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Stereodivergent S_N2@P Reactions of Borane Oxazaphospholidines: Experimental and Theoretical Studies

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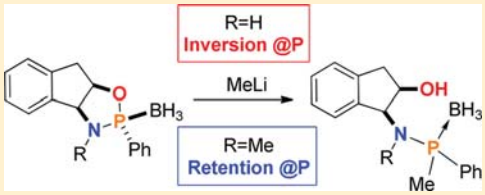
Supporting Information

ABSTRACT: The stereodivergent ring-opening of 2-phenyl oxazaphospholidines with alkyl lithium reagents is reported. N-H oxazaphospholidines derived from both (+)-*cis*-1-amino-2-indanol and (−)-norephedrine provide inversion products in a highly stereoselective process. In contrast, N-Me oxazaphospholidines yield ring-opening products with retention of configuration at the P center, as previously reported by Jugé and coworkers. As a result, from a single amino alcohol auxiliary, both enantiomers of key P-stereogenic intermediates could be synthesized. Theoretical studies of ring-opening with model oxazaphospholidines at the DFT level have elucidated the streochemical course of this process. N-H substrates react in a single step via preferential backside S_N2@P substitution with inversion at phosphorus. N-methylated substrates react preferentially via a two-step frontside S_N2@P, yielding a ring-opened product in which the nucleophilic methyl binds to P with retention of configuration. DFT calculations have shown that the BH_3 unit is a potent directing group to which the methyl lithium reagent coordinates via Li in all the reactions studied.



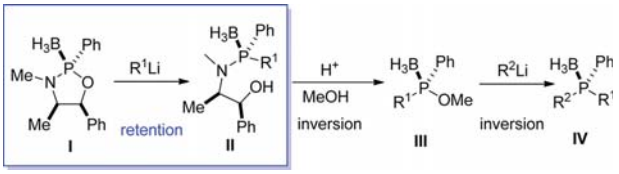
1. INTRODUCTION

Chiral phosphines have played a crucial role in the emergence of asymmetric metal catalysis as an efficient tool to produce single-enantiomer compounds.[1] One of the historical contributions in this field was the development of the P-stereogenic phosphine ligands PAMP and DIPAMP and their application in asymmetric hydrogenation for the synthesis of the anti-alzheimer drug L-DOPA.[2] Today, P-stereogenic phosphines attract increasing interest from the asymmetric catalysis community because of their capacity to impart excellent selectivities.[3,4] However, the methods for the synthesis of these compounds are scarce and limited in terms of substrate scope. One of the most well-established approaches for the synthesis of P-stereogenic ligands is the so-called "Jugé−Stephan method", which is based on the nucleophilic ring-opening of ephedrine-derived borane oxazaphospholidines (BOPs) in an S_N2@P process with alkyl lithium reagents (Scheme 1).[5,6] The main drawback of this strategy is that it is not amenable for the synthesis of bulky phosphines because of the lack of reactivity of intermediate **II**.[7]

Recently, we described that oxazaphospholidines are also amenable for the synthesis of bulky P-stereogenic aminophosphines.[8] *tert*-Butyl oxazaphospholidine **1** derived from *cis*-1-amino-2-indanol (**3**) reacted stereoselectively with alkyl lithium or Grignard reagents to furnish the corresponding ring-opening products (Scheme 2). The presence of a free N-H group in **1** was a key element for the success of the reaction. For example, N-methyl oxazaphospholidine **2** did not undergo ring-opening under the same reaction conditions (Scheme 2). Most noticeably, S_N2@P of **1** took place with unprecedented inversion of configuration at the P center, while ring-opening in the ephedrine Jugé−Stephan system (Scheme 1) takes place with retention of configuration.[5]

The opposite stereochemical pathways observed for these two systems can be attributable to the following: (a) *tert*-butyl vs phenyl substitution at the 2 position of the BOP ring; (b) hydrogen vs methyl substitution at the N atom of the BOP ring; and (c) the use of distinct 1,2-amino alcohol scaffolds. To

Scheme 1. Synthesis of P-Stereogenic Phosphines Using the Jugé−Stephan Method with Ephedrine[a]



[a]Ring-opening of BOP highlighted in blue.

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