Abstract

Reductive amination and its stepwise variant stands as a cornerstone in the synthesis of amines, crucial molecules in both natural and synthetic chemistry, especially in pharmaceutical industry. Trichlorosilane-mediated reductive amination emerges as a particularly attractive method, offering simplicity, efficacy, and versatility across various functional groups. This thesis explores the application and enhancement of this method, aiming to expand its utility, particularly focusing on the synthesis of cholesterol-lowering compounds exemplified by Ezetimibe.

The research begins with an investigation into the stability of diverse functional groups under $HSiCl_3$-mediated reductive amination conditions with dimethylformamide as a catalyst, establishing a fundamental understanding of the reaction scope. Among the stable functional groups identified is the pentafluorosulfanyl (SF_5) moiety, known for its distinct properties and potential in medicinal chemistry. The investigation delves into the applicability of this method to aldehydes and prochiral ketones, demonstrating its versatility.

Building upon this groundwork, the study progresses towards the development and application of an asymmetric version of reductive amination, targeting Ezetimibe and its analogues. The synthetic pathway involves the catalytic use of previously synthesized in our group chiral catalyst Kenamide in conjunction with trichlorosilane, offering advantages over traditional methodologies in terms of chemoselectivity and scalability.

Moreover, the thesis examines the strategic incorporation of polyfluorinated substituents, such as the SF_5 group, known for its beneficial properties in enhancing chemical and metabolic stability. By exploring compounds featuring the SF_5 and CF_3 groups, the study aims at optimization of synthetic routes not only to Ezetimibe, but also its analogues, potentially improving pharmacokinetic profiles. Preliminary biological evaluations of the synthesized derivatives provide insights into their potential pharmacological efficacy, paving the way for further exploration in drug development.

Overall, this thesis contributes to the advancement of synthetic methodologies in pharmaceutical chemistry, with implications extending to the broader scale of organic synthesis and drug discovery.