PREFACE

Organocatalysis has emerged as a powerful synthetic paradigm that is complementary to metal-catalyzed transformations and has accelerated the development of new methods to make diverse chiral molecules. In recent years, organocatalytic cascade, multi-component and multi-catalysis cascade (MCR/MCC) reactions have been utilized for the synthesis of complex enantiomerically enriched molecules having multiple stereocenters. In comparison to traditional stepwise approaches, the uninterrupted sequence of reactions in one flask reduces the number of manual operations, thereby saving time, effort and production costs. The present thesis entitled “High-yielding Stereoselective Synthesis of Bioactive Molecules through TCRA and Barbas Dienamine Platform” describes the synthesis of highly functionalized chiral molecules of Pharmaceutical and biological importance using multi-catalysis cascade (MCC) reactions. In all sections, a brief introduction is provided to keep the present work in proper perspective, the compounds are sequentially numbered (bold), and references are marked sequentially as superscript and listed at the end of the thesis. All the figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA, and in some of them uninformative areas have been cut to save the space.

Highly functionalized heterocycles such as chromenes, chromenones and xanthenones have found wide applications as pharmaceutical drugs, drug intermediates and drug ingredients. To construct such complex molecules a diversity-oriented green synthesis is required. Here we achieved using simple starting materials such as 1,3-diones, salicylic aldehydes, Hantzsch ester and diazomethane through cascade three-component reductive alkylation (TCRA) and three-component reductive alkylation/oxy-Michael/dehydration (TCRA/OM/DH) and three-component reductive alkylation/alkylation/oxy-Michael/dehydration (TCRA/A/OM/DH) reaction sequences in one-pot under stereospecific organo- and organo/Brønsted acid- and self/base-catalysis.
In continuation to the development of TCRA platform, synthesis of highly functionalized chiral building blocks achieved via three component reductive alkylation (TCRA) as an important step. Here, we developed the one-step alkylation of CH-acids with chiral aldehydes and Hantzsch ester through organocatalytic TCRA strategy. In continuation, using combination of L-proline/Brønsted acid-catalyzed cascade three-component reductive alkylation/lactonization/esterification and three-component reductive alkylation/esterification reactions of CH-acids, chiral aldehydes, Hantzsch ester constructed the highly functionalized chiral γ-butyrolactones and protected γ-carboxy-L/D-glutamic acids in good to high yields. This TCRA strategy provided access to HIV-1 protease inhibitors, phospholipase A₂ inhibitors, antibiotic agglomerins, (R)-γ-hexanolide and (+)-brefeldin-A.

In the third chapter we carried out the synthesis of highly functionalized molecules through Barbas dienamine platform. Here we developed the facile synthesis of highly functionalized cyclohexanes via proline catalyzed cascade annulations from simple substrates such as aldehydes, enones and CH-acids through olefination/Diels-Alder/epimerization and olefination/Diels-Alder/epimerization/three-component reductive alkylation reaction sequence. In this reaction we observed the novel epimerization at β-position to carbonyl of the trans-isomer to the more stable cis-isomer.

In continuation to the synthesis of bioactive molecules through Barbas dienamine platform, herein we report the amino acid-catalyzed diastereospecific three-component Diels-Alder (DTCDA) reactions that produce highly functionalized chiral spiro[5,5]undecane-1,5,9-triones from commercially available 4-substituted-3-buten-2-ones, protected glyceraldehydes and CH-acids through modern dienamine chemistry. Functionalized chiral spiro[5,5]undecane-1,5,9-triones are biologically active compounds and also attractive intermediates in the total synthesis of natural products.