## Cascade Reactions with a Twist

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2016

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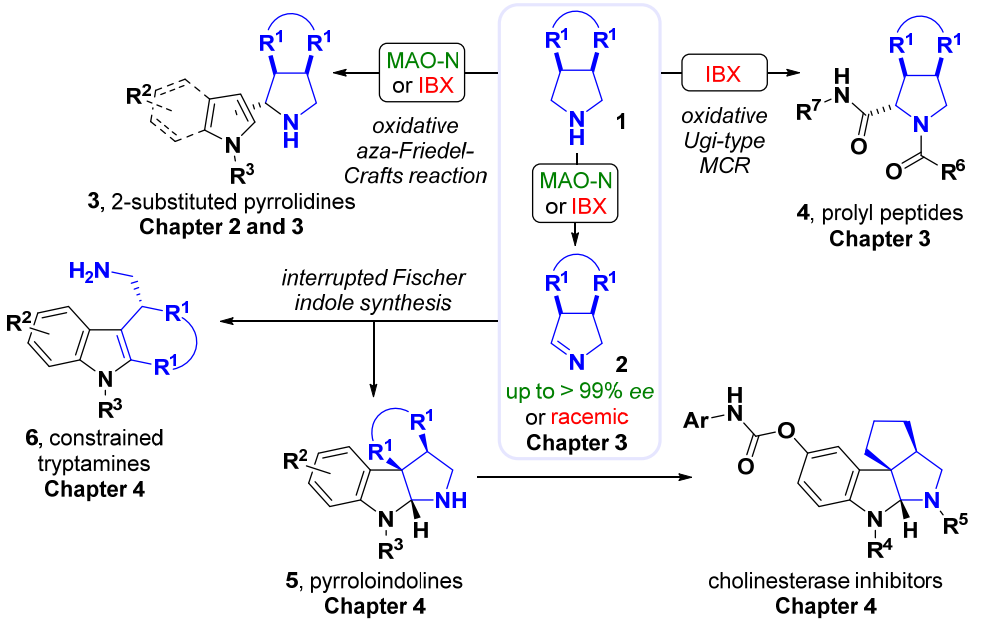
# Summary

## Cascade Reactions with a Twist

Chemoenzymatic Synthesis of Biologically Relevant Heterocycles

The synthesis of complex biologically relevant molecules is often achieved with lengthy linear syntheses. In this respect, the development of more sophisticated and efficient synthetic methods is a continuing challenge. The use of convergent strategies starting from small building blocks presents the opportunity to build novel analogs with several diversification points. Furthermore, the number of synthetic steps and the related waste production and energy consumption can be reduced by combining several chemical transformations in one pot. Important tools to achieve these goals are cascade and multicomponent reactions. Cascade reactions are defined as sequenced conversions using the product of one transformation as the substrate for the next and so on. The consecutive series of intra- or intermolecular steps of these domino reactions proceeds through highly reactive intermediates until a stable product is reached. Multicomponent reactions involve the well-defined condensation of more than two reactants to form a product that contains significant portions of all reactants, ideally all atoms.

The asymmetry in the synthesis of bioactive compounds is often introduced under the influence of organocatalysts and heavy metals, but the application of Nature as a chiral template can be an elegant alternative. This approach may involve the use of compounds that are represented in the chiral pool. Another widely applicable



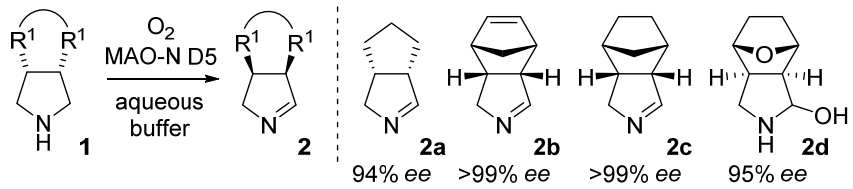

**Scheme 1.** *meso*-Pyrrolidines as templates for oxidative cascade processes.

strategy uses enzymes, the asymmetric catalysts from Nature, which offer unrivaled chemo-, regio- and stereoselectivity. The key objective of the research in this thesis is the development of novel and efficient methods for the synthesis of pharmaceutically and biologically interesting compounds. In particular, the application of **biocatalysis** for the synthesis of substrates for novel **cascade reactions** was envisioned. For an overview of the diversity of scaffolds that were synthesized with novel methods during the research for this thesis, see Scheme 1.

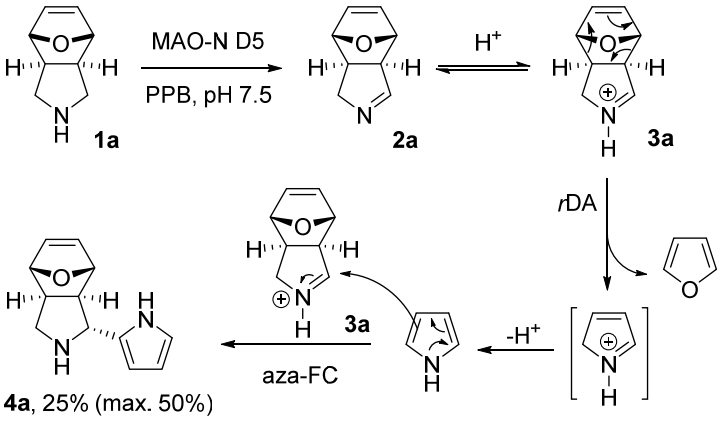
The high potential for the application of biocatalysts in organic synthesis has been clearly demonstrated in the past decades, but enzymes are still not fully integrated in the synthetic toolbox yet. We provided a guideline on how to implement biocatalysis in synthetic chemistry in **Chapter 1**. For this purpose, the most important biocatalytic strategies are summarized for the biocatalysts with the highest potential to be applied. The fruitful union of biocatalysis and organic synthesis is illustrated with some relevant highlights from the literature. Herewith, we hope to inspire the reader to think out of the box and consider biocatalysis as a reliable tool in asymmetric synthetic transformations.

Previously, we described the oxidation of *meso*-pyrrolidines with an engineered variant of monoamine oxidase (MAO-N D5) to give the corresponding bicyclic imines in high to excellent enantioselectivity (Scheme 2). Since only carbocycle-fused pyrrolidines were shown to be suitable substrates for the biocatalyst, we investigated the incorporation of an additional heteroatom in het substrate skeleton. Attractively, a *meso*-pyrrolidine derived from furan was suitable for the biocatalytic oxidation, giving stable hemiaminal **2d** in 95% *ee* and 81% yield (**Chapter 2**).

From the overview in **Chapter 1**, we noticed that the one-pot combination of enzymatic activation with synthetic transformation in benign media receives particular interest. Intriguingly, we discovered that subjecting the furan-derived *meso*-pyrrolidine **1a** to the biocatalyst in aqueous buffer results in a domino sequence

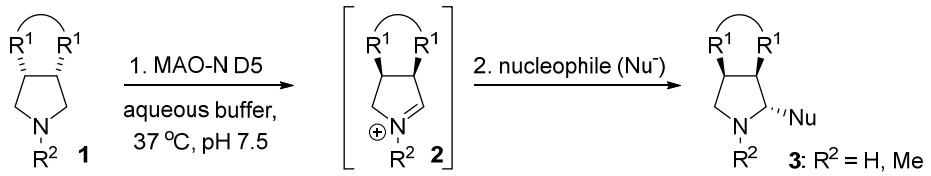



**Scheme 2.** Biocatalytic oxidation of a range of *meso*-pyrrolidines.



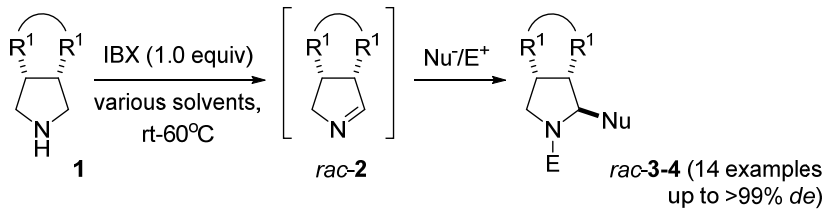

**Scheme 3.** MAO-*r*DA-aza-FC sequence. PPB = potassium phoshate buffer

of biocatalytic oxidation followed by a *retro*-Diels–Alder reaction and an aza-Friedel–Crafts addition (MAO-*r*DA-aza-FC, Scheme 3). Apparently, the aqueous buffer is a sufficiently good proton donor and/or hydrogen bond acceptor to activate the intermediate imine (**2a**) for an aza-FC reaction (and a *r*DA), while activation of this species with a strong Lewis or Brønsted acid is required in organic solvents. We opted to circumvent the *r*DA side reaction of the intermediate imine by employing *meso*-pyrrolidines that are unable to undergo this reaction. With an optimized two-stage one-pot procedure, the α-functionalization of a broad range of pyrrolidines with a variety of aromatic C-nucleophiles was achieved under benign conditions (Scheme 4, **Chapter 2**). The desired 2-substituted pyrrolidines were obtained in reasonable to good yield as single diastereoisomers and generally with high enantioselectivity. As for most synthetic methods, this strategy has some limitations *i.e.* low enantioselectivity for tertiary amines ($R^2$ = Me) and restriction to the substrate scope of the biocatalyst. However, our chemoenzymatic oxidative aza-FC reaction has clear advantages, since it is significantly more benign than many other direct α-functionalizations of pyrrolidines.




**Scheme 4.** Chemoenzymatic oxidative aza-Friedel-Crafts reaction.

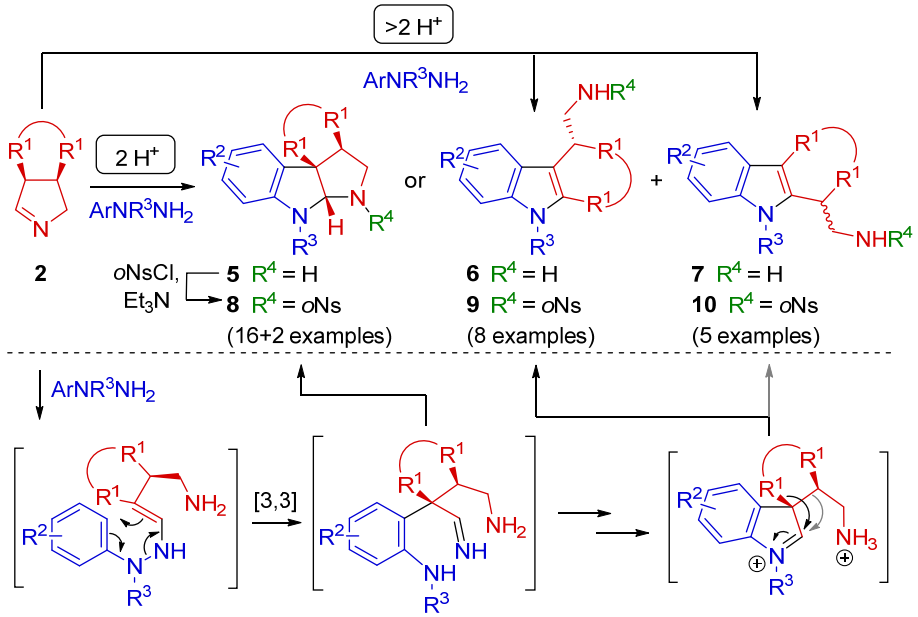
In light of our continued interest in the functionalization of imines, in particular 1-pyrrolines, we envisioned a clean and fast chemical oxidation of unactivated *meso*-pyrrolidines. Given the recent regained interest in hypervalent iodine reagents, we explored their ability to oxidize aliphatic amines. Gratifyingly, we developed the first *o*-iodoxybenzoic acid (IBX) mediated oxidation of unactivated amines (Scheme 5, **Chapter 3**). This convenient method gives access to bi- and tricyclic imines *rac*-**2**, but is limited to 1-pyrrolines that do not tautomerize under the reaction conditions. The chemical space was further explored with one-pot oxidative Ugi-type and aza-Friedel–Crafts reactions, which proved to be highly diastereoselective.




**Scheme 5.** Oxidative α-functionalizaton of *meso*-pyrrolidines **1** with IBX.

In order to develop novel methods for the synthesis of complex molecules, we explored the utility of our biocatalytically generated chiral building blocks **2** in cascade reactions by considering them as amino aldehyde synthons. We developed an asymmetric chemoenzymatic synthesis of natural product-like pyrroloindolines **5** with *cis*-junction of both [3.3.0] bicyclic systems using an interrupted Fischer indole synthesis between arylhydrazines and bicyclic imines (Scheme 6, **Chapter 4**). A wide range of electron-rich as well as electron-deficient arylhydrazines were suitable substrates for this reaction, showing an interesting trend in regioselectivity for *meta*-substituted arylhydrazines depending on the steric size of the substituent.

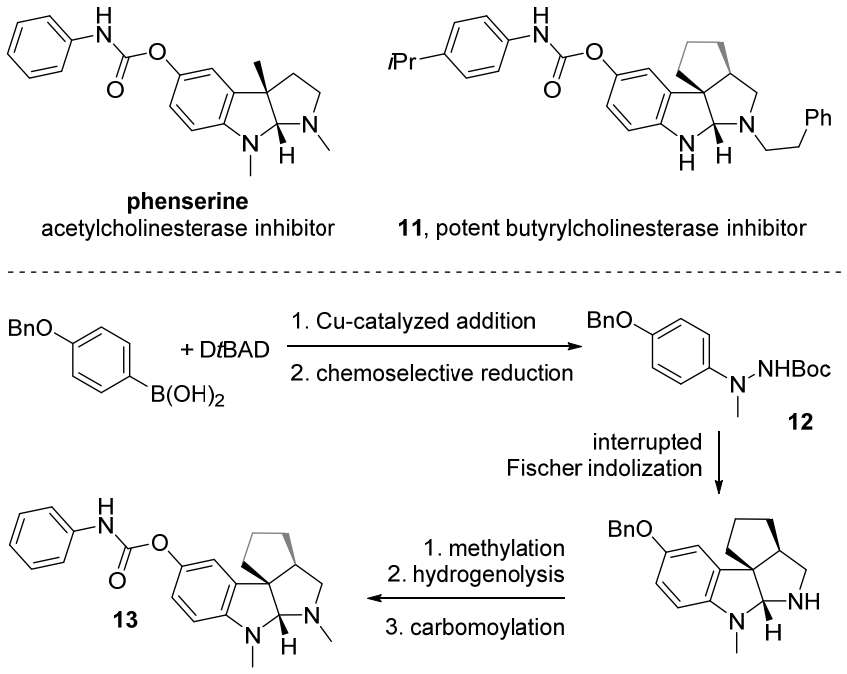
We serendipitously discovered that a subtle change in the reaction conditions of the interrupted Fischer indole synthesis in terms of stoichiometry of the acid mediator resulted in a rearrangement of the polycyclic scaffold to afford constrained tryptamine derivatives **6** and **7** selectively (Scheme 6, **Chapter 4**). This rearrangement proved quite general, as demonstrated for relatively electron-rich as well as electron-deficient systems and even heterocyclic compounds.




**Scheme 6.** Interrupted Fischer indole synthesis towards either pyrroloindolines or constrained tryptamines and key intermediates of the proposed mechanism.

For the rearrangement, interesting results in terms of regioselectivity of the migrating C-C bond were observed that were reasonably explained by electronic factors. A plausible mechanistic pathway for the formation of the pyrroloindolines and constrained tryptamines was also provided, but a thorough computational study is required to provide a better understanding of the influence of steric factors. This acid-switchable chemoenzymatic synthesis of either pyrroloindolines or serotonin analogs underlines the fruitful union of biocatalysis with cascade reactions even further.

As a result of the high therapeutic potential of phenserine and norcymserine—which exhibit a pyrroloindoline core—for Alzheimer's disease and other neurodegenerative diseases, we set out to synthesize analogs of these important lead compounds. We employed an $N_\alpha$-methylated hydrazine for the cascade reaction towards phenserine analog **13** (Scheme 7), which was synthesized *via* a novel chemoselective Boc-reduction. After the interrupted Fischer indolization between (–)-**2a** and $N_\alpha$-methylated hydrazine **12**, compound **13** was obtained by *N*-methylation, hydrogenolysis and carbamoylation.




**Scheme 7.** Cholinesterase inhibitors phenserine and phenethylnorcymserine analog **11** as well as our strategy for the synthesis of phenserine analog **13**.

As certain constrained tryptamines act on the 5-$HT_6$ receptor, an important target for novel therapeutics in the treatment of Alzheimer's disease, this compound class has several conceivable therapeutic applications. Furthermore, potent and selective inhibitors of melatonin receptors as well as the TRPV1 ion channel with the same core structure have been reported. We synthesized an antagonist of the 5-$HT_6$ receptor

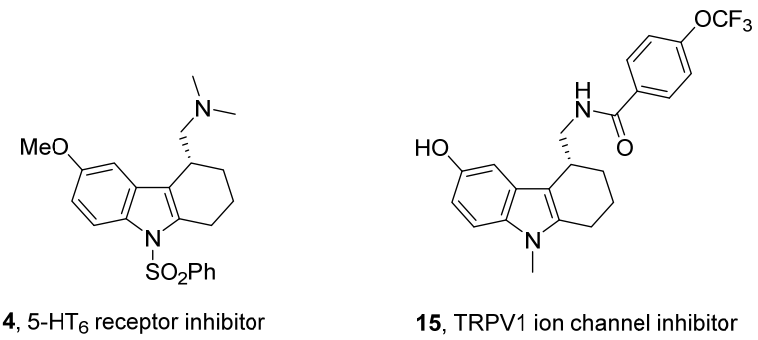



**Figure 1.** Examples of pharmaceutically relevant constrained tryptamines.

(**14**), known as the constrained analog of MS-245, by a convenient three-step synthesis based on the interrupted Fischer indole synthesis. Also, TRPV1 ion channel inhibitor **15** could be synthesized using our novel methodology. These bioactive compounds are easily accessible with our strategy in either optically pure or racemic form by employing a bicyclic imine synthesized by either biocatalytic (**Chapter 2**) or IBX-mediated oxidation (**Chapter 3**).

Future efforts will focus on investigation of the biological activity of new analogs such as **13** to identify lead compounds in drug discovery. Since both the pyrroloindolines **5** and constrained tryptamines **7** and **8** have several diversification points (see Scheme 6), a range of compounds with high therapeutic potential can be generated using our strategy.