Addition of a Catalytic Site in Varying Locations in Peptoid Catalysts to Promote Enantioselectivity

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Trifluoromethylation is the process of attaching a trifluoromethyl, or a carbon bonded to three fluorine atoms, to another carbon-containing molecule. The ability to trifluoromethylate efficiently and exactly is becoming an increasingly important task, as a growing number of commercial drugs are incorporating fluorine atoms into their chemical structures. This is because of fluorine's electronegativity, or its ability to attract electrons towards it. If a given molecule contains fluorine–or the three fluorines present in a trifluoromethyl group–the nearby functional groups will be less reactive, thus enhancing the metabolic stability of the molecule. However, to produce drugs containing a trifluoromethyl group in a manner that is economically sustainable, the process of trifluoromethylation must be reliable and fast. One method of trifluoromethylation involves using the Ruppert-Prakash reagent. This reagent utilizes "building block" chemistry, in which elements that are already part of an organic compound are added onto another molecule.[1] In the case of the Ruppert-Prakash reagent, a trifluoromethyl group is transferred from the reagent to a substrate.

When discussing the synthesis of complex molecules, particularly molecules that may be used as pharmaceuticals, it is also important to pay attention to the chirality of such molecules. Compounds that are chiral have one or more elements, most commonly carbon atoms, that form bonds with all unique groups of elements. However, if these groups are arranged in one order, the molecule as a whole may have a different function than if the groups are arranged in another order. Since pharmaceuticals need to complete very specific tasks, it is important to synthesize these products with processes that create only the desired arrangement of groups, or, in other words, processes that are enantioselective. One method of ensuring enantioselective reactions uses chiral catalysts, which is where my project comes into play.

A catalyst is a molecule that accelerates the rate of a reaction without being taken apart by it. Previous work in the Gorske lab has synthesized trifluoromethylation catalysts out of molecules known as peptoids.[2] Peptoids, not to be confused with the peptides that connect to form proteins, have a unique structure that involves an R-group, or a functional group that attaches at a carbon to the rest of the main molecule, bonded to the nitrogen of the peptoid backbone. This differs from the structure of a peptide, in which R-groups attach to another carbon in the backbone. The difference in design allows peptoid backbones to rely on electronic and steric interactions instead of hydrogen bonds that can weaken during trifluoromethylation.

My research focused on investigating how the location of the catalytic site in my catalyst affected the enantioselectivity and yield of trifluoromethylation reactions. I used 2-picolylamine as my catalytic site, which the Gorske lab previously found to be a successful enantioselective catalyst for trifluoromethylation. It is thought that the nitrogen atom on the aromatic ring on the 2-picolylamine attacks the silicon in the Ruppert-Prakash reagent, creating a better leaving group and allowing the trifluoromethyl group to detach from the rest of the reagent. I synthesized four peptoids with the 2-picolylamine residue in different R-group positions, of which there were four. The rest of my R-groups in each of my peptoids consisted of s-1-phenylethylamine residues, as this group has been shown to promote the helical shape that I desired for my peptoids.

To synthesize my peptoids, I first swelled a Rink amide resin in dimethylformamide (DMF). Then, I deprotected the resin in a 20% piperidine solution in DMF. To add each amine group, I first mixed my resin with bromoacetic acid and diisopropylcarbodiimide solutions in DMF. Then, the amine solution in DMF is mixed with the resin as well. I then repeated these last two steps until all four of my amine groups were added. To prevent an unusual truncation of my products, I acetylated my products. To cleave the peptoid from the resin, I used a 95% trifluoroacetic acid (TFA) solution in water. The TFA was then evaporated off of the product using nitrogen gas. I plan to continue this research this upcoming year for my honors project, and my next step will involve confirming the identities of my synthesis products via LC-CMS.

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References

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