Synthesis of novel homochiral phosphine ligands
by Meiqun Jiang

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Chemistry
Montana State University

Abstract:
Chiral phosphine ligands are of key importance in development of transition-metal catalysts for enantioselective reactions. Yet, despite the critical importance of P-chiral phosphines, the methodology for their enantioselective synthesis in high enantiomeric excess and without resolution or separation of diastereomers remains relatively undeveloped. We describe herein an effective enantioselective synthesis of chiral tertiary phosphines. This methodology shows promise for the synthesis of a wide range of monophosphines and diphosphines of high enantiomeric purity and could be useful for the asymmetric reactions,

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APPROVAL

of a thesis submitted by
Meiqun Jiang

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

July 21, 1994
Date

Tom Tilson
Chairperson, Graduate Committee

Approved for the Major Department

8/3/94
Date

David M Dooley
Head, Major Department

Approved for the College of Graduate Studies

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R K Brown
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Date July 18, 1994

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ABSTRACT

Chiral phosphine ligands are of key importance in development of transition-metal catalysts for enantioselective reactions. Yet, despite the critical importance of P-chiral phosphines, the methodology for their enantioselective synthesis in high enantiomeric excess and without resolution or separation of diastereomers remains relatively undeveloped. We describe herein an effective enantioselective synthesis of chiral tertiary phosphines. This methodology shows promise for the synthesis of a wide range of monophosphines and diphosphines of high enantiomeric purity and could be useful for the asymmetric reactions.

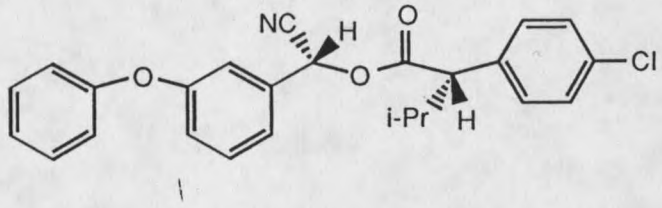
INTRODUCTION

Introduction to Enantioselective Catalysis

Chirality plays a central role in science and technology. A wide range of significant physical, chemical, and biological functions are generated through precise molecular recognition which requires strict matching of chirality. For a long time, access to enantiomerically pure compounds, at least in a practical sense, was thought to be nature's monopoly. Living organisms are masters of enantioselective catalysis. In general, when a living cell manufactures a chiral organic molecule, it selectively produces only one of the two non-superimposable mirror-image forms (enantiomers). To do otherwise is at best inefficient. Biocatalyst (enzymes and ribozymes) promote the chemistry of life with exquisite efficiency and selectivity.

Synthetic chemists have been slow to learn from nature's model. Creation of optically active organic molecules by chemical means is challenging and difficult. Only optical resolution and structural modification of naturally occurring chiral substances provide in this respect. Until recently, it was common practice for a pharmaceutical company to market a chiral drug as the racemate.[1] As recently as 1985, more than 75% of chiral drugs were sold as the racemates. This approach in effect meant that each dose of a drug was contaminated with an equal weight of an isomer, which usually had no therapeutic value but had the potential to cause unsuspected deleterious side effects. For example, the sedative thalidomide (**1**) was marketed as a

racemate,[2] the desired sedative activity resides in the R-isomer, but the contaminant S-isomer is a tetratogen, causing profound birth defects in babies born to mothers using the drug. The issue of enantiomeric purity is by no means limited to the field of pharmaceuticals. A case in point is ASANA (i-Pr=isopropyl),[3] a synthetic pyrethroid insecticide which contains two asymmetric centers(**2**).



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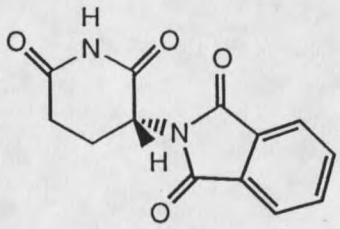


Thalidomide 1

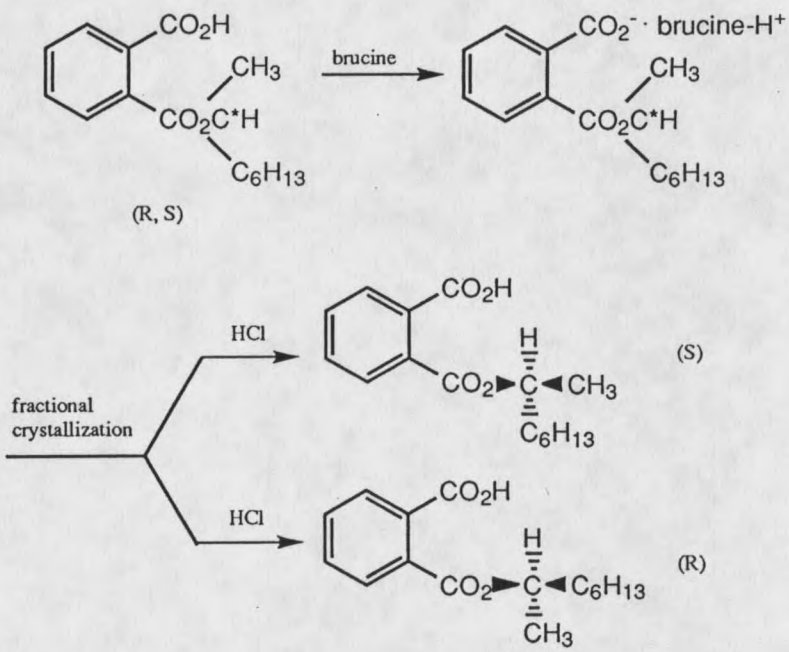
The potent insecticide activity overwhelmingly resides in just one of the four possible stereoisomers. Moreover, the non-insecticidal stereoisomers exhibit significant cytotoxicity toward certain plant species. Thus ASANA, which is sold as a single stereoisomer, can be registered and used for crops whereas the mixed stereoisomers are not suitable. Due to the need for chiral liquid crystals, enantiomerically pure polymers, and membrane components with applications in such diverse areas as drug delivery, separation technology, and

optoelectronics, it is easy to understand the growing demand for efficient methods of producing enantiomerically pure compounds.

Assiduous efforts made by synthetic organic chemists in the last two decades are converting the chemist's dreams into reality. In order to maximize synthetic efficiency, it is obviously desirable to utilize a catalytic amount of chiral source for "multiplication of chirality", namely, stereoselective production of a large quantity of a chiral target compound. Enantioselective catalysis is bringing about a revolution in asymmetric synthesis. Seldom has there been an area of chemistry where the scientific goals are so challenging and the economic benefits so obvious.

In the past, the selling of a racemic product could be defended on the grounds that the cost of manufacturing a single isomer could be prohibitive. Today, improvements in the technology for asymmetric synthesis, including the development of enantioselective catalysts based on metal complexes, make the development of new racemic drugs unacceptable. Asymmetric synthesis has advanced to the point where it should be possible to manufacture any drug as a single enantiomer.

Conventional methods of asymmetric synthesis rely on the stoichiometric use of enantiomerically pure starting materials or reagents. In resolution by differential crystallization,[4] a racemic-product mixture can be converted into a separable mixture of diastereomers by the use of a stoichiometric amount of an optically pure resolving agent (Scheme 1). This method, however, requires recovery of the resolving agent and wastefully consumes precious starting materials to make the wrong enantiomer, which must then be racemized or discarded.



Scheme 1. Conventional methods of making the chiral molecules

Perhaps the most important advantage of enantioselective catalysis, versus conventional stoichiometric procedures, is the feature of chiral multiplication. Under the right conditions, thousands of chiral product molecules can be produced by one molecule of catalyst.

Chiral multiplication is a characteristic of both biocatalysis and catalysis by chiral metal complexes. Recently, enantioselective catalysis using metal complexes has advanced to the point where it can often provide a viable alternative to biocatalysis. The strengths of metal catalysts tend to complement those of enzymes:

(i) metals can promote reactions not known to occur in nature;

(ii) the chirality of the catalyst is easily modified by appropriate changes in the ligands;

(iii) one can use substrates not accepted by enzymes;

(iv) separation and recovery of products are relatively easy (enzymes

most often work in aqueous or near aqueous environments);

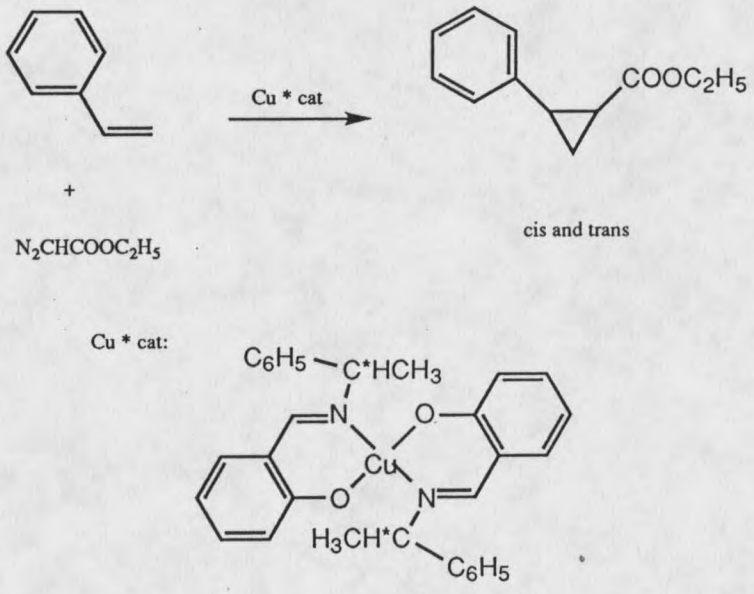
v) organometallic reagents are generally less capricious than enzymes, which are often susceptible to degradation caused by heat, oxidation, and pH.

Enantioselective catalysis using metal complexes, provides one of the most general, flexible methods for asymmetric reactions. Metallic elements possess a variety of catalytic activities, and permutation of organic ligands, or auxiliaries, that direct the steric course of the reaction is practically unlimited. Besides the choice of central metal, molecular design of the chiral modifier is a particularly significant task. Efficient ligands must be endowed with a suitable functionality, an appropriate element of symmetry, substituents capable of differentiating space either sterically or electronically, skeletal rigidity or flexibility (depending on the nature of the reaction) etc. - all of which contribute to accomplish highly enantioselective catalysts.

Chiral Phosphine Ligands

The first example of asymmetric synthesis from prochiral compounds catalyzed by homogeneous chiral metal complexes appeared in the literature in 1966.[5] A chiral Schiff base-Cu(II) complex was formed to catalyze decomposition of ethyl diazoacetate in stryrene to give cis- and trans-1-carboethoxy-2-phenylcyclopropane in <10% e.e, proving the existence of reactive Cu carbenoid placed in a chiral environment (Scheme 2).

Later, extensive systematic screening of chiral Schiff bases resulted in a dramatic improvement of the optical yield of cyclopropanation, allowing for asymmetric synthesis of chrysanthemic acid derivatives in up to 94% e.e.[6]

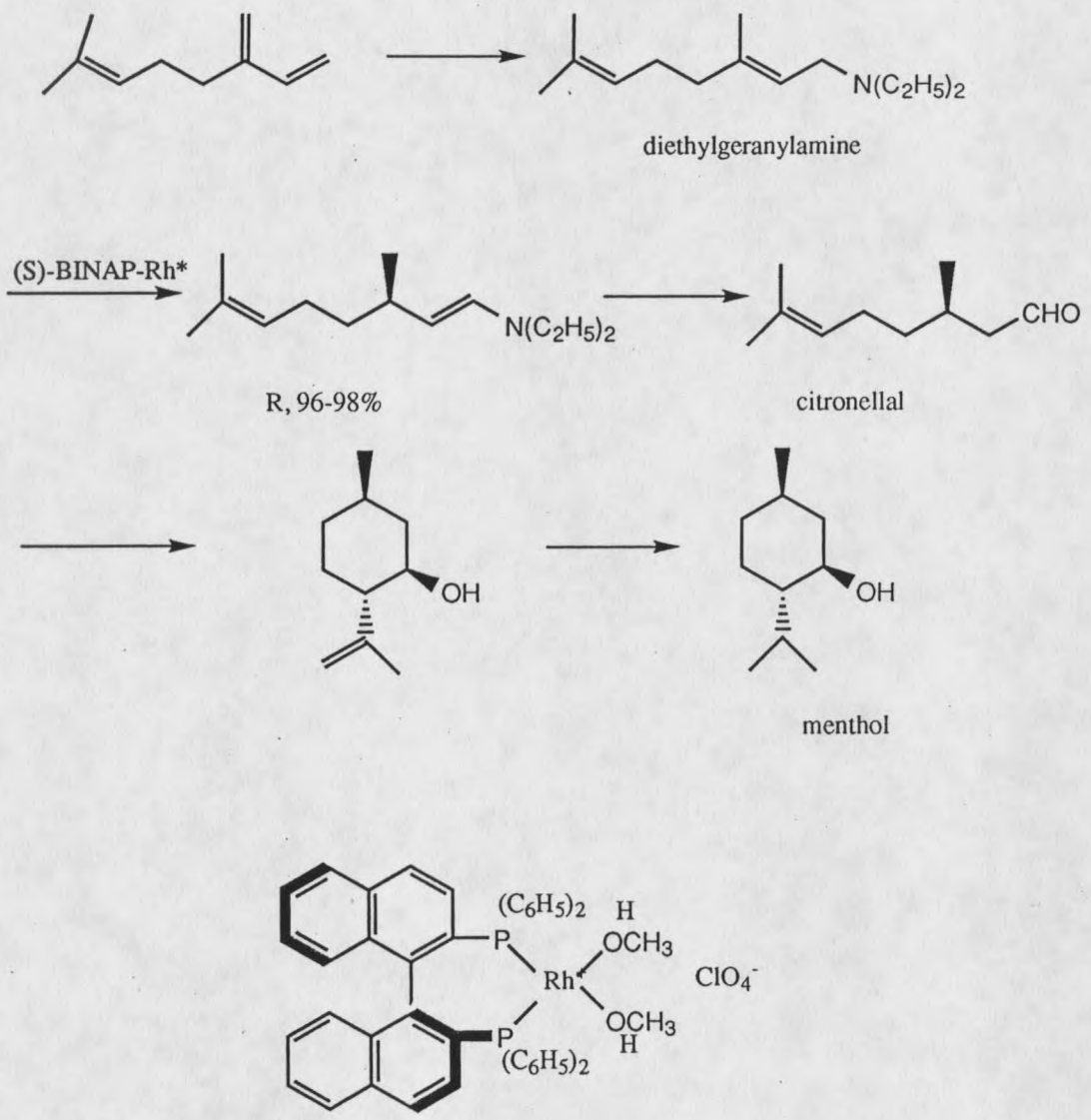


Scheme 2. Chiral Schiff base-Cu(II) complex

Perhaps the most common asymmetric catalyst used by industry at this time is utilized in the synthesis of (-)menthol (Talasage International CO, Japan)[7] (Scheme 3). The key step is the Rh-BINAP catalyzed enantioselective isomerization of diethylgeranylamine to citronellal diethylenamine proceeding in 96-98% optical yield. Here, use of an atropisomeric BINAP ligand has played a key role in the successful asymmetric transformation.

Another significant development in organotransition-metal chemistry is the discovery of soluble complexes which catalyze the asymmetric hydrogenation of prochiral olefins[8] (Scheme 4). These asymmetric reactions are achieved by homogeneous catalysts bearing chiral phosphine ligands.

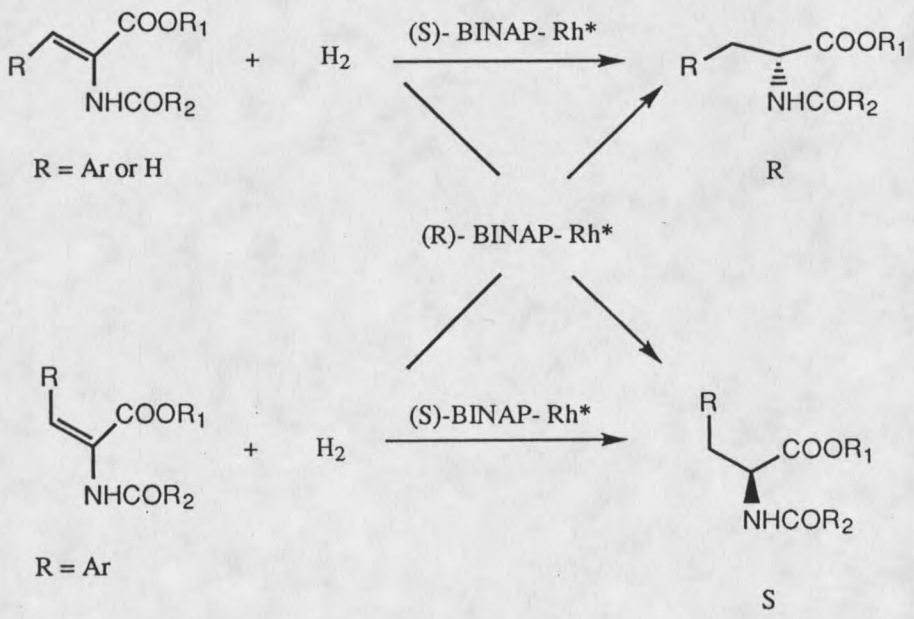
Chiral phosphines have been widely used as ligands for transition metals such as nickel, cobalt, rhodium, ruthenium, platinum, palladium and copper. These metal-chiral phosphine complexes have been used in the study of asymmetric reactions, such as reductions of ketones,[9]



Scheme 3. Synthesis of (-)menthol using the BINAP

hydrosilylations,[10] hydroformylations,[11] hydrocyanations,[12] and [4+2] cycloadditions.[13] The synthesis of well designed phosphine ligands is crucial to the development of efficient asymmetric catalysis by chiral transition-metal complexes.

Chiral phosphines can be divided into two broad classes: monophosphine and bidentate phosphine ligands.



Scheme 4. Asymmetric hydrogenation of olefins by Rh-BINAP

A. Monophosphines

There are basically two ways to design chiral monophosphines; the chirality can be located on either the side chain (**3**) or on phosphorus (**4**) (P-chiral) (Scheme 5).

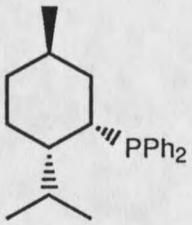
3 **4**

Scheme 5. Main types of chiral monophosphines

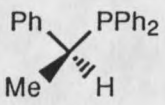
A1. Monophosphines with a Chiral Side Chain

Phosphines of the general type (**3**) (Scheme 5) are the easiest to obtain because their syntheses typically begin from a chiral natural product. Some

examples are depicted below (**5**)[14] (**6**)[15] (**7**)[16]:



5 (nmdpp)



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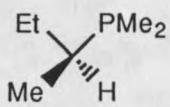

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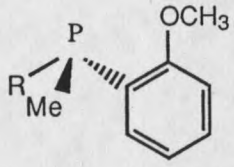
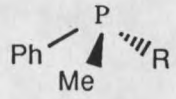
A2. Monophosphines with an Asymmetric Phosphorus Center

Optically active phosphines of type (**4**) (Scheme 5) were first used in asymmetric hydrogenation.[17] Representative P-chiral phosphines are as follows (**8**)[18] and (**9**)[19]:



8 R= Ph (pamp)

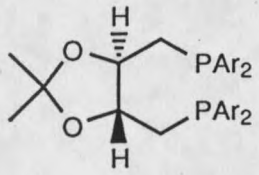


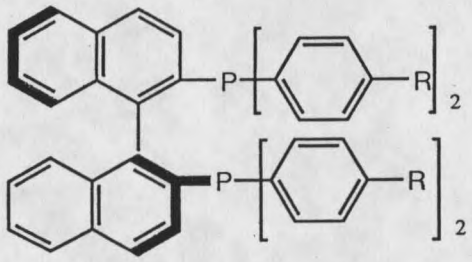
9 R = Et, n-Pr, CH_2Ph, CH_2CHCH_2, t-Bu

B. Bidentate Phosphines

The chelation of the ligand on a metallic center can occur through a chiral group connecting two achiral phosphorus atoms (**10**)[20] and (**11**)[21]. Within this class, the majority of members possess a stereogenic center, plane, or axis as an intrinsic component of the P-P linking backbone. Normally the two remaining substituents at phosphorus are aryl residues (commonly PPh_2),

although other combinations including alkylphosphines[22], alkyl(aryl)phosphines[23] and phospholanes[24] have been utilized to good effect.

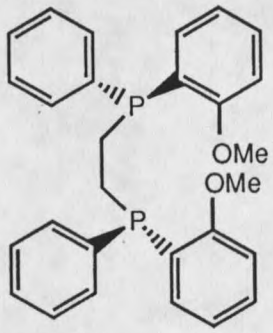




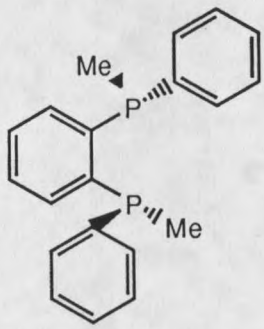
10 Ar = Ph (R,R-diop)
Ar = 2-anisyl
Ar = 3,5-dimethylphenyl

11 R = H (binap)
R = Me
R = t-Bu

Another type of bidentate chiral phosphine consists of two chiral phosphorus atoms connected by achiral backbone (**12**)[25] and (**13**)[26]. Examples of this class are relatively rare, due to the synthetic difficulty of controlling stereogenicity at phosphorus.



12 (dipamp)



13

One important objective in designing bidentate chiral phosphine ligands is to keep a suitable distance between the two chelating points in order to obtain a suitable chelate ring size. If the chelate ring is too large, the ligand will have a tendency to complex in a monodentate fashion or form a bridge between metals.

Preparation of Chiral Phosphines

A. Monophosphines

A1 Monophosphines with a Chiral Side Chain

Phosphines of the general type (**3**) (Scheme 5) are among the most easy to obtain because the synthesis can start from a chiral natural product (e.g. a terpene, sugar, etc.). The most frequent way to introduce phosphorus is to treat the tosylate (or halide) of the optically active compound (available from the chiral pool) with the diphenylphosphide anion, $^-PPh_2$ (Scheme 6):

$$R^*X + {}^-PPh_2 \longrightarrow R^*PPh_2 + X^-$$

Scheme 6. Route to monophosphines with a chiral side chain

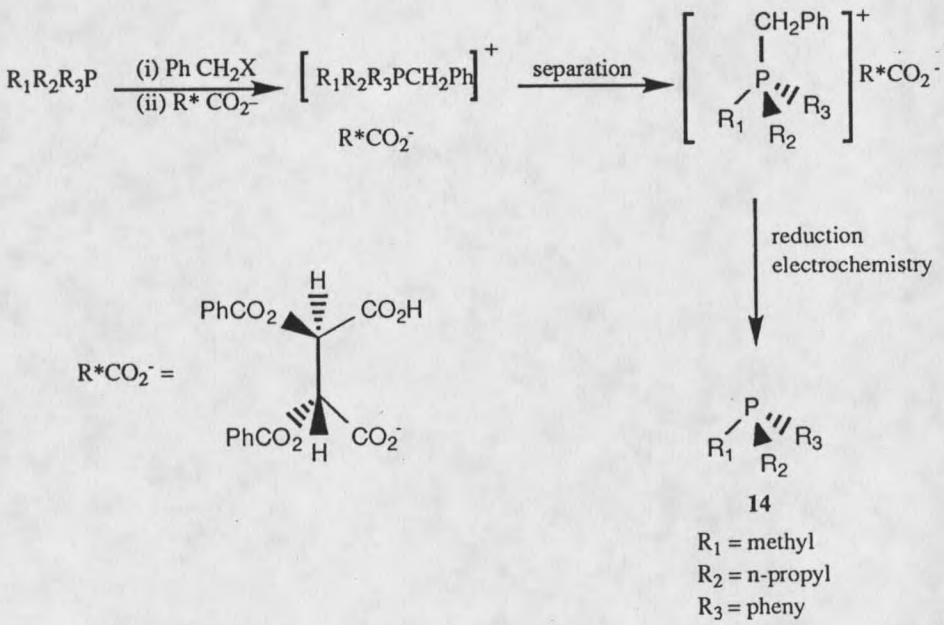
A2 Monophosphines with an Asymmetric Phosphorus Center

Optically active phophines of type (**4**) (Scheme 5) were first used in asymmetric hydrogenation.[17] There are three main transformation methods giving access to P-chiral phosphines:

- electrolytic hydrogenolysis of chiral phosphonium salts;
- reduction of chiral phosphine oxides;
- displacement of diheterocyclic phosphines

1. Electrolytic Hydrogenolysis of Chiral Phosphonium Salts

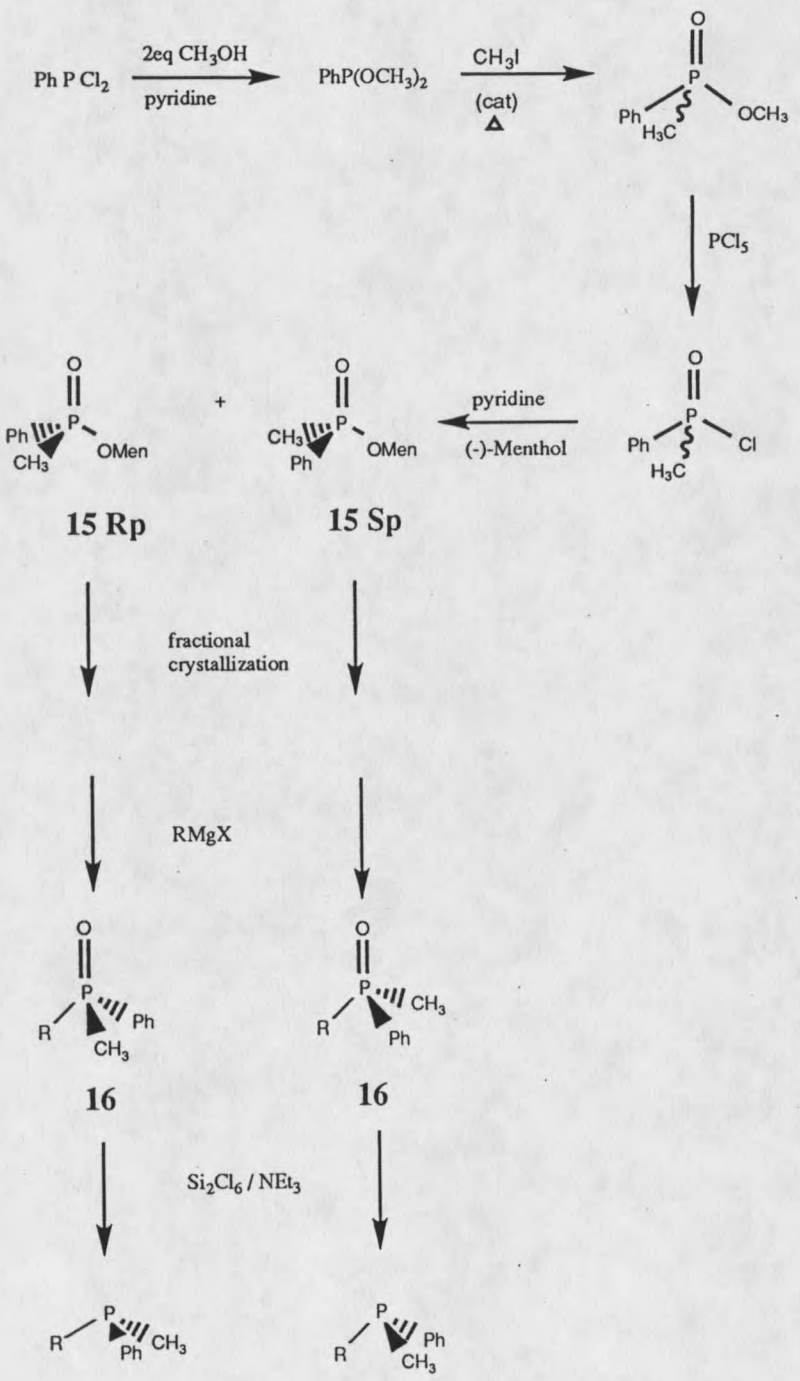
The first optically active phosphine in which the phosphorus atom is the asymmetric center in the molecule was described in 1911 by Meisenheimer and Lichtenstadt.[27] It was not until 50 years later that optically active phosphines could be routinely prepared, due to the efforts of Horner and Mentrup.[28] For example, methyl n-propylphenylphosphine **14** was obtained by electrolytic hydrogenolysis of its optically active benzylphosphonium salt (Scheme 7).



Scheme 7. Electrochemical preparation of chiral phosphines

2. Reduction of Phosphine Oxides

In 1968, a new method to create asymmetric phosphorus atoms was introduced by Mislow.[29] This approach was based on a simple observation that the diastereomeric O-menthylphosphinate **15** (*Rp*) and **15** (*Sp*) could be separated by fractional crystallization (Scheme 8).

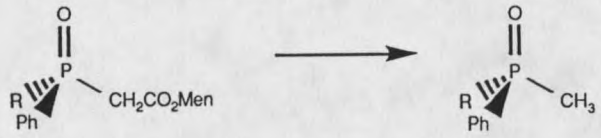


Scheme 8. Synthesis of chiral phosphines by Mislow and coworkers

The two diastereomeric phosphinates derived from the esterification of

(-)-menthol with Ph(R)PCl were separated (the most tedious step of the method). Displacement of the menthol group by an arylmagnesium halide occurred with inversion of configuration, giving (**16**) and its diastereomer. Reduction of the phosphine oxide by Si_2Cl_6 produced the related optically active phosphine with complete inversion of configuration.[29b] It had been observed that the combined reagent $HSiCl_3$-Et_3N was not stereoselective for phosphine oxide reduction whereas $PhSiH_3$ gave mainly retention of configuration.[29c] Therefore, Si_2Cl_6 seemed to be the most useful reagent for the stereospecific transformation of a phosphine oxide into a phosphine. This work led directly to the synthesis of the ligand DIPAMP {(*R*, *R*)-1,2-bis-[O-methoxyphenyl(phenyl)phosphino] ethane} **12** by Monsanto.[25]

Pietrusiewics[30] and Imamoto[31] prepared the vinyl and tert-butyl phosphine oxide (**18**) by separation of (**17**) followed by decarboxylation (Scheme 9).



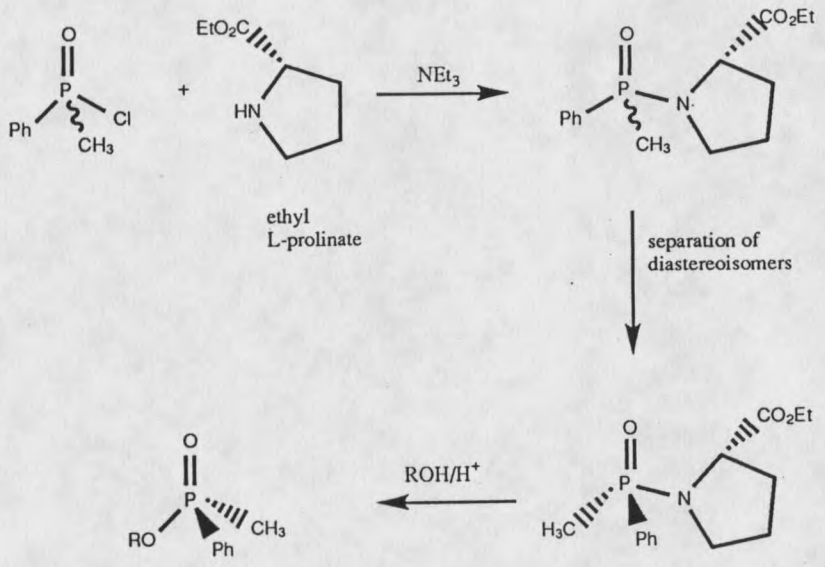
17 **18**

a) R = vinyl: (LiCl; H_2O; DMSO)/180°C

b) R = t-Bu: (i) KOH (ii) 160°C

Scheme 9. Synthesis of phosphine oxides by Pietrusiewics and Imamoto

In 1979, Koizumi and Coll[32] used this method to synthesize the phosphinate (**20**) by methanolysis of intermediate phosphinamide (**19**), derived from ethyl L-prolinate (Scheme 10).

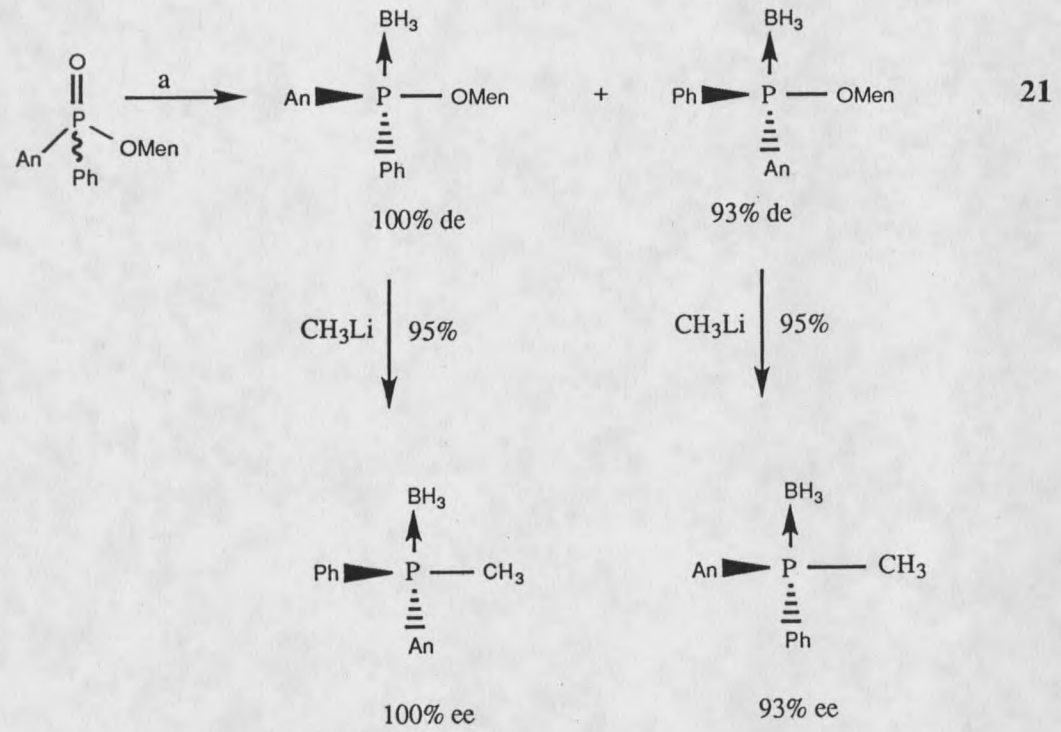


20 **19**

Scheme 10. Synthesis of phosphinates by Koizumi and Coll

Recently, Imamoto[33] described a new approach to prepare chiral phosphines. The diastereomerically pure menthyloxyphenylphosphine-boranes (**21**) and (**22**) were prepared from their phosphine oxides on treatment with $LiAlH_4$-$NaBH_4$-$CeCl_3$ (Scheme 11).

The method for the preparation of optically pure phosphines via reduction of a phosphine oxide generally involves a diastereomeric separation, low overall yields, and is not adaptable to the modification of substituents on the phosphorus atom.



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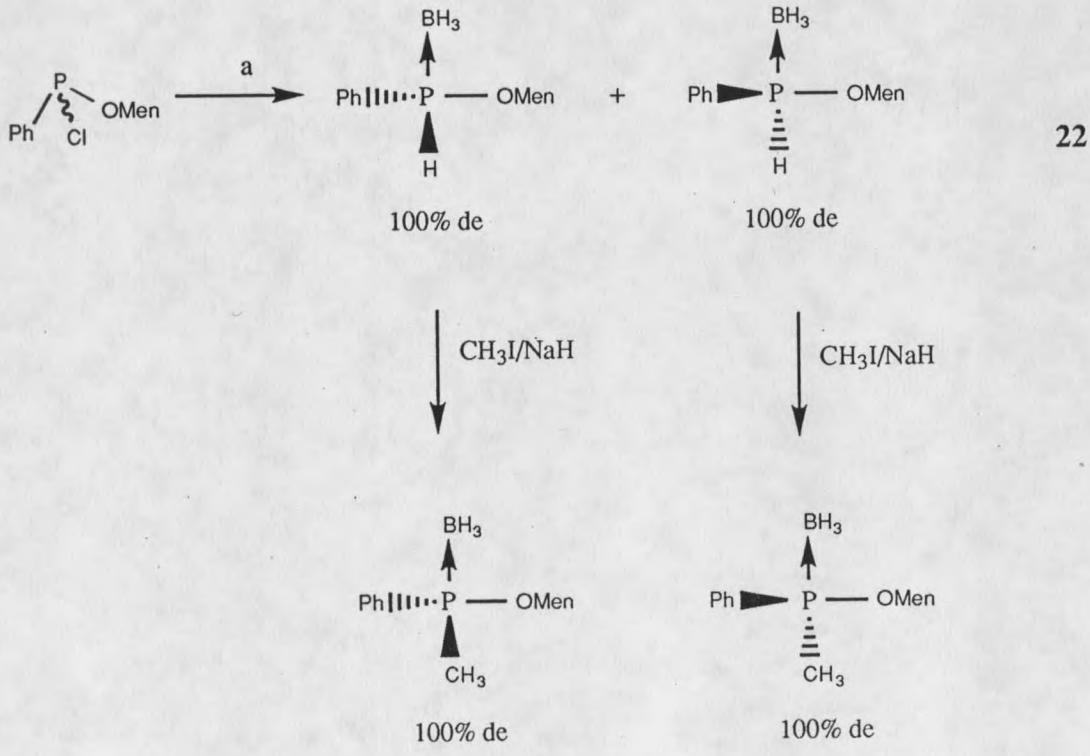
a) $LiAlH_4/NaBH_4/CeCl_3$



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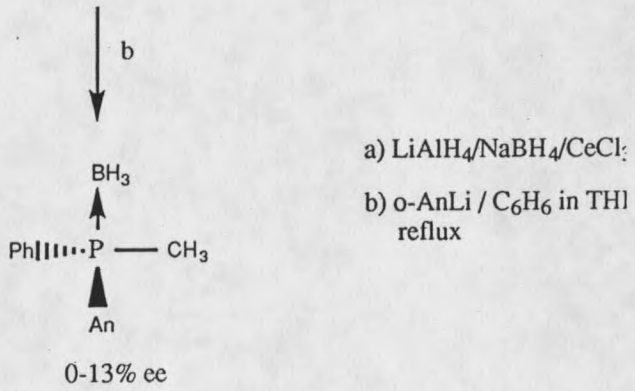
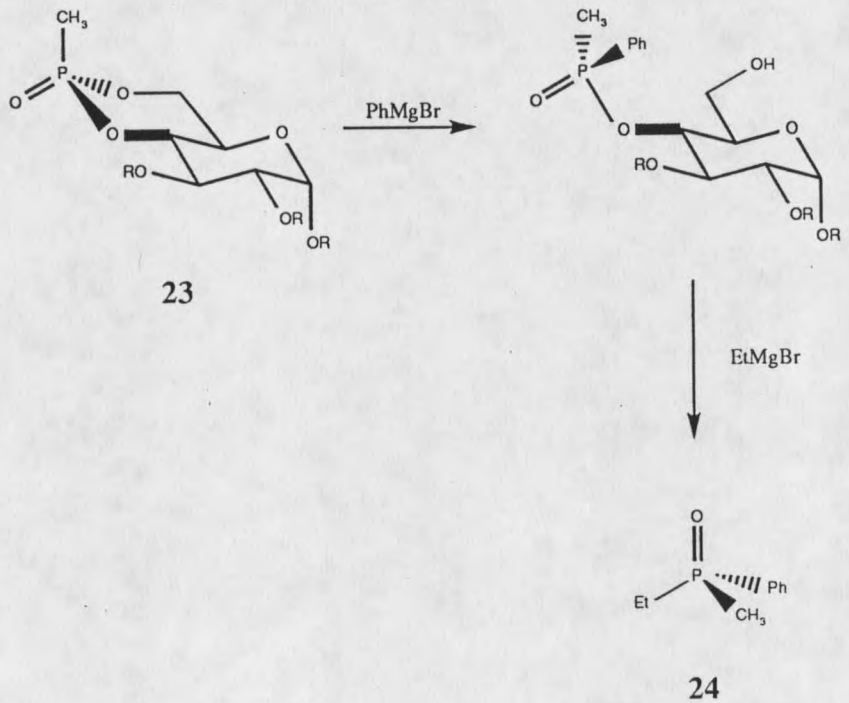


Scheme 11. Synthesis of phosphine borane complexes

3. Displacement of Diheterocycle Phosphines (Oxazaphospholidine, Oxaphosphorinane)

In 1974, Inch and Coll[34] proposed a new way to synthesize chiral phophine oxides (Scheme 12).



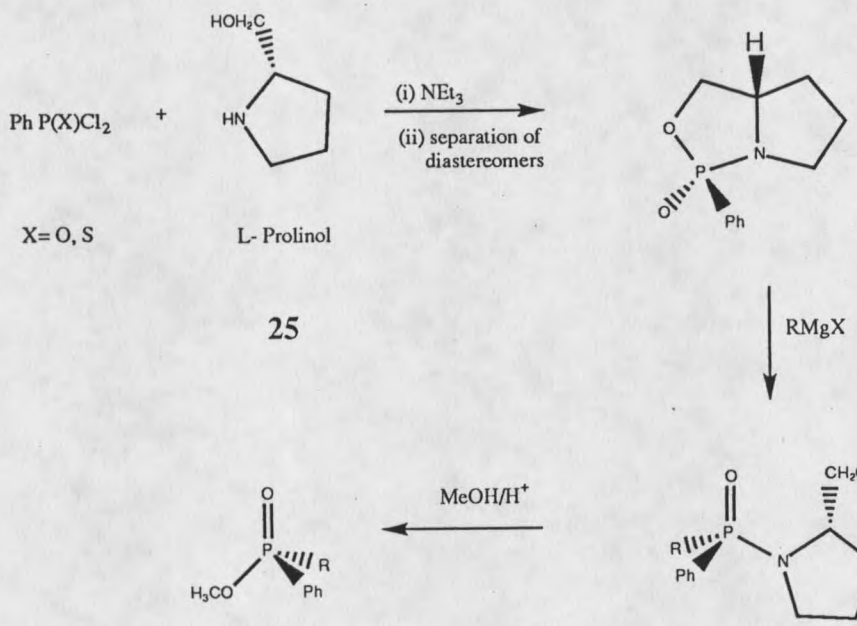
23

24

Scheme 12. Synthesis chiral phosphine oxides by Inch and Coll

The dioxaphosphorinane (**23**) was diastereoselectively formed by starting with a carbohydrate derivative. Sequential addition of phenylmagnesium bromide and ethylmagnesium bromide afforded phosphine oxide (**24**), which illustrated the utility of carbohydrates for stereospecific synthesis of optically active phosphates.

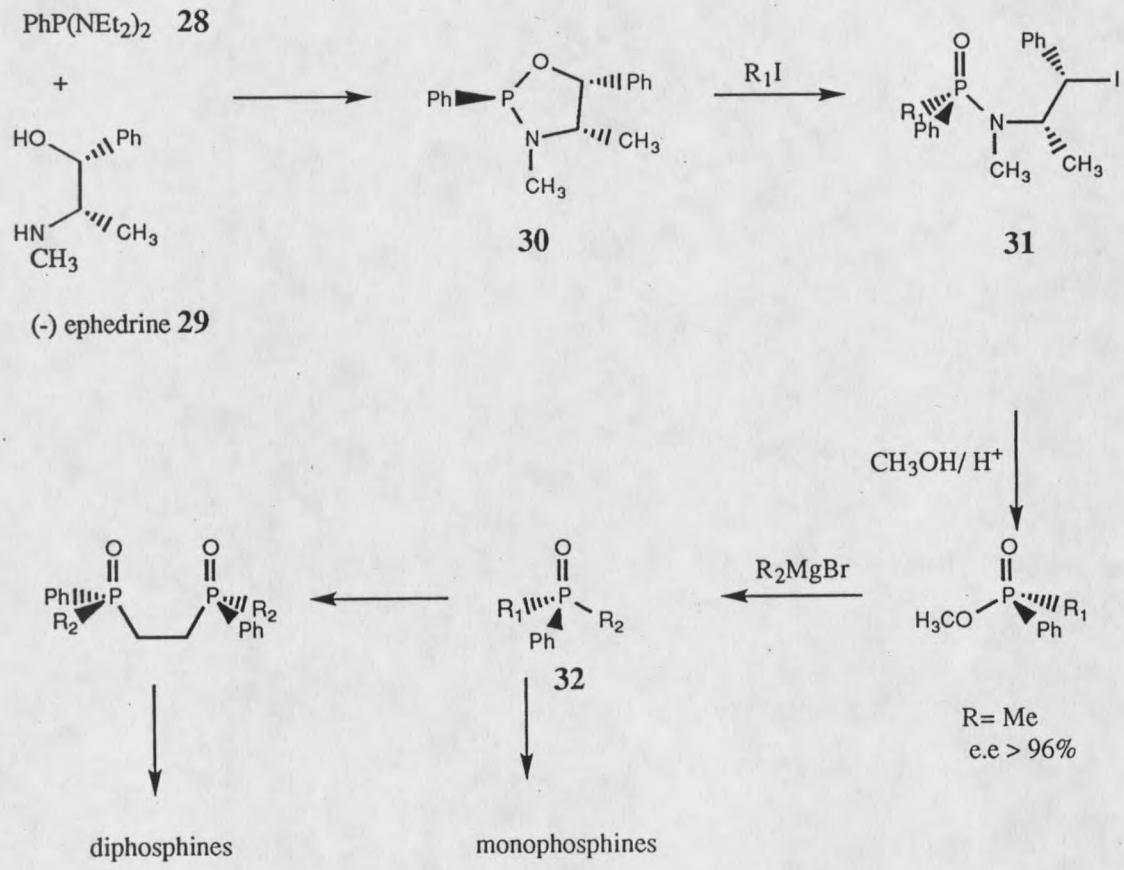
Using a related method, Koizumi and Coll[35] synthesized chiral phosphinate (**27**) by acid methanolysis of the phosphinamide (**26**), prepared by regio and stereoselective opening of oxazaphospholidine derived of L-prolinol **25** (Scheme 13).



Scheme 13. Synthesis of chiral phosphates from oxazaphospholidines

In the 1980's, Juge[36] and Brown[37] developed a new method for making

optically active phosphines (Scheme 14). This approach was based on the high diastereoselectivity observed in the formation of oxazaphospholidine (**30**) from ephedrine. Thus (**30**) reacted with MeI, EtI, or PrI to give (**31**) in a 9:1 ratio of diastereomers. The product (**31**) could be converted into diarylalkylphosphine oxides by successive acid-catalyzed methanolysis and Gringard displacement to give (**32**) in 95% e.e.

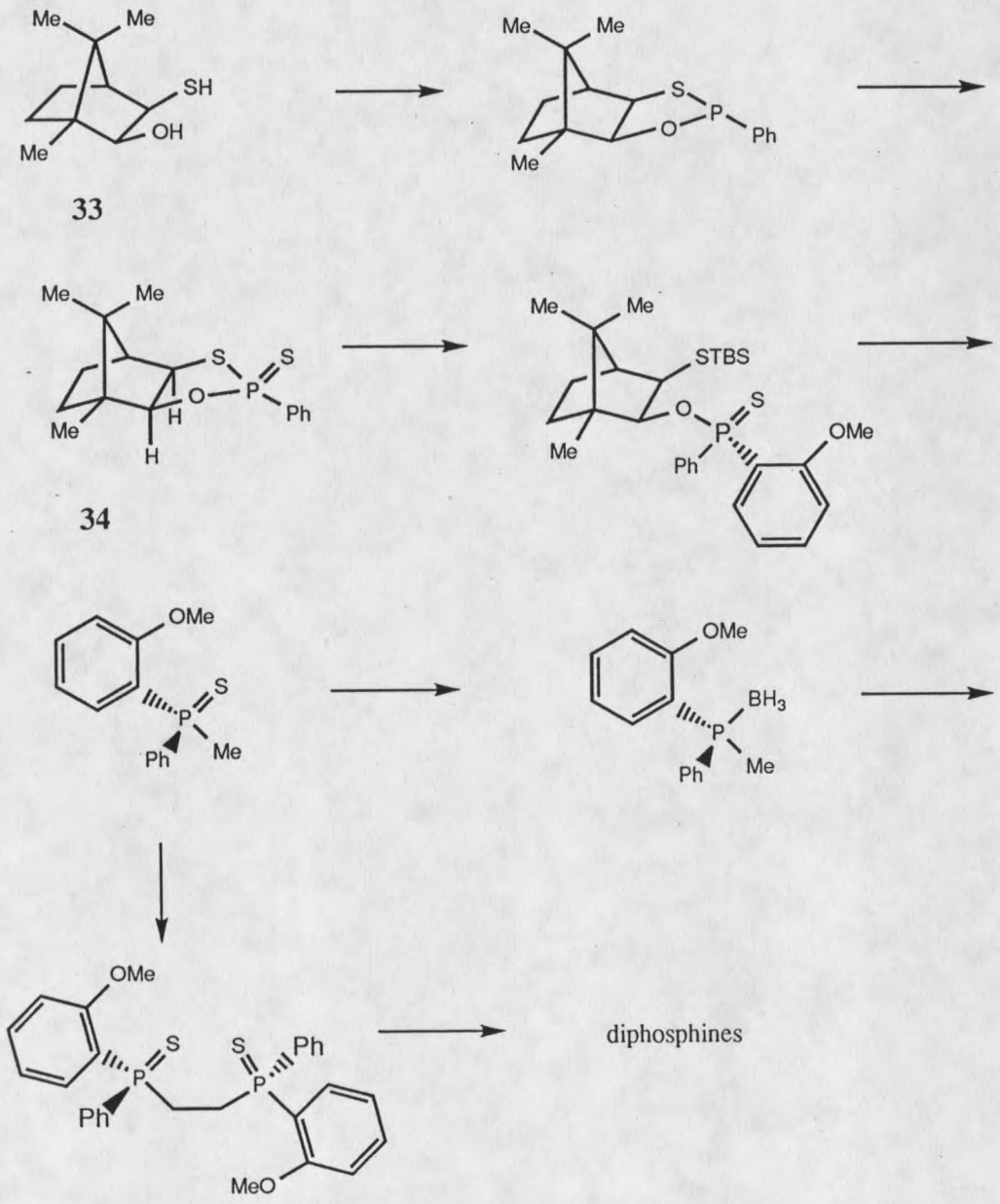


Scheme 14. Synthesis of chiral phosphine oxides by Juge and Brown

A crucial transformation that is commonly used in this method involves the thermal condensation of bis[diethyl(amino)phenyl] phosphine with (-)-ephedrine to give the corresponding oxazaphospholidine. It was quickly

determined, however, that the direct thermal condensation reaction involving (**28**) and (**29**) was a highly capricious and non-general reaction, it also gave poor yields (15-30%) along with large amounts of polar by-products.

Very recently, Corey[38] used a camphor derivative (**33**) formed a cyclic phospholidine intermediate (**34**) (Scheme 15).

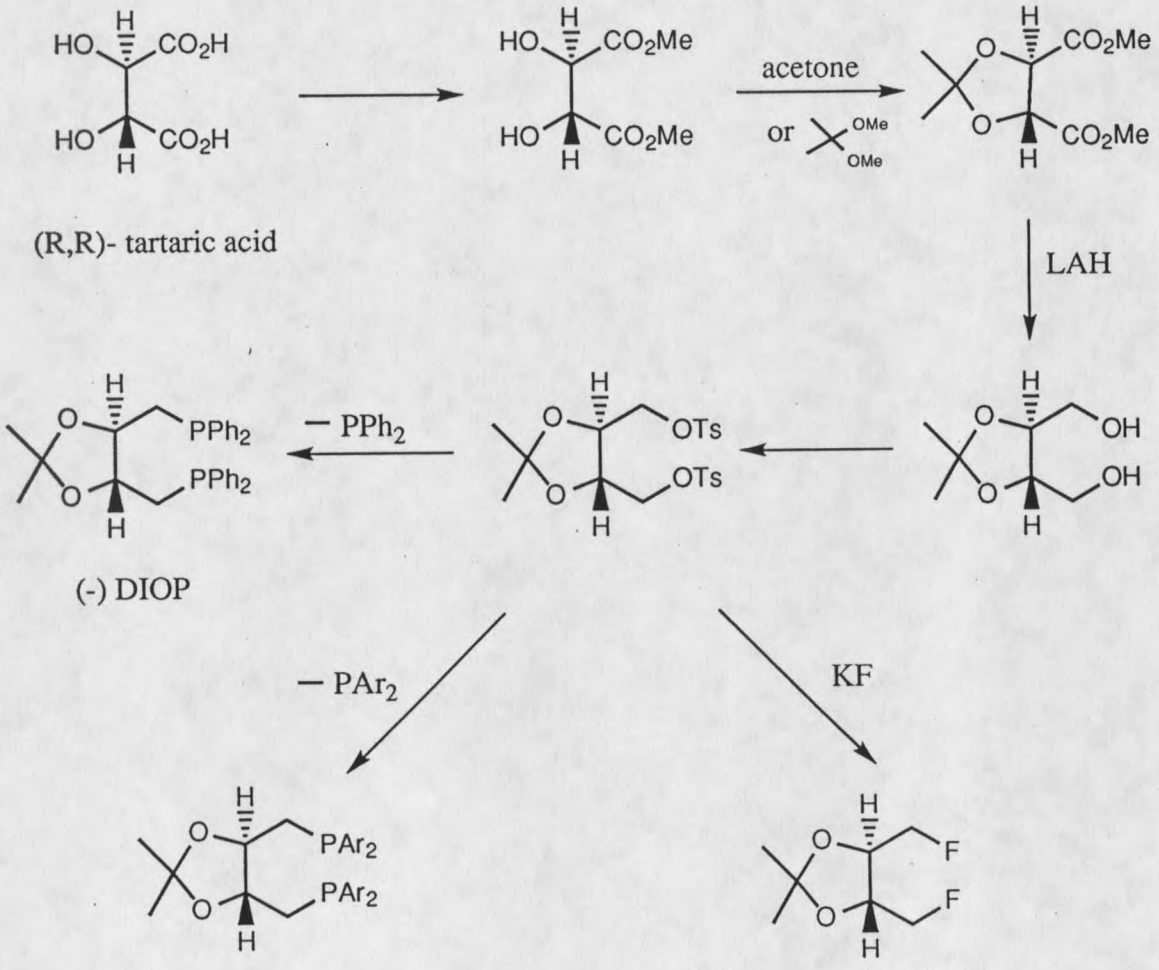


Scheme 15. Synthesis of chiral phosphine ligands by Corey

In this case, two heteroatoms attached to phosphorus can be displaced stereospecifically by nucleophilic aryl or alkyl groups.

B. Diphosphines with a Chiral Group Connecting Two Achiral Phosphorus Atoms

This family of chelating ligands expanded rapidly during the last decade because of the very high enantiomeric excess often observed in various catalytic reactions that used them. They are also relatively easy to synthesize (Scheme 16).

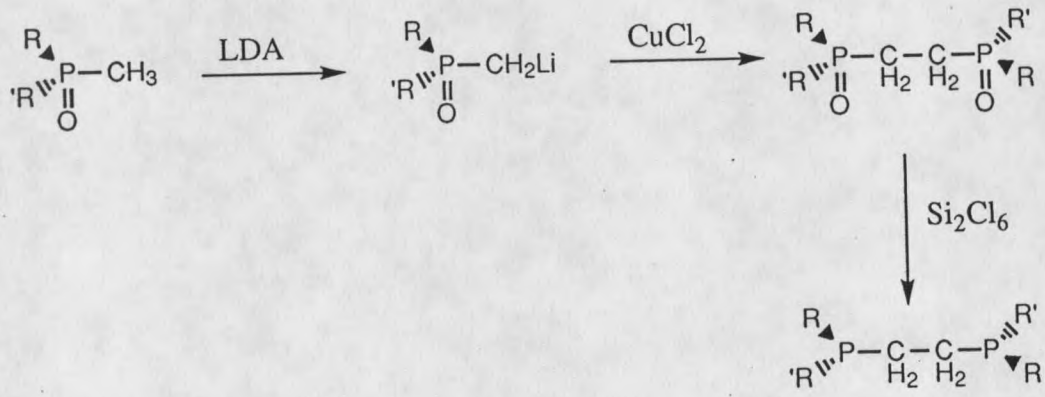


Scheme 16. Preparation of diphosphines with chiral carbon backbone

In many cases tedious resolutions could be avoided by starting with optically active natural products. Simple chemistry often allows easy introduction of the PR_2 groups (usually as PPh_2). The most common ligands are 1,4-diphosphines, 1,3-diphosphines, and 1,2-diphosphines.[39]

C. Diphosphines with Chirality on Phosphorus

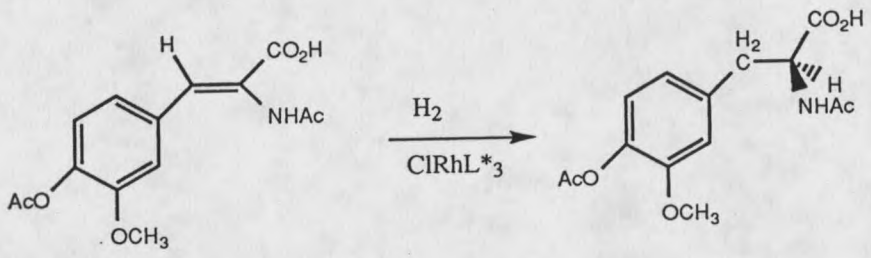
This family of chelating ligands consists of the two chiral phosphorus atoms which are separated by a carbon chain (X) of variable length: R(R')PXP(R")R"'. The connecting chain (X) has to be of suitable length and geometry to allow chelation. Up to now 1,2-diphosphines were synthesized in which X = $(CH_2)_2$, 1,2-C_6H_4, or cis-CH=CH. In many cases the two phosphorus atoms are equivalent (R = R", R' = R"'). The most general way to prepare chiral 1,2-diphosphines stereoselectively is the oxidative coupling of two chiral phosphine oxides[40] (Scheme 17).



Scheme 17. Preparation of diphosphine ligands by oxidative coupling

The stereochemistry at phosphorus during metallation and coupling is retained. By this method, Knowles made (*R*, *R*)- DIPAMP (**12**),[25] which is a very efficient rhodium catalyst for asymmetric hydrogenation and is used in industrial

asymmetric synthesis of (*S*)-DOPA, a drug for the treatment of Parkinson's disease (Scheme 18).



L*= DIPAMP

(*S*-DOPA)

Scheme 18. Industrial use of Rh-DIPAMP to make (*S*)-DOPA

Hence, the immense potential that structurally varied homochiral mono- and biphosphine ligands hold for transition metal based asymmetric synthesis has recently stimulated renewed investigation into the synthesis of these compounds.

RESULTS AND DISCUSSIONS

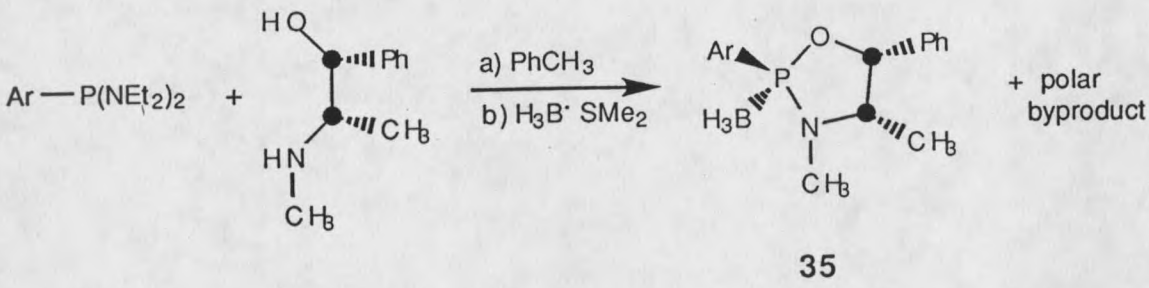
Preparation of Homochiral Oxazaphospholidine Boranes

Progress in the development of transition-metal catalysts for enantioselective reactions, especially hydrogenation processes, heavily depends on the availability of suitable chiral phosphine or diphosphine ligands. Yet, despite the critical importance of P-chiral phosphines, the methodology for their enantioselective synthesis in high enantiomeric excess and without resolution or separation of diastereomers remains relatively undeveloped. Our goal is to develop an effective methodology for the synthesis of a wide range of chiral phosphines and diphosphines.

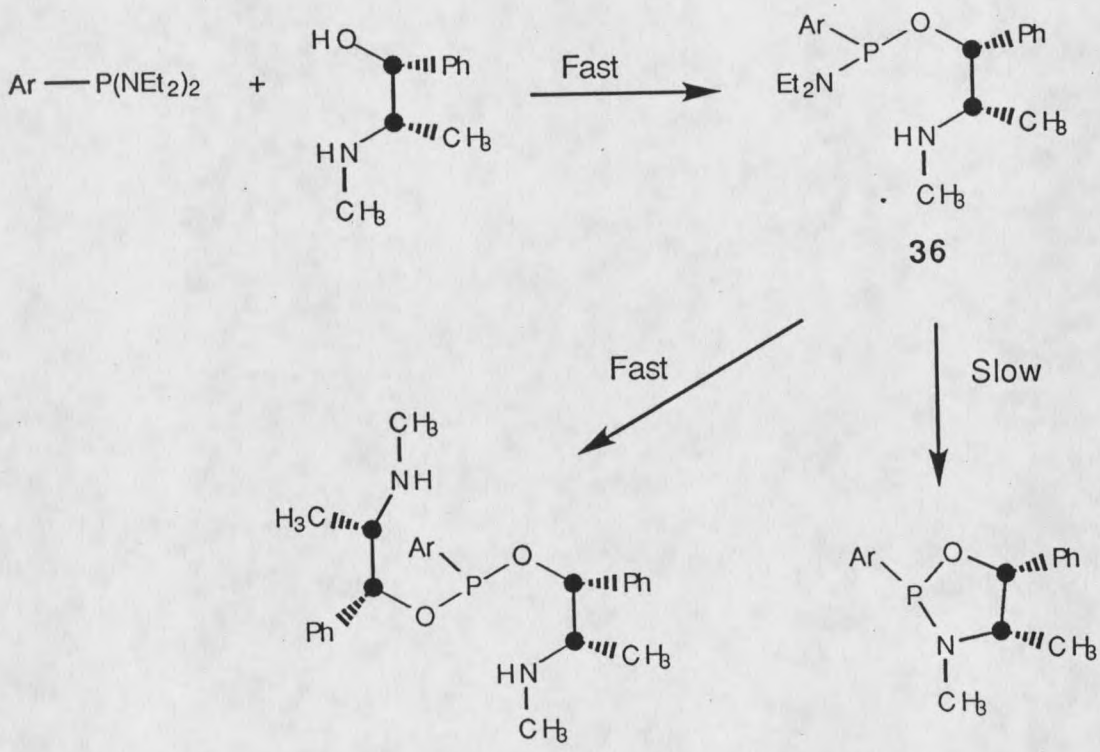
In 1990, Juge and coworkers reported a new approach for making chiral phosphine ligands.[36] One of the crucial steps in this approach is the diastereoselective synthesis of oxazaphospholidine boranes (**35**).

The diastereomerically pure complex (**35**) was prepared in one step from bis(diethylamino)phosphine, (-)ephedrine and $BH_3{\cdot}SMe_2$ (Scheme 19). A direct thermal condensation was involved in this step. For most cases we studied, this reaction gave low yields (15-30%) along with large amounts of polar by-products.

We reasoned that the polar by-product was formed because the formation of the phosphorus-nitrogen bond was relatively slow, and the non-cyclized intermediate (**36**) can react with another (-)ephedrine molecule to give dioxaphosphine products (Scheme 20).

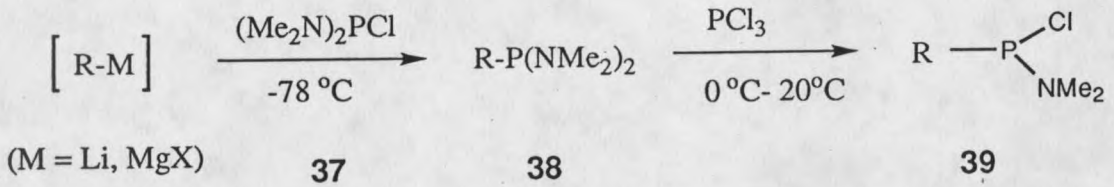


Scheme 19. Preparation of oxazaphospholidine boranes by Juge

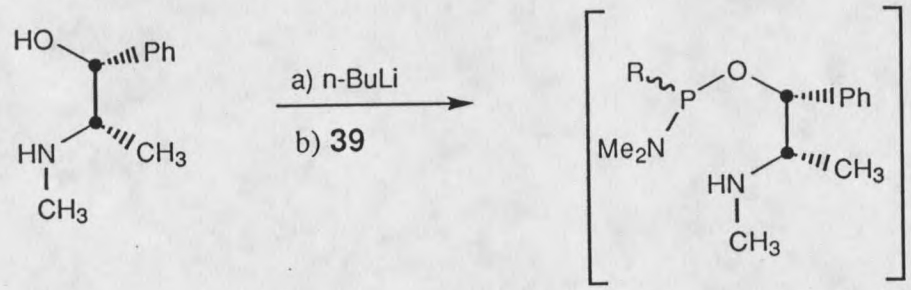


Scheme 20. Formation of the polar by-products

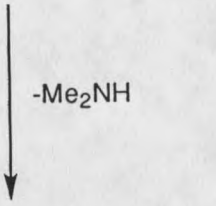
In our strategy, an efficient "ionic" coupling reaction was employed to give the initial phosphorus-oxygen bond, followed by themolytic ring closure. Using this strategy, we have made a range of electronically and sterically differentiated oxazaphospholidine boranes (**42-48**) (Scheme 21).

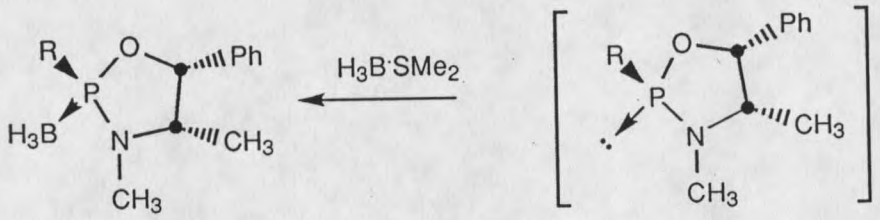


(M = Li, MgX) **37** **38** **39**



40





42-47 **41**

R = 2-$(CF_3)C_6H_4$; (**42**)

R = C_6F_5; (**43**)[41]

R = 4-$(OCH_3)C_6H_4$; (**44**)

R = 2-(CH_3)-4-$(OCH_3)C_6H_3$; (**45**)[41]

R = 2-(5-methylthienyl); (**46**)

R = cyclohexyl; (**47**)[41]

R = Ph; (**48**)

Scheme 21. Preparation of oxazaphospholidine boranes

Chloro-bis(dimethylamino)phosphine (**37**) was treated with an organolithium (or Grignard) reagent to give the bis(dimethylamino)phosphines (**38**). Exposure of (**38**) to 1.0 equiv of PCl_3 gave the chloro(dimethylamino)phosphine (**39**). The addition of (**39**) to a solution of monolithiated (-)-ephedrine (in THF or 1,2-DME) afforded the non-cyclized phosphonamidates (**40**) which the P-O bond was formed by "ionic coupling". The reaction mixture was then heated at reflux for 12 h to furnish the cyclized products (**41**). Addition of 1.1 equiv of BMS *in situ* provided the desired complexes (**42-48**).

The amine exchange reaction that results in cyclization is acid catalyzed (in the form of ammonium salts). In cases where cyclization is sluggish, as shown by the absence of copious Me_2NH evolution, a few µl of Me_3SiCl may be added as a more powerful Lewis acid catalysis.

An indication of the preparative scope of the foregoing procedure is provided by the examples in Table 1.

Table 1. Isolated yields and melting points of oxazaphospholidine derivatives

compound	**42**	**43**	**44**	**45**	**46**	**47**	**48**
yield (%)	77	72	78	70	82	76	80
mp(°C)	106	104	82	100	76	99	107

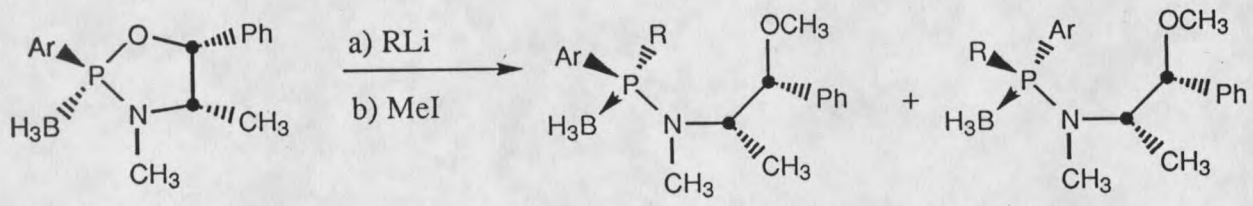
As can be seen from Table 1, the overall yields for this procedure are all in the range 70-82%, and seem to be relatively insensitive to both the electronic and steric effects of the substituent R. It is particularly worth mentioning that in this reaction sequence the borane group bonding with the phosphorous atom activates the adjacent group and at the same time it protects the phosphine

group which is generally sensitive to oxidation and electrophiles such as alkyl halides.

The new procedure used herein is characterized by its ease of execution and overall chemical efficiency. This new method permits the large scale preparation of a range of electronically and sterically differentiated homochiral monophosphine precursors.

Utilization of Oxazaphospholidine Borane Complexes in the Synthesis of Aminophosphine Boranes

Alkyl and aryllithium compounds reacted with oxazaphospholidine borane complexes at low temperatures (-78 °C) in THF, to give the corresponding aminophosphine boranes (**49-54**), by P-O bond cleavage, with a diastereomeric ratio better than 96:4 (Scheme 22).



Ar = 2-$(CF_3)C_6H_4$, R = Me; (**49**)

Ar = 2-$(CF_3)C_6H_4$, R = Ph; (**50**)

Ar = 2-$(CF_3)C_6H_4$, R = p-An; (**51**)

Ar = 4-$(CH_3O)C_6H_4$, R = Me; (**52**)

Ar = Ph, R = Me; (**53**)

Ar = Ph, R = 2-$(CH_3O)C_6H_4$; (**54**)

Scheme 22. Preparation of aminophosphine borane complexes

The complexes (**49-54**) are highly crystalline so that the separation of diastereomeric impurities at this stage by recrystallization is usually easy (e.g., methylcyclohexane). The reaction conditions and results are shown in Table 2.

Table 2. Results and conditions for preparation of aminophosphine boranes

Entry	Substrate	RM	Product	Temp (°C)	Diastere ratio
1	**42**	MeLi	**49**	-78	98:2
2	**42**	MeLi	**49**	-40	85:15
3	**42**	PhLi	**50**	-78	100:0
4	**42**	p-AnLi	**51**	-78	96:4
5	**44**	MeLi	**52**	-78	100:0
6	**48**	MeLi	**53**	-78	98:2
7	**48**	o-AnLi	**54**	-78	100:0

These reactions gave reasonable yields (80%) with high stereoselectivity. However, a lowering of stereoselectivity was observed at higher temperatures. The diastereomeric ratio of complexes (**49-54**) were determined by ^{1}H NMR spectroscopy (Figure 1) and HPLC (Figure 2).

Recently, the structure of (*Rp*)-N-methyl N-[(*1R, 2S*)-(1-hydroxyl-1-phenyl 2-propyl)] amino-methyl-phenyl-phosphine borane has been determined by X-ray crystallography[42] in order to determine the absolute configuration around the phosphorus atom (Figure 3). The absolute configuration of the phosphorus atom is R. The bond distance for the P-B bond (1.90A) is longer than the P-N bond (1.65A). The bond angles for CH_3-P-BH_3 and CH_3-P-N are 110 °. The N-P-BH_3 and Ph-P-CH_3 bond angles are 115 ° and 104 ° respectively.

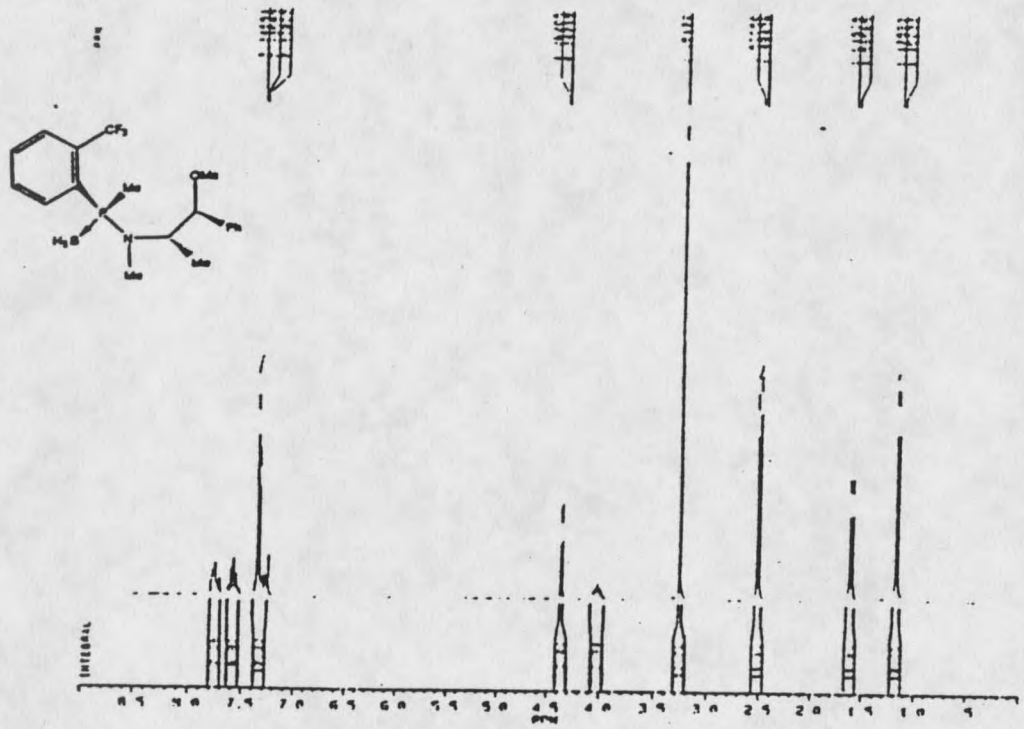


Figure 1. ^{1}H NMR of aminophosphine borane complex (**49**)

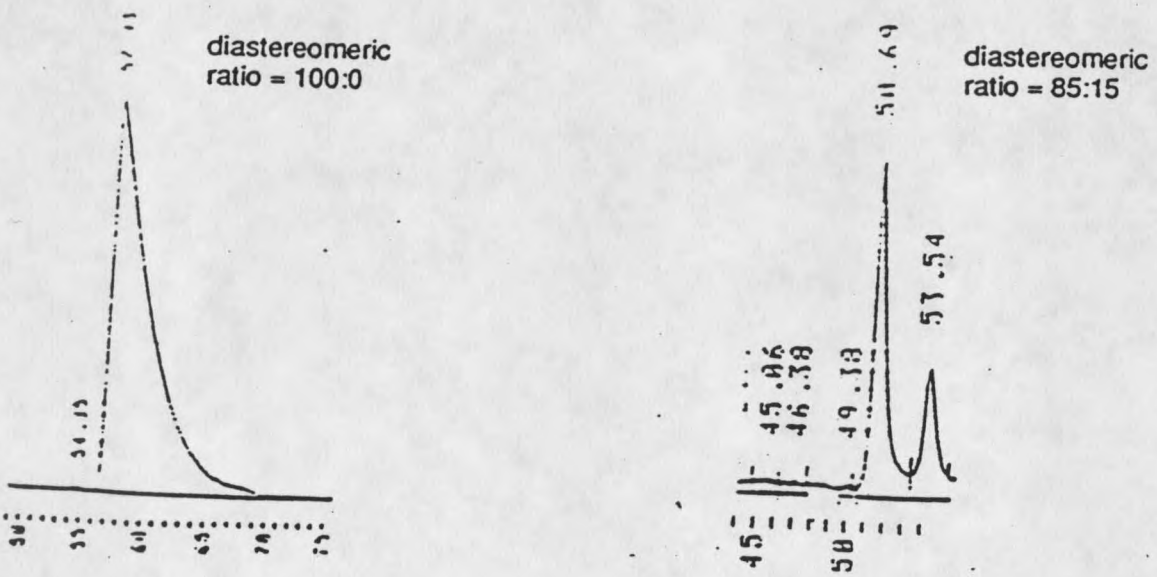
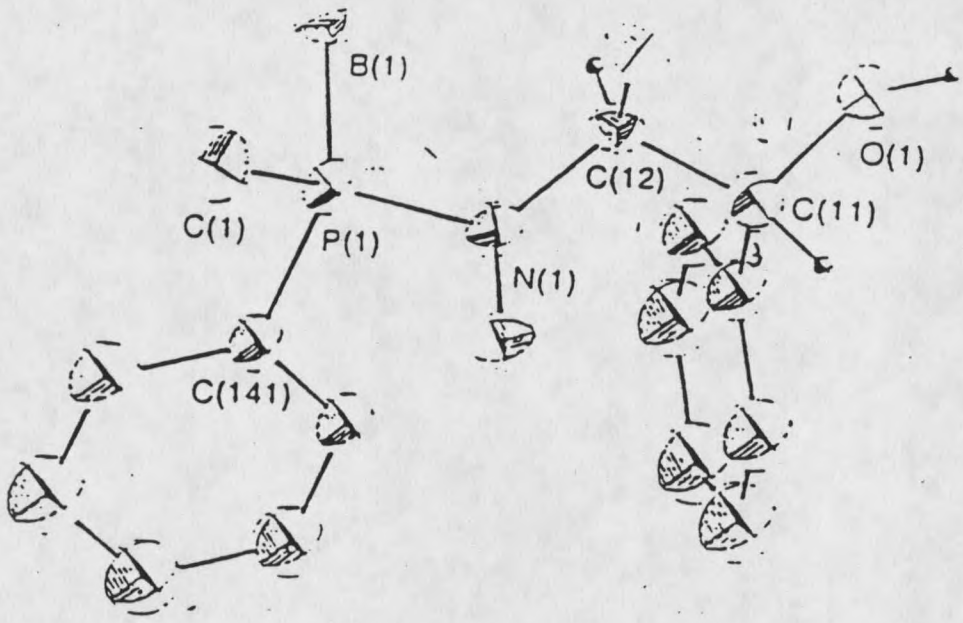


Figure 2. HPLC analysis of aminophosphine borane complex (**49**)



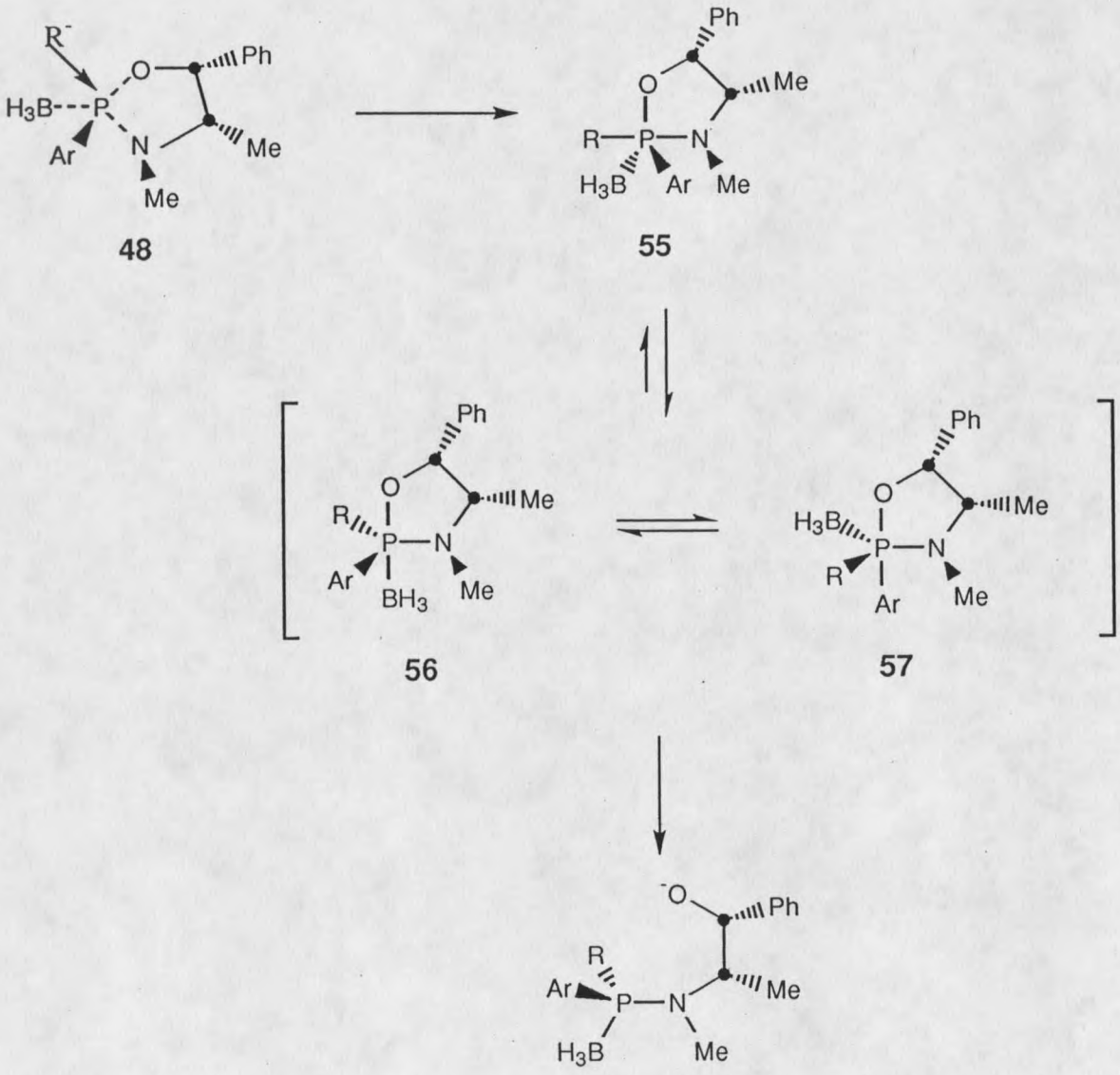
ORTEP projection at the 30% probability level. Selected distances (A) and angles (°): P(1)-C(1) 1.81; P(1)-B(1) 1.90; P(1)-N(1) 1.65; P(1)-C(141) 1.81; B(1)-P(1)-C(1) 110.2; N(1)-P(1)-C(1) 109; N(1)-P(1)-B(1) 114.5; C(141)-P(1)-C(1) 104.4; C(141)-P(1)-B(1) 112.2; C(141)-P(1)-N(1) 105.8.

Figure 3. X-ray structure of aminophosphine borane

The absolute configuration of the phosphorus atom demonstrates that P-C bond formation proceeds in this case with retention of configuration. The X-ray structure of starting material (**48**)[42] shows the methyl substituent of the nitrogen on the back side of the oxygen leaving group. Consequently, the stereochemistry of P-C bond formation is under kinetic control. Nucleophilic attack occurs at the less hindered face of the P-O bond which is opposite nitrogen (Scheme 23).

The mechanism proposed requires the formation of a pentacoordinate intermediate (**55**) which stereopermutes into another one (**56** or **57**), having

the substituents on the phosphorus atom in a staggered position with the N-methyl group. The presence of the oxygen group in the apical position of the intermediate (**56** or **57**) permits the cleavage of the P-O bond and the formation of the ring opened compound with retention of configuration.

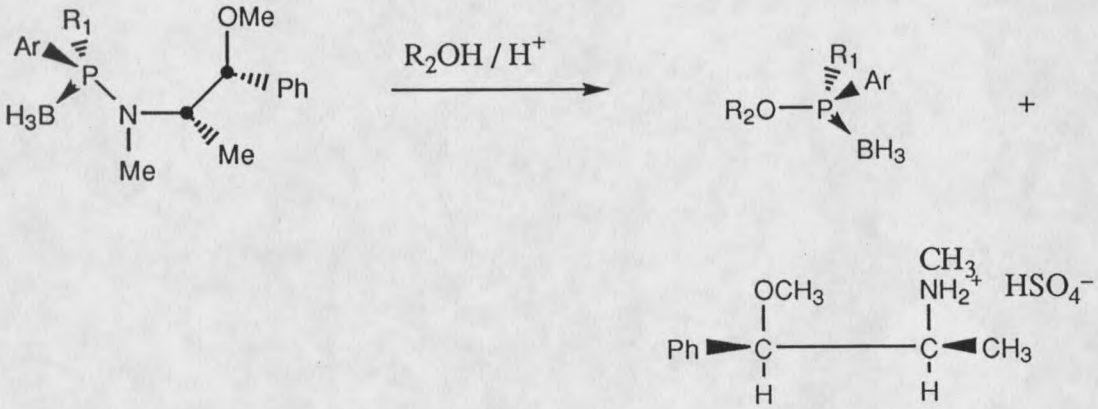


Scheme 23. Mechanism for P-C bond formation

Utilization of Aminophosphine Borane Complexes in the Synthesis of Asymmetric Phosphine Derivatives

A. Preparation of Phosphinite Borane Complexes

Aminophosphine borane complexes reacted with alcohol at room temperature in the presence of acid to give the corresponding phosphinite boranes (**58-61**) with varying degrees of inversion of configuration (Scheme 24).



Ar = 2-$(CF_3)C_6H_4$, $R_1 = CH_3$, $R_2 = CH_3$; (**58**)

Ar = 2-$(CF_3)C_6H_4$, $R_1 = CH_3$, $R_2 = CF_3CH_2$;(**59**)

Ar = 2-$(CF_3)C_6H_4$, $R_1 = CH_3$, $R_2 = H_3COCH_2CH_2$; (**60**)

Ar = Ph, R_1 = 2-$(CH_3O)C_6H_4$, $R_2 = CH_3$; (**61**)

Scheme 24. Acid alcoholysis of aminophosphine boranes

Juge has found that the enantiomeric excesses of phosphinite boranes depends on the acid concentration during methanolysis.[36] The highest

selectivity is obtained with 0.125M H_2SO_4. Our reaction conditions and results are shown in Table 3.

Table 3. Results and conditions of the acid alcoholysis

Entry	Substrate	Product	Acid Conc. (M)	e.e	Yield
1	**49**	**58**	0.125	>98%	95%
2	**49**	**58**	4.00	84%	90%
3	**49**	**59**	0.125	20 %	40%
4	**49**	**60**	0.125	30%	60%
5	**54**	**61**	0.125	>98%	90%

In general, the acid catalyzed methanolysis of aminophosphine boranes was very efficient, it gave quantitative yields and high stereoselectivities (Table 3, entry 1, 5). The reactions were less efficient in terms of yield and stereoselectivity when 2-trifluoroethanol or 2-methoxyethanol were used (CH_3SO_3H as acid). These resulted in 40% and 60% yield respectively. Also the e.e dropped from 98:2 to 52:48 (Table 3, entry 4). All enantiomeric excesses were determined by chiral HPLC (Figure 4) (hexane/isopropanol 90:10)

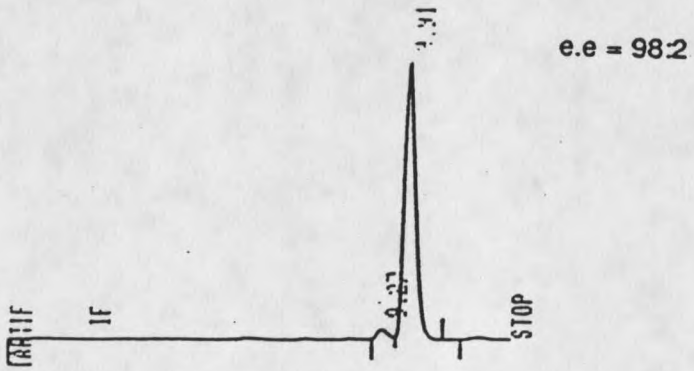
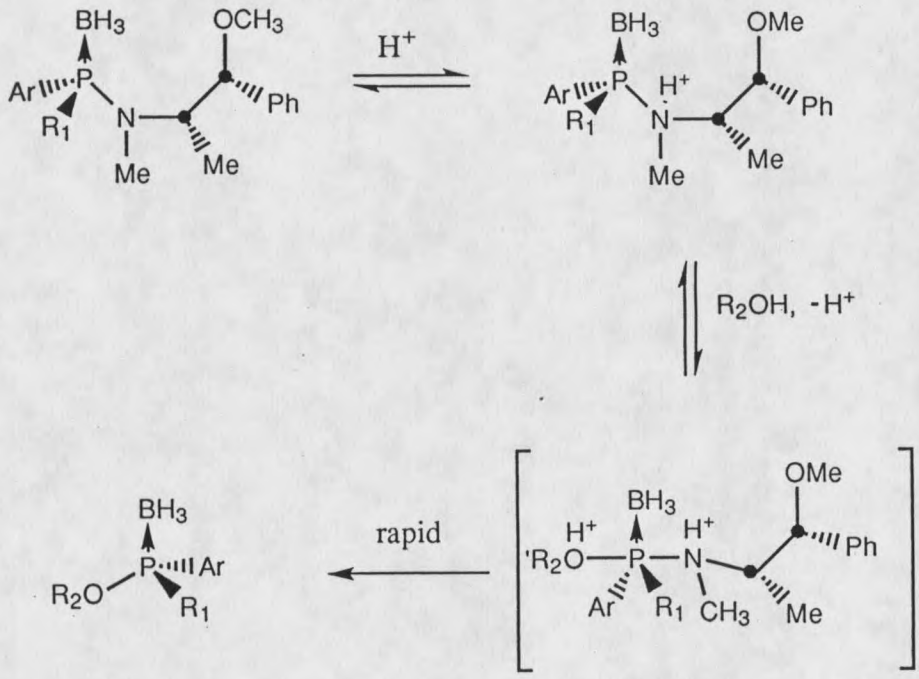


Figure 4. HPLC analysis of the phosphinite borane (**49**)

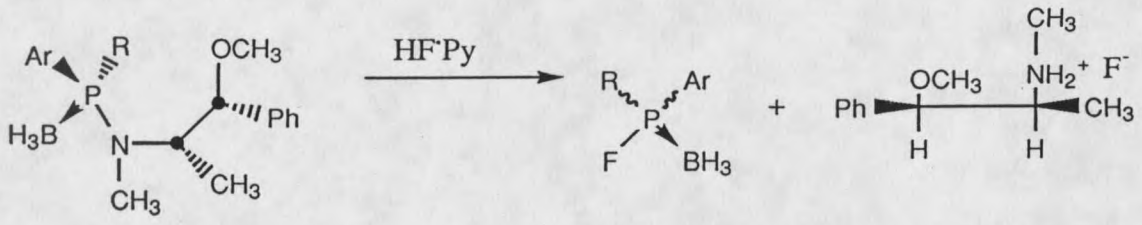
The proposed S_N2 mechanism for alcoholysis of aminophosphine boranes is shown below (Scheme 25). The nitrogen of the aminophosphine borane is first protonated by the acid, then the nucleophile attacks the phosphorus to form a pentacovalent intermediate. At this stage the ammonium group quickly dissociates from the phosphorus, affording the product with inversion of configuration.



Scheme 25. Mechanism for the alcoholysis of aminophosphine boranes

B. Preparation of Fluorophosphine Borane Complexes

Aminophosphine boranes react with HF·py at -25 °C to give the fluorophosphine borane complexes (**62-65**) (Scheme 26).



Ar = 2-$(CF_3)C_6H_4$, R = CH_3; (**62**)

Ar = 2-$(CF_3)C_6H_4$, R = Ph; (**63**)

Ar = 4-$(CH_3O)C_6H_4$, R = CH_3; (**64**)

Ar = Ph, R = 2-$(CH_3O)C_6H_4$; (**65**)

Scheme 26. Preparation of fluorophosphine borane complexes

None of the examples we studied gave enantiomerically pure products. The enantiomeric ratios were measured by chiral HPLC (99:1 of hexane:isopropanol). The reaction conditions and results are shown in Table 4.

The reactions of aminophosphine borane complexes with HF·py gave >80% yield, and the corresponding fluorophosphine boranes were stable at 0 °C. Comparing hydrofluorination with acid methanolysis, the former is much faster. The electronic characteristics and steric characteristics of the substituents on the asymmetric phosphorus seemed not to influence the stereoselectivity of hydrofluorination.

Umezawa has demonstrated that HF-amine reagents were in equilibrium with a small amount of free hydrogen fluoride.[43] The concentration of free hydrogen fluoride would increase by lowering the basicity of the amine in an HF-amine reagent (i-Pr_2NH > n-Bu_3N > pyridine). Fluoride ions are known to be high phosphophilic,[44] and it is this higher reactivity with phosphorus that may cause the racemization. In the two solvent systems: $CHCl_3/CH_3CN$

Table 4. Results and conditions for hydrofluorination

Entry	Substrate	Solvent	[HF] (M)	Product	e.e
1	**49**	toluene	>4.0	**62**	46:54
2	**49**	toluene	0.1	**62**	45:55
3	**49**	$CHCl_3/CH_3CN$	>3.0	**62**	48:52
4	**49**	toluene/MTHP	>3.0	**62**	48:52
5	**49**	CH_2Cl_2/MTHP	>3.0	**62**	50:50
6	**50**	toluene	>4.0	**63**	48:52
7	**52**	toluene	>4.0	**64**	46:54
8	**54**	toluene	> 4.0	**65**	48:52
9	**49**	toluene(half done)	0.1	**62**	46:54
10	**49**	toluene(over done)	0.1	**62**	48:52

and CH_2Cl_2/2-methyltetrahydropyran (MTHP), the concentration of free hydrogen fluoride could possibly decrease due to "chelation" of the lone pair electrons of the nitrogen (CH_3CN) and oxygen (MTHP). It was interesting to find that the results obtained with these two solvent systems are almost the same as those with toluene solvent system. It is possible that the ability of CH_3CN and 2-methyltetrahydrogenpyran to chelate the hydrogen fluoride is not strong enough, so the concentration of fluoride ion in the solution is still high. Currently under investigation in our group, is the utilization of $BF_3 \cdot OEt_2$ which may lower the concentration of fluoride ion more effectively (Scheme 27).

$$BF_3 \cdot OEt_2 \quad + \quad F^- \text{ ---------- } BF_4^-$$

Scheme 27. Reaction of $BF_3 \cdot OEt_2$ with F^-