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"To immigrants and exiles everywhere,

the uprooted,

the re-rooted,

the rootless,

And to the trees we left behind,

rooted in our memories ..."

— **Elif Shafak**, *The Island of Missing Trees*

Contents

Aim and Outline

Chemocatalysis is a process that involves the use of chemical catalysts (e.g. metal catalysts or organocatalysts) to facilitate chemical reactions. When an enzyme is used for the acceleration of the chemical reaction, instead of a chemical catalyst, the process is referred to as biocatalysis. Biocatalytic systems have inherent properties that offer several advantages over traditional chemocatalysts. These advantages include the ability to perform reactions under ambient conditions and the use of environmentally friendlier water as a solvent. Moreover, biocatalysts can provide precise control over chemo-, enantio-, and regioselectivity, which can be particularly useful in addressing difficult chemical transformations.[1] Enzymes and their engineered variants, therefore, offer superior or at least comparable performance to chemical alternatives in many instances. Furthermore, the relatively mild operating conditions of biocatalytic reactions, the safe disposal of the biodegradable enzyme and renewability make biocatalysis ideal for the much needed transition into a sustainable future.[2-4] In the context of sustainable chemical synthesis, light-assisted methods that employ enzymes as a critical component for important synthetic transformations have also gathered significant attention.[5]

The utilization of light-induced (photocatalytic) radical reactions has been extensively studied in organic synthesis.[6] Nevertheless, the implementation of enzymatic systems that harness the potential of such powerful mechanisms remains relatively scarce.[7] The integration of light-driven and photocatalyst-assisted radical reactions within the active site of enzymes confers several advantages over conventional methods due to the characteristic nature of the biocatalytic systems. For example, water-compatible substrates that are not suitable for use in traditional catalysis in organic solvents but are unique to the biocatalytic realm may be used for discovering completely new reactivity. The complex protein environment may also result in novel reactivities not seen in small-molecule catalysts. Other benefits include the improved handling of enzymes and the possibility of enzyme evolution for tailoring the photoenzymatic systems, including the enhancement of activity, selectivity and photostability.[8]

The work described in this thesis aimed to develop novel chemoenzymatic and photobiocatalytic methodologies for the synthesis of nitrogen-containing pharmaceutical building blocks and chiral alcohols. Retrosynthetic analysis, substrate design, and enzymatic and photobiocatalytic reaction optimization were used to achieve the asymmetric synthesis of *N*-containing heterocycles and non-canonical amino-acids, as well as selective reductions for the synthesis of various chiral alcohols and aliphatic amines and amino-, azoxy- and azo-aromatics.

Chapter 1 gives a brief overview of the functional, structural and mechanistic properties of ethylenediamine-*N,N′*-disuccinic acid (EDDS) lyase and nitroreductases, which were applied as biocatalysts in the synthetic applications described in this thesis.

In **Chapter 2**, we describe an efficient chemoenzymatic method for the asymmetric synthesis of *N*-containing heterocyles: dihydrobenzoxazinones (DHBs) and dihydroquinoxalinones (DHQs). These valuable scaffolds are widely used for the production of pharmaceuticals, herbicides and fungicides. The use of EDDS lyase for the key chemo- and stereoselective carbon-nitrogen bond-forming step highlights the importance of biocatalytic systems as effective tools for the step-economic synthesis of complex molecules.

In **Chapter 3**, we report the use of EDDS lyase for the multigram-scale synthesis of Toxin A, an important chiral precursor for the synthesis of Aspergillomarasmine A, Aspergillomarasmine B, and Lycomarasmine, which are inhibitors of the bacterial metallo-beta-lactamase NDM-1. In addition, we developed new chemoenzymatic routes for the synthesis of various Toxin A derivatives, including a photocaged Aspergillomarasmine B, with moderate to good overall yields (23-66%).

Chapter 4 describes the use of the nitroreductase BaNTR1, assisted by the photocatalyst $[Ru(bpy)_3]Cl_2$ and blue light irradiation, for the asymmetric reduction of substituted aryl ketones to give chiral alcohols with high conversions (up to >99%) and high enantiopurity (up to >99:1 enantiomeric ratio). Notably, this photobiocatalytic system allowed for the chemoselective reduction of various α,ß-unsaturated ketones to give the desired enantioenriched alcohols without reducing the C=C or C≡C bond.

In **Chapter 5**, we report the tailoring of two photobiocatalytic systems, based on the nitroreductases BaNTR1 and EcNR and chlorophyll as photocatalyst, for the selective synthesis of aliphatic amines and amino-, azoxy- and azo-aromatics from the corresponding nitro compounds with high conversions (up to 99%) and excellent yield (up to 97%).

Finally, in **Chapter 6**, we summarize the results presented in this thesis and suggest some perspectives for future research.