trans-1,2-Diaminocyclohexane Derivatives as Chiral Reagents, Scaffolds, and Ligands for Catalysis: Applications in Asymmetric Synthesis and Molecular Recognition

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Received March 18, 1997 (Revised Manuscript Received August 1, 1997)

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I. Introduction

Asymmetric synthesis has witnessed a burgeoning activity in the discovery, development, and application of numerous methods for the creation of stereogenic centers with high levels of enantio- and/or diastereoselectivity in recent years.[1] Indeed, the development of stereoselective reactions to form C−H, C−C, C−O, C−halogen, C−N, C−S, C−P, N−O, and S−O bonds using a stoichiometric or a catalytic[2] quantity of a chiral reagent has reached unprecedented levels of diversity, efficiency, and applicability. Some of these chiral motifs have become the reagents of choice in daily research activities, as well as for large-scale production of drugs and fine chemicals.[3] The sources of these reagents are numerous, ranging from enantiopure readily available compounds[4,5] to designed variants

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S0009-2665(94)00757-0 CCC: $28.00

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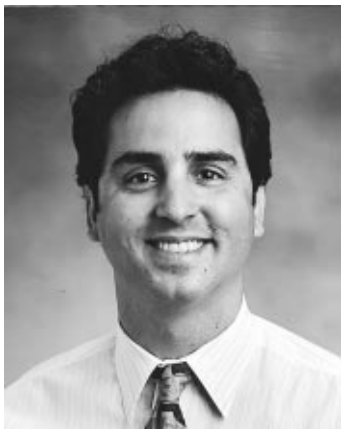
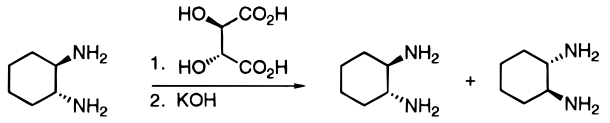


Dr. Youssef L. Bennani grew up in Casablanca, Morocco. In 1980 he moved to Montreal, Canada, where he received his B.Sc. (1984), M.Sc. (1986), and Ph.D. (1991) from the Université de Montréal, under the guidance of Professor Stephen Hanessian. His doctoral work involved development of phosphorus based-synthetic methodology, synthesis, and crystallographic studies. After a postdoctoral stay with Professor K. Barry Sharpless at The Scripps Research Institute working on the osmium tetraoxide catalyzed asymmetric dihydroxylation of olefins, he joined Ligand Pharmaceuticals, working in the area of retinoids and oncology. Since 1996, he has been a Group Leader at Abbott Laboratories first in Metabolic Diseases Research and now in Infectious Diseases Research. His research interests include organic and medicinal chemistry and molecular biology with applications to therapeutically relevant biological systems.

which bear the appropriate structural and electronic features for the intended specific reaction. As developments in the field of asymmetric synthesis progress, the choice of chiral reagents for any transformation is made by a combination of *efficiency, availability, and economy*. In this article, we shall review the utility of enantiomerically pure *trans*-1,2-diaminocyclohexane derivatives as broad-range chiral reagents and ligands for catalytic cycles in the field of asymmetric synthesis. A brief overview of the fascinating aspects of applications in the field of molecular recognition will also be given.

trans-1,2-diaminocyclohexane (*trans*-DACH, **1**) was first reported in 1926 by Wieland and co-workers,[6] who obtained it from hexahydrophthalic acid by conversion to the hydrazide followed by a Curtius reaction. A variety of syntheses have been reported since.[7] Today, this C_2 symmetrical diamine is commercially available[8] at relatively low cost, since it is a component in a byproduct amine stream generated during the purification of 1,6-hexanediamine, which is used in the manufacture of Nylon 66.[9] It is easily resolved in aqueous medium using D- or L-tartaric acid to give the (*R,R*)-**1.2** or the (*S,S*)-**1.3** enantiomer, respectively, in enantiopure form (Scheme 1).[10]

Scheme 1



1.1 Rac.-*Trans* **1.2** *(R,R)* **1.3** *(S,S)*

The pure enantiomers are generally derivatized to serve as powerful stereodirecting reagents or ligands in asymmetric synthesis, as chiral stationary phases in chromatographic separation, in molecular recognition, and as chelating agents for many minerals and metals. In spite of its ready availability, its utility in asymmetric organic reactions remained unexploited for many years until the studies by Fujita and co-workers[11] in asymmetric hydrogenation of α-acylaminoacrylic acids (see section 4.1) and by Hanessian and co-workers[12] in asymmetric C−C bond forming reactions (see section 1.1). A host of other asymmetric processes based on this chiral motif have been developed since then, which are highlighted in this review.

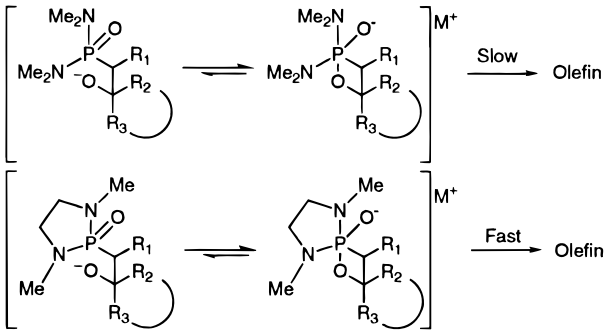
II. Asymmetric C–C Bond Forming Reactions

A. Olefination

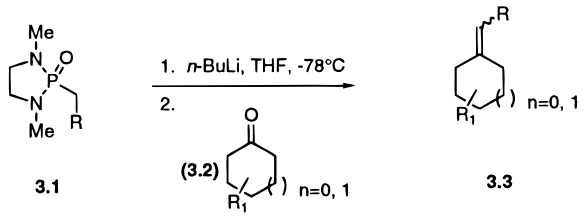
The formation of olefinic bonds is one of the cornerstones in synthetic organic chemistry. The most widely used methods to form C=C bonds are the Wittig[13] and the Horner−Emmons−Wadsworth[14] reactions and their variants. The first successful method for the direct asymmetric olefination of achiral cycloalkanones with preparatively significant enantio- and diastereoselectivity was reported in 1984, utilizing derivatives of cyclic phosphoric acid amides (hereafter referred to as "phosphonamides") prepared from enantiomerically pure (*R,R*)- and (*S,S*)-1,2-diaminocyclohexane.[12] The reaction of achiral acyclic phosphonamide anions with aldehydes and ketones has been reported by Corey and co-workers.[15] Although the carbanions derived from these reagents showed good reactivity toward ketones, the corresponding β-alkoxy phosphonamide anions required heating to effect elimination to the desired olefins. Stereoelectronic requirements, the nature and orientation of the substituents, and the phenomenon of pseudorotation at phosphorus play critical roles in such eliminations.[16,17] It is well-known that the apical positions are preferentially occupied by the more electronegative groups (O, N, etc.), while the charged oxide anion adopts an equatorial position (Scheme 2).[18]

It was of interest to investigate the reactivity of anions derived from cyclic phosphonamides toward ketones and aldehydes (Scheme 3).[19] Interestingly, the anions of these alkyl cyclic phosphonamides added to a variety of ketones and aldehydes to give, after quenching with acetic acid at −78 °C, the

Scheme 2



Scheme 3

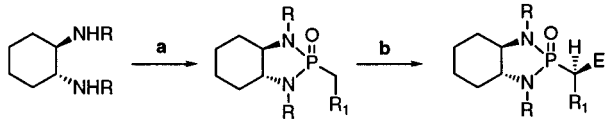


R= Me; Et, Allyl; Crotyl; -CH_2Ph, -CH_2CO_2Me

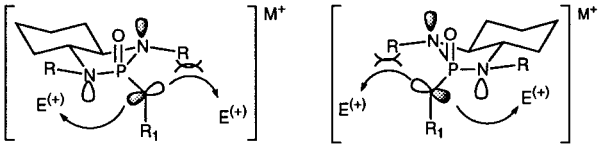
corresponding olefins in good yields. The facile fragmentation of the cyclic phosphonamides at much lower temperatures compared to the analogous oxaphosphetanes in the acyclic series[15] is noteworthy. Trisubstituted olefins have been prepared with anions of monocyclic β-ketophosphonamides and ketones.[20,21]

Hanessian and co-workers[22] had previously considered the design of an asymmetric version of this reaction by exploiting *trans*-1,2-diaminocyclohexane as a chiral framework. Because of the C_2 symmetry of this molecule, the stereoelectronic requirements on the two nitrogen atoms attached to the phosphorus atom in a bicyclic rigidified core, and the overall topology of the resulting enantiomerically pure alkyl phosphonamides, it was expected that the corresponding stabilized carbanions would exhibit diastereofacial bias in their reaction with electrophiles as illustrated in Scheme 4.

Scheme 4



a. $Cl_2P(O)CH_2R_1$; **b**. Base, Electrophile $E^{(+)}$

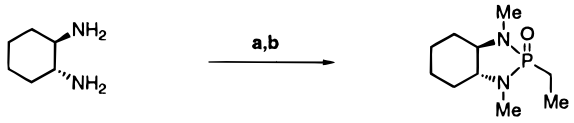


Favored ,"Left cleft" Enantiofacial approach **A**

Favored "right cleft" Enantiofacial approach **B**

It has subsequently been demonstrated through deprotonation/deuteration/alkylation experiments that the carbanions derived from ethyl and benzyl phosphonamides have a planar geometry.[23] The observed enantioselectivities (see section 1.6.2) are the result of a combination of the positioning and size of the *N*-alkyl groups, the reaction temperature, and the nature of the electrophile. From the preparative standpoint, (*R,R*)-1,2-diaminocyclohexane was converted to the corresponding *N,N′*-dimethyl derivative[24] which, upon treatment with alkyl phosphonic dichlorides in the presence of triethylamine, gave enantiomerically pure alkyl phosphonamides of type **5.2** in good overall yields (Scheme 5). Although other *N,N′*-dialkyl derivatives were prepared, the bulk of the work was done with the *N,N′*-dimethyl derivative which proved to be quite efficient. Two other preparations of these bicyclic phosphonamides were recently reported.[25]

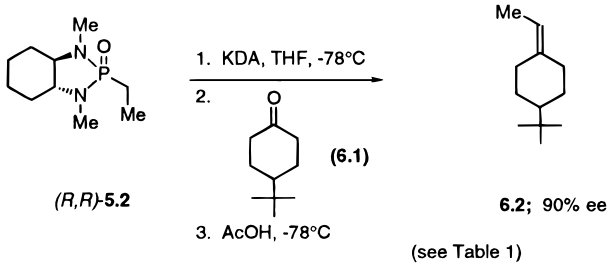
Scheme 5



a. i. $ClCO_2Et$, NaOH, C_6H_6; ii. LAH, THF
b. $Cl_2P(O)Et$, Et_3N, C_6H_6, 25°C

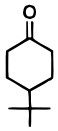
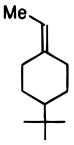
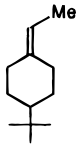
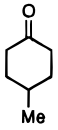
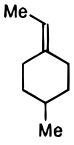
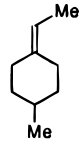
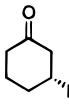
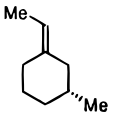
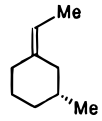
Several novel *N,N′*-dimethyl and *P*-alkyl bicyclic phosphonamides[12,25−27] were prepared, and their reactivities as asymmetric olefination reagents were evaluated. For example, treatment of the (*R,R*)-ethyl phosphonamide **5.2** with KDA at low temperature, followed by the addition of a symmetrical ketone such as 4-*tert*-butylcyclohexanone (**6.1**) and a quench of the reaction at −78 °C with acetic acid gave (*R*)-4-*tert*-butylethylidenecyclohexane (**6.2**) in a good yield (82%) and high enantionselectivity (90% ee) (Scheme 6). The enantiomeric (*S*)-4-*tert*-butylethylidenecyclohexane was similarly obtained from the (*S,S*)-ethyl phosphonamide. A variety of bases, solvents, temperatures, additives, and ketones were surveyed. In the case of the ethyl phosphonamides, the use of KDA led to the olefins with higher enantio- or diasteroselectivities compared to those of LDA (Table 1).[26]

Scheme 6

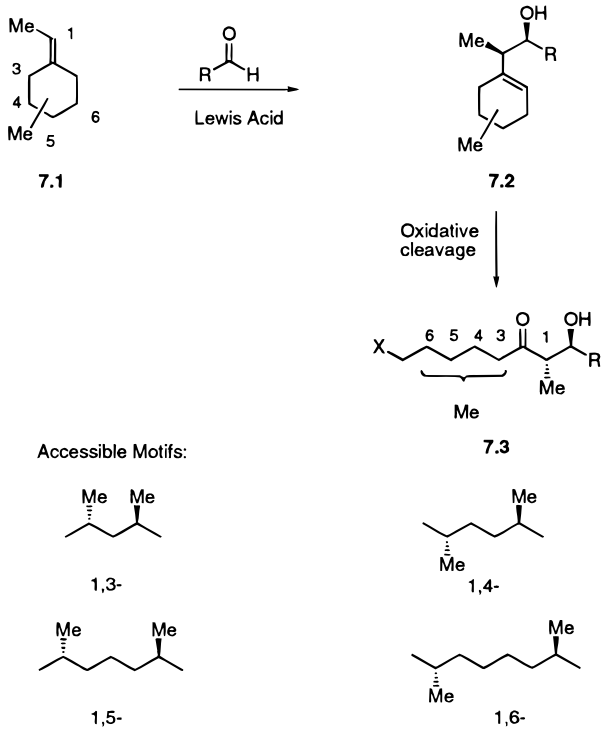


It has also been recently demonstrated that these olefinic adducts can serve as versatile stereogenically defined precursors for alicyclic and acyclic compounds with alternate and remote *C*-methyl substitution patterns via sequential asymmetric olefination−ene reactions, followed by oxidative ring opening (Scheme 7).[27]

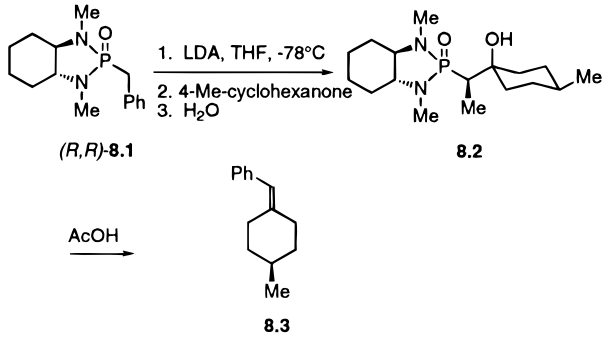
Table 1. Asymmetric Olefination of Cyclic Ketones with Ethyl Phosphonamide (*R,R*)-5.2 and Its (*S,S*)-Antipode

Entry	Ketone	Reagent	Olefin	ee	Entry	Reagent	Olefin	ee
1		*(R,R)*-**5.2**		90%	4	*(S,S)*		90%
2		*(R,R)*-**5.2**		69%	5	*(S,S)*		70%
3		*(R,R)*-**5.2**		86%	6	*(S,S)*		86%

Scheme 7



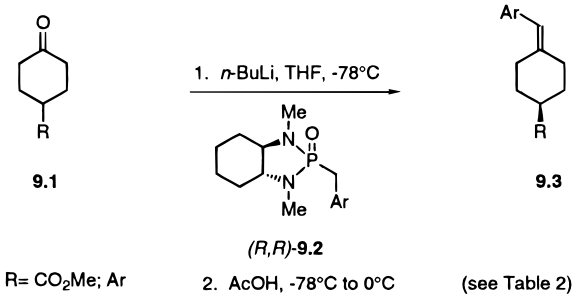
Scheme 8



Benzylidene Cyclohexanes. The lithium anions derived from (*R,R*)-benzyl phosphonamide **8.1** and its enantiomer can be used for the asymmetric benzylidation of cyclohexanones with high levels of enantiomeric and diastereomeric purities and excellent yields (Table 2). Kinetic resolution was achieved with α-substituted cyclohexanones where stereodifferentiation could be maximized in the transition state[26] (Scheme 8). The structures of the products, and the absolute configurations at the newly formed stereogenic centers in the intermediate β-hydroxy phosphonamides were conclusively established by X-ray analysis in a number of cases. The isolation of intermediates such as **8.2** corroborated the predictions made for the approach of the electrophile in the original model (Scheme 4). It is of interest that the mismatched pair of (*S,S*)-reagent and ketone gave a product with a lower diastereomeric ratio compared to that of the matched pair (Table 2, entries 6 and 3, respectively).

Recently, Schuster and co-workers[28] prepared chiral 4-substituted benzylidenecycloalkanes by the above procedure (Scheme 9), and they disclosed their use as photoswitchable chiroptical liquid crystalline materials. Enantiomeric excesses up to 88% were recorded in these substituted cycloalkane systems.

Scheme 9

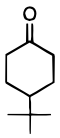
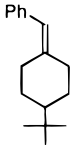
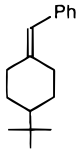
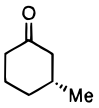
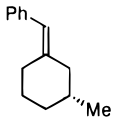
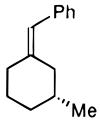
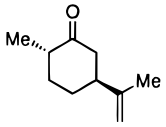
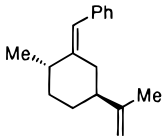
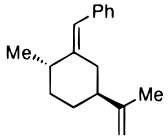


Allylidene Cyclohexanes. Asymmetric olefination of substituted cyclohexanones with (*R,R*)-allyl phosphonamide **10.1** (and its *S,S*-enantiomer) gave the corresponding dienes essentially as single enantiomers or diastereomers (Scheme 10).[26]

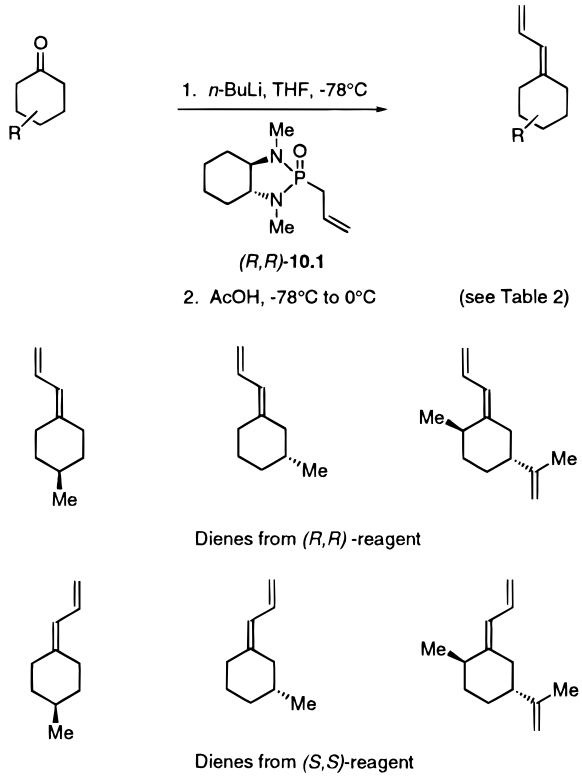
B. 1,4-Conjugate Additions

1,4-Conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is an important and well-documented method for functionalizing organic molecules.[29,30] In these reactions, the addition occurs at the β-carbon of an electron-deficient

Table 2. Asymmetric Olefination of Cyclic Ketones with Benzyl Phosphonamide (*R,R*)-8.1 and Its (*S,S*)-Antipode

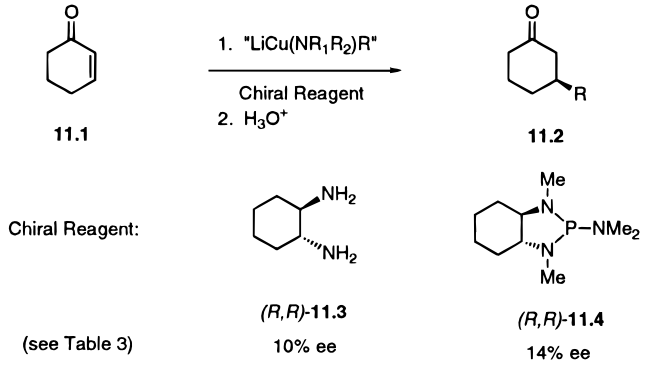
Entry	Ketone	Reagent	Olefin	Ratio	Entry	Reagent	Olefin	Enantiomer or Diastereomer Ratio
1		*(R,R)*-**8.1**		>99:1	4	*(S,S)*		99:1
2		*(R,R)*-**8.1**		98:2	5	*(S,S)*		98:2
3		*(R,R)*-**8.1**		99:1	6	*(S,S)*		61:39

Scheme 10



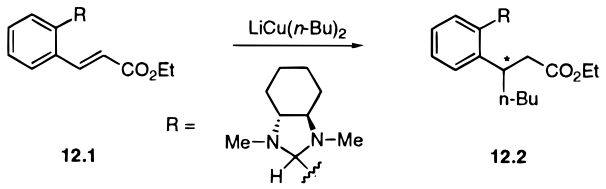
alkene, giving first an enolate which can be quenched with an electrophile to give the corresponding vicinally substituted adduct. α,β-Unsaturated derivatives of ketones, aldehydes, esters, amides, sulfoxides, phosphonates, or nitro compounds are usually used in this reaction. The following paragraphs will outline the use of 1,2-diaminocyclohexane derivatives as chiral reagents in asymmetric conjugate additions. The addition of phenylmagnesium bromide in the presence of a copper salt and (*R,R*)-1,2-diaminocyclohexane to 2-cyclohexenone gave the expected conjugate addition product in 66% yield and a low ee (10%).[31a] A related reaction in the presence of (*R,R*)-*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane gave a racemic adduct.[31b] In another case, modest levels of enantioselectivity in the reaction of dibutyl lithiocuprate with 2-cyclohexenone in the presence of phospholane **11.4** were reported[32] (Scheme 11).

Scheme 11



The same authors have reported a great increase in diastereoselectivities in the addition of lithium dimethylcuprate to ethyl cinnamate bearing chiral acetals, oxazolines, and *N,N′*-dimethyl-1,2-diaminocyclohexane-derived imidazolidines in the *ortho* position. The enantiomeric excesses ranged from 15% to 96% ee (Scheme 12, Table 3).[33]

Scheme 12

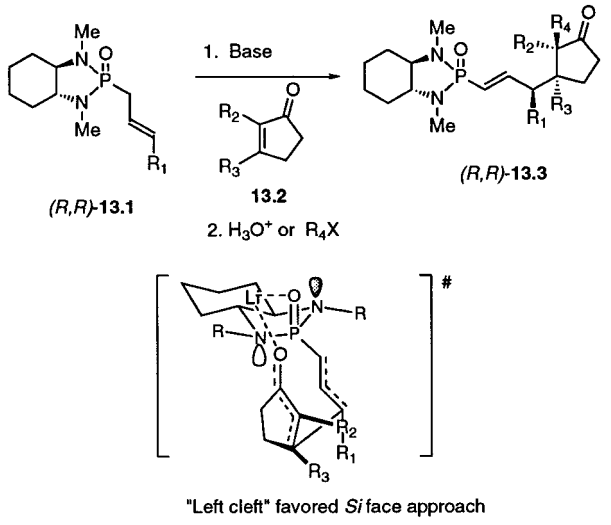


In spite of the significant recent advances in asymmetric 1,4-conjugate addition reactions involving catalysts or substrates having chiral substituents, relatively few examples are known in which the transferred carbon moiety is an allylic-type anion and part of the chiral reagent.[34] Highly stereocontrolled asymmetric 1,4-conjugate additions to α,β-unsaturated cyclic ketones, lactones, lactams, and esters with anions of enantiomerically pure chiral allyl and crotyl

Table 3. Asymmetric 1,4-Cuprate Addition to Cinnamic Imidazolines of Type 12.1

Entry	Cuprate	% Yield	% ee	*R/S*
1	$LiCuMe_2$	85	94	*S*
2	$LiCu(n\text{-}Bu)_2$	90	95	*S*
3	$LiCuPh_2$	84	96	*R*
4	$LiCu(CH{=}CHCH_2CH_3)_2$	80	90	*R*
5	EtMgBr, CuI	73	93	*R*

Scheme 13



phosphonamides were recently reported.[35a] Thus, it is possible to generate as many as three contiguous stereogenic centers containing a combination of secondary, tertiary, and quaternary substituents, at will, in a single step (Scheme 13). The consistently high diastereoselectivities in these 1,4-conjugate addition reactions in the examples shown, can be rationalized on the basis of the highly organized lithium-chelated entities resulting from the reagent **13.1** and the enone. A model that rationalizes the sense of enantioselectivity involves a favored transition state in which the lithium-chelated enones are best accommodated within the "left-cleft" of the (*R,R*)-reagent (Scheme 13). The stereochemical outcome of this reaction for a number of substrates is summarized in Table 4.

The adducts from this addition reaction can be further cleaved by ozonolysis to the corresponding aldehydes and the latter reduced to alcohols, respectively, as shown in Scheme 14. Many highly functionalized and diastereomerically enriched products could be expediently prepared using this method, and applications in natural products synthesis are emerg-

Scheme 14

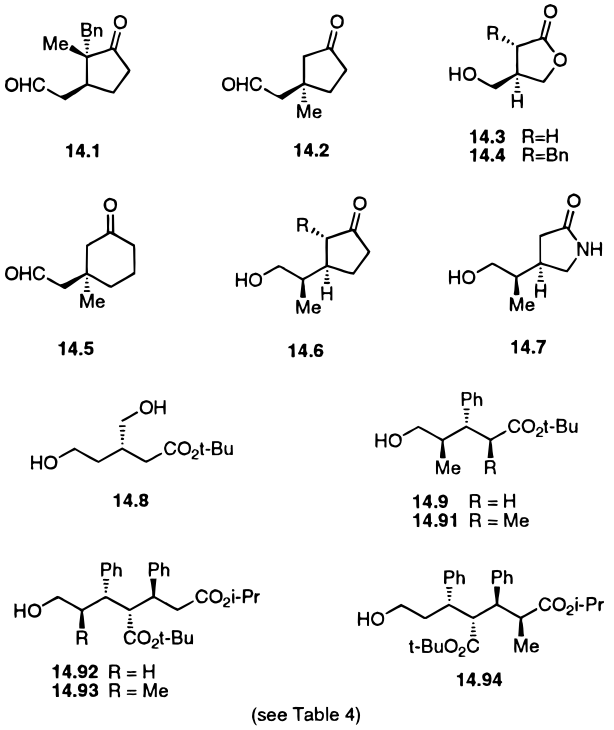
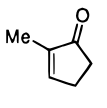
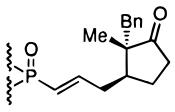
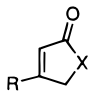
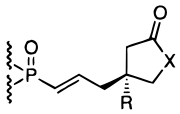
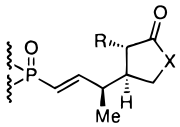
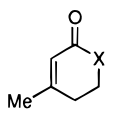
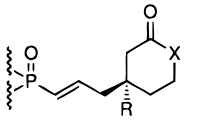
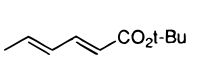
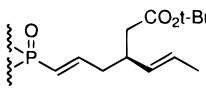
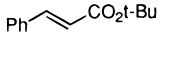
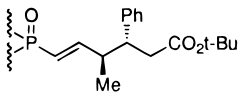
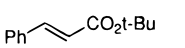
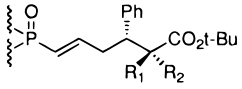


Table 4. Asymmetric 1,4-Conjugate Addition of Phosphonamide (*R,R*)-13.1 to α,β-Unsaturated Carbonyl Systems

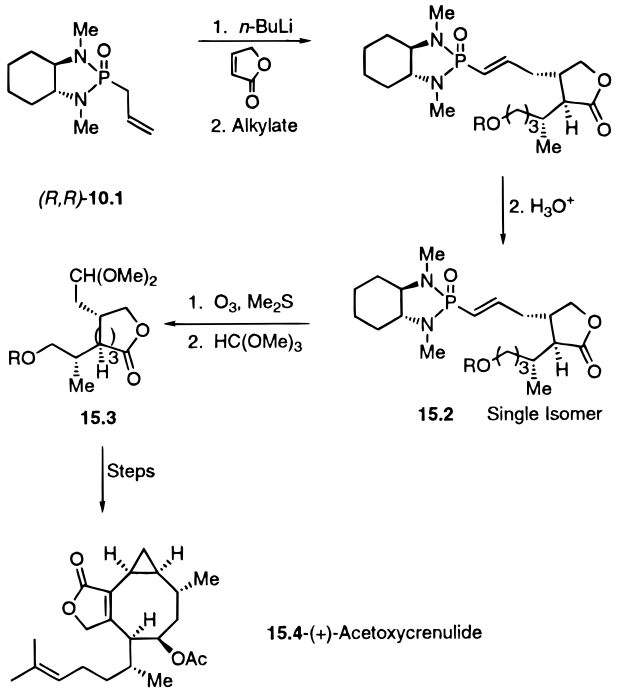
Entry	Substrate	Product	Diastereomer Ratio, ^{31}P
1			>99:1
			
2	X=C, R=Me		95:5
3	X=NPNB, R=H		99:1
			
4	X=C, R=H		96:4
5	X=O, R=H or Bn		99:1
6	X = NPNB, R = H		95:5

Entry	Substrate	Product	Diastereomer Ratio, ^{31}P
			
7	X=C, R = Me		90:10
8	X=O, R = H		93:7
9			99:1
10			99:1
11			99:1

R_1 = H, R_2 = Me; R_1 = Me, R_2 = H

ing. For example, a key step in the total synthesis of (+)-acetoxycrenulide by Paquette and co-workers[36] utilizes such a technology (Scheme 15). In this

Scheme 15



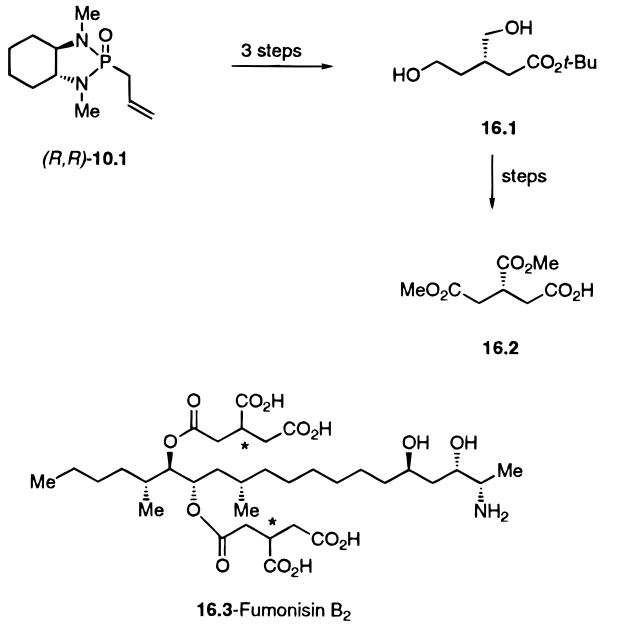
synthesis, butenolide **15.1**, underwent clean asymmetric 1,4-conjugate addition with the anion derived from allyl phosphonamide **10.1**, to give the addition product **15.2** as a single isomer in 81% yield.

The configurations at both α and *β* positions were fixed as a direct consequence of the inherent chirality of phosphonamide **10.1**. The absolute stereochemistry was assigned based on the proposed model,[35a] and further confirmed by arriving to the natural product after several steps.

Boyle and Kishi[37] reported the utilization of the same allyl phosphonamide **10.1** in studies aimed at establishing the absolute stereochemistry of fumonisin B_2 **16.3**, which is a member of a family of mycotoxins (Scheme 16). The addition of the lithium anion of phosphonamide **10.1** to *tert*-butyl sorbate gave, after oxidative cleavage and functionalization, the corresponding dimethyl ester monocarboxylic acid **16.2**. Similarly, the (*S,S*)-allyl phosphonamide enantiomer of **10.1** gave the ester of opposite configuration to **16.2**.

The phosphonamide anion technology has also been successfully applied to effect sequential Michael-type additions to cinnamate esters.[35b] Thus as many as four contiguous stereogenic centers could be generated in a one-pot reaction with high diastereoselectivity when two cinnamate esters are added in sequence (Scheme 14).

Scheme 16

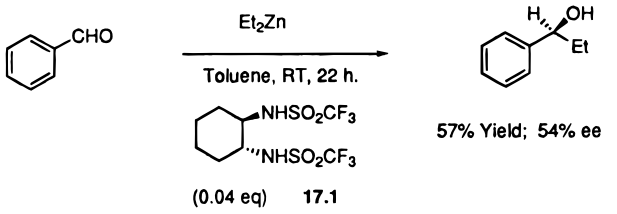


C. 1,2-Nucleophilic Additions

1. Addition to Aldehydes

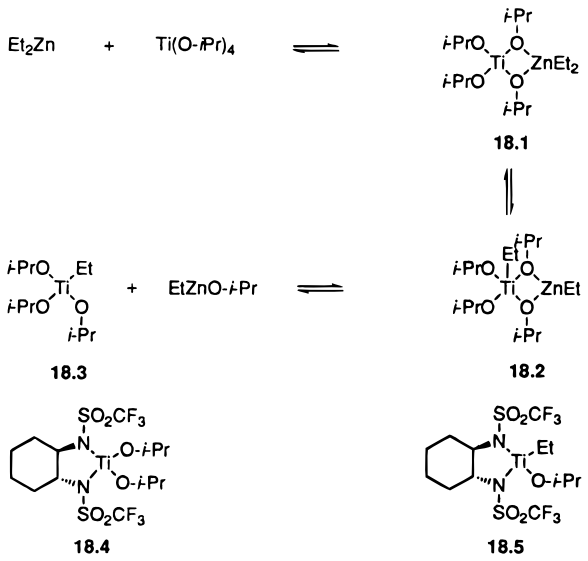
Nucleophilic addition reactions to aldehydes and ketones are important chemical transformations that create chirality at secondary and tertiary carbon centers, respectively. To achieve this reaction in a highly enantioselective and catalytic fashion has been the focus of much research efforts in the past decade. Originally, Lewis acids (LAs) modified by chiral alcohols and amines were utilized as reagents for chiral induction and catalysis in the addition of diethyl zinc to a variety of aromatic aldehydes.[38] To achieve a more efficient catalytic process, Kobayashi and co-workers[38] reasoned that, in addition to the stereocontrol and the facile exchange of the product with the substrate on the catalyst, the rate accelerating effect of the catalyst could be important. On the basis of these considerations, a modified LA with an electron-withdrawing group on the amines of the chiral ligand derived from *trans*-1,2-diaminocyclohexane was considered. In such a modified LA, the ligand will not only provide the chiral environment but also increase the acidity of the LA. Accordingly, the addition of Et_2Zn, and (*R,R*)-*N,N′*-bis(trifluoromethanesulfonyl)-1,2-diaminocyclohexane (**17.1**) to benzaldehyde in toluene gave the addition product in 57% yield and 54% ee (Scheme 17).

Scheme 17



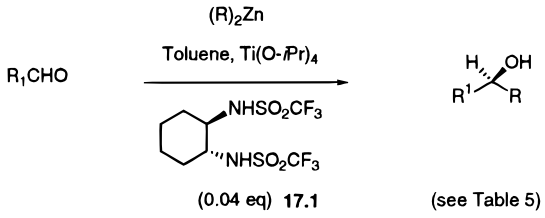
Subsequently, it was found that the addition of a catalytic amount of Ti(O-*i*-Pr)$_4$ accelerated the reaction and enhanced the enantiomeric excess (Scheme 18). ^{1}H-NMR studies[38] suggested that the treatment of Et_2Zn with Ti(O-*i*-Pr)$_4$ generates an equilibrium mixture of species such as **18.1**−**18.5**, in either a monomeric or complex polymeric state. The chiral ethyltitanium species **18.5**, possibly generated from Et_2Zn and complex **18.4**, might be more reactive than any other ethylmetal species due to its attachment to an electron-withdrawing sulfonamide. Many alkyl sulfonamides, dialkyl zinc reagents, and aldehydes

Scheme 18



using a variety of catalyst-to-reagent ratios at different temperatures were screened as listed in Table 5 (Scheme 19).

Scheme 19



Although the exact structures of the active species are not clear, a possible catalytic cycle is shown in Scheme 20. The chiral ethyltitanium species **20.3** might be initially generated by the reaction of the chiral titanate **20.2** and the achiral ethyltitanium species A (and/or Et_2Zn). Intermediate **20.3** reacts with an aldehyde to form dialkoxytitanium **20.5**, which in turn reacts with the ethyltitanium species **20.1** (or Et_2Zn) to regenerate **20.3**, thus establishing the catalytic cycle. The remarkable efficiency observed in this system is the result of the high reactivity of ethyltitanium species **20.3** and the extremely facile regeneration of **20.3** from **20.5**.

Table 5. Enantioselective Addition of Dialkylzinc Reagents to Aldehydes[a]

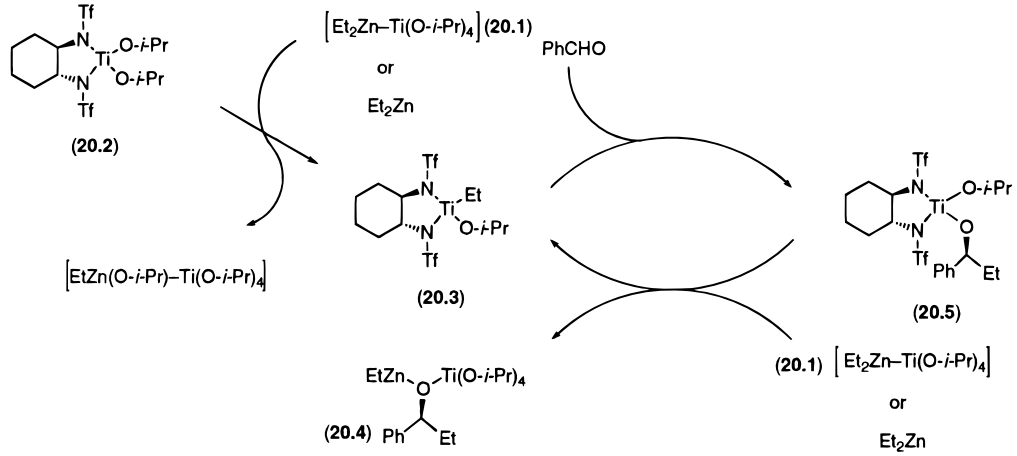
Entry	Aldehyde	Ti(O-*i*-Pr)$_4$ (eq.)	$R^2{}_2Zn$	% Yield	% ee
1	PhCHO	1.3~1.5	$(CH_3)_2Zn$	99	73
2	PhCHO	1.3~1.5	$(n\text{-}C_4H_9)_2Zn$	98	97
3	PhCHO	1.3~1.5	$(n\text{-}C_5H_{11})_2Zn$	99	99
4	PhCH=CHCHO	0.3	$(C_2H_5)_2Zn$	85	99
5	$PhCH_2CH_2CHO$	0.6	$(C_2H_5)_2Zn$	Quant.	92
6	$n\text{-}C_5H_{11}CHO$	0.6	$(C_2H_5)_2Zn$	78	99

[a] Catalyst: entries 1, 5, and 6, 0.04 equiv; entries 2−4, 0.02 equiv.

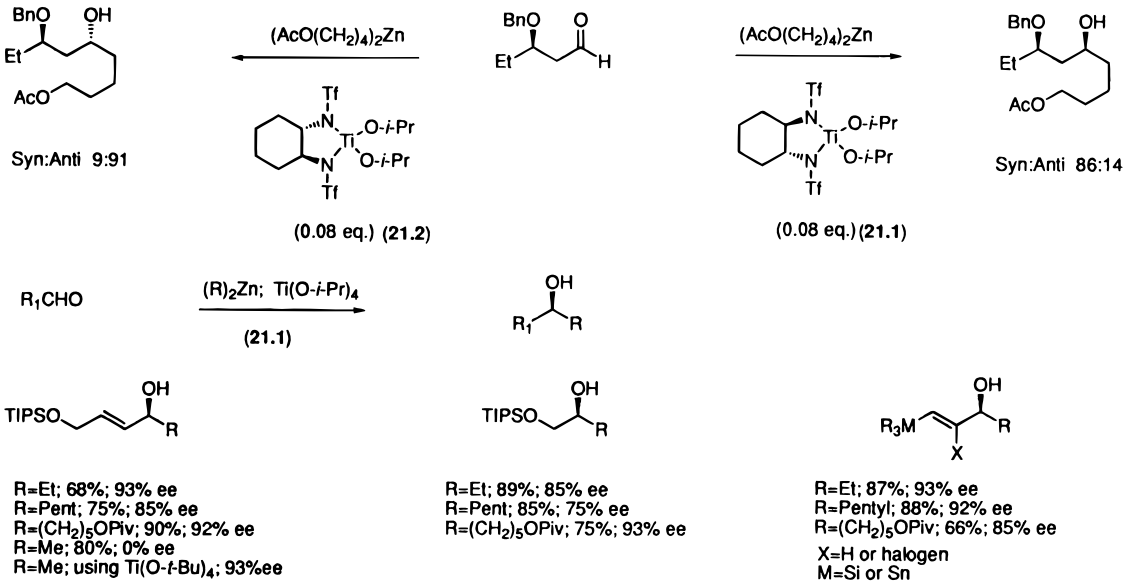
Dialkylzinc reagents are now readily available through either the iodine−zinc exchange reaction or its copper salt catalyzed version. Various applications of this methodology were recently reported by Knochel and co-workers,[39,40] who utilized the Kobayashi ligand[38] (**21.1** or **21.2**), to prepare many functionalized secondary alcohols, in a highly enantioselective fashion. Addition of these dialkylzinc reagents to simple as well as functionalized α,β-unsaturated aldehydes was achieved in a highly efficient and stereoselective manner (Scheme 21).[39,40]

Knochel and co-workers[40] propose a slightly modified catalytic cycle for the above dialkylzinc addition to aldehydes. The *N*-trifluoromethanesulfonyl groups of the C_2 symmetrical ligand are responsible for the orientation and conformation of the two isopropoxy ligands, which influences the position of the coordinated aldehyde. The coordination of the dialkylzinc organometallic species to the two isopropoxy ligands prior to the transfer of the alkyl group to the carbonyl moiety should also be favored and will lead to the highly ordered bimetallic complex **B** (Scheme 22). The role of Ti(O-*i*-Pr)$_4$ is to remove the zinc alkoxide from the titanium center by forming the mixed complex (R^1−OZnR−Ti(O-*i*-Pr)$_4$ such as **C**, which then gives the alcohol upon treatment with water.

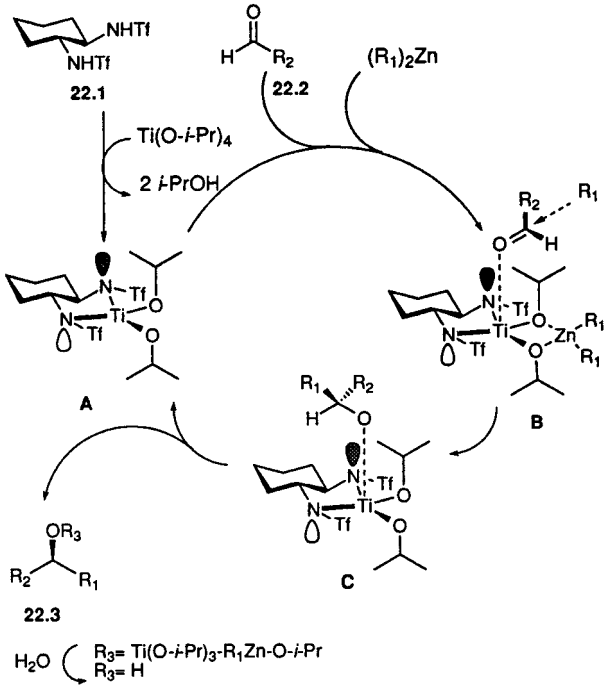
Scheme 20



Scheme 21



Scheme 22



Variations on the same theme for the enantioselective addition of diethylzinc to aldehydes were recently reported by Zhang and co-workers.[41] Tetradentate titanium ligands, based on *trans*-1,2-diaminocyclohexane *o*-hydroxybenzene sulfonamides, were prepared, and their levels of asymmetric control during this reaction were determined. The best results were obtained in the case of aromatic aldehydes.

In another approach, Shono and co-workers[42] reported that electroreduction of diimines, derived from (*S*,*S*)-1,2-diaminocyclohexane and aromatic aldehydes in acidic media, gave the corresponding intramolecularly coupled 2,3-diarylpiperazines stereoselectively. These piperazines served as highly efficient catalysts in the 1,2-nucleophilic addition of diethylzinc to aldehydes (Scheme 23, Table 6).

Scheme 23

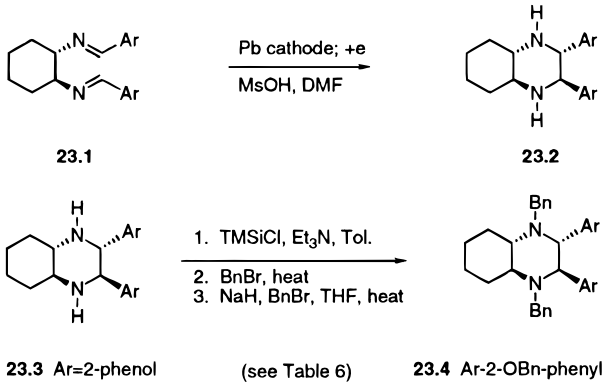


Table 6. 1,2-Nucleophilic Addition of Diethylzinc to Aldehydes Catalyzed by Diarylpiperazines of Type 23.4

Entry	Aldehyde	% Yield	% ee
1	PhCHO	85	99
2	PhCH=CHCHO	90	88
3	4-MeO-PhCHO	95	99
4	*n*-C_6H_{13}CHO	91	81

2. Addition to Hydrazones

Chiral aminals used as auxiliaries and protective reagents of glyoxal monohydrazone undergo a stereoselective 1,2-nucleophilic addition reaction.[43] Hydrogenation and hydrolysis of the addition products gave the corresponding α-aminoaldehydes in optically pure form (Scheme 24).

Better selectivities were obtained in the case of aminals derived from (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diamino-1,2-diphenylethane (**24.4**) compared to those derived from (*S*,*S*)-1,2-diaminocyclohexane (**24.3**). Interestingly, dramatic effects were observed upon the variation of solvents and additives such as LiBr with enantioselectivities reaching up to 95% (Table 7).

Scheme 24

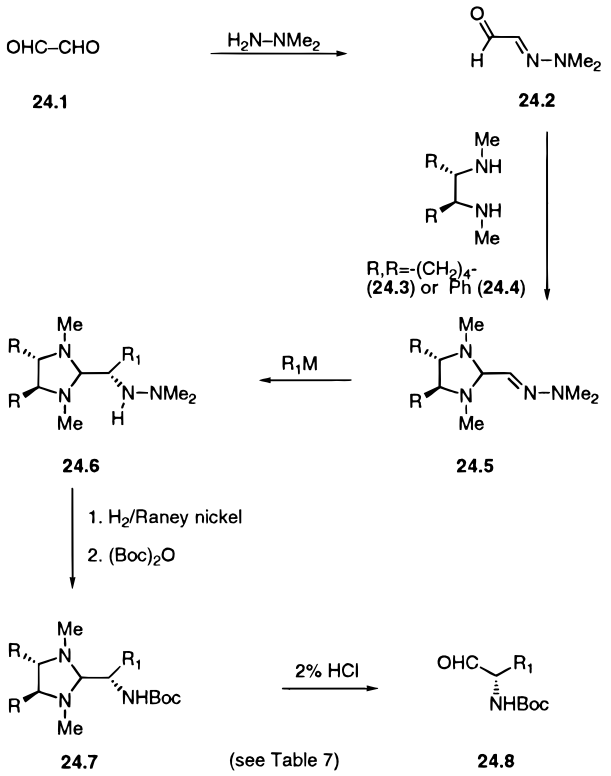


Table 7. Addition of Dialkyllithium Reagents to Aminals of Type 24.5

Entry	Aminal	Organometallic reagent R^1M	% Yield	% de
1	**24.3**	MeLi-LiBr (in Et_2O)	90%	20
2	**24.3**	MeLi-LiBr (in THF)	90%	40
3	**24.4**	MeLi-LiBr (in THF)	90%	96
4	**24.4**	*n*-BuLi (in THF)	90%	99
5	**24.4**	PhLi-LiBr (in THF)	90%	99
6	**24.4**	Me_2C=CHLi-LiBr (in THF)	85%	99

3. Addition to Imidazolidines

Monoprotected phthalaldehydes bearing a chiral imidazolidine auxiliary derived from (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diamino-1,2-diphenylethane and (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diaminocyclohexane were reacted with various organometallic reagents to give the corresponding secondary alcohols.[44] While lithium organocuprates gave almost exclusively one diastereomer, organomanganese reagents gave the opposite diastereomer. Hydrolysis of the aminal moiety afforded the enantiomerically pure lactols (Scheme 25). In this case, both chiral auxiliaries displayed high degrees of asymmetric induction, albeit in opposite directions (Table 8).

This intriguing inversion in the sense of asymmetric induction was rationalized on the basis of chelation and steric factors as depicted in Scheme 26 for the corresponding (*R*,*R*)-diamine derivative. Thus, considering a front-side attack on the carbonyl group with a 109° angle, conformer B would be favored over A. In a related case, it has been demonstrated that the addition of lower alkyl cuprates onto imidazolidines derived from 3-formylpyridine proceeded with

Scheme 25

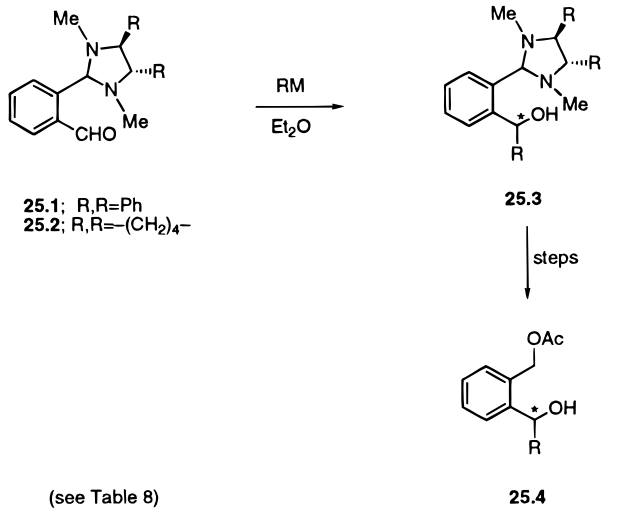
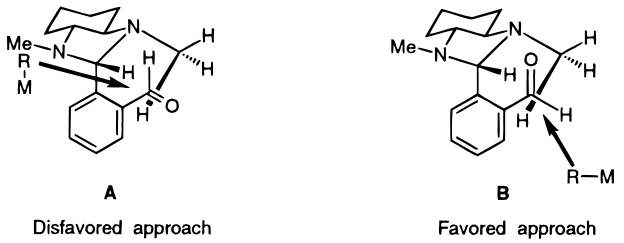


Table 8. Addition of Organometallic Reagents to Chiral Imidazoles of Type 25.1 and 25.2

Entry	Imidazolidine	Organometallic reagent	% Yield	% de	Confg.
1	**25.1**	BuMnBr	64	99	R
2	**25.1**	Bu_2CuLi	70	100	S
3	**25.1**	Me_2CuLi	71	100	S
4	**25.1**	Ph_2CuLi	72	9	S
5	**25.2**	Bu_2CuLi	89	90	R
6	**25.2**	Me_2CuLi	55	90	R
7	**25.2**	Ph_2CuLi	70	98	R
8	**25.2**	$(Et\text{-}CH{=}CH)_2CuLi$	42	72	R

Scheme 26



up to 80% de when *N*,*N*′-dimethyl-1,2-diamino-1,2-diphenylethane was used as chiral auxiliary. Derivatives of 1,2-diaminocyclohexane gave ~10% ee in this addition reaction.

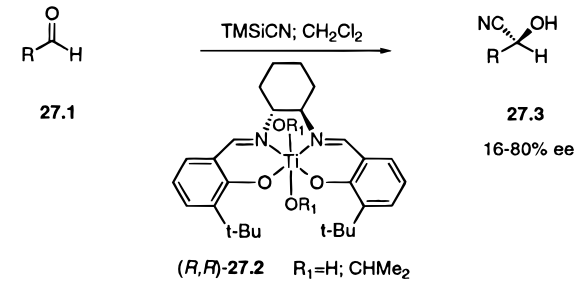
4. Addition to Prochiral Ketones and Aldehydes

Various derivatives of *trans*-1,2-diaminocyclohexane have been utilized in asymmetric reactions that involve the addition of optically active chelated organometallic compounds with various counterions (Li, Be, Mg, Zn, etc.) to prochiral unsaturated substrates. For example, the addition of (*R*,*R*)- or (*S*,*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane–$LiAlH_4$ complex to acetophenone or to benzaldehyde afforded the corresponding alcohols. The optical purities of the adducts ranged from 4–19% ee depending on the ratios of chelate to substrate and the solvent used.[45]

5. Trimethylsilylcyanation of Aldehydes

Recently, chiral (salen)-Ti(IV) catalysts prepared in situ from Ti(O-*i*-Pr)$_4$ and (*R,R*)-[*N,N′*-bis(2′-hydroxy-3′-*tert*-butylbenzylidene)]-1,2-diaminocyclohexane were used in the synthesis of trimethylsilyl cyanohydrins of a set of aromatic and α,β-unsaturated aldehydes. The recorded ee's were in the range 40−80% (Scheme 27).[46]

Scheme 27

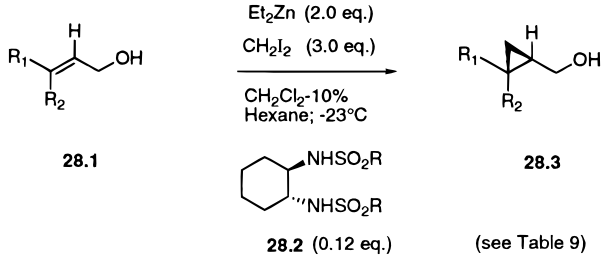


D. Asymmetric Cyclopropanation

1. Catalytic Asymmetric Cyclopropanation of Allylic Alcohols

Within the class of catalytic and enantioselective C−C bond forming reactions, cycloadditions of the [4 + 2], [2 + 2], and [2 + 1] types have attracted continued and increasing attention.[47] In particular, enantioselective cyclopropanation has been the focus of much research since the seminal work of Nozaki and co-workers[48] in 1966. Thus, highly efficient enantioselective cyclopropanations catalyzed by bis(oxazoline)copper complexes have been reported using diazoacetate derivatives as the source of electrophilic carbon.[49] It is known that cyclopropanation of an allylic alcohol or its ether derivative proceeds much faster than that of a simple olefin under the Simmons−Smith conditions (Et$_2$Zn−CH$_2$I$_2$).[50] The enhancement of reactivity is attributed to a strong affinity between the organozinc reagent and the oxygen atom.[51] In a catalytic and enantioselective system, it is believed that the Lewis acidity plays a crucial role in the turnover rate and selectivity. On the basis of these facts, Kobayashi and co-workers[52] reported in 1992 the first example of an enantioselective and catalytic version of the Simmons−Smith cyclopropanation of an allylic alcohol with Et$_2$Zn−CH$_2$I$_2$, using a chiral *trans*-1,2-diaminocyclohexane *N,N′*-disulfonamide as a ligand (Scheme 28).

Scheme 28

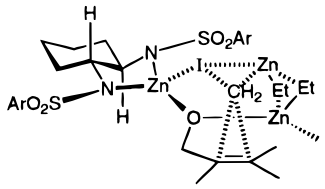


A variety of substituted aryl sulfonamides were screened as Lewis acid catalysts for this reaction. Cyclopropanation of a variety of allylic alcohols at −23 °C using Et$_2$Zn:CH$_2$I$_2$:(*R,R*)-1,2-diaminocyclohexane *N,N′*-dibenzenesulfonamide, in a 2:3:0.12 ratio in dichloromethane−hexanes (9:1), was achieved in good yields and with enantioselectivities up to 82% ee (Table 9). It is noteworthy that by using (*R,R*)-**28.2** the cyclopropanation occurred from the same face of the olefin regardless of its geometry. Presumably, a zinc complex such as that depicted in Scheme 29 was generated in situ from the chiral disulfonamide and diethylzinc.

Table 9. Catalytic Asymmetric Cyclopropanation of Allylic Alcohols of Type 28.1

Entry	R	R_1	R_2	% Yield	% ee
1	Ph	Ph	H	75	68
2	*o*-NO_2Ph	Ph	H	92	75
3	*m*-NO_2Ph	Ph	H	72	33
4	*p*-NO_2Ph	Ph	H	82	76
5	*p*-NO_2Ph	H	Ph	71	75
6	*p*-NO_2Ph	$PhCH_2CH_2$-	H	100	82
7	*p*-NO_2Ph	TrO-CH_2-	H	86	80
8	*p*-NO_2Ph	H	TrO-CH_2-	79	66

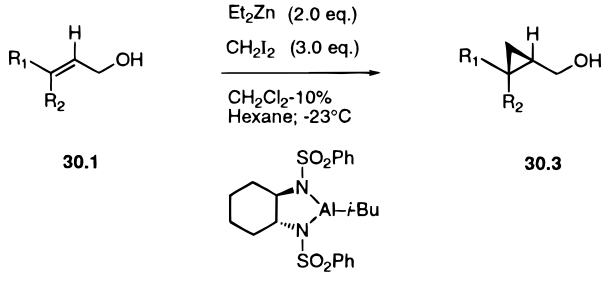
Scheme 29



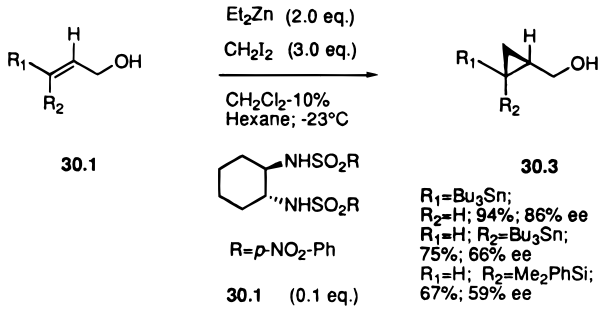
Although no experimental evidence is available on how the chiral zinc complex participates in the transition state of this reaction, it is possible that both the allylic zinc alkoxide and the iodine atom of Et$_2$Zn coordinate to the Lewis acid complex (Scheme 29). The formation of such a trinuclear complex could well account for the difference in enantioselectivity between an allylic alcohol and its methyl ether. Additionally, the coordination of the zinc atom in a complex and the involvement of the iodine atom as depicted in Scheme 29 could be responsible for the rate acceleration and the efficient turnover for catalyst **28.2**.

A variety of aluminum-based ligands derived from (*R,R*)-*N,N′*-arylsulfonyl-1,2-diaminocyclohexane derivatives have been shown to act as efficient catalysts for the cyclopropanation of cinnamyl alcohol[53] (Scheme 30). The most interesting features of these reactions

Scheme 30



Scheme 31



are (1) no decrease of enantioselectivity was observed even at higher concentrations, probably due to the solubility of the pre-prepared catalyst in dichloromethane as compared to the zinc analogue and (2) the fact that both zinc and aluminum catalysts afforded the cyclopropane adducts with similar enantioselectivities and sense of asymmetric induction. As an application of this catalytic reaction, the cyclo propanation of (*E*)- and (*Z*)-γ-silyl and γ-stannyl allylic alcohols was examined (Scheme 31).

Following Kobayashi's[52] cyclopropanations, Denmark and co-workers[54] have reported studies on the effects of various chiral diamines, temperatures, additives, solvents, and order of addition of the reagents and substrates under Simmons−Smith conditions. Modest improvement in enantiomeric excess (from 80% to 86% ee) was observed in the cyclopropanation of cinnamyl alcohol, when a full equivalent of zinc iodide was used which helps to accelerate the reaction in an autocatalytic fashion. The preformation of ethylzinc cinnamyl oxide and bis(iodomethyl)zinc plays a crucial role in this reaction. Mechanistic details of this process have not yet been reported.

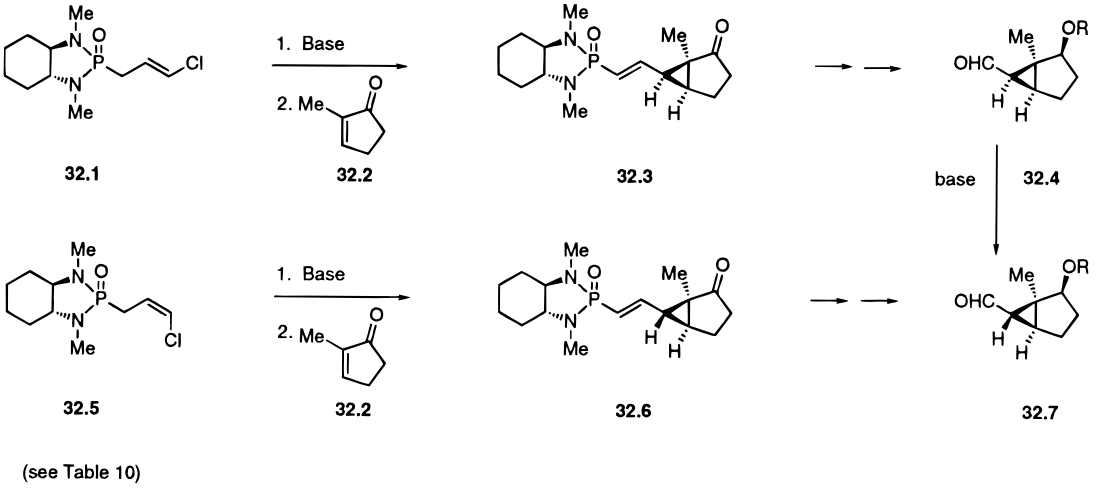
2. Catalytic Asymmetric Cyclopropanation of Unfunctionalized Olefins

Jacobsen and co-workers[55] reported preliminary results on the $CuPF_6$-catalyzed cyclopropanation of 1,2-dihydronaphthalene with ethyl diazoacetate in the presence of variety of aryl Schiff base derivatives of *trans*-1,2-diaminocyclohexane. By analogy to the corresponding copper(I)-catalyzed aziridination, it was found that the cyclopropanation proceeds through discrete monomeric copper intermediates.

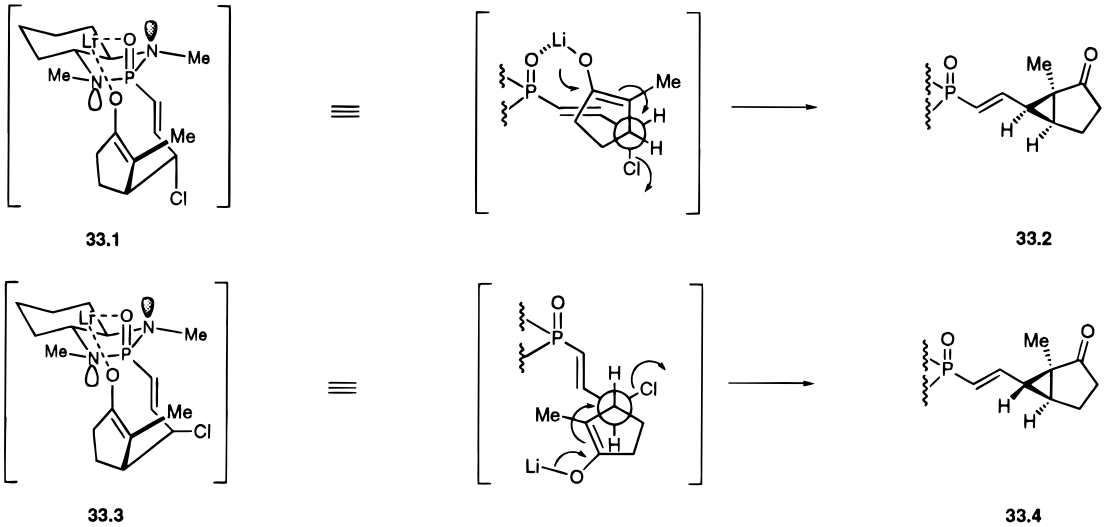
3. Asymmetric Cyclopropanation of α-Phosphoryl Carbanions

A novel method for the asymmetric synthesis of fully functionalized cyclopropanes has recently been

Scheme 32



Scheme 33



found based on Hanessian's phosphonamide technology.[56] Thus, treatment of 2-methylcyclopentenone with the lithium anion derived from phosphonamide **32.1** led to the corresponding trisubstituted cyclopropane **32.3** derivative in high diastereomeric excess (Scheme 32). The *cis*-vinyl chloride reagent **32.5** gave the diastereomeric adduct **32.6**. These highly stereoselective cyclopropanations have also been extended to cyclic enones, α,β-unsaturated lactones, and lactams as well as *tert*-butyl sorbate and cinnamate.

The outcome of these reactions can be rationalized on the basis of the approach of the carbonyl group (*e.g.*, 2-methylcyclopentenone), from the more accessible "left cleft" of the (*R,R*)-reagent. This results in a favorable trajectory of attack of the γ-chloroallylic anion on the *Si*-face of the cyclic enone, leading to a Li-chelated enolate intermediate, which expels chloride to give the observed product (Scheme 33). It is remarkable that a high level of stereochemical character is maintained in the anionic transition state, leading to clean intramolecular S_N2-like ejection of the intermediate chloride by the enolate.

Oxidative cleavage of the vinylic phosphonamides afforded highly functionalized and stereochemically defined monocyclic or bicyclic cyclopropanes (Table 10). In essence, the chiral chloroalkyl phosphonamides are sources of a "chiral acetaldehyde" in these reactions. These compounds should find use in the synthesis of natural and unnatural products as well as scaffolds for molecular diversity.

It was also recently found that treatment of chloromethyl phosphonamide **34.1** with a strong base such as LDA in THF, followed by the addition of *tert*-butyl cinnamate (**34.2**, R = Ph) afforded the corresponding cyclopropane derivative **34.3** (Scheme 34).[57] The additions to other α,β-unsaturated esters were also highly diastereoselective, particularly when the γ-substituent was bulky or electronically biased. Further manipulations allowed the preparation of interesting trisubstituted cyclopropyl phosphonates. The sense of asymmetric induction has been confirmed using X-ray crystallography for a number of products. It is noteworthy that the intermediate 1,4-conjugate addition product can be trapped at low temperatures prior to cyclization to the corresponding cyclopropane.

Scheme 34

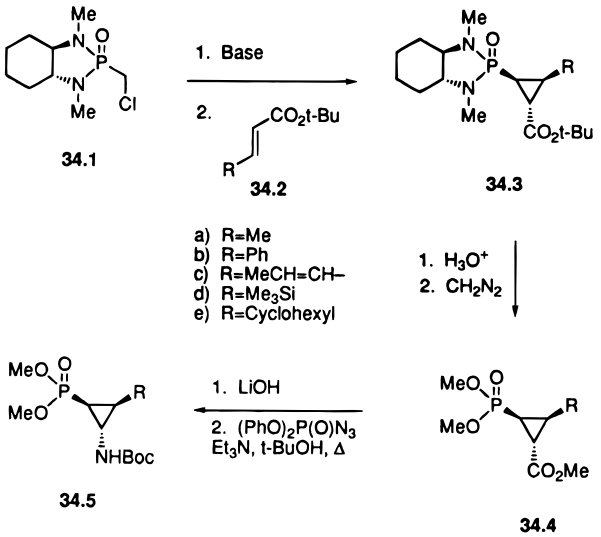


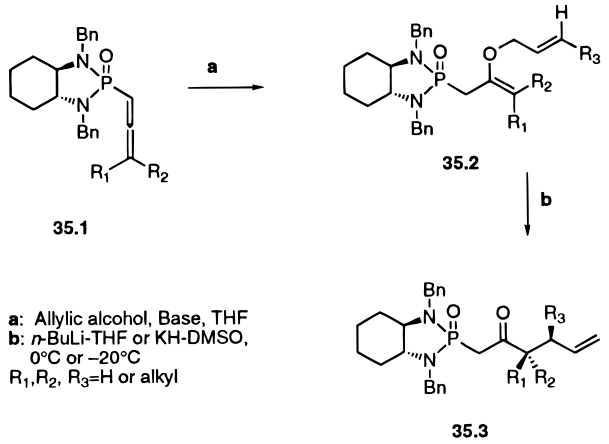
Table 10. Asymmetric Cyclopropanation of α,β-Unsaturated Carbonyl Compounds by 1,4-Conjugate Addition of Phosphonamides 32.1 and 32.5

Entry	Substrate	Product	Diastereomer Ratio ^{31}P
1	X=C		96:4
2	X=O		99:1
3	X=NPNB		99:1
4	X=C, R=Me		95:5
5	X=O, R=H		92:8
6	Ph, CO_2t-Bu		99:1
7	Me, CO_2t-Bu		99:1

E. Carbanion-Accelerated Claisen Rearrangements

Denmark and co-workers[58] have reported on the utilization of various cyclic phosphonamides in their studies on carbanion-accelerated Claisen rearrangements of allyl vinyl ethers. An extensive survey of chiral auxiliaries has helped to identify the phosphonamide derivative **35.2** to be optimal for better stereoselectivities. These phosphonamides readily rearranged (*n*-BuLi, −20 °C) to the γ-unsaturated ketones with complete regioselectivity and in good yields (Scheme 35).

Scheme 35

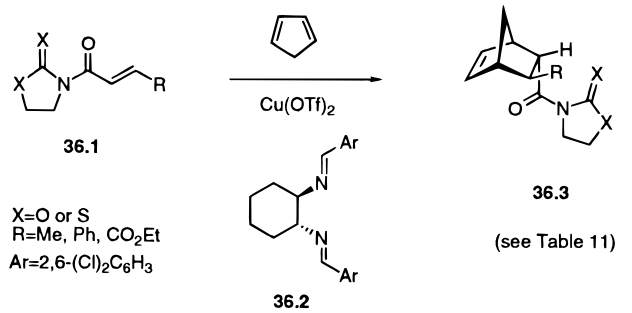


1. Asymmetric [4 + 2]-Cycloaddition

Asymmetric versions of the venerable Diels−Alder reaction have been a topic of interest in recent years. Reports of catalytic and enantioselective reactions utilizing a variety of metals and chiral auxiliaries are known in the literature.[59] Evans and co-workers[60] have reported on the reaction of cyclopentadiene with dienophiles derived from α,β-unsaturated oxazolidinones in the presence square-planar $Cu(OTf)_2$-bis-

(*trans*-1,2-diaminocyclohexane arylimine) complexes as catalysts (Scheme 36).

Scheme 36



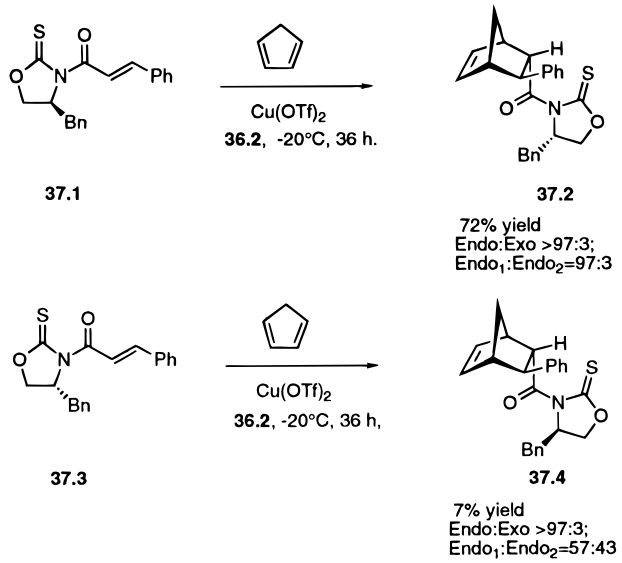
The 2,6-dichlorophenyl-substituted ligand **36.2** was found to be the most effective for a range of substrates, affording products with ee values of 83−94%. A higher *endo:exo* diastereoselection was observed in the case of thiazolidine-2-thione analogues **36.3** (X = S) (Table 11).

Table 11. Asymmetric [4 + 2]-Cycloaddition Catalyzed by Schiff baSe 36.2

Entry	X	R	%Yield	Endo:Exo ds	%Endo ee
1	O	H	87	80:20	92
2	O	Me	90	65:35	83
3	O	Ph	83	60:40	85
4	O	CO_2Et	90	55:45	94
5	S	Me	86	93:7	91
6	S	Ph	83	92:8	92
7	S	CO_2Et	99	90:10	88

Additionally, double stereodifferentiating cycloadditions catalyzed by **36.2**-$Cu(OTf)_2$ were examined. In the matched case, the chirality of the ligand and the substrate had a cooperative effect (72% yield, *endo:exo* = 97:3; $endo_1$:exo_2 = 97:3). In the mismatched case, poor conversion (7%) was observed and a mixture of diastereomers was obtained (Scheme 37).

Scheme 37



F. Asymmetric Alkylations

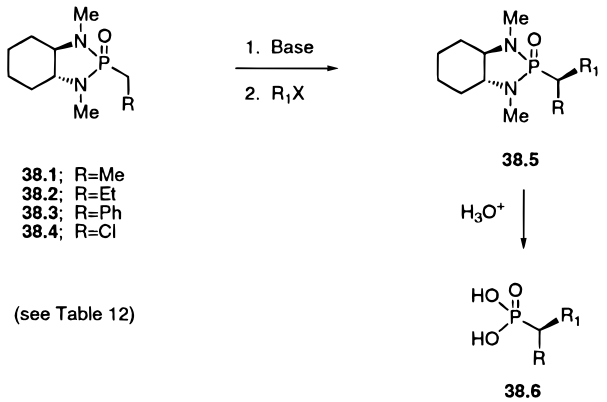
1. Alkylations of Phosphoryl α-Carbanions

Stereoselective alkylations of α-phosphoryl carbanions were carried out by Hanessian and co-workers[12,20] conducted in conjunction with the asymmetric olefination of prochiral ketones using phosphonamides derived from *trans-N,N′*-dimethyl-1,2-diaminocyclohexane to substantiate the sense of asymmetric induction. These initial results have been extended to include highly stereoselective alkylations of structurally related alkyl, aryl, and chloromethyl phosphonamides (Scheme 38, Table 12).[61] Subsequent hydrolysis of the alkylated products led to the synthesis of enantiomerically pure or highly enriched α-substituted alkyl phosphonic acids.

Table 12. Asymmetric α-Alkylation of Phosphonamides of Type 38.1−38.4

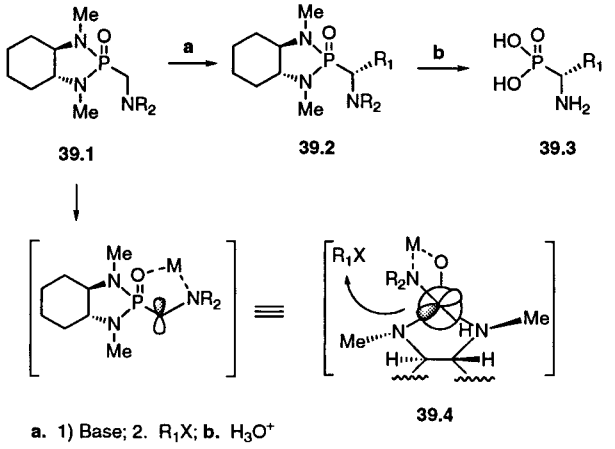
Entry	R	R^1	%Yield	Diastereomer Ratio ^{31}P
1	Me	Et	76	95:5
2	Me	C_3H_5–	83	94:6
3	Me	Bn	83	97:3
4	Me	$TPSO(CH_2)_3$–	71	99:1
5	Et	Me	82	79:21
6	Ph	Me	95	84:16
7	Ph	C_3H_5–	91	89:11
8	Ph	Bn	93	90:10
9	Cl	Me	87	90:10
10	Cl	Et	78	98:2
11	Cl	Bn	86	98:2
12	$N=C(SR)_2$	Me	87	10:90
13	$N=C(SR)_2$	Et	78	5:95
14	$N=C(SR)_2$	Bn	86	2:98

Scheme 38



Aminomethyl phosphonamides of type **39.1** were also alkylated in a highly stereoselective manner. These alkylations proceeded with the opposite sense of asymmetric induction as compared to the above-mentioned alkyl series **38.1**−**38.4**. This inversion could be explained by the intermediacy of a chelated species, where the opposite face of the carbanion is exposed to the approaching electrophile (Scheme 39).[62] The high levels of enantioselectivity are believed to arise from the unique topology of these enantiomerically pure phosphonamides. It was demonstrated that planar α-carbanions are involved as intermediates and that the levels of stereoselectivity are the result of the size and reactivity of electrophiles, the substituents on the nitrogen atoms, and the temperature of the alkylation reactions.[23] Excerpts from these studies,[61,62] which are summarized in Table 12, show the diversity and high diastereoselectivities observed in these alkylations An *ab initio* study of the P−C bond rotation in phosphoryl-stabilized carbanions has been disclosed by Denmark and co-workers.[63] The merits of conformational rigidity in bicyclic phosphonamides derived from 1,2-*trans*-diaminocyclohexanes such as **4.2** (Scheme 4) and related structures were discussed.

Scheme 39

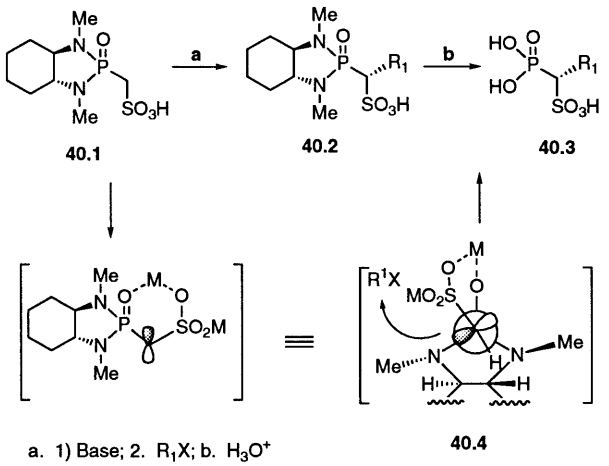


Recently, researchers from Bristol-Myers-Squibb reported that alkylation of phosphonamide sulfonate **40.1**, through its corresponding dianion, proceeded in up to 25:1 diastereomeric ratio to give the desired compounds of type **40.2** (Scheme 40).[64] The sense of asymmetric induction, which was found to be opposite that in the alkylation of nonfunctionalized α-alkyl phosphonamides, was explained on the basis of the previously established chelation-controlled Hanessian-model **39.4**. Subsequent hydrolysis of phosphonamide **40.2** gave the corresponding phosphonosulfonic acid of type **40.3**, which showed higher potency as a squalene synthase inhibitor compared to its enantiomer.[64]

2. Additions of Phosphoryl α-Carbanions

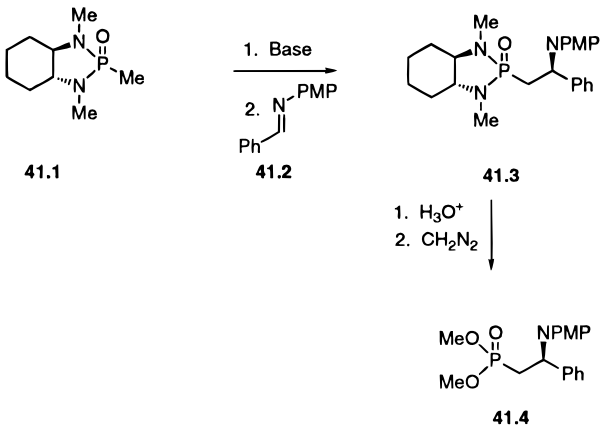
The addition of alkyl phosphonamide α-carbanions to *N*-substituted imines has been reported.[65] Reaction of the lithium anion of **41.1** with the Schiff base **41.2** resulted in the formation of the corresponding

Scheme 40



β-amino phosphonamide **41.3** in 80% yield and in a diastereomeric ratio of 88:12 (Scheme 41). Acid hydrolysis of **41.3**, followed by treatment with diazomethane, gave the corresponding dimethyl phosphonate derivative **41.4** in good yield.

Scheme 41



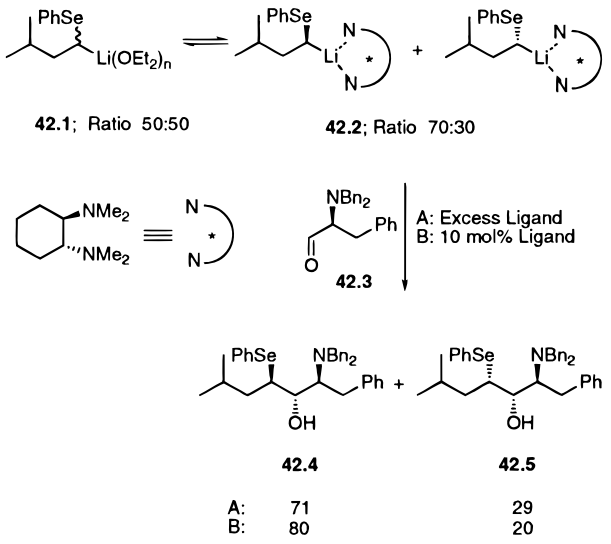
3. Stereoselective Additions of α-Selenocarbanions

In 1993, Hoffmann and co-workers[66] reported studies toward delineating the factors which determine asymmetric induction in the enantioselective transformations of configurationally labile (α-selenoalkyl)-lithium compounds, using (*R,R*)-*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane as a chiral complexing agent (Scheme 42). The overall results from these kinetic studies were that the organolithium compound **42.1** formed complexes of type **42.2** with the chiral *trans*-1,2-diaminocyclohexane ligand which reacted more rapidly with an aldehyde, as compared to the uncomplexed reagent. The addition of the diastereomeric complexes to the electrophile was much faster than their equilibration. The enantiomeric ratio of the adducts **42.4** and **42.5** corresponded to the diastereomeric ratio of the complex **42.3**. Although the enantioselectivities were not very high (70:30), this model was chosen on the basis of the maximum information obtained by NMR spectroscopy.

4. Enolate Alkylations

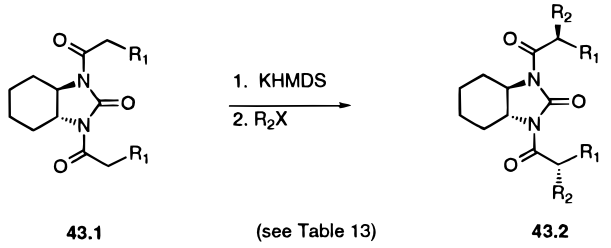
Enolate alkylation is a powerful synthetic method for the asymmetric formation of C−C bonds. The

Scheme 42



high levels of diastereoselection attained so far require conformational restriction of an enolate of specific geometry, as well as the differential enantiofacial shielding of the nucleophilic enolate carbon. The parameters governing the accessibility of the two faces of the enolate are believed to be mainly steric due to the presence of a suitable stereogenic center promoting the reaction from the opposite side and restriction of the enolate geometry through chelation to a suitable lone pair donor on the chiral auxiliary. Two of the most successful examples of asymmetric C-alkylations of enolates rely on Evans' *N*-acyl oxazolidinones,[67] and Oppolzer's camphor sultams[68] as chiral auxiliaries. Recently, Davies and co-workers[69] reported that the stereoselective alkylation of potassium enolates of 1,3-diacylimidazolidin-2-ones, such as **43.1** derived from *trans*-1,2-diaminocyclohexane, led to clean and highly diastereoselective alkylation reactions with reactive alkyl halides at low temperatures (Scheme 43). The sense of asymmetric induc-

Scheme 43



tion is consistent with the intermediacy of a chelated *syn* enolate and the approach of the electrophile from the *exo*-face (Table 13). The chiral auxiliary was cleaved by reduction to give the corresponding α-alkylated alcohols. It is of interest that the use of *trans*-1,2-diamino-1,2-diphenylethane as a chiral auxiliary resulted in much lower levels of diastereoselectivity compared to the cyclohexane analogue **43.1**.

G. Allylic Alkylation

Although transition-metal-catalyzed allylations have emerged as versatile and powerful reactions, until recently, they were not widely applicable in enantioselective processes. The difficulty in this process lies in the spatial relationships between the breaking bond, the newly forming bond, and the metal with its residing ligands. As an example, the generally accepted mechanism for the palladium-catalyzed allylation reaction with a soft nucleophile is depicted in Scheme 44. The basic catalytic cycle consists of Pd−olefin complexation followed by ionization, alkylation, and then decomplexation. To induce asymmetrization, the asymmetric environment provided by the metal ligands must be "felt" on the opposite face of the π-allyl system, derived from the substrate, where bond breaking and bond formation are taking place.

Table 13. Asymmetric Alkylation of 1,3-Dialkylimidazolidin-2-one 43.1

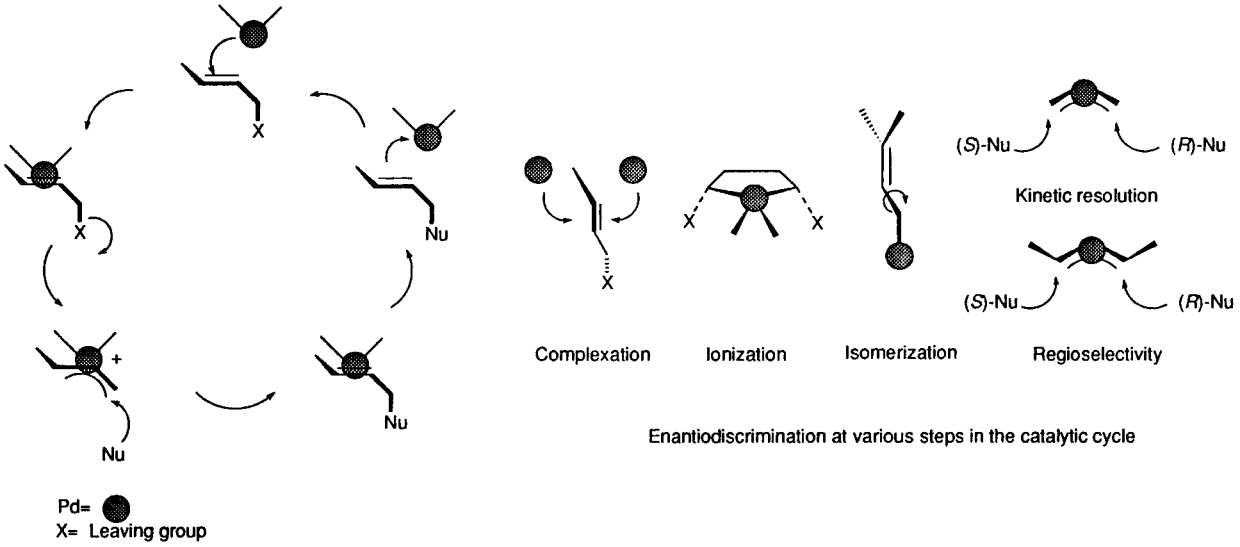
Entry	R^1	R^2	%Yield	Diastereomer Ratio ^{31}P
1	Me	Bn	72	97:3
2	Me	CH=CHCH$_2$–	81	98:2
3	Me	Et	64	92:8
4	Et	Me	66	88:12
5	Bn	Me	72	92:8
6	Bn	Et	71	88:12

Trost and co-workers[70] have devised an efficient new class of ligands based on 2-(diphenylphosphino)-benzoic acid amides derived from *trans*-1,2-diaminocyclohexane and various other C_2 symmetric diamines, for the asymmetric allylic alkylation reaction. The structural requirements for a good and practical ligand to effect these types of transformations have been probed through rational and stepwise changes in the chiral ligand structure. The synthesis of unsymmetrical 1,4-disubstituted cyclopentenes with excellent enantioselectivies has been achieved using this strategy utilizing prochiral allylic carbonates (Scheme 45).

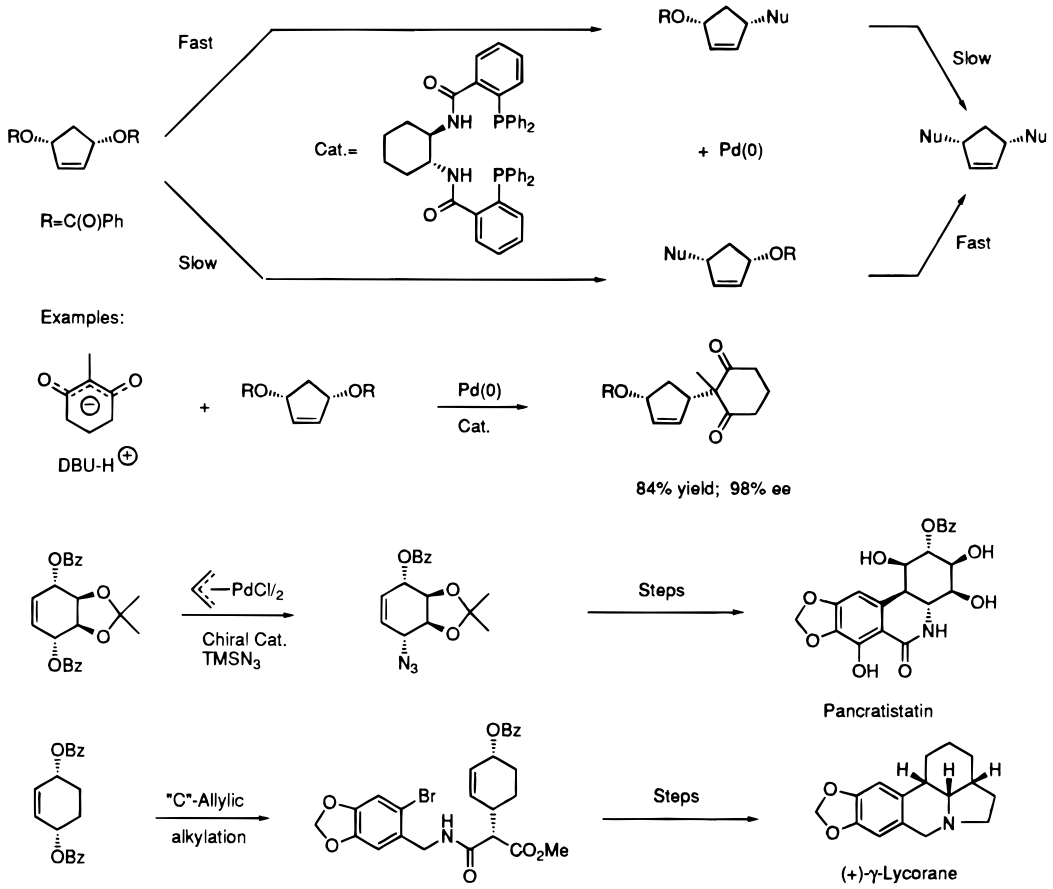
The following features which make this transformation a good model for developing effective ligands can be enumerated: (1) the enantio-determining step, ionization, occurs early in the catalytic cycle during this mechanistically defined reaction; (2) only palladium−olefin complexation *anti* to the leaving group will lead to product; (3) the diasterofacial inversion of the metallophosphine is prevented by the ring; (4) the nucleophile attacks intramolecularly and it has a defined trajectory; (5) the uncatalyzed reaction does not compete with the catalyzed one; and (6) there are no competing side reactions. Many ligands have been prepared and screened for this transformation, giving the cyclized product with up to 88% ee. The best ligands with regard to overall efficiency and ready availability are those derived from *trans*-1,2-diaminocyclohexane.

Since asymmetric induction arises in the ionization step, this approach appears to be generally applicable for allylic alkylations involving inter- and intramolecular processes utilizing carbon and heteroatom nucleophiles. The highest enantioselectivity obtained in the intermolecular alkylations is >98% ee. The mechanistic rationale that emerges using 2-(diphen-

Scheme 44. Catalytic Cycle for the Palladium Catalyzed Allylic Alkylation



Scheme 45



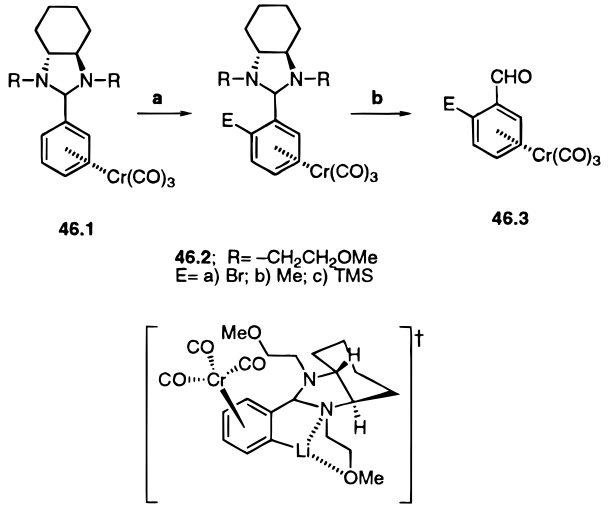
ylphosphino)benzoyl derivatives of chiral diols and diamines strongly supports their involvement as bidentate ligands through both phosphines. It seems that the source of chiral recognition resides in the conformational disposition and chirality of the diphenylphosphino moieties. Several synthesis of natural products such as pancratistatin, (+)-γ-lycorane, and (−)-epibatidine have been addressed and completed on the basis of this methodology. In addition, the development and optimization of other nucleophilic additions (azide, sulfonyl anions, malonates, etc.) are under study. A detailed review article on this subject has recently been published,[71a] and new applications continue to enrich the area.[71b]

H. Enantioselective *ortho*-Lithiation of Aminals

There has been a recent interest in the enantioselective *ortho*-metalation of arene chromium tricarbonyl complexes through either deprotonation with a chiral base or the functionalization of a chiral acetal derivative. The major difficulty associated with these methods resides in the cleavage of the chiral auxiliary. A newly developed method relies on the use of *N*,*N*′-bis(2-methoxyethyl)-*trans*-1,2-diaminocyclohex-

ane derivatives. The aminal formed from this chiral auxiliary with benzaldehyde chromium tricarbonyl complex (**46.1**), can be *ortho*-lithiated in a highly selective manner. Treatment of this intermediate with an electrophile such as methyl iodide gave, after mild hydrolysis, the desired *o*-methylbenzaldehyde chromium complex in essentially enantiopure form. The stereochemical outcome of this asymmetric deprotonation may be ascribed to a bidentate chelation of the lithium atom (Scheme 46, Table 14).[72]

Scheme 46



46.1 46.3

46.2; R= $-CH_2CH_2OMe$
E= a) Br; b) Me; c) TMS

a. 1. *n*-BuLi, 2. E^+; **b.** H_3O^+ (see Table 14)

Table 14. Enantioselective *ortho*-Lithiation–Alkylation of Arene–Chromium Tricarbonyl Aminal Complexes of Type 46.1

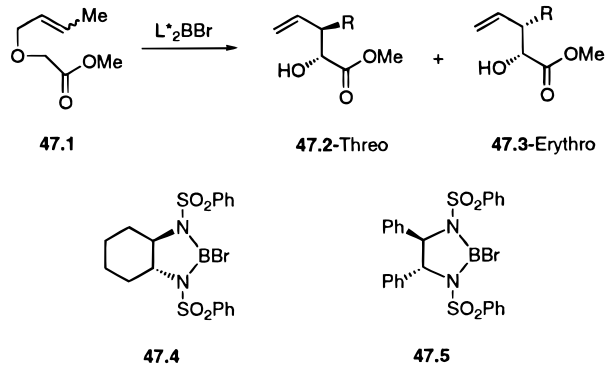
Entry	R	E	%Yield	Ratio *o*: *m*: *p*	de
1	Me	Me	95	10;90	99
2	$-(CH_2)_2OMe$	Me	95	76:24	99
3	$-(CH_2)_2OMe$	Me_3Si	95	90:10	99
4	$-(CH_2)_2OMe$	Br	95	95:5	99

I. Enantioselective [2,3]-Wittig Rearrangement

The "enolate"-[2,3]-sigmatropic Wittig rearrangement involves an enolate as the migrating terminus to provide α-hydroxy-β-alkyl carboxylic acid derivatives which are of paramount synthetic importance. The first example of an enantioselective [2,3]-sigmatropic Wittig rearrangement was reported by Nakai and co-workers.[73] The key to this successful transformation was the use of a chiral boron enolate terminus containing bis(*N*-arylsulfonyl) derivatives of enantiopure *trans*-1,2-diaminocyclohexane or 1,2-diamino-1,2-diphenylethane as the controller ligands (Scheme 47). While the resultant *threo:erythro* ratios were moderate, the respective enantiomeric excesses were better for the *threo* products. Different selectivities and product distributions were obtained in the case of substrates with β-substituted and nonsubstituted *cis* or *trans* allylic ether moieties.

Although no definitive explanation to accommodate the stereochemical outcome of this rearrangement

Scheme 47

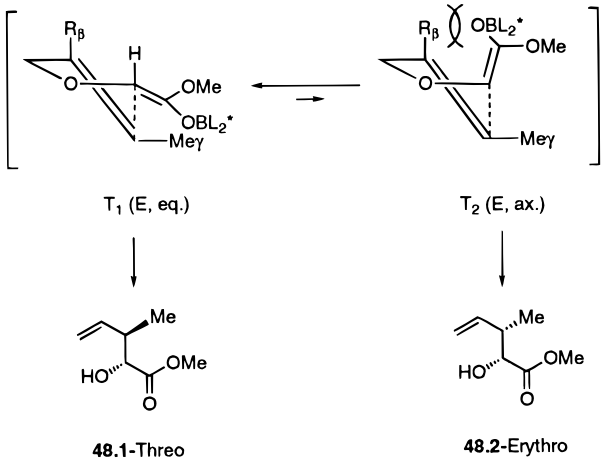


47.1 47.2-Threo 47.3-Erythro

47.4 47.5

was advanced, the high *threo* selection obtained from the *E*-substrates could be the result of a more sterically favorable transition state T_1 compared with T_2 (Scheme 48).

Scheme 48



T_1 (E, eq.) T_2 (E, ax.)

48.1-Threo 48.2-Erythro

III. Asymmetric C–O Bond Forming Reactions

A. Epoxidation of Unfunctionalized Olefins and Related Oxidations

The Katsuki–Sharpless titanium tartrate-catalyzed enantioselective epoxidation of allylic alcohols is one of the most powerful methods for the synthesis of optically active organic compounds.[74] Since the original report in 1980, much effort has been aimed at developing asymmetric-catalytic methods for the stereoselective epoxidation of unfunctionalized olefins, where selectivity is determined solely through nonbonded interactions. A recent review that incorporates various existing strategies for the asymmetric epoxidation of olefinic substrates other than allylic alcohols was recently published.[76] The following section summarizes the developmental stages and recent findings in the Mn-(salen)-catalyzed asymmetric epoxidation of olefins with an emphasis on the use of enantiopure *trans*-1,2-diaminocyclohexane derivatives as chiral ligands. In 1990, Jacobsen and co-workers[75] reported that Mn(III) complexes derived from Schiff's base of 1,2-diamino-1,2-diphenylethane, and subsequently from (*R*,*R*)-1,2-diaminocyclohexane, were effective catalysts for the asymmetric epoxidation of unfunctionalized olefins. Recent process improvements and refinements in catalyst design by electronic and structural tuning led to the

emergence of the Mn(salen)-catalyzed epoxidation as a practical method for the synthesis of a wide variety of epoxides with high levels of enantioselectivity. The Jacobsen epoxidation employs sodium hypochlorite as a stoichiometric oxidant and is most effective with *cis*-disubstituted and with some trisubstituted alkenes (Scheme 49, Table 15).

Scheme 49

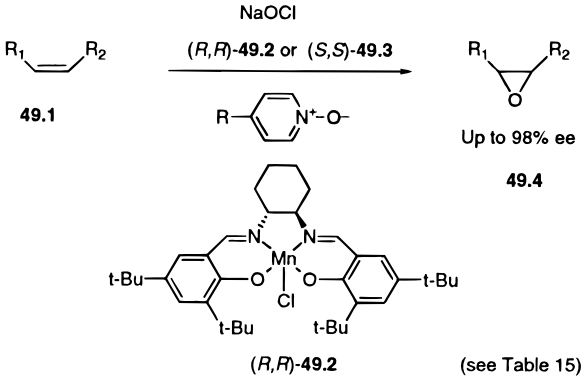


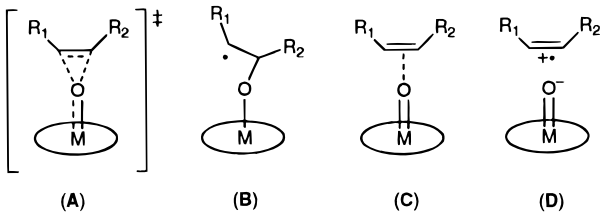
Table 15. Asymmetric Catalytic Epoxidation of Olefins Using Mn Schiff Base 49.2

Entry	Olefin	%Yield	%ee
1	Ph, Me	84	91
2		67	92
3		87	98
4		80	88
5	Me_3Si, C_6H_{11}	65	98
6		63	94
7	Ph, CO_2Et	67	97
8	Ph	75	92

From the mechanistic standpoint, the "side-on" approach mechanism, proposed earlier in porphyrin-based oxygen transfer catalytic systems, suggested the possible involvement of several different initial interactions between the alkene and the metal oxo species. The simplest possible mechanism is shown in Scheme 50, and it involves intermediate **A**, where concerted (not necessarily synchronous) formation of both oxygen and carbon bonds takes place. Other possibilities involve a stepwise bond formation through polar or nonpolar intermediates as in **B**, a rate-limiting electron transfer as in **C**, or charge transfer complex formation as expressed in **D**.[76]

In the chiral Mn(salen)-catalyzed epoxidations, the latter two possibilities can potentially be excluded, since the observed levels of enantioselectivity are consistent with a highly ordered stereo-determining

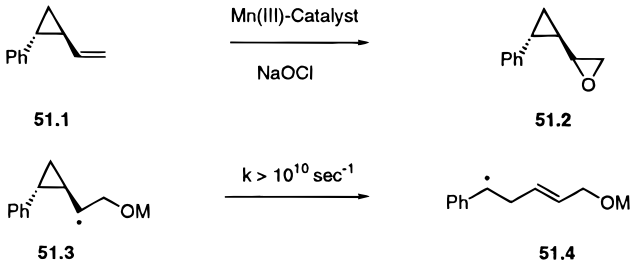
Scheme 50



transition state, which is difficult to rationalize on the basis of noncovalent interactions. Nevertheless, both pathways **C** and **D** could constitute initial, reversible steps in the concerted and stepwise mechanisms **A**/**B**.

Several lines of evidence, supported by experimental results, suggest a substrate-class-dependent mechanism. In the case of *cis* olefins (including conjugated alkenes), a stepwise mechanism involving a radical intermediate such as **D** (Scheme 50), which undergoes competitive collapse to *cis* epoxide and rotation/collapse to give a *trans* epoxide, seems likely. In the case of isolated olefins, the epoxidation reaction seems to proceed through a concerted mechanism. This is supported by several lines of evidence: (a) the low levels of enantioselectivity obtained, (b) the slow rate of reactivity as compared to sterically similar but conjugated olefins, and (c) the fact that epoxidation of the hypersensitive radical clock **51.1** by catalyst **49.2** gave epoxide **51.2** as the only reaction product. This excludes the intermediacy of a radical species such as **51.3**, which is believed to rearrange irreversibly to **51.4** at a rate of $\geq 10^{10}$ s^{-1} (Scheme 51).[77] More details underlying the dramatic difference in enantioselectivities observed in the epoxidation of isolated and conjugated olefins with (salen)-Mn(III) catalysts from a mechanistic point of view have recently been put forward by Jacobsen,[78] Norrby,[79] Katsuki,[80] and their respective co-workers.

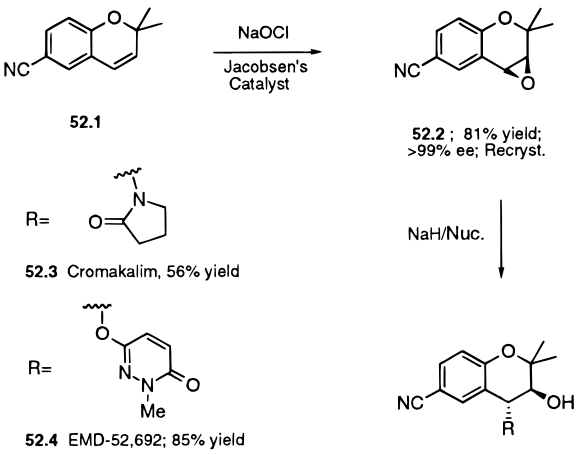
Scheme 51



Although the synthetic utility of the chiral (salen)-Mn(III) epoxidation catalysts remains to be extended to other classes of olefins, applications of this methodology to the synthesis of medicinally important drugs, synthetic intermediates, and fine chemicals are evident. For example, the epoxidation of 2,2-dimethylchromene **52.1** with catalyst **49.2** and sodium hypochlorite proceeds in good yield to give epoxide **52.2** in >99% ee after one recrystallization. This epoxide was further transformed in one step to either Cromakalim, an antihypertensive agent or its related analogues EMD-52-692 (Scheme 52).[81]

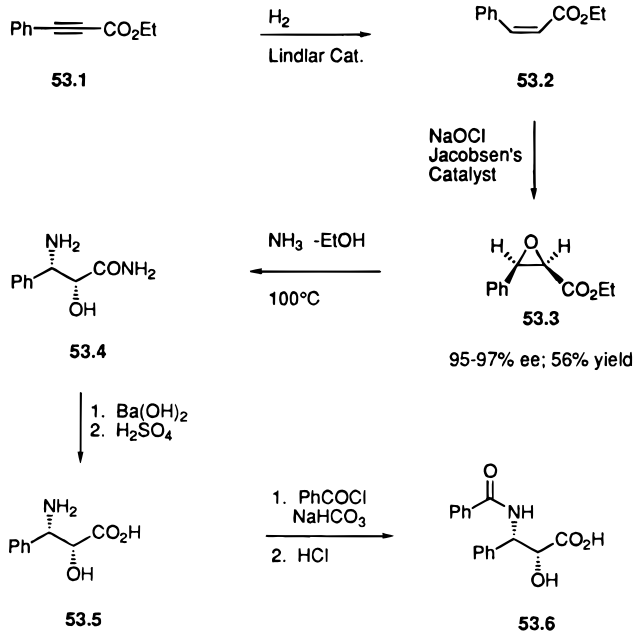
In another application of this methodology, epoxidation of *cis*-ethyl cinnamate (**53.2**), using similar conditions as above, gave epoxide **53.3** in 56% yield

Scheme 52



and 95−97% ee (in addition to 13% *trans*-epoxide) (Scheme 53). Regioselective epoxide opening followed

Scheme 53



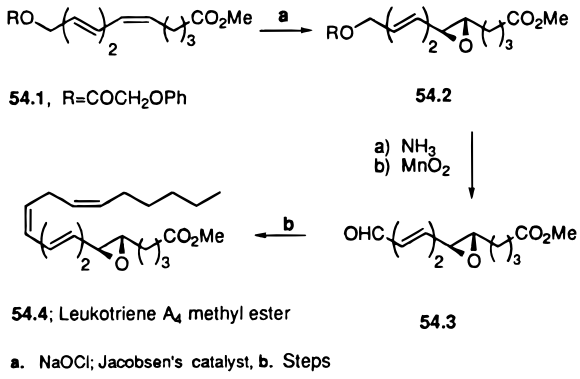
by hydrolysis and acylation gave the Taxol side chain in an expedient manner.[82]

Similar methodology was applied in the synthesis of leukotriene LTA_4, where triene ester **54.1** was selectively epoxidized at the *cis*-olefin (8:1 *trans:cis*; 62% yield) to give the corresponding ester **54.2** in 82% ee (Scheme 54).[83] The latter was further transformed using standard methodology to the desired leukotriene methyl ester **54.4**.

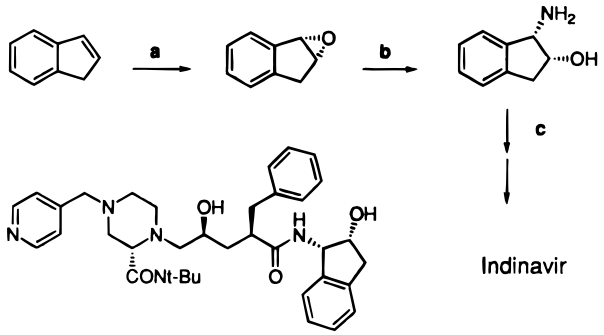
The enantioselective synthesis of Indinavir, an HIV protease inhibitor developed and now marketed by Merck and Co., required the utilization of the Jacobsen methodology to efficiently prepare the 1-amino-2-hydroxyindane moiety (Scheme 55). This was accomplished through the asymmetric epoxidation of 1-indene followed by treatment of the resulting epoxide under Ritter conditions to afford the desired amino alcohol.[84]

Interestingly, stereoselective oxidation of benzylic C−H bonds, to their corresponding alcohols, was

Scheme 54



Scheme 55[a]



[a] (a) Jacobsen epoxidation. (b) Ritter reaction. (c) Several steps.

recently reported first by Larrow and Jacobsen[85] and more recently by Katsuki and co-workers.[86] Oxidations using 1,2-diamino-1,2-diphenylethane−Mn complexes gave better results than their *trans*-1,2-diaminocyclohexane counterparts.

Adam and co-workers[87] have disclosed an asymmetric synthesis of α-hydroxy ketones and esters via the oxidation of the corresponding silyl enol ethers and ketone acetals with the (salen)Mn(II) catalyst **49.2** in the presence of oxidants. Enantiomeric excesses ranging from 20 to 81% were observed.

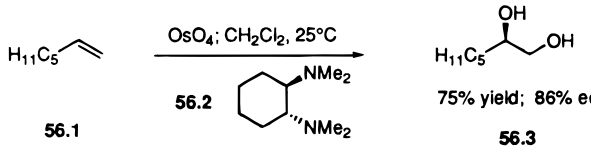
B. Dihydroxylation of Olefins

The asymmetric dihydroxylation of olefins using osmium tetraoxide in the presence of a chiral ligand or catalyst has received considerable attention in recent years due to its enormous potential in the synthesis of enantiopure molecules. Since the early seminal contributions of Sharpless and co-workers in 1980,[88] several protocols dealing with the asymmetric conversion of *cis* and *trans* olefins to the corresponding diols have appeared in the literature.[88] The recently developed catalytic systems for the dihydroxylation of olefins by Sharpless and co-workers[89] utilizing Cinchona alkaloids as ligands for OsO_4 offer high levels of efficiency and practicability for this reaction.

An early report by Snyder and Tokles[90] described the utilization of (*R,R*)-*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane as a chiral ligand in the osmium tetraoxide mediated dihydroxylation of a limited number of olefins. The reactions were carried out at 25 °C in dichloromethane with 1.1 equiv of OsO_4,

and the best level of enantiomeric excess was 86% ee with 1-heptene (Scheme 56). To the best of our

Scheme 56



knowledge these results have not be validated or exploited further.

Asymmetric dihydroxylations using a variety of other chiral ligands with good to excellent enantioselectivities have also been reported.[91] After screening a number of *N,N′*-dialkyl-*trans*-1,2-diaminocyclohexanes, Hanessian and co-workers[92] reported optimum levels of asymmetric induction in a wide selection of olefins utilizing a stoichiomeric amount of OsO_4 and (*R,R*)-*N,N′*-dineopentyl-1,2-diaminocyclohexane as a chiral ligand at −90 °C in toluene (Scheme 57, Table 16). Most of the substrates

Scheme 57

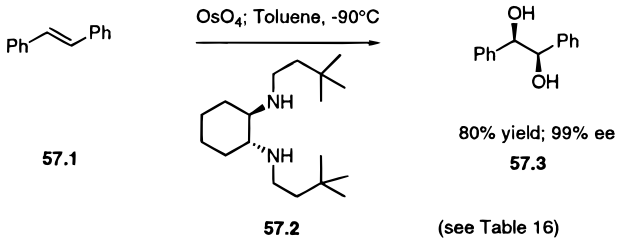
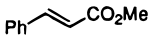
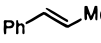
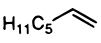
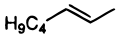
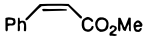
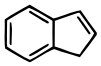


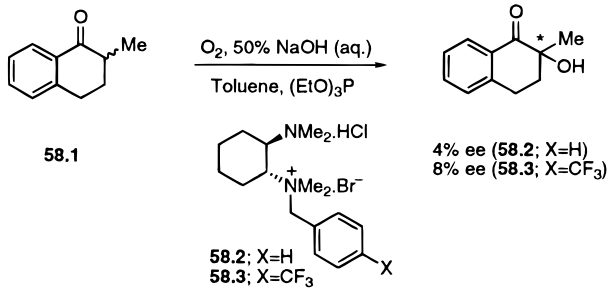
Table 16. Asymmetric Dihydroxylation of Olefins Using the (*R,R*)-*N,N′*-Dineopentyl-1,2-diaminocyclohexane 57.2/OsO_4 System

Entry	Olefin	%Yield	%ee
1		80	99
2		82	95
3		70	99
4		70	65
5		61	90
6		60	87
7		80	77
8		70	80

(terminal, mono-, di-, and tri-substituted olefins) showed ee's above 90% with particular success with *cis*-olefins such as *cis*-methyl cinnamate and dimethyl fumarate. Interestingly, an intermediate product resulting from the addition of *trans*-stilbene, diamine **57.2**, and OsO_4 was isolated and its crystal structure solved. This structure showed the discreet intermediacy of a five-coordinate square-based pyramidal Os^{VI} complex which could also be seen by ^1H- and ^{13}C-NMR. Recently, Corey and co-workers[93] have reported their X-ray and NMR studies on the structure of a highly reactive bidentate (*R,R*)-1,2-bis(*N*-pyrrolidino)cyclohexane−OsO_4 complex with formally a 20-electron outer valence shell.

In 1988, Shiori and co-workers reported that the monobenzyl quaternary salt derived from (*R,R*)-*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane was utilized as a phase transfer catalyst in the oxidation of achiral ketones with molecular oxygen.[94] Unfortunately, virtually insignificant levels of enantioselectivity (4−8%) were recorded (Scheme 58).

Scheme 58

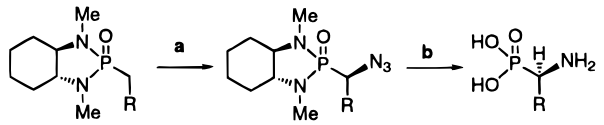


IV. Asymmetric C–N Bond Forming Reactions

A. Amination

The stereoselctive formation of C−N bonds through electrophilic amination of enolates has been successfully demonstrated in the oxazolidinone[67] and camphor sultam[68] systems. As part of general studies on the use of chiral nonracemic bicyclic phosphonamides derived from enantiomerically pure 1,2-diaminocyclohexane in organic synthesis, the amination of carbanions derived from phosphonamides of type **59.1**−**59.3** was investigated.[95] The electrophilic asymmetric amination (azidation) of these carbanions proceeds in good yields to give products with diastereomeric ratios ranging from 84:16 to 90:10 (Scheme 59, Table 17). The azido bicyclic systems of type **59.4**−**59.6** were hydrolyzed and reduced to the corresponding α-amino phosphonic acids. The stereochemical outcome of these reactions follows the models previously proposed for related reactions (Scheme 4).

Scheme 59[a]



[a] (a) 1. *n*-BuLi, THF, −78 °C, 2. Ar-SO_2N_3. (b) 1. H_3O^+, 2. H_2, PtO_2. See Table 17.

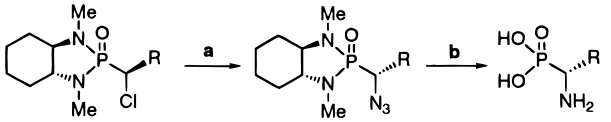
Table 17. Asymmetric Azidation of Phosphonamides 59.1−59.3

Entry	Azides			Amino acids	
	R	%Yield	Ratio	%Yield	%ee
1	Me	72	84:16	85	67
2	Et	68	82:18	89	63
3	Ph	90	90:10	92	99

B. Nucleophilic Displacement by Azide

α-Amino phosphonic acids can be prepared through the nucleophilic displacement of chiral (α-chloroalkyl)phosphonamides with azide ion (Scheme 60; Table 18).[62] The α-azido phosphonamides of type

Scheme 60[a]



(R,R)-**60.1** *(R,R)*-**60.2** *(R)*-**60.3**

[a] (a) NaN_3, DMF, 140 °C. (b) 1. H_3O^+, 2. H_2, PtO_2. See Table 18.

Table 18. Azide Nucleophilic Displacement of α-Chloro α-Alkyl Phosphonamide 60.1

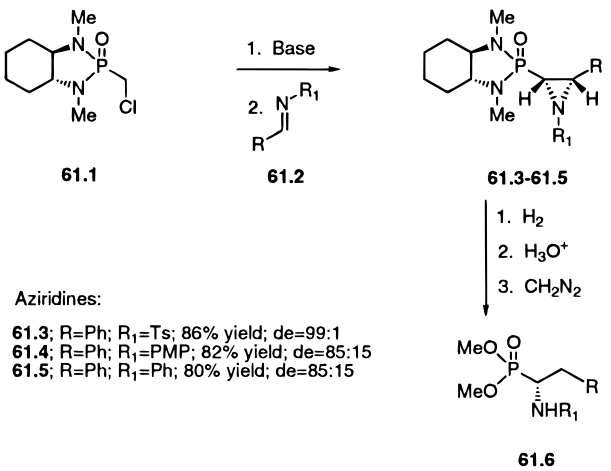
Entry		Azides		Amino acids	
	R	%Yield	Ratio	%Yield	%ee
1	Me	62	90:10	95	78
2	Et	65	99:1	98	98
3	Pr	65	99:1	96	98
4	*i*-Bu	66	89:11	95	78

60.2 thus obtained were hydrolyzed and reduced to give the corresponding α-amino phosphonic acids in good yields and in high enantiomeric excesses. This method leads to α-amino acids that are enantiomeric to the ones obtained by the direct azidation route described above (Scheme 59).

C. Formation of Aziridines from α-Phosphoryl Carbanions

The carbanion derived from the α-chloromethyl bicyclic phosphonamide **61.1** adds to imines in a highly diastereoselective fashion to give the corresponding aziridines of type **61.4**−**61.6**. For example, treatment of **61.1** with *n*-BuLi in THF at −100 °C, followed by the addition of *N*-(*p*-tolylsulfonyl)benzylideneimine led to the isolation of aziridine **61.3** as a single enantiomer (>99:1) in 86% yield (Scheme 61).[65] The corresponding *N*-*p*-methoxyphenyl (PMP)

Scheme 61



61.1 **61.2** **61.3-61.5**

Aziridines:

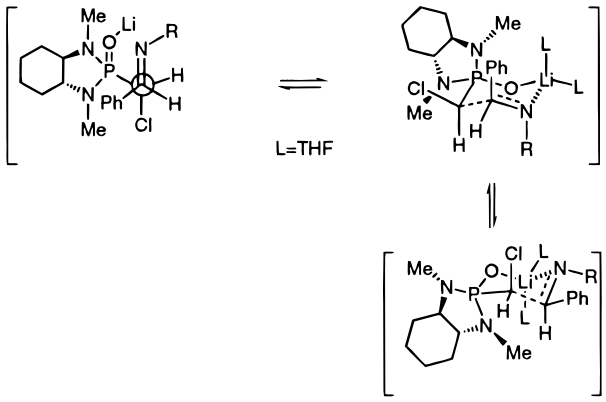
61.3; R=Ph; R_1=Ts; 86% yield; de=99:1
61.4; R=Ph; R_1=PMP; 82% yield; de=85:15
61.5; R=Ph; R_1=Ph; 80% yield; de=85:15

61.6

and *N*-phenyl analogues were also formed in high yields with diastereoselectivities exceeding 85:15 (at −78 °C). Since the isomers could be separated by chromatography, individual enantiopure products were available in this series. Hydrogenolytic cleavage of the aziridine moiety in **61.4**−**61.6** took place in a site-selective manner to give the corresponding α-amino phosphonamide derivative in quantitative yield. Acid hydrolysis and treatment with diazomethane afforded the corresponding phosphonates of type **61.6**.

The formation of the major products in the addition of the phosphonamide anion from **61.1** to the benzylidene imines can be rationalized on the basis of previous observations in alkylations in the same series (Scheme 4). Attack takes place from the "*pro-S*" (left-cleft) side of the planar anion, possibly through a Li-coordinated intermediate, as shown for the product arising from the benzaldehyde imine (Scheme 62).

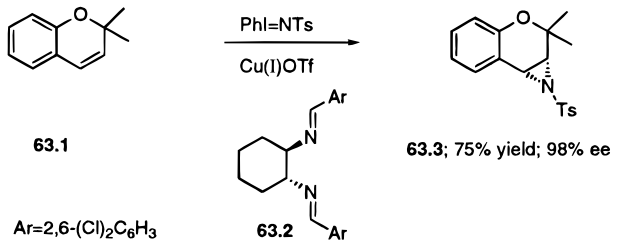
Scheme 62



D. Catalytic Asymmetric Aziridination

While the development of catalysts for the enantioselective alkene functionalization has been reported, examples of reactions that involve catalytic enantioselective nitrogen-group transfer have emerged only recently. In 1993, Jacobsen and co-workers[96a] reported that catalysis in the aziridination of alkenes was achieved using copper(I) complexes derived from dibenzylidene derivatives of (*R,R*)-1,2-diaminocyclohexane and (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (Scheme 63). While the levels of enantioselec-

Scheme 63



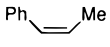
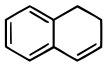
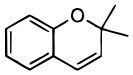
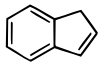
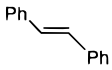
63.1 **63.2** **63.3**; 75% yield; 98% ee

Ar=2,6-$(Cl)_2C_6H_3$

tivity were high with only few systems, such as 6-cyano-2,2-dimethylchromene, the reaction offers great potential for improvement, given the ease of preparation of the chiral catalysts (Table 19).

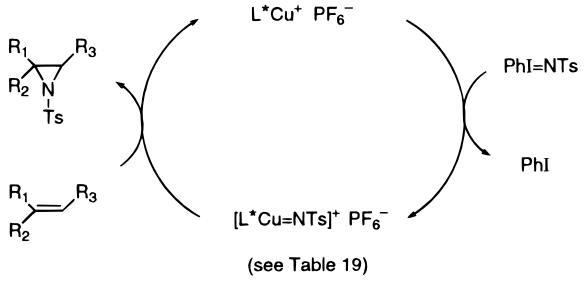
From the mechanistic standpoint, it was recently reported that this (diimine)copper(I)-catalyzed aziri-

Table 19. Asymmetric Catalytic Aziridination of Unfunctionalized Olefins Using Catalyst 63.2

Entry	Olefin	%Yield	%ee
1		79 (cis)	67
2		70	87
3		75	98
4		50	58
5		79	66
6		nd	30

dination reaction involves the intermediacy of a discrete monomeric Cu(III)-nitrene species[96b] and suggests a remarkable similarity in the geometries of transition structure in asymmetric cyclopropanation and aziridination (Scheme 64).

Scheme 64



E. Catalytic Asymmetric Epoxide Opening with $TMSiN_3$

New developments in the utilization of chiral-metal salen catalysts have recently been reported by Jacobsen and co-workers.[97] Schiff-base−Cr complexes such as **65.2** catalyze the ring opening of racemic cyclohexene oxide with $TMSiN_3$ to give α-azido alcohols in >80% yield and 80% ee. A variety of five- and six-membered *meso* epoxides were ring-opened in 81−98% ee and good yields (Scheme 65, Table 20). This epoxide-ring opening catalyzed by **65.2** was extended to a study of the kinetic resolution of other chiral racemic epoxides. In the case of styrene oxide, treatment with 0.7 mol equiv of Me_3SiN_3 and 2 mol % of catalyst **65.2** resulted in a complex mixture of

Scheme 65

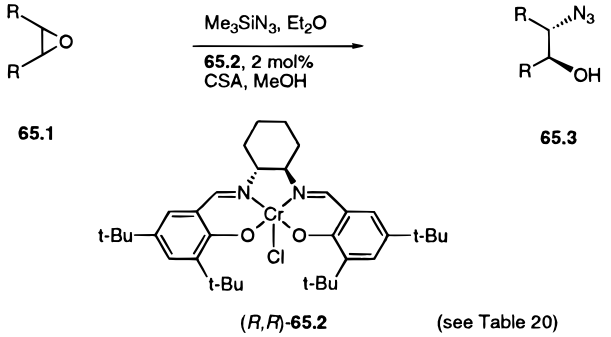
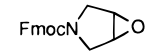
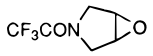


Table 20. Asymmetric Catalytic $TMSN_4$-Epoxide Opening Using Cr Schiff Base 65.2

Entry	Epoxide	%Yield azide	%ee
1		80	88
2		72	81
3		80	94
4		80	98
5		80	95
6		90	95

products with 76% conversion. The ee of the remaining unreacted epoxide was 98%!

The successful ring opening of racemic 3,4-epoxycyclopentanone followed by elimination of azide offers a new route to the cyclic core of prostaglandins.[98] Additionally, various chiral 1,2-diamine titanium and chromium complexes were tested for similar nucleophilic opening of cyclohexane epoxide with azide; however, low ee's were recorded in this case.[99]

V. Asymmetric C–H Bond Forming Reactions

A. Hydrogenation

Chiral diphosphine Rh(I) catalysts derived from enantiomerically pure *trans*-1,2-diaminocyclohexane were reported by Fujita and co-workers[11] in 1978, and by Onuma and co-workers[100,101] shortly thereafter, for the asymmetric hydrogenation of α-acylaminoacrylic acids. The resulting *N*-acylated amino acids were obtained in excellent yields and with ee's up to 93% (Scheme 66, Table 21).

Scheme 66

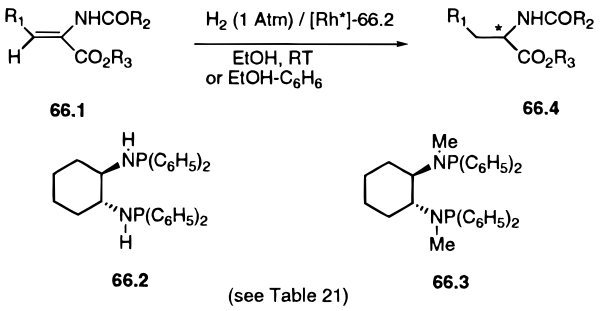


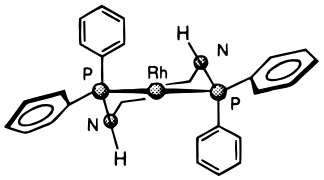
Table 21. Asymmetric Hydrogenation of α-Acylamine Acrylates Catalyzed by 66.2

Entry	R_1	R_2	R_3	Rh-Cat.	%ee
1	Ph	Me	OH	Ent-**66.2**	72 (*S*)
2	Ph	Me	NH_2	Ent-**66.2**	92 (*S*)
3	Ph	Ph	OH	Ent-**66.2**	60 (*S*)
4	Ph	Ph	NH_2	Ent-**66.2**	70 (*S*)
5	*i*-Pr	Ph	OH	**66.3**	93 (*S*)
6	Ph	Me	OH	**66.3**	73 (*S*)

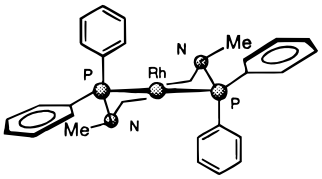
While (*S*)-amino acids were obtained using (*R*,*R*)-1,2-bis(*N*-diphenylphosphino-*N*-methylamino)cyclohexane (**66.3**), (*R*)-amino acids were obtained using (*R*,*R*)-1,2-bis(*N*-(diphenylphosphino)amino)cyclohexane (**66.2**).

This inversion of the sense of stereoselectivity was rationalized in terms of chiral helical conformations of the phenyl groups attached to the phosphorus atom in the rhodium complexes. The seven-membered chelate ring consisting of the rhodium and the two phosphorus atoms is in a twist-chair conformation, thus reducing the repulsion between the phenyl groups and the cyclohexane. In the case of ligand **67.1** (*N*-H), the hydrogen atom may adopt a quasi-axial position while the methyl group in **67.2** (*N*-Me) could be in a quasi-equatorial position (Scheme 67).

Scheme 67



67.1 Left-Handed Helicity

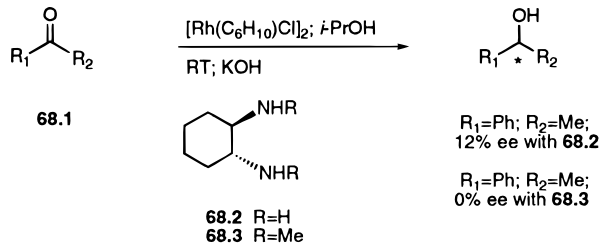


67.2 Right-Handed Helicity

This inversion of substituents around the nitrogen atoms might exert significant effects on the orientation of the phenyl groups which will result in a reversal of the helical orientation. This could explain the reversal in stereoselectivity between the closely related chiral ligands.[102]

Recently, Lemaire and co-workers[103] reported the catalytic asymmetric reduction of prochiral ketones by hydride transfer using C_2 symmetrical chiral diamines as rhodium(I) complexes (Scheme 68).

Scheme 68



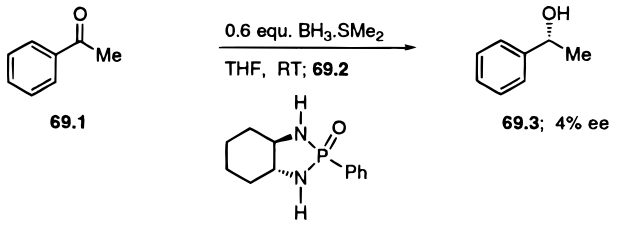
68.1

68.2 R=H
68.3 R=Me

Although complexes of (*R*,*R*)-1,2-diaminocyclohexane (**68.2**) and its *N*,*N*′-dimethyl derivative **68.3** were screened, better results were obtained with 1,2-diphenylethylenediamine.

Wills and co-workers[104] described a number of phosphorus-based derivatives for the reduction of ketones with borane−dimethyl sulfide complex. Virtually insignificant enantiomeric excesses were observed with **69.2** (Scheme 69).

Scheme 69



69.1

69.3; 4% ee

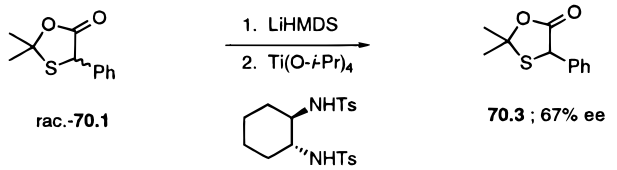
69.2

More recently, Noyori and co-workers[105a,b] described the asymmetric transfer hydrogenation of aromatic ketones catalyzed by a new type of chiral ruthenium(II) complexes. (*S*,*S*)-*N*-(*p*-Toluenesulfonyl)-1,2-diamino-1,2-diphenylethane was efficiently utilized as a chiral controller in the reduction of prochiral ketones ([$RuCl_2$(π^6-mesitylene)$_2$; 2-propanol; 25 °C) to give the corresponding alcohols in excellent yield and enantioselectivities up to 98% ee. Related 1,2-diaminocyclohexane catalysts have also been described with X-ray crystal structure data.[105b] A variety of aryl monosulfonamides derived from (*R*,*R*)-1,2-diaminocyclohexane have been reported by Knochel and co-workers[105c] as efficient ligands for the asymmetric transfer hydrogenation of ketones at 30 °C in HCOOH/Et_3N with up to 96% ee. Additionally, the enantioselective reduction of ketones with sodium borohydride catalyzed by optically active (*β*-oxoaldiminato)cobalt(II)−1,2-diaryl-1,2-diaminoethane complexes was reported by Mukaiyama and co-workers.[106] In a separate system, Buckwald and co-workers[107] reported that the Ti(O-*i*-Pr)$_4$−(*R*,*R*)-1,2-(dibenzylamino)cyclohexane complex catalyzes the reduction of prochiral ketones with triethoxysilane in THF. For example methylphenylcarbinol was obtained with an ee of 37%.

B. Asymmetric Protonation

Protonation of the lithium enolate from **70.1** using LiHMDS and Ti(O-*i*-Pr)$_4$ the presence of (*R*,*R*)-*N*,*N*′-bis(*p*-toluenesulfonyl)-1,2-diaminocyclohexane as the proton source gave the chiral compound **70.3** in 67% ee (Scheme 70). Various sources of chiral protonating agents were also screened.[108]

Scheme 70



rac.-**70.1**

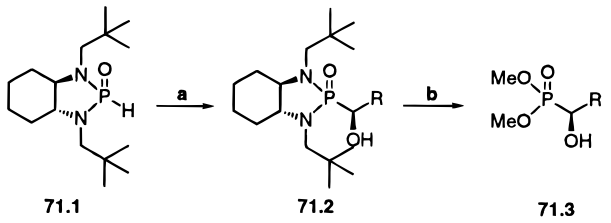
70.2

70.3 ; 67% ee

VI. Asymmetric C–P Bond Forming Reactions

Spilling and co-workers[109] reported that the addition of chiral phosphorus acid diamides derived from *N*,*N*′-disubstituted-*trans*-1,2-diaminocyclohexane to aldehydes proceeded in good yield and high diastereoselectivity (Scheme 71). On the basis of previously established methodology, these authors reported the asymmetric synthesis of a variety of α-hydroxy phosphonic acids and their corresponding phosphonates (Table 22).

Scheme 71[a]



71.1 71.2 71.3

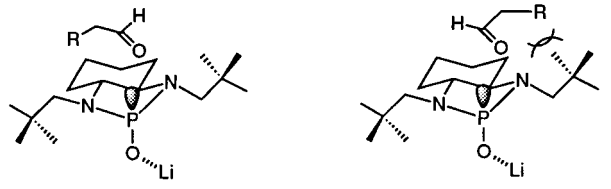
[a] (a) 1. LDA, THF, 2. RCHO. (b) 1. H_3O^+, 2. CH_2N_2.

Table 22. Asymmetric Addition of Phosphite 71.1 to Aldehydes

Entry	Aldehyde	% Yield	Diastereomer Ratio ^{31}P
1	Cinnamaldehyde	68%	7.9:1
2	Crotonaldehyde	91	6.9:1
3	β-Naphthaldehyde	58	14:1
4	α-Naphthaldehyde	91	29:1
5	Benzaldehyde	49	25:1
6	Isovaleraldehyde	82	3.4:1
7	Heptaldehyde	80	4:1

The *N,N′*-substituents seem to play an important role in enantiofacial discrimination in the formation of the P−C bond (1.82 Å). The authors explain that the *N,N′*-substituents are expected to exert their stereodirecting effect with better selectivity compared to that of the α-phosphoryl C−C bond formation. Additionally, the aldehyde is expected to interact with the lone pair of diamide anions with a trajectory of approach from above and slightly in front of the plane of the five-membered ring (Scheme 72). Steric interactions with the *gem*-dimethyl moiety of the neopentylic group in the transition state can be avoided by addition to the aldehyde from the *Si*-face.

Scheme 72

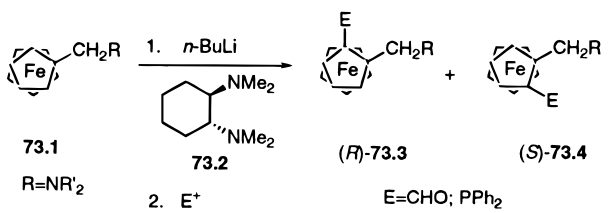


Si- face attack Re- face attack

(see Table 22)

The enantioselective *ortho*-lithiation−phosphorylation and formylation of substituted ferrocenes were reported to proceed with up to 80% ee in the presence of (*R,R*)-*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane (Scheme 73). Although other C_2 symmetrical tertiary amines such as sparteine and (*R,R*)-*N,N′*-tetramethylbinaphthylamine were screened, the best results were obtained with *trans*-1,2-diaminocyclohexane derivatives.[110]

Scheme 73

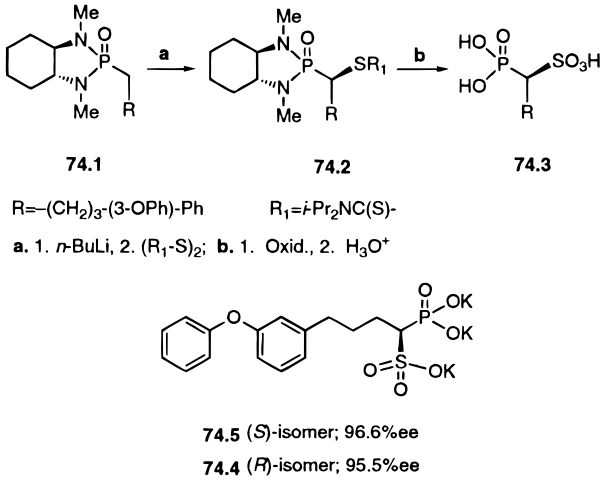


73.1 R=NR′$_2$ 73.2 (*R*)-73.3 (*S*)-73.4 E=CHO; PPh_2

VII. Asymmetric C–S Bond Forming Reactions

Carbon−sulfur bond formation was achieved in an enantioselective manner utilizing Hanessian's *N,N′*-dimethyl-1,2-diaminocyclohexane-based phosphonamide methodology.[111] Thus, the addition of α-alkyl phosphonamide **74.1** to dithiuram proceeded with good yield diastereomeric excess (Scheme 74). Further oxidation and hydrolysis of the resulting phosphonamide **74.2** led to the desired phosphonosulfonic acid **74.5**, which is a potent and selective inhibitor of squalene synthase in both rats and humans.

Scheme 74



74.1 74.2 74.3

R=–$(CH_2)_3$-(3-OPh)-Ph R_1=*i*-$Pr_2NC(S)$-

a. 1. *n*-BuLi, 2. $(R_1\text{-}S)_2$; **b.** 1. Oxid., 2. H_3O^+

74.5 (*S*)-isomer; 96.6%ee

74.4 (*R*)-isomer; 95.5%ee

VIII. Asymmetric S–O Bond Forming Reactions

The development of methods to prepare chiral sulfoxides in high enantiomeric purity has been the focus of intense research in the last two decades. In 1984, Kagan and co-workers[112] demonstrated high levels of enantioselectivity using, a Sharpless-type of catalytic system Ti(O-*i*-Pr)$_4$/(+)-DET/H_2O and *t*-BuOOH as a stoichiometric oxidant for the stereoselective oxidation of sulfides to sulfoxides.

In 1986, Nakajima and co-workers[113] reported that chiral oxotitanium(IV)−Schiff base complexes derived from 2,3-diaminobutane or 1,2-diamino-1,2-diphenylethane have better catalytic efficiency profiles compared to those of the Kagan system. However, these catalysts showed lower enantiomeric excesses. In the early 1990's, the same researchers described that complexes derived from the reaction of (*R,R*)-1,2-diaminocyclohexane and $TiCl_4$ catalyzed the oxidation of methyl phenyl sulfide by trityl hydroperoxide in methanol at 0 °C in 53% ee.[114] Similar Schiff-base complexes of oxovanadium(IV) and oxovanadium(V) complexes led to lower ee's.[115] In 1992, Jacobsen and co-workers[116] used *trans*-1,2-diaminocyclohexane (salen)Mn(III) complexes as catalysts for the oxidation of methyl aryl sulfides using buffered hydrogen peroxide as an oxidant in acetonitrile. Enantioselectivities ranging from 34−68% ee were reported (Scheme 75, Table 23).

Scheme 75

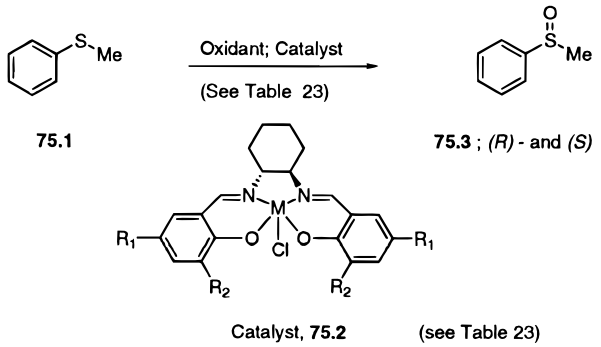


Table 23. Asymmetric Oxidation of Sulfides Using Metal Schiff Bases of Type 75.2

Entry	R_1	R_2	M	Oxidant	% Yield	%ee
1	H	MeO	V	CHP	70	40(*S*)
2	MeO	H	V	CHP	87	13 (*S*)
3	H	H	Ti	THP	98	62 (*R*)
4	H	H	Ti	CHP	32	19 (*R*)
5	MeO	*t*-Bu	Mn	H_2O_2	90	47 (*S*)

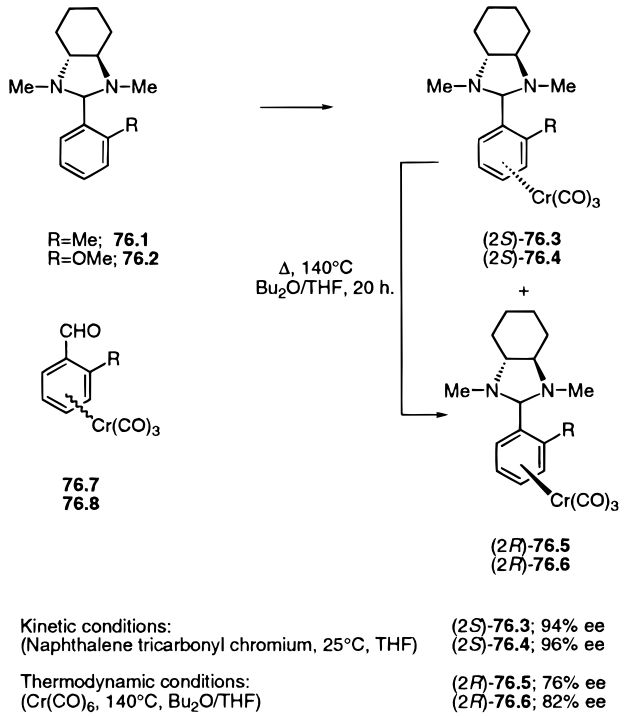
IX. Asymmetric Arene–Chromium Complex Forming Reactions

Chiral chromium tricarbonyl arene complexes are useful synthons in asymmetric synthesis, and their preparation has relied on enzymatic enantioselection or resolution techniques. In 1992, Alexakis and co-workers[117] reported that enantioselective complexation (resolution) can be achieved with *ortho*-substituted chiral aminal derivatives of (*R*,*R*)-*N*,*N*′-dimethyl-1,2-diaminocyclohexane as a chiral reagent (Scheme 76). Under thermodynamic conditions ($Cr(CO)_6$; 140 °C; Bu_2O−THF), a 88:12 *R:S* ratio was obtained (76% yield). In the case where R = OMe, a 91:9 *R:S* ratio was obtained (55% yield). However, under kinetic conditions (naphthalene tricarbonyl chromium, 25 °C, THF, 4 days), the opposite (2*S*) diastereomer complex was obtained in 80% yield and 94% de. The inversion of selectivity might be due either to a chelation of one of the nitrogen atoms of the imidazolidine ring or to the steric requirements of the aminal group itself, which behaves differently in the presence of naphthalene tricarbonylchromium. In each case, the diastereomers could be easily separated by chromatography and subjected to hydrolysis to give the corresponding enantiomerically pure chromium complex aldehydes in 94−96% ee and near-quantitative yields.

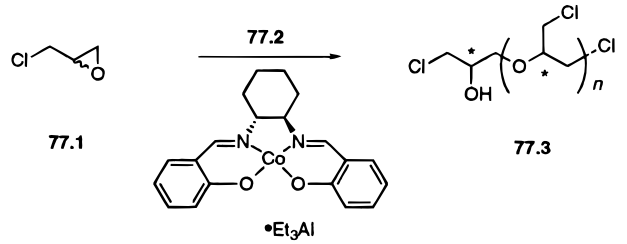
X. Stereoselective Oligomerizations and Polymerizations

Asymmetric selective polymerization is known to provide useful ways for synthesizing optically active polymers from racemic monomers.[118] In 1983, Tsuruta and co-workers[119] reported that chloromethyloxirane underwent asymmetric selective oligomerization with a binary catalyst system comprised of triethylaluminum and the (*N*,*N*′-disalicylidene-(*R*,*R*)-1,2-cyclohexanediyldiaminato)cobalt(II) complex (**77.2**) (Scheme 77). Two kinds of linear optically active oligomers were produced with epoxy- and halohydrin end groups such as **77.3**.

Scheme 76

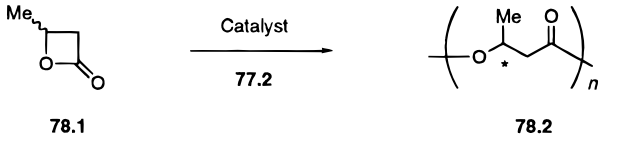


Scheme 77



The stereoselective polymerization of racemic β-butyrolactone complex **77.2** was reported by Takeichi and co-workers[120] (Scheme 78). The optically active polyester obtained was essentially the same material as the naturally occurring optically active poly(β-hydroxybutyrate).

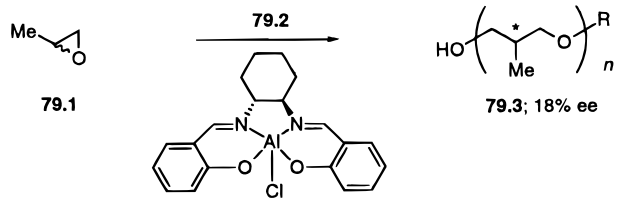
Scheme 78



Bifunctional oligoethers have interesting applications as in the synthesis of liquid-crystalline polymers and crown ethers. These can be prepared in an enantioselective manner by oligomerization of oxiranes using suitable chiral initiators. Le Borgne and co-workers[121] reported the formation of a chiral aluminum complex from the reaction of (*R*,*R*)-*N*,*N*′-bis(2-hydroxybenzylidene)-1,2-diaminocyclohexane.

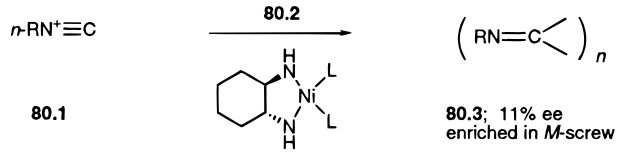
This complex demonstrated an "asymmetric initiator" character leading to the preferential oligomerization of one enantiomer (up to 18% ee) over the other, from a racemic monomeric mixture (Scheme 79).

Scheme 79



Poly(isocyanides) (RN=C<) were prepared enantioselectively from readily available isocyanides and a chiral Ni(II) initiator complex. In 1988, Drenth and co-workers[122] described the preparation and utilization of a variety of chiral amine−nickel complexes in this polymerization reaction. Poly(isocyanides) were obtained with up to 83% ee with one screw sense from an achiral monomer. However, the complex derived from (*R*,*R*)-1,2-diaminocyclohexane gave only 11% ee. This low level of enantioselectivity was believed to arise from the fact that each amino group can react simultaneously with a coordinated isocyanide (Scheme 80).

Scheme 80



XI. Molecular Recognition

An important challenge in the field of molecular recognition[123] is the creation of synthetic molecules that can simulate properties similar to those of biological substances such as antibodies, enzymes, and biological receptors.[124] Various host molecules have been used to mimic important biological reactions such as the catalytic activity of pyridoxamine,[125] thiamine,[126] and the binding ability of FADH.[127] Thus, the search for hosts that can function in catalytic cycles, particularly in aqueous media, is of paramount importance. Reports describing the synthesis and utilization of artificial hosts of biological molecules derived from *trans*-1,2-diaminocyclohexane are emerging as illustrated in the following sections.

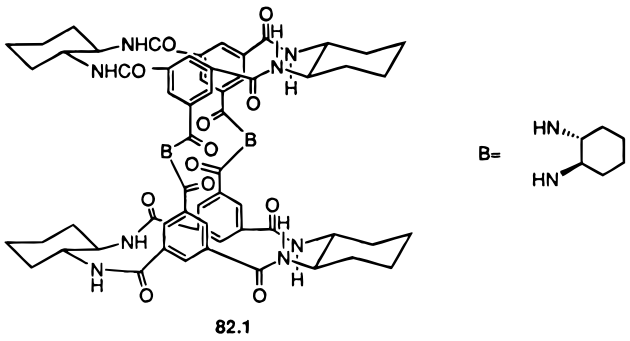
A. Hydride Transfer

Recently, Wennerstrom and Skog[128] reported a new macrocyclic host molecule derived from four nicotineamide units linked by two *p*-xylene groups and two chiral *trans*-1,2-diaminocyclohexane units. In this positively charged, tetravalent, D_2-symmetric, water-soluble host, the two *p*-xylene groups cooperate to form a hydrophobic cavity where small charged or polar guests can be included. It was found that this host molecule forms a complex in water with *N*-benzyldihydronicotinamide from which hydride ion is transferred from the guest to the host (Scheme 81). It was also observed that the dianion from terephthalic acid binds to **81.1** while phthalic acid dianion does not.

B. Receptor Design

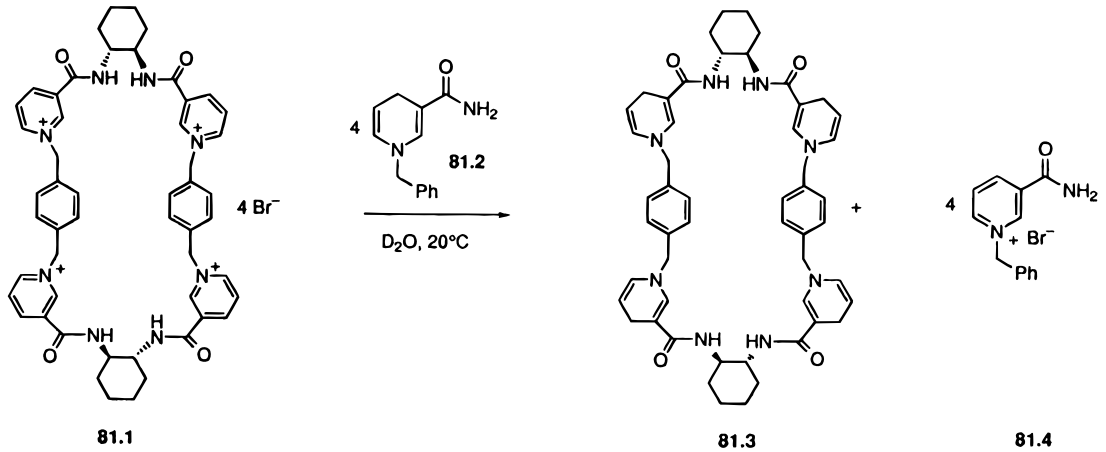
Sequence selective peptide binding in water with a synthetic receptor derived from a *trans*-1,2-diaminocyclohexane was recently described by Still and coworkers.[129] The cyclooligomer **82.1** obtained from (*R*,*R*)-1,2-diaminocyclohexane and trimesic acid was found to selectively bind L-α-amino acids (70−99% ee) and to more specifically select for amino acid side chains having a particular size (Ph ≫ Bn ≫ Et ≫ Me) (Scheme 82).

Scheme 82



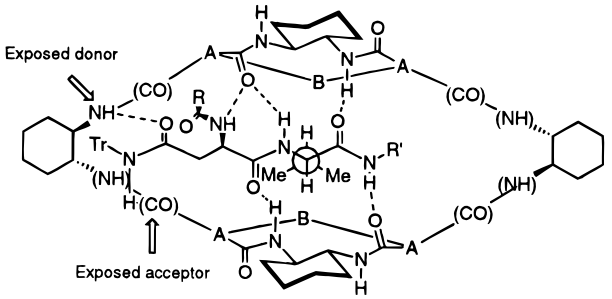
In conjunction with developing solid phase assays and combinatorial chemistry techniques, a labeled receptor was prepared on the basis of a *trans*-1,2-diaminocyclohexane scaffold and it was studied for

Scheme 81



selective binding toward a variety of peptides. After decoding the peptide sequences that showed the strongest binding to receptor **83.1**, a preference was demonstrated for L-valine. This finding was in agreement with previous NMR data obtained by Still and co-workers.[129] Further decoding and analyses showed that receptor **83.1** preferentially binds the tripeptide consensus sequence n-V-S and its relatives q-V-S, n-V-G, and q-V-G. A receptor−ligand structure based on molecular mechanics and ^{1}H-NMR is depicted in Scheme 83. Related studies in carboxylate recognition[129c] and in "chemical selection" during a cyclization reaction[129d] have been reported.

Scheme 83

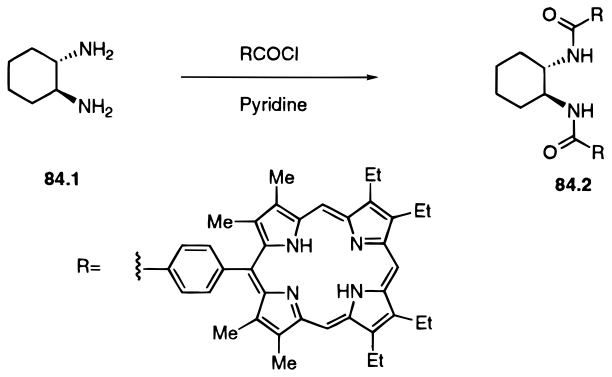


83.1

C. Chiral Porphyrin Dimers

Porphyrins are spatially arranged in the naturally occurring proteins such cytochrome *c* oxidase. It is documented that the distance and orientation between two porphyrins are significant factors in the efficiencies of electron transfer and in the catalytic activities. Recently, Ema and co-workers[130] described the synthesis and CD spectrum of a novel chiral C_2 symmetrical porphyrin dimer derived from (*S*,*S*)-1,2-diaminocyclohexane (Scheme 84).

Scheme 84

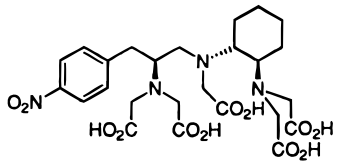


84.1 **84.2**

D. Complexes for Radioimmunotherapy

1,2-Diaminocyclohexane derivatives with potential therapeutic value in radioimmunotherapy against cancer have been reported in connection with using α-particle emmiter-labeled antibodies. The α-decay produces cytocidal, densely ionizing radiation of very high energy over a range of a few cell diameters, which limits toxicity to small areas of tissue. The design of a chelating agent to label immunoproteins with ^{212}Bi requires that the complex be thermodynamically stable and kinetically inert resulting from an irreversible binding of the radioisotope to the protein. Several C-functionalized cyclohexyldiethylenetriaminepentaacetic acids of type **85.1** were synthesized by Brechbiel and Gansow[131] for labeling monoclonal antibodies with a ^{212}Bi α-particle emitter (Scheme 85). In these systems, the *p*-nitro group was further transformed into the corresponding isocyanate to be conjugated with a monoclonal antibody.

Scheme 85

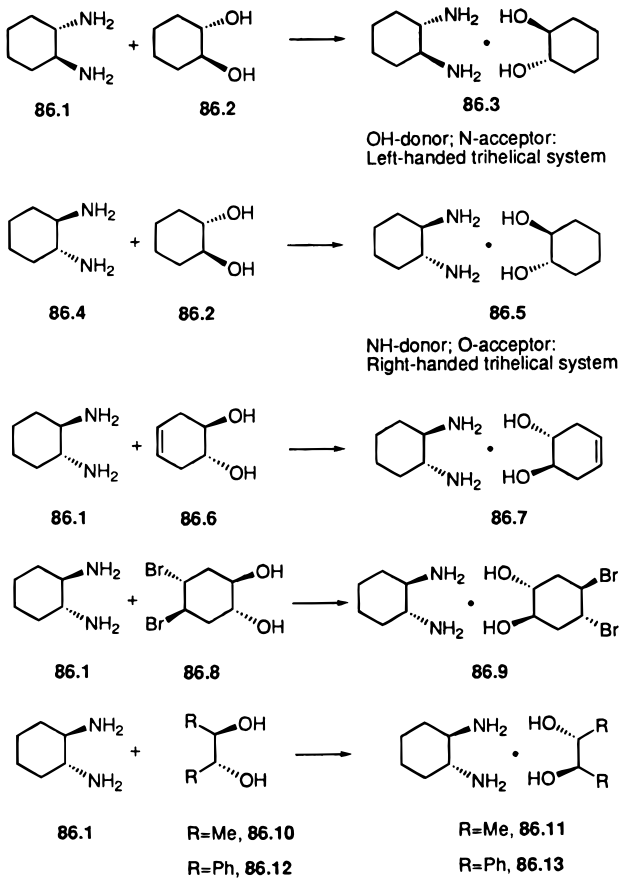


85.1

E. Self-Assembly: Non-amidic Hydrogen Bonding

Hanessian and co-workers[132a−d] have disclosed a new class of supramolecular structures that are self-assembled on the basis of H-bonding between pairs of vicinal diamines and diols such as *trans*-1,2-cyclohexanediols, 2,3-butanediols, 1,2-diphenyl-1,2-ethanediols, and related compounds. The two enantiomers of *trans*-1,2-diaminocyclohexane form well-defined supramolecular structures (supraminols) with appropriately paired C_2-symmetrical 1,2-diols that are assembled by H-bonding. Depending on the structure and chirality of the diamine, it is possible to form left- and right-handed trihelicate structures consisting of polar cores and hydrophobic outer residues (Scheme 86).

Scheme 86



86.1 **86.2** **86.3**

86.4 **86.2** **86.5**

86.1 **86.6** **86.7**

86.1 **86.8** **86.9**

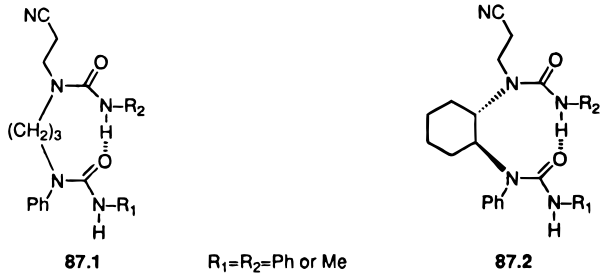
86.1 R=Me, **86.10** R=Ph, **86.12** R=Me, **86.11** R=Ph, **86.13**

These structures can be sublimed without change, and they slowly adsorb carbon dioxide to eventually give polymeric amorphous fibers. Heating these materials regenerates the original 1:1 adducts as supramolecular entities with evolution of CO_2. The parent (*R,R*)-1,2-diaminocyclohexane forms a crystalline ammonium carbonate salt with carbon dioxide which exists as a layered right-handed trihelicate structure. Other charged supramolecular structures are formed from the (*R,R*)-diamine and the enantiomeric tartaric acids. *trans*-1,2-Diaminocyclohexane and related vicinal diamines are superb assemblers of neutral and charged structures by accommodating preferred diol and acid partners in their crystal lattices.[132a−d]

F. Molecular Scaffolds: Intramolecular Hydrogen Bonding

U-turns are important architectural elements of both natural and unnatural molecules. Much effort has been devoted to the development of U-turns as β-turn mimics, which are potentially useful for the creation of synthetic peptide analogues able to simulate the biological activities of natural peptide hormones. Results from the development of acyclic molecules in which intramolecular hydrogen bonding creates conformationally well-defined structures (U-turns) have been recently reported by Nowick and co-workers.[133] 1,2-Diaminoethane ureas were compared to diurea analogues prepared from 1,2-diaminocyclohexane. On the basis of spectroscopic studies, it was found that the intramolecular hydrogen bond was stronger in **87.1** than in **87.2**, hence the conclusion that the former could be a better scaffold for U-turn mimics (Scheme 87). Gelation and "chiral aggregation" has been observed with bis(ureido) and bis(alkylamido) derivatives of (*R,R*)-1,2-diaminocyclohexane.[134a,b]

Scheme 87



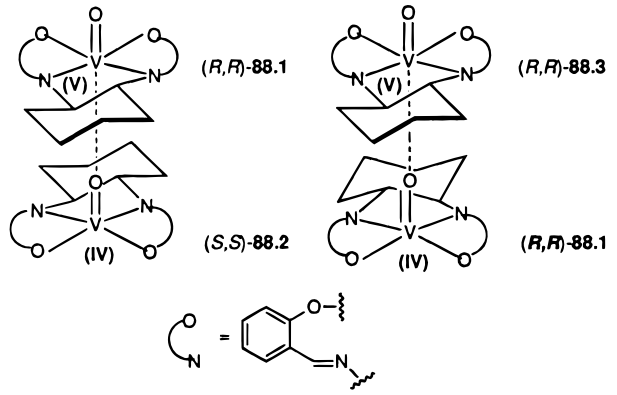
G. Molecular Recognition in the Epimerization of Aldoses

Studies on the epimerization and isomerization of aldoses using various nickel(II) and calcium(II) diamine complexes were originally reported by Osanai and co-workers.[135a] From these studies, it became apparent that the epimerization at C-2 of D-glucose (to D-mannose), in the presence of Ni(II) diamine, proceeded through a stereospecific rearrangement of the carbon skeleton, rather than via the enediol rearrangement. On the basis that the coordination state of the intermediate complex consists of the metal Ni(II)−diamine complex and sugar, several diamines were screened to evaluate their influence on the rate and degree of this epimerization. It was found that the epimerization of D-glucose at 0 °C gave a greater yield of D-mannose using (*R,R*)-*N,N′*-diethyl-1,2-diaminocyclohexane than the (*S,S*)-isomer.[135b] The opposite was found when D-mannose was used as the starting material. Overall, the equilibrium of the reaction shifted in accordance with the chirality of the diamine ligand employed.

H. Chiral Recognition in Electron-Transfer Reactions

It has been recently shown that the isomerization between the diastereomeric pair of optically active Schiff base−oxovanadium(IV) complexes **88.1** and **88.2** is catalyzed by the oxidized oxovanadium(V) species.[136] The electron-transfer reaction between the oxovanadium(IV) and oxovanadium(V) complexes was suggested to have an important role in this isomerization. Recent kinetic studies using *trans*-1,2-diaminocyclohexane (DACH)−oxovanadium Schiff base complexes demonstrated that the rate constant of the electron transfer between [VO{3-MeOSal-(*S,S*)-DACH}] and [VO{3-MeOSal-(*R,R*)-DACH}]$^+$ (k_{SS-RR}) and that between [VO{3-MeOSal-(*R,R*)-DACH}] and [VO{3-MeOSal-(*R,R*)-DACH}]$^+$ (k_{RR-RR}) was 2.0 at 25 °C. The proposed structures of the intermediate in the electron-transfer reaction are depicted in Scheme 88. The observed activation parameters suggest that the reaction between **88.1** and **88.2** requires more thermal energy than that between **88.1** and **88.3**. It was also suggested that the chiral recognition must be due to the difference in the nonbonding steric interactions between the ligands in the two intermediate structures.

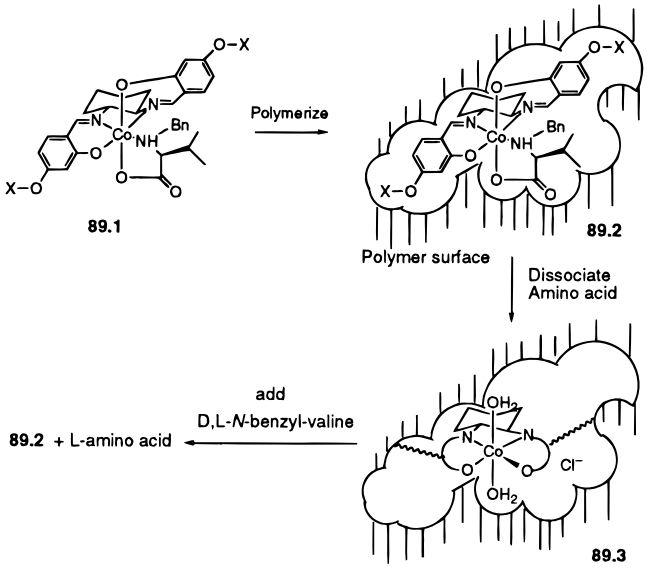
Scheme 88



I. Molecular Imprinting

Considerable advances have been made in the field of molecular imprinting, particularly in resolutions, enzyme mimicking, selective hydrolysis of D,L-amino esters, and regioselective steroid reduction, to name a few.[137] In one example, template polymer complex **89.2** was synthesized by copolymerization of Δ-β2-[Co{(*R,R*)-*N,N′*-bis[4-(*p*-vinylbenzyloxy)salicylidene]-1,2-DACH} (*N*-benzyl-D-valine)], **89.1**, styrene, and divinylbenzene, followed by dissociation of the coordinated amino acid (Scheme 89).[138] Interestingly, this polymer incorporated *N*-benzyl-D-valine with almost 100% stereoselectivity, reflecting on the high level of optical resolution in this Co^+ binding mode.

Scheme 89



The primary utility of this form on molecular recognition lies in the field of chromatographic separations.

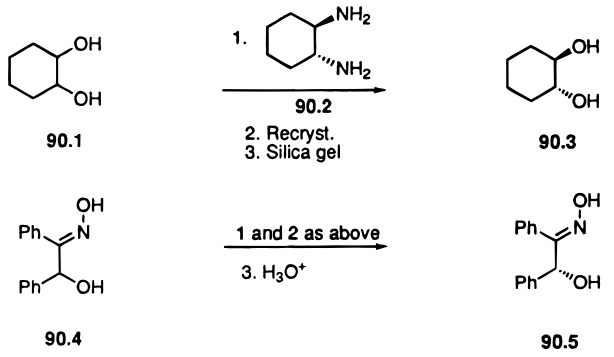
J. Metal Ion Size-Based Selectivity

Selective complexation of metal ions for biomedical applications is currently of major scientific interest.[139] An important example is the synthesis of ligands for the complexation of Gd^{3+} in magnetic resonance imaging. In 1995, de Sousa and Hancock[140] reported on the complexing ability of molecules prepared from the reaction of (*R,R*)- or (*S,S*)-1,2-diaminocyclohexane with cyclohexene oxide toward various metal ions such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}. In other medically oriented applications, 1,2-diaminocyclohexane−platinum derivatives were synthesized as cisplatin analogues. It was found that these compounds exhibit lower toxicity and lack cross resistance over the parent compound while maintaining good biological activities. Miller and co-workers[141] reported a theoretical study for the binding of these diaminocyclohexane derivatives to DNA and concluded that these compounds [(*R,R*), (*S,S*), (*R,S*), and (*S,R*)] fit into the active site equally well. Quantum mechanical calculations of the intrinsic ligand binding energies of these compounds demonstrate that the (*R,R*)- and (*S,S*)-isomers bind better to DNA by 1.7 kcal/mol than the (*R,S*)- and (*S,R*)-isomers, in agreement with the corresponding biological activities. Hanessian and Wang[142] described the preparation of hydroxy and alkoxy derivatives of *trans*-1,2-diaminocyclohexane−Pt complexes. Monoclonal antibodies have been raised against a ((*R,R*)-1,2-diaminocyclohexyl)platinum(II)−DNA adduct.[143] Many applications on the preparation of these platinum complexes and their utility in cancer therapy can be found in the patent literature.

K. Resolutions

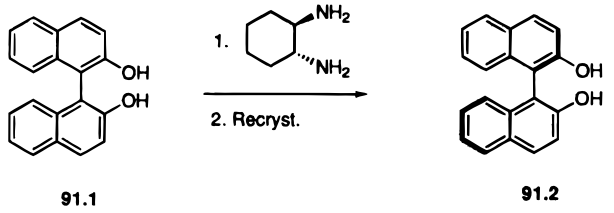
1,2-Diaminocyclohexane and its derivatives have been used in many other applications that are not related to asymmetric chemical reactions. This section will briefly highlight the miscellaneous uses of this compound in resolution and for the determination of enantiomeric excess. Direct optical resolutions of vicinal diols such as *trans*-1,2-cyclohexanediol (**90.1**), 2,3-butanediol, and stilbenediol as well as α-hydroxy oxime **90.4** were successfully accomplished by Kawashima and Hirayama[144] by utilizing enantiomerically pure *trans*-1,2-diaminocyclohexane (**90.2**) (Scheme 90).

Scheme 90



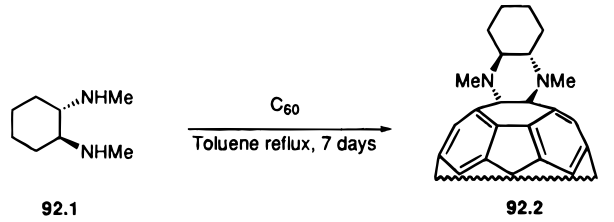
They also studied the optical resolution of 2,2′-dihydroxy-1,1′-binaphthyl (**91.1**) using (*R,R*)-1,2-diaminocyclohexane, which afforded the (*R*)-binaphthol **91.2** in 94% ee after its separation from the complex by treatment with acid (Scheme 91).[145a] Related studies have been reported by Toda and co-workers.[145b] Racemic *trans*-cyclohexenediol can be resolved to >99% ee enantiopurity by complexation with (*R,R*)- or (*S,S*)-1,2-diaminocylohexane.[132d]

Scheme 91



Recently, Prato and co-workers[146] reported that the addition of (*S,S*)-*N,N*′-dimethyl-1,2-diaminocyclohexane to C_{60} in refluxing toluene, for 1 week, led to the two enantiomers of chiral C_{60} derivative **92.2**, which possesses C_2 symmetry (Scheme 92). The circular dichroism spectra of the two isomers showed a very intense chirospectroscopic response.

Scheme 92



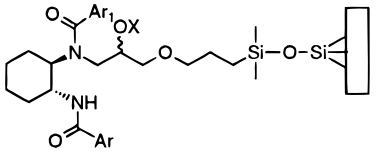
XII. Applications to Analytical Methods

A. Chromatography

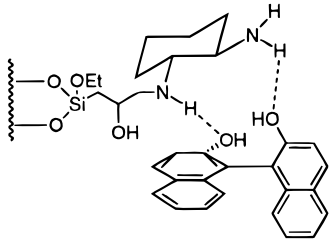
Separation and spectroscopic techniques for accurate and reliable determination of enantiomeric purity are primordial tools in modern asymmetric

organic synthesis. Separation sciences, especially enantioselective liquid chromatography (LC), gas chromatography (GC), supercritical fluid chromatography (SFC), and capillary electrophoresis (CE), have greatly advanced the analysis of organic molecules.[147] Direct chromatographic techniques based on chiral stationary phases (CSPs) are the most frequently used on analytical as well as for preparative scales. In addition, the use of chiroptical detectors greatly extends the usefulness of these stationary phases in solving stereochemical problems.[148] A number of chiral stationary phases derived from enantiomerically pure (*R,R*)- and (*S,S*)-1,2-diaminocyclohexane were designed and synthesized by Sinibaldi,[149] Pirkle,[150] and Misiti[151] and their respective co-workers (Scheme 93).

Scheme 93



93.1; CSP 1; Ar=Ar$_1$=3,5-NO$_2$(C$_6$H$_3$); X=H,Ar
93.2; CSP 2; Ar=Ar$_1$=(C$_6$F$_5$); X=H,Ar
93.3; CSP 3; Ar=1-Naphthyl; Ar$_1$-CO=H; X=H



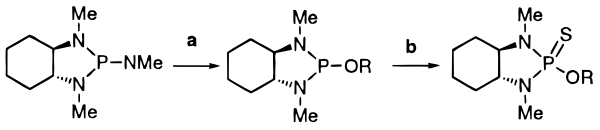
93.4; Chiral Recognition of β-Naphthol

These low-molecular-weight CSPs show good levels of enantioselectivity, high chemical and thermal inertness, and "tunable" selectivity toward specific compounds, obtained by functional group modifications on the 1,2-diaminocyclohexane core.

B. NMR-Spectroscopic Applications

As discussed in the previous section, chromatography techniques have proven to be excellent methods for the determination of the optical purity of organic molecules. The use of NMR spectroscopy with the aid of a chiral derivatizing agent also allows such a precise analysis, and many chiral derivatizing agents (CDA's) have been developed for this purpose.[152] Although Mosher's esters[153] have been widely used over the years, phosphorus reagents derived from (*R,R*)-1,2-diaminocyclohexane such as phospholane **94.1** have been recently reported for their enantiodifferentiating abilities using ^{31}P NMR (Scheme 94).[154] Treatment of an enantiomeric alcohol mixture with phospholane **94.1** followed by the addition of S_8 gave rise to a mixture of thiophosphonamides of type **94.4**, the diastereomeric content of which could be easily assessed by ^{31}P-NMR. The diastereomeric excesses of a variety of alcohols,

Scheme 94[a]



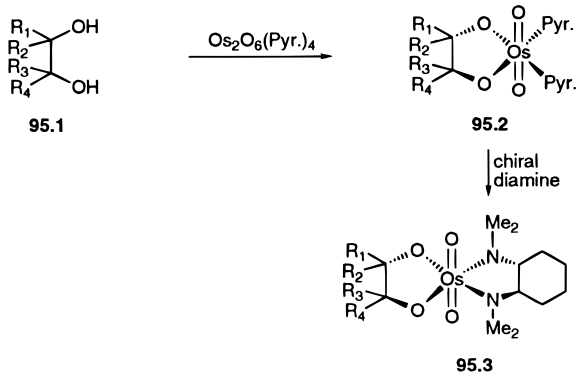
94.1 **94.3** **94.4**

[a] (a) ROH. (b) S_8.

primary alcohols, and thiols were successfully determined utilizing this method.

In 1981, Meinwald and Resch[155] reported that osmate(VI) esters chelated with (*R,R*)-*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane were useful derivatives for the (reversible) detection of sub-milligram quantities of glycols by ^{1}H-NMR (Scheme 95).

Scheme 95



95.1 **95.2** **95.3**

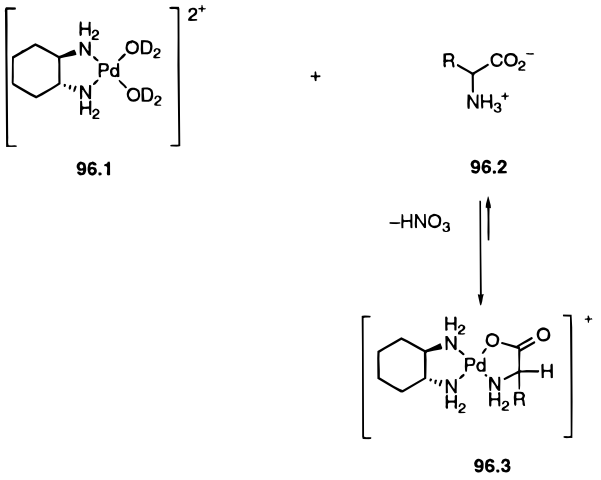
Thus, glycols **95.1** were reacted with $Os_2O_6(pyr)_4$ in aqueous pyridine to form diamagnetic pyridyl osmate esters **95.2**, which underwent facile ligand exchange with the chiral nonracemic tertiary amine to give complexes of type **95.3**. The levels of enantiomeric purity and determinations of absolute configuration were based on the chemical shifts of the *N*-Me groups. This method was employed in the determination of the absolute stereochemistry of the pyrrolizidine alkaloids and trachelanthic and viridifloric acids.

More recently, Staubach and Baddrus[156] reported on a new method for the determination of the optical purity of unprotected α-amino acids by NMR spectroscopy utilizing C_2-symmetrical chiral diamine palladium complexes. On the basis of the known reactivity of [Pd(H$_2$NCH$_2$CH$_2$NH$_2$)(H$_2$O)$_2$(NO$_3$)$_2$] with α-amino acids in water, the method was extended using a chiral 1,2-diaminocyclohexane (Scheme 96). The enantiomeric excesses of the complexed α-amino acids were easily determined by ^{1}H-NMR.

XIII. Conclusions and Perspectives

When we decided to write this review article, we did not expect to find such a broad range of applications for 1,2-diaminocyclohexanes in the chemical literature. It is interesting to see the range of applications reported since the first asymmetric hydrogenation[11] and C−C bond forming reactions[12] performed utilizing this chiral motif. Additionally, this unique molecule is being exploited in much broader areas of organic, bioorganic, and analytical chemistry, as well as in material and physical sciences.[157] Thus, we foresee other significant and

Scheme 96



diversified applications as "designer" chiral ligands, reagents, and auxiliaries in the quest for new asymmetric processes in the near future.

XIV. References

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