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

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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Bradley H. Wolfe

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APPROVAL

of a thesis submitted by

Bradley Hamilton Wolfe

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 stereoinduction 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 stereoinduction 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.

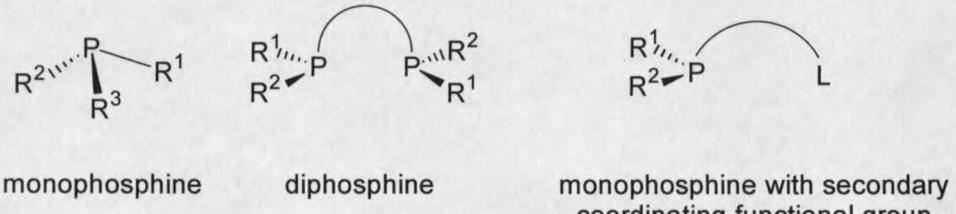


Figure 1. Three major types of *P*-chiral phosphine ligands

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

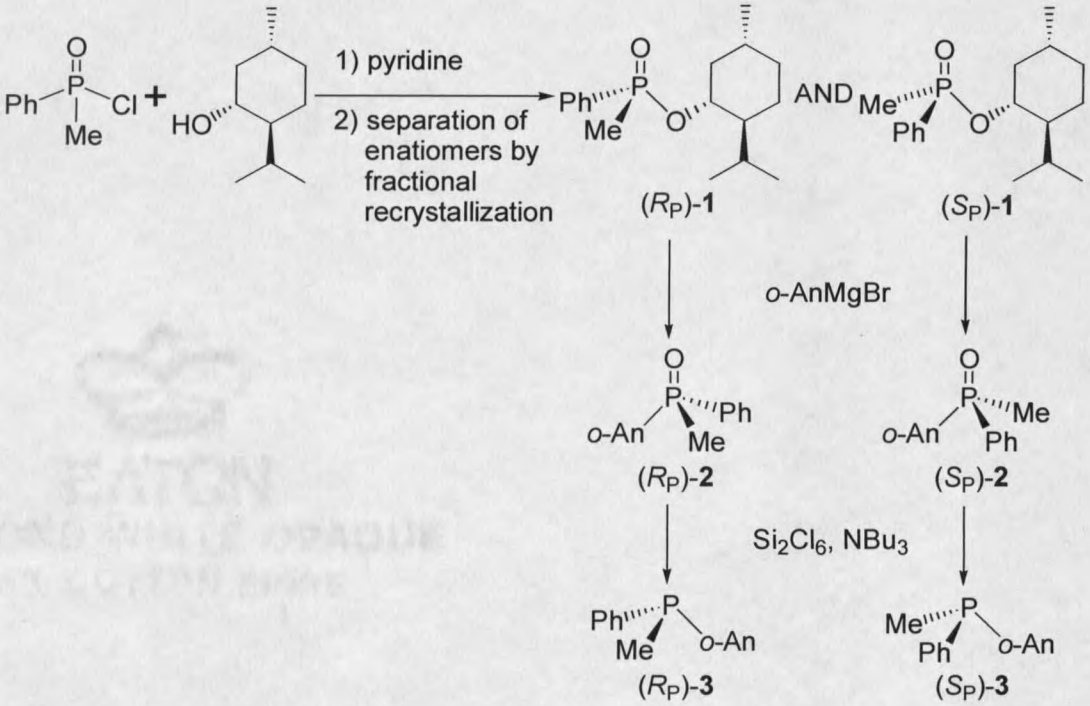
Direct Resolution of Enantiomers

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.

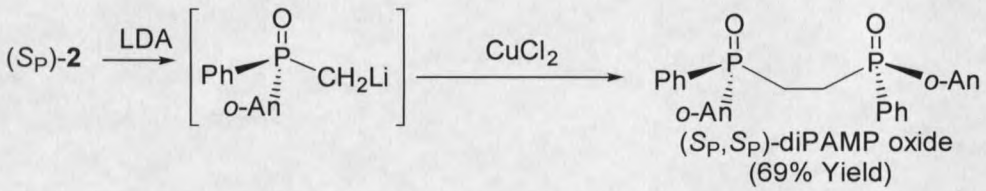
Recently, resolutions of *P*-chiral phosphines have been primarily accomplished by coupling a racemic mixture of phosphinates with an optically pure natural product. Subsequent separation of diastereomers by fractional crystallization and removal of the chiral resolving agent provides the scalemic *P*-chiral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

One of the first preparations of optically pure phosphines, in which menthyloxymethylphenylphosphinate (**1**) was prepared from methylphenylphosphinyl chloride, menthol (Men) and pyridine (**Scheme1**), 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 phenylanisolemethylphospine (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 Cl_3SiH 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(phenylanisolephospino)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**).