PhD Thesis: "**Chiral organocatalysts mediated asymmetric oxyfunctionalization and tandem reactions**"

Sara Meninno

Dipartimento di Chimica e Biologia, Università degli Studi di Salerno, Via Giovanni Paolo II, 132, 84084, Fisciano (SA)

smeninno@unisa.it

Abstract

Asymmetric organocatalysis is a new rapidly growing field whose huge potential is becoming more and more evident.[1] This PhD project has been conceived and developed in the context of non-covalent organocatalysis.

The aim of this work has been to design, plan and develop new organocatalytic methodologies for the synthesis of optically active, densely functionalized, organic molecules whose functional groups are susceptible to further manipulation. The target molecules represent important motifs present in many biologically active natural and non-natural substances.

The catalysts used are small chiral organic molecules, in particular the attention has been focused on bifunctional organocatalysts. The main features of the catalysts are their non-toxicity, stability to air and moisture and the ability to work under mild conditions that make them convenient tools in organic chemistry. These promoters are able to synergistically activate both the electrophile and the nucleophile through multiple hydrogen-bonding interactions provided by their acid and basic groups with the reactive groups of the reagents.[2] The best-performing chiral scaffold of the bifunctional organocatalysts, employed in the methodologies herein developed, has been selected screening the activity of previously reported promoters such as ureas, thioureas, squaramides, amino alcohols. However, the design and synthesis of new optically pure bifunctional organocatalysts, modifying the chiral backbone and by tuning their stereoelectronic features, has been one of the objectives of this doctoral project. The stereoselective construction of a quaternary stereocentre, especially when it is an all-carbon quaternary stereocentre, is one of the most difficult goals in organic synthesis due to the steric congestion imposed by the four attached substituents.[3] In this project, the synthesis of challenging molecules, bearing quaternary stereocentres in their structure, has been accomplished.

The methodologies developed aimed to the stereocontrolled construction of carbon-carbon and carbon-heteroatom bonds to give access to new and important cyclic compounds of different nature and size (such as epoxides, tetrahydrothiophenes, γ-butyrolactones) and non-cyclic compounds, such as α-hydroxy β-ketoamides (Figure 1).

In order to access the cyclic compounds, the one-pot tandem organocatalytic methodologies developed, such as Michael/Michael, aldol/lactonization, allowed us to obtain the densely functionalized molecules with a minimum number of synthetic operations. Unquestionably, these

processes are becoming of considerable synthetic interest in terms of sustainability and advantageous in terms of time, costs saving issues and minimal manual operations.[4]

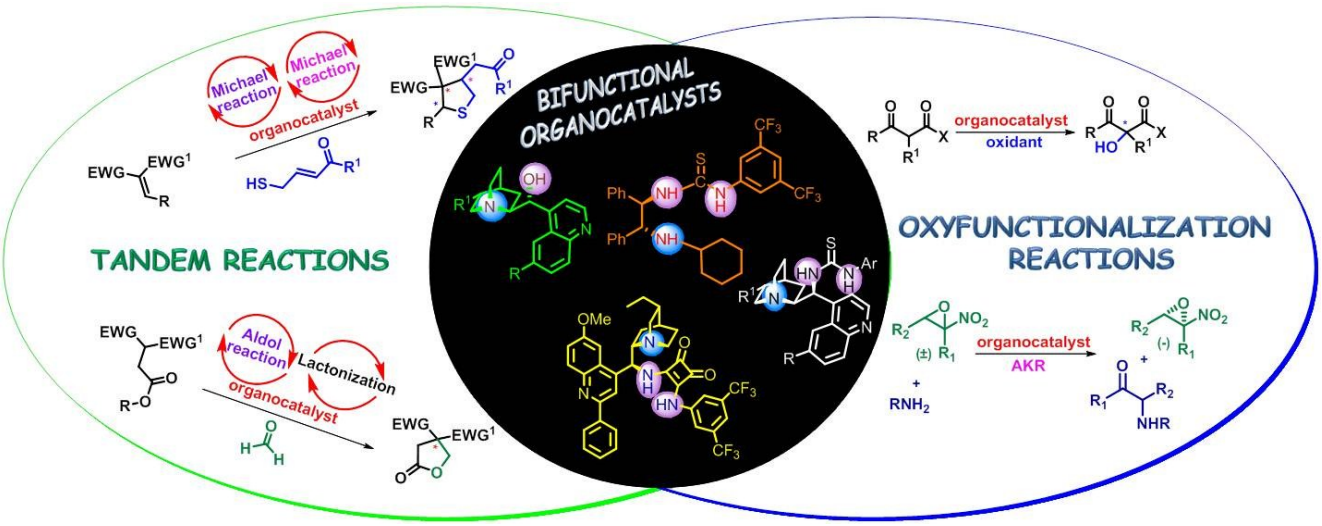

Figure 1. Goals of the PhD project: development of new asymmetric oxyfunctionalization and tandem reactions promoted by bifunctional organocatalysts.

In this doctoral work, the first stereoselective cascade sulfa-Michael/Michael reaction for the synthesis of tetrahydrothiophenes from *trans*-α-carbonyl-β-substituted acrylonitriles has been developed, by using a novel readily available secondary amine thiourea. Highly functionalized tetrahydrothiophenes, bearing three contiguous stereocentres, one of them quaternary, were formed by means of a highly stereoselective cascade transformation. This work represents an unprecedented case in which the stereochemical outcome of an asymmetric synthesis of tetrahydrothiophenes has been controlled exclusively by a dinamic kinetic resolution process.[5]

The first straighforward approach to enantioenriched β,β-disubstituted γ-butyrolactones has been achieved through a cascade aldol/lactonization process. [6] From simple starting materials and working under mild reaction conditions, highly challenging γ-butyrolactones, bearing an all-carbon quaternary stereocentre at the remote β-position were obtained. Remarkably, this work represents the first example of an enantioselective hydroxymethylation reaction of 2-substituted-1,3-dicarbonyl compounds catalyzed by an organocatalyst.

Moreover, we demonstrated that these products can be elaborated to prepare valuable hydroxy γ-butyrolactones, bearing contiguous tertiary and quaternary stereocentres, so far inaccessible via alternative methods.

Another important goal of this project concerned the development of a first approach to enantiomerically enriched aromatic α-nitroepoxides. [7] An aminolytic kinetic resolution of racemic aromatic α-nitroepoxides with aniline, catalyzed by an easily accessible cinchona alkaloid-derived thiourea, was devised as a successful strategy. The first demonstration of synthetic utility of the chiral

epoxides obtained has been reported: they have been transformed into highly valuable *anti*-1,2-amino alcohols through an one-pot stereoselective ring-opening reaction followed by reduction.

Finally, the first enantioselective α-hydroxylation reaction of α-substituted β-ketoamides, organocatalyzed by a commercially available HQN/TBHP system, has been realized in this PhD project. This protocol enables a facile access to functionalized tertiary alcohols bearing a tetrasubstituted stereocentre, substituted with both ketone and amido groups, amenable to chemoselective manipulation.[8]

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