2010

Quinine/Sodium Borohydride Complexes as Chiral Reductive Catalysts

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James Gallagher and William Dasher

Introduction:

Due to the critical importance of chirality in bio-chemical systems, asymmetric synthesis is currently one of the most important areas in chemistry research. Two enantiomers can have very different properties within a biological system. For example, many pharmaceutical drugs have only one active enantiomer. However the field of asymmetric chemistry is still in its infancy. Given the thousands of different types of reactions used in medicinal chemistry, there is much room for the development of various asymmetric catalysts that are both cost-effective and able to efficiently produce high yields.

Quinine, a naturally occurring alkaloid compound found in the bark of the Cinchona tree, is one promising asymmetric catalyst. Recently quinine and its derivatives have been shown to effectively catalyze reactions asymmetrically.[1,2] This property is due to the chiral pocket it forms at its stereocenter (figure 1).

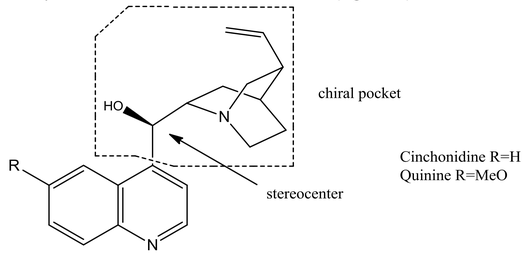
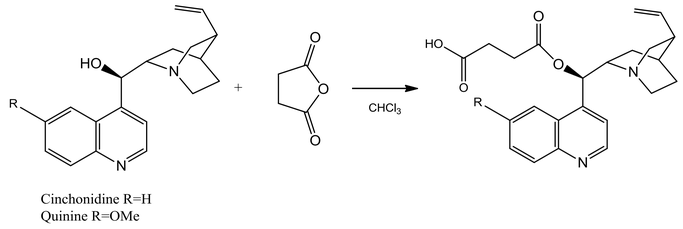


Figure 1. Quinine and Cinchonidine

Reduction reactions are a particularly appealing class of reactions that could be catalyzed asymmetrically by quinine as they often result in an alcohol which can then be elaborated further in a variety of different ways. Sodium Borohydride ($NaBH_4$) is a commonly used reductant due to its ability to reduce ketones in the presence of other functional groups such as esters. Additionally, its Lewis Acid properties give the possibility of forming a quinine/$NaBH_4$ complex. The goal of this research is to investigate the properties of quinine/$NaBH_4$ derivatives as asymmetric catalysts in reduction reactions.

Modification of Quinine/Cinchonidine:

Quinine and cinchonidine were modified by addition of succinic anhydride at the beta alcohol site (scheme 1). This particular sort of derivative is a promising candidate to create a chiral $NaBH_4$ reagent. The acidic functionality created by adding the anhydride group should covalently bind $NaBH_4$, resulting in better complexion. Complexion of the $NaBH_4$ is critical for asymmetric synthesis since any $NaBH_4$ that is not attached to the quinine derivative will reduce a carbonyl in a symmetric fashion.



Scheme 1

Formation of the quinine hemisuccinate adduct was confirmed by ^{1}H-NMR. The appearance of a four proton singlet at 2.5ppm indicates the presence of the succinic protons, while the shift of the carbinol proton from 5.5ppm to 6.0ppm suggests an alteration at the beta alcohol location.

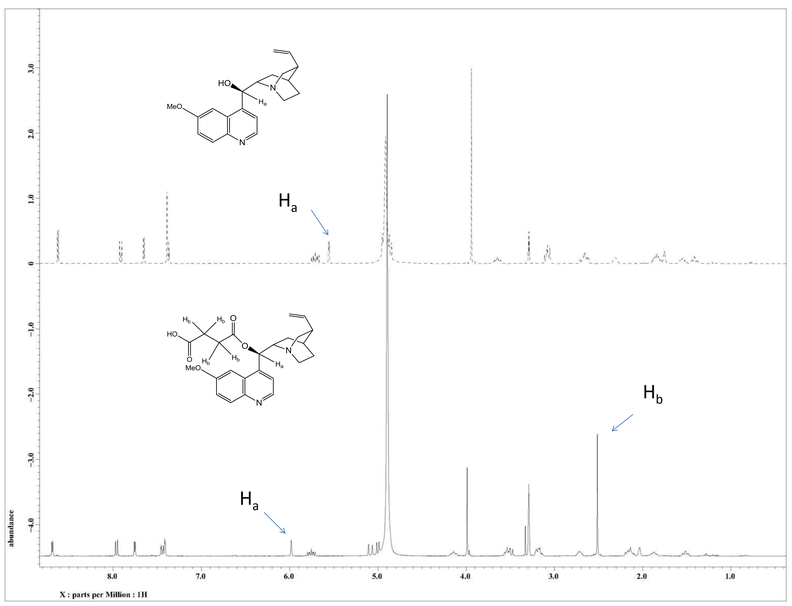


Figure 2. ^{1}H-NMR overlay spectra of quinine and quinine hemisuccinate in CD_3OD.

References

[1] Maruoka, K. *Org. Process Res. Dev.*, **2008**, 12 (4), 679–697.

[2] Hoffmann, H.M.R.; Frackenpohl, *J. Eur. J. Org. Chem.*, **2004**, 4293-4312.

HPLC was also performed, with the unmodified quinine standard eluting at 5.9 minutes (figure 3a). While the HPLC spectrum of the quinine hemisuccinate adduct does exhibit a peak at 5.9 minutes, the relative size compared to the standard suggests that unmodified quinine exists only in trace amounts in the product (figure 3b).

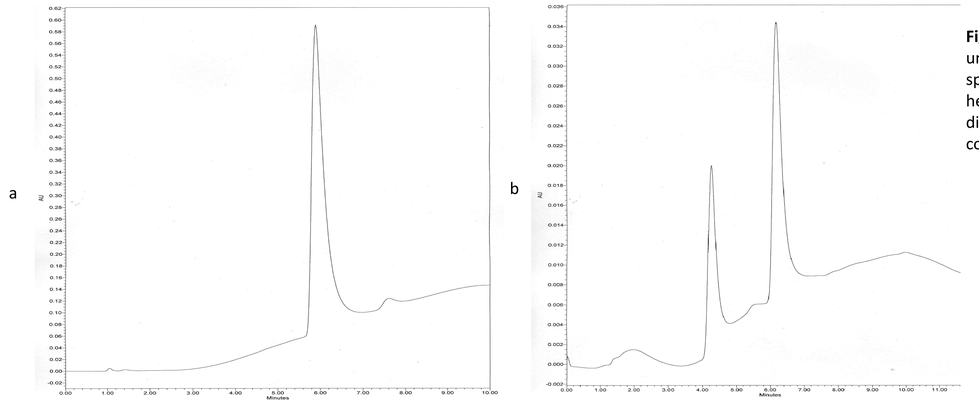
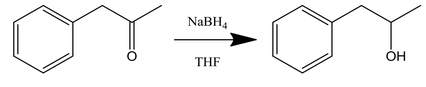


Figure 3 a) HPLC spectrum of unmodified quinine. **b**) HPLC spectrum of quinine hemisuccinate. Note difference in y-axis scaling compared to **3a.**

Determination of Reductive Properties:

Reduction of phenyl-2-propanone with free $NaBH_4$ was performed for standardization (scheme 2). GC/MS post work up shows near complete conversion to product, while the approximately 1:1 ratio of eluent peaks in the chiral GC spectrum indicates the reaction proceeded in a symmetric manner (figure 4).



Scheme 2

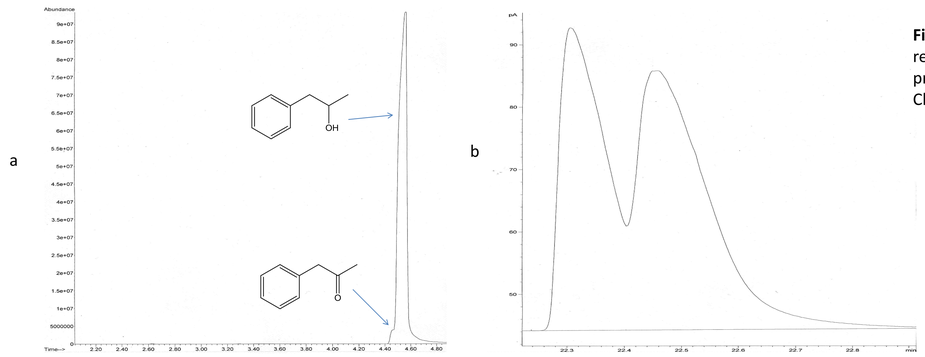


Figure 4 a) GC/MS spectrum for reduction of phenyl-2-propanone with free $NaBH_4$. **b)** Chiral GC of purified product

Reduction of phenyl-2-propanone was then attempted in the presence of the quinine hemisuccinate/$NaBH_4$ adduct with identical reaction conditions (scheme 3). GC/MS post work up showed only starting material (figure 5). Insolubility of the adduct in THF prompted attempting the reaction in glyme. While this greatly increased solubility no reduction took place. Using the cinchonidine hemisuccinate/$NaBH_4$ adduct yielded identical results.

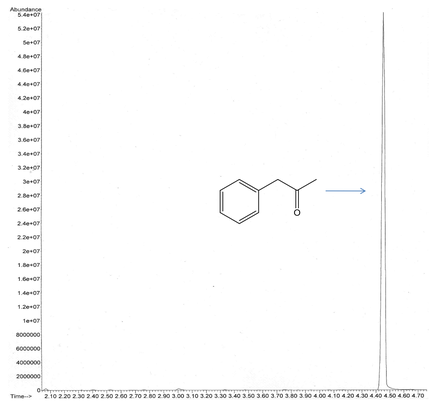
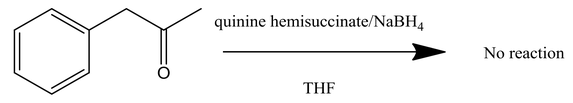


Figure 5. GC/MS of attempted reduction of phenyl-2-propanone with quinine hemisuccinate/$NaBH_4$ adduct.



Scheme 3

Future Research:

The inability of quinine and cinchonidine hemisuccinate/NaBH4 adducts to reduce phenyl-2-propanone might be the result of using an unsuitable substrate. Using alternative ketones as substrates is one possible area of future work. Another possible explanation is that the adducts bind to NaBH4 too tightly to allow reduction to occur. The degree of complexation can be tuned by altering the length and composition of the chain at the beta alcohol site.

Acknowledgements:

I would like to thank the University of Puget Sound for providing the resources to make my research possible, and professors William Dasher and John Hanson for their guidance.