Asymmetric Hydroboration-Oxidation of Methylstyrene

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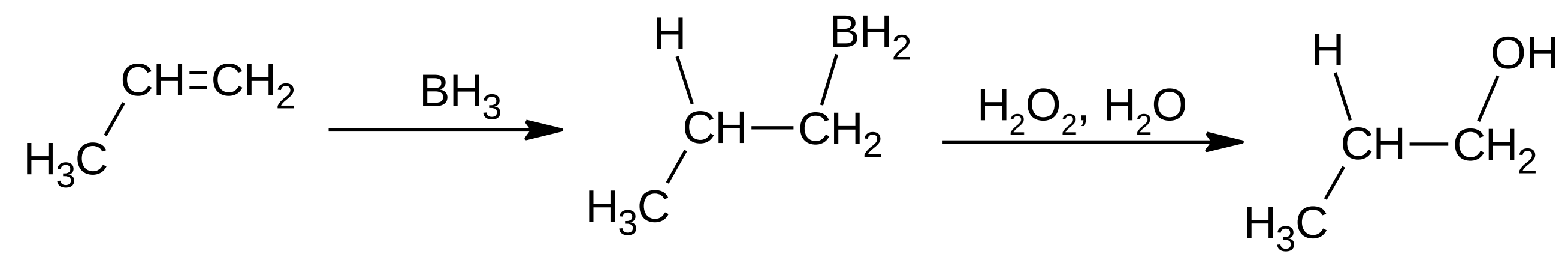
Introduction

Hydroboration reactions involve the addition of hydrogen-boron bonds to C-C double and triple bonds, as well as other carbon double bonds, though this paper will focus on C-C double bonds (alkenes). Because of the reversed B-H polarity, boron typically adds to the less-substituted carbon of the double bond (anti-Markovnikov) as its hydrogen adds to the more substituted carbon.[1] This unique regioselectivity makes hydroboration a good intermediate for synthesis of primary alcohols (1), amines, etc.[2] A significant implication of the thalidomide tragedy is that the syntheses of alcohols and such molecules for medicine and other applications require excellent optical activity achieved via asymmetric synthesis and catalysis. Asymmetric hydroboration is the selective synthesis of only one enantiomer over the other.[3]

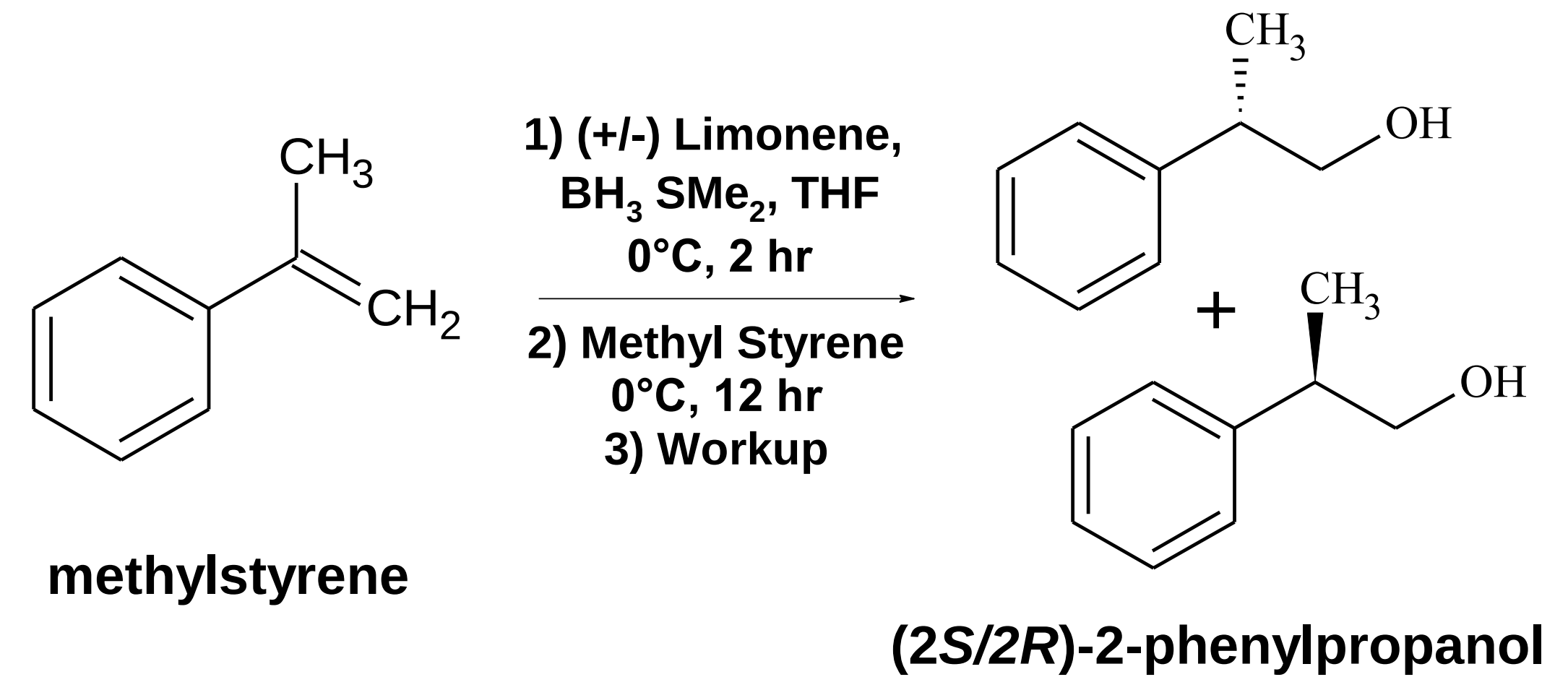
(1)



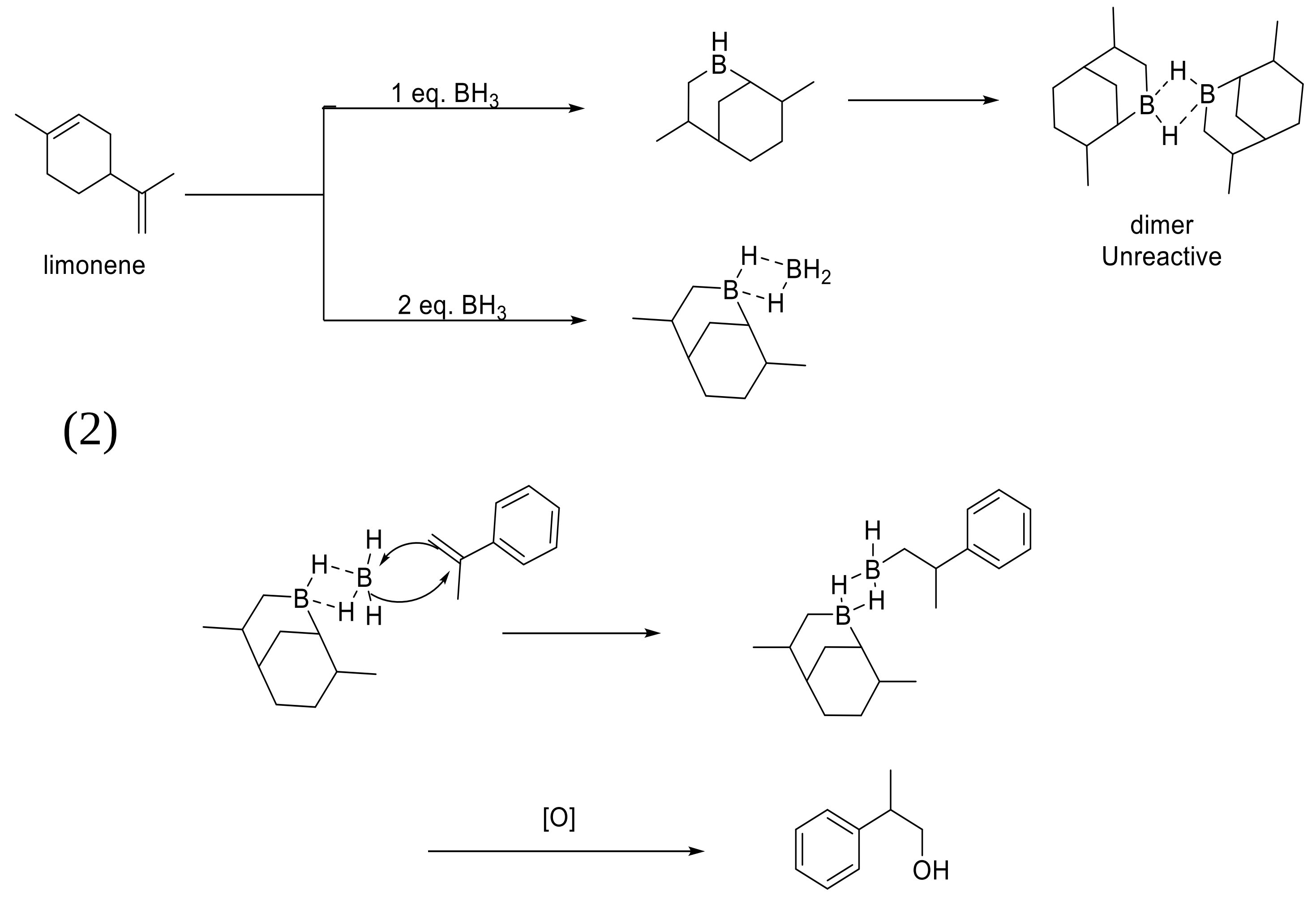
Current asymmetric hydroboration methods include the use of reagents like Diisopinocampheylborane (ipc_2BH) which reliably produce stereoselective compounds in up to a 99% ratio.[3] However, the polarity of the byproduct is highly similar to the desired product, 2-phenylpropanol, making separation of the two via column chromatography very difficult. A reagent like 9-BBN results in a diol product, making it more easily separable, but it does not react asymmetrically.[4] By using hydroborated, optically active limonene instead (2-BBN), the diol byproduct can be easily separated and stereoselectivity can be achieved (2). Thus, co-hydroboration and separation of methylstyrene and (+/-) limonene can produce the asymmetric diol in high yields.

Experimental

1. THF, (+/-) limonene, and borane dimethylsulfide were added to a flask under nitrogen at 0^{o}C and stirred for 2 hours.
2. Methyl styrene was added and let stir overnight before NaOH and H_2O_2 were added, followed by acid workup.
3. Enantiomeric ratio was determined by reacting the alcohol with (-)-menthyl chloroformate (3).



Results



(2)

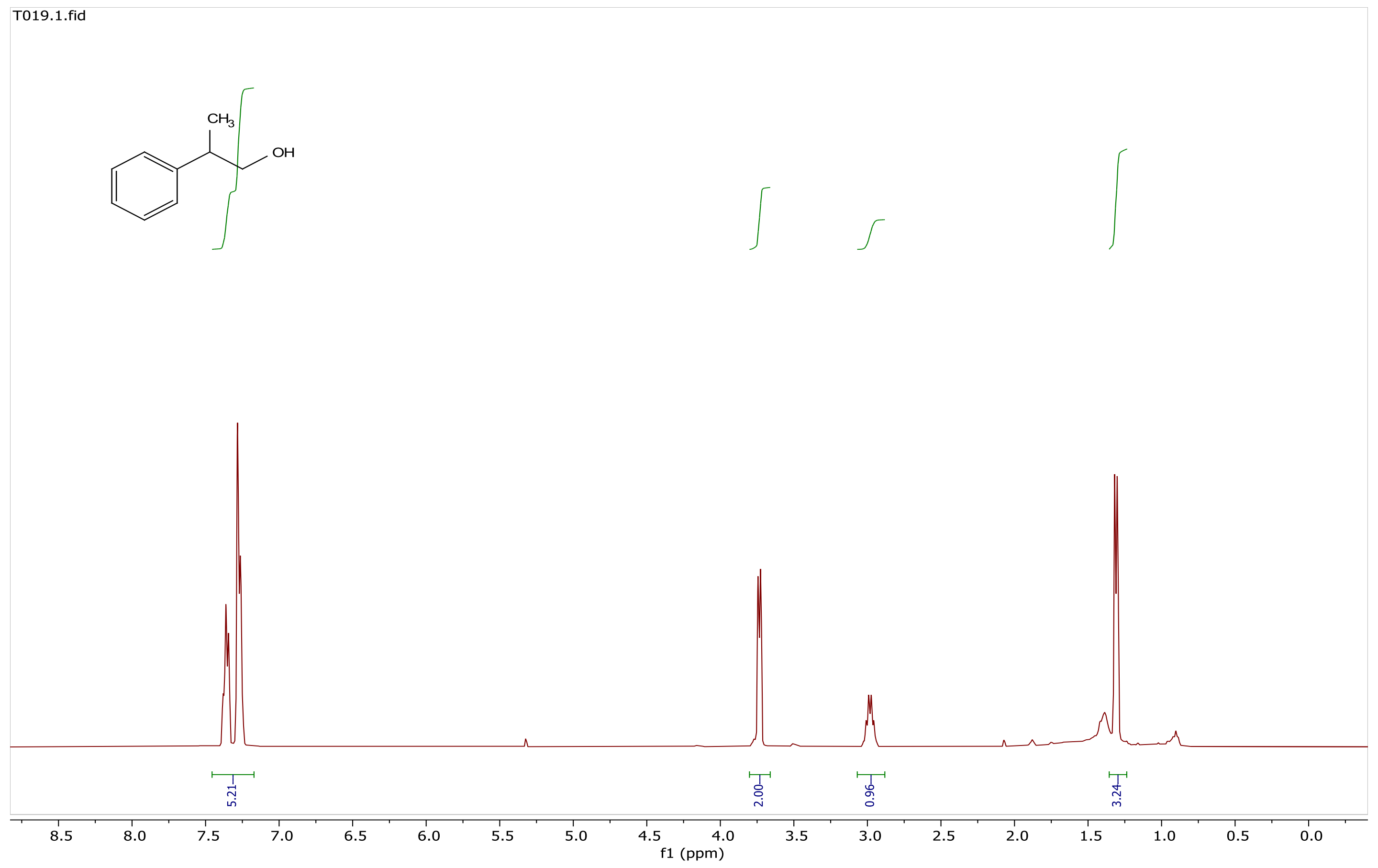
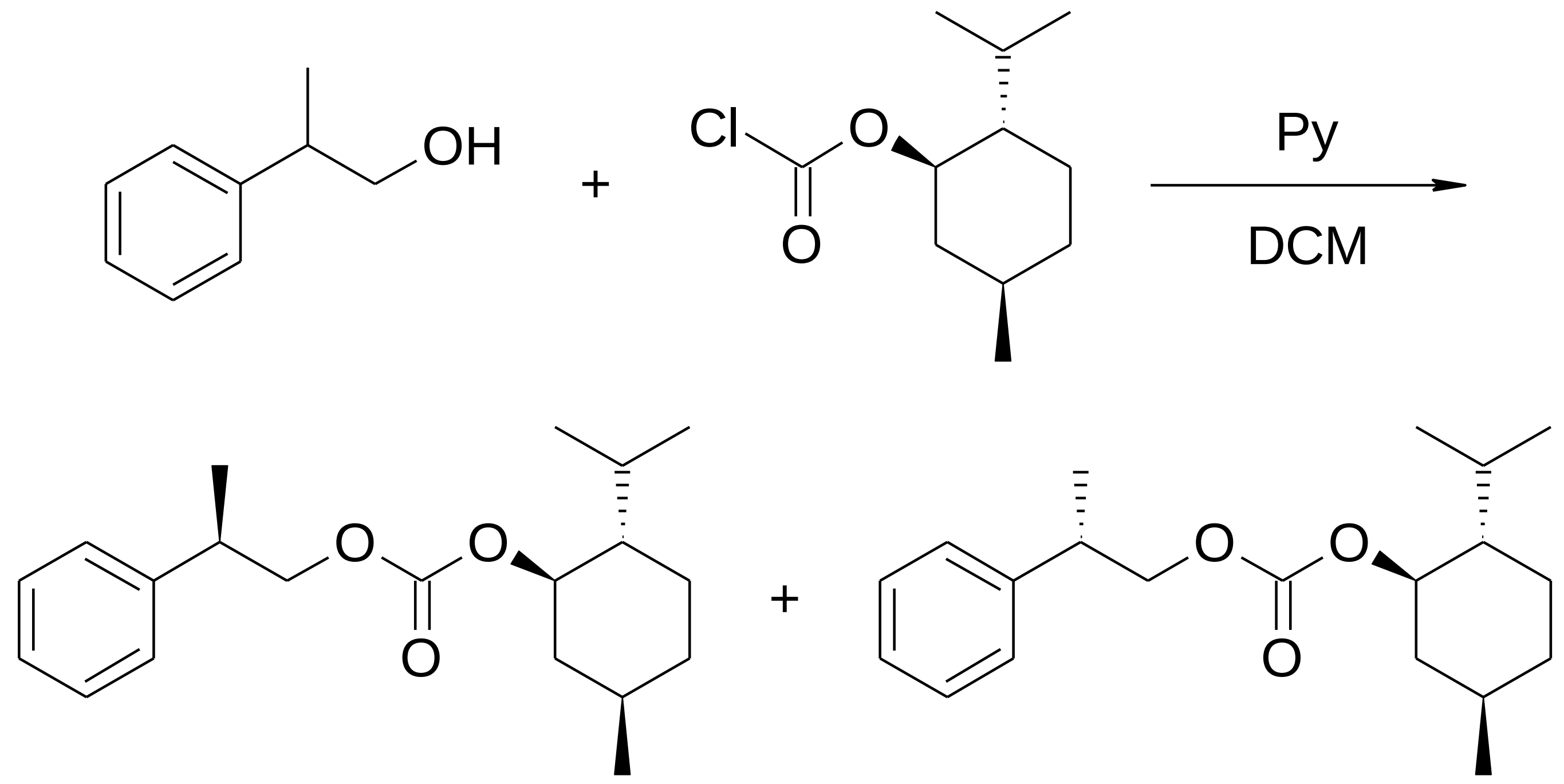


Figure 1. PNMR of 2-phenylpropanol product (T019).

(3)



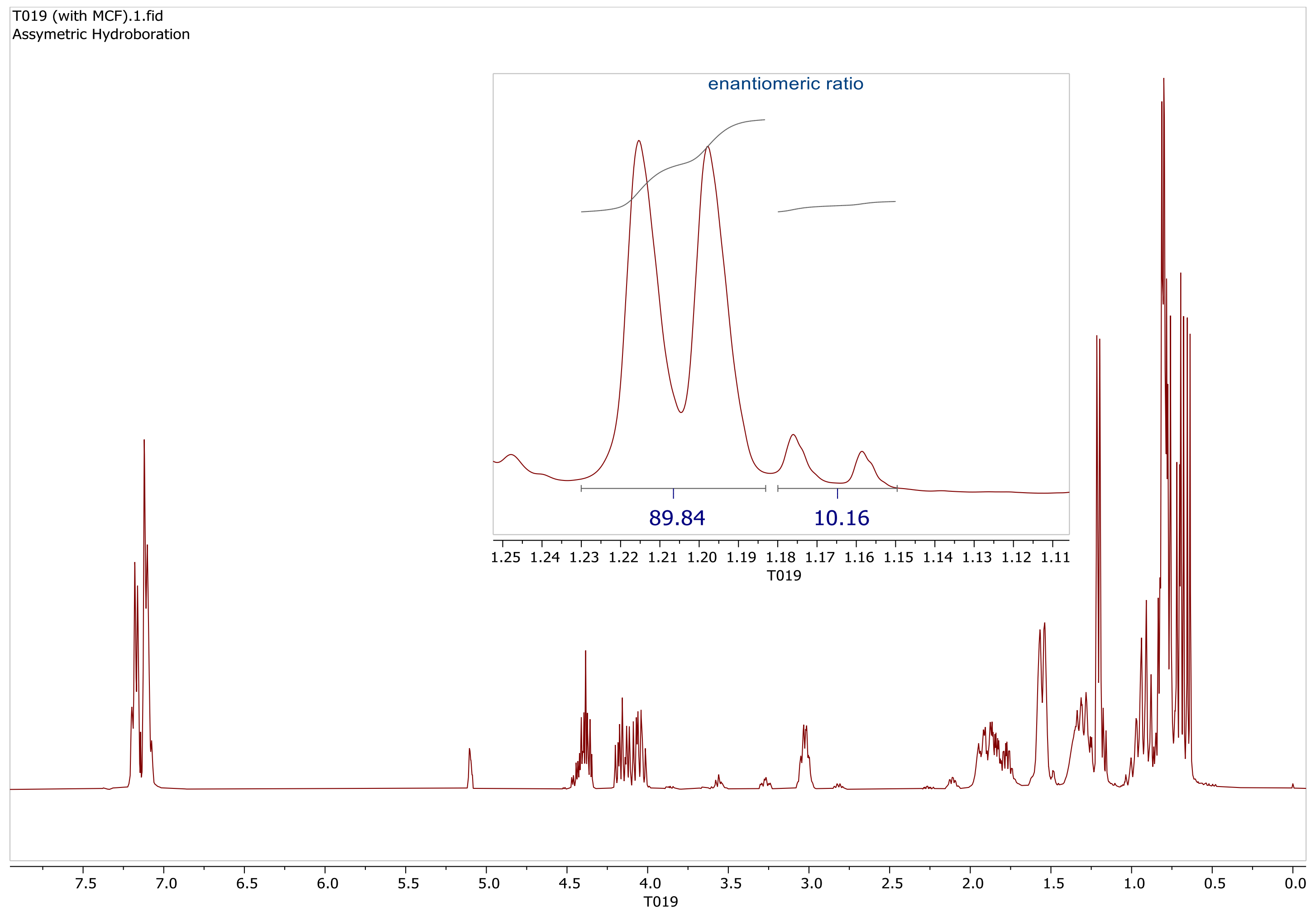


Figure 2. PNMR of menthyl chloroformate derivative of 2-phenylpropanol.

The ratio of the benzyl methyl protons (doublet at ~1.2ppm) showed a diastereomeric ratio of 90:10 (Figure 2) corresponding to the er of the alcohol. Similar ratio was observed for some carbons in the C-13 NMR. In a racemic mixture (non-asymmetric) the ratio would be 50:50.

Conclusion

The co-hydroboration of α-methylstyrene and limonene has furnished the resultant 2-phenylpropanol in a 90:10 enantioselective ratio.

References

(1) Brown, H. C. Hydroboration-a Powerful Synthetic Tool. Tetrahedron 1961, 12 (3), 117–138. https://doi.org/10.1016/0040-4020(61)80107-5.

(2) Rathke, M. W.; Inoue, N.; Varma, K. R.; Brown, H. C. A Stereospecific Synthesis of Alicyclic and Bicyclic Amines via Hydroboration. Journal of the American Chemical Society. American Chemical Society 1966, pp 2870–2871. https://doi.org/10.1021/ja00964a057.

(3) Brown, H. C.; Zweifel, G. Hydroboration as a Convenient Procedure for the Asymmetric Synthesis of Alcohols of High Optical Purity. Journal of the American Chemical Society. American Chemical Society January 20, 1961, pp 486–487. https://doi.org/10.1021/ja01463a055.

(4) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. Hydroboration. 45. New, Convenient Preparations of Representative Borane Reagents Utilizing Borane-Methyl Sulfide. J. Org. Chem. 1977, 42 (8), 1392–1398. https://doi.org/10.1021/jo00428a028.

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