Applications and Industrial Viability of Organocatalysed Mannich Reactions

Proefschrift

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door

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te Eindhoven
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<tr>
<td>ABTS</td>
<td>2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>ADHD</td>
<td>attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>Alb</td>
<td>α-aminoisobutyric acid</td>
</tr>
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<td>Ar</td>
<td>aryl</td>
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<td>ATH</td>
<td>asymmetric transfer hydrogenation</td>
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<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
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<td>1,1'-bi-2-naphthol</td>
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<td>BINS</td>
<td>binaphthyl disulfonic acid</td>
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<td>BBA</td>
<td>Brønsted acid-assisted chiral Brønsted acid</td>
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<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
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<td>BOP</td>
<td>benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate</td>
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<td>Bn</td>
<td>benzyl</td>
</tr>
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<td>diastereomeric excess</td>
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<td>diethyl azodicarboxylate</td>
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<td>DEAD</td>
<td>diisopropylazodicarboxylate</td>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<td>Dess-Martin periodinane</td>
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<td>dimethyl sulfide</td>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<td>DPEN</td>
<td>1,2-diphenyl-1,2-ethylenediamine</td>
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<td>Ed.</td>
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</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>El</td>
<td>electron ionisation</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
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<td>ESI</td>
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</tr>
<tr>
<td>HIV</td>
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</tr>
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<td>HOBt</td>
<td>1-hydroxynaphthalene-2,3-dicarboxylic acid</td>
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<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<td>isopropyl</td>
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<td>IR</td>
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</tr>
<tr>
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<td>low resolution mass spectrometry</td>
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<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
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<tr>
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<td>milli</td>
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<td>multiplep</td>
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<td>M</td>
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</tr>
<tr>
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<td>MTBE</td>
<td>methyl tert-butyl ether</td>
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<td>N-methylpyrrolidinone</td>
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<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>nPr</td>
<td>n-propyl</td>
</tr>
<tr>
<td>Ns</td>
<td>para-nitro-toluene sulfonyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Meaning</td>
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<td>--------------</td>
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<tr>
<td>o.n.</td>
<td>over night</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PBP</td>
<td>pyridinium bromide perbromide</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-methoxyphenyl protecting group</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
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<td>proline</td>
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<td>benzotriazol-1-yl-oxytriazenyl-2,2,6,6-tetramethyl-1-piperidinyloxyl-trifluoroacetophosphate</td>
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<tr>
<td>PTC</td>
<td>phase transfer catalyst</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
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<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SDS</td>
<td>sodium dodecyl sulfate</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>SMP</td>
<td>(S)-2-methoxy-methylpyrrolidine</td>
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GENERAL INTRODUCTION

1.1 Introduction

The concept of organocatalysis was recognised as early as in 1928 by Wolfgang Langenbeck\(^1\) (Fig. 1). Its synthetic potential, however, was for a long time not recognised until approximately one decade ago, when it was reinvented as a viable approach for producing enantiomerically pure compounds.

Figure 1 Early recognition of organocatalysis.\(^{1}\)

Dalko and Moisan\(^2\) defined organocatalysis as "the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal ion."

While for a long time only isolated cases existed, around the year 2000 numerous successful examples of asymmetric organocatalytic reactions had been developed.\(^3\) In this Chapter we aim to address organocatalytic versions of the well-known Mannich reaction in particular.\(^4\) Key element in Mannich reactions is an iminium intermediate 2, which is susceptible to nucleophilic attack by a variety of nucleophiles such as enolised ketones (1) or equivalents thereof, resulting in carbon-carbon bond formation adjacent to the nitrogen atom (Scheme 1).

Scheme 1 Essentials of the Mannich reaction.

The products, so-called Mannich bases (3), are β-amino ketones, which are versatile intermediates in organic synthesis and have especially proven their value in the synthesis of alkaloids. The Mannich reaction by now has also been firmly established as a viable approach to prepare the Mannich bases in enantiomERICALLY pure form via organocatalysis.\(^5,6\) In the following overview, several organocatalytic approaches will be highlighted, which can be divided in catalysis by chiral amines (via enamine formation) (Section 1.2), chiral Brønsted bases (Section 1.3), chiral Brønsted acids (Section 1.4) and phase transfer catalysts and other quaternary (internal) salts (Section 1.5).
1.2 Catalysis by enamine forming chiral amines

Chiral amines have the potential to react with so-called Mannich donors such as ketones or aldehydes. The resulting chiral enamines can react with a Mannich acceptor, usually a prochiral aldime, thereby introducing one or two chiral centres in the Mannich product. The catalytic cycle is completed by regeneration of the amine catalyst through hydrolysis. The products are β-amino aldehydes or β-amino ketones, which are optionally substituted at the α-position.

1.2.1 Syn-selective approaches
1.2.1.1 N-PMP-substituted Mannich acceptors

In the 1970s, the research groups of Hajos–Parrish and Eder–Sauer–Wiechert independently found that proline could enantioselectively catalyse an intramolecular aldol reaction. Not until 2000, List et al. hypothesised that proline might catalyse, besides the aldol reaction, analogous Mannich reactions in an asymmetric fashion. They reported that a one-pot three-component reaction involving a ketone, an aldehyde and a primary amine provided the desired Mannich product in enantiopure form. As an example, reaction of L-proline, p-nitrobenzaldehyde (4), acetone (5) and p-anisidine (6) in DMF led to the desired Mannich adduct 10 in 50% yield with an ee of 94% (Scheme 2). This proceeds via the chiral proline-derived enamine 8, which reacts with the in situ formed prochiral iminium intermediate 7 in a stereoselective manner. The initially formed iminium adduct 9 hydrolyses in the process and the released proline can enter the next catalytic cycle. The corresponding aldol product (reaction of acetone with the aldehyde 4) is formed as a side-product.

Scheme 2 The first proline-catalysed asymmetric Mannich reaction.
Chapter 1

After this discovery, an evaluation of the scope and optimal reaction conditions was initiated. Various proline-resembling compounds were examined as potential catalysts. Several ketones such as butanone, methoxyacetone and hydroxyacetone also furnished the desired products in high yields (92–96%) and with excellent ee (>99%) (Scheme 3). Importantly, in all instances a high syn-selectivity (95% de) was observed. While in case of methoxy and hydroxy substituents single regioisomers were formed, a methyl substituent (butanone) provided a 2.5:1 regioisomeric mixture of products.

Scheme 3 Variation of the ketone component.

Structurally diverse aldehydes were also tested in the asymmetric Mannich reaction. α-Unbranched aldehydes appeared efficient substrates providing yields up to 90% combined with good to excellent ee values. Evaluation of the scope of the primary amine showed the necessity of a p-methoxy substituent on the aromatic ring. Remarkably, replacement of p-anisidine with p-chloroaniline caused a marked decrease in enantioselectivity (84% ee), and introduction of α-hydroxy- or α-methoxyaniline led to almost complete disappearance of enantioselectivity (<10% ee). A distinct advantage of the use of p-anisidine is that the Mannich reaction leads to p-methoxyphenyl (PMP)-protected amines, which can be oxidatively converted into the corresponding free amines (vide infra). While optimising the reaction conditions, it also appeared that the proline loading could be reduced to 10 mol% and the product could still be obtained in good yield (>90%) in a reasonable reaction time (~5 h).

Shortly after List, the Barbas group published similar results on proline-catalysed asymmetric Mannich reactions. They independently discovered the previously mentioned one-pot three-component proline-catalysed asymmetric Mannich reaction. However, their focus quickly turned to conditions involving preformed imines. For example, in 2002 a highly enantioselective proline-catalysed reaction of ketones with N-PMP ethyl iminoglyoxylate was reported, which gave the corresponding β-amino acid derivatives in high yields. Exploration of the scope involving several ketones showed that all reactions proceeded smoothly, typically affording the desired products in good yields (70–80%) and high stereoselectivity (d.r. >95:5 (syn/anti), ee up to >99%). When unsymmetric methyl ketones were used, reaction with the imine mostly occurred with the
most substituted enamine intermediate. Mannich reactions of ketones with PMP-protected iminoglyoxylate 14 proceeded well in a wide variety of organic solvents including dimethyl sulfoxide (DMSO).

Mechanistically, the stereochemical outcome of all of these reactions can be explained by invoking a transition state as depicted in Fig. 2. The stereochemical repulsion between the PMP group and the proline moiety, in combination with protonation of the imine by the acid functionality of proline, accounts for a si-face attack of the (E)-aldimine (from p-anisidine and acceptor aldehyde) by the si-face of the (E)-enamine formed by the ketone and proline. This model explains the stereochemical outcome of many similar reactions that have appeared in literature.

In order to extend the scope of the proline-catalysed asymmetric Mannich reaction, Barbas and co-workers investigated the application of unmodified aldehydes (rather than ketones) as the donor. In 2002, they discovered that the reaction of isovaleraldehyde (16, R°1 = iPr) with ethyl iminoglyoxylate 14 in DMSO afforded the Mannich adducts 17 (R°1 = iPr) in high yield (80%) with good stereoselectivity (d.r. > 10:1 (syn/anti), 87% ee). To broaden the scope of this transformation, a number of aliphatic aldehydes 16 were reacted with 14 under the same conditions (Scheme 5).

While the obtained ee was always higher than 90%, it was shown that better diastereoselectivities were obtained with larger substituents on the aldehyde donor (R°1 = Me < Et < iPr < n-pentyl). It was also observed that the obtained diastereomeric ratios resulting from aldehydes with smaller α-substituents (e.g. R°1 = Et, iPr) were significantly different.
higher if determined immediately after aqueous work-up than after additional column chromatography. This indicates that epimerisation takes place during the purification on silica gel. The undesired epimerisation could be successfully suppressed by slow addition of propionaldehyde (18) to a solution of aromatic N-PMP-protected aldimines 19 in DMF in the presence of L-proline, followed by in situ reduction of the aldehyde function. This yielded the intended 1,3-amino alcohols 20 in reasonable yields, excellent enantioselectivities (90–99\% ee) and modest to good diastereoselectivities (d.r. up to > 10:1 (syn/anti)) (Scheme 6). The diastereoselectivity was virtually complete (>19:1 (syn/anti)) when heptanal was used as the donor (not shown).

Scheme 6 Synthesis of 1,3-amino alcohols.

As a next step, Barbas, Córdova and Hayashi simultaneously reported the viability of a one-pot three-component asymmetric Mannich reaction between two different aldehydes (cross-Mannich reaction).\textsuperscript{12,13,14} The temperature appeared to be a crucial factor for a successful outcome. Typical reaction temperatures of −20 to −10 °C were necessary in order to suppress side reactions such as the cross- and homo-aldol reaction.\textsuperscript{12,14} The reaction was also highly solvent dependent, proceeding poorly in acetonitrile, dichloromethane, THF and toluene, but giving high yields and selectivities in DMF and NMP instead.\textsuperscript{14}

Under optimised conditions, addition of an aliphatic donor aldehyde 16 to a mixture of \( p \)-anisidine, an acceptor aldehyde 21 and L-proline, followed by subsequent in situ reduction, afforded 1,3-amino alcohols 22 in good yields with excellent enantioselectivities (up to >99\% ee) and good diastereoselectivities (d.r. up to >19:1 (syn/anti)) (Scheme 7). The immediate reduction step suppresses decomposition or epimerisation of the \( \beta \)-amino aldehydes during work-up.

The scope of this reaction was extensively investigated by the aforementioned groups. Various aliphatic aldehydes were used as Mannich donors 16 and generally good results were obtained. However, it was observed that use of acetaldehyde and 2-substituted acetaldehydes did not result in the expected products.

The scope of the acceptor aldehyde 21 was also explored. Benzaldehyde, substituted benzaldehydes and heteroaromatic aldehydes appeared suitable Mannich acceptors, whereas the use of aliphatic aldehydes not in all cases led to high selectivities and yields. In the absence of a second aldehyde, proline catalysed the direct asymmetric Mannich reaction of one aliphatic aldehyde being both the donor and acceptor component.\textsuperscript{12,14}
Ethyl glyoxylate was also successfully employed as acceptor aldehyde in the proline-catalysed one-pot three-component reaction with aliphatic donor aldehydes and p-anisidine. The resulting β-formyl-α-amino acid derivatives were isolated as such (without reduction) in good yields and excellent diastereo- and enantioselectivities.

Córdova also reported that the reaction of ketones 13 with aqueous formaldehyde (23) and an aromatic amine 24 furnished α-aminomethylated ketones 25a and 25b in very good yields and selectivities (Scheme 8). When acyclic ketones with R1 = H were employed, product 25a was predominantly formed. Bolm and co-worker showed that this proline-catalysed α-aminomethylation was accelerated, e.g. with the use of a microwave. They also demonstrated that the catalyst loading could be lowered to 0.5% while still obtaining the desired product in acceptable yields and selectivities.

Hayashi et al. then developed a new strategy to stereoselectively synthesise syn- or anti-γ-amino secondary alcohols (Scheme 9). Instead of reducing the Mannich product 26 with NaBH4, it was directly reacted with a Ph-nucleophile (Ph2CuLi or Ph3ZnLi) to generate a secondary alcohol. Because this step proceeded only with poor diastereoselectivity, the resulting alcohol was oxidised to the ketone and by adding LiAlH(OtBu)3 or catecholborane, the latter was subsequently reduced to syn- or anti-27, respectively.

In 2005, the first direct catalytic enantioselective Mannich reaction that provides β-amino-α-oxoaldehydes 28 and 3-amino tetroses 29 was reported by Córdova et al.
were obtained through a proline-catalysed homo-Mannich reaction of protected glycolaldehydes 31 (Scheme 10). The enantioselectivity of this reaction was high (up to >99% ee), but the diastereoselectivity was disappointing with a d.r. ranging from 1:1 to 4:1 (syn/anti).

The analogous proline-catalysed addition of protected glycolaldehydes to aromatic imines afforded β-amino-α-oxyaldehydes in good yields (up to 96%) and high enantioselectivity (up to 99% ee). The diastereoselectivity was generally moderate (Scheme 11).

Córdova et al. also investigated the influence of water on the proline-catalysed Mannich reaction. As an example, a one-step synthesis of carbohydrate derivatives via amino acid-mediated Mannich reactions with protected dihydroxyacetone derivative as the nucleophile was successfully developed (Scheme 12). It was shown that the reaction proceeded more successfully than under water-free conditions. Still, the stereochemical outcome of this one-pot reaction was in accordance with that of previously reported proline-catalysed Mannich reactions. Hence, this methodology provides a direct enantioselective entry for the catalytic synthesis of amino sugars. A small excess of water potentially facilitates proton transfer in the transition state, which both lowers the LUMO of the incoming electrophile and directs the enantioselectivity of the newly formed stereocentres. The higher Brønsted acidity of the amino acid in the presence of water and polar aprotic organic solvents plausibly accounts for the observed higher stereoselectivity.
Fustero et al. developed a direct and convenient strategy for the synthesis of acyclic fluorinated α-alkyl-β-amino acid derivatives 38 involving a Mannich condensation of fluorinated aldimines 37 with aliphatic aldehydes 16 in the presence of L- or D-proline, followed by reduction of the resulting aldehyde with NaBH4 (Scheme 1). Although the yields were moderate (31–50%), the selectivity was outstanding in all cases (d.r. >19:1 (syn/anti), ee 99%; R' = CF3, C2F5, CF3Cl and CF3Ph). This strategy can be used for the selective synthesis of syn-γ-fluorinated, α-alkyl-β-amino esters and allows the introduction of diversity into both the β-fluoroalkyl and α-alkyl groups of these compounds.

Westermann et al. reported the employment of protected dihydroxyacetone 35 and imine 14 in Mannich reactions (Scheme 4). In polar solvents (formamide or 2,2,2-trifluoroethanol (TFE)) and in the presence of L-proline as the catalyst, the desired product 39 was obtained (yields up to 76%, d.r. up to 97:3 (syn/anti), ee up to 99%). The reaction was accelerated by the use of microwaves. After 10 min irradiation at 300 W, product 39 was obtained in 72% yield with high diastereoselectivities and enantioselectivities (d.r. 90:10 (syn/anti), ee 94%). A decrease in irradiating power led to a lower yield, although the selectivities remained the same.
The group of Enders also reported a direct organocatalytic synthesis of carbohydrate fragments starting from the acetonide of dihydroxyacetone (35). Various protected carbohydrates and amino sugars could be assembled in one step by an almost completely diastereoselective proline-catalysed reaction with the \textit{in situ} formed imine of \( p \)-anisidine (6) and an acceptor aldehyde (Scheme 15). Suitable reaction temperatures ranged from 2 °C to ambient temperature. At lower temperatures a decrease in diastereoselectivity and enantioselectivity was observed. The use of catalyst (37) generally led to an enhancement of the reaction rate, due to its superior solubility properties.

![Scheme 15](image_url)

\textit{Scheme 15} Protected dihydroxyacetone as Mannich donor.  

So far, only proline or derivatives thereof were used in the asymmetric three-component Mannich reaction. Córdova \textit{et al.} reported the use of alternative linear chiral amines and amino acids to catalyse the direct Mannich reaction with high enantioselectivities (Scheme 16). By stirring cyclohexanone (41), \( p \)-anisidine (6), \( p \)-nitrobenzaldehyde (4), L-serine (43a) and DMSO for 48 h, the corresponding Mannich product (42) was formed in 60% yield, 6:1 d.r. (syn/anti) and 94% ee (Scheme 15). In comparison, the same reaction using proline as catalyst gave (42) in a 50% yield with a d.r. of 2:1 and 84% ee. Several acyclic chiral amines and amino acids were screened for the direct one-pot three-component Mannich reaction. A large number of amino acids catalysed the reaction with high enantioselectivities. After a reaction time of 14 h in the presence of \( l \)-alanine (43b) as the catalyst, (42) was isolated in 42% yield and 98% ee. Increasing the reaction time to 48 h with the addition of 5 equiv of water increased the yield to 68%, however, the ee decreased to 86%. Loss of enantioselectivity occurred at prolonged reaction times. In order to increase the nucleophilicity of the amine and the yield of the Mannich product, one equivalent of dicyclohexylamine was added to the reaction mixture, which also reduced the ee decrease of (42). The aliphatic amino acids (43a, 43c, 43h) and (43j) catalysed the asymmetric formation of (42) with 2:1–6:1 d.r. and 91–94% ee. The addition of a small amount of water slightly improved the yield of (39). The use of amino derivatives such as (43j) improved the solubility as well as the catalytic efficiency of the organocatalysts in the asymmetric formation of (42) (yield 89%, d.r. 3:1, ee 94%, 12 h).
Hence, Córdova demonstrated that there are a large number of novel, simple organocatalysts that can be derived from acyclic natural and nonproteogenic amino acids, which could potentially be used as catalysts for the direct Mannich reaction.

Scheme 16 Screening of various catalysts.

Despite the fact that proline has often been shown to catalyse reactions in high enantio- and diastereoselectivity, a few drawbacks to the use of proline exist. Firstly, the proline-catalysed reaction is generally conducted in solvents such as DMF, dioxane, DMSO and NMP, due to the relatively low solubility of proline in apolar solvents. Secondly, high levels of catalyst loading (10–30 mol%) are usually required. Ley et al. identified three relatively small organocatalysts 44, 45 and 46, which proved to work as efficiently in apolar solvents such as DCM at significantly lower catalyst loadings (Scheme 17).

Scheme 17 Non-amino acid organocatalysts.

A representative example is the reaction of cyclohexanone with N-PMP-protected glyoxylate ester 14 giving the corresponding product by using only 1–5 mol% of catalyst 44 in various organic solvents (e.g., DCM, MeCN, THF) without affecting the yield and enantioselectivity of the reaction. More generally, the reaction of ketone 47 with 14 proceeded with at least the same efficiency as the corresponding proline-catalysed reaction (Scheme 18). The applicability of these new catalysts in apolar solvents looks promising in case of ketone donors, but whether they are also useful with aldehyde donors was not disclosed. Extension to one-pot three-component reactions has also not been reported to the best of our knowledge.
Recently, a new application of catalyst 44 was developed by Barbas et al. It appeared effective in catalysing the reaction between masked 2-amino ketones and N-PMP-protected imines. The use of masked 2-amino ketones was considered of interest due to the instability of the free amines. After optimising the conditions, a series of azido ketones 49 was reacted with p-anisidine (6) and an aldehyde 21 in the presence of catalyst 44 (Scheme 19). The azido ketones reacted regioselectively affording the α-azido-β-amino ketones 50 in high yields (80–96%), enantio- and diastereoselectivities (ee 82–99%, d.r. up to 91:9 (syn/anti)).

Remarkably, when phthalimidoacetone (N-phthaloyl-protected amino acetone) 51 was employed, reversed regioselectivity was observed. Reaction with N-PMP-protected imines provided Mannich products 52 in good yields and reasonable selectivities (Scheme 20).

In 2004, Wang et al. disclosed another alternative for proline catalysis. They discovered that pyrrolidine-sulfonamide catalyst 53 was able to induce stereoselectivity in the reaction of cyclohexanone 41 and N-PMP-protected ethyl glyoxylate (14). The Mannich adduct 54 was obtained in very high syn-selectivity and excellent enantioselectivity (Scheme 21).
A solvent screening revealed high activities in both protic and aprotic solvents. Yields varying from 76% in MeNO$_2$ up to 90% in DMSO were observed whereas the solvent did not significantly influence the stereochemical outcome of the reaction. Compound 54 was in all cases obtained with >95% ee and a d.r. of >95:5 (syn/anti). This catalyst has a broad scope, affords products with excellent selectivity and is applicable in various solvents, thus it might in selected cases be an attractive alternative to proline. However, from an economic point of view proline is favoured, since both enantiomers are commercially available at low cost.

The solubility problem in proline catalysis also prompted Hayashi and co-workers to develop a more soluble catalyst. They identified trans-4-tert-butylidimethylsiloxy-L-proline 40 as a more active variant of proline (Scheme 15). For instance, the one-pot three-component reactions of ketones, p-anisidine and aldehydes which was extremely slow in DMF with proline as the catalyst, proceeded within 20–24 h in moderate yields (48–63%) and excellent enantioselectivity (90–98% ee) with catalyst 40.

In 2012, Kumar et al. elegantly exploited proline-catalysis in a formal (3+2) cycloaddition of succinaldehyde and N-PMP-aldehydes. The Mannich reaction was followed by an acid-promoted in situ reductive amination, leading to highly functionalised trans-substituted pyrrolidines (Scheme 22).

In the preceding reactions, the p-methoxyphenyl (PMP) group was used as the imino protecting group. For quite some time, ceric ammonium nitrate (CAN) has been advocated as the method of choice for the oxidative removal of the PMP group. This proceeds via oxidation of the anisidine moiety into the corresponding iminoquinone 58, followed by aqueous hydrolysis of the imine to liberate the amine (Scheme 23). Mainly due to the moderate reproducibility and laborious nature of the CAN-mediated deprotection, more efficient, alternative methods have been developed in recent years for PMP removal. These
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methods will be discussed in Chapters 2 and 3.

**Scheme 23** PMP deprotection.

1.2.1.2 **N-oxy carbonyl- and N-acyl substituted Mannich acceptors**

Enders and co-workers reported the first example of *tert*-butoxycarbonyl (Boc) as the imine protecting group in proline-catalysed Mannich reactions (Scheme 24). The resulting products were formed in good yields and selectivities (e.g. $R^1 = \text{Ph}$, 85%, de $> 99\%$, ee $= 96\%$).

**Scheme 24** Boc-protected Mannich acceptors.

Soon thereafter, Córdova and List almost simultaneously reported extensive studies on the use of N-Boc imines as Mannich acceptors (Scheme 25). The Córdova group reported that proline, but also (R,S)-4-hydroxyproline was able to stereoselectively catalyse the Mannich reaction between aryl-substituted N-Boc imines and aliphatic aldehydes in high yields (62–85%) and selectivities (d.r. >19:1, ee up to >99%). The rather moisture-sensitive N-Boc protected imines 60 can be prepared via a two-step protocol, involving reaction of *tert*-butyl carbamate (62), *p*-toluenesulfinic acid (63) (or alike) and an aldehyde (36), followed by basic elimination (Scheme 25).

**Scheme 25** Synthesis of N-Boc imines.

Córdova later realised that the second step could be conducted *in situ* and found that the proline-catalysed reaction of 64 with aldehydes 65 in the presence of KF as the base smoothly produced the desired $\beta$-amino aldehydes 66 with high selectivities (Scheme 26).
Virtually simultaneously, Melchiorre and co-workers disclosed the same concept, but instead of proline they employed pyrrolidine-substituted tetrazole \( \text{44} \) as the catalyst for syn-selective reactions. They added \( \text{Cbz} \) to the list of applicable imine protecting groups.\(^{32}\)

As mentioned above, List also reported the synthesis of \( \text{N-Boc} \)-protected amino aldehydes \( \text{71} \) employing proline as the catalyst (Scheme 27), but additionally found that acetone could be used as Mannich donor (73% yield, ee >98%).\(^{33}\) It was recognised that this method is limited by the requirement of preformation of the imines and the incompatibility with aliphatic imines. Both limitations do not apply to \( \text{N-PMP} \)-protected imines. The group of List later discovered that also acetaldehyde could be employed as the Mannich donor.\(^{34}\)

The aforementioned solubility issues were also dealt with by Carter and co-worker.\(^{35}\) They developed a cheap and soluble proline derivative \( \text{70} \) which effectively catalyses the reaction of a variety of ketones and aldehydes \( \text{67} \) with \( \text{N-Boc} \)- and \( \text{N-PMP} \)-protected imines \( \text{71} \) in apolar solvents such as DCE, DCM and the industrially more attractive 2-Me-THF.

A protected taxol side chain (\( \text{76} \)), obviously an interesting target structure (see: Chapter 6), was elegantly constructed by Córdova et al. via a \( d \)-proline-catalysed reaction of \( \text{Bn} \)-protected
hydroxyacetaldehyde 73 with N-phenacyl-protected imine 74, followed by NaClO₂ oxidation (Scheme 29).

\[
\begin{align*}
73 & \underset{\text{O-proline}}{\xrightarrow{\text{CH₃CN, rt, 16 h}}} 75 \\
74 & \xrightarrow{\text{NaClO}_2} 76
\end{align*}
\]

Scheme 29 Synthesis of protected taxol side chain via proline catalysis.

Tan et al. developed an interesting route for the synthesis of α-fluorinated Mannich products. They discovered that the bicyclic guanidine catalyst 77 smoothly catalysed the reaction of β-keto acetyl oxazolidinone 79 with N-protected imines 78. Subsequent ethanolysis, deacetylation and protonation led to the syn-fluorinated product 81 (Scheme 30), albeit without full retention of diastereoselectivity (decrease from 99:1 to 4:1).

\[
\begin{align*}
\text{Et}_2\text{CO} & \underset{\text{IBu}^+}{\xrightarrow{\text{N,N,N,N-}} 77} \text{K}_\text{CO}_3 \underset{\text{EtOH}}{\rightarrow} 82
\end{align*}
\]

Scheme 30 Synthesis of α-fluorinated β-amino esters.

The same bicyclic guanidine catalyst was also capable of catalysing the reaction between malonic acid half thioesters 82 and N-tosylimines 83. Unfortunately, only low diastereoselectivities were observed, but enantioselectivities were reasonable.

\[
\begin{align*}
\text{Et}_2\text{CO} & \underset{\text{IBu}^+}{\xrightarrow{\text{N,N,N,N-}} 77} \text{K}_\text{CO}_3 \underset{\text{EtOH}}{\rightarrow} 84
\end{align*}
\]

Scheme 31 Mannich reaction of malonic acid half thioesters.

The organocatalysed Mannich reaction of acetaldehyde (85) and N-benzoyl imine 87 using pyrrolidine derived 89 as the catalyst was elegantly linked up to an electrophilic amination with di-tert-butylazodicarboxylate (86) by the group of Greck. A one-pot procedure including NaBH₄ reduction led to the formation of product 88 in moderate yields but excellent selectivities.
As reported by Maruoka et al., vicinal diamines 91 were also accessible when N-Cbz-protected amino acetaldehydes 90 were employed as Mannich donors in the presence of L-proline as the catalyst.

They screened various catalysts in the reaction of isovaleraldehyde (16, R^1 = iPr) and found that commercially available SMP gave optimal results affording the desired β-formyl-functionalised leucine derivative 93 (R^1 = iPr) in 48% yield, reasonable ee (69%) and with high diastereoselectivity (d.r. >1:10 (syn/anti)). The ee could be improved to 82% by switching the solvent from dioxane to DMSO. Reaction of other aldehydes (e.g. R^1 = Et, nBu, iPr, n-pentyl) also afforded products 93 in modest to good ee (74–92%) and with a diastereomeric ratio that increased with the bulkiness of the aldehyde donor. Similar to proline-catalysis, reactions of aldehydes with smaller α-substituents (e.g. R^1 = Et, iPr) resulted in significantly higher diastereomeric ratios if determined immediately after aqueous work-up than after additional column chromatography, indicating that epimerisation readily takes place.
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Scheme 3.4 anti-Selective Mannich reactions using SMP as the organocatalyst

The stereochemical outcome of the SMP-catalysed reaction was explained through assuming the transition state, depicted in Fig. 3. The si-face of the N-PMP imine is attacked by re-face of the SMP-enamine. In proline-catalysed reactions, the si-face of N-PMP-imines is attacked by the si-face of the proline-enamine (Fig. 2).

Figure 3 Mechanistic rationale for the anti-stereoselectivity of SMP-catalysed reactions.

Unfortunately, the scope of this reaction seemed rather limited. For example, it was not possible to obtain the anti-adduct from an SMP-catalysed reaction of propionaldehyde and the imine formed from p-nitrobenzaldehyde and p-anisidine. In this case, low diastereomeric and enantioselectivity was observed. Jørgensen and co-workers demonstrated that silylated α,α-diarylprolinol 89 (Scheme 3.4) catalyses the reaction depicted in Scheme 3.4 with significantly improved selectivity. Diastereomeric ratios up to 92:8 and ee values in the range of 94–98% were observed. The same catalyst was utilised by Hayashi et al. to catalyse the reaction of in situ generated N-Ts and N-Ns imines, which also afforded anti-products.

A related catalyst (MeSi-protected α,α-diphenylprolinol) was used by Fustero et al. to prepare fluorinated amino alcohols. Not surprisingly, employment of this catalyst and of catalyst 91 gave anti-products, whereas the use of proline afforded the corresponding syn-products (vide supra). Melchiorre and co-workers successfully employed a silylated α,α-diarylprolinol as the catalyst for the Mannich reaction of in situ generated N-Boc and N-Chz imines. Another catalyst variation was reported by Palomo et al. They introduced a 4-hydroxy substituted MeSi-protected α,α-diarylprolinol, which in the presence of p-nitrobenzoic acid, effectively catalysed the reaction of N-tosyl and N-nosyl imines to afford anti-products.

The group of Maruoka developed new chiral amino sulfonamide catalysts for the formation of the anti-Mannich product of aldehydes and α-imino esters (Scheme 3.5). The first designed catalyst 96a (5 mol%) was tested in the Mannich reaction of isovaleraldehyde 16 (R1 = iPr) and α-imino ester 94 (R2 = Et) in dioxane giving aldehyde 95 in 60% yield, but
without significant diastereoselectivity. Modification of the catalyst to 96b resulted in excellent reactivity and stereoselectivity (yield 93%, d.r. >1:20 (syn/anti), 99% ee). Reactions between other aldehydes 16 and α-imino esters 94 were carried out in dioxane at room temperature. In the case of primary alkyl aldehydes (R1 = Me, nBu, Bn), 1 mol% of 96b was sufficient to synthesise products 95 with excellent selectivities (yield >92%, d.r. >11:1, ee >99%).

Scheme 35 Chiral amino sulfonamide-catalysed Mannich reactions.

A few years later, it was reported that 96b could also efficiently catalyse the reaction between N-Boc imines and acetaldehyde in a stereoselective manner. When substituted acetaldehydes were employed, predominantly anti-products were obtained. Vicinal diamines were accessible when N-Cbz-protected amino acetaldehydes were used as Mannich donors. This method was utilised in the total synthesis of marine alkaloid (-)-agelastatin A, a potent antitumor agent. In 2006, the same group reported the synthesis of a novel pyrrolidine-based catalyst 97, giving good results (yield 82–93%, d.r. >11:1 (anti/sym), ee 90–95%) with aldehydes (R1 = H, R2 = nPr, iPr, tBu) as the nucleophiles (Scheme 35). Less reactive ketones could also be used as nucleophiles, leading to the corresponding anti-β-amino ketones in good yields and selectivities (yield 95–99%, d.r. >20:1 (anti/sym), ee > 93%).

Scheme 36 Use of the novel pyrrolidine-based catalyst 97.

Barbas and co-workers also contributed to the search for anti-selective organocatalysts. They designed a novel pyrrolidine-derived catalyst with substituents on the 3- and 5-
positions (98), showing excellent anti-selectivity in the reaction of aldehydes with \( N \)-PMP-protected glyoxylate esters (Scheme 37).

![Scheme 37 Use of the 3,5-disubstituted pyrrolidine catalyst 98 in Mannich reactions.](image)

Remarkably, the Mannich reaction with ketones and 98 as the catalyst was not very effective, but it was shown that the demethylated congener 101 efficiently catalysed the latter reaction. Both cyclic and linear ketones could be successfully applied, affording the corresponding \( \beta \)-amino ketones in good yields and excellent selectivities (Scheme 38).

![Scheme 38 Use of the 3-substituted pyrrolidine catalyst 101 in Mannich reactions.](image)

Interestingly, with \( \alpha \)-hydroxyketones as donors, no diastereoselectivity was observed. In case linear \( \alpha \)-amino acids (L-Trp and O-tBu-L-Thr) were applied as catalysts, \( \alpha \)-hydroxy-\( \beta \)-amino ketones were formed in moderate to high selectivities (d.r. up to >19:1 (anti/syn), ee up to 98%) (Scheme 39).

![Scheme 39 L-Trp- and O-tBu-L-Thr-catalysed Mannich reaction with anti-selectivity.](image)

Córdova and co-workers also reported highly enantioselective anti-catalysts for the asymmetric Mannich reactions. Readily prepared Me\(_3\)Si-protected diphenyl- and di(2-naphthyl)prolinol appeared effective in catalysing the reaction of aldehydes with \( N \)-PMP-protected ethyl iminoglyoxylate, giving rise to \( \beta \)-amino aldehydes in good yields and selectivities. Additionally it was found that \( \beta \)-amino acids and in particular \( \beta \)-homovaline could be effectively used as a catalyst in the reaction of ketones and \( N \)-PMP-protected \( \alpha \)-iminooethyl glyoxylate, giving anti-\( \beta \)-amino ketones.
Threonine-derived organocatalysts were reported by the group of Lu as effective catalysts in purely aqueous systems. 

For example, O-TBDPS-protected threonine could catalyse the reaction of O-benzyl hydroxyacetone (104) with a variety of in situ formed p-anisidine-derived imines with reasonable selectivities (ee 62–97%, d.r. 3:2 to 20:1 (anti/syn)) (Scheme 40). Aliphatic aldehydes were also investigated, but gave decreased yields and selectivities.

Scheme 40 O-Benzyl hydroxyacetone as donor.

Peng et al., who discovered an anti-selective secondary amine-thiourea catalyst 105 (Fig. 4), also observed another interesting phenomenon. While the outcome of the organocatalysed Mannich reaction is generally mainly catalyst controlled, they reported an example with solvent-controlled selectivity.

Figure 4 Secondary amine thiourea catalyst.

They observed that in the presence of threonine-derived catalyst 103, the reaction of isatin imines 104 with hydroxyacetone (105), conducted in Et₂O leads to predominant formation of anti-products 106, whereas employment of toluene as the solvent affords syn-products 107 (Scheme 41).

Scheme 41 Solvent-controlled selectivity.

Another interesting approach came from the Glorius group. Instead of designing a new catalyst, they reasoned that proline, although generally affording syn-products, could be forced to deliver anti-products when the starting imine would be locked in a Z-configuration. This hypothesis was
confirmed via the synthesis of a series of amino ketones 112. The protecting group could be readily removed through hydrogenolysis in EtOH/H₂O.

Scheme 42 Forced anti-selective catalysis with proline.

1.3 Catalysis by Brønsted bases

In the previous section, the crucial C-C-bond forming step in a Mannich reaction occurred through the reaction of an enamine nucleophile with a protonated imine. The protonation of the imine is essential to render it sufficiently electrophilic to react with the enantiomerically pure nucleophilic enamine. It is, however, also possible to react nucleophiles with neutral imines, although in these cases generally an electron-withdrawing substituent on the imine nitrogen is required to enhance its electrophilicity. The nucleophile is often an active methylene compound which, upon deprotonation by a chiral amine, provides a chiral intimate ion pair of which the anion reacts with the Mannich acceptor in an enantioselective fashion. The presence of a thiourea moiety can assist, most likely through cooperative hydrogen bonding with the imine precursor, thereby rendering it more active towards nucleophilic attack. In addition, the hydrogen bonding properties of the thiourea moiety can also be invoked to account for increased reactivity of the nucleophile (vide infra).

1.3.1 Use of cinchona alkaloid-derived bases

Chincona alkaloids have proven to be exceptionally effective in catalysing a plethora of asymmetric transformations, including the Mannich reaction. Schaus and co-workers have developed a diastereo- and enantioselective direct Mannich reaction of β-ketoesters 114 with acyl aryl imines 115 catalysed by the alkaloids cinchonine (116) and cinchonidine (117) (Scheme 43) to synthesise enantioenriched dihydropyrimidones and β-amino alcohols. Employment of 116 or 117 led to opposite enantioselectivities. The stereoselective control was explained through complexation of the chiral alkaloid with the nucleophile. Reaction of β-ketoester 114 with aryl methyl carbamate 115 (R² = OMe) in the presence of catalyst 116, proceeded in good yield with moderate enantio- and varying diastereoselectivity. They expanded the scope of this reaction by including α-substituted β-keto esters and β-diketones as donors, thereby gaining access to structures with α-quaternary centres. Additionally, aryl-propenyl acylimines appeared suitable as Mannich acceptors.
Chan et al. reported that a cinchona alkaloid derivative served as a catalyst for the Mannich type formal (2+3) cyclisation of N-tosyl imines with methyl isocyanoacetate. The diastereoselectivity of this reaction was reasonable while the enantioselectivity was low. The Schaus group reported that the hydroquinine-derived thiourea could serve as an effective catalyst. The reaction between dimethyl malonate and a variety of methyl carbamate-protected aromatic imines afforded the corresponding Mannich adducts in good selectivities and almost quantitative yields (Scheme 4). Computational modelling studies established that malonate anion stabilisation via a chiral ion pair with the hydroquinine moiety and simultaneous hydrogen bonding of the thiourea part of the molecule with the anion accounted for the excellent selectivity of this reaction.

Catalyst also effectively facilitated the stereoselective reaction of glycine-derived Schiff bases and in situ generated N-Boc imines. Well aware of the beneficial effect of co-operative hydrogen-bonding catalysis with readily available cinchona alkaloids, Deng and co-workers investigated the use of cinchona alkaloids bearing a thiourea functionality as catalysts (123 and 124) for the addition of malonates to N-Boc-protected imines (Fig. 5). After optimisation of reaction conditions, the desired
products were obtained in excellent yields (up to 99%) and enantioselectivities (ee up to 99%). The imine scope was not limited to aromatic imines, but also aliphatic acceptors could be applied. β-Keto esters could also be used as donors, providing access to β-keto amines albeit with only moderate diastereomeric control. Dixon et al. reported comparable results for reactions with Boc- and Cbz-protected aldimes catalysed by a slightly different catalyst.63

Figure 5 Cinchona alkaloids 123 and 124 with thiourea moiety.

A major drawback of the use of N-Boc-protected imines is the low stability of particularly aliphatic imines. This was recognised by Deng et al. and overcome by the implementation of gradual and in situ generation of N-alkyloxycarbonyl-protected imines from stable α-amino sulfones.64 This also led to higher optical purities when employing catalyst 124 due to the relatively high concentration of the catalyst compared to the imine. In one example, with the same amount of catalyst, 95% ee was obtained with in situ generation of the imine, whilst employment of a preformed imine afforded the desired product in only 74% ee. Additional examples involving the use of N-alkyloxycarbonyl-protected α-amino sulfones and dibenzylmalonate provided further insight into the scope of this reaction (Scheme 4 5).

Scheme 4 5 Addition of dibenzyl malonate to in situ generated N-alkyloxycarbonyl-protected imines.

An interesting variation on this motif was reported by the Jørgensen group. They described a highly enantioselective procedure for the reaction of α-aryl-substituted cyanoacetates 128 with N-Boc protected iminoglyoxylates 129 in the presence of a chiral tertiary amine catalyst (Scheme 46).65
Various catalysts were screened for the reaction of 128 (R₁ = nPr; Ar = Ph) with 129 (R₂ = Et), and commercially available (DHQD)₂PYR (131) gave the best diastereo- and enantioselectivity (Fig. 6). The scope of α-aryl-substituted cyanoacetates was investigated and it was found that in all cases similarly high selectivities could be observed, but in the case of a 2-bromosubstituted aryl moiety, the nature of the ester group of 129 seemed to direct the selectivity. An ethyl group completely inverted the diastereoselectivity, whereas the enantioselectivity disappeared almost completely.

Figure 6 (DHQD)₂PYR.

The substrate tolerance of the catalytic system was further demonstrated by the use of the cyclic β-ketoester 132 (Scheme 47). The reaction smoothly afforded Mannich base 134 in a high yield and essentially as a single isomer in excellent ee.

Scheme 47 Cyclic β-keto ester 132 as Mannich donor.

The concept of combining the basic amine functionality of cinchona alkaloids with the acidic protons of (thio)urea moieties was also picked up by Coltart et al.⁶⁶ They utilised organocatalyst 138 to simultaneously activate and deprotonate thioester 135. The resulting enolate attacks N-sulfonyl imines 136 to eventually afford Mannich products 137 in good diastereoselectivity. Unfortunately, the enantioselectivity was low.
Lu et al. found a moderately enantioselective approach to enhance the low reactivity of aryl methyl ketones (e.g. acetophenone). They employed cinchonine-based bifunctional \( \text{139} \) as the catalyst for the decarboxylative addition of \( \beta \)-keto esters \( \text{140} \) to \( N\text{-SO}_2\text{PMP} \) imines \( \text{141} \).^{37}

Another cinchona-based thiourea was disclosed by the Yang group. They developed catalyst \( \text{143} \) (Fig. 7), which catalysed the reaction of diethyl malonates with \( N\text{-benzothiazole} \) imines.\(^{69}\) The observed enantioselectivities were moderate and the reaction times were long.

**Figure 7** Cinchona-derived catalyst \( \text{143} \).

A one-pot enolate-mediated Mannich reaction, promoted by the bifunctional quinidine thiourea catalyst \( \text{146} \), was recently disclosed by Zhao et al.\(^{49}\) After condensation of \( \text{Ts-amine (144)} \) with an aromatic aldehyde, the enolised ketone attacks the resulting imine, resulting in the enantio- and diastereoselective formation of \( N\text{-tosylated} \) \( \beta\text{-amino ketones 147} \).
1.3.2 Use of other chiral bases

The results achieved with cinchona alkaloid-derived thiourea catalysts prompted Takemoto et al. to investigate potential of the simple thiourea compound 150 in the Mannich reaction.\textsuperscript{79} It effectively catalysed the reaction of diethyl malonate with \(N\)-Boc-protected aldimines as opposed to other \(N\)-protected aldimines. Although the thiourea catalyst led to high enantioselectivities for reacting \(\beta\)-keto esters with aldimines, no diastereoselectivity was observed. This was possibly due to epimerisation of the product. Subsequently, cyclic 1,3-dicarbonyl compounds 149 were used as substrates (Scheme 51). The product 151 was obtained in 89% yield and the selectivities were good (ee 88%, d.r. 92:8). A series of reactions with cyclic substrates was disclosed, but the selectivities were generally fairly modest. The authors suggested that a dual activation of the electrophile and the nucleophile accounted for the observed selectivity, but no definite proof was provided.

A more sterically hindered congener of 150 was employed by Yan et al. for the synthesis of \(O\)-ethyl tetronic acid derivatives 151.\textsuperscript{71} After the Mannich reaction between ethyl 4-chloro-3-oxobutanoate (152) and \(N\)-Boc imines (153) catalysed by thiourea derivative 154, a triethylamine-mediated cyclisation in the same pot afforded the desired products in good yields and moderate to good selectivity.
Thiourea-catalysed reactions had already been reported previously by Jacobsen and co-workers in 2002. At that time, they recognised that the conditions required for the removal of N-aryl protecting groups posed a serious drawback to the organocatalysed reactions described above. As a result, they reported an efficient route to N-Boc-protected β-amino acids via the enantioselective addition of silyl ketene acetal to N-Boc aldimines catalysed by thiourea catalyst 156 (Fig. 8).

Addition of silyl ketene acetal 157 to N-Boc-protected α-, m-, p- and unsubstituted arylimines 70 proceeded with generally good enantioselectivity (88–93% yield, up to 97% ee) to afford the Mannich bases 158 (Scheme 5.3). It is however noteworthy that reactions were conducted at –40 to –30 °C to suppress the non-catalytic (racemic) pathway. Aliphatic N-Boc-protected imines were not investigated since no useful method was available for their synthesis.

The same catalyst was later found to efficiently catalyse the reaction of N-Boc imines 159 with benzothiazol-2-ylxoyl-derived ketones 160. The products could be converted to allylic amines 161 through reduction with NaBH₄, whereas treatment with NaSEt gave rise to β-amino ketones 162.
Kim and Kang developed a set of catalysts with both axial and central chiral elements of which 164 appeared to perform best in the reaction of β-keto ester 163 and N-Boc aldimines 153.\(^{74}\)

Long reaction times were generally employed but the selectivities were virtually complete. A similar reaction could be catalysed by rosin-derived amine-thiourea 166 (Fig. 9), developed by Wang et al. Besides β-keto esters, their system also accepted lactones as the Mannich donors.\(^{75}\) A modified version (167) was developed for the synthesis of cyclic thioureas.\(^{76}\)

Only secondary and tertiary amine thiourea catalysts were reported to effectively catalyse the Mannich reaction until Tsogoeva et al.\(^{77}\) found that the reaction of ketones 13 and N-benzoylhydrazones 168 proceeds in the presence of primary amine 169 (Scheme 56). Despite the high enantioselectivity, a virtual absence of diastereoselectivity in the reaction renders this catalyst less suitable for substituted ketones as the Mannich donors. As an addition, the authors found evidence based on \(^{18}\)O studies that this reaction not exclusively follows an enamine pathway, but also partially proceeds through an enol mechanism.
1.4 Catalysis by chiral Brønsted acids

A third pathway for enantioselective organocatalysed Mannich reactions proceeds via enantiopure Brønsted acids. Instead of reacting with an enantiopure nucleophile (Section 1.2), the imine is protonated by the chiral acid, which leads to the formation of an iminium ion with an enantiopure counterion. This counterion directs the incoming nucleophile and leads to an optically active Mannich product. Most often, the acids involved are readily accessible enantiopure phosphoric acids.

An early example was reported by Akiyama and co-workers. They synthesised a series of chiral phosphate catalysts, of which phosphoric acid 173 proved to give the best results. For example, reaction of the aromatic aldimines 171 with silyl ketene acetal 172 (R1 = R2 = Me) catalysed by 173 afforded the Mannich bases 174 in excellent yield (98–100%) and reasonable enantioselectivity (80–89% ee) (Scheme 56). Addition of monosubstituted silyl ketene acetals 172 (R1 = H, R2 = Me, Bn) to aromatic aldimines 171 led to highly selective reactions (d.r. 87:13 to 95:5 (syn/anti)), while the enantioselectivity was also maintained (81–96% ee). In addition, it was concluded that the hydroxy-substituent on the o-position of the protecting group was essential to ensure high levels of enantioselectivity.

In a later report, Ishihara et al. demonstrated that the performance of chiral phosphoric acid catalyst (175) largely depends on the counterion. The reaction of N-Boc aldimines 70 with acetylacetone (176) proceeded with opposite enantioselectivity when the counterion was exchanged from H+ to Ca2+. The steric demand of the Ar-substituent also appeared of great
importance. When it was changed from 4-(β-naph)-C₆H₄ to 9-Anthryl, a lower and opposite enantioselectivity was observed. This implies a match/mismatch condition. With H⁺ as the counterion, the presence of the more demanding 9-anthryl substituent is preferred to obtain high enantioselectivity. With Ca²⁺ as the counterion, 4-(β-naph)-C₆H₄ as the Ar-substituent led to higher and opposite enantioselectivity. Scheme 58 shows the most successful combinations.

Scheme 58 Influence of aryl-substituent and counterion on enantioselectivity with 172 as the catalyst.

Expecting to have different electronic and steric properties, the novel Brønsted acid 178, based on the well-known TADDOL scaffold, was prepared by the group of Akiyama (Fig. 10). By varying the Ar functionality and the alkyl groups on the acetal moiety, the catalyst initially showed only modest selectivity (ee 31–73%) for the Mannich reaction of aromatic aldimines and ketene silyl acetals. However, when the imine protective group was changed from o-hydroxyphenyl to o-hydroxy-p-methylphenyl, a dramatic increase of the enantiomeric excesses to 85–92% was observed without diminishing the yields.

Figure 10 TADDOL-based catalyst.

Yamamoto et al. reported the introduction of the concept of Brønsted acid-assisted chiral Brønsted acid (BBA) catalysis for the design of 179 as a new asymmetric Mannich catalyst (Scheme 59). The BBA catalyst bears two acidic protons. Mechanistically, the imine 180 is activated by the reasonably acidic hydroxy group, while the bis(triflyl)methyl proton simultaneously fixes the OH-N bond, thereby stabilising the configuration of the chiral transition state. Attack of the silyl ketene acetals 181 affords products 182. The chemical yield initially did not exceed 53%, but the reactivity was improved by adding 2,6-xylenol as an achiral proton source to trap the silicon species resulting from the reaction. Various N-phenyl-protected β-amino esters were obtained with a maximum ee of 77%. It was also
shown that the \(N\)-protective group could be replaced by a diarylmethyl moiety, giving enantioselectivities up to 87%.

Terada et al. used the chiral phosphoric acid catalyst 183 to catalyse the enantioselective addition of acetylacetone 176 to the \(p\)- and \(o\)-substituted \(N\)-Boc-protected aromatic aldimines 70, providing the Mannich bases 184 in high yields (93–99%) and high enantioselectivity (90–98% ee) (Scheme 60).22

Schoepke et al. reported the first enantioselective Brønsted acid-assisted chiral Brønsted acid-catalysed direct Mannich reaction of the poorly reactive acetophenone.23 They reasoned that activation of the aldimine should occur via ion pair formation with the chiral Brønsted acid, while activation of the ketone donor must be mediated by an achiral acid which cannot form an ion pair with the aldimine. Elaborating this concept, the reaction of acetophenone with the \(N\)-4-chlorophenyl-protected aldimine 185 was investigated using the chiral BINOL-phosphate 187 in combination with acetic acid, which led to a high selectivity (76% ee) (Scheme 61). The scope was also evaluated to show that aromatic and heteroaromatic aldimines could be applied in the reaction with acetophenone to afford the corresponding \(\beta\)-amino ketones in moderate yields and selectivities.
The use of acetophenone as the Mannich donor was also reported by Dixon and co-worker, but they had to preactivate the ketone as its enamine with morpholine. They tested a variety of modified BINOL structures as catalysts in the reaction of enamine 190 with the N-Boc protected aldimine 189 and found that the best results were obtained with (S)-H-BINOL 191. Only aromatic substrates were reported as acceptable donors and acceptors for this catalyst. Yields were good, but enantiomeric excesses were generally moderate (mostly in 60–80% range) (Scheme 62).

Ishihara et al. developed an asymmetric route towards binaphthyl-disulfonic acid (195, BNSA). In combination with two equiv of an achiral organic base (196), it could serve as an effective catalyst for the enantioselective addition of diketones to N-alkyloxycarbonylimines.

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Scheme 61 Brønsted acid-assisted chiral Brønsted acid-catalysis.

Scheme 62 Preactivated acetophenone as Mannich donor.

Scheme 63 Combined Brønsted acid/base-catalysed Mannich reaction.
The previous examples showed enantioselective Brønsted-catalysed reactions, leading to compounds with only one chiral centre. Gong et al. were the first to report anti-selective examples of chiral Brønsted acid-catalysed reactions. Reasonable diastereoselectivities (d.r. in the 80:20 to 98:2 range) were observed in the reaction of cyclic ketones with aniline and aromatic aldehydes and catalysts 198b or 198d (Scheme 63), while enantioselectivities were generally high (90–95% ee). In the presence of 198a or 198c, the reaction of acyclic ketones with aromatic aldehydes in the presence of (substituted) aniline also proceeded with high enantioselectivities (up to 86% ee). No diastereoselective examples were reported.

Maruoka et al. expanded the field of Brønsted-acid catalysis by introducing axially chiral dicarboxylic acids. After identification of the optimal reaction conditions and catalyst design (Scheme 65), it was found that besides tert-butyl diazoacetate (R^1 = CO_2Bu), also dimethyl (diazomethyl)phosphonate (R^1 = PO(OMe)_2) and tolyl (diazomethyl)sulphone (R^1 = SO_2Tol) could be used as effective Mannich donors in the reaction with N-Boc imines.

Another effective catalyst for the reaction of dialkyl diazomethylphosphonates with N-alkyloxycarbonyl imines was described by the Peng group. An extensive catalyst screening
revealed that phosphoric acid 208 efficiently promotes the deprotonation of the diazo carbon of 207, while it simultaneously protonates the N-alkyloxycarbonyl imine 206 in an asymmetric fashion. In the presence of a diminutive amount of catalyst (0.1 mol%), the resulting Mannich products were formed in very high yield and selectivity.

Scheme 6A Axially chiral phosphoric acid catalysis.

1.5 Phase transfer catalysts and quaternary salts

As the final class, the group of phase transfer catalysts and other quaternary salts is discussed. Similar to chiral Brønsted acids, these catalysts form well-defined complexes with the electrophile. Thereby, one side of this electrophile is shielded, which paves the way for an enantioselective outcome of the catalytic Mannich reaction.

Maruoka et al. disclosed an N-spiro C$_2$-symmetric chiral quaternary ammonium bromide (211)-catalysed reaction of glycinate Schiff base 210 with N-PMP protected imine 14. This early example of a phase-transfer-catalysed Mannich reaction proceeded with a high enantio- but only moderate diastereoselectivity (Scheme 6B).

Scheme 6B N-spiro C$_2$-symmetric chiral quaternary ammonium bromide-catalysed Mannich reaction.

The in situ formation of N-alkyloxycarbonyl-protected imines and their use as Mannich acceptors was also reported by Sgarzani and co-workers. Cinchona alkaloid 216 was designed, which showed excellent enantioselectivity in the reaction of p-anisyl malonate 214.
with various *in situ* generated *N*-Boc- or *N*-Cbz-protected aldimines. Both aliphatic and aromatic α-amido p-tolylsulfones were tolerated. The enantiomeric excesses were generally in the 84–98% range (Scheme 68).

![Scheme 68](image)

**Scheme 68** *In situ* generation of *N*-alkyloxycarbonyl-protected imines.

A Mannich-type addition of β-phenylsulfonyl acetonitriles to *N*-Boc protected α-amido sulfones or imines catalysed by quinidine derived 217 was reported by Palomo *et al.* Although the yields were reasonable, the enantioselectivities were far from optimal. 

**Figure 11** A quinidine-derived PTC.

Another quinidine-derived catalyst 218 was employed to catalyse for the first time the reaction of arylsulfonylacettes 219 with *in situ* formed *N*-Boc imines. The resulting Mannich products 221 were formed in low diastereoselectivity but the enantioseletivities were high. The authors transformed the adducts into compounds 222 and 223 (Scheme 69) which lacked chirality at the previously sulfonyl-bonded carbon atom. Since these products were eventually obtained in high enantioselectivity it was proven that the formation of the initially observed mixture of diastereomers was caused by epimerisation of the aforementioned chiral centre.
The first example of betaine catalysis was disclosed by Ooi et al.\textsuperscript{93} They developed a new catalyst design with catalyst \textsuperscript{226} as the best performing example in terms of product yield and selectivity. \(\alpha\)-Nitrocarboxylates were reacted with \(N\)-Boc imines in the presence of the catalyst which resulted in the formation of the desired products with high enantioselectivities but only moderate diastereoselectivities (Scheme 70).

A much more simple betaine type catalyst was developed a couple of years later by the same group.\textsuperscript{94} Catalyst \textsuperscript{228} appeared to be the most successful of a set of \(C_1\)-symmetric internal ion pairs in the catalysis of the reaction of \(N\)-Boc imines and 2-benzyloxythiazol-5(4H)-ones (Scheme 71).
The products could be obtained in high ee and a reasonable anti-selectivity was observed. For $R_1^1$ and $R_2^2 = \text{Ph}$, it was shown that 229 could easily be converted into the corresponding $\alpha$-aryl-$\alpha,\beta$-diamino acid ester and amide.

Another interesting contribution from the Ooi group to the field of ion pair catalysis was the incorporation of a participating anion, which influence was previously neglected. They found a significant rate enhancement for the reaction of $N$-sulfonyl imines 231 with azlactones 230, when substituting the formate anion for a pivalate anion. Unfortunately, this replacement did not improve the initial virtual absence of enantioselectivity. By altering its geometry from ($M$,S) to ($P$,S) the authors ultimately prepared an efficient and stereoselective catalyst. Products 233 could be obtained with high enantiomeric excesses, but diastereoselectivities stayed behind (Scheme 72).

Scheme 72: Tetraamino phosphonium carboxylate-catalysed Mannich-type reaction.

Maruoka et al. after having discovered that chiral quaternary phosphonium salt 235 could effectively catalyse the asymmetric Michael addition, found that the same catalyst was also applicable as a catalyst for the Mannich reaction of 3-aryloxindoles with $N$-Boc imines (Scheme 73).

Scheme 73: Chiral phosphonium salt catalysis.

Products 236 were obtained in near quantitative yields and excellent diastereoselectivities. Unfortunately, the observed enantioselectivity was somewhat lower.
A new catalyst design was reported by the Gong group in 2012. They developed a complex chiral bis(betaine) catalyst with multiple functionalities for the reaction of azlactones and aliphatic imines. The products were obtained in high enantio- but low diastereoselectivity.

![Scheme 7: Bis(betaine)-catalysed Mannich reaction.](image)

### 1.6 Discussion

This survey of organocatalytic Mannich reactions leads us to conclude that this is a promising field from which many new applications in the synthesis of biologically active compounds will emerge. It also becomes evident that the use of proline as the catalyst gives easy access to syn-products in high yields with high regio-, chemo-, diastereo- and enantioselectivity. Since proline is commercially available in L- and D-form, the products can also be obtained in both enantiomeric forms. Both one-pot three-component reactions and reactions with preformed imines have extensively been studied using unmodified ketones and aldehydes as Mannich donors. It should be noted that a relatively high catalyst loading is generally used (typically 10–30 mol%). Some research groups have developed new, more soluble catalysts to increase the dissolved catalyst concentration. However, this led to more expensive catalysts of which the scope still needs to be fully investigated. Moreover, since proline catalysis only gives access to syn-adducts, the development of anti-directing catalysts was also desired. Nowadays, a series of enamine-forming amines are available that affords the anti-products in good selectivity.

Besides catalysis by proline and derivatives, other chiral bases such as cinchona alkaloids have been successfully employed in combination with electron-poor imines and active methylene compounds. Success in this particular reaction is often facilitated by introducing thiourea moieties, that interact with the system through cooperative hydrogen bonding.

Chiral Brønsted acids (mostly phosphoric acids) have been employed to include the iminium ion in a chiral intimate ion pair, which also results in enantioselective addition to the...
iminium species.

Some very recent reports disclose the use of quaternary (internal) salts as effective catalysts. The structure of most of these catalysts is based on the axially chiral binaphthyl core.

1.7 Thesis outline

During the past decade, substrate scope and product accessibility in the field of organocatalysis massively increased. Unfortunately, this development came with a price: catalyst structures became increasingly intricate rendering their larger scale applications more costly. Even after more than 10 years of research since its discovery, the sheer low cost and high selectivity of proline still gives this catalyst a special position in the field of organocatalysis.

The purpose of this Thesis is to further anchor the proline-catalysed Mannich reaction between currently well-established synthetic methods. This includes gaining further insight in optimal reaction conditions overcoming protecting group difficulties, and transforming the resulting products into relevant synthetic targets or building blocks. Moreover, this Thesis is one of the fruits of a collaboration of the Radboud University Nijmegen with DSM, Syncom and the University of Groningen. In this joint project (termed Ultimate Chiral Technologies), we focussed on the development of (new) stereoselective routes to multichiral centre compounds and the evaluation of the industrial viability thereof. In this context, Chapter 2 describes a novel oxidative method to replace the ceric ammonium nitrate-mediated removal of the often used p-methoxyphenyl N-protecting group. In Chapter 3, the expansion of the collection of aforementioned deprotection methods with an enzymatic approach is described. Chapter 4 covers the selective transformation of β-amino ketones into the corresponding syn- and anti-1,3-amino alcohols. In Chapter 5, an entry into the synthesis of tetrahydroisoquinolines, starting from Mannich adducts is presented. Chapter 6 describes the development of an industrially viable reaction sequence, which enables the one-pot conversion of enantiopure 1,3-N-PMP-protected amino alcohols into protecting group-free β-2,3-disubstituted amino acids amino acids. This methodology has also been employed in an approach towards a synthesis of dioctatin A. In Chapter 7, the total synthesis of the naturally occurring alkaloid lasubine II is expounded. In the final Chapter 8, the research described in this thesis will be contemplated and some outlook and suggestions for future investigations will be presented.
1.8 References


General introduction


Chapter 1

MILD AND EFFICIENT DEPROTECTION OF
THE AMINE PROTECTING \( p \)-
METHOXYPHENYL (PMP) GROUP

2.1 Introduction
As described in Chapter 1, asymmetric Mannich reactions catalysed by L- or D-proline proceed smoothly using p-anisidine-derived Schiff bases of aldehydes and ketones. Moreover, in the advent of new catalytic strategies to produce enantiopure products, p-anisidine stands out as the starting material of choice for a variety of processes that involve imine intermediates. Other applications involve the (asymmetric) reduction of p-methoxyphenyl (PMP)-protected imines, the involvement of p-anisidine in a three-component reaction to form N-PMP-protected amino acid amides, and application in asymmetric Diels–Alder reactions. Furthermore, a Cu-catalysed procedure for introduction of the PMP group as a protecting group for amino functions has been described. Obviously, all of these strategies at one point require liberation of the desired amine by oxidative deprotection of the p-methoxyphenyl function (Scheme 1).

Scheme 1 Deprotection of PMP-protected amines.

The deprotection of the PMP group was identified by us as a crucial and important drawback for scale-up and commercial application of any type of methodology involving N-PMP intermediates, including the proline-catalysed Mannich reaction. Most literature refers to oxidative removal with ceric ammonium nitrate (CAN), but appears to neglect the serious disadvantages associated with it. Usually, a large excess of CAN (4 to 5 equiv) is required, the reaction has a laborious workup procedure involving column chromatography, CAN is expensive, and highly toxic. Some of these arguments also hold for phenyl iodoacetate (PhI(OAc)_2), which has also been reported as a deprotecting agent. In recognition of these drawbacks, the Mioskowski group – in a search for better deprotection methods – reported an electrochemical procedure for the oxidative removal of the PMP substituent. However, electrochemical reactions are poorly amenable to scale-up because specific production equipment is required.

2.2 Screening of various oxidants
Based on these arguments, we set out to develop a new methodology that can be broadly applied for deprotection of the PMP group with cheap reagents and beneficial atom economy for potential large scale application in an industrial setting. We decided that the readily accessible reduced Mannich product 4 would be a useful starting point to search for oxidation reagents that might be effective in realising PMP deprotection. Initially, an HPLC assay was adopted that allowed us to determine the conversion in time (after 8 and 20 h) of PMP-protected amine 4 into...
the corresponding free amine upon treatment with varying amounts (1 or 4 equiv) of oxidant. As can be seen from Table 1, CAN and Phl(OAc)₃ in the presence of one equivalent of sulfuric acid indeed were effective in doing so, albeit with moderate conversions. We were, however, pleasantly surprised to find that under these acidic conditions readily available and cheap oxidants such as trichloroisocyanuric acid (TCCA) and periodic acid (H₅IO₆) were effectively capable of removing the PMP group (Table 1, entries 7–12). The data show that the addition of a strong protic acid is crucial in the deprotection reactions, since without the acid the oxidants do not give any product formation at all (Table 1, entries 7 and 10). This is in agreement with the mechanism involving initial formation of the benzoquinone-derived imine, which is under the reaction conditions hydrolysed to the desired free amine (Scheme 1).

**Table 1 Deprotection of PMP-protected amine 4** using various oxidants.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv Oxidant</th>
<th>Conversion to 5 at t = 8 h (%)</th>
<th>Conversion to 5 at t = 20 h (%)</th>
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<tr>
<td>1</td>
<td>1 CAN</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>4 CAN</td>
<td>71</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>4 Phl(OMe)₂</td>
<td>54</td>
<td>47</td>
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<tr>
<td>4</td>
<td>4 Phl(OMe)₂</td>
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<td>63</td>
</tr>
<tr>
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Conditions: a) 1 or 4 equiv oxidant, 1 equiv H₂SO₄, 5 mol% benzoic acid (internal standard), MeCN/H₂O 1:1, rt. b) Conversions were determined using HPLC (Inertsil ODS-3 column) on crude samples from the reaction mixture. c) Carried out without addition of H₂SO₄. d) Several byproducts were detected by HPLC. (DMF = Dess-Martin periodinane, PBP = pyridinium bromide perbromide, NCS = N-chlorosuccinimide, NBS = N-bromosuccinimide, NIS = N-iodosuccinimide). *d.r. and ee of 4 not determined for this screening.
The decrease in yield upon going from 1 to 4 equiv of TCCA (Table 1, entries 8 and 9) may be explained by oxidation of the liberated amino alcohol in the latter case. Periodic acid shows a relatively low conversion after 8 h, but a very good conversion after 20 h (Table 1, entry 11), while additional equivalents of oxidant yielded no improvement (Table 1, entry 12). Other halogen containing oxidants have also been tested under these acidic conditions, such as the hypervalent Dess-Martin reagent (Table 1, entries 5 and 6), hypochlorous acid (Table 1, entries 13 and 14), and a series of electrophilic halide reagents (Table 1, entries 15–25). Without exception, in all cases conversion of 4 into 5 was observed, but with reduced efficiency compared to TCCA and periodic acid. Finally, several inorganic oxidants were applied, but appeared unsuccessful in this transformation (Table 1, entries 26–30).

2.3 Preparative H$_5$IO$_6$ and TCCA induced deprotection of N-PMP-protected substrates

To verify the results of our initial screening, we performed a series of preparative scale experiments on the initial substrate 4 as well as on the PMP-protected amines 6–11 with TCCA and periodic acid (Table 2). As can be judged from Table 2, the corresponding free amines 5 and 12–17 were formed with satisfactory results. Subjection of PMP-protected benzylamine (6) to TCCA provided the free amine 12 in good yield, but the deprotection proceeded poorly with periodic acid which led us to conclude that for these conditions a substituent at the benzylic position is desirable (Table 2, entries 1 and 2). From NMR analysis of the concentrated combined DCM layers from the workup, it was concluded that benzaldehyde was formed in the H$_5$IO$_6$ experiment. Indeed, PMP-protected α-methylbenzylamine (7) gave good yields of the desired product 13 with both oxidants (Table 2, entries 3 and 4). N-PMP-protected 4-phenylbutan-2-amine (8) underwent facile deprotection in similar efficiency to give 4-phenylbutan-2-amine (14) (Table 2, entries 5 and 6). Deprotection of the reduced Mannich adducts 4 and 9–10 also proceeded readily to furnish the corresponding amines in excellent yield (Table 2, entries 7–12). Finally, the tertiary amine 11 was subjected to the same conditions, and showed a good yield in case of TCCA deprotection, but did not produce a pure product when H$_5$IO$_6$ was used. It may be expected that the yields may be further increased by optimisation of the reaction conditions. It should be noted that these new PMP removal procedures are accompanied by a straightforward and practical workup, which is in sharp contrast with the laborious CAN chromatography protocol. In all cases, after completion of the reaction, workup involved washing the aqueous mixture with DCM (to remove benzoquinone) before adjustment to high pH (>10) and extraction with ethyl acetate. Upon acidification of the organic layer with a solution of HCl in ethyl acetate and subsequent concentration, the
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Deprotected amines were obtained in high purity as the corresponding HCl-salts and chromatography was not needed for further purification.

Table 2 Preparative scale N-PMP deprotections.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-PMP amine</th>
<th>oxant</th>
<th>product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH$_2$PMP</td>
<td>TCCA</td>
<td>NH$_2$HCl</td>
</tr>
<tr>
<td>2</td>
<td>NH$_2$PMP</td>
<td>H$_5$IO$_6$</td>
<td>12 (72%)</td>
</tr>
<tr>
<td>3</td>
<td>NH$_2$PMP</td>
<td>TCCA</td>
<td>NH$_2$HCl</td>
</tr>
<tr>
<td>4</td>
<td>NH$_2$PMP</td>
<td>H$_5$IO$_6$</td>
<td>4 (61%)</td>
</tr>
<tr>
<td>5</td>
<td>NH$_2$PMP</td>
<td>TCCA</td>
<td>NH$_2$HCl</td>
</tr>
<tr>
<td>6</td>
<td>NH$_2$PMP</td>
<td>H$_5$IO$_6$</td>
<td>5 (68%)</td>
</tr>
<tr>
<td>7</td>
<td>NH$_2$PMP</td>
<td>TCCA</td>
<td>NH$_2$HCl</td>
</tr>
<tr>
<td>8</td>
<td>NH$_2$PMP</td>
<td>H$_5$IO$_6$</td>
<td>5 (60%)</td>
</tr>
<tr>
<td>9</td>
<td>NH$_2$PMP</td>
<td>TCCA</td>
<td>NH$_2$HCl</td>
</tr>
<tr>
<td>10</td>
<td>NH$_2$PMP</td>
<td>H$_5$IO$_6$</td>
<td>7 (73%)</td>
</tr>
<tr>
<td>11</td>
<td>NH$_2$PMP</td>
<td>TCCA</td>
<td>NH$_2$HCl</td>
</tr>
<tr>
<td>12</td>
<td>NH$_2$PMP</td>
<td>H$_5$IO$_6$</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>13</td>
<td>NH$_2$PMP</td>
<td>TCCA</td>
<td>NH$_2$HCl</td>
</tr>
<tr>
<td>14</td>
<td>NH$_2$PMP</td>
<td>H$_5$IO$_6$</td>
<td>8 (95%)</td>
</tr>
</tbody>
</table>

$^*$Conditions: 1 equiv H$_2$SO$_4$, 1 equiv H$_5$IO$_6$ or 0.5 equiv TCCA, MeCN/H$_2$O 1:1, rt
2.4 Mechanism

Although we have not studied the mechanism of oxidative PMP deprotection methods, in this section, two possible mechanisms will be discussed: 1. \( N \)-halogenation (Scheme 2) and 2. single-electron transfer (SET) (Scheme 3). Both mechanisms entail the formation of an iminoquinone species, which upon hydrolysis leads to formation of the free amine and benzoquinone as the side product. The difference between both mechanisms lies in the oxidative first step. The first mechanism starts with attack of the free electron pair of the aniline nitrogen on the electrophilic halide source (e.g. \( \text{H}_2\text{IO}_6 \) or TCCA). Attack of water on the cationic intermediate in the second step followed by elimination of methanol gives rise to the aforementioned iminoquinone species. However, halide-elimination may also occur via \( S_N2 \)-type attack of water on the OMe-group.

![Scheme 2](image)

\textit{Scheme 2} \( N \)-dearylation via \( N \)-halogenation.

The SET mechanism is initiated by abstraction of an electron from the electron-rich aromatic ring by the oxidant. The resulting radical cation is subsequently trapped with water, after which proton abstraction leads to a neutral radical. The desired iminoquinone is formed by H-atom abstraction, followed by recombination of an electron pair.

![Scheme 3](image)

\textit{Scheme 3} \( N \)-dearylation via single electron transfer.
2.5 Deprotection of α-hydroxy-substituted PMP-protected amines

To further explore scope of the substrate of the deprotection method, we synthesised substrate 19 with a hydroxy group β to the amino function (Scheme 4), which is a common reaction product of Mannich reactions.

![Scheme 4 Synthesis of 2,3-dihydroxy amines from hydroxyacetone.](attachment:Scheme_4.png)

α-Hydroxy-β-amino ketone 18 was prepared via the proline-catalysed Mannich reaction as depicted in Scheme 4. Because β-amino ketone 18 displayed only limited stability, we reduced the ketone functionality prior to deprotection of the amino group. NaBH₄ reduction gave diol 19 in quantitative yield with a diastereomeric ratio of 4:1 for the resulting alcohols. Subsequent treatment of 19 with H₂O₂ did not produce a pure product, presumably due to oxidative cleavage of the diol. Unfortunately, also by applying TCCA, diol 19 could not be obtained in reasonable purity. In both reactions, benzaldehyde was formed as a side product as could be concluded from ¹H NMR analysis of the concentrated combined DCM layers.

As described in Section 2.4, oxidation of the PMP group results in the formation of an iminoquinone species. The second step in the deprotection is the acidic hydrolysis of this iminoquinone. However, a hydroxyl function adjacent to the PMP-amino group, presumably C-C bond cleavage occurs, leading to formation of 2-hydroxypropionaldehyde and imine 21 (Scheme 5). The latter compound is subsequently hydrolysed to p-hydroxyaniline and benzaldehyde. In the presence of a second equivalent of the oxidising agent, p-hydroxyaniline might be further oxidised, and upon hydrolysis, ultimately lead to the formation of ammonia and benzoquinone.

![Scheme 5 Mechanism of benzaldehyde formation through oxidative cleavage.](attachment:Scheme_5.png)
We envisioned that this undesired cleavage could be circumvented through protection of the β-OH group. We realised that selective protection of the desired secondary OH groups would be cumbersome.

![Scheme 6 Bis-OH protection followed by PMP removal.](image)

Protection of diol 19 with TBSCl resulted in formation of the fully protected diol 22 in 89% yield. Subsequent subjection to TCCA conditions enabled us to isolate the free amine in 77% yield, which proved the importance of protection of β-hydroxyl groups during N-PMP deprotection.

### 2.6 Deprotection of other N-aryl protected amines

Although less often employed as an amine protecting group, we also studied the removal of the o-methoxy-, p-hydroxy-, o-hydroxy- and p-methoxyphenyl groups. To this end, a series of N-aryl protected amines was synthesised via a reductive amination procedure starting from 4-phenylbutan-2-one.

N-Aryl-protected amines 24-27 were exposed to oxidative deprotection conditions (H$_2$O$_2$ or TCCA). We found that p-hydroxy- and p-methoxy-substituted aryl groups could be removed without extensive side-product formation. However, with an electron-donating substituent in the o-position, reactions proceeded less efficiently. To demonstrate the importance of an electron-donating substituent on the aromatic ring, we also included an unsubstituted N-phenyl-protected amine and found that the desired deprotected amine could only be obtained in trace amounts.
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2.7 Conclusions
In conclusion, the extensive use of the PMP-group in asymmetric organocatalysis requires facile and scalable deprotection procedures in order to render these processes economically viable. We have developed novel oxidative cleavage conditions involving a series of electrophilic halide reagents, which are effective if the deprotection is carried out at low pH. Periodic acid and trichloroisocyanuric acid were identified as particularly effective for N-deprotection, requiring only 1 and 0.5 equiv, respectively, to give a high yield of the desired amine. In case of 1,2-amino alcohols, protection of the hydroxyl substituent is required in order to avoid undesired oxidative C-C-bond cleavage. In addition, we found that our method is also applicable for other N-aryl (including o-OMe-, p-OH- and o-OH-phenyl) protected amines.

2.8 Experimental section

General remarks
All chemicals were obtained from commercial sources and used without further purification unless stated otherwise. All reactions were carried out under ambient atmosphere unless stated otherwise. Rf values were obtained using thin layer chromatography (TLC), which was carried out on silica gel-coated plates (Merck 60 F254). Column chromatography was carried out using silica gel. Melting points were analysed...
with Büchi melting point B-545. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer, or a Bruker Tensor 27 FTIR spectrometer. NMR spectra were recorded on a Bruker DMX300, Varian Inova 400 or Bruker DPX200 spectrometer. \( ^1H \) NMR chemical shifts are reported in parts per million (ppm) relative to a residual proton peak of the NMR solvent (δ = 7.26 ppm for CDCl\( _3 \), δ = 3.31 ppm for CD\( _3 \)OD, δ = 4.79 ppm for D\( _2 \)O). \( ^13C \) NMR chemical shifts are reported in ppm relative to CDCl\( _3 \) (77.0 ppm), CD\( _3 \)OD (49.0 ppm) or DMSO-d\( _6 \) (39.5 ppm).

Optical rotation were determined with a Perkin Elmer 241 polarimeter. High resolution mass spectra were recorded on a JEOL AccuTOF-CS or JEOL AccuTOF-GCv spectrometer. HPLC analysis was carried out on various Shimadzu HPLC-configurations using the stated columns and eluents. Detection was carried out using UV light.

### (2S,3S)-3-((4-Methoxyphenyl)amino)-2-methyl-3-phenylpropan-1-ol (4)

Benzaldehyde (4.8 mL, 5.0 g, 47.1 mmol) was dissolved in NMP (50 mL). \( p \)-Anisidine (6.38 g, 51.8 mmol) and \( L \)-proline (0.54 g, 4.71 mmol) were added. The resulting mixture was stirred for 1 h and cooled to \(-20^\circ C\), followed by addition of propionaldehyde (10.2 mL, 8.19 mL, 141 mmol). The mixture was stirred for 22 h and quenched by addition of 50 mL potassium phosphate buffer (pH 7, 50 mM). The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na\( _2 \)SO\( _4 \)) and concentrated.

The residue was dissolved in MeOH (250 mL) and cooled to 0 \(^\circ C\). Solid NaBH\( _4 \) was slowly added to the reaction mixture while monitoring the temperature of the reaction mixture (T<10 \(^\circ C\)). The reaction mixture was stirred for an additional 30 min and quenched with aqueous NaHCO\( _3 \) (100 mL). EtOAc (350 mL) and water (400 mL) were added and after separation, the aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were dried (Na\( _2 \)SO\( _4 \)) and concentrated. The residue was taken up in diisopropyl ether (100 mL) and water (100 mL). After separation, the organic layer was washed with water (100 mL), saturated aqueous NaHCO\( _3 \) (100 mL), dried (Na\( _2 \)SO\( _4 \)) and concentrated. The product was obtained as a white solid after crystallisation from diisopropyl ether (2.63 g, 9.69 mmol, 21%). The mother liquor was concentrated and the residue was purified by column chromatography (EtOAc/heptane 1/6 → 1/1). The product was obtained as a white solid (5.58 g, 20.6 mmol, 44%).

Characterisation of product obtained from crystallisation.

\(^1H\) NMR (CDCl\( _3 \), 300 MHz) δ (ppm) 7.38–7.18 (m, 5H), 6.71–6.64 (m, 2H), 6.55–6.48 (m, 2H), 4.51 (d, \( J = 4.3 \) Hz, 1H), 3.68 (s, 3H), 3.65–3.62 (m, 2H), 2.25–2.09 (m, 1H), 0.93 (d, \( J = 7.1 \) Hz, 3H). \(^13C\) NMR (CDCl\( _3 \), 75 MHz) δ (ppm) 152.2, 141.7, 141.3, 128.4, 127.0, 126.9, 115.1, 114.7, 66.2, 61.3, 55.7, 41.5, 12.1; HPLC: ee 95% (Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention times: minor enantiomer 7.6 min, major enantiomer 8.8 min); d.r. \((^1H\) NMR) > 19:1; \(^1H\) NMR (CD\( _3 \)OD, 300 MHz) δ (ppm) 7.40–7.10 (m, 5H), 6.66–6.57 (m, 2H), 6.56–6.44 (m, 2H), 4.43 (d, \( J = 5.2 \) Hz, 1H), 3.62 (s, 3H), 3.55 (dd, \( J = 10.7, 6.6 \) Hz, 1H), 3.38 (dd, \( J = 10.7, 5.8 \) Hz, 1H), 2.11–1.97 (m, 1H), 0.95 (d, \( J = 7.0 \) Hz, 3H). \(^1H\) NMR spectral data are in accordance with previously reported data.

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Characterisation of the product obtained from column chromatography.

\[^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta (ppm) 7.36-7.17 (m, 5H), 6.73-6.65 (m, 2H), 6.56-6.47 (m, 2H), 4.51 (d, J = 4.3 Hz, 1H), 3.68 (s, 3H), 3.65-3.62 (m, 2H), 2.26-2.09 (m, 1H), 0.93 (d, J = 7.1 Hz, 3H); \]^13\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta (ppm) 152.1, 141.8, 141.3, 128.3, 127.0, 126.9, 115.1, 114.7, 66.2, 61.2, 55.7, 41.5, 12.0; ee > 99\% (HPLC, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention times: minor enantiomer 7.8 min, major enantiomer 8.8 min), d.r. (\[^1\text{H} \text{NMR}) > 15:1.

(\textit{E})-4-Methoxy-N-(1-phenylethylidene)aniline (7a)

Acetophenone (7.1 mL, 7.32 g, 60.9 mmol) was dissolved in toluene (100 mL). After addition of \textit{p}-anisidine (5.00 g, 40.6 mmol) and \textit{p}-toluenesulfonic acid monohydrate (17 mg, 0.089 mmol), the mixture was heated to reflux in a Dean–Stark apparatus during 1.5 h. The mixture was concentrated and the residue was crystallised from heptane. (yellow solid; 4.84 g, 26.9 mmol, 66\%).

\[^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta (ppm) 8.03-7.93 (m, 2H), 7.51-7.37 (m, 3H), 6.98-6.89 (m, 2H), 6.80-6.72 (m, 2H), 3.82 (s, 3H), 2.26 (s, 3H); \]^13\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta (ppm) 165.7, 155.9, 144.8, 139.7, 130.3, 128.3, 127.1, 120.7, 114.2, 55.4, 17.3.

NMR data are in accordance with previously reported data.

4-Methoxy-N-(1-phenethyl)aniline (7)

Under an atmosphere of argon, (\textit{E})-4-Methoxy-N-(1-phenylethylidene)aniline (7a) (vide supra) (2.00 g, 11.1 mmol) was dissolved in dry THF (50 mL), followed by addition of acetic acid (3.2 mL, 3.33 g, 55.5 mmol) and Na\text{BH}_4 (1.26 g, 33.3 mmol). The resulting mixture was heated to reflux, stirred 30 min and cooled to rt. Saturated aqueous NaHCO\textsubscript{3} was added (50 mL). The resulting mixture was extracted with \textit{Et}_2\text{O} (50 mL). The organic phase was dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The residue was purified by column chromatography (\textit{EtOAc/heptane 1/6}), to afford 1.80 g (7.92 mmol, 71\%) of a colorless oil, which crystallised upon standing.

\[^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta (ppm) 7.39-7.27 (m, 4H), 7.26-7.18 (m, 1H), 6.74-6.65 (m, 2H), 6.51-6.43 (m, 2H), 4.42 (q, J = 6.7 Hz, 1H), 3.70 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H); \]^13\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta (ppm) 151.9, 145.4, 141.5, 128.6, 128.3, 127.1, 120.7, 114.7, 114.6, 55.7, 54.3, 25.1.

NMR data in accordance with previously reported data.

4-Methoxy-N-(4-phenylbutan-2-yl)aniline (8)

Under an argon atmosphere, \textit{p}-anisidine (1.83 g, 0.0149 mol) was dissolved in DCM (30 mL). Benzylacetone (1.0 mL, 1.0 g, 6.7 mmol), acetic acid (0.05 mL, 0.095 g, 14.9 mmol) and Na\text{OAc}.\text{BH} (4.01 g, 0.0189 mol) were added. The mixture was stirred for 2 h and quenched with aqueous saturated NaHCO\textsubscript{3}. After dilution with DCM (50 mL), the layers were separated. The organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The residue was purified through column chromatography (Et\textit{OAc/heptane 1/9). Yield: 1.66 g (6.50 mmol, 97\%) of a yellow oil. \[^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta (ppm)

Characterisation of the product obtained from column chromatography.
Spectral data are in accordance with previously reported data.\(^\text{15}\)

(2S,3S)-3-Amino-2-methyl-3-phenylpropan-1-ol hydrochloride (5.HCl) (entry 7)

(2S,3S)-3-((4-Methoxyphenyl)amino)-2-methyl-3-phenylpropan-1-ol (4) (271 mg, 1.0 mmol) was dissolved in MeCN/H\(_2\)O (1:1, 20 mL), aqueous H\(_2\)SO\(_4\) (1 M, 1 mL) was added followed by trichloroisocyanuric acid (116 mg, 1.0 mmol) and the resulting mixture was stirred for 16 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). All layers were combined and separated. Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The residue was taken up in EtOAc and concentrated. The residue was taken up in DCM (50 mL) and concentrated (2×). The product was obtained as an off-white/red solid (198 mg, 0.98 mmol, 98%) \(^1\)H NMR (CD\(_3\)OD, 300 MHz) \(\delta\) (ppm) 7.54–7.35 (m, 5H), 4.30 (d, \(J = 6.6\) Hz, 1H), 3.44–3.32 (m, 2H), 2.38–2.21 (m, 1H), 1.03 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (CD\(_3\)OD, 75 MHz) \(\delta\) (ppm) 136.6, 130.1 (2C), 128.7, 64.5, 60.0, 40.0, 13.7.

Spectral data are in accordance with data obtained from 5.HCl (entry 8) \(^{\text{vide infra}}\).

(2S,3S)-3-Amino-2-methyl-3-phenylpropan-1-ol hydrochloride (5.HCl) (entry 8)

(2S,3S)-3-((4-Methoxyphenyl)amino)-2-methyl-3-phenylpropan-1-ol (4) (271 mg, 1.0 mmol) was dissolved in MeCN/H\(_2\)O (1:1, 20 mL), aqueous H\(_2\)SO\(_4\) (1 M, 1 mL) was added followed by K\(_2\)IO\(_4\) (228 mg, 1.0 mmol) and the resulting mixture was stirred for 19 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as an off-white solidifying oil (181 mg, 0.90 mmol, 90%) \(^1\)H NMR (CD\(_3\)OD, 300 MHz) \(\delta\) (ppm) 7.56–7.35 (m, 5H), 4.32 (d, \(J = 6.5\) Hz, 1H), 3.43–3.32 (m, 2H), 2.41–2.21 (m, 1H), 1.04 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (CD\(_3\)OD, 75 MHz) \(\delta\) (ppm) 136.7, 130.0 (2C), 128.7, 64.5, 59.9, 40.0, 13.8; IR (cm\(^{-1}\)) 3332, 3113, 2975, 2872, 1488, 1025, 705, 558; HRMS [ESI+ (m/z)]: calcd for C\(_{10}\)H\(_{16}\)NO (M+H\(^+\)) 166.12319, found 166.12458.
Mild and efficient deprotection of the amine protecting p-methoxyphenyl (PMP) group

A mixture of p-nitrobenzaldehyde (7.12 g, 47.1 mmol), NMP (50 mL), p-anisidine (6.38 g, 51.8 mmol) and l-proline (0.54 g, 4.71 mmol) was stirred for 1.5 h and cooled to –20 °C. Propionaldehyde (10.2 mL, 8.19 g, 141 mmol) was added slowly. The resulting mixture was stirred for 2 days and cooled to 0 °C. NaBH₄ was added slowly. Subsequently, the reaction mixture was poured out in a mixture of a saturated aqueous NH₄Cl and water (200 mL/200 mL). The mixture was extracted with diisopropyl ether (200 mL). The organic layer was washed with water (3 × 200 mL), aqueous saturated NaHCO₃ (200 mL), dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1:6 → 1:1). After concentration, the orange solid (8.45 g) was dissolved in boiling diisopropyl ether. Some insoluble solids were filtered off and the hot solution was left standing for crystallisation. The product was obtained as orange crystals (5.31 g, 16.8 mmol, 36%) ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.22–8.13 (m, 2H) (both diastereomers), 7.56–7.46 (m, 2H) (both diastereomers), 6.73–6.63 (m, 2H) (both diastereomers), 6.47–6.40 (m, 2H) (both diastereomers), 4.65 (d, J = 4.0 Hz, 1/19H) (major diastereomer), 4.38 (d, J = 7.1 Hz, 1/19H) (minor diastereomer), 3.68 (s, 3H) (both diastereomers), 3.76–3.58 (m, 2H) (both diastereomers), 2.28–2.11 (m, 1H) (both diastereomers), 0.91 (d, J = 7.1 Hz, 18/19 × 3H) (major diastereomer), 0.89 (d, J = 6.90 Hz, 1/19 × 3H) (minor diastereomer); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 152.3, 150.4, 147.0, 140.7, 128.0, 123.6, 114.7, 65.6, 60.5, 55.7, 41.4, 11.6; HPLC: d.r. 19:1 (Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention times: minor diastereomer 15.4 min, major diastereomer 17.2 min) ee > 99% (HPLC, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention times: minor enantiomer 10.5 min, major diastereomer 17.2 min); HRMS [ESI⁺ (m/z)]: calcld for C₁₇H₂₁N₂O₄ (M+H⁺) 317.15013, found 317.15000.

NMR spectral data are in accordance with previously reported data.

(2S,3S)-3-((4-Methoxyphenyl)amino)-2-methyl-3-(4-nitrophenyl)propan-1-ol (9)

To a solution of p-anisidine in DMSO (20 mL) were added benzaldehyde (1.6 mL, 1.72 g, 16.2 mmol) and L-proline (373 mg, 3.24 mmol). After 2 h of stirring, acetone (80 mL) was added. The resulting mixture was stirred for 18 h, quenched with aqueous saturated NaHCO₃ (100 mL) and extracted with a 1:1 mixture of EtOAc and heptane (2 × 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1:9 → 1:4). The product was obtained as a yellow oil, which crystallised partially upon storage in freezer (1.83 g, 6.79 mmol, 42%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.44–7.19 (m, 5H), 6.73–6.66 (m, 2H), 6.57–6.47 (m, 2H), 4.77 (t, J = 6.5 Hz, 1H), 3.69 (s, 3H), 2.90 (d, J = 6.5 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 207.2, 152.4, 142.7, 140.9, 128.7, 127.3, 126.3, 115.3, 114.7, 55.6, 55.3, 51.3, 38.7; HPLC: ee: 95% (Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention times: minor enantiomer 10.0 min, major enantiomer 12.7 min.

NMR data are in accordance with previously reported data.
Chapter 2

(4S)-4-((4-Methoxyphenyl)amino)-4-phenylbutan-2-ol (10)

Under an atmosphere of argon, (S)-4-((4-methoxyphenyl)amino)-4-phenylbutan-2-one (10a) (425 mg, 1.58 mmol) (vide supra) was dissolved in MeOH (10 mL) and the resulting mixture was cooled to 0 °C. Solid NaBH₄ (66 mg, 1.74 mmol) was added. After 20 min of stirring, saturated aqueous NaClO₃ (20 mL) was added. The aqueous mixture was extracted with DCM (2 × 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified through column chromatography. The product was obtained as an off-white solid (152 mg, 72%). ¹H NMR data are in accordance with previously reported data.¹⁸

(2S,3S)-3-((4-Methoxyphenyl)(methyl)amino)-2-methyl-3-(4-nitrophenyl)propan-1-ol (11)

Under an atmosphere of argon, (2S,3S)-3-((4-methoxyphenyl)(methyl)amino)-2-methyl-3-(4-nitrophenyl)propan-1-ol (9) (3.0 g, 9.48 mmol) was dissolved in dry MeCN (50 mL). K₂CO₃ (2.63 g, 19 mmol) and MeI (2.9 mL, 29 mmol) were added. The mixture was heated to 40 °C, stirred for 5 days, allowed to come to rt, filtered and concentrated. The residue was purified by column chromatography (EtOAc/heptane 3/1). The product was obtained as a red oil (2.63 g, 82%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.14–8.07 (m, 2H), 7.30–7.23 (m, 2H), 6.79 (s, 4H), 4.63 (d, J = 9.9 Hz, 1H), 3.75 (s, 3H), 3.58 (dd, J = 10.8, 4.1 Hz, 1H), 3.37 (dd, J = 10.7, 5.2 Hz, 1H), 2.58 (s, 3H), 2.62–2.47 (m, 1H), 1.20 (d, J = 6.7 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 153.4, 147.0, 145.1, 144.7, 128.8, 123.3, 118.7, 114.5, 67.7, 65.1, 55.6, 35.7, 34.1, 14.8; IR (cm⁻¹): 3393, 2932, 2363, 1509, 1345; HRMS [ESI⁺ (m/z)]: calcld for C₂₉H₂₅N₂O₄Na (M+Na⁺) 535.14773, found 535.14829; Rf: 0.44 (EtOAc/heptane 1:1).

Benzylation hydrochloride (12) (entry 1)

N-Benzyl-4-methoxyaniline (213 mg, 1.0 mmol) was dissolved in MeCN/H₂O (1:1, 20 mL), aqueous H₂SO₄ (1 mL, 1M) was added followed by trichloroisocyanuric acid (116 mg, 0.5 mmol) and the resulting mixture was stirred overnight and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as an off-white solid (103 mg, 0.72 mmol, 72%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.56–7.34 (m, 5H), 4.12 (s, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 134.4, 130.2, 130.0, 44.3. ¹H NMR data are in accordance with previously reported data.¹⁷

¹H NMR data are in accordance with previously reported data.¹⁷

¹H NMR data are in accordance with previously reported data.¹⁷

¹H NMR data are in accordance with previously reported data.¹⁷

¹H NMR data are in accordance with previously reported data.¹⁷
Mild and efficient deprotection of the amine protecting p-methoxyphenyl (PMP) group

Benzylamine hydrochloride (12) (entry 2)

*N*-Benzyl-4-methoxyaniline (213 mg, 1.0 mmol) was dissolved in MeCN/H₂O (1:1, 20 mL), aqueous H₂SO₄ (1 mL, 1M) was added followed by H₅IO₆ (228 mg, 0.5 mmol) and the resulting mixture was stirred overnight and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as an off-white solid (47 mg, 0.33 mmol, 33%).

1H NMR (CD₃OD, 300 MHz) δ (ppm) 7.60–7.33 (m, 5H), 4.12 (s, 2H); 13C NMR (CD₃OD, 75 MHz) δ (ppm) 134.4, 130.2, 130.0, 44.4. Spectral data are in accordance with data obtained from 12 (entry 1).

1-Phenylethanamine hydrochloride (13) (entry 3)

4-Methoxy-N-(1-phenylethyl)aniline (7) (227 mg, 1.0 mmol) was dissolved in MeCN/H₂O (1:1, 20 mL), aqueous H₂SO₄ (1M, 1 mL) was added followed by trichloroisocyanuric acid (116 mg, 0.50 mmol). The resulting mixture was stirred for 19 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (3 × 50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (148 mg, 0.94 mmol, 94%).

1H NMR (CD₃OD, 300 MHz) δ (ppm) 7.49–7.36 (m, 5H), 4.45 (q, J = 6.9 Hz, 1H), 1.63 (d, J = 6.9 Hz, 3H); 13C NMR (CD₃OD, 75 MHz) δ (ppm) 139.6, 130.3, 130.2, 127.6, 52.4, 20.7. 1H NMR data are in accordance with previously reported data.¹⁹

1-Phenylethanamine hydrochloride (13) (entry 4)

4-Methoxy-N-(1-phenylethyl)aniline (7) (227 mg, 1.0 mmol) was dissolved in MeCN/H₂O (1:1, 20 mL), aqueous H₂SO₄ (1 mL, 1M) was added followed by H₅IO₆ (228 mg, 1.0 mmol). The mixture was stirred for 19 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as an off-white solid (128 mg, 0.81 mmol, 81%).

1H NMR (CD₃OD, 300 MHz) δ (ppm) 7.56–7.34 (m, 5H), 4.47 (q, J = 6.9 Hz, 1H), 1.65 (d, J = 6.9 Hz, 3H); 13C NMR (CD₃OD, 75 MHz) δ (ppm) 139.6, 130.3, 130.1, 127.7, 52.4, 20.8. NMR data are in accordance with NMR data obtained from 13 (entry 3).
4-Phenylbutan-2-amine hydrochloride (14) (entry 5)

4-Methoxy-N-(4-phenylbutan-2-yl)aniline (14) (255 mg, 1.0 mmol) was dissolved in MeCN/H2O (1:1, 20 mL), aqueous H2SO4 (1M, 1 mL) was added followed by trichloroisocyanuric acid (116 mg, 1.0 mmol) and the resulting mixture was stirred for 16 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na2SO4). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (169 mg, 91%, 1H NMR (CD3OD, 300 MHz) δ (ppm) 8.37–8.28 (m, 2H), 7.84–7.74 (m, 2H), 4.57 (d, J = 6.6 Hz, 1H), 3.47 (dd, J = 6.6 Hz, 3H); 13C NMR (CD3OD, 75 MHz) δ (ppm) 141.8, 129.7, 129.3, 127.3, 48.6, 37.7, 32.5, 18.5; IR (cm⁻¹) 2890, 1516, 765, 745, 700; HRMS [ESI⁺ (m/z)]: calcd for C24H18N·H2SO4·HCl 483.1000, found 483.0970. NMR data are in accordance with NMR data obtained from 14 (entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 6)

4-Methoxy-N-(4-phenylbutan-2-yl)aniline (14) (255 mg, 1.0 mmol) was dissolved in MeCN/H2O (1:1, 20 mL), aqueous H2SO4 (1M, 1 mL) was added followed by H2O2 (228 mg, 1.0 mmol) and the resulting mixture was stirred for 20 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na2SO4). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (125 mg, 67%, 1H NMR (CD3OD, 300 MHz) δ (ppm) 7.33–7.15 (m, 5H), 3.33–3.19 (m, 1H), 2.82–2.60 (m, 2H), 2.06–1.75 (m, 2H), 1.34 (d, J = 6.6 Hz, 3H); 13C NMR (CD3OD, 75 MHz) δ (ppm) 141.8, 129.7, 129.3, 127.3, 48.6, 37.6, 32.5, 18.5. NMR data are in accordance with NMR data obtained from 14 (entry 5).

(2S,3S)-3-Amino-2-methyl-3-(4-nitrophenyl)propan-1-ol hydrochloride (15) (entry 9)

(2S,3S)-3-((4-Methoxyphenyl)amino)-2-methyl-3-(4-nitrophenyl)propan-1-ol (9) (316 mg, 1.0 mmol) was dissolved in MeCN/H2O (1:1, 20 mL), aqueous H2SO4 (1M, 1 mL) was added followed by trichloroisocyanuric acid (116 mg, 0.5 mmol) and the resulting mixture was stirred for 18 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na2SO4). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The residue was taken up in EtOAc (50 mL) and concentrated. The residue was taken up in DCM (50 mL) and concentrated. The product was obtained as an off-white solid (249 mg, 1.0 mmol, 100%) 1H NMR (CD3OD, 300 MHz) δ (ppm) 8.37–8.28 (m, 2H), 7.84–7.74 (m, 2H), 4.57 (d, J = 6.4 Hz, 1H), 3.47 (dd, J = 6.4 Hz, 3H); 13C NMR (CD3OD, 300 MHz) δ (ppm) 289.57, 151.65, 129.66, 129.31, 127.36, 48.62, 37.63, 32.51, 18.51; IR (cm⁻¹) 3410, 2980, 1675, 1516, 765, 745, 700; HRMS [ESI⁺ (m/z)]: calcd for C24H18N4O6·HCl·H2O 490.0926, found 490.0907. NMR data are in accordance with NMR data obtained from 15 (entry 9).
Mild and efficient deprotection of the amine protecting p-methoxyphenyl (PMP) group

(2S,3S)-3-Amino-2-methyl-3-(4-nitrophenyl)propan-1-ol hydrochloride (15) (entry 10)

(2S,3S)-3-((4-Methoxyphenyl)amino)-2-methyl-3-(4-nitrophenyl)propan-1-ol (9)

(16 mg, 1.0 mmol) was dissolved in MeCN/H₂O (1:1, 20 mL), aqueous H₂SO₄ (1M, 1 mL) was added followed by H₂SO₄ (228 mg, 1.0 mmol) and the resulting mixture was stirred for 18 h and subsequently washed with DCM (3 × 25 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The residue was taken up in EtOAc (50 mL) and concentrated. The product was obtained as a white solid (222 mg, 0.90 mmol, 90%) 1H NMR (CDCl₃, 300 MHz) δ (ppm) 9.37–8.28 (m, 2H), 7.79–7.67 (m, 2H), 4.52 (d, J = 6.3 Hz, 1H), 3.45 (dd, J = 11.0, 4.7 Hz, 1H), 3.33 (dd, J = 10.3, 6.2 Hz, 1H), 2.45–2.28 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H); 13C NMR (CDCl₃, 75 MHz) δ (ppm) 149.4, 143.8, 130.3, 124.9, 64.3, 59.2, 39.8, 13.6; IR (cm⁻¹) 3353, 2966, 2882, 1529, 1346; HRMS [ESI⁺(m/z)]: calcd for C₁₃H₁₄NO₂Cl (M+H) 211.10916, found 211.10916.

(4S)-4-Amino-4-phenylbutan-2-ol hydrochloride (16) (entry 11)

(4S)-4-((4-Methoxyphenyl)amino)-4-phenylbutan-2-ol (10) (44 mg, 0.162 mmol) was dissolved in MeCN/H₂O (1:1, 10 mL), aqueous H₂SO₄ (0.16 mL, 1M) was added followed by trichloroisocyanuric acid (19 mg, 0.001 mmol). The resulting mixture was stirred for 18 h and subsequently washed with DCM (3 × 25 mL). Aqueous KOH was added (0.3 mL, 5 M) and the aqueous solution was extracted with EtOAc (25 mL). Aqueous KOH was added (0.15 mL, 5 M), and the aqueous solution was extracted with EtOAc (25 mL). Aqueous KOH was added (0.15 mL, 5 M), and the aqueous solution was extracted with EtOAc (25 mL). The combined organic layers were dried (Na₂SO₄) and slightly concentrated. 0.16 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (24 mg, 0.119 mmol, 73%). 1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.53–7.34 (m, 5H, both diastereomers), 4.55–4.41 (m, 1H, both diastereomers), 3.88–3.74 (m, 2/3H, major diastereomer), 3.73–3.58 (m, 1/3H minor diastereomer), 2.20–1.91 (m, 2H, both diastereomers), 1.21 (d, J = 6.2 Hz, 4/3H, major diastereomer), 1.18 (d, J = 6.2 Hz, 2/3H, minor diastereomer); 13C NMR (CDCl₃, 75 MHz) δ (ppm) 138.5 (major diastereomer), 138.4 (major diastereomer), 138.3 (major diastereomer), 130.3 (major diastereomer), 130.1 (minor diastereomer), 128.4 (minor diastereomer), 128.0 (major diastereomer), 66.2 (minor diastereomer), 64.8 (major diastereomer), 55.7 (minor diastereomer), 54.2 (major diastereomer), 43.8 (minor diastereomer), 43.7 (major diastereomer), 24.5 (minor diastereomer), 23.4 (major diastereomer). NMR spectral data are in accordance with data obtained from 16 (entry 12) (vide infra).
(4S)-4-Amino-4-phenylbutan-2-ol hydrochloride (16) (entry 12)

(4S)-4-((4-Methoxyphenyl)amino)-4-phenylbutan-2-ol (10) (44 mg, 0.162 mmol) was dissolved in MeCN:H2O (1:1, 10 mL), aqueous H2SO4 (0.16 mL, 1M) was added followed by H5IO6 (37 mg, 0.162 mmol). The resulting mixture was stirred for 16 h and subsequently washed with DCM (3 × 25 mL). Aqueous KOH was added (0.3 mL, 5 M) and the aqeous solution was extracted with EtOAc (25 mL). Aqueous KOH was added (0.15 mL, 5 M), and the aqueous solution was extracted with EtOAc (25 mL). Aqueous KOH was added (0.15 mL, 5 M), and the aqueous solution was extracted with EtOAc (25 mL). The combined organic layers were dried (Na2SO4), 0.16 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (26 mg, 0.129 mmol, 80 %). 1H NMR (CD3OD, 300 MHz) δ (ppm) 7.53–7.36 (m, 5H, both diastereomers), 4.53–4.42 (m, 1H, both diastereomers), 3.87–3.73 (m, 2/3H, major diastereomer), 3.73–3.59 (m, 1/3H minor diastereomer), 2.17–1.93 (m, 2H, both diastereomers), 1.21 (d, J = 6.2 Hz, 4/3H minor diastereomer), 1.18 (d, J = 6.2 Hz, 2/3H, major diastereomer); 13C NMR (CD3OD, 75 MHz): δ (ppm) 138.5 (major diasteromer), 138.4 (minor diastereomer), 130.3 (major diastereomer 2C), 130.1 (minor diastereomer 2C), 128.4 (minor diastereomer), 128.0 (major diastereomer), 66.2 (minor diastereomer), 64.8 (major diastereomer), 55.7 (minor diastereomer), 54.2 (major diastereomer), 43.8 (minor diastereomer), 43.7 (major diastereomer), 24.5 (minor diastereomer), 23.4 (major diastereomer); IR (cm−1) 3278, 2963, 2441, 2218, 699; HRMS [ESI+ (m/z)]: calcd for C10H16NO (M–Cl–) 166.12319, found 166.12382.

(2S,3S)-2-Methyl-3-(methylamino)-3-(4-nitrophenyl)propan-1-ol hydrochloride (17)

(2S,3S)-3-((4-Methoxyphenyl)(methyl)amino)-2-methyl-3-(4-nitrophenyl)propan-1-ol (11) (0.33 g, 1.0 mmol) was dissolved in MeCN:H2O (1:1, 20 mL), aqueous H2SO4 (1 mL, 1M) was added followed by trichloroisocyanuric acid (116 mg, 0.5 mmol) and the resulting mixture was stirred for 21 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na2SO4) and concentrated. The residue was dissolved in 20 mL EtOAc, 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as an off-white solid (247 mg, 0.95 mmol, 95 %). 1H NMR (CD3OD, 300 MHz) δ (ppm) 8.39–8.32 (m, 2H), 7.81–7.73 (m, 2H), 4.48 (d, J = 4.5 Hz, 1H), 3.54 (dd, J = 10.8, 4.7 Hz, 1H), 3.28 (dd, J = 10.8, 9.1 Hz, 2H), 2.58 (t, 3H), 2.69–2.49 (m, 3H), 0.90 (d, J = 7.0 Hz, 3H); 13C NMR (CD3OD, 75 MHz): δ (ppm) 149.8, 140.0, 131.4, 125.0, 68.8, 64.2, 38.2, 33.0, 13.8; IR (cm−1) 3360, 3207, 1522, 1349; HRMS [ESI+ (m/z)]: calcd for C11H17N2O3 (M+H+) 225.12392, found 225.12475.
(3S,4R)-3-Hydroxy-4-((4-methoxyphenyl)amino)-4-phenylbutan-2-one (18)

Benzaldehyde (8.2 mL, 86 g, 81 mmol) was dissolved in DMSO (480 mL). p-Anisidine (10.0 g, 81 mmol) and L-proline (1.84 g, 0.016 mmol) were added. The resulting mixture was stirred for 2 h followed by addition of hydroxyacetone (18 mL, 90% pure). The reaction mixture was stirred for 17 h, poured out in water (500 mL) and extracted with a 1:1 mixture of EtOAc/heptane (2 × 500 mL, 1 × 100 mL). The combined organic layers were washed with water (3 × 500 mL) and saturated aqueous NaHCO₃ (200 mL). The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/3 → 1/1). The fractions containing the product were concentrated until the product precipitated. The suspension was left standing for 1 h and filtered off. The residue was washed with heptane (100 mL), dried, dissolved in EtOAc (50 mL) and concentrated. The product was obtained as an off-white solid (8.72 g, 30.6 mmol, 38%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.40–7.22 (m, 5H), 6.72–6.65 (m, 2H), 6.54–6.47 (m, 2H), 4.89 (d, J = 2.6 Hz, 1H), 4.41 (d, J = 1.8 Hz, 1H), 4.37 (bs, bs, 1H), 3.78 (bs, 1H), 3.68 (s, 3H), 2.31 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 207.4, 152.4, 140.1, 139.3, 128.6, 127.5, 127.0, 115.1, 114.8, 80.7, 59.1, 55.6, 25.2. d.r. (NMR) >19:1 (one stereoisomer visible) HPLC ee > 99% (Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention times: minor diastereomer 9.1 min, major diastereomer 13.6 min).

NMR spectral data are in accordance with previously reported data.¹

(1R,2S)-1-((4-Methoxyphenyl)amino)-1-phenylbutane-2,3-diol (19)

Under an atmosphere of argon, (3S,4R)-3-hydroxy-4-((4-methoxyphenyl)amino)-4-phenylbutan-2-one (18) was dissolved in DCM/MeOH (40 mL/40 mL). NaBH₄ (2.65 g, 70 mmol) was added. The mixture was stirred for 1 h and quenched with aqueous HCl (20 mL, 5 M). Subsequently, aqueous NaOH (50 mL) was added. The mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was taken up in DCM and concentrated. The product was obtained as a white solidifying oil (2.03 g, 7.1 mmol, quant.). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.36–7.20 (m, 5H, both diastereomers), 6.76–6.49 (m, 4H (both diastereomers), 4.54 (d, J = 4.3 Hz, 1H, both diastereomers), 4.43 (d, J = 3.9 Hz, 1H, minor diastereomer), 4.00–3.50 (m, 2H, both diastereomers), 3.68 (s, 3H, both diastereomers), 1.37–1.15 (m, 3H, both diastereomers); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 152.6, 140.7, 128.8, 128.7, 127.5, 127.1, 115.9, 115.8, 114.7, 78.7, 77.2, 68.5, 67.6, 61.5, 59.8, 55.6, 20.2, 18.8. IR (cm⁻¹) 3419, 2966, 2932, 1513, 1028, 810; HRMS [ESI⁺ (m/z)]: calcd for C₁₇H₂₁NO₃Na (M+Na⁺) 310.14191, found 310.14250; Rf 0.33 (EtOAc/heptane 1:1).
Chapter 2

\(N'-(1R,2S,3R)-3,3\text{-bis((tert-butylmethyldiisilyl)oxy)}\text{-1-phenylbutyl}-4\text{-methoxyaniline (22)}\)

A flask was loaded with tert-butylmethyldiisilyl chloride (2.62 g, 17.4 mmol) and placed under argon. DMF (20 mL), \((1R,2S,3R)-(4\text{-methoxyphenyl})\text{amino)}\text{-1-phenylbutane-2,3-diol (19)}\) (1.00 g, 3.48 mmol) and imidazole (2.37 g, 34.8 mmol) were added and the mixture was heated to 80 °C for 16 h and subsequently allowed to cool to rt. Saturated aqueous \(\text{NH}_4\text{Cl}\) (50 mL) was added and the resulting mixture was extracted with diethyl ether (100 mL). The organic layer was washed with water (100 mL), saturated aqueous \(\text{NaHCO}_3\) dried (\(\text{Na}_2\text{SO}_4\)) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1:2). The product was obtained as a colorless oil (1.60 g, 3.10 mmol, 89%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ (ppm) 7.36–7.13 (m, 5H), 6.75–6.63 (m, 2H), 6.45–6.34 (m, 2H), 4.74–4.50 (m, 2H), 3.97–3.70 (m, 2H), 3.69 (2 × s, 3H), 1.19 (d, \(J = 6.2\) Hz, 3H), 0.96–0.52 (2 × TMS, 30H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) δ (ppm) 128.3, 128.2, 127.5, 126.8, 126.4, 114.9, 114.7, 114.2, 113.5, 82.9, 83.8, 81.9, 79.5, 58.5, 55.7, 54.7, 26.2, 26.0, 25.9, 25.7, 20.0, 18.3, 18.0, 17.8, 17.0, -2.9, -3.7, -4.2, -5.0, -5.5 (complex NMRs of mixture of diastereomers), IR (cm\(^{-1}\)) 3430, 2953, 2929, 2896, 2856, 1512, 834; HRMS [ESI (m/z)]: calcd for \(C_{42}H_{34}NO_5Si_2\) (M+H\(^{+}\)) 516.33292, found 516.33212; \(R\) (EtOAc/heptane 1:9) 0.68.

\((1R,2S,3R)-3,3\text{-bis((tert-butylmethyldiisilyl)oxy)}\text{-1-phenylbutan-1-amine (23)}\)

To a solution of \(N'-(1R,2S,3R)-3,3\text{-bis((tert-butylmethyldiisilyl)oxy)}\text{-1-phenylbutyl}-4\text{-methoxyaniline (22)}\) (41 mg, 0.079 mmol) in a mixture of MeCN/H\(_2\)O (6 mL, 1:1) was added aqueous \(\text{H}_2\text{SO}_4\) and trichloroisocyanuric acid (9.3 mg, 0.040 mmol). The mixture was stirred for 20.5 h and \(\text{H}_2\text{O}\) (2 mL) and saturated aqueous \(\text{Na}_2\text{CO}_3\) (1 mL) were added. The mixture was stirred or 30 min and \(\text{H}_2\text{O}\) was added (10 mL). The aqueous mixture was extracted with DCM (2 × 10 mL). The combined organics were dried (\(\text{Na}_2\text{SO}_4\)) and concentrated. The product was obtained as a slightly coloured film (25 mg, 0.061 mmol, 77%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ (ppm) 7.51–7.16 (m, 5H), 3.99–3.58 (m, 2H), 1.35–0.69 (m, 21H), 0.18–0.34 (m, 12H); IR (cm\(^{-1}\)) 2955, 2929, 2896, 2857, 1255, 1099, 834, 777; HRMS [ESI (m/z)]: calcd for \(C_{22}H_{22}NO_3Si_2\) (M+H\(^{+}\)) 410.29106, found 410.29124.

\(4\text{-((4-Phenylbutan-2-yl)amino)phenol (24)}\)

Under an atmosphere of argon, acetic acid (0.57 mL, 0.60 g, 10 mmol) was dissolved in DCM (30 mL). Benzylacetone (1.40 g, 1.5 mL, 10 mmol), 4-aminophenol (1.09 g, 10 mmol) and Na\((\text{OAc})_2\)BH (2.97 g, 14 mmol) were added. The resulting mixture was stirred for 18 h and quenched with saturated aqueous \(\text{NaHCO}_3\). After separation, the aqueous layer was extracted with DCM (30 mL). The combined organic layers were dried (\(\text{Na}_2\text{SO}_4\)) and concentrated. Diisopropyl ether (10 mL) was added to the residue upon which the product crystallised. After filtration, the crystals were washed with diisopropyl ether (20 mL). The product was obtained as a white solid (1.33 g, 5.51 mmol, 55%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ (ppm) 7.35–7.14 (m, 5H), 6.75–6.61 (m, 2H), 6.55–6.35 (m, 2H), 4.40–3.00 (bs,
Mild and efficient deprotection of the amine protecting p-methoxyphenyl (PMP) group

2H) 3.48–3.30 (m, 1H), 2.72 (t, J = 7.8 Hz, 2H), 1.93–1.65 (m, 2H), 1.20 (d, J = 6.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ (ppm) 147.5, 142.0, 141.6, 128.4, 128.4, 125.8, 116.2, 115.1, 49.1, 38.8, 32.4, 20.8.

NMR Spectral data are in accordance with previously reported data.\(^\text{20}\)

2-Methoxy-N-(4-phenylbutan-2-yl)aniline (25)

Under an atmosphere of argon, acetic acid (1.26 mL, 1.32 g, 22 mmol) was dissolved in DCM (30 mL). Benzylacetone (1.5 mL, 1.48 g, 10 mmol), o-anisidine (2.5 mL, 2.71 g, 22 mmol) and Na(OAc)$_3$BH (5.93 g, 28 mmol) were added. The resulting mixture was stirred for 18 h. Aqueous HCl (1M, 100 mL) was added. After separation, the aqueous layer was extracted with DCM (50 mL). The combined organic layers were washed with aqueous NaOH (1M, 50 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/9). The product was obtained as a colorless oil (2.40 g, 9.40 mmol, 94%).

$^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 7.31–7.15 (m, 5H), 6.88–6.80 (m, 1H), 6.77 (dd, J = 7.9, 1.4 Hz, 1H), 6.63 (dd, J = 7.9, 7.5, 1.6 Hz, 1H), 6.52 (dd, J = 8.0, 1.3 Hz, 1H), 4.15–4.00 (m, 1H), 3.85 (s, 3H), 3.58–3.41 (m, 1H), 2.74 (t, J = 7.9 Hz, 2H), 2.02–1.73 (m, 2H), 1.24 (d, J = 6.3 Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ (ppm) 146.8, 142.1, 137.4, 128.4, 128.3, 125.8, 121.3, 115.8, 110.1, 109.5, 55.4, 47.5, 38.8, 32.5, 20.9; IR (cm$^{-1}$), 3419, 3024, 2960, 1511, 1220, 1029, 735; HRMS [ESI$^+$ (m/z)]: calcd for C$_{17}$H$_{22}$NO (M+H$^+$) 256.17014, found 256.16907; Rf (EtOAc/heptane 1/9) 0.55.

2-(4-Phenylbutan-2-yl)amino)phenol (26)

Under an atmosphere of argon, acetic acid (0.57 mL, 0.60 mL, 10 mmol) was dissolved in DCM (30 mL). Benzylacetone (1.5 mL, 1.48 g, 10 mmol), o-aminophenol (1.09 g, 10 mmol) and Na(OAc)$_3$BH (2.97 g, 14 mmol) were added. The resulting mixture was stirred for 20 h. Aqueous HCl (1M, 100 mL) was added. After separation, the DCM was evaporated. After filtration, the residue was taken up in methanol (10 mL) and DCM (50 mL). The organic mixture was washed with saturated aqueous NaHCO$_3$. The organic layer was dried (Na$_2$SO$_4$) and concentrated. The product was obtained as a dark oil (1.46 g, 6.65 mmol, 61%). $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 7.35–7.15 (m, 5H), 7.05–6.35 (m, 4H), 3.60–3.25 (m, 1H), 2.75 (t, J = 7.9 Hz, 2H), 2.03–1.70 (m, 2H), 1.23 (d, J = 6.2 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ (ppm) 142.0, 128.4, 128.4, 125.8, 32.4, 22.8 (also some broad signals present, no chemical shifts reported); IR (cm$^{-1}$), 3419, 3024, 2960, 1511, 1220, 1029, 735; HRMS [ESI$^+$ (m/z)]: calcd for C$_{16}$H$_{20}$NO (M+H$^+$) 242.15449, found 242.15464; Rf (EtOAc/heptane 1/3) 0.46.
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N-(4-Phenylbutan-2-yl)aniline (27)

Under an atmosphere of argon, acetic acid (1.26 mL, 1.32 g, 22 mmol) was dissolved in DCM (30 mL). Benzylacetone (1.5 mL, 1.48 g, 10 mmol), aniline (2.0 mL, 2.05 g, 22 mmol) and Na(OAc)₃BH (5.93 g, 28 mmol) were added. The resulting mixture was stirred for 20 h. Aqueous HCl (1M, 100 mL) was added. After separation, the aqueous layer was extracted with DCM (50 mL). The combined organic layers were washed with aqueous NaOH (1M, 50 mL). The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/9). The product was obtained as a slightly yellow oil (2.36 g, 10 mmol, 100%).

¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.35–7.12 (m, 7H), 6.69 (tt, J = 7.4, 1.1 Hz, 1H), 6.59–6.52 (m, 2H), 3.59–3.45 (m, 1H), 3.43 (bs, 1H), 2.75 (t, J = 7.9 Hz, 2H), 2.00–1.70 (m, 2H), 1.24 (d, J = 6.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 147.5, 142.0, 129.3, 128.4, 128.4, 125.8, 116.9, 113.1, 47.9, 38.8, 32.5, 20.8.

NMR spectral data are in accordance with previously reported data.

Table 3:

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<th>4-Phenylbutan-2-amine hydrochloride (14) (entry 3)</th>
</tr>
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| 4-[(4-Phenylbutan-2-yl)amino]phenol (24) (241 mg, 1.0 mmol) was dissolved in MeCN/H₂O (1:1, 20 mL), aqueous H₂SO₄ (1 mL, 1M) was added, followed by trichloroisocyanuric acid (116 mg, 0.5 mmol) and the resulting mixture was stirred for 24 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (138 mg, 0.74 mmol, 74%). ¹H NMR (CD₂OD, 300 MHz) δ (ppm) 7.33–7.13 (m, 5H), 3.35–3.19 (m, 1H), 2.81–2.63 (m, 2H), 2.13–1.71 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H); ¹³C NMR (CD₂OD, 75 MHz) δ (ppm) 141.8, 129.6, 129.3, 127.3, 48.6, 37.6, 32.5, 18.6. NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 4)

4-[(4-Phenylbutan-2-yl)amino]phenol (24) (241 mg, 1.0 mmol) was dissolved in MeCN/H₂O (1:1, 20 mL), aqueous H₂SO₄ (1 mL, 1M), was added, followed by H₅IO₆ (228 mg, 1.0 mmol) and the resulting mixture was stirred for 25 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (125 mg, 0.67 mmol, 67%). ¹H NMR (CD₂OD, 300 MHz) δ (ppm) 7.36–7.13 (m, 5H), 3.33–3.19 (m, 1H), 2.82–2.57 (m, 2H), 2.09–1.75.
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\( \delta (\text{ppm}) 141.8, 129.6, 129.3, 127.3, 48.6, 37.6, 32.5, 18.5. \)

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 5)

2-Methoxy-\( N \)-(4-phenylbutan-2-yl)aniline (25) (255 mg, 1.0 mmol) was dissolved in MeCN/H\( _2 \)O (1:1, 20 mL), aqueous H\( _2 \)SO\( _4 \) (1 mL, 1M) was added, followed by trichloroisocyanuric acid (116 mg, 1.0 mmol) and the resulting mixture was stirred for 18 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na\( _2 \)SO\( _4 \)), 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (84 mg, 0.45 mmol, 45%).

\( \delta (\text{ppm}) 7.35–7.12 (\text{m, 5H}), 3.35–3.20 (\text{m, 1H}), 2.83–2.61 (\text{m, 2H}), 2.11–1.77 (\text{m, 2H}), 1.35 (\text{d, } J = 6.6 \text{ Hz, 3H}). \)

\( 13\text{C} \) NMR (CD\( _3 \)OD, 75 MHz) \( \delta (\text{ppm}) 141.8, 129.6, 129.3, 127.3, 48.6, 37.6, 32.5, 18.5. \)

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 6)

2-Methoxy-\( N \)-(4-phenylbutan-2-yl)aniline (25) (0.26 g, 1.0 mmol) was dissolved in MeCN/H\( _2 \)O (1:1, 20 mL), aqueous H\( _2 \)SO\( _4 \) (1 mL, 1M) was added, followed by H\( _5 \)IO\( _6 \) (228 mg, 1.0 mmol) and the resulting mixture was stirred for 18 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na\( _2 \)SO\( _4 \)), 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (78 mg, 0.42 mmol, 42%).

\( \delta (\text{ppm}) 7.34–7.12 (\text{m, 5H}), 3.36–3.16 (\text{m, 1H}), 2.83–2.56 (\text{m, 2H}), 2.09–1.76 (\text{m, 2H}), 1.35 (\text{d, } J = 6.6 \text{ Hz, 3H}). \)

\( 13\text{C} \) NMR (CD\( _3 \)OD, 75 MHz) \( \delta (\text{ppm}) 141.8, 129.6, 129.3, 127.3, 48.6, 37.6, 32.5, 18.5. \)

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 7)

2-[(4-Phenylbutan-2-yl)amino]phenol (26) (0.24 g, 1.0 mmol) was dissolved in MeCN/H\( _2 \)O (1:1, 20 mL), aqueous H\( _2 \)SO\( _4 \) (1 mL, 1M) was added, followed by trichloroisocyanuric acid (116 mg, 0.5 mmol) and the resulting mixture was stirred for 15 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na\( _2 \)SO\( _4 \)), 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a white solid (88 mg, 0.43 mmol, 43%).

\( \delta (\text{ppm}) 7.35–7.11 (\text{m, 5H}), 3.36–3.16 (\text{m, 1H}), 2.83–2.56 (\text{m, 2H}), 2.09–1.76 (\text{m, 2H}), 1.34 (\text{d, } J = 6.6 \text{ Hz, 3H}). \)

\( 13\text{C} \) NMR (CD\( _3 \)OD, 75 MHz) \( \delta (\text{ppm}) 141.8, 129.6, 129.3, 127.3, 48.6, 37.6, 32.5, 18.5. \)

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).
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ml HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a dark oil (115 mg, 0.62 mmol, 62%) 1H NMR (CD3OD, 300 MHz) δ (ppm) 7.36-7.07 (m, 5H), 3.35-3.18 (m, 1H), 2.85-2.62 (m, 2H), 2.15-1.74 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H); 13C NMR (CD3OD, 75 MHz) δ (ppm) 141.8, 129.6, 129.3, 127.3, 48.6, 37.6, 32.5, 18.5.

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 6)

2-[(4-Phenylbutan-2-yl)amino]phenol (26) (0.24 g, 1.0 mmol) was dissolved in MeCN/H2O (1:1, 20 mL), aqueous H2SO4 (1 mL, 1M) was added, followed by H5IO6 (228 mg, 1.0 mmol) and the resulting mixture was stirred for 15 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na2SO4), 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as an off-white solid (59 mg, 0.32 mmol, 32%) 1H NMR (CD3OD, 300 MHz) δ (ppm) 7.36–7.05 (m, 5H), 3.35–3.18 (m, 1H), 2.84–2.62 (m, 2H), 2.11–1.75 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H); 13C NMR (CD3OD, 75 MHz) δ (ppm) 141.8, 129.6, 129.3, 127.3, 48.6, 37.6, 32.5, 18.5.

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 9)

N-(4-Phenylbutan-2-yl)aniline (27) (225 mg, 1.0 mmol) was dissolved in MeCN/H2O (1:1, 20 mL), aqueous H2SO4 (1 mL, 1M) was added, followed by trichloroisocyanuric acid (116 mg, 1.0 mmol) and the resulting mixture was stirred for 18 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EtOAc (50 mL). The combined organic layers were dried (Na2SO4). 1 mL HCl in EtOAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as an off-white wax/solid (5.1 mg, 0.027 mmol, 3%). 1H NMR (CD3OD, 300 MHz) δ (ppm) 7.34–7.10 (m, 5H), 3.30–3.19 (m, 1H), 2.82–2.61 (m, 2H), 2.04–1.74 (m, 2H), 1.34 (d, J = 6.6 Hz, 3H); 13C NMR (CD3OD, 75 MHz) δ (ppm) 141.8, 129.7, 129.3, 127.3, 48.6, 37.7, 32.5, 18.5.

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

4-Phenylbutan-2-amine hydrochloride (14) (entry 10)

N-(4-Phenylbutan-2-yl)aniline (27) (225 mg, 1.0 mmol) was dissolved in MeCN/H2O (1:1, 20 mL), aqueous H2SO4 (1 mL, 1M) was added, followed by H3O0 (228 mg, 1.0 mmol) and the resulting mixture was stirred for 19 h and subsequently washed with DCM (3 × 50 mL). Aqueous KOH was added (0.6 mL, 5 M) and the aqueous solution was extracted with EtOAc (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with
Ethr (50 mL). Aqueous KOH was added (0.3 mL, 5 M), and the aqueous solution was extracted with EthAc (50 mL). The combined organic layers were dried (Na₂SO₄), 1 mL HCl in EthAc (~2.3 M) was added and the mixture was concentrated. The product was obtained as a slightly brown oil (2.9 mg, 0.016 mmol, 2%).

$^1$H NMR (CDCl₃, 300 MHz) $δ$ (ppm): 7.34–7.13 (m, 5H), 3.34–3.19 (m, 1H), 2.86–2.52 (m, 2H), 2.12–1.56 (m, 2H), 1.34 (d, $J = 6.6$ Hz, 2H).

$^{13}$C NMR (CDCl₃, 75 MHz) $δ$ (ppm): 141.8, 129.7, 120.0, 128.5, 120.1, 112.3, 105.5, 101.5.

NMR data are in accordance with NMR data obtained from 14 (Table 2, entry 5).

2.9 References


3.1 Introduction

The para-methoxyphenyl (PMP) group is, as described in Chapter 2, increasingly used as a nitrogen protecting group for amines and imines. At the start of our research, the PMP protecting group was generally considered a crucial element in proline-catalysed asymmetric Mannich reactions for reaching high enantioselectivities. Industrial application of the PMP-protecting group had, however, been thwarted by a lack of cheap and practical deprotection methods. In most cases, a large excess of ceric ammonium nitrate (CAN) was used for deprotection, which is expensive and highly toxic. Phenyl iodoacetate and also electrochemical deprotection have been proposed instead, but both approaches do not provide viable alternatives for industrial application. Recently however, we demonstrated that the cheap oxidants trichloroisocyanuric acid (TCCA) and periodic acid can be both efficiently applied for PMP deprotection of amines (Chapter 2). Parallel to this chemical PMP deprotection and due to the growing need for green and sustainable catalytic deprotection strategies, we also aimed to develop an oxidative enzymatic method for effective removal of the PMP group from amines. Since we previously showed (Section 2.2) that a rather large variety of oxidative reagents can be employed for PMP removal, we reasoned that this transformation might also be effectuated using oxidative enzymes. In view of the many applications of laccases (E.C. 1.10.3.2) in oxidative transformations, we envisioned that these enzymes are potential candidates for selective PMP removal as well. Laccases are multi-copper oxidases found in several trees and fungi, catalysing the oxidation of various types of compounds with concomitant reduction of oxygen to water, avoiding the formation of hazardous hydrogen peroxide.

3.2 Screening of laccases and optimising reaction conditions

Our investigation into the applicability of laccases for PMP group removal commenced with developing an HPLC assay to screen laccases by monitoring the conversion of starting material, i.e. the N-PMP protected amine, into the desired free amine. As a benchmark substrate, we chose the protected 1,3-amino alcohol 1 (Scheme 1).
A thorough screen of reaction conditions was carried out in which co-solvents and the pH were varied. Two commercially available laccases were employed as such, namely laccase T (from *Trametes versicolor*) and laccase AB (from *Agaricus bisporus*).

**Table 1** Screening of reaction parameters.

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*Conditions: A mixture of laccase T or AB (4 mg), benzoic acid (internal standard, 1 mg), PMP-amine 1 (1 mg), buffer and co-solvent (1 mL) was shaken at rt. Conversions were determined using HPLC (Inertsil ODS-3 column) on crude samples after filtration. *Values >100% are due to inaccuracy in assay.*

Because of the generally low solubility of organic substrates in aqueous solution, we decided to investigate the use of co-solvents from the start. We considered this especially important, since earlier studies revealed that laccases are often deactivated by organic solvents. Thus, a series of experiments were carried out in a buffer (50 mM, pH 5)/co-solvent mixture, thereby varying the co-solvent. The conversions of substrate 1 into the free amine 3, as determined by HPLC, are depicted in Table 1 (entries 1–8). These results led us to conclude that the laccase-mediated PMP deprotection proceeds smoothly in homogeneous systems, but we found biphasic systems...
(e.g. with EtOAc, toluene, MTBE) also applicable (not shown in Table 1). Additionally, it must be noted that higher amounts of co-solvent, although rendering the substrate more soluble, significantly decreased the conversion through enzyme deactivation. Considering these initial results, we continued with evaluation of the pH dependence of the reaction in a buffer/MeCN mixture (4:1) using both laccases T and AB (Table 1, entries 9–24). Clearly, the conversions increased with lower pH values, albeit that highly acidic conditions (pH < 3) led to enzyme deactivation. Having concluded that 3 was the optimum pH value and laccase T the more suited enzyme, a series of industrially viable solvents were evaluated in varying ratios with the buffer solution (Table 1, entries 25–48). No real solvent limitations were identified in these experiments. We have therefore identified the combination of a water miscible solvent and acidic water (pH 3) as optimal.

Subjection of protected amino alcohol 1 to laccase AB gave a maximum conversion of 38% (buffer pH 5/MeCN 4:1, Table 1, entry 13). To improve this conversion we envisaged the usage of so-called mediators, which are known to enlarge the scope of laccases. Mediators are usually small organic molecules, which act as ‘electron shuttles’ between the enzyme and the substrate to overcome a limited substrate scope. Hence, they might make the necessity of a fit of the substrate in the active site of the enzyme redundant.

We investigated the influence of mediators (Fig. 1) on the efficiency of this particular reaction. Mechanistically, the mediator is, after being oxidised by laccase, responsible for the conversion of the substrate into its oxidised form. Since the reduced mediator can be reoxidised by the enzyme, both laccase and mediator can be used in a catalytic fashion using oxygen as the stoichiometric oxidant thereby producing water as the by-product (Scheme 2).
Laccase-mediated deprotection of p-methoxyphenyl (PMP)-protected amines

Figure 1 Tested mediators for laccase-catalysed deprotection.

The best result was obtained with 2,2’-azinobis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS, 5) (introduced as the corresponding diammonium salt) as the mediator leading to 81% conversion into 3, instead of 38% in entry 13, 19 h, rt, 0.1 equiv of ABTS).

3.3 Preparative scale experiments
To validate the screening results, we performed a series of preparative experiments using the initial substrate 1 as well as substrates 10, 13–16 with laccases T and AB (Table 2). Surprisingly, subjection of PMP-protected benzylamine 12 to these enzymes did not produce benzylamine (17) itself. Possibly, laccase-mediated formation of benzaldehyde had taken place (see Chapter 2). In most other cases, however, the corresponding crude amines 2, 11, 18, 19 and 21 were isolated after workup in reasonable to good crude yields.
Table 2 Preparative deprotections using laccase T and AB. \(^a\)

<table>
<thead>
<tr>
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<th>laccase</th>
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<td>1</td>
<td>12</td>
<td>T</td>
<td>17 (0%) HCl</td>
</tr>
<tr>
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<td>A0</td>
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<td>T</td>
<td>18 (43%) Me-Ph</td>
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<tr>
<td>4(^a)</td>
<td>13</td>
<td>A0</td>
<td>18 (43%) Nicl</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>T</td>
<td>2 (0%) Me-Ph</td>
</tr>
<tr>
<td>6(^a)</td>
<td>1</td>
<td>A0</td>
<td>2 (74%)</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>T</td>
<td>19 (61%) Me-N2HCl</td>
</tr>
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<td>8(^a)</td>
<td>14</td>
<td>A0</td>
<td>19 (66%)</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>T</td>
<td>19 (66%) Me-N2HCl</td>
</tr>
<tr>
<td>10(^a)</td>
<td>15</td>
<td>A0</td>
<td>19 (47%)</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>T</td>
<td>21 (49%) Me-N2HCl</td>
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<tr>
<td>12(^a)</td>
<td>16</td>
<td>A0</td>
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<td>11 (40%) Me-Ph</td>
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<tr>
<td>14(^a)</td>
<td>10</td>
<td>A0</td>
<td>11 (23%)</td>
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\(^a\) Conditions: PMP-protected amine (0.92 mmol), laccase (120 mg), THF-buffer mixture (1:4, pH 3, 200 mL), rt, o.n. \(^b\) Reaction conducted in the presence of ABTS.2NH\(_3\) (mediator) (10 mol%).

In entries 9 and 10, the demethylated deprotected product 19 was recovered, indicating isomerisation of the intermediate quinimide 22 to iminium ion 23 and subsequent hydrolysis to the corresponding amine. The resulting \(\text{p-hydroxyphenyl-protected ammonium ion 24 is again prone to laccase-mediated oxidation, so that eventually the unsubstituted amine 19 is formed (Scheme 3).}

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[Page 84]
Finally, realising that more concentrated reaction mixtures are desirable to render processes industrially viable, we repeated one of the deprotection experiments in a 10 mg/mL suspension to find that the desired product was isolated in a somewhat lower yield (58 vs 82% in entry 5).

3.4 Conclusions
In conclusion, the increasing use of the \( p \)-methoxyphenyl (PMP) group in organic synthesis requires cost-efficient, environmentally friendly and scalable deprotection procedures to render these processes industrially viable. We have developed a novel enzymatic oxidative deprotection procedure for \( N \)-PMP-protected amines involving laccases, which is effective at a pH below 4. Additionally, we have found that the use of ABTS leads to an increase in conversions in a specific example. The yields and purities of the products obtained with the ‘chemical’ deprotection (Chapter 2) are generally higher, which makes it the preferential method. However, when functional groups are present which do neither tolerate periodic acid nor trichloroisocyanuric acid, enzymatic deprotection followed by purification of the crude product may be the better option.

3.5 Acknowledgement
Dr. Lieke van Hemert is kindly acknowledged for her contribution to this chapter.

3.6 Experimental section
For general remarks, see section 2.8. Enzymes used for the experiments described in Tables 1 and 2 were purchased from Sigma-Aldrich as light brown powders (activity laccase T from \textit{Trametes versicolor}: 13.6 U/mg; activity laccase AB from \textit{Agaricus bisporus}: 8.0 U/mg)
Synthetic procedures for compounds 1, 10, 13, 14 and 15 have been described in Chapter 2.

(4S)-4-(3,4-Dimethoxyphenyl)-4-[(4-methoxyphenyl)amino]butan-2-ol (16)

Under argon: To a solution of (S)-4-(3,4-dimethoxyphenyl)-4-[(4-methoxyphenyl)amino]butan-2-one (1.08 g, 3.28 mmol) (see Chapter 4, ((S)-1) in a mixture of MeOH and DCM (1:1, 100 mL) was added NaBH₄ (0.124 g, 3.28 mmol). The mixture was stirred for 1 h, quenched with saturated aqueous NaHCO₃ (100 mL) and diluted with DCM (100 mL). After separation, the aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to give product 16 as a white/colorless solid glass (1.10 g, 3.32 mmol, quant.) ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 6.91–6.77 (m, 3H, both diastereomers), 6.73–6.64 (m, 2H, both diastereomers), 6.60–6.47 (m, 2H, both diastereomers), 4.50 (dd, J = 7.3, 5.3 Hz, 2/3H, major diastereomer), 4.38 (dd, J = 9.0, 5.1 Hz, 1/3H, minor diastereomer), 4.09–3.93 (m, 1H, both diastereomers), 3.86–3.82 (m, 6H, both diastereomers), 3.69 (s, 1H, minor diastereomer), 3.69 (s, 2H, major diastereomer), 2.01–1.71 (m, 2H), 1.24 (d, J = 6.3 Hz, 2H, major diastereomer), 1.22 (d, J = 6.6 Hz, 1H, minor diastereomer).

¹H NMR spectral data are in accordance with data in Chapter 4: Compound 2

Procedure for the laccase-mediated PMP-deprotection. To a solution of the substrate (0.92 mmol) in THF (40 mL) and phosphate buffer (160 mL, pH 3, 50 mM) was added laccase AB or T (120 mg) and if stated ABTS (10 mol%). The resulting suspension was stirred in an open flask (except entry 6) o.n. at rt, acidified to pH 1 with 5 N HCl and optionally filtrated over Celite. The filtrate was washed with DCM (3 × 100 mL). The resulting aqueous phase was subsequently brought to pH ~12 via addition of 5 N aqueous NaOH or KOH and extracted with EtOAc (4 × 75 mL). Before each extraction, the mixture was adjusted to pH ~12 with 5 N aqueous NaOH or KOH. The combined organic fractions were dried, filtered and concentrated after addition of HCl/EtOAc (2.3 M, 1 mL).

1-Phenylethanamine hydrochloride (18) (entry 3)
The product was obtained using laccase T as a dark oil (62 mg, 0.39 mmol, 43%). ¹H NMR (CD₂OD, 300 MHz) δ (ppm) 7.52–7.36 (m, 5H), 4.46 (q, J = 6.9 Hz, 1H), 1.64 (d, J = 6.9 Hz, 3H).

¹H NMR spectral data are in accordance with data previously obtained (See Chapter 2, compound 13).

1-Phenylethanamine hydrochloride (18) (entry 4)
The product was obtained using laccase AB as a dark oil (64 mg, 0.41 mmol, 44%). ¹H NMR (CD₂OD, 300 MHz) δ (ppm) 7.61–7.32 (m, 5H), 4.47 (q, J = 6.9 Hz, 1H), 1.65 (d, J = 6.9 Hz, 3H).

¹H NMR spectral data are in accordance with data previously obtained (See Chapter 2, compound 13).
Laccase-mediated deprotection of p-methoxyphenyl (PMP)-protected amines

(2S,3S)-3-Amino-2-methyl-3-phenylpropan-1-ol hydrochloride (2) (entry 5)

The product was obtained using laccase T as a dark oil (137 mg, 0.68 mmol, 74%). 1H NMR (CD3OD, 300 MHz) δ (ppm) 7.56–7.28 (m, 5H), 4.31 (d, J = 6.7 Hz, 1H), 3.44–3.32 (m, 2H), 2.38–2.22 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 5.HCl).

(2S,3S)-3-Amino-2-methyl-3-phenylpropan-1-ol hydrochloride (2) (entry 6)

The product was obtained using laccase AB as a dark oil (137 mg, 0.56 mmol, 61%). 1H NMR (CD3OD, 300 MHz) δ (ppm) 8.38–8.25 (m, 2H), 7.83–7.72 (m, 2H), 4.55 (d, J = 6.4 Hz, 1H), 3.46 (dd, J = 11.0, 4.8 Hz, 1H), 3.35 (dd, J = 11.0, 6.7 Hz, 1H), 2.46–2.32 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 5.HCl).

(2S,3S)-3-Amino-2-methyl-3-(4-nitrophenyl)propan-1-ol hydrochloride (entry 7)

The product was obtained using laccase T as an off-white solid (138 mg, 0.56 mmol, 61%). 1H NMR (CD3OD, 300 MHz) δ (ppm) 8.28 (m, 2H), 7.79 (m, 2H), 8.25 (m, 2H), 7.83 (m, 2H), 3.32 (m, 4H), 3.35 (dd, J = 11.0, 6.7 Hz, 1H), 2.46–2.33 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 15).

(2S,3S)-3-Amino-2-methyl-3-(4-nitrophenyl)propan-1-ol hydrochloride (entry 8)

The product was obtained using laccase AB as an off-white solid/oil (213 mg, 0.86 mmol, 94%). 1H NMR (CD3OD, 300 MHz) δ (ppm) 8.41–8.22 (m, 2H), 7.87–7.68 (m, 2H), 4.57 (d, J = 6.3 Hz, 1H), 3.47 (dd, J = 11.0, 4.8 Hz, 1H), 3.36 (dd, J = 11.0, 6.7 Hz, 1H), 2.56–2.31 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 15).

(2S,3S)-2-Methyl-3-(methylamino)-3-(4-nitrophenyl)propan-1-ol hydrochloride (19) (entry 9)

The product was obtained using laccase T as a dark solidifying oil (194 mg, 0.79 mmol, 86%). 1H NMR (CD3OD, 300 MHz) δ (ppm) 4.40–4.25 (m, 2H), 7.83–7.77 (m, 2H), 4.55 (d, J = 6.3 Hz, 1H), 3.46 (dd, J = 11.0, 4.8 Hz, 1H), 3.35 (dd, J = 11.0, 6.7 Hz, 1H), 2.46–2.32 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 15).

(2S,3S)-2-Methyl-3-(methylamino)-3-(4-nitrophenyl)propan-1-ol hydrochloride (19) (entry 10)

The product was obtained using laccase AB as a colorless oil (106 mg, 0.43 mmol, 47%). 1H NMR (CD3OD, 300 MHz) δ (ppm) 8.38–8.28 (m, 2H), 7.79–7.73 (m, 2H), 7.72–7.67 (m, 1H), 4.54 (d, J = 6.3 Hz, 1H), 3.46 (dd, J = 11.0, 4.8 Hz, 1H), 3.35 (dd, J = 11.0, 6.8 Hz, 1H), 2.45–2.32 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 15).
(4S)-4-Amino-4-(3,4-dimethoxyphenyl)butan-2-ol (21) (entry 11)

The product was obtained using laccase T as a dark oil (mixture of diastereomers) (119 mg, 0.45 mmol, 49%). 1H NMR (CD$_3$OD, 300 MHz) δ (ppm) 7.15–6.95 (m, 3H, both diastereomers), 4.65–4.38 (m, both diastereomers), 3.88 (s, minor diastereomer) + 3.87 (s, major diastereomer), 3H), 3.83 (s, 3H, both diastereomers), 3.92–3.52 (m, 1H, both diastereomers), 2.20–1.75 (m, 2H, both diastereomers), (1.22 (d, J = 6.1 Hz, major diastereomer) + 1.19 (d, J = 6.2 Hz, minor diastereomer), 3H). 13C NMR (for major isomer) (CD$_3$OD, 75 MHz): δ (ppm) 151.0, 150.9, 130.9, 120.9, 113.1, 111.8, 64.8, 56.7, 56.5, 54.0, 43.7, 23.3. IR (cm$^{-1}$): 3348, 2966, 2935, 1520, 1262, 1145, 1021; HRMS [ESI$^+$ (m/z)]: calcd for C$_{12}$H$_{20}$NO$_3$ (M+H$^+$) 226.14432, found 226.14462.

The product was obtained using laccase AB as a dark oil (mixture of diastereomers) (119 mg, 0.45 mmol, 49%). 1H NMR (CD$_3$OD, 300 MHz) δ (ppm) 7.15–6.95 (m, 3H, both diastereomers), (4.64–4.54 (m, minor diastereomer) + 4.48–4.39 (m, major diastereomer), 1H) (3.88 (s, minor diastereomer) + 3.87 (s, major diastereomer), 3H), 3.83 (s, 3H, both diastereomers), 3.90–3.56 (m, 1H, both diastereomers), 2.30–1.65 (m, 2H, both diastereomers), (1.22 (d, J = 6.2 Hz, major diastereomer) + 1.19 (d, J = 6.2 Hz, minor diastereomer), 3H). 13C NMR (for major isomer) (CD$_3$OD, 75 MHz): δ (ppm) 151.0, 150.9, 130.9, 120.9, 113.1, 111.8, 64.8, 56.7, 56.5, 54.0, 43.7, 23.3. IR (cm$^{-1}$): 3365, 2966, 2936, 1520, 1264, 1144, 1023; HRMS [ESI$^+$ (m/z)]: calcd for C$_{12}$H$_{20}$NO$_3$ (M+H$^+$) 226.14432, found 226.14460.

4-Phenylbutan-2-amine hydrochloride (11) (entry 12)

The product was obtained using laccase AB as a dark oil (mixture of diastereomers) (119 mg, 0.45 mmol, 49%). 1H NMR (CD$_3$OD, 300 MHz) δ (ppm) 7.15–6.95 (m, 3H, both diastereomers), 4.64–4.54 (m, minor diastereomer) + 4.48–4.39 (m, major diastereomer), 1H) (3.88 (s, minor diastereomer) + 3.87 (s, major diastereomer), 3H), 3.83 (s, 3H, both diastereomers), 3.90–3.56 (m, 1H, both diastereomers), 2.30–1.65 (m, 2H, both diastereomers), (1.22 (d, J = 6.2 Hz, major diastereomer) + 1.19 (d, J = 6.2 Hz, minor diastereomer), 3H). 13C NMR (for major isomer) (CD$_3$OD, 75 MHz): δ (ppm) 151.0, 150.9, 130.9, 120.9, 113.1, 111.8, 64.8, 56.7, 56.5, 54.0, 43.7, 23.4. IR (cm$^{-1}$): 3365, 2965, 2936, 1520, 1264, 1144, 1023; HRMS [ESI$^+$ (m/z)]: calcd for C$_{12}$H$_{20}$NO$_3$ (M+H$^+$) 226.14432, found 226.14460.

The product was obtained using laccase T as a dark oil (mixture of diastereomers) (68 mg, 0.37 mmol, 40%). 1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 14).

4-Phenylbutan-2-amine hydrochloride (11) (entry 13)

The product was obtained using laccase T as a dark oil (68 mg, 0.37 mmol, 40%). 1H NMR (CD$_3$OD, 300 MHz) δ (ppm) 7.40–7.11 (m, 5H), 3.35–3.21 (m, 1H), 2.83–2.57 (m, 2H), 2.13–1.67 (m, 2H), 1.39 (d, J = 6.6 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 14).

4-Phenylbutan-2-amine hydrochloride (11) (entry 14)

The product was obtained using laccase AB as a slightly colored solidifying oil (37 mg, 0.20 mmol, 22%). 1H NMR (CD$_3$OD, 300 MHz) δ (ppm) 7.34–7.10 (m, 5H), 3.29–3.21 (m, 1H), 2.82–2.57 (m, 2H), 2.06–1.75 (m, 2H), 1.34 (d, J = 6.6 Hz, 3H).

1H NMR spectral data are in accordance with previously obtained data (Chapter 2, compound 14).
Laccase-mediated deprotection of p-methoxyphenyl (PMP)-protected amines

3.7 References


STEREOSELECTIVE SYNTHESIS OF N-PMP-PROTECTED 1,3-AMINO ALCOHOLS

4.1 Introduction

With the growing number of enantio- and diastereomerically pure pharmaceutical compounds, the need for stereoselective synthetic methodologies is increasing. Since the 1,3-amino alcohol moiety is often encountered in drugs and drug-like molecules, general procedures are desired to selectively prepare all possible diastereomers of such compounds. Examples of drugs containing this structural motif are depicted in Figure 1. Ritonavir and lopinavir are both drugs with anti-HIV properties. 4-Hydroxyleucine derivatives show activity in the treatment of fat metabolism and obesity.

Figure 1 Examples of pharmaceutically relevant 1,3-amino alcohols.

Other pharmaceutically active 1,3-amino alcohols are used for the treatment of psychiatric disorders such as depression (e.g. fluoxetine and duloxetine) and ADHD (e.g. atomoxetine) (Figure 2). Zhang et al. described an elegant rhodium-catalysed hydrogenation of the ketone precursor as the key step in the synthesis of the former compounds.

Figure 2 Psychoactive 1,3-amino alcohols.

Additionally, the 1,3-amino alcohol pattern is found in antibiotics as a building block of negamycin, clavalanine and biphenomycins A and B (Figure 3).
Stereoselective synthesis of N-PMP-protected 1,3-amino alcohols

Figure 3 1,3-Amino alcohols as important structural elements of antibiotics.

Various natural products also contain 1,3-amino alcohol moieties. Selected examples include lythracea alkaloids,9 sedum alkaloids,10 paliclavine,11 and dysherbaine.12 On a different note, an excellent review of Keay and co-workers extensively describes the application of 1,3-amino alcohols as chiral transfer agents in asymmetric transformations.13 Despite its abundance in synthetically relevant targets, relatively few stereoselective methods are available for the construction of the 1,3-amino alcohol moiety. Undoubtedly, the most straightforward route would involve stereoselective reduction of Mannich products of which the ketone function is reduced by employing hydride donors. While several methods for the reduction of α-chiral amino ketones have been reported,14,15,16 only a small number of reports on the reduction of β-amino ketones, with the amine and ketone separated by only a methylene group, have been disclosed. Dias and co-workers reported a diastereoselective reduction of acyclic N-aryl-β-amino ketones, using LiEt₃BH or Zn(BH₄)₂.17 Berkes et al. published a diastereoselective reduction of β-amino ketones using MnCl₂.18 The group of Truong described that both syn- and anti-1,3-amino alcohols could be prepared through treatment of β-amino ketones with SmI₂ in methanol, with the nitrogen-protecting group as the stereodirecting unit.19 A recent paper of the Davis group described a diastereoselective reduction of acyclic N-sulfonyl β-amino ketones. Both anti- and syn-amino alcohols could be prepared in moderate to excellent selectivity by using LiEt₃BH or Li(BuO)₃AlH. They applied their newly developed methodology in a formal total synthesis of (−)-pinidinol and (+)-epipinidinol.20

As an alternative, amino alcohols can be prepared through ruthenium-catalysed hydrogenation of β-amino ketones, although these methodologies are generally reported for the synthesis of targets without α-chirality.21 Rhodium-catalysed examples have also been published, however, none of them dealing with chiral amines.22 As a third method, Ellman and co-workers reported a diastereoselective reduction of N-sulfonyl protected 1,3-hydroxylimines.23 Menche et al. described a syn-selective reductive amination of β-hydroxyketones with p-anisidine and polymethylhydroisloxane as the reducing agent in the presence of Ti((OPr)₄). They employed their method in the synthesis of the hydroxylamine core of ritonavir/lopinavir (Fig. 1).24 The list of stereoselective methods to transform β-amino ketones into the corresponding alcohols is completed by biocatalytic reductions with enzymes or baker’s yeast. Only a few examples have
been published involving β-amino ketones, which are mostly rather substrate specific and therefore not generally applicable. In 2010, Bäckvall et al. published a method for the synthesis of syn- and anti-1,3-amino alcohols via dynamic kinetic resolution of N-Boc-protected 1,3-amino ketones.

We envisaged that enantioselective access to N-PMP-protected β-amino ketones via the proline-catalysed Mannich reaction and the recently discovered cheap and efficient methods for the removal of the PMP protecting group (vide Chapters 2 and 3) could provide a new general entry into the synthesis of 1,3-amino alcohols. In this chapter, our results in converting the N-PMP-protected β-amino ketones into syn- and anti-1,3-amino alcohols in a diastereoselective manner are described.

4.2 Hydride reductions

As described in Section 4.1, a straightforward way to convert ketones into alcohols proceeds through reduction with a borohydride reagent. We chose to screen reaction conditions on amino ketone 1, because it was available as a single enantiomer and readily synthesised on large scale (see Chapter 7). The formation of both possible alcohols was monitored using HPLC.

With NaBH₄ as reductant, amino alcohol 2 was formed in a 1:3 ratio of diastereomers (entry 1, Table 1). In case of Zn(BH₄)₂ the desired amino alcohols were formed in a reversed 5:1 ratio. The relative configurations were tentatively assigned based on chelation-controlled reduction, with Zn²⁺ acting as a chelator between the ketone and amine functions, thereby favouring syn-product formation (Scheme 2, pathway a). Consequently, it was assumed that Felkin-Anh-controlled NaBH₄ reduction (Scheme 2, pathway b) produced predominantly the anti-product. The small difference in steric demand of the Ar and NHPMP substituents in the latter model accounts for the observed low diastereoselectivity.
Stereoselective synthesis of N-PMP-protected 1,3-amino alcohols

Scheme 2 Chelation- and Felkin–Anh controlled reduction.

We subsequently tested a series of boro- and aluminiumhydrides, but unfortunately in none of these cases a sufficiently high diastereoselectivity was observed (Table 1).

Table 1 Screening of various reductants for the reduction of \((S)-1\).

<table>
<thead>
<tr>
<th>entry</th>
<th>reductant</th>
<th>T (°C)</th>
<th>ratio ((R,S)/Z/(S,S)-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>21</td>
<td>75.25</td>
</tr>
<tr>
<td>2</td>
<td>LiBH₄</td>
<td>0</td>
<td>69.31</td>
</tr>
<tr>
<td>3</td>
<td>LiEt₂BH</td>
<td>21</td>
<td>63.37</td>
</tr>
<tr>
<td>4</td>
<td>Li₂BH₄</td>
<td>0</td>
<td>66.34</td>
</tr>
<tr>
<td>5</td>
<td>Li(dBu)₂BH</td>
<td>21</td>
<td>68.32</td>
</tr>
<tr>
<td>6</td>
<td>Li(dBu)₃BH</td>
<td>0</td>
<td>68.32</td>
</tr>
<tr>
<td>7</td>
<td>Li(dBuO₂)₃BH</td>
<td>21</td>
<td>61.39</td>
</tr>
<tr>
<td>8</td>
<td>Li(dBuO₂)₃BH</td>
<td>0</td>
<td>60.40</td>
</tr>
<tr>
<td>9</td>
<td>Zn(BH₄)₂</td>
<td>21</td>
<td>17.83</td>
</tr>
</tbody>
</table>

Apparently, the influence of the existing chiral center was too small to induce chirality at the second chiral center, which prompted us to investigate other approaches.

4.3 Iridium-catalysed transfer hydrogenation: anti-amino alcohols

Both hydrogenation and transfer hydrogenation have found a plethora of applications in stereoselective reduction of alkenes, alkenes, imines and ketones. Surprisingly, no literature precedence on the diastereoselective (transfer) hydrogenation of chiral β-amino ketones existed at the start of our research, while on the other hand β-hydroxy ketones have shown to be suitable hydrogenation substrates.\(^{27,28}\) In transfer hydrogenations, 2-propanol or a mixture of formic acid/triethylamine is used as the source of hydrogen, which is reversibly transferred to the substrate molecule. Due to this reversibility, a careful analysis of the reaction progress and selectivity is required. We started our investigations on N-PMP-protected β-amino ketone 1. Using the well-established Ru/TsDPEN complex as the catalyst, we observed a clean conversion...
into the desired 1,3-amino alcohols with a moderate diastereomeric excess (60%), which irrespective of the existing chiral center depended on the catalyst chirality (Figure 4).

Scheme 2 Ru/(R,R)-TsDPEN-catalysed transfer hydrogenation of 1.

Encouraged by these initial results we explored the use of iridium-based catalysts. We prepared efficient asymmetric transfer hydrogenation (ATH) catalysts 5 by heating a solution of an iridium precursor (i.e. [IrCp*Cl₂]₂) and an amino acid amide in the presence of an inorganic base (e.g. K₂CO₃) (Scheme 3) according to a modified protocol disclosed by Verzijl.²⁹

Scheme 3 Synthesis of Ir-based amino acid amide catalysts 5.

The inorganic base was removed by filtration to suppress possible elimination of the N-PMP group prior to reduction. Preferably, α,α-disubstituted amino acids were employed to avoid the risk of catalyst racemisation. To our satisfaction, exposure of benchmark substrate 1 to these catalysts resulted in very high diastereoselectivities. When D-α-Me-phenylglycine amide was used as the ligand, conversion of (S)-1 into the corresponding (R,S)-amino alcohol (R,S)-2 proceeded with a diastereomeric ratio of 96:4, while the (R)-amino ketone led to a 1:1 formation of amino alcohols. This implies that the existing chiral center has a large impact on the stereochemical outcome of the transfer hydrogenation. The influence of the preexisting chirality in terms of a match and mismatch with the ligand was confirmed by employing achiral Aib-NH₂ as the ligand. In the presence of the achiral catalyst, a diastereomeric ratio of 84:16 was observed for the products. A limited ligand screening (Table 2) showed that the diastereostereoselectivity could be increased to 100:0 (entry 7).
Table 2 Screening of Ir-based amino acid amide catalysts for ATH of amino ketone 1.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R¹</th>
<th>R²</th>
<th>ratio (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S-1</td>
<td>Ph</td>
<td>Me</td>
<td>96:4 (R,S)/(S,S)</td>
</tr>
<tr>
<td>2</td>
<td>S-1</td>
<td>Me</td>
<td>Me</td>
<td>94:16 (R,S)/(S,S)</td>
</tr>
<tr>
<td>3</td>
<td>S-1</td>
<td>Br</td>
<td>Ph</td>
<td>47:53 (R,S)/(S,S)</td>
</tr>
<tr>
<td>4</td>
<td>S-1</td>
<td>Me</td>
<td>Br</td>
<td>63:37 (R,S)/(S,S)</td>
</tr>
<tr>
<td>5</td>
<td>R-1</td>
<td>Ph</td>
<td>Me</td>
<td>50:50 (R,R)/(S,R)</td>
</tr>
<tr>
<td>6</td>
<td>R-1</td>
<td>Me</td>
<td>Me</td>
<td>not determined</td>
</tr>
<tr>
<td>7</td>
<td>R-1</td>
<td>Br</td>
<td>Ph</td>
<td>0:100 (R,R)/(S,R)</td>
</tr>
<tr>
<td>8</td>
<td>R-1</td>
<td>Me</td>
<td>Br</td>
<td>2:98 (R,R)/(S,R)</td>
</tr>
</tbody>
</table>

Although we obtained better results with α-benzylphenylglycinamide as the ligand, we explored the substrate scope of the stereoselective ATH with the D-α-methylphenylglycine amide-based catalyst because of its larger availability at the time. Substrates were prepared via the asymmetric proline-catalysed Mannich reaction (See Section 4.7). It should be noted that in some instances, Mannich ketones were prone to partial racemisation over time. We hypothesise that racemisation occurs via catalysis by impurities in the Mannich ketone samples, because ketones 6–9 were oils and purified by troublesome column chromatography, whereas 1 was purified through crystallisation and the resulting crystals appeared more stable.

Table 3 Preparative asymmetric transfer hydrogenation of β-amino ketones.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R¹</th>
<th>product</th>
<th>d.r. (R,S)/(S,S)</th>
<th>yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-1</td>
<td>3,4-(MeO)₂C₆H₄</td>
<td>2</td>
<td>96:4</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>F</td>
<td>10</td>
<td>90:5</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>2-ClC₆H₄</td>
<td>11</td>
<td>97:3</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>iBu</td>
<td>12</td>
<td>76:24</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>CO₂Et</td>
<td>13</td>
<td>79:21</td>
<td>100</td>
</tr>
</tbody>
</table>

Conditions: ketone (1.0 equiv), [(IrCpCl)₂] (0.02 equiv), D-α-Me-phenylglycine-NH₂ (0.20 equiv), K₂CO₃ (3 equiv), 2-propanol, rt, 1.5–20 h. a determined by HPLC. b isolated yield.

a absolute configuration = (R,R):(S,R).
The results shown in Table 3 led us to conclude that the asymmetric transfer hydrogenation of β-amino ketones with an iridium based catalyst is widely applicable. In all examples we observed a reasonable to good diastereoselectivity, with the best selectivities obtained for \( R^1 = \text{Ar} \).

With a method for the anti-selective preparation of 1,3-amino alcohols in hand, we realised that extensive screening of other metal/ligand combinations could possibly deliver 1,3-amino alcohols with syn-selectivity. However, at the time we simultaneously explored the option of hydrogenation instead of transfer hydrogenation, which is outlined in Section 4.4.

### 4.4 Rhodium-catalysed hydrogenation: syn-amino alcohols

Since with asymmetric transfer hydrogenation, only the anti-1,3-amino alcohols were accessible, we resorted to hydrogenation with molecular hydrogen for the synthesis of the syn-congeners. We discovered that hydrogenation of β-amino ketones in the presence of the catalyst derived from monovalent Rh(I) and a C\(_2\)-symmetric ligand such as \((\text{R})\)-BINAP (15), (Scheme 4), produced the desired syn-1,3-amino alcohols in excellent diastereoselectivity.

![Scheme 4: Formation of Rh-based (R)-BINAP catalyst](image)

Again we observed a strong effect of the existing chiral center on the diastereoselectivity. Upon hydrogenation of \((S)\)-1 with Rh/(R)-BINAP, pure \((S,S)\)-2 was obtained, whereas with Rh/(S)-BINAP the ratio \((R,S)\) vs \((S,S)\) was 70:30. DCM appeared to be the most suitable solvent with respect to solubility of the starting material, diastereoselectivity and reaction rate. To investigate the scope and limitations, we subsequently hydrogenated a number of aromatic, aliphatic and carboxylic β-amino ketones on preparative scale (Table 4).
Table 4 Preparative asymmetric hydrogenation of β-amino ketones.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R¹</th>
<th>cat. (mol%)</th>
<th>t (h)</th>
<th>dr</th>
<th>[d]. [[(R,S) (S,S)]</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-1</td>
<td>3,4-(OMe)₂C₆H₃</td>
<td>30</td>
<td>19</td>
<td>2</td>
<td>&gt;1:19</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>4-FC₆H₄</td>
<td>5</td>
<td>44</td>
<td>10</td>
<td>&lt;1:19</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>2-MeC₆H₄</td>
<td>5</td>
<td>44</td>
<td>11</td>
<td>&gt;1:19</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>iBu</td>
<td>30</td>
<td>15</td>
<td>12</td>
<td>&lt;1:19^d</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>CO₂Et</td>
<td>30</td>
<td>17</td>
<td>13</td>
<td>&lt;1:19</td>
<td>96</td>
</tr>
</tbody>
</table>

^a Conditions: substrate (1.0 equiv), Rh(COD)-BF₄ (0.05 or 0.30 equiv), (R)-BINAP (0.05 or 0.030 equiv). ^b determined by HPLC. ^c isolated yields. ^d absolute configuration = (R,R)-[(S,S).  

Unfortunately, the reactions proceeded rather slowly, which prompted us to use relatively high catalyst loadings. Gratefully, in all cases near-exclusive formation of the desired syn-stereoisomer was observed.

Finally, to verify the assigned stereochemical outcome, we prepared (S,S)-2 on a larger scale and X-ray crystallographic analysis of the product proved that Rh/(R)-BINAP hydrogenation of (S)-1 indeed led to formation of the syn-product ((S,S)-2) (Figure 5).^20

Figure 5 Crystal structure representation of (S,S)-2.
4.5 Conclusions

In conclusion, we have developed two complementary methods for the hydrogenation of β-amino ketones to the corresponding 1,3-amino alcohols. The anti-products can be obtained through asymmetric transfer hydrogenation, in which 2-propanol is employed as the hydrogen donor and an Ir/α-substituted-amino acid amide complex as the catalyst. Syn-products are accessible by hydrogenation under increased hydrogen pressure in the presence of a Rh-based BINAP catalyst. In combination with the proline-catalysed Mannich reaction, these methods have now proven to be powerful tools for the enantio- and diastereoselective synthesis of all four diastereomers of 1,3-amino alcohols.

4.6 Acknowledgements

Jan M. M. Smits is kindly acknowledged for performing the X-ray crystallographic analysis presented in section 4.4. Ferdi van der Pijl is kindly acknowledged for performing the experiments presented in Table 1.

4.7 Experimental section

Amino acid amides were obtained from DSM, Geleen, The Netherlands.

For general remarks, see section 2.8.

\((5\text{-}4\text{-}(3,4\text{-Dimethoxyphenyl})\text{-}4\text{-}(4\text{-methoxyphenyl})\text{amino})\text{butan-2-one} (15)\text{-}1\)

To a mixture of DMSO (45 mL) and acetone (180 mL) was added 3,4-dimethoxybenzaldehyde (10.5 g, 63.2 mmol), p-anisidine (7.78 g, 63.2 mmol) and L-proline. The resulting reaction mixture was stirred for 23 h. The reaction mixture was quenched with 100 mL potassium phosphate buffer (0.5 M, pH 7, 100 mL). Subsequently, a total of 150 mL of potassium phosphate buffer (0.5 M, pH 7) was added in portions. The reaction mixture was cooled to 0 °C and the flask was scratched with a spatula, which induced precipitation. After stirring for 20 min, the suspension was filtered off and the residue was washed with water (0 °C, 50 mL). The product was dried in vacuo. The product was obtained as an off-white powder (12.7 g). The product was recrystallised from EtOAc and obtained as white crystals (10.2 g, 31.0 mmol, 49%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) 6.92–6.86 (m, 2H), 6.84–6.77 (m, 1H), 6.73–6.65 (m, 2H), 6.57–6.48 (m, 2H), 4.69 (t, \(J = 6.5\) Hz, 1H), 3.85 (s, 6H), 3.70 (s, 3H), 2.89 (d, \(J = 6.5\) Hz, 2H), 2.11 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) (ppm) 207.4, 152.4, 149.2, 148.1, 141.0, 135.4, 118.2, 115.4, 114.7, 111.3, 109.5, 55.9 (2C), 55.7, 55.2, 51.4, 30.8; HRMS [ESI\(^+\) (m/z)]: calcld for C\(_{19}\)H\(_{23}\)NO\(_4\)Na (M+Na\(^+\)) 352.15248, found 352.15249; HPLC: ee: >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-heptane/2-propanol 80/20, retention time: major enantiomer 19.0 min, minor enantiomer: 15.8 min.

NMR spectral data are in accordance with data in Chapter 7 (Ch.7, compound ent-7)
Stereoselective synthesis of N-PMP-protected 1,3-amino alcohols

(5)-4-(4-Fluorophenyl)-4-((4-methoxyphenyl)amino)butan-2-one (6)

p-Anisidine (2.00 g, 16.2 mmol) was dissolved in DMSO (20 mL) and 4-fluorobenzaldehyde (1.74 mL, 2.00 g, 16.2 mmol) and L-proline (373 mg, 3.24 mmol) were added. After 2 h of stirring, acetone was added (80 mL). The resulting mixture was stirred for 22 h and quenched with saturated aqueous NaHCO₃ (100 mL). It was subsequently extracted with a mixture of EtOAc and heptane (1:1, 2 × 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified using column chromatography (EtOAc/heptane 1/9 → 1/4). Yield: 1.40 g (4.87 mmol, 30%) of an orange oil. 1H NMR (CDCl₃, 300 MHz) δ (ppm): 7.38–7.29 (m, 2H), 7.05–6.95 (m, 6H), 6.72–6.65 (m, 2H), 6.53–6.46 (m, 2H), 4.74 (t, J = 6.5 Hz, 1H), 4.15 (bs, 1H), 3.70 (s, 3H), 2.89 (d, J = 6.5 Hz, 2H), 2.11 (s, 3H). 13C NMR (CDCl₃, 75 MHz): δ (ppm) 187.7, 153.9, 141.0, 134.7, 131.0, 129.9, 129.1, 128.5, 128.2, 115.6, 51.2, 30.7, 19.1. IR (cm⁻¹): 3383, 3003, 2831, 1710, 1509, 1235, 820. HRMS [ESI⁺ (m/z)]: calcd for C₂₃H₁₇FNO Na(M+Na⁺) 310.1219, found 310.1205; calcd for C₂₃H₁₇FNO Na(M+Na⁺) 310.12193, found 310.12059; HRMS: ee: 91%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-heptane/2-propanol 80/20, retention time: major enantiomer 14.6 min; minor enantiomer: 9.9 min; R₁ 0.26 (EtOAc/heptane 1/2).

(5)-4-((4-Methoxyphenyl)amino)-4-(o-tolyl)butan-2-one (7)

p-Anisidine (2.00 g, 16.2 mmol) was dissolved in DMSO (20 mL) and o-toluic acid (1.88 mL, 2.00 g, 16.2 mmol) and L-proline (373 mg, 3.24 mmol) were added. After 2 h of stirring, acetone was added (80 mL). The resulting mixture was stirred for 19 h and quenched with saturated aqueous NaHCO₃ (100 mL). It was subsequently extracted with a mixture of EtOAc and heptane (1:1, 2 × 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified using column chromatography (EtOAc/heptane 1/9 → 1/4). Yield: 2.34 g (8.26 mmol, 51%) of an orange oil. 1H NMR (CDCl₃, 300 MHz) δ (ppm): 7.41–7.30 (m, 3H), 7.19–7.12 (m, 3H), 6.73–6.65 (m, 2H), 6.50–6.40 (m, 2H), 4.96 (dd, J = 7.9, 3.5 Hz, 1H), 4.07 (bs, 1H), 3.69 (s, 3H), 2.87 (dd, J = 15.7, 5.1 Hz, 1H), 2.80 (dd, J = 15.9, 7.9 Hz, 1H), 2.45 (s, 3H), 2.14 (s, 3H). 13C NMR (CDCl₃, 75 MHz) δ (ppm): 207.3, 152.3, 141.0, 140.4, 134.7, 130.8, 127.1, 126.6, 125.2, 115.0, 114.8, 51.6, 49.0, 30.5, 19.1, 10.0. IR (cm⁻¹): 3383, 3022, 2947, 2831, 1708, 1510, 1237. HRMS [ESI⁺ (m/z)]: calcd for C₂₃H₂₀NO Na(M+Na⁺) 306.14700, found 306.14873; HPLC: ee: 96%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-heptane/2-propanol 80/20, retention time: major enantiomer 11.9 min, minor enantiomer: 7.7 min; R₁ 0.33 (EtOAc/heptane 1/2).

(R)-4-((4-Methoxyphenyl)amino)-6-methylheptan-2-one (8)

p-Anisidine (2.00 g, 16.2 mmol) was dissolved in DMSO (20 mL) and isovaleraldehyde (1.74 mL, 2.00 g, 16.2 mmol) and L-proline (373 mg, 3.24 mmol) were added. After 2 h of stirring, acetone was added (80 mL). The resulting mixture was stirred for 18 h and quenched with saturated aqueous NaHCO₃ (100 mL). It was subsequently extracted with a mixture of EtOAc and heptane (1:1, 2 × 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified using
column chromatography (EtOAc/heptane 1/9 → 1/4). Yield: 2.16 g (8.66 mmol, 53%) of a yellow oil. 

\[ \text{\(^1\)H NMR (CDCl}_3, 300 MHz) \delta (ppm) 6.80–6.73 (m, 2H), 6.62–6.54 (m, 2H), 3.85–3.75 (m, 1H), 3.73 (s, 3H), 2.65 (dd, \( J = 16.1, 5.0 \text{ Hz, 1H}\), 2.54 (dd, \( J = 16.2, 6.5 \text{ Hz, 1H}\), 2.12 (s, 3H), 1.83–1.65 (m, 1H), 1.47 (ddd, \( J = 14.2, 8.2, 6.1 \text{ Hz, 1H}\), 1.32 (ddd, \( J = 13.7, 8.0, 5.7 \text{ Hz, 1H}\), 0.92 (d, \( J = 6.6 \text{ Hz, 3H}\), 0.90 (d, \( J = 6.5 \text{ Hz, 3H}\)); 

\[ \text{\(^{13}\)C NMR (CDCl}_3, 75 MHz) \delta (ppm) 208.4, 152.2, 141.3, 115.0, 114.9, 55.7, 49.1, 48.1, 44.7, 31.0, 25.0, 22.3; \]

HPLC: ee: 84%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-heptane/2-propanol 80/20, retention time: major enantiomer 5.8 min, minor enantiomer: 6.5 min.

Spectral data are in accordance with literature values.

\((E)-\text{Ethyl 2-((4-methoxyphenyl)imino)acetate (9a)\)}\)

Under an atmosphere of argon, ethyl glyoxylate (10 mL, ~50% in toluene) was dissolved in anhydrous toluene (250 mL). Molsieves (4Å, 50 g) and \( p \)-anisidine (5.54 g, 45 mmol) were added. The mixture was stirred for 22 h and filtered over celite. The filtrate was concentrated. The product was obtained as a dark yellow oil (9.28 g, 44.8 mmol, quant.); \n
\[ \text{\(^1\)H NMR (CDCl}_3, 300 MHz) \delta (ppm) 7.94 (s, 1H), 7.40–7.33 (m, 2H), 6.98–6.89 (m, 2H), 4.41 (q, \( J = 7.1 \text{ Hz, 2H}\), 3.84 (s, 3H), 1.40 (t, \( J = 7.1 \text{ Hz, 3H}\)); 

\[ \text{\(^{13}\)C NMR (CDCl}_3, 75 MHz): \delta (ppm) 163.6, 160.5, 148.0, 141.4, 123.6, 114.5, 61.9, 55.5, 14.2. \]

Spectral data are in accordance with literature values.

\((E)-\text{Ethyl 2-((4-methoxyphenyl)amino)-4-oxopentanoate (9)\)}\)

\((E)-\text{Ethyl 2-((4-methoxyphenyl)imino)acetate (9a)\)} (3.36 g, 16.2 mmol) was dissolved in DMSO (20 mL) and acetone (80 mL) and \( L \)-proline were added. The resulting mixture was stirred for 18 h and quenched with aqueous NaHCO\(_3\). The resulting mixture was extracted with a mixture of EtOAc and heptane (1:1, 2 × 200 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated. The product could be obtained as an orange oil in pure form without further purification (3.16 g, 11.9 mmol, 73%); \n
\[ \text{\(^1\)H NMR (CDCl}_3, 300 MHz) \delta (ppm) 6.83–6.71 (m, 2H), 6.70–6.57 (m, 2H), 4.33 (t, \( J = 5.6 \text{ Hz, 1H}\), 4.17 (q, \( J = 7.2 \text{ Hz, 2H}\), 3.74 (s, 3H), 2.96 (d, \( J = 5.6 \text{ Hz, 2H}\), 2.18 (s, 3H), 1.23 (t, \( J = 7.0 \text{ Hz, 3H}\)); \n
\[ \text{\(^{13}\)C NMR (CDCl}_3, 75 MHz): \delta (ppm) 205.8, 173.0, 153.1, 140.5, 115.8, 114.0, 61.4, 55.7, 54.3, 45.8, 30.4, 14.1; \]

HPLC: ee: >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-heptane/2-propanol/ethanol 80/10/10, retention time: major enantiomer 16.8 min; minor enantiomer: 16.0 min.

Spectral data are in accordance with literature values.
Stereoselective synthesis of N-PMP-protected 1,3-amino alcohols

(2R,4S)-4-(3,4-Dimethoxyphenyl)-4-((4-methoxyphenyl)amino)butan-2-ol ((R,S)-2)

D-α-Methylphenylglycinamide (4.12 mg, 0.025 mmol), K₂CO₃ (50 mg, 0.361 mmol) and IrCp*Cl₂ (2 mg, 2.51 μmol) were taken up in MeCN (dry, 5 mL). The mixture was stirred for 30 min at 70 °C and cooled to 0 °C. The solution was filtered and concentrated. (2R,4S)-4-(3,4-Dimethoxyphenyl)-4-((4-methoxyphenyl)amino)butan-2-one ((R,S)-1) (41 mg, 0.125 mmol) was added to the catalyst together with dry 2-propanol (10 mL). The resulting reaction mixture was stirred for 20 h under argon, poured out in a mixture of saturated aqueous NaHCO₃ (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc in heptane, 1/9 → 3/7). The product was obtained as an off-white sticky oil (quant. yield). ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.04–6.43 (m, 7H), 4.49 (t, J = 6.1 Hz, 1H), 4.18–3.95 (m, 1H), 3.84 (s, 6H), 3.69 (s, 3H), 2.01–1.70 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 152.1, 149.1, 147.8, 141.4, 136.5, 118.1, 115.1, 114.7, 111.2, 109.4, 65.3, 56.2, 55.8 (2C), 55.7, 54.6, 23.7. IR (cm⁻¹): 3383, 2933, 2832, 1511, 1234; HRMS [ESI⁺ (m/z)]: calcd for C₂₂H₂₃NO₄ (M+H⁺) 332.18618, found 332.18618; HPLC: d.r.: 96.4 Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-heptane/2-propanol 80/20, retention time: major diastereomer 15.7 min, minor diastereomer: 24.0 min. R: 0.17 (EtOAc/heptane 1:1).

(2R,4S)-4-(4-Fluorophenyl)-4-((4-methoxyphenyl)amino)butan-2-ol ((R,S)-10)

D-α-Methylphenylglycinamide (8.24 mg, 0.050 mmol), K₂CO₃ (100 mg, 0.723 mmol) and IrCp*Cl₂ (4 mg, 52.0 μmol) were taken up in MeCN (dry, 5 mL). The mixture was stirred for 30 min at 70 °C and cooled to 0 °C. The solution was filtered and concentrated. The residue was taken up in 4 mL dry 2-propanol. (S)-4-(4-Fluorophenyl)-4-((4-methoxyphenyl)amino)butan-2-one ((R,S)-10) (36 mg, 0.125 mmol) was dissolved in dry 2-propanol (8 mL), followed by addition of 2 mL of the catalyst mixture. The resulting reaction mixture was stirred under argon for 2 h and poured out in a mixture of a half-saturated aqueous NaHCO₃ (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc/n-heptane, 1/9 → 3/7). The product was obtained as an off-white solid (32 mg, 0.111 mmol, 80%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.36–7.18 (m, 2H), 7.09–6.89 (m, 2H), 6.68 (d, J = 8.6 Hz, 2H), 6.47 (d, J = 8.7 Hz, 2H), 4.56 (dd, J = 6.9, 5.1 Hz, 0.9H), 4.43 (dd, J = 8.8, 5.0 Hz, 0.1H), 4.10–3.90 (dt, J = 19.0, 4.5 Hz, 1H), 3.69 (s, 3H), 1.98–1.76 (m, 2H), 1.24 (d, J = 6.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 161.69 (d, J = 244.5 Hz), 152.11 (s), 141.16 (s), 139.51 (s), 127.71 (d, J = 7.9 Hz), 115.41 (d, J = 21.3 Hz), 114.91 (s), 114.76 (s), 65.24 (s), 55.70 (s), 55.58 (s), 46.74 (s), 23.81 (s); IR (cm⁻¹): 3381, 2969, 1510, 1235; HRMS [ESI⁺ (m/z)]: calcd for C₂₀H₁₈FN₄O₂ (M+H⁺) 290.15563, found 290.15600; HPLC: d.r.: 95.5 Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-heptane/2-propanol 80/20, retention time: major diastereomer 13.7 min, minor diastereomer: 24.1 min. R: 0.17 (EtOAc/heptane 1:2).
Chapter 4

(2R,4S)-4-((4-Methoxyphenyl)amino)-4-(o-toly)butan-2-ol ((R,S)-11)

D-α-Methylphenylglycinamide (8.24 mg, 0.050 mmol), K$_2$CO$_3$ (100 mg, 0.723 mmol) and IrCp*Cl$_2$ (4 mg, 5.02 μmol) were taken up in MeCN (dry, 5 mL). The mixture was stirred for 30 min at 70 °C and cooled to 0 °C. The solution was filtered and concentrated. The residue was taken up in 4 mL dry 2-propanol. (S)-4-((4-Methoxyphenyl)amino)-4-(o-toly)butan-2-one ((S)-12) (0.125 mmol) was dissolved in dry 2-propanol (8 mL), followed by addition of 2 mL of the catalyst mixture. The resulting reaction mixture was stirred for 1.5 h under argon and quenched with half-saturated aqueous NaHCO$_3$ (30 mL) and DCM (30 mL). After separation, the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/19 → 3/7). The product was obtained as a yellow oil (27 mg, 0.095 mmol, 76%).

1H NMR (CDCl$_3$, 300 MHz) δ (ppm) 7.50–7.33 (m, 2H), 7.22–7.06 (m, 3H), 6.68 (d, $J = 8.6$ Hz, 2H), 6.45 (d, $J = 8.0$ Hz, 2H), 4.94–4.72 (m, 1H), 4.20–4.00 (m, 1H), 3.68 (s, 3H), 2.34 (s, 3H), 1.92–1.72 (m, 2H), 1.26 (d, $J = 6.1$ Hz, 3H); 13C NMR (CDCl$_3$, 75 MHz): δ (ppm) 152.1, 141.5, 141.3, 134.5, 130.7, 126.6, 126.4, 125.2, 114.0, 65.5, 55.7, 52.3, 45.0, 23.0, 19.1; IR (cm$^{-1}$) 3391, 2966, 1511, 1235, 1040, 819; HRMS [ESI$^+$ (m/z)]: calcd for C$_{16}$H$_{19}$NO$_2$ (M+H$^+$) 286.18070, found 286.18151

Under an atmosphere of argon, D-α-Methylphenylglycinamide (8.24 mg, 0.050 mmol), K$_2$CO$_3$ (100 mg, 0.723 mmol) and IrCp*Cl$_2$ (4 mg, 5.02 μmol) were taken up in MeCN (dry, 5 mL). The mixture was stirred for 30 min at 70°C and cooled to 0°C. The solution was filtered and concentrated. The residue was taken up in 4 mL dry 2-propanol. (R)-4-((4-Methoxyphenyl)amino)-6-methylheptan-2-one ((R,R)-12) (33 mg, 0.125 mmol) was placed under argon and dissolved in dry 2-propanol (8 mL). 2 mL of the catalyst solution was added and the mixture was stirred for 18 h. The reaction mixture was poured out in a mixture of an aqueous half-saturated solution of NaHCO$_3$ (20 mL) and DCM (20 mL). After separation, the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/9 → 1/4). The product was obtained as a yellow oil (31 mg, 0.123 mmol, 99%).

1H NMR (CDCl$_3$, 300 MHz) δ (ppm) 6.82–6.61 (m, 4H, both diastereomers), 4.14–4.02 (m, 1H, both diastereomers), 3.75 (s, 3/5H, minor diastereomer), 3.74 (s, 12/5H, major diastereomer), 3.59 (qd, $J = 7.0$, 135 Hz, 4/5H, major diastereomer), 3.52–3.41 (m, 1/5H, minor diastereomer), 3.40–2.75 (bs, 2H, both diastereomers), 1.83–1.58 (m, 2H, both diastereomers), 1.56–1.24 (m, 3H, both diastereomers), 1.21 (d, $J = 6.3$ Hz, 12/5H, major diastereomer), 1.20 (d, $J = 6.2$ Hz, 3/5H, minor diastereomer), 0.92 (d, $J = 6.6$ Hz, 12/5H, minor diastereomer), 0.87 (d, $J = 6.6$ Hz, 3/5H, minor diastereomer), 0.88 (d, $J = 6.5$ Hz, 12/5H, 0.84 (d, $J = 6.6$ Hz, 3/5H); 13C NMR (CDCl$_3$, 75 MHz): δ (ppm) 153.3 (minor diastereomer), 152.5 (major diastereomer), 141.8 (major diastereomer), 140.7 (minor diastereomer), 117.1 (minor diastereomer), 115.5 (major diastereomer), 114.9 (major diastereomer), 114.8 (minor diastereomer), 86.8 (minor diastereomer), 65.3 (major diastereomer), 55.7 (major diastereomer), 55.6 (minor diastereomer), 114.0 (minor diastereomer)
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diastereomer), 54.9 (minor diastereomer), 50.4 (major diastereomer), 45.6 (minor diastereomer), 44.9 (major diastereomer), 42.9 (minor diastereomer), 25.0 (major diastereomer), 24.9 (minor diastereomer), 24.0 (both diastereomers), 23.3 (minor diastereomer), 23.0 (major diastereomer), 22.5 (major diastereomer), 22.0 (minor diastereomer). IR (cm⁻¹, film from DCM) 3367, 2955, 1510, 1236; HRMS [ESI⁺ (m/z)]: calcd for C₁₂H₂₆N₁O₂ (M+H⁺) 252.19635, found 252.19628; HPLC: d.r. 76:24 (Chiralpak AD-H (250 × 4.6 mm), flow 0.3 mL/min, n-heptane/2-propanol/ethanol 80/15/5, retention time: major diastereomer 20.7 min; minor diastereomer 21.7 min; R₁ 0.29 (EtOAc/heptane 1/2).

(2S,4R)-Ethyl 4-hydroxy-2-(((4-methoxyphenyl)amino)pentanoate ((R,S)-13)

Under an atmosphere of argon, D-α-methylphenylglycinamide (8.24 mg, 0.050 mmol), K₂CO₃ (100 mg, 0.723 mmol) and IrCp*Cl₂ (4 mg, 5.02 μmol) were taken up in MeCN (dry, 5 mL). The mixture was stirred for 30 min at 70°C and cooled to 0°C. The solution was filtered and concentrated. The residue was taken up in 4 mL dry 2-propanol. (R)-4-(((4-Methoxyphenyl)amino)-6-methylheptan-2-one (9) (33 mg, 0.12 mmol) was placed under argon and dissolved in dry 2-propanol (8 mL). 2 mL of the catalyst solution was added and the mixture was stirred for 18 h. The reaction mixture was poured out in a mixture of an aqueous half-saturated solution of NaHCO₃ (20 mL) and DCM (20 mL). After separation, the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/9 → 1/4 → 1/2). The product was obtained as a yellow oil (33 mg, 0.12 mmol, 100%)

1H NMR (CDCl₃, 300 MHz) δ 6.82–6.63 (m, 4H, both diastereomers), 4.25–3.99 (m, 2H), 4.16 (q, J = 7.0 Hz, 2H, both diastereomers), 3.74 (s, 0.18 × 3H, minor diastereomer), 3.73 (s, 0.82 × 3H, major diastereomer), 2.00–1.68 (m, 2H, both diastereomers), 1.25 (d, J = 6.3 Hz, 3H, both diastereomers), 1.23 (t, J = 7.1 Hz, 0.92 × 3H, major diastereomer), 1.22 (t, J = 7.1 Hz, 0.18 × 3H, minor diastereomer); 13C NMR (CDCl₃, 75 MHz): δ (ppm) 174.4 (major diastereomer), 173.7 (minor diastereomer), 154.0 (minor diastereomer), 153.2 (major diastereomer), 140.9 (major diastereomer), 140.2 (minor diastereomer), 117.4 (minor diastereomer), 115.9 (major diastereomer), 114.8 (major diastereomer), 114.8 (minor diastereomer), 114.8 (minor diastereomer), 67.6 (minor diastereomer), 65.2 (major diastereomer), 61.2 (minor diastereomer), 61.2 (major diastereomer), 59.2 (minor diastereomer), 56.2 (major diastereomer), 55.6 (major diastereomer), 55.6 (minor diastereomer), 41.2 (both diastereomers), 23.8 (major diastereomer), 23.6 (minor diastereomer), 14.2 (both diastereomers); IR (cm⁻¹) 3368, 2968, 1720, 1513, 1238; HRMS [ESI⁺ (m/z)]: calcd for C₁₄H₂₂N₁O₄ (M+H⁺) 268.15488, found 268.15511 HPLC: d.r. 79:21 (Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol/ethanol 80/10/10, retention time: major diastereomer 11.2 min; minor diastereomer: 14.6 min; R₁ 0.12 (EtOAc/heptane 1/2).
Yield: 32 mg (77%) of a white solid.

The combined organic layers were dried (NaSO₄) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/3). Yield: 32 mg (77%) of a white solid. 1H NMR (CDCl₃, 300 MHz) δ (ppm) 6.89–6.75 (m, 3H), 6.69 (d, J = 8.6 Hz, 2H), 6.57 (d, J = 8.6 Hz, 2H), 4.39 (dd, J = 8.5, 5.1 Hz, 1H), 4.18–3.94 (m, 1H), 3.84 (s, 6H), 3.70 (s, 3H), 1.98 (s, 3H), 1.90–1.74 (m, 2H), 1.23 (d, J = 6.1 Hz, 3H). 13C NMR (CDCl₃, 75 MHz): δ (ppm) 152.9, 149.2, 141.0, 136.5, 125.9, 118.1, 116.6, 114.6, 111.2, 109.2, 68.0, 59.9, 55.9 (2C), 55.7, 46.9, 24.3; IR (cm⁻¹): 3367, 2966, 2934, 1511, 1234, 1028; HRMS [ESI⁺ (m/z)]: calcd for C₂₁H₂₂NO₄Na (M+Na⁺) 354.16813, found 354.16781; HPLC: d.r. >99:1 (2931, 1510, 1234); HRMS [ESI⁺ (m/z)]: calcd for C₂₀H₂₁F₂N₂O₂ (M+H⁺) 299.15563, found 299.15677; HPLC: d.r. >99:1 (syn/anti) Chiralpak AD-H (250 x 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention time: major diastereomer 23.5 min; minor diastereomer: n/a. (see (R,S)-10); Rf 0.38 (EtOAc/heptane 1/1).

After separation, the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried (NaSO₄) and concentrated. The residue was purified by column chromatography (EtOAc/heptane 1/9 → 3/7). Yield: 27 mg (74%) of an off-white solid. 1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.31–7.22 (m, 2H), 7.03–6.93 (m, 2H), 6.72–6.65 (m, 2H), 6.57–6.50 (m, 2H), 4.44 (dd, J = 9.0, 5.0 Hz, 1H), 4.09–3.94 (m, 1H), 3.69 (s, 3H), 1.95–1.72 (m, 2H), 1.23 (d, J = 6.2 Hz, 3H); 13C NMR (CDCl₃, 75 MHz): δ (ppm) 161.84 (d, J = 245.5 Hz), 160.2, 153.0, 140.3, 139.3, 127.73 (d, J = 7.9 Hz), 116.6, 115.51 (d, J = 21.4 Hz), 114.7. IR (cm⁻¹): 3366, 2966, 2931, 1510, 1234; HRMS [ESI⁺ (m/z)]: calcd for C₂₁H₂₂F₂N₂O₂ (M+H⁺) 299.15563, found 290.15677; HPLC: d.r. >99:1 (syn/anti) Chiralpak AD-H (250 x 4.6 mm), flow 1.0 mL/min, heptane/2-propanol 80/20, retention time: major diastereomer 23.5 min; minor diastereomer: n/a. (see (R,S)-10); Rf 0.38 (EtOAc/heptane 1/1).
Stereoselective synthesis of N-PMP-protected 1,3-amino alcohols

**25**

(25,4S)-4-(((4-Methoxyphenyl)amino)-4-((o-tolyl)butan-2-ol (5S)-11)

![Molecule diagram]

Rh(COD)\(_2\)BF\(_3\) (15.2 mg, 0.037 mmol) and (R)-BINAP (22.35 mg, 0.037 mmol) were taken up in 2 mL DCM. Catalyst solution (0.33 mL) was added to a tube, containing (S)-4-(((4-methoxyphenyl)amino)-4-((o-tolyl)butan-2-one (7) (36 mg, 0.125 mmol) in DCM (5 mL). Hydrogen pressure was applied (25 bar) and the mixture was stirred at 300 K for 44 h. The reaction mixture was concentrated and purified by column chromatography (heptane → 30% EtOAc in heptane). Yield: 29 mg (81%) of colorless wax. \( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) (ppm) 7.37-7.27 (m, 1H), 7.19-7.09 (m, 3H), 6.73-6.65 (m, 2H), 6.56-6.47 (m, 2H), 4.75-4.63 (m, 1H), 4.11 (dd, \( J = 12.2, 6.1 \) Hz, 1H), 3.69 (s, 3H), 2.38 (s, 3H), 1.85-1.74 (m, 2H), 1.24 (t, \( J = 6.2 \) Hz, 3H); \( ^{13}C \) NMR (CDCl\(_3\), 75 MHz) \( \delta \) (ppm) 152.8, 141.7, 140.8, 134.5, 130.7, 126.7, 126.6, 124.6, 116.2, 114.7, 68.6, 56.0, 55.6, 45.9, 24.2, 19.2; IR (cm\(^{-1}\)) 3761, 2985, 2900, 1406, 1393, 1066, 1055; HRMS [ESI\(^+\) (m/z)]: calcd for C\(_{36}\)H\(_{37}\)N\(_2\)O\(_2\) 598.2926, found 598.2918. The product was purified by column chromatography (EtOAc/heptane 1/9 → 3/7) and obtained as an off-white solid. Yield: 29 mg (81%).

**25**

(25,4R)-4-(((4-Methoxyphenyl)amino)-6-methylheptan-2-ol (5R)-12)

Rh(COD)\(_2\)BF\(_3\) (16.24 mg, 0.040 mmol) and (R)-BINAP (25 mg, 0.040) were taken up in 2 mL DCM and heated to 50°C for 30 min. The catalyst solution was added to a solution of (R)-4-(((4-methoxyphenyl)amino)-6-methylheptan-2-one (8) (41 mg, 0.125 mmol) in DCM (10 mL) in an autoclave. Hydrogen pressure was applied (25 bar) and the mixture was heated to 50°C and stirred for 15 h. The mixture was diluted with DCM (20 mL) and an aqueous solution of NaHCO\(_3\) (20 mL). After separation, the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated. The product was purified by column chromatography (EtOAc/heptane 1/9 → 3/7) and obtained as a brown oil. Yield: 77%.

\( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) (ppm) 6.84-6.75 (m, 2H), 6.74-6.64 (m, 2H), 4.13-4.00 (m, 1H), 3.76 (s, 3H), 3.53-3.39 (m, 1H), 1.78-1.16 (m, 5H), 1.20 (t, \( J = 6.2 \) Hz, 3H), 0.94-0.76 (m, 6H); \( ^{13}C \) NMR (CDCl\(_3\), 75 MHz) \( \delta \) (ppm) 153.3, 140.7, 117.2, 114.8, 68.7, 55.7, 54.9, 45.7, 43.2, 24.9, 24.0, 23.3, 22.1; IR (cm\(^{-1}\)) 3367, 2954, 2929, 1510, 1236; HRMS [ESI\(^+\) (m/z)]: calcd for C\(_{21}\)H\(_{23}\)NO\(_2\) (M+H\(^+\)) 286.18070, found 286.18105. The product was taken up in 2 mL DCM and heated to 50°C for 15 h. The mixture was diluted with DCM (20 mL) in an autoclave. Hydrogen pressure was applied (25 bar) and the mixture was heated to 50°C and stirred for 44 h. The reaction mixture was concentrated and purified by column chromatography (EtOAc/heptane 1/9 → 3/7) and obtained as a brown oil. Yield: 77%.

**25**

(25,4S)-3-((4-Methoxyphenyl)amino)pentanoate (5S)-13)

Rh(COD)\(_2\)BF\(_3\) (16.24 mg, 0.040 mmol) and (R)-BINAP (25 mg, 0.040) were taken up in 2 mL DCM and heated to 50°C for 30 min. The catalyst solution was added to a solution of (S)-3-((4-methoxyphenyl)amino)pentanoic acid (9) (33 mg, 0.125 mmol) in DCM (10 mL) in an autoclave. Hydrogen pressure was applied (25 bar) and the mixture was heated to 50°C and stirred for 17 h. The mixture was diluted with DCM (20 mL) and an aqueous solution of NaHCO\(_3\) (20 mL). After separation, the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated. The product was purified by column chromatography (EtOAc/heptane 1/9 → 3/7) and obtained as an off-white solid. Yield: 29 mg (81%).
19 mg (0.070 mmol, 56%) 1H NMR (CDCl3, 300 MHz) δ (ppm) 6.81–6.69 (m, 4H), 4.22–4.04 (m, 4H), 3.74 (s, 3H), 1.94 (ddd, J = 14.2, 4.3, 2.5 Hz, 1H), 1.78 (dt, J = 14.3 Hz, 9.5 Hz, 1H), 1.23 (d, J = 6.3 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H). 13C NMR (CDCl3, 75 MHz) δ (ppm) 173.7, 154.0, 140.2, 117.5, 114.8, 67.7, 61.3, 59.3, 55.6, 41.2, 23.6, 14.1; IR (cm⁻¹) 3367, 2967, 2932, 1728, 1511, 1236; HRMS [ESI⁺ (m/z)]: calcd for C14H22NO4 (M+H⁺) 268.15488, found 268.15450.

HPLC: d.r. >99:1 Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, heptane/2-propanol/ethanol 80/10/10, retention time: major diastereomer 14.5 min, minor diastereomer: n/a. (see (R,S)-13), Rf 0.30 (EtOAc/heptane 1/1).

Larger scale synthesis of (S,S)-2

(2S,4S)-4-(3,4-Dimethoxyphenyl)-4-((4-methoxyphenyl)amino)butan-2-ol (S,S)-2

Rh(COD)2BF4 (31 mg, 0.076 mmol) and (R)-BINAP (47 mg, 0.076 mmol) were dissolved in DCM (5 mL). (S)-4-(3,4-dimethoxyphenyl)-4-((4-methoxyphenyl)amino)butan-2-one (S)-1 (500 mg, 1.52 mmol) was added and the mixture was put under H2 (autoclave, 25 bar) and stirred for 3 days. After release of the H2 pressure, the reaction mixture was diluted with DCM (50 mL) and washed with saturated aqueous NaHCO3. The organic layer was dried (Na2SO4) and concentrated. The residue was purified by column chromatography (silica eluted with EtOAc/heptane 1/2 → 1/1), which yielded an off-white solid (211 mg, 0.64 mmol, 42%). 1H NMR (CDCl3, 300 MHz) δ (ppm) 6.86–6.76 (m, 3H), 6.73–6.66 (m, 2H), 6.61–6.53 (m, 2H), 4.39 (dd, J = 8.9, 4.9 Hz, 1H), 4.11–3.99 (m, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H), 1.96–1.76 (m, 2H), 1.23 (d, J = 6.2 Hz, 3H). 1H NMR data in accordance with data obtained from (S,S)-2.

Suitable crystals for X-ray analysis were grown from EtOAc. The resulting crystals were analysed by X-ray analysis (Table 5).

**Table 5 Crystal data and structure refinements for (S,S)-2.**

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<thead>
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<th>Crystal colour</th>
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<tr>
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<td>F(000)</td>
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Stereoselective synthesis of N-PMP-protected 1,3-amino alcohols

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4.8 References

9 See Chapter 7


For a review on the stereoselective synthesis of 1,3-diols, including (transfer) hydrogenation of 1,3-hydroxy ketones: Bode, S. E.; Wolberg, M.; Müller, M. Synthesis, 2006, 557–588.


A PICTET–SPENGLER ENTRY
INTO 3,4-DISUBSTITUTED
TETRAHYDROISOQUINOLINES
5.1 Introduction

5.1.1 General introduction

The tetrahydroisoquinoline skeleton is frequently encountered in naturally occurring alkaloids such as salsolinol (1), which plays a role in Parkinson’s disease, addiction and physiological regulatory functions, and michellamine B (2), an alkaloid that shows anti-HIV-1 properties. The tetrahydroisoquinoline motif is also present in other drug or drug-like molecules, e.g. the ACE-inhibitor quinapril (3).

![Figure 1 Salsolinol (1), michellamine B (2) and quinapril (3).](image)

Consequently, many synthetic methods to prepare members of this biologically relevant class of molecules have been developed over the years. An important strategy proceeds through a Pictet-Spengler condensation of β-arylethylamines (4) with an aldehyde or a ketone or a synthetic equivalent thereof (Scheme 1).

![Scheme 1 The original Pictet-Spengler reaction.](image)

In the Pictet-Spengler reaction, a β-arylethylamine 6 is converted into a hemiaminal upon treatment with the carbonyl compound 7. This hemiaminal is then dehydrated under acidic conditions to form the iminium ion 8, which undergoes a 6-endo-trig cyclisation to form the six-membered ring structure (Scheme 2). The Pictet-Spengler reaction, which in fact is an electrophilic aromatic substitution, usually proceeds most effectively when electron rich β-arylethylamines are employed.
5.1.2 Stereoselective Pictet–Spengler approaches to tetrahydroisoquinolines

Although many asymmetric stereoselective routes have been developed throughout the years, only a few give access to enantio- and diastereomerically pure 3,4-disubstituted tetrahydroisoquinolines. As has been described in this thesis, the proline-catalysed Mannich reaction is an outstanding tool to prepare $\alpha,\beta$-disubstituted amines from enolisable aldehydes (13) and imines (14). We envisaged to take advantage of the excellent control of chirality in this reaction for the synthesis of enantio- and diastereomerically pure 3,4-disubstituted tetrahydroisoquinolines (10), by transforming the Mannich bases (12) into these valuable target compounds (Scheme 3).

Scheme 3 Retrosynthesis of 3,4-disubstituted tetrahydroisoquinolines.

5.2 Non-activated phenylacetaldehyde as the Mannich donor

We set out preparing the Mannich product of phenylacetaldehyde and an acceptor imine. Phenylacetaldehyde is commercially available and has been described as suitable donor aldehyde in the proline-catalysed Mannich reaction. While various examples of aldehydes as Mannich donors appeared in the literature starting from 2000, the first example of employing phenylacetaldehyde (15) in the proline-catalysed Mannich reaction was reported by the group of Janey in 2006. They observed that the reaction of phenylacetaldehyde (15) with the $N$-PMP imine of ethyl glyoxylate (16) in the presence of l-proline and with THF as the solvent led to the formation of $\alpha$-aryl-$\beta$-amino aldehyde (17) in a stereoselective manner. Acetic acid was added in the reduction step to prevent lactonisation and epimerisation. As a final step, the ethyl ester was transformed into amide (19) (Scheme 4).

To our delight, while we were performing our research, Pietruszka and co-workers reported the discovery of a new catalyst ((S)-indoline-3-carboxylic acid), which also accepts phenylacetaldehyde as the Mannich donor. Unlike proline, its use leads to anti-selective
formation of the desired β-amino aldehydes (18) (Scheme 4), which can obviously be converted into the corresponding alcohols.

Scheme 4 Syn- and anti-selective formation of 2-phenyl-3-amino aldehydes 17 and 18.

Following the reaction protocol of the Janey group, unfortunately we did not observe any conversion into the desired β-amino aldehyde. Interestingly, after adding a small amount of water to the reaction mixture, the desired product started to form promptly. Upon subsequent reduction and amidation, the hydroxy amide 19 was indeed obtained fully stereoselectively in 41% yield.

Initially, the N-PMP protected amino alcohol 19 was subjected to Pictet-Spengler conditions (paraformaldehyde, formic acid, 80 °C), which as anticipated would lead to the corresponding iminium ion 21. Not entirely unexpectedly, iminium ion 21, which is possibly in equilibrium with aminal 22, was subsequently reduced by formic acid, following the Eschweiler–Clarke pathway. To our surprise, the methylated intermediate 24 underwent lactonisation, despite the presence of the relatively unreactive pyrrolidine amide, to form 25 as the major product (Scheme 5).
Possibly, lactonisation takes place prior to reduction, which leads to the formation of a trans-substituted lactone 23 and consequently renders the resulting iminium ion inaccessible for attack by the phenyl ring. To prevent the lactonisation, the primary alcohol was protected as a tert-butyldiphenylsilyl (TBDPS) ether. Subsequently, the PMP group was removed through oxidation with periodic acid (See Chapter 2) giving rise to amine 26.

We attempted to prepare the tetrahydroisoquinolines through treatment with either paraformaldehyde or ethyl glyoxylate under acidic conditions, but in neither of these cases, the desired products were isolated (Scheme 6). Because we were not able to prepare the cyclised products with unactivated phenylacetaldehydes, we decided to investigate the employment of more electron rich aromatic analogues.
5.3 Activated phenylacetaldehydes as the Mannich donors

Unlike phenylacetaldehyde, which was used as the Mannich donor in the preceding section, its electron-rich congener 29 was not commercially available. We attempted to oxidise precursor 28 to the aldehyde employing pyridinium chlorochromate (PCC) as the oxidant, but observed that the desired product was accompanied by the formation of veratraldehyde. This phenomenon has previously been described in detail by Kumar and Fernandes.\textsuperscript{11} We speculate that after formation of the chromate ester, formaldehyde is released, giving rise to a stabilised cation, which is subsequently attacked by HCrO\textsubscript{3}. After deprotonation, veratraldehyde is formed.

Swern oxidation also appeared unsuccessful in our hands, but treatment with Dess–Martin periodinane (DMP) furnished 29 in 67% yield.

As a next step, the modified conditions of the Janey group were applied to prepare amino alcohol 30. To prevent lactonisation, the primary alcohol was protected with a TBDPS group afterwards. The resulted protected amino alcohol 31 was then treated with 1 equiv of trifluoroacetic acid (TFA) and 1 equiv of ethyl glyoxylate. LRMS (ESI) analysis of the crude reaction mixture showed the formation of a major product with a mass of 709 (M+1), while we expected to find a mass of 711 (M+1) (Scheme 7).

![Scheme 7](image_url)

Although the mass spectrum of the crude reaction mixture showed a predominance of the side product, after workup and purification we unexpectedly obtained 32 as the main product (with a mass of 711) in 81% yield and a 3:1 ratio of diastereoisomers (Figure 2). We analysed the side...
A Pictet–Spengler entry into 3,4-disubstituted tetrahydroisoquinolines

product (with a mass of 709), but neither $^1$H and $^{13}$C NMR spectroscopy nor IR spectroscopy enabled us to elucidate its structure. According to the $^1$H NMR spectrum (Figure 3), only one of the diastereoisomers was converted into the side product with the lower mass.

Figure 2 $^1$H NMR Spectrum of 32 (M = 711).

Figure 3 $^1$H NMR Spectrum of 34 (M = 709).

Upon treatment of 28 with paraformaldehyde, we found similar behaviour: a new product was formed, but LRMS showed a mass of 637 instead of 639 (Scheme 7).

These results in our view clearly indicate an oxidative process. Additionally, the $^1$H NMR signal of one the ethyl esters seems distorted. We hypothesise that in the presence of oxygen the N-oxide is formed, which under ESI conditions eliminates to form the product with (M+1) of 709,
although we have not been able to find direct evidence. To impede spontaneous oxidation of the amine, we removed the electron-rich PMP group via treatment with periodic acid. The free amine was then treated with ethyl glyoxylate and TFA. We were pleased to find that the cyclic product 34 was readily formed as a 3:1 mixture of diastereoisomers (Scheme 8). Moreover, $^1$H NMR analysis showed that the attack of the aromatic ring had occurred regioselectively.

Scheme 8 Oxidative removal of PMP-protecting group followed by Pictet–Spengler cyclisation.

As a next step we investigated the use of other aldehydes besides ethyl glyoxylate. Tetrahydroisoquinoline 35 was obtained in moderate yield when paraformaldehyde was employed (Scheme 8). Employing benzaldehyde, we were not able to isolate any of the desired cyclised product at all.

We subsequently prepared a second amino alcohol to further evaluate the scope of our route. Aldehyde 37 was prepared by ozonolysis of commercially available safrole (36). Subsequent Mannich reaction followed by reduction with NaBH$_4$ afforded amino alcohol 38 as a single stereoisomer. After TBDPS protection and PMP removal, the corresponding amine 40 was subjected to Pictet-Spengler conditions. Whereas cyclisation in the presence of ethyl glyoxylate led to formation of the desired product 41 in a 4:1 diastereomeric ratio, albeit in rather low yield, cyclisation with formaldehyde did not lead to the desired compound (Scheme 9).
To account for the low yield of 41, we analysed the major side product by $^1$H and $^{13}$C NMR and found that the α-keto ester 44 had been formed as well. A plausible mechanistic explanation involves initial formation of iminium ion 42, which could isomerise to the more stable trisubstituted iminium ion 43 if not attacked sufficiently fast by the electron-rich aromatic ring. During workup, the imine was then hydrolysed to the corresponding ketone (Scheme 10).

5.4 Conclusions and outlook

In conclusion, we have shown that the products of the Mannich reaction of ethyl glyoxylate-derived imines and electron-rich phenylacetaldehydes are suitable precursors for the Brønsted acid-catalysed Pictet-Spengler reaction with activated aldehydes. Considering the fact that organocatalysts are available to produce all four isomers of the starting amino alcohol, we have demonstrated the proof-of-principle of a promising new route to 3,4-substituted tetrahydroisoquinolines. Unfortunately, within the timeframe of this research, we did not have the opportunity to fully explore the scope of this methodology. Moreover, some limitations of this route have already emerged. The aromatic rings of the amino aldehydes should be
sufficiently activated to capture the initially formed iminium ion and not all aldehydes, employed as acceptors in the Pictet-Spengler reaction always give rise to the formation of the desired product. Future research could inter alia include the synthesis of 1,3-amino alcohols starting from indole-, thiophene-, or furan-containing aldehydes to evaluate whether the scope of the methodology extends beyond the use of electron-rich aromatic phenylacetaldehydes.

Furthermore, in this study we have only tested a limited number of conditions to effect the Pictet-Spengler reaction. We believe that the use of other (Lewis- or Brønsted) acids and other aldehydes or synthetic equivalents might lead to further extension of this method.

5.5 Experimental section

For general remarks, see section 2.8.

(2S,3S)-4-Hydroxy-2-[(4-methoxyphenyl)amino]-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one (17)

To a solution of (E)-ethyl 2-[(4-methoxyphenyl)imino]acetate (See Chapter 4) (4.0 g, 19.3 mmol) in anhydrous THF (50 mL) were added water (2.5 mL) and L-proline (378 mg, 3.28 mmol). After stirring at rt for 15 min, the reaction mixture was cooled to -5 °C, and freshly distilled phenylacetaldehyde (2.26 mL, 19.3 mmol) was added. The resulting mixture was stirred for 18 h before addition of acetic acid (3.8 mL). After careful addition of NaBH₄ (825 mg, 21.8 mmol), the resulting mixture was stirred at -5 °C for 2 h and subsequently quenched with concentrated aqueous NaHCO₃. The aqueous solution was extracted with EtOAc (100 mL). The organic layer was dried (Na₂SO₄) and concentrated. The residue was dissolved in THF (50 mL) and pyrrolidine (1.7 mL, 1.45 g, 20.4 mmol) and Na₂CO₃ (354 mg, 3.34 mmol) were added. The resulting mixture was heated to 50 °C and stirred for 2 h. After quenching with saturated aqueous NaHCO₃ (100 mL), the mixture was extracted with EtOAc (100 mL). The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 3/1 → EtOAc), and the product was obtained as a white solid (2.80 g, 7.90 mmol, 41%).

1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.36–7.22 (m, 5H), 6.79–6.72 (m, 2H), 6.67–6.60 (m, 2H), 4.59–4.43 (m, 1H), 4.37–4.15 (m, 1H), 4.17–3.90 (m, 2H), 3.73 (s, 3H), 3.53–3.25 (m, 4H), 3.08–2.88 (m, 2H), 1.89–1.60 (m, 4H); 13C NMR (CDCl₃, 75 MHz) δ (ppm) 171.0, 152.8, 141.1, 138.8, 128.6, 128.5, 127.3, 115.9, 114.9, 63.2, 59.8, 55.7, 49.6, 46.5, 46.0, 26.0, 23.9.

NMR spectral data are in accordance with literature values.8
A Pictet–Spengler entry into 3,4-disubstituted tetrahydroisoquinolines

Under an atmosphere of argon, (2S,3S)-4-hydroxy-2-((4-methoxyphenyl)amino)-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one (22) (0.51 mmol) was dissolved in DCM (30 mL) and cooled to 0 °C. tert-Butyl(chloro)diphenylsilane (1.46 mL, 5.56 mmol) was added followed by imidazole (304 mg, 5.64 mmol). The resulting mixture was stirred for 5 min and then allowed to come to rt. After 30 min, saturated aqueous NaHCO$_3$ (25 mL) was added. After separation, the organic layer was dried (Na$_2$SO$_4$) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/9 → 1/3 → 1/1), which yielded the product as a white solid (1.57 g, 94%).$^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 7.66–7.59 (m, 2H), 7.57–7.50 (m, 2H), 7.46–7.27 (m, 6H), 7.26–7.19 (m, 3H), 7.12–7.04 (m, 2H), 6.73 (s, 4H), 4.76 (dd, $J$ = 8.6, 3.8 Hz, 1H), 4.26 (dd, $J$ = 10.1, 8.0 Hz, 1H), 4.06 (bs, 1H), 3.88 (dd, $J$ = 10.1, 4.5 Hz, 1H), 3.55–3.30 (m, 4H), 3.18 (dt, $J$ = 8.6, 4.3 Hz, 1H), 1.94–1.72 (m, 4H), 1.14–1.06 (s, 9H).$^{13}$C NMR (CDCl$_3$, 75 MHz) δ (ppm) 171.0, 152.7, 142.5, 137.6, 135.6, 135.5, 133.5, 133.0, 129.7, 129.9, 129.0, 128.0, 127.7, 127.6, 127.1, 116.2, 114.8, 64.2, 57.8, 55.8, 50.4, 46.4, 45.8, 26.9 (3C), 26.1, 24.0, 19.2; IR (cm$^{-1}$) 3069, 2952, 2874, 2858, 2832, 1643, 1512, 1428, 1112, 701; HRMS [ESI $^+$ (m/z)]: calcd for C$_{30}$H$_{39}$N$_2$O$_2$Si (M+H$^+$) 487.27808, found 487.27664; R$_f$ 0.43 (MeOH/DCM 1/9).

(25S,3S)-2-Amino-4-((tert-butyldiphenylsilyloxy)-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one (23)

(25S,3S)-4-((tert-Butyldiphenylsilyloxy)-2-((4-methoxyphenyl)amino)-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one (22) (0.30 g, 0.51 mmol) was dissolved in MeOH/H$_2$O (30 mL/15 mL). Aqueous H$_2$SO$_4$ was added (1M, 0.51 mL) followed by H$_2$O$_2$ (116 mg, 0.51 mmol). The mixture was stirred for 15 h and water (50 mL) and saturated aqueous Na$_2$CO$_3$ (3 mL) were added. The aqueous mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The residue was purified via column chromatography (MeOH/DCM 1/99 → 2/98 → 5/95). After concentration of the pure product containing fractions, the residue was dissolved in DCM, filtered and concentrated. The product was obtained as a brown sticky oil (181 mg, 0.37 mmol, 73%).$^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 7.56–7.49 (m, 2H), 7.42–7.26 (m, 10H), 7.25–7.18 (m, 3H), 4.15 (d, $J$ = 7.5 Hz, 1H), 3.95 (dd, $J$ = 10.1, 5.7 Hz, 1H), 3.82 (dd, $J$ = 10.1, 4.5 Hz, 1H), 3.63–3.33 (m, 4H), 3.13 (dt, $J$ = 7.4, 5.1 Hz, 1H), 1.98–1.69 (m, 4H), 1.04–0.96 (m, 9H).$^{13}$C NMR (CDCl$_3$, 75 MHz) δ (ppm) 172.6, 138.8, 135.5, 133.5, 133.3, 132.9, 129.6, 129.5, 129.3, 128.2, 127.6, 127.5, 127.0, 64.9, 53.2, 52.5, 46.4, 45.8, 26.8, 25.9, 24.1, 19.1; IR (cm$^{-1}$): 2929, 2856, 1640, 1427, 1108, 701; HRMS [ESI $^-$ (m/z)]: calcd for C$_{38}$H$_{37}$N$_2$O$_2$Si (M$^-$H$^+$) 487.27808, found 487.27664; R$_f$ 0.43 (MeOH/DCM 1/9).
**Chapter 5**

2-(3,4-Dimethoxyphenyl)acetaldehyde (26)

2-(3,4-Dimethoxyphenyl)ethanol (2.00 g, 11.0 mmol) was dissolved in DCM (50 mL). Dess–Martin periodinane (4.67 g, 11.0 mmol) was added and the resulting mixture was stirred at rt for 1.5 h, filtered over celite and washed with a 1:1 mixture of saturated aqueous NaHCO₃ and 10% aqueous Na₂S₂O₃ (100 mL). The aqueous layer was extracted with DCM (50 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/2). The product was obtained as a yellow liquid (1.68 g, 9.32 mmol, 85%).

**¹H NMR (CDCl₃, 300 MHz) δ (ppm) 9.72 (t, J = 2.5 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.76 (ddt, J = 8.1, 2.0, 0.5 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 3.87 (s, 6H), 3.62 (d, J = 2.4 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 199.4, 149.3, 148.4, 124.1, 121.8, 112.6, 111.6, 55.9 (2C), 50.1; HRMS [EI⁺ (m/z)]: calcd for C₁₀H₁₂O₃ (M⁺) 180.07864, found 180.07880.

NMR data are in accordance with literature values.²

(2S,3S)-Ethyl 3-(3,4-dimethoxyphenyl)-4-hydroxy-2-((4-methoxyphenyl)amino)butanoate (27)

To a solution of (E)-Ethyl 2-((4-methoxyphenyl)imino)acetate (16) (1.38 g, 6.66 mmol) in anhydrous THF (20 mL) were added, water (1 mL) and L-proline (130 mg, 1.13). The mixture was stirred for 15 min, cooled to −5 °C. After addition of 2-(3,4-dimethoxyphenyl)acetaldehyde (26) (1.2 g, 6.66 mmol), the resulting mixture was stirred for 17.5 h. Acetic acid (1.3 mL) was added and after 10 min of stirring, NaBH₄ (0.28 g, 7.33 mmol) was added in portions. The reaction was stirred for 2 h and poured out in a saturated aqueous solution of NaHCO₃ (50 mL). The aqueous solution was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/3 → 1/2 → 1/1 → 2/1). The product was obtained as a yellow sticky wax (1.74 g, 4.47 mmol, 67%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 6.86-6.72 (m, 5H), 6.69–6.62 (m, 2H), 4.42 (bs, 1H), 4.21–3.91 (m, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H), 3.35 (dt, J = 7.6, 5.5 Hz, 1H), 1.95 (bs, 1H), 1.23 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 173.5, 153.1, 149.0, 148.6, 141.4, 129.7, 120.7, 116.1, 114.8, 111.8, 111.3, 63.9, 61.2, 60.2, 55.8 (2C), 55.7, 50.0, 44.3 (m); IR (cm⁻¹): 3372, 2956, 2834, 1729, 1512, 1237, 1026; HRMS [ESI⁺ (m/z)]: calcd for C₂₁H₂₈N₁O₆ (M+H⁺) 390.19166, found 390.19232; HPLC: ee > 99% Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, 2-propanol/heptane 20/80, retention time: major enantiomer 25.6 min, minor enantiomer: 51.4 min. Rf 0.27 (EtOAc/heptane 1/1).
A Pictet–Spengler entry into 3,4-disubstituted tetrahydroisoquinolines

(2S,3S)-Ethyl 4-(((tert-butyldiphenylsilyl)oxy)-3-(3,4-dimethoxyphenyl)-2-((4-methoxyphenyl)amino)butanoate (28)

(2S,3S)-Ethyl 3-(3,4-dimethoxyphenyl)-4-hydroxy-2-((4-methoxyphenyl)amino)butanoate (1.50 g, 3.85 mmol) (27) was dissolved in DCM (25 mL) and cooled to 0 °C. tert-Butylchlorodiphenylsilane (2.00 mL, 2.12 g, 7.7 mmol) and imidazole (524 mg, 7.7 mmol) were added. The resulting mixture was allowed to come to rt, stirred for 1.5 h and quenched with saturated aqueous NaHCO₃. After separation, the aqueous layer was extracted with DCM (50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/4). This yielded a colorless oil (2.30 g, 3.66 mmol, 95%).

1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.69–7.58 (m, 4H), 7.45–7.27 (m, 6H), 6.74 (d, J = 8.2 Hz, 5H), 6.74 (s, 4H), 6.62 (dd, J = 8.2, 1.9 Hz, 1H), 6.57 (d, J = 1.9 Hz, 1H), 4.67 (dd, J = 7.7, 3.6 Hz, 1H), 4.20 (t, J = 9.8 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.87–3.73 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.35 (dt, J = 9.0, 4.4 Hz, 1H), 1.21 (t, J = 7.1 Hz, 1H), 1.12–1.08 (m, 9H);

13C NMR (CDCl₃, 75 MHz) δ (ppm) 173.8, 152.9, 148.7, 148.3, 142.1, 135.7, 135.6, 133.4, 129.8, 129.7, 129.6, 127.7, 127.6, 120.7, 116.1, 114.8, 111.9, 111.0, 64.1, 60.9, 55.8 (2C), 55.7, 50.3, 26.9, 19.2, 14.3;

IR (cm⁻¹) 3373, 2931, 2856, 1734, 1511, 1237, 1109, 1028, 703;

HRMS [ESI⁺ (m/z)]: calcd for C₃₇H₄₆NO₆Si (M+H⁺) 628.30944, found 628.30744; Rf 0.65 (EtOAc/heptane 1/1).

(2S,3S)-Ethyl 2-amino-4-(((tert-butyldiphenylsilyl)oxy)-3-(3,4-dimethoxyphenyl)butanoate (33)

(2S,3S)-Ethyl 4-(((tert-butyldiphenylsilyl)oxy)-3-(3,4-dimethoxyphenyl)-2-((4-methoxyphenyl)amino)butanoate (28) (1.71 g, 2.72 mmol) was dissolved in a mixture of MeCN and water (150 mL/75 mL). Aqueous H₂SO₄ was added (1M, 2.7 mL) followed by addition of H₅IO₆ (0.62 g, 2.72 mmol). The resulting mixture was stirred for 17 h. Saturated Na₂CO₃ (20 mL) and water (100 mL) were added. The aqueous solution was extracted with EtOAc (2 × 300 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/2 → 1/1). The product was obtained as a dark oil (1.09 g, 2.09 mmol, 77%).

1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.67–7.56 (m, 4H), 7.46–7.31 (m, 6H), 6.78–6.71 (m, 1H), 6.70–6.63 (m, 2H), 4.17–4.02 (m, 4H), 3.83 (s, 3H), 3.82 (dd, J = 10 Hz, 5.5 Hz, 2H), 3.78 (s, 3H), 3.25 (dt, J = 8.4, 5.3 Hz, 1H), 1.25 (q, J = 7.1 Hz, 1H), 1.05 (s, 9H);

13C NMR (CDCl₃, 75 MHz) δ (ppm) 175.2, 148.6, 148.1, 135.6, 135.6, 133.6, 133.5, 130.5, 129.6, 127.6, 120.9, 112.1, 111.0, 64.6, 60.8, 55.8, 55.0, 50.8, 26.9, 19.2, 14.3; IR (cm⁻¹) 3373, 2931, 2857, 1734, 1516, 1110, 704;

HRMS [ESI⁺ (m/z)]: calcd for C₂₀H₂₄NO₃Si (M+H⁺) 522.26757, found 522.26700; Rf 0.23 (EtOAc/heptane 1/1).
(3S,4S)-Diethyl 4-(((tert-butyldiphenylsilyl)oxy)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1,3-dicarboxylate (34)

(23S)-Ethyl 2-amino-4-(((tert-butyldiphenylsilyl)oxy)-3-(3,4-dimethoxyphenyl)butanoate (33) (50 mg, 0.096 mmol) was dissolved in dry DCM and put under an atmosphere of argon. Ethylglyoxylate (50% wt% in toluene, 19 μL, 0.096 mmol) and TFA (7.4 μL, 0.096 mmol) were added and the resulting mixture was stirred at rt for 2 h. Aqueous saturated NaHCO₃ (10 mL) and DCM (10 mL) were added and the layers were separated. The aqueous phase was extracted with DCM (10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/5 → 1/1). The product was obtained as a colorless oil (20 mg, 0.037 mmol, 39%). ^1H NMR (CDCl₃, 300 MHz) δ (ppm) 7.78-7.54 (m, 4H), 7.50-7.29 (m, 6H), 6.45 (s, 1H), 6.26 (s, 1H), 4.25-4.04 (m, 4H), 3.97-3.74 (m, 3H), 3.80 (s, 3H), 3.68 (s, 3H), 3.28-3.16 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H); ^13C NMR (CDCl₃, 75 MHz) δ (ppm) 173.7, 174.7, 174.4, 135.7 (2C), 135.6 (2C), 133.4, 129.1, 129.6 (4C), 127.4, 124.9, 111.8, 108.7, 67.3, 60.8, 55.5, 44.3, 41.7, 29.7, 26.9, 19.2, 14.2; IR (cm⁻¹), 2931, 2856, 1729, 1517, 1227, 1111, 704; HRMS [ESI⁺ (m/z)]: calcd for C₃₁H₄₀N₂O₅Si (M+H⁺) 606.28870, found 606.28617; Rf (EtOAc/heptane 1/1).
A Pictet–Spengler entry into 3,4-disubstituted tetrahydroisoquinolines

2-(Benzo[d][1,3]dioxol-5-yl)acetaldehyde (37)

Safrole (36) (5.0 mL, 5.48 g, 33.8 mmol) was dissolved in DCM (50 mL) in an oxygen flushed flask. The solution was flushed with oxygen for 10 min and cooled to –78 °C. An ozone stream was led through to the solution for 4 h. The reaction mixture was flushed with oxygen. Dimethylsulfide (3.2 mL) was added and the reaction mixture was placed under argon and stirred under reflux overnight. After cooling down, the reaction mixture was concentrated and the residue was purified via column chromatography (EtOAc/heptane 1/9). The product was obtained as a slightly yellow liquid (2.66 g, 16.2 mmol, 48%).

\[ \delta (ppm) 9.71 (t, J = 2.3 Hz, 1H), 6.82–6.78 (m, 1H), 6.71–6.63 (m, 2H), 5.96 (s, 2H), 3.59 (d, J = 2.3 Hz, 2H) \]

\[ \delta (ppm) 199.3, 148.2, 147.0, 125.3, 122.8, 109.9, 108.7, 101.1, 50.1 \]

IR (cm\(^{-1}\)): 3424, 2891, 1721, 1489, 1245, 1037; HRMS [EI\(^{+}\) (m/z)]: calcd for C\(_9\)H\(_8\)O\(_3\) (M\(^{+}\)) 164.04734, found 164.04801; R\(_f\) (EtOAc/heptane 1/1) 0.58.

(2S,3S)-Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-4-hydroxy-2-((4-methoxyphenyl)amino)butanoate (38)

To a solution of (E)-Ethyl 2-((4-methoxyphenyl)imino)acetate (16) (1.09 g, 5.26 mmol) in anhydrous THF (20 mL) were added water (1 mL) and L-proline (130 mg, 1.13 mmol). The mixture was stirred for 15 min and cooled to –5 °C. After addition of 2-(benzo[d][1,3]dioxol-5-yl)acetaldehyde (37) (0.86 g, 5.26 mmol), the resulting mixture was stirred for 20.5 h. Acetic acid (1.0 mL) was added and NaBH\(_4\) (0.22 g, 5.82 mmol) was added in portions. The reaction mixture was poured out in saturated aqueous NaHCO\(_3\) (50 mL). The aqueous solution was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/3 → 1/2 → 1/1). The product was obtained as a yellow oil (0.784 g, 2.11 mmol, 40%).

\[ \delta (ppm) 6.80–6.63 (m, 7H), 5.95 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.5 Hz, 1H), 4.40 (d, J = 5.1 Hz, 1H), 4.14 (q, J = 7.1 Hz, 3H), 4.05 (dd, J = 10.8, 7.8 Hz, 1H), 3.93 (dd, J = 10.8, 5.7 Hz, 1H), 3.73 (s, 3H), 3.33 (dt, J = 7.6, 5.4 Hz, 1H), 1.23 (s, J = 7.1 Hz, 3H) \]

\[ \delta (ppm) 173.4, 153.2, 147.9, 147.1, 141.4, 138.9, 121.9, 116.2, 114.8, 108.7, 108.4, 101.1, 63.8, 61.2, 60.2, 55.7, 50.1, 14.3, 0.0 \]

IR (cm\(^{-1}\)): 3404, 2900, 1727, 1512, 1241, 1035; HRMS [ESI\(^{+}\) (m/z)]: calcd for C\(_{20}\)H\(_{24}\)NO\(_6\) (M+H\(^{+}\)) 374.16036, found 374.15986; R\(_f\) (EtOAc/heptane 1/1) 0.47 HPLC: ee > 99% Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, 2-propanol/heptane 20/80, retention time: major enantiomer 18.5 min, minor enantiomer: 33.1 min.
(25S,3S)-Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-4-((tert-butyldiphenylsilyl)oxy)-2-((4-methoxyphenyl)amino)butanoate (39)

To a solution of (25S,3S)-ethyl 3-(benzo[d][1,3]dioxol-5-yl)-4-hydroxy-2-((4-methoxyphenyl)amino)butanoate (38) (694 mg, 1.86 mmol) was dissolved in anhydrous DCM (25 mL), placed under an atmosphere of argon and cooled to 0 °C. After addition of tert-butylchlorodiphenylsilane (0.96 mL, 1.02 g, 3.72 mmol) and imidazole (253 mg, 3.72 mmol), the mixture was stirred for 5 min, allowed to come to rt and stirred for an additional 18 h. Saturated aqueous NaHCO₃ (50 mL) was added. After separation, the aqueous layer was extracted with DCM (50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/4 + EtOAc/heptane 1/9 → 1/6). The product was obtained as a brown oil (474 mg, 76%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.71–7.50 (m, 4H), 7.47–7.28 (m, 6H), 6.76 (s, 4H), 6.68 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 1.6 Hz, 1H), 6.51 (dd, J = 8.0, 1.7 Hz, 1H), 5.91 (d, J = 1.4 Hz, 1H), 5.90 (d, J = 9.4, 5.3 Hz, 1H), 4.67 (dd, J = 8.0, 3.3 Hz, 1H), 4.18 (t, J = 7.9 Hz, 1H), 4.12 (q, J = 7.1 Hz, 1H), 3.76 (dd, J = 9.4, 5.3 Hz, 1H), 3.75 (s, 3H), 3.34 (dt, J = 9.51, 4.35 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.11 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 173.7, 152.9, 147.5, 146.8, 142.1, 135.6, 133.4, 133.3, 130.9, 129.7, 129.6, 127.7, 127.7, 121.8, 114.2, 114.7, 108.8, 108.1, 100.9, 64.0, 61.0, 59.1, 55.7, 50.3, 26.9, 19.2, 14.3; IR (cm⁻¹), 2930, 2879, 1737, 1512, 1237, 1038; HRMS [ESI⁺ (m/z)]: calcd for C₃₂H₃₆NO₅Si (M+H⁺) 506.2367; found 506.2367.

To a solution of (25S,3S)-ethyl 3-(benzo[d][1,3]dioxol-5-yl)-4-hydroxy-2-((4-methoxyphenyl)amino)butanoate (39) (759 mg, 1.24 mmol) in MeCN/H₂O (90 mL/45 mL) was added aqueous H₂SO₄ (1M, 1.24 mL) and periodic acid (283 mg, 1.24 mmol). The resulting mixture was stirred for 16 h and saturated aqueous Na₂CO₃ (10 mL) and water (50 mL) were added. The aqueous mixture was extracted with EtOAc (2 × 150 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/2). The product was obtained as a brown oil (474 mg, 0.94 mmol, 76%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.67–7.59 (m, 4H), 7.45–7.32 (m, 6H), 6.60 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 1.7 Hz, 1H), 6.55 (dd, J = 8.0, 1.7 Hz, 1H), 5.91 (s, 2H), 4.17–3.99 (m, 1H), 3.78 (dd, J = 10.0, 5.4 Hz, 1H), 3.24 (dt, J = 8.8, 5.1 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 175.2, 147.4, 146.6, 135.6, 133.5, 131.5, 129.7, 127.6, 122.0, 109.1, 108.0, 100.0, 64.5, 60.8, 54.8, 50.7, 35.4, 31.9, 26.9, 19.2, 14.3; IR (cm⁻¹), 2931, 2856, 1733, 1488, 1249, 1110, 704; HRMS [ESI⁺ (m/z)]: calcd for C₃₂H₃₆NO₅Si (M+H⁺) 506.2367; found 506.2367; Rf (EtOAc/heptane 1/1) 0.57.
A Pictet–Spengler entry into 3,4-disubstituted tetrahydroisoquinolines

(7S,8S)-Diethyl 8-(((tert-butyldiphenylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline-5,7-dicarboxylate (41)

To a solution of (2S,3S)-ethyl 2-amino-3-(benzo[d][1,3]dioxol-5-yl)-4-(((tert-butyldiphenylsilyl)oxy)butanoate (40) (50 mg, 0.099 mmol) in dry DCM (5 mL) was added ethyl glyoxylate (~50 wt% solution in toluene, 19 μL, 0.096 mmol) and TFA (7.4 μL, 11 mg, 0.096 mmol). The mixture was stirred for 20 h and quenched with saturated aqueous NaHCO₃. After addition of DCM (10 mL), the layers were separated. The aqueous phase was extracted with DCM (10 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via column chromatography (EtOAc/heptane 1/9 → 1/6 → 1/3). Yield: 10 mg (0.017 mmol, 18%). Yield of side product 44: 17 mg (0.034 mmol, 35%). Characterisation for 41: ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.72–7.30 (m, 10H, both diastereomers), 6.79 (s, 4/5H, major diastereomer), 6.70 (s, 1/5H), 6.46 (s, 1/5H, minor diastereomer), 6.23 (s, 4/5H, major diastereomer), 5.90 (d, J = 1.4 Hz, 1/5H, minor diastereomer), 5.89 (d, J = 1.4 Hz, 1/5H, minor diastereomer), 5.87 (d, J = 1.4 Hz, 4/5H, major diastereomer), 5.83 (d, J = 1.4 Hz, 4/5H, major diastereomer), 4.95 (s, 4/5H, major diastereomer), 4.58 (s, 1/5H, minor diastereomer), 4.34–4.00 (m, 4H+1/5H, both + minor diastereomer), 4.34 (d, J = 2.5 Hz, 4/5H, major diastereomer), 4.00–3.69 (m, 2H, both diastereomers), 3.21–3.11 (m, 1H, both diastereomers), 1.18 (t, J = 7.1 Hz, 1H, both diastereomers), 1.07 (m, 36/5H, major diastereomer), 1.01 (s, 9/5H, minor diastereomer); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 173.4, 172.7, 146.7, 135.7, 135.6, 133.5, 133.4, 129.8, 129.7, 127.7, 126.6, 124.7, 109.2, 108.7, 106.7, 106.4, 100.9, 77.2, 66.2, 61.6, 60.9, 57.0, 53.7, 43.1, 29.7, 26.9, 26.8, 14.2, 14.1 (complex mixture of diastereomers); IR (cm⁻¹), 2929, 1736, 1455, 1208, 1111, 1038, 705; HRMS [ESI⁺ (m/z)]: calcd for C₃₃H₄₀NO₇Si (M+H⁺) 590.25740, found 590.25616; Rf (EtOAc/heptane 1/1) 0.74.

5.6 References

SYNTHESIS OF β-2,3-DISUBSTITUTED AMINO ACIDS

6.1 Introduction

β-2,3-Disubstituted amino acids are privileged structural elements, which are frequently encountered in biologically active substances such as cocaine (1), taxol® (2), penicillin V (3), dolastatin 11 (4) and diocatin A (5) (Figure 1).

**Figure 1** Biologically active β-amino acids: cocaine (1), taxol (2), penicillin V (3), dolastatin 11 (4) and diocatin A (5).

Cocaine has been isolated from the coca plant (Erythroxylaceae family) and has a plethora of pharmacological effects, including influence on the central nervous system, body temperature, sympathetic nervous system and nerve conduction. It was initially recognised as a potent therapeutic agent, but is nowadays mostly associated with drug abuse. Taxol®, a tubulin-targeting cytoskeletal drug, initially isolated from the Taxus brevifolia, is currently on the market as a drug (Paclitaxel) against ovarian cancer. Paclitaxel inhibits the disassembly of microtubules. As a consequence, the increased concentration of microtubules instigates cell death. Unfortunately, the biological availability of paclitaxel is limited and although total syntheses of paclitaxel have been reported, it can be more economically synthesised in a semi-synthetic manner, starting from a suitably protected variant of the less scarce 10-deacetylbaccatin III (7) and a protected derivative of the N-benzoyl-β-2,3-disubstituted amino acid side chain 6 (Fig. 1).

β-Lactam antibiotics such as penicillin V are cyclised β-2,3-disubstituted amino acids, which are used in the treatment of bacterial infections. The marine depsipeptide dolastatin 11 (4) was
isolated from the mollusk Dolabella auricularia and has been studied for its cytotoxic effects. Dioctatin A (5) is a naturally occurring tripeptide, consisting of two β-amino acids and a dehydroamino acid, which inhibits the aflatoxin production of fungi (see: Section 6.3). On account of the great importance of β-2,3-disubstituted amino acids, numerous synthetic methods for their preparation have been developed throughout the years.1,9 Barbas et al. recognised that the 1,3-amino aldehydes obtained from the proline-catalysed Mannich reaction could be further elaborated into the corresponding 1,3-amino acids, but ignored the removal of the N-PMP-group.10 Furthermore, isolation and purification of the intermediate β-amino aldehydes may lead to undesired epimerisation. Janey and co-workers developed a three-step protocol to synthesise an N-Boc-protected amino amide, starting from an N-PMP-protected amino alcohol.11 In this chapter we describe a general method to convert N-PMP-protected 1,3-amino alcohols into protecting group-free β-2,3-disubstituted amino acids in a one-pot procedure.

### 6.2 Synthesis of β-2,3-disubstituted amino acids

As described in Chapter 1, proline, amongst other catalysts, effectively catalyses the Mannich reaction between PMP-protected imines and aldehydes. β-Amino aldehydes are formed with high diastereoselectivity and are best immediately transformed into the corresponding 1,3-amino alcohols to prevent epimerisation during purification. Chapter 2 describes the oxidative deprotection of N-PMP-protected amines with usage of periodic acid. Alsters et al. disclosed a method to convert alcohols into the corresponding ketones or carboxylic acids, employing catalytic sodium dichromate with sodium periodate as the stoichiometric oxidant.12 Since both methodologies in fact make use of the same oxidant, we envisioned combining these two synthetic methods, with the aim to convert N-PMP-protected amino alcohols directly into the corresponding protecting group-free β-2,3-disubstituted amino acids.

When preparing the amino alcohols 16–21, it appeared crucial to monitor the initial conversion of imines 10–13 into the amino aldehydes by HPLC analysis in order to obtain good yields. We observed that the retro-Mannich reaction was favoured at higher temperatures; above −10 °C, the initially formed Mannich product relapsed to the starting materials in the presence of the catalyst. The starting aldehydes 8–9 might eventually undergo a self-aldol reaction, leading to hydroxy aldehydes 15 (Table 1).13 The low temperature that was required rendered initial HPLC monitoring of the conversion troublesome. However, by preparing HPLC samples at low temperatures (−20 to −10 °C) and immediately injecting them on the HPLC column, the
conversion of the imine into the amino aldehyde could be adequately monitored in time. Upon quenching of the reaction with NaBH₄, the β-amino aldehydes 14 were irreversibly transformed into the 1,3-amino alcohols 16–21.

Table 1 Synthesis of 1,3-amino alcohols.

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<th>R²</th>
<th>t (h)</th>
<th>Product</th>
<th>d.r</th>
<th>ee (%)</th>
<th>Yield (%)</th>
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<td>&gt;99</td>
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<td>n-Bu (9)</td>
<td>4-NO₂C₆H₄H (16)</td>
<td>48</td>
<td>&gt;19:1</td>
<td>&gt;99</td>
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<tr>
<td>3</td>
<td>Me (8)</td>
<td>4-NC₆H₄H (11)</td>
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<td>&gt;99</td>
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<tr>
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<td>n-Bu (9)</td>
<td>4-NC₆H₄H (11)</td>
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<td>&gt;19:1</td>
<td>&gt;99</td>
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<td>&gt;19:1</td>
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</table>

* Imine was formed in situ (vide infra)

As becomes clear from the results in Table 1, amino alcohols with aromatic R² groups were synthesised in good yields and complete selectivities (entries 1–4). Additionally, we prepared amino alcohol 21 starting from two aliphatic aldehydes. However, since the imine of p-anisidine and hexanal (13, R² = n-pentyl) was considered less stable and therefore more difficult to purify, we prepared the imine in situ without workup afterwards (entry 6). The imine formation could be monitored by HPLC, but we were not able to push the equilibrium further than ca. 70% by adding dehydrating agents. When the imine formation stopped proceeding, the donor aldehyde was added and product formation was again monitored by HPLC. The desired product 21 could be isolated after reduction and purification in 14% yield and complete selectivity. We then synthesised the Mannich adduct of propionaldehyde (8) and N-PMP ethyl glyoxylate (12). Barbas et al. previously reported that aldehyde 14 (R¹ = Me; R² = CO₂Et) was isolated without any diastereoselectivity, but we showed that by direct reduction of the aldehyde, the alcohol could be obtained in complete selectivity albeit in 16% yield (entry 5). With the enantiomeric and diastereomerically pure amino alcohols 16–21 in hand, we intended to convert these products in a one-pot process into the corresponding free β-2,3-disubstituted amino acids.

In Chapter 2 we described a method to mildly remove the PMP-group from an amine. This deprotection method was further extended to the synthesis of β-2,3-disubstituted amino acids via a one-pot deprotection-oxidation sequence (Table 2). First, the reduced Mannich adducts
were treated with periodic acid to effect PMP removal and upon completion, a catalytic amount of sodium dichromate and an additional 5 equiv of periodic acid were added to the aqueous solution, resulting in oxidation of the alcohol to the carboxylic acid. The crude mixture was purified using ion-exchange chromatography to yield the corresponding β-2,3-disubstituted amino acids. Given the vast number of N-PMP-1,3-amino alcohols that are accessible via the asymmetric Mannich reaction, the latter pathway represents a facile and efficient entry into a large variety of β-amino acids. This was shown by transforming a series of 1,3-amino alcohols into the amino acids 23–27 as depicted in Table 2.

Table 2 Formation of β-2,3-disubstituted amino acids.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>Me</td>
<td>Me</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>n-Bu</td>
<td>n-Bu</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>n-Bu</td>
<td>n-Bu</td>
<td>4-NCC$_6$H$_4$</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>Me</td>
<td>n-pentyl</td>
<td>26</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>Me</td>
<td>C$_6$H$_5$</td>
<td>27</td>
<td>68</td>
</tr>
</tbody>
</table>

*a ee and c.f. not determined*

Following the aforementioned procedure, we obtained β-2,3-disubstituted amino acids 23–27 in good yields. Starting from 20 ($R^1$ = Me, $R^2$ = CO$_2$Et), the corresponding amino acid could also be prepared according to mass spectroscopic analysis of the reaction mixture. Purification however, was more troublesome due to the base labile ester functionality in the molecule. Since ion-exchange chromatography requires elution of the product with a 2 M NH$_4$OH solution, we assumed this purification method to be incompatible with the ethyl ester functionality.

6.3 Synthesis of a dioctatin A building block

Aflatoxins (e.g. aflatoxin B$_1$ (28), Figure 2), strongly carcinogenic substances that belong to the class of mycotoxins, are mainly produced by strains of Aspergillus flavus and Aspergillus parasiticus and affect crops such as maize and peanuts.
To prevent its malevolent consequences, effective methods to reduce the aflatoxin contamination of crops are desired. Research has previously been directed towards the synthesis of anti-fungal agents, but no compounds have been discovered which are sufficiently active and safe at the same time. On the other hand, Sakuda et al. discovered that dioctatin A (5) inhibits the aflatoxin production,\textsuperscript{16,17} without inhibiting the growth of the aflatoxin-producing microorganism. Dioctatin A (5) is a tripeptide consisting of dehydro-\(\alpha\)-amino acid 31, and two \(\beta\)-amino acids (2R,3S)-29 and 30 (Scheme 1).

The retrosynthesis depicted in Scheme 1 leads to a seemingly short route to dioctatin A. However, it does not start from commercially available amino acids. \(\beta\)-2,3-Disubstituted amino acid (2R,3S)-29 was prepared by Sakuda starting from 2-octenoic acid ethyl ester in only 6% overall yield. Moreover, a laborious low-yielding chromatographic separation of the two diastereoisomers was included in the route, which rendered it less applicable for scale-up. Additionally, Sakuda claims that the stereochemical configuration of the 2-position of amino acid 29 is \(R\) (as depicted in Scheme 1),\textsuperscript{17} although no substantial proof was provided. In his synthetic route, amino acid 29 was initially produced as a mixture of diastereoisomers (epimers at the 2-position), which were separated by chromatography. Two tripeptides, prepared from either (2R,3S)-29 or from (2S,3S)-29, were tested for anti-aflatoxin production activity. The peptide with the highest activity was concluded to be the naturally occurring stereoisomer after comparison of their analytical data. However, the absolute configuration of the 2-position remained unproven. The development of a straightforward and efficient protocol for the synthesis of \(\beta\)-2,3-disubstituted amino acids from \(N\)-PMP-protected 1,3-amino alcohols (Section 6.2) prompted us to pursue a synthesis of building block (2R,3S)-29. Synthesis of the preceding 1,3-amino alcohol via proline catalysis would lead to a syn-configuration of the substituents; \textit{i.e.}
(2R,3S)-29 (using D-proline) or 26 ((2S,3R-configuration)) (using L-proline), and comparison of the $^1$H NMR data of the resulting β-2,3-disubstituted amino acids with those of the epimers prepared by Sakuda, would deliver the stereochemical proof.

The D-proline-catalysed Mannich reaction produced the intermediate amino alcohol 32 with excellent selectivity, while the subsequent conversion into the β-2,3-disubstituted amino acid (2R,3S)-29 proceeded as expected (Scheme 2). We compared its $^1$H NMR data with the data from 26 and with the data of the presumed (2R,3S)-diastereomer produced by Sakuda. The spectral data were identical which proves that C2 is indeed $R$-configured.

Since our protocol requires no separation of stereoisomers and the overall yield (18%) is significantly higher than in the Sakuda route, it might contribute to a more efficient future synthesis of dioctatin A.

6.4 Conclusion and outlook

In conclusion, we have developed a new and efficient protocol for the synthesis of enantio- and diastereomerically pure β-2,3-disubstituted amino acids. After formation of N-PMP-protected 1,3-amino alcohols via the asymmetric proline-catalysed Mannich reaction, these valuable compounds can be transformed in high yields into the corresponding protecting group-free amino acids by treatment with periodic acid and sodium dichromate in a one-pot two-step protocol. In addition, we have shown that the development of this new route paves the way for an easier and more scalable access into one of the key building blocks for the synthesis of the naturally occurring aflatoxin production inhibitor dioctatin A. Through comparison with literature data, we have additionally confirmed the tentatively assigned stereochemistry of the 2-position of the N-terminal β-amino acid of dioctatin A.
6.5 Acknowledgements
Moniek Pillen is kindly acknowledged for her contribution to this chapter. Dr. Paul Alsters (DSM Innovative Synthesis, Geleen, The Netherlands) is kindly acknowledged for the useful discussions.

6.6 Experimental section
For general remarks, see section 2.8.

\((E)-4\text{-Methoxy-N-(4-nitrobenzylidene)aniline (10)}\)

A solution of \(p\)-anisidine (30.0 g, 244 mmol) and 4-nitrobenzaldehyde (36.9 g, 244 mmol) in 1,2-DCE (300 mL) was heated to 90 °C and stirred for 1 h under an atmosphere of argon. The solvent was then removed until crystallisation started. The mixture was cooled to 0 °C. The obtained crystals were filtered off and washed with cold EtOAc. The product was obtained as a yellow solid (41.2 g, 0.16 mmol, 66%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) 8.58 (s, 1H), 8.32 (d, \(J = 6.3\) Hz, 2H), 8.06 (d, \(J = 6.6\) Hz, 2H), 7.31 (d, \(J = 6.9\) Hz, 2H), 6.96 (d, \(J = 6.9\) Hz, 2H), 3.86 (s, 3H). Spectral data are in accordance with literature values.

\((E)-4\text{-((4-Methoxyphenyl)imino)methyl}benzonitrile (11)\)

A solution of \(p\)-anisidine (2.96 g, 24.0 mmol) and 4-cyanobenzaldehyde (3.48 g, 24.0 mmol) in MeOH (120 mL) was stirred for 1h at rt under an atmosphere of argon. After concentration, the residue was recrystallised from EtOAc (50 mL). The product \(10\) (2.1 g, 8.89 mmol, 37%) was obtained as a yellow solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) 8.52 (s, 1H), 7.99 (d, \(J = 8.1\) Hz, 2H), 7.75 (d, \(J = 8.4\) Hz, 2H), 7.29 (d, \(J = 9.0\) Hz, 2H), 6.95 (d, \(J = 9.0\) Hz, 2H), 3.85 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\) 75 MHz) \(\delta\) (ppm) 159.1, 155.3, 143.7, 140.3, 132.5, 128.8, 122.5, 118.5, 114.5, 113.9, 55.5; IR (cm\(^{-1}\)) 2955, 2837, 2220, 1586, 1505, 1246, 1034, 838, 559; HRMS [ESI (m/z)] calcd for C\(_{15}\)H\(_{13}\)N\(_2\)O (M+H\(^+\)) \(237.10279\), found 237.10304; R\(_f\) = 0.72 (EtOAc/heptane, 1:1); Mp 116–117 °C.

\((E)-\text{Ethyl 2-((4-methoxyphenyl)imino)acetate (12)}\)

To a solution of \(p\)-anisidine (6.21 g, 50.4 mmol) in anhydrous toluene (100 mL) was added ethyl glyoxylate (−50 wt%) (10.3 g, 50.4 mmol). The resulting mixture was stirred for 5 min, filtered and concentrated at 40 °C. The product was obtained as a brown oil (9.99 g, 47.8 mmol, 95%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) 7.94 (s, 1H), 7.36 (d, \(J = 9.0\) Hz, 2H), 6.93 (d, \(J = 9.0\) Hz, 2H), 4.41 (q, \(J = 7.2\) Hz, 2H), 3.84 (s, 3H), 1.40 (t, \(J = 7.2\) Hz, 3H).

\(^1\)H NMR data are in accordance with data in Chapter 4 (p 109).
Synthesis of β-2,3-disubstituted amino acids

(2S,3S)-(4-Methoxyphenylamino)-2-methyl-3-(4-nitrophenyl)propan-1-ol (16)

(4)-4-Methoxy-N-(4-nitrobenzylidene)aniline (10) (300 mg, 1.17 mmol) and l-proline (23 mg, 0.23 mmol) were dissolved in a mixture of NMP (19 mL) and water (1 mL). After cooling to −14 °C freshly distilled propionaldehyde (0.25 mL, 3.5 mmol) was added. The reaction mixture was stirred for 144 h and cooled to 0 °C before addition of NaBH₄ (133 mg, 3.51 mmol). Saturated aqueous NaHCO₃ (30 mL) was added and the mixture was three times extracted with a 1:1 mixture of EtOAc and heptane. The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was purified via column chromatography (EtOAc/heptane, 0 → 75%). The product was obtained as a brown oil (201 mg, 0.64 mmol, 54%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.17 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 6.43 (d, J = 9.0 Hz, 2H), 4.65 (d, J = 3.9 Hz, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 3.67 (d, J = 1.5 Hz, 1H), 3.65 (d, J = 3.6 Hz, 1H), 2.24–2.19 (m, 1H), 0.92 (d, J = 7.2 Hz, 3H).

Data are in accordance with data in Chapter 2 (Ch. 2, Compound 9).

(5)-2-(((4)-4-Methoxyphenylamino)(4-nitrophenyl)methyl)hexan-1-ol (17)

(4)-4-Methoxy-N-(4-nitrobenzylidene)aniline (10) (100 mg, 0.390 mmol) and l-proline (7.73 mg, 0.078) were dissolved in NMP (9.5 mL) and water (0.5 mL). The reaction mixture was cooled to −16 °C before addition of freshly distilled hexanal (0.16 mL, 1.2 mmol) and stirred for 48 h. The mixture was cooled to 0 °C and NaBH₄ (44 mg, 1.2 mmol) was added. Saturated aqueous NaHCO₃ (10 mL) was added and the mixture was extracted with a mixture of EtOAc and heptane (1:1, 3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was purified via column chromatography (EtOAc/heptane, 0 → 25%). The product was obtained as a brown oil (102 mg, 0.28 mmol, 73%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.17 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 6.42 (d, J = 9.0 Hz, 2H), 4.70 (m, 1H), 3.76–3.63 (m, 2H), 3.60 (s, 3H), 2.00 (m, 1H), 1.38–1.18 (m, 6H), 0.83 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 152.4, 150.2, 147.0, 140.7, 128.1, 123.6, 114.9, 114.8, 63.6, 60.7, 55.7, 46.4, 29.9, 25.4, 22.7, 13.9; IR (cm⁻¹) 2931, 1512, 1345, 610, 586; HRMS (ESI) (m/z) calcd for C₂₀H₁₆N₂O₂ (M+H)⁺ 359.1970, found 359.19548; HPLC ee >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-hexane/2-propanol 80/20, retention times 25.1 min (major isomer), 8.5 min (minor isomer); d.r. >19:1 (determined by ¹H NMR); [α]D = 0.49 (EtOAc/heptane, 1:1); [α]D = −50.4 (c 0.395, CHCl₃).

4-((15S,25S)-3-Hydroxy-1-(4-methoxyphenylamino)-2-methylpropyl)benzonitrile (18)

A solution of l-proline (8.33 mg, 0.084 mmol) and (4)-4-(((3-methoxyphenyl)imino)methyl)benzonitrile (11) (100 mg, 0.420 mmol) in a mixture of NMP (9.5 mL) and water (0.5 mL) was cooled to −20 °C. Propionaldehyde (0.09 mL, 1.27 mmol) was added and the resulting mixture was stirred for 72 h. The mixture was cooled to 0°C before NaBH₄ (48 mg, 1.3 mmol) was added. Saturated aqueous NaHCO₃ (10 mL) was added and the mixture was extracted with a mixture of EtOAc and heptane (1:1, 3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was purified via column chromatography (CHCl₃/EtOAc, 1:1).
concentrated. The residue was purified via column chromatography (EtOAc/heptane, 0 → 25%). The product was obtained as a brown oil (45.1 mg, 0.152 mmol, 36%). 1H NMR (CDCl3, 300 MHz) δ (ppm) 7.60 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 6.42 (d, J = 8.7 Hz, 2H), 4.49 (d, J = 3.6 Hz, 1H), 3.68 (s, 3H), 3.64 (m, 2H), 2.27–2.09 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H); 13C NMR (CDCl3, 75 MHz) δ (ppm) 152.2, 148.2, 140.7, 132.2, 127.9, 118.9, 114.8, 114.7, 110.6, 65.6, 60.6, 55.7, 41.3, 11.6;

IR (cm⁻¹) 3403, 2931, 2227, 1512, 1235, 1035, 820; HRMS [ESI (+)] calcd for C18H13NO3 (M+H)⁺ 339.20725, found: 339.20686; HPLC ee >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-hexane/2-propanol 80/20, retention times 15.4 min (major enantiomer), 9.3 min (minor enantiomer); d.r. >19:1 (determined with 1H NMR); Rf = 0.31 (EtOAc/heptane, 1:1); [α]D²⁰ = -50.9 (c 0.615, CHCl₃).

4-(15S,23S)-2-(Hydroxymethyl)-1-(4-methoxyphenylamino)hexyl benzonitrile (19)

A solution of L-proline (8.33 mg, 0.084 mmol) and (E)-4-(((4-methoxyphenyl)imino)methyl)benzonitrile (11) (100 mg, 0.420 mmol) in a mixture of NMP (9.5 mL) and water (0.5 mL) was cooled to -16 °C. Freshly distilled hexanal (0.18 mL, 1.3 mmol) was added and the resulting mixture was stirred for 96 h. The reaction mixture was cooled to 0 °C and NaN₃H (48 mg, 0.615 mmol) was added. Saturated aqueous NaHCO₃ (10 mL) was added and the mixture was extracted with a mixture of EtOAc and heptane (1:1, 3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was purified via column chromatography (EtOAc/heptane, 0 → 25%). The product was obtained as a brown oil (112.3 mg, 0.332 mmol, 79%). 1H NMR (CDCl3, 300 MHz) δ (ppm) 7.60 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 6.42 (d, J = 9.0 Hz, 2H), 4.64 (d, J = 3.9 Hz, 1H), 3.74–3.62 (m, 2H), 3.69 (s, 3H), 2.01–1.97 (m, 1H), 1.38–1.17 (m, 6H), 0.83 (t, J = 6.6 Hz, 3H); 13C NMR (CDCl3, 75 MHz) δ (ppm) 152.3, 148.0, 140.8, 132.2, 128.0, 118.9, 114.8, 114.8, 110.7, 63.6, 60.8, 55.7, 46.3, 29.9, 25.4, 22.7, 13.9; IR (cm⁻¹) 3389, 2929, 2227, 1512, 1237, 1037, 820; HRMS [ESI (m/z)] calcd for C₂₉H₂₄N₃O₂ (M+H)⁺ 439.20725, found: 439.20686; HPLC ee >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-hexane/2-propanol 80/20, retention times 21.6 min (major enantiomer), 8.4 min (minor enantiomer); d.r. >19:1 (determined with 1H NMR); Rf = 0.56 (EtOAc/heptane, 1:1); [α]D²⁰ = -28.8 (c 0.225, CHCl₃).

(2S,3S)-Ethyl 4-hydroxy-2-(4-methoxyphenylamino)-3-methylbutanoate (20)

A solution of L-proline (191 mg, 1.93 mmol) and N-PMP ethylglyoxalate (12) (2.00 g, 9.65 mmol) in NMP (95 mL) and water (5 mL) was cooled to -20 °C. After addition of freshly distilled propionaldehyde (2.08 mL, 28.9 mmol) the mixture was stirred for 24 h at -20 °C. NaN₃H (1.1 g, 29 mmol) was added (with T < 0 °C). After addition of water (30 mL) and saturated aqueous NaHCO₃ (120 mL), the mixture was extracted with EtOAc/heptane (1:1, 3 × 100 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was purified via column chromatography (EtOAc/heptane, 0 → 60%). The product was obtained as a brown oil (412 mg, 1.54 mmol, 16%). 1H NMR (CDCl3, 300 MHz) δ (ppm) 6.77 (d, J = 8.1 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 4.23–4.11 (m, 3H), 3.76 (dd, J = 10.8 Hz, J = 4.2 Hz, 1H), 3.74 (s, 3H), 3.66 (dd, J = 10.8 Hz, J = 7.2 Hz, 1H), 2.92–2.19 (m, 1H), 1.24 (t, J = 6.9 Hz, 3H), 1.0 (d, J = 7.2 Hz, 3H); 13C NMR (CDCl3, 75 MHz) δ (ppm) 173.9, 153.3,
Synthesis of β,3-disubstituted amino acids

141.4, 116.5, 114.0, 65.8, 61.1, 61.0, 55.7, 38.1, 14.2, 11.7; IR (cm\(^{-1}\)) 2933, 1725, 1512, 1235, 1034, 822, 609; HRMS [ESI (m/z)] 268.15488, found: 268.15428; HPLC ee >99%, retention times 8.1 min (major enantiomer), 9.8 min (minor enantiomer); d.r. >19:1 (determined via \(^1\)H NMR); \(R_e = 0.35\) (EtOAc/heptane, 1:1); [\(\alpha\)]\(^D\) = −49.4 (c 1.085, CHCl\(_3\)).

(25S,3R)-3-(4-Methoxyphenylamino)-2-methylpropan-1-ol (21)

A solution of \(p\)-anisidine (100 mg, 0.812 mmol) en hexanal (66 µL, 0.81 mmol) in NMP (5 mL) was stirred for 2.5 h. \(\tau\)-Proline (16.1 mg, 0.162 mmol) was added and the reaction mixture was cooled to −16 °C. After addition of freshly distilled propionaldehyde (180 µL, 2.44 mmol) the mixture was stirred for 16 h. After allowing the reaction mixture to warm to 0 °C, NaBH\(_4\) (92.2 mg, 2.44 mmol) was added. Saturated aqueous NaHCO\(_3\) (10 mL) was added and the mixture was extracted with EtOAc/heptane (1:1, 3 × 20 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was purified via column chromatography (EtOAc/heptane, 0 → 25%). The product was obtained as a brown oil (31 mg, 14%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) 6.77 (d, \(J = 8.7\) Hz, 2H), 6.65 (d, \(J = 8.7\) Hz, 2H), 3.74 (s, 3H), 3.67 (d, \(J = 5.4\) Hz, 2H), 3.43 (m, 1H), 2.93 (m, 1H), 1.98 (m, 1H), 1.51 (m, 1H), 1.26 (m, 6H), 0.95 (d, \(J = 6.9\) Hz, 3H), 0.85 (m, 3H); \(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) (ppm) 152.5, 142.1, 115.8, 114.9, 67.1, 57.9, 55.8, 37.1, 32.4, 31.9, 26.5, 22.6, 14.0, 11.0; IR (cm\(^{-1}\)) 2360, 2339, 1557, 1509, 667, 610, 511, 418; HRMS [ESI (m/z)] calcd for \(C_{25}H_{33}NO_2\) (M+H\(^+\)) 266.21200, found: 266.21167; HPLC ee >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-hexane/2-propanol 95/5, retention times 15.9 min (major enantiomer) and 14.2 min (minor enantiomer); d.r. >19:1 (determined via \(^1\)H NMR); \(R_e = 0.56\) (EtOAc/heptane, 1:1); [\(\alpha\)]\(^D\) = −40.0 (c 0.445, CHCl\(_3\)).

(25S,3S)-3-Amino-2-methyl-3-(4-nitrophenoxy)propanoic acid (23)

Under an inert atmosphere, to a solution of (25S,3S)-3-[(4-methoxyphenylamino)-2-methyl-3-(4-nitrophenoxy)propan-1-ol\(^+\) (16) (7.00 g, 22.1 mmol) in MeCN/water (1:1, 150 mL) were added \(H_2S\)\(_2O\) (1M, 22.1 mL, 22.1 mmol) and periodic acid (5.04 g, 22.1) and the resulting mixture was stirred for 3.5 h. Subsequently, Na\(_2\)Cr\(_2\)O\(_7\)-2H\(_2\)O (0.33 g, 1.1 mmol) and periodic acid (25.2 g, 110.5 mmol) were added. After stirring for 16 h, the mixture was washed with DCM (3 × 80 mL). After purification via ion exchange chromatography (DOWEX 50W × 8) the product was obtained as white-brown crystals (3.841 g, 77% yield). \(^1\)H NMR (D\(_2\)O, 300 MHz) \(\delta\) (ppm) 8.33 (d, \(J = 8.4\) Hz, 2H), 7.68 (d, \(J = 8.7\) Hz, 2H), 4.92 (d, \(J = 8.4\) Hz, 1H), 3.28 (m, 1H), 1.34 (d, \(J = 7.2\) Hz, 3H); \(^13\)C NMR (D\(_2\)O, 75 MHz) \(\delta\) (ppm) 175.5, 147.7, 140.9, 128.1, 123.9, 55.5, 42.9, 12.5; IR (cm\(^{-1}\)) 2941, 1757, 1575, 1515, 1398, 1346, 1108, 858, 698; HRMS [ESI (m/z)] 225.08753, found: 225.08874; [\(\alpha\)]\(^D\) = +16.8 (c 0.975, H\(_2\)O).

*ee and d.r. of this batch were not determined, for a stereoselective synthesis See Chapter 2.
(S)-2-((S)-Amino(4-nitrophenyl)methyl)hexanoic acid (24)

To a solution of (S)-2-((S)-4-methoxyphenylamino)-4-nitrophenyl)methyl)hexan-1-ol (17) (0.10 g, 0.28 mmol) in MeCN/H₂O (1:1, 5 mL) were added H₂SO₄ (1M, 0.28 mL) and periodic acid (63.8 mg, 0.28 mmol). After stirring for 3.5 h, Na₂Cr₂O₇; 2H₂O (42 mg, 0.14 mmol) and periodic acid (319 mg, 1.40 mmol) were added and the mixture was stirred for an additional 19.5 h. The resulting reaction mixture was washed with DCM (3 × 10 mL). After purification via ion exchange chromatography, the product was obtained as a white powder (252 mg, 97%). ¹H NMR (D₂O, 300 MHz) δ (ppm) 8.21 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 9.0 Hz, 2H), 4.43 (d, J = 9.3 Hz, 1H), 2.79–2.71 (m, 1H), 1.54 (m, 2H), 1.25 (m, 4H), 0.78 (m, 3H); ¹³C NMR (D₂O, 75 MHz): δ (ppm) 129.1, 124.9, 57.4, 53.8, 29.5, 29.2, 22.5, 13.7. (quaternary carbons invisible due to low solubility of product in D₂O; IR (cm⁻¹) 3748, 2360, 2332, 1522, 1347, 668, 415; HRMS [ESI (m/z)] calcd for C₂₀H₁₄NO₂ (M+H)⁺ 267.13381, found: 267.13448, [α]D₂₀ +11.5 (c 0.38, DMSO).

(5)-2-((S)-Amino(4-cyanophenyl)methyl)hexanoic acid (25)

To a solution of 4-((15S,21S)-2-(hydroxymethyl)-1-(4-methoxyphenylamino)hexyl)benzonitrile (19) (0.1 g, 0.3 mmol) in MeCN/H₂O (1:1, 5 mL) were added H₂SO₄ (1M, 0.3 mL, 0.3 mmol) and periodic acid (63.4 mg, 0.30 mmol). After stirring for 3.5 h, Na₂Cr₂O₇; 2H₂O (45 mg, 0.15 mmol) and periodic acid (342 mg, 1.50 mmol) were added and the mixture was stirred for an additional 19.5 h. The resulting reaction mixture was washed with DCM (3 × 10 mL). After purification via ion exchange chromatography, the product was obtained as a brown powder (55.4 mg, 75%). ¹H NMR (D₂O, 300 MHz) δ (ppm) 7.73 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.30 (d, J = 9.3 Hz, 1H), 2.72–2.64 (m, 1H), 1.52 (m, 2H), 1.22 (m, 4H), 0.78 (m, 3H); ¹³C NMR (D₂O, 75 MHz): δ (ppm) 133.7, 128.6, 57.7, 54.3, 29.6, 29.2, 22.5, 13.7 (quaternary carbons invisible due to low solubility of product in D₂O; IR (cm⁻¹) 3748, 2360, 2339, 1558, 1540, 1507, 668, 418; [α]D₂₀ −1.8 (c 0.375, DMSO).

(2S,3R)-3-Amino-2-methyloctanoic acid (26)

To a solution of (2S,3R)-3-(4-methoxyphenylamino)-2-methyloctan-1-ol (21) (400 mg, 1.50 mmol) in MeCN/H₂O (1:1, 20 mL) were added H₂SO₄ (1M, 1.5 mL, 1.5 mmol) and periodic acid (342 mg, 1.50 mmol). After stirring for 16 h, Na₂Cr₂O₇; 2H₂O (22 mg, 0.075 mmol) and periodic acid (1.71 g, 7.50 mmol) were added. The mixture was stirred for an additional 3 h and washed with DCM (3 × 50 mL). After purification via ion exchange chromatography, the product was obtained as a white powder (252 mg, 97%). ¹H NMR (D₂O, 300 MHz) δ (ppm) 3.43 (m, 1H), 2.60 (m, 1H), 1.66–1.64 (m, 2H), 1.35 (m, 6H), 1.18 (d, J = 7.2 Hz, 3H), 0.89 (br s, 3H); ¹³C NMR (DMSO-d₆, 75 MHz): δ (ppm) 176.7, 52.0, 31.1, 30.1, 24.8, 21.9, 13.9, 11.7; IR (cm⁻¹) 2927, 2867, 1564, 1400, 1364, 1263, 1167, 1107, 734, 703; HRMS [ESI (m/z)] calcd for C₁₀H₁₅NO (M+H)⁺ 174.14940, found 174.14928.
(2S,3S)-3-Amino-2-methyl-3-phenylpropanoic acid (27)

Under an inert atmosphere: To a solution of (2S,3S)-3-((4-methoxyphenyl)amino)-2-methyl-3-phenylpropan-1-ol (22)* (5.99 g, 22.1 mmol) in 1:1 acetonitrile/water (150 mL) were added H₂SO₄ (1M, 22.1 mL, 22.1 mmol) and periodic acid (5.04 g, 22.1 mmol) and the resulting mixture was stirred for 1h. Subsequently, Na₂Cr₂O₇·2H₂O (0.33 g, 1.1 mmol) and periodic acid (25.2 g, 110.5 mmol) were added. After stirring for 16 h, the dark brown mixture was diluted with DCM (3 × 80 mL). After purification via ion exchange chromatography (DOWEX 50W × 8) the product was obtained as off-white crystals (3.142 g, 79% yield). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.47 (m, 5H), 4.46 (d, J = 7.2 Hz, 1H), 3.05 (m, 1H), 1.28 (d, J = 6.9 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 178.9, 134.6, 126.7, 128.6, 57.0, 44.9, 13.3; IR (cm⁻¹): 2972, 1562, 1454, 1398, 1359, 1074, 755, 706; HRMS [ESI (m/z)]: calcd for C₇₇H₅₇N₂O₇: 180.10245, found: 180.10176; [α]D 20° = 9.5 (c 0.840, H₂O).

*ee and d.r. of this batch were not determined, for a stereoselective synthesis, see Chapter 2.

(2R,3S)-3-((4-Methoxyphenyl)amino)-2-methyloctan-1-ol (32)

A solution of p-anisidine (1 g, 8.12 mmol) and hexanal (1.998 mL, 16.24 mmol) in EtOAc/NMP (40 mL, 7:1) was stirred for 15 min. The EtOAc was evaporated under reduced pressure. The reaction mixture was diluted with NMP (5 mL) and cooled to −20 °C. D-proline (187 mg, 1.62 mmol) was added and the reaction was stirred for 10 min. After addition of propionaldehyde (1.415 g, 24.36 mmol) the reaction mixture was warmed to 16 h at −20 °C. NaBH₄ (922 mg, 24.36 mmol) was added and the reaction was quenched with saturated NaHCO₃ (150 mL). The reaction mixture was extracted with n-heptane/EtOAc (3 × 100 mL, 1:1), washed with brine (100 mL), dried (Na₂SO₄), and concentrated. The residue was purified by column chromatography (n-heptane/EtOAc, 0 → 25%) to afford 19 (600 mg, 28%) as a brown oil. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 6.77 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.7 Hz, 2H), 3.74 (s, 3H), 3.66 (d, J = 5.4 Hz, 2H), 3.42 (m, 1H), 1.98 (m, 1H), 1.47 (m, 3H), 1.26 (m, 6H), 0.94 (d, J = 6.9 Hz, 3H), 0.86 (m, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 152.5, 142.0, 115.7, 114.9, 66.9, 57.8, 55.7, 37.1, 32.3, 31.8, 22.5, 14.0, 11.1. IR (cm⁻¹): 2928, 1510, 1463, 1232, 1037, 819; HRMS [ESI (m/z)]: calcd for C₉H₈NO₂: (M+H)⁺ 266.21200, found 266.21173. HPLC ee >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min (n-hexane/2-propanol 95/5), retention times 14.2 min for 19 and 15.9 for ent-19; d.r. >19:1 (determined by ¹H NMR); Rf 0.59 (n-heptane/EtOAc, 1:1); [α]D 20° +43.0 (c 0.445, CHCl₃).

(2R,3S)-2-Amino-2-methyloctanoc acid (2R,3S)-29

(2RS)-3-((4-Methoxyphenyl)amino)-2-methyloctan-1-ol (39) (500 mg, 1.884 mmol) was dissolved in MeCN/water (1:1, 10 mL). Aqueous H₂SO₄ (1M, 1.884 mL, 1.884 mmol) and periodic acid (429 mg, 1.884 mmol) were subsequently added. The reaction was stirred for 16 h and Na₂Cr₂O₇·2H₂O (28 mg, 0.094 mmol) and periodic acid (2.15 g, 9.42 mmol) were added subsequently. The reaction was warmed for 3 h. The mixture was washed with DCM (3 × 50 mL). The product was purified with ion exchange column chromatography and obtained via lyophilisation. Yield 212 mg (1.22 mmol, 65%). ¹H NMR (400 MHz, D₂O) δ (ppm) 3.55–3.27
(m, 1H), 2.75–2.52 (m, 1H), 1.76–1.52 (m, 2H), 1.50–1.25 (m, 6H), 1.17 (d, $J = 6.3$ Hz, 3H), 0.95–0.77 (m, 3H).

1H NMR data are in accordance with data obtained for 26 (opposite enantiomer).

6.7 References

TOTAL SYNTHESIS OF LASUBINE II

7.1 Introduction
The quinolizidine skeleton is widely encountered in drug-like compounds and natural products, displaying a large array of biological activities. Quinolizidine-based natural products have been mostly isolated from plants, trees and herbs. Lasubine I (1a) and II (1b, Scheme 1) represent two of these alkaloids and were isolated from the leaves of the Lagerstroemia subcostate Koehne by Fuji et al. in 1978. Synthetic efforts by various groups have resulted in a number of racemic and enantioselective routes to lasubine II. In conjunction with recent work from our group on the total synthesis of quinolizidine-based natural products, and in view of the potentially interesting properties of the lasubines, we set out to develop a new pathway to lasubine II based on the asymmetric proline-catalysed Mannich reaction. We reasoned that the commercial availability of both the D- and L-form of the catalyst would provide an entry to both enantiomers of lasubine II.

7.2 Retrosynthetic analysis
Retrosynthetic analysis of lasubine II (1b) leads to the bicyclic lactam 2 as a suitable precursor, of which the unsaturated ring was projectc to result from ring-closing metathesis of diene 3. We envisioned that the latter compound could be formed via an intramolecular Mannich cyclisation of imine 4, which in turn would be accessible via an asymmetric proline-catalysed Mannich reaction involving acetone, veratryl aldehyde (5) and p-anisidine (6).

Scheme 1 Lasubine I (1a) and retrosynthetic analysis of lasubine II (1b).

7.3 Results
With this plan in mind, we set out to study the intended asymmetric three-component Mannich reaction (Scheme 2), employing D-proline which would lead to the unnatural enantiomer (+)-lasubine II. This reaction was investigated previously by the group of Hayashi, that was unable
to isolate the desired aminoketone with proline as the catalyst. Instead, they used a more expensive protected 4-hydroxyproline derivative. In our hands, careful analysis of the \( \beta \)-proline-catalysed Mannich reaction (20 mol\% \( \beta \)-proline, DMSO, rt) revealed that the product was formed, but accompanied by the formation of enone 9. We discovered that enone 9 was formed under the reaction conditions via elimination of \( \beta \)-anisidine from the desired product 7. Gratifyingly, by employing \( \beta \)-proline as the catalyst and by careful monitoring of the reaction progress by HPLC and quenching the reaction mixture at ca. 50\% conversion, we were able to isolate the \( \left( R \right) \)-aminoketone 7 by precipitation from the reaction mixture as a crystalline solid in 50\% yield and >99\% ee. This crystallisation protocol allowed us to scale up the reaction to 10 g, furnishing the product in the same yield and enantiopurity. The \( \left( S \right) \)-enantiomer was also prepared in comparable yield and selectivity with \( \beta \)-proline as the catalyst.

Scheme 2 Synthesis of 1,3-aminoketone 8.

Subsequently, we deprotected \( \alpha \)-PMP amine 7 employing \( \text{H}_2\text{IO}_6 \) under acidic conditions. Although cleavage to the free amine proceeded smoothly, isolation of the \( \beta \)-amino ketone appeared troublesome due to side-reactions (e.g. condensation) during concentration of the organic layer after workup. This problem was circumvented by formation of the \( \text{HCl} \) salt 8 prior to concentration.

Inspired by our own research on iminium ion type cyclisations, we envisioned that conversion of compound 8 into the corresponding imine 4 should lead to a precursor that would be prone to a Mannich cyclisation. This idea was underlined by work of Davis and co-workers, who carried out similar types of Mannich cyclisations that involved furan nucleophiles. The precursor imine 4 was prepared by condensation of 8 with cinnamaldehyde in the presence of triethylamine as a base to liberate the amino group. The condensation was carried out in 1,2-dichloroethane via repetitive concentration of the reaction mixture under reduced pressure to azeotropically remove water. Because this experiment was conducted in a rotatory evaporator, fresh triethylamine and 1,2-dichloroethane were repeatedly added to the residue after each
concentration step until nearly complete consumption of cinnamaldehyde was observed by HPLC analysis. The Mannich cyclisation was then effected by stirring a solution of the crude imine 4 in 1,2-dichloroethane at 60 °C in the presence of an excess of (+)-camphorsulfonic acid (CSA) to yield piperidone 10 as a single diastereoisomer. It appeared to be crucial to dry the CSA prior to use and conduct the reaction under exclusion of moisture, since imine 4 was extremely prone to acidic hydrolysis. Without purification of the resulting 2,6-disubstituted piperidinone 10, the amine function was immediately acylated with vinylacetic acid via standard DCC-coupling, leading to the stable piperidinone 12. The yield of 12 after silica gel purification was 44% over the three steps (Scheme 3).

Scheme 3 Mannich cyclisation, followed by ring-closing metathesis and reduction to give 13.

Similar steps were also carried out by using the l-proline route resulting in ent-10 with a comparable yield and complete diastereoselectivity. HPLC analysis and 1H NMR studies (NOESY, Figure 1) on the purified product ent-10 proved that it was formed as a cis-disubstituted diastereoisomer. This outcome can be rationalised by invoking the chairlike cationic intermediate 11 (Scheme 3), in which both the aryl and the styrenyl substituent will preferentially occupy the least hindered equatorial positions.
To avoid lactam reduction at a later stage, we tried to N-alkylate the crude piperidinone ent-10 with 4-bromo-1-butene to obtain a metathesis precursor without this lactam functionality (Scheme 4). Although mass spectrometry of the reaction mixture showed formation of a product with the expected mass, we were unable to isolate the desired product, possibly due to decomposition.

Scheme 4: Unsuccessful alkylation of ent-10.

Anticipating on the required conversion of the ketone into the alcohol at a later stage in the synthesis, we reduced product ent-10 with LS-Selectride® and observed the formation of products 14a and b in a 14:1 ratio, favouring the product with the desired stereochemistry (Scheme 5). However, alkylation of 14a/b with 4-bromo-1-butene also failed and acylation under the aforementioned conditions only led to poor conversion into the desired amide. The mixture of stereoisomers in combination with the unsuccessful attempts to transform 14a/b into a suitable ring-closing metathesis precursor led us to return to the earlier described route (Scheme 3).
In the D-proline-based route, we observed that treatment of piperidinone \(12\) with the Grubbs 2\textsuperscript{nd} generation catalyst (6 mol%), followed by straightforward hydrogenation of the resulting unsaturated lactam moiety led to the bicyclic structure \(13\) in good overall yield (Scheme 3).

As the next step, we investigated the stereoselective reduction of the ketone functionality of \(13\). Both small and more sterically demanding borohydride reducing agents were evaluated, but all attempts led to undesired stereochemistry at the C4 carbon. This was proven by subsequent LiAlH\(_4\) reduction of lactam \(13\), which provided 2-epi-lasubine II \((15)\) as the exclusive diastereoisomer in all cases, as demonstrated by \(^1\)H NMR data comparison with the literature\(^{3c}\) (Scheme 6). Thus, both carbonyls were reduced simultaneously with LiAlH\(_4\) as the reducing agent. The resulting 2-epi-lasubine \((15)\) was transformed into (+)-lasubine II \((+)-1b\) via a protocol from Zhu \textit{et al.} (Scheme 6).

In addition, cyclisation product \(\text{ent-10}\) was converted via an identical pathway into natural (–)-lasubine II \((–)-1b\) (Scheme 7).

Analytical data of both lasubine II enantiomers were in agreement with literature data (see section 7.6).
7.4 Conclusion
In conclusion, we developed a new stereoselective route to both enantiomers of lasubine II. Key steps include an enantioselective D- or L-proline-catalysed Mannich reaction, which employs commercially available starting compounds, and a diastereoselective Mannich cyclisation.

7.5 Acknowledgements
Ferdi van der Pijl and Dr. Marian Willems are kindly acknowledged for their contribution to this chapter.

7.6 Experimental section
For general remarks, see section 2.8.

7.6.1 (+)-Lasubine II and intermediates

(R)-4-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenylamino)butan-2-one (7)

To a mixture of DMSO (45 mL) and acetone (180 mL) was added 3,4-dimethoxybenzaldehyde (10.5 g, 63.2 mmol), p-anisidine (7.75 g, 62.9 mmol) and D-proline (1.52 g, 13.2 mmol). The resulting mixture was stirred for 24 h at rt. The reaction was quenched by the addition of potassium phosphate buffer (0.5 M, pH 7, 100 mL). The resulting mixture was stirred for another 10 min until a precipitate was formed. The precipitate was isolated by filtration and dried in vacuo to afford 7 (10.3 g, 31.3 mmol, 50%) as a white solid.

$^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 6.92–6.87 (m, 2H), 6.83–6.79 (m, 1H), 6.73–6.67 (m, 2H), 6.55–6.49 (m, 2H), 4.69 (t, $J = 6.5$ Hz, 1H), 4.11 (br s, 1H), 3.85 (s, 6H), 3.70 (s, 3H), 2.89 (d, $J = 6.5$ Hz, 2H), 2.11 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ (ppm) 207.4, 152.4, 149.2, 148.1, 141.0, 135.4, 118.2, 115.4, 114.7, 111.3, 109.5, 55.9, 55.7, 55.2, 51.4, 30.8; IR (cm$^{-1}$) 3382, 1705, 1506, 1251, 1229, 1139, 1022, 819; HRMS [ESI (m/z) calcd for C$_{19}$H$_{24}$NO$_4$ (M+H)$^+$: 330.17053, found: 330.17086; HPLC: ee: >99%, Chiralpak AD-H (250 × 4.6 mm), flow 1.0 mL/min, n-hexane/2-propanol 80/20, retention time: 7: 14.9 min, ent-7: 18.4 min; $R_f = 0.26$ (EtOAc/heptane, 1:1); Mp 152–154 °C; $[\alpha]_{20}^{20}$ +2.7 ($c = 0.93$, CHCl$_3$).

(R)-4-Amino-4-(3,4-dimethoxyphenyl)butan-2-one hydrochloride (8)

To a solution of (R)-4-(3,4-dimethoxyphenyl)-4-(4-methoxyphenylamino)butan-2-one (7) (9.3 g, 28 mmol) in MeCN/H$_2$O (250 mL, 1:1) was added aqueous H$_2$SO$_4$ (1M, 28 mL, 28 mmol) and H$_2$O (66 g, 29 mmol). The mixture was stirred for 4 h at rt. The mixture was washed with DCM (3 × 125 mL) and the resulting aqueous phase was diluted with 125 mL DCM. While stirring the mixture vigorously, the pH of the aqueous layer was brought to 9 via addition of 5 M aqueous KOH. The layers were separated and the aqueous layer was extracted with DCM (3 × 125 mL). The combined organic layers were dried (Na$_2$SO$_4$) and HCl/EtOAc (20 mL) was added. The resulting mixture was concentrated until the product precipitated. The product was isolated by filtration.
and dried in vacuo to afford 8 (3.6 g, 13.9 mmol, 49%) as a pale yellow solid. 1H NMR (CD$_3$OD, 300 MHz) δ (ppm) 7.06–7.04 (m, 1H), 7.00–6.98 (m, 2H), 4.62 (dd, J = 7.3, 6.3 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.20 (d, J = 7.5 Hz, 1H), 3.20 (d, J = 6.1 Hz, 1H), 2.20 (s, 3H); 13C NMR (CDCl$_3$, 75 MHz) δ (ppm) 207.4, 151.3, 151.0, 130.3, 121.1, 113.1, 112.1, 56.6, 56.5, 52.1, 47.6, 30.0; IR (cm$^{-1}$): 3399, 2919, 1709, 1515, 1256, 1143, 1022; HRMS [ESI (m/z)] calcd for C$_{17}$H$_{15}$NO$_3$: 246.11061, found: 246.10966; Rf = 0.38 (MeOH/DCM, 1:1); Mp 158–161 °C; [α]$_D$-21.2 (c 0.94, MeOH).

**Chapter 7**

(−)-4-(3,4-Dimethoxyphenyl)butan-2-one (9)

Analytical data of compound 9, which was isolated as a side product during the development of the route towards (−)-lasubine II: 1H NMR (CDCl$_3$, 300 MHz) δ (ppm) 7.42 (d, J = 16.3 Hz, 1H), 7.08 (dd, J = 2.1 Hz, J = 1.6 Hz, 1H); 7.06 (d, J = 2.1 Hz, 1H), 6.84 (d, J = 10.3 Hz, 1H), 6.57 (d, J = 16.2 Hz, 1H), 3.88 (s, 3H), 3.23 (s, 3H); 13C NMR (CDCl$_3$, 75 MHz) δ (ppm) 198.3, 151.4, 143.3, 143.5, 127.3, 125.3, 123.0, 111.1, 109.6, 56.0, 55.9, 27.3; IR (cm$^{-1}$): 2962, 1664, 1504, 1250, 1018, 976, 805, 557; (M+H$^+$) (LRMS): 207.0; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min, n-hexane/2-propanol 80/20): retention time 7.7 min.

**(2R,6S)-1-Butenyl-2-(3,4-dimethoxyphenyl)-6-styrylpiperidin-4-one (12)**

To a solution of (R)-4-amino-4-(3,4-dimethoxyphenyl)butan-2-one hydrochloride (8) (3.5 g, 13.5 mmol) in dry 1,2-dichloroethane (200 mL) was added triethylamine (1.45 mL, 10.3 mmol) and trans-cinnamaldehyde (1.30 ml, 10.3 mmol). The mixture was concentrated in vacuo. To the residue was added dry 1,2-dichloroethane (150 mL) and triethyamine (1.5 mL, 11 mmol). The mixture was concentrated again in vacuo. Dry 1,2-dichloroethane (150 mL), triethylamine (1.5 mL, 11 mmol) and trans-cinnamaldehyde (0.38 mL, 3.0 mmol) were added to the residue. The resulting mixture was concentrated in vacuo. To the residue was added dry 1,2-dichloroethane (125 mL) and triethylamine (1.5 mL, 11 mmol). The resulting mixture was concentrated in vacuo to afford the crude imine. The crude imine 4 was dissolved in dry 1,2-dichloroethane (360 mL) and the resulting mixture was added dropwise to a stirring solution of dry (−)-10-camphorsulfonic acid (20.2 g, 87 mmol) in dry 1,2-dichloroethane (230 mL) at 60 °C. The mixture was stirred for 5 h at 60 °C under an inert atmosphere. The mixture was washed with an aqueous half saturated NaHCO$_3$ (3 × 350 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo affording the crude piperidinone 10. Vinylic acid (3.8 ml, 45 mmol) and DCC (3.20 g, 15.5 mmol) were dissolved in dry DCM (100 mL) and stirred for 1 h at rt. The precipitate was removed by filtration and the solution was diluted with DCM (500 mL). The crude piperidinone 10 and DMAP (2.38 g, 19.5 mmol) were added to this solution. The mixture was stirred for 16 h under an argon atmosphere at rt. The mixture was washed with aqueous HCl (0.2 M, 500 mL), aqueous NaHCO$_3$ (1 M, 500 mL) and brine (500 mL). The mixture was then dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography (EtOAc/acetone, 1:2–1:1) to afford 12 (2.43 g, 5.99 mmol, 44% over three steps) as a yellow oil. 1H NMR (CDCl$_3$, 200 MHz, T = 323K) δ (ppm) 7.37–7.04 (m, 5H), 6.90–6.70 (m, 3H), 6.51–6.33 (m, 1H), 6.11–5.78 (m, 3H), 5.47 (br s, 1H), 5.26–5.05 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 3.33–3.20 (m, 2H), 3.12 (dd, J = 16.4, 5.2 Hz, 1H), 2.80 (dd, J = 16.5 Hz, 6.8 Hz, 1H) 2.74 (d, J = 5.4 Hz, 2H); 13C NMR (CDCl$_3$, 75 MHz) δ (ppm)
Total synthesis of lasubine II

206.6, 171.3, 149.3, 148.4, 135.8, 133.8, 131.6, 131.3, 129.1, 128.4, 128.0, 126.2, 118.7, 110.7, 110.2, 111.1, 110.0, 55.8, 55.7, 55.0–42.0 (br, 4C), 39.5; IR (cm⁻¹) 1719, 1642, 1516, 1401, 1254, 1146, 1025; HRMS [ESI (m/z)] calcd for C₉H₁₈N₂O₄Na (M+Na)⁺: 428.18378, found: 428.18379; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min n-hexane/2-propanol 80/20, retention times: 12: 12.4 min, ent-12: 11.5 min; Rₛ = 0.18 (EtOAc/heptane, 1:1); [α]D₂⁰ +32 (c 0.095, CHCl₃).

(4R,9aS)-4-(3,4-Dimethoxyphenyl)-3,4-dihydro-1H-quinolizine-2,6(7H,9aH)-dione (16)

To a solution of (2R,6S)-1-but-3-enyl-2-(3,4-dimethoxyphenyl)-6-styrylpiperidin-4-one (12) (2.36 g, 5.82 mmol) in degassed DCM (125 mL) was added Grubbs 2nd generation catalyst (280 mg, 5.7 mol%). The mixture was stirred for 2 h at 40 °C under an inert atmosphere. The mixture was concentrated in vacuo and the residue was purified by column chromatography (MeOH/EtOAc, 0% → 1%) to afford 16 (1.30 g, 43.1 mmol, 74%) as an off-white solid. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 6.75 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1H), 6.63 (ddt, J = 8.2, 2.2, 0.7 Hz, 1H), 6.03 (ddt, J = 9.9, 4.6, 2.7 Hz, 1H), 5.80 (dd, J = 6.2, 2.0 Hz, 1H), 5.73 (dt, J = 9.9, 1.9 Hz, 1H), 4.85–4.70 (m, 1H), 3.82 (s, 3H), 3.01 (s, 3H), 3.19 (dt, J = 21.0, 4.1 Hz, 1H), 3.18 (dd, J = 16.5 Hz, 6.3 Hz, 1H), 3.06 (ddt, J = 21.5, 6.3, 2.8 Hz, 1H), 2.92 (dd, J = 16.4, 2.3 Hz, 1H), 2.63 (d, J = 9.0 Hz, 1H), 2.63 (d, J = 7.9 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 206.0, 168.4, 149.2, 148.2, 133.6, 123.7, 117.0, 111.2, 109.1, 55.8, 55.7, 52.9, 51.9, 45.3, 45.0, 33.4; IR (cm⁻¹) 2359, 1722, 1646, 1515, 1406, 1318, 1255, 1135, 1024; HRMS [ESI (m/z)] calcd for C₂₁H₁₇NO₄Na (M+Na)⁺: 324.12118, found: 324.12128; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min, n-hexane/2-propanol 80/20, retention times: 16: 24.5 min, ent-16: 34.9 min; Rₛ = 0.21 (EtOAc/MeOH, 49:1); Mp 148–151 °C; [α]D₂⁰ +67 (c 0.20, CHCl₃).

(4R,9aR)-4-(3,4-Dimethoxyphenyl)tetrahydro-1H-quinolizine-2,6(7H,9H)-dione (13)

To a solution of (4R,9aS)-4-(3,4-dimethoxyphenyl)-3,4-dihydro-1H-quinolizine-2,6(7H,9aH)-dione (16) (1.19 g, 3.95 mmol) in MeOH (60 mL) was added 10% Pd/C (459 mg, 11 mol%). A hydrogen atmosphere was applied (balloon) and the mixture was stirred for 16 h at rt. The catalyst was removed by filtration over celite and the solution was concentrated in vacuo. The residue was purified by column chromatography (MeOH/EtOAc, 0% → 2%) to afford 13 (885 mg, 2.92 mmol, 74%) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 6.76 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 2.1 Hz, 1H), 6.65 (dd, J = 8.2, 2.2, 0.9 Hz, 1H), 5.84 (dd, J = 5.9, 2.3 Hz, 1H), 4.15–3.98 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.10 (dd, J = 16.7, 6.0 Hz, 1H), 2.94 (dd, J = 16.7, 2.4 Hz, 1H), 2.67–2.53 (m, 2H), 2.46 (d, J = 6.8 Hz, 1H), 2.46 (d, J = 9.2 Hz, 1H), 2.10–1.60 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 206.3, 170.2, 149.1, 148.1, 133.8, 117.0, 111.0, 109.2, 55.8, 55.7, 52.9, 52.2, 45.2, 44.8, 32.1, 30.8, 20.4; IR (cm⁻¹) 2941, 1722, 1639, 1511, 1441, 1410, 1255, 1143, 1024; HRMS [ESI (m/z)] calcd for C₁₅H₁₃NO₃ (M⁺): 304.15488, found: 304.15461; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min, n-hexane/2-propanol 80/20, retention times: 13: 23.9 min, ent-13: 27.8 min; Rᵣ = 0.54 (DCM/MeOH, 9:1); Mp 181–183 °C; [α]D₂⁰ +122 (c 0.26, CHCl₃).
(+)-2-epi-Lasubine II (15)

To a solution of (4R,9aR)-4-(3,4-dimethoxyphenyl)tetrahydro-1H-quinoline-2,6(7H,8H)-dione (13) (787 mg, 2.59 mmol) in dry THF (50 mL) was added LiAlH₄ (496 mg, 13.1 mmol). The mixture was brought to 60 °C and stirred for 3 h under an inert atmosphere. The reaction was quenched by adding H₂O (644 mg, 1.3 mg/mg LiAlH₄), NaOH (15% solution in H₂O, 644 mg, 1.3 mg/mg LiAlH₄) and H₂O (1.61 g, 3.25 mg/mg LiAlH₄). The resulting mixture was stirred vigorously for 10 min and the precipitate was removed by filtration. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (MeOH/EtOAc, 0% → 7.5%) to afford 15 (698 mg, 2.40 mmol, 92%) as a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.10–6.60 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81–3.65 (m, 1H), 2.91 (dd, /j = 11.6, 2.6 Hz, 1H), 2.72–2.63 (m, 1H), 2.05–1.89 (m, 3H), 1.75–1.14 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 147.9, 136.6, 120.0–119.0 (broad, 2C), 111.6–109.0 (broad, 2C), 68.4, 68.2, 60.9, 55.9, 52.9, 45.1, 42.8, 33.6, 26.0, 24.6; IR (cm⁻¹) 3353, 2934, 2354, 1504, 1453, 1259, 1225, 1136, 1030, 738; HRMS [ESI (+)] calcd for C₁₇H₂₆NO₃ (M+H)+: 292.19127, found: 292.18986; Rf = 0.07 (EtOAc/MeOH, 9:1); [α]D²₀ +44 (c 0.56, MeOH).* ¹H NMR data are in accordance with literature values. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 6.98–6.73 (m, 3H), 6.60 (m, 3H), 4.17–4.11 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.31 (dd, /j = 11.2, 3.1 Hz, 1H), 2.77–2.62 (m, 1H), 2.50–2.30 (m, 1H), 1.98–1.18 (m, 12H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 149.0, 147.8, 137.2, 119.7, 110.9, 110.4, 65.0, 63.4, 56.4, 55.9, 55.8, 53.2, 42.8, 40.3, 33.6, 26.1, 24.8; IR (cm⁻¹) 2928, 1591, 1510, 1459, 1258, 1134, 1028; HRMS [ESI (m/z)] calcd for C₁₀H₁₀NO₂ (M+H)+: 292.19127, found: 292.19127; Rf = 0.07 (EtOAc/MeOH, 9:1); [α]D²₀ +44 (c 0.56, MeOH).* ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.10–6.60 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81–3.65 (m, 1H), 2.91 (dd, /j = 11.6, 2.6 Hz, 1H), 2.72–2.63 (m, 1H), 2.05–1.89 (m, 3H), 1.75–1.14 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 147.9, 136.6, 120.0–119.0 (broad, 2C), 111.6–109.0 (broad, 2C), 68.4, 68.2, 60.9, 55.9, 52.9, 45.1, 42.8, 33.6, 26.0, 24.6; IR (cm⁻¹) 3353, 2934, 2354, 1504, 1453, 1259, 1225, 1136, 1030, 738; HRMS [ESI (+)] calcd for C₁₇H₂₆NO₃ (M+H)+: 292.19127, found: 292.19127; Rf = 0.07 (EtOAc/MeOH, 9:1); [α]D²₀ +44 (c 0.56, MeOH).* ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 6.98–6.73 (m, 3H), 6.60 (m, 3H), 4.17–4.11 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.31 (dd, /j = 11.2, 3.1 Hz, 1H), 2.77–2.62 (m, 1H), 2.50–2.30 (m, 1H), 1.98–1.18 (m, 12H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 149.0, 147.8, 137.2, 119.7, 110.9, 110.4, 65.0, 63.4, 56.4, 55.9, 55.8, 53.2, 42.8, 40.3, 33.6, 26.1, 24.8; IR (cm⁻¹) 2928, 1591, 1510, 1459, 1258, 1134, 1028; HRMS [ESI (m/z)] calcd for C₁₀H₁₀NO₂ (M+H)+: 292.19127, found: 292.19127; Rf = 0.07 (EtOAc/MeOH, 9:1); [α]D²₀ +44 (c 0.56, MeOH).*
Total synthesis of lasubine II

Previously reported values: ([α]_20^D = +43.4 (c = 1.0, CHCl_3)); ([α]_20^D = +50 (c = 0.3, MeOH)).

Previously reported value for (-)-lasubine II: [α]_23^D = -47.5 (c 3.7, MeOH).

NMR data are in accordance with literature values.

7.6.2 (-)-Lasubine II and intermediates

Optimised experimental procedures are provided for the synthesis of (+)-lasubine II (Section 7.6.1). Only analytical data are provided for the synthesis of the natural isomer (-)-lasubine II and the intermediates.

(5)-4-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenylamino)butan-2-one (ent-7)

\[\text{H NMR (CDCl}_3, 300 MHz) \delta (ppm) 6.92–6.86 (m, 2H), 6.83–6.78 (m, 1H), 6.73–6.66 (m, 2H), 6.65–6.49 (m, 2H), 4.69 (d, J = 6.5 Hz, 1H), 4.11 (br s, 1H), 3.85 (s, 6H), 3.70 (s, 3H), 2.89 (d, J = 6.5 Hz, 2H), 2.11 (s, 3H); 13C NMR (CDCl}_3, 75 MHz) \delta (ppm) 207.3, 152.4, 149.2, 148.1, 141.0, 135.3, 118.2, 115.3, 114.7, 114.4, 109.5, 55.8(2C), 55.6, 55.2, 51.4, 30.8; IR (cm}^{-1}) 3385, 1708, 1510, 1253, 1235, 1139, 1027, 821; HRMS [ESI (m/z)] calcd for C_{38}H_{46}N_2O_8Na (2M+Na)^+: 681.31518, found: 681.31567; HPLC: ee: >99%, Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min, n-hexane/2-propanol 80/20, retention time: 7: 14.9 min, ent-7: 18.4 min; Mp 147–151 °C; [α]_20^D +2.4 (c 0.41, CHCl_3).

(25,6R)-1-But-3-enoyl-2-(3,4-dimethoxyphenyl)-6-styrylpiperidin-4-one (ent-12)

\[\text{H NMR (CDCl}_3, 300 MHz, T = 324K) \delta (ppm) 7.25–7.16 (m, 3H), 7.13–7.05 (m, 2H), 6.90–6.82 (m, 2H), 6.78–6.73 (m, 1H), 6.49–6.36 (m, 1H), 6.11–5.75 (m, 3H), 5.48 (br s, 1H), 5.25–5.10 (m, 2H), 3.79 (s, 3H), 3.70 (s, 3H), 3.32–3.24 (m, 2H), 3.21 (dd, J = 16.4, 5.2 Hz, 1H), 2.81 (dd, J = 16.4, 6.9 Hz, 1H), 2.75 (d, J = 6.5 Hz, 2H); 13C NMR (CDCl}_3, 75 MHz) \delta (ppm) 206.6, 171.3, 149.3, 148.4, 135.8, 133.8, 131.7 (br), 131.3, 129.1, 128.5, 128.0, 126.2, 118.8 (br) 118.2, 111.1, 110.0 (br), 55.8, 55.7, 55.5–52.0 (br, 4C), 39.5; IR (cm}^{-1}) 1721, 1642, 1516, 1404, 1256, 1143, 1025; HRMS [ESI (m/z)] calcd for C_{25}H_{27}NO_4Na (M+Na)^+: 428.18378, found: 428.18447; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min, n-hexane/2-propanol 80/20); retention times: 12: 12.4 min, ent-12: 11.5 min; Rf = 0.13 (EtOAc/heptane, 1:1); [α]_20^D = -16 (c 0.76, CHCl_3).
(4S,9αR)-4-(3,4-Dimethoxyphenyl)-3,4-dihydro-1H-quinolizine-2,6(7H,9αH)-dione (ent-16)

\[
\text{H}^1 \text{NMR (CDCl}_3, 400 \text{ MHz}) \delta (\text{ppm}) \ 6.75 (d, J = 8.3 \text{ Hz}, 1H), 6.65 (d, J = 2.1 \text{ Hz}, 1H), 6.62 (ddd, J = 0.8, 2.2, 8.3 \text{ Hz}, 1H), 6.02 (ddt, J = 9.9, 4.7, 2.6 \text{ Hz}, 1H), 5.79 (dd, J = 6.2, 2.0 \text{ Hz}, 1H), 5.75–5.69 (m, 1H), 4.81–4.70 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.17 (dd, J = 16.4, 6.3, 1H), 3.06 (ddt, J = 21.5, 6.4, 2.8 \text{ Hz}, 1H), 2.91 (dd, J = 16.4, 2.2 \text{ Hz}, 1H), 2.62 (d, J = 8.9, 1H), 2.62 (d, J = 7.9, 1H); \quad \text{C}^{13} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta (\text{ppm}) \ 206.0, 168.4, 149.1, 148.1, 133.6, 125.6, 124.3, 116.9, 111.2, 109.0, 55.8, 55.8, 52.9, 51.9, 45.3, 45.0, 33.3; \quad \text{IR (cm}^{-1}) \ 1722, 1647, 1515, 1406, 1318, 1256, 1135, 1024; \quad \text{HRMS [ESI (m/z)]} \ \text{calcd for C}_{37}H_{31}N_6O_2Na \} \] (M+Na): 542.17943, found: 542.17904; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min n-hexane/2-propanol 80/20, retention times: 16: 24.5 min, ent-16: 34.9 min; Rr = 0.20 (EtOAc/MeOH, 49:1); Mp 143–147 \textdegree C; [\alpha]_D^{20} +31 (c 0.08, CHCl,).

(4S,9aS)-4-(3,4-Dimethoxyphenyl)tetrahydro-1H-quinolizine-2,6(7H,8H)-dione (ent-13)

\[
\text{H}^1 \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta (\text{ppm}) \ 6.76 (d, J = 8.3, 1H), 6.70 (d, J = 2.0 \text{ Hz}, 1H), 6.66 (ddd, J = 0.8, 2.2, 8.3, 1H), 5.95 (dd, J = 5.8, 2.0 \text{ Hz}, 1H), 4.11–3.98 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.11 (dd, J = 16.7, 6.0 \text{ Hz}, 1H), 2.95 (dd, J = 16.7, 2.4 \text{ Hz}, 1H), 2.73–2.50 (m, 2H), 2.47 (d, J = 6.8, 1H), 2.47 (d, J = 9.1, 1H), 2.10–1.57 (m, 4H); \quad \text{C}^{13} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta (\text{ppm}) \ 206.3, 170.2, 149.1, 148.1, 133.8, 117.0, 111.2, 109.2, 55.9, 55.8, 52.9, 52.3, 45.2, 44.9, 32.1, 30.8, 20.5; \quad \text{IR (cm}^{-1}) \ 1721, 1636, 1514, 1409, 1255, 1141, 1024; \quad \text{HRMS [ESI (m/z)]} \ \text{calcd for C}_{37}H_{31}N_6O_2Na \} \} \] (M+Na): 542.18379, found: 542.18324; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min n-hexane/2-propanol 80/20, retention times: 13: 23.9 min, ent-13: 27.8 min; Rr = 0.51 (DCM/MeOH, 9:1); Mp 174–179 \textdegree C; [\alpha]_D^{20} +90 (c 0.32, CHCl,).

(-)-2-epi-Lasubine II (ent-15)

\[
\text{H}^1 \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta (\text{ppm}) \ 7.10–6.60 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80–3.60 (m, 1H), 2.96–2.80 (m, 1H), 2.78–2.56 (m, 1H), 2.05–0.70 (m, 13H); \quad \text{C}^{13} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta (\text{ppm}) \ 147.9, 136.7, 120.0–119.0 (br, 2C), 111.0–109.0 (br, 2C), 68.5, 68.2, 60.9, 56.0, 55.8, 52.9, 45.2, 42.0, 33.7, 26.1, 24.6; \quad \text{IR (cm}^{-1}) \ 3350, 2933, 1512, 1463, 1262, 1130, 1029, 731; \quad \text{HRMS [ESI (m/z)]} \ \text{calcd for C}_{37}H_{31}N_6O_2Na \} \} \] (M+Na): 529.19127, found: 529.19038; HPLC: Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min, n-hexane/2-propanol 80/20, retention times: 15: 6.8 min, ent-15: 8.2 min; Rr = 0.23 (DCM/MeOH, 9:1); [\alpha]_D^{20} –49 (c 1.7, MeOH). \quad \text{H}^1 \text{NMR data in accordance with literature values.}

(-)-Lasubine II ((-)1b)

\[
\text{H}^1 \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta (\text{ppm}) \ 7.10–6.69 (m, 3H), 4.30–4.10 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.36–3.33 (m, 1H), 2.90–2.60 (m, 1H), 2.43 (br s, 1H), 2.04–0.70 (m, 12H); \quad \text{C}^{13} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta (\text{ppm}) \ 149.1, 147.0, 137.1, 119.8, 110.9, 110.5, 65.0, 63.5, 56.6, 56.0, 55.8, 53.2, 42.6, 40.2, 33.5, 26.0, 24.8; \quad \text{IR (cm}^{-1}) \ 2928, 1514, 1463.
Total synthesis of lasubine II

1260, 1260, 1136, 1027; HRMS [ESI (m/z) calcd for C_{17}H_{26}NO_3 (M+H)^+]: 292.19127, found: 292.19027; \( \alpha \) = 0.06 (EtOAc/MeOH, 9:1); \([\alpha]_D^{20} = -56 (c = 0.32, MeOH)."

'See Section 7.6.1 for literature values of ent-15 and (-)-lasubine II
NMR data are in accordance with literature values\(^{(n)}\) ((+)-lasubine).

7.6.3 Procedure, \(^1\)H NMR, \(^{13}\)C NMR for ent-10

A stock solution was prepared by mixing dry toluene (375 mL), dry DCM (125 mL), and dry triethylamine (10 mL). To a mixture of \((S)-4\)-amino-4-(3,4-dimethoxyphenyl)butan-2-one hydrochloride (ent-8) (6.33 g, 24.4 mmol) and trans-cinnamaldehyde (3.05 mL, 24.2 mmol) was added 150 mL of stock solution. The resulting mixture was concentrated in vacuo. To the residue was added 150 mL stock solution and the resulting mixture was concentrated again in vacuo. 150 mL of stock solution was added to the residue and the resulting mixture was concentrated in vacuo to afford the crude imine. The crude imine was dissolved in dry 1,2-dichloroethane (350 mL) and dry (+)-camphorsulfonic acid (14.39 g, 61.9 mmol) was added. The mixture was stirred for 16 h at 60 °C under an inert atmosphere. The mixture was washed with half saturated aqueous Na_2CO_3 (3 × 350 mL) and concentrated in vacuo. The residue was purified by two successive column chromatography steps (toluene/EtOAc, 4:1 and MeOH/DCM, 1:99, respectively) to afford ent-10. \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) (ppm) 7.41–7.22 (m, 5H), 6.99 (d, \( J \) = 2.0 Hz, 1H), 6.95 (dd, \( J \) = 8.5, 2.0 Hz, 1H), 6.85 (d, \( J \) = 8.2 Hz, 1H), 6.61 (d, \( J \) = 15.9, 7.3 Hz, 1H), 3.97 (dd, \( J \) = 10.8, 3.9 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.73 (dddd, \( J \) = 9.8, 7.3, 4.9, 0.83 Hz, 1H), 2.61–2.45 (m, 4H). \(^{13}\)C NMR (CDCl₃, 75 MHz) \( \delta \) (ppm) 207.9, 149.2, 148.7, 136.4, 135.2, 131.3, 130.5, 128.6, 127.9, 126.4, 118.7, 111.2, 109.6, 60.7, 59.3, 56.0 (2C), 50.4, 48.0; \( \alpha \) = 0.18 (toluene/MeAc, 4:1).

7.7 References

Chapter 7


REFLECTION
8.1 Ultimate Chiral Technology

The research project Ultimate Chiral Technology was performed within a consortium of industrial and academic partners. Industry showed a great interest in the development of new industrially applicable routes towards multi-chiral centre compounds. The large scale accessibility of all stereoisomers of these chiral building blocks was considered important to custom manufacturing of pharmaceuticals (and pharmaceutical intermediates) since druglike molecules increasingly carry multiple chiral centres. To this end the consortium set the objective to develop new chiral technologies for the synthesis of these high value targets. The newly developed proline-catalysed Mannich reaction was considered a promising approach to the industrial synthesis of optically pure 1,3-amino alcohols and heterocycles. We identified the following three challenges for rendering the organocatalysed Mannich reaction applicable to the industrial synthesis of multichiral centre compounds:

1. Is it possible to find a cost-efficient and a more environmentally friendly alternative for the commonly used ceric ammonium nitrate (CAN) deprotection of the N-PMP group?
2. Can we identify industrially attractive methods to transform chiral β-amino ketones into all stereoisomers of the corresponding 1,3-amino alcohols?
3. Can we transform Mannich products into other valuable (stereoisomerically pure) compounds?

This thesis contains the results of the efforts to answer these questions.

8.2 Results

The research started with the evaluation of alternative N-deprotection methods, which resulted in the discovery of a new chemical and a new enzymatic method for this transformation. We substituted CAN for electrophilic halogen reagents (Chapter 2) and found that the desired free amines could in most cases be obtained without laborious chromatographic procedures, which is most desirable from environmental and cost perspectives. We developed an enzymatic method for the PMP-group removal using laccases (Chapter 3), but the obtained crude products were not as pure as with the chemical method. Moreover, the employed laccase amounts were high and within the timeframe of this project, we have not been able to evaluate their recycling. From an industrial point of view, the use of trichloroisocyanuric acid (TCCA) could be recommended as the best alternative for CAN-deprotection, because of its extremely low cost and environmental impact. The industrial applicability of the PMP-deprotection by TCCA was further demonstrated by the synthesis of amino acid derivative 5 (Scheme 1) in the pilot plant facility at DSM in Geleen, one of the consortium partners. A one-pot two-step protocol was developed and carried out on 345 g (p-anisidine) scale. The desired product 5 was obtained in ~50% yield and of sufficient purity after TCCA deprotection.
We subsequently set out to diastereoselectively transform β-amino ketones into anti- or syn-1,3-amino alcohols (Chapter 4). After an unsuccessful screening of borohydride reductions, we discovered two catalytic approaches, which can provide all desired stereoisomers. Asymmetric transfer hydrogenation in the presence of an Ir-based homogeneous catalyst gave rise to the formation of anti-1,3-amino alcohols. Short reaction times and low catalyst loadings were sufficient to efficiently allow the β-amino ketones to be diastereoselectively transformed into the corresponding 1,3-amino alcohols. The cheap, practical and easy-to-perform protocol meets the conditions for industrial application. The synthesis of syn-1,3-amino alcohols was achieved through asymmetric hydrogenation with a Rh/BINAP-based catalyst. Despite the extremely high selectivities of this reaction, industrial implementation is presently still hampered due to high catalyst loadings and long reaction times. Future research could include the development of a more active catalyst system with equally high diastereoselectivity.

We have subsequently shown that the proline-catalysed Mannich reaction forms an interesting starting point for the industrial synthesis of two important compound classes, i.e. tetrahydroisoquinolines (Chapter 5) and β-amino acids (Chapter 6). In the final Chapter 7, we have shown that the excellent selectivity of the reaction can be applied for the synthesis of both enantiomers of the natural product lasubine II.

Furthermore, the synthesis of a range of Mannich products using literature procedures was required for our investigations, which provided us with a view on the industrial scope and limitations of the proline-catalysed Mannich reaction. In the early stage of our investigations we encountered difficulties in reproducing previously reported results. Our observed yields and enantio- and diastereoselectivities were often lower than literature values. This initially hampered the progress of our research. Later we found that careful temperature control is required to obtain the desired results (e.g. during the exothermic NaBH₄ reduction), which is a factor that should be taken into account during industrial application. Furthermore, the incriminating racemisation of the acetone-derived N-PMP-protected β-amino ketones during column chromatography and prolonged storage should be avoided by using alternative...
purification methods (such as crystallisation, as was demonstrated in the synthesis of lasubine II) or by performing a consecutive synthetic step prior to purification.

8.3 Conclusions

To our opinion, the results described in this thesis have brought the proline-catalysed Mannich reaction closer to industrial application. It can be considered a realistic option when developing strategies toward target molecules, which contain the β-amino ketone, γ-amino alcohol or β-amino acid structural element. However, the limitations described in Section 8.2 must be taken into account during the process of route scouting. Naturally, the process of determining the best route is a unique process for each individual target compound but we nevertheless feel that our efforts have demonstrated the value of the proline-catalysed Mannich reaction and further established it amongst other chemical transformations.
Summary

In the continuous search for biological activity, there is a clear trend that the complexity of molecules being evaluated in lead discovery research is increasing. This includes an increased focus on small molecules which contain multiple stereocentres, so-called multichiral centre compounds. As a result, the demand for new and efficient enantio- and diastereoselective routes to synthesise such pharmaceutically relevant molecules has increased considerably. In this thesis, it was our goal to evaluate the industrial applicability of the organocatalysed Mannich reaction (Scheme 1), and to explore novel downstream chemistry to synthesise enantiomerically pure 1,3-amino alcohols and heterocycles, representing specific examples of multichiral centre compounds. This research was performed within a consortium of industrial and academic partners, called the Ultimate Chiral Technology project.

We identified the following three scientific challenges for rendering the organocatalysed Mannich reaction applicable to the industrial synthesis of multichiral centre compounds:

1. Develop a cost-efficient and environmentally more friendly alternative for the commonly used ceric ammonium nitrate (CAN) deprotection of the nitrogen protecting \( \text{p}-\text{methoxyphenyl (N-PMP)} \) group
2. Identify industrially attractive methods to transform enantiopure \( \beta \)-amino ketones diastereoselectively into the corresponding 1,3-amino alcohols
3. Transform Mannich products into other high value stereoisomerically pure products

This thesis contains the results of our efforts to meet these challenges. In this perspective, Chapter 1 describes recent developments in the field of organocatalysed Mannich reactions and provides an overview of the current state-of-the-art. It was concluded that despite the increasing number of organocatalytic systems, proline still holds a special position as a cheap and readily available catalyst for the synthesis of a plethora of highly valuable \( \beta \)-amino carbonyl compounds.

In Chapter 2, a novel oxidative method to replace the CAN-mediated removal of the N-PMP group is described. Periodic acid and trichloroisocyanuric acid (TCCA) were identified as particularly effective reagents for the deprotection, requiring only 1 and 0.5 equiv of oxidant, respectively, under acidic conditions to afford the desired products in high yields (Scheme 2).
Scheme 2 Periodic acid- and TCCA-mediated deprotection of N-PMP protected amines.

In addition, we found that this method is applicable for the deprotection of other N-aryl (including o-MeO-, p-HO- and o-HO-phenyl)-protected amines.

Chapter 3 describes a novel enzymatic oxidative deprotection procedure for N-PMP-protected amines involving laccases, which is effective at a pH below 4. Although the yields and purities of the products obtained with the ‘chemical’ deprotection (Chapter 2) are generally higher, the enzymatic procedure can be an alternative method when functional groups are present which do neither tolerate periodic nor trichloroisocyanuric acid.

In Chapter 4, we detail two complementary methods for the hydrogenation of β-amino ketones to the corresponding 1,3-amino alcohols. The anti-products can be obtained through asymmetric transfer hydrogenation, in which 2-propanol is employed as the hydrogen donor and an Ir/α-substituted-amino acid amide complex as the catalyst. Syn-products are accessible by hydrogenation under increased hydrogen pressure in the presence of a Rh-based BINAP catalyst (Scheme 3). In combination with the proline-catalysed Mannich reaction, these methods have appeared powerful tools for the enantio- and diastereoselective synthesis of all four diastereomers of 1,3-amino alcohols.

In Chapter 5, we show that the products of the proline-catalysed Mannich reaction of ethyl glyoxylate-derived N-PMP-protected imines and electron-rich phenylacetaldehydes are, after periodic acid-mediated removal of the N-PMP-protecting group, suitable precursors for the Brønsted acid-catalysed Pictet-Spengler reaction with activated aldehydes. Thus, we have demonstrated a proof of principle of a promising new route to 3,4-disubstituted tetrahydroisoquinolines (Scheme 4).
In Chapter 6, the development of a new and efficient protocol for the synthesis of β-2,3-disubstituted amino acids is described. After formation of N-PMP-protected 1,3-amino alcohols via the asymmetric proline-catalysed Mannich reaction, these compounds can be transformed in high yields into the corresponding valuable free amino acids by treatment with periodic acid and sodium dichromate in a two-step one-pot protocol (Scheme 5). In addition, this new route paves the way for an easier and more scalable access to one of the key building blocks for the synthesis of the naturally occurring aflatoxin production inhibitor dioxidatin A.

Scheme 5 One-pot synthesis of β-2,3-disubstituted amino acids.

In Chapter 7, a new stereoselective route to both enantiomers of lasubine II is disclosed (Scheme 5). Key steps include an enantioselective D- or L-proline-catalysed Mannich reaction, which employs commercially available starting compounds, and a diastereoselective Mannich cyclisation.

Scheme 6 A new stereoselective route to lasubine II.
In Chapter 8, it is contemplated to what extent the aforementioned challenges have been met. It is concluded that the organocatalysed Mannich reaction has the potential to establish itself as an industrial applicable method for the synthesis of target molecules, which contain the β-amino ketone, γ-amino alcohol or β-amino acid structural elements.
Samenvatting

In de voortdurende zoektocht naar nieuwe biologisch actieve verbindingen is een duidelijke trend waarnembaar, waarbij de structuren van de onderzochte moleculen steeds complexer worden en het aantal stereocentra toeneemt. De toenemende interesse in deze zogenaamde multichiral centre compounds zorgt ervoor dat de vraag naar nieuwe, effectieve enantio- en diastereoselectieve routes voor het synthetiseren van deze farmaceutisch relevante moleculen de laatste jaren is toegenomen. In dit promotieonderzoek hebben we ons als doel gesteld om te bestuderen of de organogekatalyseerde Mannich reactie (Schema 1) industriëel toepasbaar is. Tevens hebben we de mogelijkheden onderzocht om de producten van deze reactie om te zetten in enantiomeerzuivere 1,3-aminoalcoholen en daarvan afgeleide ringstructuren. Dit onderzoek werd uitgevoerd binnen een consortium van industriële en academische partners, die samen het Ultimate Chiral Technology project vormden.

Schema 1 De organogekatalyseerde Mannich reactie.

Om de organogekatalyseerde Mannich reactie industriëel toepasbaar te maken voor de synthese van enantiomeerzuivere β-aminoketonen en daarvan afgeleide multichiral centre compounds zijn in dit project de volgende drie wetenschappelijke uitdagingen geadresseerd:

1. Het ontwikkelen van een goedkoop en duurzaam alternatief voor het gebruik van ceriumammoniumnitraat als reagens voor de ontscherming van N-PMP-beschermde aminen
2. Het ontwikkelen van methoden om enantiomeerzuivere β-aminoketonen diastereoselectief om te zetten in de overeenkomstige 1,3-aminoalcoholen
3. Het omzetten van Mannich producten in andere klassen hoogwaardige druglike producten

In dit proefschrift wordt beschreven hoe deze uitdagingen zijn opgepakt en welke resultaten hierbij zijn behaald. Het inleidende Hoofdstuk 1 beschrijft de recente ontwikkelingen op het gebied van organogekatalyseerde Mannich reacties. Hieruit wordt duidelijk wat momenteel de mogelijkheden en beperkingen zijn van deze reactie. Proline blijkt, als een van de eerst ontdekte organokatalysatoren voor de Mannich reactie, nog steeds een bijzondere positie te hebben in het veld. De lage prijs en goede verkrijgbaarheid maken proline nog altijd van waarde voor de synthese van een keur aan sterk gefunctionaliseerde β-aminocarbonylverbindingen.
In **Hoofdstuk 2** wordt een nieuwe oxidatieve ontschermingsmethode van de N-PMP-groep beschreven. De oxidatiemiddelen perjoodzuur en trichloorisocyanuurzuur, waarvan respectievelijk slechts 1 en 0,5 equivalent nodig was, bleken efficiënt te werken onder zure omstandigheden om de gewenste producten in hoge opbrengsten te verkrijgen.

![Schema 2](attachment:schema2.png)

**Schema 2** Ontscherming van N-PMP-aminen door middel van perjoodzuur of trichloorisocyanuurzuur (TCCA).

We ontdekten dat deze methode ook toepasbaar was voor de ontscherming van andere elektronenrijke N-aryl-beschermde aminen. Zowel de o-MeO- als de o-HO-fenylgroep konden hiermee goed worden verwijderd.

In **Hoofdstuk 3** wordt beschreven hoe N-PMP-beschermde aminen in aanwezigheid van oxidatieve enzymen, zogenaamde laccases, kunnen worden ontschermd. Door middel van deze methode, die werkt bij een pH lager dan 4, worden de gewenste producten verkregen in een wat lagere opbrengst en zuiverheid dan via de in Hoofdstuk 2 beschreven ‘chemische’ methode. Echter kan de enzymatische methode wel een alternatief bieden voor de chemische variant indien de substraten en/of producten niet bestand zijn tegen perjood- dan wel trichloorisocyanuurzuur.

In **Hoofdstuk 4** wordt uitgezet hoe β-aminoketonen door middel van hydrogenering kunnen worden omgezet in de daaraan verwante 1,3-amino alcoholen. Asymmetrische transferhydrogenering in de aanwezigheid van 2-propanol en een katalysator op basis van iridium en een α-gesubstitueerd aminozuuramide leidt tot de vorming van de overeenkomstige anti-producten. Syn-producten kunnen worden verkregen met behulp van hydrogenering onder verhoogde waterstofdruk. In dit geval werd een op rhodium gebaseerde BINAP-katalysator gebruikt. Door de proline-gelinkte Mannich reactie nu te combineren met elk van de diastereoselectieve hydrogeningsmethoden is een generieke strategie ontwikkeld waarmee de vier mogelijke stereoisomeren van specifieke 1,3-aminoalcoholen kunnen worden gesynthetiseerd.

![Schema 3](attachment:schema3.png)

**Schema 3** Asymmetrische synthese van anti- en syn-1,3-aminoalcoholen.
In Hoofdstuk 5 wordt aangetoond dat de producten van de proline-gekatalyseerde Mannich-reactie van N-PMP-beschermde iminen afgeleid van ethylglyoxylaat met elektronenrijke fenylacetaldehyden, na ontscherming door middel van perjoodzuur, geschikte grondstoffen zijn voor de Brønstedzuur-gekatalyseerde Pictet-Spengler reactie met geactiveerde aldehyden. De methodologie, die in dit hoofdstuk beschreven wordt, biedt een veelbelovende nieuwe route naar 3,4-digesubstitueerde tetrahydroisochinolines (Schema 4).

De ontwikkeling van een nieuwe en effectieve procedure voor de synthese van \( \beta \)-2,3-digesubstitueerde aminozuren wordt beschreven in Hoofdstuk 6. Door behandeling met perjoodzuur en natriumdichromaat kunnen N-PMP-beschermde 1,3-aminoalcoholen, bereid via de asymmetrische proline-gekatalyseerde Mannich reactie, met hoge opbrengsten worden omgezet in de overeenkomstige hoogwaardige vrije aminozuren. De ontscherming en oxidatie van de primaire alcoholen kunnen na elkaar in hetzelfde reactievat worden uitgevoerd zonder tussentijdse opwerking (Schema 5). Met behulp van deze methode kan ook één van de aminozuurbouwstenen van diocatine A op een eenvoudigere en meer opschaalbare manier worden gemaakt dan tot nu toe is beschreven. Diocatine A is een in de natuur voorkomende remmer van de productie van aflatoxines.

In Hoofdstuk 7 wordt uiteengezet hoe met de proline-gekatalyseerde Mannich reactie van commercieel verkrijgbare grondstoffen als uitgangspunt en een diastereoselectieve cyclisatie op een later moment, beide enantiomeren van lasubine II afzonderlijk kunnen worden
gesynthetiseerd. Het gebruik van L-proline als katalysator leidt uiteindelijk tot de synthese van het in de natuur voorkomende (-)-enantiomeer (Schema 6).

Schema 6 Een nieuwe stereoselectieve route naar lasubine II.

In Hoofdstuk 8 wordt geëvalueerd in hoeverre de doelstellingen van het project zijn gehaald. Na een terugblik op de eerder genoemde wetenschappelijke uitdagingen is de conclusie dat de organogekatalyseerde Mannich reactie de mogelijkheid biedt om zich in de toekomst te bewijzen als een industrieel toepasbare methode voor de synthese van doelmoleculen met een β-aminoketon-, γ-aminoalcohol- of β-aminozuurmotief in hun structuur.
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Jorge
List of publications and patents

Curriculum Vitae

Jorge Verkade was born in Eindhoven, the Netherlands in 1980 and was raised in Sint-Oedenrode. He attended Gymnasium Beekvliet (Sint-Michielsgestel, 1992-1998) and subsequently studied Chemistry at the Catholic University Nijmegen (later Radboud University Nijmegen) and performed his major traineeship in the group of prof. dr. F. P. J. T. Rutjes under supervision of dr. ir. B. W. T. Gruijters (title: *A non-covalent linking concept through self-complementary quadruple hydrogen-bond formation*). A minor industrial traineeship (subject: peptide synthesis) was performed at DSM, Geleen (NL) under supervision of dr. ir. P. J. L. M. Quaedflieg. He obtained his M.Sc. degree (*cum laude*) in 2005. After an additional short stay at DSM, he joined the group of prof. Rutjes as a Ph.D. student. His research was focused on finding new applications and evaluating the industrial viability of organocatalysed Mannich reactions. The results of the project are described in this Thesis. Jorge is currently employed as a Research Associate at SynAffix B.V., focusing at the development of click chemistry and application in site-specific protein conjugation.
Curriculum Vitae
