Reductive Functionalization of Carbonyl Group in Fluoroalkyl Amides

M. Sc. Eng. Paweł Czerwiński
supervisor: prof. dr hab. Bartłomiej Furman

This dissertation is devoted to the development of a method for the reduction of fluoroalkyl amides to the corresponding imines and their further use in nucleophilic functionalization reactions. This type of reductive amide functionalization has not previously been used to synthesize of fluorinated molecules. These, in turn, are often difficult or impossible to obtain due to the limited availability of highly reactive fluoroalkyl aldehydes or their surrogates. To overcome this problem, I used zirconocene chloride hydride, $Cp_2Zr(H)Cl$ (Schwartz's reagent), which was the only one among the partial amide reduction methods that allowed a chemoselective reduction reaction of the amide to an imine and a subsequent addition leading to a functionalized amine. The reduction/addition sequence proceeds without the separation of transition compounds, making the developed process highly useful.

I applied the developed method to the synthesis of various fluorinated amines and determined the scope of the protocol for a variety of secondary fluoroalkyl amides with synthetically relevant functional groups in their structure, as well as another class of nucleophiles. The protocol was applied to the synthesis of bioisosteres of two commercially available drugs.

My interest in alternative reaction methods led me to develop a mechanochemical variant of the reaction. After detailed optimization, the process, in which the Schwartz's reagent is generated in situ from stable precursors, allowed the synthesis of fluoroalkyl amines with virtually no solvent. Additionally, I have developed a solvent-minimizing method for purifying products with acidic ion exchange resin, which made the process more sustainable and environmentally friendly.

The final step in this work was the application of amides as sources of fluoroalkyl motifs. In previous study, I obtained a molecule resulting from the formal addition of a nucleophile to a trifluoroacetaldehyde as a by-product. By optimizing the reaction to this product, I have shown that tertiary amides can act as fluoroalkyl aldehydes surrogate. I obtained a series of symmetrical as well as unsymmetrical bis(heteroaryl)methanes using the developed method, and the utility of the method was confirmed by the synthesis of a multifluorinated porphyrin building block and a fluoroalkylated BODIPY dye.