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Synthesis of a Modified Cinchonidine Catalyst for Use in the Asymmetric Michael Reaction

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Background:
• Quinine, an alkaloid found in the trees of the genus Cinchona, has found historical importance due to its use as an anti-malarial treatment and a tonic water ingredient. The compound cinchonidine comes from the same tree source as quinine and has a pseudo-enantiomer of the name cinchonine.
• Progress in the field of asymmetric synthesis has proven important in the development of pharmaceuticals and other biologically active compounds. By quaternizing the nucleophilic nitrogen of quinine, EJ Corey developed an efficient quinine-based catalyst that found use in the synthesis of amino acids. Successes such as Corey’s sparked an increased interest in the research of quinine-based chiral catalysts for use in asymmetric synthesis. The availability, stability, and synthetic potential of the cinchona alkaloids also contribute to their popularity in the field.

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Purpose:
The goal of our research is to synthesize a novel cinchonidine-based organocatalyst that can improve the catalytic capabilities of cinchonidine in the asymmetric Michael Reaction.

Results:

Synthesis of Modified Cinchonidine Catalyst

1st Step) Synthesis of protected 4-hydroxyphenylacetic acid

Michael Reaction
• The catalyst used in the control Michael reaction consisted of Vitride, a reducing aluminum agent, and cinchonidine bonded as a complex in solution. Optimal catalytic activity was achieved using a 20% catalytic load.
• Multiple enones and malonate combinations were tested using plain cinchonidine as the catalyst in order to maximize yield and %ee.

2nd Step) Esterification of cinchonidine with protected 4-hydroxyphenylacetic acid

In cinchonidine, the hydrogen bonded to the carbonyl carbon is depicted in its H NMR spectrum as a doublet near 5.6 ppm. After the acid is tethered to the cinchonidine, this doublet shifts downward to roughly 6.4 ppm.

3rd Step) Deprotection of final modified cinchonidine catalyst

Final product appeared as a yellow glass. The weight of the final product was roughly 220 mg.

Summary of Results:
• Using the new method of protecting the phenolic hydroxyl group, the synthesis of the specified cinchonidine catalyst proved to be very successful. Although, improvements could be made to optimize yield of some reactions, future researcher students could easily reproduce the synthesis.
• The Michael reaction was run with the cinchonidine catalyst and the procedure was altered to optimize the reaction’s yield and decrease its scale. The reaction was also performed with multiple combinations of reactants to achieve the highest %ee achievable.
• The Michael reaction was then run with the modified cinchonidine catalyst. After analysis, it was determined that our catalyst had achieved an enantiomeric excess of 7% of the opposite enantiomer.

Future Research
• Based on the results from this summer, it would be beneficial to synthesize more of the modified cinchonidine catalyst and run the Michael reaction with a variety of enone and malonate combinations to find the reagents that optimize the %ee.
• Although cinchonidine was used exclusively for my research this summer, future research could focus on the use of other cinchona alkaloids, such as cinchonidine’s pseudo-enantiomer cinchonine, as bases for synthetic modification.
• Initial steps were taken this summer to attach other “tethers” to the cinchonidine base, such as 2-hydroxyphenylacetic acid and 3-hydroxyphenylacetic acid. Further exploration in developing a catalyst with a variant tether may prove beneficial in developing a more effective catalyst.

References: