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**Chiral Lithium N,P-amide Complexes**  
**Synthesis, applications and structural studies by NMR and DFT**

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Akademisk avhandling för filosofie doktorsexamen i kemi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras onsdagen den 21 december 2011, kl. 9.00 i KE, Institutionen för kemi, Kemigården 4, Göteborgs Universitet och Chalmers Tekniska Högskola, Göteborg.

Fakultetsopponent är Tell Tuttle, Senior lecturer in physical organic chemistry at the University of Strathclyde, Glasgow, UK.

Avhandlingen kommer att försvaras på engelska.

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### ABSTRACT

Enantiospecific synthesis reactions are of intense interest, owing to the increasing request for enantiopure compounds in both research and industry. Lithium amides containing a secondary chelating group are a class of powerful ligands for asymmetric addition reactions. Based on earlier experiences with lithium N,O and N,S amides, synthesis and properties of chiral lithium N,P amides and their use in asymmetric addition are investigated in the present thesis.

Several chiral amines were synthesized with previously published methods, which were improved in different ways. A new synthetic route towards chiral aminophosphines via cyclic sulfamidates has been developed. The use of silica in the synthesis of sulfamidate and the chiral aminophosphine shortened the reaction time considerably, compared to previous methods. The reactions are fast, clean and high-yielding. Furthermore, the synthesis could successfully be scaled up with no loss in yield or purity and gives a general and simple route to a wide variety of chiral N,P-ligands from cheap and readily available amino acids.

Solution studies using low temperature  $^6\text{Li}$ -NMR showed that the chiral lithium N,P-amides form various types of dimers depending on solvent and substituents in the amino acid backbone. The Li-P interactions in these complexes proved much stronger than expected, as indicated by the  $^6\text{Li}$ - $^{31}\text{P}$  coupling constant. A stability study on the aminophosphines with  $^{31}\text{P}$ -NMR proved they are relatively air stable.

The newly synthesized lithium N,P amides were used as ligands in the asymmetric 1,2-addition of *n*-BuLi to benzaldehyde. The chiral N,P-ligands were found to induce asymmetry to similar or better extent, compared to previously reported chiral N,O- and N,S-ligands. Enantiomeric ratios up to 98:1 were obtained at  $-116\text{ }^\circ\text{C}$ .

The experiments were complemented by quantum-chemical calculations employing Density-Functional Theory and Molecular Mechanics (MM), in order to rationalize the experimental findings. For the MM calculations, a tailored force field was developed to allow a proper description of the Li-N interaction. Both the aggregation and solvation of the ligand and the reaction mechanism were investigated. The predicted solvation and aggregation states as well as the enantioselectivities were in good accordance with experiment, provided that dispersion interaction was taken into account in a proper way. It was found that Li- $\pi$  and  $\pi$ - $\alpha$ -H interactions and solvation within the complexes are the major contributions to the energy differences between the more stable (*R*)-transition state compared to its corresponding (*S*)-transition state.

**Keywords:**  $^6\text{Li}$  NMR, Asymmetric synthesis, N,P-ligands, DFT, Molecular mechanics.