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Quinine/Sodium Borohydride Complexes as Chiral Reductive Catalysts

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. Asymmetric catalysts that are both cost-effective and able to efficiently produce high yields.

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 (NaBH₄) 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/NaBH₄ complex. The goal of this research is to investigate the properties of quinine/NaBH₄ 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 NaBH₄ reagent. The acidic functionality created by adding the anhydride group should covalently bind NaBH₄, resulting in better complexation. Complexation of the NaBH₄ is critical for asymmetric synthesis since any NaBH₄ that is not attached to the quinine derivative will reduce a carbonyl in a symmetric fashion.

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

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).

References

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.

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