Development of a Peptoid Catalyst for the Enantioselective Trifluoromethylation of Ketones

Jonathan Ryss, 2012

The introduction of chiral trifluoromethyl moieties (-CF$_3$) into pharmaceuticals allows unique manipulation of drug properties. The -CF$_3$ group can be used in conjunction with other organic functional groups to precisely adjust electronic and spatial properties of drug molecules. These groups also increase the membrane permeability of drugs, increasing drug bioavailability. They are rare in nature and consequently are resistant to biological degradation. Trifluoromethyl groups are often located at chiral centers, potentially forming one of a pair of isomers known as enantiomers, which are mirror images of each other. Transformations that produce such chiral centers must be controlled to produce an excess of one enantiomer because often only one enantiomer is desired in a target molecule. Asymmetric peptide catalysts, which consist of an achiral catalytic group covalently bonded to a peptide scaffold, have been shown to enantioselectively catalyze transformations. Recently, catalytic groups attached to non-natural scaffolds such as peptoids have also been shown to enantioselectively catalyze reactions. Asymmetric peptoid catalysts are modular and can easily be modified with different catalytic groups, suggesting that they could be useful for a wide range of reactions, including enantioselective trifluoromethylation reactions.

This summer, I developed the synthesis of a peptoid catalyst utilizing an amine N-oxide catalytic group to catalyze the enantioselective trifluoromethylation of ketones (Fig. 1). This catalytic group activates the Ruppert-Prakash Reagent, the source of -CF$_3$, for nucleophilic addition to a substrate ketone, producing a chiral center with attached -CF$_3$ and alcohol (-OH) groups. A monomeric catalyst containing just one peptoid side chain was selected as the first target catalyst in order to probe the minimum structural complexity required for enantioselectivity. This monomer approach is advantageous because it utilizes solution phase chemistry, which can be done on a larger scale than traditional peptoid solid-phase techniques. A larger scale synthesis produces larger amounts of the catalyst, making it easier to optimize the reaction conditions.

![Figure 1](image)

**Figure 1:** Overall reaction scheme of enantioselective trifluoromethylation. The trifluoromethyl group is added to the carbonyl group of the substrate ketone, producing a chiral trifluoromethylated alcohol. One enantiomer of product is produced in excess of the other, preferably with > 99% enantiomeric excess.

Using organic synthesis methods obtained from literature sources, a total synthesis of a peptoid monomer catalyst from an amine starting material was developed and carried out. The chiral scaffold of the catalyst was successfully synthesized and only the final reaction step producing the active catalytic
group remains to be completed in the construction of the target monomer catalyst. Future work entails the completion of this monomeric catalyst, the optimization of reaction conditions to increase yields, and the testing of catalyst performance in enantioselective trifluoromethylation reactions. Larger peptoids will then be synthesized as needed until an optimal catalyst is obtained. Such a catalyst would facilitate the synthesis of biologically active compounds and pharmaceuticals.

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