Synthesis of C2-symmetric P-chiral bis(phosphine borane)s and their application in rhodium(I) catalyzed asymmetric transformation
by Holly Ann Heath

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

Abstract:
A new development for the synthesis C2-Synnnetric P-Chiral Bis(phosphine borane) ligands is reported, These ligands are based on the asymmetric induction of prochiral phosphine ligands with organolithium/chiral diamine complexes. These ligands have been evaluated in asymmetric rhodium(I) catalyzed hydrogenation and [4 + 2] cycloisomerization reactions. Enantiomeric excesses as high as 99% were obtained for ene-diene cycloadditions.

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APPROVAL

of a dissertation submitted by

Holly Ann Heath

This dissertation has been read by each member of the dissertation 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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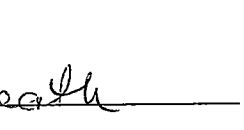
Signature 

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ABSTRACT

A new development for the synthesis C_2-Symmetric *P*-Chiral Bis(phosphine borane) ligands is reported. These ligands are based on the asymmetric induction of prochiral phosphine ligands with organolithium/chiral diamine complexes. These ligands have been evaluated in asymmetric rhodium(I) catalyzed hydrogenation and [4 + 2] cycloisomerization reactions. Enantiomeric excesses as high as 99% were obtained for ene-diene cycloadditions.

CHAPTER 1

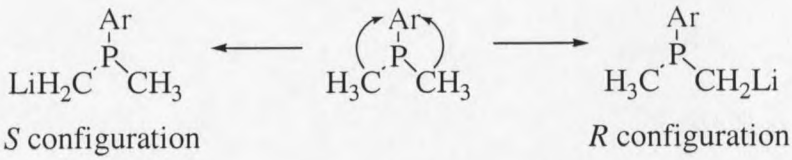
INTRODUCTION

Enantiomerically pure substances are of economic importance in industry. The need for efficient enantioselective syntheses remains a constant challenge. One of the most common methods to obtain stereoisomerically pure compounds involves the use of a stoichiometric quantity of a chiral resolving agent. This method, however, requires the recovery of the resolving agent which can be time consuming and costly. Hence, the development of chiral catalysis is of great interest because of its potential to be more economically feasible and efficient.

Chiral phosphine ligands have been used in transition metal complexes as catalysts for production of enantiomerically pure compounds. There are a variety of reactions where these ligands are not efficient in their reactivity or selectivity and a continued search for well designed chiral ligands remain an important goal. The objective of the research described herein was to design new C_2-symmetric *P*-chiral phosphine ligands for use as enantiocontrollers in asymmetric rhodium(I) catalyzed [4 + 2] cycloisomerizations of olefins. These new ligands were also evaluated to determine their efficacy in asymmetric reduction of C=C linkages.

The synthesis and application of new chiral diphosphine ligands are reported herein. A key feature of these ligands is that the chirality is at the phosphorus atom. In catalytic processes involving phosphine ligands reactivity can be fine-tuned by altering

the environment surrounding the phosphorus atom. These alterations result in a change in the steric and/or electronic environment around the phosphorus. Therefore, the reactivity of phosphorus ligands were studied by preparing a number of chiral phosphine-borane ligands starting with prochiral phosphine-borane (Figure 1).



S configuration *R* configuration

Figure 1. Prochiral Aryldimethylphosphine.

A new method to prepare chiral phosphine-borane ligands was achieved by starting with prochiral phosphine-borane (Figure 1). Asymmetric induction of prochiral phosphine ligands with organolithium/chiral diamine complexes allowed for an efficient method for asymmetric synthesis of new phosphine-borane ligands. The fundamental concepts of organolithium/chiral diamine complexes for asymmetric induction of prochiral phosphine ligands will be discussed. An overview will be given of the use and versatility of these complexes.

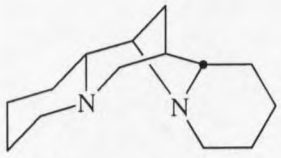
The logic behind the design and development of homochiral phosphine ligands during the course of this research will be discussed as well as the evaluation of these ligands in asymmetric catalytic hydrogenation and rhodium(I) catalyzed [4 + 2] cycloisomerization reactions.

CHAPTER 2

BACKGROUND

Organolithium/Chiral Diamine Complexes

The use of complexes formed between organolithium reagents and enantiopure ligands in asymmetric chemistry offers convenient approaches to syntheses of enantioenriched compounds.

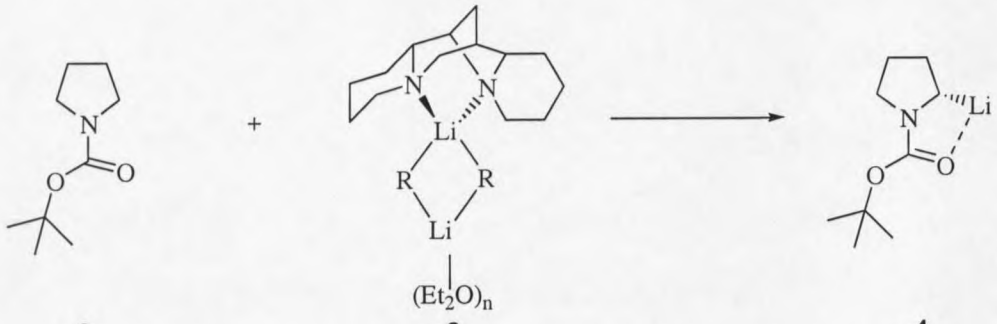


(-)-sparteine
(**1**)

Figure 2. Chiral Diamine (-)-Sparteine (**1**).

Hoppe and co-workers reported that *sec*-BuLi and the C_1 symmetric diamine (-)-sparteine (**1**) (Figure 2) form a complex that can be used to lithiate a nonconjugated oxygen-substituted system.[1,2,3] Beak and co-workers later reported a highly enantioselective deprotonation using **3** for a nonconjugated nitrogen system (Scheme 1).[4] Complex **3** was determined to be configurationally stable at –78 °C and to react with

electrophiles with retention of configuration.[5] NMR spectroscopy established the structure of RLi/(-)-sparteine to be an unsymmetrical dimer in which one of the lithium atoms is complexed by (-)-sparteine and the other lithium atom is complexed by Et_2O. Asymmetric deprotonation of Boc-pyrrolidine (**2**) with **3** resulted in a configurationally stable lithiated species **4** which could be trapped with various electrophiles to give 2-substituted Boc-pyrrolidines in high enantioenrichment (Scheme 1)[4].

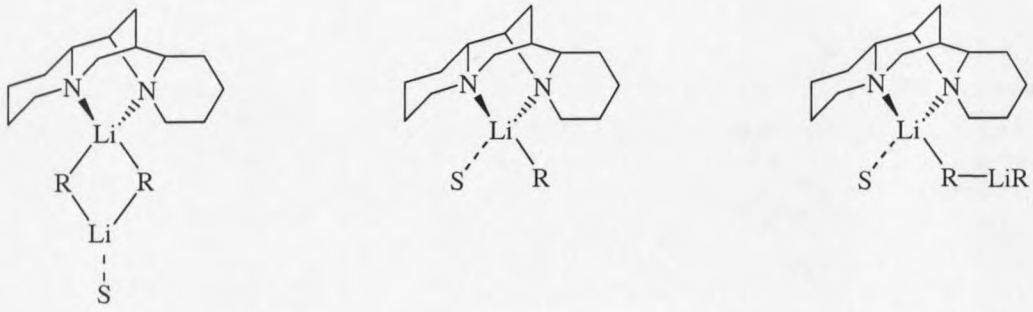


2 **3** **4**

Scheme 1. Asymmetric Deprotonation of Boc-pyrrolidine (**2**).

A kinetic investigation of the reaction strongly suggests that deprotonation is the rate-determining step and that the complexation/decomplexation equilibrium is fast relative to the deprotonation reaction. The predominant species in solution is the prelithiation complex and though the structure is speculative there are three possibilities (Figure 3).[4] Complex **5** is consistent with the kinetic investigation data; however, the distance between the substrate and (-)-sparteine makes it difficult to envision how asymmetric induction occurs. Complex structures **6**[4] and **7**,[6] however, allow the substrate

to be in closer proximity to the chirality introduced by the (-)-sparteine. There has been support for both complexes **6** and **7**. While Beak suggests a transition state that would proceed from the monomeric **6**,[4] Collum proposes a linear dimer **7** based on the lithium dialkylamide transition states.[6]



5 **6** **7**

Figure 3. Proposed Prelithiation Complexes of (**1**).

A variety of ligand systems including (-)-sparteine (**1**) were investigated by Beak, of particular interest were, (-)-isosparteine (**8**), 3-benzyl-6-methyl-3,6-diaza-bicyclo[3.2.1]octnane (**9**), and trans-1,2-bis(dimethylamino)cyclohexane (**10**) (Figure 4). Beak found ligands **8** and **9** provided useful enantiomeric excess (ee) with low conversion to product, while **10** gave no enantioselectivity but provided a good conversion to product (~90%).[5]