Synthesis of the Chiral Cyclic Amines 1-aminoindan and 1,2,3,4-tetrahydronaphthalen-1-amine by Reduction of Imine Precursors with Activated Metal Borohydrides

Lucy Kuhn ‘22, Isobelle McClements ‘23,
Professor Joe Tanski (CHEM)

Introduction

Chirality is a crucial aspect of chemicals used in an array of applications from pharmaceuticals to foods. The same molecule with different chirality may have completely different properties. The goal of this experiment was to find safe and more effective ways to stereoselectively reduce the two diphenylphosphinic protected imines of 1-aminoindan oxime and 3,4-dihydronaphthalen-1(2H)-one oxime using various metal borohydride complexes.

Methods

The first successful reduction was made using $Zr(BH_4)_4$ in THF. $ZrCl_4$ and $NaBH_4$ were allowed to react in THF and left to stir for 24 hours under nitrogen in a glove box to synthesize $Zr(BH_4)_4$. 100 mg of diphenylphosphinic protected imine 1-aminoindan oxime were then added and the solution was left to stir for another 24 hours. This procedure was repeated for the diphenylphosphinic protected imine of 3,4-dihydronaphthalen-1(2H)-one oxime, with two trials for each imine for a total of four vials.

A washing procedure using HCl, NaOH, and brine was used to isolate the organic layer, which was dried with magnesium sulfate.

In hopes of synthesizing enantiomerically rich products, this procedure was amended by adding (*R*) and (*S*) BINOL.

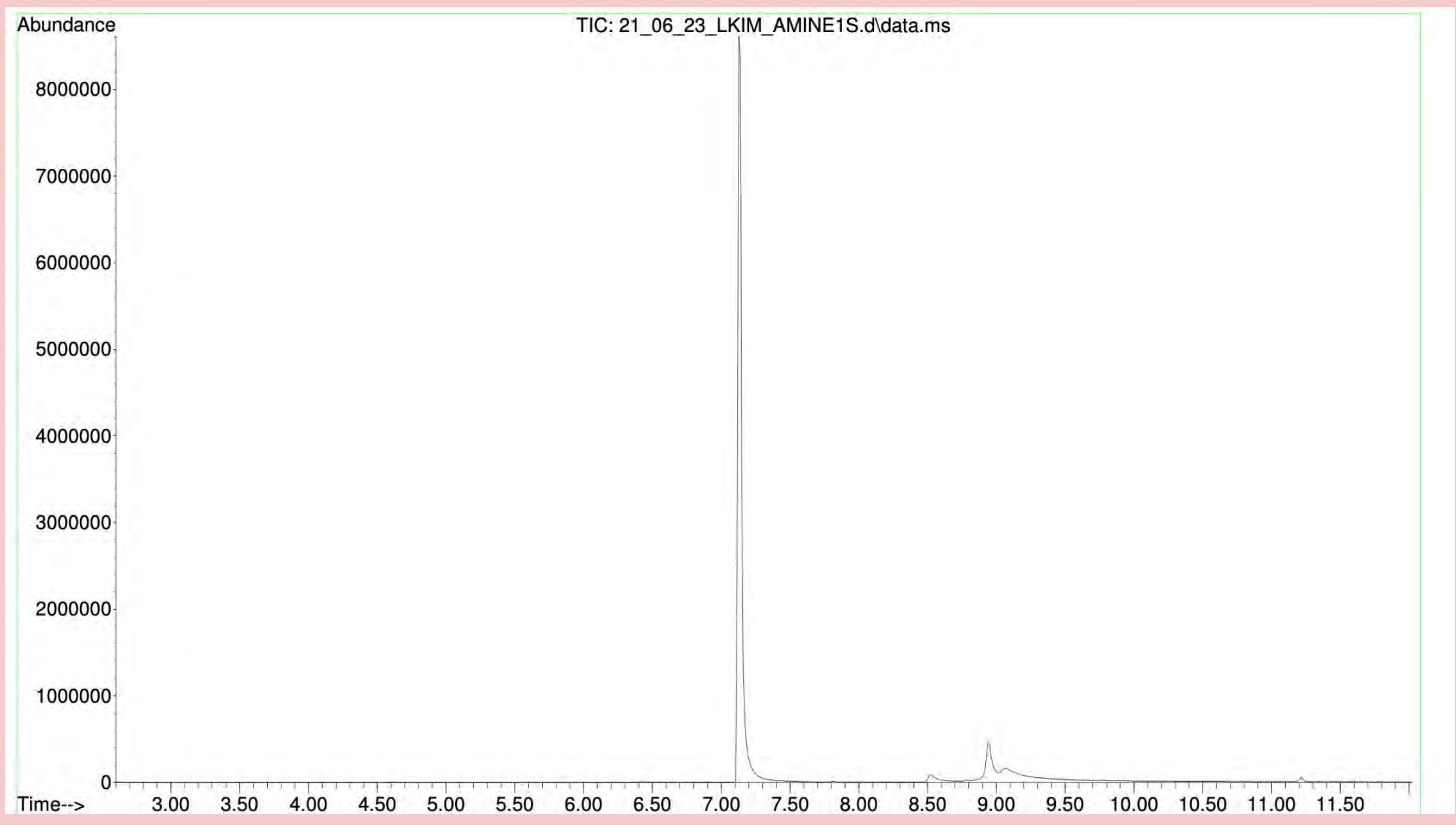
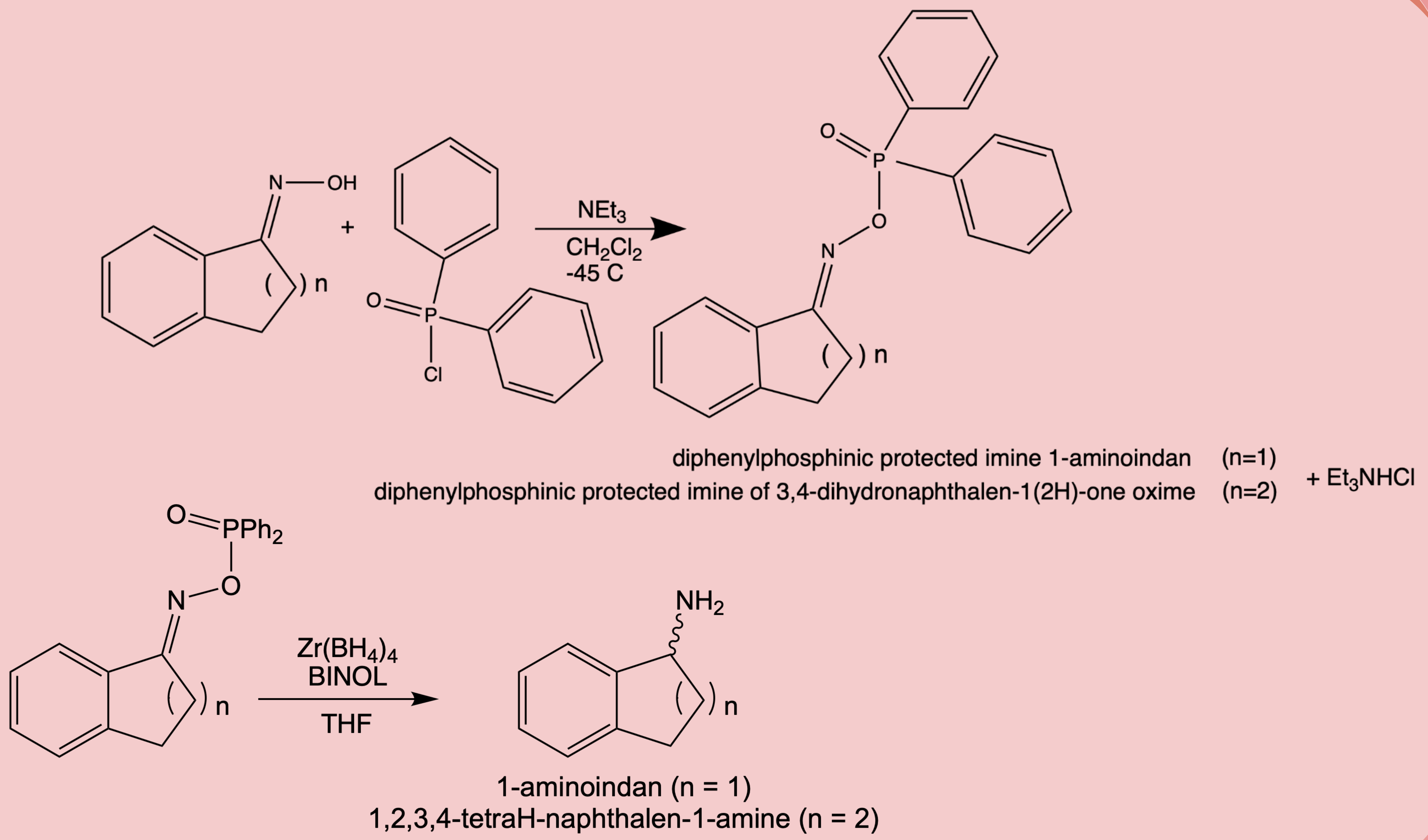


Figure 2. GC-MS Spectra of pure amine purchased from Sigma Aldrich showing that the retention time of pure 1-aminoindan is 7.10 minutes



Future Work

Future work will continue with examining effects of BINOL on the stereospecificity of the reduction with the ultimate goal of creating enantiomeric excess within the amine product.

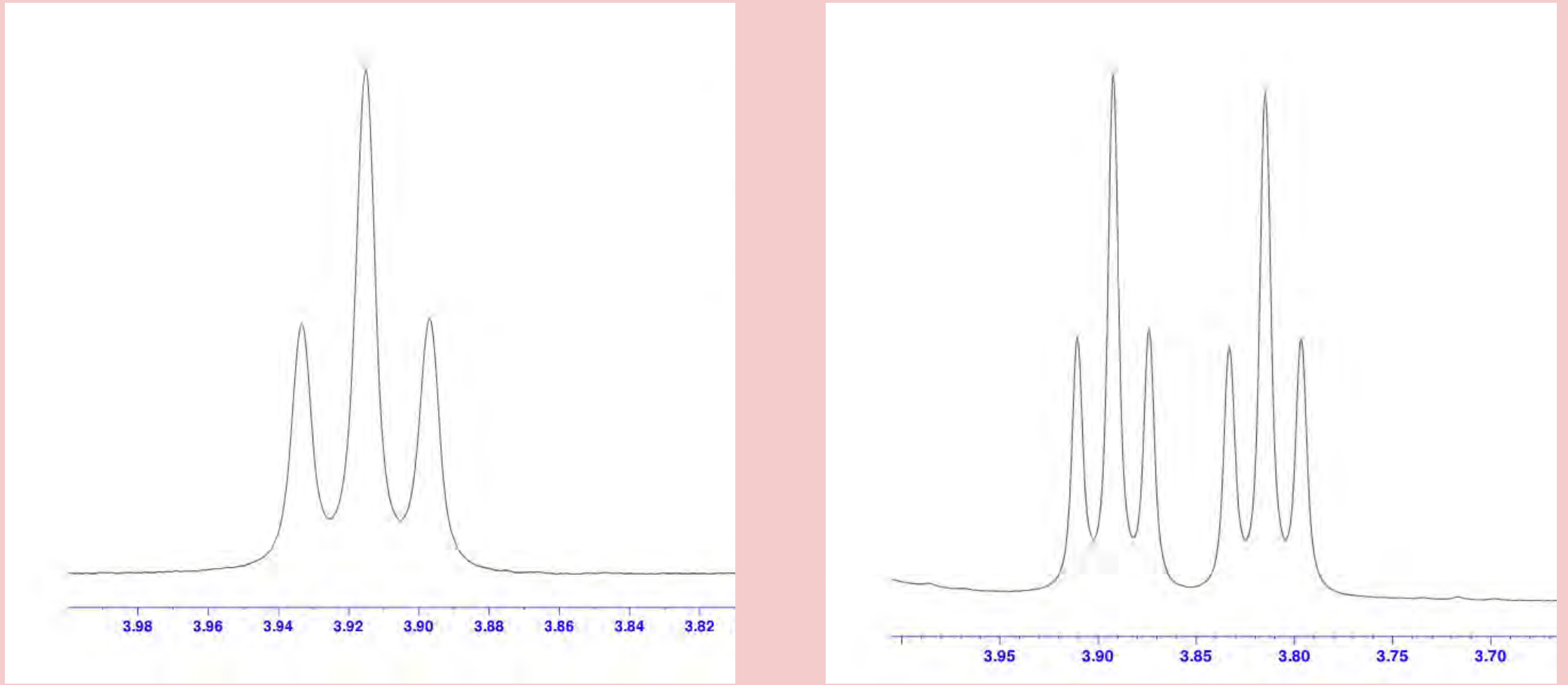
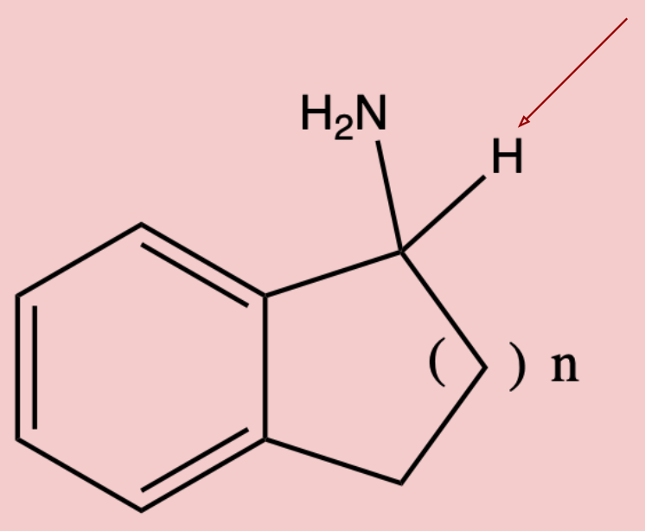


Figure 3. NMR spectra of (*S*) isomer 1-aminoindan (right) and racemic 1-aminoindan spiked with binol (left).



The NMR shift for the hydrogen indicated on the left is different depending on the chirality of the amine as it interacts with BINOL, so integrating its peak could be used to determine e.e.

Results

Simple borohydrides are ineffective at reducing the deactivated imines. Trials were performed using $NaBH_4$,$[(C_6H_5)_3P]_2CuBH_4$, and $(C_2H_5)_4N(BH_4)$ as reducing agents in a variety of solvents, and none yielded amine products. $Zr(BH_4)_4$ in THF acted as an effective reducing agent for the deactivated imines. (*R*) and (*S*) isomers of BINOL were introduced to the reaction in order to yield enantiomerically enriched products. NMR shift studies point to enriched amine products, but further study needs to be done in order to determine the effectiveness of this method.

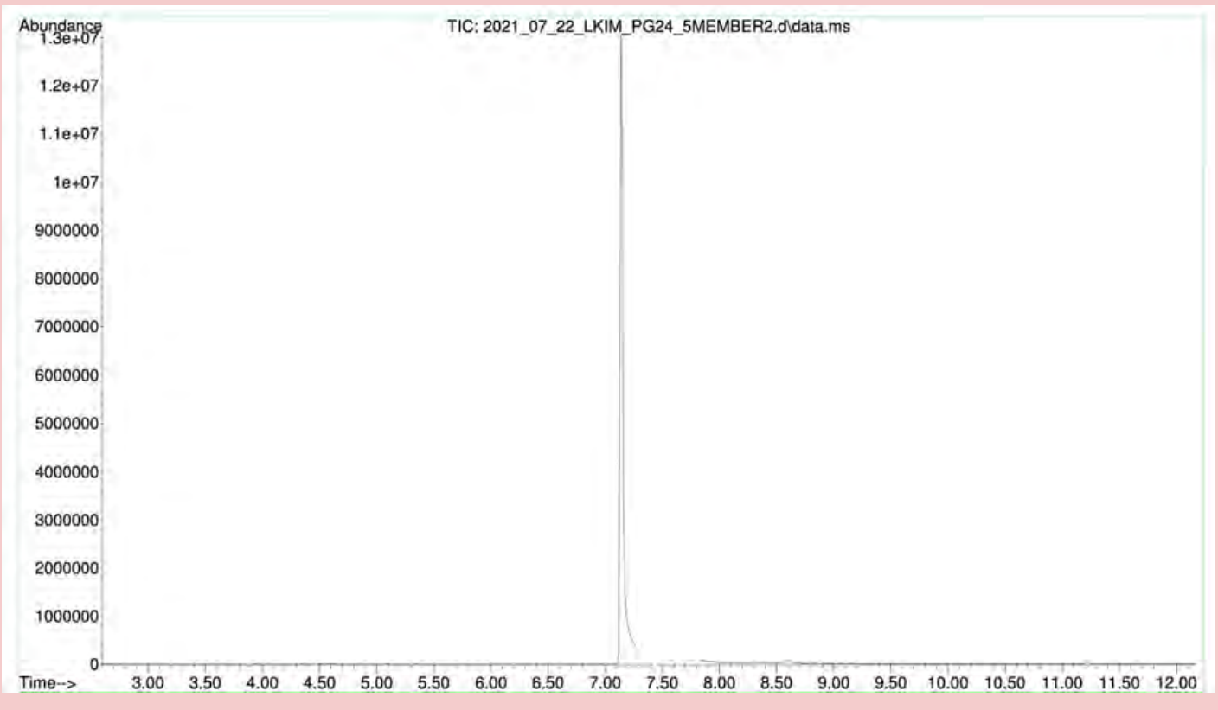


Figure 4. GC-MS spectra of product from $Zr(BH_4)_4$ reduction, showing presence of amine product.

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