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„New asymmetric methods for the synthesis of biologically important heterocyclic compounds"

Design of new reaction pathways leading to the desired structural motifs constitutes an important task in modern organic chemistry. Particularly challenging is the development of enantioselective strategies using chiral catalysts and resulting in optically active products. Asymmetric organocatalysis is a useful tool in the stereocontrolled organic synthesis and constitutes a convenient method for the introduction of chirality into target molecules. Among available methods of catalytic activation of substrates, aminocatalytic strategies are of great importance, with a considerable part of this dissertation being devoted to this problem. In this PhD thesis, new asymmetric methods for the synthesis of heterocyclic compounds with known or potential biological activity are presented.

The first part of the study deals with the development of an enantioselective method for the synthesis of benzo[1,5]oxazocine derivatives. The elaborated "one-pot" reaction cascade offers a facile and stereoselective entry to target products. The designed synthetic strategy is realized under dienamine activation and includes a condensation reaction of the corresponding aniline with salicylaldehyde, the subsequent hetero-Diels-Alder [4+2]-cycloaddition between imine and dienamine, elimination of the catalyst, terminated with an intramolecular oxy-Michael addition.

The next part of the thesis is focused on the use of 4-substituted-oxazol-5(4*H*)-one derivatives, which are important precursors of α,α-disubstituted α-amino acids. The conditions for the Michael addition of 4-substituted-oxazol-5(4*H*)-one to tetraethyl methylenebisphosphonate have been elaborated. In order to obtain optically active products, cinchona alkaloid derivatives were used as chiral catalysts. The opening of the oxazol-5(4*H*)-one ring under acidic conditions constitutes a facile route to α,α-disubstituted α-amino acids containing a geminal bisphosphonate moiety.

Employing the aminocatalytic strategies, the task of spirocyclic furan-2(3*H*)-ones synthesis based on trienamine activation has been undertaken. The trienamine intermediate (formed *in situ* from the $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde and aminocatalyst) plays an important role in the catalytic cycle reacting with 3-alkylidenofuran-2(3*H*)-one to yield target products.

In this work the synthesis of spirocyclic tetrahydrothiophene derivatives containing furan-2(3*H*)-one or oxazol-5(4*H*)-one ring has been also presented. The developed synthetic pathway utilizes a cascade reaction that includes thia-Michael addition of 2-mercaptoacetaldehyde (generated *in situ* from 1,4-dithiane-2,5-diol) to alkylidene derivatives of furan-2(3*H*)-one or oxazole-5(4*H*)-one and the subsequent intramolecular aldol reaction. The synthesis has been carried out with the chiral Brønsted base resulting in the expected products. Best results were obtained using dimeric dihydroquinine derivative as catalyst.

Further research on the development of asymmetric strategies for the synthesis of biologically relevant compounds has been focused on the development of method for the synthesis of 3,4-dihydrocoumarin derivatives bearing α,α-disubstituted α-amino acid moiety. The elaborated project is based on the cascade reaction between 4-substituted-oxazol-5(4*H*)-ones and 2-hydroxychalcones. It is initiated by a chiral Brønsted base-catalyzed Michael reaction followed by the 4-substituted-oxazol-5(4*H*)-ones ring opening to construct 3,4-dihydrocoumarin framework. The stereochemistry of the reaction was controlled by a bifunctional squaramide catalyst derived from cinchona alkaloids.

The last part of the study has been devoted to the development of enantioselective methods for the synthesis of dihydro-2*H*-thiopyran derivatives. The synthesis of 3,4-dihydro-2*H*-thiopyrans derivatives is based on the dienamine activation. The corresponding dienamine is formed by the condensation of α,β-unsaturated aldehyde with an aminocatalyst and subsequent deprotonation of γ-position and isomerization. It participates in the inverse-electron-demand hetero-Diels–Alder reaction (IEDHDA) with thiochalcones used as heterodienes. In such a way, a series of products with high regio-, diastereo- and enantioselectivity have been obtained. 3,6-Dihydro-2*H*-thiopyrans derivatives have been also successfully synthesized using trienamine activation strategy. The trienamine intermediate (generated *in situ* from 2,4-dienal reaction and aminocatalyst) reacts in the thia-Diels-Alder reaction with thioketones, which have been used as heterodienophiles in asymmetric synthesis for the first time.

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