



New methods for preparing scalemic P-chiral secondary phosphine-boranes and enantiomerically pure phosphine ligand precursors
by Bradley H Wolfe

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
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Abstract:

ABSTRACT With the increasing importance of asymmetric transition metal catalysis using scalemic (non-racemic) phosphine ligands in organic synthesis, there has been an increase in demand for enantiomerically pure phosphine ligands with phosphorus centered chirality (P-chiral). However, due to the difficulty of preparation of P-chiral phosphine ligands, there are a limited number of general methods for their synthesis. Three efficient methods for the preparation of P-chiral phosphine-borane ligand precursors were developed that take advantage of the high nucleophilicity and stereointegrity of lithiated scalemic P-chiral secondary phosphine-boranes. The first method involves the reductive elimination of enantiomerically pure P-chiral secondary phosphine-boranes from esters derived from asymmetric deprotonation of aryldimethylphosphine-boranes. The second method, involves preparing scalemic P-chiral phosphine-borane ligand precursors directly from enantiomerically pure secondary phosphine-borane surrogates via a novel nucleophilic vinyl ipso substitution reaction. The final approach is an unprecedented- direct synthesis of P-chiral phosphine-boranes via dynamic thermodynamic resolution of lithiated tert-butylphenylphosphine-borane with (-)-sparteine. The three approaches are among the most efficient known methods for the preparation of enantiomerically pure P-chiral phosphine-borane ligand precursors and are well suited for rapid ligand screening in asymmetric transition metal catalysis.

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NEW METHODS FOR PREPARING SCALEMIC *P*-CHIRAL
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by
Bradley H. Wolfe

A thesis submitted in partial fulfillment
of the requirements for the degree

of
Doctor of Philosophy
in
Chemistry

Montana State University
Bozeman, Montana

February, 2000

D378
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APPROVAL

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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.

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ABSTRACT

With the increasing importance of asymmetric transition metal catalysis using scalemic (non-racemic) phosphine ligands in organic synthesis, there has been an increase in demand for enantiomerically pure phosphine ligands with phosphorus centered chirality (*P*-chiral). However, due to the difficulty of preparation of *P*-chiral phosphine ligands, there are a limited number of general methods for their synthesis. Three efficient methods for the preparation of *P*-chiral phosphine-borane ligand precursors were developed that take advantage of the high nucleophilicity and stereointegrity of lithiated scalemic *P*-chiral secondary phosphine-boranes. The first method involves the reductive elimination of enantiomerically pure *P*-chiral secondary phosphine-boranes from esters derived from asymmetric deprotonation of aryldimethylphosphine-boranes. The second method, involves preparing scalemic *P*-chiral phosphine-borane ligand precursors directly from enantiomerically pure secondary phosphine-borane surrogates via a novel nucleophilic vinyl ipso substitution reaction. The final approach is an unprecedented direct synthesis of *P*-chiral phosphine-boranes via dynamic thermodynamic resolution of lithiated *tert*-butylphenylphosphine-borane with (-)-sparteine. The three approaches are among the most efficient known methods for the preparation of enantiomerically pure *P*-chiral phosphine-borane ligand precursors and are well suited for rapid ligand screening in asymmetric transition metal catalysis.

INTRODUCTION

Over the past twenty five years there has been a virtual explosion in the number of methodologies for asymmetric induction in chemical synthesis. This is illustrated by the recent publication of numerous books and periodicals entirely devoted to the subject.¹ The interest is due to several factors, the foremost being the superior economic efficiency of asymmetric synthesis over racemic methods.² For example, in the pharmaceutical industry the mixture of enantiomers produced by racemic methods can make drugs less effective and possibly even dangerous.^{3,4} In addition, resolution of the enantiomers is often costly and time consuming. In contrast, many asymmetric syntheses can produce products that are virtually free of the unwanted enantiomer. For this reason, the development of asymmetric methods is making racemic synthesis obsolete in the pharmaceutical industry.

Although a large variety of asymmetric transformations now exist, many require a stoichiometric amount of a chiral auxiliary. The recovery of the auxiliary upon completion of the reaction is not always cost-effective or practical. Conversely, asymmetric catalytic transformations require only substoichiometric amounts of chiral auxiliary, alleviating the need to recover the chiral auxiliaries upon completion of the reaction.

A large proportion of asymmetric catalytic transformations employ transition metals with scalemic (non-racemic) phosphine ligands as chiral auxiliaries.⁵ Despite the widespread

use of chiral phosphines, it is often necessary to match a scalemic phosphine ligand to a given substrate to optimize enantioselectivity and yield.⁶ Thus, a variety of scalemic phosphine ligands need to be screened to optimize a particular reaction. Extensive optimization is not always possible because there are only a few enantiomerically pure phosphine ligands commercially available, and the preparation of scalemic ligands is often quite lengthy.⁷ It is, therefore, desirable to develop efficient and general methods for the preparation of enantiomerically pure phosphine ligands.

There are three general classes of scalemic phosphine ligands; those that have chiral carbon skeletons (*C*-chiral phosphine ligands), those that have phosphorus centered chirality (*P*-chiral phosphine ligands), and finally, those that have both a chiral backbone and phosphorus centered chirality (*C,P*-chiral phosphine ligands).^{5b} In catalytic systems it is anticipated that *P*-chiral phosphine ligands would provide superior stereinduction because the ligand's chirality would be very close to the site of stereogenesis. However, many more examples of *C*-chiral and *C,P*-chiral phosphine ligands are used in asymmetric transition metal catalysis than *P*-chiral phosphine ligands due to the difficulty involved in stereinduction around phosphorus.⁸

With the recent success of many asymmetric transformations employing known *P*-chiral phosphine ligands, there has been an increased emphasis on the discovery of more general and efficient syntheses of these types of ligands.^{1a-b,5a} Described herein are three approaches for the rapid preparation of *P*-chiral phosphine ligands that can be readily screened in asymmetric transition metal catalyzed reactions.

BACKGROUND

Most *P*-Chiral phosphine ligands synthesized to date can be placed into one of three categories (**Figure 1**); monophosphines, diphosphines or monophosphines with a secondary coordinating functional group.⁷ Although scalemic (non-racemic) monophosphines have been used in asymmetric catalysis, they are generally prepared as intermediates in the synthesis of the more complicated bidentate phosphine ligands of the other two categories. There are many ways to prepare scalemic *P*-chiral monophosphines, but all follow one of two general routes: resolution or asymmetric synthesis.

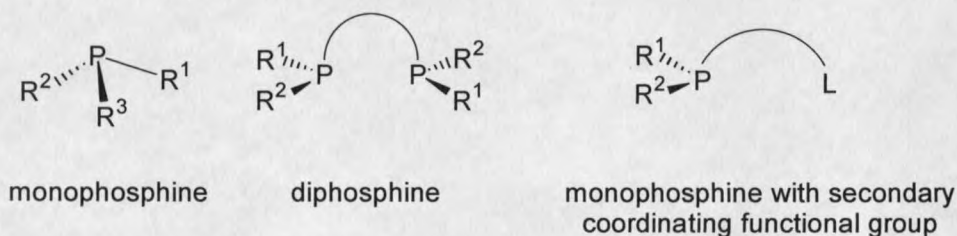


Figure 1. Three major types of *P*-chiral phosphine ligands

Resolution of Racemic *P*-Chiral Monophosphines
and Preparation of Diphosphines

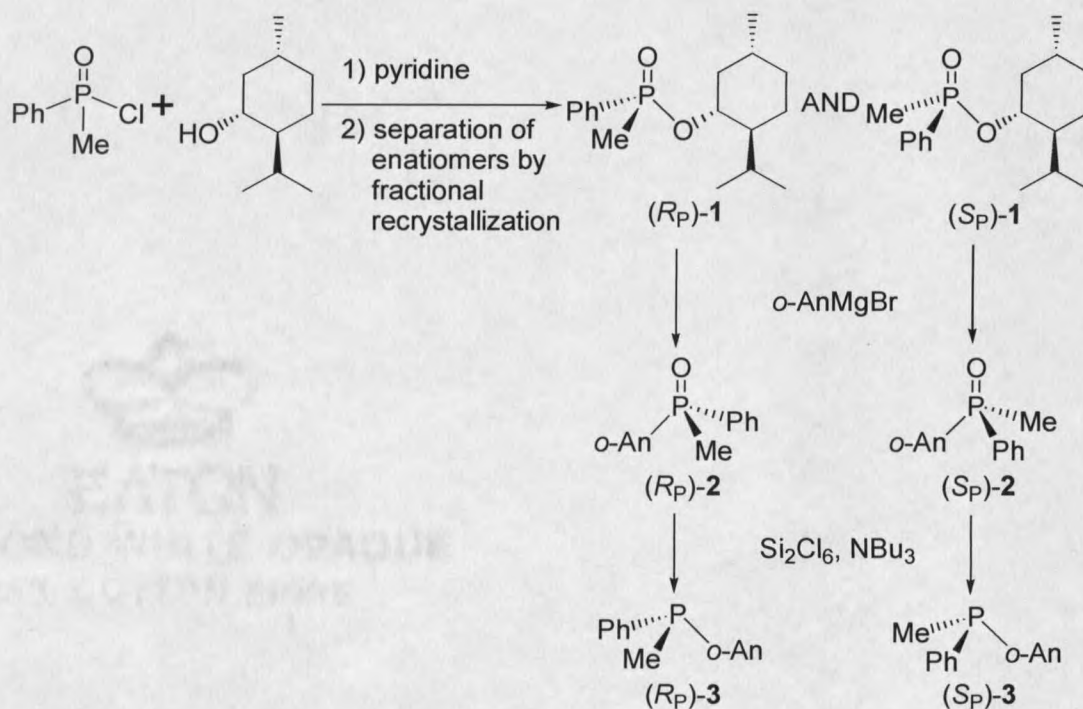
Direct Resolution of Enantiomers

The first preparation of an optically pure *P*-chiral phosphine oxide was in 1911 by Meisenheimer and co-workers.⁹ Meisenheimer resolved the weakly basic

ethylmethylphenylphosphine oxide and benzylmethylphenylphosphine oxide by fractional crystallization with (+)-bromocamphorsulfonic acid and (+)-camphorsulfonic acid, respectively. With one exception, this method has not been successful for the preparation of any other monophosphine oxides.^{8b} It was not until the early 1960's that a general approach to the synthesis of scalemic *P*-chiral phosphines was discovered.

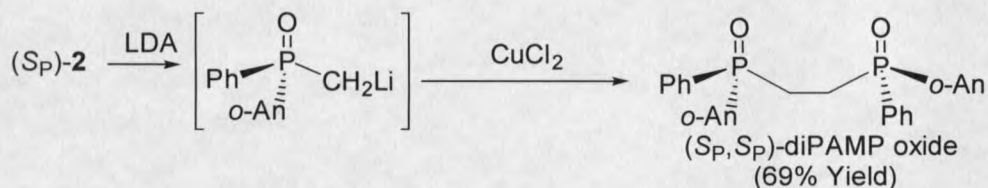
Recently, resolutions of *P*-chiral phosphines have been primarily accomplished by coupling a racemic mixture of phosphinates with an optically pure natural product. Subsequent separation of diastereomers by fractional crystallization and removal of the chiral resolving agent provides the scalemic *P*-chiral phosphine oxide.

One of the first preparations of optically pure phosphines, in which menthylloxymethylphenylphosphinate (**1**) was prepared from methylphenylphosphinyl chloride, menthol (Men) and pyridine (**Scheme 1**), was reported by Mislow and coworkers in the early 1960's.¹⁰ Isolation of both (*S_p*)-**1** and (*R_p*)-**1** diastereomers was achieved by fractional crystallization, although the (*R_p*)-**1** isomer could be only obtained after much effort and in a low yield. Displacement of the menthyloxy moiety of both (*S_p*)-**1** and (*R_p*)-**1** with the Grignard reagent of 2-bromoanisole yielded phenylanisolemethylphosphine (PAMP) oxide with inversion of stereoconfiguration at phosphorus ((*S_p*)-**2**, (*R_p*)-**2**, respectively). The (*R*)-**2** and (*S*)-**2** phosphine oxides were subsequently reduced to PAMP with Cl₃SiH and tributylamine, yielding (*R_p*)-**3** and (*S_p*)-**3** with inversion of the configuration at



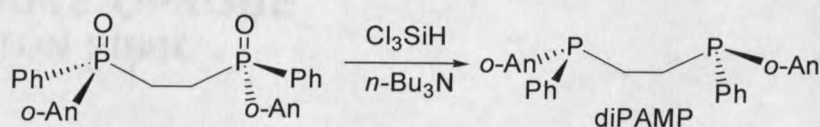
Scheme 1

phosphorus. The diphosphine (*S,S*)-1,2-di(phenylanisolephosphino)ethane ((*S,S*)-diPAMP) oxide was prepared from (*S*)-2 by deprotonation of the methyl group with lithium diisopropylamide (LDA), followed by oxidative coupling with cupric chloride (Scheme 2).¹¹



Scheme 2

The diphosphine oxide was reduced to the free diPAMP phosphine ligand with trichlorosilane and tributylamine, again with inversion of the configuration of phosphorus (Scheme 3).

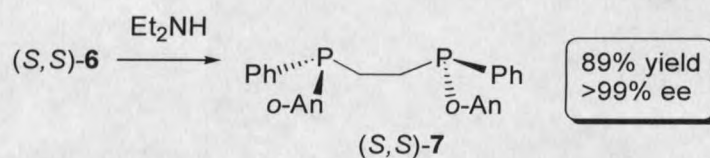


Scheme 3

Although several *P*-chiral phosphine ligands have been prepared using this methodology (*vide supra*), the final reduction step presents a problem.¹² The reduction of scalemic phosphine oxides is usually accompanied by various levels of stereodegradation depending on the substrate and reaction conditions.¹³ For this reason, oxide protecting groups are not desirable intermediates for the synthesis of optically enriched phosphines. Consequently, other phosphorus protecting groups, such as borane, have proven to be more useful than oxide.

Resolution of Phosphine-Boranes

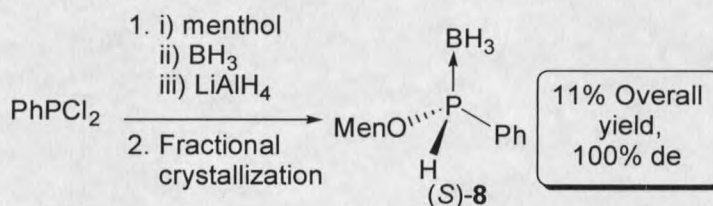
Imamoto and coworkers first demonstrated the versatility of borane as a protecting group in the preparation of phosphine ligands.¹⁴ Imamoto prepared menthylphenoxyphenyl-anisolephosphine-borane (**4**) in a one-pot synthesis by treating dichlorophenylphosphine with *o*-anisylmagnesium bromide, followed by menthol/pyridine, and then borane-THF complex. The resulting diastereomers, (*S*)-**4** and (*R*)-**4**, were then separated by preparative TLC (**Scheme 4**). Subsequent displacement of the menthylphenoxy with methyllithium yielded PAMP-borane without loss of stereointegrity ((*S*)-**5** and (*R*)-**5**).



Scheme 6

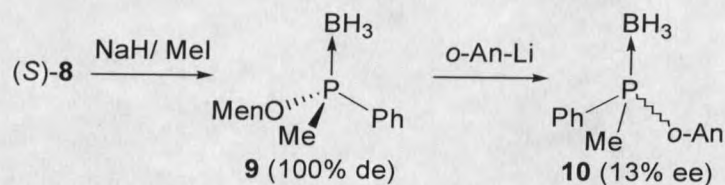
Resolution of Secondary Phosphine-Boranes

Imamoto also demonstrated the first preparation of enantiomerically pure *P*-chiral secondary phosphine-boranes (2° -phosphine-boranes).¹⁵ The synthesis involved coupling menthol with dichlorophenylphosphine, followed by boronation of the phosphorus and reductive removal of the remaining chloride with lithium aluminum hydride (LAH). Fractional crystallization of the diastereomeric mixture of 2° -phosphine-boranes afforded the scalemic (*S*)-menthyloxyphenylphosphine-borane ((*S*)-**8**) (Scheme 7).

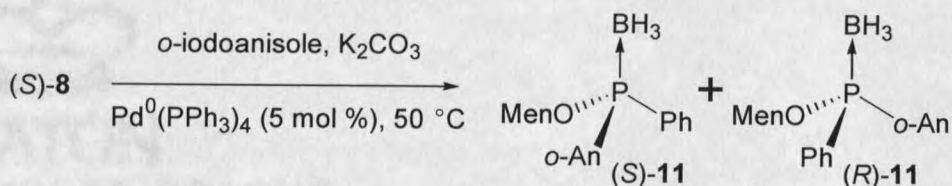


Scheme 7

Imamoto and coworkers were able to methylate (*S*)-**8** with sodium hydride in the presence of methyl iodide to yield menthyloxymethylphenylphosphine-borane (**9**) with 100% diastereomer excess (de). Subsequent displacement of the menthyloxy moiety with *o*-anisyllithium provided PAMP-borane (**10**) with almost complete loss of stereointegrity (13% ee). Because subsequent attempts to improve the stereocontrol of the displacement of the methoxy group resulted in limited success, other methods of arylation were found.¹⁶



Imamoto and coworkers successfully coupled the diastereomerically pure (*S*)-**8** with *o*-iodoanisole using tetrakis(triphenylphosphine) palladium ($\text{Pd}(\text{PPh}_3)_4$) at 50 °C with good results (**Scheme 9**).¹⁷ Imamoto found that control of the stereoconfiguration of the coupled product was strongly solvent dependent. If the reaction was performed in acetonitrile, the product was formed with complete retention of stereochemistry at phosphorus ((*S*)-**11**). If THF was used, the coupling resulted in inversion of the product ((*R*)-**11**).

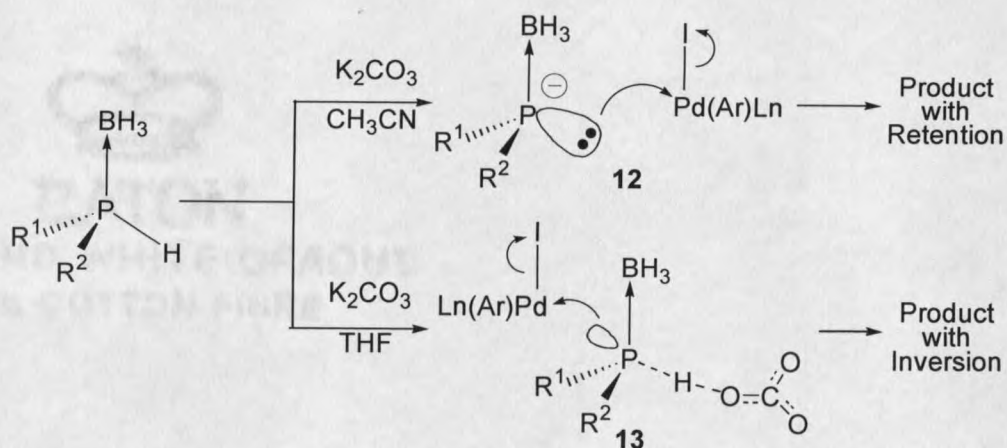


Solvent	Time (h)	Yield (%)	(<i>S</i>)- 11 : (<i>R</i>)- 11
CH ₃ CN	16	89	100:0
THF	48	76	4:96

Scheme 9

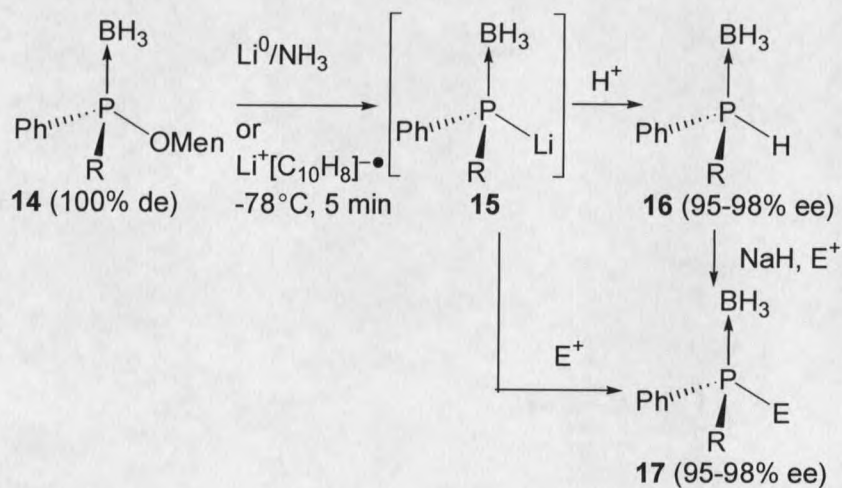
Imamoto proposed that the dramatic solvent effect in the palladium coupling of (*S*)-**8** with *o*-iodoanisole was the result of solvation of the base and intermediate anion (**Scheme 10**).¹⁷ In a polar solvent such as acetonitrile, the potassium carbonate readily deprotonates the 2°-phosphine-borane, yielding the solvated “naked” phosphorus anion **12**. Subsequent transmetalation and reductive elimination yielded the product with retention of configuration

at the phosphorus. Conversely, in a less polar solvent, THF, the proton abstraction and transmetalation occur simultaneously **13**, yielding inversion of the phosphorus configuration in the final product.



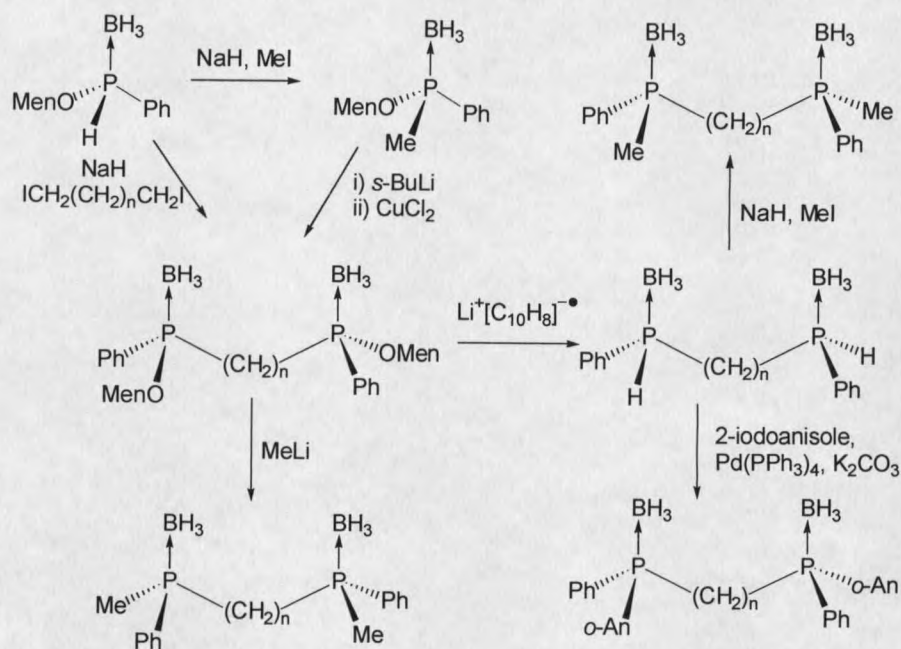
Scheme 10

Imamoto also demonstrated that the menthyloxy group of **14** derived from (*S*)-**8** could be removed by reduction with either lithium in ammonia or lithium naphthalenide in THF at $-78\text{ }^{\circ}\text{C}$ (Scheme 11).¹⁸ The resulting lithiated 2°-phosphine-borane intermediate **15** was protonated to produce the 2°-phosphine-borane **16** with good yield and high retention of the



Scheme 11

configuration at phosphorus. The alkylated product **17** could also be prepared by addition of an appropriate electrophile directly to intermediate **15**, or by deprotonation of **16** with sodium hydride followed by alkylative addition, again in a high yield and with little loss of stereointegrity. Imamoto went on to demonstrate the utility of scalemic *P*-chiral 2°-phosphine-boranes as intermediates for the preparation of enantiomerically pure *P*-chiral diphosphine ligand precursors using the methods discussed earlier (**Scheme 12**).¹⁹



Scheme 12

In the previous examples, optical enrichments of the final phosphines were derived from the resolution of diastereomers that arose from the coupling racemic phosphorus compounds with scalemic natural products. This type of synthesis is inherently inefficient, time consuming, and has limitations. First, it may be possible to isolate only one diastereomer effectively, and the desired phosphine may only be available from the unnatural chiral

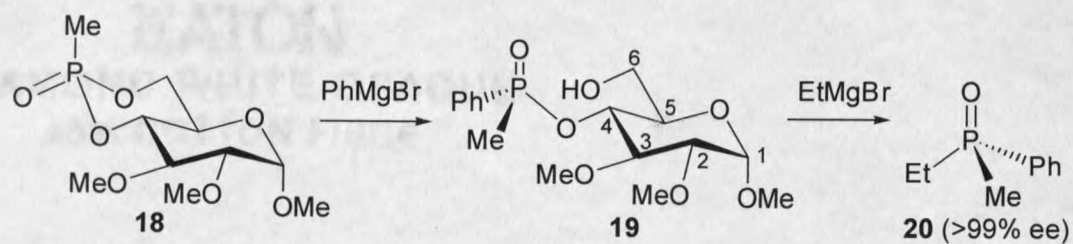
resolving agent. Second, the processes of fractional crystallization and chromatography are not general; even a small change in chemical structure can render a nonseparable mixture of diastereomers or a noncrystalline mixture. Together these problems make it difficult to prepare a rational series of enantiomerically pure *P*-chiral phosphine ligands via resolution for testing in catalytic systems. A way to avoid the problems associated with fractional crystallization of diastereomers is to directly prepare the desired phosphine asymmetrically.

Asymmetric Synthesis of *P*-Chiral Phosphine Ligands

Systematic Displacement of Phosphorus Heterocycles

Chiral heterocycles that incorporate phosphorus in the ring are valuable precursors for the preparation of optically enriched *P*-chiral phosphines. In these systems, the stereochemistry of the substituents on the ring sets the absolute stereochemistry at the phosphorus. The ring moiety is then systematically removed, yielding the optically active phosphine.

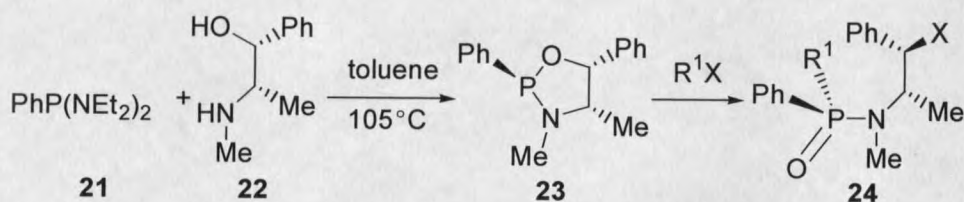
Inch and coworkers demonstrated the preparation of optically pure chiral phosphine oxides from glucose-derived cyclic phosphinate **18** (Scheme 13).²⁰ Treatment of **18** with phenylmagnesium bromide provided phosphinite **19** as a single diastereomer, producing only



Scheme 13

a trace of the product from the P-O bond cleavage at the 4-position of the sugar moiety. After purification, **19** was treated with ethylmagnesium bromide, yielding optically pure *P*-chiral (*R*)-ethylmethylphenylphosphine oxide (**20**) in 10% overall yield. Inch remarked that the displacement of the carbohydrate unit was very dependent on the nature of the groups attached to phosphorus, however he did not demonstrate the synthesis of any other monophosphine oxides by this approach.

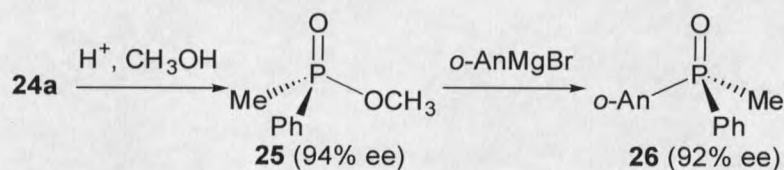
Jugé later demonstrated the preparation of scalemic *P*-chiral phosphine oxides from the oxazaphospholidine **23**.^{21,22} Compound **23** was prepared as a single diastereomer from ephedrine (**21**) and bis(diethylamino)phenylphosphine (**22**) in refluxing toluene (Scheme 14).²³ Treatment of **23** with alkyl halides provided phosphinamides **24a-c** with inversion of stereochemistry via the Michaelis-Arbuzov rearrangement. The de of the Michaelis-Arbuzov rearrangement products was highly dependent on the alkyl halides. The larger the alkyl halide, the lower the de of the resultant phosphinamides (**24a-c**).



entry	R ¹ X	conditions	yield (%)	de (%)
24a	MeI	25°C, 1 d	85	85
24b	EtBr	80°C, 14 min	80	70
24c	PhCH ₂ Br	25°C, 2 d	90	40

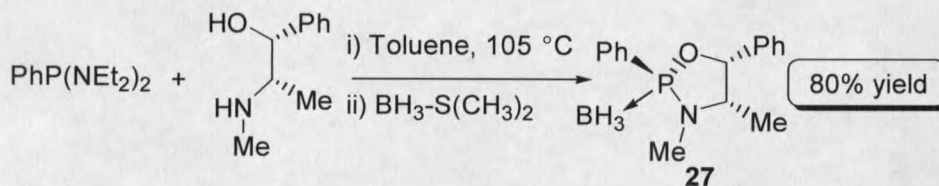
Scheme 14

Enantiomerically pure **24a** was obtained by fractional crystallization and then treated with acidic methanol, providing phosphinate **25** with stereoinversion and little loss of stereoconfiguration (94% ee) (**Scheme 15**). Substitution of the methoxy group with *o*-anisylmagnesium bromide (*o*-AnMgBr) provided PAMP oxide (**26**) with inversion of stereochemistry and little loss of stereointegrity (92% ee).



Scheme 15

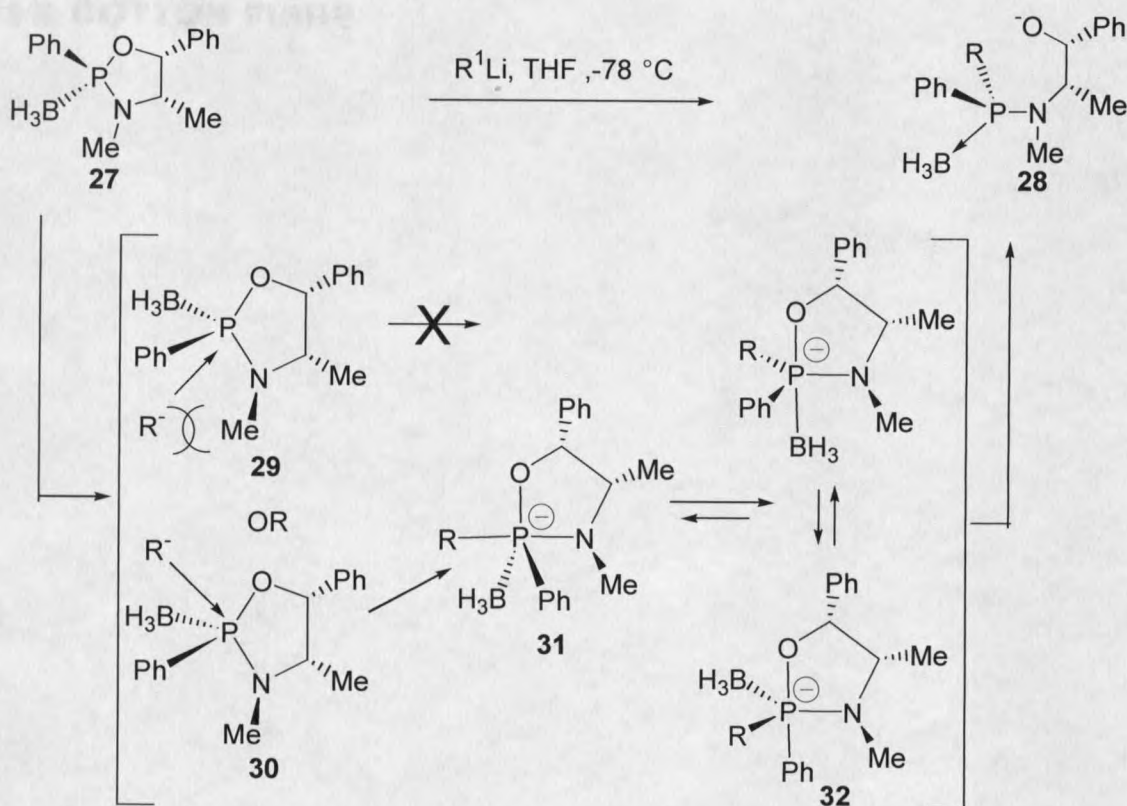
Jugé and co-workers later demonstrated that the borane complex of the oxazaphospholidine (described above) was an excellent starting material for the preparation of scalemic *P*-chiral phosphine-boranes (**Scheme 16**).^{24,25} Complex **27** was prepared as a single diastereomer from bis(diethylamino)phenylphosphine in refluxing toluene (**Scheme 14**).



Scheme 16

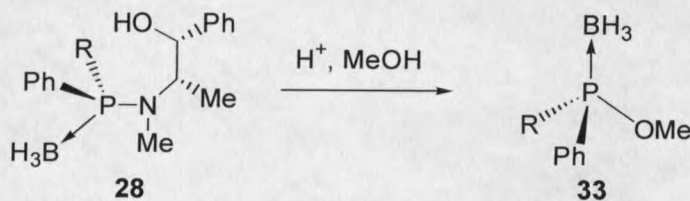
Interestingly, the addition of aryl- or alkylolithiums to oxazaphospholidine-borane **27** displaced the oxygen moiety, providing the phosphinamide **28** with retention of stereochemistry around the phosphorus (**Scheme 17**). This result can be contributed to steric congestion from the methyl on the nitrogen opposite the oxygen leaving group (**29**).

Therefore, the organometallic reagent must approach the phosphorus via its less hindered face opposite the nitrogen (**30**) to form a pentacoordinate phosphorus intermediate **31**. A pseudorotation of the phosphorus places the oxygen in the axial position where it can dissociate from the phosphorus to provide **28** with a diastereomeric excess of 84% (R= *o*-anisoyl).



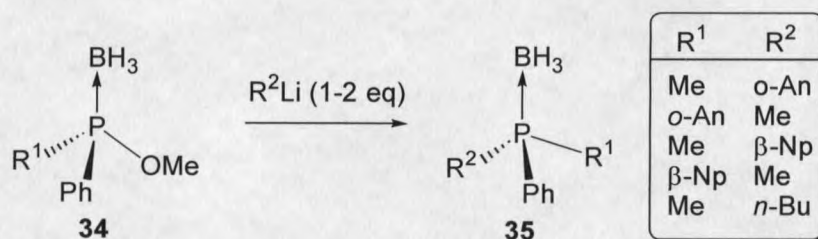
Scheme 17

The ephedrine functionality was removed from **28** by acidic methanolysis, yielding the methyl phosphite-borane **33** with inversion of stereochemistry at phosphorus in nearly a quantitative yield (Scheme 18). The degree of stereodegradation in the methanolysis step was highly dependant on the substituents of the phosphorus.²⁶



Scheme 18

Substitution of the methoxy group with aryl- or alkylolithiums yielded scalemic 3°-phosphines **35** with inversion of stereochemistry and high yields (89-98% ee) (Scheme 19). Several *P*-chiral monophosphines were prepared by Jugé and others²⁷ via this method, including those with β -naphthalene (β -Np), *o*-anisole (*o*-An), methyl, and *n*-butyl (*n*-Bu) substituents. The monophosphines can then be transformed into diphosphines or other more complicated scalemic *P*-chiral phosphine ligand precursors.

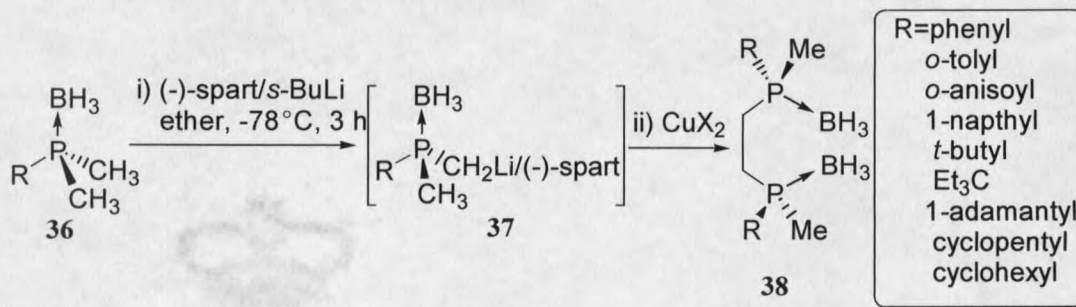


Scheme 19

A useful aspect of this methodology is that, in some instances, both enantiomers of a monophosphine-borane can be prepared from the same starting material by reversing the sequence of addition of the organolithium reagents. However, the lack of generality of the methanolysis step and overall length of this type synthesis, make it cumbersome for the preparation of scalemic *P*-chiral phosphine ligands for asymmetric transition metal catalysis.

Asymmetric Deprotonation

Evans²⁸ and Imamoto²⁹ have recently demonstrated the asymmetric deprotonation of aryl- or alkyldimethylphosphine-boranes **36** with *s*-butyllithium/(-)-sparteine complex. The scalemic lithio derivatives **37** were oxidatively coupled with copper (II) to yield the corresponding bisphosphine-boranes **38** very rapidly (**Scheme 17**). The optical enrichment of the asymmetric deprotonation ranged from 79% to 87% ee, with an absolute conformation of (*S*). Moreover, upon coupling the phosphine-boranes together, the ee's were amplified to greater than 98%, with a small amount of the corresponding meso contaminate being prepared. The asymmetric deprotonation method gave good results for a large variety of R groups, allowing for the rapid preparation of a variety of ligand precursors. Some of the ligands prepared in this way have already begun to show promise in transition metal catalysis.^{30,31}



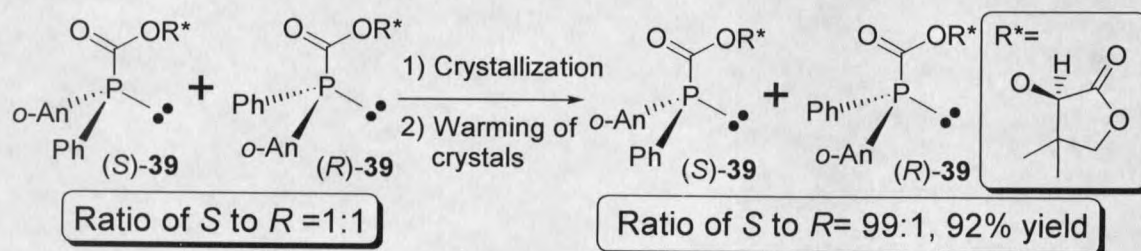
Scheme 20

The generality of the asymmetric deprotonation of functionalized dimethylphosphine-boranes can be attributed to the fact that asymmetry is not derived from nucleophilic substitution on the phosphorus as in most other synthetic approaches. This is important because the pentacovalent intermediate resulting from nucleophilic substitution undergoes

racemization to varying degrees depending on the substituents on phosphorus as well as the nucleophile.

Crystallization-Induced Dynamic Resolution

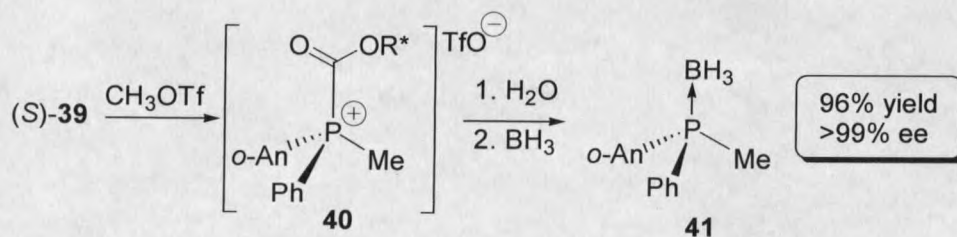
Vedejs and coworkers have recently demonstrated a very interesting method of stereoselection around phosphorus via crystallization-induced dynamic resolution.³² This process takes advantage of the rapid rate of phosphorus epimerization of the diastereomeric mixture of *P*-alkoxycarbonylphosphines **39** relative to the rate of crystallization, thus allowing for preferential crystallization of one diastereomer. Vedejs demonstrated that when a 1:1 mixture of (*S*)-**39** and (*R*)-**39** was crystallized from ethanol, the diastereomeric ratio of the crystals increased to 25-32:1 in a yield of 92% (**Scheme 21**). Surprisingly, further improvement of the diastereomeric ratio of (*S*)-**39** to (*R*)-**39** from 25-32:1 to 99:1 was obtained by simply warming the solid mixture to 50 °C for 22 h.



Scheme 21

Compound (*S*)-**39** was then transformed to PAMP-borane by alkylation of with methyl trifluoromethanesulfonate (CH₃OTf). The resulting phosphonium salt **40** was hydrolyzed with water, followed by protection with borane, providing **41** in 96% yield and greater than 99% ee (**Scheme 22**). Although Vedejs gave little indication of the generality of the crystallization-

induced dynamic resolution methodology to prepare other scalemic *P*-chiral monophosphines, it is a very efficient route to PAMP-borane and its derivatives.



Scheme 22



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RESULTS AND DISCUSSION

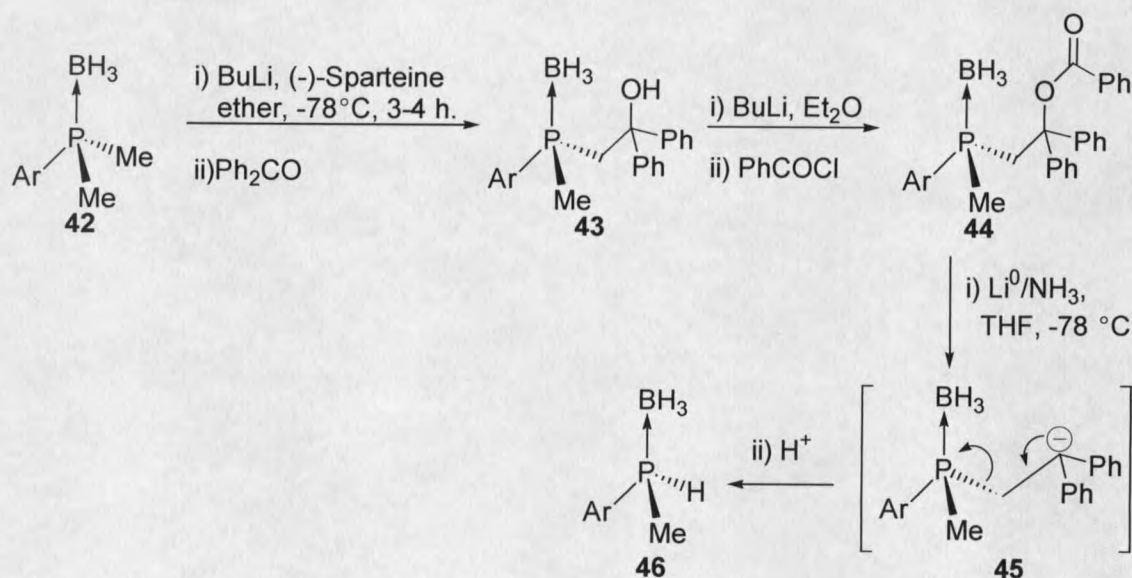
Enantiomerically pure *P*-chiral 2°-phosphine-boranes have been demonstrated to be versatile starting materials for the synthesis of scalemic transition metal ligands.¹⁹ Unfortunately, there are a limited number of preparations of scalemic 2°-phosphine-boranes in the literature.^{17,18} In order to further advance asymmetric transition metal catalysis with scalemic *P*-chiral phosphine ligands, it is necessary to develop methods for the rapid and general preparation of enantiomerically pure 2°-phosphine ligands. The Livinghouse group has been working toward the development of efficient routes to scalemic *P*-chiral 2°-phosphine-boranes that can be used for the synthesis of a variety of enantiomerically pure *P*-chiral phosphine ligands for rapid screening in transition metal catalysis.³³

In this discussion, three approaches to the preparation of enantiomerically pure phosphine-borane ligand precursors from scalemic lithiated *P*-chiral 2°-phosphine-boranes will be examined. The first method is to directly prepare enantiomerically pure *P*-chiral 2°-phosphine-boranes and subsequently convert them to scalemic phosphine-borane ligand precursors. The second approach utilizes novel chemistry to prepare stable scalemic 2°-phosphine-borane surrogates that can be converted directly into enantiomerically pure *P*-chiral phosphine-borane ligand precursors. The final approach is to prepare scalemic *P*-chiral

phosphines-borane ligand precursors by an unprecedented dynamic thermodynamic resolution of racemic lithiated *t*-butylphenylphosphine-borane with (-)-sparteine.

Preparation of Scalemic 2°-Phosphine-Boranes

A route begun by Dr. Gullapalli Kumaraswamy in the Livinghouse laboratory utilized the asymmetric deprotonation of functionalized aryldimethylphosphine-boranes developed by Evans (*vide supra*).²⁸ This method of stereoinduction was chosen because it had been established to give high optical purity with a large variety of alkyl- and aryldimethylphosphine-boranes. Kumaraswamy's method ultimately involved reductive removal of the methyl group that was originally selectively deprotonated by the (-)-sparteine/*s*-butyllithium complex.



Scheme 23

In Kumaraswamy's method, the enantiomerically enriched lithiated aryl dimethylphosphine-boranes **42** from asymmetric deprotonation were trapped with benzophenone (**Scheme 23**). Next, the resulting alcohols **43** were deprotonated with *n*-butyllithium and subsequently acylated with benzoyl chloride. The esters **44** were then reduced with lithium in ammonia, forming the scalemic *P*-chiral 2°-phosphine-boranes **46** upon collapse of the intermediate benzylic anion **45** and proton quench.

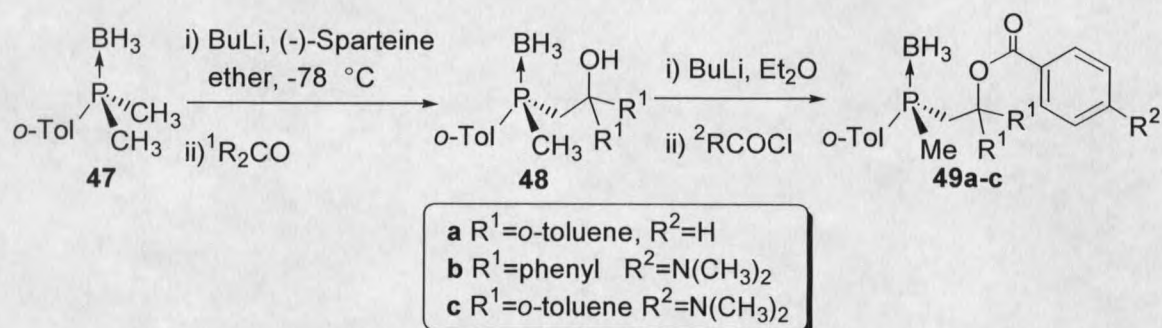
While all the reactions in the synthetic pathway were high-yielding and took place with total conservation of stereointegrity, there were limited opportunities for enantiomeric enrichment due to the scarcity of crystalline intermediates. The ee provided by asymmetric deprotonation had to be carried through to the scalemic *P*-chiral 2°-phosphine-borane products (70% to 95% ee depending on the Ar group). Thus, it was necessary to prepare crystalline derivatives along the pathway so that the enantiomeric purity could be improved by fractional crystallization. This goal proved to be more difficult than originally anticipated.

Pursuit of Crystalline Derivatives

Derivatives of Benzophenone and Benzoyl Chloride. Numerous approaches to forming crystalline derivatives originating from the asymmetric deprotonation of aryl and alkyl dimethylphosphine-boranes were attempted. Originally, changes made to Kumaraswamy's method to improve the crystallinity of the intermediate phosphine-boranes, included variations of the ketone and acylating group. The enantiomerically enriched lithio derivative from the asymmetric deprotonation *o*-tolyl dimethylphosphine-borane **47** was trapped with bis(4-methylphenyl)methanone. The resulting alcohol **48a** was then acylated

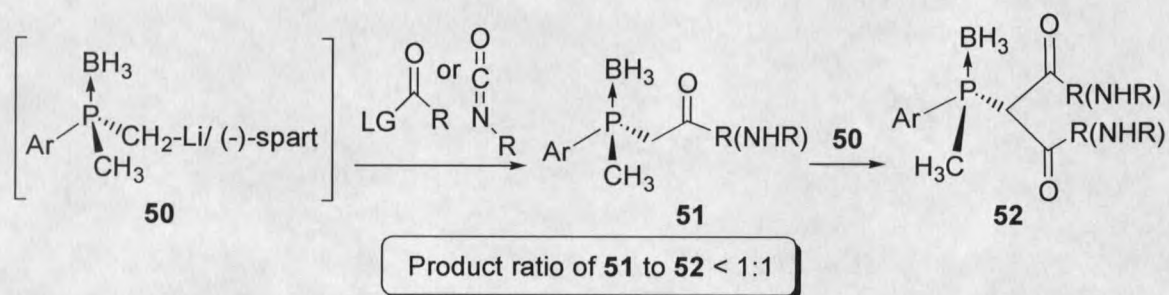
with benzoyl chloride (**49a**) (**Scheme 24**). It was assumed that the added bulk and symmetry would improve the chances of crystallinity. However, this was not the case; and a solid foam was all that resulted.

Another approach was to exchange the benzoyl acyl group with a *p*-dimethylaminobenzoyl moiety (**49b**) in the hope that the added functionality would improve dipole-dipole interactions and lead to a crystalline solid. Unfortunately, a solid foam was all that could be attained. The combination of bis(4-methylphenyl)-methanone trap with the *p*-dimethylaminobenzoyl acyl group (**49c**) was also not crystalline.



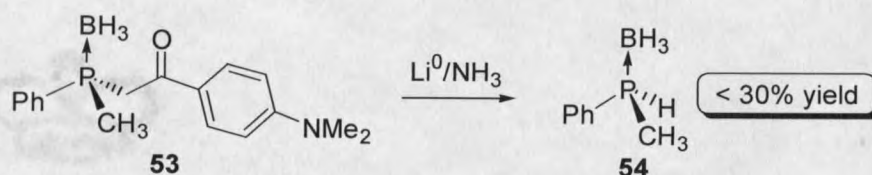
Scheme 24

Direct Acylation. Direct acylation of the enantiomerically enriched (**50**) proved to be problematic and yielded noncrystalline products (**Scheme 25**). Direct acylation of **50** with



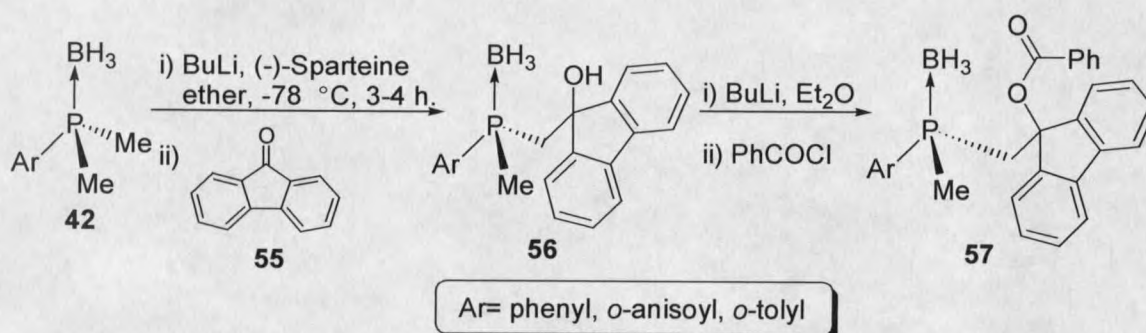
Scheme 25

isocyanate, acid chlorides and anhydrides provided primarily double acylation (**52**), while nitriles failed to react. Direct acylation as a means to prepare *P*-chiral 2°-phosphine-boranes was abandoned when it was demonstrated that reduction of **53** with dissolved lithium in ammonia at -78 °C provided methylphenylphosphine-borane (**54**) in less than 30% yield (**Scheme 26**).



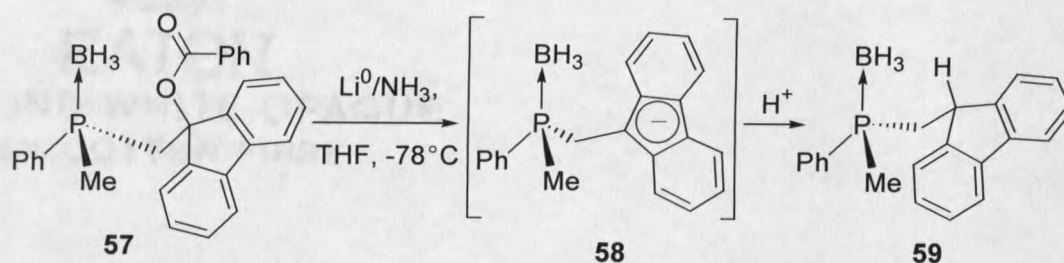
Scheme 26

Alkylative Trap with 9-Fluorenone. The benzoyl esters **57** that were derived from the alkylation of the enantiomerically enriched lithio derivatives of **42** with 9-fluorenone (**55**) proved to be crystalline (**Scheme 27**). The reduction of **57** (Ar = phenyl) with lithium and



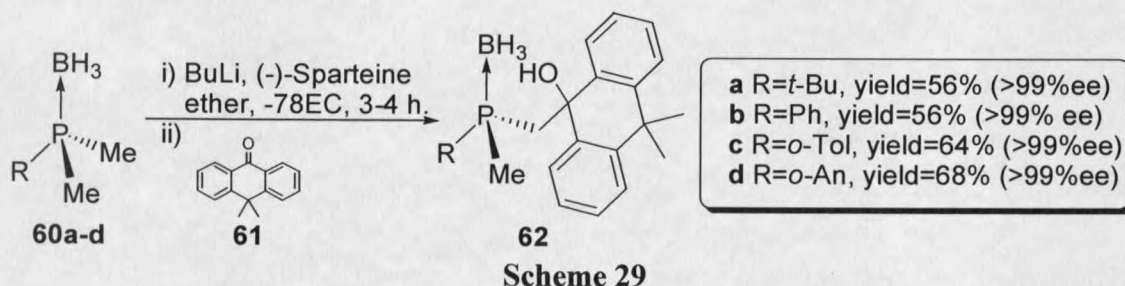
Scheme 27

ammonia formed an aromatic cyclopentadienyl anion derivative **58** that did not collapse to form the 2°-phosphine-borane anion. Instead, the protonated product **57** was isolated (**Scheme 28**).



Scheme 28

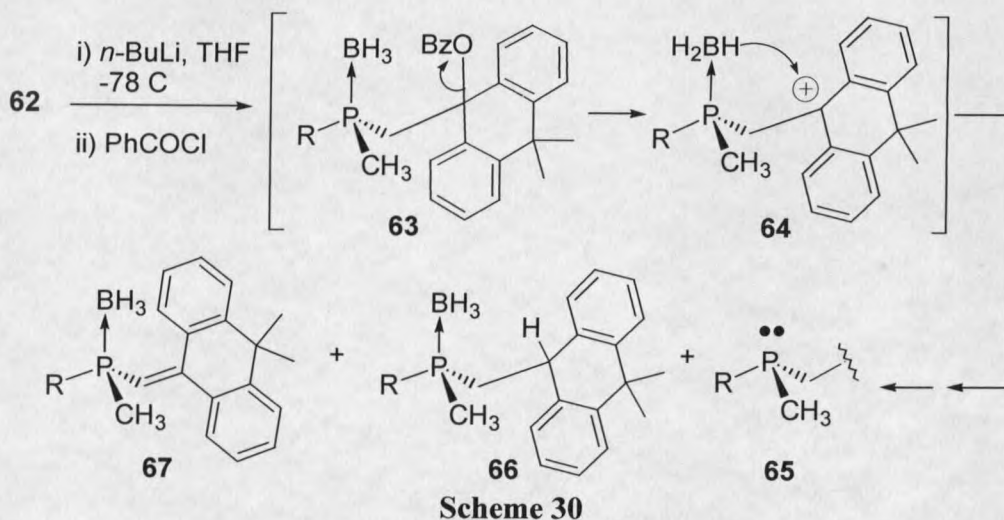
Alkylative Trap with 10,10-Dimethylanthrone. The alkylative trap of scalemic anions **60a-d** with 10,10-dimethylanthrone (**61**) resulted in highly crystalline alcohols **62a-d**. These alcohols were readily recrystallized to greater than 99% ee in all cases (**62a-d**, Scheme 29).³⁴



Scheme 29

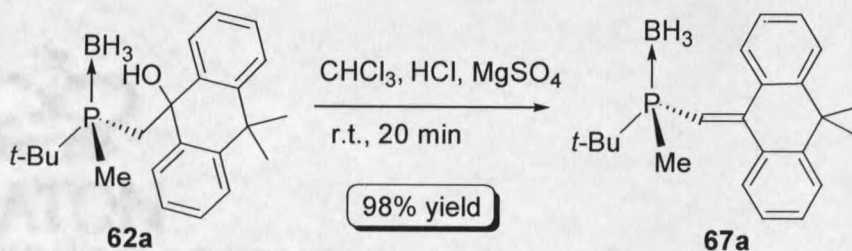
It was found that acylation of **62** by deprotonation with *n*-butyllithium, followed by the addition of benzoyl chloride, did not afford the desired benzyl ester (Scheme 30). The products of the reaction consisted primarily of the elimination product **67**, as well as a substantial amount of the reduced product **66**, and a variety of deboronated side products **65** (10-20%). This result is thought to be derived from the disassociation of the benzoate moiety (**63**) after acylation, yielding a highly stabilized cationic intermediate **64**. This cationic

intermediate **64** can collapse to form either **67**, or it can be directly reduced by hydride abstraction from the borane moiety ultimately forming **65** and **66**.³⁵



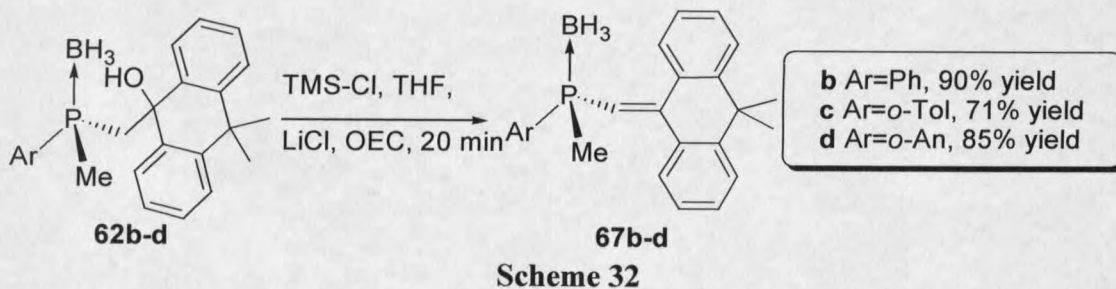
Later, production of the benzoyl esters **62a-d** was discovered to be unnecessary because the dehydrated products underwent reductive elimination when treated with lithium in ammonia, yielding the *P*-chiral 2°-phosphine-boranes (*vide infra*). Therefore, mild conditions for the acidic dehydration of **62a-d** had to be found to prevent self-reduction of the cationic intermediate (similar to **64**).

Dehydration of **62a** could be performed with acidic chloroform³⁶ and anhydrous magnesium sulfate providing **67a** with a high yield and less than 1% self-reduction (Scheme

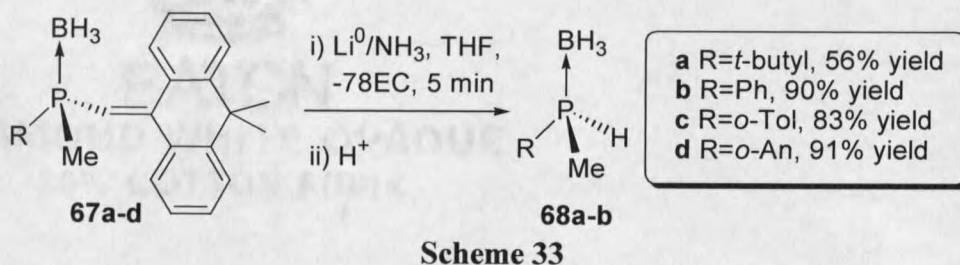


Scheme 31

31). Alcohols **62b-d** were dehydrated by treatment with chlorotrimethylsilane (TMS-Cl) in the presence of excess lithium chloride at 0 °C, providing the vinyl phosphines **67b-d** in good yields (Scheme 32).



Reductive elimination of vinyl phosphine-boranes **67a-d** with lithium and ammonia provided the *P*-chiral 2°-phosphine-boranes **68a-d** (Scheme 33). The yields for the reductions were all good, with the exception of **67a**, where the poor yield was attributed to the high volatility of *t*-butylmethylphosphine-borane (**68a**). This volatility issue will be addressed in the following section.

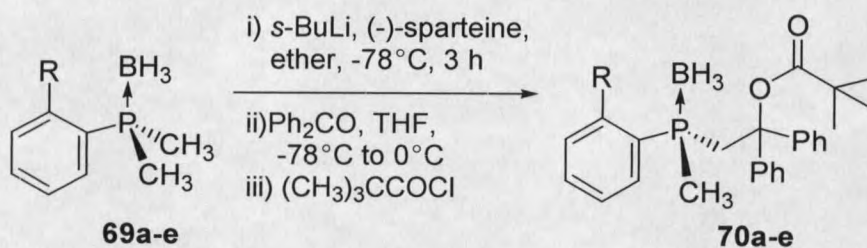


The advantage of the above methodology over Kumaraswamy's original synthesis of scalemic *P*-chiral 2°-phosphine-boranes is that the intermediate alcohol can be recrystallized to greater than 99% ee. However, the multiple steps for the preparation of 10,10-dimethylanthrone make this methodology for the synthesis of scalemic *P*-chiral phosphine-

boranes cumbersome. If this synthesis is to be truly useful, more readily obtainable starting materials must be found.

Pivaloyl Esters of the Benzophenone Adduct. Deprotonation of the aryldimethylphosphineboranes **69a-e** with (-)-sparteine/*s*-butyllithium complex, followed by alkylation with benzophenone and *in situ* acylation with pivaloyl chloride, yielded the pivaloyl esters **70a-e**. Pivaloyl chloride was chosen due to its steric bulk, thus decreasing the rotational and conformational modes in the resulting esters, which would increase the probability that the products would be crystalline. The pivaloyl esters **70a-e** were indeed very crystalline and were readily recrystallized to greater than 99% ee, in good yields (**Table 1**).

Table 1. Yield of Enantiomerically Pure Pivaloyl Esters.^d



Entry 70	R	% ee before recrystallization	% yield (>99% ee)
a	H	75	69 ^a
b	<i>i</i> -propyl	>99	70 ^b
c	CH ₃	87	76 ^a
d	OCH ₃	83	46 ^a
e	CF ₃	87	- ^c

^a Percent ee determined by chiral HPLC fitted with a CHIRALPAK[®] AD column. ^b Percent ee determined by analogy to the corresponding alcohol **108** (see experimental). ^c Recrystallization not optimized due to poor results in subsequent reactions. ^d Absolute stereochemistry of **70a-d** was assigned to be (*S*) by analogy to Evans studies (*vide supra*).²⁸

