Cascade Reactions with a Twist

Chemoenzymatic Synthesis of Biologically Relevant Heterocycles

Corien de Graaff

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Chemoenzymatic Synthesis of Biologically Relevant Heterocycles

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door
Corien de Graaff
geboren te Alkmaar

promotor: prof.dr.ir. R.V.A. Orru

copromotor: dr. E. Ruijter

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List of Abbreviations

n-D	n-dimensional (n = 1–3)
n-CR	n-component reaction (n = 1–4)
AADH	amino acid dehydrogenase
AAO	amino acid oxidase
Ac	acetate
AD	Alzheimer's disease
ADH	alanine dehydrogenase
aq.	aqueous
Ar	aryl
ATA	amine transaminase
aza-FC	*aza*-Friedel-Crafts
BBE	berberine bridge enzyme
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad (IR)
BVMO	Baeyer–Villiger monooxygenase
*c*Hex	cyclohexyl
CHMO	cyclohexanone monooxygenase
COSY	correlation spectroscopy
CPMO	cyclopentanone monooxygenase
d	doublet (NMR)
DCE	1,2-dichloroethane
de	diastereomeric excess
DHPM	3,4-dihydropyridimidin-2(1*H*)-one
DKR	dynamic kinetic resolution
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DYKAT	dynamic kinetic asymmetric transformation
e.g.	*exempli gratia* (for example)
EC	Enzyme Commission
ee	enantiomeric excess
EKR	enzymatic kinetic resolution
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
et al.	*et alii* (and others)
FAD	flavin adenine dinucleotide
FDH	formate dehydrogenase
FMN	flavin mononucleotide
G6PDH	glucose-6-phosphate dehydrogenase
GDH	glucose dehydrogenase
h	hour
HAPMO	4-hydroxyacetophenone monooxygenase
HCV	hepatitis C virus
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

HMBC	heteronuclear multiple-bond correlation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
HT	hydroxytryptamine
Hz	hertz
IC_{50}	half maximal inhibitory concentration
i.e.	*id est* (that is)
IA	iodic acid
IBX	2-iodoxybenzoic acid
*i*Pr	isopropyl
IR	infrared (spectroscopy)
J	coupling constant
k	rate constant
LDH	lactate dehydrogenase
m	*meta*
m	medium (IR)
M	molar (mol/L)
max.	maximum
m.p.	melting point
MAO	monoamino oxidase
MCR	multicomponent reaction
Me	methyl
min	minutes
NAD(H)	nicotinamide adenine dinucleotide
NADP(H)	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ns	nosyl, 2-nitrobenzenesulfonyl
Nu	nucleophile
o	*ortho*
OYE	old yellow enzyme
p	*para*
PAMO	phenylacetone monooxygenase
Pd/C	palladium on carbon
Ph	phenyl
PIFA	bis(trifluoroacetoxy)iodobenzene
PIDA	(diacetoxy)iodobenzene
PLP	pyridoxal 5′-phosphate
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTDH	phosphite dehydrogenase
q	quartet (NMR)
quant.	quantitative
*r*DA	*retro*-Diels-Alder
ref.	reference
rt	room temperature
s	strong (IR)
s	singlet (NMR)
t	triplet (NMR)

TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
Tris	tris(hydroxymethyl)amino-methane
TRPV1	transient receptor potential vanilloid type 1
TS	transition state
TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
w	weak (IR)
zgn.	zogenaamd (so-called)
δ	delta
ω-TA	amine transaminase
µW	microwave

Chapter I

Biocatalytic Strategies in Organic Synthesis

Introduction

1.1 Introduction

Biocatalysis has evolved over the past decades towards a reliable tool in the field of organic chemistry.[1] However, the use of enzymes is still not fully integrated in the synthetic community. To provide a better understanding of this important field, some essential background information on biocatalysis will be provided. Furthermore, enzymes that have found broad application in organic synthesis are briefly summarized in this chapter, being categorized according to the type of reaction that they catalyze. For each enzyme, the relevant biocatalytic strategies for their application are presented.

Excellent reviews on the use of enzymes in organic chemistry have appeared in the literature, mostly focusing on the application of biocatalysis in the synthesis of either natural products or pharmaceuticals.[2] To provide a guideline on how to further implement biocatalysis in organic synthesis, the most important asymmetric strategies in which enzymes can be applied are outlined, *i.e.* kinetic resolution (1), desymmetrization (2), deracemization (3), and stereoselective conversions of prochiral substrates (4). Stereoselective conversions of prochiral substrates can actually be considered as desymmetrization techniques (*i.e.* prochiral substrates have an internal mirror plane). However, we differentiate between symmetric molecules that have two identical reactive substituents (2) and prochiral molecules in which the attack of one side of a reactive moiety is favored (4). The relevant biocatalysts for the research in this thesis *i.e.* monoamine oxidases, transaminases and Baeyer-Villiger monooxygenases are categorized under the most important asymmetric strategies that exist for their application. As there is a plethora of total syntheses that exploit an enzymatic step, only a few examples that are illustrative to the topic of discussion will be discussed to underline the synthetic relevance of these asymmetric strategies.

1.2 Biocatalysis

Catalysts are substances which affect the rate of a reaction by lowering the activation energy.[3] In this process, the catalyst is not consumed and may therefore be recovered after the reaction is complete. A large part of the proteins found in nature have this unique ability. Generally, catalysts from nature are known as enzymes and are produced in the cells of living organisms to *a.o.* accelerate reactions in metabolic

pathways.[4] The application of enzymes as catalysts for chemical transformations in synthesis is referred to as biocatalysis.

Enzymes are environmentally benign catalysts as a consequence of among others their reactivity under mild conditions and complete biodegradability. Biotransformations are generally performed in aqueous medium, although some enzymes tolerate high concentrations of organic solvents. Another advantageous property of biocatalysis is the exceptionally high efficiency of enzymes. Generally, significantly lower catalyst loadings are required in comparison with chemical catalysts. The most important strength of enzymes is their ability to exert high chemo-, regio- and stereoselectivity. The chemically unmatched, highly specific binding pocket of enzymes is responsible for this exceptional selectivity. In the ideal case, the substrate enters the binding pocket that is pre-organized in such a way that it will only allow a specific moiety (*i.e.* chemo- and regioselectively) to enter in a particular orientation (*i.e.* stereoselectively). Although this pathway follows the lowest energy barrier for the transformation and represents the preferred binding of the substrate to the enzyme, other binding modes can participate as well (Figure 1). The high selectivity of enzymes has many advantages such as fewer side reactions than chemical catalysis. Moreover, biocatalysts can be used in complex transformations as well as multi-enzyme cascades without the need for intermediate functional group protection and deprotection steps.

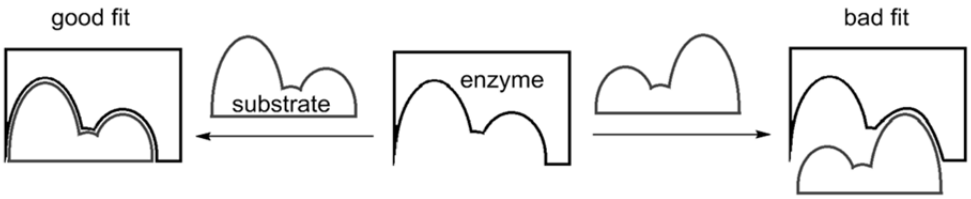


Figure 1. A schematic representation of the specific binding pocket of enzymes.

The use of enzymes also presents some disadvantages such as the fact that they are often unstable outside their natural environment. Although chemical reactions can be optimized by screening temperatures, solvents, additional reagents and other factors, enzymes maintain a much narrower optimization window.[3] Moreover, the efficiency of enzymes can be negatively affected by the presence of high concentrations of organic compounds. Although the use of a low enzyme concentration is a favorable aspect, high substrate concentrations often lead to substrate or product inhibition.[6]

Furthermore, substrates suitable for biotransformation are generally small. However, alteration of enzyme function and properties can be achieved by directed evolution, a method to evolve enzymes by mimicking the natural selection process.[5] Most biocatalytic conversions are performed in aqueous medium, which is a major advantage in terms of sustainability. However, low solubility of the reagents in water is often an issue when combining a biotransformation with diversifying chemical reactions in one pot. For this reason, co-solvents are frequently used to increase the solubility of the reagents. Some enzymes require a specific cofactor (*e.g.* NAD(P)H, flavin, heme) to catalyze the desired reaction. This is a major drawback as these cofactors are rather expensive and unstable. Additional enzymes are often required for regeneration of the cofactors or to drive the equilibrium towards the desired product.

1.3 Enzymes

The Enzyme Commission (EC) number nomenclature[7] is a classification of specific enzymes into enzyme categories based on the type of reaction that they catalyze. The six main categories are: oxidoreductases (EC 1), transferases (EC 2), hydrolases (EC 3), lyases (EC 4), isomerases (EC 5) and ligases (EC 6). In this section, enzymes that have found broad application in organic synthesis will be described, which belong to categories EC 1–3. Other types of enzymes are not discussed, as their impact on organic chemistry has been relatively small. We categorized the selected enzymes according to the type of reaction that they catalyze and in order of popularity *i.e.* hydrolytic reactions, reduction and oxidation reactions, and finally followed by transfer reactions. For each enzyme, the relevant biocatalytic strategies for their application are discussed.

1.3.1 Hydrolytic reactions

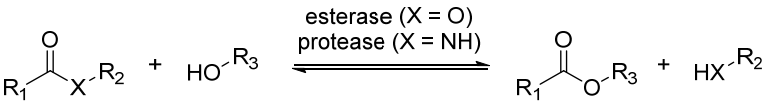
The class of enzymes that catalyzes hydrolytic transformations of functional groups is referred to as hydrolases (EC 3). Of these reactions, the hydrolysis of amides and esters has clearly received major interest throughout the years.[8] These reactions are readily performed with either proteases (to hydrolyze amide bonds, EC 3.4) or esterases (to hydrolyze ester bonds, EC 3.1). Lipases are a subclass of the esterases

that specifically hydrolyze lipids in nature. The key features that promote the popularity of hydrolases are the lack of cofactor requirement, their wide substrate scopes as well as high availability and stability. The reverse reaction to synthesize amide and ester bonds is most frequently performed in organic solvents to shift the thermodynamic equilibrium.[9-11] Other hydrolases such as nitrilases (EC 3.5) and epoxide hydrolases (EC 3.3) have a smaller impact on organic chemistry, but their potential has been clearly demonstrated.[12-15]

1.3.1.1 Proteases, lipases and other esterases

In synthetic chemistry, proteases and esterases can be applied in (trans)esterification reactions or hydrolyses. Lipases are certainly the most widely applied biocatalysts in organic chemistry, as they have several advantageous characteristics.[16] Since the natural function of lipases is the catabolism of a wide variety of nutrients in the digestion process, lipases accept a broad range of natural as well as non-natural substrates. Various lipases are commercially available and highly stable both in organic solvents and at elevated temperatures, while exhibiting high stereoselectivity.

Esterases and proteases are ideal for kinetic resolutions and desymmetrizations of carboxylic acids, alcohols, amides and amines (Scheme 1).[8-10] In the past two decades, dynamic kinetic resolution methods have gained attention, predominantly for the deracemization of secondary alcohols by combining a lipase with a racemizing additive (*e.g.* bases, metal complexes, racemases).[11]

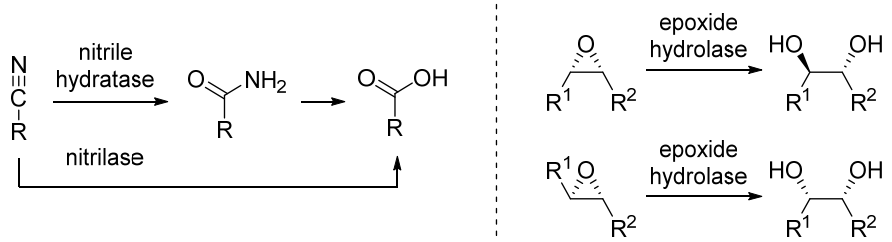


Scheme 1. Generalized reaction catalyzed by esterases and proteases.

1.3.1.2 Nitrilases

Nitrilases catalyze the hydrolysis of cyano groups to the corresponding carboxylic acid derivative and ammonia (Scheme 2). Since the first nitrilase was discovered in the 1960s,[17] many different examples have been identified in animals, plants and micro-organisms. Nevertheless, there is still little understanding of the biological function of most nitrilases. Research on nitrilases and their role in plant-microbe interactions has been reviewed by Preston.[18] Nitrilases have been applied in several

industrial biotransformations.[19] Since their properties are comparable to lipases, nitrilases can also be applied in kinetic resolution, desymmetrization and deracemization strategies.[12,20]



Scheme 2. Generalized reaction catalyzed by nitrile hydratases, nitrilases and epoxide hydrolases.

1.3.1.3 Epoxide hydrolases

Epoxide hydrolases are present in every living organism to catalyze the hydrolysis of epoxides into vicinal diols with inversion of one stereocenter (Scheme 2). The main functions of epoxide hydrolases are detoxification, catabolism, and regulation of signaling molecules. Micro-organisms are generally the source of epoxide hydrolases in organic synthesis, as they are easy to culture on large scale and hence give relatively fast access to large quantities of the biocatalyst.[21] Epoxide hydrolases offer several advantageous properties. Like lipases, these enzymes do not require a cofactor and often exhibit high regio- and stereoselectivity. Moreover, epoxide hydrolases typically remain active in the presence of organic solvents. As a result of their ubiquity in nature, a large variety of epoxide hydrolases can be applied on various types of substrates.[22] Epoxide hydrolases can logically be used in kinetic resolution[13] and desymmetrization.[14] However, a more interesting application is deracemization.[15]

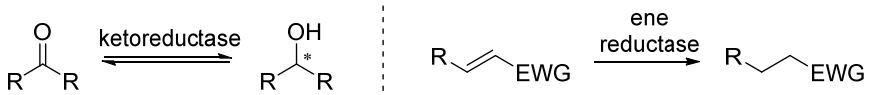
1.3.2 Reduction reactions

Enzymes that catalyze redox reactions, called oxidoreductases (EC 1), can be classified into three important categories: dehydrogenases, oxygenases and oxidases.[23] The EC classification depends on among others the donor molecule and cofactor. Since oxygenases and oxidases consume molecular oxygen during oxidation, these enzymes cannot be applied in reduction reactions. Dehydrogenases catalyze oxidation reactions by transferring hydrogen from a donor substrate to an acceptor cofactor such as a

ketone or an alkene. The redox cofactor is NAD(H) or NADP(H) in most cases. The reverse reaction (reduction) can be catalyzed by dehydrogenases as well, depending on the redox state of the cofactor. With the intention to avoid confusion, dehydrogenases used in reduction reactions are generally called reductases *e.g.* an alcohol dehydrogenase that is used for the reduction of a ketone, is then called ketoreductase. The most widely applied enzymes for reduction reactions are ketoreductases and ene reductases.

1.3.2.1 Ketoreductases

Carbonyl moieties are present in various endogenous (*e.g.* hormones, mediators, cofactors) and exogenous (*e.g.* food ingredients, drugs) compounds, and often play a vital role in the biological activity of these compounds. Therefore, an important function of ketoreductases (Scheme 3) is to regulate the concentration of these biologically active compounds in living organisms. Since these carbonyl compounds differ greatly in their chemical backbone, ketoreductases can accept a wide range of carbonyl compounds.[24] There are several chemical processes equivalent to enzymatic ketoreduction, which have shown to be very robust and versatile.[25] Nevertheless, ketoreductases deliver many advantages over chemical approaches in terms of regio- and stereoselectivity, reaction conditions (*i.e.* mild conditions), lack of H_2 consumption or release, and low catalyst costs. A drawback of ketoreductases is that cofactors are required. Ketoreductases are mainly used in stereoselective transformations.[26] In addition, some examples of kinetic resolution[27] and deracemization[28] are reported as well.



Scheme 3. Generalized reaction catalyzed by ketoreductases and ene reductases.

1.3.2.2 Ene reductases

Enzymes belonging to the old yellow enzyme (OYE) family are surely the most commonly used ene reductases in organic chemistry. In 1932, Warburg and Christian were the first to isolate an OYE from brewers' bottom yeast (*Saccharomyces pastorianus*).[29] Homologous enzymes have been found in other yeasts, plants, bacteria and parasitic eukaryotes.[30]

Ene reductases catalyze the reduction of C=C bonds (Scheme 3) that are activated by electron-withdrawing groups (*e.g.* esters, ketones, amides). Although chemical equivalents are still very popular (*i.e.* Knowles and Noyori received the Nobel Prize for their work on asymmetric hydrogenation in 2001), ene reductases are gaining attention due to their high stereo- and regioselectivity, and rather broad substrate scopes. Most ene reductases use flavin mononucleotide (FMN) as the hydride donor, which is recycled during the reaction by NADH.[31] Notably, the OYE family owes its name to the yellow color of oxidized FMN in aqueous solution. As might be expected, ene reductases are only applied in the stereoselective transformation of prochiral substrates.[32]

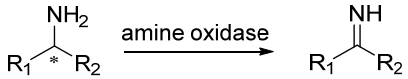
1.3.3 Oxidation reactions

Oxidoreductases such as oxygenases and oxidases are widely applied as catalysts for oxidation reactions.[23] The name of the oxygenase subclass originates from their ability to transfer oxygen atoms from molecular oxygen to a substrate. Monooxygenases (EC 1.14) transfer a single oxygen atom as a hydroxyl group to the substrate and reduce the other oxygen atom to water using cofactor NADPH or NADH. In most cases, activation of oxygen is achieved with a cofactor such as heme or flavin. Dioxygenases (EC 1.13) transfer both oxygen atoms to the substrate using an iron cofactor *e.g.* in the form of heme. Oxidases catalyze the abstraction of hydrogen from a donor substrate to molecular oxygen, which is reduced to water or hydrogen peroxide in the process. In contrast to dehydrogenases that generally use NAD(H) or NADP(H) as cofactor, oxidases are not able to catalyze the reverse reaction. The most widely applied oxidoreductases for oxidation reactions are amine oxidases (EC 1.4.3), dioxygenases and monooxygenases.

1.3.3.1 Amine oxidases

Amine oxidases are divided in type I (quinone-dependent family) and type II (flavin-dependent family). For synthetic chemists, enzymes of type I are less interesting as the product will be covalently bound to the enzyme.[33] Monoamine oxidases of type II are enzymes that catalyze the oxidation of primary aliphatic and aromatic amines as well as some secondary and tertiary amines to imines (Scheme 4). Imines are generally unstable and readily hydrolyzed to the corresponding aldehyde or ketone and amine. In the human body, these enzymes function in the oxidative

deamination of neurotransmitters and exogenous amines.[34] The monoamine oxidase from fungus *Aspergillus niger* (MAO-N) is so far the only monoamine oxidase that is well established in organic chemistry. This enzyme was identified by Schilling and Lerch[35] in 1995, after which Sablin *et al.*[36] overexpressed the gene in *E. coli*. In contrast to mammalian MAOs, MAO-N is soluble, peroxisomal, readily extractable and easy to isolate. Moreover, MAO-N shows no tendency to aggregate and the flavin cofactor FAD is non-covalently linked. Although wild-type MAO-N only catalyzes the oxidation of simple amines, several rounds of directed evolution[5] have successfully broadened the substrate scope of this enzyme.[37]



Scheme 4. Generalized reaction catalyzed by amine oxidases.

While kinetic resolution and deracemization strategies of chiral amines are possible, all resolution protocols can in principle be converted into a dynamic kinetic resolution (see Chapter 1.4.3.2). Owing to the stability of cyclic imines, MAO-N is especially suitable for the desymmetrization of prochiral cyclic amines (see Chapter 1.4.2.2).

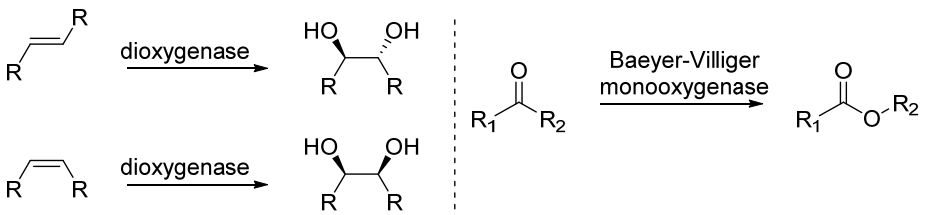
1.3.3.2 Dioxygenases

A key step in the catabolism of aromatic compounds by micro-organisms is *cis*-dihydroxylation catalyzed by microbial dioxygenases. In the presence of molecular oxygen, the biocatalyst oxidizes aromatic compounds towards the corresponding diols. In addition, this process is also crucial in the detoxification of aromatic pollutants.[38,39] Dioxygenases have been applied in numerous asymmetric syntheses,[40] as two stereocenters are generated with high stereospecificity for a broad range of aromatic substrates. Alkenes have also been used, albeit in conjugation with an aryl group or another olefin (Scheme 5).[41] Chemical dihydroxylations are well known, although most methods are only applicable on alkenes. As the substrates are generally achiral, these types of enzymes are only used in stereoselective biotransformations of prochiral substrates.[42]

1.3.3.3 Baeyer-Villiger monooxygenases

Baeyer-Villiger monooxygenases (BVMOs) are oxidoreductases that catalyze the conversion of ketones to esters (Scheme 5). BVMOs can be classified as type I or II

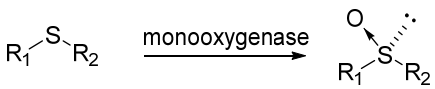
based on the difference in cofactors (*i.e.* type I uses FAD and NADPH, type II uses FMN and NADH) and structure.[43] Only BVMOs of type I, exclusively found in bacteria and fungi, are integrated in organic chemistry. In Nature, these enzymes play a vital role in several degradation pathways and in the biosynthesis of complex molecules (*e.g.* steroids).[44] Chemically, a Baeyer-Villiger reaction is performed with a ketone and a peroxy acid. Besides the fact that peroxy acids are non-selective, these oxidants are also harsh, toxic reagents. Highly stereoselective catalytic methods based on transition metals have been developed using less harsh reaction conditions. Nevertheless, BVMOs are superior in terms of sustainability, chemo-, regio-, and stereoselectivity, using molecular oxygen as the oxidant.[45] Although BVMOs are well-known biocatalysts, not many applications in asymmetric synthetic strategies have appeared in the literature thus far. BVMOs are mostly applied in desymmetrization (Chapter 1.4.2.1) and deracemization strategies (Chapter 1.4.3.1). Examples of kinetic resolutions are known,[46] but synthetic applications are lagging behind.



Scheme 5. Generalized reaction catalyzed by dioxygenases and Baeyer-Villiger monooxygenases.

1.3.3.4 Miscellaneous monooxygenases

Sulfoxides are chiral molecules that are represented in various biologically active compounds. In addition, sulfoxides are used in asymmetric synthesis as chiral auxiliaries. Although asymmetric strategies to oxidize sulfides by means of organocatalysis[47] or transition metal catalysis[48] have been reported, biocatalysts remain superior in terms of enantioselectivity. Many types of oxidases catalyze this



Scheme 6. Generalized reaction catalyzed by monooxygenases.

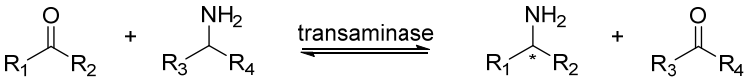
reaction, but no specific enzymes exist that only catalyze sulfur oxidation (Scheme 6).[49] To obtain enantiopure sulfoxides using biocatalysis, kinetic resolution can be applied by oxidation of one of the enantiomers to its corresponding sulfone.[50] However, stereoselective transformations of prochiral thioethers are a more attractive strategy.[51]

1.3.4 Transfer reactions

Enzymes that transfer specific functional groups from donor molecules to acceptor molecules are referred to as transferases (EC 2). Transaminases (EC 2.6.1) are the most popular and widely applied transferases in organic chemistry.

1.3.4.1 Transaminases

Transaminases are ubiquitous in nature, as these enzymes play a vital role in the biosynthesis of amino acids. The reaction that transaminases catalyze is the exchange of an amine moiety of one molecule with the carbonyl moiety of another molecule utilizing the cofactor pyridoxal 5'-phosphate (PLP). Formally, the molecule with the carbonyl moiety is reduced and the compound with the amine functionality is oxidized (Scheme 7). These enzymes are usually named α-transaminases if α-amino acids are formed. However, when a transaminase is also able to accept aliphatic ketones and amines as substrates, they are referred to as ω-transaminases. Alternatively, the latter class is named amine transaminases (ATAs).[52] Unlike other biocatalytic reductions, transaminases do not require expensive redox cofactors. In addition to transaminases that produce L-amino acids, transaminases producing D-amino acids have also been identified in bacterial species.[53] Consequently, both enantiomers of a desired amine may be produced by selecting enantio-complementary enzymes from different sources.



Scheme 7. Generalized reaction catalyzed by transaminases.

In Nature, transamination reactions are in constant equilibrium, which is undesirable when full conversion of the substrate is pursued. This drawback can be overcome by removing the undesired coproduct from the reaction by the use of additional

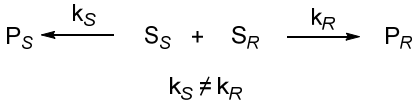
enzymatic systems, or using a large excess of a sacrificial amine or ketone cosubstrate. Transaminases are mostly used in the stereoselective transformation of prochiral compounds (see Chapter 1.4.4.1) and in the kinetic resolution of racemic amines (see Chapter 1.4.1.1), but deracemization methods have been developed as well (see Chapter 1.4.3.3).

1.4 Biocatalytic Strategies

Biocatalytic strategies that have found wide application in organic chemistry are outlined in this section. Furthermore, some interesting examples of their application in organic synthesis are presented for three important enzyme categories, namely Baeyer-Villiger monooxygenases, monoamine oxidases and transaminases.

1.4.1 Kinetic resolution

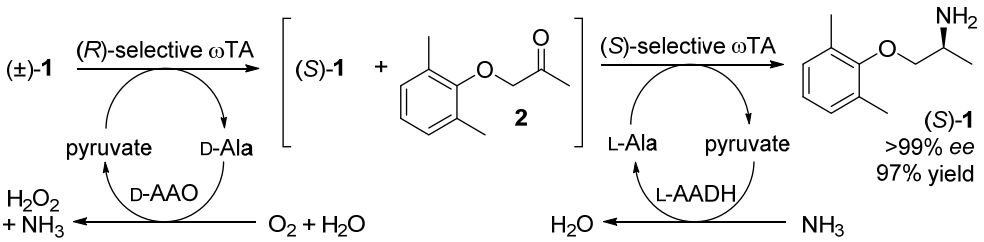
Enzymatic kinetic resolution (EKR) is of prime importance in asymmetric synthesis, both in industry and academia. Although many synthetic chemists regard this strategy as inelegant, it is still probably the most widely applied biocatalytic strategy in organic synthesis. The success of EKR depends on the difference in activation energy of the two enantiomers when reacted in the presence of an enzyme (*i.e.* $k_R \neq k_S$). The higher the difference in activation energy, the higher the preference for one of the enantiomers (Scheme 8). If both enantiomers of a natural compound or drug are desired, EKR is a highly suitable strategy. Unfortunately, the undesired enantiomer is generally a waste product after kinetic resolution. In this case, a purification step is required that is commonly rather laborious.



Scheme 8. The principle of kinetic resolution.

1.4.1.1 Transaminases

The yield limitation of EKR is frequently a justified reason for avoiding a resolution step in total syntheses. However, an example by Kroutil *et al.* shows an ingenious sequence consisting of a kinetic resolution step followed by a stereoselective amination with oppositely enantioselective transaminases (TAs, Scheme 9). This two-step deracemization strategy affords optically pure mexiletine (**1**). By simply switching the order of the enzymatic reactions, both enantiomers could be obtained as optically-pure products in near quantitative yields (97%).[54] Although Kroutil and coworkers have demonstrated the resolution power of transaminases, preference is generally given to stereoselective conversions of prochiral ketones. Only if the racemic amine is more easily accessible than the prochiral ketone, such a deracemization strategy is an interesting alternative.



Scheme 9. A one-pot two-step deracemization procedure towards mexiletine (*S*)-**1**.

1.4.2 Desymmetrization

Enzymatic desymmetrization is a powerful tool in numerous total syntheses. Unlike kinetic resolution, desymmetrization does not have the drawback of a maximal theoretical yield of 50%, as the substrates are achiral. The strategy is based on having two equivalent substituents of which only one will undergo a biocatalytic transformation. When the substrate is prochiral, transformation of one of these groups will lead to a chiral compound. Since enzymes have the beneficial property of having a very specific binding pocket, the substrate will usually be oriented in such a way that high selectivity can be achieved.

1.4.2.1 Baeyer-Villiger monooxygenases

BVMOs have been applied in many desymmetrization approaches using cyclic prochiral ketones. Some examples of interesting products with predominantly high enantiopurity are shown in Figure 2. Although several BVMOs have been applied on a wide variety of substrates, the number of applications in total synthesis is lagging behind.[55] However, optically pure lactones have proven to be versatile building blocks in the synthesis of various high-value target molecules, in particular β-aryl-γ-lactones. For instance, lactone **4** is introduced as a key intermediate in the total synthesis of biologically active (*R*)-baclofen.[56] Another example is bicyclic lactone **8**—an important building block in the synthesis of scholarisine A[57]—which is generally synthesized by a lipase-catalyzed desymmetrization strategy,[58] followed by several synthetic steps. Although this procedure is applicable on a large scale, it may be interesting to consider a BVMO-catalyzed desymmetrization to provide this chiral intermediate.

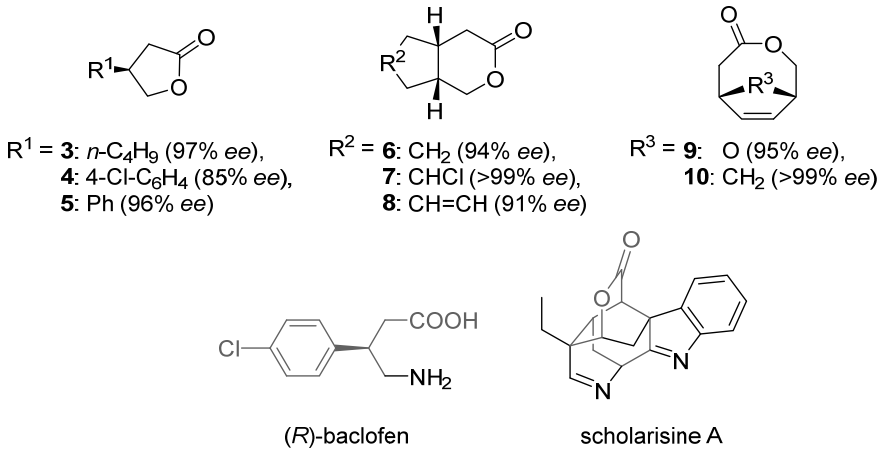


Figure 2. Interesting products attained by BVMOs.

1.4.2.2 Amine oxidases

Turner *et al*. subjected a series of *meso*-pyrrolidines to amine oxidation by an *Aspergillus niger* MAO-N mutant (Figure 3). Oxidation proved to be faster for substrates with increased bulk and lipophilicity. Stable bi- and tricyclic imines could be isolated with high enantioselectivity (>94% *ee*) as either the monomer, or the

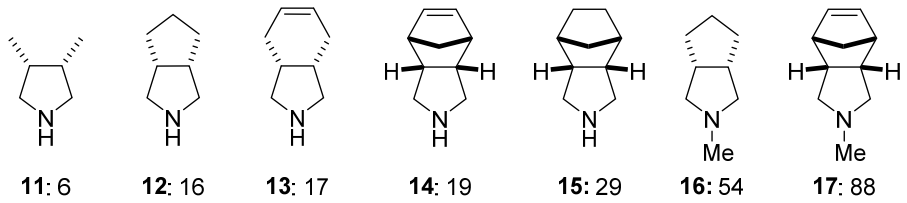
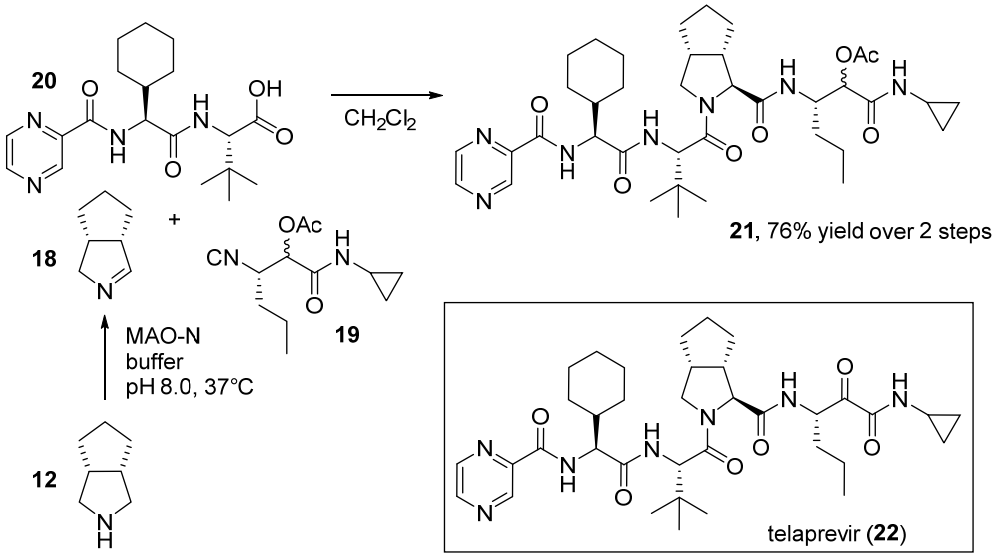


Figure 3. Relative rates of biocatalytic oxidation with MAO-N D5 for pyrrolidines **11**–**17**. Rates are relative to (*S*)-α-methylbenzylamine (rate= 100).

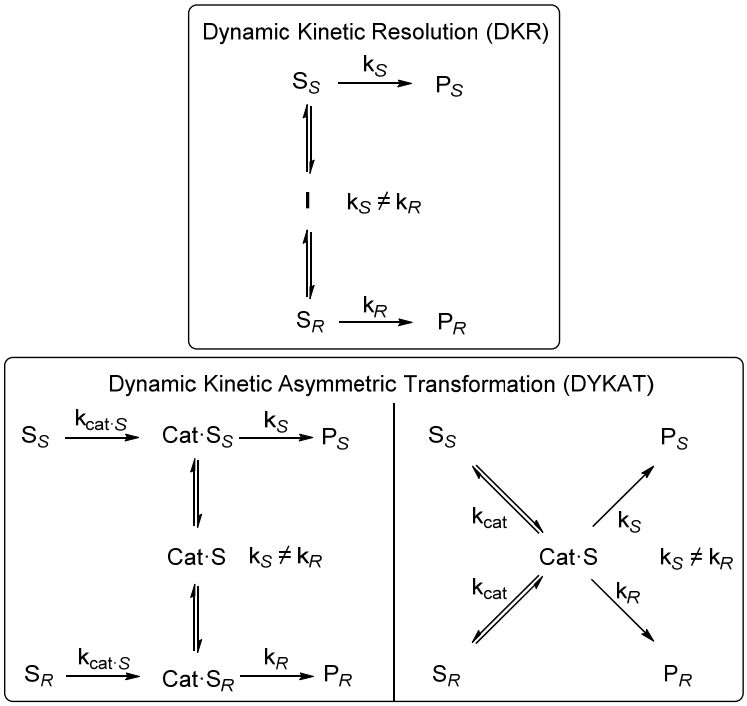
trimer.[59] To date, no chemical procedures have been reported that can accomplish this asymmetric transformation. Imines are intermediates in various multicomponent reactions (MCRs), which is a category of reactions that create a high degree of diversity and complexity in a single step. Orru *et al.* illustrated the applicability of the biocatalytically generated 1-pyrrolines in Ugi-type MCRs to access enantio-enriched prolyl peptides in good yields (60–85%) and with high stereoselectivity (84–98% *de*, 94–99% *ee*).[60] This combination of biocatalysis and multicomponent reactions was later applied in the synthesis of the hepatitis C virus protease inhibitor telaprevir (**22**, Scheme 10).[61] In addition, a tandem MAO-N oxidation, Ugi 3CR, Adams Carroll-type cyclization sequence for rapid synthesis of alkaloid-like polycyclic structures was described.[62]



Scheme 10. Chemoenzymatic total synthesis of hepatitis C virus protease inhibitor telaprivir.

1.4.3 Deracemization

Deracemization strategies have gained much attention over the past decade, since the obvious disadvantages of kinetic resolution (50% maximum yield) and desymmetrization (limited substrate scope) are avoided. Although some enzymes can deracemize a substrate, most processes require an additional chemical reagent or enzyme for *in situ* deracemization. Deracemization strategies also include dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DYKAT) (Scheme 11). DYKAT is a process in which interconversion of the starting material takes place on the chiral catalyst. DYKATs proceed either by binding of either enantiomer to the chiral catalyst (*i.e.* giving two diastereomeric catalysts) after which one is converted by means of epimerization, or by eliminating the stereocenter (*i.e.* hence forming only one substrate/enzyme complex) after which addition to one side is preferred.[63] This is in contrast with the DKR, in which racemization is induced by an

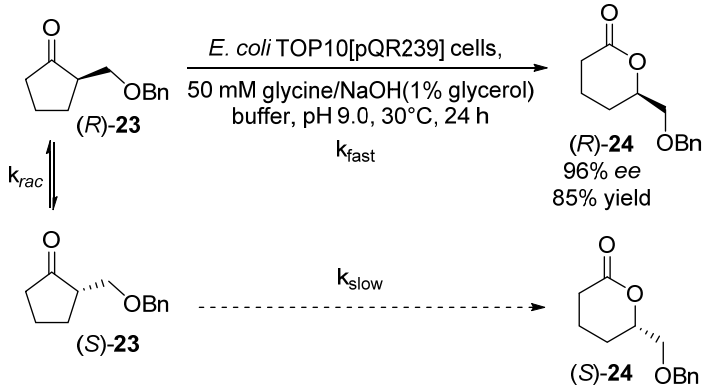


Scheme 11. Schematic representation of dynamic kinetic resolution and dynamic kinetic asymmetric transformation.

achiral reagent or catalyst. The first examples of enzyme-catalyzed DKR procedures originate from the past century. These methods often benefit from the generally undesired racemization of base-sensitive substrates.[64] Other methods are based on racemization by transition metals and racemases.[65]

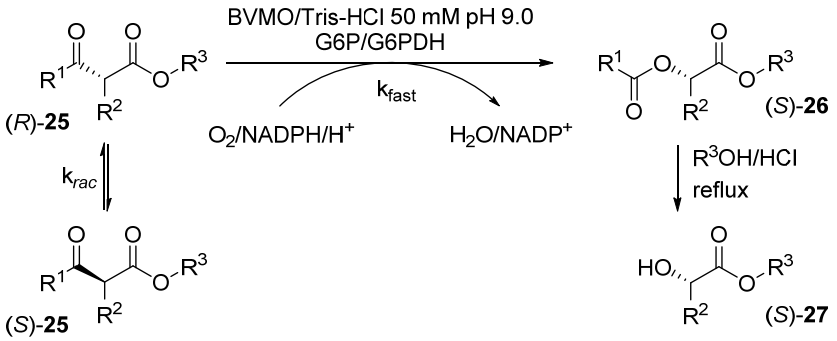
1.4.3.1 Baeyer-Villiger monooxygenases

BVMOs hold great potential in deracemization strategies, although examples and applications are limited in the literature. The first DKR method employing a BVMO was reported by Furstoss *et al.*, in which α-substituted cyclopentanone **23** was converted to lactone **24** (Scheme 12). The authors performed the oxidation at pH 9 to induce racemization of **23**. The product could be obtained in 85% yield with high optical purity (96% *ee*).[66]



Scheme 12. Conversion of (±)-**23** to lactone (*R*)-**24** via a BVMO-catalyzed DKR procedure.

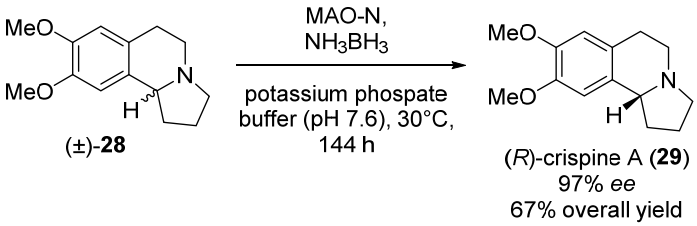
A more recent example was reported by Gotor *et al.*, in which α-substituted β-ketoesters **25** were subjected to biocatalyzed Baeyer-Villiger oxidations (Scheme 13).[67] Of the three BVMOs tested, phenylacetone monooxygenase (PAMO) and 4-hydroxyacetophenone monooxygenase (HAPMO) displayed superior activity and selectivity. The resulting α-acylated hydroxyl esters **26** are valuable synthetic building blocks in various industrial processes. Most products were obtained in high optical purity, with high conversion within 2 days. Gotor and coworkers have also published other DKR methods with BVMOs, yet resulting in less attractive products for synthetic applications.[68]



Scheme 13. Conversion of acyclic α-substituted β-ketoesters to α-acylated hydroxyl esters via a BVMO-catalyzed DKR procedure followed by hydrolysis.

1.4.3.2 Amine oxidases

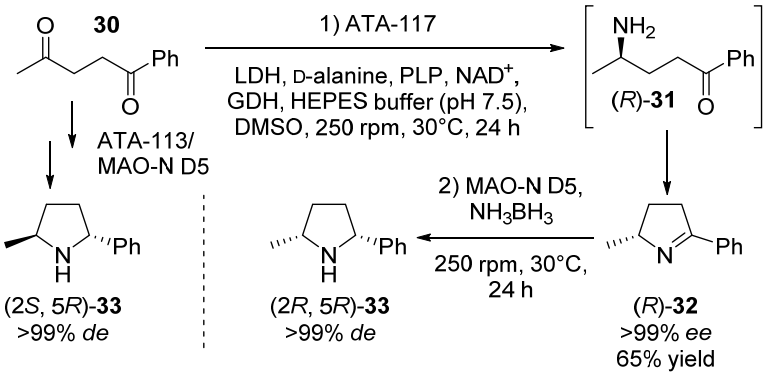
Deracemization methods that utilize amine oxidases are distinct from other deracemization processes, as amine oxidases selectively symmetrize chiral compounds. Combining the biocatalytic oxidation of one enantiomer with non-selective reduction of the imine allows the synthesis of enantiomerically pure amines after several redox cycles. Turner *et al*. were the first to illustrate this principle by combining a MAO-N-catalyzed oxidation with ammonia borane reduction in one pot. This method could be applied on a wide variety of structurally different amines giving high enantioselectivity (83–99% *ee*).[69] The fact that the substrate scope includes tertiary amines is considered a great asset for synthetic chemistry, since these compounds are typically difficult to oxidize enantioselectively.[70] This method was successfully applied in the total synthesis of tetrahydroisoquinoline alkaloid (*R*)-crispine A (**29**, Scheme 14).[71] The synthetic utility was further illustrated by the synthesis of active pharmaceutical ingredients solifenacin and levocetirizine, as well as natural products (*R*)-coniine, (*R*)-eleagnine and (*R*)-leptaflorine.[37] In addition, one



Scheme 14. MAO-N catalyzed DKR strategy in the total synthesis of (*R*)-crispine A (**29**).

of their MAO-N mutants was able to catalyze an exotic Pictet-Spengler/deracemization sequence towards (*R*)-harmicine in high yield and optical purity.[37]

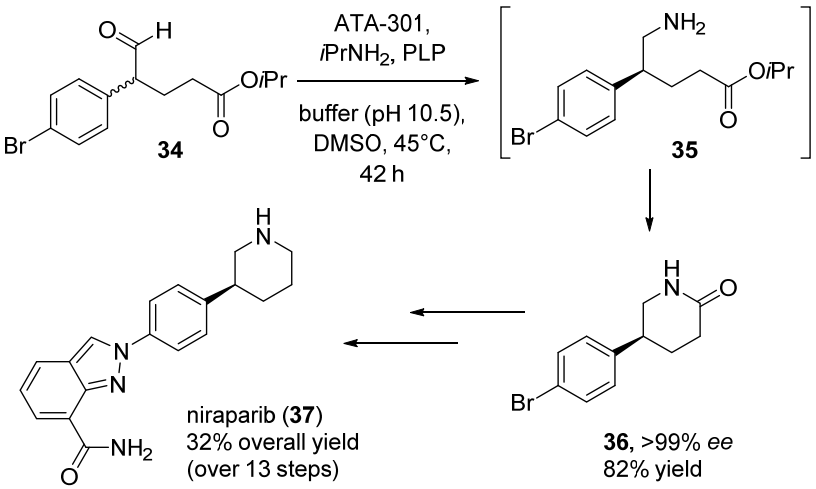
Kroutil *et al*. combined a MAO-N-based deracemization with berberine bridge enzyme (BBE) to provide a one-pot cascade transformation. Full conversion towards the desired berberin products with high enantioselectivity (>97% *ee*) was achieved within two days.[72] To date, no chemical reagent (or other biocatalyst) is able to perform either of the two biotransformations. Turner *et al.* showed that commercially available (*S*)-selective transaminase ATA-113 and (*R*)-selective transaminase ATA-117 can regioselectively convert 1,4-diketone **30** to optically-pure pyrrolines **33** in good yields via a transamination/cyclization sequence. Subsequently, this method was successfully combined in one pot with MAO-N catalyzed deracemization to provide a small range of pyrrolidines with excellent stereoselectivity (Scheme 15).[73,74]



Scheme 15. A regio- and stereoselective ATA/MAO cascade towards pyrrolidines **33**.

1.4.3.3 Transaminases

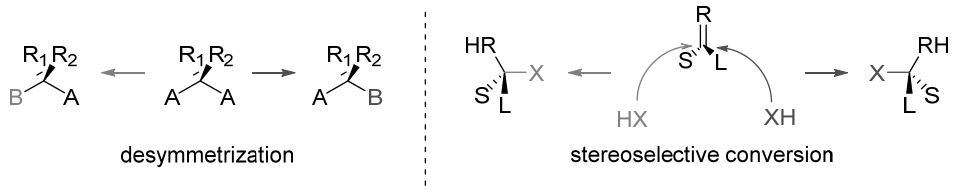
Deracemization methods with transaminases are based on keto-enol tautomerization of the prochiral carbonyl substrate. Gotor *et al.* performed the deracemization of acyclic α-substituted β-keto esters with several (*S*)- and (*R*)-selective transaminases.[75] Although high *ee´*s were achieved in general, high diastereoselectivities (94–96% *de*) were only achieved with cyclic analogs. Chung *et al.* used a deracemization strategy followed by lactamization in the synthesis of niraparib (**37**).[76] Superior results were obtained in rather basic media (pH 10.5), using pyridoxal 5'-phosphate (PLP) as a cofactor and isopropylamine as the amine donor (Scheme 16).



Scheme 16. Transaminase DKR strategy in the total synthesis of niraparib (**37**).

1.4.4 Stereoselective biotransformations of prochiral compounds

Stereoselective biotransformations of prochiral compounds are strictly speaking desymmetrization reactions, as the achiral starting material is converted to a chiral product. However, stereoselective conversions of prochiral compounds by favored attack from one side of the reactive moiety, can be considered substantially different than preferential conversion of one of two identical moieties to give a chiral molecule during a desymmetrization. This distinction is more clearly depicted in scheme 17.

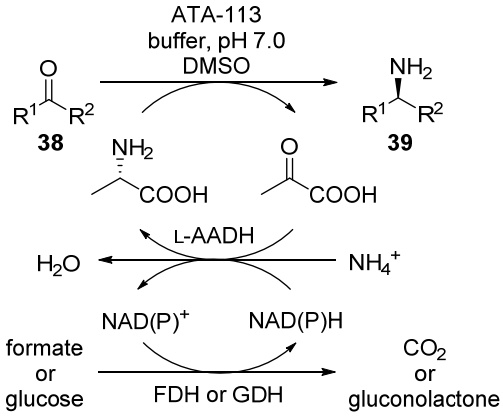


Scheme 17. A discrimination between desymmetrization and stereoselective conversion.

1.4.4.1 Transaminases

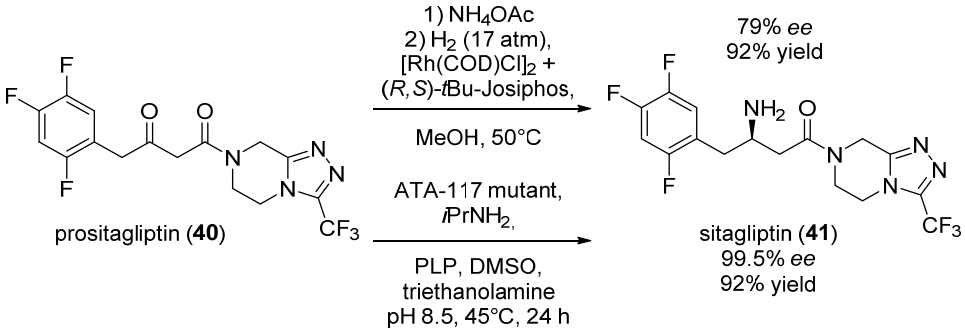
Transaminases are mainly used in the stereoselective conversion of achiral ketones or aldehydes, which are synthetically easily accessible. However, these types of biotransformations require ingenious techniques to obtain high quantities of the

chiral amine, owing to the thermodynamic equilibrium. Kroutil and coworkers have developed such a method using ammonium as a cheap stoichiometric amine donor (Scheme 18).[77] This process requires three enzymes: 1) a transaminase, 2) an amino acid dehydrogenase (AADH), and 3) a formate/glucose dehydrogenase. The transaminase (ATA-113) carries out the desired transformation with alanine as the direct amine donor. Pyruvate is subsequently recycled by L-alanine dehydrogenase (L-ADH) and ammonium. The third enzyme, formate dehydrogenase (FDH) or glucose dehydrogenase (GDH), is required for cofactor recycling. High conversions and *ee´*s were obtained with a variety of ketone substrates. The advantage of this cycle is that product inhibition by pyruvate is prevented. Nevertheless, an excess of alanine (5 equiv) is required to achieve high conversion.



Scheme 18. The use of ammonium as stoichiometric amine donor in biocatalytic transamination.

Transaminases have already been included in many synthetic strategies, mostly to optimize a certain transformation. This surely applies for the enzymatic conversion of prositagliptin (**40**) to sitagliptin (**41**, Scheme 19).[78] Sitagliptin could be synthesized in 92% yield and 99.5% *ee* from the corresponding ketone using an engineered transaminase (ATA-117 mutant). The fact that ATA-117 (an enzyme that is only capable of converting small ketone substrates) could be modified to accept rather large ketones like prostagliptin, shows the great potential of directed evolution for the implementation of enzymes in total synthesis. The enzymatic route was clearly superior over the transition-metal based approach in both *ee* and sustainability and therefore represents a landmark of modern biocatalysis.



Scheme 19. Improvement of the chemical conversion of prositagliptin (**40**) to sitagliptin (**41**) by use of transaminase ATA-117.

1.5 Conclusion & Outlook

Enzymes are able to perform transformations that are chemically either less effective or not (yet) possible. Although chemical procedures are improving, the binding pocket of enzymes is chemically unmatched. The greatest strength that biocatalysts exhibit is their high chemo-, regio-, and enantioselectivity. Moreover, the diverse selection of biocatalytic strategies and biocatalysts gives access to a variety of building blocks.

Biocatalysts have some obvious disadvantages, such as high substrate specificity, cofactor dependence and narrow optimization possibilities. Fortunately, the use of directed evolution provides the possibility to alter the properties of enzymes in order to overcome these drawbacks. In addition, new enzymes are discovered every day, and there is still a large domain of biocatalysts which remains unexplored. By accepting biocatalysis as an important tool in the synthetic toolbox, more handles are available to solve the chemical problems that we encounter.

1.6 Acknowledgements

J. M. Saya (VU University) is gratefully acknowledged for his contribution to this chapter.

1.7 Outline of this Thesis

From this introductory chapter, it becomes clear that biocatalytic strategies have great potential for synthetic chemistry. Although numerous examples of the use of biotransformations in total syntheses have been described, only a limited number of enzymes is considered suitable for organic chemistry. Many enzymes find only little application because of limitations in their substrate scope and their instability in the presence of organic solvents and many reagents. However, directed evolution has provided some tailored variants of otherwise difficult-to-use enzymes with wider substrate scopes. In **Chapter 2**, we will describe the one-pot combination of a biocatalytic oxidation of *meso*-pyrrolidines—using an engineered monoamine oxidase (MAO-N D5)—with chemical transformations. This highly stereoselective chemoenzymatic cascade sequence provides 2-substituted pyrrolidines in a sustainable manner. Although this biocatalytic oxidation was previously only described for carbocycle-fused pyrrolidines, we were delighted to find that the incorporation of an oxygen atom in the substrate was allowed. Hereby, we show that MAO-N can be used for the synthesis of a wider variety of 1-pyrrolines in high optical purity. Since MAO-N only provides one of the enantiomers, we set out to develop a convenient chemical oxidation providing racemic 1-pyrrolines. In **Chapter 3**, we will describe the first *o*-iodoxybenzoic acid (IBX) mediated oxidation of unactivated pyrrolidines to the corresponding imines. We further explored the chemical space with one-pot oxidative diastereoselective Ugi-type and aza-Friedel–Crafts reactions. With convenient methods towards either racemic or optically pure bicyclic imines in hand, we investigated their application in novel cascade reactions by considering them as amino aldehyde synthons. In **Chapter 4**, we will describe a switchable chemoenzymatic interrupted Fischer indole synthesis of either pyrroloindolines or constrained tryptamines. To account for the switch in reaction outcome based on the stoichiometry of the acid mediator, we will describe a plausible reaction mechanism. Furthermore, the synthetic utility of our method is illustrated with the synthesis of pharmaceutically relevant examples of both product classes. In **Chapter 5**, we will describe other envisioned opportunities for the use of monoamine oxidase in organic synthesis, using *meso*-pyrrolidines as a template. Evidently, other biocatalyst have great potential to be applied in synthetic chemistry as well. Therefore, we will also describe possibilities for the application of other biocatalysts *i.e.* Baeyer-Villiger monooxygenases and transaminases.

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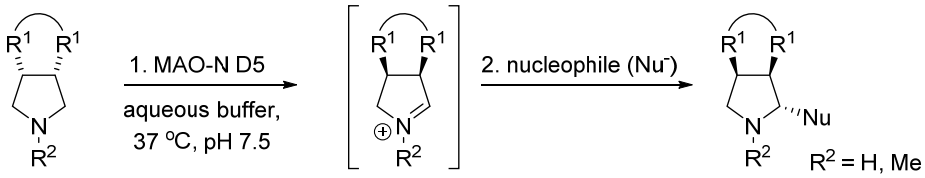
Chapter 2

Stereoselective Chemoenzymatic Oxidative aza-Friedel–Crafts Reactions in Aqueous Buffer



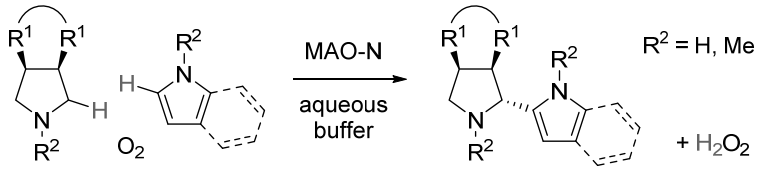
Abstract: *We disclose a highly diastereoselective chemoenzymatic oxidative aza-Friedel–Crafts reaction of meso-pyrrolidines in aqueous buffer providing valuable enantioenriched 2-substituted pyrrolidines. A range of secondary as well as tertiary amines were shown to be suitable substrates for the biocatalytic oxidation and subsequent addition of variety of C-nucleophiles.*

Adv. Synth. Catal., accepted.

2.1 Introduction

In the transition to sustainable chemistry, the demand for more sophisticated and efficient chemical processes that utilize and generate less hazardous chemicals is ever increasing.[1,2] In order to reduce waste production and energy consumption, the one-pot combination of substrate activation and synthetic transformations in benign media is of great interest. Biocatalysis is particularly useful in this respect, as enzymes are often able to mediate otherwise difficult activation of building blocks under mild conditions with unrivaled chemo-, regio- and stereoselectivity. The power of chemoenzymatic approaches has been convincingly demonstrated in the synthesis of well-known pharmaceuticals such as sitagliptin,[3] singulair,[4] posaconazole[5] and telaprevir.[6]

In recent years, direct asymmetric α-functionalizations towards 2-substituted pyrrolidines have attracted great attention in view of the importance of this structural motif in organocatalysis (*e.g.* proline derivatives).[7-9] Herein, we present a novel one-pot chemoenzymatic oxidative aza-Friedel–Crafts sequence for the synthesis of such chiral 2-substituted pyrrolidines under mild conditions. This approach combines the biocatalytic oxidation of cyclic amines to the corresponding imine derivatives with the subsequent addition of C-nucleophiles in aqueous buffer to yield formally double C–H activation products (Scheme 1).



Scheme 1. One-pot chemoenzymatic oxidative aza-Friedel-Crafts sequence.

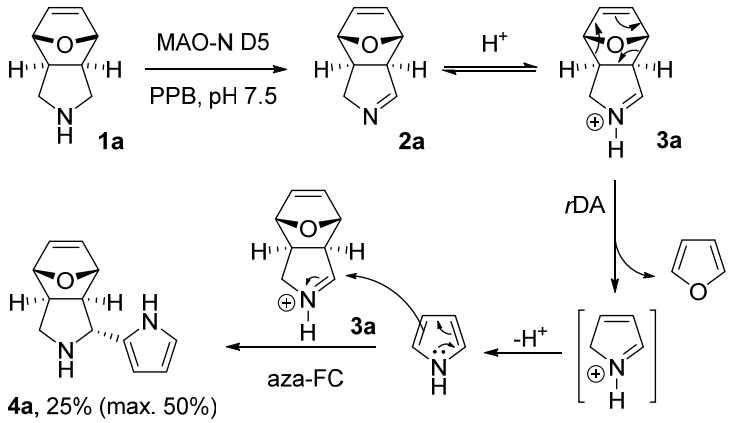
The aza-Friedel–Crafts (aza-FC) reaction[10] can be defined as the 1,2-addition of aromatic and hetero-aromatic compounds to imine derivatives. This transformation typically requires organic solvents and strong Lewis or Brønsted acid catalysis, with the exception of a limited number of examples of activator-free phenolic Mannich reactions in aqueous medium.[11] In these cases, the alcohol functionality is proposed to be responsible for both imine activation and regioselectivity control as a result of hydrogen bond formation. Other examples of aqueous aza-FC reactions without an

additional catalyst require a highly electrophilic imine.[12,13] Besides the drawback of limited application, these procedures employ imine derivatives that are accessed through additional synthesis and purification steps which is undesirable from a green perspective.

2.2 Results and Discussion

We previously reported a biocatalytic oxidation of *meso*-pyrrolidines with an engineered monoamine oxidase (MAO-N D5) to give 1-pyrrolines with high enantioselectivity.[14] In continuation of this research, we investigated the biocatalytic oxidation of *exo*-configured *meso*-pyrrolidine **1a** in aqueous buffer.[15] Intriguingly, 2-pyrrolyl pyrrolidine **4a** was obtained as the reaction product rather than the expected imine **2a**. To unravel which chemoenzymatic reaction cascade is responsible for the formation of **4a**, we investigated this reaction outcome in greater detail.

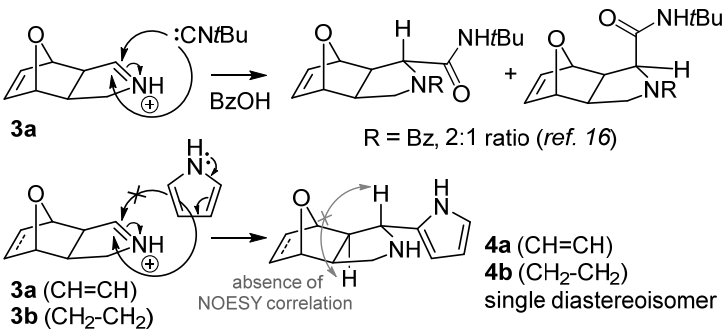
The mechanism for the formation of **4a** likely starts with the usual biocatalytic oxidation of **1a** to give imine **2a** (Scheme 2). However, **2a** is apparently unstable under the reaction conditions and undergoes a *retro*-Diels-Alder (*r*DA) reaction to give furan and pyrrole. Since *rac*-**2a** can readily be prepared with a different method,[16] we hypothesize that the *r*DA reaction proceeds only from protonated **2a** under aqueous conditions. Test experiments showed no reaction



Scheme 2. Proposed mechanism for the formation of 2-pyrrolyl pyrrolidine **4a**.
PPB = potassium phosphate buffer

between *rac*-**2a** and pyrrole in organic solvents such as dichloromethane, methanol and acetonitrile, while **4a** was isolated as a single product for the identical reaction in aqueous buffer. Based on these results, we believe that the aqueous buffer is a sufficiently good proton donor and/or hydrogen bond donor to activate **2a** toward a *r*DA reaction or an aza-FC reaction. Therefore, the formed pyrrole adds to unconverted (protonated) **2a** via an aza-FC reaction to afford the 2-pyrrolyl pyrrolidine **4a** (25%) in a maximum theoretical yield of 50%. This one-stage sequence consisting of biocatalytic oxidation, *r*DA and aza-FC requires only a single purification step, which is a major advantage.

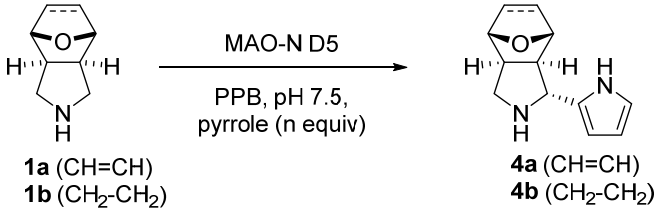
In terms of stereochemistry, we were delighted to obtain 2-pyrrolyl pyrrolidine **4a** as a single diastereoisomer, albeit with 70% *ee*.[14] The excellent diastereoselectivity of this aza-FC reaction is a highly interesting feature, since the corresponding Ugi-type three-component reaction (Ugi-type 3CR) with *tert*-butyl isocyanide and benzoic acid proceeds with only moderate diastereoselectivity (Scheme 3).[16] The fact that a reaction between *rac*-**2a** and pyrrole in the presence of a Brønsted acid (TFA) is completely diastereoselective as well, implies that the *C*-nucleophile is responsible for the degree of stereoinduction rather than the reaction medium. Considering the steric properties of the nucleophile, *tert*-butyl isocyanide is rather linear compared to pyrrole with an sp-hybridized nitrogen separating the sp-hybridized nucleophilic carbon from the steric bulk. Therefore, the excellent diastereoselectivity towards **4a** presumably results from a significantly larger stereodifferentiation between the diastereotopic faces of **3a**,**b** by pyrrole compared to *tert*-butyl isocyanide.



Scheme 3. Representation of diastereoselectivity for the aza-Friedel–Crafts reaction of *exo*-configured **3a**,**b** with pyrrole compared to the Ugi-type 3CR with *tert*-butyl isocyanide.

Given these interesting observations, we proceeded to optimize the oxidative aza-FC reaction of *meso*-pyrrolidine **1a**. Our initial oxidation of **1a** with the biocatalyst afforded 2-pyrrolyl pyrrolidine **4a** in 25% isolated yield (Table 1, entry 1). We slightly increased the yield by including pyrrole (2 equiv) in the reaction mixture (entry 2), but the *r*DA reaction of protonated **2a** impeded further improvements. To circumvent this issue, we opted to employ a similar *meso*-pyrrolidine (**1b**) that is unable to undergo the *r*DA reaction. To our delight, product **4b** was obtained with considerably increased enantioselectivity and yield compared to **4a** (entries 2 and 4) while maintaining the diastereoselectivity. However, a side product was formed which is plausibly the addition product of **4b** to iminium ion **3b** (double aza-FC).[17] In order to further optimize the reaction conditions, we performed the oxidative aza-FC reaction

Table 1. Optimization of reaction conditions for the stereoselective oxidative aza-Friedel–Crafts reaction of *meso*-pyrrolidines **1a**,**b**.[a]

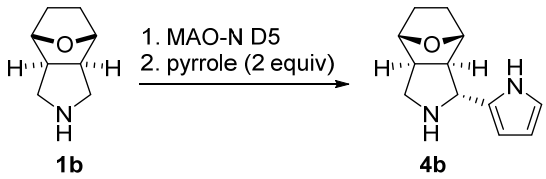


Entry	Pyrrolidine	Product	n	Yield[b] (%)	*ee*[c] (%)
1	**1a**	**4a**	0	25	70
2	**1a**	**4a**	2	36	70
3	**1b**	**4b**	1	55[d] [12][e]	98
4	**1b**	**4b**	2	56[d] [6][e]	92
5	**1b**	**4b**	5	23[d]	89
6	**1b**	**4b**	10	trace[d]	75
7[f]	**1b**	**4b**	2	67	95

[a] Conditions (one stage): pyrrolidine **1** (1 equiv), pyrrole (n equiv), MAO-N D5 freeze-dried whole cells (500 mg per mmol of **1**), PPB (50 mL per mmol of **1**, 200 mM, pH 7.5), 37 °C, 400 rpm shaking, 17 h. [b] Isolated yield, unless stated otherwise. [c] Determined with chiral HPLC by comparison with the racemic mixture. [d] Yield determined by NMR spectroscopy with 2,5-dimethylfuran (0.5 equiv) as an internal standard. [e] Yield of the proposed side product[17] in square brackets as determined by NMR spectroscopy with 2,5-dimethylfuran (0.5 equiv) as an internal standard. [f] Conditions (two stages): pyrrolidine **1** (1 equiv), MAO-N D5 freeze-dried whole cells (500 mg per mmol of **1**), PPB (50 mL per mmol of **1**, 200 mM, pH 7.5), 37 °C, 400 rpm shaking, 17 h; then pyrrole (2 equiv), 37 °C, 400 rpm shaking, 24 h.

of **1b** with varying equivalents of pyrrole (entries 3–6). A significant decrease in conversion was observed with increasing pyrrole stoichiometry, which is probably caused by competitive enzyme inhibition by the excess of pyrrole. To our surprise, the enantioselectivity was also found to decrease with increasing pyrrole stoichiometry. Binding of pyrrole in one or more hydrophobic pockets in the enzyme may alter its conformation, thereby affecting the enantioselectivity. In order to maximize both yield and enantioselectivity, we performed the oxidative aza-FC reaction as a two-stage one-pot protocol, in which pyrrole (2 equiv) is added after the oxidation is complete (17 h). Using this procedure, **4b** was isolated in improved yield and with high enantioselectivity without the formation of any side product (entry 7). We

Table 2. Optimization of the reaction conditions for the asymmetric oxidative aza-Friedel–Crafts reaction of *meso*-pyrrolidines **1b**.[a]



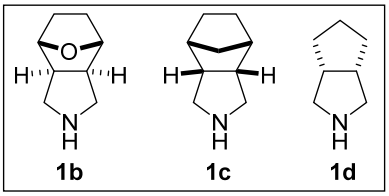
Entry	Buffer	pH	Yield[b] (%)	*ee*[c] (%)
1	200 mM PPB	7.5	66	95%
2	200 mM PPB	6.5	67	93%
3	200 mM PPB	7.0	73	94%
4	200 mM PPB	8.0	56	94%
5	200 mM PPB	8.5	49	92%
6	100 mM PPB	7.5	63	95%
7	500 mM PPB	7.5	65	95%
8	50 mM Tris-HCl	7.5	66	92%
9	20 mM HEPES	7.5	68	93%
10[d]	200 mM PPB	7.5	63	94%
11[e]	200 mM PPB	7.5	68	n.d.
12[f]	200 mM PPB	7.5	54 [7][g]	n.d.

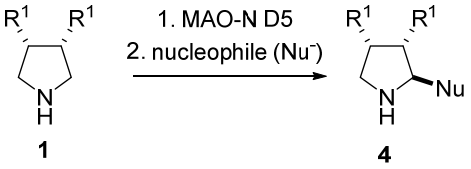
[a] Conditions (two stages): 1. pyrrolidine **1** (1 equiv), MAO-N D5 freeze-dried whole cells (500 mg per mmol of **1**), PPB (50 mL per mmol of **1**, 200 mM, pH 7.5), 37 °C, 400 rpm shaking, 17 h; 2. pyrrole (2 equiv), 37 °C, 400 rpm shaking, 24 h. [b] Crude yield (>95% purity). [c] Determined with chiral HPLC by comparison with the racemic mixture. [d] Reaction performed at 30 °C. [e] Second stage: 5 h. [f] Second stage: 1 h. [g] Yield of the corresponding imine (**2b**) in square brackets, calculated by the molar ratio in NMR spectroscopy.

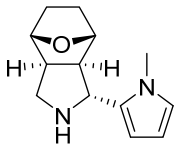
further explored the reaction conditions in terms of molarity, pH and type of buffer, but these factors did not significantly affect the reaction outcome (Table 2, entries 1–8). Notably, the aza-FC reaction proved to be relatively fast, since full conversion of **2b** was reached in a few hours (entries 11–12).

With the optimized conditions in hand, the scope of the nucleophile was explored with a range of pyrroles and indoles. To our delight, the desired products **4c**–**i** were obtained in moderate to good yields with high enantioselectivity (Table 3). In all cases, a clean conversion to single diastereoisomers of the products was observed. In order to determine the relative and absolute configuration of these adducts, 2-pyrrolyl pyrrolidine **4f** was crystallized and its structure was confirmed by X-ray crystallography.[18] The analogous products **4a**–**e** and **4g** were assumed to have

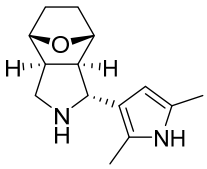
Table 3. Scope exploration for oxidative aza-Friedel—Crafts reaction.[a]



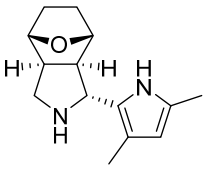




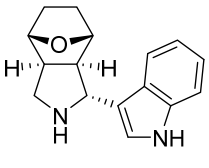
4c, 59%, 93% *ee*



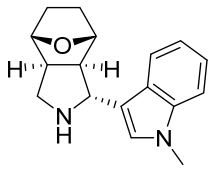
4d, 42%, 95% *ee*



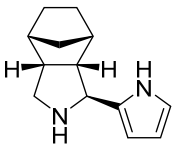
4e, 62%, 94%[b] *ee*



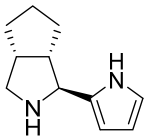
4f, 52%, 95% *ee*



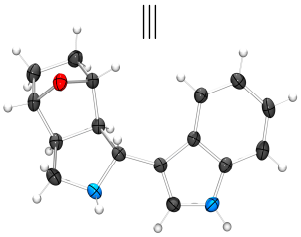
4g, 20%, 94% *ee*



4h, 85%, >99% *ee*



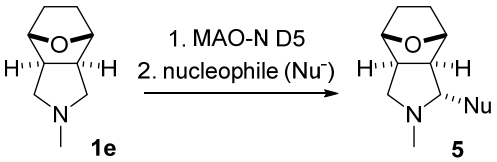
4i, 67%, 97% *ee*

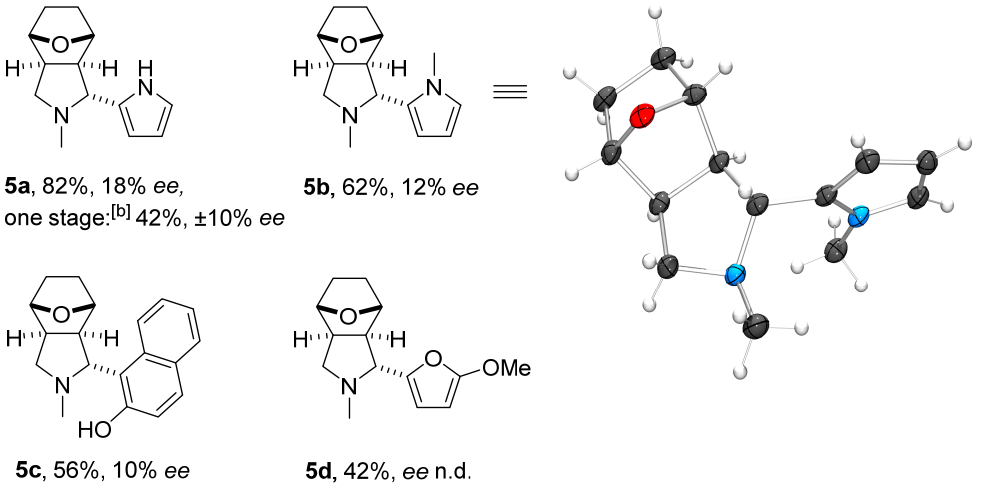


X-ray structure of **4f** with displacement ellipsoids drawn at 50% probability level.[18] [a] Conditions (two stages): 1. pyrrolidine **1** (1 equiv), MAO-N D5 freeze-dried whole cells (500 mg per mmol of **1**), PPB (50 mL per mmol of **1**, 200 mM, pH 7.5), 37 °C, 400 rpm shaking, 17 h; 2. pyrrole (2 equiv) and DMSO (5% v/v, only for **4f,g**), 37 °C, 400 rpm shaking, 24 h. Single diastereoisomers were observed by NMR analysis of the crude product. [b] Approximate value as a result of overlap with small impurities in the HPLC chromatogram.

the same relative configuration,[19] which is supported by the absence of a NOESY correlation between the protons at the 2- and 3-positions of the pyrrolidine (as indicated in Scheme 3). Other heteroaromatic nucleophiles, including 3-methylindole, 2-methylfuran, 2-methoxyfuran and *N*-phenyl pyrrole, were found to be unreactive towards **2b**[20] under these conditions. Further investigation showed that a range of other C-nucleophiles (*N*,*N*-dimethylaniline, 1,3-dimethoxy-benzene, *p*-cresol, 1-phenyl-1-trimethylsiloxyethylene, ethyl vinyl ether and 4-(cyclohex-1-en-1-yl)-morpholine) did not show significant reactivity either. To further evaluate the reaction scope, we tested different *meso*-pyrrolidines. Pleasingly, the examined

Table 4. Oxidative aza-Friedel–Crafts reaction with *N*-methylpyrrolidines **1e**.[a]

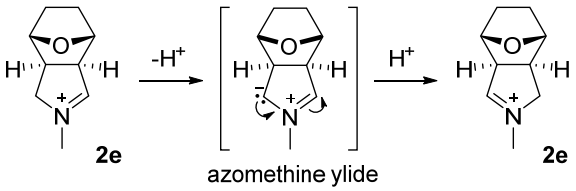




X-ray structure of **5b** with displacement ellipsoids drawn at 50% probability level.[18] [a] Conditions (two stages): 1. pyrrolidine **1e** (1 equiv), MAO-N D5 *freeze-dried* whole cells (500 mg per mmol of **1e**), PPB (50 mL per mmol of **1e**, 200 mM, pH 7.5), 37 °C, 400 rpm shaking, 17 h; 2. pyrrole (2 equiv) and DMSO (10% v/v, only for **5c**), 37 °C, 400 rpm shaking, 24 h. Single diastereoisomers were observed with NMR spectroscopy of the crude mixture. [b] Conditions (one stage): pyrrolidine **1e** (1 equiv), pyrrole (2 equiv), MAO-N D5 freeze-dried whole cells (500 mg per mmol of **1e**), PPB (50 mL per mmol of **1e**, 200 mM, pH 7.5), 37 °C, 400 rpm shaking, 17 h. Compound **5a** was isolated as an inseparable mixture with **6** (6%) and the yields were calculated based on the molar ratio as determined by NMR analysis.[22]

substrates **1c** and **1d** underwent clean conversion to the desired 2-pyrrolyl pyrrolidines **4h** and **4i** as single diastereoisomers. Their relative and absolute configurations were deduced from our previous studies on diastereoselective α-functionalizations of **1c,d**.[8c]

Next, we investigated the application of *N*-methyl pyrrolidine **1e** in the oxidative aza-FC reaction with different nucleophiles. To our delight, a wider variety of aromatic and heteroaromatic nucleophiles could be combined with this substrate, presumably as a result of the increased electrophilicity of the iminium ion **2e**. The desired 2-substituted pyrrolidines **5a**–**d** were obtained in reasonable to good yield and as single diastereoisomers (Table 4). In order to determine the relative stereochemistry, 2-pyrrolyl pyrrolidine **5b** was crystallized and its structure was corroborated by X-ray crystallography.[18] Disappointingly, products **5a**–**c** were isolated with low optical purity (≤16% *ee*). Possibly, the biocatalyst has low stereoselectivity in the oxidation of *meso*-pyrrolidine **1e**. However, in this case one would expect to find identical *ee* values for **5a**–**d**. Another plausible explanation is a post-oxidation racemization by an internal redox-neutral hydride transfer mechanism, as commonly observed for cyclic iminium ions.[21] This racemization has been described to proceed through an azomethine ylide intermediate as depicted in Scheme 4. The low optical purity of **5a**–**c** may be caused by a combination of low stereoselectivity during the biocatalytic oxidation of **1e** and subsequent partial racemization.[22] Despite the decreased enantioselectivity for **1e**, our method is significantly more benign than many other direct α-functionalizations of tertiary amines.[7] Moreover, the synthesis of *rac*-**5a**–**c** (as racemic standards for *ee* determination) required a laborious three-step protocol involving oxidation, Brønsted acid-mediated addition and *N*-methylation.[23] Thus, our one-pot oxidative aza-FC reaction has many advantages over conventional chemical synthesis of 2-substituted pyrrolidines.



Scheme 4. Proposed mechanism for racemization of **2e** through an internal redox-neutral hydride transfer.

2.3 Conclusion

We developed an one-pot chemoenzymatic oxidative aza-Friedel–Crafts reaction under benign conditions for the direct α-functionalization of a range of pyrrolidines including both secondary and tertiary amines. These typically unreactive substrates were activated by means of biocatalytic oxidation in aqueous buffer, followed by the addition of a variety of C-nucleophiles without the requirement of an additional catalyst. The desired 2-substituted pyrrolidines were obtained in reasonable to good yield and as single diastereoisomers with generally high enantioselectivity. This contribution demonstrates the high potential of one-pot chemoenzymatic transformations to produce functionalized chiral small molecules in a sustainable manner.

2.4 Acknowledgements

We thank E. Janssen (VU University) for technical assistance, S. Bouwman (VU University) for HRMS measurements, and Dr. A. W. Ehlers (VU University) for NMR maintenance. S. Alvarez (Utrecht University) is kindly acknowledged for her contribution to the experimental part. The X-ray diffractometers employed were purchased with support from the Hercules Foundation (project AUGE/11/029 "3D-SPACE: 3D Structural Platform Aiming for Chemical Excellence") NSF Grant 1337296. The authors thank M. Zeller (Youngstown State University) and K. Vanhecke (Ghent University) for collecting the data sets and Dr. C. M. L. Vande Velde (University of Antwerp) for the refinement of **4f** and **5b**. M. Rentsch (Waters) is kindly acknowledged for UPC2-MS analysis of **4h** and **4i**.

2.5 Experimental Section

General comments

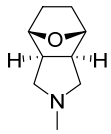
Starting materials were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics and used without treatment. Unless stated otherwise, the solvents were purchased from VWR Chemicals or Biosolve and were used without further treatment. Cyclohexane (*c*Hex) was purified by distillation before use. The *meso*-pyrrolidines **1a-d** and racemic imines *rac*-**2a** and **S2c-d** were synthesized according to previously

reported procedures.[16] The procedure for *in situ* biocatalytic oxidation of *meso*-pyrrolidines with an engineered monoamine oxidase was adapted from a previously reported procedure.[14] Celite® 512 medium was purchased from Sigma Aldrich. Column Chromatography was performed on Silica-P Flash Silica Gel (particle size 40-63 µm, pore diameter 60 Å) from Silicycle or aluminiumoxide (activated, basic, Brockmann I) from Sigma Aldrich. Thin Layer Chromatography (TLC) was performed using TLC plates F_{254} (silica gel 60 on aluminium) from Merck Serono KGaA (Darmstadt) and compounds were visualized by UV detection (254 or 366 nm) and stained with basic aq. $KMnO_4$ or ninhydrin/ethanol. ^1H, ^{13}C, COSY, HSQC, HMBC and NOESY nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (500.23 MHz for ^1H and 125.78 MHz for ^{13}C) in $CDCl_3$ using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR) or Bruker Avance 400 (400.13 MHz for ^1H and 100.62 MHz for ^{13}C) using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR) or Bruker Avance 250 (250.13 MHz for ^1H) in $CDCl_3$ using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet) and m (multiplet) or combinations thereof. The COSY-, HMBC- and HSQC-NMR spectra were used for the assignment of the proton signals. The APT-NMR spectra were used for the assignment of the carbon signals. NMR data was processed using MestReNova. Names of chemical structures were deduced from generic names and/or important functionalities. Electrospray Ionization (ESI) high resolution mass spectrometry (HRMS) was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Infrared (IR) spectra were recorded neat using a FTIR-8400s from Shimadzu. Signal intensities are described as strong (s), medium (m), weak (w) or broad (br). Melting points were recorded on a Büchi M-565 and are not corrected. Chiral HPLC was recorded using a LC10VP with a SCL-10A *VP* system controller, LC-10AT *VP* liquid chromatograph, SPD-M10A *VP* diode array detector and CTO-10AC *VP* column oven from Shimadzu. Data was processed using Shimadzu Labsolutions. UPC2-MS analysis was recorded using an Acquity UPC^2 system consisting of a SFC Manager, Column Manager, Sample Manager, Binary Solvent Manager, SFC PDA Detector, Isocratic Solvent Manager, QDa Detector from Waters using Acquity Trefoil method development strategy. Specific rotations were measured with an automatic AA-10 polarimeter. X-ray single crystal data for **4f** were collected at 101K on an Agilent Supernova diffractometer, with Cu microsource and mirror optics. ω-scans were employed, to collect a full sphere of reflections to θ=66.97°. 44692 reflections were measured, of which 2643 unique, with R_{int} 6.91%. Data were reduced and corrected for absorption with the Agilent CrysAlisPro software v1.171.37.35.[26] For **5b**, data were collected on a Bruker X8 Prospector diffractometer with Cu microsource and focusing optics, and an ApexII detector. Here also, a full sphere of reflections was collected with ω-scans up to θ=66.97°. 11332 reflections were measured, of which 2174 were unique, with R_{int} = 5.44%. Data were reduced with Bruker SAINT v8.34A[27] and corrected for absorption with SADABS 2012/1.[28] The structures were solved and refined with the SHELX suite of software[29] and the shelXle graphical interface.[30] Nu unusual values were encountered in the bond distances and angles, and the crystal packing also contained no unusual or unexpected features. Figures were prepared with Ortep3 for Windows.[31] In both cases, the space group was chiral, and the absolute configuration of the enantiomers could be derived from the Friedel differences. Using Parsons's method,[32] for **4f**, the Flack parameter is -0.18(10) , whereas for **5b**, it equals -0.13(12). The significance of these values was cross checked by using the Bayesian approach of Hooft[33] with PLATON.[34] For **4f**, this leads to a probability that the absolute configuration is incorrectly assigned of 10^{-29}, and a probability that the crystal is a racemic twin of 10^{-9}. Hooft y equals -0.15(10). For **5b**, those same probabilities are 10^{-27} and 10^{-8}, respectively. Hooft y equals -0.11(10).

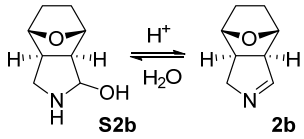
General procedure for the reaction of *rac*-2a with pyrrole in organic solvent: To a solution of imine *rac*-**2a** (0.25 mmol, 1.0 equiv) in solvent (0.2 M) was added nucleophile pyrrole (0.50 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 17 h and quenched by the addition of sat. aq. Na_2CO_3 (10 mL), extracted with DCM (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was analyzed with NMR spectroscopy. No conversion of rac-2a was observed in the investigated solvents: MeOH, MeCN and DCM.

General procedure for the reaction of *rac*-2a with pyrrole in aqueous buffer: To a solution of imine *rac*-**2a** (0.25 mmol, 1.0 equiv) in aq. sodium phosphate buffer (0.2 M, 200 mM, pH 7.5) was added nucleophile pyrrole (0.50 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 17 h, after which the pH was adjusted to 12-13 with 2M aq. NaOH. The aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The yield of **4a** (42%) was determined with ^{1}H-NMR spectroscopy after dissolving the crude product in $CDCl_3$ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 equiv) as internal standard.

Substrate synthesis



pyrrolidine 1e: To a solution of pyrrolidine **1b** (2.10 g, 15.1 mmol, 1.0 equiv) in methanol (100 mL) at 0 °C under N_2 atmosphere were added formaldehyde (1.68 mL, 22.5 mmol, 1.5 equiv), acetic acid (1.75 mL, 30.0 mmol, 2.0 equiv) and sodium cyanoborohydride (1.46 g, 22.5 mmol, 1.5 equiv). The reaction mixture was stirred for 2 h at rt and quenched by the addition of sat. aq. Na_2CO_3 (100 mL), extracted with DCM (3 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved with flash chromatography (SiO_2) with an eluent gradient of MeOH (1-5%) in DCM to obtain compound **1e** (1.70 g, 11.1 mmol, 74%) as a light orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.24 (dd, *J* = 3.2, 2.3 Hz, 2H, C*H*O), 3.10 – 3.04 (m, 2H, C*H*$_2$NC*H*$_2$), 2.42 – 2.37 (m, 2H, NCH$_2$C*H*), 2.29 (s, 3H, NC*H*$_3$), 1.98 – 1.91 (m, 2H, C*H*$_2$NHC*H*$_2$), 1.69 – 1.63 (m, 2H, C*H*$_2$C*H*$_2$), 1.40 – 1.34 (m, 1H, C*H*$_2$C*H*$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 78.9 (CH), 60.6 (CH_2), 49.3 (CH), 41.3 (CH), 28.5 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2949 (m), 2783 (m), 1655 (w), 1448 (m), 1219 (m), 1136 (m), 972 (m), 928 (s), 806 (s), 592 (s). **HRMS** (ESI): *m/z* calculated for $C_9H_{16}NO$ $[M+H]^+$: 154.1226, found: 154.1232.



hemiaminal S2b and 1-pyrroline 2b:[33,34] To a suspension of rehydrated freeze-dried MAO-N cells (6 x 125 mg, 30 min, 37 °C, 400 rpm) in aq. phosphate buffer (6 x 12.5 mL, 200mM, pH 7.5) was added pyrrolidine (6 x 36 mg, 1.5 mmol, 1.0 equiv). The reaction mixture was shaken for 17 h (400 rpm, 37 °C). The suspension was centrifuged (1 h, 4000 rpm, 4 °C)[35] and the supernatant was collected, adjusted to pH 12-13 with 2M aq. NaOH, extracted with DCM (3 x 150 mL), dried (Na_2SO_4) and concentrated *in vacuo*, to obtain compound **S2b** (180 mg, 1.21 mmol, 81%) as a light yellow

solid without the need of purification. **m.p.**: 152 – 155 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.34 – 4.30 (m, 1H, CH(OH)CHC*H*O), 4.26 – 4.21 (m, 1H, CH_2CHC*H*O), 3.15 (t, *J* = 8.0 Hz, 1H, NHCH_2), 2.47 (d, *J* = 6.7 Hz, 1H, NHC*H*OH), 2.39 (q, *J* = 8.0 Hz, 1H, NHCH$_2$C*H*), 2.18 – 2.09 (m, 2H, NHCH_2CHC*H*CH(OH)), 1.74 – 1.62 (m, 2H, CH_2CH_2), 1.44 – 1.35 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 86.1 (CH), 78.5 (CH), 78.0 (CH), 52.8 (CH), 51.4 (CH_2), 47.5 (CH), 28.8 (CH_2), 28.6 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2949 (m), 1655 (w), 1393 (m), 1315 (m), 1225 (s), 1215 (s), 1175 (s), 1047 (m), 972 (s), 924 (s), 805 (s), 623 (s). **HRMS** (ESI): *m/z* calculated for $C_8H_{12}NO$ $[M+H]^+$: 138.0913, found: 138.0916. **Specific rotation**: $[\alpha]_D^{20}$ = +4 ° (c = 0.5, $CHCl_3$).

hemiaminal *rac*-S2b and 1-pyrroline *rac*-2b:[36] To a solution of *meso*-pyrrolidine **1b** (2.72 g, 19.2 mmol, 1.0 equiv) in DCM (120 mL) was slowly added *N*-chlorosuccinimide (2.64 g, 19.2 mmol, 1.0 equiv) at 0°C. The reaction mixture was stirred for 2 h at rt, washed with H_2O (2 x 100 mL) and brine (1 x 100 mL), extracted with DCM (2 x 75 mL), dried (Na_2SO_4) and concentrated to 50 mL *in vacuo.* The resulting solution was slowly added this to a solution of KOH (1.62 g, 28.8 mmol, 1.5 equiv) in EtOH (25 mL). The reaction mixture was stirred for 24 h at rt, after which it was concentrated *in* vacuo. The crude product was then redissolved in DCM (100 mL), washed with sat. $NaHCO_3$ (50 mL), extracted with DCM (2 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (DCM → 19:1 v/v DCM:MeOH) to obtain compound *rac*-**S2b** (2.25 mg, 16.4 mmol, 75%) as a light yellow solid without the need of purification. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.33 – 4.30 (m, 1H, CH(OH)CHC*H*O), 4.28 – 4.21 (m, 1H, CH_2CHC*H*O), 3.15 (t, *J* = 8.0 Hz, 1H, NHCH_2), 2.47 (d, *J* = 6.8 Hz, 1H, NHC*H*OH), 2.40 (q, *J* = 7.8 Hz, 1H, NHCH$_2$C*H*), 2.20 – 2.08 (m, 2H, NHCH_2CHC*H*CHOH), 1.75 – 1.59 (m, 2H, CH_2CH_2), 1.43 – 1.33 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 86.2 (CH), 78.5 (CH), 78.0 (CH), 52.8 (CH), 51.4 (CH_2), 47.5 (CH), 28.8 (CH_2), 28.6 (CH_2) ppm.

Synthetic procedures and spectral data

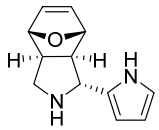
General procedure 1 (two stages): To a suspension of rehydrated freeze-dried MAO-N cells (500 mg per mmol of **1**, 30 min, 37 °C, 400 rpm) and aq. phosphate buffer (50 mL per mmol, 200mM, pH 7.5) was added pyrrolidine **1** (1.0 equiv). The reaction mixture was shaken for 17 h (400 rpm, 37 °C) after which the nucleophile (2.0 equiv) were added, followed by continued shaking for 24 h. The suspension was centrifuged (1 h, 4000 rpm, 4 °C)[35] and the supernatant was collected, adjusted to pH 12-13 with 2M aq. NaOH, extracted with DCM (3 x 100 mL per mmol of **1**), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved with flash chromatography (SiO_2) with an eluent gradient of MeOH (1- 5%) in DCM.

General procedure 2 (two stages with DMSO): To a suspension of rehydrated freeze-dried MAO-N cells (500 mg per mmol of **1**, 30 min, 37 °C, 400 rpm) and phosphate buffer (50 mL per mmol of **1**, 200mM, pH 7.5) was added pyrrolidine **1** (1.0 equiv). The reaction mixture was shaken for 17 h (400 rpm, 37 °C) after which the nucleophile (0.50 mmol, 2.0 equiv) and DMSO (10% v/v) were added, followed by continued shaking for 24 h. The workup was performed as described in *general procedure 1*.

General procedure 3 (one stage): To a suspension of rehydrated freeze-dried MAO-N cells (500 mg per mmol of **1**, 30 min, 37 °C, 400 rpm) and phosphate buffer (50 mL per mmol of **1**, 200mM, pH 7.5) was added pyrrolidine **1** (1.0 equiv) and pyrrole (2.0 equiv). The reaction mixture was shaken for 17 h (400 rpm, 37 °C) and the workup was performed as described in *general procedure 1*.

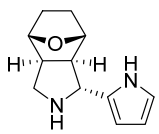
General procedure 4: To a solution of nucleophile (1.0 equiv) in DCM (0.2 M) were added imine **2** (1.1 equiv) and TFA (2.0 equiv). The reaction mixture was stirred for 30 min at 60°C under microwave irradiation and quenched by the addition of sat. aq. Na_2CO_3 (10 mL per mmol of **2**), extracted with DCM (2 x 10 mL per mmol of **2**), dried (Na_2SO_4) and concentrated *in vacuo*.

General procedure 5: To a solution of nucleophile (2.0 equiv) in DCM (0.2 M) were added imine **2** (1.0 equiv) and TFA (2.0 equiv). The reaction mixture was stirred for 30 min at 60°C under microwave irradiation and quenched by the addition of sat. aq. Na_2CO_3 (10 mL per mmol of **2**), extracted with DCM (2 x 10 mL per mmol of **2**), dried (Na_2SO_4) and concentrated *in vacuo*.



pyrrolyl pyrrolidine 4a: Prepared from pyrrolidine **1a** (118 mg [13% THF], 0.75 mmol, 1.0 equiv) and nucleophile pyrrole (105 µL, 1.5 mmol, 2.0 equiv) according to *general procedure 3* to obtain compound **4a** (55 mg, 0.27 mmol, 36%) as a light brown solid. **m.p.**: >152 °C (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.30 (bs, 1H, N*H*C*), 6.74 (q, *J* = 2.5 Hz, 1H, C*NHC*H*), 6.38 (s, 2H, C*H*=C*H*), 6.13 (q, *J* = 2.8 Hz, 1H, C*NHCHC*H*), 6.06 – 6.03 (m, 1H, C*NHCHCHC*H*), 4.82 (s, 1H, NHCHCHC*H*O), 4.72 (s, 1H, NHCH$_2$CHC*H*O), 4.09 (d, *J* = 4.9 Hz, 1H, NHC*H*C*), 3.18 (bs, 1H, N*H*CH$_2$), 3.06 (dd, *J* = 11.1, 7.7 Hz, 1H, NHC*H*$_2$), 2.78 (dd, *J* = 11.1, 5.2 Hz, 1H, NHC*H*$_2$), 2.50 – 2.38 (m, 2H, NHCH$_2$C*H*C*H*CHO) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.8 (CH), 136.7 (CH), 132.1 (C*), 117.7 (CH), 108.2 (CH), 105.5 (CH), 82.7 (CH), 82.0 (CH), 59.7 (CH), 52.6 (CH), 49.6 (CH$_2$), 46.8 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3258 (w), 3126 (w), 2997 (w), 1437 (m), 1028 (s), 932 (m), 897 (s), 814 (s), 714 (s), 696 (s), 609 (m). **HRMS** (ESI$^+$) calculated for $C_{12}H_{15}N_2O$ (MH$^+$) 203.1179, found 203.1184. **Chirality:** 70% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 235 nm, t (major) = 10.205 min, t (minor) = 13.011 min]. **Specific rotation**: $[\alpha]_D^{20} = -8$ ° (c = 0.5, EtOH).

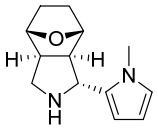
***rac*-pyrrolyl pyrrolidine 4a:** Prepared from hemiaminal **S2b** (75.4 mg, 0.55 mmol, 1.0 equiv) and nucleophile pyrrole (76.3 µL, 1.10 mmol, 2.0 equiv) according to *general procedure 5* to obtain compound *rac*-**4a** (100 mg, 0.50 mmol, 90%) as a light brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.92 (bs, 1H, C*N*H*), 6.72 (s, 1H, C*NHCHCHC*H*), 6.38 (s, 2H, C*H*=C*H*), 6.15 (s, 1H, C*NHCHC*H*), 6.04 (s, 1H, NHC*C*H*), 4.85 (s, 1H, NHCHCHC*H*O), 4.73 (s, 1H, NHCH$_2$CHC*H*O), 4.08 (d, *J* = 4.4 Hz, 1H, NHC*H*C*), 3.07 (dd, *J* = 11.0, 7.3 Hz, 1H, NC*H*$_2$), 2.83 (dd, *J* = 11.2, 4.6 Hz, 1H, NC*H*$_2$), 2.59 – 2.36 (m, 2H, NCH$_2$CHCHCOH), 2.33 (s, 1H, CH$_2$N*H*) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.9 (CH), 136.7 (CH), 133.3 (C*), 117.0 (CH), 108.4 (CH), 104.9 (CH), 83.0 (CH), 82.2 (CH), 59.9 (CH), 53.1 (CH), 50.1 (CH$_2$), 47.1 (CH) ppm.



pyrrolyl pyrrolidine 4b: Prepared from pyrrolidine **1b** (151 mg, 1.09 mmol, 1.0 equiv) and nucleophile pyrrole (150 µL, 2.18 mmol, 2.0 equiv) according to *general procedure 1* to obtain compound **4b** (149 mg, 0.73 mmol, 67%) as an off-white solid. **m.p.**: >115 °C (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.81 (s, 1H, N*H*C*), 6.73 (s, 1H, C*NHC*H*), 6.15 (s, 1H, C*NHCHC*H*), 6.05 (s, 1H, C*NHCHCHC*H*), 4.49 – 4.39 (m, 1H, NHCHCHC*H*O), 4.36 – 4.29 (m, 1H, NHCH$_2$CHC*H*O), 3.93 (d, *J* = 5.5 Hz, 1H, NHC*H*C*), 3.20 – 3.12 (m, 1H, NHC*H*$_2$), 2.71 (dd, *J* =

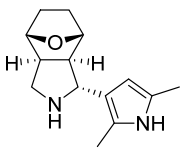
10.3, 6.2 Hz, 1H, NHC*H*$_2$), 2.43 – 2.31 (m, 2H, NHCH$_2$C*H*CHCHO), 2.15 – 2.01 (m, 1H, N*H*CH$_2$), 1.76 – 1.61 (m, 2H, C*H*$_2$C*H*$_2$), 1.47 – 1.37 (m, 2H, C*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 132.6 (C*), 117.6 (CH), 108.1 (CH), 105.2 (CH), 80.4 (CH), 79.6 (CH), 61.6 (CH), 56.3 (CH), 51.5 (CH_2), 50.0 (CH), 28.7 (CH_2), 28.6 (CH_2) ppm. **IR** (cm^{-1}): ν_{max} = 3263 (m), 2968 (m), 2864 (m), 2750 (m), 1456 (m), 1427 (m), 1294 (m), 1222 (m), 1199 (m), 1097 (m), 1022 (s), 960 (s), 927 (s), 881 (s), 798 (s), 711 (s), 609 (s). **HRMS** (ESI^+) calculated for $C_{12}H_{17}N_2O$ (MH^+) 205.1335, found 205.1331. **Chirality:** 95% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 90/10, v = 0.7 mL/min, column temperature: 30 °C, λ = 220 nm, t (major) = 14.115 min, t (minor) = 21.383 min]. **Specific rotation**: $[\alpha]_D^{20}$ = –28 ° (c = 0.5, EtOH).

***rac*-pyrrolyl pyrrolidine 4b:** Prepared from hemiaminal **S2b** (273 mg, 1.75 mmol, 1.1 equiv) and nucleophile pyrrole (110 µL, 1.59 mmol, 1.0 equiv) according to *general procedure 4* to obtain compound *rac*-**4b** (231 mg, 1.13 mmol, 71%) as an off-white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.90 (s, 1H, N*H*C*), 6.74 (s, 1H, C*NHC*H*), 6.16 – 6.12 (m, 1H, C*NHCHC*H*), 6.06 (s, 1H, C*NHCHCHC*H*), 4.42 (d, *J* = 3.7 Hz, 1H, NHCHCHC*H*O), 4.32 (d, *J* = 3.8 Hz, 1H, NHCH$_2$CHC*H*O), 3.93 (d, *J* = 5.5 Hz, 1H, NHC*H*C*), 3.17 (dd, *J* = 10.5, 7.9 Hz, 1H, NHC*H*$_2$), 2.70 (dd, *J* = 10.5, 5.9 Hz, 1H, NHC*H*$_2$), 2.43 – 2.33 (m, 2H, NHCH$_2$C*H*CH), 2.01 (bs, 1H, NHC*H*$_2$), 1.75 – 1.62 (m, 2H, C*H*$_2$C*H*$_2$), 1.42 (d, *J* = 7.2 Hz, 2H, C*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 132.7 (C*), 117.5 (CH), 108.2 (CH), 105.1 (CH), 80.5 (CH), 79.6 (CH), 61.6 (CH), 56.3 (CH), 51.6 (CH_2), 50.0 (CH), 28.7 (CH_2), 28.6 (CH_2) ppm.



***N*-methylpyrrolyl pyrrolidine 4c:** Prepared from pyrrolidine **1b** (147 mg, 1.05 mmol, 1.0 equiv) and nucleophile *N*-methylpyrrole (186 µL, 2.10 mmol, 2.0 equiv) according to *general procedure 1* to obtain compound **4c** (135.2 mg, 0.62 mmol, 59%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.63 – 6.58 (m, 1H, NC*H*), 6.09 – 6.03 (m, 2H, NCHC*H*C*H*), 4.38 – 4.29 (m, 2H, C*H*OC*H*), 3.78 (d, *J* = 6.9 Hz, 1H, NHC*H*), 3.69 (s, 3H, NC*H*$_3$), 3.27 (dd, *J* = 11.5, 8.0 Hz, 1H, NHC*H*$_2$), 2.63 (dd, *J* = 11.5, 6.9 Hz, 1H, NHC*H*$_2$), 2.52 – 2.45 (m, 1H, NHCHC*H*), 2.45 – 2.36 (m, 1H, NHCH$_2$C*H*), 1.82 (bs, 1H, N*H*), 1.75 – 1.65 (m, 2H, C*H*$_2$C*H*$_2$), 1.47 – 1.39 (m, 2H, C*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.1 (C*), 123.0 (CH), 106.5 (CH), 105.9 (CH), 80.2 (CH), 79.5 (CH), 60.6 (CH), 56.1 (CH), 52.2 (CH_2), 51.2 (CH), 34.3 (CH_3), 28.8 (CH_2), 28.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2957 (m), 1491 (w), 1298 (m), 1088 (w), 926 (m), 812 (m), 729 (s), 709 (s), 600 (m). **HRMS** (ESI^+) calculated for $C_{13}H_{19}N_2O$ (MH^+) 219.1492, found 219.1498. **Chirality:** 93% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 90/10, v = 0.7 mL/min, column temperature: 30 °C, λ = 220 nm, t (minor) = 14.309 min, t (major) = 34.281 min].

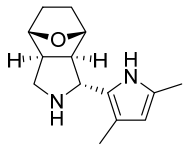
***rac*-*N*-methylpyrrolyl pyrrolidine 4c:** Prepared from hemiaminal **S2b** (109 mg, 0.70 mmol, 1.1 equiv) and nucleophile *N*-methylpyrrole (55.9 µL, 0.63 mmol, 1.0 equiv) according to *general procedure 4* to obtain compound *rac*-**4c** (109 mg, 0.50 mmol, 79%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.63 – 6.58 (m, 1H, NC*H*), 6.08 – 6.03 (m, 2H, NCHC*H*C*H*), 4.39 – 4.28 (m, 2H, C*H*OC*H*), 3.77 (d, *J* = 6.8 Hz, 1H, NHC*H*), 3.69 (s, 3H, NC*H*$_3$), 3.27 (dd, *J* = 11.5, 8.0 Hz, 1H, NHC*H*$_2$), 2.63 (dd, *J* = 11.2, 7.1 Hz, 1H, NHC*H*$_2$), 2.52 – 2.46 (m, 1H, NHCHC*H*), 2.45 – 2.36 (m, 1H, NHCH$_2$C*H*), 1.79 – 1.59 (m, 3H, N*H*, C*H*$_2$C*H*$_2$), 1.48 – 1.39 (m, 2H, C*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.2 (C*), 123.0 (CH), 106.5 (CH), 105.9 (CH), 80.3 (CH), 79.5 (CH), 60.6 (CH), 56.1 (CH), 52.3 (CH_2), 51.2 (CH), 34.3 (CH_3), 28.8 (CH_2), 28.8 (CH_2) ppm.



2,5-dimethylpyrrolyl pyrrolidine 4d: Prepared from pyrrolidine **1b** (161 mg, 1.15 mmol, 1.0 equiv) and nucleophile 2,5-dimethylpyrrole (233 µL, 2.30 mmol, 2.0 equiv) according to *general procedure 1* to obtain compound **4d** (112 mg, 0.48 mmol, 42%) as a brown solid. **m.p.**: 84 – 87 °C.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (s, 1H, N*H*C*), 5.80 (s, 1H, NHC*C*H*), 4.30 (dd, *J* = 7.7, 3.8 Hz, 2H, C*H*OC*H*), 3.65 (d, *J* = 7.6 Hz, 1H,

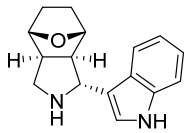
NHC*H*), 3.33 (t, *J* = 9.3 Hz, 1H, NHC*H*$_2$), 2.60 (t, *J* = 8.9 Hz, 1H, NHC*H*$_2$), 2.43 (q, *J* = 8.2 Hz, 1H, NHCH$_2$C*H*), 2.30 – 2.17 (m, 7H, NHCH$_2$C*H*, C(C*H*$_3$)NHC(C*H*$_3$)), 1.74-1.61 (m, 2H, C*H*$_2$CH$_2$), 1.47 – 1.31 (m, 2H, CH$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 126.0 (C*), 123.6 (C*), 119.7 (C*), 104.2 (CH), 79.7 (CH), 78.9 (CH), 60.4 (CH), 57.9 (CH), 51.6 (CH_2), 50.8 (CH), 28.7 (CH_2), 28.6 (CH_2), 13.09 (CH_3), 11.3 (CH_3) ppm. **IR** (cm^{-1}): ν_{max} = 2950 (s), 2871 (w), 1458 (s), 1218 (s), 1159 (m), 1027 (s), 987 (s), 925 (s), 896 (s), 856 (w), 792 (s), 713 (m), 599 (s), 567 (m). **HRMS** (ESI$^+$) calculated for $C_{14}H_{21}N_2O$ (MH^+) 233.1648, found 233.1636. **Chirality:** 95% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 90/10, v = 0.7 mL/min, column temperature: 30 °C, λ = 220 nm, t (minor) = 27.338 min, t (major) = 34.831 min]. **Specific rotation**: $[\alpha]_D^{20}$ = –4 ° (c = 0.5, EtOH).

***rac*-2,5-dimethylpyrrolyl pyrrolidine 4d:** Prepared from hemiaminal **S2b** (106 mg, 0.68 mmol, 1.1 equiv) and nucleophile 2,5-dimethylpyrrole (64.1 µL, 0.63 mmol, 1.0 equiv) according to *general procedure 4* to obtain compound *rac*-**4d** (101 mg, 0.43 mmol, 69%) as a brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (s, 1H, NHC*H*), 5.78 (s, 1H, NHC*H*C*H*), 4.30 (dd, *J* = 7.6, 4.1 Hz, 2H, C*H*OC*H*), 3.63 (d, *J* = 7.5 Hz, 1H, NHC*H*), 3.33 (t, *J* = 9.3 Hz, 1H, NHC*H*$_2$), 2.59 (t, *J* = 9.5 Hz, 1H, NHC*H*$_2$), 2.42 (q, *J* = 8.2 Hz, 1H, NHCH$_2$C*H*), 2.24 – 2.12 (m, 7H, NHCH$_2$C*H*, C(C*H*$_3$)NHC(C*H*$_3$)), 1.66 (s, 2H, C*H*$_2$CH$_2$), 1.45 – 1.30 (m, 2H, CH$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 125.8 (C*), 123.3 (C*), 120.0 (C*), 103.9 (CH), 79.6 (CH), 78.8 (CH), 60.3 (CH), 58.0 (CH), 51.7 (CH_2), 50.9 (CH), 28.7 (CH_2), 28.6 (CH_2), 13.0 (CH_3), 11.1 (CH_3) ppm.



2,4-dimethylpyrrolyl pyrrolidine 4e: Prepared from pyrrolidine **1b** (145 mg, 1.04 mmol, 1.0 equiv) and nucleophile 2,4-dimethylpyrrole (214 µL, 2.08 mmol, 2.0 equiv) according to *general procedure 1* to obtain compound **4e** (150 mg, 0.64 mmol, 62%) as a brown solid. **m.p.**: >70 °C (decomposition). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.71 (s, 1H, CH$_3$C*N*H), 5.65 (d, *J* = 2.1 Hz, 1H, CH$_3$C*C*H), 4.36 (d, *J* = 4.6 Hz, 1H, NHCHCHC*H*O), 4.29 (d, *J* = 4.4 Hz, 1H, NHCH$_2$CHC*H*O), 3.91 (d, *J* = 7.9 Hz, 1H, NHC*H*), 3.29 (t, *J* = 8.9 Hz, 1H, NHC*H*$_2$), 2.64 (t, *J* = 8.6 Hz, 1H, NHC*H*$_2$), 2.48 – 2.39 (m, 2H, N*H*CH$_2$C*H*), 2.28 (t, *J* = 8.3 Hz, 1H, NHCHC*H*), 2.21 (s, 3H, C*H*$_3$), 2.05 (s, 3H, C*H*$_3$), 1.73 – 1.62 (m, 2H, C*H*$_2$CH$_2$), 1.43 – 1.30 (m, 2H, CH$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 126.7 (C*), 125.9 (C*), 115.4 (C*), 107.7 (CH), 79.4 (CH), 78.6 (CH), 58.8 (CH), 56.4 (CH), 50.7 (CH_2), 49.1 (CH), 28.5 (CH_2), 28.3 (CH_2), 12.9 (CH_3), 11.0 (CH_3) ppm. **IR** (cm^{-1}): ν_{max} = 2962 (w), 2931 (w), 2871 (m), 1683 (s), 1436 (s), 1400 (s), 1267 (w), 1218 (s), 1201 (s), 1056 (s), 985 (s), 921 (s), 850 (s), 800 (s), 661 (m), 607 (s). **HRMS** (ESI$^+$) calculated for $C_{14}H_{21}N_2O$ (MH^+) 233.1648, found 233.1636. **Chirality:**[37] ±94% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 90/10, v = 0.7 mL/min, column temperature: 30 °C, λ = 220 nm, t (major) = 8.950 min, t (minor) = 11.879 min]. **Specific rotation**: $[\alpha]_D^{20}$ = –20 ° (c = 0.3, $CHCl_3$).

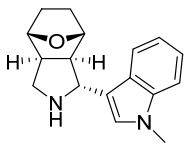
***rac*-2,4-dimethylpyrrolyl pyrrolidine 4e:** Prepared from hemiaminal **S2b** (109 mg, 0.70 mmol, 1.1 equiv) and nucleophile 2,4-dimethylpyrrole (64.9 µL, 0.63 mmol, 1.0 equiv) according to *general procedure 4* to obtain compound *rac*-**4e** (109 mg, 0.47 mmol, 67%) as a brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, CH$_3$C*N*H), 5.66 (s, 1H, CH$_3$C*C*H), 4.37 (d, *J* = 4.7 Hz, 1H, NHCHCHC*H*O), 4.29 (d, *J* = 4.7 Hz, 1H, NHCH$_2$CHC*H*O), 3.92 (d, *J* = 7.8 Hz, 1H, NHC*H*), 3.28 (t, *J* = 9.0 Hz, 1H, NHC*H*$_2$), 2.71 – 2.59 (m, 1H, NHC*H*$_2$), 2.44 (q, *J* = 8.3 Hz, 1H, NHCH$_2$C*H*), 2.28 (t, *J* = 8.3 Hz, 1H, NHCHC*H*), 2.20 (s, 3H, C*H*$_3$), 2.05 (s, 3H, C*H*$_3$), 1.78 – 1.62 (m, 2H, C*H*$_2$CH$_2$), 1.55 – 1.28 (m, 2H, CH$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 127.2 (C*), 125.0 (C*), 116.0 (C*), 107.9 (CH), 79.5 (CH), 78.7 (CH), 59.0 (CH), 56.2 (CH), 50.5 (CH_2), 49.0 (CH), 28.5 (CH_2), 28.3 (CH_2), 13.0 (CH_3), 11.0 (CH_3) ppm.



indolyl pyrrolidine 4f: Prepared from pyrrolidine **1b** (210 mg, 1.51 mmol, 1.0 equiv), nucleophile indole (354 mg, 3.02 mmol, 2.0 equiv) and DMSO (5% v/v) according to *general procedure 2* to obtain compound **4f** (200 mg, 0.79 mmol, 52%)

as a yellow solid. **m.p.**: >136 °C (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.52 (bs, 1H, NHC*), 7.74 (d, *J* = 7.8 Hz, 1H, NHC*C*CH), 7.35 (d, *J* = 8.0 Hz, 1H, NHC*CH), 7.21 (t, *J* = 7.5 Hz, 1HC, NHC*CHCH), 7.19 – 7.12 (m, 2H, NHC*CHCHCH/C*NHCH), 4.48 (d, *J* = 3.5 Hz, 1H, NHCHCHCHO), 4.37 (d, *J* = 3.4 Hz, 1H, $NHCH_2CHCHO$), 4.10 (d, *J* = 6.5 Hz, 1H, CH_2NHCH), 3.40 (dd, *J* = 10.5, 7.7 Hz, 1H, $NHCH_2$), 2.75 (dd, *J* = 10.5, 6.9 Hz, 1H, $NHCH_2$), 2.57 – 2.44 (m, 2H, $NHCH_2CHCH$CHO), 1.99 (bs, 1H, CH_2NH), 1.76 – 1.63 (m, 2H, CH_2CH_2), 1.48 – 1.33 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.8 (C*), 126.4 (C*), 122.2 (CH), 121.8 (CH), 119.54 (CH), 119.52 (CH), 117.4 (C*), 111.6 (CH), 80.0 (CH), 79.4 (CH), 61.0 (CH), 57.0 (CH), 51.8 (CH_2), 50.8 (CH), 28.71 (CH_2), 28.67 (CH_2) ppm. **IR** (cm^{-1}): ν_{max} = 3317 (m), 3037 (w), 2858 (w), 2800 (w), 1448 (s), 1402 (s), 1323 (m), 1218 (s), 1174 (m), 1110 (s), 991 (s), 964 (s), 925 (s), 877 (m), 811 (m), 792 (m), 750 (s), 603 (s), 572 (m). **HRMS** (ESI^+) calculated for $C_{16}H_{19}N_2O$ (MH^+) 255.1492, found 255.1494. **Chirality:** 95% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 90/10, v = 0.7 mL/min, column temperature: 30 °C, λ = 220 nm, t (minor) = 37.513 min, t (major) = 42.266 min]. **Specific rotation**: $[\alpha]_D^{20}$ = –28 ° (c = 0.5, EtOH).

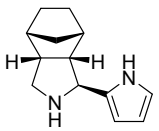
***rac*-indolyl pyrrolidine 4f:** Prepared from hemiaminal **S2b** (106 mg, 0.68 mmol, 1.1 equiv) and indole (73 mg, 0.62 mmol, 1.0 equiv) according to *general procedure 4* to obtain compound *rac*-**4f** (118 mg, 0.47 mmol, 75%) as a light brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.60 (bs, 1H, NHC*), 7.73 (d, *J* = 7.9 Hz, 1H, NHC*C*CH), 7.36 (d, *J* = 8.1 Hz, 1H, NHC*CH), 7.20 (t, *J* = 7.5 Hz, 1H, NHC*CHCH), 7.16 – 7.08 (m, 2H, NHC*CHCHCH/C*NHCH), 4.47 (d, *J* = 4.0 Hz, 1H, NHCHCHCHO), 4.37 (d, *J* = 4.0 Hz, 1H, $NHCH_2CHCHO$), 4.10 (d, *J* = 6.5 Hz, 1H, CH_2NHCH), 3.40 (dd, *J* = 9.5, 3.5 Hz, 1H, $NHCH_2$), 2.75 (dd, *J* = 10.3, 7.0 Hz, 1H, $NHCH_2$), 2.57 – 2.43 (m, 2H, $NHCH_2CHCH$CHO), 1.98 (bs, 1H, CH_2NH), 1.76 – 1.64 (m, 2H, CH_2CH_2), 1.48 – 1.33 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.8 (C*), 126.3 (C*), 122.2 (CH), 121.7 (CH), 119.64 (CH), 119.57 (CH), 117.7 (C*), 111.5 (CH), 80.0 (CH), 79.4 (CH), 61.1 (CH), 57.0 (CH), 51.9 (CH_2), 50.8 (CH), 28.7 (CH_2), 28.7 (CH_2) ppm.



***N*-methylindolyl pyrrolidine 4g:** Prepared from pyrrolidine **1b** (216 mg, 1.55 mmol, 1.0 equiv), nucleophile *N*-methylindole (407 mg, 3.10 mmol, 2.0 equiv) and DMSO (5% v/v) according to *general procedure 2* to obtain compound **4g** (100.2 mg [17% CH_2Cl_2], 0.31 mmol, 20%) as a light brown solid. **m.p.**: 155 – 156 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 1H, NC*C*CH), 7.31 (d, *J* = 8.1 Hz, 1H, NC*CH). 7.24 (t, *J* = 8.1 Hz, 1H, NC*C*CHCH), 7.12 (t, *J* = 7.4 Hz, 1H, NC*CHCH), 7.08 (s, 1H, CH_3NCH), 4.45 (s, 1H, NHCHCHCHO), 4.35 (s, 1H, $NHCH_2CHCHO$), 4.10 (d, *J* = 6.9 Hz, 1H, NHCH), 3.75 (s, 3H, NCH_3), 3.39 (t, *J* = 9.3 Hz, 1H, $NHCH_2$), 2.73 (t, *J* = 8.4 Hz, 1H, $NHCH_2$), 2.52 – 2.47 (m, 2H, $NHCHCHCHCH_2$), 2.01 (s, 1H, NH), 1.70 (s, 2H, CH_2CH_2), 1.45 – 1.25 (m, 2H, CH_2CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.2 (2x C*), 128.1 (CH), 126.8 (C*), 122.2 (CH), 119.7 (CH), 119.5 (CH), 109.6 (CH), 79.4 (CH), 78.8 (CH), 60.3 (CH), 56.2 (CH), 50.4 (CH_2), 49.0 (CH), 32.9 (CH_3), 28.4 (CH_2), 28.2 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2949 (m), 1393 (m), 1223 (s), 1175 (s), 1140 (w), 972 (s), 926 (s), 806 (s), 721 (s), 623 (s). **HRMS** (ESI^+) calculated for $C_{17}H_{21}N_2O$ (MH^+) 269.1648, found 269.1657. **Chirality:** 94% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 90/10, v = 0.7 mL/min, column temperature: 30 °C, λ = 220 nm, t (major) = 18.527 min, t (minor) 31.832 = min].

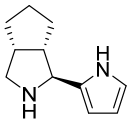
***rac*-*N*-methylindolyl pyrrolidine 4g:** Prepared from hemiaminal **S2b** (109 mg, 0.70 mmol, 1.1 equiv) and nucleophile *N*-methylindole (82.6 mg, 0.63 mmol, 1.0 equiv) according to *general procedure 4* to obtain compound *rac*-**4g** (147 mg, 0.55 mmol, 87%) as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.9 Hz, 1H, NC*C*CH), 7.30 (d, *J* = 8.2 Hz, 1H, NC*CH), 7.24 (t, *J* = 7.6 Hz, 1H, NC*C*CHCH), 7.13 (d, *J* = 7.2 Hz, 1H, NC*CHCH), 7.09 (s, 1H, CH_3NCH), 4.44 (d, *J* = 4.4 Hz, 1H, NHCHCHCHO), 4.33 (d, *J* = 4.4 Hz, 1H, $NHCH_2CHCHO$), 4.09 (d, *J* = 6.7 Hz, 1H, NHCH), 3.74 (s, 3H, NCH_3), 3.36 (dd, *J* = 10.6, 7.5 Hz, 1H, $NHCH_2$), 2.70 (dd, *J* = 10.4, 6.9 Hz, 1H, $NHCH_2$), 2.59 – 2.42 (m, 2H, $NHCHCHCHCH_2$), 1.83 – 1.65 (m, 2H, CH_2CH_2), 1.51 –

1.28 (m, 2H, CH_2CH_2) ppm.



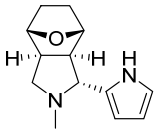
pyrrolyl pyrrolidine 4h: Prepared from pyrrolidine **1b** (134 mg, 0.97 mmol, 1.0 equiv) and nucleophile pyrrole (139 µL, 1.94 mmol, 2.0 equiv) according to *general procure 1* to obtain compound **4h** (168 mg, 0.82 mmol, 85%) as an orange solid. **m.p.**: 89 – 93 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.92 (bs, 1H, C*NHC*H*), 6.69 (s, 1H, C*NHC*H*), 6.14 (s, 1H, C*NHCHC*H*), 5.94 (s, 1H, C*NHCHCHC*H*), 4.19 (s, 1H, CH_2NHC*H*), 2.89 (d, *J* = 12.0 Hz, 1H, NHC*H*$_2$), 2.79 – 2.66 (m, 1H, NHC*H*$_2$, NHCHC*H*), 2.59 – 2.48 (m, 2H, N*H*CH_2C*H*), 2.35 (s, 1H, NHCHCHC*H*CH_2CH), 2.19 (s, 1H, NHCH_2CHC*HC*H*$_2$), 1.67 – 1.33 (m, 6H, C*H*$_2$CHC*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.8 (C*), 116.6 (CH), 108.4 (CH), 104.2 (CH), 56.5 (CH), 52.5 (CH), 46.48 (CH_2), 46.45 (CH), 43.4 (CH_2), 40.62 (CH), 40.55 (CH), 23.6 (CH_2), 22.8 (CH_2) ppm. **IR** (cm^{-1}): ν_{max} = 2945 (s), 1392 (m), 1328 (m), 1301 (m), 1286 (m), 1130 (s), 1105 (s), 1024 (s), 950 (s), 919 (s), 879 (s), 763 (s), 711 (s). **HRMS** (ESI^+) calculated for $C_{13}H_{19}N_2O$ (MH^+) 203.1543, found 203.1551. **Chiral SFC**: >99% ee [Acquity Trefoil CEL2 (2.1 x 150 mm, 2.5 µm), modifier: EtOH/ACN (1:1) + 0.2% TFA, t = 3.30 min]. **Specific rotation**: $[\alpha]_D^{20}$ = +26 ° (c = 0.5, EtOH).

***rac*-pyrrolyl pyrrolidine 4h:** Prepared from imine **S2c** (106 mg, 0.68 mmol, 1.0 equiv) and nucleophile pyrrole (94.3 µL, 1.36 mmol, 2.0 equiv) according to *general procedure 5* to obtain the compound *rac*-**4h** (111 mg, 0.55 mmol, 81%) as a light brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.96 (bs, 1H, C*NH*H*), 6.69 (s, 1H, C*NHC*H*), 6.14 (s, 1H, C*NHCHC*H*), 5.94 (s, 1H, C*NHCHCHC*H*), 4.18 (s, 1H, CH_2NHC*H*), 2.88 (d, *J* = 12.0 Hz, 1H, NHC*H*$_2$), 2.80 – 2.65 (m, 2H, NHC*H*$_2$, NHCHC*H*), 2.61 – 2.44 (m, 2H, N*H*CH_2C*H*), 2.34 (s, 1H, NHCHCHC*H*CH_2), 2.19 (s, 1H, NHCH_2CHC*H* C*H*$_2$), 1.64 – 1.35 (m, 6H, C*H*$_2$CHC*H*$_2$C*H*$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.2 (C*), 116.5 (CH), 108.4 (CH), 104.1 (CH), 56.5 (CH), 52.6 (CH), 46.6 (CH_2), 46.5 (CH), 43.4 (CH_2), 40.7 (CH), 40.6 (CH), 23.7 (CH_2), 22.8 (CH_2).

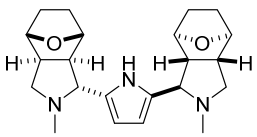


pyrrolyl pyrrolidine 4i: Prepared from pyrrolidine **1b** (89.0 mg, 0.80 mmol, 1.0 equiv) and nucleophile pyrrole (111 µL, 1.60 mmol, 2.0 equiv) according to *general procedure 1* to obtain compound **4i** (94.5 mg, 0.54 mmol, 67%) as a yellow solid. **m.p.**: 90 – 93 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.99 (bs, 1H, C*NH*H*), 6.74 (s, 1H, C*NHC*H*), 6.14 (s, 1H, C*NHCHC*H*), 6.06 (s, 1H, C*NHCHCHC*H*), 3.64 (d, *J* = 7.3 Hz, 1H, CH_2NHC*H*), 3.30 (t, *J* = 9.3 Hz, 1H, NHC*H*$_2$), 2.77 – 2.64 (m, 1H, NHCH_2C*H*), 2.62 – 2.53 (m, 1H, NHCHC*H*), 2.52-2.42 (m, 1H, NHC*H*$_2$), 2.12 (bs, 1H, CH_2N*H*), 1.68 – 1.34 (m, 6H C*H*$_2$C*H*$_2$C*H*$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.7 (C*), 117.3 (CH), 108.0 (CH), 104.9 (CH), 63.7 (CH), 54.0 (CH_2), 51.1 (CH), 44.3 (CH), 32.2 (CH_2), 31.2 (CH_2), 25.4 (CH_2). **IR** (cm^{-1}): ν_{max} = 2927 (s), 2854 (m), 1436 (s), 1444 (s), 1288 (s), 1132 (s), 1027 (m), 987 (s), 927 (s), 916 (w), 881 (m), 856 (m), 790 (s), 711 (s). **HRMS** (ESI^+) calculated for $C_{11}H_{17}N_2$ (MH^+) 177.1386, found 177.1390. **Chiral SFC**: 97% ee [Acquity Trefoil AMY1 (2.1 x 150 mm, 2.5 µm), modifier: EtOH/IPA (1:1) + 0.2% TFA, t (minor) = 3.75 min, t (major) = 3.94 min]. **Specific rotation**: $[\alpha]_D^{20}$ = +38 ° (c = 0.5, EtOH).

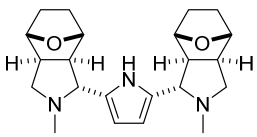
***rac*-pyrrolyl pyrrolidine 4i:** Prepared from imine **S2d** (76.4 mg, 0.70 mmol, 1.0 equiv) and nucleophile pyrrole (97.1 µL, 1.40 mmol, 2.0 equiv) according to *general procedure 5* to obtain compound *rac*-**4i** (120 mg, 0.68 mmol, 97%) as a light brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.95 (bs, 1H, C*NH*H*), 6.74 (s, 1H, C*NHCHCHC*H*), 6.13 (s, 1H, C*NHCHC*H*), 6.06 (s, 1H, NHC**C*H*), 3.64 (d, *J* = 7.2 Hz, 1H, CH_2NHC*H*), 3.28 (t, *J* = 9.3 Hz, 1H, NHC*H*$_2$), 2.75 – 2.63 (m, 1H, NHCH_2C*H*), 2.63 – 2.52 (m, 1H, NHCHC*H*), 2.48 (t, *J* = 7.9 Hz, 1H, NHC*H*$_2$), 2.24 (bs, 1H, CH_2N*H*), 1.71 – 1.35 (m, 6H C*H*$_2$C*H*$_2$C*H*$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.4 (C*), 117.4 (CH), 108.0 (CH), 104.9 (CH), 63.6 (CH), 53.8 (CH_2), 51.0 (CH), 44.2 (CH), 32.1 (CH_2), 31.2 (CH_2), 25.4 (CH_2).



pyrrolyl pyrrolidine 5a: Prepared from pyrrolidine **1e** (124 mg, 0.77 mmol, 1.0 equiv) and nucleophile pyrrole (109 µL, 1.54 mmol, 2.0 equiv) according to *general procedure 1* to obtain compound **5a** (137 mg, 0.63 mmol, 82%) as an off-white solid. **m.p.**: 89 – 92 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.67 (s, 1H, N*H*), 6.76 (bs, 1H, NHC*H*), 6.13 (d, *J* = 10.8 Hz, 2H, NHCHC*HCH*), 4.35 (d, *J* = 3.8 Hz, 1H, NCHCHC*H*O), 4.28 (d, *J* = 3.7 Hz, 1H, NCH_2CHCHO), 3.30 (t, *J* = 8.6 Hz, 1H, NCH_2), 2.95 (d, *J* = 8.0 Hz, 1H, NC*H*C*), 2.40 (q, *J* = 8.4 Hz, 1H, NCHC*H*), 2.25 (t, *J* = 8.3 Hz, 1H, NCH_2), 2.10 (s, 3H, NCH_3), 2.06 (t, *J* = 8.8 Hz, 1H, NCH_2CH), 1.68 (s, 2H, CH_2CH_2), 1.51 – 1.21 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.8 (C*), 117.9 (CH), 108.0 (CH), 107.1 (CH), 79.2 (CH), 78.4 (CH), 68.9 (CH), 61.0 (CH_2), 57.7 (CH), 47.3 (CH), 40.1 (CH_3), 28.6 (CH_2), 28.3 (CH_2) ppm. **IR** (cm^{-1}): ν_{max} = 1463 (s), 1444 (s), 1288 (s), 1220 (s), 1213 (w), 1132 (s), 1091 (s), 1027 (s), 987 (s), 927 (s), 881 (m), 856 (m), 790 (s), 711 (s). **HRMS** (ESI^+) calculated for $C_{13}H_{19}N_2O$ (MH^+) 219.1492, found 219.1498. **Chirality:** 18% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 98/2, v = 0.3 mL/min, column temperature: 30 °C, λ = 215 nm, t (minor) = 27.635 min, t (major) = 31.723 min].



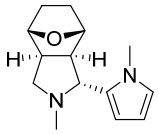
C_2-symmetric **6'**



meso-**6**

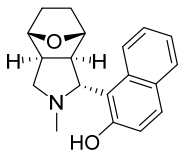
pyrrolyl pyrrolidines 5a and 6/6' (one-stage procedure):[38] Prepared from pyrrolidine **1e** (132 mg, 0.75 mmol, 1.0 equiv) and nucleophile pyrrole (106 µL, 1.50 mmol, 2.0 equiv) according to *general procedure 3* to obtain a mixture of compound **5a** (69 mg, 0.32 mmol, 42%) and **6/6'** (15 mg, 0.041 mmol, 5%) in a 7.6:1 ratio as an off-white solid. **6/6': ^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.69 (bs, 1H, N*H*), 6.00 (dd, *J* = 5.3, 2.6 Hz, 2H, NCHC*CH*), 4.35 (d, *J* = 3.8 Hz, 2H, NCHCHC*H*O),[39] 4.28 (d, *J* = 3.7 Hz, 2H, NCH_2CHCHO),[39] 3.29 – 3.23 (m, 2H, NCH_2), 2.90 (dd, *J* = 8.0, 3.0 Hz, 2H, NC*H*C*), 2.40 (q, *J* = 8.4 Hz, 2H, NCHC*H*),[39] 2.25 (t, *J* = 8.3 Hz, 2H, NCH_2),[39] 2.10 (s, 6H, NCH_3),[39] 2.06 (t, *J* = 8.8 Hz, 2H, NCH_2CH),[39] 1.68 (s, 4H, CH_2CH_2),[39] 1.51 – 1.21 (m, 4H, CH_2CH_2)[39] ppm. **^{13}C NMR** (126 MHz, $CDCl_3$):[39] δ 132.0 (C*), 106.6 (CH), 79.2 (CH), 78.4 (CH), 68.9 (CH), 61.0 (CH_2), 57.7 (CH), 47.3 (CH), 40.1 (CH_3), 28.6 (CH_2), 28.3 (CH_2) ppm. **HRMS** (ESI^+) calculated for $C_{22}H_{32}N_3O_2$ (MH^+) 370.2489, found 370.2494. **5a**: **Chirality: ±**10% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 98/2, v = 0.3 mL/min, column temperature: 30 °C, λ = 215 nm, t (minor) = 29.306 min, t (major) = 33.845 min].

***rac*-pyrrolyl pyrrolidine 5a**: Prepared from hemiaminal **S2b** (77 mg, 0.50 mmol, 1.0 equiv) and nucleophile pyrrole (69.4 µL, 1.0 mmol, 2.0 equiv) according to *general procedure 5*. To a solution of the crude product in methanol (5 mL) were added sodium cyanoborohydride (49 mg, 0.75 mmol, 1.5 equiv), acetic acid (58 uL, 1.0 mmol, 2.0 equiv) and aq. formaldehyde (56 µL [37%], 0.75 mmol, 1.5 equiv) at 0 °C under N_2-atmosphere. The reaction mixture was stirred for 2 hours at rt and quenched by de addition of sat. aq. Na_2CO_3 (15 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain compound *rac*-**5a** (80 mg, 0.37 mmol, 73%) as an off-white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 6.76 (q, *J* = 1.1 Hz, 1H, NHC*H*), 6.17 – 6.08 (m, 2H, NHCHC*HCH*), 4.35 (d, *J* = 4.8 Hz, 1H, NCHCHC*H*O), 4.28 (d, *J* = 4.8 Hz, 1H, NCH_2CHCHO), 3.30 (t, *J* = 8.6 Hz, 1H, NCH_2), 2.96 (d, *J* = 8.0 Hz, 1H, NC*H*C*), 2.40 (q, *J* = 8.4 Hz, 1H, NCHC*H*), 2.25 (t, *J* = 8.3 Hz, 1H, NCH_2), 2.11 (s, 3H, NCH_3), 2.06 (t, *J* = 8.9 Hz, 1H, NCH_2CH), 1.73 – 1.62 (m, 2H, CH_2CH_2), 1.42 – 1.24 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.9 (C*), 117.8 (CH), 108.0 (CH), 107.0 (CH), 79.2 (CH), 78.4 (CH), 68.9 (CH), 61.0 (CH_2), 57.8 (CH), 47.3 (CH), 40.1 (CH_3), 28.6 (CH_2), 28.3 (CH_2) ppm.



pyrrolyl pyrrolidine 5b: Prepared from pyrrolidine **1e** (132 mg, 0.758 mmol, 1.0 equiv) and nucleophile *N*-methylpyrrole (136 µL, 1.52 mmol, 2.0 equiv) according to *general procedure 1* to obtain compound **5b** (109 mg, 0.47 mmol, 62%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) 6.57 (t, *J* = 2.2 Hz, 1H, C*N(CH_3)C*H*), 6.08 (d, *J* = 2.2 Hz, 2H, C*N(CH_3)CHC*HCH*), 4.30 (dd, *J* = 15.5, 4.8 Hz, 2H, C*HOCH*), 3.70 (s, 3H, C*NC*H*$_3$), 3.29 (t, *J* = 8.4 Hz, 1H, NC*H*$_2$), 2.96 (d, *J* = 8.0 Hz, 1H, NC*H*C*), 2.48 – 2.34 (m, 2H, NCHC*HCH*CHO), 2.07 (s, 3H, CH_2NC*H*$_3$), 2.00 (t, *J* = 8.7 Hz, 1H, NC*H*$_2$), 1.74 – 1.62 (m, 2H, C*H*$_2$C*H*$_2$), 1.45 – 1.28 (m, 2H, C*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.9 (C*), 123.0 (CH), 108.5 (CH), 106.9 (CH), 79.1 (CH), 78.3 (CH), 68.2 (CH), 60.8 (CH_2), 57.0 (CH), 47.3 (CH), 39.9 (CH_3), 34.6 (CH_3), 28.5 (CH_2), 28.4 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2947 (m), 1497 (w), 1292 (m), 1221 (m), 1146 (m), 928 (s), 793 (s), 706 (s), 588 (s). **HRMS** (ESI^+) calculated for $C_{14}H_{21}N_2O$ (MH^+) 233.1648, found 233.1659. **Chirality:** 12% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 99/5, v = 0.2 mL/min, column temperature: 30 °C, λ = 240 nm, t (minor) = 23.293 min, t (major) = 24.837 min].

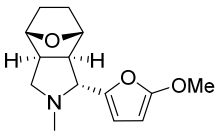
***rac*-pyrrolyl pyrrolidine 5b:** Prepared from hemiaminal **S2b** (82 mg, 0.53 mmol, 1.0 equiv) and nucleophile *N*-methylpyrrole (47 µL, 0.53 mmol, 1.0 equiv) according to *general procedure 3*. To a solution of the crude product in methanol (5 mL) were added sodium cyanoborohydride (52 mg, 0.79 mmol, 1.5 equiv), acetic acid (62 uL, 1.06 mmol, 2.0 equiv) and aq. formaldehyde (59 µL [37%], 0.79 mmol, 1.5 equiv) at 0 °C under N_2-atmosphere. The reaction mixture was stirred for 2 hours at rt and quenched by de addition of sat. aq. Na_2CO_3 (15 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain compound *rac*-**5b** (122 mg, 0.53 mmol, 99%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.56 (t, *J* = 2.3 Hz, 1H, C*N(CH_3)C*H*), 6.11 – 6.05 (m, 2H, C*N(CH_3)CHC*HCH*), 4.30 (dd, *J* = 14.9, 4.8 Hz, 2H, C*HOCH*), 3.70 (s, 3H, C*NC*H*$_3$), 3.29 (t, *J* = 8.4 Hz, 1H, NC*H*$_2$), 2.97 (d, *J* = 8.0 Hz, 1H, NC*H*C*), 2.47 – 2.34 (m, 2H, NCHC*HCH*CHO), 2.07 (s, 3H, CH_2NC*H*$_3$), 2.01 (t, *J* = 8.7 Hz, 1H, NC*H*$_2$), 1.74 – 1.62 (m, 2H, C*H*$_2$C*H*$_2$), 1.46 – 1.29 (m, 2H, C*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.8 (C*), 123.0 (CH), 108.4 (CH), 106.8 (CH), 79.1 (CH), 78.3 (CH), 68.1 (CH), 60.7 (CH_2), 56.9 (CH), 47.2 (CH), 39.8 (CH_3), 34.6 (CH_3), 28.5 (CH_2), 28.4 (CH_2) ppm.



pyrrolyl pyrrolidine 5c: Prepared from pyrrolidine **1e** (132 mg, 0.758 mmol, 1.0 equiv), nucleophile 2-napthol (221 mg, 1.52 mmol, 2.0 equiv) and DMSO (10% v/v) according to *general procedure 2* to obtain compound **5c** (127 mg [1% CH_2Cl_2], 0.423 mmol, 56%) as a light yellow foamy solid. **m.p.**: >116 °C (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 1H, C(OH)C*C*C*H*), 7.78 (d, *J* = 8.0 Hz, 1H, C(OH)CHCHC*C*H*), 7.70 (d, *J* = 8.8 Hz, 1H, C(OH)CHC*H*), 7.50 – 7.44 (m, 1H, C(OH)C*C*CHC*H*), 7.30 (t, *J* = 7.3 Hz, 1H, C(OH)CHCHC*CHC*H*), 7.12 (d, *J* = 8.8 Hz, 1H, C(OH)C*H*), 4.60 (d, *J* = 5.3 Hz, 1H, NCHCHC*H*O), 4.37 (d, *J* = 5.2 Hz, 1H, NCH_2CHC*H*O), 4.08 (d, *J* = 8.1 Hz, 1H, NC*H*), 3.52 – 3.46 (m, 1H, NC*H*$_2$), 2.57 (q, *J* = 8.5 Hz, 1H, NCH_2C*H*), 2.48 (t, *J* = 8.4 Hz, 1H, NCHC*H*), 2.31 – 2.25 (s, 4H, C*H*$_3$, NC*H*$_2$), 1.77 – 1.57 (m, 2H, C*H*$_2$C*H*$_2$), 1.44 – 1.35 (m, 1H, C*H*$_2$$CH_2$), 1.29 – 1.18 (m, 1H, CH_2C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.0 (C*), 133.1 (C*), 129.4 (CH), 129.1 (CH), 128.6 (C*), 126.6 (CH), 122.6 (CH), 121.2 (CH), 119.7 (CH), 115.0 (C*), 79.1 (CH), 78.3 (CH), 69.3 (CH), 60.1 (CH_2), 57.7 (CH), 47.8 (CH), 39.3 (CH_3), 28.5 (CH_2), 28.3 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2949 (w), 1620 (m), 1466 (m), 1271 (m), 1240 (s), 1140 (m), 959 (m), 872 (s), 748 (s), 592 (s). **HRMS** (ESI^+) calculated for $C_{19}H_{22}NO_2$ (MH^+) 296.1645, found 296.1657. **Chirality:** 10% *ee* [Dr. Maisch Chiral AM, heptane/IPA = 95/5, v = 0.9 mL/min, column temperature: 30 °C, λ = 230 nm, t (minor) = 7.096 min, t (major) = 9.297 min].

***rac*-pyrrolyl pyrrolidine 5c:** To a solution of hemiaminal **S2b** (80 mg, 0.52 mmol, 1.0 equiv) in DCM (2.5 mL) was added nucleophile 2-napthol (75 mg, 0.52 mmol, 1.0 equiv). The reaction mixture was stirred for

17 h at rt and quenched by the addition of sat. aq. Na_2CO_3 (2.5 mL), extracted with DCM (3 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo.* To a solution of the crude product in EtOAc (5 mL) were added sodium cyanoborohydride (50 mg, 0.77 mmol, 1.5 equiv), acetic acid (60 uL, 1.03 mmol, 2.0 equiv) and aq. formaldehyde (58 µL [37%], 0.77 mmol, 1.5 equiv) at 0 °C under N_2-atmosphere. The reaction mixture was stirred for 17 h at rt and quenched by de addition of sat. aq. Na_2CO_3 (15 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain compound *rac*-**5c** (132 mg, 0.47 mmol, 87%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.6 Hz, 1H, C(OH)C*C*C*H*), 7.78 (d, *J* = 8.0 Hz, 1H, C(OH)CHCHC*C*H*), 7.73 (d, *J* = 8.8 Hz, 1H, C(OH)CHC*H*), 7.51 – 7.45 (m, 1H, C(OH)C*C*CHC*H*), 7.34 – 7.29 (m, 1H, C(OH)CHCHC*CHC*H*), 7.22 (d, *J* = 8.9 Hz, 1H, C(OH)C*H*), 4.54 (d, *J* = 5.2 Hz, 1H, NCHCHC*H*O), 4.38 (d, *J* = 5.2 Hz, 1H, NCH_2CHCHO), 4.24 (d, *J* = 7.6 Hz, 1H, NC*H*), 3.77 – 3.70 (m, 1H, NCH_2), 2.72 – 2.61 (m, 2H, NCH_2CHCH), 2.47 – 2.32 (m, 4H, CH_3NCH_2), 1.78 – 1.59 (m, 2H, CH_2CH_2), 1.44 – 1.34 (m, 1H, CH_2CH_2), 1.28 – 1.21 (m, 1H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.5 (C*), 133.0 (C*), 130.2 (CH), 129.1 (CH), 128.6 (C*), 127.0 (CH), 122.8 (CH), 120.7 (CH), 119.7 (CH), 113.2 (C*), 78.9 (CH), 78.2 (CH), 69.6 (CH), 59.8 (CH_2), 56.4 (CH), 47.3 (CH), 39.1 (CH_3), 28.2 (CH_2), 28.1 (CH_2) ppm.



pyrrolyl pyrrolidine 5d: Prepared from pyrrolidine **1e** (132 mg, 0.758 mmol, 1.0 equiv) and nucleophile 2-methoxyfuran (72 µL, 0.758 mmol, 1.0 equiv) according to *general procedure 1* to obtain compound **5d** (81 mg, 0.33 mmol, 43%) as a light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.10 (d, *J* = 3.1 Hz, 1H, C(OMe)CHC*H*), 5.04 (d, *J* = 3.1 Hz, 1H, C(OMe)C*H*), 4.31 – 4.23 (m, 2H, C*H*OC*H*), 3.80 (s, 3H, OCH_3), 3.30 (t, *J* = 8.5 Hz, 1H, NCH_2), 2.73 (d, *J* = 8.0 Hz, 1H, NC*H*), 2.51 (t, *J* = 8.3 Hz, 1H, NCHC*H*), 2.42 (q, *J* = 8.4 Hz, 1H, NCH_2CH), 2.14 (s, 3H, NCH_3), 1.99 (t, *J* = 8.8 Hz, 1H, NCH_2), 1.72 – 1.60 (m, 2H, CH_2CH_2), 1.44 – 1.30 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.7 (C*), 143.6 (C*), 109.3 (CH), 79.6 (CH), 79.2 (CH), 78.3 (CH), 68.5 (CH), 61.0 (CH_2), 57.8 (CH_3), 55.0 (CH), 47.1 (CH), 39.8 (CH_3), 28.5 (CH_2), 28.3 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2947 (m), 1751 (m), 1616 (m), 1583 (s), 1439 (m), 1259 (s), 1219 (m), 1146 (m), 1007 (s), 926 (s), 789 (m), 735 (m), 592 (m). **HRMS** (ESI^+) calculated for $C_{14}H_{20}NO_3$ (MH^+) 250.1438, found 250.1446.

2.6 References and Notes

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15 The choice of substrate is based on the envisioned use of furan as a chiral auxiliary, that can be removed by a *r*DA reaction after diastereoselective α-functionalization (see Chapter 5.2.1.1).

16 C. de Graaff, L. Bensch, M. J. van Lint, E. Ruijter and R. V. A. Orru, *Org. Biomol. Chem.* **2015**, *13*, 10108–10112.

17 This hypothesis is based on similarities in the ^{1}H NMR spectrum when compared to side product **6/6'** (ref. 22) that was obtained using a one-stage protocol with substrate **1e**. In correspondence with our expectation, the proposed side product (using substrate **1b**) was formed to a higher extent with a lower concentration of pyrrole (Table 1, entry 3–4) and was not observed at higher concentration (Table 1, entries 5–6).

18 CCDC 1434414 (**4f**) and CCDC 1434415 (**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

19 The absolute stereochemistry is determined during the biotransformation and should thus be the same for all products derived from **1b**.

20 Imine (–)-**2b** was isolated as a stable hemiaminal by the biocatalytic oxidation of *meso*-pyrrolidine **1b** with MAO-N. Imine *rac*-**2b** was isolated as a stable hemiaminal by a two-step protocol of *N*-halogenation of *meso*-pyrrolidine **1b** followed by base-mediated elimination or in dehydrated form by IBX-mediated oxidation as in ref. 16.

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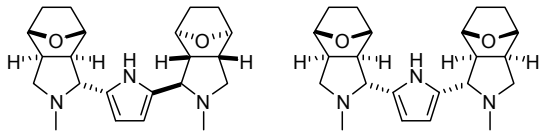
22 In an attempt to trap the iminium ion before racemization, we performed the reaction with a one-stage protocol having pyrrole present during the biocatalytic oxidation. However, the *ee* decreased even further in this case. The negative influence of pyrrole on the enantioselectivity of the biocatalyst as observed earlier (See Table 1, entries 3–6) presumably cancels out the *ee* gain of reduced racemization. Using this one-stage protocol, a side product (**6** or **6'**) was formed that we isolated as a mixture with the desired product **5a**. The proposed structures are based on 1D- and 2D-NMR, and MS analysis of the product mixture. Due to difficulties in isolation of the side product, we were unable to differentiate between *meso*-**6** and the C_2-symmetric **6'**. The mechanism to its formation is proposed to proceed through addition of the pyrrole moiety of **5a** to iminium ion **2e**. We speculate that this reaction occurs in a hydrophobic pocket of the enzyme, since it was only observed with the one-stage procedure. The maximum theoretical yield for **6/6'** is 50%.



C_2-symmetric **6'** *meso*-**6**

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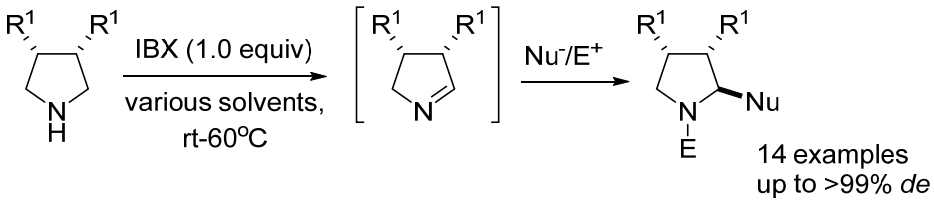
33 The reaction was performed with six separate batches that were combined during the work-up. Compounds **2b** and **S2b** are in equilibrium in aqueous medium and the molar ratio of **2b**/**S2b** in the product can therefore vary between batches.
34 As a result of HCl traces in $CDCl_3$, hemiaminal **S2b** slowly equilibrates to a mixture of **S2b** and imine **2b**.
35 Low temperature is not required, but the centrifuge is located in a cold room.
36 For complete characterization of **2b**, see ref. 16.
37 Approximate value of enantiomeric excess as a result of peak overlap with small impurities.
38 Yields of **5a** and **6/6'** were calculated using the molar ratio in NMR spectroscopy.
39 Peak overlaps with the corresponding signals of **5a**.

Chapter 3

IBX-Mediated Oxidative Ugi-type MCRs and aza-Friedel–Crafts reactions



Abstract: *The first o-iodoxybenzoic acid (IBX) mediated oxidation of unactivated amines to imines is described. A range of meso-pyrrolidines were shown to be suitable substrates. The chemical space was further explored with one-pot oxidative Ugi-type and aza-Friedel–Crafts reactions, which proved to be highly diastereoselective.*

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3.1 Introduction

The chemistry of hypervalent iodine reagents (Figure 1) has received major interest in recent years as a result of the increasing number of new reagents and their application in diverse chemical transformations.[1] In particular, *o*-iodoxy-benzoic acid (IBX)[2] has experienced increasing attention owing to its broad applicability and high chemoselectivity. Santagostino *et al.* developed a convenient and cost-efficient synthesis of high purity IBX by the treatment of 2-iodobenzoic acid with oxone in aqueous medium,[3] which renders IBX an easily accessible reagent. Chemical transformations mediated by IBX include the selective oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones as well as dehydrogenation of aldehydes and ketones to α,β-unsaturated carbonyl compounds. Nicolaou *et al.* described the oxidation of benzylic amines as well as amines that aromatize upon oxidation,[4,5] however, the oxidation of unactivated aliphatic amines with IBX was not investigated.[6]

The direct *α*-functionalization of amines is a highly interesting transformation that attracted great attention in recent years.[7] Consequently, transition metal-catalyzed oxidative versions of important C–C bond-forming reactions such as Mannich, Strecker, aza-Henry and aza-Friedel–Crafts reactions have been developed.[8] A limited number of examples of the application of IBX in oxidative multicomponent reactions has been described, *i.e.* oxidative Strecker,[9] Passerini,[10] Ugi and Ugi-type[11] reactions. Although unactivated alcohols were suitable substrates, the scope of the amine component is basically unexplored with the exception of a small selection of α-activated amines, such as benzylic amines, α-amino nitriles and α-amino esters.

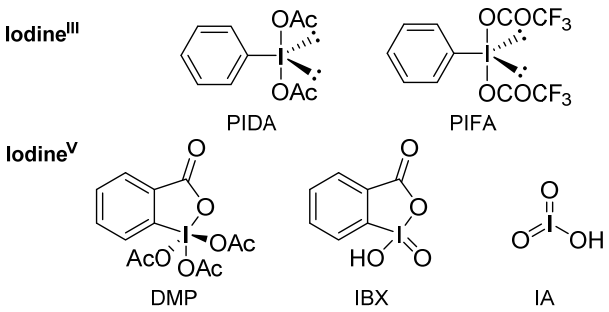


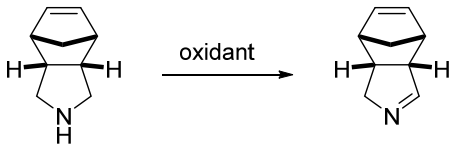
Figure 1. A selection of commonly used and commercially available hypervalent iodine reagents and their acronyms.

In this Chapter, we describe a mild and selective oxidation of unactivated cyclic amines with IBX to access the corresponding imines. The oxidation can be combined in one pot with the addition of C-nucleophiles, providing oxidative Ugi-type and aza-Friedel–Crafts reactions.

3.2 Results and Discussion

In light of our continued interest in the functionalization of imines, in particular 1-pyrrolines,[12] we envisioned a clean and fast oxidation of unactivated *meso*-pyrrolidines. Examination of the currently available methods revealed that the oxidation of unactivated secondary amines is rather challenging.[13] Given the recent regained interest in hypervalent iodine reagents, we decided to explore their ability to

Table 1. Optimization of reaction conditions for the oxidation of *meso*-pyrrolidine **1a**.[a]



1a **2a**

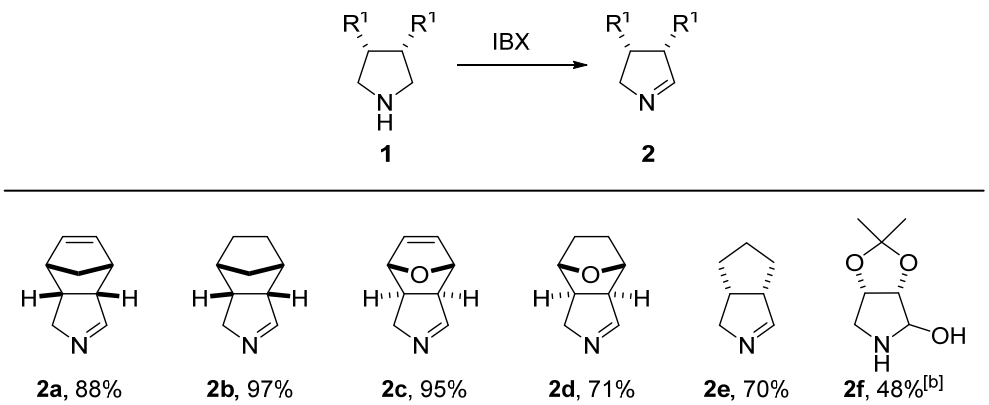
Entry	Oxidant	Solvent	T, t	Yield[b]
1	PIDA	DMSO	rt, 30 min	38%
2	PIFA	DMSO	rt, 30 min	33%
3	DMP	DMSO	rt, 30 min	55%
4	IBX	DMSO	rt, 30 min	90%
5	IBX	DMF	rt, 30 min	92%
6	IBX	MeCN	rt, 1h	19%
7[c]	IBX	MeCN	60 °C, 1h	78%
8[c]	IBX	MeOH	60 °C, 1h	81%
9[c]	**IBX**	**CH_2Cl_2**	**60 °C, 1h**	**95%**
10[c]	IBX	THF/DMSO (9:1)	60 °C, 1h	94%
11[c]	IBX	THF	60 °C, 1h	58%
12[c]	IBX	CF_3CH_2OH	60 °C, 1h	47%
13[c]	IBX	$(MeO)_2CO$	60 °C, 1h	31%
14[c]	IBX	EtOAc	60 °C, 1h	19%
15[c]	IBX	toluene	60 °C, 1h	10%

[a] Conditions: amine (1.0 equiv), oxidant (1.0 equiv), solvent (0.2 M). [b] Yield determined by adding 2,5-dimethylfuran (0.5 equiv) after the reaction workup as standard for NMR spectroscopy. [c] Closed vessel.

oxidize aliphatic amines. We started our investigation with the oxidation of *meso*-pyrrolidine **1a** with different commercially available hypervalent iodine reagents at room temperature in the typically used solvent DMSO (Table 1, entries 1–4).[4] The desired 1-pyrroline (**2a**) was obtained in high yield with only 1.0 equiv of IBX (entry 4), while oxidants such as (diacetoxy)iodobenzene (PIDA), bis(trifluoroacetoxy)iodobenzene (PIFA) and Dess-Martin periodinane (DMP) gave poor to moderate yields (entry 1–3). A solvent screen (entries 5–15) revealed that the oxidation proceeds well in a range of protic as well as aprotic solvents in which IBX is virtually insoluble, although an increased temperature and reaction time were sometimes required. Superior results were obtained using CH_2Cl_2 (entry 9),[14] which prompted us to select this solvent for a screening of the substrate scope.

To our delight, a range of aliphatic *meso*-pyrrolidines was selectively oxidized by IBX towards the corresponding 1-pyrrolines in good to excellent yield (Table 2, 70–97%). Hemiaminal **2f** is a highly interesting building block for the synthesis of aza-sugars, but was obtained in moderate yield presumably as a result of instability due to its increased electrophilicity.[15,16] Under the same conditions, reactions of monocyclic pyrrolidines gave mixtures of the corresponding 1-pyrrolines and pyrroles. We hypothesize that this overoxidation is caused by tautomerization of the initially formed imines to the corresponding enamines, which subsequently undergo a second oxidation leading to pyrroles. In case of bi- and tricyclic 1-pyrrolines **2a**–**f**, tautomerization is prevented and overoxidation does not occur. Piperidine

Table 2. Scope study for oxidation of *meso*-pyrrolidines **1** with IBX.[a]



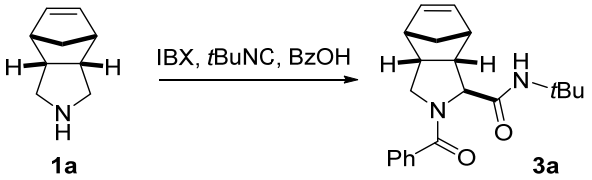
[a] Conditions: amine (1.0 equiv), IBX (1.0 equiv), CH_2Cl_2 (0.2 M), 60 °C, 1h, closed vessel. Isolated yield, unless stated otherwise. [b] MeCN as solvent. Yield determined by adding 2,5-dimethylfuran (0.5 equiv) after the reaction workup as standard for NMR spectroscopy and proposed compound **2f** was not isolated.[15]

derivatives and acyclic secondary amines were not converted under these conditions.

Imines are interesting inputs for a wide variety of complexity-generating reactions as a result of their electrophilic as well as nucleophilic character. For example, imines serve as templates for many multicomponent reactions (MCRs), a category of reactions that create a high degree of diversity and complexity in a single step.[17] One of the most studied and widely applied MCRs is the Ugi reaction, which has proven to be a powerful tool for rapid synthesis of lead compounds in drug discovery.[18] Consequently, we envisioned a diastereoselective oxidative Ugi-type three-component reaction for the synthesis of *N*-acylprolyl amide derivatives.[19]

For a screening of the reaction conditions, the reaction between *meso*-pyrrolidine **1a**, benzoic acid and *tert*-butyl isocyanide was investigated (Table 3). In agreement with earlier reports,[10,11] a high concentration of reagents proved to be beneficial for the reaction outcome (entries 1–2). The solvent of choice for most Ugi reactions, MeOH, was used as reaction medium with modest efficiency (entry 3). Competing oxidation of the solvent could pose a problem, although previous reports suggest that the oxidation of amines is generally much faster than alcohols.[4,11c] Considering the complexity of the reaction, satisfactory results were obtained using either MeCN or CH_2Cl_2 as the solvent (entries 4–5). As a consequence of the superior results obtained for the oxidation of a variety of *meso*-pyrrolidines in CH_2Cl_2, this solvent was selected for investigation of the reaction scope.

Table 3. Optimization of reaction conditions for the oxidative Ugi-type three-component reaction.[a]



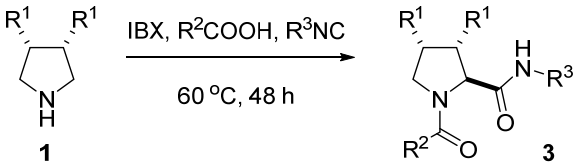
1a **3a**

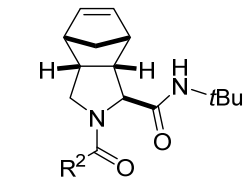
Entry	Solvent	T	Yield[b]
1	DMSO[c]	rt	26%
2	DMSO	rt	37%
3	MeOH	60 °C	25%
4	MeCN	60 °C	50%
5	**CH_2Cl_2**	**60 °C**	**54%**

[a] Conditions: amine (1.0 equiv), benzoic acid (1.5 equiv), *tert*-butyl isocyanide (1.5 equiv), IBX (1.0 equiv), solvent (0.5 M), 60 °C, 24 h, closed vessel. [b] Yield determined by adding 2,5-dimethylfuran (0.5 equiv) after the reaction workup as standard for NMR spectroscopy. [c] 0.2 M.

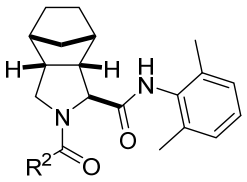
Gratifyingly, we could employ a large variety of inputs for the one-pot oxidative Ugi-type three-component reaction (Table 4). In total, 10 examples of prolyl peptide **3** were synthesized in modest to good yields (35–61%) using 6 isocyanides, 6 secondary amines and 6 carboxylic acids. A range of electronically diverse carboxylic acids were suitable reaction partners, although it should be noted that lower yields were observed for aliphatic acids such as acetic acid (**3e**, 43%). Despite the instability of the intermediate hemiaminal **2f** upon isolation, Ugi adduct **3h** could be obtained in 45% yield as a single diastereoisomer. Notably, 3,3-dimethylindoline—with blocked benzylic positions to prevent benzylic oxidation[20]—could also be applied with modest efficiency (**3j**, 35%).[21] For the majority of examples, a single diastereoisomer of the

Table 4. Oxidative Ugi-type three-component reaction[a]

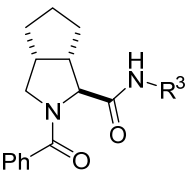




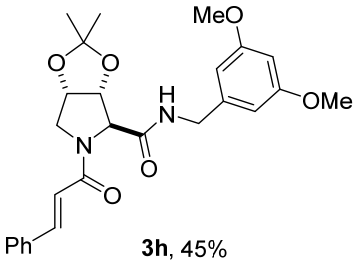
3a, R^2 = Ph, 59%
3b, R^2 = *p*-$NO_2C_6H_4$, 52%
3c, R^2 = PMB, 56%



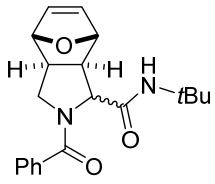
3d, R^2 = Ph, 61%
3e, R^2 = Me, 43%



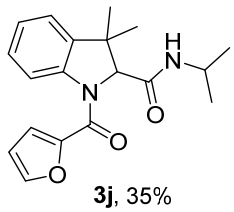
3f, R^3 = *c*Hex, 54%
3g, R^3 = Bn, 41%



3h, 45%

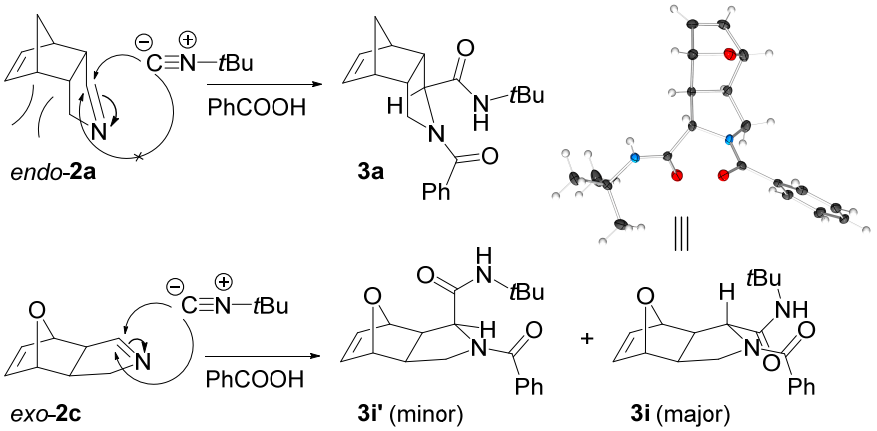


3i, 57%, dr 2:1[b]



3j, 35%

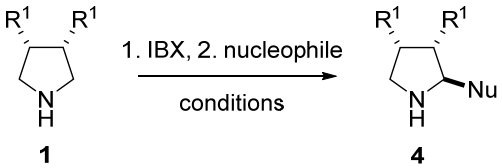
[a] Conditions: amine (1.0 equiv), carboxylic acid (1.5 equiv), isocyanide (1.5 equiv), IBX (1.0 equiv), CH_2Cl_2 (0.5 M), 60 °C, 48 h, closed vessel. Isolated yield. Only one diastereoisomer observed, unless stated otherwise. [b] Ratio determined by NMR analysis of the crude mixture.[22,23]

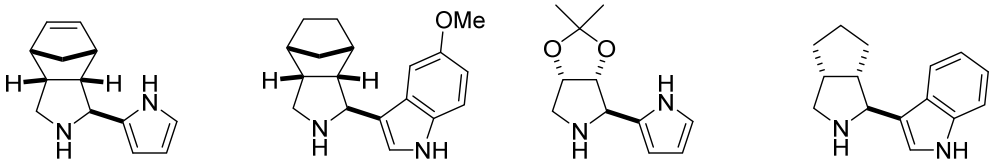


Scheme 1. Steric rationalization for superior diastereoselectivity for the Ugi-type reaction of *endo*-configured **2a** compared to *exo*-**2c**. X-ray structure of major diastereoisomer **3i** with displacement ellipsoids drawn at 50% probability.[23]

dipeptide was isolated (**3a**–**h**). However, *exo*-configured dipeptide **3i** was obtained as a mixture of diastereoisomers.[22] The increased diastereoselectivity with *endo*-configured imines[12b] such as **2a** is explained by steric congestion on the concave face of the molecule, facilitating selective attack of the nucleophile from the other side (Scheme 1). For *exo*-configured **2c**, the steric effect is expected to be less pronounced.

Table 5. Oxidative aza-Friedel–Crafts reaction[a]





4a, 48% **4b**, 60% **4c** (major), 52%, dr >13:1[b] **4d**, 75%

[a] Conditions: 1. amine (1.0 equiv), IBX (1.0 equiv), CH_2Cl_2 (0.2 M), 60 °C, 1 h; 2. nucleophile (2.0 equiv), TFA (2.0 equiv), 60 °C, 1 h, closed vessel. Isolated yield. Only a single diastereoisomer was observed, unless stated otherwise. [b] Diastereomeric ratio determined by NMR analysis of the crude mixture.

In order to expand the molecular diversity available by reactions of *in situ*-generated bicyclic pyrrolines, we decided to explore the aza-Friedel–Crafts reaction.[24] Our one-pot methodology showed to be effective in an oxidative aza-Friedel–Crafts reaction with pyrrole and indoles as a two-step procedure, giving 2-substituted pyrrolidines in modest to good yields (Table 5, 48–75%) and with high to excellent diastereoselectivities. The yield of pyrrolidine **4c** even exceeded the yield of its hemiaminal intermediate **2f**, supporting our hypothesized instability of the latter species. Unfortunately, 6-nitro- and 3-methyl-substituted indoles were not suitable reaction partners, presumably as a result of their reduced nucleophilicity.

3.3 Conclusion

We have developed the first IBX-mediated oxidation of unactivated aliphatic amines. This method gives access to bi- and tricyclic imines, but is limited to 1-pyrrolines that do not tautomerize under the reaction conditions. An efficient one-pot protocol for diastereoselective α-functionalization of *meso*-pyrrolidines in oxidative Ugi-type and aza-Friedel–Crafts reactions was presented as well.

3.4 Acknowledgements

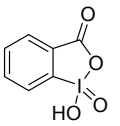
We thank E. Janssen (VU University) for technical assistance, S. Bouwman (VU University) for HRMS measurements, and Dr. A. W. Ehlers (VU University) for NMR maintenance. R. C. Cioc (VU University) is kindly acknowledged for his contribution to this chapter. We kindly acknowledge Dr. M. Zeller (Youngstown State University) for collecting the X-ray data and Dr. C. M. L. Vande Velde (University of Antwerp) for the refinement of the X-ray structure of **3i**. The diffractometer was funded by NSF Grant 1337296.

3.5 Experimental Section

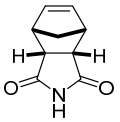
3.5.1 General comments

Starting materials were purchased from Sigma Aldrich, Fisher Scientific and Acros Organics and were used without purification, unless stated otherwise. (3a*R*,6a*S*)-Octahydrocyclopenta[*c*]pyrrole hydrochloride was purchased from AK Scientific and dissolved in CH_2Cl_2, washed with sat. aq. Na_2CO_3, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated *in vacuo* before use. Unless stated otherwise, the solvents were purchased from VWR Chemicals and were used without further treatment. Cyclohexane (*c*Hex) was purified by distillation before use. THF was distilled from sodium/benzophenone under nitrogen before use. Celite® 512 medium was purchased from Sigma Aldrich. Column Chromatography was performed on Silica-P Flash Silica Gel (particle size 40-63 µm, pore diameter 60 Å) from Silicycle. Preparative thin layer chromatography was performed on Silica Gel plates F_{254} (20 x 20 cm, 2000 µm, pore diameter 60 Å) from Silicycle. Thin Layer Chromatography (TLC) was performed using TLC plates F_{254} (silica gel 60 on aluminium) from Merck Serono KGaA (Darmstadt) and compounds were visualized by UV detection (254 or 366 nm) and stained with basic aq. $KMnO_4$ or ninhydrin/ethanol. ^1H, ^{13}C, COSY, HSQC, HMBC and NOESY nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (500.23 MHz for ^1H and 125.78 MHz for ^{13}C) in $CDCl_3$ or DMSO-d_6 using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR, DMSO-d_6: δ = 2.50 for ^1H NMR and δ = 39.52 for ^{13}C NMR) or Bruker Avance 400 (400.13 MHz for ^1H and 100.62 MHz for ^{13}C) using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR, DMSO-d_6: δ = 2.50 for ^1H NMR and δ = 39.52 for ^{13}C NMR). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet) and m (multiplet) or combinations thereof. The COSY-, HMBC- and HSQC-NMR spectra were used for the assignment of the proton signals and the NOESY-NMR spectra were used for the assignment of the relative stereochemistry. The APT-NMR spectra were used for the assignment of the carbons. Names of chemical structures were deduced from generic names and/or important functionalities. Electrospray Ionization (ESI) high resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Infrared (IR) spectra were recorded neat using a FTIR-8400s from Shimadzu. Signal intensities are described as strong (s), medium (m), weak (w) or broad (br). Melting points were determined on a Büchi M-565 and are not corrected. X-ray single crystal data were collected at 100Kon a Bruker X8 Prospector with Cu microsource and focusing optics, and Apex II detector. Data were integrated and corrected for absorption with SAINT V8.34A and SADABS 2012/1, and the structure was solved and refined with SHELX 2014 and shelXle. Hydrogen atoms were detected in the Fourier difference maps, those on C were refined with constraints on bond lengths and angles, those on N were refined freely.

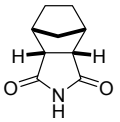
3.5.2 Substrate synthesis



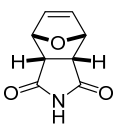
***o*-iodoxybenzoic acid (IBX, S1):**[3] To a solution of Oxone® (74.3 g, 242 mmol, 6.0 equiv) in H_2O (0.2 M) was added 2-iodobenzoic acid (10.0 g, 40.3 mmol, 1.0 equiv). The reaction mixture was stirred for 3 h at 70 °C and then cooled to rt. The solid was filtered off, washed with cold H_2O (500 mL) and cold acetone (300 mL) and dried *in vacuo* (60 °C, 18 h). Compound **S1** (7.17 g, 25.5 mmol, 63%) was obtained without the need of purification as an off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.15 (d, J = 8.0 Hz, 1H), 8.06 – 7.97 (m, 2H), 7.84 (t, J = 7.3 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, DMSO-d_6): δ 167.6 (C*), 146.6 (C*), 133.5 (CH), 133.1 (CH), 131.5 (C*), 130.1 (CH), 125.1 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3097 (w), 1636 (m), 1560 (w), 1331 (m), 1294 (s), 1246 (m), 1138 (m), 831 (m), 773 (m), 748 (s), 692 (s), 673 (s), 648 (m), 592 (s), 577 (s).



imide S2a: To a solution of maleimide (7.28 g, 75.0 mmol, 1.0 equiv) in diethyl ether (0.68 M) was added cyclopentadiene (7.0 mL, 80.0 mmol, 1.06 equiv) dropwise. The reaction mixture was stirred for 2 h at rt. The product was filtered off and washed with diethyl ether. Compound **S2a** (12.0 g, 73.5 mmol, 98%) was obtained without the need of purification as an off-white solid. **R_f** = 0.30 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 184.4 – 188.6 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.47 (bs, 1H, N*H*), 6.17 (d, J = 2.0 Hz, 2H, C*H*=C*H*), 3.36 (s, 2H, C(O)CHC*H*CH_2), 3.31 – 3.22 (m, 2H, C(O)C*H*), 1.72 (d, J = 8.8 Hz, 1H, CH_2), 1.51 (d, J = 8.8 Hz, 1H, CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 178.5 (C*), 134.7 (CH), 52.4 (CH_2), 47.4 (CH), 45.0 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3159 (m), 2991 (m), 1753.17 (m), 1697 (s), 1352 (m), 1294 (m), 1186 (s), 1120 (s), 991 (m), 839 (s), 829 (s), 729 (s), 660 (s), 604 (s). **HRMS** (ESI): *m/z* calulated for $C_9H_{10}NO_2$ $[M+H]^+$:164.0706, found: 164.0711.

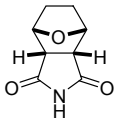


imide S2b: To a solution of palladium on carbon 10% (15 mg, 0.04 mol%) in CH_2Cl_2 (0.1 mL) and methanol (27 mL) was added imide **S2a** (6.56 g, 4.0 mmol). The reaction mixture was stirred for 63 h at rt under H_2 atmosphere (1 atm.). The reaction mixture was filtered over Celite®, washed with methanol and concentrated *in vacuo*. Compound **S2b** (5.86 g, 36.3 mmol, 90%) was obtained without the need of purification as an off-white solid. **R_f** = 0.21 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 175 – 177 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.01 (bs, 1H, N*H*), 3.10 (s, 2H, C(O)C*H*), 2.72 (s, 2H, C(O)CHC*H*CH_2), 1.76 – 1.48 (m, 4H, CH_2CHCH_2CH_2), 1.46 – 1.25 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 179.6 (C*), 50.3 (CH), 42.2 (CH_2), 39.3 (CH), 24.8 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3173 (w), 1695 (s), 1350 (m), 1177 (s), 995 (m), 822 (m), 588 (s), 459 (s). **HRMS** (ESI): *m/z* calulated for $C_9H_{11}NNaO_2$ $[M+Na]^+$:188.0682, found: 188.0689.

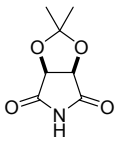


imide S2c: To a solution of maleimide (1.46 g, 15 mmol, 1.0 equiv) in H_2O (1.07 M) was added furan (1.34 mL, 18 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred for 1 h at 90 °C under microwave irradiation and then cooled to rt. The product was filtered off and washed with H_2O (100 mL) and diethyl ether (20 mL). Compound **S2c** (1.38 g,

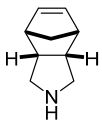
0.84 mmol, 54%) was obtained without the need of purification as an off-white solid. $\mathbf{R_f}$ = 0.23 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 168.6 - 171.3 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 8.15 (bs, 1H, N*H*), 6.52 (s, 2H, C*H*=C*H*), 5.32 (s, 2H, OC*H*), 2.89 (s, 2H, C(O)C*H*) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 176.1 (C*), 136.7 (CH), 81.1 (CH), 48.9 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3148 (w), 1772 (m), 1701 (s), 1352 (m), 1287 (m), 1204 (m), 1186 (s), 897 (m), 820 (s), 733 (s), 633 (s), 582 (s). **HRMS** (ESI): *m/z* calulated for $C_8H_7NNaO_3$ $[M+Na]^+$: 188.0318, found: 188.0320.



imide S2d: To a solution of palladium on carbon 10% (0.10 g, 0.04 mol%) in CH_2Cl_2 (0.1 mL) and methanol (100 mL) was added imide **S2c** (10.19 g, 62.0 mmol). The reaction mixture was stirred for 48 h at rt under H_2 atmosphere (1 atm.). The reaction mixture was filtered over Celite®, washed with methanol and concentrated *in vacuo*. Compound **S2d** (9.9 g, 59.0 mmol, 96%) was obtained without the need of purification as an off-white solid. $\mathbf{R_f}$ = 0.21 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 184 - 186 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 8.76 (bs, 1H, N*H*), 4.94 – 4.86 (m, 2H, OC*H*), 2.91 (s, 2H, NC(O)C*H*), 1.90 – 1.83 (m, 2H, CH_2CH_2), 1.62 – 1.54 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 177.8 (C*), 79.2 (CH), 51.4 (CH), 28.6 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3004 (w), 1672 (s), 1306 (m), 1182 (s), 899 (m), 839 (m), 815 (s), 559 (m), 455 (s).

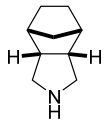


imide S2f:[25] To a solution of $Mn(ClO_4)_2$·6 H_2O (15 mg, 0.3 mol%) in acetone (100 mL) was added picolic acid (44 mg, 1.8 mol%) and maleimide (1.94 g, 20.0 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C and an aq. sodiumacetate solution (1.0 mL, 0.6 M) and hydrogen peroxide (2.58 mL, 30.0 mmol, 1.5 equiv) were added. The solution was stirred for 29 h at rt, after which it was quenched with solid sodium thiosulfate. The suspension was filtered, washed with acetone, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was diluted in acetone (100 mL) and 2,2-dimethoxypropane (9.2 mL, 74.9 mmol, 4.0 equiv) and *p*-toluenesulfonic acid monohydrate (356 mg, 1.9 mmol, 0.1 equiv) were added. The solution was stirred 144 h at rt (until conversion was complete according to TLC). The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (3 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2) with an eluent gradient (10:1 → 1:1 v/v *c*Hex:EtOAc) to obtain compound **S2f** (740 mg, 4.30 mmol, 22%) as a colourless oil. $\mathbf{R_f}$ = 0.31 (cHex:EtOAc 1:1 v/v). **m.p.:** 143.4 – 146.4 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 8.13 (bs, 1H, N*H*), 4.88 (s, 2H, C*H*), 1.51 (s, 3H, CH_3), 1.44 (s, 3H, CH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 172.2 (C*), 116.5 (C*), 76.1 (CH), 26.8 (CH_3), 25.7 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3205 (m), 3094 (w), 1717 (s), 1375 (m), 1354 (m), 1192 (s), 1153 (m), 1097 (s), 987 (m), 849 (m), 756 (s), 712(m), 633 (w), 575 (s).

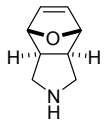


pyrrolidine 1a: To a solution of $LiAlH_4$ (3.5 g, 92.0 mmol, 1.5 equiv) in THF (500 mL, anh.) was slowly added imide **S2a** (10.0 g, 61.0 mmol, 1.0 equiv) under N_2 atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 45 °C, after which the reaction was quenched with H_2O (5 mL) to remove the excess of $LiAlH_4$. The suspension was filtered over Celite®, washed

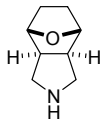
with THF and concentrated *in vacuo* to give compound **1a** (3.0 g, 22.0 mmol, 36%) as a yellow solid. $\mathbf{R_f}$ = 0.09 (CH_2Cl_2:MeOH:NEt_3 100:1:0.5 v/v). **m.p.:** 100.5 – 109.4 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.24 – 6.15 (m, 2H, C*H*=C*H*), 2.84 – 2.78 (m, 2H, NHCH$_2$CHC*H*CH$_2$), 2.76 – 2.64 (m, 3H, NHC*H*$_2$C*H*), 2.57 (d, *J* = 12.2 Hz, 2H, NHC*H*$_2$), 1.78 (bs, 1H, N*H*), 1.47 – 1.36 (m, 2H, CHC*H*$_2$CH) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 135.8 (CH), 53.1 (CH_2), 50.1 (CH_2), 48.2 (CH), 46.5 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3051 (w), 2957 (m), 2930 (s), 1344 (m), 1250 (m), 1092 (m), 895 (m), 870 (m), 800 (s), 743 (s), 689 (m). **HRMS** (ESI): *m/z* calculated for $C_9H_{14}N$ $[M+H]^+$: 136.1121, found: 136.1126.



pyrrolidine 1b: To a solution of $LiAlH_4$ (2.0 g, 54.0 mmol, 1.5 equiv) in THF (300 mL, anh.) was slowly added imide **S2b** (5.8 g, 36.0 mmol, 1.0 equiv) under N_2 atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 70 °C, after which the reaction was quenched with H_2O (4 mL) to remove the excess of $LiAlH_4$. The suspension was filtered over Celite®, washed with THF and concentrated *in vacuo* to give compound **1b** (3.6 g, 26.0 mmol, 72%) as a yellow solid. $\mathbf{R_f}$ = 0.66 (CH_2Cl_2:MeOH:NEt_3 100:1:0.5 v/v). **m.p.:** 96.8 – 103.3 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.91 (d, *J* = 12.0 Hz, 2H, NHC*H*$_2$), 2.64 – 2.55 (m, 2H, NHC*H*$_2$), 2.41 – 2.35 (m, 2H, NHCH$_2$C*H*), 2.13 (s, 2H, NHCH$_2$CHC*H*CH$_2$), 1.88 (bs, 1H, N*H*), 1.54 – 1.26 (m, 6H, C*H*$_2$CHC*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 48.3 (CH_2), 45.8 (CH), 43.0 (CH_2), 41.1 (CH), 23.3 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2937 (s), 2864 (m), 1290 (m), 1250 (m), 1221 (w), 1184 (w), 1111 (m), 1005 (m), 961 (w), 910 (m), 843 (s), 797 (m), 598 (s). **HRMS** (ESI): *m/z* calculated for $C_9H_{16}N$ $[M+H]^+$: 138.1277, found: 138.1291.



pyrrolidine 1c: To a solution of $LiAlH_4$ (1.7 g, 45.0 mmol, 1.5 equiv) in THF (250 mL, anh.) was slowly added imide **S2c** (5.0 g, 30.0 mmol, 1.0 equiv) under N_2 atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 40 °C, after which the reaction was quenched with H_2O (4 mL) to remove the excess of $LiAlH_4$. The suspension was filtered over Celite®, washed with THF and concentrated *in vacuo* to give compound **1c** (3.1 g, 20.0 mmol, 65%) as a red oil. $\mathbf{R_f}$ = 0.07 (CH_2Cl_2:MeOH:NEt_3 100:1:0.5 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.36 (s, 2H, C*H*=C*H*), 4.70 (s, 2H, OC*H*), 2.92 – 2.83 (m, 4H, C*H*$_2$), 2.45 (bs, 1H, N*H*), 2.30 – 2.22 (m, 2H, CH$_2$C*H*) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 137.1 (CH), 83.9 (CH), 51.6 (CH_2), 46.8 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3258 (w), 2991 (w), 2926 (w), 1308 (w), 1067 (w), 949 (m), 891 (s), 964 (s), 843 (s), 810 (s), 712 (s), 692 (s), 590 (s). **HRMS** (ESI): *m/z* calculated for $C_8H_{12}NO$ $[M+H]^+$: 138.0913, found: 138.0920.



pyrrolidine 1d: To a solution of $LiAlH_4$ (3.4 g, 86.0 mmol, 1.5 equiv) in THF (500 mL, anh.) was slowly added imide **S2d** (9.6 g, 58.0 mmol, 1.0 equiv) under N_2 atmosphere at 0 °C. The reaction mixture was stirred for 19 h at 45 °C, after which the reaction was quenched with H_2O (5 mL) to remove the excess of $LiAlH_4$. The suspension was filtered over Celite®, washed with THF and concentrated *in vacuo* to give compound **1d** (6.0 g, 43.0 mmol, 75%) as a yellow oil. $\mathbf{R_f}$ = 0.07 (CH_2Cl_2:MeOH:NEt_3 100:1:0.5 v/v). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.30 – 4.23 (m, 2H, OC*H*), 2.92 (dd, *J* = 11.3 Hz, 6.4 Hz, 2H, NC*H*$_2$), 2.69 (dd, *J* = 11.3, 2.4 Hz, 2H, NC*H*$_2$), 2.40 (bs, 1H, N*H*), 2.24 – 2.20 (m, 2H,

NCH_2CH), 1.64 – 1.56 (m, 2H, CH_2CH_2), 1.42 – 1.35 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 81.3 (CH), 53.3 (CH_2), 49.9 (CH), 28.9 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3173 (m), 2945 (s), 2909 (m), 2853 (s), 1221 (m), 1182 (s), 1082 (s), 1024 (s), 1005 (s), 989 (s), 959 (s), 912 (s), 901 (s), 795 (s), 629 (s), 584 (s). **HRMS** (ESI): *m/z* calculated for $C_8H_{14}NO$ $[M+H]^+$:140.1070, found: 140.1069.

pyrrolidine 1f: To a solution of $LiAlH_4$ (230 mg, 6.1 mmol, 1.5 equiv) in THF (35 mL, anh.) was slowly added imide **S2f** (700 mg, 4.1 mmol, 1.0 equiv) under N_2 atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 55 °C, after which the reaction was quenched with H_2O (2 mL) to remove the excess of $LiAlH_4$. The suspension was filtered over Celite®, washed with THF and concentrated *in vacuo* to give compound **1f** (444 mg, 3.1 mmol, 51%) as a colourless oil. $\mathbf{R_f}$ = 0.16 (CH_2Cl_2:MeOH:NEt_3 100:1:0.5 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.65 (s, 2H, $NHCH_2CH$), 3.11 (d, *J* = 14.0 Hz, 2H $NHCH_2$), 2.51 (d, *J* = 13.3 Hz, 2H, $NHCH_2$), 1.75 (bs, 1H, NH), 1.45 (s, 3H, CH_3), 1.31 (s, 3H, CH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 110.3 (C*), 81.7 (CH), 54.4 (CH_2), 26.1 (CH_3), 23.9 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2980 (m), 2928 (s), 1373 (m), 1207 (s), 1150 (m), 1080 (m), 1034 (s), 897 (m), 851 (s), 822 (m), 625 (m). **HRMS** (ESI): *m/z* calculated for $C_7H_{14}NO_2$ $[M+H]^+$: 144.1019, found: 144.1025.

3.5.3 Synthetic procedures and spectral data

General procedure for optimization of the reaction conditions for the oxidation of *meso*-pyrrolidine 1a with IBX in Table 1: To a solution of pyrrolidine **1a** (0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) was added IBX (70 mg, 0.25 mmol, 1.0 equiv). The reaction mixture was stirred for 0.5 - 1 h at rt or 60 °C (oil bath, closed vessel). The reaction mixture was cooled to rt, quenched with sat. aq. $Na_2S_2O_4$ (1 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Subsequently, the yield of **2a** was determined with ^{1}H-NMR spectroscopy after dissolving the crude product in $CDCl_3$ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 equiv) as standard for NMR spectroscopy.

General procedure for optimization of the reaction conditions for the oxidative Ugi-type reaction in Table 3: To a solution of pyrrolidine **1a** (0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 m) were added IBX (70 mg, 0.25 mmol, 1.0 equiv), benzoic acid (0.375 mmol, 1.5 equiv) and *tert*-butyl isocyanide (0.375 mmol, 1.5 equiv). The reaction mixture was stirred for 24 h at rt or 60 °C (oil bath, closed vessel). The suspension was cooled to rt, quenched with sat. aq. $Na_2S_2O_4$ (1 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Subsequently, the yield of **3a** was determined with ^{1}H-NMR spectroscopy after dissolving the crude product in $CDCl_3$ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 equiv) as standard for NMR spectroscopy.

General procedure 1 for the oxidation of *meso*-pyrrolidines 1: To a solution of the pyrrolidine (0.5 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) was added IBX (140 mg, 0.5 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The reaction was cooled to rt, quenched with sat. aq.

$Na_2S_2O_4$ (2 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with CH_2Cl_2 (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. If necessary, the crude product was purified by flash chromatography.

General procedure 2 for oxidative Ugi-type three-component reactions: To a solution of the pyrrolidine (0.5 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 M) were added IBX (140 mg, 0.5 mmol, 1.0 equiv), the carboxylic acid (0.75 mmol, 1.5 equiv) and the isocyanide (0.75 mmol, 1.5 equiv). The reaction mixture was stirred for 48 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt, quenched with sat. aq. Na2S2O4 (2 mL), washed with sat. aq. Na2CO3/brine (3:1, 20 mL), extracted with CH_2Cl_2 (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. If necessary, the crude product was purified by flash chromatography or preparative thin layer chromatography. Two sets of resonances were observed in all ^1H and ^{13}C spectra, corresponding to different rotamers. Incomplete coalencence was observed at 100 °C for **3b**, as depicted in Figure 2.

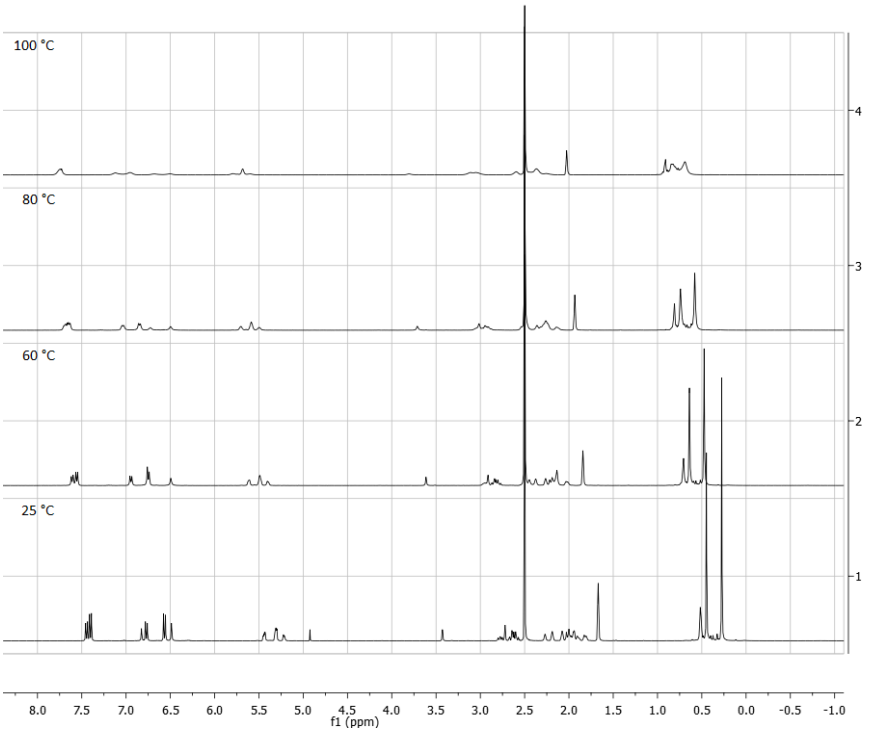
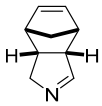


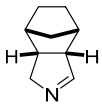
Figure 2. High temperature NMR spectra of **3b** in DMSO-d_6, showing incomplete coalescence at 100 °C.

General procedure 3 for oxidative aza-Friedel–Crafts reaction: To a solution of the pyrrolidine (0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.25 M) were added IBX (70 mg, 0.25 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt and

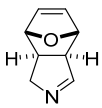
trifluoroacetic acid (38 μL, 0.5 mmol, 2.0 equiv) and the pyrrole or indole (0.5 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt, quenched with sat. aq. $Na_2S_2O_4$ (2 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with CH_2Cl_2 (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. If necessary, the crude product was purified by flash chromatography.



1-pyrroline 2a: Prepared from pyrrolidine **1a** (69 mg, 0.50 mmol, 1.0 equiv) according to *general procedure 1*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (1:1 → 1:2 v/v *c*Hex:EtOAc, 100:1 → 50:1 v/v CH_2Cl_2:MeOH), to obtain compound **2a** (59 mg, 0.44 mmol, 88%) as a light yellow solid. $\mathbf{R_f}$ = 0.24 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 81.0 – 85.0 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.28 (s, 1H, N=C*H*), 6.11 – 5.94 (m, 2H, *H*C=C*H*), 3.72 – 3.62 (m, 1H, NCH_2), 3.55 – 3.41 (m, 1H, N=CHC*H*), 3.24 – 3.11 (m, 1H, NCH_2), 3.03 (s, 1H, N=CHCHC*H*CH$_2$), 2.92 (s, 1H, NCH$_2$CHC*H*CH$_2$), 2.83 – 2.73 (m, 1H, NCH$_2$C*H*), 1.52 (d, *J* = 8.1 Hz, 1H, CHCH_2CH), 1.36 (d, *J* = 8.2 Hz, 1H, CHCH_2CH) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 167.2 (CH), 135.5 (CH), 133.6 (CH), 62.9 (CH_2), 60.3 (CH), 51.1 (CH_2), 45.4 (CH), 44.2 (CH), 41.0 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2958 (m), 2918 (m), 2798 (m), 1339 (s), 1207 (m), 1182 (s), 1096 (m), 953 (m), 899 (m), 841 (m), 800 (m), 739 (*s*), 725 (s). **HRMS** (ESI): *m/z* calculated for $C_9H_{12}N$ $[M+H]^+$: 134.0964, found: 110.0966.

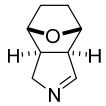


1-pyrroline 2b: Prepared from pyrrolidine **1b** (73 mg, 0.50 mmol, 1.0 equiv) according to *general procedure 1*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (1:1 v/v *c*Hex:EtOAc, 100:1 v/v CH_2Cl_2:MeOH), to obtain compound **2b** (65 mg, 0.48 mmol, 97%) as a light yellow solid. $\mathbf{R_f}$ = 0.24 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 81.0 – 88.1 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.41 (s, 1H, N=C*H*), 3.84 – 3.77 (m, 1H, NCH_2), 3.70 – 3.61 (m, 1H, NCH_2), 3.23 – 3.13 (m, 1H, N=CHC*H*), 2.64 – 2.53 (m, 1H, NCH$_2$C*H*), 2.50 (s, 1H, N=CHCHC*H*CH$_2$), 2.16 (s, 1H, NCH$_2$CHC*H*CH$_2$), 1.52 (d, *J* = 9.4 Hz, 1H, CHCH_2CH), 1.43 (d, *J* = 9.0 Hz, 1H, CHCH_2CH), 1.31 (d, *J* = 6.3 Hz, 2H, CH_2CH_2), 1.19 (d, *J* = 7.4 Hz, 2H, CH_2CH_2) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$): *δ* 169.2 (CH), 60.9 (CH_2), 58.3 (CH), 42.6 (CH), 42.1 (CH_2), 40.0 (CH), 38.5 (CH), 26.0 (CH_2), 22.1 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2945 (s), 2860 (m), 1670 (w), 1381 (w), 1298 (m), 1225 (m), 1177 (m), 1161 (m), 1119 (s), 1092 (s), 1018 (w), 995 (w), 889 (m), 822 (w), 656 (w). **HRMS** (ESI): *m/z* calculated for $C_9H_{14}N$ $[M+H]^+$: 136.1121, found: 136.1125.



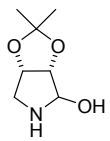
1-pyrroline 2c: Prepared from pyrrolidine **1c** (79 mg, 0.50 mmol, 1.0 equiv) according to *general procedure 1*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (1:1 v/v cHex:EtOAc, 100:1 → 10:1 v/v CH_2Cl_2:MeOH), to obtain compound **2c** (66 mg [3% *c*Hex], 0.47 mmol, 95%) as a reddish brown solid. $\mathbf{R_f}$ = 0.18 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 100.0 – 109.2 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.49 – 7.36 (m, 1H, N=C*H*), 6.46 – 6.29 (m, 2H, C*H*=C*H*), 4.95 (s, 1H, NCH$_2$CHC*H*O), 4.75 (s, 1H, N=CHCHC*H*O), 4.04 – 3.86 (m, 1H, NCH_2), 3.72 – 3.59 (m, 1H, NCH_2), 3.10 (dd, *J* = 7.1 Hz, *J* = 2.9 Hz, 1H, N=CHC*H*), 2.57 – 2.44 (m, 1H, NCH$_2$C*H*) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 164.1 (CH), 137.5 (CH), 136.2 (CH), 84.2 (CH), 79.7 (CH), 63.6 (CH_2), 59.7 (CH), 42.3 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) =

2978 (m), 1458 (w), 1342 (m), 1229 (m), 1190 (m), 1157 (s), 1032 (s), 997 (m), 949 (s), 897 (s), 866 (m), 810 (s), 723 (s), 692 (s), 681 (s), 625 (s). **HRMS** (ESI): *m/z* calculated for $C_8H_{10}NO$ $[M+H]^+$: 136.0757, found: 136.0758.

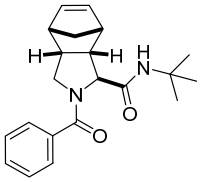


1-pyrroline 2d: Prepared from pyrrolidine **1d** (72 mg, 0.50 mmol, 1.0 equiv) according to *general procedure 1*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (1:1 cHex:EtOAc, 100:1 → 20:1 v/v CH_2Cl_2:MeOH), to obtain compound **2d** (60 mg [17% CH_2Cl_2], 0.36 mmol, 71%) as a light yellow solid. $\mathbf{R_f}$ = 0.18 (CH_2Cl_2:MeOH 100:1 v/v).**m.p.:** 150.6 – 157.2 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35 (d, J = 3.3 Hz, 1H, N=C*H*), 4.51 (d, J = 4.7 Hz, 1H, NCH_2CHCHO), 4.34 (d, J = 4.7 Hz, 1H, N=CHCHC*H*O), 4.10 – 4.00 (m, 1H, NCH_2), 3.74 – 3.65 (m, 1H, NCH_2), 3.03 (dd, J = 7.8 Hz, J = 2.9 Hz, 1H, N=CHC*H*), 2.42 – 2.34 (m, 1H, NCH_2CH), 1.79 – 1.64 (m, 2H, CH_2CH_2), 1.58 – 1.43 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.1 (CH), 82.6 (CH), 77.4 (CH), 67.9 (CH_2), 61.1 (CH), 44.1 (CH), 29.3 (CH_2), 28.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2949 (m), 1655 (w), 1393 (m), 1315 (m), 1225 (s), 1215 (s), 1175 (s), 1047 (m), 972 (s), 924 (s), 805 (s), 623 (s). **HRMS** (ESI): *m/z* calculated for $C_8H_{12}NO$ $[M+H]^+$: 138.0913, found: 138.0916.

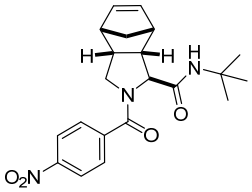
1-pyrroline 2e:[26] Prepared from pyrrolidine **1e** (56 mg, 0.50 mmol, 1.0 equiv) according to *general procedure 1*. Compound **2e** (38 mg, 0.35 mmol, 70%) was obtained without the need of purification as a light yellow solid. $\mathbf{R_f}$ = 0.38 (CH_2Cl_2:MeOH 100:1 v/v). **m.p.:** 99.8 – 111.7 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32 – 7.28 (m, 1H, NHC*H*), 4.11 – 3.98 (m, 1H, NHCH_2), 3.57 – 3.46 (m, 1H, NHCH_2), 3.27 (t, J = 8.9 Hz, 1H, NHCHC*H*), 2.72 – 2.57 (m, 1H, $NHCH_2CH$), 1.73 – 1.19 (m, 6H, $CH_2CH_2CH_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.6 (CH), 70.3 (CH_2), 55.2 (CH), 38.7 (CH), 34.8 (CH_2), 29.4 (CH_2), 25.0 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2931 (s), 2901 (m), 1466 (m), 1306 (m), 1204 (s), 1182 (s), 1157 (m), 1134 (s), 1070 (m), 932 (s),. **HRMS** (ESI): *m/z* calculated for $C_7H_{12}N$ $[M+H]^+$: 110.0964, found: 110.0973.



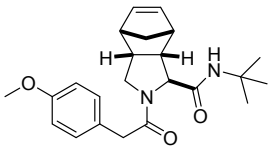
α-hydroxypyrrolidine 2f:[15] To a solution of pyrrolidine **1f** (0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) was added IBX (70 mg, 0.25 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 60 °C in an oil bath. The reaction was cooled to rt, quenched with sat. aq. $Na_2S_2O_4$ (1 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Compound **2f** was obtained in 48% yield, as determined with ^{1}H-NMR spectroscopy after dissolving the crude product in $CDCl_3$ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 equiv) as standard for NMR spectroscopy. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.72 – 4.66 (m, 1H, $NHCH_2CH$), 4.37 (dd, J = 7.1, 3.9 Hz, 1H, NHCHOC*H*), 3.33 (dd, J = 9.9, 6.1 Hz, 1H, NHCH_2), 3.26 (d, J = 4.1 Hz, 1H, NHC*H*O), 2.59 (dd, J = 9.8, 3.5 Hz, 1H, NHCH_2), 1.51 (s, 1H, CH_3), 1.32 (s, 1H, CH_3) ppm.**^{13}C NMR** (126 MHz, $CDCl_3$) δ 113.6 (C*), 85.4 (CH), 80.8 (CH), 77.4 (CH), 52.5 (CH_2), 27.0 (CH_3), 25.2 (CH_3).



prolyl peptide 3a: Prepared from pyrrolidine **1a** (69 mg, 0.50 mmol, 1.0 equiv), benzoic acid (92 mg, 0.75 mmol, 1.5 equiv) and *t*-butyl isocyanide (87 µL, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (4:1 → 2:1 v/v *c*Hex:EtOAc), to obtain compound **3a** (99 mg, 0.29 mmol, 59%) as an off-white solid. $\mathbf{R_f}$ = 0.48 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 191.0 – 193.7 °C (decomposition).**^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.45 – 7.32 (m, 5H, *Ph*), 6.64 (s, 1H, N*H*), 6.20 (dd, *J* = 5.7 Hz, *J* = 3.0 Hz, 1 H, $NCH_2CHCHCH$=CH), 5.91 (dd, *J* = 5.7 Hz, *J* = 3.0 Hz, 1H, C(O)CHCHCHC*H*=CH), 4.43 (s, 1H, C(O)C*H*), 3.55 (dd, *J* = 11.7 Hz, *J* = 8.6 Hz, 1H, NCH_2), 3.45 – 3.38 (m, 1H, C(O)CHC*H*), 3.08 – 2.98 (m, 2H, $NCH_2CHCHCH_2CH$), 2.93 – 2.84 (m, 1H, $NCH_2CHCHCH_2$), 2.82 – 2.74 (m, 1H, NCH_2CH), 1.49 – 1.36 (m, 2H, $CHCH_2CH$), 1.32 (s, 9H $C(CH_3)_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.3 (C*), 169.7 (C*), 136.7 (C*), 134.9 (CH), 134.4 (CH), 130.1 (CH), 128.5 (CH), 126.6 (CH), 63.0 (CH), 52.1 (CH_2), 51.7 (CH_2), 47.1 (CH), 46.6 (CH), 45.6 (CH), 45.0 (CH), 28.8 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3300 (w), 2935 (w), 1670 (m), 1599 (s), 1566 (s), 1535 (s), 1410 (s), 1389 (m), 1317 (m), 1223 (m), 1205 (m), 731 (m), 716 (s), 621 (m). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{27}N_2O_2$ $[M+H]^+$: 339.2067, found: 339.2056.

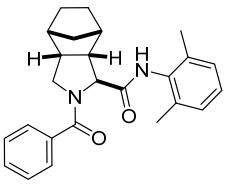


prolyl peptide 3b: Prepared from pyrrolidine **1a** (69 mg, 0.50 mmol, 1.0 equiv), 4-nitrobenzoic acid (125 mg, 0.75 mmol, 1.5 equiv) and *t*-butyl isocyanide (87 µL, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (4:1 → 2:1 v/v *c*Hex:EtOAc), to obtain compound **3b** (114 mg [12% CH_2Cl_2], 0.26 mmol, 52%) as an off-white solid. $\mathbf{R_f}$ = 0.40 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** >150 °C decomposition. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.3 Hz, 2H, $C(NO_2)CH$), 7.59 – 7.51 (m, 2H, $C(NO_2)CHCH$), 6.40 (s, 1H, N*H*), 6.22 (dd, *J* = 5.7 Hz, *J* = 3.0 Hz, 1H, CH=C*H*), 5.93 (dd, *J* = 5.8 Hz, *J* = 3.0 Hz, 1H, C*H*=CH), 4.37 (d, *J* = 2.0 Hz, 1H, NC*H*), 3.60 (dd, *J* = 11.7 Hz, *J* = 8.9 Hz, 1H, NCH_2), 3.43 –3.31 (m, 1H, NCH_2), 3.04 (s, 1H, C*H*), 2.97 – 2.89 (m, 2H, C*H*), 2.81 (s, 1H, C*H*), 1.51 (d, *J* = 8.6 Hz, 1H, $CHCH_2CH$), 1.42 (d, *J* = 8.6 Hz, 1H, $CHCH_2CH$), 1.34 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.9 (C*), 167.4 (C*), 148.7 (C*), 142.6 (C*), 135.1 (CH), 134.5 (CH), 127.8 (CH), 124.0 (CH), 63.5 (CH), 52.2 (CH_2), 51.8 (CH_2), 51.4 (C*), 47.0 (CH), 46.7 (CH), 45.7 (CH), 28.9 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3308 (m), 2976 (m), 2932 (m), 1599 (m), 1520 (s), 1437 (m), 1340 (s), 1313 (m), 1227 (m), 1209 (m), 1016 (w), 854 (m), 831 (m), 602 (m). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{26}N_3O_4$ $[M+H]^+$: 384.1918, found: 384.1908.

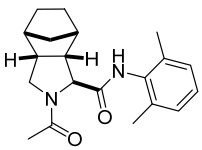


prolyl peptide 3c: Prepared from pyrrolidine **1a** (69 mg, 0.50 mmol, 1.0 equiv), 2-(4-methoxyphenyl)acetic acid (126 mg, 0.75 mmol, 1.5 equiv) and *t*-butyl isocyanide (87 µL, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (10:1 → 1:1 v/v *c*Hex:EtOAc), to obtain compound **3c** (103 mg, 0.28 mmol, 56%) as an off-white solid. $\mathbf{R_f}$ = 0.34 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 133.7 – 140.9 °C (decomposition). **^{1}H NMR** (500 MHz,

$CDCl_3$): δ 7.12 (d, *J* = 9.0 Hz, 2H, C(OMe)CHC*H*), 6.84 (d, *J* = 8.0 Hz, 2H, C(OMe)C*H*), 6.10 – 6.03 (m, 1H, CH=C*H*), 5.74 – 5.63 (m, 1H, C*H*=CH), 4.14 (s, 1H, NC*H*), 3.78 (s, 3H, H_3CO), 3.52 – 3.45 (m, 2H, C*CH_2), 3.36 – 3.22 (m, 2H, NCH_2, C*H*), 3.24 – 3.15 (m, 1H, NCH_2), 2.94 (s, 1H, C*H*), 2.91 – 2.87 (m, 1H, C*H*), 2.83 (s, 1H, C*H*), 1.66 (s, 1H, N*H*), 1.39 – 1.34 (m, 1H, CHCH_2CH), 1.31 – 1.25 (m, 10H, C(CH_3)$_3$, CHCH_2CH) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.5 (C*), 170.0 (C*), 158.7 (C*), 135.2 (CH), 134.5 (CH), 129.9 (CH), 126.3 (C*), 114.2 (CH), 63.2 (CH), 55.4 (CH_3), 51.7 (CH_2), 51.1 (C*), 50.0 (CH_2), 47.1 (CH), 46.6 (CH), 45.8 (CH), 45.2 (CH), 41.8 (CH_2), 28.8 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3283 (w), 2934 (w), 1647 (s), 1626 (s), 1516 (m), 1389 (w), 1290 (w), 1277 (w), 1250 (s), 1219 (m), 1024 (m), 856 (w), 820 (m), 735 (m). **HRMS** (ESI): *m/z* calculated for $C_{23}H_{31}N_2O_3$ $[M+H]^+$: 383.2329, found: 383.2331.

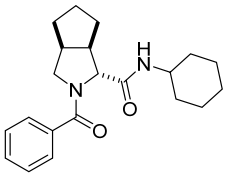


prolyl peptide 3d: Prepared from pyrrolidine **1b** (73 mg, 0.50 mmol, 1.0 equiv), benzoic acid (92 mg, 0.75 mmol, 1.5 equiv) and 1,3-dimethylbenzene isocyanide (98 mg, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:1 → 5:1 v/v *c*Hex:EtOAc), to obtain compound **3d** (118 mg, 0.30 mmol, 61%) as an off-white solid. $\mathbf{R_f}$ = 0.64 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 77.7 – 91.8 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09 (bs, 1H, N*H*), 7.59 – 7.37 (m, 5H, *Ph*), 7.12 – 7.01 (m, 3H, C(CH_3)C*HCHCH*), 5.22 (s, 1H, NC*H*), 3.62 (dd, *J* = 11.9 Hz, *J* = 8.4 Hz, 1H, NCH_2), 3.49 (d, *J* = 12.0 Hz, 1H, NCH_2), 3.30 – 3.17 (m, 1H, NCHC*H*), 2.78 – 2.66 (m, 1H, NCH_2C*H*), 2.42 (s, 1H, NCHCHC*H*CH_2CH), 2.33 – 2.14 (m, 7H, CH_3, CH_3, NCH_2CHC*H*CH_2), 1.72 – 1.19 (m, 6H, CH_2CHCH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.57 (C*), 169.58 (C*), 136.1 (C*), 135.2 (C*), 133.9 (C*), 130.5 (CH), 128.6 (CH), 128.3 (CH), 127.3 (CH), 126.8 (CH), 60.6 (CH), 50.3 (CH_2), 44.4 (CH), 44.3 (CH), 42.0 (CH_2), 41.5 (CH), 41.0 (CH), 23.3 (CH_2), 22.9 (CH_2), 18.6 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3263 (br), 2953 (w), 1684 (s), 1609 (s), 1516 (s), 1447 (s), 1420 (s), 1398 (s), 1375 (s), 1296 (w), 1175 (m), 881 (m), 766 (s), 721 (s), 698 (s). **HRMS** (ESI): *m/z* calculated for $C_{25}H_{29}N_2O_2$ $[M+H]^+$: 389.2224, found: 389.2221.

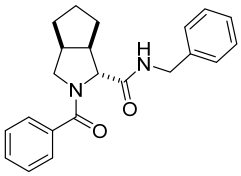


prolyl peptide 3e: Prepared from pyrrolidine **1b** (73 mg, 0.50 mmol, 1.0 equiv), acetic acid (43 µL, 0.75 mmol, 1.5 equiv) and 1,3-dimethylbenzene isocyanide (98 mg, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by preparative thin layer chromatography (SiO_2, *c*Hex:EtOAc 1:1 v/v), to obtain compound **3e** (70 mg, 0.22 mmol, 43%) as an off-white solid. Two-step procedure: To a solution of pyrrolidine **1b** (72 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) were added IBX (140 mg, 0.5 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt and acetic acid (43 µL, 0.75 mmol, 1.5 equiv) and 1,3-dimethylbenzene isocyanide (98 mg, 0.75 mmol, 1 equiv) were added, after which stirring was proceeded for 23 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt, quenched with sat. aq. $Na_2S_2O_4$ (2 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with CH_2Cl_2 (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by preparative thin layer chromatography (SiO_2, *c*Hex:EtOAc 1:1 v/v), to obtain compound **3e** (88 mg, 0.27 mmol, 54%) as an off-white solid. $\mathbf{R_f}$ = 0.73 (*c*Hex:EtOAc 1:1 v/v). **m.p.:**

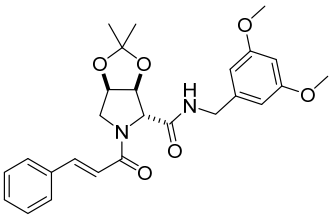
171.6 – 179.5 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.18 (bs, 1H, N*H*), 7.16 – 7.00 (m, 3H, *Ar*), 4.89 (s, 1H, NC*H*), 3.62 (d, *J* = 11.5 Hz, 1H, NCH_2), 3.47 (dd, *J* = 11.7 Hz, *J* = 8.3 Hz, 1H, NCH_2), 3.18 (dd, *J* = 10.9 Hz, *J* = 4.9 Hz, 1H, NCHC*H*), 2.81 – 2.68 (m, 1H, NCH_2CH), 2.44 – 2.34 (m, 1H, NCHCHC*H*CH_2), 2.34 – 2.30 (m, 1H, $NCH_2CHCHCH_2$), 2.18 (d, *J* = 5.1 Hz, 6H, CH_3), 1.60 – 1.58 (m, 1H, CHCH_2CH), 1.54 – 1.49 (m, 1H, CHCH_2CH), 1.45 – 1.39 (m, 2H, CH_2CH_2), 1.35 – 1.27 (m, 2H, CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.8 (C*), 169.6 (C*), 135.2 (C*), 134.0 (C*), 128.2 (CH), 127.1 (CH), 77.4 (CH), 60.2 (CH), 48.4 (CH_2), 44.6 (CH), 43.8 (CH), 42.0 (CH_2), 41.5 (CH), 40.9 (CH), 23.3 (CH_2), 22.9 (CH_2), 22.6 (CH_3), 18.5 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3309 (w), 1647 (s), 1506 (m), 1471 (m), 1406 (s), 1375 (m), 1192 (m), 1034 (w), 847 (w), 773 (m), 640 (m). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{26}N_2NaO_2$ $[M+Na]^+$: 349.1886, found: 349.1879.



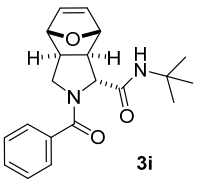
prolyl peptide 3f: Prepared from pyrrolidine **1e** (56 mg, 0.50 mmol, 1.0 equiv), benzoic acid (92 mg, 0.75 mmol, 1.5 equiv) and cyclohexyl isocyanide (95 µL, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:1 → 8:1 v/v *c*Hex:EtOAc), to obtain compound **3f** (96 mg, 0.27 mmol, 54%) as a yellow oil. $\mathbf{R_f}$ = 0.45 (*c*Hex:EtOAc 1:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.52 – 7.32 (m, 5H, *Ph*), 6.73 (d, *J* = 8.3 Hz, 1H N*H*), 4.65 – 4.54 (m, 1H, C*H*C(O)), 3.85 – 3.67 (m, 2H, NCH_2, NCHC*H*), 3.29 (d, *J* = 11.3 Hz, 1H, NCH_2), 3.24 – 3.13 (m, 1H, NCH_2CH), 2.75 – 2.68 (m, 1H, C(O)NHC*H*), 2.02 – 1.51 (m, 10H, CH_2),[27] 1.42 – 1.03 (m, 6H, CH_2)[27] ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.6 (C*), 170.1 (C*), 136.3 (C*), 130.3 (CH), 128.6 (CH), 127.0 (CH), 66.6 (CH), 56.0 (CH_2), 48.3 (CH), 44.3 (CH), 43.4 (CH), 33.1 (CH_2), 32.8 (CH_2), 26.3 (CH_2), 25.6 (CH_2), 24.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3302 (br), 2928 (s), 1616 (s), 1541 (s), 1522 (m), 1418 (s), 1225 (w), 891 (w), 725 (m), 698 (s). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{29}N_2O_2$ $[M+H]^+$: 341.2224, found: 341.2207.



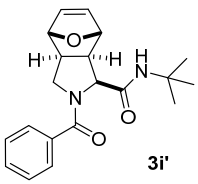
prolyl peptide 3g: Prepared from pyrrolidine **1e** (56 mg, 0.50 mmol, 1.0 equiv), benzoic acid (92 mg, 0.75 mmol, 1.5 equiv) and benzyl isocyanide (86 µL, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:1 → 2:1 v/v *c*Hex:EtOAc) and by preparative thin layer chromatography (SiO_2, *c*Hex:EtOAc 1:1 v/v), to obtain compound **3g** (72 mg, 0.21 mmol, 41%) as a yellow oil. $\mathbf{R_f}$ = 0.35 (*c*Hex:EtOAc 1:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.46 – 7.09 (m, 10H, *Ph*),[27] 4.63 (s, 1H, C*H*C(O)), 4.47 – 4.31 (m, 2H, NHCH_2),[27] 3.67 (dd, *J* = 11.3Hz, *J* = 7.4 Hz, 1H, NCH_2), 3.26 (dd, *J* = 11.2 Hz, *J* = 2.8 Hz, 1H, NCH_2), 3.22 – 3.12 (m, 1H, NCHC*H*), 2.78 – 2.58 (m, 1H, NCH_2CH), 1.97 – 1.16 (m, 6H, $CH_2CH_2CH_2$)[27] ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.1 (C*), 170.7 (C*), 138.5 (C*), 136.1 (C*), 128.5 (CH), 128.4 (CH), 127.6 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 66.5 (CH), 56.0 (CH_2), 44.6 (CH), 43.6 (CH_2), 43.5 (CH), 33.1 (CH_2), 32.7 (CH_2), 31.1 (CH_2), 26.3 (CH_2), 25.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3290 (br), 2945 (w), 1616 (s), 1541 (m), 1497 (m), 1447 (m), 1418 (s), 1361 (w), 1228 (m), 721 (m), 696 (s), 677 (m), 663 (m). **HRMS** (ESI): *m/z* calculated for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1911, found: 349.1895.



prolyl peptide 3h: Prepared from pyrrolidine **1f** (72 mg, 0.50 mmol, 1.0 equiv), cinnamic acid (109 mg, 0.75 mmol, 1.5 equiv) and 1-(isocyanomethyl)-3,5-dimethoxybenzyl (117 µL, 0.75 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (20:1 → 1:2 v/v *c*Hex:EtOAc) and by preparative thin layer chromatography (SiO_2, *c*Hex:EtOAc 1:1 v/v), to obtain compound **3h** (110 mg [3% CH_2Cl_2], 0.23 mmol, 45%) as a yellow solid. $\mathbf{R_f}$ = 0.34 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 52.1 – 61.5 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 15.4 Hz, 1H, C(O)C*H*=C*H*), 7.53 (dd, *J* = 6.5 Hz, *J* = 3.0 Hz, 2H, *Ph*), 7.43 – 7.35 (m, 3H, *Ph*), 7.12 (d, *J* = 8.0 Hz, 1H, CH_2C*C*H), 6.72 (d, *J* = 15.5 Hz, 1H, C(O)C*H*=C*H*), 6.43 – 6.37 (m, 2H, CH_2C*C*HC(OMe)C*H*), 5.13 (d, *J* = 5.7 Hz, 1H, NC*H*), 4.95 – 4.89 (m, 2H, C*H*O), 4.41 – 4.33 (m, 1H, NHCH_2), 4.31 – 4.23 (m, 1H, NHCH_2), 4.00 (d, *J* = 11.9 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.72 – 3.66 (m, 1H, NCH_2), 1.75 (bs, 1H, N*H*), 1.41 (s, 3H, C*CH_3), 1.32 (s, 3H, C*CH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.7 (C*), 165.8 (C*), 160.6 (C*), 158.6 (C*), 143.7 (CH), 134.9 (C*), 130.2 (CH), 129.0 (CH), 128.1 (CH), 118.6 (C*), 117.2 (CH), 112.0 (C*), 103.9 (CH), 98.6 (CH), 80.6 (CH), 79.8 (CH), 65.7 (CH), 55.5 (CH_3), 53.2 (CH_2), 39.1 (CH_2), 26.9 (CH_3), 24.9 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3294 (br), 2935 (w), 1647 (s), 1610 (m), 1578 (w), 1508 (s), 1418 (s), 1373 (m), 1261 (m), 1205 (s), 1155 (s), (m), 1034 (m), 974 (m), 764 (m), 702 (m), 565 (w). **HRMS** (ESI): *m/z* calculated for $C_{26}H_{31}N_2O_6$ $[M+H]^+$: 467.2177, found: 467.2167.



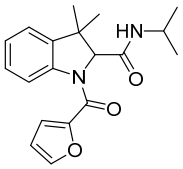
3i



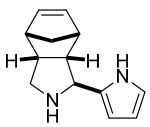
3i'

prolyl peptide 3i (major) and prolyl peptide 3i' (minor): Prepared from pyrrolidine **1c** (40 mg [87% pure], 0.25 mmol, 1.0 equiv), benzoic acid (46 mg, 0.38 mmol, 1.5 equiv) and *t*-butyl isocyanide (44 µL, 0.38 mmol, 1.5 equiv) according to *general procedure 2*. Purification was achieved by preparative thin layer chromatography (SiO_2, *c*Hex:EtOAc 1:3, v/v), to obtain the compound **3i** (32 mg, 0.09 mmol, 38%) as an off-white solid and the diastereoisomer **3i'** (16 mg, 0.05 mmol, 19%) as an off-white solid in a 2:1 diastereoisomeric ratio. **3i**: $\mathbf{R_f}$ = 0.14 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 176.8 – 185.3 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49 – 7.38 (m, 5H, *Ph*), 6.93 (s, 1H, N*H*), 6.42 (dd, *J* = 6.1 Hz, *J* = 1.9 Hz, 1H, NCH_2CHCHC*H*=CH), 6.35 (dd, *J* = 1.5 Hz, *J* = 1.5 Hz, 1H, $NCH_2CHCHCH$=C*H*), 4.95 – 4.84 (m, 2H, NCH_2CHC*H*O, NC*H*), 4.65 (s, 1H, NCHCHC*H*O), 3.73 (dd, *J* = 11.9 Hz, *J* = 8.3 Hz, 1H, NCH_2), 3.52 (dd, *J* = 12.0 Hz, *J* = 1.9 Hz, 1H, NCH_2), 2.98 (d, *J* = 7.1 Hz, 1H, NCHC*H*), 2.42 (t, *J* = 7.8 Hz, 1H, NCH_2C*H*), 1.35 (s, 9H, C(CH_3)$_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.1 (C*), 169.8 (C*), 137.1 (CH), 136.6 (CH), 136.2 (CH), 130.3 (CH), 128.6 (CH), 127.0 (C*), 84.0 (CH), 83.7 (CH), 64.1 (CH), 52.9 (CH_2), 51.4 (C*), 44.7 (CH), 44.3 (CH), 28.8 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3292 (w), 2966 (w), 1676 (s), 1601 (s), 1570 (s), 1541 (s), 1447 (m), 1425 (s), 1356 (m), 1281 (w), 1259 (w), 1223 (m), 1030 (w), 941 (w), 903 (s), 868 (w), 847 (w), 719 (s), 692 (s), 665 (s), 619 (m). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1860, found: 341.1849. **3i'**: $\mathbf{R_f}$ = 0.10 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 184.0 – 190.0 °C (decomposition). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.59 – 7.19 (m, 5H, *Ph*), 6.50 – 6.31 (m, 2H, *H*C=C*H*), 4.86 (s, 1H, C*H*O), 4.78 – 4.59 (m, 2H, NC*H*,

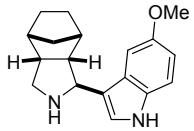
C*H*O), 3.53 (t, *J* = 9.7 Hz, 1H), 3.40 – 3.30 (m, 1H, NC*H*$_2$),[28] 2.68 – 2.56 (m, 1H, NHCH$_2$C*H*), 2.54 – 2.40 (m, 1H, NCHC*H*),[27] 1.30 (s, 9H, C(C*H*$_3$)$_3$,) ppm.[27] **^{13}C NMR** (126 MHz, DMSO-d_6): δ 168.4 (C*), 168.0 (C*), 137.2 (CH), 137.1 (C*), 136.7 (CH), 130.3 (CH), 128.7 (CH), 127.6 (CH), 79.4 (CH, CH), 60.5 (CH), 53.0 (CH$_2$), 50.7 (C*), 47.2 (CH), 45.4 (CH), 29.1 (CH$_3$) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2974 (w), 1670 (s), 1624 (s), 1418 (s), 1313 (w), 1223 (m), 1142 (m), 986 (m), 951 (m), 906 (m), 822 (w), 661 (m). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1860, found: 341.1850.



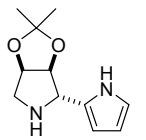
prolyl peptide 3j: To a solution of 3,3-dimethylindoline (37 mg, 0.25 mmol, 1.0 equiv) in DMSO (0.5 M) were added IBX (70 mg, 0.25 mmol, 1.0 equiv), furoic acid (43 mg, 0.38 mmol, 1.5 equiv) and *i*-propyl isocyanide (35 µL, 0.38 mmol, 1.5 equiv). The reaction mixture was stirred for 48 h at rt. The suspension was quenched with sat. aq. $Na_2S_2O_4$ (2 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with CH_2Cl_2 (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:1 → 5:1 v/v *c*Hex:EtOAc) and by preparative thin layer chromatography (SiO_2, *c*Hex:EtOAc 1:1, v/v), to obtain compound **3j** (32 mg [13% CH_2Cl_2], 0.09 mmol, 35%) as a yellow solid. **R$_f$** = 0.32 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 63.2 – 73.8 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.2 Hz, 1H, NC*C*H), 7.59 – 7.55 (m, 1H, OC*H*CHC*H*), 7.31 – 7.27 (m, 2H, OC*H*CHC*H*, NC*CHC*H*), 7.20 – 7.13 (m, 2H, NC*C*C*H*CH*), 6.54 (dd, *J* = 3.5 Hz, *J* = 1.8 Hz, 1H, OCHC*H*), 5.43 – 5.35 (m, 1H, N*H*) 4.95 (s, 1H, NC*H*), 4.07 – 3.93 (m, 1H, NHC*H*), 1.43 (s, 3H, C*C*H$_3$*), 1.40 (s, 3H, C*C*H$_3$*), 0.94 (dd, *J* = 13.5 Hz, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.6 (C*), 158.1 (C*), 147.5 (C*), 145.3 (CH), 141.1 (C*), 139.9 (C*), 128.3 (CH), 125.5 (CH), 122.5 (CH), 118.4 (CH), 118.0 (CH), 112.2 (CH), 75.0 (CH), 45.0 (C*), 41.4 (CH), 32.7 (CH$_3$), 29.8 (C*), 22.9 (CH$_3$), 22.6 (CH$_3$), 22.4 (CH$_3$) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3285 (br), 2966 (w), 1653 (s), 1558 (m), 1477 (s), 1456 (s), 1394 (s), 1366 (s), 1283 (m), 1171 (w), 885 (w), 750 (s), 594 (w). **HRMS** (ESI): *m/z* calculated for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1703, found: 327.1707.



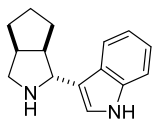
pyrrolyl pyrrolidine 4a: Prepared from pyrrolidine **1a** (33 mg, 0.25 mmol, 1.0 equiv) and pyrrole (35 µL, 0.50 mmol, 2.0 equiv) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:0 → 20:1 v/v CH_2Cl_2:MeOH), to obtain compound **4a** (24 mg, 0.12 mmol, 48%) as a grey solid. **R$_f$** = 0.32 (CH_2Cl_2:MeOH 20:1 v/v). **m.p.:** > 86.3 °C decomposition. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.04 (bs, 1H, C*N*H*), 6.72 – 6.64 (m, 1H,C*NHC*H*), 6.32 – 6.21 (m, 2H, *H*C=C*H*), 6.20 – 6.14 (m, 1H, C*NHCHC*H*), 6.05 – 5.95 (m, 1H, C*NHCHCHC*H*), 3.82 (d, *J* = 4.5 Hz, 1H, C*C*H*NH), 3.06 (dt, *J* = 9.0 Hz, *J* = 4.4 Hz, 1H, NHCHC*H*), 3.00 – 2.95 (m, 1H, CHCH$_2$C*H*), 2.93 – 2.78 (m, 3H, C*H*CH$_2$CH, NHCH$_2$C*H*), 2.50 (dd, *J* = 11.8 Hz, *J* = 4.6 Hz, 1H, NHC*H*$_2$), 2.29 – 2.06 (bs, 1H, CH$_2$N*H*), 1.60 (dt, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H, CHC*H*$_2$CH), 1.52 (dt, *J* = 8.2 Hz, *J* = 1.5 Hz, 1H, CHC*H*$_2$CH) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.5 (C*), 136.5 (CH), 116.7 (CH), 108.5 (CH), 104.4 (CH), 58.7 (CH), 54.7 (CH), 53.6 (CH$_2$), 49.0 (CH$_2$), 48.7 (CH), 46.0 (CH), 45.8 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3072 (w), 2934 (m), 2862 (m), 1448 (w), 1414 (w), 1028 (w), 918 (m), 879 (m), 833 (m), 725 (s), 563 (w). **HRMS** (ESI): *m/z* calculated for $C_{13}H_{17}N_2$ $[M+H]^+$: 201.1386, found: 201.1394.



pyrrolyl pyrrolidine 4b: Prepared from pyrrolidine **1b** (38 mg, 0.26 mmol, 1.0 equiv) and 5-methoxy-1*H*-indole (77 µL, 0.52 mmol, 2.0 equiv) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:0 → 20:1 v/v CH_2Cl_2:MeOH), to obtain compound **4b** (44 mg, 0.16 mmol, 60%) as a dark yellow oil. $\mathbf{R_f}$ = 0.66 (CH_2Cl_2:MeOH 50:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.94 (bs, 1H, C*N*H*), 7.23 (d, *J* = 8.7 Hz, 1H, NHC*C*H*), 7.09 (s, 1H, C*C*HC*(OMe)), 6.98 (s, 1H, C*NHC*HC**), 6.85 (d, *J* = 9.0 Hz, 1H, C(OMe)C*H*), 4.45 (s, 1H, CH_2NHC*H*), 3.86 (s, 3H, OCH_3), 3.03 – 2.91 (m, 2H, NHCH_2), 2.78 – 2.54 (m, 2H, NHCH_2C*H*, NHCHC*H*), 2.46 – 2.36 (m, 1H, NHCH_2CHCHCH_2C*H*), 2.27 – 2.19 (m, 1H, NHCH_2CHC*H*CH_2), 2.01 (bs, 1H, CH_2N*H*), 1.80 (t, *J* = 9.4 Hz, 1H, CH_2), 1.71 – 1.36 (m, 5H, CH_2CHCH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 154.0 (C*), 131.9 (C*), 126.8 (C*), 121.4 (CH), 119.9 (C*),[29] 112.3 (CH), 112.0 (CH), 101.0 (CH), 56.1 (CH), 55.0 (CH_3), 52.0 (CH), 46.4 (CH_2), 45.9 (CH), 43.4 (CH_2), 40.9 (CH), 40.8 (CH), 23.6 (CH_2), 23.1 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (w), 1481 (m), 1437 (m), 1290 (w), 1209 (s), 1171 (m), 1101 (w), 1051 (w), 1028 (m), 924 (m), 795 (m), 733 (m), 640 (m), 606 (m). **HRMS** (ESI): *m/z* calculated for $C_{18}H_{23}N_2O$ $[M+H]^+$: 283.1805, found: 283.1801.



pyrrolyl pyrrolidine 4c: Prepared from pyrrolidine **1f** (36 mg, 0.25 mmol, 1.0 equiv) and pyrrole (35 µL, 0.50 mmol, 2.0 equiv) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:0 → 20:1 v/v CH_2Cl_2:MeOH), to obtain compound **4c** (27 mg, 0.13 mmol, 52%, *dr* > 13:1) as a brown solid. $\mathbf{R_f}$ = 0.92 (CH_2Cl_2:MeOH 50:1 v/v). **m.p.:** 112.0 – 124.2 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.80 (bs, 1H, N*HC**), 6.77 – 6.65 (m, *J* = 3.1 Hz, *J* = 1.7 Hz, 1H, C*NHC*H*), 6.16 (q, *J* = 2.9 Hz, 1H, C*NHCHC*H*), 6.05 – 6.00 (m, 1H, C*NHCHCHC*H*), 4.95 (d, *J* = 5.4 Hz, 1H, NHCHC*H*), 4.67 (dd, *J* = 5.4 Hz, *J* = 3.7 Hz, 1H, NHCH_2C*H*), 4.34 (s, 1H, NHC*H*C*), 3.03 (d, *J* = 13.6, 1H, NHCH_2), 2.63 (dd, *J* = 13.6, 3.9 Hz, 1H, NHCH_2), 2.47 (bs, 1H, CH_2N*H*), 1.50 (s, 3H, C*CH_3), 1.36 (s, 3H, C*CH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 129.3 (C*), 116.7 (CH), 110.6 (C*), 108.8 (CH), 105.1 (CH), 86.0 (CH), 82.3 (CH), 62.5 (CH), 52.6 (CH_2), 26.1 (CH_3), 23.9 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3265 (w), 1381 (w), 1367 (w), 1204 (m), 1090 (m), 1045 (m), 1030 (s), 947 (w), 891 (m), 881 (m), 866 (m), 851 (m), 710 (s), 604 (s). **HRMS** (ESI): *m/z* calculated for $C_{18}H_{23}N_2O$ $[M+H]^+$: 209.1285, found: 209.1279.



pyrrolyl pyrrolidine 4d: Prepared from pyrrolidine **1e** (29 mg, 0.25 mmol, 1.0 equiv) and indole (60 mg, 0.50 mmol, 2.0 equiv) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:0 – 20:1 v/v CH_2Cl_2:MeOH), to obtain compound **4d** (43 mg, 0.19 mmol, 75%) as a brown solid. $\mathbf{R_f}$ = 0.10 (CH_2Cl_2:MeOH 20:1 v/v). **m.p.:** > 69.8 °C decomposition.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (bs, 1H, N*HC**), 7.74 (d, *J* = 7.9 Hz, 1H, NHC*C*C*H*), 7.35 (d, *J* = 8.0 Hz, 1H, NHC*C*H*), 7.23 – 7.06 (m, 3H, C*H*NHC*CHC*HCH*), 3.92 (d, *J* = 7.1 Hz, 1H, NHC*H*CH), 3.40 (dd, *J* = 10.7, 8.0 Hz, 1H, NHCH_2), 2.89 – 2.73 (m, 2H, NHCH_2C*HCH*), 2.55 (dd, *J* = 10.7, 7.1 Hz, 1H, NHCH_2), 2.40 (bs, 1H, N*H*CH_2), 1.74 – 1.43 (m, 6H,

CH_2CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.7 (C*), 126.6 (C*), 122.2 (CH), 122.0 (CH), 119.6 (CH), 119.6 (CH), 117.1 (C*), 111.5 (CH), 63.1 (CH), 53.7 (CH_2), 50.8 (CH), 44.3 (CH), 32.1 (CH_2), 31.4 (CH_2), 25.5 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2930 (w), 2860 (w), 1456 (w), 1448 (w), 1339 (w), 735 (s), 608 (m), 426 (m). **HRMS** (ESI): *m/z* calculated for $C_{15}H_{19}N_2$ $[M+H]^+$: 227.1543, found: 227.1542.

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14 The oxidation was amenable to scale up (4 mmol) with minor changes to the general procedure (0.4 M, 2 h), affording imine **2a** in 76% yield.

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21 The oxidation of dihydroindoline and tetrahydroquinoline was only selective when using an excess of IBX (2.0 equiv) and a stoichiometric amount of radical inhibitor TEMPO (1.0–1.5 equiv), providing the aromatized products. This observation supports previous hypotheses by Nicolaou *et al.* that the oxidation of amines with IBX proceeds via an ionic mechanism, while benzylic oxidation towards acetophenone derivatives follows a single electron transfer (SET) mechanism. TEMPO itself does not facilitate the oxidation.

22 The relative configurations of the major diastereoisomer **3i**, determined by X-ray crystallography, and minor diastereoisomer **3i'** are depicted in Scheme 1.

23 CCDC 1400648 contains the supplementary crystallographic data for **3i**. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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26 Signals of the trimerized product were visible in the NMR spectrum.

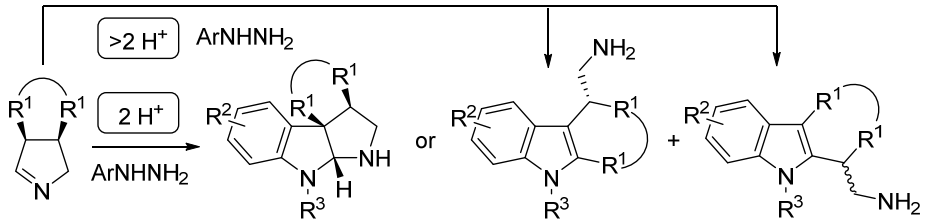
27 Signals are overlapped with the signals of the rotamers and/or the solvent.

28 Signal is overlapped with the H_2O peak. The H_2O was an impurity in the solvent MeOD-d_4.

29 Very weak signal assigned by HMBC.

Chapter 4

Switchable Cascade Reaction towards either Pyrroloindolines or Constrained Tryptamines



Abstract: *The interrupted Fischer indole synthesis of arylhydrazines and biocatalytically generated chiral bicyclic imines selectively affords either tetracyclic pyrroloindolines or tricyclic tryptamine analogs depending on the reaction conditions. We demonstrate that the reaction is compatible with a variety of functional groups. The products are obtained in high optical purity and in reasonable to good yield. We present a plausible reaction mechanism to explain the observed reaction outcome depending on the stoichiometry of the acid mediator. To demonstrate the synthetic utility of our method, pharmaceutically relevant examples of both product classes were synthesized in highly efficient reaction sequences, including a phenserine analog as a potential cholinesterase inhibitor and constrained tryptamine derivatives as selective inhibitors of the 5-HT$_6$ serotonin receptor and the TRPV1 ion channel.*

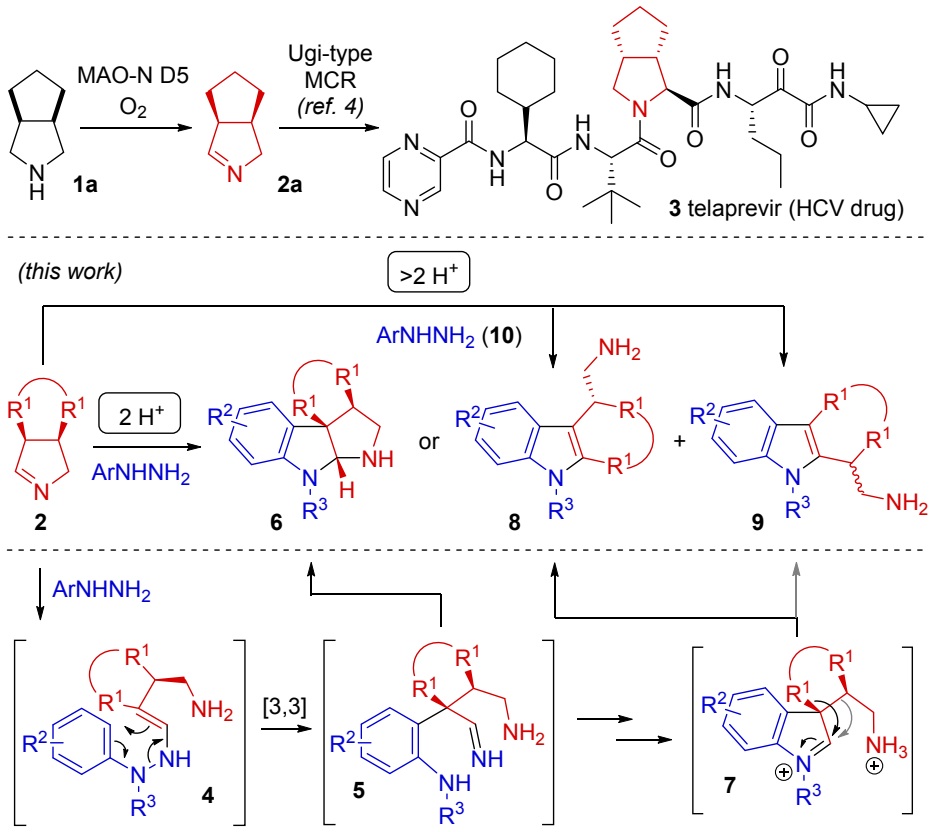
Published in: *Angew. Chem. Int. Ed.* **2015**, *54*, 14133–14136.

4.1 Introduction

Nature has been a major inspiration in the development of new reactions and the quest for novel bioactive compounds. As Waldmann's Biology-Oriented Synthesis (BIOS) concept states, the chemical space can be effectively explored by the application of natural product scaffolds as starting points for selective diversification in order to identify potent bioactive molecules.[1] Certainly, this strategy has provided several new molecular probes for the selective and reversible modulation of cellular functions.[2] Besides its chiral pool of molecules, Nature provides another attractive tool for the introduction of asymmetry in the form of enzymes, which offer unrivaled chemo-, regio- and stereoselectivity. For example, we employed an engineered monoamine oxidase[3] in the synthesis of the hepatitis C drug telaprevir (Scheme 1).[4]

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. Moreover, the number of synthetic steps and related waste production and energy consumption can be reduced by combining several chemical transformations in one pot. Cascade reactions are important tools to achieve these goals.[5]

Indole derivatives exhibit a privileged position within the rich molecular diversity of natural products as well as in lead discovery.[6] As a result, numerous synthetic strategies were developed to construct and modify indoles. We envisioned direct access to complex polycyclic indole derivatives in a stereoselective fashion by employing readily available reactants in novel cascade reactions. Our success in chemoenzymatic multicomponent processes[4] prompted us to investigate the utility of biocatalytically generated chiral building blocks such as bicyclic imines **2** in cascade reactions by considering them as amino aldehyde synthons. We hypothesized a reaction between **2** and arylhydrazines to afford pyrroloindolines **6** with *cis*-junction of both [3.3.0] bicyclic systems *via* an 'interrupted' Fischer indole synthesis (Scheme 1).[7,8] Herein, we describe the acid-switchability of this reaction to provide either pyrroloindolines **6** or constrained tryptamines **8** and **9** by a Plancher rearrangement of the former species.



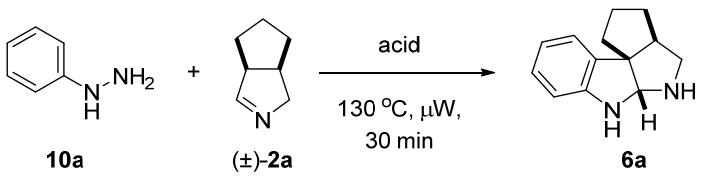
Scheme 1. The application of biocatalytically generated chiral bicyclic imines **2** in the synthesis of telaprevir (**3**) and tetracyclic pyrroloindolines **6** or constrained tryptamines **8**/**9**.

Although several representatives of the pyrroloindoline natural product class have been prepared—generally by electrophilic C_3-alkylation of 3-substituted indoles[9,10]—these synthetic routes do not allow straightforward systematic variation of the substituents and scaffold. The application of the interrupted Fischer indole synthesis in pyrroloindoline synthesis was shown in a limited number of examples. Most significantly, Garg and List described a convergent synthesis of pyrroloindolines by a cascade reaction between arylhydrazines and cyclic hemiaminals.[7] An asymmetric variant of the interrupted Fischer indolization to form pyrroloindolines was reported by List, who used a sterically congested chiral phosphoric acid.[11] However, the presence of a N_β-benzyl group on the hydrazine fragment was essential for high enantioselectivity.

4.2 Results and Discussion

We started our investigations with the benchmark reaction between bicyclic imine[12] (±)-**2a** and phenylhydrazine **10a** for the synthesis of pyrroloindoline **6a**. Our initial screening with a range of solvents and acid mediators resulted in only modest success (Table 1, entries 1–6). To our delight, the envisioned stereoselective interrupted Fischer indolization proceeded smoothly with a range of Brønsted acids in toluene (entries 7–10). Additional experiments showed that increasing or decreasing the temperature led to slightly reduced yields (data not shown). Although microwave heating did not have a beneficial effect compared to conventional heating in an oil bath (entries 10–11), the microwave was used for convenience. Optimal conversion of (±)-**2a** to the desired tetracyclic pyrroloindoline **6a** was achieved with phenylhydrazine hydrochloride (**10b**) and 1.0 equiv of TsOH in toluene with

Table 1. Exploration of reaction conditions for the interrupted Fischer indole synthesis.



10a (±)-**2a** **6a**

Entry	Acid		Solvent	Yield[a]
1	-	excess	AcOH	<5%
2	HCl [1.25 M]	excess	MeOH	<5%
3	HCl [4.0 M]	excess	dioxane	36%
4	TsOH	2.0 equiv	MeOH	30%
5	TsOH	2.0 equiv	DCE	44%
6	TsOH	2.0 equiv	$(MeO)_2CO$	36%
7	F_3CSO_3H	2.0 equiv	toluene	46%
8	$EtSO_3H$	2.0 equiv	toluene	52%
9	$MeSO_3H$	2.0 equiv	toluene	60%
10	TsOH	2.0 equiv	toluene	68%
11[b]	TsOH	2.0 equiv	toluene	68%
12[c]	**TsOH**	**1.0 equiv**	**toluene**	**71%**

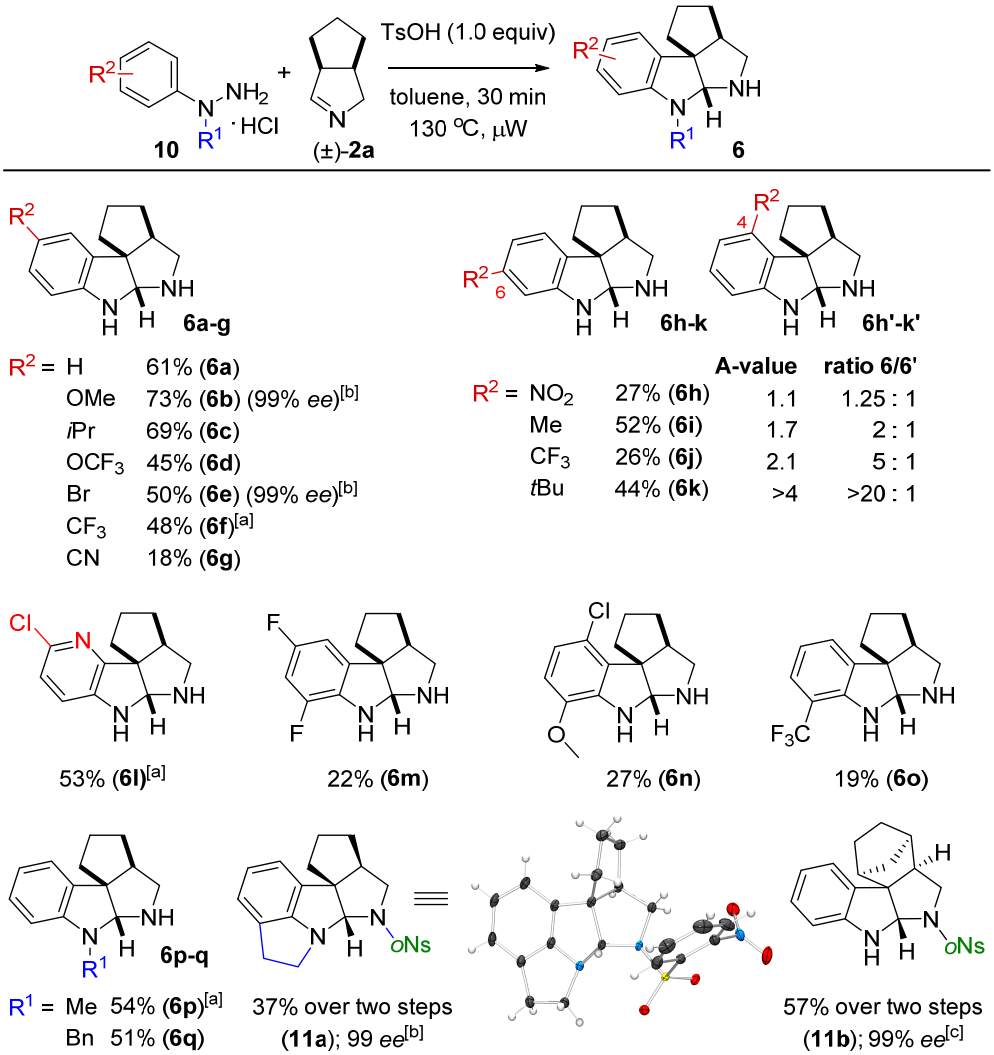
[a] Yield determined by adding 2,5-dimethylfuran (0.5 equiv) after the reaction workup as standard for NMR spectroscopy. [b] Conventional heating (oil bath). [c] Phenylhydrazine·HCl salt (**10b**) was used.

microwave heating to 130 °C for 30 min (entry 12).

With the optimized reaction conditions in hand, we explored the reaction scope with respect to *para*-, *meta*-, and *ortho*-substituents on phenylhydrazine employing (±)-**2a** (Scheme 2).[13] To our delight, a range of electronically and sterically diverse *para*-substituted arylhydrazines were suitable substrates, giving the corresponding pyrroloindolines **6b**–**g** in modest to good yield (18–73%). Electron-rich inputs with substituents such as methoxy and isopropyl were readily converted (**6b**,**c**) and even a more challenging trifluoromethoxy substituent was tolerated (**6d**). A bromide substituent was also allowed at the *para*-position (**6e**), providing a convenient handle for a multitude of transition metal-catalyzed cross-coupling reactions. Interestingly, strongly electron-withdrawing substituents could be introduced (**6f**,**g**), while previous reports on interrupted Fischer indole syntheses showed only trace amounts of product.[7a,b] The lower efficiency of these substrates is most likely caused by slower formation of the hydrazone intermediate and/or slower sigmatropic rearrangement. The application of *meta*-substituted arylhydrazines gave rise to the formation of two regioisomeric pyrroloindolines in modest to reasonable yield (26–52%). The 6-substituted regioisomers **6h**–**k** were formed as the major products in all cases, in combination with varying amounts of the 4-substituted isomers **6h'**–**k'**. We recognized that the regioselectivity is mainly governed by the steric properties of the *meta*-substituent that are most accurately described by the Winstein-Holness A-values.[14] In correspondence with increasing steric bulk, the ratio between 6-substituted and 4-substituted pyrroloindolines increases moving from substituents with a low to a high A-value. Complete regioselectivity could be induced by a *meta*-substituent with a sufficiently high A-value, such as *tert*-butyl (**6k**). Notably, pyrroloazaindoline **6l** could be obtained in reasonable yield as a single regioisomer as a result of electronic control.[15] In agreement with earlier reports on the classic Fischer indole synthesis, the use of *ortho*-substituted arylhydrazines led to a more sluggish reaction.[16] Nevertheless, the desired pyrroloindolines **6m**–**o** could be isolated in modest yield (19–27%).

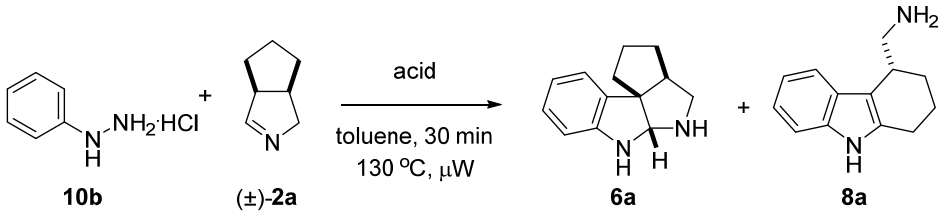
To further evaluate the reaction scope, we tested N_α-substituted arylhydrazines in the interrupted Fischer indolization. Gratifyingly, the application of both N_α-methyl and N_α-benzyl phenylhydrazine resulted in the formation of the desired pyrroloindolines **6p,q** in moderate yield (51–54%). Furthermore, highly strained pentacyclic pyrroloindoline derivative **11a** could be isolated in optically pure form after *o*-nosylation by the application of enantiopure (–)-**2a** (99% *ee*). After

crystallization, the structure of **11a** was confirmed by X-ray crystallography.[17] As expected, (−)-**2a** could be used for the synthesis of **6b** and **6e** in excellent optical purity (99% *ee*) as well. During our investigation of the behavior of tricyclic imine



Scheme 2. Synthesis of diverse pyrroloindolines **6** and **11**. X-ray structure of **11a** with displacement ellipsoids drawn at 50% probability level.[17] [a] Free hydrazine used (instead of HCl salt) in combination with 2.0 equiv TsOH. [b] Determined by comparison with the racemate using HPLC on a chiral stationary phase. (−)-**2a** was used. [c] Determined by comparison with the racemate using HPLC on a chiral stationary phase. Tricyclic imine (−)-**2b** was used in combination with 1.0 equiv PPTS and a reaction time of 5 min.

Table 2. Exploration of the acid switchability of the cascade sequence.[19]



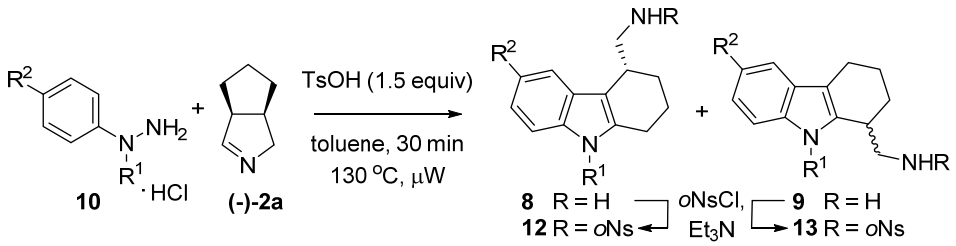
Entry	Acid		Yield for **6a**[a]	Yield for **8a**[a]
1	TsOH	1.0 equiv	71%	14%
2	TsOH	1.5 equiv	-	61%
3[b]	TsOH	1.5 equiv	-	61%
4	PPTS	1.0 equiv	76%	<5%
5	PPTS	1.5 equiv	70%	9%
6	TFA	1.0 equiv	73%	<5%
7	TFA	1.5 equiv	64%	<5%

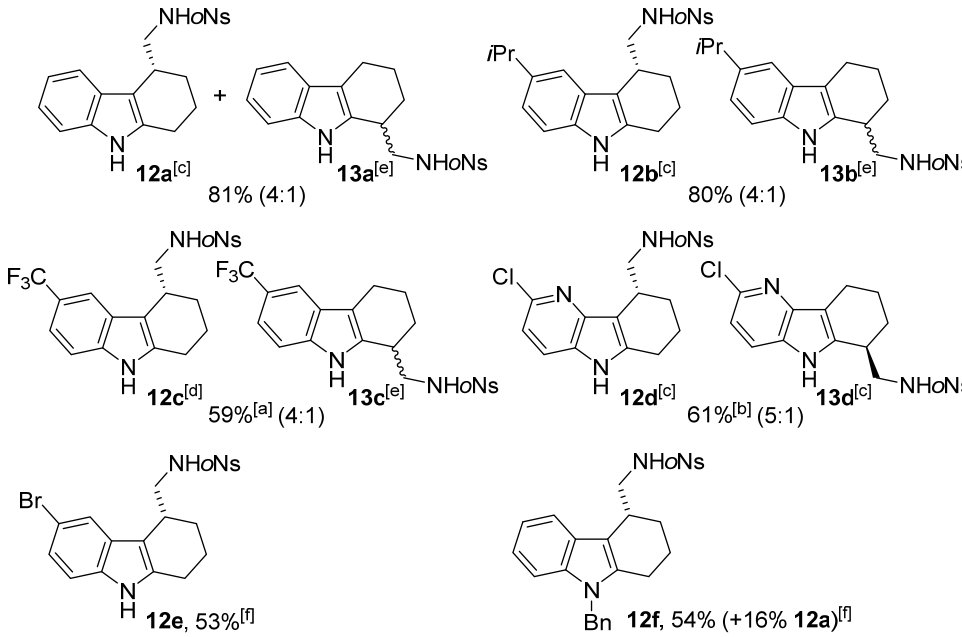
[a] Yield was determined with ^{1}H NMR using 2,5-dimethylfuran as standard. [b] Reaction time of 5 min.

(−)-**2b** in the interrupted Fischer indole synthesis, we found that the desired pyrroloindoline could only be obtained by the use of 1.0 equiv of the mild acid pyridinium *para*-toluenesulfonate (PPTS) and by shortening the reaction time (5 min). Subsequent *o*-nosylation afforded the desired pentacyclic pyrroloindoline **11b** in 57% yield with 99% *ee*.

During additional experiments regarding the reaction mechanism, we discovered that the yield of **6** is highly dependent on the stoichiometry and strength of the acid mediator.[18] Under otherwise identical conditions, the use of 1.5 equiv of TsOH (instead of 1.0 equiv) led to full conversion to tricyclic tryptamine derivative **8a** (Table 2, entries 1–2), along with its regioisomer **9a**.[19] The pyrroloindoline product **6a** was not observed under these conditions. Most likely, **8a** and **9a** are formed *via* a rearrangement of **6a** (see page 95–98). Intriguingly, this highly complex cascade reaction consisting of the interrupted Fischer indolization and rearrangement was completed within 5 minutes (entry 3). When exploring different acid mediators, we observed that weaker acids such as TFA and PPTS were not able to facilitate this selective product switch (entries 4–7). Although we synthesized the library of pyrroloindolines (Scheme 2) with TsOH, TFA and PPTS proved to be more efficient and selective acid mediators for the formation of **6a**.

To facilitate separation of regioisomers **8a** and **9a**, the constrained tryptamines were subjected to *in situ o*-nosylation. With a two-stage procedure, we could synthesize compounds **12a**–**d** and **13a**–**d** in a ~4:1 ratio and very good yields considering the complexity of the transformation (59–81%, Scheme 3). Advantageously, regioisomers **12** and **13** were readily separated by flash chromatography. We showed the generality of this strategy by the synthesis of relatively electron-rich as well as

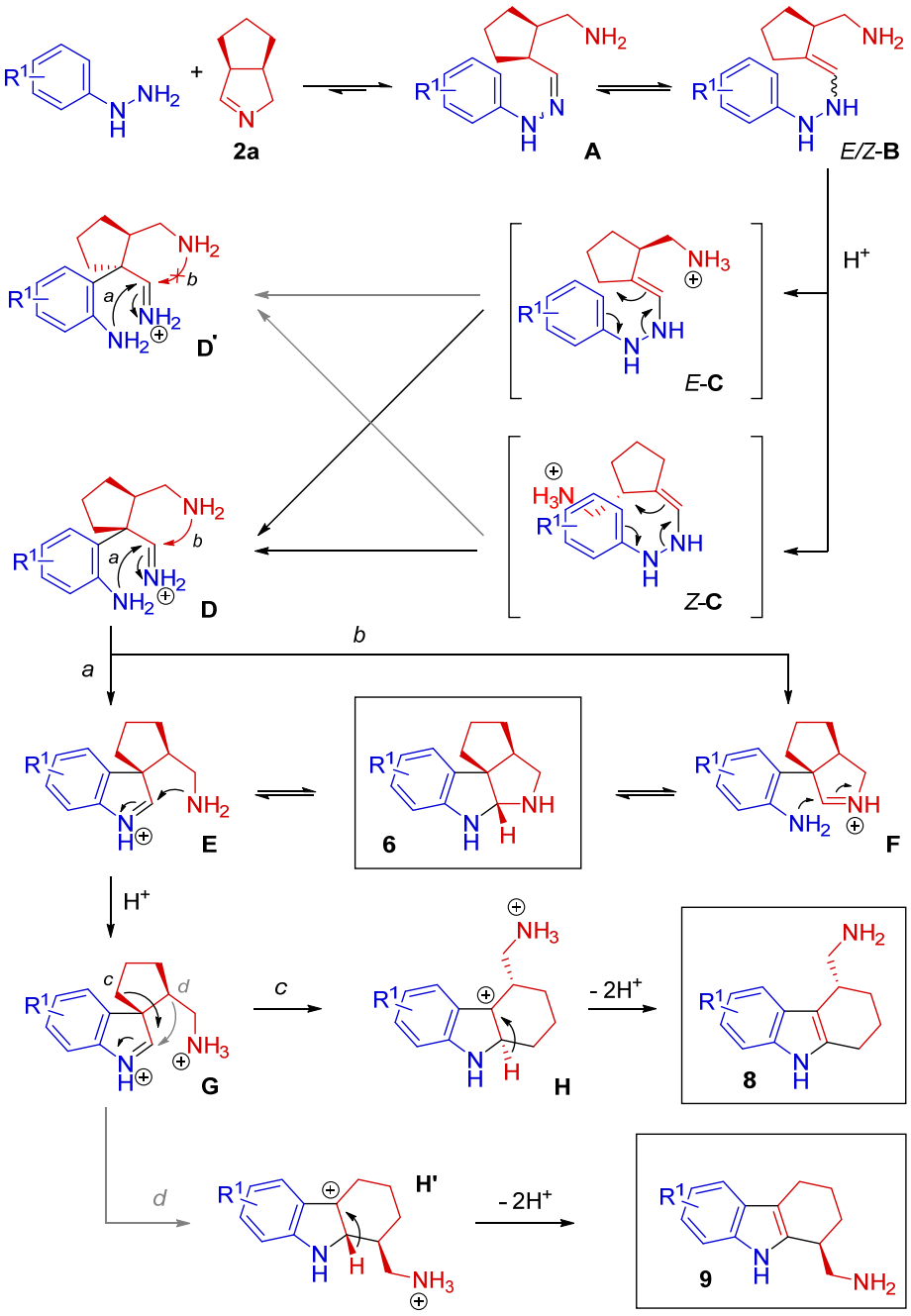




Scheme 3. Synthesis of tricyclic tryptamine analogs **12** and regioisomers **13**. [a] Free hydrazine used (instead of HCl salt) in combination with 2.5 equiv TsOH. [b] Free hydrazine used; TsOH (3.5 equiv), 150 °C, 60 min. [c] *ee* = 99% (**12a**,**b**) *ee* = 98% (**12d**, **13d**). Determined by comparison with the racemate using HPLC on a chiral stationary phase. [d] Presumed optically pure by detection of a single peak by HPLC (chiral stationary phase) and in analogy to **12a**, **12b** and **12d**. [e] (Partially) racemized as determined by chiral HPLC comparison with the racemate (**13a,b**) or by detection of two peaks by HPLC analysis on a chiral stationary phase (**13c**). [f] (±)-**2a** was used.

electron-poor systems and even heteroaromatic derivatives. The minor regioisomer of *para*-bromo and *N*-benzyl derivatives **12e**–**f** was not isolated, however, the debenzylated product **12a** was isolated as a side product in the latter case. By employing (–)-**2a**, the major regioisomers **12a**–**d** were isolated in excellent optical purity (98–99% *ee*). However, the minor regioisomers **13a**–**c** were found to be partially or completed racemized. We hypothesize that the racemization is acid mediated and occurs only after the cascade process (see page 98–100). In contrast to **13a**–**c**, heteroaromatic derivative **13d** was obtained with high optical purity, presumably because of the presence of the additional basic nitrogen.

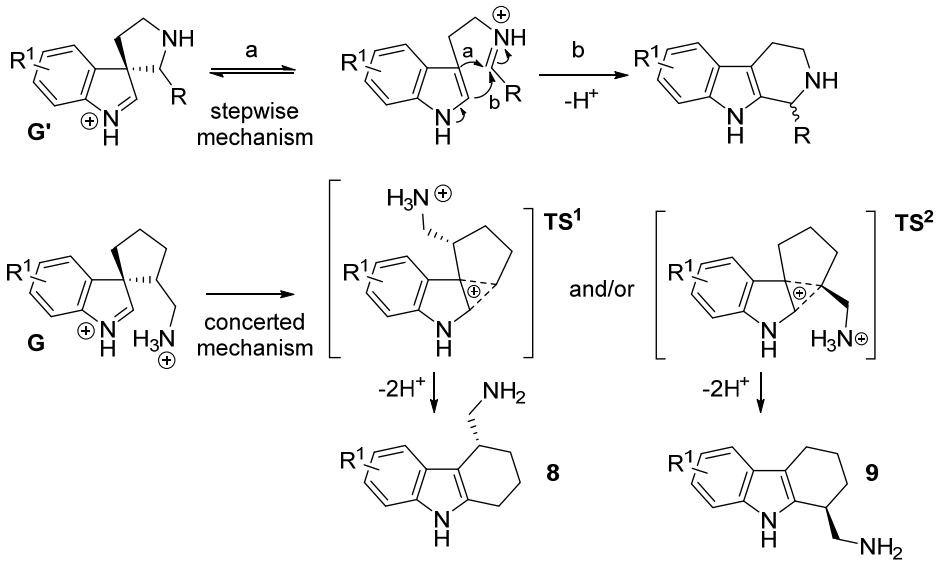
Thus, our novel cascade reaction provides either pyrroloindolines **6** or constrained tryptamines **8** and **9** based on the stoichiometry of the acid mediator. To account for these experimental observations, we propose the following mechanism (Scheme 4). As envisioned, amino aldehyde synthon **2a** undergoes a "transimination" reaction with arylhydrazine **10** to form hydrazone intermediate **A**. This intermediate is in tautomeric equilibrium with ene-hydrazine **B** that undergoes a [3,3]-sigmatropic rearrangement *via* either *E*-**C** or *Z*-**C** to produce iminium ion **D** or **D'**. Evidently, **D'** cannot provide **6** and also is not able to undergo an addition of the aliphatic amine to the iminium ion as it would lead to an energetically unfavorable system of *trans*-fused five-membered rings. If **D'** is formed at all, we hypothesize that it might undergo addition of the aromatic amine to the iminium ion to give the *trans*-isomer of **E** followed by acid-mediated migration. However, **6** was obtained as the major product experimentally, which is plausibly formed *via* **D**. The clear selectivity for the formation of **D** over **D'** is hypothesized to be induced during the sigmatropic rearrangement of *Z*-ene-hydrazine **C**, as a result of chirotopic shielding by the cationic ammonium group.[20] Subsequently, intermediate **D** undergoes intramolecular addition of either the aromatic (pathway *a*) or aliphatic (pathway *b*) amine to the iminium moiety to afford intermediates **E** and **F**, respectively, with loss of an ammonium ion. The Fischer indole synthesis is then interrupted by an intramolecular addition of the pendant amino group to give (protonated) pyrroloindoline **6** due to the lack of a proton at C_3 necessary for indole formation.[7] Plausibly, the latter species is in dynamic equilibrium with intermediates **E** and **F** under the reaction conditions. Only in the presence of additional strong acid, intermediate **E** can undergo a second protonation to bivalent cation **G**.[21] This highly reactive intermediate can undergo a Wagner–Meerwein-type cationic shift known as the Plancher rearrangement[22] *via* either pathway *c* of *d*. Pathway *c* will give cationic intermediate **H** that produces regioisomer **8** after loss of



Scheme 4. Proposed mechanism for the formation of **6**, **8** and **9**.

two protons. Similarly, pathway *d* affords regioisomer **9**. The formation of these regioisomeric products directly results from the presence of two inequivalent migratory carbons in intermediate **G**. An evident regiopreference (4:1 for **12a–d/13a–d**) was observed in favor of the regioisomer that is formed by migration of the secondary carbon instead of the tertiary carbon. Tertiary carbons can generally stabilize (partial) positive charges more efficiently than secondary carbons. However, destabilization of the partial positive charge on the tertiary carbon by the nearby cationic ammonium group plausibly explains the regioselectivity in our case.

Two possible mechanisms exist for the Plancher rearrangement, *i.e.* concerted or stepwise migration (Scheme 5). The concerted mechanism proceeds through a three-center-two-electron-type transition state with preservation of stereochemistry at the migrating carbon. The stepwise mechanism proceeds through bond scission and subsequent bond formation with concomitant epimerization at the migratory carbon. You *et al.* investigated the Plancher rearrangement of sp^3 carbons in C_3-spiroindolenines—such as **G** and **G'**—with theoretical calculations and experimental tests.[23] This study showed that the higher the ability of the migratory group to stabilize the accumulating positive charge, the easier migration occurs and the more likely the reaction mechanism is stepwise rather than concerted. For example,



Scheme 5. Stepwise and concerted mechanism of the Plancher rearrangement.

when a nitrogen atom is attached to the migratory carbon, a *retro*-Mannich/Mannich equilibrium can exist with concomitant racemization at the migratory carbon.[24] The migration can then occur through a stepwise *retro*-Mannich/Mannich mechanism, but participation of the concerted mechanism should not be excluded. However, in the absence of an electron-donating substituent next to the migratory group, migration almost certainly occurs by a concerted process through a three-center-two-electron-type transition state.[23,25] The alternative would be scission of the bond between the spirocarbon and migrating carbon, which is highly implausible in this case. Therefore, we propose a concerted mechanism for the Plancher rearrangement of bivalent cationic intermediate **G** with preservation of stereochemistry at the migratory carbon. We believe that the observed racemization of **13a**–**c** is acid-mediated and occurs only after the cascade process through imine/enamine tautomerization. Based on this hypothesis, we envisioned that the treatment of 2,3-dimethylindole with TsOD (130 °C, 30 min, μW) would lead to deuteration at the C_3' position (Scheme 6). Indeed, a mixture of compounds (**14**–**16**) with varying degree of deuteration at the C_3'-position was obtained, as determined by ^{13}C NMR analysis (Figure 1). Thus, a racemizing imine/enamine equilibrium in protonated indoles proved to be feasible.

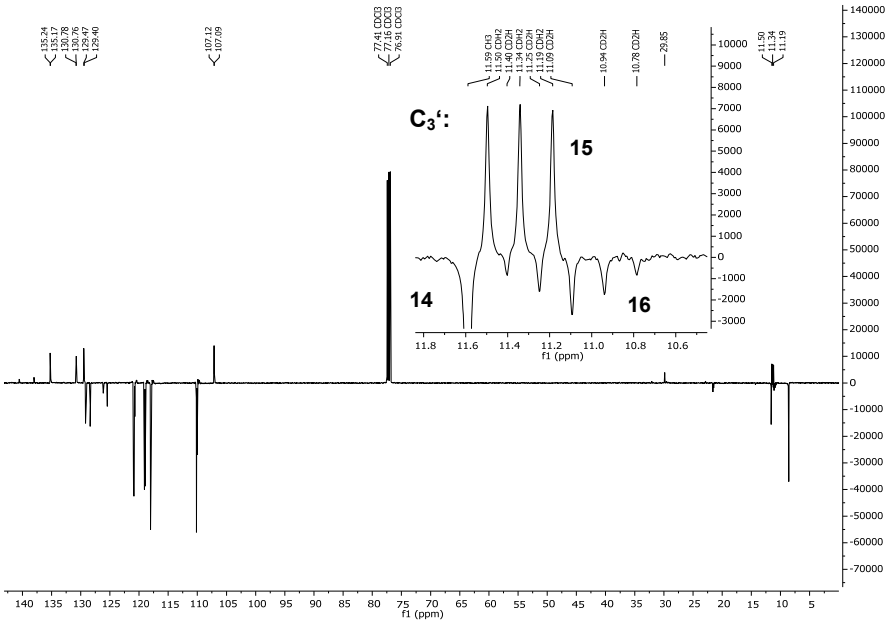
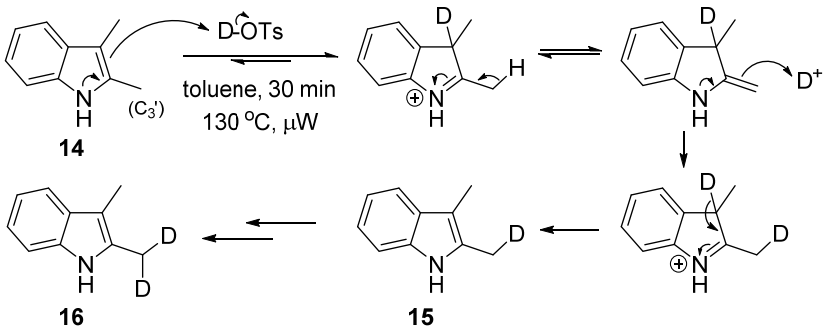


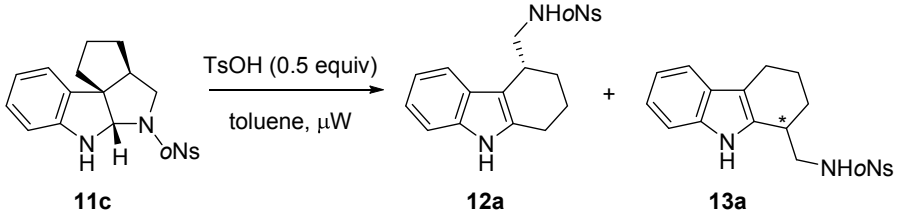
Figure 1. ^{13}C NMR spectrum after treatment of 2,3-dimethylindole with TsOD.



Scheme 6. Working hypothesis for C_3' deuteration of 2,3-dimethylindole with TsOD.

To investigate the temperature dependence of the racemization of **13a** after the rearrangement, we used **11c** in a temperature screen (Table 3). As a result of the low basicity of the *o*-nosylated amine group, it cannot scavenge protons and formation of a bivalent cation is not required for migration. Therefore, 0.5 equiv of TsOH is sufficient to facilitate the rearrangement of **11c**. Although full racemization of **13a** was observed at temperatures of 100 °C and higher (entries 1–2), **13a** was only partially racemized at 85 °C with complete conversion of **11c** (entry 3). Racemization was even further reduced by shortening the reaction time (entry 4). Moreover, no racemization

Table 3. Screening to investigate temperature and time dependence of the racemization of **13a**.

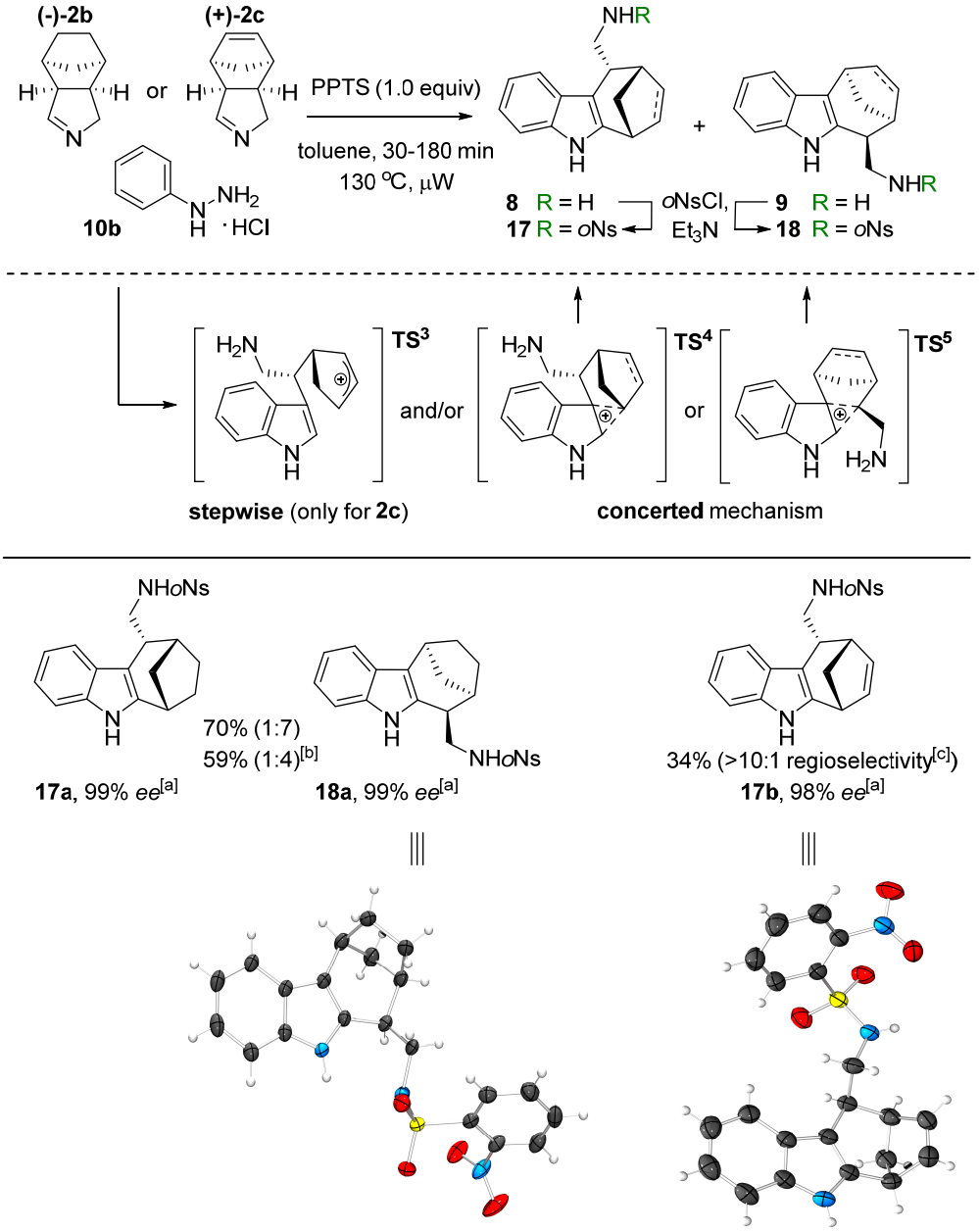


Entry	Temperature	Time (min)	Conversion of **11c**[a]	*ee*[b] **12a**	*ee*[b] **13a**
1	130	30	>99%	99%	~0%
2	100	30	>99%	99%	~0%
3	85	30	>99%	99%	57%
4	85	15	>95%	99%	88%
5	70	30	31%	99%	99%

[a] Determined by NMR spectroscopy according to the molar ratio between **11c** and **12a/13a**.
[b] Determined by comparison with the racemate using HPLC on a chiral stationary phase.

of **13a** was observed at 70°C, but the conversion of **11c** was only 31% in 30 min. Thus, we observed a clear temperature as well as time dependence for the racemization of **13a**, which supports our hypothesis of a post-cascade racemization.

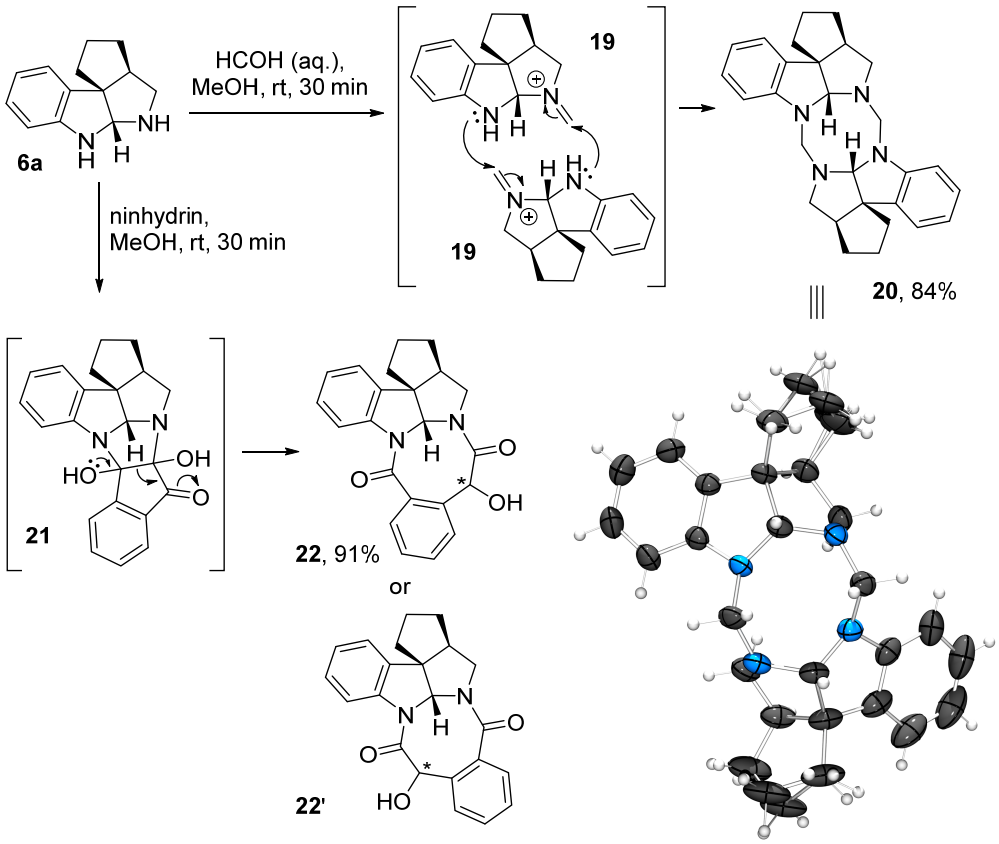
When investigating the behavior of tricyclic imines *e.g.* (–)-**2b** in the interrupted Fischer indole synthesis, we observed that the resulting pentacyclic pyrroloindolines are more prone to undergo a rearrangement than their tetracyclic analogs, presumably as a result of increased strain. A clean conversion towards **17a**/**18a** was achieved with 1.0 equiv of the mild acid PPTS after a reaction time of 3 hours (Scheme 7). Since the corresponding pyrroloindoline **11b** was obtained under identical conditions but with a shorter reaction time (5 min, see page 92), this reaction proves to be time switchable. An interesting phenomenon is the observed inversion of regioselectivity for the Plancher rearrangement towards **17a**/**18a** (1:7) compared to **12a**–**d**/**13a**–**d** (4:1). In contrast to the requirement of bivalent cationic intermediate **G** for the formation of **12**/**13**, a doubly protonated species is plausibly not formed in the synthesis of **17a**/**18a** when using the mild acid PPTS. Therefore, the pendant amine can presumably stabilize (rather than destabilize) the partial positive charge accumulating on the migrating carbon in **TS⁵** by neighboring group participation, leading to preferred formation of **18a** over **17a**. We anticipated that the use of an excess of strong acid (TsOH) would result in partial protonation of the pendant amine. In this case, one would expect that migration through a bivalent cationic transition state would predominantly give **17a** and a monovalent cationic transition state would favor formation of **18a** based on electronic arguments. We observed that the use of 1.5 equiv of TsOH (130 °C, 30 min, μW) led to the formation of **17a**/**18a** in 1:4 regioisomeric ratio (compared to 1:7 when using 1.0 equiv PPTS). This may either imply that the rearrangement proceeds predominantly *via* the monoprotonated intermediate, or that other factors (e.g. sterics, strain release) are responsible for the observed regioselectivity. Epimerization at the C_3' position of **18a** under acidic conditions apparently does not occur, since a single diastereoisomer was obtained. A plausible explanation is that an imine/enamine equilibrium does not exist in this case, because of the increased strain that it would cause. By the application of (+)-**2c**, a double bond is introduced that presumably provides allylic stabilization of the accumulating positive charge during the Plancher rearrangement. We hypothesize that this stabilization favors **TS⁴** over **TS⁵** in the concerted mechanism and could also induce participation of a stepwise mechanism (**TS³**) to a certain extent. Therefore, the regioselectivity is again reversed and **17b** is the main product of this cascade reaction,



Scheme 7. Synthesis of tetracyclic tryptamine analogs **17** and regioisomers **18**. X-ray structures of *ent*-**18a** and (±)-**17b** with displacement ellipsoids drawn at 50% probability level.[17] [a] Determined by comparison with the racemate using HPLC on a chiral stationary phase. [b] 1.5 equiv TsOH instead of 1.0 equiv PPTS. [c] An isomer of **17b** was observed in the crude ^{1}H NMR spectrum, but could not be isolated.

albeit in low yield (34%). In order to verify the reversed regioselectivity of the migration when using **2b** or **2c**, the corresponding major regioisomers **18a** and **17b** were crystallized and their structures were corroborated by X-ray crystallography (Scheme 7). Although we provided a plausible explanation for the regioselectivity of the migration—using either substrate **2a**, **2b** or **2c**—based on electronic arguments, a thorough computational study is required to investigate the importance of strain release and/or steric factors.

Having established some mechanistic understanding of the switchability of our reaction to form either **6** or **8/9**, we set out to investigate applications of our methodology in the synthesis of bioactive compounds with high pharmaceutical relevance. Pyrroloindoline alkaloids constitute a diverse class of natural products that exhibit interesting biological properties including antibacterial[26] and antitumor[27] activity. The acetylcholinesterase inhibitor (−)-physostigmine (**23**, Scheme 9) has been applied in the treatment of neurodegenerative diseases,[28] but suffers from short duration of action, low therapeutic window and negative side effects.[29] Its semisynthetic derivative phenserine (**24**) advanced as far as Phase III clinical trials for the treatment of Alzheimer's disease (AD) owing to its more beneficial characteristics in terms of activity and selectivity.[29,30] Interestingly, its enantiomer *ent*-**24** (posiphen) is currently also in clinical development for the treatment of AD, but seems to have a different mode of action.[31] We soon realized that phenserine analog **28** should be rapidly accessible *via* our interrupted Fischer indole synthesis in a stereoselective fashion. However, initial studies showed that post-cascade methylation of the aromatic NH is rather challenging. In an attempt to reductively methylate both nitrogen atoms of pyrroloindoline **6a** with formaldehyde, we observed the formation of a highly crystalline compound in very good yield with significantly reduced polarity compared to **6a** (Scheme 8). X-ray structural analysis revealed that this compound (**20**) has a dimeric structure with an eight-membered ring consisting of alternating carbon and nitrogen atoms. Notably, the reductive methylation of the corresponding phenserine precursor did not lead to formation of the analog of dimer **20**.[32] We propose that compound **20** is formed through iminium ion formation of the more nucleophilic aliphatic nitrogen of **6a** with formaldehyde to form **19**, followed by a dimerization reaction with a second molecule of **19**. Although aminal formation between two aliphatic nitrogens from different molecules of **6a** and formaldehyde plausibly occurs, this reaction does not lead to a stable product and is expected to be

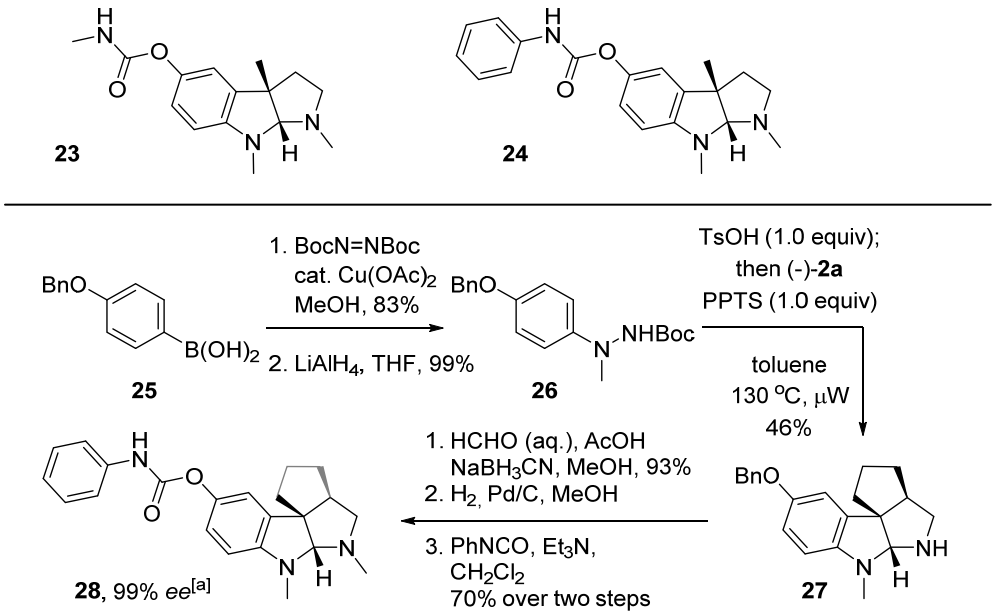


Scheme 8. Reactivity of tetracyclic pyrroloindoline **6a** with ninhydrin and formalin. X-ray structure of **20** with displacement ellipsoids drawn at 50% probability level.[17]

reversible. However, intermolecular double addition of the aromatic nitrogen atom of **19** to the iminium functionality of another molecule of **19** and vice-versa apparently leads to a stable dimer (**20**). During a screening of the reactivity of **6a** with other electrophilic carbonyl compounds, we found that ninhydrin selectively reacts with **6a** to form an eight-membered ring compound in excellent yield as a single regio- and stereoisomer. Plausibly, the mechanism proceeds through double hemiaminal formation between the nitrogen atoms of **6a** and two carbonyl functionalities of ninhydrin to form **21**, followed by a ring expansion step and tautomerization to give **22**. Its regioisomer **22'**, can be formed from the regioisomer of **21**. Initial bond formation between the more nucleophilic aliphatic nitrogen of **6a** with the central and most electrophilic carbonyl of ninhydrin is most probable and will lead to regioisomer

22. However, we were not able to distinguish between the regioisomers by means of NMR analysis and attempts to crystallize the product were thus far unsuccessful.

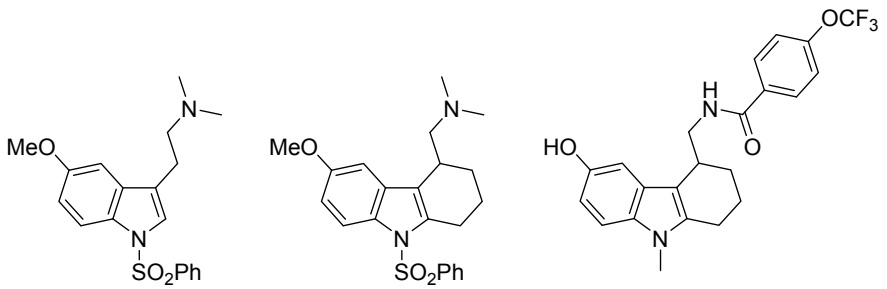
To circumvent the necessity of post-cascade methylation of the aromatic NH in the synthesis of **28**, we opted to employ an N_α-methylated hydrazine derivative in the cascade process (Scheme 9). Conveniently, di-$N_\alpha N_\beta$-Boc-protected arylhydrazines can be prepared by Cu^{II}-catalyzed addition of boronic acids to di-*tert*-butyl azodicarboxylate.[33] We discovered that chemoselective reduction of the N_α-Boc group can be achieved with $LiAlH_4$ at room temperature to provide N_α-Me-N_β-Boc-protected arylhydrazine **26**. The cascade reaction of **26** and (–)-**2a** with *in situ* Boc deprotection (1.0 equiv TsOH, 60 °C, 1 h), proceeded most smoothly with 1.0 equiv of PPTS. After isolation of **27**, *N*-methylation of the aliphatic nitrogen atom was readily achieved by reductive methylation with formaldehyde. Finally, phenserine analog **28** was readily synthesized by hydrogenolysis of the benzyl ether and subsequent carbamoylation. The corresponding (±)-**28**—that provides access to the posiphen analog—was conveniently produced by employing readily available (±)-**2a**.

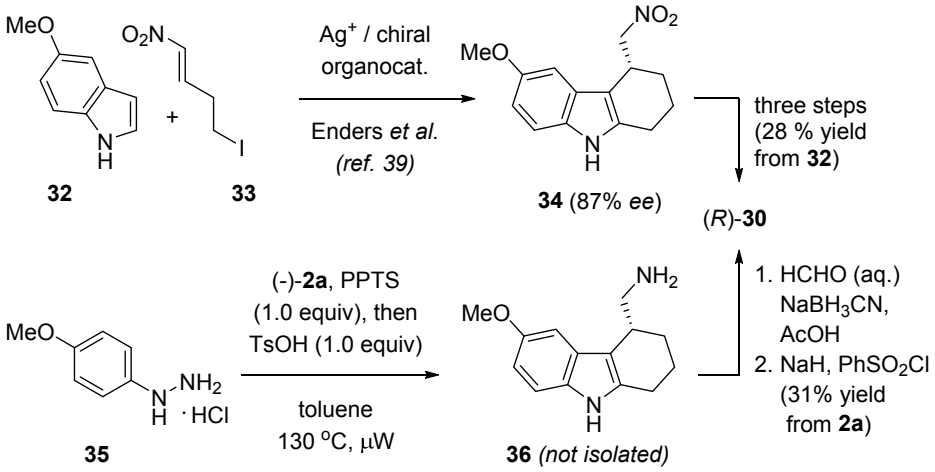


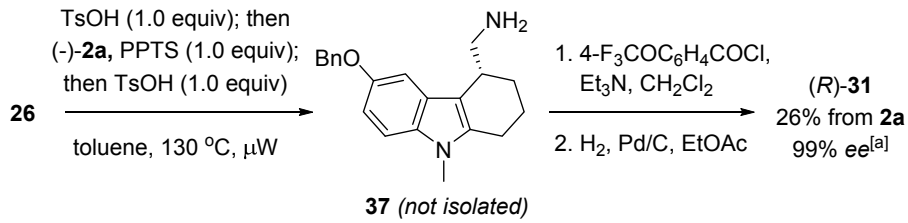
Scheme 9. Synthesis of phenserine analog **28**.

[a] Determined by comparison with the racemate using HPLC on a chiral stationary phase.

Like the pyrroloindoline compound class, tricyclic constrained tryptamine analogs have been reported to have several conceivable therapeutic applications. For example, they are potent and selective inhibitors of serotonin[34] and melatonin[35] receptors as







Scheme 10. Stereoselective synthesis of serotonin receptor inhibitor **30** and TRPV1 inhibitor **31**.
[a] Determined by comparison with the racemate using HPLC on a chiral stationary phase.

well as the TRPV1 (transient receptor potential vanilloid 1) ion channel.[36] The important lead compound MS-245 (**29**) is a tryptamine derivative with potent 5-HT_6 receptor inhibitor activity (IC_{50} = 2.1 nM).[34] By acting on this receptor, MS-245 has high therapeutic potential for the treatment of Alzheimer's disease.[38] The constrained tricyclic analog of this species (*rac*-**30**) is an even more potent inhibitor (IC_{50} = 1.5 nM).[37] Enders and co-workers described the asymmetric synthesis of (*R*)-**30** by an organocatalytic cascade reaction *via* a Plancher rearrangement.[39] They reacted 5-methoxyindole (**32**) and iodonitroalkene **33** to obtain precursor **34** with 87% *ee* before recrystallyzation (Scheme 10). Finally, they obtained (*R*)-**30** after an additional three-step reaction sequence. We envisioned the application of our cascade methodology to provide a more efficient and selective process, starting from readily available substrates arylhydrazine **35** and (−)-**2a** (Scheme 10). The cascade reaction was found to proceed most efficiently in a one-pot, two-stage process involving the interrupted Fischer indolization (1.0 equiv PPTS, 130 °C, 30 min.) and the rearrangement (1.0 equiv TsOH, 130 °C, 30 min.). The resulting tricyclic tryptamine derivative **36** was then modified by *N*-methylation and sulfonylation of the indole nucleus, without purification of the intermediates. To our delight, we obtained (*R*)-**30** in excellent enantioselectivity and in a more time- and step-efficient manner than Enders' route.

As a potent and selective inhibitor of the TRPV1 ion channel, (±)-**31** has therapeutic potential in the treatment of neuropathic pain.[36] We envisioned rapid and stereoselective access to this compound with our methodology (Scheme 10). In this case, the *in situ* Boc deprotection (1.0 equiv TsOH, toluene, 60 °C, 1 h) of **26** was followed by the cascade reaction with (−)-**2a** as developed for **35** (1.0 equiv PPTS, 130 °C, 30 min., then 1.0 equiv TsOH, 130 °C, 30 min.). After acylation of tricyclic tryptamine derivative **37**, hydrogenolysis of the benzyl ether afforded (*R*)-**31** in 26% overall yield with excellent enantioselectivity (99% *ee*).

4.3 Conclusion

We developed an acid-switchable chemoenzymatic interrupted Fischer indole synthesis of either tetracyclic pyrroloindolines **6** or tricyclic tryptamines derivatives **8** and **9** with multiple diversification points. This novel cascade process either affords **6** or can undergo an additional Plancher rearrangement to give **8** and **9** depending on

the stoichiometry of the acid mediator. Both compounds classes 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**). A range of electron-rich and deficient arylhydrazines were compatible with this cascade process in combination with a small range of chiral bicyclic imines. We applied our concise methodology in the synthesis of pharmaceutically releveant compounds in high optical purity. Notably, examples from both scaffold types have high therapeutic potential in the treatment of Alzheimer's disease. These findings clearly illustrate the fruitful union of biocatalysis and cascade reactions.

4.4 Acknowledgements

We thank Dr. G. Barreca (Chemessentia S.r.L.) for a generous gift of (−)-**2a**, Dr. A. W. Ehlers (VU University) for assistance with NMR spectroscopy and S. Bouwman (VU University) for HRMS measurements. We kindly acknowledge Dr. M. Zeller (Youngstown State University) for collecting the X-ray data and Dr. C. M. L. Vande Velde (University of Antwerp) for the refinement of the X-ray structure of **11a**, **18b**, **17b** and **20**. M. Hazewinkel and E. van Echten (Syncom BV) are acknowledged for chiral SFC analysis of **12d**.

4.5 Experimental Section

General comments

Starting materials were purchased from Sigma Aldrich, Alfa Aesar, Apollo Scientific, Enamine, Acros Organics and used without treatment. Unless stated otherwise, the solvents were purchased from VWR Chemicals or Biosolve and were used without further treatment. Cyclohexane (*c*Hex) was purified by distillation before use. (3a*R*,6a*S*)-Octahydrocyclopenta[*c*]pyrrole hydrochloride was purchased from AK Scientific and dissolved in CH_2Cl_2, washed with sat. aq. Na_2CO_3, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated *in vacuo* before use. Enantioenriched 1-pyrrolines **2** were be synthesized by biocatalytic oxidation with an engineered monoamine oxidase according to a previously reported procedure.[3] A batch of (–)-**2a** (99% *ee*) was generously provided by Dr. G. Barreca (Chemessentia S.r.L.). Celite® 512 medium was purchased from Sigma Aldrich. All yields were calculated taking the solvent traces into account. Column Chromatography was performed on Silica-P Flash Silica Gel (particle size 40-63 µm, pore diameter 60 Å)

from Silicycle or aluminiumoxide (activated, basic, Brockmann I) from Sigma Aldrich. Preparative thin layer chromatography was performed on Silica Gel plates F_{254} (20 x 20 cm, 2000 µm, pore diameter 60 Å) from Silicycle. Thin Layer Chromatography (TLC) was performed using TLC plates F_{254} (silica gel 60 on aluminium) from Merck Serono KGaA (Darmstadt) and compounds were visualized by UV detection (254 or 366 nm) and stained with basic aq. $KMnO_4$ or ninhydrin/ethanol. ^1H, ^{13}C, COSY, HSQC, HMBC and NOESY nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (500.23 MHz for ^1H and 125.78 MHz for ^{13}C) in $CDCl_3$ using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR) or Bruker Avance 400 (400.13 MHz for ^1H and 100.62 MHz for ^{13}C) using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet) and m (multiplet) or combinations thereof. The COSY-, HMBC- and HSQC-NMR spectra were used for the assignment of the proton signals. The APT-NMR spectra were used for the assignment of the carbon signals. NMR data was processed using MestReNova. Names of chemical structures were deduced from generic names and/or important functionalities. Electrospray Ionization (ESI) high resolution mass spectrometry (HRMS) was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Infrared (IR) spectra were recorded neat using a FTIR-8400s *from Shimadzu. Signal intensities are described as strong (s), medium (m), weak (w) or broad (br). Melting points were recorded on a* Büchi M-565 and are not corrected. *Chiral* HPLC was recorded using a LC10VP with a SCL-10A *VP* system controller, LC-10AT *VP* liquid chromatograph, SPD-M10A *VP* diode array detector and CTO-10AC *VP* column oven from Shimadzu. Data was processed using Shimadzu Labsolutions. Chiral SFC analysis was recorded using an Acquity UPC^2 system consisting of a Convergence Manager, Sample Manager FL, Binary Solvent Manager, PDA Detector, Isocratic Solvent Manager, QDa Detector and 30S column manager from Waters. Specific rotations were measured with an automatic AA-10 polarimeter. Microwave assisted reactions were performed in a sealed vessel using a Biotage Initiator+ and reaction temperatures were measured using IR. Reaction times refer to the hold time at the desired set temperature and not to total irradiation time. The external standard was added to the reaction mixture after the work up. X-ray single crystal data were collected at 100Kon a Bruker X8 Prospector with Cu microsource and focusing optics, and Apex II detector. Data were integrated and corrected for absorption with SAINT V8.34A and SADABS 2012/1, and the structure was solved and refined with SHELX 2014 and shelXle. Hydrogen atoms were detected in the Fourier difference maps, those on C were refined with constraints on bond lengths and angles, those on N were refined freely.

Substrate synthesis

1-pyrroline *rac*-2a:[3] To a solution of *meso*-pyrrolidine **1a** (2.00 g, 18 mmol, 1.0 equiv) in DCM (108 mL) was slowly added *N*-chlorosuccinimide (2.50 g, 18.9 mmol, 1.05 equiv) at 0°C. The reaction mixture was stirred for 3 hours at room temperature. The resulting solution was washed with H_2O (2 x 50 mL) and brine (1 x 50 mL). The combined organic layers were dried (Na_2SO_4) and

concentrated *in vacuo.* The resulting solution was added this to a solution of KOH (2.00 g, 36 mmol, 2.0 equiv) in EtOH (25 mL). The reaction mixture was stirred for 24 hours at room temperature, after which it was concentrated *in* vacuo. The crude product was then dissolved in 100 mL of DCM, washed with sat. $NaHCO_3$ and subsequently the water layer was extracted with DCM (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (1:1 v/v *c*Hex/EtOAc → 19:1 v/v DCM:MeOH), to obtain compound (±)-**2a** (752 mg, 6.90 mmol, 38%) as a light yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 1H, NHC*H*), 4.11 – 3.98 (m, 1H, NHCH_2), 3.57 – 3.46 (m, 1H, NHCH_2), 3.27 (t, J = 8.9 Hz, 1H, NHCHC*H*), 2.72 – 2.57 (m, 1H, NHCH_2C*H*), 1.73 – 1.19 (m, 6H, CH_2CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.6 (CH), 70.3 (CH_2), 55.2 (CH), 38.7 (CH), 34.8 (CH_2), 29.4 (CH_2), 25.0 (CH_2) ppm.

Synthetic procedures and spectral data

General procedure for optimization of reaction conditions of interrupted Fischer indole reaction in Table 1: To a solution of 1-pyrroline **2a** (0.10 mmol, 1.0 equiv) in solvent (0.1 M) were added phenylhydrazine **10a** (1.05 equiv) and the source of acid (0.20 mmol, 2.0 equiv) under nitrogen. The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Subsequently, the yield of pyrroloindoline **6a** was determined with ^{1}H-NMR spectroscopy after dissolving the crude product in $CDCl_3$ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 equiv) as internal standard.

General procedure for exploration of the acid switchability of the reaction outcome of the interrupted Fischer indole synthesis in Table 2: To a solution of 1-pyrroline **2a** (30 mg, 0.25 mmol, 1.0 equiv) in toluene (0.1 M) were added phenylhydrazine hydrochloride **10b** (0.26 mmol, 1.05 equiv) and the source of acid (48 mg, 0.25 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Subsequently, the yield was determined with ^{1}H-NMR spectroscopy after dissolving the crude product in $CDCl_3$ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 equiv) as internal standard.

Procedure for deuteration experiment in Scheme 6: To a solution of 2,3-dimethylindole (1.0 equiv) in toluene (0.1 M) was added *p*-TsOD (3.0 equiv; prepared by dissolving *p*TsOH monohydrate in D_2O and subsequent concentration *in vacuo*). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in methanol (3 mL), washed with sat. aq. Na_2CO_3 (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was analysed with NMR spectroscopy, clearly showing a combination of the non-deuterated **14**, mono-deuterated **15** and di-deuterated **16** species. This experiment shows the feasibility of an

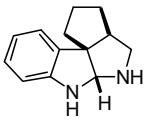
imine/enamine equilibrium (see working hypothesis) in protonated indoles, plausibly accounting for the observed racemization of **13a-c**. The product was analyzed with NMR spectroscopy.

Procedure for the screening of temperature and time dependence of the racemization of 13a in Table 3: To a solution of *o*-nosylated pyrroloindoline **11c** (1.0 equiv) in toluene (0.1 M) was added TsOH (0.5 equiv). The reaction mixture was stirred at elevated temperature under microwave irradiation. The suspension was cooled to rt, washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Subsequently, conversion was determined by analysis with NMR spectroscopy according to the molar ratio between **11c** and **12a**/**13a**. The enantiomeric excess of **12a** and **13a** was determined by comparison with the racemates using HPLC on a chiral stationary phase.

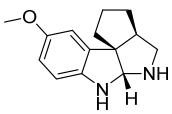
Pyrroloindoline synthesis

General procedure 1: To a solution of 1-pyrroline **2a** (30 mg, 0.25 mmol, 1.0 equiv) in toluene (0.1 M) were added the hydrazine hydrochloride **10** (0.26 mmol, 1.05 equiv) and *p*-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. If necessary, the crude product was purified by flash chromatography.

General procedure 2: To a solution of 1-pyrroline **2a** (30 mg, 0.25 mmol, 1.0 equiv) in toluene (0.1 M) were added the hydrazine **10** (0.26 mmol, 1.05 equiv) and *p*-toluenesulfonic acid monohydrate (95 mg, 0.50 mmol, 2.0 equiv). The reaction was proceeded as described in *general procedure 1*.

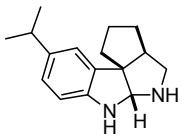


pyrroloindoline 6a: Prepared from phenylhydrazine hydrochloride (38 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 20:1 v/v DCM:MeOH), to obtain compound **6a** (31 mg, 0.15 mmol, 61%) as a red oil. $\mathbf{R_f}$ = 0.78 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 7.4 Hz, 1H, NHC*C*C*H*), 7.02 (t, *J* = 7.5 Hz, 1H, NHC*CHC*H*), 6.73 (t, *J* = 7.4 Hz, 1H, NHC*C*CHC*H*), 6.56 (d, *J* = 7.8 Hz, 1H, CHC*CH), 4.88 (s, 1H, NHCHNH), 3.14 (dd, *J* = 11.0, 6.6 Hz, 1H, NHCH_2), 2.79 – 2.73 (m, 1H, NHCH_2), 2.52 – 2.43 (m, 1H, NHCH$_2$C*H*), 2.13 – 1.71 (m, 6H, CHCH_2CH_2CH_2, N*H*), 1.53 – 1.42 (m, 1H, NHCH$_2$CHCH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 149.5 (C*), 135.5 (C*), 127.7 (CH), 123.2 (CH), 119.0 (CH), 108.8 (CH), 87.2 (CH), 65.4 (C*), 54.5 (CH), 51.4 (CH_2), 40.7 (CH_2), 33.5 (CH_2), 27.8 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3275 (br), 2941 (m), 2858 (m), 1607 (m), 1485 (m), 1466 (m), 1396 (m), 1248 (m), 1196 (w), 903 (w), 636 (m). **HRMS** (ESI): *m/z* calculated for $C_{13}H_{17}N_2$ $[M+H]^+$: 201.1386, found: 201.1393.

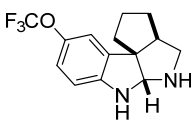


5-methoxypyrroloindoline 6b: Prepared from 4-methoxyphenylhydrazine hydrochloride (39 mg, 0.26 mmol, 1.05 eq) and (–)-**2a** according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (100:1 → 20:1 v/v DCM:MeOH), to obtain compound **6b** (44 mg [2.5% CH_2Cl_2], 0.19 mmol, 73%) as a dark red oil. $\mathbf{R_f}$ = 0.73 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ

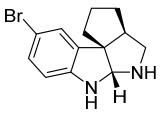
6.67 (d, *J* = 2.6 Hz, 1H, NHC*C*C*H*), 6.60 (dd, *J* = 8.4, 2.6 Hz, 1H, NHC*CHC*H), 6.51 (d, *J* = 8.4 Hz, 1H, NHC*C*H), 4.85 (s, 1H, NHC*H*NH), 3.75 (s, 3H, C*H*$_3$), 3.16 (dd, *J* = 10.8, 6.7 Hz, 1H, NHC*H*$_2$), 2.74 (dd, *J* = 10.8, 3.0 Hz, 1H, NHC*H*$_2$), 2.52 – 2.44 (m, 1H, NHCH$_2$C*H*), 2.09 – 1.72 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$, N*H*), 1.53 – 1.42 (m, 1H, NHCH$_2$CHC*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 153.9 (C*), 143.4 (C*), 137.4 (C*), 112.5 (CH), 110.1 (CH), 109.7 (CH), 87.6 (CH), 65.8 (C*), 56.1 (CH_3), 54.2 (CH), 51.3 (CH_2), 40.5 (CH_2), 33.5 (CH_2), 27.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3281 (br), 2932 (m), 2858 (m), 1489 (s), 1435 (w), 1205 (s), 1176 (m), 1140 (w), 1099 (w), 1032 (s), 845 (w), 804 (m), 602 (w). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{19}N_2O$ $[M+H]^+$: 231.1492, found: 231.1497. **Chiral HPLC** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 260 nm, t (major) = 17.926, t (minor) = 31.018 min]. **Specific rotation**: $[\alpha]_D^{20} = -42$ ° (c = 1.0, EtOH).



5-(*iso*-propyl)pyrroloindoline 6c: Prepared from 4-isopropylphenyl-hydrazine hydrochloride (50 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 20:1 v/v DCM:MeOH), to obtain compound **6c** (42 mg, 0.17 mmol, 69%) as a dark red oil. **R$_f$** = 0.82 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 6.97 – 6.87 (m, 2H, C*H*C(*i*Pr)C*H*), 6.51 (d, *J* = 7.8 Hz, 1H, NHC*C*H), 4.86 (s, 1H, NHC*H*NH), 3.16 (dd, *J* = 10.9, 6.7 Hz, 1H, NHC*H*$_2$), 2.82 (hept, *J* = 6.9 Hz, 1H, C*H*(CH_3)$_2$), 2.73 (dd, *J* = 10.9, 2.8 Hz, 1H, NHC*H*$_2$), 2.52 – 2.45 (m, 1H NHCH$_2$C*H*), 2.12 – 1.65 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$, N*H*), 1.55 – 1.43 (m, 1H, NHCH$_2$CHC*H*$_2$), 1.21 (d, *J* = 6.9 Hz, 6H, C*H*$_3$CHC*H*$_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 147.8 (C*), 140.3 (C*), 136.0 (C*), 125.7 (CH), 121.5 (CH), 109.1 (CH), 87.8 (CH), 65.8 (C*), 54.5 (CH), 51.7 (CH_2), 41.0 (CH_2), 34.1 (CH), 33.8 (CH_2), 28.0 (CH_2), 24.9 (CH_3), 24.8 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2951 (s), 2862 (m), 1616 (m), 1489 (s), 1447 (w), 1396 (w), 1362 (w), 1333 (w), 1257 (m), 1190 (w), 1101 (w), 881 (w), 812 (s), 613 (m). **HRMS** (ESI): *m/z* calculated for $C_{15}H_{23}N_2$ $[M+H]^+$: 243.1856, found: 243.1860.

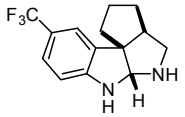


5-(trifluoromethoxy)pyrroloindoline 6d: Prepared from 4-(trifluormethoxy)phenylhydrazine hydrochloride (61 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 50:1 v/v DCM:MeOH), to obtain compound **6d** (32 mg, 0.11 mmol, 45 %) as a dark red oil. **R$_f$** = 0.80 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 6.90 – 6.84 (m, 2H, NHC*CHC*H*, NHC*C*C*H*), 6.48 (d, *J* = 8.4 Hz, 1H, NHC*C*H), 4.93 (s, 1H, NHC*H*NH), 4.29 (bs, 1H, N*H*), 3.14 (dd, *J* = 10.9, 6.6 Hz, 1H, NHC*H*$_2$), 2.77 (dd, *J* = 11.0, 2.7 Hz, 1H, NHC*H*$_2$), 2.51 – 2.44 (m, 1H, NHCH$_2$C*H*), 2.25 (s, 1H, N*H*), 2.08 – 1.99 (m, 2H, C*H*$_2$CH$_2$C*H*$_2$), 1.98 – 1.90 (m, 1H, CHCH$_2$CH$_2$C*H*$_2$), 1.90 – 1.73 (m, 2H, CHCH$_2$C*H*$_2$), 1.52 – 1.46 (m, 1H, NHCH$_2$CHC*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 148.1 (C*), 142.0 (C*), 136.9 (C*), 120.82 (q, *J* = 255.6 Hz, C*), 120.80 (CH), 116.9 (CH), 108.5 (CH), 87.6 (CH), 65.4 (C*), 54.6 (CH), 51.3 (CH_2), 40.6 (CH_2), 33.4 (CH_2), 27.7 (CH_2) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): *δ* -58.39 ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2943 (w), 2866 (w), 1489 (s), 1244 (s), 1213 (s), 1148 (s), 873 (w), 816 (m), 800 (w), 613 (m), 600 (m). **HRMS** (ESI): *m/z* calculated $C_{14}H_{16}F_3N_2O$ $[M+H]^+$: 285.1209, found: 285.1205.

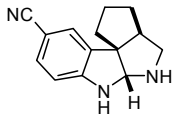


5-bromopyrroloindoline 6e: Prepared from 4-bromophenylhydrazine hydrochloride (59 mg, 0.26 mmol, 1.05 eq) and (–)-**2a** according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 50:1 v/v DCM:MeOH), to obtain compound **6e** (34 mg, 0.12 mmol, 50%) as a red solid.

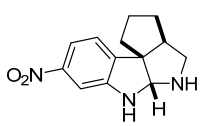
R_f = 0.59 (DCM:MeOH 100:1 v/v). **m.p.:** 80.0 – 94.8 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.12 (d, J = 2.0 Hz, 1H, CBrC*H*), 7.09 (dd, J = 8.2, 2.1 Hz, 1H, NHC*CHC*H*) 6.42 (d, J = 8.3 Hz, 1H, NHC*CH*), 4.90 (s, 1H, NHC*H*NH), 3.11 (dd, J = 11.1, 6.7 Hz, 1H, NHCH_2), 2.76 (dd, J = 11.1, 2.6 Hz, 1H, NHCH_2), 2.52 – 2.41 (m, 1H, NHCH$_2$C*H*), 2.09 – 1.96 (m, 2H, CH_2CH$_2$CH_2), 1.94 – 1.87 (m, 1H, CHCH$_2$CH$_2$CH_2), 1.85 – 1.70 (m, 2H, CHCH$_2$CH_2), 1.52 – 1.40 (m, 1H, NHCH$_2$CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 148.5 (C*), 137.9 (C*), 130.3 (CH), 126.2 (CH), 110.3 (C*), 110.0 (CH), 87.4 (CH), 65.4 (C*), 54.7 (CH), 51.2 (CH_2), 40.6 (CH_2), 33.4 (CH_2), 27.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3171 (br), 2926 (m), 2858 (m), 1601 (m), 1475 (s), 1448 (m), 1420 (m), 1261 (s), 1097 (m), 901 (m), 864 (m), 837 (m), 800 (s), 741 (w), 671 (m), 561 (m). **HRMS** (ESI): *m/z* calculated for $C_{13}H_{16}BrN_2$ $[M+H]^+$: 279.0491, found: 279.0490. **Chiral HPLC** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 95/5, v = 0.9 mL/min, column temperature: 30 °C, λ = 210 nm, t (major) = 22.180, t (minor) = 28.864 min]. **Specific rotation**: $[\alpha]_D^{20}$ = +8 ° (c = 0.5, EtOH).



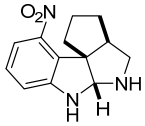
5-(trifluoromethyl)pyrroloindoline 6f: Prepared from 4-(trifluormethyl)phenylhydrazine (48 mg, 0.26 mmol, 1.05 eq) according to *general procedure 2*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (100:1 → 20:1 v/v DCM:MeOH), to obtain compound **6f** (32 mg, 0.12 mmol, 48%) as a red solid. **R_f** = 0.62 (DCM:MeOH 100:1 v/v). **m.p.:** 97.4 – 113.7 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33 – 7.17 (m, 2H, NHC*CHC*H*, NHC*C*C*H*), 6.52 (d, J = 8.1 Hz, 1H, NHC*CH*), 4.96 (s, 1H, NHC*H*NH), 4.45 (bs, 1H, N*H*), 3.11 (dd, J = 11.1, 6.4 Hz, 1H, NHCH_2), 2.81 (dd, J = 11.1, 2.3 Hz, 1H, NHCH_2), 2.55 – 2.39 (m, 1H, NHCH$_2$C*H*), 2.15 – 1.76 (m, 6H, CH_2CH_2CH_2, N*H*), 1.53 – 1.38 (m, 1H, NHCH$_2$CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.2 (C*), 135.4 (C*), 125.4 (q, J = 4.0 Hz, CH), 125.1 (q, J = 271.5 Hz, C*), 120.2 (q, J = 32.3 Hz, C*), 120.1 (q, J = 3.6 Hz, CH), 107.0 (CH), 87.4 (CH), 64.9 (C*), 54.9 (CH), 51.3 (CH_2), 40.5 (CH_2), 33.4 (CH_2), 27.7 (CH_2) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): δ -60.54 ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3178 (br), 2943 (m), 2862 (m), 1616 (s), 1506 (m), 1323 (s), 1269 (s), 1153 (s), 1140 (s), 1121 (s), 1080 (s), 1055 (s), 986 (m), 901 (s), 841 (m), 812 (s), 642 (m). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{16}F_3N_2$ $[M+H]^+$: 269.1260, found: 269.1260.



5-cyanopyrroloindoline 6g: Prepared from 4-hydrazinobenzonitrile hydrochloride (44 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (200:1 → 20:1 v/v DCM:MeOH), to obtain compound **6g** (10 mg [4.0% CH_2Cl_2], 0.04 mmol, 18%)[40] as a dark yellow oil. **R_f** = 0.53 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 2H, C*H*C(CN)C*H*), 6.48 (d, J = 8.2 Hz, 1H, NHC*C*H*), 5.00 (s, 1H, NHC*H*NH), 4.90 (s, 1H, N*H*), 3.14 (s, 1H, N*H*), 3.06 (dd, J = 11.2, 6.4 Hz, 1H, NHCH_2), 2.82 (dd, J = 11.3, 1.8 Hz, 1H, NHCH_2), 2.50 – 2.43 (m, 1H, NHCH$_2$C*H*), 2.12 – 1.99 (m, 2H, CH_2CH$_2$CH_2), 1.96 – 1.75 (m, 3H, CHCH$_2$CH_2CH_2), 1.50 – 1.39 (m, 1H, NHCH$_2$CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.0 (C*), 135.8 (C*), 133.3 (CH), 126.8 (CH), 120.8 (C*), 107.5 (CH), 100.0 (C*), 87.2 (CH), 64.8 (C*), 55.2 (CH), 51.1 (CH_2), 40.5 (CH_2), 33.3 (CH_2), 27.8 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2928 (s), 2856 (s), 2206 (s), 1609 (s), 1558 (m), 1522 (m), 1491 (s), 1458 (s), 1271 (m), 1167 (m), 1103 (m), 814 (m), 600 (m), 567 (w). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{16}N_3$ $[M+H]^+$: 226.1339, found: 226.1340.



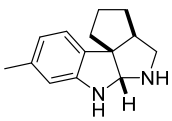
6h



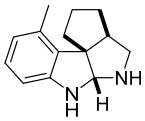
6h'

6-nitropyrroloindoline 6h and 4-nitropyrroloindoline 6h': Prepared from 3-nitrophenylhydrazine hydrochloride (50 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (SiO_2)

with an eluent gradient (200:1 → 50:1 v/v DCM:MeOH), to obtain compounds **6h** and **6h'** (16 mg, 0.07 mmol, 27%) in a 1.25:1 ratio as determined with the crude NMR spectrum. Pure fractions of both compound **6h** (major), as an orange foam, and compound **6h'** (minor), as a red oil, were used for full identification. **6h: R_f** = 0.56 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.1, 1.8 Hz, 1H, C(NO_2)C*H*CH), 7.29 – 7.21 (m, 1H, NHC*C*H*), 7.09 (d, *J* = 8.1 Hz, 1H, C(NO_2)CHC*H*), 5.01 (s, 1H, NHC*H*NH), 4.46 (s, 1H, N*H*), 3.13 (dd, *J* = 10.9, 6.5 Hz, 1H, NHCH_2), 2.83 (dd, *J* = 10.9, 2.0 Hz, 1H, NHCH_2), 2.53 – 2.44 (m, 1H, NHCH_2C*H*), 2.19 – 1.78 (m, 6H, CH_2CH_2CH_2), 1.54 – 1.43 (m, 1H, NHCH_2CHCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3 (C*), 148.5 (C*), 143.2 (C*), 122.9 (CH), 114.5 (CH), 102.3 (CH), 87.7 (CH), 65.1 (C*), 55.4 (CH), 51.4 (CH_2), 40.5 (CH_2), 33.6 (CH_2), 28.1 (CH_2). **6h':**[40] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2 Hz, 1H, C(NO_2)C*H*), 7.15 (t, *J* = 8.0 Hz, 1H, C(NO_2)CH*CH*), 6.81 (d, *J* = 7.8 Hz, 1H, NHC*C*H*), 4.82 – 4.66 (m, 2H, N*HCH*NH), 3.14 (dd, *J* = 11.0, 7.3 Hz, 1H, NHCH_2), 3.07 – 2.98 (m, 1H, NHCH_2C*H*), 2.68 (dd, *J* = 11.1, 4.3 Hz, 1H, NHCH_2), 2.35 – 2.20 (m, 2H, C*CH_2CH_2CH_2), 1.99 – 1.80 (m, 2H, C*CH_2CH_2CH_2), 1.77 – 1.62 (m, 1H, C*CH_2), 1.58 – 1.51 (m, 1H, C*CH_2CH_2CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.3 (C*), 146.5 (C*),[41] 129.0 (CH), 128.2 (C*), 114.8 (CH), 113.8 (CH), 87.2 (CH), 67.3 (C*), 52.1 (CH_2), 51.3 (CH), 37.0 (CH_2), 33.3 (CH_2), 26.4 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2935 (m), 2862 (m), 1614 (w), 1522 (s), 1340 (s), 1250 (w), 1074 (w), 907 (m), 856 (w), 816 (w), 727 (s), 644 (w). **HRMS** (ESI): *m/z* calculated for $C_{13}H_{16}N_3O_2$ $[M+H]^+$: 246.1237, found: 246.1228.

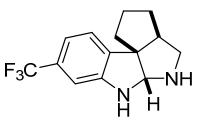


6i

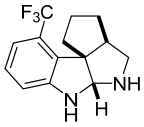


6i'

6-methylpyrroloindoline 6i and 4-methylpyrrolo-indoline 6i': Prepared from *m*-tolylhydrazine hydrochloride (42 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 20:1 v/v DCM:MeOH), to obtain compounds **6i** and **6i'** (28 mg, 0.13 mmol, 52%, inseparable mixture) as a dark yellow oil in a 2.0:1 ratio as determined with the crude NMR spectrum. **R_f** = 0.38 (DCM:MeOH 100:1 v/v). **IR** (neat): ν_{max} (cm^{-1}) = 2941 (m), 2860 (m), 1616 (w), 1591 (w), 1259 (m), 1159 (w), 1078 (s), 1013 (s), 945 (w), 793 (s), 737 (m), 696 (w), 679 (w), 596 (w). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{19}N_2$ $[M+H]^+$: 215.1543, found: 215.1549. **6i**: **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 6.94 (d, *J* = 7.3 Hz, 1H, NHC*C*C*H*),[42] 6.57 – 6.54 (m, 1H, C(CH_3)C*H*), 6.40 (s, 1H, NHC*C*H*), 4.86 (s, 1H, NHC*H*NH), 3.17 – 3.07 (m, 1H, NHCH_2), 2.77 – 2.71 (m, 1H, NHCH_2),[42] 2.47 – 2.40 (m, 1H, NHCH_2C*H*), 2.26 (s, 3H, C*H*$_3$), 2.12 – 1.97 (m, 2H, CH_2CH_2CH_2),[42] 1.94 – 1.85 (m, 1H, CHCH_2CH_2CH_2),[42] 1.84 – 1.68 (m, 2H, CHCH_2CH_2),[42] 1.48 – 1.40 (m, 1H, NHCH_2CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 149.7 (C*), 137.5 (C*), 132.6 (C*), 122.8 (CH), 119.6 (CH), 109.5 (CH), 87.4 (CH), 65.1 (C*), 54.4 (CH), 51.4 (CH_2), 40.6 (CH_2), 33.5 (CH_2), 27.7 (CH_2), 21.6 (CH_3) ppm. **6i': ^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 6.98 – 6.92 (m, 1H, NHC*CHC*H*),[42] 6.55 (d, *J* = 7.9 Hz, 1H, *Ar*), 6.45 (d, *J* = 7.7 Hz, 1H, *Ar*), 4.59 (s, 1H, NHC*H*NH), 3.17 – 3.07 (m, 1H, NHCH_2),[42] 2.77 – 2.71 (m, 1H, NHCH_2),[42] 2.61 – 2.58 (m, 1H, NHCH_2C*H*), 2.29 (s, 3H, C*H*$_3$), 2.12 – 1.97 (m, 2H, CH_2CH_2CH_2),[42] 1.94 – 1.85 (m, 2H, CHCH_2CH_2CH_2),[42] 1.84 – 1.68 (m, 1H, CHCH_2CH_2),[42] 1.58 – 1.52 (m, 1H, NHCH_2CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 149.5 (C*), 134.5 (C*), 131.2 (C*), 127.8 (CH), 121.4 (CH), 107.0 (CH), 87.0 (CH), 66.1 (C*), 51.5 (CH_2), 50.7 (CH), 37.2 (CH_2), 32.6 (CH_2), 26.3 (CH_2), 18.4 (CH_3) ppm.



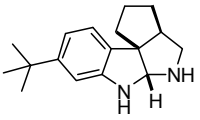
6j



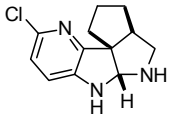
6j'

6-(trifluoromethyl)pyrroloindoline 6j and 4-trifluoromethylpyrroloindoline 6j': Prepared from 3-(trifluormethyl)phenylhydrazine hydrochloride (57 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3

basic) with an eluent gradient (200:1 → 50:1 v/v DCM:MeOH), to obtain compounds **6j** and **6j'** (16 mg, 0.06 mmol, 26%) in a 1:0.2 ratio as determined with the crude NMR spectrum. A pure fraction of compound **6j** (major), as an orange foam, was used for full identification. **6j**: $\mathbf{R_f}$ = 0.62 (DCM:MeOH 100:1 v/v). **m.p.:** 35.1 – 44.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.7 Hz, 1H, NHC*C*C*H*), 6.96 (d, *J* = 7.7 Hz, 1H, NHC*C*CHC*H*), 6.73 (s, 1H, NHC*C*H), 4.95 (s, 1H, NHC*H*NH), 4.37 (bs, 1H, N*H*), 3.13 (dd, *J* = 11.0, 6.7 Hz, 1H, NHCH_2), 2.79 (dd, *J* = 11.1, 2.6 Hz, 1H, NHCH_2), 2.53 – 2.42 (m, 1H, NHCH$_2$C*H*), 2.26 – 1.74 (m, 6H, N*H*, CH_2CH_2CH_2), 1.55 – 1.41 (m, 1H, NHCH$_2$CHCH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 149.7 (C*), 139.3 (C*), 130.1 (q, *J* = 32 Hz, C*), 124.7 (q, *J* = 272 Hz, C*), 123.0 (CH), 115.6 (q, *J* = 4.1 Hz, CH), 104.6 (q, *J* = 3.7 Hz, CH), 87.2 (CH), 65.0 (C*), 54.8 (CH), 51.2 (CH_2), 40.4 (CH_2), 33.4 (CH_2), 27.7 (CH_2) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): δ -62.25 ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2934 (w), 2862 (w), 1614 (w), 1336 (m), 1317 (s), 1155 (m), 1107 (s), 1059 (m), 984 (w), 857 (m), 810 (m), 737 (w), 700 (m), 679 (w), 665 (m). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{16}F_3N_2$ $[M+H]^+$: 269.1260, found: 269.1254. **6j':**[43] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.16 – 7.11 (m, 1H, NHC*CHC*H*), 6.99 (d, *J* = 7.7 Hz, 1H, NHC*C*H), 6.77 (d, *J* = 7.8 Hz, 1H, NHC*CHCHC*H*), 4.78 (s, 1H, NHC*H*NH), 3.13 (dd, *J* = 11.4, 7.1 Hz, 1H, NHCH_2), 2.96 – 2.89 (m, 1H, NHCH$_2$C*H*), 2.71 (dd, *J* = 11.4, 4.3 Hz, 1H, NHCH_2), 2.24 – 1.50 (m, 6H, CH_2CH_2CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 150.9 (C*), 128.7 (CH), 127.0 (q, *J* = 32 Hz, C*), 124.7 (q, *J* = 273 Hz, C*) 117.2 (CH), 112.5 (CH), 87.0 (CH), 66.9 (C*), 51.4 (CH_2), 51.3 (CH), 38.2 (CH_2), 32.6 (CH_2), 25.9 (CH_2). **^{19}F NMR** (235 MHz, $CDCl_3$): δ -57.11 ppm.

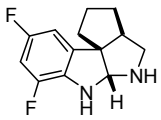


6-(*tert*-butyl)pyrrolodindoline 6k: Prepared from 3-(*t*-butyl)phenyl-hydrazine hydrochloride (53 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 50:1 v/v DCM:MeOH), to obtain compound **6k** (28 mg, 0.11 mmol, 44%) as a yellow solid. $\mathbf{R_f}$ = 0.47 (DCM:MeOH 100:1 v/v). **m.p.:** 80.0 – 100.1 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.98 (d, *J* = 7.6 Hz, 1H, NHC*C*C*H*), 6.77 (dd, *J* = 7.8, 1.8 Hz, 1H, NHC*C*CHC*H*), 6.63 (d, *J* = 1.8 Hz, 1H, NHC*C*H), 4.88 (s, 1H, NHC*H*NH), 3.16 (dd, *J* = 10.9, 6.7 Hz, 1H, NHCH_2), 2.75 (dd, *J* = 11.0, 2.8 Hz, 1H, NHCH_2), 2.52 – 2.43 (m, 1H, NHCH$_2$C*H*), 2.14 – 1.96 (m, 4H, N*H,* CH_2CH$_2$CH_2), 1.95 – 1.87 (m, 1H, CHCH$_2$CH$_2$CH_2), 1.86 – 1.71 (m, 2H, CHCH$_2$CH_2), 1.55 – 1.42 (m, 1H, NHCH$_2$CHCH_2), 1.32 – 1.20 (m, 9H, C(CH_3)$_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 151.2 (C*), 149.4 (C*), 132.6 (C*), 122.5 (CH), 116.2 (CH), 106.4 (CH), 87.4 (CH), 65.2 (C*), 54.1 (CH), 51.4 (CH_2), 40.6 (CH_2), 34.8 (C*), 33.5 (CH_2), 31.7 (CH_3), 27.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2947 (s), 2926 (s), 2905 (s), 2858 (s), 1611 (m), 1458 (s), 1448 (s), 1362 (w), 1261 (m), 1099 (m), 1086 (m), 852 (m), 803 (s), 737 (s), 654 (s). **HRMS** (ESI): *m/z* calculated for $C_{17}H_{25}N_2$ $[M+H]^+$: 257.2012, found: 257.2003.

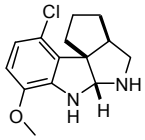


pyrroloazaindoline 6l: Prepared from 2-chloro-5-hydrazinylpyridine (39 mg, 0.26 mmol, 1.05 eq) according to *general procedure 2*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (100:1 → 20:1 v/v DCM:MeOH), to obtain compound **6l** (36 mg [3.1% CH_2Cl_2, 9.4% acetone], 0.13 mmol, 53%) as a dark red oil. $\mathbf{R_f}$ = 0.46 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.90 (d, *J* = 8.2 Hz, 1H, NHC*CHC*H*), 6.72 (d, *J* = 8.2 Hz, 1H, NHC*C*H), 4.95 (s, 1H, NHC*H*NH), 4.29 (s, 1H, N*H*), 3.10 (dd, *J* = 11.0, 6.5 Hz, 1H, NHCH_2), 2.84 (dd, *J* = 11.1, 2.5 Hz, 1H, NHCH_2), 2.76 – 2.67 (m, 1H, NHCH$_2$C*H*), 2.36 – 2.27 (m, 1H, CHCH$_2$CH$_2$CH_2), 2.14 – 2.00 (m, 1H, NHCH$_2$CHCH_2), 1.97 – 1.82 (m, 2H, CHCH$_2$CH_2CH_2), 1.81 – 1.70 (m, 1H, CHCH$_2$CH_2), 1.52 – 1.41 (m, 1H, NHCH$_2$CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.4 (C*), 142.5 (C*), 140.3 (C*), 122.1 (CH), 116.8 (CH), 86.1 (CH), 65.7 (C*), 53.2 (CH), 51.7 (CH_2), 38.5 (CH_2), 33.4 (CH_2), 27.5 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3277 (w), 2935 (m), 2864 (m), 1593 (m), 1429 (s), 1356 (w), 1244 (m),

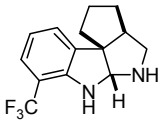
2298 (m), 1101 (m), 903 (w), 816 (m), 733 (w), 683 (w), 602 (m). **HRMS** (ESI): *m/z* calculated for $C_{12}H_{15}ClN_3$ $[M+H]^+$: 236.0949, found: 236.0938.



3,5-difluoropyrroloindoline 6m: Prepared from 2,4-difluorophenylhydrazine hydrochloride (48 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 50:1 v/v DCM:MeOH), to obtain compound **6m** (13 mg, 0.06 mmol, 22%) as a dark red oil. $\mathbf{R_f}$ = 0.66 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.64 – 6.52 (m, 2H, C*H*CFC*H*), 4.97 (s, 1H, NHC*H*NH), 3.19 (dd, *J* = 10.7, 6.6 Hz, 1H, NHCH_2), 2.80 (dd, *J* = 10.7, 2.8 Hz, 1H, NHCH_2), 2.51 – 2.43 (m, 1H, NCH_2C*H*), 2.08 – 1.97 (m, 2H, CH_2CH_2CH_2), 1.98 – 1.89 (m, 1H, CHCH_2CH_2CH_2), 1.86 – 1.77 (m, 2H, CHCH_2CH_2), 1.57 – 1.44 (m, 1H, NHCH_2CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.6 (dd, *J* = 238.5, 9.6 Hz, C*), 147.1 (dd, *J* = 243.4, 12.7 Hz, C*), 139.6 (dd, *J* = 8.6, 6.0 Hz, C*), 132.6 (dd, *J* = 12.3, 2.0 Hz, C*), 105.9 (dd, *J* = 23.4, 3.4 Hz, CH), 102.3 (dd, *J* = 27.2, 21.8 Hz, CH), 87.8 (CH), 66.1 (C*), 54.2 (CH), 51.2 (CH_2), 40.3 (CH_2), 33.4 (CH_2), 27.7 (CH_2) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): δ -122.77 (t, *J* = 8.6 Hz), -131.99 (d, *J* = 10.1 Hz) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (m), 2862 (m), 1607 (w), 1489 (s), 1418 (w), 1340 (m), 1215 (m), 1094 (m), 982 (m), 845 (m), 735 (w), 721 (w), 638 (w), 588 (m). **HRMS** (ESI): *m/z* calculated for $C_{13}H_{15}F_2N_2$ $[M+H]^+$: 237.1198, found: 237.1200.

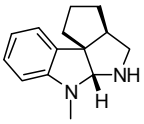


3-methoxy-6-chloropyrroloindoline 6n: Prepared from 5-chloro-2-methoxy-phenylhydrazine hydrochloride (56 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 20:1 v/v DCM:MeOH), to obtain compound **6n** (18 mg, 0.07 mmol, 27%) as a dark yellow oil. $\mathbf{R_f}$ = 0.54 (DCM:MeOH 100:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.64 (d, *J* = 8.6 Hz, 1H, OC*C*H*), 6.58 (d, *J* = 8.5 Hz, 1H, OC*CHC*H*), 4.69 (s, 1H, NHC*H*NH), 4.36 (s, 1H, N*H*), 3.79 (d, *J* = 3.2 Hz, 3H, CH_3), 3.18 – 3.05 (m, 1H, NHCH_2), 2.93 – 2.80 (m, 1H, NHCH_2C*H*), 2.64 (dd, *J* = 10.9, 4.8 Hz, 1H, NHCH_2), 2.32 (ddd, *J* = 12.8, 10.3, 7.1 Hz, 1H, CHCH_2CH_2CH_2), 2.11 – 2.02 (m, 1H, NHCH_2CHCH_2), 2.00 – 1.91 (m, 1H, CHCH_2CH_2), 1.88 – 1.63 (m, 3H, N*H*, CHCH_2CH_2CH_2), 1.56 – 1.46 (m, 1H, NHCH_2CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 143.5 (C*), 139.9 (C*), 130.6 (C*), 122.4 (C*), 119.4 (CH), 110.6 (CH), 86.9 (CH), 67.2 (C*), 55.6 (CH_3), 51.3 (CH_2), 50.3 (CH), 36.4 (CH_2), 32.4 (CH_2), 26.4 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2932 (m), 2858 (m), 1612 (w), 1583 (w), 1481 (s), 1460 (m), 1439 (m), 1275 (m), 1213 (s), 1180 (w), 1092 (m), 1003 (w), 924 (w), 777 (m), 655 (w), 635 (w). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{18}ClN_2O$ $[M+H]^+$: 265.1102, found: 265.1095.

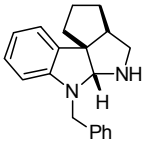


3-(trifluoromethyl)pyrroloindoline 6o: Prepared from 2-(trifluormethyl)phenylhydrazine hydrochloride (56 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (100:0 → 100:1 v/v DCM:MeOH), to obtain compound **6o** (13 mg, 0.05 mmol, 19%) as a dark yellow solid. $\mathbf{R_f}$ = 0.88 (DCM:MeOH 100:1 v/v). **m.p.:** 36.2 – 47.6 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.9 Hz, 1H, CF_3C*C*H*), 7.15 (d, *J* = 7.3 Hz, 1H, NHC*C*C*H*), 6.71 (t, *J* = 7.6 Hz, 1H, F_3CC*CHC*H*), 4.99 (d, *J* = 2.3 Hz, 1H, NHC*H*NH), 4.71 (s, 1H, N*H*), 3.14 (dd, *J* = 10.9, 6.4 Hz, 1H, NHCH_2), 2.81 (dd, *J* = 10.9, 2.3 Hz, 1H, NHCH_2), 2.49 – 2.40 (m, 1H, NHCH_2C*H*), 2.11 – 1.77 (m, 6H, N*H,* CH_2CH_2CH_2), 1.51 – 1.42 (m, 1H, NHCH_2CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 146.8 (C*), 137.5 (C*), 126.3 (CH), 125.1 (q, *J* = 272 Hz, C*), 124.3 (q, *J* = 4.4 Hz, CH), 109.0 (q, *J* = 29.6 Hz, C*), 87.4 (CH), 64.5 (C*), 55.2 (CH), 51.3 (CH_2), 40.7 (CH_2), 33.6 (CH_2), 28.0 (CH_2) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): δ -61.75 ppm. **IR**

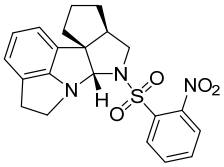
(neat): ν_{max} (cm^{-1}) = 3236 (w), 2932 (m), 2868 (m), 1603 (m), 1354 (m), 1313 (m), 1281 (m), 1163 (s), 2092 (s), 1080 (s), 1064 (s), 1032 (s), 988 (m), 854 (m), 785 (w), 746 (m). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{16}F_3N_2$ $[M+H]^+$: 269.1260, found: 269.1250.



***N*¹-methylpyrroloindoline 6p:** Prepared from 1-methyl-1-phenylhydrazine (32 µL, 0.26 mmol, 1.05 eq) according to *general procedure 2*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (200:1 → 50:1 v/v DCM:MeOH), to obtain compound **6p** (29 mg, 0.14 mmol, 54%) as a yellow oil. $\mathbf{R_f}$ = 0.94 (DCM:MeOH 100:1 v/v). **¹H NMR** (500 MHz, $CDCl_3$): δ 7.07 (t, *J* = 7.4 Hz, 1H, $CH_3NC^*C^*CHCH$), 7.03 (d, *J* = 7.2 Hz, 1H, $CH_3NC^*C^*CH$), 6.65 (t, *J* = 7.3 Hz, 1H, CH_3NC^*CHCH), 6.35 (d, *J* = 7.8 Hz, 1H, CH_3NC^*CH), 4.52 (s, 1H, $NCHNH$), 3.08 (dd, *J* = 11.1, 6.6 Hz, 1H, $NHCH_2$), 2.81 (s, 3H, CH_3), 2.81 – 2.76 (m, 1H, $NHCH_2$), 2.43 (q, *J* = 7.1 Hz, 1H, $NHCH_2CH$), 2.21 – 1.97 (m, 3H, $CH_2CH_2CH_2$, NH), 1.87 – 1.76 (m, 3H, $CHCH_2CH_2CH_2$), 1.48 – 1.38 (m, 1H, $NHCH_2CHCH_2$) ppm. **¹³C NMR** (126 MHz, $CDCl_3$): δ 151.2 (C*), 135.8 (C*), 127.7 (CH), 122.5 (CH), 117.3 (CH), 105.5 (CH), 94.6 (CH), 63.7 (C*), 54.8 (CH), 51.9 (CH_2), 40.9 (CH_2), 34.2 (CH_2), 32.5 (CH_3), 28.3 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (m), 2856 (m), 1605 (s), 1489 (s), 1448 (w), 1296 (w), 1252 (w), 1099 (w), 1022 (w), 941 (w), 920 (w), 843 (w), 733 (s), 635 (w), 602 (w). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{19}N_2$ $[M+H]^+$: 215.1543, found: 215.1547.

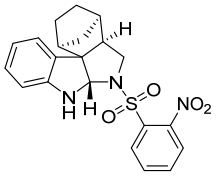


***N*¹-methylpyrroloindoline 6q:** Prepared from 1-benzyl-1-phenylhydrazine hydrochloride (61 mg, 0.26 mmol, 1.05 eq) according to *general procedure 1*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (100:0 → 100:1 v/v DCM:MeOH), to obtain compound **6q** (37 mg, 0.13 mmol, 51%) as a dark yellow oil. $\mathbf{R_f}$ = 0.86 (DCM). **¹H NMR** (500 MHz, $CDCl_3$): δ 7.32 – 7.28 (m, 5H, *Ph*), 7.12 – 6.96 (m, 2H, $NC^*C^*CHCHCH$), 6.70 (td, *J* = 7.4, 1.0 Hz, 1H, NC^*C^*CHCH), 6.37 (d, *J* = 7.8 Hz, 1H, NC^*CH), 4.84 (s, 1H, $NCHNH$), 4.62 – 4.46 (m, 2H, NCH_2), 3.19 (dd, *J* = 11.0, 6.6 Hz, 1H, $NHCH_2$), 2.90 (dd, *J* = 11.1, 2.2 Hz, 1H, $NHCH_2$), 2.59 – 2.53 (m, 1H, $NHCH_2CH$), 2.20 – 2.00 (m, 2H, $CH_2CH_2CH_2$), 1.95 – 1.79 (m, 3H, $CHCH_2CH_2CH_2$), 1.63 – 1.53 (m, 1H, $NHCH_2CHCH_2$) ppm. **¹³C NMR** (126 MHz, $CDCl_3$): δ 150.1 (C*), 138.4 (C*), 134.8 (C*), 128.8 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 122.6 (CH), 118.1 (CH), 106.3 (CH), 91.8 (CH), 63.9 (C*), 54.2 (CH), 50.7 (CH_2), 50.0 (CH_2), 40.6 (CH_2), 33.5 (CH_2), 27.9 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (m), 2858 (m), 1603 (s), 1489 (s), 1452 (m), 1354 (m), 1296 (w), 1267 (w), 1252 (w), 1157 (w), 1099 (w), 1028 (w), 941 (w), 920 (w), 841 (w), 799 (w), 733 (s), 696 (s), 633 (s), 606 (m), 540 (s). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{23}N_2$ $[M+H]^+$: 291.1856, found: 291.1840.

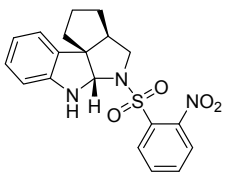


pentacyclic pyrroloindoline 11a: Prepared from 1-pyrroline (–)-**2a** (30 mg, 0.25 mmol, 1.0 equiv) and 1-amineindoline hydrochloride (46 mg, 0.26 mmol, 1.05 equiv), according to *general procedure 1*. The crude product was dissolved DCM (0.1 M), after which Et_3N (42 µL, 0.30 mmol, 1.2 equiv) and *o*-nosyl chloride (68 mg, 0.30 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 2 h at rt, washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was impregnated on SiO_2 and purification was achieved by flash chromatography (SiO_2) with an eluent gradient (20:1 → 10:1 v/v *c*Hex:EtOAc), to obtain the compound **11a** (43 mg, 0.093 mmol, 37 %) as a light yellow foam. Crystallization was achieved by slow evaporation from dichloromethane. $\mathbf{R_f}$ = 0.33 (*c*Hex:EtOAc 4:1 v/v). **m.p.:** >157 °C (decomposition). **¹H NMR** (500 MHz, $CDCl_3$): δ 8.25 – 8.15 (m, 1H, $C(NO_2)CH$), 7.78 – 7.68 (m, 3H, *o*-NO_2Ph), 6.94 (d, *J* = 7.2 Hz,

1H, CH_2C^*CH), 6.81 (d, *J* = 7.3 Hz, 1H, $CH_2C^*CHCHCH$), 6.66 (t, *J* = 7.3 Hz, 1H, CH_2C^*CHCH), 5.24 (s, 1H, NC*H*N), 3.87 (dd, *J* = 10.1, 7.4 Hz, 1H, NCH_2CH), 3.62 (t, *J* = 8.2 Hz, 1H, NCH_2CH_2), 3.43 (dd, *J* = 10.2, 1.6 Hz, 1H, $NHCH_2CH$), 3.32 (m, 1H, NCH_2CH_2), 3.22 – 3.14 (m, 1H, NCH_2CH_2), 3.09 (dd, *J* = 14.5, 7.8 Hz, 1H, NCH_2CH_2), 2.76 (q, *J* = 6.6 Hz, 1H, C*H*), 2.19 – 2.12 (m, 1H, $CH_2CH_2CH_2CH$), 2.09 – 2.00 (m, 1H, CH_2CH_2CH), 1.91 – 1.82 (m, 1H, $CH_2CH_2CH_2CH$), 1.82 – 1.65 (m, 2H, CH_2CH_2CH), 1.45 – 1.32 (m, 1H, CH_2CH_2CH) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.4 (C*), 148.1 (C*), 133.8 (C*), 133.7 (CH), 132.0 (CH), 130.6 (CH), 127.3 (C*), 124.7 (CH), 123.3 (CH), 123.1 (C*), 120.7 (CH), 119.7 (CH), 95.8 (CH), 72.2 (C*), 56.7 (CH_2), 54.5 (CH_2), 51.1 (CH), 39.7 (CH_2), 34.3 (CH_2), 34.1 (CH_2), 27.4 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2949 (w), 2864 (w), 1537 (s), 1348 (s), 1330 (m), 1169 (s), 1122 (m), 1040 (m), 1026 (m), 763 (m), 308 (m), 561 (s). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{21}N_3NaO_4S$ $[M+Na]^+$: 434.1145, found: 434.1135. **Chiral HPLC** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 220 nm, t (minor) = 9.703, t (major) = 15.158 min]. **Specific rotation**: $[\alpha]_D^{20}$ = −72 ° (c = 0.18, EtOH).



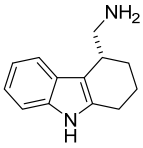
pentacyclic pyrroloindoline 11b: To a solution of 1-pyrroline (–)-**2b** (29 mg, 0.20 mmol, 1.0 equiv) in toluene (2.5 mL) were added phenylhydrazine hydrochloride (31 mg, 0.21 mmol, 1.05 equiv) and pyridinium *p*-toluenesulfonic acid (52 mg, 0.20, 1.0 equiv). The reaction mixture was stirred for 5 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in methanol (3 mL), washed with sat. aq. Na_2CO_3 (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved DCM (2.5 mL), after which Et_3N (34 µL, 0.25 mmol, 1.2 equiv) and *o*-nosyl chloride (55 mg, 0.25 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 2 h at rt, washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was impregnated on SiO_2 and purified by flash chromatography (SiO_2) with an eluent gradient (6:100 → 10:100 v/v acetone/*c*Hex), to obtain compound **11b** (51 mg, 0.12 mmol, 57%) as a light yellow oil. $\mathbf{R_f}$ = 0.53 (cHex:acetone 2:1 v/v). **m.p.:** 154 – 160 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 1H, $C(NO_2)CH$), 7.78 – 7.70 (m, 2H, $C(NO_2)C^*CHCHCH$), 7.69 – 7.63 (m, 1H, SO_2C^*CH), 7.23 (d, *J* = 7.5 Hz, 1H, NHC^*C^*CH), 7.04 (t, *J* = 7.6 Hz, 1H, NHC^*CHCH), 6.75 (t, *J* = 7.5 Hz, 1H, NHC^*C^*CHCH), 6.50 (d, *J* = 7.8 Hz, 1H, NHC^*CH), 5.95 (d, *J* = 2.4 Hz, 1H, NHCHN), 4.83 (s, 1H, NH), 3.73 (d, *J* = 10.1 Hz, 1H, NCH_2), 3.46 (dd, *J* = 10.0, 7.7 Hz, 1H, NCH_2), 2.59 – 2.54 (m, 1H, C^*CHCH_2CH), 2.49 – 2.44 (m, 1H, NCH_2CH), 2.43 – 2.39 (m, 1H, C^*CHCH_2CH), 2.17 (d, *J* = 9.9 Hz, 1H, C^*CHCH_2CH), 1.79 – 1.68 (m, 2H, C^*CHCH_2CH, CH_2CH_2), 1.64 – 1.55 (m, 1H, CH_2CH_2), 1.50 – 1.35 (m, 2H, CH_2CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.5 (C*), 148.2 (C*), 134.2 (C*), 133.7 (CH), 133.0 (C*), 131.9 (CH), 130.4 (CH), 128.1 (CH), 124.2 (CH), 122.8 (CH), 119.5 (CH), 109.1 (CH), 81.8 (CH), 64.2 (C*), 55.4 (CH), 47.5 (CH_2), 47.1 (CH), 42.7 (CH_2), 41.4 (CH), 24.0 (CH_2), 21.8 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2957 (w), 1541 (s), 1350 (s), 1168 (m), 1153 (m), 1128 (m), 1041 (m), 1026 (m), 989 (m), 734 (s), 605 (s), 569 (m). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{22}N_3O_4S$ $[M+H]^+$: 412.1326, found: 412.1321. **Chiral HPLC** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 210 nm, t (minor) = 29.300, t (major) = 46.092 min]. **Specific rotation**: $[\alpha]_D^{20}$ = −49.0 ° (c = 0.5, $CDCl_3$).



pyrroloindoline 11c: To a solution of 1-pyrroline (–)-**2a** (450 mg, 4.12 mmol, 1.0 equiv) in toluene (10 mL) were added phenylhydrazine hydrochloride (631 mg, 4.32 mmol, 1.05 equiv) and TFA (52 mg, 3.18 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in methanol (5 mL), washed with sat. aq.

Na_2CO_3 (50 mL), extracted with DCM (3 x 35 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved DCM (2.5 mL), after which Et_3N (692 µL, 4.94 mmol, 1.2 equiv) and *o*-nosyl chloride (1115 mg, 4.94 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 2 h at rt, washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was impregnated on SiO_2 and purified by flash chromatography with an eluent gradient (6:100 → 12:100 v/v acetone:*c*Hex), to obtain compound **11c** (1022 mg, 2.65 mmol, 64%) as a yellow oil. $\mathbf{R_f}$ = 0.21 (cHex:EtOAc 4:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 1H, C(NO_2)C*H*), 7.74 – 7.63 (m, 3H, C(SO_2)C*H*C*H*C*H*), 7.05 (t, *J* = 6.5 Hz, 2H, NHC*C*C*H*CHC*H*), 6.76 (t, *J* = 7.4 Hz, 1H, NHC*CHC*H*), 6.55 (d, *J* = 8.0 Hz, 1H, NHC*C*H*), 5.53 (s, 1H, NHC*H*N), 4.89 (s, 1H, N*H*), 3.48 (dd, *J* = 9.9, 6.4 Hz, 1H, NCH_2), 3.41 (d, *J* = 10.1 Hz, 1H, NCH_2), 2.64 – 2.56 (m, 1H, NCH_2C*H*), 2.11 – 2.01 (m, 3H, CHCH_2CH_2CH_2), 1.81 (q, *J* = 6.9 Hz, 2H, CHCH_2CH_2), 1.52 – 1.41 (m, 1H, CHCH_2CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7 (C*), 148.2 (2 x C*), 133.7 (CH), 133.0 (C*), 131.9 (CH), 130.7 (CH), 128.3 (CH), 124.3 (CH), 122.6 (CH), 119.5 (CH), 109.0 (CH), 85.9 (CH), 65.6 (C*), 52.6 (CH_2), 52.5 (CH), 40.1 (CH_2), 33.1 (CH_2), 26.8 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2947 (w), 2866 (w), 1541 (s), 1344 (m), 1164 (m), 1029 (m), 850 (m), 739 (s), 729 (s), 600 (m), 569 (m). **HRMS** (ESI): *m/z* calculated for $C_{19}H_{20}N_3O_4S$ $[M+H]^+$: 386.1169, found: 386.1159. **Chiral HPLC** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 80/20, v = 0.9 mL/min, column temperature: 30 °C, λ = 210 nm, t (minor) = 27.055, t (major) = 38.032 min]. **Specific rotation**: $[\alpha]_D^{20}$ = −82 ° (c = 1.15, EtOH).

Synthesis of constrained tryptamines

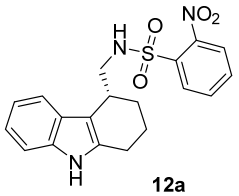


constrained tryptamine 8a: To a solution of 1-pyrroline **2a** (30 mg, 0.25 mmol, 1.0 equiv) in toluene (0.1 M) were added phenylhydrazine hydrochloride (38 g, 0.26 mmol, 1.05 equiv) and *p*-toluenesulfonic acid monohydrate (71 mg, 0.38 mmol, 1.5 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (Al_2O_3 basic) with an eluent gradient (100:1 → 10:1 v/v DCM:MeOH), to obtain compound **8a** (20 mg, 0.10 mmol, 40%)[40] as a yellow solid. $\mathbf{R_f}$ = 0.05 (DCM:MeOH 100:1 v/v). **m.p.:** 62.0 – 72.5 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.83 (s, 1H, N*H*), 7.57 (d, *J* = 7.7 Hz, 1H, NHC*C*C*H*), 7.29 (d, *J* = 8.0 Hz, 1H, NHC*C*H*), 7.11 (t, *J* = 7.1 Hz, 1H, NHC*CHC*H*), 7.07 (t, *J* = 7.4 Hz, 1H, NHC*C*CHC*H*), 3.17 (dd, *J* = 12.5, 3.9 Hz, 1H, NH_2CH_2), 3.11 – 3.04 (m, 1H, NH_2CH_2C*H*), 2.99 (dd, *J* = 12.5, 7.9 Hz, 1H, NH_2CH_2), 2.75 – 2.70 (m, 2H, NHC*CH_2), 2.07 – 1.69 (m, 6H, NH_2, NHC*CH_2CH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 135.8 (C*), 135.3 (C*), 127.5 (C*), 121.1 (CH), 119.4 (CH), 118.6 (CH), 111.2 (C*), 110.7 (CH), 46.1 (CH_2), 35.9 (CH), 26.5 (CH_2), 23.5 (CH_2), 20.2 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2922 (m), 2862 (m), 1618 (w), 1580 (w), 1452 (m), 1325 (m), 1261 (w), 1234 (w), 1012 (w), 912 (w), 808 (w), 735 (s). **HRMS** (ESI): *m/z* calculated for $C_{13}H_{14}N$ $[M+H-NH_3]^+$: 184.1121, found: 184.1117.

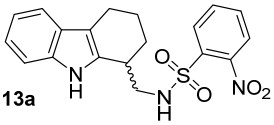
General procedure 3: To a solution of 1-pyrroline **2a** (1.0 equiv) in toluene (0.1 M) were added the hydrazine hydrochloride **10** (1.05 equiv) and *p*-toluenesulfonic acid monohydrate (1.5 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in MeOH (3 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved DCM (0.1 M), after which Et_3N (1.2 equiv) and *o*-nosyl chloride (1.2 equiv) were added. The reaction mixture was stirred for 2 h at rt,

washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was impregnated on SiO_2 and purified by flash chromatography.

General procedure 4: To a solution of 1-pyrroline **2a** (1.0 equiv) in toluene (0.1 M) were added the hydrazine **10** (1.05 equiv) and *p*-toluenesulfonic acid monohydrate (2.5 equiv). The reaction was proceeded as described in *general procedure 3*.

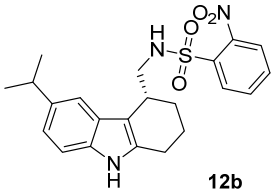


12a

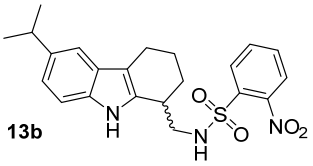


13a

tricyclic tryptamine 12a and 13a: Prepared from 1-pyrroline (–)-**2a** (61 mg, 0.56 mmol, 1.0 equiv) and phenylhydrazine hydrochloride (85 mg, 0.59 mmol, 1.05 equiv) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (10:100 → 20:100 v/v acetone:*c*Hex), to obtain a mixture of compounds **12a** and **13a** (175 mg, 0.45 mmol, 81%) in a 4:1 ratio as determined by NMR analysis of the crude mixture. Pure fractions of both compound **12a** (major), a light yellow solid, and compound **13a** (minor), a yellow oil, were used for full identification. **12a:** $\mathbf{R_f}$ = 0.31 (*c*Hex:acetone 2:1 v/v). **m.p.:** 79 – 82 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.1, 1.9 Hz, 1H, C(NO_2)C*H*), 7.84 (s, 1H, C*N*H), 7.75 – 7.64 (m, 3H, C(NO_2)CHC*H*C*H*C*H*), 7.29 – 7.17 (m, 2H, NHC*C*H*CHCHC*H*), 7.05 (t, *J* = 7.6 Hz, 1H, NHC*CHC*H*), 6.86 (t, *J* = 7.5 Hz, 1H, NHC*C*CHC*H*), 5.39 – 5.34 (m, 1H, N*H*CH_2), 3.60 – 3.52 (m, 1H, NHCH_2), 3.39 – 3.23 (m, 2H, NHCH_2C*H*), 2.75 – 2.62 (m, 2H, NHC*CH_2), 2.00 – 1.89 (m, 3H, CHCH_2CH_2), 1.86 – 1.76 (m, 1H, CHCH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.7 (C*), 136.4 (C*), 135.8 (C*), 133.5 (CH), 133.3 (C*), 132.8 (CH), 131.1 (CH), 126.6 (C*), 125.7 (CH), 121.2 (CH), 119.5 (CH), 117.6 (CH), 110.9 (CH), 108.4 (C*), 47.1 (CH_2), 32.5 (CH), 26.5 (CH_2), 23.2 (CH_2), 20.2 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2949 (w), 1541 (m), 1489 (m), 1342 (m), 1165 (m), 1126 (m), 1026 (m), 731 (s), 608 (m), 569 (m). **HRMS** (ESI): *m/z* calculated for $C_{19}H_{19}N_3NaO_4S^+$ [M+Na]$^+$: 408.0988, found: 408.0976. **Chiral HPLC:** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 220 nm, t (minor) = 35.787, t (major) = 37.930 min]. **Specific rotation**: $[\alpha]_D^{20}$ = +2 ° (c = 0.5, EtOH). **13a:**[40] $\mathbf{R_f}$ = 0.36 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (s, 1H, C*N*H*), 8.07 (dd, *J* = 7.5, 1.7 Hz, 1H, C(NO_2)C*H*), 7.83 (dd, *J* = 7.6, 1.5 Hz, 1H, C(NO_2)C*C*H*), 7.71 – 7.62 (m, 2H, C(NO_2)CHC*H*C*H*), 7.43 (d, *J* = 7.8 Hz, 1H, NHC*C*C*H*), 7.30 (d, *J* = 8.0 Hz, 1H, NHC*C*H*CH), 7.14 (t, *J* = 7.5 Hz, 1H, NHC*CHC*H*), 7.07 (t, *J* = 7.1 Hz, 1H, NHC*C*CHC*H*), 5.66 (t, *J* = 6.3 Hz, 1H, N*H*CH_2), 3.40 – 3.27 (m, 2H, NHC*H*$_2$), 3.19 – 3.11 (m, 1H, NHCH_2C*H*), 2.74 – 2.56 (m, 2H, NHC*C*C*H*$_2$), 2.02 – 1.85 (m, 2H, CHC*H*$_2$C*H*$_2$), 1.83 – 1.73 (m, 1H, CHCH_2C*H*$_2$), 1.70 – 1.60 (m, 1H, CHC*H*$_2$CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.0 (C*), 136.0 (C*), 133.8 (CH), 133.7 (C*), 133.2 (C*), 133.0 (CH), 131.1 (CH), 127.2 (C*), 125.5 (CH), 121.9 (CH), 119.4 (CH), 118.2 (CH), 111.7 (C*), 111.1 (CH), 48.3 (CH_2), 34.4 (CH), 27.3 (CH_2), 21.2 (CH_2), 21.0 (CH_2) ppm. **HRMS** (ESI): *m/z* calculated for $C_{19}H_{19}BrN_3O_4S$ [M+H]$^+$: 408.0988, found: 408.0975. **Chiral HPLC:** *rac* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 220 nm, t = 25.789, 31.172 min].



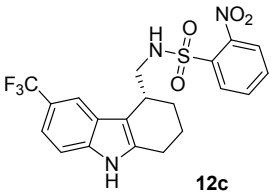
12b



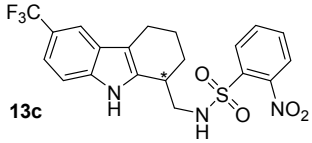
13b

tricyclic tryptamine 12b and 13b: Prepared from 1-pyrroline (–)-**2a** (30 mg, 0.27 mmol, 1.0 equiv) and 4-isopropylphenylhydrazine hydrochloride (55 mg, 0.29 mmol,

1.05 equiv) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (10:100 → 15:100 v/v acetone:*c*Hex), to obtain a mixture of compounds **12b** and **13b** (94 mg, 0.22 mmol, 80%) in a 4:1 ratio as determined by NMR analysis of the crude mixture. Pure fractions of both compound **12b** (major), as a grey solid, and compound **13b** (minor), as light yellow foam, were used for full identification. **12b: R_f** = 0.29 (*c*Hex:acetone 2:1 v/v). **m.p.:** >118 °C (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 5.9, 3.3 Hz, 1H, C(NO_2)C*H*), 7.79 (dd, *J* = 5.9, 3.3 Hz, 1H, C(NO_2)C*C*H), 7.72 (s, 1H, C*NH), 7.67 (dd, *J* = 5.9, 3.4 Hz, 2H, C(NO_2)CHC*HCH*), 7.20 (m, 2H, C*H*CHC(*i*Pr)C*H*), 7.00 (d, *J* = 8.3 Hz, 1H, NHC*CHC*H*), 5.46 – 5.40 (m, 1H, N*H*CH_2), 3.62 – 3.53 (m, 1H, NHCH_2), 3.34 – 3.21 (m, 2H, NHCH_2C*H*), 2.91 (hept, *J* = 6.9 Hz, 1H, CH_3C*H*CH_3), 2.73 – 2.59 (m, 2H, NHC*CH_2), 1.98 – 1.86 (m, 3H, CHCH_2CH_2), 1.86 – 1.74 (m, 1H, CHCH_2CH_2), 1.26 (dd, *J* = 14.2, 6.9 Hz, 6H, CH_3CHCH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.9 (C*), 140.2 (C*), 136.2 (C*), 134.3 (C*), 133.7 (C*), 133.5 (CH), 132.8 (CH), 131.2 (CH), 126.8 (C*), 125.5 (CH), 120.4 (CH), 114.9 (CH), 110.6 (CH), 108.7 (C*), 47.2 (CH_2), 34.3 (CH), 32.7 (CH), 26.2 (CH_2), 24.9 (CH_3), 24.7 (CH_3), 23.2 (CH_2), 19.8 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2957 (w), 1535 (m), 1491 (m), 1342 (m), 1161 (s), 1124 (m), 731 (m), 694 (m), 652 (m), 582 (m), 571 (m). **HRMS** (ESI): *m/z* calculated for $C_{22}H_{25}N_3O_4S^+$ $[M+H]^+$: 450.1458, found: 450.1457. **Chiral HPLC:** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 88/12, v = 0.9 mL/min, column temperature: 30 °C, λ = 220 nm, t (major) = 34.608 min, t (minor) = 44.359]. **Specific rotation**: $[\alpha]_D^{20}$ = −23 ° (c = 2.5, EtOH). **13b:**[40] **R_f** = 0.34 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 – 8.02 (m, 2H, C*NH, C(NO_2)C*H*), 7.84 (dd, *J* = 7.6, 1.5 Hz, 1H, C(NO_2)C*C*H), 7.74 – 7.61 (m, 2H, C(NO_2)CHC*HCH*), 7.23 (d, *J* = 8.3 Hz, 2H, C*H*CHC(*i*Pr)C*H*), 7.05 (d, *J* = 8.3 Hz, 1H, C(*i*Pr)C*H*CH), 5.62 (t, *J* = 6.3 Hz, 1H, N*H*CH_2), 3.39 – 3.29 (m, 2H, NHCH_2), 3.22 – 3.08 (m, 1H, NHCH_2C*H*), 3.06 – 2.90 (m, 1H, CH_3C*H*CH_3), 2.77 – 2.56 (m, 1H, NHC*C*CH_2), 2.04 – 1.84 (m, 2H, CHCH_2CH_2), 1.83 – 1.71 (m, 1H, CHCH_2CH_2), 1.69 – 1.59 (m, 1H, CHCH_2CH_2), 1.30 (d, *J* = 6.9 Hz, 6H, CH_3CHCH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.0 (C*), 140.3 (C*), 134.6 (C*), 133.9 (C*), 133.8 (CH), 133.3 (C*), 133.0 (CH), 131.1 (CH), 127.3 (C*), 125.5 (CH), 121.1 (CH), 115.1 (CH), 111.6 (C*), 110.8 (CH), 48.3 (CH_2), 34.5 (CH), 34.4 (CH), 27.4 (CH_2), 24.92 (CH_3), 24.91 (CH_3), 21.2 (CH_2), 21.1 (CH_2) ppm. **HRMS** (ESI): *m/z* calculated for $C_{22}H_{25}N_3O_4S^+$ $[M+H]^+$: 450.1458, found: 450.1457. **Chiral HPLC:** *rac* [Dr. Maisch Chiral AM, heptane/2-propanol = 88/12, v = 0.9 mL/min, column temperature: 30 °C, λ = 275 nm, t = 30.697, 41.988 min].



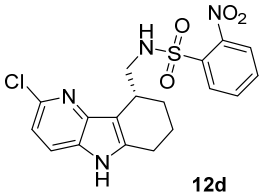
12c



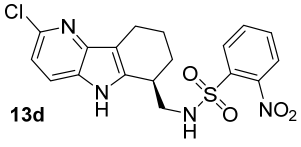
13c

tricyclic tryptamine 12c and 13c: Prepared from 1-pyrroline (–)-**2a** (59 mg, 0.55 mmol) and 4-(trifluoromethyl)phenylhydrazine (105 mg, 0.57 mmol, 1.05 equiv) according to *general procedure 4*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (10:100 → 22.5:100 v/v acetone:*c*Hex), to obtain a mixture of compounds **12c** and **13c** (145 mg, 0.32 mmol, 59%) in a 4:1 ratio as determined by NMR analysis of the crude mixture. Pure fractions of both compound **12c** (major), a light yellow foamy oil, and compound **13c** (minor), a yellow oil, were used for full identification. **12c: R_f** = 0.32 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.1 Hz, 1H, C(NO_2)C*H*), 8.02 (s, 1H, C*NH), 7.75 – 7.65 (m, 3H, C(NO_2)C*CHCHCH*), 7.43 (s, 1H, C(CF_3)C*HC*), 7.34 – 7.28 (m, 2H, NHC*C*HCH*), 5.31 – 5.26 (m, 1H, N*H*CH_2), 3.57 – 3.48 (m, 1H, NHCH_2), 3.40 – 3.30 (m, 2H, NHCH_2C*H*), 2.82 – 2.67 (m, 2H, NHC*CH_2), 2.08 – 1.95 (m, 3H, CHCH_2CH_2), 1.91 – 1.81 (m, 1H, CHCH_2CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.7 (C*), 138.6 (C*), 137.3 (C*), 133.9 (CH), 132.9 (CH), 132.8 (C*), 131.3 (CH), 126.0 (C*), 125.7 (CH), 125.3 (C*, q, *J* = 277 Hz), 121.6 (C*, q, *J* = 38 Hz),

118.3 (CH), 115.2 (CH), 111.0 (CH), 109.4 (C*), 47.0 (CH_2), 32.3 (CH), 26.4 (CH_2), 23.2 (CH_2), 20.2 (CH_2) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): δ -60.03 ppm. **IR** (neat): ν_{max} (cm^{-1}) = 1533 (s), 1362 (m), 1319 (m), 1161 (m), 1124 (m), 1103 (m), 1051 (m), 740 (m), 586 (m), 507 (m). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{18}F_3N_3NaO_4S$ $[M+Na]^+$: 476.0862, found: 476.0860. **Chiral HPLC:** *enantiopure*[44] [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 285 nm, t (major) = 19.060 min]. **Specific rotation**: $[\alpha]_D^{20}$ = −3 ° (c = 1.27, EtOH). **13c: R_f** = 0.37 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (s, 1H, C*N*H*), 8.07 (dd, *J* = 7.4, 1.7 Hz, 1H, C(NO_2)C*H*), 7.84 (dd, *J* = 7.4, 1.7 Hz, 1H, C(NO_2)C*C*H*), 7.72 – 7.64 (m, 3H, C(NO_2)CHC*HCH*, NHC*CHC*H*), 7.36 (s, 2H, C*H*CHC(CF_3)C*H*), 5.75 (s, 1H, N*H*CH_2), 3.40 – 3.29 (m, 2H, NHC*H*$_2$), 3.23 – 3.14 (m, 1H, NHCH_2C*H*), 2.76 – 2.60 (m, 2H, NHC*C*C*H*$_2$), 2.05 – 1.87 (m, 2H, CHC*H*$_2$C*H*$_2$), 1.84 – 1.74 (m, 1H, CHCH_2C*H*$_2$), 1.69 – 1.60 (m, 1H, CHC*H*$_2$$CH_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.9 (C*), 137.4 (C*), 135.8 (C*), 134.0 (CH), 133.1 (CH), 133.0 (C*), 126.6 (CH), 125.6 (C*, q, *J* = 272 Hz), 125.6 (CH), 121.7 (C*, q, *J* = 32 Hz), 118.5 (CH), 116.0 (CH), 112.5 (C*), 111.2 (CH), 48.2 (CH_2), 34.5 (CH), 27.3 (CH_2), 21.1 (CH_2), 20.8 (CH_2). **^{19}F NMR** (235 MHz, $CDCl_3$): δ -60.15 ppm. **IR** (neat): ν_{max} (cm^{-1}) = 1541 (s), 1361 (m), 1323 (m), 1161 (m), 1124 (m), 1101 (m), 1047 (m), 740 (m), 654 (m), 586 (m), 507 (m). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{18}F_3N_3NaO_4S$ $[M+Na]^+$: 476.0862, found: 476.0860. **Chiral HPLC:** ±13% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 88/12, v = 0.8 mL/min, column temperature: 30 °C, λ = 225 nm, t (minor) = 32.682 min, t (major) = 35.450 min].



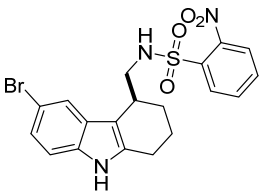
12d



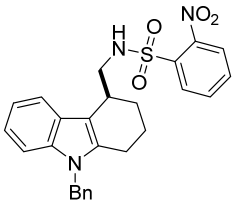
13d

tricyclic azaindole 12d and 13d: Prepared from 1-pyrroline (–)-**2a** (52 mg, 0.48 mmol) and 2-chloro-5-hydrazinylpyridine (76 mg, 0.50 mmol, 1.05 equiv) according to *general procedure 4* with the following adjustments: *p*-toluenesulfonic acid monohydrate (3.5 equiv), 1 h, 150°C. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (17.5:100 → 27.5:100 v/v acetone:*c*Hex), to obtain a mixture of compounds **12d** and **13d** (122 mg, 0.29 mmol, 61%) in a 5:1 ratio as determined by NMR analysis of the crude mixture. Pure fractions of both compound **12d** (major), as a light brown foamy oil, and compound **13d** (minor), as a light brown foam, were used for full identification. **12d: R_f =** 0.23 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H, C*N*H*), 8.22 – 8.13 (m, 1H, C(NO_2)C*H*), 7.97 – 7.89 (m, 1H, N*H*CH_2), 7.73 – 7.62 (m, 3H, C(NO_2)CHC*HCHCH*), 7.50 (d, *J* = 8.4 Hz, 1H, NHC*C*H*), 6.94 (d, *J* = 8.4 Hz, 1H, NHC*CHC*H*), 3.63 (m, 1H, NHC*H*$_2$), 3.24 (m, 1H, NHC*H*$_2$), 3.17 – 3.09 (m, 1H, NHCH_2C*H*), 2.76 – 2.67 (m, 2H, NHC*C*H*$_2$), 2.06 – 1.94 (m, 2H, CHC*H*$_2$C*H*$_2$), 1.80 – 1.70 (m, 1H, CHCH_2C*H*$_2$), 1.65 – 1.52 (m, 1H, CHC*H*$_2$$CH_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1 (C*), 144.5 (C*), 142.9 (C*), 141.7 (C*), 134.0 (C*), 133.3 (CH), 132.5 (CH), 131.0 (CH), 127.4 (C*), 124.9 (CH), 120.3 (CH), 116.0 (CH), 110.8 (C*), 48.1 (CH_2), 33.8 (CH), 27.5 (CH_2), 23.63 (CH_2), 21.6 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2939 (w), 1541 (s), 1398 (w), 1361 (w), 1339 (w), 1163 (m), 1043 (w), 741 (m), 656 (m), 586 (m), 507 (m). **HRMS** (ESI): *m/z* calculated for $C_{18}H_{17}ClN_4NaO_4S$ $[M+H]^+$: 443.0551, found: 443.0546. **Chiral HPLC:** n.d. [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, λ = 225 nm, t (major) = 27.787 min, t (minor) = 28.739 min]. **Chiral SFC**: 98% ee [Daicel Chiralpak ID-3 SFC, CO_2/MeOH = gradient, v = 1.2 mL/min, column temperature: 40 °C, t (minor) = 5.517 min, t (major) = and 5.628 min]. **Specific rotation**: $[\alpha]_D^{20}$ = + 19 ° (c = 0.53, EtOH). **13d: R_f** = 0.27 (*c*Hex:acetone 2:1 v/v). **m.p.:** >197 °C (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.78 (s, 1H, C*N*H*), 8.09 (dd, *J* = 7.5, 1.5 Hz, 1H, C(NO_2)C*H*), 7.87 (dd, 1H, C(NO_2)C*C*H*), 7.78 – 7.68 (m, 2H, C(NO_2)CHC*HCH*), 7.53 (d, *J* = 8.4 Hz, 1H,

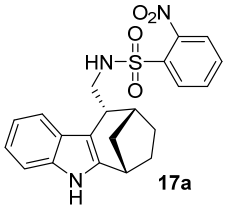
NHC*C*HCH), 7.04 (d, *J* = 8.4 Hz, 1H, NHC*CHC*H*), 5.80 (dd, 1H, N*H*CH$_2$), 3.40 – 3.27 (m, 2H, NHC*H*$_2$), 3.25 – 3.17 (m, 1H, NHCH$_2$C*H*), 2.87 – 2.78 (m, 1H, NHC*C*C*H*$_2$), 2.76 – 2.66 (m, 1H, NHC*C*C*H*$_2$), 2.04 – 1.85 (m, 2H, CHC*H*$_2$C*H*$_2$), 1.81 – 1.71 (m, 1H, CHCH$_2$C*H*$_2$), 1.65 – 1.57 (m, 1H, CHC*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1 (C*), 144.7 (C*), 143.7 (C*), 139.6 (C*), 134.2 (CH), 133.2 (CH), 132.8 (C*), 131.3 (CH), 127.7 (C*), 125.7 (CH), 120.6 (CH), 116.4 (CH), 112.0 (C*), 48.2 (CH_2), 34.8 (CH), 27.4(CH_2), 21.1(CH_2), 20.1(CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2941 (w), 1533 (s), 1340 (m), 1163 (s), 729 (s), 654 (m), 586 (m), 569 (m), 420 (w). **HRMS** (ESI): *m/z* calculated for $C_{18}H_{17}N_4NaO_4S$ $[M+Na]^+$: 443.0551, found: 443.0531. **Chiral HPLC:** 98% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, column temperature: 30 °C, λ = 225 nm, t (major) = 30.934 min, t (minor) = 38.702 min]. **Specific rotation**: $[\alpha]_D^{20} = -7$ ° (c = 0.73, $CHCl_3$).

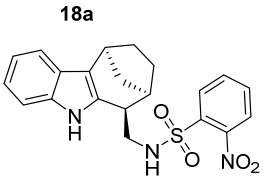


tricyclic tryptamine 12e: Prepared from 1-pyrroline (±)-**2a** (62 mg, 0.57 mmol, 1.0 eq) and 4-bromophenylhydrazine hydrochloride (135 mg, 0.60 mmol, 1.05 eq) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (12:100 → 20:100 v/v acetone:*c*Hex), to obtain compound **12e** (143 mg [1.1% acetone], 0.30 mmol, 53%) as a yellow-brown oil. $\mathbf{R_f}$ = 0.32 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.5 Hz, 1H, C(NO_2)C*H*), 7.99 (s, 1H, C*N*H*), 7.79 – 7.69 (m, 3H, C(NO_2)CHC*HCHCH*), 7.18 (s, 1H, C(Br)C*H*), 7.12 – 7.05 (m, 2H, C(Br)C*HCH*), 5.31 – 5.25 (m, 1H, N*H*CH$_2$), 3.53 – 3.43 (m, 1H, NHC*H*$_2$), 3.36 – 3.27 (m, 1H, NHC*H*$_2$), 3.26 – 3.18 (m, 1H, NHCH$_2$C*H*), 2.76 – 2.60 (m, 2H, NHC*C*H*$_2$), 2.03 – 1.88 (m, 3H, CHC*H*$_2$C*H*$_2$), 1.84 – 1.75 (m, 1H, CHCH$_2$C*H*$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.5 (C*), 138.3 (C*), 134.5 (C*), 134.1 (CH), 132.9 (CH), 132.6 (C*), 131.2 (CH), 128.2 (C*), 125.8 (CH), 123.9 (CH), 120.1 (CH), 112.5 (C*), 112.3 (CH), 107.9 (C*), 47.0 (CH_2), 32.1 (CH), 26.5 (CH_2), 23.1 (CH_2), 20.3 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2927 (w), 1535 (s), 1439 (m), 1339 (m), 1161 (s), 1047 (m), 852 (m), 781 (m), 731 (s), 584 (s). **HRMS** (ESI): *m/z* calculated for $C_{19}H_{18}BrN_3NaO_4S$ $[M+Na]^+$: 486.0094, found: 486.0091.

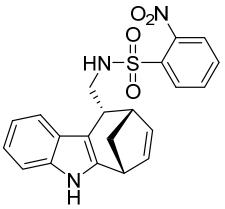


tricyclic *N*-benzyltryptamine 12f: Prepared from 1-pyrroline (±)-**2a** (31 mg, 0.28 mmol, 1.0 equiv) and 1-benzyl-1-phenylhydrazine hydrochloride (71 mg, 0.30 mmol, 1.05 eq) according to *general procedure 3*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (12:100 → 20:100 v/v acetone:*c*Hex), to obtain compound **12f** (72 mg, 0.15 mmol 54%) a yellow oil and debenzylated **12a** (17 mg, 0.04 mmol, 16%) as a light yellow solid. $\mathbf{R_f}$ = 0.38 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.0 Hz, 1H, C(NO_2)C*H*), 7.76 – 7.63 (m, 3H, C(NO_2)CHC*HCHCH*), 7.30 – 7.14 (m, 5H, NC*C*HCHCHC*H*, CH$_2$C*CHC*HCHCH*), 7.04 (t, *J* = 7.6 Hz, 1H, NHC*CHC*H*), 6.97 (d, *J* = 7.4 Hz, 2H, CH$_2$C*C*H*), 6.88 (t, *J* = 7.5 Hz, 1H, NHC*C*CHC*H*), 5.43 – 5.35 (d, *J* = 5.2 Hz, 1H, N*H*CH$_2$), 5.22 (s, 2H, NC*H*$_2$C*), 3.64 – 3.53 (m, 1H, NHC*H*$_2$), 3.42 – 3.27 (m, 2H, NHC*H*$_2$C*H*), 2.66 – 2.50 (m, 2H, NC*C*H*$_2$), 1.99 – 1.77 (m, 4H, CHC*H*$_2$C*H*$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.8 (C*), 137.8 (C*), 136.9 (C*), 133.5 (CH), 133.5 (C*), 132.8 (CH), 131.2 (CH), 128.9 (CH), 127.4 (CH), 126.3 (C*), 126.2 (CH), 125.7 (CH), 121.1 (CH), 119.3 (CH), 117.7 (CH), 109.5 (CH), 108.3 (C*), 47.1 (CH_2), 46.4 (CH_2), 32.8 (CH), 26.2 (CH_2), 22.1 (CH_2), 20.0 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 2949 (w), 1541 (m), 1342 (m), 1164 (m), 1124 (m), 1026 (m), 729 (s), 606 (m), 569 (m). **HRMS** (ESI): *m/z* calculated for $C_{26}H_{25}N_3NaO_4S$ $[M+H]^+$: 498.1458, found: 498.1439.



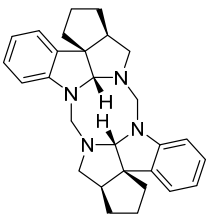


tetracyclic tryptamine 17a and 18a: To a solution of 1-pyrroline (–)-**2b** (80 mg, 0.47 mmol, 1.0 equiv) in toluene (5 mL) were added phenylhydrazine hydrochloride **10b** (72 mg, 0.50 mmol, 1.05 equiv) and pyridinium *p*-toluenesulfonic acid (121 mg, 0.47 mmol, 1.0 equiv). The reaction mixture was stirred for 3 h at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in methanol (3 mL), washed with sat. aq. Na_2CO_3 (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved DCM (5 mL), after which Et_3N (79 µL, 0.57 mmol, 1.2 equiv) and *o*-nosyl chloride (128 mg, 0.57 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 2 h at rt, washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was impregnated on SiO_2 and purified by flash chromatography with an eluent gradient (10:100 → 15:100 v/v acetone:*c*Hex), to obtain a mixture of the compounds **17a** and **18a** (137 mg, 0.33 mmol, 70%) as a 1:4 ratio as determined by NMR analysis of the crude mixture. Pure fractions of both compound **17a** (major), a foamy orange oil, and compound **18a** (minor), a red oil, were used for full identification. **17a: R_f** = 0.33 (cHex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 5.9, 3.3 Hz, 1H, C(NO_2)C*H*), 7.88 (dd, *J* = 5.8, 3.4 Hz, 1H, C(NO_2)C*C*H), 7.82 (s, 1H, C*NH*) 7.74 (dd, *J* = 5.8, 3.4 Hz, 2H, C(NO_2)CHC*HCH*), 7.36 (d, *J* = 7.8 Hz, 1H, NHC*CHCHCHC*H*), 7.28 (d, *J* = 8.1 Hz, 1H, NHC*C*H*CH), 7.08 (t, *J* = 7.1 Hz, 1H, NHC*CHC*H*), 7.01 (t, *J* = 7.5 Hz, 1H, NHC*CHCHC*H*), 5.50 (t, 1H, N*H*CH_2, 4.13 – 4.02 (m, 1H, NHCH_2), 3.52 – 3.41 (m, 1H, NHCH_2C*H*), 3.20 – 3.09 (m, 1H, NHCH_2), 3.05 (s, 1H, NHCH_2CHC*C*C*H*), 2.77 – 2.72 (m, 1H, NHCH_2CHC*H*), 1.96 – 1.83 (m, 3H, CH_2CH_2), 1.79 (t, *J* = 10.0 Hz, 1H, CHCHCH_2CH_2), 1.71 – 1.54 (m, 2H, CHCHCH_2CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.2 (C*), 142.5 (C*), 135.4 (C*), 133.7 (C*), 133.7 (CH), 133.0 (CH), 131.4 (CH), 126.9 (C*), 125.6 (CH), 120.8 (CH), 119.7 (CH), 118.8 (CH), 111.2 (CH), 104.8 (C*), 44.4 (CH_2), 40.6 (CH), 38.1 (CH_2), 35.9 (CH), 35.3 (CH), 34.5 (CH_2), 22.0 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 1533 (s), 1418 (m), 1362 (m), 1339 (m), 1161 (m), 739 (m), 725 (m), 581 (m). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{21}N_3NaO_4S$ $[M+Na]^+$: 434.1145, found: 434.1140. **Chiral SFC**: 99% ee [Daicel Chiralpak ID-3 SFC, CO_2/MeOH = gradient, v = 1.2 mL/min, column temperature: 40 °C, t (major) = 5.813 min, t (minor) = and 5.958 min]. **18a: Rf** = 0.36 (cHex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (s, 1H, C*N*H*), 8.20 – 8.14 (m, 1H, C(NO_2)C*H*), 7.94 – 7.87 (m, 1H, C(NO_2)C*C*H*), 7.80 – 7.73 (m, 2H, C(NO_2)CHC*HCH*), 7.50 (d, *J* = 7.6 Hz, 1H, NHC*C*C*H*CH), 7.31 (d, *J* = 8.0 Hz, 1H, NHC*C*H*CHCH), 7.10 (dt, *J* = 20.6, 7.3 Hz, 2H, NHC*CHC*HCH*), 5.70 (d, *J* = 7.4 Hz, 1H, N*H*CH_2), 3.55 – 3.39 (m, 2H, NHCH_2C*H*), 3.33 (s, 1H, NHC*C*C*H*CH_2), 3.15 – 3.07 (m, 1H, NHCH_2), 2.55 (s, 1H, NHCH_2CHC*H*), 1.90 – 1.81 (m, 3H, CH_2CHCH_2CH_2), 1.77 (t, *J* = 10.1 Hz, 1H, CH_2CHCH_2CH_2), 1.71 – 1.62 (m, 1H, CH_2CHCH_2CH_2), 1.51 – 1.44 (m, 1H, CH_2CHCH_2CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.3 (C*), 136.1 (C*), 134.2 (CH), 133.2 (CH), 132.7 (C*), 131.8 (C*), 131.7 (CH), 125.7 (CH), 125.4 (C*), 121.4 (CH), 119.4 (CH), 118.5 (C*), 117.8 (CH), 111.2 (CH), 46.5 (CH_2), 42.1 (CH), 39.2 (CH_2), 37.5 (CH), 34.9 (CH_2), 32.6 (CH), 23.0 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = 1533 (s), 1362 (m), 1331 (m), 1163 (m), 1122 (m), 656 (m), 584 (m). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{21}N_3NaO_4S$ $[M+Na]^+$: 434.1145, found: 434.1142. **Chirality** 99% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, λ = 285 nm, t (minor) = 30.677 min, t (major) = 36.187 min].



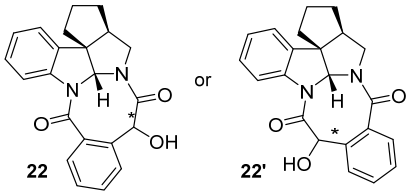
tetracyclic tryptamine 17b: To a solution of 1-pyrroline (+)-**2c** (71 mg, 0.53 mmol, 1.0 equiv) in toluene (5 mL) were added phenylhydrazine hydrochloride (81 mg, 0.56 mmol, 1.05 equiv) and pyridinium *p*-toluenesulfonic acid (136 mg, 0.53 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in methanol (3 mL), washed with sat. aq. Na_2CO_3 (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved DCM (5 mL), after which Et_3N (88 µL, 0.64 mmol, 1.2 equiv) and *o*-nosyl chloride (144 mg, 0.64 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 2 h at rt, washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was impregnated on SiO_2 and purified by flash chromatography (SiO_2) with an eluent gradient (10:100 → 15:100 v/v acetone:*c*Hex), to obtain a mixture of the compound **17b** (74 mg, 0.18 mmol, 34%) as a brown oil. $\mathbf{R_f}$ = 0.29 (cHex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 1H, C(NO_2)C*H*), 7.94 (bs, 1H, N*H*C*) 7.83 – 7.78 (m, 1H, C(NO_2)C*C*H*), 7.74 – 7.69 (m, 2H, C(NO_2)CHC*HCH*), 7.28 – 7.23 (m, 1H, NHCH_2CHC*C*CHCHCHC*H*), 7.15 (d, *J* = 7.9, 1H, NHCH_2CHC*C*C*H*), 7.01 (t, *J* = 8.1 Hz, 1H, NHCH_2CHC*C*CHCHC*H*), 6.86 (t, *J* = 7.9 Hz, 1H, NHCH_2CHC*C*CHC*H*), 6.49 (dd, *J* = 5.7, 2.9 Hz, 1H, NHC*CHC*H*=CH), 5.90 (dd, *J* = 5.6, 2.9 Hz, 1H, NHC*CHCH=C*H*), 5.49 – 5.44 (m, 1H, N*H*CH_2), 3.81 – 3.73 (m, 1H, NHC*H*$_2$), 3.49 – 3.42 (m, 1H, NHCH_2C*H*), 3.38 – 3.34 (m, 1H, NHC*C*H*CH_2), 3.29 – 3.24 (m, 1H, NHCH_2CHC*H*), 3.16 – 3.08 (m, 1H, NHC*H*$_2$), 2.46 – 2.40 (m, 1H, CHC*H*$_2$CH), 2.02 (d, *J* = 9.8 Hz, 1H, CHC*H*$_2$CH) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.0 (C*), 141.6 (CH), 141.2 (C*), 134.6 (C*), 133.7 (CH), 133.5 (C*), 132.9 (CH), 131.4 (CH), 130.7 (CH), 127.5 (C*), 125.8 (CH), 120.5 (CH), 119.8 (CH), 117.7 (CH), 111.2 (CH), 103.5 (C*), 44.4 (CH_2), 44.3 (CH_2), 42.0 (CH), 39.0 (CH), 37.1 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2953 (w), 1535 (s), 1404 (w), 1340 (m), 1163 (s), 852 (m), 743 (s), 729 (s), 652 (m), 582 (s). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{20}N_3O_4S$ $[M+Na]^+$: 410.1169, found: 410.1173. **Chirality** 98% *ee* [Dr. Maisch Chiral AM, heptane/2-propanol = 85/15, v = 0.9 mL/min, λ = 225 nm, t (major) = 33.248 min, t (minor) = 40.842 min]. **Specific rotation**: $[\alpha]_D^{20}$ = +22.5 ° (c = 0.4, EtOH).

Synthesis of pharmaceutically relevant compounds

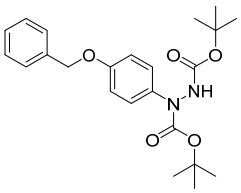


dimeric pyrroloindoline 20: To a solution of pyrroloindoline **6a** (124 mg, 0.60 mmol, 1.0 equiv) in MeOH (3 mL) was added aq. formaldehyde (45 uL [37%], 0.60 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at rt, showing (partial) precipitation of the product after 1 min. The suspension was diluted with DCM (20 mL), washed with sat. aq. Na_2CO_3 (20 mL), extracted with DCM (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient of EtOAc in *c*Hex (10:1 v/v *c*Hex:EtOAc), to obtain compound **20** (108 mg, 0.254 mmol, 84 %) as a white solid. $\mathbf{R_f}$ = 0.59 (*c*Hex:EtOAc 4:1 v/v). **m.p.:** 194 – 196 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 – 6.94 (m, 4H, NC*C*C*H*CHC*H*), 6.66 (t, *J* = 7.3 Hz, 2H, NC*C*CHC*H*), 6.48 (d, *J* = 7.9 Hz, 2H, NC*C*H*), 4.69 (s, 2H, NC*H*N), 4.61 (d, *J* = 15.2 Hz, 2H, NC*H*$_2$N), 4.48 (d, *J* = 15.2 Hz, 2H, NC*H*$_2$N), 3.25 – 3.19 (m, 2H, NC*H*$_2$CH), 2.76 (d, *J* = 8.7 Hz, 2H, NC*H*$_2$CH), 2.31 (q, *J* = 7.4 Hz, 2H, NCH$_2$C*H*), 2.28 – 2.18 (m, 2H, CHCH$_2$CH$_2$C*H*$_2$), 2.18 – 2.05 (m, 2H, NCH$_2$CHC*H*$_2$), 2.02 – 1.71 (m, 6H, CHCH$_2$C*H*$_2$C*H*$_2$), 1.69 – 1.47 (m, 2H, NCH$_2$CHC*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* 152.4 (C*), 136.2 (C*), 127.5 (CH), 121.7 (CH), 117.7 (CH), 105.7 (CH), 98.6 (CH), 67.1 (CH_2), 62.9 (C*), 54.3 (CH), 53.5 (CH_2), 41.5

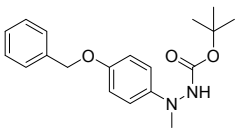
(CH_2), 35.6 (CH_2), 29.0 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (m), 2851 (m), 1603 (m), 1481 (s), 1346 (s), 1273 (s), 1159 (s), 1086 (w), 914 (s), 723 (s), 635 (w), 582 (w). **HRMS** (ESI): *m/z* calculated for $C_{28}H_{33}N_4$ $[M+H]^+$: 425.2700, found: 425.2689. **Specific rotation**: $[\alpha]_D^{20}$ = +57.0 ° (c = 0.5, $CDCl_3$).



bisamide pyrroloindoline 22 or 22': To a solution of pyrroloindoline **6a** (43 mg, 0.21 mmol, 1.0 equiv) in MeOH (3 mL) was added ninihydrin (42 mg, 0.23 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min at rt. The suspension was diluted with DCM (10 mL), washed with sat. aq. Na_2CO_3 (10 mL), extracted with DCM (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient of EtOAc in *c*Hex (10:1 → 4:1 v/v *c*Hex:EtOAc), to obtain compound **22** or **22'** (69 mg, 0.19 mmol, 91 %) as an off-white solid. $\mathbf{R_f}$ = 0.13 (*c*Hex:EtOAc 4:1 v/v). **m.p.:** 77 – 80 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.2 Hz, 1H, NC*C*HCH), 7.74 (d, *J* = 7.8 Hz, 1H, CH(OH)C*C*H), 7.62 – 7.53 (m, 2H, C(O)C*C*HCHCH), 7.44 (t, *J* = 7.5 Hz, 1H, C(O)C*CHCH), 7.31 – 7.23 (m, 1H, NC*CHCH), 7.14 (d, *J* = 7.1 Hz, 2H, NC*C*CHCH), 5.50 – 5.46 (m, 1H, CH(OH)), 5.33 (s, 1H, NCHN), 5.14 (d, *J* = 2.1 Hz, 1H, CH(OH)), 4.36 (dd, *J* = 12.6, 2.1 Hz, 1H, NCH_2), 3.53 (dd, *J* = 12.6, 7.5 Hz, 1H, NCH_2), 2.72 – 2.63 (m, 1H, NCH_2CH), 2.21 – 2.07 (m, 2H, $CHCH_2CH_2$), 1.93 – 1.81 (m, 1H, CHC*CH_2), 1.79 – 1.58 (m, 3H, $CHCH_2CH_2CH_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0 (C*), 168.6 (C*), 141.4 (C*), 135.5 (C*), 135.2 (C*), 134.5 (C*), 131.8 (CH), 129.0 (CH), 128.8 (CH), 126.7 (CH), 126.2 (CH), 125.7 (CH), 122.6 (CH), 116.7 (CH), 86.9 (CH), 70.9 (CH), 64.5 (C*), 52.7 (CH), 50.4 (CH_2), 40.7 (CH_2), 33.9 (CH_2), 27.3 (CH_2). **IR** (neat): ν_{max} (cm^{-1}) = (2947 (w), 2866 (w), 1645 (s), 1479 (m), 1418 (m), 1398 (m), 1350 (m), 1271 (m), 1188 (m), 1084 (m), 1063 (m), 744 (s), 470 (m). **HRMS** (ESI): *m/z* calculated for $C_{22}H_{21}N_2O_3$ $[M+H]^+$: 361.1547, found: 361.1535. **Specific rotation**: $[\alpha]_D^{20}$ = −108.0 ° (c = 0.5, EtOH).

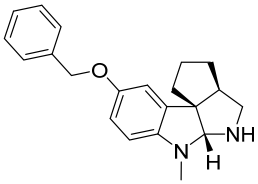


di-N_α,N_β-Boc-protected hydrazine S1: To a solution of di-*tert*-butyl azodicarboxylate (3.36 g, 14.6 mmol, 1.0 equiv) in MeOH (0.4 M) were added 4-(benzyloxy)phenylboronic acid **25** (4.95 g, 21.0 mmol, 1.5 equiv) and copper(II) acetate (217 mg, 1.09 mmol, 0.05 equiv). The reaction mixture was stirred for 4 h at rt. The crude product was impregnated on SiO_2 and purified by flash chromatography (SiO_2) with an eluent gradient (10:100 → 50:100 v/v EtOAc:*c*Hex), to obtain compound **S1** (5.05 g, 12.2 mmol, 83%) as a beige solid. $\mathbf{R_f}$ = 0.43 (*c*Hex:EtOAc 4:1 v/v). **m.p.:** 110 – 118 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 7H, Ph, NC*C*H), 6.92 (d, *J* = 8.9 Hz, 2H, NC*CHCH), 6.78 (s, 1H, NH), 5.05 (s, 2H, OCH_2), 1.49 (s, 18H, $C(CH_3)_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.9 (C*), 155.5 (C*), 154.1 (C*), 137.0 (C*), 135.6 (C*), 128.7 (CH), 128.1 (CH), 127.6 (CH), 114.8 (CH), 82.1 (C*), 81.5 (C*), 70.3 (CH_2), 28.3 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3281 (w), 2981 (w), 1734 (m), 1686 (s), 1510 (m), 1366 (s), 1242 (s), 1153 (s), 1003 (m), 827 (m), 758 (m), 741 (m), 696 (m). **HRMS** (ESI): *m/z* calculated for $C_{23}H_{30}N_2NaO_5$ $[M+Na]^+$: 437.2047, found: 437.2038.

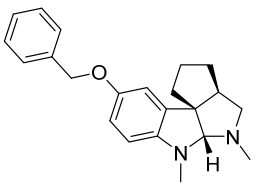


N_β-Boc-N_α-methylhydrazine 26: To a solution of di-N_α,N_β-Boc-protected hydrazine **S1** (1.11 g, 2.69 mmol, 1.0 equiv) in THF[45] (0.25 M) was slowly added $LiAlH_4$ (322 mg, 8.06 mmol, 3 equiv) under inert atmosphere (N_2) at 0°C. The reaction mixture was stirred for 4 h at rt and quenched by the addition of drops of water (stoichiometric). The crude product was filtered over Celite and concentrated *in vacuo* to

obtain compound **26** (870 mg, 2.65 mmol, 99%) as a beige solid. $\mathbf{R_f}$ = 0.43 (*c*Hex:EtOAc 4:1 v/v). **m.p.:** 90 – 94 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.28 (m, 5H, Ph), 6.96 – 6.87 (m, 2H, NC*CHC*H*), 6.85 – 6.75 (m, 2H, NC*C*H*), 6.40 (s, 1H, N*H*), 5.01 (s, 2H, OCH_2), 3.13 (s, 3H, NCH_3), 1.60 – 1.28 (m, 9H, C(CH_3)$_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9 (C*), 152.8 (C*), 144.5 (C*), 137.5 (C*), 128.6 (CH), 127.9 (CH), 127.6 (CH), 115.8 (CH), 114.6 (CH), 80.9 (C*) , 70.7 (CH_2), 41.8 (CH_3), 28.4 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3366 (w), 2982 (w), 1712 (m), 1514 (m), 1487 (m), 1452 (m), 1366 (m), 1240 (w), 1163 (w), 1049 (m), 812 (m), 731 (m), 694 (m), 519 (m), 467 (m). **HRMS** (ESI): *m/z* calculated for $C_{19}H_{24}N_2NaO_3$ $[M+Na]^+$: 351.1679, found: 351.1672.

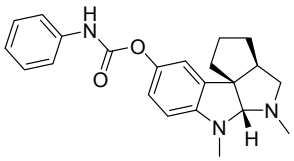


***N*-methylpyrroloindoline 27:** To a solution of N_β-Boc-N_α-methylhydrazine **26** (189 mg, 0.58 mmol, 1.1 equiv) in toluene (0.1 M) was added *p*-toluenesulfonic acid monohydrate (101 mg, 0.53 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 60 °C in an oil bath. To this solution was added 1-pyrroline (–)-**2a** (60.4 mg, 0.53 mmol, 1.0 equiv) and PPTS (135 mg, 0.53 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in MeOH (3 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (33:100 → 50:100 v/v EtOAc/*c*Hex and 5:100 → 10:100 v/v MeOH:DCM), to obtain compound **27** (158 mg [3.1% CH_2Cl_2], 0.478 mmol, 46%) as a brown oil. $\mathbf{R_f}$ **=** 0.22 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.4 Hz, 2H, CH_2C*C*H*), 7.41 (t, *J* = 7.5 Hz, 2H, CH_2C*CHC*H*), 7.34 (t, *J* = 7.3 Hz, 1H, CH_2C*CHCHC*H*), 6.81 (d, *J* = 2.6 Hz, 1H, C(OBn)C*H*C*), 6.75 (dd, *J* = 8.4, 2.6 Hz, 1H, C(OBn)C*H*CH), 6.31 (d, *J* = 8.4 Hz, 1H, C(OBn)CHC*H*), 5.01 (s, 2H, OCH_2), 4.49 (s, 1H, NC*H*NH), 3.16 (dd, *J* = 10.8, 6.8 Hz, 1H, NHCH_2), 2.86 – 2.75 (m, 5H, N(CH_3)CHN*HCH*$_2$), 2.51 – 2.41 (m, 1H, NHCH$_2$C*H*), 2.20 – 2.01 (m, 2H, CHCH_2CH$_2$CH_2), 1.88 – 1.78 (m, 3H, CHCH$_2$CH_2CH_2), 1.51 – 1.40 (m, 1H, CHCH_2CH$_2$CH$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 151.9 (C*), 145.8 (C*), 137.6 (C*), 137.2 (C*), 128.4 (CH), 127.7 (CH), 127.5 (CH), 112.9 (CH), 111.4 (CH), 105.8 (CH), 95.0 (CH), 71.1 (CH_2), 63.5 (C*), 54.2 (CH), 51.6 (CH_2), 40.6 (CH_2), 34.0 (CH_2), 33.5 (CH), 28.1 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (w), 2856 (w), 1493 (s), 1447 (m), 1271 (m), 1223 (m), 1190 (m), 1024 (m), 735 (m), 696 (m), 524 (m). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{25}N_2O$ [M]: 321.1961, found: 321.1954. **Specific rotation**: $[\alpha]_D^{20}$ = +12 ° (c = 0.5, EtOH).

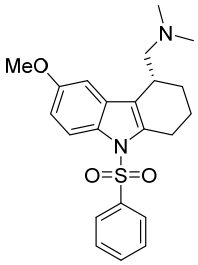


***N,N'*-dimethylpyrroloindoline *S*2:** To a solution of *N*-methylpyrroloindoline **27** (224 mg, 0.688 mmol, 1.0 equiv) in MeOH (0.2 M) were added sodium cyanoborohydride (67 mg, 1.03 mmol, 1.5 equiv), formaldehyde (76.8 µL, 1.03 mmol, 1.5 equiv) and acetic acid (80.4 µL, 1.38 mmol, 2.0 equiv) under inert atmosphere (N_2). The reaction mixture was stirred for 2 h at rt. The mixture was quenched with sat. aq. Na_2CO_3 (20 ml), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated in *vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (0:100 → 2:100 v/v MeOH:DCM), to obtain compound **S2** (214 mg, 0.640 mmol, 93%) as a brown oil. $\mathbf{R_f}$ **=** 0.53 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2H, CH_2C*C*H*), 7.38 (t, *J* = 7.5 Hz, 2H, CH_2C*CHC*H*), 7.32 (t, *J* = 7.2 Hz, 1H, CH_2C*CHCHC*H*), 6.75 (d, *J* = 6.9 Hz, 2H, OC*C*H*), 6.41 (d, *J* = 9.0 Hz, 1H, NC*C*H*), 4.99 (s, 2H, OCH_2), 4.17 (s, 1H, NC*H*N), 2.93 (s, 3H, C*NCH_3), 2.90 – 2.84 (m, 1H, NCH_2), 2.54 (s, 4H, CH_2NCH_3), 2.48 (s, 1H, NCH$_2$C*H*), 2.05 – 1.76 (m, 5H, CH_2CH_2CH_2), 1.73 – 1.64 (m, 2H, CHCH_2CH$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.7 (C*), 146.4 (C*), 138.0 (C*), 137.6 (C*),

128.5 (CH), 127.8 (CH), 127.6 (CH), 113.3 (CH), 110.7 (CH), 108.0 (CH), 98.9 (CH), 71.1 (CH_2), 63.8 (C*), 58.7 (CH_2), 52.2 (CH), 41.0 (CH_2), 38.3 (CH_3), 37.6 (CH_3), 33.5 (CH_2), 27.6 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (w), 2858 (w), 1491 (s), 1445 (m), 1271 (m), 1221 (m), 1191 (m), 1022 (m), 734 (m), 696 (m), 526 (w). **HRMS** (ESI): *m/z* calculated for $C_{22}H_{27}N_2O$ [M]: 335.2118, found: 335.2132. **Specific rotation**: $[\alpha]_D^{20}$ = +4 ° (c = 0.5, EtOH).

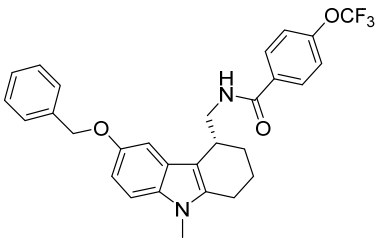


phenserine analog 28: To a solution of *N*,*N*'-dimethylpyrroloindoline **S2** (148 mg, 0.443 mmol, 1 equiv) in MeOH (0.2 M) was added 10% palladium on carbon (24 mg, 0.022 mmol, 0.05 equiv). The reaction mixture was stirred under hydrogen atmosphere overnight at rt. The mixture was filtered over Celite and concentrated *in vacuo*. The crude product was dissolved DCM (0.1 M), after which Et_3N (254 µL, 1.77 mmol, 4 equiv) and phenyl isocyanate (59 uL, 0.53 mmol, 1.5 equiv) were added. The reaction mixture was stirred overnight at rt, washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (0:100 → 5:100 v/v MeOH:DCM), to obtain compound **28** (128 mg [11.7% CH_2Cl_2], 0.311 mmol, 70%) as a brown oil. $\mathbf{R_f}$ **=** 0.35 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 2H, NHC*C*H*), 7.29 (t, *J* = 7.9 Hz, 2H, NHC*CHC*H*), 7.22 (s, 1H, N*H*), 7.07 (t, *J* = 7.4 Hz, 1H, NHC*CHCHC*H*), 6.87 (dd, *J* = 8.4, 2.4 Hz, 1H, NC*CHC*H*), 6.83 (d, *J* = 2.4 Hz, 1H, NC*C*C*H*), 6.39 (d, *J* = 8.4 Hz, 1H, NC*C*H*), 4.09 (s, 1H, NC*H*N), 2.93 (s, 3H, C*NC*H*$_3$), 2.84 (t, *J* = 8.9 Hz, 1H, NC*H*$_2$), 2.53 (s, 3H, CH_2NCH_3), 2.47 – 2.40 (m, 2H, NC*H*$_2$C*H*), 2.03 – 1.88 (m, 3H, CHC*H*$_2$CH$_2$C*H*$_2$), 1.86 – 1.71 (m, 2H, CHCH$_2$C*H*$_2$CH$_2$), 1.61 – 1.51 (m, 1H, CHC*H*$_2$CH$_2$CH$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.7 (C*), 149.9 (C*), 142.9 (C*), 138.0 (C*), 137.8 (C*), 129.1 (CH), 123.6 (CH), 120.3 (CH), 118.7 (CH), 115.8 (CH), 107.1 (CH), 98.9 (CH), 63.6 (C*), 59.1 (CH_2), 52.4 (CH), 41.1 (CH_2), 38.2 (CH_3), 37.6 (CH_3), 33.8 (CH_2), 27.7 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2943 (w), 2858 (w), 1718 (m), 1599 (m), 1541 (m), 1488 (s), 1439 (m), 1313 (m), 1202 (s), 1178 (s), 1007 (m), 993 (m), 752 (m), 692 (m). **HRMS** (ESI): *m/z* calculated for $C_{22}H_{26}N_3O_2$ [M]: 364.2020, found: 364.2030. **Chirality** 99% *ee* [Dr. Maisch Chiral AM, heptane/isopropanol = 93/7, v = 0.6 mL/min, column temperature: 30 °C, λ = 310 nm, t (minor) = 21.023 min, t (major) = 24.221 min]. **Specific rotation**: $[\alpha]_D^{20}$ = −8 ° (c = 0.4, EtOH).



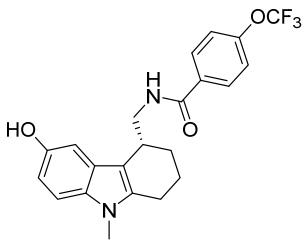
constrained tryptamine (*R*)-30: To a solution of 1-pyrroline (–)-**2a** (60 mg, 0.52 mmol, 1.0 equiv) in toluene (0.1 M) were added 4-methoxyphenylhydrazine hydrochloride **35** (98 mg, 0.55 mmol, 1.05 equiv) and pyridinium *p*-toluenesulfonic acid monohydrate (134 mg, 0.52 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. After addition of *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol, 1.0 equiv), the reaction mixture was stirred for an additional 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in MeOH (3 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. To a solution of the crude product (**36**) in MeOH (0.2 M) were added sodium cyanoborohydride (68 mg, 1.04 mmol, 2.0 equiv), formaldehyde (121.8 µL, 1.30 mmol, 2.5 equiv) and acetic acid (97.0 µL, 2.08 mmol, 4 equiv) under inert atmosphere (N_2). The reaction mixture was stirred for 2 h at rt and quenched[46] with sat. aq. Na_2CO_3 (20 ml), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. To a solution of NaH (60% in mineral oil, 42 mg, 1.04 mmol, 2.0 equiv) in DMF (2 mL) – that was extracted with pentane (2 x 2 mL) previously – was added a solution of the secondary crude

product in DMF (2 mL). Subsequently, benzenesulfonyl chloride (100.8 µL, 0.78 mmol, 1.5 equiv) was added at 0 °C. The reaction mixture was stirred overnight at rt and quenched with sat. aq. Na_2CO_3 (20 ml), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (25:100 → 100:100 v/v acetone:*c*Hex), to obtain compound (*R*)-**30** (65 mg, 0.16 mmol, 31%) as a brown oil. $\mathbf{R_f}$ = 0.24 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.0 Hz, 1H, NC*C*H*), 7.72 (d, *J* = 8.1 Hz, 2H, SO_2C*C*H*), 7.51 (t, *J* = 7.5 Hz, 1H, SO_2C*CHCHC*H*), 7.40 (t, *J* = 7.8 Hz, 2H, SO_2C*CHC*H*), 6.93 (d, *J* = 2.4 Hz, 1H, C(OMe)C*H*C*), 6.86 (dd, *J* = 9.0, 2.5 Hz, 1H, NC*CHC*H*), 3.83 (s, 3H, OC*H*$_3$), 3.16 – 3.05 (m, 1H, NC*C*H*$_2$), 3.04 – 2.96 (m, 1H, NCH_2C*H*), 2.87 – 2.75 (m, 1H, NC*C*H*$_2$), 2.45 – 2.37 (m, 2H, NC*H*$_2$), 2.31 (s, N(C*H*$_3$)$_2$), 2.07 – 1.98 (m, 1H, NCH_2CHCH_2), 1.94 – 1.75 (m, 2H, NC*CH_2C*H*$_2$), 1.72 – 1.58 (m, 1H, NCH_2CHCH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.4 (C*), 139.1 (C*), 137.2 (C*), 133.6 (CH), 131.1 (C*), 130.9 (C*), 129.3 (CH), 126.4 (CH), 120.7 (CH), 115.5 (C*), 111.6 (CH), 102.4 (CH), 62.7 (CH_2), 55.8 (CH_3), 46.1 (CH_3), 30.3 (CH), 24.93 (CH_2), 24.91 (CH_2), 19.0 (CH_2) ppm. **IR** (neat): ν_{max} (cm-1) = 2937 (w), 1607 (w), 1472 (m), 1447 (m), 1366 (m), 1209 (m), 1175 (m), 1150 (s), 1136 (m), 1088 (m), 1034 (m), 725 (s), 685 (m), 561 (s). **Chirality** 99% *ee* [Dr. Maisch Chiral AM, heptane/EtOH = 97/3, v = 0.7 mL/min, column temperature: 30 °C, λ = 300 nm, t (minor) = 12.267 min, t (major) = 12.971 min]. **Specific rotation**: $[\alpha]_D^{20}$ = −31 ° (c = 0.75 [$CHCl_3$]), Lit.: α_D^{20} = − 62 ° (c = 0.62 [$CHCl_3$]).[39]



tricyclic tryptamine S3: To a solution of *N*$_\beta$-Boc-*N*$_\alpha$-methylhydrazine **26** (143 mg, 0.581 mmol, 1.1 equiv) in toluene (0.1 M) was added *p*-toluenesulfonic acid monohydrate (102 mg, 0.528 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h in an oil bath (60 °C). To this solution was added 1-pyrroline (–)-**2a** (60.6 mg, 0.528 mmol, 1.0 equiv) and PPTS (135 mg, 0.528 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 130 °C under microwave irradiation. Subsequently, *p*-toluenesulfonic acid monohydrate (102 mg, 0.528 mmol, 1.0 equiv) was added and the reaction mixture was stirred again for 30 min at 130 °C under microwave irradiation. The suspension was cooled to rt, dissolved in MeOH (3 mL), washed with sat. aq. Na_2CO_3/brine (3:1, 20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The aforementioned steps were repeated and the crude products were combined. The crude product (**37**) was dissolved DCM (0.1 M), after which Et_3N (585 µL, 4.22 mmol, 4.0 equiv) and 4-(trifluoromethoxy)phenylbenzoyl chloride (204 µL, 1.27 mmol, 1.2 equiv) were added. The reaction mixture was stirred overnight at rt, washed with brine (20 mL), extracted with DCM (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (10:100 → 12.5:100 v/v EtOAc/*c*Hex), to obtain compound **S2** (170 mg, 0.345 mmol, 33%) as a grey solid. $\mathbf{R_f}$ **=** 0.31 (*c*Hex:acetone 2:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 2H, C(O)C*C*H*), 7.42 – 7.25 (m, 5H, Ph), 7.22 – 7.17 (m, 4H, C*H*C(OBn)CHC*H*, C(OCF$_3$)C*H*), 6.91 (d, *J* = 8.8 Hz, 1H, C(OBn)C*H*CH), 6.35 – 6.38 (m, 1H, N*H*), 5.00 – 4.86 (m, 2H, OC*H*$_2$), 3.87 – 3.72 (m, 2H, NHC*H*$_2$), 3.61 (s, 3H, NC*H*$_3$), 3.37 – 3.31 (m, 1H, $NHCH_2$C*H*), 2.69 (dd, *J* = 17.1, 10.4 Hz, 2H, NC*C*H*$_2$), 2.09 – 1.98 (m, 1H, NC*CH_2C*H*$_2$), 1.91 (dd, *J* = 29.0, 7.5 Hz, 3H, NC*CH_2C*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.3 (C*), 153.2 (C*), 151.4 (C*), 137.8 (C*), 137.6 (C*), 133.2 (C*), 132.5 (C*), 129.0 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.0 (C*), 120.6 (CH), 120.3 (q, *J* = 260 Hz, C*), 111.2 (CH), 109.6 (CH), 109.1 (C*), 102.4 (CH), 71.0 (CH_2), 44.3 (CH_2), 32.5 (CH), 29.3 (CH_3), 26.9 (CH_2), 22.3 (CH_2), 19.6 (CH_2) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): *δ* -57.70 ppm. **HRMS** (ESI): *m/z* calculated for $C_{29}H_{28}F_3N_2O_3$ [M+H]: 509.2047, found:

509.2039.



tricyclic tryptamine (*R*)-31: To a solution of tricyclic tryptamine **S3** (42 mg, 0.085 mmol, 1 equiv) in EtOAc (0.2 M) was added 10% palladium on carbon (5 mg, 0.0043 mmol, 0.05 equiv). The reaction mixture was stirred under hydrogen atmosphere overnight at rt. The mixture was filtered over Celite and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (5:100 → 20:100 v/v EtOAc:*c*Hex), to obtain compound (*R*)-**19** (28 mg, 0.068 mmol, 80%) as a yellow solid. **R_f =** 0.23 (*c*Hex:acetone 2:1 v/v). **m.p.:** 84 – 90 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 2H, C(O)C*C*H*), 7.17 (d, *J* = 8.3 Hz, 2H, C(OCF$_3$)C*H*), 7.14 – 7.07 (m, 2H, C*H*C(OH)CHC*H*), 6.77 (dd, *J* = 8.7, 2.4 Hz, 1H, C(OH)C*H*CH), 6.47 (t, *J* = 5.9 Hz, 1H, N*H*), 5.91 (bs, 1H, O*H*), 3.89 – 3.81 (m, 1H, NHC*H*$_2$), 3.70 – 3.63 (m, 1H, NHC*H*$_2$), 3.57 (s, 3H, NC*H*$_3$), 3.30 – 3.22 (m, 1H, NHCH$_2$C*H*), 2.75 – 2.59 (m, 2H, NMeC*C*H*$_2$), 2.06 – 1.74 (m, 4H, CHC*H*$_2$C*H*$_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8 (C*), 151.5 (C*), 149.9 (C*), 138.0 (C*), 133.0 (C*), 132.3 (C*), 128.9 (CH), 127.2 (C*), 120.7 (CH), 120.4 (q, *J* = 252 Hz, C*), 110.4 (CH), 109.6 (CH), 108.5 (C*), 103.2 (CH), 44.2 (CH$_2$), 32.6 (CH), 29.3 (CH$_3$), 26.9 (CH$_2$), 22.2 (CH$_2$), 19.7 (CH$_2$) ppm. **^{19}F NMR** (235 MHz, $CDCl_3$): *δ* -57.72 ppm. **IR** (neat): ν_{max} (cm-1) = 3310 (w), 2932 (w), 1636 (m), 1541 (m), 1474 (m), 1252 (s), 1207 (s), 1150 (s), 1016 (w), 848 (m), 792 (m), 734 (m), 698 (m), 546 (m). **HRMS** (ESI): *m/z* calculated for $C_{22}H_{22}F_3N_2O_3$ [M+H]: 419.1577, found: 419.1569. **Chirality** 99% *ee* [Dr. Maisch Chiral AM, heptane/isopropanol = 80/20, v = 0.9 mL/min, column temperature: 30 °C, λ = 220 nm, t (minor) = 43.168 min, t (major) = 46.346 min]. **Specific rotation**: $[\alpha]_D^{20}$ = +30 ° (c = 0.5, EtOH).

4.6 References and Notes

1 S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 10800–10826.

2 H. van Hattum and H. Waldmann, *J. Am. Chem. Soc.* **2014**, *136*, 11853–11859.

3 V. Köhler, K. R. Bailey, A. Znabet, J. Raftery, M. Helliwell, N. J. Turner, *Angew. Chem. Int. Ed.* **2010**, *49*, 2182–2184. This article also reports the preparation of racemic imines such as (±)-**2** by treatment of the amine with NCS followed by KOH.

4 (*a*) A. Znabet, E. Ruijter, F. J. J. de Kanter, V. Köhler, M. Helliwell, N. J. Turner, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2010**, *49*, 5289–5292. (*b*) A. Znabet, M. M. Polak, E. Janssen, F. J. J. de Kanter, N. J. Turner, R. V. A. Orru, E. Ruijter, *Chem. Commun.* **2010**, *46*, 7918–7920.

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18 The pyrroloindoline synthesis was only amenable to scale-up with a milder acid, such as PPTS and TFA.

19 Regioisomer **9a** was present but not taken into account because it could not be isolated and fully characterized. However, the corresponding *o*-nosylated compound **13a** was fully characterized.

20 A thorough computational study on the mechanistic aspects of this reaction is required for more insight into the relative stability of the intermediates.

21 This additional protonation seems to be essential for the formation of **8** and **9**, as the use of 1.5 equiv of a weaker acid such as PPTS did not lead to the formation of **8** and **9**.

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40 Less than 10% of an unknown impurity present.

41 Very weak signal, assigned by HMBC correlation.

42 Signals are overlapped with the signals of the regioisomer.

43 Minor regioisomer **6j'** was fully characterized by NMR spectroscopy, but was isolated in a mixed fraction with **6j**.

44 Presumed optically pure by detection of a single peak by HPLC (chiral stationary phase) and in analogy to **12a**, **12b** and **12d**.

45 Distilled under nitrogen from sodium/benzophenone before use

46 Caution: Formation of a small amount of toxic HCN.

Chapter 5

Future Directions

5.1 Introduction

Thus far, we described several novel methods for the synthesis of diverse and complex scaffolds using *meso*-pyrrolidines as a template. For example, bi- and tricyclic imines were synthesized in either optically pure or racemic form by biocatalytic (**Chapter 2**) and IBX-mediated oxidation (**Chapter 3**), respectively. These methods were also applied for direct α-functionalizations of *meso*-pyrrolidines in a diastereoselective fashion by oxidative aza-Friedel–Crafts and Ugi-type reactions. Furthermore, an acid-switchable chemoenzymatic interrupted Fischer indole synthesis of either pyrroloindolines or constrained tryptamines was developed (**Chapter 4**). Given the multiple diversification points that this strategy provides, we could synthesize several compounds with conceivable therapeutic applications such as in the treatment of Alzheimer's disease. With these examples, we illustrated the fruitful union of biocatalysis and synthetic chemistry. Exploration of the use of other enzymes in organic chemistry will certainly lead to major opportunities in the future.

5.2 Future Directions

In this Chapter, we describe future directions for the application of biocatalysis in organic synthesis. Besides the potential of monoamine oxidase in the synthesis of other biologically and synthetically relevant compounds, possibilities for the application of other biocatalysts *i.e.* Baeyer-Villiger monooxygenases and transaminases are presented.

5.2.1 Monoamine oxidases

Although the applicability of monoamine oxidases in synthetic chemistry was clearly demonstrated in this thesis, the ubiquity of 2-substituted pyrrolidines in nature and synthetic chemistry promotes further exploration of this methodology.

5.2.1.1 Auxiliary-assisted synthesis of dehydropropyl peptides

Dehydroprolyl peptides constitute the core structure of a family of natural products called the phomopsins, isolated from the fungus *Phomopsis leptostromiformis* (Figure 1).[1] These hexapeptides—displaying a 3,4-dehydroprolyl peptide as their core structure—are potent microtubule depolymerizers.[2] Moreover, dehydroprolyl peptides provide a convenient handle for functionalization towards a class of natural products called the astins. Astins A–C (Figure 1) are cyclic pentapeptides with a dichlorinated proline residue exhibiting potent antitumor activity.[3] To the best of our knowledge, a total synthesis of this interesting class of molecules has not been published yet, except for astin G that exhibits a different core structure.[4]

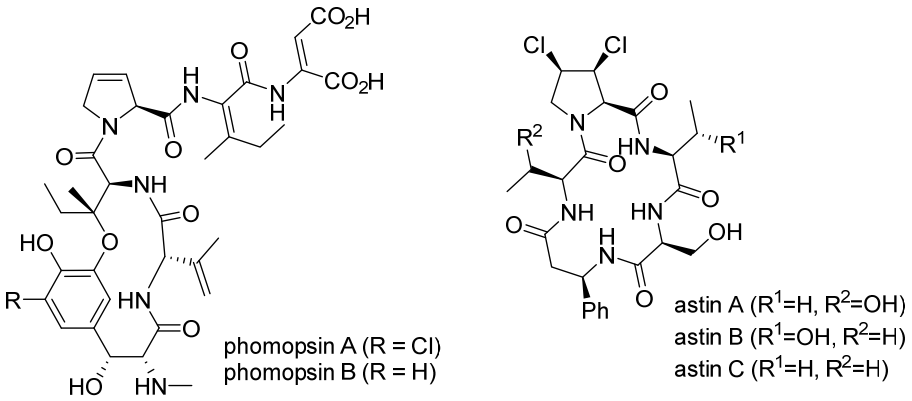
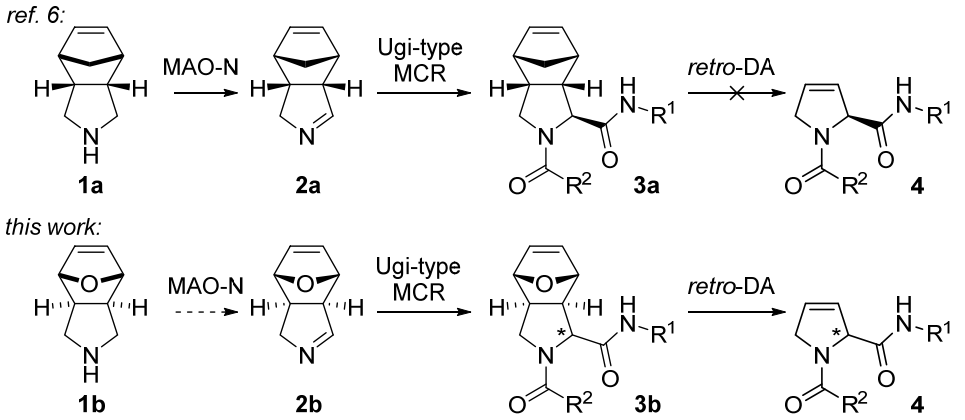


Figure 1. Phomopsin A–B and astin A–C

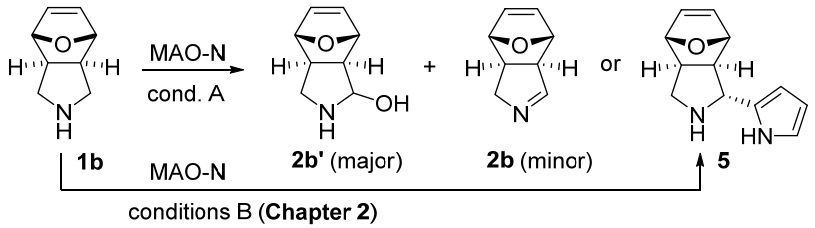
Our group previously reported a highly efficient combination of monoamine oxidase-N catalyzed desymmetrization of cyclic *meso*-pyrrolidines with an Ugi-type multicomponent reaction (MAO-MCR) to access 3,4-substituted prolyl peptides in excellent diastereo- and enantioselectivity (Scheme 1).[5,6] Based on this research, we envisioned to employ a chiral auxiliary on a pyrrolidine core to induce enantioselectivity in the biocatalytic oxidation as well as diastereoselectivity in the Ugi-type 3CR. Herein, we describe a chemoenzymatic multicomponent approach to the asymmetric synthesis of 3,4-dehydroprolyl peptides using a furan auxiliary. With this method, the MAO-MCR sequence is followed by a *retro*-Diels–Alder reaction in order to remove the auxiliary (MAO-MCR-*r*DA, Scheme 1). The 3,4-dehydroprolyl peptide constitutes a versatile synthon for follow-up chemistry.



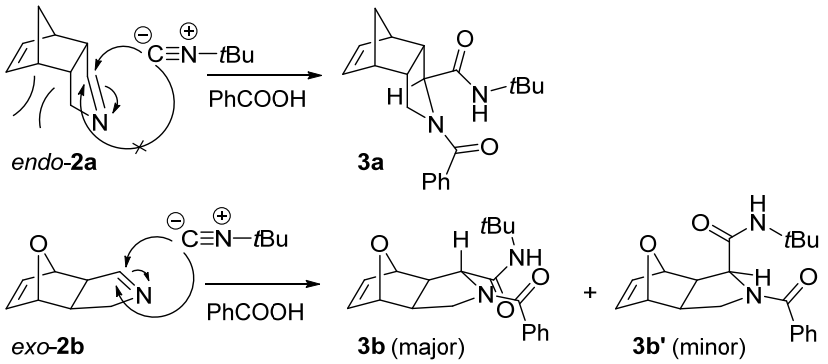
Scheme 1. MAO-Ugi-*retro*-DA sequence

The previously described MAO-MCR sequence uses a cyclopentadiene adduct (**1a**) for chiral induction.[6] Therefore, we initially investigated the application of cyclopentadiene as an auxiliary in the MAO-MCR sequence (Scheme 1). However, its removal from dipeptide **3a** by a thermal *retro*-Diels–Alder (*r*DA) reaction proved to be challenging, as no conversion was observed at elevated temperature (250 °C). To facilitate a more thermodynamically favored *r*DA reaction, we envisioned the use of a diene that contributes to aromaticity, such as furan. Synthesis of the corresponding *meso*-pyrrolidine **1b** with an *exo*-configuration was readily achieved by a Diels–Alder reaction between furan and maleimide followed by reduction of the imide functionality.[7] IBX-mediated oxidation of **1b** afforded the desired imine *rac*-**2b** (**Chapter 3**), while biocatalytic oxidation with MAO-N resulted in an interesting domino reaction of oxidation, *r*DA reaction and pyrrole addition to give 2-pyrrolyl pyrrolidine **5** (**Chapter 2**). After extensive screening of the reaction conditions, we found that imine **2b** has a lower tendency to undergo a *r*DA reaction when the mixing method for the biocatalytic oxidation is stirring instead of shaking (Scheme 2). However, we have no plausible explanation for this unusual observation. Under optimized conditions (37 °C, 400 rpm stirring), we isolated a surprisingly stable hemiaminal (**2b'**) that results from the addition of water to imine **2b**. The rather low isolated yield (54%, 2:98 ratio **2b**:**2b'**) can be rationalized by the occurrence of a *r*DA reaction to a certain extent. Since we were not yet successful in scaling up the biocatalytic oxidation, we performed the following steps of the MAO-MCR-*r*DA

sequence with the racemic imine. The Ugi-type three-component reaction of readily



Scheme 2. Biocatalytic oxidation with mixing by stirring or shaking. Conditions A: pyrrolidine (0.25 mmol), MAO-N D5 *freeze-dried* whole cells (125 mg), PPB (12.5 mL, 200 mM, pH 7.5), 37 °C, 400 rpm stirring, 17 h. Conditions B: Shaken, not stirred.



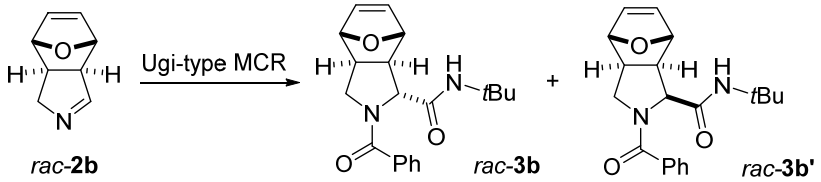
Scheme 3. Steric rationalization for diastereoselectivity in the Ugi-type reaction with *endo*-**2a** and *exo*-**2b**.

available *rac*-**2b**, *tert*-butyl isocyanide and benzoic acid provided prolyl peptides **3b** and **3b'**. However, the diastereoselectivity was significantly decreased compared to the equivalent reaction with *endo*-configured imine **2a**[6,7] as a result of the smaller difference in steric congestion between the diastereotopic faces of imine **2b** (Scheme 3). Fortunately, the diastereoisomers were readily separated by silica gel chromatography, which would allow synthesis of both enantiomers of the target molecule **4** starting from (–)-**2b**. After a screening with various solvents (Table 1), we found that superior diastereoselectivity in the Ugi-type MCR is achieved in MeCN (entry 11). The relative stereochemistry of major diastereoisomer **3b** was corroborated by X-ray crystallography (**Chapter 3**).

With the major diastereoisomer of the Ugi adduct (*rac*-**3b**) in hand, we performed a temperature screening for the *r*DA reaction of **3b** under microwave

irradiation (Table 2). Gratifyingly, high conversion towards *rac*-**4** was achieved in only

Table 1. Solvent screen for the Ugi-type three-component reaction of imine **2b**.[a]



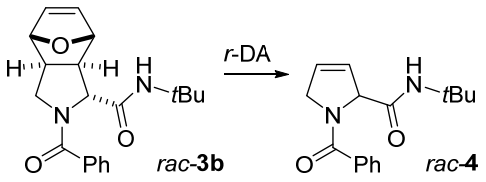
rac-**2b** *rac*-**3b** *rac*-**3b'**

Entry[a]	Solvent	Yield[b]	*dr*[c]	Entry[a]	Solvent	Yield[b]	*dr*[c]
1	dioxane	48%	1.0:1	7	EtOAc	76%	2.2:1
2	toluene	89%	1.2:1	8	DMSO	50%	2.9:1
3	*n*BuOH	79%	1.8:1	9	MeOH	84%	3.1:1
4	$(MeO)_2CO$	71%	1.8:1	10	DMF	44%	3.6:1
5	EtOH	79%	2.0:1	11	MeCN	79%	4.8:1
6	CH_2Cl_2	86%	2.2:1				

[a] Conditions: imine *rac*-**2b** (1.0 equiv), *tert*-butyl isocyanide (1.2 equiv) and benzoic acid (1.2 equiv) in solvent (0.2 M), rt, 4 days. [b] Yield of the crude **3b**/**3b'** mixture (>95% purity). [c] Determined with HPLC by comparison with a 1:1 mixture of diastereoisomers.

15 minutes at temperatures above 200 °C in DMSO (entries 3–4). Under optimized conditions (225 °C, 15 min), the dehydroprolyl peptide *rac*-**4** was obtained in 86% isolated yield (entry 4). Although these preliminary experiments show the high potential of our MAO-Ugi-*retro*-DA sequence with furan as chiral auxiliary, optimization of the biocatalytic oxidation of **1b** is required to further suppress the undesired *r*DA reaction.

Table 2. *retro*-Diels–Alder reaction of furan-based prolyl peptide **3b**.[a]



rac-**3b** *rac*-**4**

Entry	T (°C)	Conv.[b]	Yield[c]
1	150	1%	n.d.
2	175	27%	n.d.
3	200	90%	n.d.
4	225	100%	86%

[a] Conditions: DMSO-d_6 (0.3 M), 15 min, T, μW [b] Conversion calculated by the product to substrate ratio in the ^{1}H NMR spectrum of the crude mixture. [c] Isolated yield.

5.2.1.2 Chemoenzymatic strategy to the synthesis of proline-derived tetrazole organocatalysts

In light of our interest in chiral 2-substituted pyrrolidines with high relevance in synthetic chemistry, we investigated the applicability of our biocatalytic *meso*-pyrrolidine oxidation in the synthesis of proline-like organocatalysts with a tetrazole moiety. Tetrazoles are gaining importance in medicinal chemistry[8] as well as in organocatalysis.[9] Since 5-substituted-1*H*-tetrazoles are commonly known as isosteres of carboxylic acids,[10] having a similar pK_a value, proline derivatives with a 1*H*-tetrazole fragment are becoming a widely used alternative for the well-known organocatalyst proline.[11] Unlike proline, the corresponding tetrazole derivative is soluble in a wide range of organic solvents. As a result, a much wider range of reactions can be catalyzed with proline-derived tetrazoles, such as asymmetric (nitroso)aldol,[12] Mannich[13] and nitro-Michael[9] reactions. The general strategy for their synthesis starts from commercially available proline derivatives, which limits molecular diversity. Thus far, only a handful of chiral proline-derived tetrazole catalysts have been synthesized (Figure 2).[11,14,15] The development of novel sterically encumbered proline-derived tetrazole catalysts is of high interest in order to improve stereoselectivity in asymmetric organocatalytic transformations.

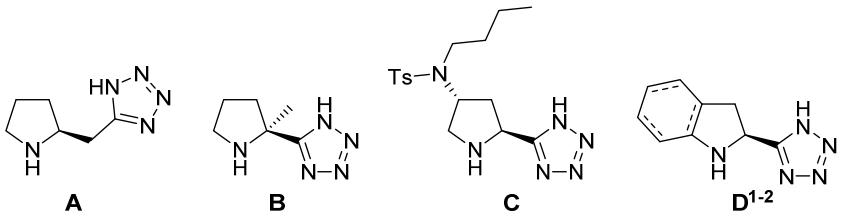
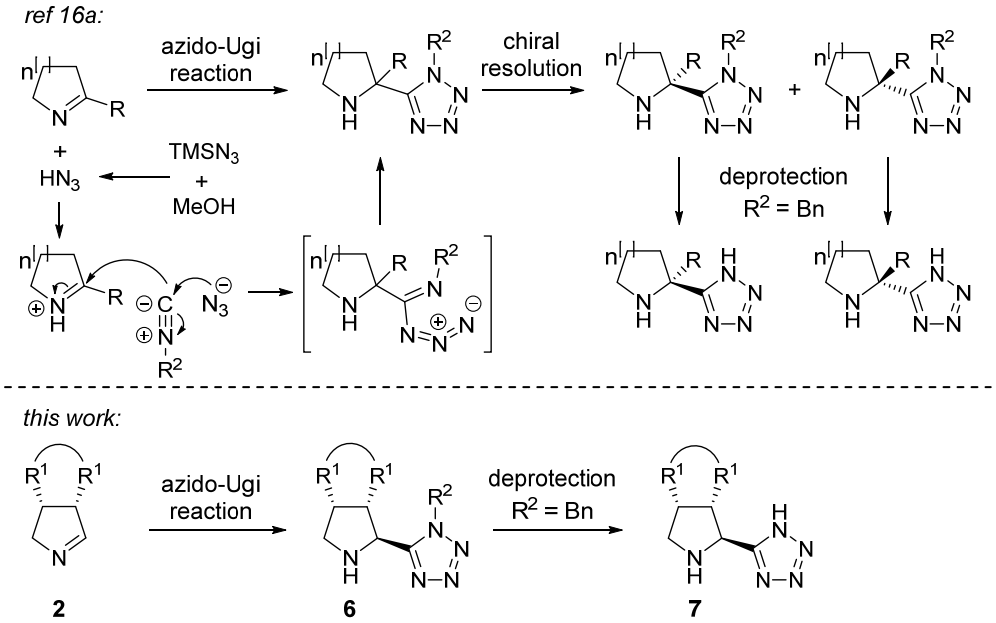


Figure 2. Examples of chiral proline-derived tetrazole organocatalysts.

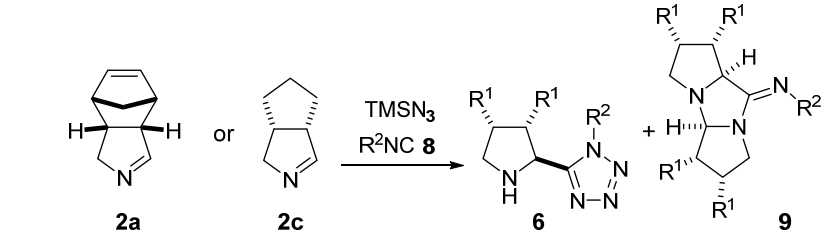
Nenajdenko *et al.* showed the application of cyclic imines in the azido-Ugi reaction with trimethylsilyl azide and isocyanides for the synthesis of racemic organocatalyst precursors (Scheme 4).[16] Chiral resolution and benzyl deprotection were required to provide an optically enriched proline-derived tetrazole organocatalyst.[16a] We envisioned direct access to novel asymmetric organocatalyst precursors **6** by the use of enantio-enriched imines **2**. Conveniently, bi- and tricyclic imines can be obtained in high to excellent enantiopurity by a biocatalytic oxidation of *meso*-pyrrolidines.[5] For the synthesis of the corresponding racemic proline-derived tetrazoles, the imine substrates can be obtained by IBX-mediated oxidation (**Chapter 3**).[7]

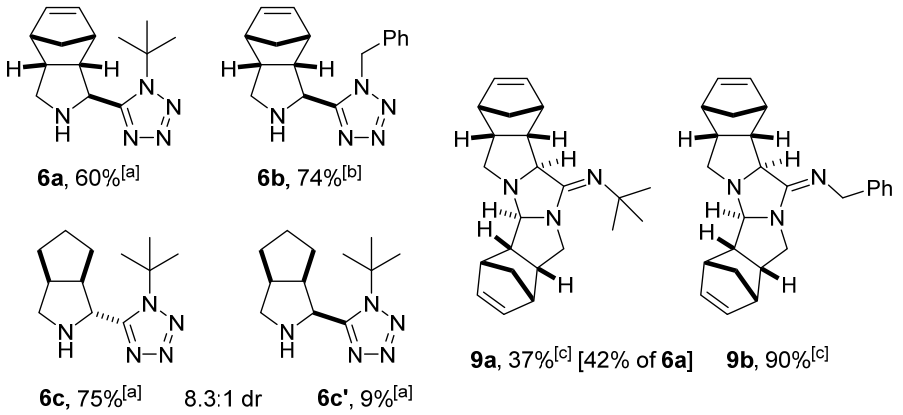


Scheme 4. Synthesis of novel organocatalysts from cyclic imines *via* an azido-Ugi reaction.

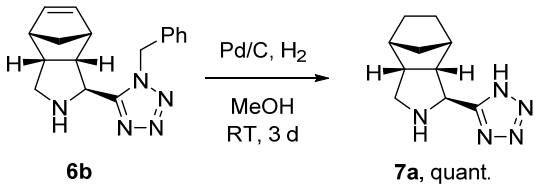
We started our investigation of the reaction conditions and substrate scope by a reaction between readily available *rac*-**2a**, isocyanides **8** and trimethylsilyl azide in methanol as the reaction medium (2 d, 40 °C). To our surprise, the main product (**9**) of our initial attempts had an isocyanide molecule inserted into a dimer of the imine substrate (Table 3). Isocyanide-inserted dimeric structure **9b** derived from benzyl isocyanide was obtained in high yield (90%) as a single diastereoisomer. However, the corresponding dimer derived from *tert*-butylisocyanide (**9a**) was obtained in only modest yield, together with 42% of tetrazole **6a**. Intriguingly, we obtained the desired 1,5-disubstituted tetrazoles **6** as the sole products after changing the reaction medium from methanol to 2,2,2-trifluoroethanol (TFE). Under optimized reaction conditions (TFE, 2 d, 40 °C, Table 3), the desired 1,5-disubstituted tetrazoles **6a** and **6b** derived from *rac*-**2a** and either *tert*-butyl or benzyl isocyanide could be isolated in good yields (60–74%) and as single diastereoisomers. Subsequently, the scope of the bicyclic imines was further explored with bicyclic imine *rac*-**2c**. As a consequence of the decreased steric congestion on the concave face of **2c**, the adducts **6c** and **6c'** were obtained as a 8.3:1 diastereoisomeric mixture, albeit in high yield.

Table 3. Azido-Ugi reaction for the synthesis of **6a–c** and **9a**,**b**.





[a] Conditions: imine *rac*-**2** (1.0 equiv), $TMSN_3$ (1.1 equiv), isocyanide **8** (1.1 equiv) in TFE, 2 d, 40 °C. [b] Conditions: imine *rac*-**2** (1.0 equiv), $TMSN_3$ (2.0 equiv), isocyanide **8** (2.0 equiv) in TFE, 2 d, 40 °C. [c] Conditions: imine *rac*-**2** (2.0 equiv), $TMSN_3$ (1.5 equiv), isocyanide **8** (1.5 equiv) in MeOH, 2 d, 40 °C.

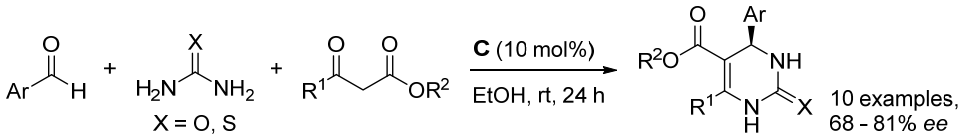


Scheme 5. Benzyl deprotection of organocatalyst precursor **6b**.

Synthesis of a novel asymmetric organocatalyst was achieved by employing optically-pure imine (+)-**2a**, derived from the corresponding *meso*-pyrrolidine by biocatalytic oxidation.[5] Debenzylation gave access to proline-derived tetrazole **7a** as a single diastereoisomer (Scheme 5).

To conclude, we developed the first stereoselective azido-Ugi reaction with cyclic imines. Facile deprotection provided a novel 3,4-substituted multicyclic proline-derived tetrazole organocatalyst (**7a**). We envision its application in the

asymmetric Biginelli MCR towards 3,4-dihydropyridimidin-2(1*H*)-one (DHPM) derivatives.[15] Thus far, only moderate enantioselectivity (68–81% *ee*) was obtained in asymmetric Biginelli reactions catalyzed by proline-derived tetrazoles (Scheme 6). Since superior results were obtained with a bulky group on the 4-position of the pyrrolidine (Figure 2, **C**), our sterically encumbered 3,4-substituted proline-derived tetrazoles appear to have high potential for this application.

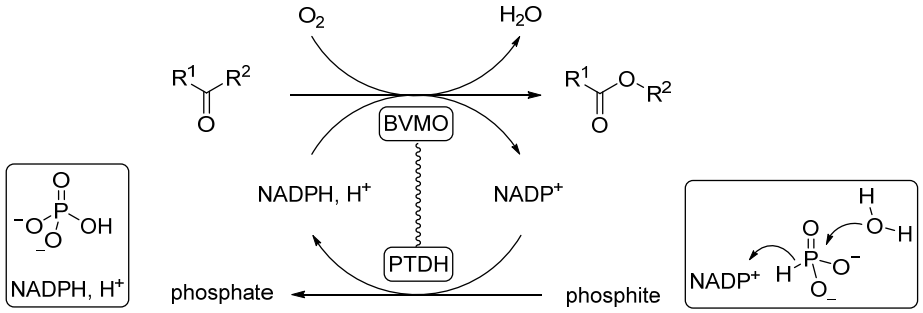


Scheme 6. Asymmetric Biginelli MCR catalyzed by proline-derived tetrazole catalyst **C**.[15]

5.2.2 Baeyer-Villiger monooxygenases

The application of Baeyer-Villiger monooxygenases (BVMOs) in organic chemistry is not widespread, but their potential has been demonstrated in several reports (**Chapter 1**).[17] Of the known subtypes of BVMOs, the most widely applied are cyclohexanone (CHMO), cyclopentanone (CPMO), hydroxyacetophenone (HAPMO) and phenylacetone monooxygenase (PAMO).[18] Their partially overlapping broad substrate scopes are depicted in Figure 3,[19a] representing the most important substrates per subtype.

As described in **Chapter 1**, a cofactor regeneration system is essential when using BVMOs as a result of the stoichiometrically consumed cofactor. Fraaije *et al.*



Scheme 7. Coenzyme regeneration by PTDH/BVMO fusion enzymes.

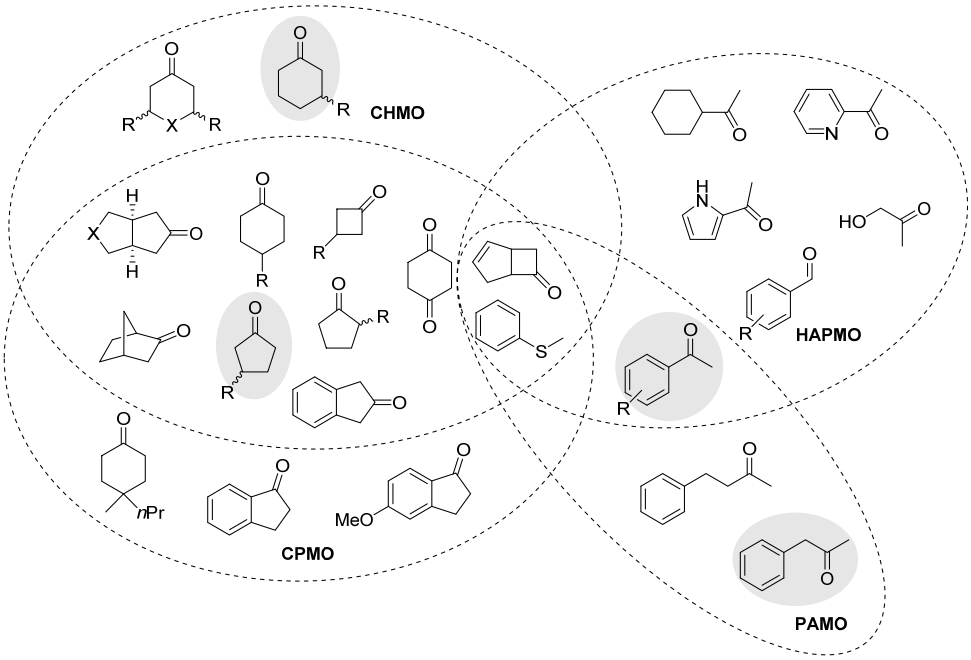


Figure 3. A representation of the substrate scopes of the four most important BVMO subtypes.[19a]

conveniently linked different types of BVMOs to phosphite dehydrogenase (PTDH) which is the vital part of the cofactor regeneration system in this case (Scheme 7).[19] The only additional requirements are oxygen and phosphite as a cheap and sacrificial electron donor. The application of these self-sufficient BVMOs reduces the labor of enzyme cultivation, expression and isolation by half, since a single fusion protein performs the task of two separate biocatalysts.

A particularly interesting biocatalytic strategy in terms of further applications is the dynamic kinetic resolution (DKR) of α-substituted β-ketoesters and β-diketones using BVMOs. The fast racemization of these substrates in aqueous medium through a keto-enol equilibrium allows an asymmetric and regioselective Baeyer-Villiger oxidation with full conversion to generate α-hydroxy esters or ketones (**Chapter 1**).[20] Further broadening the substrate scope is expected to boost the application of this method in the total synthesis of biologically active molecules.

We investigated the reaction conditions required for the dynamic kinetic resolution of α-substituted β-diketones with different fusion proteins developed by Fraaije and coworkers. A symmetric β-diketone (**10a**) was used for the benchmark

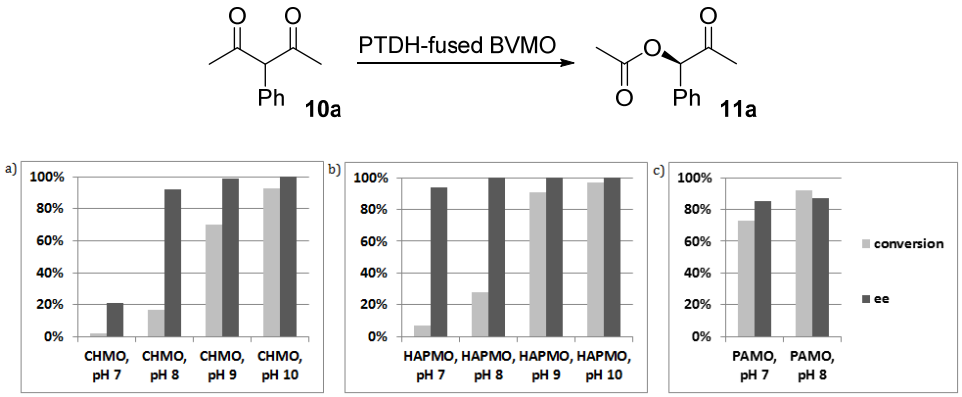
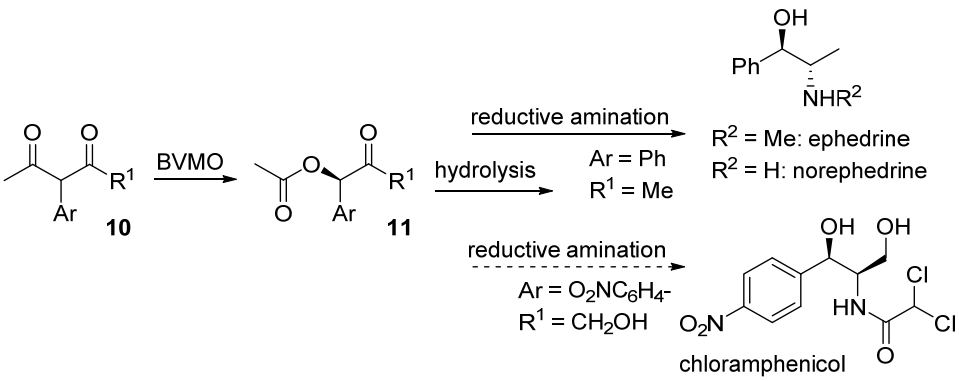
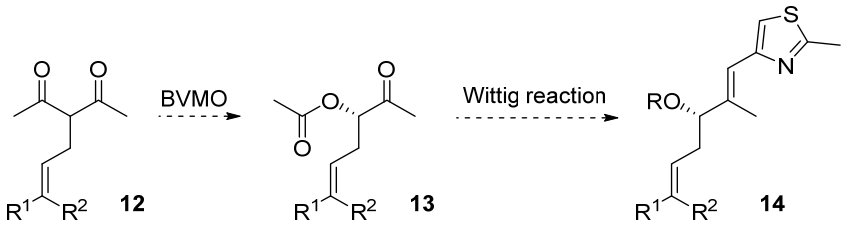


Figure 4. Biocatalytic Baeyer-Villiger oxidation of substrate **10a** with a PTDH protein fused to a) HAPMO, b) CHMO, or c) non-fused PAMO and PTDH.

reaction, in which case the biocatalytic strategy should be annotated desymmetrization rather than dynamic kinetic resolution. For the biocatalytic monooxygenation of **10a**, we observed an interesting correlation between pH and activity as well as enantioselectivity (Figure 4). Surprisingly, both HAPMO and CHMO showed superior activity (>90% conversion after 2h) and excellent enantioselectivity at a particularly high pH of 10. In contrast, PAMO only showed selective conversion to the desired product at pH 7 and 8 with up to 88% *ee*. Next, we investigated the substrate scope with an indirect phosphate assay, which indicated high conversion for a diverse library of substrates. Thus far, we were not successful in scaling up the biocatalytic Baeyer-Villiger oxidation to isolate the products. However, recent publications show wide substrate scopes for related compounds.[20a,21] It is important



Scheme 8. Total synthesis of (nor)ephedrine and hypothesized synthesis of chloramphenicol.



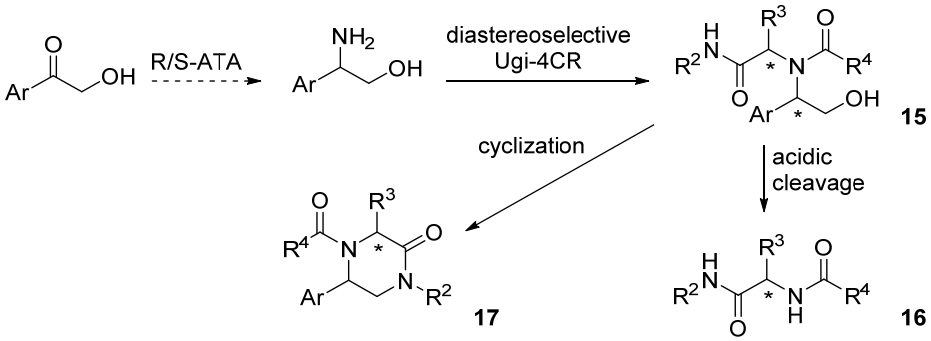
Scheme 9. Biocatalytic approach towards the synthesis of epothilone building block **14**.

to note that not much optimization work was performed, because of our lack of experience with the required conditions for these isolated enzymes. Furthermore, our focus shifted towards the other projects described in this thesis.

The potential of this strategy is illustrated by its application in the synthesis of stimulant (nor)ephedrine[20b] and our hypothesized synthesis of antibiotic chloramphenicol (Scheme 8). Furthermore, we envision the synthesis of a key chiral building block (**14**) of macrocycle epothilone B,[22] a potent anticancer drug. The asymmetric element in this building block is hypothesized to be established by a biocatalytic Baeyer-Villiger oxidation of **12** followed by a Wittig reaction (Scheme 9). Since the proposed syntheses are just examples of the potential utility of BVMOs in dynamic kinetic resolution strategies for total syntheses, we expect significant progress in the application of BVMOs in organic synthesis in the future.

5.2.3 Transaminases

Optically active amines are important building blocks for the preparation of pharmaceuticals and agrochemicals. The most appealing biocatalytic strategy for the synthesis of α-chiral primary amines is desymmetrization of the corresponding ketone with a transaminase (**Chapter 1**).[23] Although the application of many (*S*)-selective transaminases is widely described, only a few (*R*)-selective transaminases were identified, only one of which is commercially available (ATA-117). Bornscheuer *et al.* published the synthesis of enantio-enriched aliphatic, aromatic and arylaliphatic amines with (*R*)-selective amine transaminases.[24] Although the reported substrates generally have a methyl group as one of the α-substituents, an amine transaminase from *Chromobacterium violaceum* is known to accept a hydroxymethyl substituent on that position.[25] Interestingly, Nenajdenko *et al.* showed the utility of such a hydroxymethyl substituent in the formation of a zinc chelate to facilitate a



Scheme 10. Application of transaminases in organic synthesis.

diastereoselective Ugi MCR for the synthesis of dipeptides.[26] With this information in hand, we envisioned the biocatalytic desymmetrization of α-hydroxy ketones to give optically pure β-hydroxy amines which can be applied as chiral auxiliary for the Ugi MCR. An electron-rich aryl group on the chiral auxiliary would allow subsequent acidic cleavage to access enantio-enriched dipeptides with three diversification points (**16**). Other opportunities include the cyclization of **15** to provide oxopiperazines **17** (Scheme 10). We found that the Ugi MCR and subsequent acidic cleavage proceed well, as well as the cyclization of **15** to **17**. However, the transamination was not explored yet and the diastereoselectivity of the Ugi MCR proved to be only moderate in our hands. Although just two examples are highlighted in this section, the possibilities for the application of optically active primary amines in organic synthesis are limitless. Therefore, the use of transaminases in total synthesis is expected to receive increasing interest in the future.

5.3 Acknowledgements

Prof. N. J. Turner and Dr. B. Bechi (University of Manchester) are gratefully acknowledged for the fruitful collaboration on monoamine oxidases. Prof. M. W. Fraaije, Dr. H. L. van Beek, Dr. P. B. Brondani and G. van Heel (University of Groningen) are gratefully acknowledged for fruitful discussions, the opportunity to join the Fraaije group for three weeks and the collaboration on Baeyer-Villiger monooxygenases. Prof. U. T. Bornscheuer, Dr. M. Höhne and Dr. F. Steffen-Munsberg (Greifswald University) are acknowledged for fruitful discussions and our collaboration on transaminases. M.

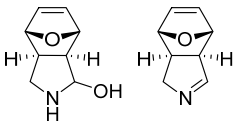
J. van Lint (VU University) is kindly acknowledged for fruitful discussions, E. Janssen (VU University) for technical assistance, S. Bouwman (VU University) for HRMS measurements, and Dr. A. W. Ehlers (VU University) for NMR maintenance.

5.4 Experimental Section

General comments

Starting materials were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics and used without treatment. Unless stated otherwise, the solvents were purchased from VWR Chemicals or Biosolve and were used without further treatment. Cyclohexane (*c*Hex) was purified by distillation before use. The *meso*-pyrrolidines and racemic or enantioenriched imines were synthesized according to previously reported procedures.[5,7] Celite® 512 medium was purchased from Sigma Aldrich. Column Chromatography was performed on Silica-P Flash Silica Gel (particle size 40-63 µm, pore diameter 60 Å) from Silicycle. Thin Layer Chromatography (TLC) was performed using TLC plates F_{254} (silica gel 60 on aluminium) from Merck Serono KGaA (Darmstadt) and compounds were visualized by UV detection (254 or 366 nm) and stained with basic aq. $KMnO_4$ or ninhydrin/ethanol. ^1H, ^{13}C, COSY, HSQC, HMBC and NOESY nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (500.23 MHz for ^1H and 125.78 MHz for ^{13}C) using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR) or Bruker Avance 400 (400.13 MHz for ^1H and 100.62 MHz for ^{13}C) using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR, MeOD-d_4: δ = 3.31 for ^1H NMR and δ = 49.00 for ^{13}C NMR) or Bruker Avance 250 (250.13 MHz for ^1H) in $CDCl_3$ using the residual solvent as internal standard ($CDCl_3$: δ = 7.26 for ^1H NMR, DMSO-d_6: δ = 2.50 for ^1H NMR). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet) and m (multiplet) or combinations thereof. The COSY-, HMBC- and HSQC-NMR spectra were used for the assignment of the proton signals. The APT-NMR spectra were used for the assignment of the carbon signals. NMR data was processed using MestReNova. Names of chemical structures were deduced from generic names and/or important functionalities. Electrospray Ionization (ESI) high resolution mass spectrometry (HRMS) was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Infrared (IR) spectra were recorded neat using a FTIR-8400s from Shimadzu. Signal intensities are described as strong (s), medium (m), weak (w) or broad (br). Melting points were recorded on a Büchi M-565 and are not corrected.

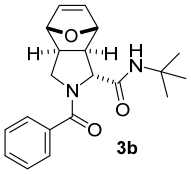
Synthetic procedures and spectral data

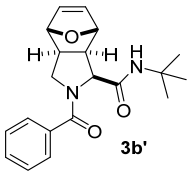


2b' **2b**

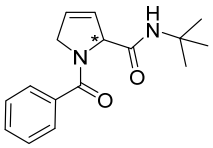
2-hydroxypyrrolidine 2b' and 1-pyrroline 2b: To a solution of rehydrated *freeze-dried* MAO-N cells (4 x 125 mg, 30 min, 37 °C, 400 rpm) in phosphate buffer (4 x 12.5 mL, 200mM, pH 7.5) was added pyrrolidine **1b** (147 mg, 1.04 mmol). The reaction mixture was stirred for 17 hr (400 rpm, 37 °C), after which the suspension was centrifuged until the supernatant had clarified (1 hr,

4000 rpm, 4 °C). The pH of the supernatant was adjusted to 11 with 2M aq. NaOH and extracted with DCM (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*, to afford a mixture of compounds **2b'** and **2b** (85.0 mg, 0.56 mmol, 54%) as a white solid in a 49:1 ratio as determined by NMR spectroscopy. **IR** (cm^{-1}): ν_{max} = 2978 (s), 2797 (s), 1394 (m), 1304 (s), 1129 (s), 1157 (s), 1032 (s), 949 (s), 897 (s), 814 (s), 723 (s), 692 (s). **HRMS** (ESI^+) calculated for C_8H_9NO (MH^+) 136.0757, found 136.0762. **2b':**[27] **^{1}H NMR** ($CDCl_3$, 250.1 MHz): δ 6.40-6.32 (m, 2H *H*C=C*H*), 4.75 (s, 1H, NCHCHC*H*O), 4.67 (s, 1H, NCH_2CHCHO), 3.21 (t, *J* = 7.8 Hz, 1H, NCH_2), 2.78 (d, *J* = 6.0 Hz, 1H, NHC*H*OH), 2.46-2.37 (m, 1H, NCH_2CHCHO), 2.26 (t, *J* = 7.5 Hz, 1H, NCH_2), 2.19 (dd, *J* = 8.0, 6.2 Hz, 1H, NCHOHC*H*) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 136.5 (CH), 136.0 (CH), 84.8 (CH), 80.7 (CH), 80.0(CH), 50.1 (CH_2), 48.7 (CH), 44.0 (CH). **2b:**[7] **^{1}H NMR** ($CDCl_3$, 250.1 MHz): δ 7.41 (s, 1H, NC*H*), 6.40-6.34 (m, 2H *H*C=C*H*), 4.95 (s, 1H, NCHCHC*H*O), 4.76 (s, 1H, NCH_2CHCHO), 4.02-3.91 (m, 1H, NCH_2), 3.72-3.63 (m, 1H, NCH_2), 3.11 (d, *J* = 7.0 Hz, 1H, NCHC*H*), 2.53-2.45 (m, 1H, NCH_2CH) ppm. **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 164.1 (CH), 137.5 (CH), 136.2 (CH), 84.3 (CH), 79.8 (CH), 63.7 (CH_2), 59.7 (CH), 42.4 (CH).

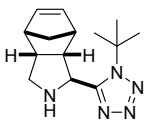




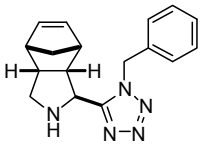
2,3-*trans*-prolyl peptide *rac*-3b (major) and 2,3-*cis*-prolyl peptide *rac*-3b' (minor): To a solution of *rac*-**2b** (654 mg, 4.84 mmol, 1.0 equiv) in DCM (25 mL) was added benzoic acid (0.71 g, 5.81 mmol, 1.2 equiv) and *tert*-butyl isocyanide (670 µL, 5.81 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 4 days, after which it was quenched by the addition of sat. aq. Na_2CO_3 (25 mL), extracted with DCM (3 x 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (4:1 → 1:2 v/v *c*Hex:EtOAc), to obtain compound *rac*-**3b** (793 mg, 2.33 mmol, 52%) and *rac*-**3b'** (428 mg, 1.26 mmol, 26%) in a 2.0:1 diastereoisomeric ratio as off-white solids. **3b**: **R_f** = 0.14 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 176.8 – 185.3 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.49 – 7.38 (m, 5H, *Ph*), 6.93 (s, 1H, N*H*), 6.42 (dd, *J* = 6.1 Hz, *J* = 1.9 Hz, 1H, NCH_2CHCHC*H*=CH), 6.35 (dd, *J* = 1.5 Hz, *J* = 1.5 Hz, 1H, $NCH_2CHCHCH$=C*H*), 4.95 – 4.84 (m, 2H, NCH_2CHCHO, NC*H*), 4.65 (s, 1H, NCHCHC*H*O), 3.73 (dd, *J* = 11.9 Hz, *J* = 8.3 Hz, 1H, NCH_2), 3.52 (dd, *J* = 12.0 Hz, *J* = 1.9 Hz, 1H, NCH_2), 2.98 (d, *J* = 7.1 Hz, 1H, NCHC*H*), 2.42 (t, *J* = 7.8 Hz, 1H, NCH_2CH), 1.35 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 170.1 (C*), 169.8 (C*), 137.1 (CH), 136.6 (CH), 136.2 (CH), 130.3 (CH), 128.6 (CH), 127.0 (C*), 84.0 (CH), 83.7 (CH), 64.1 (CH), 52.9 (CH_2), 51.4 (C*), 44.7 (CH), 44.3 (CH), 28.8 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3292 (w), 2966 (w), 1676 (s), 1601 (s), 1570 (s), 1541 (s), 1447 (m), 1425 (s), 1356 (m), 1281 (w), 1259 (w), 1223 (m), 1030 (w), 941 (w), 903 (s), 868 (w), 847 (w), 719 (s), 692 (s), 665 (s), 619 (m). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1860, found: 341.1849. **3b'**: **R_f** = 0.10 (*c*Hex:EtOAc 1:1 v/v). **m.p.:** 184.0 – 190.0 °C (decomposition). **^{1}H NMR** (500 MHz, MeOD-d_4): *δ* 7.59 – 7.19 (m, 5H, *Ph*), 6.50 – 6.31 (m, 2H, *H*C=C*H*), 4.86 (s, 1H, C*H*O), 4.78 – 4.59 (m, 2H, NC*H*, C*H*O), 3.53 (t, *J* = 9.7 Hz, 1H), 3.40 – 3.30 (m, 1H, NCH_2),[28] 2.68 – 2.56 (m, 1H, $NHCH_2CH$), 2.54 – 2.40 (m, 1H, NCHC*H*),[28] 1.30 (s, 9H, $C(CH_3)_3$,) ppm.[29] **^{13}C NMR** (126 MHz, MeOD-d_4): *δ* 168.4 (C*), 168.0 (C*), 137.2 (CH), 137.1 (C*), 136.7 (CH), 130.3 (CH), 128.7 (CH), 127.6 (CH), 79.4 (CH, CH), 60.5 (CH), 53.0 (CH_2), 50.7 (C*), 47.2 (CH), 45.4 (CH), 29.1 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2974 (w), 1670 (s), 1624 (s), 1418 (s), 1313 (w), 1223 (m), 1142 (m), 986 (m), 951 (m), 906 (m), 822 (w), 661 (m). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1860, found: 341.1850. **IR** (cm^{-1}): ν_{max} = 3294 (m), 2961 (m), 1676 (s), 1601 (s), 1570 (s), 1541 (s), 1425 (m), 1223 (m), 903 (s), 719 (s), 665 (s). **HRMS** (ESI^+) calculated for $C_{20}H_{24}N_2O_3$ (MH^+) 341.1860, found 341.1864.



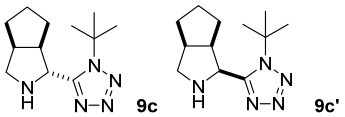
dehydroprolyl peptide *rac*-4: A solution of *rac*-**3b** (0.35 g, 1.00 mmol) in DMSO (3.5 mL) was stirred for 15 min at 225 °C under microwave irradiation, after which the reaction was quenched by the addition of H_2O (5 mL), extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain compound *rac*-**4** (0.24 g, 0.86 mmol, 86%) as a brown solid. **m.p.:** 189.3 – 190.1 °C. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.63 – 7.33 (m, 5H, Ph), 6.87 (s, 1H, N*H*), 5.99 – 5.85 (m, 2H, C*H*=C*H*), 5.48 – 5.40 (m, 1H, NCH_2CH), 4.52 – 4.41 (m, 1H, NCH_2), 4.17 – 4.03 (m, 1H, NCH_2), 1.36 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.6 (C*), 169.1 (C*), 135.9 (C*), 130.8 (CH), 128.7 (CH), 127.3 (CH), 126.9 (CH), 126.7 (CH), 68.2 (CH), 57.1 (CH_2), 51.5 (C*), 28.8 (CH_3) ppm. **IR** (cm^{-1}): ν_{max} = 3292 (s), 3067 (m), 2972 (m), 2864 (m), 1682 (s), 1632 (s), 1610 (s), 1603 (s), 1551 (s), 1418 (s), 1356 (s), 1263 (s), 1223 (m), 1003 (s), 852 (s), 785 (s), 725 (s), 702 (s), 660 (m). **HRMS** (ESI^+) calculated for $C_{16}H_{20}N_2O_2$ (MH^+) 273.1598, found 273.1599.



tetrazolyl pyrrolidine *rac*-6a: To a solution of imine **2a** (33 mg, 0.25 mmol, 1.0 equiv) in TFE (0.2 M) were added $TMSN_3$ (38 µl, 0.28 mmol, 1.1 equiv) and *t*-butyl isocyanide (32 µL, 0.28 mmol, 1.1 equiv). The reaction mixture was stirred for 48 hr at 40 °C. The suspension was concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent of EtOAc, to obtain compound *rac*-**6a** (39 mg, 0.15 mmol, 60 %) as a yellow solid. **R_f** = 0.09 (EtOAc). **m.p.:** 85.5 – 89.3 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 6.36 (dd, *J* = 5.9 Hz, *J* = 3.1 Hz, 1H, $NHCH_2CHCHCH$=), 6.26 (dd, *J* = 5.9, 3.0 Hz, 1H, NHCHCHCHCH=), 4.11 (d, *J* = 3.6 Hz, 1H, NHC*H*), 3.41 (dt, *J* = 8.6 Hz, *J* = 3.9 Hz, 1H, NHCHC*H*), 3.20 – 3.05 (m, 2H, $NHCH_2$, $NHCH_2CH$), 2.90 (s, 2H, $NHCH_2CHCH_2CH$), 2.54 (dd, *J* = 11.9 Hz, *J* = 3.7 Hz, 1H, $NHCH_2$), 2.11 (s, 1H, N*H*), 1.74 (s, 9H, CH_3), 1.63 – 1.54 (m, 2H, $CHCH_2CH$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 157.1 (C*), 137.6 (CH), 134.8 (CH), 61.2 (C*), 56.7 (CH), 54.8 (CH), 53.8 (CH_2), 49.9 (CH_2), 49.8 (CH), 46.1 (CH), 45.8 (CH), 30.2 (CH_3) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3337 (w), 2964 (m), 2937 (m), 1431 (w), 1389 (m), 1086 (m), 1032 (w), 862 (s), 833 (s), 800 (s), 748 (s), 708 (s), 681 (s). **HRMS** (ESI): *m/z* calculated for $C_{14}H_{22}N_5$ $[M+H]^+$: 260.1870, found: 260.1880.

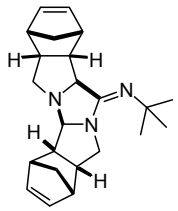


tetrazolyl pyrrolidine *rac*-6b: To a solution of imine **2a** (33 mg, 0.25 mmol, 1.0 equiv) in TFE (0.05 M) were added $TMSN_3$ (70 µl, 0.50 mmol, 2.0 equiv) and benzyl isocyanide (59 µL, 0.50 mmol, 2.0 equiv). The reaction mixture was stirred for 48 hr at 40 °C. The suspension was concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent of EtOAc, to obtain compound *rac*-**6b** (55 mg, 0.19 mmol, 74 %) as a yellow oil. **R_f** = 0.09 (EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.44 – 7.31 (m, 3H, *Ph*), 7.23 – 7.18 (m, 2H, *Ph*), 6.33 – 6.25 (m, 1H, $NHCH_2CHCHCH$=), 6.15 – 6.06 (m, 1H, NHCHCHCHCH=), 5.81 – 5.61 (m, 2H, $PhCH_2$), 3.79 (d, *J* = 3.5 Hz, 1H, NHC*H*), 3.51 – 3.43 (m, 1H, NCHC*H*), 3.03 – 2.94 (m, 1H, $NHCH_2CH$), 2.87 (s, 1H $NHCH_2CHCH$), 2.84 – 2.74 (m, 2H, $NHCH_2$, NHCHCHC*H*), 2.59 (dd, *J* = 12.4 Hz, *J* = 3.6 Hz, 1H, $NHCH_2$), 1.88 (s, 1H, N*H*), 1.55 – 1.45 (m, 2H, $CHCH_2CH$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 156.5 (C*), 137.0 (CH), 135.4 (CH), 134.3 (C*), 129.2 (CH), 128.8 (CH), 127.8 (CH), 55.6 (CH), 53.4 (CH_2), 52.6 (CH), 51.2 (CH_2), 49.6 (CH_2), 48.8 (CH), 46.4 (CH), 46.0 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2962 (w), 1497 (m), 1481 (w), 1456 (m), 1437 (m), 1248, 1165 (m), 1101 (s), 1076 (w), 864 (w), 723 (s), 710 (s), 662 (m), 619 (m). **HRMS** (ESI): *m/z* calculated for $C_{17}H_{20}N_5$ $[M+H]^+$: 294.1713, found: 294.1705.

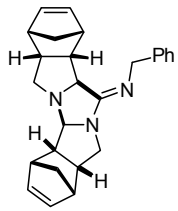


2,3-*trans*-tetrazolyl pyrrolidine *rac*-6c (major) 2,3-*cis*-tetrazolyl pyrrolidine *rac*-6c' (minor): To a solution of imine **2c** (28 mg, 0.25 mmol, 1.0 equiv) in TFE (0.2 M) were added

$TMSN_3$ (38 µl, 0.28 mmol, 1.1 equiv) and *t*-butyl isocyanide (32 µL, 0.28 mmol, 1.1 equiv). The reaction mixture was stirred for 48 hr at 40 °C. The suspension was concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient (100:5 → 100:10 v/v DCM:MeOH), to obtain compounds *rac*-**6c** (44 mg, 0.19 mmol, 75 %) as a yellow solid and *rac*-**6c'** (6 mg, 0.02 mmol, 9 %) as a yellow oil in a 8.3:1 diastereoisomeric ratio. **6c**: $\mathbf{R_f}$ = 0.18 (EtOAc). **m.p.:** 70.2 – 76.6 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.14 (d, *J* = 4.9 Hz, 1H, NHC*H*), 3.45 (dd, *J* = 11.4 Hz, *J* = 8.2 Hz, 1H, CH_2NH), 3.18 – 3.08 (m, 1H, NHCHC*H*), 2.94 – 2.80 (m, 1H, $NHCH_2CH$), 2.58 (dd, *J* = 11.6 Hz, *J* = 5.8 Hz, 1H, CH_2NH), 2.30 – 2.15 (m, 1H, N*H*), 1.87 – 1.79 (m, 2H, $NHCH_2CHCH_2CH_2CH_2$), 1.77 (s, 9H, $(CH_3)_3$), 1.72 – 1.59 (m, 2H, $CHCH_2CH_2$), 1.51 – 1.38 (m, 2H, $NHCH_2CHCH_2CH_2CH_2$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.5 (C*), 61.5 (C*), 61.1 (CH), 54.8 (CH_2), 51.5 (CH), 45.3 (CH), 32.7 (CH_2), 32.5 (CH_2), 30.3 (CH_3), 26.4 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3288 (w), 2961 (m), 1458 (w), 1389 (m), 1294 (w), 1236 (m), 1144 (m), 1115 (w), 1101 (m), 1082 (w), 860 (s), 837 (m), 708 (m), 609 (m), 581 (m). **HRMS** (ESI): *m/z* calculated for $C_{12}H_{22}N_5$ $[M+H]^+$: 236.1870, found: 236.1875. **6c'**: $\mathbf{R_f}$ = 0.01 (EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.55 (d, *J* = 7.3 Hz, 1H, NHC*H*), 3.15 – 3.08 (m, 1H, N*H*), 3.00 (d, *J* = 4.5 Hz, 2H, NHCH_2), 2.90 – 2.81 (m, 1H, NHCHC*H*), 2.79 – 2.71 (m, 1H, $NHCH_2CH$), 2.03 – 1.96 (m, 1H, $NHCH_2CHCH_2$), 1.75 (s, 9H, $(CH_3)_3$), 1.73 – 1.68 (m, 1H, $NHCH_2CHCH_2CH_2$), 1.40 – 1.20 (m, 3H, $NHCH_2CHCH_2CH_2CH_2$), 1.11 – 1.00 (m, 1H $NHCHCHCH_2$) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 153.8 (C*), 61.4 (C*), 58.4 (CH), 53.2 (CH_2), 48.9 (CH), 46.4 (CH), 34.2 (CH_2), 30.2 (CH_3), 28.8 (CH_2), 28.1 (CH_2) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2941 (s), 2862 (s), 1448 (m), 1340 (m), 1211 (w), 1059 (w), 633 (s), 534 (s). **HRMS** (ESI): *m/z* calculated for $C_{12}H_{22}N_5$ $[M+H]^+$: 236.1870, found: 236.1866.

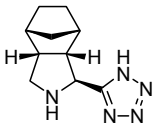


imidazolidin-4-imine *rac*-9a:[30] To a solution of imine **2a** (66 mg, 0.50 mmol, 2.0 equiv) in TFE (0.4 M) were added $TMSN_3$ (52 µl, 0.38 mmol, 1.5 equiv) and *t*-butyl isocyanide (43 µL, 0.38 mmol, 1.5 equiv). The reaction mixture was stirred for 48 hr at 40 °C. The suspension was concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient of MeOH in DCM (100:0.5 → 100:20 v/v DCM:MeOH), to obtain compound *rac*-**9a** (37 mg, 0.11 mmol, 42 %) as a yellow solid. $\mathbf{R_f}$ = 0.27 (DCM:MeOH 20:1 v/v). **m.p.:** 105.0 – 118.4 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.31 – 6.12 (m, 4H, C*H*=C*H*), 3.83 (t, *J* = 11.1 Hz, 1H, C*H*), 3.78 – 3.65 (m, 2H,C*H*), 3.39 – 3.16 (m, 2H, C^*NCH_2CH, C*H*), 3.04 – 2.98 (m, 2H, C*H*), 2.92 – 2.62 (m, 7H, C^*NCH_2CH, C*H*), 2.22 (dd, *J* = 13.0 Hz, *J* = 8.6 Hz, 1H, C*H*), 1.81 (d, *J* = 8.3 Hz, 1H, CH_2), 1.64 (dd, *J* = 13.3 Hz, *J* = 8.5 Hz, 2H, CH_2, C*H*), 1.48 (d, *J* = 8.4 Hz, 1H, C*H*), 1.36 (s, 9H, $(CH_3)_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.9 (C*), 138.0 (CH), 137.6 (CH), 136.3 (CH), 134.9 (CH), 85.3 (CH), 54.4 (CH_2), 50.4 (CH_2), 50.1 (CH), 49.7 (CH), 45.5 (CH), 45.0 (CH), 44.5 (CH), 31.5 (CH_3), 29.8 (C*) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 3053 (w), 2959 (m), 2868 (m), 2008 (s), 1649 (s), 1450 (w), 1387 (w), 1339 (w), 1221 (m), 1186 (m), 1107 (w), 1094 (w), 843 (w), 793 (m), 731 (s). **HRMS** (ESI): *m/z* calculated for $C_{23}H_{32}N_3$ $[M+H]^+$: 350.2591, found: 350.2597.



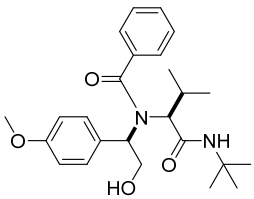
imidazolidin-4-imine *rac*-9b:[30] To a solution of imine **2a** (66 mg, 0.50 mmol, 2.0 equiv) in TFE (0.4 M) were added $TMSN_3$ (52 µl, 0.38 mmol, 1.5 equiv) and benzyl isocyanide (44 µL, 0.38 mmol, 1.5 equiv). The reaction mixture was stirred for 48 hr at 40 °C. The suspension was concentrated *in vacuo*. Purification was achieved by flash chromatography (SiO_2) with an eluent gradient of MeOH in DCM (100:0.5 → 100:20 v/v DCM:MeOH), to obtain compound *rac*-**9b** (87 mg, 0.23 mmol, 90 %) as a yellow solid. $\mathbf{R_f}$ = 0.61 (DCM:MeOH 20:1 v/v). **m.p.:** 77.7 – 88.7 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35 – 7.16 (m, 5H, *Ph*), 6.17 (d, *J* = 21.2 Hz, 4H, C*H*=C*H*), 4.48 (d, *J* = 14.9 Hz, 1H, CH_2Ph), 4.33 (d, *J* =

15.0 Hz, 1H, CH_2Ph), 3.83 (t, *J* = 10.8 Hz, 1H, C*NCH_2), 3.77 (d, *J* = 4.1 Hz, 1H, C*H*), 3.52 (d, *J* = 7.0 Hz, 1H, C*NC*H*), 3.29 – 3.17 (m, 2H, C*NCH$_2$C*H*, C*H*), 2.85 (d, *J* = 3.9 Hz, 1H, C*H*), 2.80 – 2.73 (m, 3H, C*H*), 2.71 (s, 1H, C*H*), 2.64 – 2.59 (m, 2H, C*NCH_2, C*CHNCH_2), 2.28 (dd, *J* = 13.0 Hz, *J* = 7.7 Hz, 1H, C*CHNCH_2), 1.69 (d, *J* = 8.0 Hz, 1H, CHCH_2CH), 1.60 (d, *J* = 8.4 Hz, 1H, CHCH_2CH), 1.54 (d, *J* = 8.4 Hz, 1H, CHCH_2CH), 1.45 (d, *J* = 8.6 Hz, 1H, CHCH_2CH) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 165.5 (C*), 140.5 (C*), 137.3 (CH), 137.1 (CH), 136.7 (CH), 135.5 (CH), 128.6 (CH), 127.3 (CH), 126.9 (CH), 87.6 (CH), 69.0 (CH), 55.4 (CH), 54.3 (CH_2), 54.1 (CH_2), 53.4 (CH_2), 52.8 (CH_2), 52.7 (CH_2), 49.9 (CH), 48.9 (CH_2), 45.3 (CH), 45.0 (CH), 44.5 (CH), 44.3 (CH) ppm. **IR** (neat): ν_{max} (cm^{-1}) = 2015 (w), 1649 (s), 1452 (m), 1310 (w), 1296 (m), 1254 (m), 1219 (w), 1090 (w), 1022 (w), 731 (s), 696 (s), 696 (s), 577 (m). **HRMS** (ESI): *m/z* calculated for $C_{26}H_{30}N_3$ $[M+H]^+$: 384.2434, found: 384.2430.

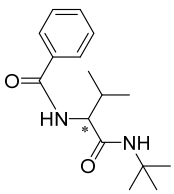


proline-derived tetrazole 7b: To a solution of 10% palladium on carbon (38 mg, 0.1 equiv) in DCM (0.1 mL) and methanol (4 mL) was added 1,5-disubstituted tetrazole **6b** (23 mg, 0.07 mmol). The reaction mixture was stirred for 72 hr at rt under a hydrogen atmosphere (1 atm.). The reaction mixture was filtered over Celite®, washed with methanol and concentrated *in vacuo*. No purification was necessary. Compound **7b** (14 mg, 0.07 mmol) was obtained as a yellow solid.

General procedure for screening in Figure 4: A 50 mM aq. Tris-HCl buffer solution (total volume: 500 µL) containing 2.5 mM substrate **10a**, 1 µM BVMO, 10 mM phosphite, 5 µM PTDH (only for PAMO), 20 µM NADPH, 0.25 mM acetanilide as internal standard and DMSO (5% v/v) was shaken at 400 rpm for 4 h at rt. The solution was extracted with EtOAc (3 x 500 µL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in *iso*-propanol and analyzed with HPLC.

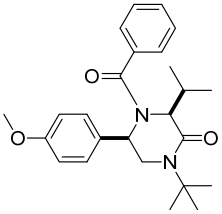


dipeptide *rac*-15a (major): To a solution of *rac*-2-amino-2-(4-methoxyphenyl)ethan-1-o l (0.08 g, 0.50 mmol) in the solvent of choice (4.5 mL), were added isobutyraldehyde (46.0 µL, 0.50 mmol), benzoic acid (61 mg, 0.50 mmol) and 2-isocyano-2-methylpropane (70 µL, 0.60 mmol). The mixture was stirred for 72 h at rt and the solvent was evaporated *in vacuo*. Purification by flash chromatography (SiO_2) with an eluent gradient (3:1 → 0:1 v/v *c*-Hex:EtOAc) yielded compound *rac*-**15a** (154 mg, 0.18 mmol, 36%) as a white solid. **^{1}H NMR** ($CDCl_3$, 400.1 MHz) : δ 7.79 (bs, 1H, O*H*), 7.56–7.53 (m, 2H, Ph), 7.50–7.43 (m, 3H, Ph), 7.10 (d, *J* = 8.4 Hz, 2H, C(OMe)CHC*H*), 6.80 (d, *J* = 8.4 Hz, 2H, C(OMe)C*H*), 5.08 – 5.04 (m, 1H, C*H*CH$_2$), 4.43 (dd, *J* = 11.2, 10.8 Hz, 1H, CH_2), 3.80 – 3.74 (m, 1H, CH_2), 3.77 (s, 3H, OCH_3), 3.25 (d, *J* = 10.8 Hz, 1H, NCHCH), 2.92 – 2.84 (m, 1H, C*H*(CH$_3$)$_2$), 1.39 (s, 9H, C(CH_3)$_3$), 0.85 (d, *J* = 6.4 Hz, 3H, CHCH_3), 0.22 (d, *J* = 6.8 Hz, 3H, CHCH_3) ppm. **^{13}C NMR** ($CDCl_3$, 500.2 MHz): δ 174.3 (C*), 172.3 (C*), 159.4 (C*), 137.6 (C*), 133.3 (CH), 129.9 (CH), 129.0 (CH), 128.2 (C*), 127.0 (CH), 114.2 (CH), 68.6 (CH), 63.3 (CH), 61.2 (CH_2), 55.3 (CH_3), 51.3 (C*), 28.6 (CH_3), 27.5 (CH), 20.3 (CH_3), 19.2(CH_3) ppm.



dipeptide *rac*-16a: Dipeptide **15a** (0.11 g, 0.25 mmol) was dissolved in TFA (1 mL) and the mixture was stirred for 1 h at rt. After evaporation of the solvent *in vacuo*, purification by flash chromatography (SiO_2) with an eluent system of *c*Hex and EtOAc (4:1 v/v) yielded the compound *rac*-**16a** (0.04 g, 0.14 mmol, 55%) as a white solid. **^{1}H NMR** ($CDCl_3$, 400.1 MHz) : δ 8.83 (d, 2H, *J* = 7.6 Hz, C(O)C*C*H*), 7.51 – 7.42 (m, 5H,

Ph), 5.83 (bs, 1H, N*H*), 4.33 (dd, *J* = 7.6, 8.0 Hz, 1H, NHC*H*), 3.81 (bs, 1H, N*H*), 2.20 – 2.05 (m, 1H, C*H*CH$_3$), 1.37 (s, 9H, C(C*H*$_3$)$_3$), 1.01 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$) ppm.



piperazin-2-one *rac*-17a: To a solution of dipeptide **15a** (184 mg, 0.4 mmol) in THF (4 mL), were added DEAD (469 mg, 1.1 mmol) and PPh$_3$ (229, 0.9 mmol). The mixture was stirred for 2 h at 55 °C, after which the solvent was evaporated *in vacuo*. Purification by flash chromatography (SiO_2) with an eluent system of MeOH in CH_2Cl_2 (1:100 v/v) yielded compound *rac*-**17a** (124 mg, 0.3 mmol, 76%) as a white solid. **^{1}H NMR** ($CDCl_3$, 400.1 MHz): δ 7.54 – 7.52 (m, 2H, C(O)C*C*H), 7.44 – 7.37 (m, 3H, Ph), 7.13 (d, *J* = 8.4 Hz, 2H, C(OMe)CHC*H*), 6.78 (d, *J* = 8.4 Hz, 2H, C(OMe)C*H*), 4.48 – 4.42 (m, 2H, CHC*H*$_2$), 4.03 – 3.98 (m, 1H, C*H*CH$_2$), 3.76 (s, 3H, OC*H*$_3$), 3.41 (d, *J* = 7.6 Hz, 1H, NC*H*CH), 2.11 – 2.06 (m, 1H, C*H*CH$_3$), 1.38 (s, 9H, C(C*H*$_3$)$_3$), 1.21 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 0.71 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$) ppm.

5.5 References and Notes

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27 Proposed structure **2b'** was determined with ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR spectroscopy.

28 Signal is overlapped with H_2O or MeOH. The H_2O was an impurity in the solvent MeOD-d_4.

29 Signals are overlapped with the signals of the rotamers.

30 The relative configuration was deduced according to previous diastereoselective functionalizations of imine **2a** (see ref. 6) and by minimum energy calculations with Chem3D Pro (double 2,3-*trans* diastereoisomer (**9a**): E = 111.1919 kcal/mol versus double-*cis* diastereoisomer: E = 163.4718 kcal/mol.

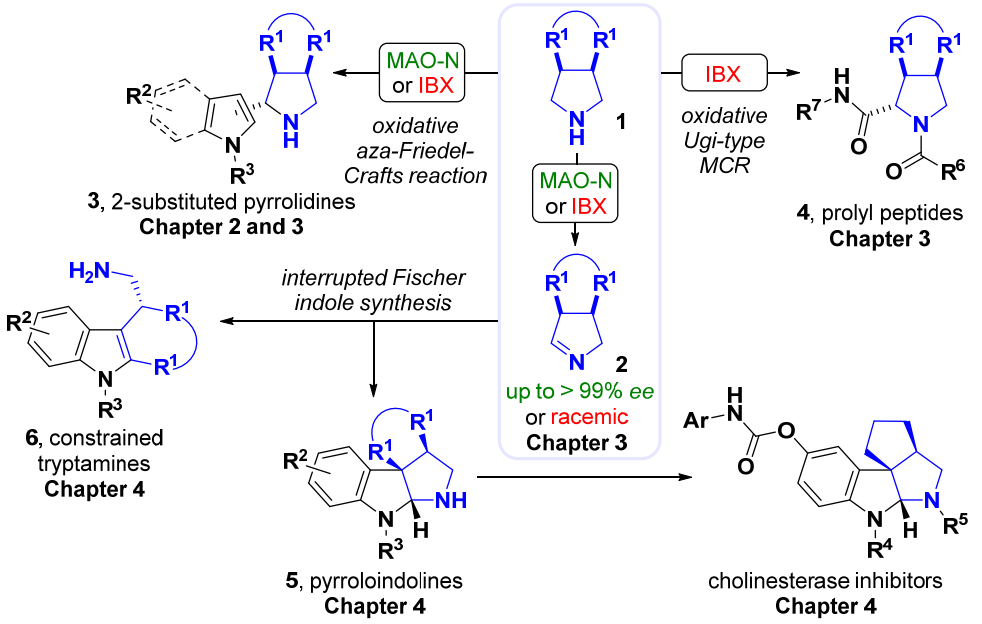
Summary

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



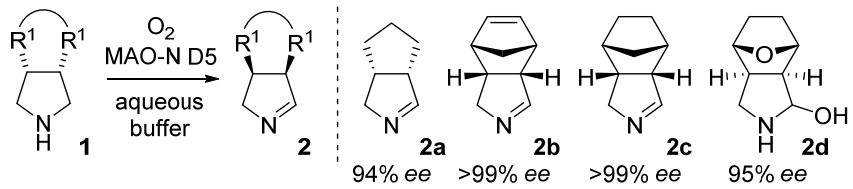
Scheme 1. *meso*-Pyrrolidines as templates for oxidative cascade processes.

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.

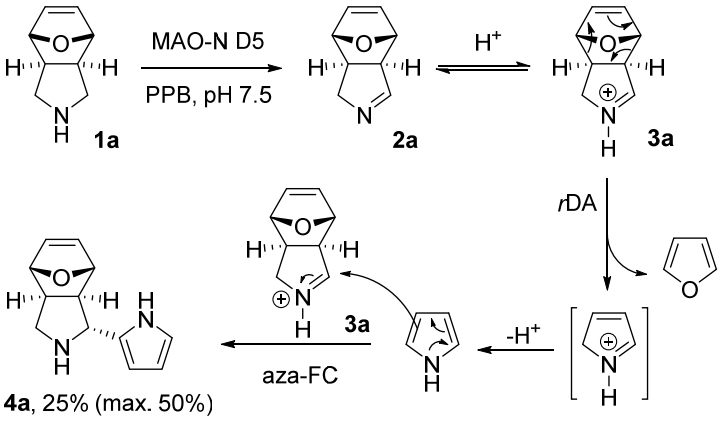
The high potential for the application of biocatalysts in organic synthesis has been clearly demonstrated in the past decades, but enzymes are still not fully integrated in the synthetic toolbox yet. We provided a guideline on how to implement biocatalysis in synthetic chemistry in **Chapter 1**. For 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

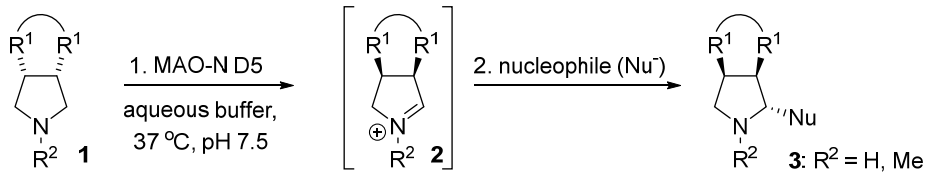


Scheme 2. Biocatalytic oxidation of a range of *meso*-pyrrolidines.



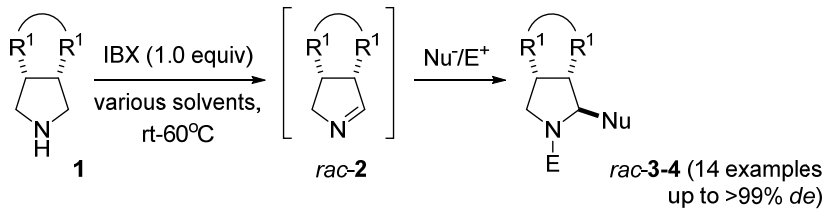
Scheme 3. MAO-*r*DA-aza-FC sequence. PPB = potassium phoshate buffer

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.

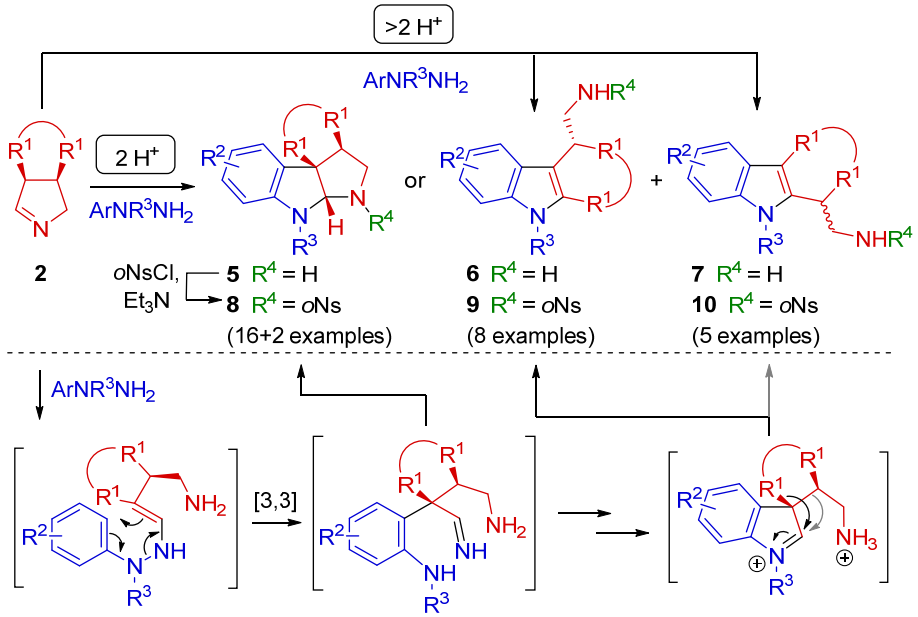
In light of our continued interest in the functionalization of imines, in particular 1-pyrrolines, we envisioned a clean and fast chemical oxidation of unactivated *meso*-pyrrolidines. Given the recent regained interest in hypervalent iodine reagents, we explored their ability to oxidize aliphatic amines. 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.

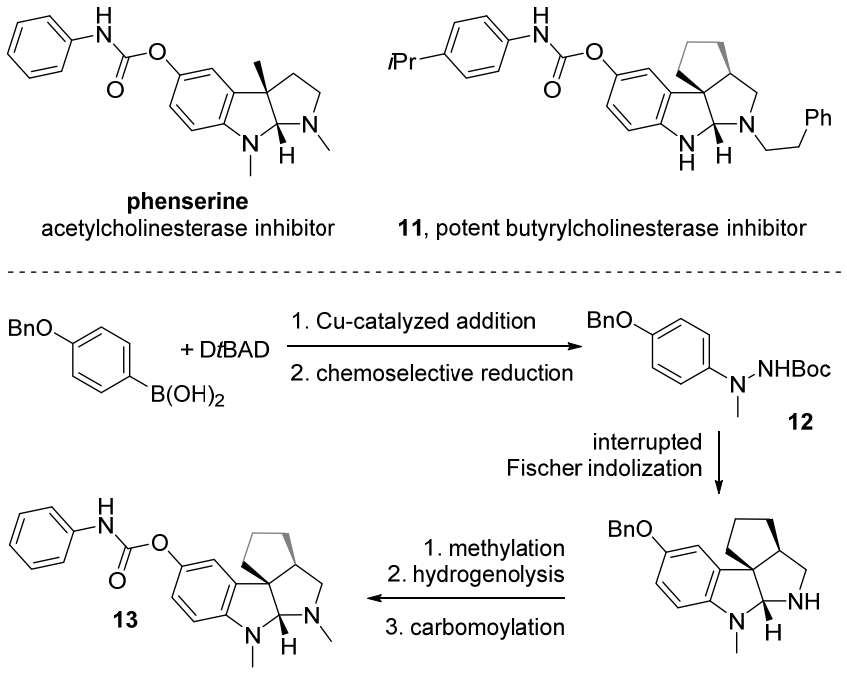
We serendipitously discovered that a subtle change in the reaction conditions of the interrupted Fischer indole synthesis in terms of stoichiometry of the acid mediator resulted in a rearrangement of the polycyclic scaffold to afford constrained tryptamine derivatives **6** and **7** selectively (Scheme 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_α-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_α-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

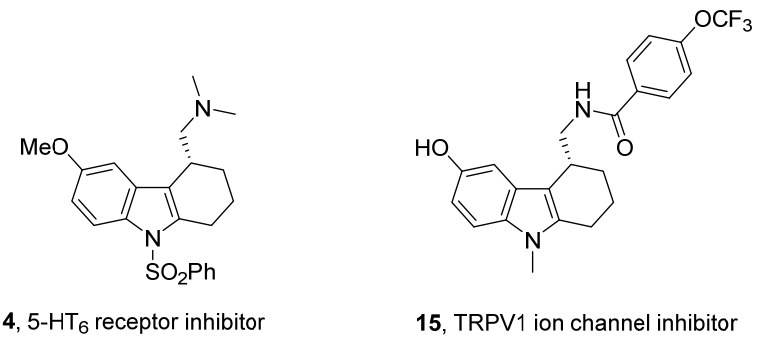


Figure 1. Examples of pharmaceutically relevant constrained tryptamines.

(**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.

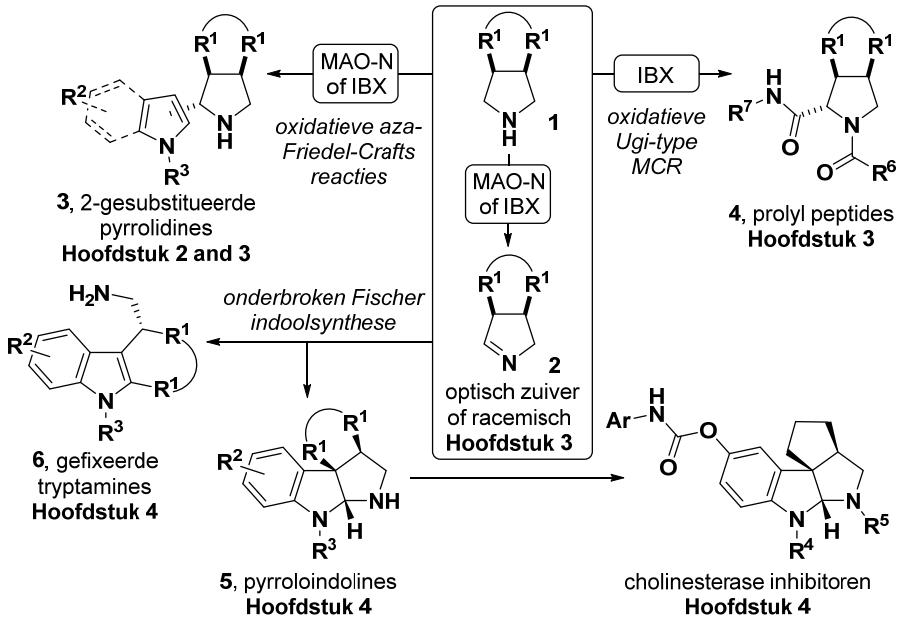
Samenvatting

Cascadereacties met een Twist

Chemoenzymatische Synthese van Biologisch Relevante Verbindingen

De synthese van complexe en biologisch relevante moleculen wordt vaak gerealiseerd met lange lineaire syntheses. De ontwikkeling van slimmere en efficiëntere synthetische methoden is in dit opzicht een voortdurende uitdaging. Het gebruik van convergente strategieën vanuit kleine chemische bouwstenen stelt ons in staat om nieuwe analogen met meerdere punten voor diversificatie te synthetiseren. Bovendien kunnen het aantal synthetische stappen en de daaraan gerelateerde afvalproductie en energieverbruik gereduceerd worden door meerdere chemische omzettingen te combineren in één reactievat. Cascade- en multicomponentreacties zijn belangrijke hulpmiddelen om deze doelen te bereiken. Cascadereacties worden gedefinieerd als sequentiële conversies waarbij het product van de eerste transformatie gebruikt wordt als het substraat van de volgende, enzovoorts. Deze dominoreeks van intra- en intermoleculaire reactiestappen verloopt via reactieve intermediairen totdat een stabiel product gevormd wordt. Multicomponentreacties zijn selectieve reacties tussen meer dan twee reactanten waarbij een product gevormd wordt dat significante delen (idealiter alle atomen) van alle reagentia bevat.

De asymmetrie in de synthese van bioactieve verbindingen wordt vaak geïntroduceerd door het gebruik van organokatalysatoren en zware metalen, terwijl de toepassing van de natuur als chiraal template vaak een elegant alternatief is. Deze

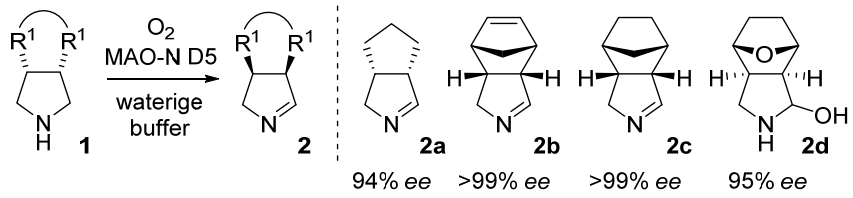


Schema 1. *meso*-Pyrrolidines als startpunt voor oxidatieve cascadereacties.

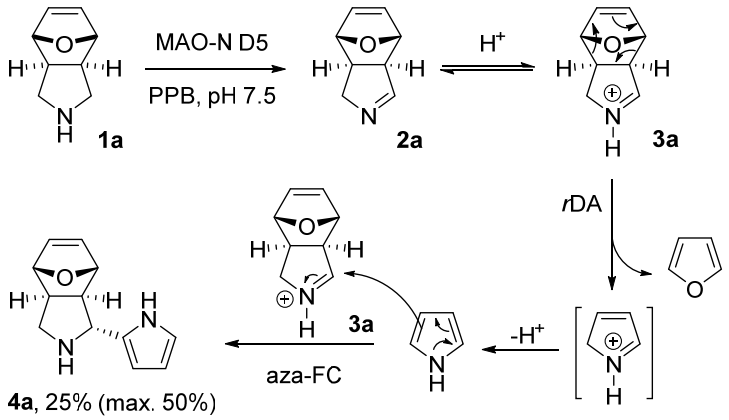
aanpak kan worden gerealiseerd door het gebruik van chirale moleculen uit de natuur als uitgangsmateriaal. Een andere veel gebruikte aanpak is het gebruik van enzymen, de asymmetrische katalysatoren van de natuur, die ongeëvenaarde chemo-, regio- en stereoselectiviteit bieden. De doelstelling van het onderzoek in dit proefschrift is de ontwikkeling van nieuwe en efficiënte methoden voor de synthese van farmaceutisch en biologisch interessante verbindingen. De toepassing van **biokatalyse** voor de synthese van substraten voor innovatieve **cascadereacties** was daarbij een belangrijke doelstelling. Voor een overzicht van de diversiteit aan verbindingen die met innovatieve methoden tijdens het onderzoek voor dit proefschrift gesynthetiseerd zijn, zie Schema 1.

Het hoge potentieel voor de toepassing van biokatalysatoren in organische synthese is in de laatste decennia duidelijk aangetoond, maar enzymen zijn nog steeds niet volledig geïntegreerd in de zgn. synthetische toolbox. In **Hoofdstuk 1** hebben wij een handleiding geschreven voor de toepassing van biokatalyse in de synthetische chemie. Hiervoor hebben we de belangrijkste biokatalytische strategieën achter elkaar gezet. De vruchtbare vereniging van biokatalyse en organische synthese is geïllustreerd met een aantal relevante voorbeelden. Hiermee hopen we de lezer te inspireren om buiten hun referentiekader te denken en biokatalyse te beschouwen als een betrouwbaar middel in asymmetrische synthetische transformaties.

De oxidatie van *meso*-pyrrolidines met een gemodificeerde variant van monoamine oxidase (MAO-N D5) voor de synthese van bicyclische imines in (zeer) hoge enantioselectiviteit was eerder beschreven door onze groep. Wij hebben vervolgens onderzocht of het enzym een substraat met een extra heteroatoom accepteert, omdat alleen koolstofring-gefuseerde pyrrolidines bekend zijn als geschikte substraten voor de biokatalysator (Schema 2). Tot onze tevredenheid bleek een substraat met een zuurstof atoom in de gefuseerde ring van het *meso*-pyrrolidine ook geschikt voor de biokatalytische oxidatie. Hemiaminal **2d** werd geïsoleerd als het



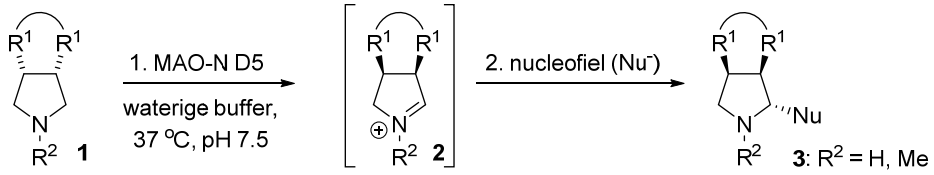
Schema 2. Biokatalytische oxidatie van verschillende *meso*-pyrrolidines.



Schema 3. MAO-*r*DA-aza-FC cascadereactie. PPB = kalium fosfaatbuffer

product van deze reactie is 95% enantiomere overmaat (*ee*) en 81% opbrengst (**Hoofdstuk 2**).

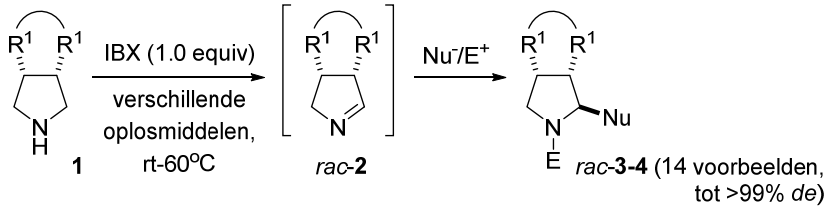
Het overzicht in **Hoofdstuk 1** geeft onder andere weer dat de combinatie van enzymatische activering met synthetische transformaties in milieuvriendelijke oplosmiddelen bijzonder interessant is. Wij ondervonden dat de biokatalytische oxidatie van het furaan-gebaseerde *meso*-pyrrolidine **1a** in een waterige buffer resulteerde in een dominoreactie van oxidatie gevolgd door een *retro*-Diels–Alder reactie en een aza-Friedel–Crafts additie (MAO-*r*DA-aza-FC, Schema 3). Blijkbaar is de waterige buffer een voldoende effectieve proton en/of waterstofbrug donor om het intermediaire imine **2a** te activeren voor een aza-FC reactie (en een *r*DA), terwijl activering van deze verbinding met een sterk Lewis- of Brønstedzuur nodig is in organische oplosmiddelen. We voorzagen de mogelijkheid om de *r*DA nevenreactie van het intermediaire imine te voorkomen door een *meso*-pyrrolidine te gebruiken die deze reactie niet kan ondergaan. Met een geoptimaliseerde twee-fase procedure in één reactievat hebben we de α-functionalisering van een reeks pyrrolidines met een verscheidenheid aan koolstof nucleofielen onder milieuvriendelijke condities gerealiseerd (Schema 4, **Hoofdstuk 2**). De gewenste 2-gesubstitueerde pyrrolidines werden verkregen als enkele diastereoisomeren in redelijke tot goede opbrengst en een over het algemeen hoge enantioselectiviteit. Deze strategie heeft net zoals de meeste methoden een aantal beperkingen, namelijk de lage enantioselectiviteit met tertiaire amines (R^2 = Me) en de beperking tot het substraatbereik van de biokatalysator. Onze chemoenzymatische oxidatieve aza-FC reactie heeft echter



Schema 4. Chemoenzymatische oxidatieve aza-Friedel-Crafts reactie.

duidelijke voordelen, omdat deze significant milieuvriendelijker is dan de gemiddelde α-functionalisering van pyrrolidines.

Gezien onze interesse in de functionalisering van imines, met name 1-pyrrolines, wilden we een snelle en schone chemische oxidatie van ongeactiveerde *meso*-pyrrolidines ontwikkelen. Vanwege de recente hernieuwde interesse in hypervalente joodreagentia hebben we hun vermogen om alifatische amines te oxideren onderzocht. Tot ons genoegen hebben we de eerste *o*-jodoxybenzoëzuur (IBX) gemedieerde oxidatie van ongeactiveerde amines ontwikkeld (Schema 5, **Hoofdstuk 3**). Deze doeltreffende methode geeft toegang tot bi- en tricyclische imines (±)-**2**, maar beperkt zich tot 1-pyrrolines die niet tautomeriseren onder de reactiecondities. De chemische ruimte is verder onderzocht door middel van oxidatieve Ugi-type en aza-FC reacties, welke zeer diastereoselectief bleken te zijn.

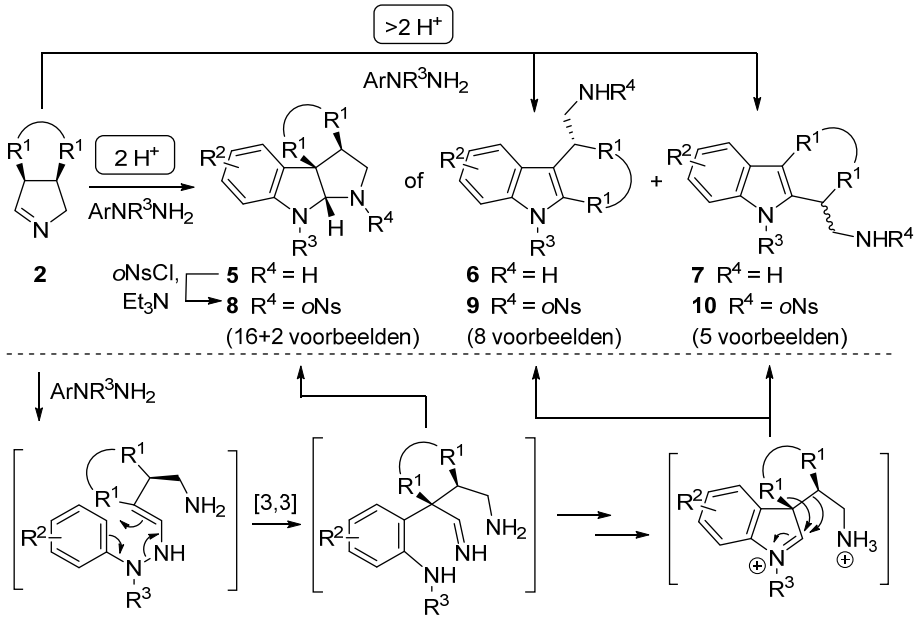


Schema 5. Oxidatieve α-functionalisering van *meso*-pyrrolidines **1** met IBX.

Om nieuwe methoden voor de synthese van complexe moleculen te ontwikkelen, hebben we de toepasbaarheid van onze biokatalytisch gegenereerde chirale bouwstenen **2** in cascadereacties onderzocht door ze als aminoaldehydes te beschouwen. We hebben een asymmetrische chemoenzymatische synthese van natuurstofachtige pyrroloindolines **5** met een *cis*-configuratie van beide [3.3.0] bicyclische systemen ontwikkeld door middel van een onderbroken Fischer indoolsynthese tussen arylhydrazines en bicyclische imines (Schema 6, **Hoofdstuk 4**). Een breed scala aan elektronenrijke en elektronenarme arylhydrazines bleken

geschikte substraten voor deze reactie. Voor *meta*-gesubstitueerde arylhydrazines was een interessante trend zichtbaar afhankelijk van de sterische grootte van het substituent.

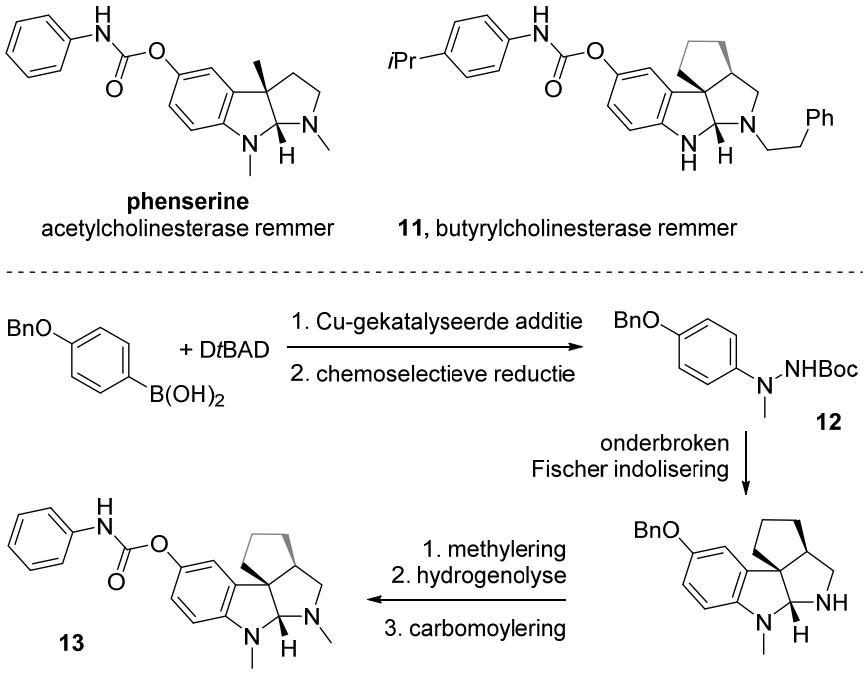
We ontdekten dat een kleine verandering in de reactiecondities van de onderbroken Fischer indoolsynthese wat betreft de stoechiometrie van het zuur resulteerde in een selectieve omlegging van het polycyclische molecuul **5** naar de gefixeerde tryptaminederivaten **6** en **7** (Schema 6, **Hoofdstuk 4**). Deze omlegging bleek te werken voor relatief elektronenrijke en elektronenarme systemen en zelfs voor heteroaromatische verbindingen en is dus breed toepasbaar.



Schema 6. Onderbroken Fischer indoolsynthese van pyrroloindolines of gefixeerde tryptamines en essentiële intermediairen in het voorgestelde mechanisme.

De omlegging gaf interessante resultaten qua regioselectiviteit van de migrerende koolstof–koolstof binding, die goed verklaarbaar zijn op basis van elektronische argumenten. Verder hebben we ook een plausibel mechanisme omschreven voor de vorming van de pyrroloindolines en gefixeerde tryptamines, maar een uitgebreide computationele studie is nodig om de invloed van sterische factoren te onderzoeken. Deze schakelbare chemoenzymatische synthese van pyrroloindolines of serotonine analogen onderstreept de vruchtbare combinatie van biokatalyse en cascadereacties.

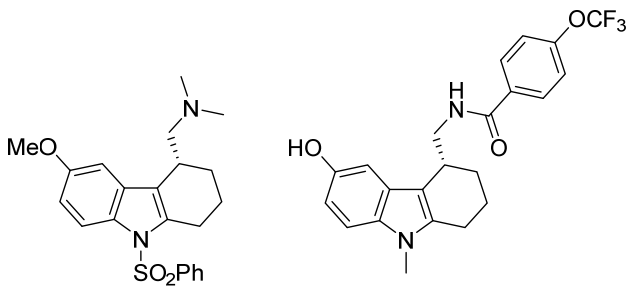
De pyrroloindoline-gebaseerde verbindingen phenserine en norcymserine hebben een hoog therapeutisch potentieel tegen de ziekte van Alzheimer en andere neurodegeneratieve ziektes. Daarom wilden we analogen synthetiseren van deze farmaceutisch relevante verbindingen. Via een innovatieve chemoselectieve Boc-reductie konden we het N_{α}-gemethyleerde hydrazine **12** genereren als uitgangsmateriaal voor de cascadesynthese van phenserine-analoog **13** (Scheme 7). Na de onderbroken Fischer indoolreactie tussen **12** en het imine (–)-**2a** werd analoog **13** verkregen na *N*-methylering, hydrogenolyse en carbamoylering.



Schema 7. Cholinesterase remmers phenserine en phenethylnorcymserine analoog **11** en onze strategie voor de synthese van phenserine-analoog **13**.

Aangezien bepaalde gefixeerde tryptamines invloed kunnen uitoefenen op de 5-HT_6 receptor, een belangrijk doelwit van nieuwe medicijnen voor onder andere de behandeling van de ziekte van Alzheimer, hebben deze verbindingen veel denkbare therapeutische toepassingen. Daarnaast zijn moleculen met deze basisstructuur bekend als selectieve remmers van melatonine receptoren en ook het TRPV1 ionkanaal. Wij hebben een bekende antagonist van de 5-HT_6 receptor (**14**), beter bekend als het gefixeerde analoog van MS-245, gesynthetiseerd door middel van een

driestapssynthese gebaseerd op de onderbroken Fischer indoolsynthese. Daarnaast hebben we de TRPV1 ionkanaal remmer **15** gesynthetiseerd met onze innovatieve methodologie. Deze bioactieve verbindingen zijn met onze methode goed toegankelijk in optisch zuivere of racemische vorm door de toepassing van het bicyclische imine gesynthetiseerd door middel van biokatalytische (**Hoofdstuk 2**) of IBX-gemedieerde oxidatie (**Hoofdstuk 3**).



14, 5-HT_6 receptor remmer **15**, TRPV1 ionkanaal remmer

Figuur 1. Farmaceutisch relevante gefixeerde tryptamines.

Toekomstig onderzoek zal zich voornamelijk richten op de biologische activiteit van nieuwe analogen zoals **13** om nieuwe derivaten voor de farmaceutische industrie te identificeren. Aangezien zowel pyrroloindolines **5** als gefixeerde tryptamines **7** en **8** meerdere diversificatiepunten hebben, kunnen we een reeks van verbindingen met hoog therapeutisch potentieel genereren met onze strategie.

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List of Publications

Stereoselective Chemoenzymatic Oxidative aza-Friedel–Crafts Reactions of *meso*-Pyrrolidines in Aqueous Buffer
C. de Graaff, B. Oppelaar, O. Péruch, C. M. L. Vande Velde, B. Bechi, N. J. Turner, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.*, accepted.

Asymmetric Synthesis of Tetracyclic Pyrroloindolines and Constrained Tryptamines by a Switchable Cascade Reaction
C. de Graaff, L. Bensch, S. J. Boersma, R. C. Cioc, M. J. van Lint, E. Janssen, N. J. Turner, R. V. A. Orru, and E. Ruijter, *Angew. Chem., Int. Ed.* **2015**, *54*, 14133–14136.

IBX-Mediated Oxidation of Unactivated Cyclic Amines: Application in Highly Diastereoselective Oxidative Ugi-type and aza-Friedel–Crafts Reactions
C. de Graaff, L. Bensch, M. J. van Lint, E. Ruijter and R. V. A. Orru, *Org. Biomol. Chem.* **2015**, *13*, 10108–10112.

Recent Developments in Asymmetric Multicomponent Reactions
C. de Graaff, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969–4009.