Addition of Hydrogen Bonding Groups to Peptoid Catalysts to Increase Enantioselectivity

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As the need for new medicines and pharmaceuticals continues to rise, the addition of a fluorine atom to a pharmaceutical compound has become an increasingly popular way to address some of the largest challenges facing the drug development industry, including metabolic stability and bioavailability.[1] About a quarter of pharmaceutical compounds on the market or in clinical trials contain at least one fluorine atom.[2] Trifluoromethyl groups, three fluorines attached to a singular carbon, are especially common additives, as the effects of fluorine are additive.[3] In order to ensure drug safety and effectiveness, the trifluoromethyl group must be added on enantioselectively, which means the group must be in the correct three dimensional manner relative to the other atoms on the molecule. Because this complication of fluorine addition can impede the study and development of new drugs, further research into effective enantioselective trifluoromethylation can help address existing gaps in the pharmaceutical industry.

A common source for enantioselective trifluoromethylation is the Ruppert-Prakash reagent, which requires a catalyst to complete the reaction.[4] Peptoids, biological mimics of peptides, are a promising catalyst for the reaction, as they maintain their secondary structure in the presence of polar solvents and are easily modifiable. A peptoid's ability to perform enantioselective catalysis can be affected by steric and electronic interactions as a result of altering the peptoid side chains. In her 2020 Honors project, Rebecca Londoner proposed that adding side chains with the ability to hydrogen bond could activate the ketone substrate to promote enantioselective trifluoromethylation.[5]

My summer project sought to design a peptoid that had hydrogen bonding capabilities and an effective catalytic site. As the exact mechanism for this type of catalysts is unknown, I began my project by testing a variety of amines and oxidized amines to learn about the role of the catalytic nitrogen. I performed trifluoromethylation reactions with the Ruppert-Prakash reagent, 4-chlorobenzaldehyde substrate, and various catalytic sites, including pyridine, 2-picolyl amine, nicotinic acid, 2-picolinic acid, triethylamine, and triethylamine N-oxide, in dimethylformamide solvent.

I analyzed the trifluoromethylation results using normal-phase high-performance liquid chromatography (HPLC). Results showed that triethylamine and triethylamine N-oxide successfully catalyzed the reaction, with consistently high peak ratios of starting material to product. The ability of triethylamine to catalyze the reaction was a particularly promising result, as this, to our lab's knowledge, has not been reported in previous literature, and similar tertiary amines can easily be added to peptoids.

The next step was to add a tertiary amine on to the end of a peptoid with hydrogen bonding capabilities. I successfully synthesized two peptoids, each with a singular L-alaninamide sidechain, which has hydrogen bonding capabilities, and three S-1-phenylethylamine side chains (Figure 1). Peptoid A has a dimethylamine catalytic site that is expected to behave similar to triethylamine. Peptoid B has a dimethyl-L-phenylalanine catalytic site, which is expected to act in a similar manner to the triethylamine but contains more steric bulk. This may help to stabilize the reaction. Both products were synthesized via solid-phase synthesis, and their identity was confirmed via low resolution liquid chromatography/mass spectrometry.

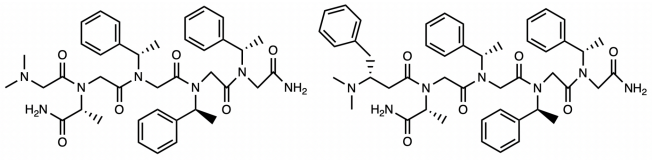

Figure 1. Peptoids A and B were successfully synthesized using solid-phase synthesis.

In future work, I plan to purify both peptoids using reverse-phase HPLC. Once isolated, the peptoids will be tested as catalysts in the trifluoromethylation reaction. The products will be analyzed using normal-phase HPLC to determine enantioselectivity.

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References

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