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Nitrogen-embedding heterocyclic nucleophiles in catalytic asymmetric vinylogous Mannich reactions

Coordinatore: Prof. Marco Mor

Tutore: Prof. Franca Zanardi

Dottoranda: Beatrice Ranieri

Nitrogen-embedding heterocyclic nucleophiles in catalytic asymmetric vinylogous Mannich reactions

Thesis by
Beatrice Ranieri

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Contents

List of schemes

CHAPTER 2

The Mannich reaction: from antipyrine to vinylogy

CHAPTER 3

Silver(I)-catalyzed asymmetric vinylogous Mukaiyama Mannich reactions with pyrrole-based silicon dienolates

CHAPTER 4

Investigations into the asymmetric vinylogous Mannich reaction with 3-alkylidene-2-oxindoles: synthesis of hexahydro-α-carbolines

CHAPTER 5

A short economical and scalable synthesis of homobenzotetramisole and related organocatalysts

List of figures

CHAPTER 2

The Mannich reaction: from antipyrine to vinylogy

CHAPTER 3

Silver(I)-catalyzed asymmetric vinylogous Mukaiyama Mannich reactions with pyrrole-based silicon dienolates

CHAPTER 4

Investigations into the asymmetric vinylogous Mannich reaction with 3-alkylidene-2-oxindoles: synthesis of hexahydro-α-carbolines

CHAPTER 5

A short economical and scalable synthesis of homobenzotetramisole and related organocatalysts

List of tables

List of charts

CHAPTER 3

Silver(I)-catalyzed asymmetric vinylogous Mukaiyama Mannich reactions with pyrrole-based silicon dienolates

Chapter 1

General introduction

"*The aminoalkylation of CH-acidic compounds was described by several authors as early as the 19th century. However, it was Carl Mannich who was the first to recognize the enormous significance of this reaction type, and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. Since then this reaction that now carries his name has developed into one of the most important C-C bond-forming reactions in organic chemistry*."[1] This is the introduction of the famous review on the Mannich reaction "Modern Variants of the Mannich Reactions", probably universally known for the frog on its front cover and the question "What does Carl Mannich have to do with frogs?" Surely the authors knew how to catch chemist readers' attention (maybe not just chemists).

The review was written at the end of the XX century, now someone could argue that it is quite outdated. I would not define it in this way; instead I would like to rewrite the question: *what does Carl Mannich have to do with…?* This question does not want to represent the uncertainty of our current time or of the writer but it wants to induce the reader to consider the great impact of this simple and elegant reaction. Its importance is well witnessed by many aspects of life's chemistry; from nature to medicinal compounds, plant protection, and paint and polymer chemistry.[2]

[1] Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044.
[2] a) Tramontini, M.; Angiolini, L. *Mannich-Bases, Chemistry and Uses*, CRC, Boca Raton, FL, **1994**. b) Tramontini, M.; Angiolini, L.; Ghedeni, N. *Polymer* **1988**, *29*, 771 *46*, 1791.

The aim of this *philosophiae doctor* thesis is not to celebrate Carl Mannich and describe in details all the latest developments and applications of his discover but instead it will focus on the *vinylogous Mannich reaction*- a logical extension.

The research group has always been interested in developing vinylogous reactions[3] and this reactivity can be applied to the Mannich addition as well. Furthermore in the recent years *asymmetric catalysis* has seen a growing interest in synthetic chemists' community because of its interdisciplinary impact.[4] The goal was thus to merge these concepts and trend in order to develop valuable and solid protocols for *Catalytic Asymmetric Vinylogous Mannich Reactions.*

In chapter 2 a literature state of the art is reported. The first pages describe the Mannich reaction, from its discover to recent developments; in this general part, noteworthy examples are briefly illustrated. The second section is dedicated to the vinylgous Mannich reaction, being the major topic of this philosophical doctorate degree. Particular emphasis is given to catalytic asymmetric versions.

In chapter 3 the project on catalytic asymmetric Mukaiyama Mannich reaction is illustrated. We focused our attention on pyrrole-based silicon dienolates as donors, abling to build 1,2-diaminated scaffolds, important motifs in organic synthesis.[5] Two different protocols for aromatic and alkyl-substituted imines have been developed. Therein, the optimization, the acceptor scope and the stereochemical assessment are discussed.

In chapter 4 the ongoing project on 3-alkenyl-2-oxindoles as new donor matrices for catalytic asymmetric vinylogous Mannich reaction is described. 3-Alkenyl-2-oxindoles are interesting chemical scaffolds

[3] a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.

[4] a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis I-III*, Springer-Verlag Berlin Heidelberg **1999**. b) Halpern, J.; Trost, B. *PNAS*, **2004**, *101*, 5347. c) *The growing impact of asymmetric catalysis, Aldrichimica Acta* **2007**,vol. 40 no. 3.

[5] (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. (c) Viso, A.; de la Pradilla, R. F.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167. (d) Saibabu Kotti, S. R. S; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101

occurring in Nature and medicinal chemistry as well. In order to demonstrate their synthetic versatility, the first effort towards the synthesis of 2,4-disubstituted perhydro-α-carbolines is reported.

Chapter 5 is dedicated to the work made in Professor Daniel Romo group at Texas A&M University during the period as PhD visiting student. The aim of the project was the development of a short, scalable and economical synthesis of homobenzotetramisole (HBTM) and related organocatalysts, isothiourea-based compounds which acted as chiral acylating agents.

Chapter 2

The Mannich reaction: from antipyrine to vinilogy

Mitteilung aus dem pharmazeutischen Institut der Universität Berlin.

Ueber ein Kondensationsprodukt aus Formaldehyd, Ammoniak und Antipyrin.

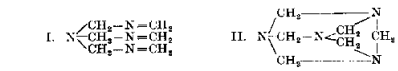
Von C. Mannich und W. Krösche.

(Eingegangen den 23. IX. 1912.)

Formaldehyd reagiert bekanntlich mit Ammoniak anders als die homologen aliphatischen Aldehyde. Als Kondensationsprodukt erhält man nicht einen Körper, der durch Vereinigung von je einem Molekül Formaldehyd und Ammoniak entstanden ist, vielmehr bildet sich ein komplizierter gebautes Molekül, das Hexamethylentetramin, gemäß der Gleichung

$$6\,CH_2O + 4\,NH_3 = 6\,H_2O + (CH_2)_6N_4.$$

Wenn man die folgenden beiden[1], [2]) für Hexamethylentetramin bevorzugten Konstitutionsformeln betrachtet,



so erkennt man, daß jede von ihnen mindestens ein Stickstoffatom enthält, das mit drei Methylengruppen in direkter Bindung steht. Man kann sich daher wohl vorstellen, daß bei der Hydrolyse des Hexamethylentetramins als Zwischenprodukt eine Substanz der Formel: $N(CH_2.OH)_3$ entsteht, die als Tri-methanolamin zu bezeichnen wäre.

In der vorliegenden Abhandlung werden nun eigenartige Kondensationsprodukte aus Formaldehyd, Ammoniak und Substanzen der Antipyrinreihe beschrieben, die als Abkömmlinge des hypothetischen Tri-methanolamins aufzufassen sind.

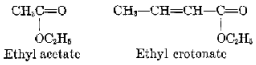
THE PRINCIPLE OF VINYLOGY

REYNOLD C. FUSON

Department of Chemistry, University of Illinois, Urbana, Illinois

Received December 20, 1934

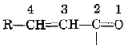
It has long been recognized that, in a molecule containing a system of conjugated double linkages, the influence of a functional group may sometimes be propagated along the chain and make itself apparent at a remote point in the molecule. For example, the methyl group in ethyl crotonate behaves in some respects as it does when it is attached directly to the ester group as in ethyl acetate.



Ethyl acetate Ethyl crotonate

Similarly, the methyl group in *p*-nitrotoluene resembles that in *o*-nitrotoluene, and both of these groups resemble the methyl group in nitromethane, which is attached directly to the nitro group. It is as though the influence of the nitro group were felt even when the methyl group is located in a distant part of the molecule.

Another characteristic property of conjugated systems is that in addition reactions the extremities of the system may be involved even though they be widely separated. The 1,4-addition of certain reagents to α,β-unsaturated ketones and esters is an example. In these cases, carbon atom 4 may be said to usurp the function of carbon atom 2:



Phenomena of the foregoing general types have been effectively correlated by many authors, notably Angeli (2, 3), Lapworth (50), Koenigs (44), Thiele (70), and Claisen (17), who have dealt with the problem primarily on an empirical basis. Others, especially in recent years, have, by reference to theoretical considerations, succeeded in greatly clarifying the problems involved.[1]

2.1 Introduction

The Mannich reaction is a very powerful tool in chemists' hand for carbon-carbon bond installation and simultaneous introduction of a nitrogen moiety. It has been employed successfully in many total syntheses of natural products, *e.g.* alkaloids, and constituted a pivotal step in the preparation of several pharmaceutical compounds.[1] Its great utility is well witnessed by Nature which elegantly orchestrates biosynthetic pathways containing the Mannich transformation as a key maneuver.[1,2]

The aim of this first part of chapter 2 is to give the readers a brief overview of the Mannich reaction from its infancy to the present, shading some light on important developments and applications.

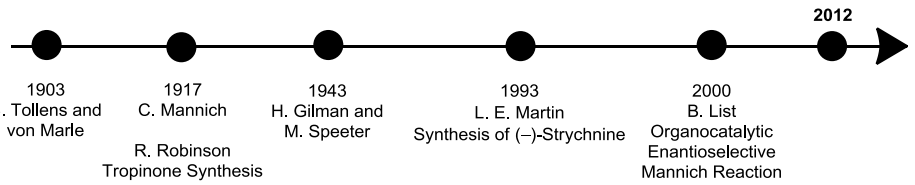


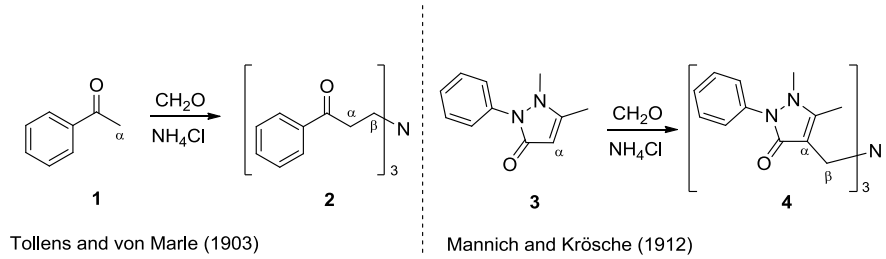
Figure 2.1. Timeline with examples that demonstrate the development of the Mannich reaction.

In Figure 2.1 a timeline regarding the evolution of the Mannich reaction is shown. Obviously, it does not want to be an exhaustive representation; it just shows the focal points that will be treated in this chapter, from the very origins of the Mannich reaction to important achievements in the field of total synthesis and enantioselective catalysis, where this addition represents a key maneuver.

[1] Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1045.
[2] Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, Wiley, **2009**, p. 311.

2.1.1 From the beginning to the definition of the Mannich reaction

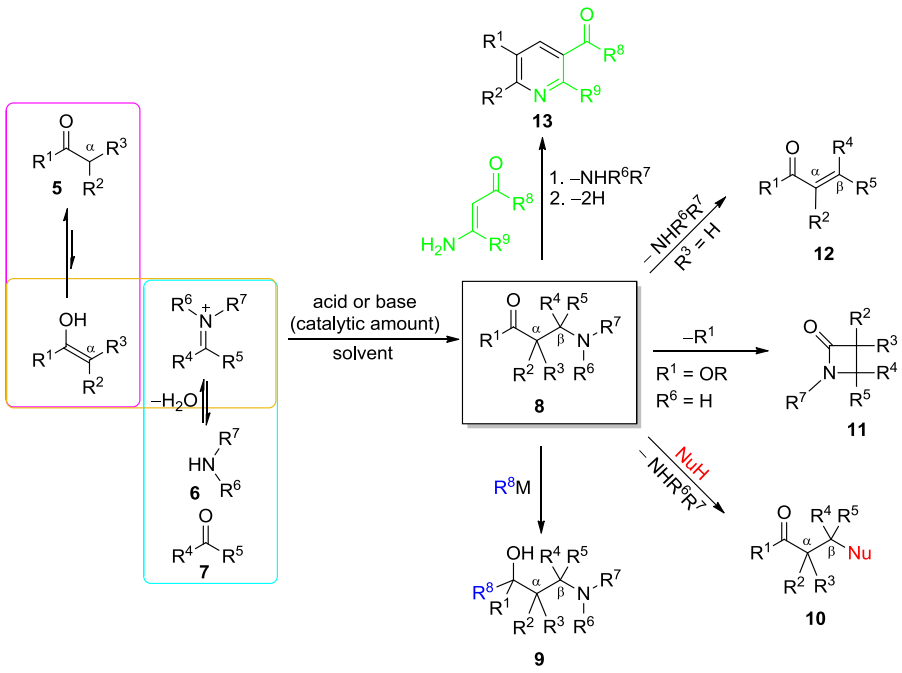
The first scientists who observed the formation of a “Mannich product”, a tertiary amine, were B. Tollens and C. von Marle in 1903.[3] They obtained keto amine **2** from the reaction of acetophenone (**1**) with formaldehyde in the presence of ammonium chloride (scheme 2.1). However, it was 14 years later that the tertiary amine **4** was isolated by Carl Mannich, who exposed antipyrine (**3**) to identical reaction conditions and recognized the generality of this transformation.[4]



Scheme 2.1. First reports on the Mannich Reaction.

Today the Mannich reaction is commonly defined as the addition reaction between an enolizable carbonyl compound of type **5** and the iminium ion derived from a primary or secondary amine **6** (or ammonia) and a non-enolizable carbonyl compound of type **7**.[5] The product is a β-amino carbonyl compound of general structure **8**, generally known as Mannich base (scheme 2.2).

[3] Von Marle, C.; Tollens B. *Ber. Dtsch. Chem. Ges.* (now part of *Eur. J. Inorg. Chem.*) **1903**, *36*, 1351.
[4] a) Mannich, C; Krösche, W. *Arch Farm.* **1912**, *250*, 647; b) Mannich, C. *Arch Farm.* **1917**, *255*, 261; c) Mannich, C. *J. Chem. Soc., Abstract,* **1917**, *112*, i634.
[5] Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Acamdemic Press, **2005**, p. 274

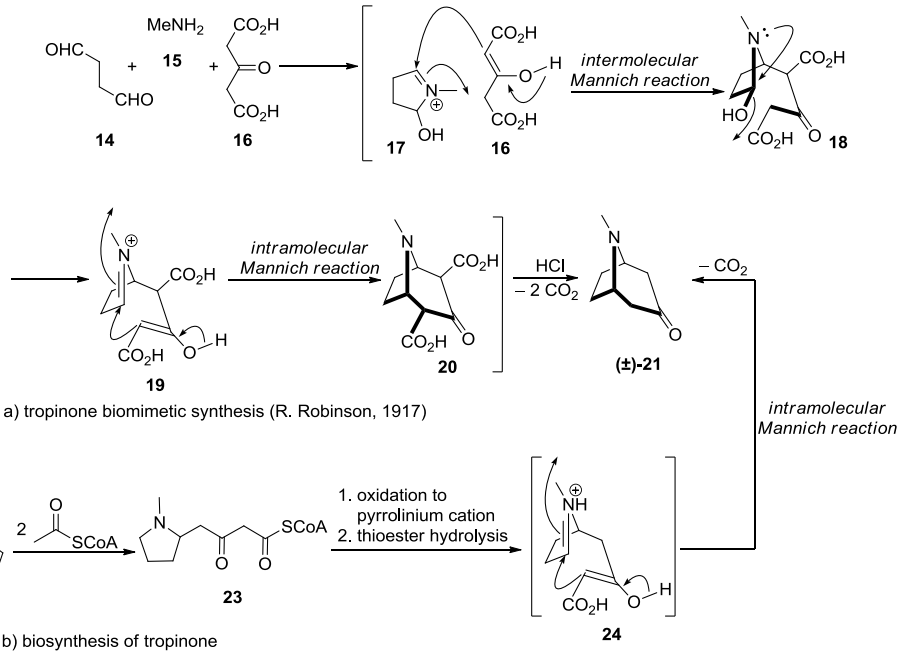


Scheme 2.2. The Mannich reaction and possible further elaborations of its product.

The Mannich bases are versatile scaffolds which –in turn– can be converted into a number of derivatives such as 1,3-amino alcohols **9**, β-functionalized carbonyl compounds **10**, β-lactams **11,** Michael acceptors of type **12** and pyridine heterocycles of general structure **13**. Due to the synthetic flexibility of the Mannich products, which makes them suitable candidates not only in an academic context but also in industry, it comes as no surprise that the organic chemistry community has always been trying to make every effort to improve this transformation at its best.

2.1.2 The Mannich reaction in Nature: the synthesis of tropinone

The very same year the article "*Eine Synthese von β-Ketonbasen*" (Synthesis of β-Ketonic Bases) by C. Mannich was published, R. Robinson reported the publication "*A Synthesis of Tropinone*".[6]



Scheme 2.3. Robinson total synthesis of tropinone and postulated biogenetic pathway.

This total synthesis has long been recognized as a masterpiece of organic synthesis and, for such reason, it has been extensively cited and presented as the first biomimetic total synthesis, pioneering multicomponent reactions and protecting-group free total synthesis.[7]

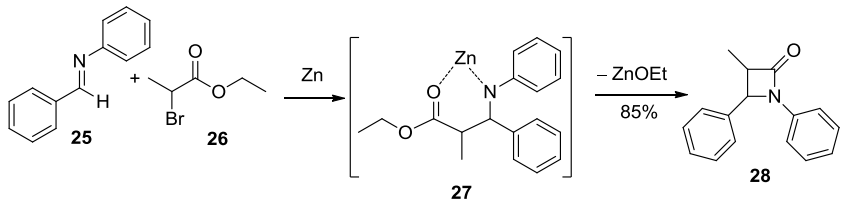
In R. Robinson's elegant synthesis of (±)-tropinone [(±)-**21**], the combination of succindialdehyde (**14**), methylamine (**15**) and acetone dicarboxylic acid (**16**) resulted in the formation of the alkaloid by two

[6] Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762.
[7] For representative reviews see a) Nicolaou, K. C., Vourloumis, D.; Wissinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44. b) Young, I. S.; Baran, P. S. *Nature Chemistry* **2009**, *1*, 193.

consecutive inter- and intramolecular Mannich reactions, key maneuvers of this synthetic strategy (scheme 2.3, part a). Robinson himself, twenty years later,[8] hypothesized that the biosynthesis of tropinone might occur following a similar route with a condensation between pyrrolinium cation **22** and an "acetone analog" (today recognized deriving from two molecules of acetyl-CoA). His proposal is holding remarkably firm nowadays.[2,9]

2.1.3 The introduction of preformed Mannich reagents

Despite the attractive multifaceted nature of Mannich bases of general structure **8**, the classical intermolecular Mannich reaction suffered from a series of disadvantages, such as poliaminoalkylation (when primary amine or ammonia are used) and the limited employment of aldehydes and ketones as nucleophiles. In order to overcome these problems, the modern versions of the transformation adopted the use of preformed Mannich reagents.[10]



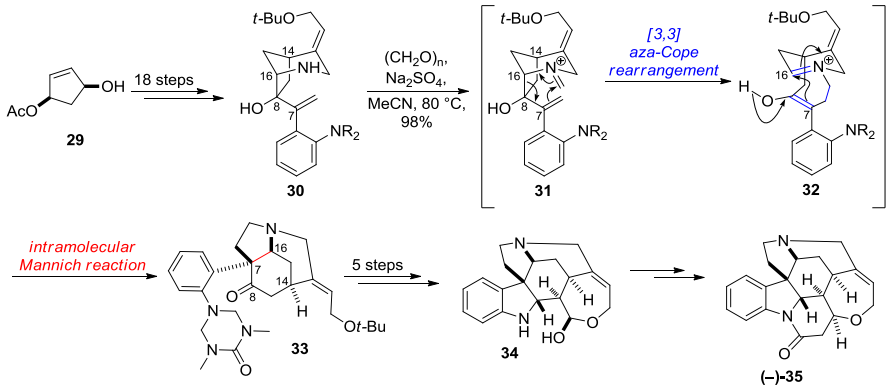
Scheme 2.4. The Mannich reaction with preformed imine *via* Reformatsky-type addition.

In 1943, H. Gilman and M. Speeter reported the first enolate-imine condensation for the synthesis of β-lactams (scheme 2.4).[11] The reaction proceeded with the *in situ* formation of the zinc enolate from compound **26** *via* Reformatsky-type reaction. Intermediate **27** cyclized one-pot to give the desired product **28** in considerable yield.

[8] Robinson, R. *The Structural Relations of Natural Products,* Clarendon Press, Oxford, 1955, p. 59.
[9] Humphrey, A, J.; O'Hagan, D. *Nat. Prod. Rep.* **2001**, *18*, 494.
[10] Kleinman, E. F. *Comprehensive Organic Synthesis, Vol.2* (edited by B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, p. 893.
[11] Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255.

2.1.4 The intramolecular Mannich reaction: synthesis of (–)-strychnine

Strychnine is the major alkaloid isolated from the seeds of the trees *Strychnos nux-vomica* and *Strychnos ignatii.* Beyond its pharmacological properties, this natural compound constituted an important target for synthetic organic chemists.[12] In 1993, L. E. Overman reported the first enantioselective synthesis of strychnine.[13]



Scheme 2.5. Key aza-Cope rearrangement and intramolecular Mannich reaction sequence in the total synthesis of (–)-strychnine.

As depicted in scheme 2.5, the cardinal step was a tandem cationic aza-Cope rearrangement/Mannich cyclization process, called “aza-Cope-Mannich” reaction.[14]

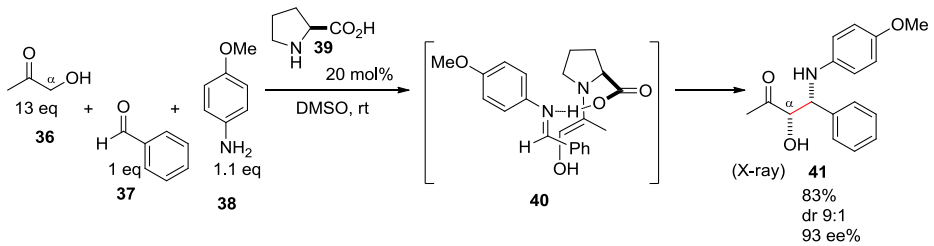
Intermediate **30** was exposed to paraformaldehyde and a dehydrating agent in order to synthesize the iminium ion **31**, which underwent an initial aza-Cope rearrangement to the isomeric iminium ion **32**. Then, the enol reacted with the vicinal electrophilic iminium cation through a highly exothermic Mannich cyclization to give compound **33** which was then

[12] Overman, L. E.; Cannon, J. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 4288.
[13] a) Knight, S. D.; Overman, L. E.; Pairaudeau, G.; *J. Am. Chem. Soc.* **1993**, *115*, 9293 b) Knight, S. D.; Overman, L. E.; Pairaudeau, G.; *J. Am. Chem. Soc.* **1995**, *117*, 5776 c) For a detailed synthetic analysis, see: Nicolaou, K. C.; Sorensen, E. J.; *Classic in Total Synthesis: Targets, Strategies, Methods*, Wiley-VCH, 1996, p.641.
[14] For a detailed explanation, see: Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.

turned into (–)-strychnine **35**. It is noteworthy that this process could be carried out under extremely mild conditions.

2.1.5 Catalytic enantioselective Mannich reaction: the advent of organocatalysis

During the XX century, the increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in pharmaceutical compounds and natural products as well. The need of enantiopure Mannich bases urged organic chemists to develop enantioselective protocols possibly employing catalytic amounts of the chiral stereodirecting reagents. Organocatalysis proved to be an advantageous tool in this regard, due to the use of non-toxic, bench-stable and cheap small chiral molecules. Here, the first organocatalyzed asymmetric Mannich reaction developed by B. List and co-workers is briefly described (scheme 2.6).[15]



Scheme 2.6. The first organocatalytic asymmetric three-component Mannich reaction.

The work was based on *enamine-catalysis*:[16] according to it, (*S*)-proline (**39**) was able to catalyze the *in situ* formation of a chiral enolate equivalent (the enamine) from ketone **36** which subsequently reacted with the imine derived from benzaldehyde (**37**) and primary amine **38**. The Mannich product **41** was obtained in good yield, diastereo- and

[15] a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. b) List, B.; Pojarliev, P.; Biller, W. T.; Martin , H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.
[16] Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B.; *Chem Rev.* **2007**, *107*, 5471.

enantioselectivity in favor of the *syn*-isomer. This type of Mannich bases are valuable scaffolds for further synthetic elaborations.

2.1.6 What's next? Vinylogy and vinylogous reactions

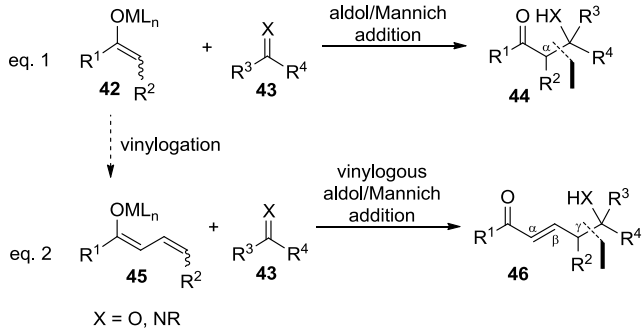
The aim of this first part of the introduction chapter was to give the reader a brief overview of the tremendous progresses of the Mannich reaction. The logical extension of the Mannich addition is the vinylogous version. Vinylogy can be defined as *the transmission of electronic effects through a conjugate system*, concept reported for the first time by R. C. Fuson.[17]

In comparison to the classical Mannich addition, the vinylogous Mannich reaction (VMnR) has been less reported. Despite the sporadic, excellent reports in this field, the potentiality of the VMnR is still to be fully disclosed. The importance of the VMnR in biosynthesis and in total syntheses, and the development of catalytic enantioselective protocols will be highlighted in the next section.

2.2 Introduction

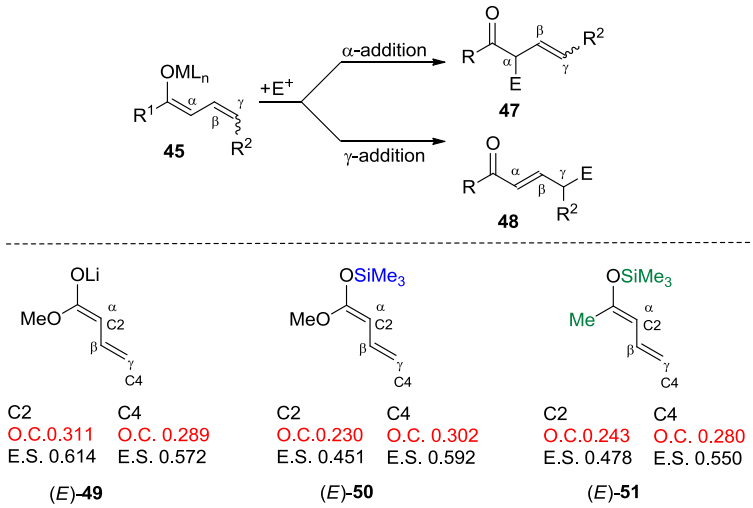
The aldol and Mannich reactions can be extended from the classical versions (eq. 1 scheme 2.7) to their vinylogous counterparts (eq. 2 scheme 2.7) by basically swapping the nucleophilic enolate **42** for dienolate **45**. The vinylogous product **46**, derived from the γ-attack of **45**, possesses one added element of stereogenicity, the double bond; for this reason it constitutes a more attractive target due to possible further manipulation.

[17] Fuson, R. C. *Chem. Rev*. **1935**, *16*, 1.



Scheme 2.7. Classical aldol-type addition and its vinylogous variant.

Because of the ambidentate nature of the dienolate **45**, the bond forming event with a generic electrophilic acceptor can occur at either the "normal" α-position or the "vinylogous" γ-position to give compounds of type **47** or vinylogous products **48** respectively (scheme 2.8).



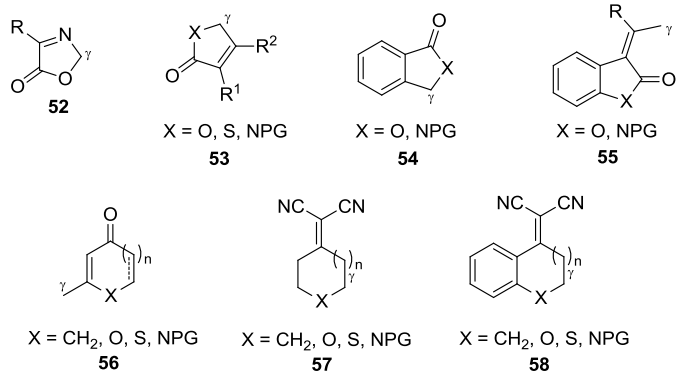
Scheme 2.8. Competitive α- *versus* γ-attack of the vinylogous addition and Fukui indices.

The site selectivity γ *versus* α strictly depends on the M substituent of the dienolate **45** and it is well illustrated by frontier-orbital density calculations by Fukui.[18] As shown in scheme 2.8, for the lithium enolate

[18] a) Fukui, K.; Yonezawa, T.; Nagata, C.; Shingu, H. *J. Chem. Phys.* **1954**, *22*, 1433. b) Denmark, S. E.; Heemstra, Jr. J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682.

(*E*)-**49** the HOMO orbital coefficient (O.C.) and the electrophilic susceptibility (E.S.) are greater at C2 than at C4 which means that the α-addition is preferred over the γ-addition.

In the case of silicon-based dienolates (*E*)-**50** and (*E*)-**51**, the O.C. and E.S. values are greater at C4 than at C2, predicting the preferential formation of the γ-addition products. The vinylogous version of carbon-carbon bond-forming reactions where the nucleophiles are carbonyl-derived silyl dienol ethers is called *vinylogous Mukaiyama reaction* (VMR), *e.g. vinylogous Mukaiyama aldol reaction* (VMAR) and *vinylogous Mukaiyama Mannich reaction* (VMMnR).



52 **53** **54** **55** **56** **57** **58**

Figure 2.2. Possible pro-nucleophiles for vinylogous aldol-type reactions.

In the aldol-related chemistry, the vinylogous addition of **45** to **43** can occur by following two different procedures: a) by preformation (and possibly isolation) of the corresponding silicon dienolate (the Mukaiyama version) as described above; or b) *in situ* sub-stoichiometric generation of the dienolate and subsequent reaction with the electrophile. This latter case is recognized as a *direct vinylogous* execution.

Enlightening examples of bidentate carbon pro-nucleophiles to be used in vinylogous aldol related reactions are reported in figure 2.2. They include heterocyclic structures **52**, **53** and **54**, acyclic 3-alkylidene-2-

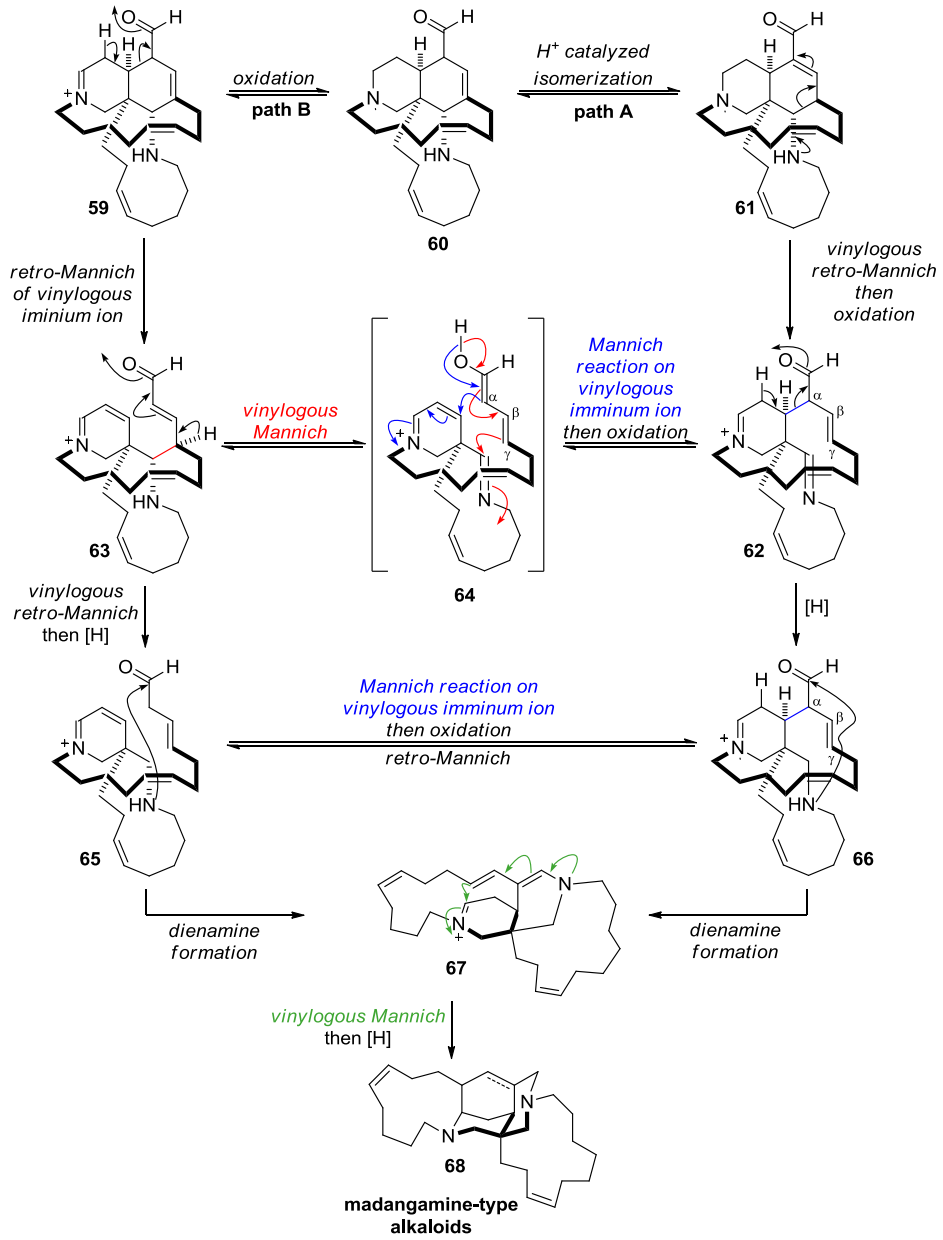
oxindole compounds[19] of type **55**, carbocycles or heterocycles **56**, and dicyanoalkylidene nucleophiles **57** and **58**.[20] Their versatility makes them unique building blocks for the synthesis of natural products, natural-like compounds and totally innovative molecules.

2.2.1 Vinylogous Mannich reaction in Nature

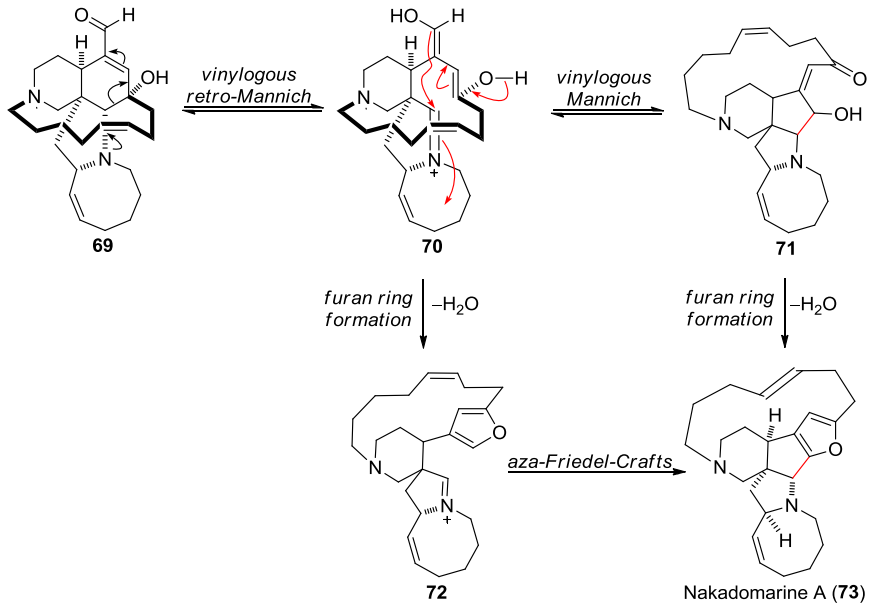
Madangamines are marine alkaloids belonging to the manzamine alkaloid class. Biosynthetically, one hypothesis asserted that they derived from pro-ircinal-type alkaloids **60** *via* two distinct pathways (path A and path B in scheme 2.9) with vinylogous Mannich reactions and 1,4-additions to vinylogous iminium as key steps.[21]

Another interesting compound from the same class is nakadomarine A (**73**) (scheme 2.10). It was postulated that alkaloid **73** could derive from ircinal A (**70**) through a vinylogous Mannich fragmentation of compound **69** and subsequent vinylogous Mannich reaction to compound **71** followed by a final aza-Friedel-Crafts reaction.

[19] Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6200.
[20] a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.
[21] Poupon, E.; Nay, B. *Biomimetic Organic Synthesis vol.1*, Wiley-VCH, 2011, p.208 and references therein.



Scheme 2.9. Postulated biosynthetic pathway of madangamine-type alkaloids.



Scheme 2.10. Biosynthesis of Nakadomarine A.

2.2.2 Application of vinylogous Mannich reaction in syntheses

Great contribution on the application of the vinylogous Mannich reaction in the total synthesis of natural products has undoubtedly been given by S. F. Martin and coworkers.[22]

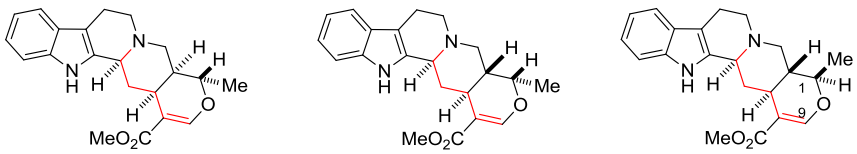


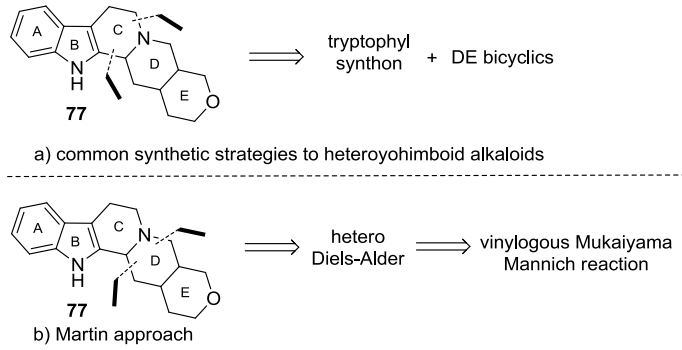
Figure 2.3. Molecules belonging to the heteroyohimboid alkaloid class.

Martin applied the vinylogous Mukaiyama Mannich reaction to the asymmetric synthesis of (–)-tetrahydroalstonine (**74**), (–)-ajmalicine (**75**)

[22] Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895.

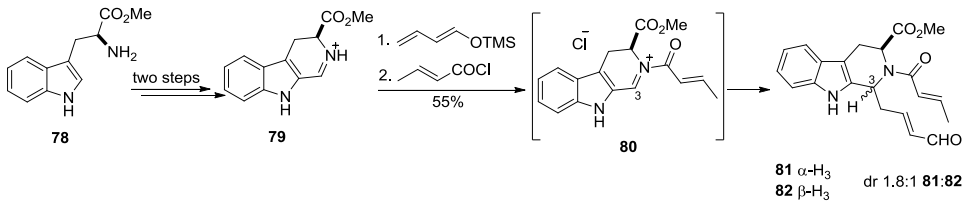
and (+)-19-*epi*-ajmalicine (**76**),[23] heteroyohimboid alkaloids which exhibit adrenergic blocking and vasodilation effects.

His approach differed from the previous common strategies, which outlined the construction of DE rings starting from a previously installed ABC tricyclic core, as outlined by key disconnections in scheme 2.11. Here, key steps for the assembly of **77** were a vinylogous Mannich reaction followed by a hetero Diels-Alder cyclization.



Scheme 2.11. Synthetic approaches towards the heteroyohimboid core.

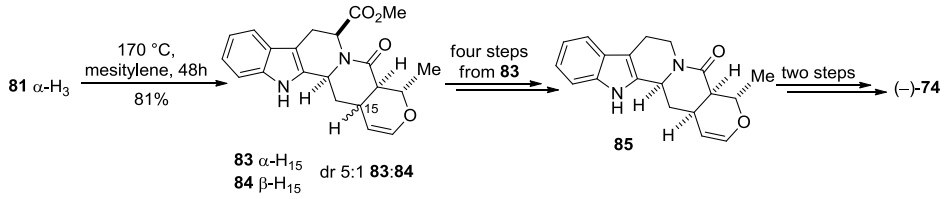
The first strategy to be applied for the construction of the heteroyohimboid skeleton was the vinylogous Mannich reaction between 1-[(trimethylsilyl)oxy]butadiene and the tryptophan-derived β-carboline iminium ion **79** in the presence of crotonyl chloride to afford isomeric compounds **81** and **82** with low diastereoselectivity. The addition proceeded *via* the *in situ* formation of *N*-acyl iminium intermediate **80** which activated C3 towards the attack from the silyl dienolate (scheme 2.12).



Scheme 2.12. VMMnR on iminium ion for the construction of the β-carboline core.

[23] Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60, 3236.*

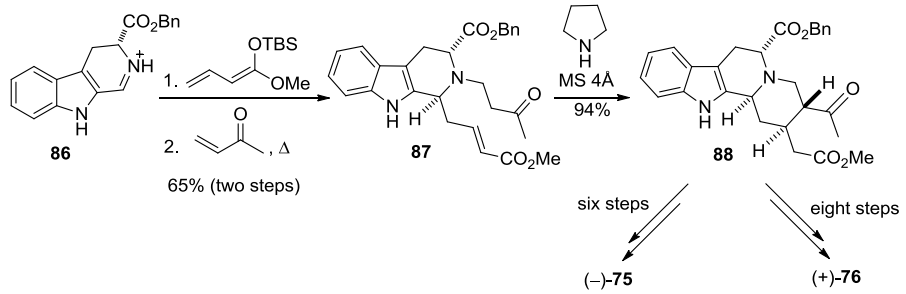
The major diastereoisomer **81** was then treated at high temperature to promote a hetero Diels-Alder reaction and a 5:1 diastereomeric mixture of **83** and **84** was obtained in good yield (scheme 2.13). The pentacyclic structure **83** was subjected to a series of chemical transformations including formation of the carboxylic acid followed by a Barton decarboxylation to **85**, the advanced intermediate to (—)-tetrahydroalstonine (**74**). The synthesis was completed in 10 steps from the readily available L-tryptophan precursor.



Scheme 2.13. Completion of the synthesis of (—)-tetrahydroalstonine (**74**).

Martin decided to apply a similar strategy towards the synthesis of (—)-ajmalicine (**75**) and (+)-19-*epi*-ajmalicine (**76**) (scheme 2.14).

In this case an improved protocol for the vinylogous Mannich reaction was used. In place of the 1-[(trimethylsilyl)oxy]butadiene of the previous addition, a more nucleophilic methyl crotonate-derived silyl ketene acetal was used, which was treated with the β-carboline iminium ion **86**, without the need of forming any reactive *N*-acyl iminium cation intermediate.

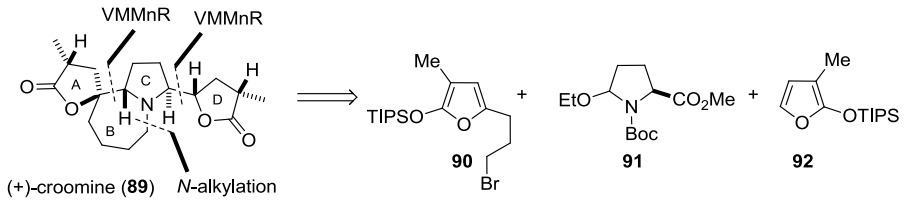


Scheme 2.14. Improvement of the VMMnR for the tricyclic core synthesis.

The reaction proceeded with a virtually complete diastereoselectivity in favor of the *trans* isomer which was then *N*-alkylated with methylvinyl

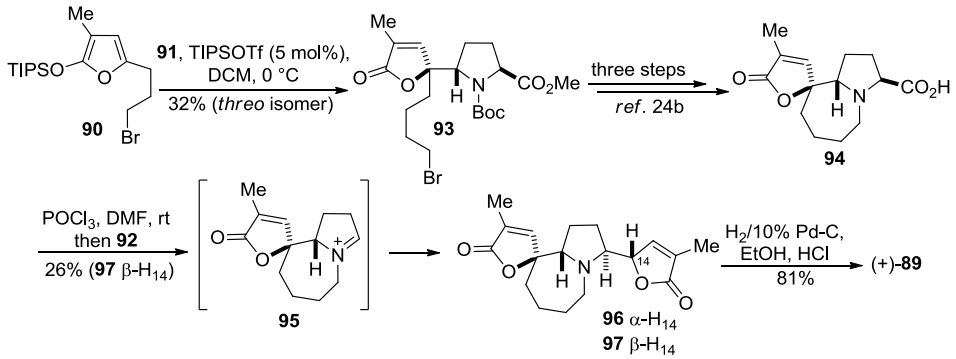
ketone to give compound **87** in good yield. Treatment of **87** with pyrrolidine gave the tetracyclic structure **88**, key intermediate for the synthesis of both (–)-ajmalicine (**75**) and (+)-19-*epi*-ajmalicine (**76**).

Another admirable example of application of the VMMnR in total synthesis of natural products is the total synthesis of *Stemona* alkaloid (+)-croomine from the same group.[24] Croomine is "*the example that perhaps best illustrates the power of VMR as a strategy for alkaloid synthesis* […]", quoting Professor S. F. Martin himself.[22]



Scheme 2.15. Synthetic disconnection of (+)-croomine.

The alkaloid structure **89** (scheme 2.15) could be regarded as a 1-azabicyclo[5.3.0]decane nucleus with two appended γ-lactone rings (A and D rings).



Scheme 2.16. Synthesis of (+)-croomine (**89**).

In Martin's strategy, (+)-croomine was disconnected into three key fragments: silyl dienol eters **90** and **92** and the chiral methoxy-pyrrolidine **91** which served as the electrophilic component *via* two-fold generation of

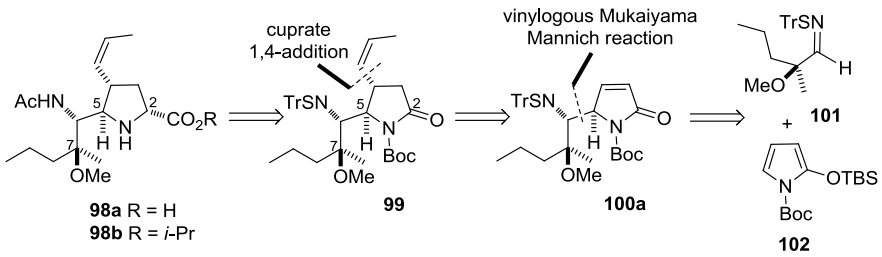
[24] a) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299. b) Martin, S. F.: Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.

iminium ion acceptors for the sequential VMMn reactions of nucleophiles **90** and **92**.

Scheme 2.16 underlines the main steps of the synthesis. The first VMMnR was catalyzed by the Lewis acid triisopropylsilyl triflate which allowed the *in situ* formation of the chiral iminium ion from **91** (not shown). A mixture of isomers was obtained and, fortunately, the desired *threo* isomer **93** crystallized in moderate yet useful yield. The stereochemical outcome of the reaction was explained through an approach of the nucleophile **90** on the iminium ion face opposite to its methyl ester functionality. In a second generation-route of the synthesis,[24b] intermediate **94**, substrate of the second VMMn reaction, was obtained from **93** in three steps. Treatment of **94** with phosphorus(V) oxychloride ($POCl_3$) afforded the iminium ion intermediate **95** that reacted with **92**, furnishing a ca. 2:1 mixture of **96** and **97** as separable isomers. Compound **96** was then subjected to catalytic hydrogenation and delivered (+)-croomine (**89**) as the sole product in notable yield.

The power of the vinylogous Mannich addition reaction is witnessed not only by academia, as illustrated above, but also by the pharmaceutical industry. The scalable synthesis of the influenza neuramindase inhibitor A-315675 **98a** and its pro-drug A-322278 **98b** (scheme 2.17)[25] from two groups of the Abbott laboratories is a clear evidence of the recognized potentiality of the vinylogous Mannich reaction in synthesis and demonstration of a successful merger of knowledge from academia and industry.

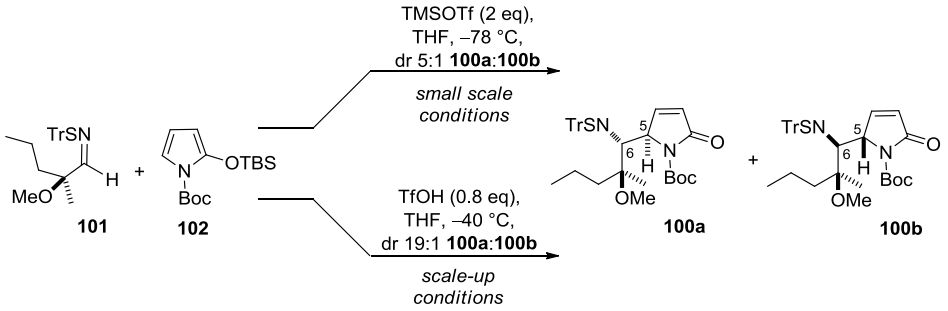
[25] a) Barnes, D. M.; McLaughlin, M. A.; Oie, T.; Rasmussen, M. W.; Stewart, K. D.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 1427. b) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445. c) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian Z.; Wittenberger, S. T. *Tetrahedron Asymm.* **2003***, 14*, 3541.



Scheme 2.17. Retrosynthesis of neuraminidase inhibitors by Abbott Pharmaceutical.

Scheme 2.17 highlights the key disconnections of the retrosynthetic route. The carboxylic acid at the C-2 position was the result of a nitrile reduction installed through a stereoselctive addition of cyanide on an *N*-acyliminium cation from intermediate **99**. The alkenyl side chain at C-4 was appended *via* conjugate addition of a cuprate reagent on pyrrolidinone compound **100** which, in turn, was synthesized by a stereoselective Mannich addition between the chiral α-alkoxy imine **101** and *N*-Boc-2-(*tert*-butyldimethylsilyloxy)pyrrole (TBSOP) (**102**).

Focusing on the VMMnR,[25a,c] after an initial screening of Lewis acids, the authors identified TMSOTf as the best choice in terms of diastereomeric ratio (dr 5:1 in favor of **100a**). During the optimization of reaction conditions, the group observed a slight increase of diastereoselectivity in favor of **100a** as the reaction proceeded, due to the reversibility of the reaction that equilibrated to a thermodynamic mixture. The use of TMSOTf demonstrated to be unsuitable for the reaction scale-up because a significant amount of the imine starting material was recovered and modification of other reaction parameters proved to be unsuccessful. It was therefore suggested that the relatively larger amount of water present in the small scale reaction was responsible for the hydrolysis of TMSOTf, thus leading to the generation of triflic acid (TfOH), able to facilitate the conversion (scheme 2.18).



Scheme 2.18. VMMnR between TBSOP (**102**) and imine **101** on different scale conditions.

This hypothesis prompted them to perform the reaction with triflic acid directly: with 0.8 eq TfOH, TBSOP **102** reacted with imine **101** in a scalable (up to 22 g of **101**) and reproducible vinylogous Mannich reaction to produce the desired compound **100a** as a 19:1 mixture of diastereoisomers. The major diastereoisomer was isolated by crystallization in 80-85% yield and diastereo- and enantioselectivity >99:1.

It is noteworthy that the C5-C6 *threo* diastereoisomers (not shown) were never observed. This high selectivity was justified by a hydrogen bonding interaction in the transition state between the trityl thioimine group and the methoxy oxygen in the aldehyde precursor.[25a]

2.2.3 Catalytic enantioselective vinylogous Mannich reactions

A major breakthrough in asymmetric synthesis during the last four decades has been the application of a chiral enantiopure catalyst to promote the conversion of achiral substrates to chiral enantiopure products. The obvious advantage is the use of small amounts of the chiral catalyst required to generate large quantities of chiral products. The tremendous economic potential of asymmetric catalysis has made it one of the most pursued research fields in the last years. Therefore, it comes

as no surprise that asymmetric catalysis has been applied to the classical Mannich reaction and its vinylogous version as well.

In the effort to point out the achievements of this area of research, the examples shown here are divided based on the catalytic system -whether metal-based or metal-free (organocatalysis)-, and on the nucleophile, in other words, indirect-type additions of silicon dienolates (vinylogous Mukaiyama Mannich reaction, VMMnR) *vs* direct additions of *in situ* generated dienolates (VMnR). Because catalytic asymmetric vinylogous Mannich reactions have been reviewed abundantly in recent reviews[19] and books,[26] for each section only noteworthy examples are taken into account and described scrupulously, whereas all the others are illustrated in a final table.

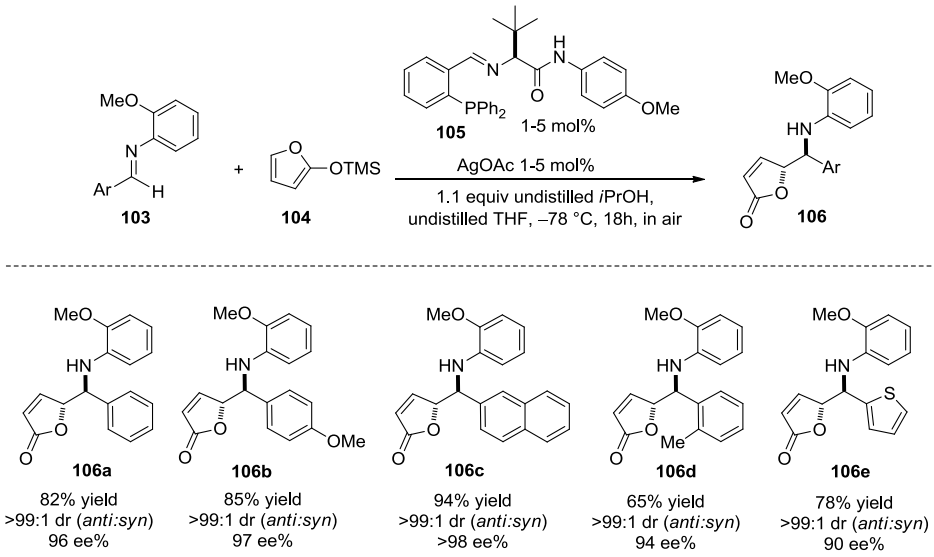
2.2.3.1 Metal-based VMMnR[27, 28a-c, 29, 30a-d, 31, 32]

In 2006 A. H. Hoveyda, M. L. Snapper and co-workers initiated extensive studies on catalytic asymmetric VMMnR of 2-silyloxyfurans based on amino acid-derived phosphine ligand/Ag complex as the catalytic system.[28a-c] In a first paper, they described the reaction with aromatic aldimines as electrophiles, by utilizing chiral ligand **105** in combination with silver(I), *i*-PrOH as additive, undistilled THF as solvent and without the need of inert atmosphere. [28a]

In scheme 2.19 a panel of synthesized compounds using this procedure is reported. The results were notable in terms of both yield, and diastereo- enantioselectivity. Relevant aspects of this methodology

[26] Schneider, C.; Sickert, M. *Chiral Amine Synthesis: Methods, Developments and Applications*. Ed. By T. C. Nugent, Wiley-ICH, 2010, p.157.
[27] Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949.
[28] a) Carswell, E.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7230; b) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961; c) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.
[29] González, A. S.; Arrayás, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335.
[30] a) Yuan, Z.-L.; Jiang, J.-J.; Shi, M. *Tetrahedron* **2009**, *65*, 6001; b) Deng, H.-P.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2009**, *351*, 2897; c) Zhao, Q.-Y.; Yuan, Z.-L.; Shi, M. *Tetrahedron Asymm.* **2010**, *21*, 943; d) Zhao, Q.-Y.; Yuan, Z.-L.; Shi, M. *Adv. Synth. Catal.* **2011**, *353*, 637.
[31] Zhang, Q.; Hui, Y.; Zhou, X.; Lin, L.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2010**, *352*, 976.
[32] Boomhoff, M.; Schneider, C. *Chem. Eur, J.* **2012***, 18*, 4185.

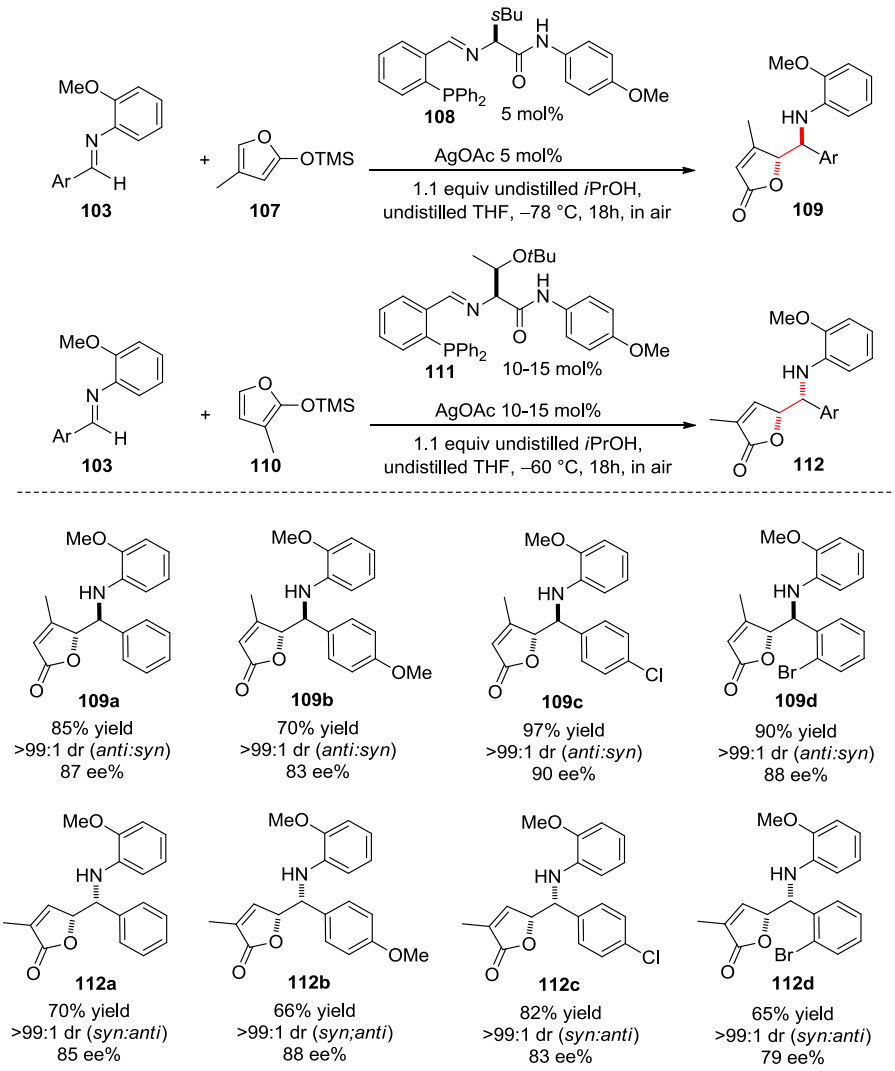
were the presence of *i*PrOH, required for high conversion, and the practicality of the execution, since undistilled solvents and air atmosphere were just needed.



Scheme 2.19. Pioneering studies on Ag-catalyzed asymmetric VMMnR by Hoveyda.

Furthermore, silver acetate (AgOAc) was commercially available and inexpensive, whereas the chiral phosphine ligands such as **105** were easily accessible via a three-step synthesis from diphenilphosphine benzaldehyde and the corresponding *N*-protected aminoacid.

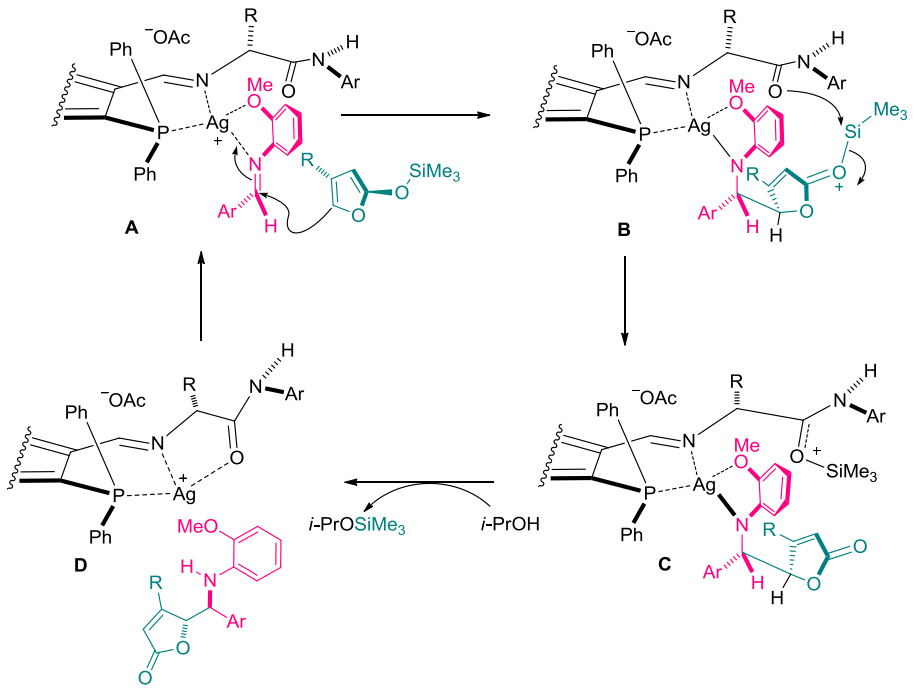
The transformation was also applied to 4- and 3-methyl-substituted silyloxyfurans **107** and **110** (scheme 2.20). The results in terms of yield, diastereo- and enantioselectivity were generally lower with respect to those in scheme 2.19, albeit an increase of the catalyst loading and different chiral ligands were employed. Surprisingly, when nucleophile **110** was used, a reversal of stereoselection was osbserved, with virtually exclusive formation of the *syn*-diastereoisomers.



Scheme 2.20. Effect of the methyl substituent of the nucleophile on Ag-catalyzed VMMnR.

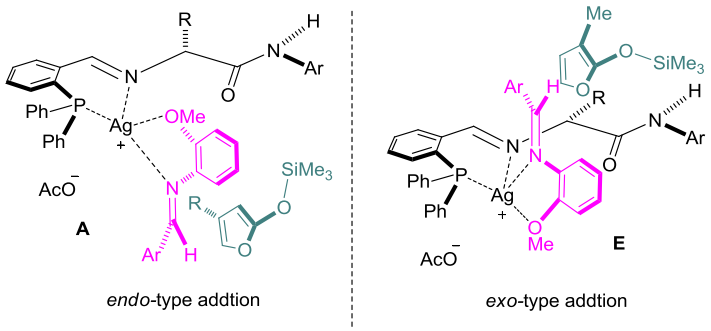
Mechanistically, a pre-association of the silver cation and the chiral ligand in order to form the Lewis acidic chiral complex was needed. The complex was postulated to form a bidentate chelation with aldimine **103** in order to promote the exposure of the *re* face towards the attack from the *si* face of nucleophiles **104** or **107** via an *endo*-type addition (structure A, scheme 2.21). Once **B** was formed, an intramolecular desilylation by

the amide moiety of the chiral ligand would furnish **C**, from which the release of the Mannich adduct and desilylation of the amide functionality could be facilitated by *i*PrOH acting as silicon scavenger.



Scheme 2.21. Mechanistic cycle of the Hoveyda's catalytic system.

The spatial arrangement **A** was not favorable when silyloxyfuran **110** was used.

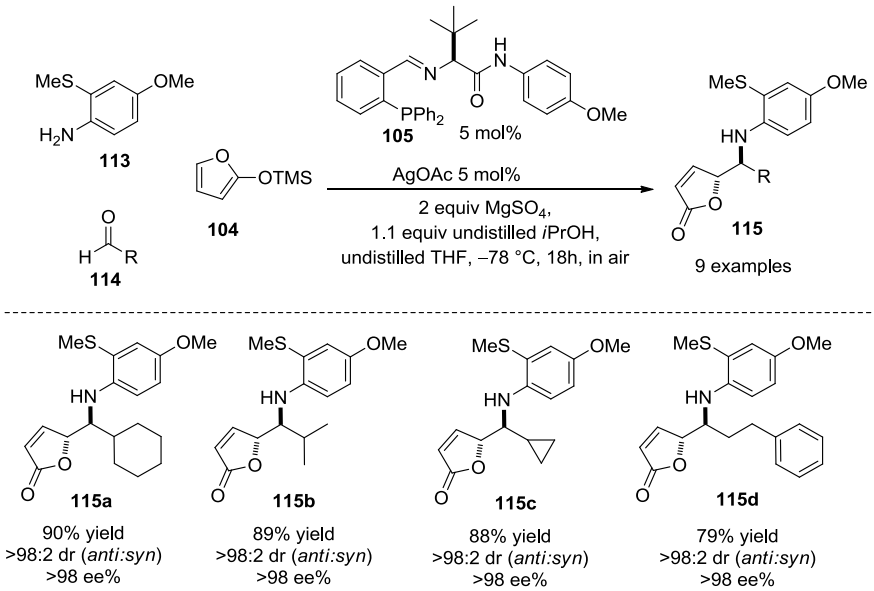


Scheme 2.22. Plausible transition states of the asymmetric Ag-catalyzed VMMnR.

In this case, an *exo*-type addition of type **E**, illustrated in scheme 2.22, might be preferred, in order to avoid steric repulsion between the *o*-anisidine ring of the imine and the methyl groups of the nucleophile.

The silver-based chiral catalytic system was then applied successfully by the same authors during VMMnR additions involving aliphatic aldimines or α-ketoimine esters.[28b,c]

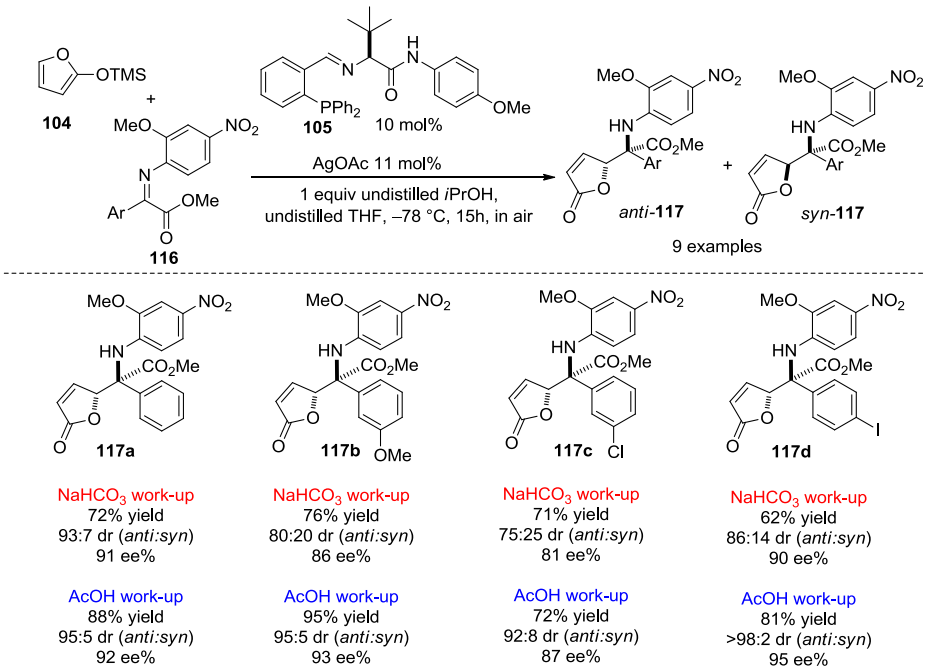
The VMMnR with aliphatic aldimines was performed in a three-component fashion due to the intrinsic instability of this kind of electrophiles.[28b] An initial screening revealed the need of modifying the *o*-anisidine moiety of the imine because of poor results in terms of efficiency and enantioselectivity. Amine **113** bearing a thiomethyl substituent at the *ortho* position and a *p*-methoxy group proved to be the right choice: the *para* methoxy substituent made the *in situ* formed aldimine less electrophilic thus less prone to decomposition, whereas the *ortho* thiomethyl appendage was suggested to create a tighter transition state responsible for improved enantiodifferentiation.



Scheme 2.23. Three-component Ag-catalyzed VMMnR.

Scheme 2.23 illustrates selected examples of this work. Results were generally good in terms of efficiency, while both diastereo- and enantiocontrol were almost complete in favor of products of type *anti*-**115**. Magnesium sulphate acted as a drying agent during the formation of the aldimine, thus facilitating the condensation between amine **113** and the generic aliphatic aldehyde **114**.

When the VMMnR was carried out with α-ketoimine esters **116**, the authors observed slight decrease in diastereo- and enantioselectivities.[28c] They reasoned that this results could be a consequence of inappropriate quenching procedure: the standard aqueous $NaHCO_3$ work-up could not be able to destroy the excess of the nucleophile **104** at –78 °C thus leading to a competitive racemic background during the warm up. The introduction of an acidic work-up resulted in improved results, due to the efficient removal of the unreacted enolsilane at low temperature.



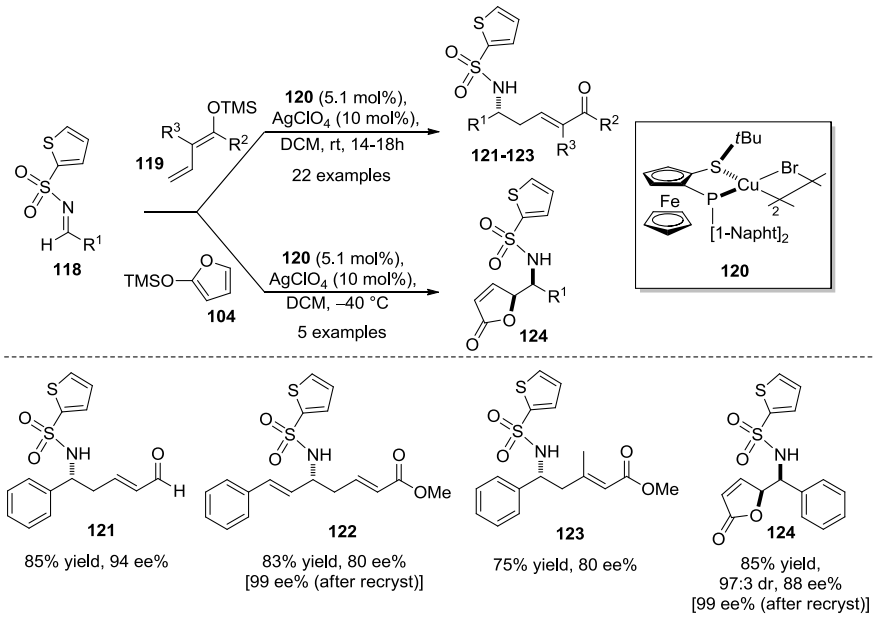
	117a	117b	117c	117d
$NaHCO_3$ work-up	72% yield 93:7 dr (*anti*:*syn*) 91 ee%	76% yield 80:20 dr (*anti*:*syn*) 86 ee%	71% yield 75:25 dr (*anti*:*syn*) 81 ee%	62% yield 86:14 dr (*anti*:*syn*) 90 ee%
AcOH work-up	88% yield 95:5 dr (*anti*:*syn*) 92 ee%	95% yield 95:5 dr (*anti*:*syn*) 93 ee%	72% yield 92:8 dr (*anti*:*syn*) 87 ee%	81% yield >98:2 dr (*anti*:*syn*) 95 ee%

Scheme 2.24. Asymmetric Ag-catalyzed VMMnR on α-keto esters-derived imines.

As depicted in scheme 2.24, swapping basic for acid quenching protocol led to improved results in both diastereo- and enantioselectivities.

Although the meticulous and detailed studies carried out by Hoveyda and co-workers, the Ag-based protocol was limited to cyclic furan-based silicon dienolates.

A broader application was achieved by J. C. Carretero and colleagues in 2008.[29] In their methodology, both cyclic and acyclic silyl dienol ethers participated efficiently in asymmetric VMMn reactions catalyzed by Fesulphos ligand-copper(I) complexes of type **120** (scheme 2.25). After an initial screening where *N*-(2-thienyl)sulphonylimines of type **118** were found to be superior to other imines of the same class, the reaction was applied successfully to different nucleophiles (scheme 2.25). The results were generally good in terms of yield, diastereo- and enantioselectivity.



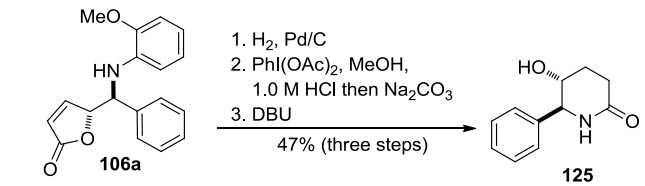
Scheme 2.25. Asymmetric VMMnR catalyzed by copper(I)-Fesulphos complex.

Furthermore, in some cases, it was possible to enhance significantly the enantiopurity of the Mannich adducts (see compounds **122** and **124**) by a single recrystallization, due to the crystalline nature of the sulfonamide products.

An issue frequently encountered during the development of Mannich reactions, be they vinylogous or not, is the removal of the protecting group from the nitrogen atom of the newly formed amine functionality.

When the nitrogen appendage is an aromatic or sulphonyl group, harsh conditions have to be used, which could affect the chemical and optical yield of the free amine products.

The merits of both Hoveyda and Carretero protocols lay in the possibility to cleave the amine protecting group in relatively mild conditions. In this manner, a panel of different enantiopure scaffolds could be prepared, thus revealing the great potential of the developed methodology. The *o*-anisidine ring was removed under mild oxidative condition using the commercially available $PhI(OAc)_2$, whereas the 2-thienyl-sulphonyl protecting group was cleaved using Mg(0) in methanol (scheme 2.26).



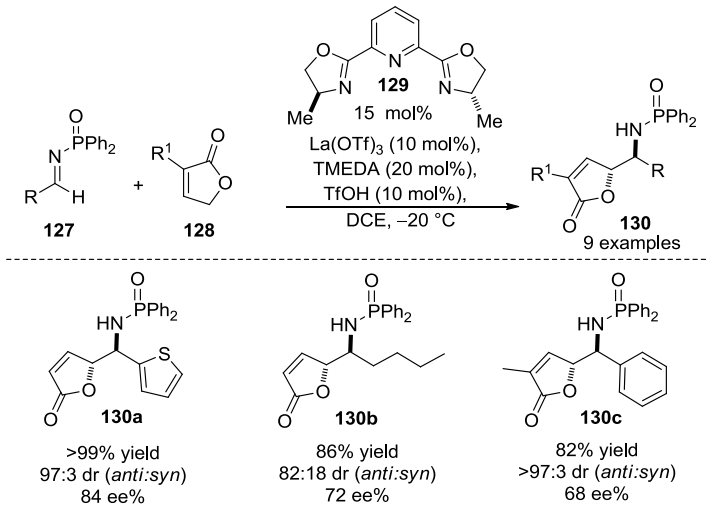
a) Hoveyda's dearilation conditions

b) Carretero's desulfonilation conditions

Scheme 2.26. Elaboration of the enantiopure Mannich butyrolactone products.

2.2.3.2 Metal-based direct VMnR[33a-b, 34, 35]

Direct vinylogous Mannich reactions represent a great achievement in the context of atom economy because they do not require the preformation of silicon dienolates for which stoichiometric amounts of the silicon reagent is needed. This area of asymmetric catalysis is still rather unexplored and examples are limited to γ-butyrolactones,[33a, 35] lactams,[33b] and dicyanoalkylidene olefins[34] as the pro-nucleophilic species.



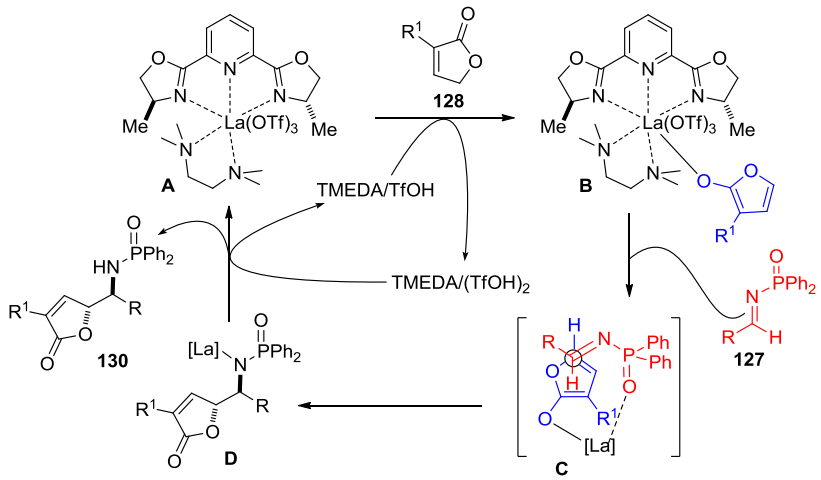
Scheme 2.27. Direct asymmetric VMnR proposed by M. Shibasaki.

In 2008 M. Shibasaki and co-workers reported the first asymmetric direct VMnR of γ-butenolides catalyzed by a combination of *in situ* generated chiral Lewis acid with an amine base and a Brønsted acid.[33a]

After an initial screening, chiral C_2-symmetric PyBox **129** in conjunction with the Lewis acid lanthanum(III) triflate [$La(OTf)_3$], the amine TMEDA and triflic acid -the Brønsted acid- was found to be the appropriate catalytic system able to promote the direct addition of γ-butenolides of general structure **128** to *N*-diphenylphosphinoyl imines **127**

[33] a) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319. b) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666.
[34] Chen, Q.-A.; Zeng, W.; Wang, D.-W.; Zhou, Y.-G. *Synlett* **2009**, 2236.
[35] Zhou, L.; Lin, L.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056.

(scheme 2.27). Low reproducibility in terms of yield and enantioselectivity was observed and this was ascribed to the small and variable amounts of TfOH within commercial lanthanum(III) triflate. The presence of triflic acid was found to be crucial and, after purification of $La(OTf)_3$, careful fixed amount of the Brønsted acid was added. From ^1H NMR studies the authors speculated that $La(OTf)_3$/Me-PyBox/TMEDA 1:1:1 might act as the active species, whileTfOH would enhance its formation.

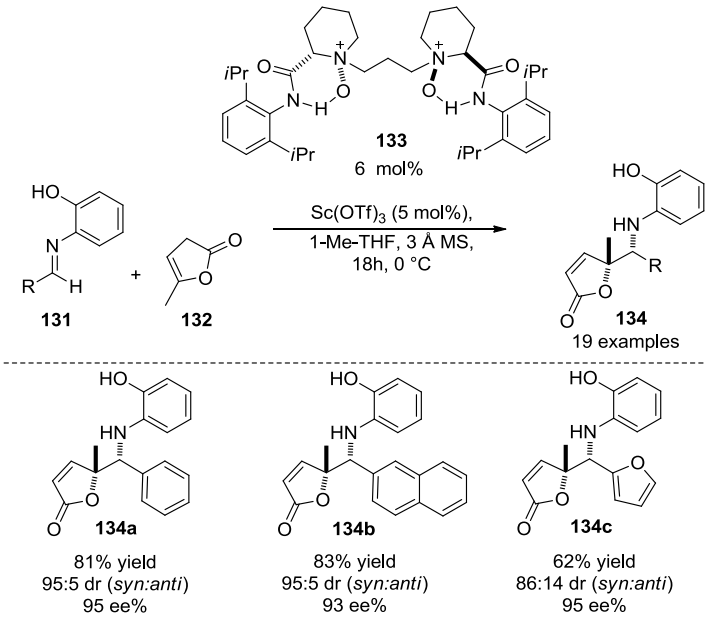


Scheme 2.28. Proposed catalytic cycle for the direct VMnR developed by Shibasaki.

A plausible catalytic cycle was proposed, as illustrated in scheme 2.28. The couple TMEDA/TfOH would deprotonate **128** which was then activated by the chiral Lewis acid complex **A** and would form the dienolate-lanthanum complex **B** and $TMEDA/(TfOH)_2$. Subsequently the dienolate in **B** could react with imine **127** *via* a synclinal transition state **C** where the oxygen of the phosphinoyl moiety coordinated the lanthanum atom, while minimizing steric repulsions. Finally, the formed adduct **D** would be protonated by $TMEDA/(TfOH)_2$ to release the final product **130** and regenerate the catalytic complex **A**.

Following in Shibasaki group footsteps, Feng and colleagues proposed the asymmetric vinylogous Mannich reaction of non-activated

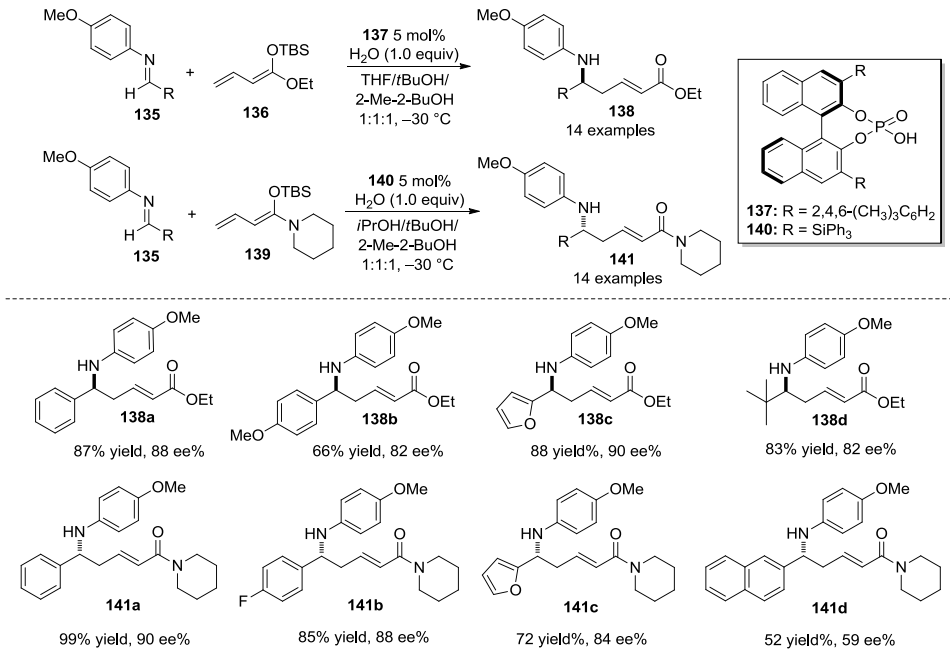
α-angelica lactone pro-nucleophile (**132**).[35] They observed that the *N,N'*-dioxide scandium complex was able to catalyze the VMn transformation *via* α-enolization of the deconjugate butenolide.



Scheme 2.29. Direct asymmetric VMMnR with pro-nucleophilic α-angelica lactone.

The Mannich adducts were obtained in good yields and high diastereo- enantioselectivities favoring compounds *syn*-**134** (scheme 2.29); the methodology was tested on aromatic aldimines exclusively. In order to better understand the reaction mechanism, the authors performed control experiments that testified the different inner reactivity between α-angelica lactone (**132**) and conjugate lactone **128**. They observed no product formation when the reaction was carried out under the optimal conditions using nucleophile **128**, suggesting a difficult γ-deprotonation by the catalytic complex.

2.2.3.3 Organocatalytic VMMnR[36a-b, 37a-f]



Scheme 2.30. Organocatalytic asymmetric VMMnR with acyclic silicon dienolates.

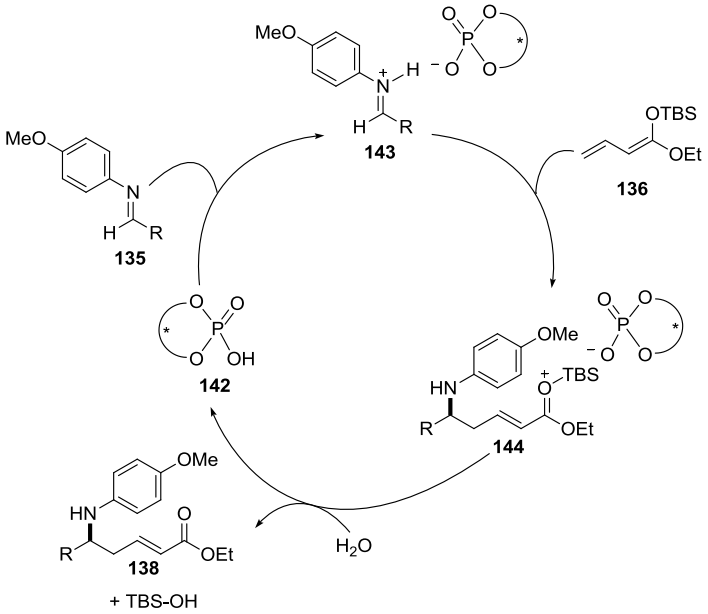
Since 2008, extensive studies and elegant applications of the vinylogous Mannich reaction were made by C. Schneider and co-workers by employing an organocatalytic approach.[37a-f] In this year, they reported for the first time an asymmetric Brønsted acid-organocatalyzed VMMnR applied to acyclic silyl dienolates.[37a]

In a first work, the authors performed the VMMnR of *p*-anisidine-derived imine **135** and silyl dienol ether **136** using chiral Brønsted acid **137** (scheme 2.30).[37a] In an initial screening, different solvents and solvent mixtures were assayed, and it was found that the alcoholic component was important to improve the reaction rate; it was also

[36] a) Itoh, J. Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; b) Akiyama, T.; Honna, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399.

[37] a) Sickert, M.; Schneider, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3631; b) Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259; c) Giera, D. S.; Sickert, M. Schneider, C. *Synthesis* **2009**, 3797; d) Sickert, M.; Abels, F.; Lang, M.; Sieler, J.; Birkemeyer, C.; Schneider, C. *Chem. Eur, J.* **2010**, *16*, 2806; e) Abels, F.; Schneider, C. *Synthesis* **2011**, 4050; f) Abels, F.; Lindemann, C.; Koch, E.; Schneider, C. *Org. Lett.* **2012**, *14*, 5972.

demonstrated that one equivalent of water further accelerated the addition, whereas 2-methyl-2-butanol was needed in order to operate at low temperature. The first series of Mannich products was obtained in good yields and enantioselectivities.

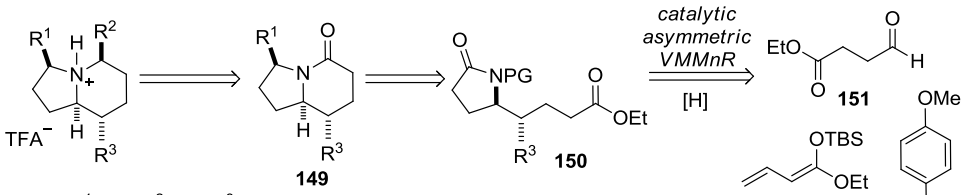


Scheme 2.31. Plausible catalytic cycle of the chiral Brønsted acid-catalyzed VMMnR.

The protocol was next extended to vinylketene silyl *N,O*-acetals;[37b] organocatalyst **140** demonstrated to be superior in promoting high enantioselectivity and products of type **141** showed an inverted configuration at the newly formed chiral amine functionality. Interestingly, it was demonstrated that the reaction could also be executed in a three-component fashion, a more straightforward approach since the pre-synthesis of the imine electrophiles was not required. Schneider and colleagues carried out ESI-MS/MS and NMR experiments in order to shed light onto the reaction mechanism.[37a,d]

As shown in scheme 2.31, it was postulated that imine **135** reacted with the chiral Brønsted acid of general structure **142**, generating the ion pair **143**, which then underwent the vinylogous attack by the silicon dienolate **136**. The new counterion pair **144** was hydrolyzed to give the Mannich product **138**, with concomitant regeneration of the chiral catalyst **142**.

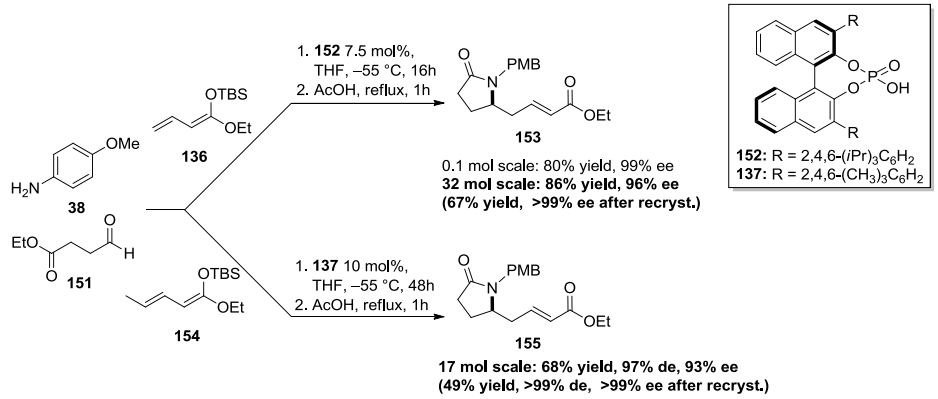
Very recently, the Schneider group reported a scalable and general synthesis of enantiopure indolizidine based alkaloids (IBAs),[37f] by applying an improved protocol for enantioselective vinylogous Mannich reaction with aliphatic imines.[37e] In the retrosynthetic plan (scheme 2.32), IBAs **145**-**148** derived from their corresponding indolizinones of general structure **149** after Grignard addition followed by stereoselective iminium ion reduction. **149**, in turn, could be prepared from the key intermediate **150**, the hydrogenated product of the catalytic asymmetric VMMnR of silicon dienolate **136** and the imine formed *in situ* from β-aldehydo-ester **151** and *p*-anisidine (**38**).



145: R^1 = H, R^2 = H, R^3 = H
146: R^1 = H, R^2 = C_3H_7, R^3 = H
147: R^1= C_4H_9, R^2 = CH_3, R^3 = H
148: R^1= H, R^2 = C_2H_5, R^3 = CH_3

Scheme 2.32. Retrosynthetic scheme of IBAs.

The modified procedure[37e] to **153** and **155** was scaled up successfully with only slight decrease in enantioselectivity. Fortunately, it was possible to improve the optical purity of the adducts with a single recrystallization (scheme 2.33).



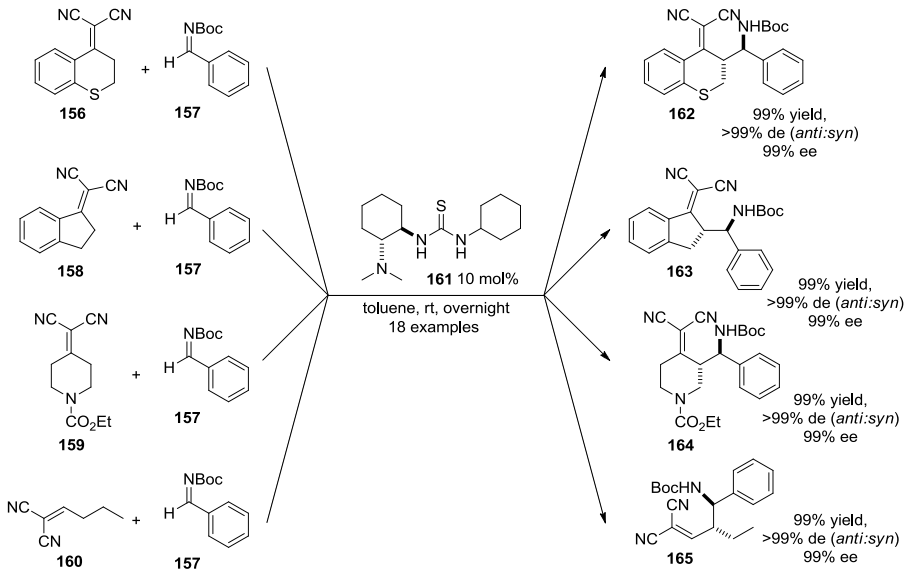
Scheme 2.33. Results of the asymmetric three-component VMMnR on different reaction scale.

The examples by Schneider and co-workers reported here represent a scrupulous and devoted study on the vinylogous Mannich reaction; indeed, application of the methodology to the total synthesis of IBAs demonstrates its versatility and practicality on both small and bigger scale.

2.2.3.4 Organocatalytic direct VMnR[38a-b, 39, 40]

Sporadic examples are reported in the literature on organocatalytic, direct executions of the vinylogous Mannich reaction. Furthermore, this approach is limited to dicyanoalkylidene olefins[38a-b, 39] and 3,4-dihalofuran-2(5*H*)-one[40] pro-nucleophiles, while detailed studies on possible reaction mechanisms and further synthetic applications are only sporadically reported.

[38] a) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878. b) Xiong, X.-F.; Jia, Z.-J.; Du, W.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Chem. Commun.* **2009**, 6994.
[39] Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 1620.
[40] Guo, Y.-L.; Bai, J.-F.; Peng, L.; Wang, L.-L.; Jia, L.-N.; Luo, X.-Y.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 8338.



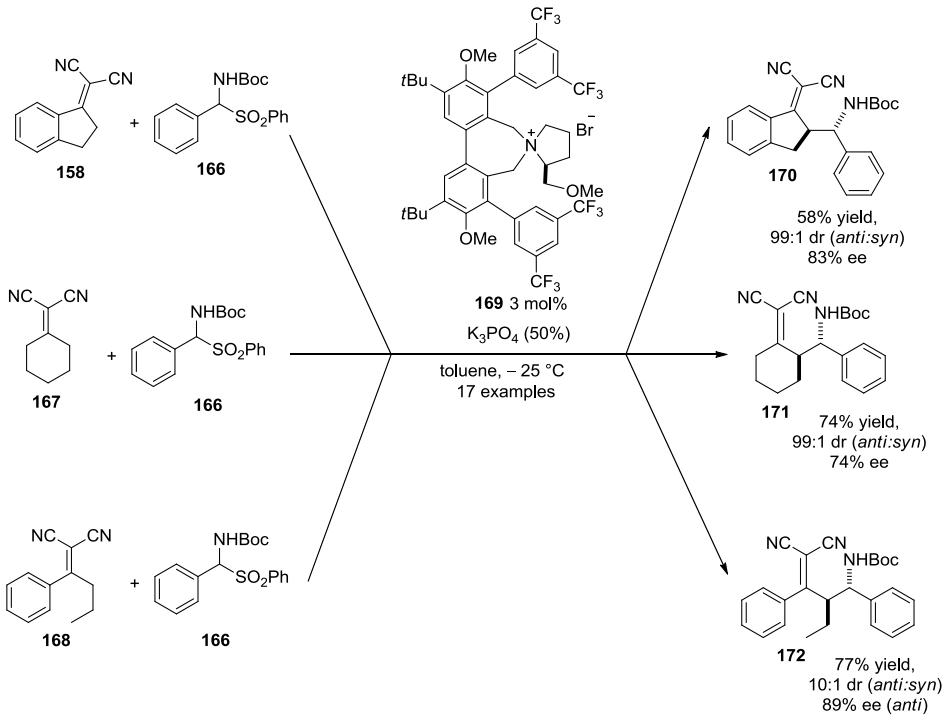
Scheme 2.34. Chiral thiourea-catalyzed direct VMnR of dicyanoalkylidene olefins.

Pioneering studies in this field were carried out independently by the Y.-C. Chen group[38a-b] and K. A. Jørgensen group.[39] In a first report, Chen and colleagues reported the asymmetric direct VMnR of a series of α,α-dicyanoolefins **156**, **158-160** with *N*-Boc aldimine **157** catalyzed by Berkessel organocatalyst **161** (scheme 2.34).

The Mannich products were generally obtained in excellent yields and with high diastereo- and enantioselectivity. Interestingly, during the screening experiments it was observed that virtually almost absolute enantioselectivity together with quantitative yield could be reached with only 0.1 mol% catalyst loading.

In the same year, Niess and Jørgensen demonstrated the ability of catalyst **169** to promote the same reaction under phase-transfer conditions (scheme 2.35).[39] Although the results were inferior with respect to the work of Chen and co-workers, the value of this methodology resided on the use of α-amido sulfone **166**, precursor of imine **157**, which allowed the *in situ* formation of the electrophile. This case can be

considered a direct vinylogous Mannich reaction for both the nucleophilic and electrophilic components.



Scheme 2.35. Asymmetric phase-transfer catalyzed VMnR.

In the following pages, a double-entry table is reported. Herein an exhaustive list of catalytic asymmetric vinylogous Mannich reactions is illustrated, covering the period 1999-2012. For each protocol, the nucleophile, the electrophile and the catalyst or catalytic system are illustrated. Not included are those processes involving chiral auxiliary-based non catalytic approaches.

Table 2.1. Summary of catalytic asymmetric VMnR developed in the period 1999-2012.

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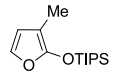
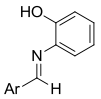
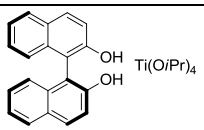
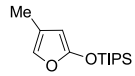
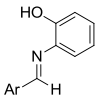
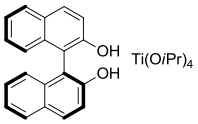
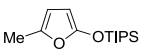
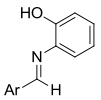
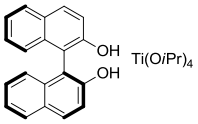
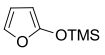
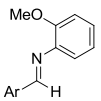
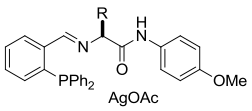
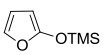
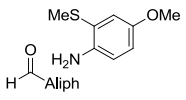
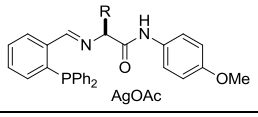
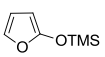
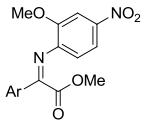
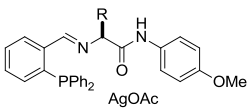
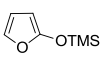
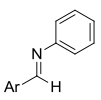
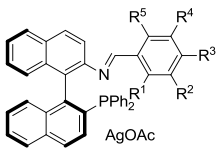
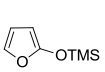
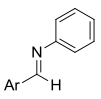
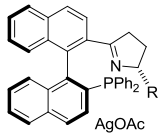
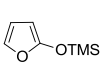
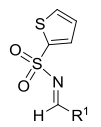
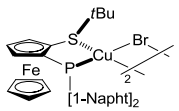
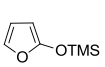
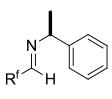
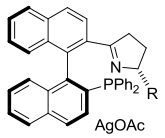
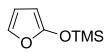
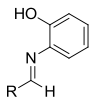
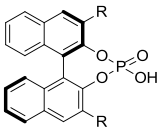
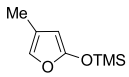
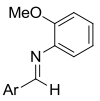
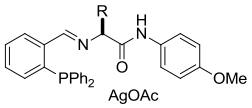
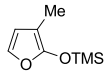
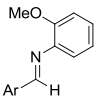
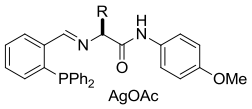
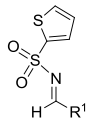
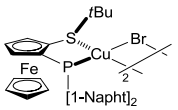
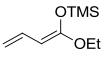
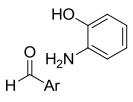
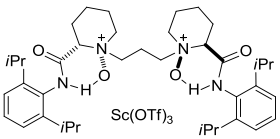
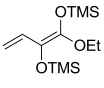
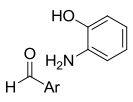
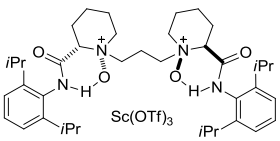
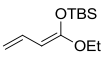
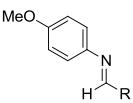
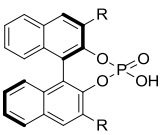
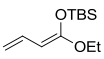
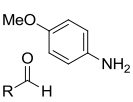
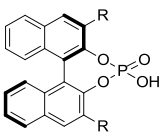
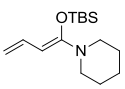
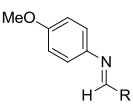
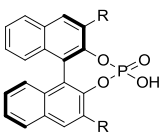
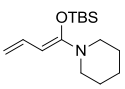
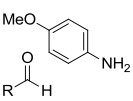
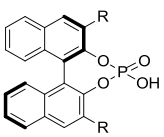
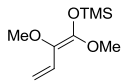
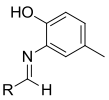
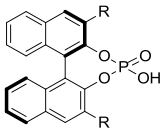
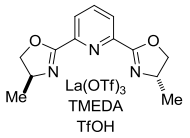
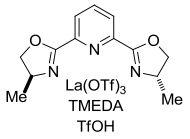
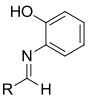
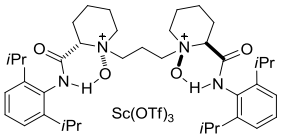
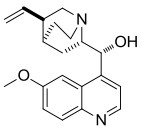
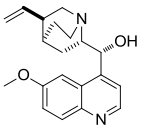
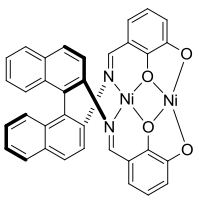
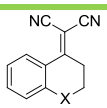
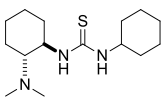
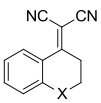
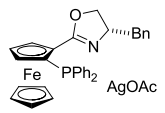
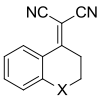
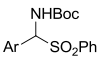
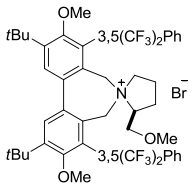
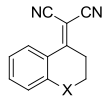
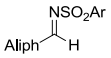
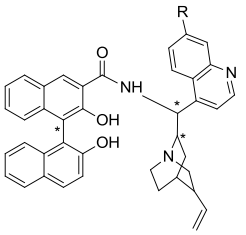
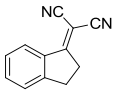
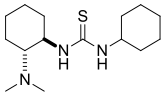
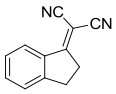
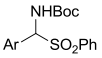
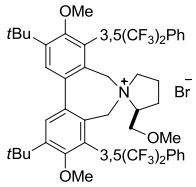
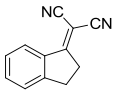
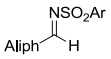
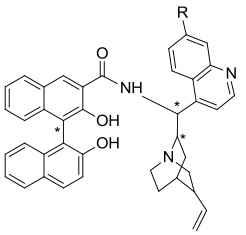
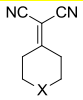
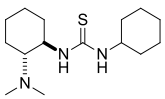
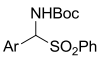
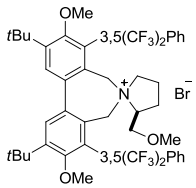
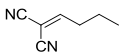
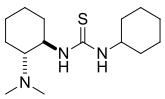
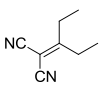
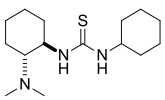
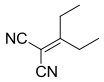
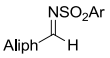
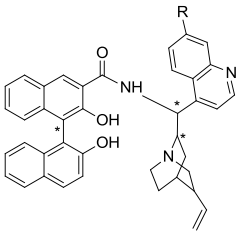
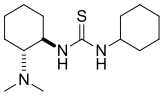
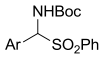
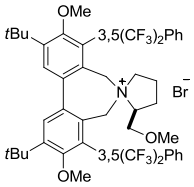
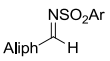
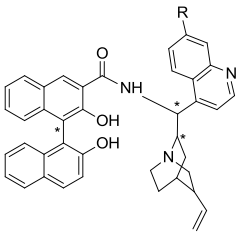
			27
			27
			27
			28a
			28b
			28c
			30a
			30b
			29
			30c,d

NUCLEOPHILE	ELECTROPHILE	CATALYST or CATALYTIC SYSTEM	REFERENCE
			36b
			28a
			28a
			29
			31
			32
			37a,c
			37a,c
			37b
			37b

NUCLEOPHILE	ELECTROPHILE	CATALYST or CATALYTIC SYSTEM	REFERENCE
			36a
			33a
			33a
			35
			40
			40
			33b
			38a
			34
			39

NUCLEOPHILE	ELECTROPHILE	CATALYST or CATALYTIC SYSTEM	REFERENCE
			38b
			38a
			39
			38b
			38a
			39
			38a
			38a

NUCLEOPHILE	ELECTROPHILE	CATALYST or CATALYTIC SYSTEM	REFERENCE
			38b
			38a
			39
			38b

2.3 Conclusions and perspectives

The aim of this chapter was to outline relevant achievements of the Mannich reaction, as well as its importance in the context of natural products synthesis and biosynthesis. In the first section, outstanding points in the history of the Mannich addition have been reported; rather than being an exhaustive report, the description was intended to map out the evolving ability of chemists in performing this key maneuver in synthetic endeavors.

A logical development of the classical Mannich reaction is the corresponding vinylogous version. Because vinylogous Mannich addition reactions are the main research topic of this PhD thesis, most of the sections have been dedicated to it. The aim of the description of the

reported examples was to underline the continuous efforts that both academia and industry made and keep on doing in order to improve the vinylogous homologation: it is indeed clear that the extended version of the Mannich reaction occupies a preeminent role in synthetic organic chemistry. The evolution history of VMMnR marks out the recently emerging urgence of developing viable and efficient catalytic and asymmetric versions of this transformation, which is in line with the general trend in contemporary organic synthesis landscape.

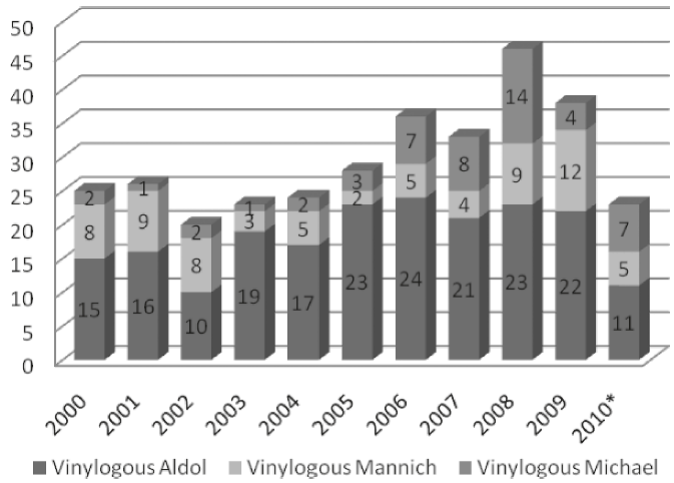


Figure 2.4. Number of research article published between 2000-2010 (*first quarter) on vinylogous aldol/Mannich/Michael reactions.

In a review-article on vinylogous aldol/Mannich/Michael reactions published in 2011, Zanardi and coworkers[19b] cleverly reported a chart illustrating the number of publications appeared in the literature on these vinylogous homologations during the decade 2000[19a]-2010 (figure 2.4). In that chart, it emerged that 51 out of 322 publications were devoted to the vinylogous Mannich reaction.[41]

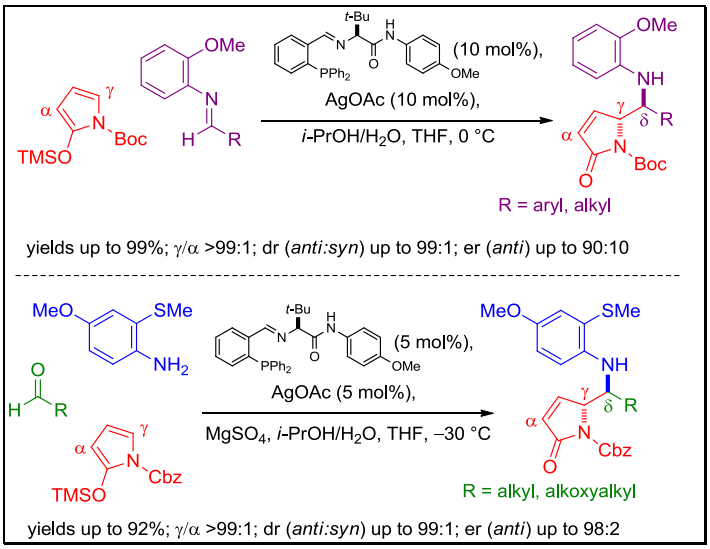
[41] Although from the chart the number of publications on vinylogous Michael reaction is lower than the number of those dedicated to the Mannich addition, in an updated chart (not published) the data appear to be reversed.

This restricted figure, far from being imputable to the scarce appealing of the reaction, could rather be ascribed to inherent difficulties posed by the vinylogous Mannich reaction concerning, for instance, the liability of certain imine electrophiles or lack of proper activation modalities. In the asymmetric catalysis context, the search for truly general and efficient catalytic systems able to govern stereocontrol is far from being established.

Conscious of the importance of the vinylogous Mannich reaction as an enabling chemical transformation and the preciousness of the Mannich products as versatile molecular scaffolds, we feel that major efforts have still to be made to render this reaction highly efficient, truly general and completely stereocontrolled.

Chapter 3

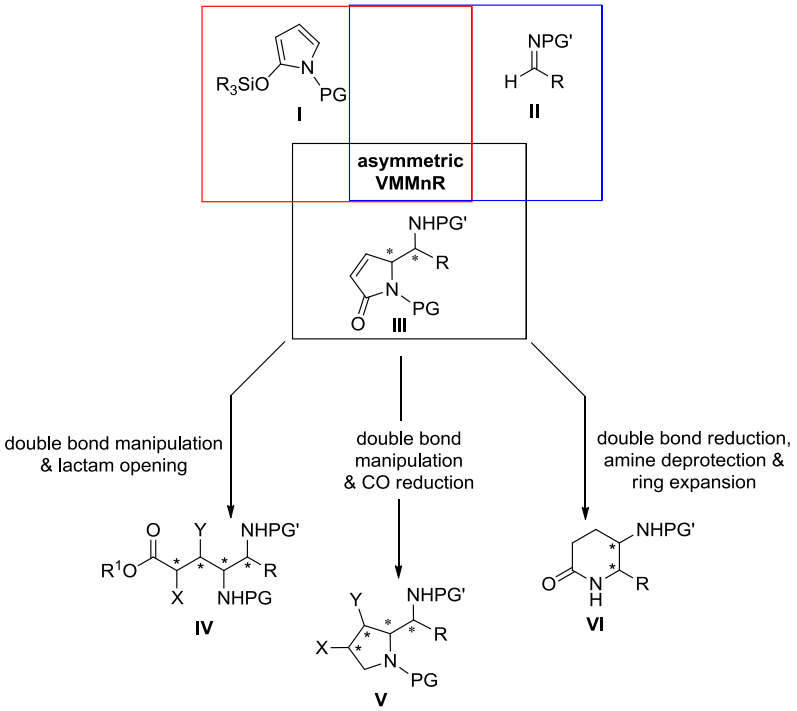
Silver(I)-catalyzed asymmetric vinylogous Mukaiyama Mannich reactions with pyrrole-based silicon dienolates[1]



[1] a) "*Anti*-Selective Catalytic Asymmetric Vinylogous Mukaiyama Mannich reactions of Pyrrole-based Silyl Dienolates with *N*-Aryl Aldimines", Curti, C.; Battistini, L.; Ranieri, B.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 2248-2252. b) "Diastereo and Enantioselective Vinylogous Mukaiyama-Mannich Reactions of Pyrrole-Based Silyl Dienolates with Alkyl-Substituted Aldehydes", Ranieri, B.; Curti, C.; Battistini, L.; Sartori, A.; Pinna, L. G.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 10291-10298.

3.1 Introduction

The vinylogous Mannich reaction (VMnR) is recognized to be a key tool for the construction of δ-amino-α,β-unsaturated carbonyl frameworks which can be identified within amplitude of multifunctional fragments and target compounds (see chapter 2). Moreover, as previously discussed, the possibility of adopting catalytic asymmetric variants in order to prepare enantiopure building blocks renders the transformation even more powerful and valuable.



Scheme 3.1. Examples of synthetic manipulations on γ-butyrolactams **III** derived from asymmetric VMMnR on pyrroles **I**.

At the time we began our work (2010), we were partially devoted to examination of the behavior of pyrrole-based silicon dienolates in vinylogous reactions, and we were quite surprised to observe that these

nucleophiles had never been exploited in catalytic enantioselective Mukaiyama Mannich reactions before.

The structural versatility of these pyrrole-based carbon nucleophiles can be well appreciated if considering simple but effective transformations. As illustrated in scheme 3.1, the reaction between a generic silyloxypyrrole **I** and imine **II** can generate α,β-unsaturated δ-amino-γ-butyrolactams of type **III** that can be subjected to different chemical modifications to deliver, for example, linear multifunctionalized carbon chains **IV**, substituted chiral pyrrolidines **V** and nitrogen-containing six-membered rings of general structure **VI**. Common feature of these twofold elaborated scaffolds is the presence of a 1,2-diamino structure, a recurring motif in the organic synthesis and medicinal chemistry arsenal of target compounds.[2]

Being aware of the synthetic potential of pyrrole-derived Mannich adducts, we decided to develop for the first time a catalytic asymmetric VMMnR using pyrrole-based silicon dienolates, a d_4 donor progeny whose utility in the catalytic asymmetric context was (and is) still substantially unexplored.

The first part of this chapter is dedicated to the analysis of the design and development of the synthetic methodology employing *N*-aryl aldimines as electrophiles; whereas in the second section of the chapter, extension and improvement of the protocol to aliphatic aldimine electrophiles will be treated in detail.

[2] For leading reviews on vicinal diamines in organic synthesis and medicinal chemistry, see: (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161; (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580; (c) Viso, A.; de la Pradilla, R. F.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167; (d) Saibabu Kotti, S. R. S; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101

3.2 Catalytic enantioselective VMMnR of pyrrole-based Si-dienolates with N-aryl aldimines

3.2.1 Results and discussion

The studies began with the catalyst screening (table 3.1). The model reaction between *N*-Boc-2-[(*tert*-butyldimethyl)silyloxy]pyrrole (TBSOP) (**1a**) and preformed arylimine **2a** was scrutinized with the chiral catalysts or catalyst systems reported in figure 3.1. The catalyst choice was made upon two main criteria: 1) tested ability of the catalyst (examples taken from recent literature) in promoting efficient vinylogous Mukaiyama aldol-type reactions and 2) commercial availability or easy preparation of the catalyst which had to be accessed in an economic way.

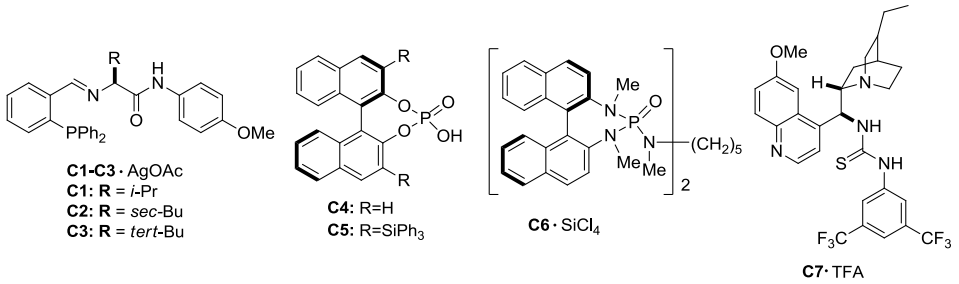


Figure 3.1. Chiral catalyst systems scrutinized for the development of the asymmetric VMMnR.

The screening included the amino-acid based chiral ligand/silver(I) complexes **C1**-**C3•**AgOAc developed by Hoveyda and Snapper,[3] the axially chiral Brønsted acids **C4** and **C5** widely investigated by Schneider and coworkers[4] (they have been extensively described in chapter 2, sections 2.2.3.1 and 2.2.3.3), Denmark's bisphosphoramide/silicon

[3] (a) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7230; (b) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961; (c) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.

[4] a) Sickert, M.; Schneider, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3631; b) Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259; c) Giera, D. S.; Sickert, M. Schneider, C. *Synthesis* **2009**, 3797; d) Sickert, M.; Abels, F.; Lang, M.; Sieler, J.; Birkemeyer, C.; Schneider, C. *Chem. Eur, J.* **2010**, *16*, 2806; e) Abels, F.; Schneider, C. *Synthesis* **2011**, 4050; f) Abels, F.; Lindemann, C.; Koch, E.; Schneider, C. *Org. Lett.* **2012**, *14*, 5972.

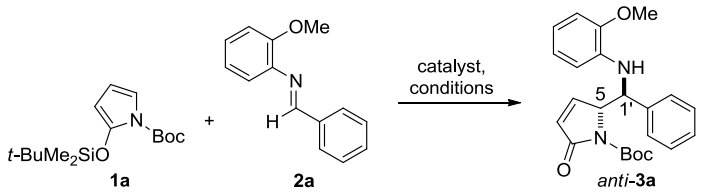
tetrachloride catalyst system **C6**•$SiCl_4$,[5,6] and the cinchona-thiourea organocatalyst **C7**•TFA.[7]

As indicated by data reported in table 3.1, initial results were quite discouraging: in the case of the Hoveyda-Snapper catalytic system, the asymmetric VMMnR proceeded using the three differently-substituted chiral ligands **C1**-**C3** with virtually absolute diastereoselection in favor of the *anti*-stereoconfigured Mannich product **3a** albeit poor efficiency and modest enantiomeric induction (entries 1, 2 and 3). Among these examples, somehow better results were detected with the peptide-like structure catalyst **C3**•AgOAc bearing a *tert*-butyl group in the ligand chain (entry 3).

Using chiral BINOL-based phosphoric acids **C4** and **C5**, reactions displayed high conversion values but scarce diastereo- and enantioselectivities (entries 4 and 5). The Denmark's catalyst system based on the combination of a weak Lewis acid –.$SiCl_4$ – and a Lewis base – the chiral bisphosphoramide – was also tested, because of its efficiency documented by ourselves in promoting asymmetric vinylogous Mukaiyama aldol reactions with the same type of nucleophiles.[5] Unfortunately, in case of the vinylogous Mannich reaction, this catalyst system proved to be completely incompetent in terms of both diastereo- and enantioselection, albeit 80% of conversion was observed (entry 6). In the same way, cinchona-thiourea organocatalyst **C7** combined with trifluoroacetic acid as cocatalyst provided compound *anti*-**3a** with low conversion, 60% diastereomeric excess and almost absent enantioselectivity (entry 7).

[5] Denmark, S.E.; Heemstra, J. R. Jr. *J. Org. Chem.* **2007**, *72*, 5668.
[6] Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F.; *Adv. Synth. Catal.* **2010**, *352*, 2011.
[7] Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558.

Table 3.1. Initial catalyst screening on the model VMMnR between pyrrole **1a** and imine **2a**.[a]



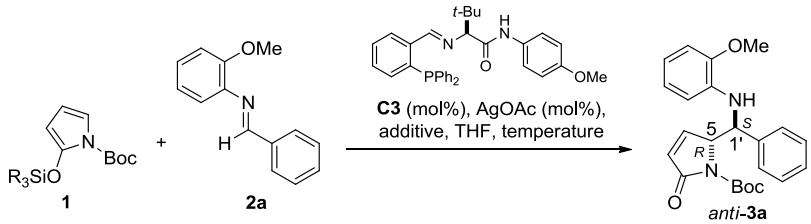
entry	catalyst	conv [%][b]	dr[c] (*anti*:*syn*)	er[d](*anti*)	ref.
1[e]	**C1**•AgOAc	20	99:1	58:42	3
2[e]	**C2**•AgOAc	15	99:1	55:45	3
3[e]	**C3**•AgOAc	30	99:1	63:37	3
4	**C4**	95	60:40	55:45[f]	4
5	**C5**	71	65:35	55:45[f]	4
6	**C6**•$SiCl_4$	80	55:45	51:49[f]	5-6
7	**C7**•TFA	30	80:20	52:48[f]	7

[a] For each catalyst system, almost the same reaction conditions as those reported in the original papers were adopted (see the corresponding references). [b] Determined by ^{1}H NMR analysis of the crude reaction. [c] Determined by HPLC analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Reaction carried out at 25 °C. [f] Determined by chiral HPLC analysis of the crude reaction mixture.

At this point it was reasoned that the nature of the pyrrole donor component could have an impact on the efficiency of the VMMnR. Two sites within the silyloxy diene could be subjected to modification: 1) the alkyl substituents at the silicon atom and, 2) the nitrogen protecting group. Initially, the attention was mainly focused on variation of the steric hindrance of the groups installed at the silicon moiety, but other reaction variables were also checked (table 3.2); the *N*-*tert*-butoxycarbonyl group was maintained, due to rapid accessibility to *N*-boc-Δ^2-pyrrolinone from pyrrole.[8]

[8] (a) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760.; (b) Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem*. **1997**, *40*, 168; (c) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Burreddu, P.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **2008**, *73*, 5446. See also: (d) Bocchi, V.; Chierici, L.; Gardini, G. P.; Mondelli, R. *Tetrahedron* **1970**, *26*, 4073; For an industrial scale production , see: Tian, Z.; Rasmussen, M.; Wittenberger, S. T. *Organic Process Research & Development* **2002**, *6*, 416.

Table 3.2. Screening of the AgOAc•C3-catalyzed VMMnR conditions.[a]



1a R_3Si = TBS
1b R_3Si = TES
1c R_3Si = TMS

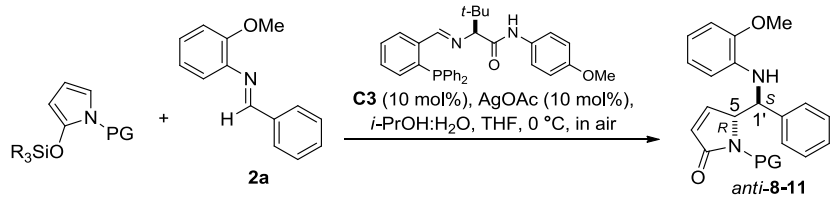
entry	**1**:**2a** [eq]	pyrrole	temp [°C]	additive (eq)	yield [%][b]	dr[c] (*anti*:*syn*)	er[d] (*anti*)[e]
1[f]	1:1	**1a**	25	*i*-PrOH (1.1)	30	99:1	63:37
2[f]	1.5:1	**1a**	–78	*i*-PrOH (1.1)	traces	nd	nd
3[f]	1.5:1	**1a**	–30	*i*-PrOH (1.1)	traces	nd	nd
4[f]	1.5:1	**1b**	–30	*i*-PrOH (1.1)	5	98:2	72:28
5[f]	1.5:1	**1c**	–30	*i*-PrOH (1.1)	10	99:1	61:38
6[g]	1.5:1	**1c**	–30	*i*-PrOH (1.5) H_2O (1.5)	12	99:1	90:10
7[f]	1.5:1	**1c**	25	*i*-PrOH (1.1)	60	99:1	68:32
8[f]	1.5:1	**1c**	0	*i*-PrOH (1.5)	65	99:1	80:20
9[g]	1.5:1	**1c**	0	*i*-PrOH (1.5)	72	99:1	85:15
10[g]	1.5:1	**1c**	0	*i*-PrOH (1.5) H_2O (1.5)	80	99:1	90:10

[a] The reactions were performed with ligand **C3**•/AgOAc (1:1), undistilled *i*-PrOH and stabilized (BHT, 250 ppm) THF, in air, for 16 h at the indicated temperature. [b] Isolated yield after silica gel flash column chromatography. [c] Determined by HPLC analysis of the crude reaction mixture. [d] Determined by HPLC analysis using Chiralcel OD-H column. [e] Enantiomeric ratio refers to *anti*-(5*R*,1'*S*)-Mannich product. [f] **C3**•AgOAc 1.0 mol% [g] **C3**•AgOAc 10 mol%.

As reported in table 3.2, lower temperatures, from –78 to –30 °C, with 1 mol% catalyst loading did not produce considerable conversion of the substrates into the Mannich products using either TBS (*tert*-butyldimethylsilyl), TES (triethylsilyl) or TMS (trimethylsilyl) groups in the nucleophile (entries 2, 3, 4 and 5). Slight improvements in terms of efficiency were observed employing the TMS group, less sterically hindered as compared to the other groups (entry 5). Performing the reaction at the same temperature but with a tenfold catalyst loading and

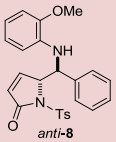
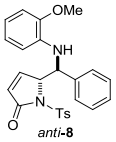
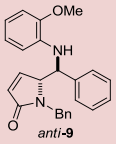
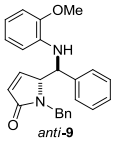
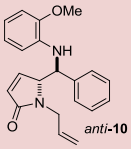
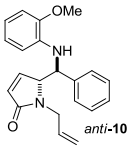
the addition of 1.5 equivalents of water as additive led to quite rewarding enantioinduction with enantiomeric ratio up to 90:10 (entry 6).

Table 3.3. Screening of the *N*-protecting groups under optimized VMMnR conditions.[a]

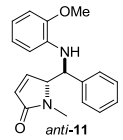
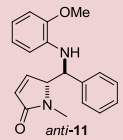


4 PG = Ts
5 PG = Bn
6 PG = allyl
7 PG = methyl

a R_3Si = TBS
c R_3Si = TMS

entry	pyrrole	product	yield [%][b]	dr (*anti*:*anti*)[c]	er[d] (*anti*)[e]
1	**4c**	 *anti*-**8**	19	99:1	96:4
2	**4a**	 *anti*-**8**	5	99:1	87:13
3	**5c**	 *anti*-**9**	61	99:1	92:8
4	**5a**	 *anti*-**9**	6	99:1	80:20
5	**6c**	 *anti*-**10**	nd	nd	nd
6	**6a**	 *anti*-**10**	14	99:1	51:49

to be continued on the next page

entry	pyrrole	product	yield [%][b]	dr (*anti*:*anti*)[c]	er[d] (*anti*)[e]
7[f]	**7a**	 *anti*-**11**	—	—	—
8[f]	**7c**	 *anti*-**11**	—	—	—

[a] The reactions were performed with silyloxy-pyrrole/imine **2a** (1.5/1.0 eq), ligand **C3**/AgOAc (1:1, 10 mol% each), undistilled *i*-PrOH:H_2O (1:1, 1.5 eq each) and stabilized (BHT, 250 ppm) THF, in air, for 16 h at 0 °C. [b] Isolated yield after silica gel flash column chromatography. [c] Determined by HPLC analysis of the crude reaction mixture. [d] Determined by HPLC analysis using Chiralcel OD-H column. [e] Enantiomeric ratio refers to *anti*-(5*R*,1'*S*)-Mannich product. [f] γ-alkylidene butyrolactam was the only isolated product.

Water was found to be crucial for high enantioselectivity to be attained, possibly due to its participation within the catalytic cycle (see scheme 2.21) by acting as scavenger of cationic silicon species which behave as achiral Lewis acids while possibly promoting competitive racemic background pathway. Optimized conditions are shown in entry 10 (table 3.2), where 10 mol% catalyst loading, at 0 °C with a premixed combination of *i*-PrOH/H_2O (1.5:1.5 equivalents) promoted the formation of the Mannich *anti*-(5*R*,1'*S*)-butyrolactam adduct *anti*-**3a** in a good 80% isolated yield, excellent diastereoselectivity (99:1 *anti:syn*), and appreciable 80% enantiomeric excess.

With this optimized conditions in hand, in a second step the role exerted by the protecting group installed on the nitrogen atom was investigated (table 3.3). The employment of the tosyl group, another electron-withdrawing protecting group more sterically hindered than Boc, led to better (entry 1) or comparable (entry 2) results in terms of enantioselectivity albeit in low isolated yield. The scarce efficiency of this reaction could be ascribed to the blockage of the nucleophile attack on the *re* face of the acceptor (see paragraph 3.4). In order to understand the role of the electronic effects exerted by the *N*-protecting group, three differently-sized electron-donating groups were scrutinized. Considerable

results were obtained using the *N*-benzyl protected TMSOP **5c** (entry 3), which approached those obtained with *N*-Boc-TMSOP, and this was a clear evidence that the electronic nature of the nitrogen appendage did not seem to exert any significant role on the asymmetric VMMnR.

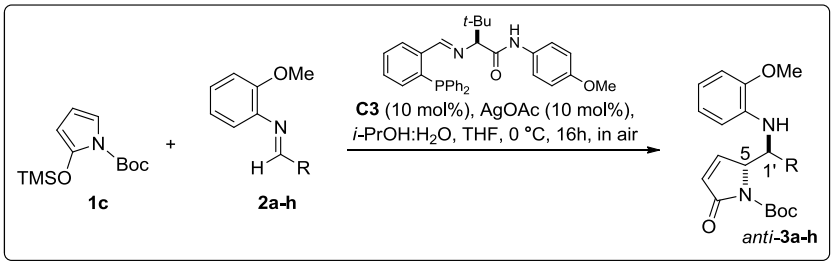
Of note, the nature of the silicon atom moiety within compound **5** – e.g. TMS for **5c** and TBS for **5a** - seemed to have a stricking impact on the reaction course: in fact, as reported in entry 4, a dramatic drop of efficiency (6% isolated yield) was observed when *N*-benzyl-2-[(*tert*-butyldimethyl)silyloxy]pyrrole (**5a**) was used. This could be due to a major reactivity attributed to TMS-syloxy pyrroles, thus more prone to react in the VMMnR and less subjected to hydrolysis to the corresponding unreactive pyrrolinone.

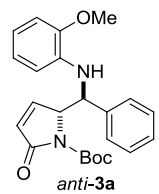
Less sterically hindered electron-donating protecting groups were not beneficial to the VMMnR: in the case of allyl substituted pyrrole **6a**, the product *anti*-**10** was isolated as a racemic mixture in 14% isolated yield, whereas *N*-methyl silyloxy-pyrroles **7a** and **7c** completely failed to give the corresponding desired Mannich adduct *anti*-**11**.

After this scrutiny, the *N*-Boc-2-[(*tert*-butyldimethyl)silyloxy]pyrrole (**1c**) was elected as the best donor agent for the Ag-catalyzed enantioselective VMMnR.

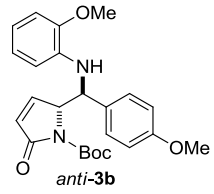
At this point the developed protocol was applied to different aromatic aldimines (table 3.4). A variety of aromatic aldimines with either electron-withdrawing or electron-donating groups on the aldehyde aromatic ring were tested and they delivered the corresponding Mannich *anti*-configured adducts in 65-99% isolated yield, excellent diastereomeric ratios (dr > 98:2) and acceptable level of enantioselectivity up to 80%.

Table 3.4. Asymmetric VMMnR between silyloxypyrrole **1c** and differently substituted *N*-arylimines **2a**-**h** catalyzed by complex **C3**•AgOAc.[a]

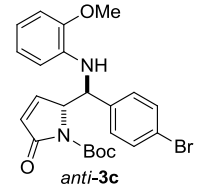




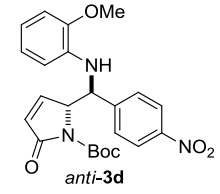
yield = 80%
dr (*anti:syn*) = 99:1
er (*anti*) = 90:10



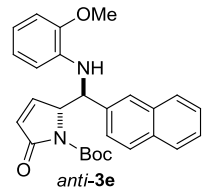
yield = 94%
dr (*anti:syn*) = 98:2
er (*anti*) = 78:22



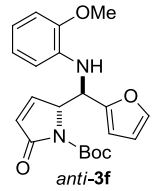
yield = 98%
dr (*anti:syn*) = 99:1
er (*anti*) = 71:29



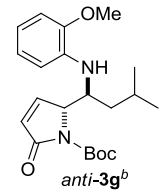
yield = 99%
dr (*anti:syn*) = 99:1
er (*anti*) = 71:29



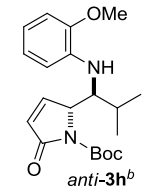
yield = 65%
dr (*anti:syn*) = 99:1
er (*anti*) = 75:25



yield = 90%
dr (*anti:syn*) = 99:1
er (*anti*) = 83:17



yield = 52%
dr (*anti:syn*) = 99:1
er (*anti*) = 82:18



yield = 36%
dr (*anti:syn*) = 87:13
er (*anti*) = 82:18

[a] Conditions as in entry 10, table 3.2. Yields refer to isolated Mannich products. Diastereomeric ratios determined by HPLC analysis of the crude reaction mixtures. Enantiomeric ratios determined by chiral HPLC analysis. [b] Three-component procedure, aliphatic imines formed *in situ*. For details see experimental data.

The substitution pattern of the phenyl ring in structure **2** did not impact the stereocontrol significantly, and heteroaromatic imine **2f** as well as 2-naphthaldehyde-derived imine **2e** proved to be viable substrates too.

In order to broaden the scope of the VMMn reaction, two aliphatic imines, **2g** and **2h**, were scrutinized, generating the Mannich lactam products *anti*-**3g** and *anti*-**3h** with results in terms of diastereo- and enantiocontrol comparable to those of aromatic aldimines. However, lower efficiency was witnessed in these cases, with isolated yields of 52%

and 36% respectively, and this pointed to the conclusion that the procedure was best suited for additions to aromatic aldimine electrophiles.

3.2.2 Stereochemical assessment

The relative configuration of the major Mannich "aromatic" product *anti*-**3a** and "aliphatic" adduct *anti*-**3g**[9] was determined by X-ray analysis of the corresponding crystalline racemates. In figure 3.2 the respective ORTEP projections are reported. The relative configuration of Mannich compounds **3b-f** and **3h** was proposed by analogy.

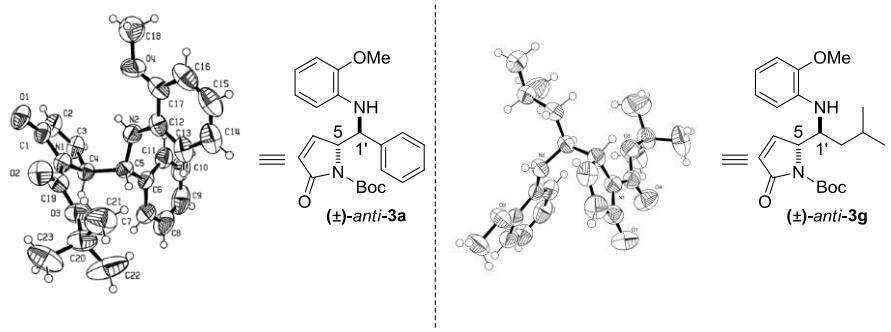
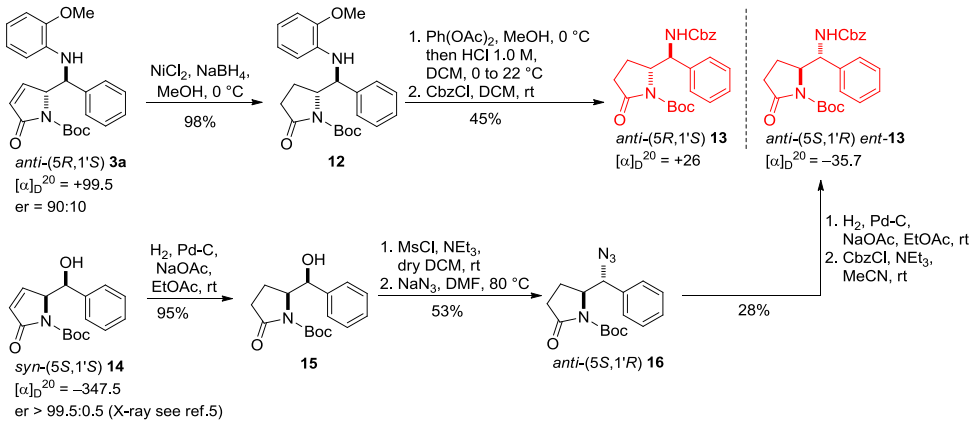


Figure 3.2. ORTEP projections of Mannich products (±)-*anti*-**3a** and (±)-*anti*-**3g** [(5*R*,1'*S*) enantiomers are shown].

The absolute configuration of *anti*-**3a** was unambiguously determined *via* chemical correlation to the known 5*S*,1'*S*-configured *syn* butyrolactam (–)-(*S*)-*N*-(*tert*-butoxycarbonyl)-5-[(*S*)-hydroxy-(phenyl)methyl]-1*H*-pyrrol-2(5*H*)-one **14**[6] as detailed in scheme 3.2.

The comparison of the optical rotatory powers of **13** and *ent*-**13** ($[\alpha]^{D}_{20}$ **13** = +26, $[\alpha]^{D}_{20}$ *ent*-**13**= –35.7) confirmed the enantiomeric relationship between the two compounds thus allowing the determination of the (5*R*,1'*S)* absolute configuration of *anti*-**3a**. Due to the fact that all the Mannich products were dextrorotatory, their absolute configuration was proposed by analogy.

[9] The ORTEP projection was published in another article, see Sartori, A.; Dell'Amico, L.; Curti, C.; Battistini, L.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2011**, *353*, 3278.



Scheme 3.2. Chemical correlation to determine the absolute configuration of *anti*-**3a**.

Furthermore, the found $[\alpha]^{D}_{20}$ values of *anti*-**3a** and **14** were perfectly in agreement with an empiric rule (the butenolidic rule) previously applied on butenolide and aza-butenolide products; it stated that optical dextrorotatory powers (positive $[\alpha]^{D}_{20}$) were symptom of *R* absolute configuration at the γ-position whereas optical levorotatory powers ($[\alpha]^{D}_{20}$) of *S*-configured γ-stereocenters.

3.3 Catalytic asymmetric three-component VMMnR of pyrrole-based Si-dienolates with alkyl-substituted aldehydes

3.3.1 Results and discussion

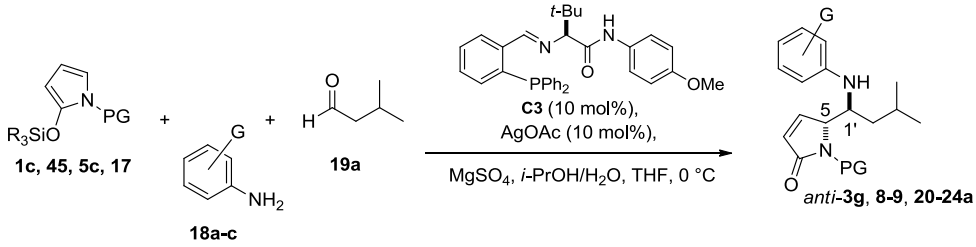
The results obtained during the previous projects, which were particularly suited for aryl-substituted aldimine electrophiles (see table 3.4), prompted us to develop an improved protocol to be best adapted to aliphatic aldimines. Due to natural instability of preformed aliphatic imines, a three-component execution, by definition the imine was directly formed *in situ* during the reaction, had to be planned.

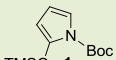
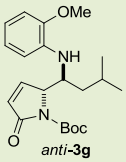
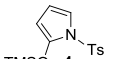
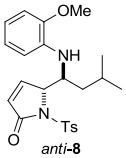
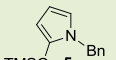
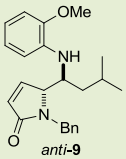
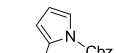
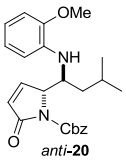
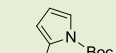
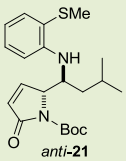
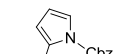
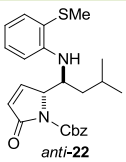
Ligand **C3**•AgOAc complex was chosen as the chiral metal-based catalyst, isovaleraldehyde **19a** was chosen as the aldehyde component, and variable *N*-protected silyloxy pyrroles and aromatic amines were initially scrutinized (table 3.5).

As shown in tables 3.4 and 3.5, the starting point was the reaction, in a three-component execution, between donor **1c**, *o*-anisidine **18a** and isovaleraldehyde **19a**, whose promising results foresaw the possibility of a more efficient protocol for this asymmetric VMMnR. At the beginning of the screening different *N*-protected pyrrole nucleophiles were tested (entries 2-4). Nucleophile **4c** bearing a *N*-tosyl group gave low conversion and modest enantioselectivity (entry 2), whereas **5c**, possessing a *N*-benzyl group, failed completely to deliver the corresponding product *anti*-**9** (entry 3). With *N*-Cbz-protected silyloxy pyrrole **17**, higher enantioselection was observed with respect to the *N*-Boc-protected pyrrole, albeit low efficiency was witnessed (entry 4 *vs* entry 1). From these premises, it was thus decided to investigate the reaction with *N*-Boc and *N*-Cbz donors **1c** and **17** by using different aromatic amines (entries 5-8).

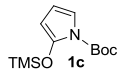
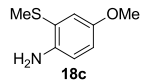
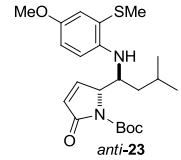
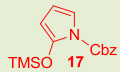
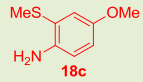
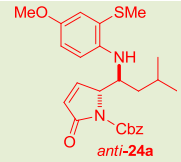
The common feature of the Mannich adducts *anti*-**3g**, **8**, and **20**, all bearing an *ortho*-anisidine appendage, was the modest enantioinduction, with ee values ranging from 42% to 68%. We reasoned that the substitution of the methoxy substituent at the *ortho* position of the aniline component with a thiomethyl group could play a role in improving enantiocontrol. As shown in entries 5 and 6, this proved to be the case, with very good ee values of 98% and 94% obtained from the corresponding Cbz- and Boc-protected pyrroles. The “soft” chelation properties of the sulfur atom could be responsible for a tighter complex to the chiral catalyst in the transition state (see later), ultimately resulting in higher face enantiodifferentiation.[3b]

Table 3.5. Evaluation of pyrrole nucleophiles and aromatic amines in the catalytic asymmetric three-component VMMnR.[a]



entry	pyrrole: R_3Si/PG	amine	product	yield [%][b]	dr (*anti*:*syn*)[c]	er (*anti*)[d,e]
1	 TMSO **1c**	 **18a**	 *anti*-**3g**	52	>99:1	81:19
2	 TMSO **4c**	 **18a**	 *anti*-**8**	9	>99:1	71:29
3	 TMSO **5c**	 **18a**	 *anti*-**9**	—	—	—
4	 TMSO **17**	 **18a**	 *anti*-**20**	40	>99:1	84:16
5	 TMSO **1c**	 **18b**	 *anti*-**21**	44	>99:1	99:1
6	 TMSO **17**	 **18b**	 *anti*-**22**	70	>99:1	97:3

to be continued on the next page

entry	pyrrole: R_3Si/PG	amine	product	yield [%][b]	dr (*anti*:*syn*)[c]	er (*anti*)[d,e]
7	 **1c**	 **18c**	 *anti*-**23**	58	>99:1	98:2
8	 **17**	 **18c**	 *anti*-**24a**	75	>99:1	97:3

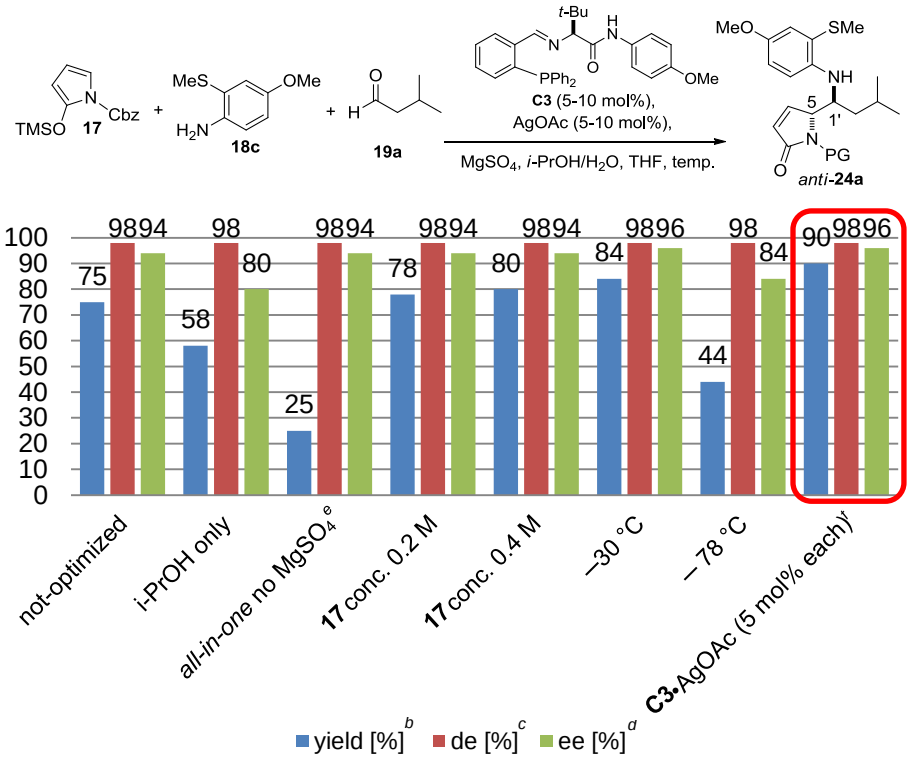
[a] The reactions were carried out using silyloxy pirroles (0.3 mmol, 1.5 eq), aldehyde **19a** (1.0 eq), amine **18a-c** (1.0 eq), $MgSO_4$ (2.0 eq), ligand **C3**/AgOAc (1:1, 10 mol% each), undistilled *i*-PrOH:H_2O (1:1, 1.5 eq each) and stabilized (BHT, 250 ppm) THF, in air, for 16 h at 0 °C, conc. 0.1 M referred to silyloxy pyrroles. [b] Isolated yield after silica gel flash column chromatography. [c] Determined by ^{1}H NMR analysis of the reaction crude. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Enantiomeric ratio refers to *anti*-(5*R*,1'*S*)-Mannich product.

Introduction of the *para*-methoxy substituent in amine **18c** increased the efficiency of the VMMnR up to 75% yield using Cbz-nucleophile **17** under unoptimized conditions (entry 8), and this was possibly due to the less electrophilic nature of the *in situ* generated aldimine, thus less prone to decomposition.

Having identified nucleophile **17** and amine **18c** as the best reactants, reaction conditions were scrupulously investigated (chart 3.1). The reaction was initially performed without water as additive (second bars) as reported in Hoveyda-Snapper protocol for furan derivatives[3] but again, as demonstrated previously by us, the presence of isopropanol alone negatively affected both yield and enantioselectivity (58 and 80% respectively): as protic scavenger of the evolving silicon ion species, water might concur in the depletion of the competitive racemic background reaction catalyzed by the silicon ions themselves, thus resulting in improved stereoselectivity. An *all-in-one* execution, mixing together the reagents and reactants without the employment of the drying agent, resulted in excellent diastereoselectivity and remarkable enantioselection albeit with much lower yield (25%). Additional

improvements in terms of efficiency were achieved by increasing the concentration of **17** from 0.1 M to 0.2 and 0.4 M (78 and 80% isolated yield), as well as lowering the temperature from 0 °C to –30 °C (84%) with a little increase of the enantiodifferentiation (96% ee) as well.

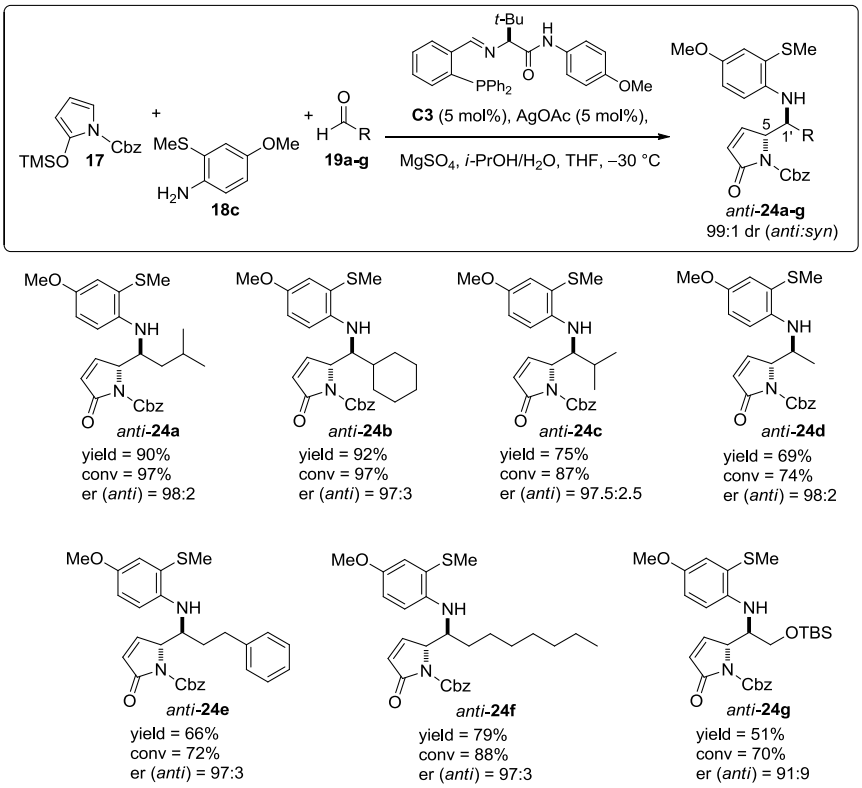
Chart 3.1. Further optimization of the asymmetric VMMnR between donor **17**, amine **18c** and isovaleraldehyde **19a**.[a]



[a] Unless otherwise stated, the reactions were carried out using **17** (0.3 mmol, 1.5 eq), aldehyde **19a** (1.0 eq), amine **18c** (1.0 eq), $MgSO_4$ (2.0 eq), ligand **C3**/AgOAc (1:1, 10 mol% each), undistilled *i*-PrOH:H_2O (1:1, 1.5 eq each) and stabilized (BHT, 250 ppm) THF, in air, for 16 h at 0 °C, conc. 0.1 M referred to **17**. [b] Isolated yield after silica gel flash column chromatography. [c] Determined by ^1H NMR analysis of the reaction crude. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Aldol product isolated. [f] Reaction carried out at –30 °C.

A temperature of –78 °C proved to be detrimental, resulting in a sluggish reaction and lower enantioselectivity (44% yield and 84% ee). Half quantity of catalyst loading did not alter the reaction course, and the Mannich adduct **24a** was obtained in 90% isolated yield, almost complete *anti*-selectivity and excellent 98:2 er.

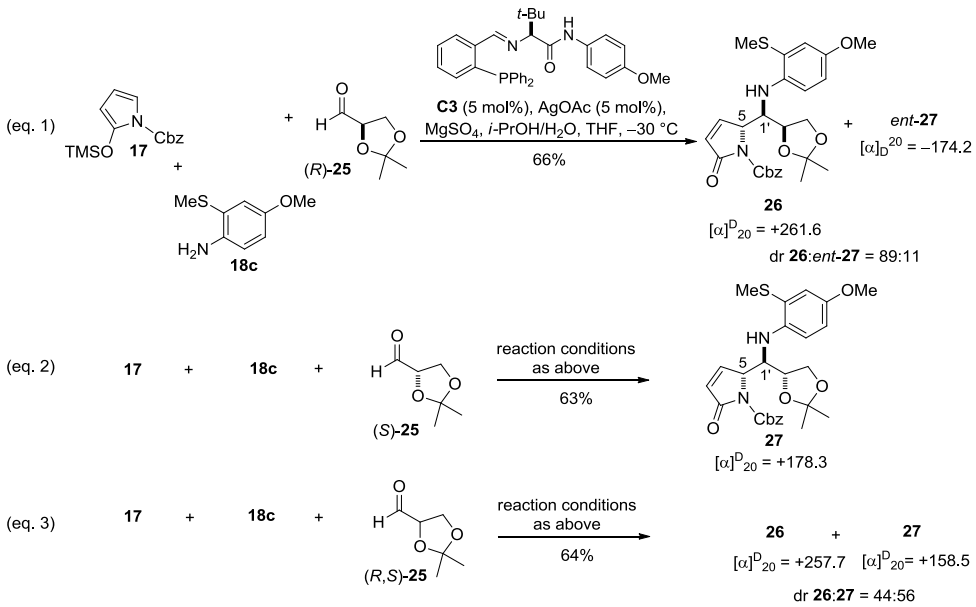
Table 3.6. Scope of the asymmetric three-component VMMnR of pyrrole **17** and amine **18c** with alkyl- and hydroxyalkyl-substituted aldehydes.[a]



[a] The reactions were carried out using **17** (1.5 eq), aldehyde **19a-g** (1.0 eq), amine **18c** (1.0 eq), $MgSO_4$ (2.0 eq), ligand **C3**/AgOAc (1:1, 5 mol% each), undistilled *i*-PrOH:H_2O (1:1, 1.5 eq each) and stabilized (BHT, 250 ppm) THF, in air, for 16 h at –30 °C, conc. 0.4 M referred to **17**. Conversions determined by ^{1}H NMR analysis of the reaction crude. Isolated yield after silica gel flash column chromatography. Diastereomeric ratio determined by ^{1}H NMR analysis of the reaction crude. Enantiomeric ratio determined by HPLC analysis on a chiral stationary phase.

Having established the optimized reaction conditions, the reaction scope

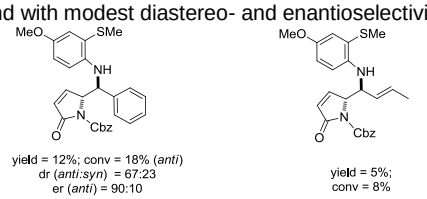
with respect to the aldehyde component was studied next (table 3.6).[10] It was demonstrated that a variety of aldehyde acceptors was compatible with the developed protocol and the Mannich adducts **24a-g** were generally isolated in good yields, excellent diastereoselectivity in favor of the *anti*-configured Mannich butyrolactams and remarkable enantiodifferentiation up to 96% ee.



Scheme 3.3. Influence of the glyceraldehyde chirality in the catalytic asymmetric **C3•**AgOAc-catalyzed VMMnR of pyrrole **17** and amine **18c**.

In order to complete our investigation, the impact of the chirality within the silver-based chiral catalyst complex on the stereochemical outcome of the VMMnR was verified in the presence of a homochiral aldehyde precursor (scheme 3.3). 2,3-*O*-Isopropylideneglyceraldehyde (**25**) was chosen for these experiments. In scheme 3.3 the results of the

[10] As illustrated by the examples below, by following the optimized conditions, the catalytic asymmetric VMMn reaction with aldimines derived from aromatic or α,β-unsaturated aldehydes proceeded in lower yields and with modest diastereo- and enantioselectivity.

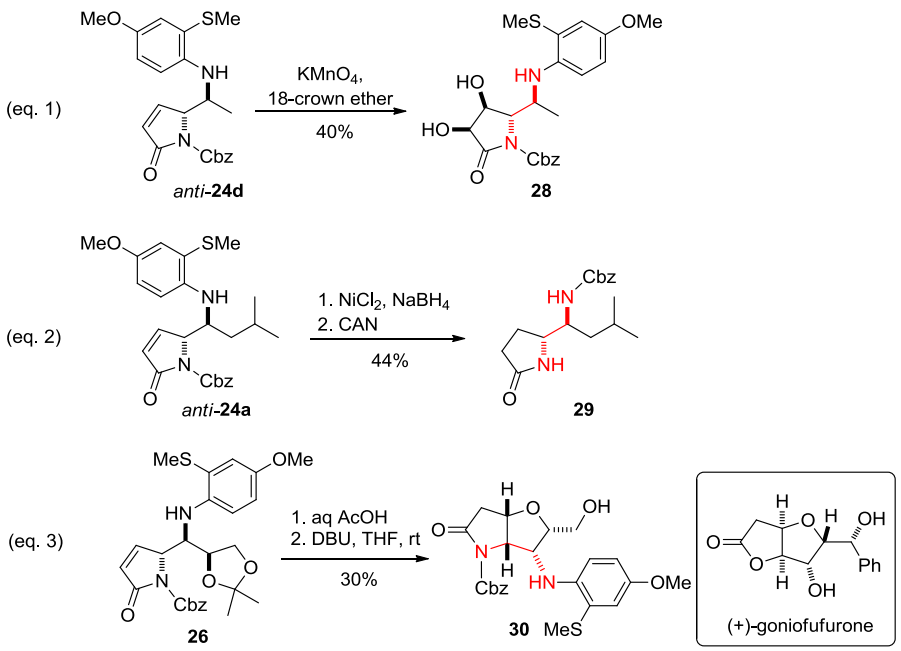


asymmetric VMMnR between pyrrole **17**, aromatic amine **18c** and aldehyde enantiomers (*R*)-**25** and (*S*)-**25** as well as the corresponding racemate in the presence of **C3**•AgOAc are reported. It was observed that the chirality resident in the aldehyde did not play a pivotal role in the catalytic asymmetric VMMnR because the employment of both the enantiomers of glyceraldehyde **25** gave the desired products **26** and **27** with almost the same efficiency and the same relative and absolute stereochemistry of the newly formed C5 and C1' stereocenters (both *anti*- and 5*R*,1'*R*-configured). Furthermore, reaction with the racemate of **25** provided a nearly equal amount of adducts **26** and **27** (albeit a small matched/mismatched case in favor of (*S*)-**25**) indicating that no kinetic resolution occurred during the vinylogous Mannich reactions.

This experiment demonstrated that the intrinsic chirality of the peptide-like ligand/silver complex catalytic system played a unique role in determining the asymmetric induction, largely overriding the inherent chirality of the aldehyde component. In truth, the optical rotation value of **27** in equation 3, arising from (*R,S*)-**25**, was slightly lower than that measured for the same isomer arising from (*S*)-**25** (eq. 2) ($[\alpha]^{D}_{20}$ = +158.5 *vs* $[\alpha]^{D}_{20}$ = +178.3), and this suggested that a small amount of *ent*-**27**, the minor product with (*R*)-**25** in eq. 1, contaminated this isomer, lowering its optical rotation value to some extent.

3.3.2 Elaboration of the Mannich products

As outlined at the beginning of the chapter, δ-aminated γ-lactam scaffolds constitute important building blocks for a variety of chemical entities. In scheme 3.1, a possibility of simple but effective elaboration of this structure was depicted. As part of this project, we wanted to turn the "ideal" chemical manipulations of scheme 3.1 into reality demonstrating, in so doing, the versatility of the synthesized Mannich butyrolactam structures (scheme 3.4).



Scheme 3.4. Skeletal elaboration of Mannich products to functionality-rich 1,2-diaminated scaffolds.

In equation 1 of scheme 3.4 is shown a simple diastereoselective dihydroxylation of the lactam double bond within *anti*-**24d** to give the 3,4-*cis*:3,5-*trans*-configured diol **28**. In the second equation, a three-step hydrogenation/dearylation/*N,N*-Cbz-migration[11] sequence to structure **29** is reported. The last transformation is a chemo- and diastereoselective oxa-Michael cyclization to rare hexahydrofuro[3,2-*b*]pyrrolone **30**, reminiscent of the fully oxygenated structure of naturally occurring (+)-goniofufurone.[12]

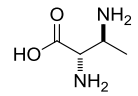
3.3.3 Stereochemical assessment

Despite plain determination of the relative and absolute configuration of the vinylogous aryl-substituted Mannich adducts was described in the

[11] For other examples on *N*-Cbz group-migration, see: (a) Bunch, L.; Norrby, P.-O.; Frydenvang, K.; Krogsgaard-Larsen, P.; Madsen, U. *Org. Lett.* **2001**, *3*, 433. (b) Quijada, F. J.; Gotor, V.; Rebolledo, F. *Org. Lett* **2010**, *12*, 3602.
[12] Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2.

previous paragraph (3.2.2), we were now facing the challenging task to determine the stereochemistry of the newly created alkyl-substituted Mannich products.

In order to determine unambiguously the absolute stereochemistry of the prepared compounds, several crystallization attempts of *anti*-**24a** using different techniques were made but they failed completely in giving suitable crystals for the X-ray analysis. It was then decided to proceed with a chemical procedure which would correlate the structure of known (2*S*,3*S*)-diaminobutanoic acid (**31**)[13] (figure 3.3) to that of *anti*-**24d**.



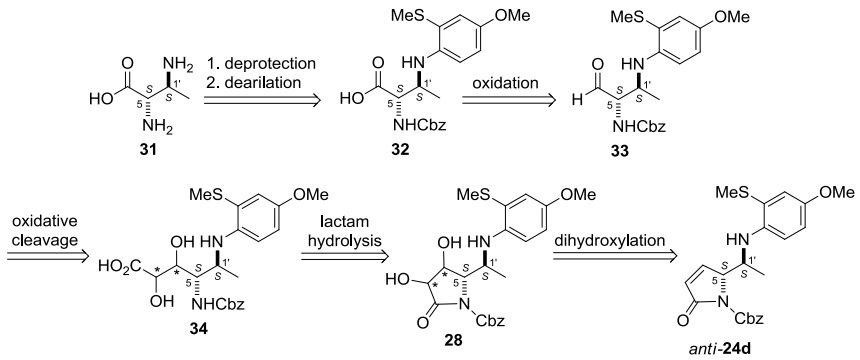
(2*S*,3*S*)-Dab (**31**)

Figure 3.3. (2*S*,3*S*)-2,3-diaminobutanoic acid (**31**) structure.

The proposed retrosynthetic strategy is shown in scheme 3.5 where (2*S*,3*S*)-dab (**31**) could be accessible in a six-step sequence starting from *anti*-**24d**. Thus, compound **28**, derived from **24d** by dihydroxylation, could be subjected to hydrolysis to deliver the linear multi-functionalized carboxylic acid **34**, which could undergo an oxidative cleavage to aldehyde **33** which, in turn, might deliver the desired compound **31** after oxidation, dearylation and final deprotection.

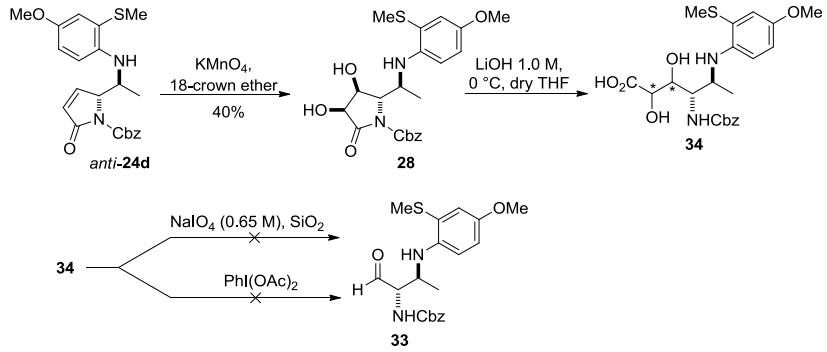
In putting this seemingly simple plan into practice, however, several problems arose. Compound *anti*-**24d** was subjected to stereoselective dihydroxylation using $KMnO_4$/18-crown ether conditions furnishing diol **28** without troubles. Compound **28** was subsequently treated with a 1.0 M aqueous LiOH solution in order to synthesize intermediate **34** (scheme 3.5).

[13] Han, H.; Yoon, J.; Janda, K. *J. Org. Chem*. **1998**, *63*, 2045.



Scheme 3.5. Proposed retrosynthetic route towards (2*S*,3*S*)-dab (**31**).

At this point, the linear dihydroxy acid **34** was subjected to oxidative cleavage conditions: a first attempt was made by using $NaIO_4$ (0.65 M) and SiO_2 (eq. 1) but these conditions failed to give aldehyde **33** probably due to concomitant dearylation of the nitrogen atom[14] at the C1' position and breakage of the C5-C1' σ bond.[15]



Scheme 3.6. Attempts towards the synthesis of intermediate **33**.

Next, $PhI(OAc)_2$ was used in a second effort towards **33** (eq. 2), but even in this case it was not possible to clearly detect the desired aldehyde intermediate.

In reasoning on the next move, we found that the solution to our problems (stereochemical assignment) could have been nearer than

[14] Verkade, J. M.M.; Van Hemert J.C. Quaedflieg J.L.M.; Alsters P.L.; Van Delft F.L.; Rutjes P.J.T. *Tetrahedron Letters* **2006**, *47*, 8109.
[15] For an example of 1,2-diamines cleavage see, Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Acamdemic Press, **2005**, p. 114 and references therein.

expected. Simple inspection of the NOESY-derived structure of bicyclic compound **30**, directly derived from the Mannich product **26**, could have furnished answers to our open questions. Thus, extensive 1D and 2D NMR analyses including NOESY correlation experiments of bicyclic compound **30** were made.

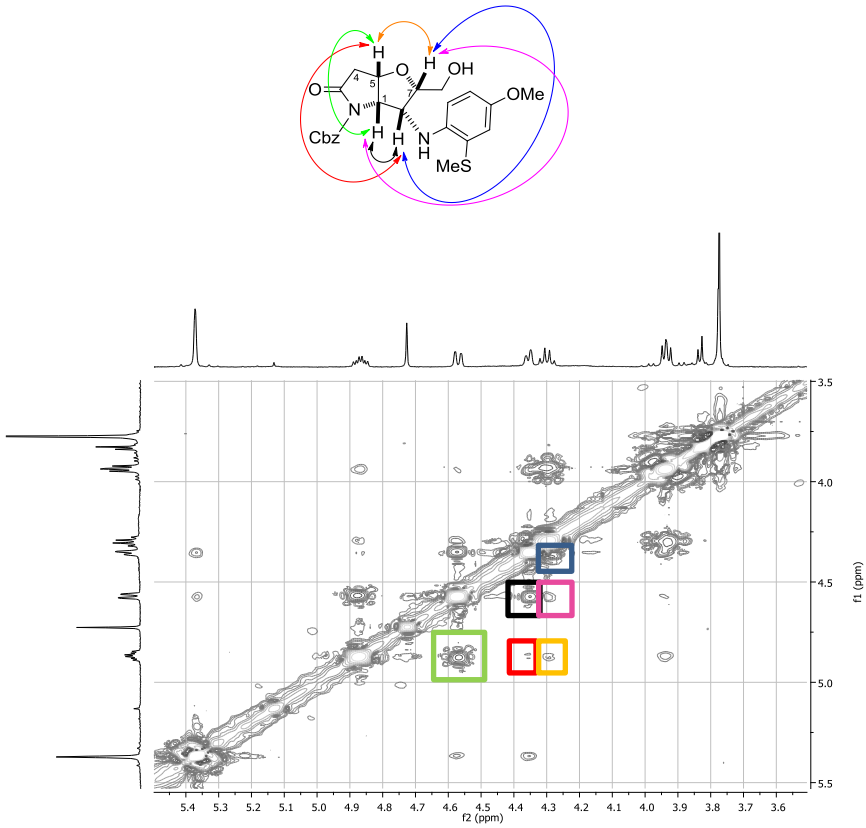


Figure 3.4. Diagnostic NOE contacts within compound **30** (^{1}H-^{1}H NMR spectrum at 300 MHz in $CDCl_3$).

This analysis provided confirmation of the relative and absolute configuration of the four embodied stereocenters (the *S*-C7 absolute configuration of **30** was certified by its origin from D-glyceraldehyde) and, ultimately, established the precursor **26** to have the 5*R*,1′*R*,2′*S*-stereochemistry. Based on this result, all structures in table 6 were assigned by analogy, in accordance with the stereoinduction trend

dictated by the chiral ligand in the silver catalyst, featuring preferential attack of the diene nucleophile (*si*-face) at the *re*-face of the imine component (see next section).[2]

As for the isomeric candidate **27** (see Scheme 3.3) the relative and absolute configuration was inferred to be 5*R*,1'*R*,2'*R* (5,1'-*anti*:1',2'-*anti*) by chiro-optical considerations[16] and strict ^{1}H and ^{13}C NMR spectral analogy to a known, related compound.[8]

3.4 Rationalization of the stereochemical outcome of the asymmetric Ag-catalyzed VMMn reactions

As mentioned in the previous sections 3.2 and 3.3, all the synthesized Mannich products arose from the preferential attack of the pyrrole donor (*si*-face) at the *re*-face of the imine acceptor. In absence of *ab initio* DFT calculations studies which could provide definitive clues on the energetic course of the reaction and possible preferred transition states, we can here speculate about three feasible transition states which could well account for the stereochemical outcome of the present VMMnR (figure 3.5).

As postulated by Hoveyda and coworkers in their work,[2] common feature for the silver-based catalyst system is the chelation between the oxygen (or the sulfur) atom of the imine aromatic ring and the silver atom; the imine substrate turns out to be positioned *anti* to the bulky R substituent of the amino acid ligand in order to avoid steric hindrance.

[16] (a) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron* **1990**, *46*, 5807; (b) Gawroński, J.; Gawrońska, K.; Kwit, M.; Kacprzak, K.; Rychlewska, U. *Chirality*, **2004**, *16*, 405; (c) Cuiper, A. D.; Brzostowska, M.; Gawroński, J. K.; Smeets, W. J. J.; Spek, A. L.; Hiemstra, H.; Kellogg, R. M.; Feringa, B. L. *J. Org. Chem.* **1999**, *64*, 2567.

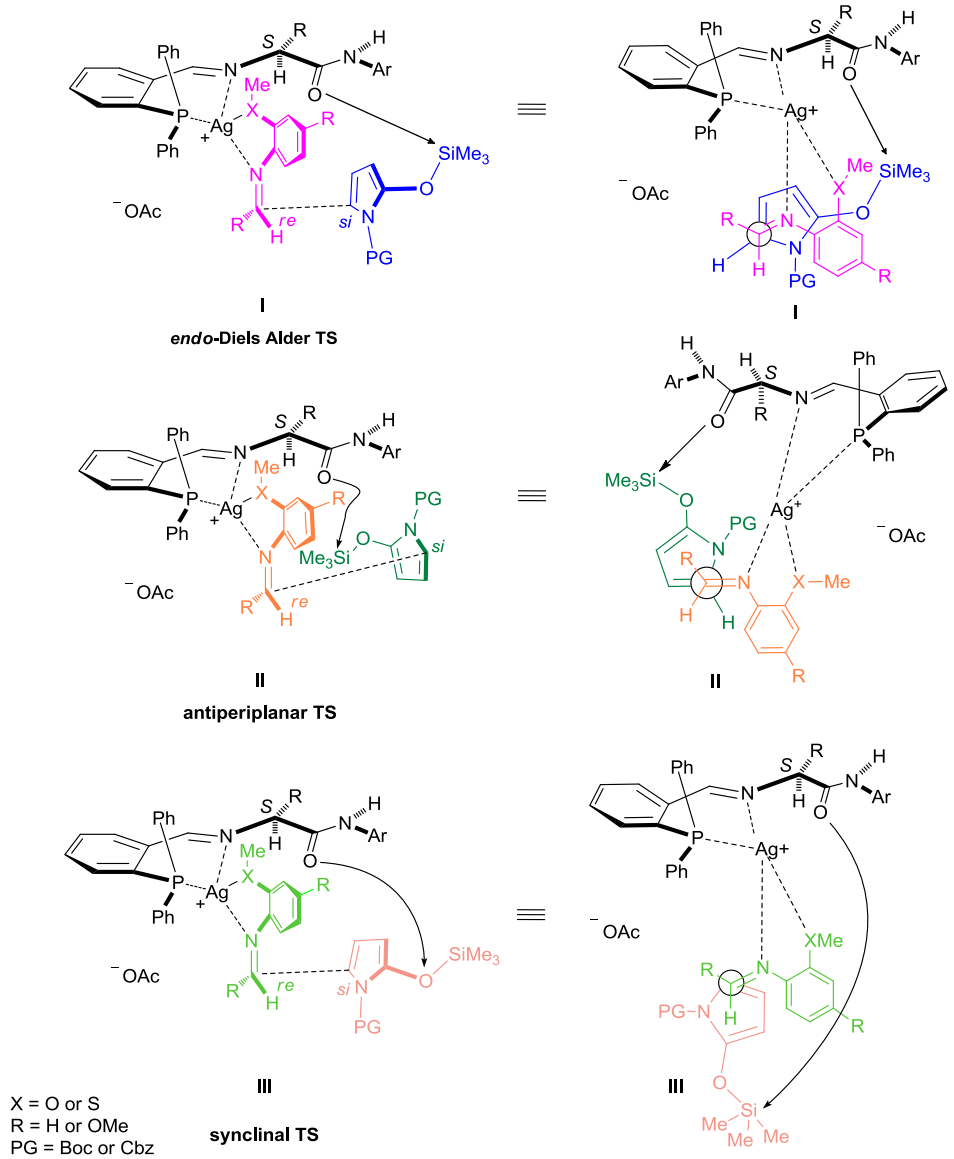


Figure 3.5. Plausible transition state structures of the asymmetric VMMnR.

It could also be invoked a supplemental interaction between the amide moiety of the chiral ligand and the silyloxypyrrole, a so-called *Lewis acid Lewis base interaction*[17] which might enhance the nucleophilicity of the

[17] a) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774-3789, and references therein; b) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67.

donor thus facilitating the delivery of the product during the catalytic cycle (see chapter 2 section 2.2.3.1). According to transition state shown in picture **I**, the donor could approach the electrophile by an *endo*-Diels Alder type addition[18] and this TS could justify low values of efficiency and enantiodifferentiation using siloxypyrroles with sterically encumbering silicon moieties. In picture **II** an antiperiplanar trajectory is proposed, by which the nucleophile is disposed *anti* with respect to the imine substrate: stabilizing π-π interactions between the aromatic ring of the acceptor (in case of aromatic aldimines) and the diene system of the nucleophile could be generated.The third model (TS **III**) shows a synclinal approach of the reactants where the silicon moiety of the donor still results far away from the imine as in TS **II**, albeit in this case favorable π-π interactions cannot be invoked.

Possibly, antiperiplanar transition state **II** could be the most favorable due to less steric hindrance and stabilizing interactions. the contribution of TS **I** as well **III** could not be ignored because the two protocols possessed structurally and electronically different nucleophiles and electrophiles and this might lead to different trajectory for the two developed VMMnR methodologies.

3.5 Conclusions

The first example of catalytic asymmetric VMMnR of pyrrole-based silyl dienolates with a series of *N*-arylimines has been reported. Good efficiency, excellent diastereoselectivity and valuable enantioselection were obtained in all cases, exploiting the amino acid-derived silver(I) catalyst system developed by Hoveyda-Snapper. In a second stage of the project, a more efficient protocol was developed for a three-component reaction with alkyl-substituted electrophile components: good yield, excellent diastereocontrol and remarkable enantiodifferentiation

[18] Burr, S. K.; Martin, S. F. *Org. Lett.* **2000**, *2*, 3445.

were generally observed, thanks to a fine tuning of the reactants and reaction conditions. The synthetic utility of the process was demonstrated by basic skeletal manipulation of the resulting vinylogous Mannich adducts. A key part of the study was dedicated to the accurate determination of the absolute and relative stereochemistry of the synthesized compound. Also, plausible transition states were proposed accounting for the observed stereoinduction.

3.6 Experimental data

General experimental methods: All reactions were performed in clean, standard laboratory glassware with rubber septa. Solvents for chromatography and filtration including hexane, ethyl acetate, dichloromethane, petroleum ether, diethyl ether, anhydrous ethanol, methanol and 2-propanol were ACS or HPLC grade and used as received. Mannich reaction solvent tetrahydrofuran (BHT, 250 ppm) was purchased from Sigma-Aldrich and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} pre-coated plates with visualization under short-wavelenght UV light and by dipping the plates with molybdate reagent (aqueous H_2SO_4 solution of ceric sulphate/ammonium molybdate) followed by heating. Flash column chromatography was performed using 40-63 μm silica gel using the indicated solvent mixtures. HPLC samples were previously filtered through Whatman Anotop 10 LC membrane filters using the indicated solvent mixtures. Analytical chiral HPLC analysis was carried out using Chiralcel OD-H column and Regis (*S,S*)-Whelk-O 1 (250×4.6 mm) column. Optical rotation data were obtained on a digital polarimeter at ambient temperature using a 100 mm cell with a 1 mL capacity and are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded at 300 MHz or 400 MHz (^{1}H) and 75 MHz or 100 MHz (^{13}C). Spectra were referenced to tetramethylsilane (0.0 ppm, ^{1}H; 0.0 ppm, ^{13}C, in $CDCl_3$). Chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hertz. ^{1}H and ^{13}C NMR assignments are corroborated by 1D and 2D experiments (gCOSY, gHSQC, and DEPT sequences). ESI-mass spectra were recorded on API 150EX apparatus and are reported in the form of (*m/z*). Octanal (**19f**) was distilled prior to use; 3-Methylbutyraldehyde (**19a**), hexahydrobenzaldehyde (**19b**), 2-methylpropionaldehyde (**19c**), ethanal (**19d**), 3-phenylpropanal (**19e**) and (*tert*-butyldimethylsilyloxy)acetaldehyde (**19g**), were commercially available and used as such without further purification. 4-Methoxy-

2(methylthio)aniline[19] (**18c**), D-glyceraldehyde[20] (*R*)-**25** and L-glyceraldehyde[21] (*S*)-**25** were prepared as reported in literature. Immine **2a** was prepared according to reported procedure.[22] Phosphino aminoacid-based ligand **C3** was prepared and characterized according to literature procedures.[2b] The purity of the ligand was ascertained by close inspection of their ^{1}H and ^{13}C NMR spectra, as well as optical rotation measurements.

Starting materials: *N*-Protected [(trialkylsilyl)oxy]pyrroles **1a-c**, **4ac-7ac** and **17** were prepared according to previously reported procedures by our laboratories.[5]

***N*-Benzyloxycarbonyl[(trimethylsilyl)oxy]pyrrole 17** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.39 (m, 5H, Ph, Cbz); 6.85 (dd, *J* = 3.9, 1.95 Hz, 1H, H3); 6.00 (dd, *J* = 3.5, 3.8 Hz, 1H, H4); 5.36 (s, 2H, CH_2, Cbz); 5.31 (dd, *J* = 3.5, 1.95 Hz, 1H, H5); 0.25 (s, 9H, $3CH_3Si$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0 (Cq, CO, Cbz); 140.0 (Cq, C2); 135.1 (Cq, Ph, Cbz); 128.6 (2CH, Ph, Cbz); 128.58 (CH, Ph, Cbz); 128.5 (2CH, Ph, Cbz); 113.2 (CH, C5); 109.1 (CH, C4); 93.0 (CH, C3); 68.4 (CH_2, Cbz); −0.4 ($3CH_3$, Si).

Representative VMMn Procedure (procedure a, table 3.4). (*R*)-5-(*N-tert*-Butoxycarbonyl)-[(*S*)-(2-methoxyphenylamino)(phenyl)methyl]-1*H*-pyrrol-2(5*H*)one (*anti*-3a). Chiral phosphine **C3** (14.0 mg, 0.02 mmol, 0.10 equiv) and AgOAc (3.5 mg, 0.02 mmol, 0.10 equiv) were dissolved in undistilled BHT-stabilized (250 ppm) THF (4 mL) and allowed to stir for5 min at 22 °C. A solution of *N*-benzylidene-2-methoxybenzenamine **2a** (44.0 mg, 0.21 mmol, 1.0 equiv) in THF (1.0 mL) was added followed by addition of a mixture of *i*-PrOH (24.0 μL, 0.31 mmol, 1.5 equiv)/H2O (6.0 μL, 0.31 mmol, 1.5 equiv) and the reaction vessel was capped with a septum. The mixture was allowed to cool to 0 °C and **1c** (82.0 mg, 0.31 mmol, 1.5 equiv) in THF (1.0 mL) was added. After 16 h the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (0.5 mL). The mixture was allowed to warm to 22 °C with vigorous stirring for 10 min, and finally extracted with EtOAc. The organic layers were collected, dried with $MgSO_4$, filtered, and concentrated in vacuo. The diastereomeric ratio of the addition products **3a** was determined to be 99.0:1.0 by analytical HPLC (see below). The crude residue was then purified by silica-gel flash chromatography (hexane/Et_2O 70:30), to yield 62 mg (80%) of (+)-*anti*-**3a** as colorless crystals: TLC, R_f = 0.38 (petroleum ether/EtOAc 70:30); $[\alpha]^{D}_{20}$ = +99.5 (c 0.99, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.30 (m, 5H, Ph), 6.92 (dd, *J* = 6.1, 2.0 Hz, 1H, H4), 6.77 (dd, *J* = 7.4, 2.1 Hz, 1H, H3″), 6.70

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(ddd, *J* = 7.5, 7.5, 1.8 Hz, 1H, H5″), 6.65 (ddd, *J* = 7.5, 7.5, 1.9 Hz, 1H, H4″), 6.32 (dd, *J* = 7.2, 2.1 Hz, 1H, H6″), 6.30 (dd, *J* = 6.0, 1.6 Hz, 1H, H3), 5.44 (bd, *J* = 3.3 Hz, 1H, H1′), 5.06 (ddd, *J* = 3.6, 1.8, 1.8 Hz, 1H, H5), 4.44 (bs, 1H, NH), 3.86 (s, 3H, CH_3), 1.56 (s, 9H, *t*-Bu, Boc); 13C NMR (75 MHz, $CDCl_3$) δ 169.0 (Cq), 149.6 (Cq), 147.3 (Cq), 146.1 (CH), 139.7 (Cq), 136.9 (Cq), 129.3 (CH), 129.1 (2C, CH), 128.0 (CH), 126.6 (2C, CH), 121.2 (CH), 117.7 (CH), 111.6 (CH), 109.8 (CH), 83.7 (Cq), 67.7 (CH), 57.3 (CH), 53.6 (CH_3), 28.3 (3C, CH_3). ESI-MS *m/z* 417.38 $[M+Na]^+$ (Calcd 417.18 $[M+Na]^+$). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.13; H, 6.78; N, 6.95. HPLC: *anti*-**3a**, t_R 11.71 min (99.0%); *syn*-**3a**, t_R 14.33 min (1.0%) (CN-100, 5μm, hexane/anhydrous EtOH 95:5, 1.0 mL/min, 254 nm) Chiral HPLC: (1′*R*,5*S*)-**3a**, t_R 8.99 min (90.0%); (1S,5*R*)-**3a**, t_R 10.14 min (10.0%) (Chiralcel OD-H, hexane/anhydrous EtOH 90:10, 1.0 mL/min, 254 nm).

(*R*)-5-(*N-tert*-Butoxycarbonyl)-[(*S*)-(4-methoxyphenyl)(2methoxyphenylamino) methyl]-1*H*pyrrol-2(5*H*)one (*anti*-3b). Lactam *anti*-**3b** was prepared according to the representative procedure described for *anti*-**3a**, utilizing *N*-(4-methoxybenzylidene)-2-methoxybenzenamine **2b** (50.0 mg, 0.21 mmol, 1.0 equiv), and **1c** (80.0 mg, 0.31 mmol, 1.5 equiv). The diastereomeric ratio of the addition products was determined to be 98.0:2.0 by analytical HPLC (see below). The crude residue was purified by silicagel flash chromatography (hexane/Et_2O 80:20), to yield 84.0 mg (94%) of (+)-*anti*-**3b** as a colorless resin. TLC, R_f = 0.29 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ = +36.4 (*c* 0.58, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H, Ar), 6.94 (m, 1H, H4), 6.93 (d, *J* = 8.6 Hz, 2H, Ar), 6.76 (dd, *J* = 7.3, 1.8 Hz, 1H, H6″), 6.70 (ddd, *J* = 7.5, 7.5, 1.9 Hz, 1H, H5″), 6.64 (m, 1H, H4″), 6.32 (dd, *J* = 6.0, 1.6 Hz, 1H, H3), 6.29 (dd, *J* = 6.2, 1.5 Hz, 1H, H3″), 5.37 (d, *J* = 3.4 Hz, 1H, H1′), 5.02 (ddd, *J* = 3.6, 1.8, 1.8 Hz, 1H, H5), 3.85 (s, 3H, OMe), 3.81 (s, 3H, OMe), 1.58 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (Cq), 159.4 (Cq), 149.7 (Cq), 147.3 (Cq), 146.3 (CH), 137.0 (Cq), 131.5 (Cq), 129.2 (CH), 127.7 (2C, CH), 121.2 (CH), 117.6 (CH), 114.5 (2C, CH), 111.6 (CH), 109.8 (CH), 83.6 (Cq), 67.8 (CH), 56.8 (CH), 55.8 (CH_3), 55.4 (CH_3), 28.3 (3C, CH_3). ESI-MS *m/z* 447.29 $[M+Na]^+$ (Calcd 447.19 $[M+Na]^+$). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.80; H, 6.77; N, 6.58. HPLC: *anti*-**3b**, t_R 10.62 min (98.4%); *syn* -**3b**, t_R 13.60 min (1.6%) (CN-100, 5 μm, hexane/*i*PrOH 90:10, 1.0 mL/min, 254 nm). Chiral HPLC: (5*R*,1′*S*)-**3b**, t_R 11.94 min (77.7%); (5*S*,1′*R*)-**3b**, t_R 18.77 min (22.3%) (Chiralcel OD-H, hexane/anhydrous EtOH 90:10, 1.0 mL/min, 254 nm).

(*R*)-5-(*N-tert*-Butoxycarbonyl)-[(*S*)-(4-bromophenyl)(2-methoxyphenylamino)

methyl]-1*H*pyrrol-2(5*H*)one (*anti*-3c). Lactam *anti*-**3c** was prepared according to the representative procedure described for *anti*-**3a**, utilizing *N*-(4-bromobenzylidene)-2-methoxybenzenamine **2c** (60.0 mg, 0.21 mmol, 1.0 equiv), and **1c** (80.0 mg, 0.31 mmol, 1.5 equiv). The diastereomeric ratio of the addition products was determined to be 99.0:1. by analytical HPLC (see below). The crude residue was purified by silicagel flash chromatography (hexane/Et_2O 70:30), to yield 95 mg (91%) of (+)-*anti*-**3c** as a colorless resin: TLC, R_f = 0.39 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ = +39.4 (*c* 1.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H, Ar), 7.33 (d, *J* = 8.4 Hz, 2H, Ar), 6.88 (dd, *J* = 6.1, 2.0 Hz, 1H, H4), 6.77 (m, 1H, H6″), 6.66-6.70 (m, 2H, H5″, H4″), 6.30 (dd, *J* = 6.1, 1.4 Hz, 1H, H3), 6.27 (dd, *J* = 7.3, 2.5 Hz, 1H, H3″), 5.37 (m, 1H, H1′), 5.01 (ddd, *J* = 3.4, 1.4, 1.4 Hz, 1H, H5), 4.43 (m, 1H, NH), 3.85 (s, 3H, OMe), 1.54 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (Cq), 149.7 (Cq), 147.3 (Cq), 145.7 (CH), 138.9 (Cq), 136.7 (Cq), 132.3 (2C, CH), 129.6 (CH), 128.4 (2C, CH), 121.9 (Cq), 121.2 (CH), 117.9 (CH), 111.5 (CH), 109.8 (CH), 83.8 (Cq), 67.4 (CH), 56.9 (CH), 55.8 (CH_3), 28.3 (3C, CH_3). ESI-MS *m/z* 495.05 $[M+Na]^+$ (Calcd 495.09 $[M+Na]^+$). Anal. Calcd for $C_{23}H_{25}BrN_2O_4$: C, 58.36; H, 5.32; N, 5.92. Found: C, 58.41; H, 5.44; N, 5.81. HPLC: *anti*-**3c**, t_R 10.65 min (98.9%); *syn* -**3c**, t_R 14.46 min (1.1%) (CN-100, 5 μm, hexane/*i*PrOH 95:5, 1.0 mL/min, 254 nm). Chiral HPLC: (5*R*,1'*S*)-**3c**, t_R 11.04 min (71.1%); (5*S*,1'*R*)-**3c**, t_R 16.84 min (28.9%) (Chiralcel OD-H, hexane/anhydrous EtOH 90:10, 1.0 mL/min, 254 nm).

(*R*)-5-(*N-tert*-Butoxycarbonyl)-[(*S*)-(2-methoxyphenylamino)(4-nitrophenyl) methyl]-1*H*pyrrol-2(5*H*)one (*anti*-3d). Lactam *anti*-**3d** was prepared according to the representative procedure described for *anti*-**3a**, utilizing *N*-(4-nitrobenzylidene)-2-methoxybenzenamine **2d** (53.5 mg, 0.21 mmol, 1.0 equiv), and **1c** (80.0 mg, 0.31 mmol, 1.5 equiv). The diastereomeric ratio of the addition products was determined to be 99.0:1.0 by analytical HPLC (see below). The crude residue was purified by silica-gel flash chromatography (hexane/EtOAc 75:25) to yield 91 mg (98%) of (+)-*anti*-**3d** as a colorless resin: TLC, R_f = 0.36 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ +40.0 (*c* 0.18, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.6 Hz, 2H, Ar), 7.65 (d, *J* = 8.5 Hz, 2H, Ar), 6.87 (dd, *J* = 6.1, 1.5 Hz, 1H, H4), 6.79 (m, 1H, H6″), 6.70 (m, 2H, H5″, H4″), 6.33 (bd, *J* = 5.2 Hz, 1H, H3), 6.25 (m, 1H, H3″), 5.51 (bd, *J* = 2.9 Hz, 1H, H1′), 5.18 (m, 1H, H5), 3.87 (s, 3H, OMe), 1.54 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (Cq), 149.9 (Cq), 147.9 (Cq), 147.5 (Cq), 147.3 (Cq,),145.0 (CH), 136.1 (Cq), 130.0 (CH), 127.8 (2C, CH), 124.4 (2C, CH), 121.2 (CH), 118.7 (CH), 111.8 (CH), 110.02 (CH), 84.1 (Cq), 66.9 (CH), 57.6 (CH), 55.9 (CH_3), 28.2 (3C, CH_3). ESI-MS *m/z* 462.24 $[M+Na]^+$ (Calcd 462.16 $[M+Na]^+$). Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 62.98; H, 6.80; N, 9.49. HPLC: *anti*-**3d**, t_R 27.89 min (98.8%); *syn*-**3d**, t_R 41.32 min (1.2%) (CN-100,

5 μm, hexane/*i*PrOH 95:5, 1.0 mL/min, 254 nm). Chiral HPLC: (5*R*,1'*S*)-**3d**, t_R 28.70 min (71.0%); (5*S*,1'*R*)-**3d**, t_R 34.52 min (29.0%) (Chiralcel OD-H, hexane/anhydrous EtOH 90:10, 1.0 mL/min, 254 nm).

(*R*)-5-(*N*-*tert*-Butoxycarbonyl)-[(*S*)-(2-methoxyphenylamino)(naphthalen-2-yl)methyl]-1*H*pyrrol-2(5*H*)one (*anti*-3e). Lactam *anti*-**3e** was prepared according to the representative procedure described for *anti*-**3a**, utilizing 2-methoxy-*N*-[(naphthalen-2-yl)methylene]benzenamine **2e** (54.5 mg, 0.21 mmol, 1.0 equiv), and **1c** (80.0 mg, 0.31 mmol, 1.5 equiv). The diastereomeric ratio of the addition products was determined to be 99.0:1.0 by analytical HPLC (see below). The crude residue was purified by silica-gel flash chromatography (hexane/EtOAc 70:30), to yield 60 mg (65%) of (+)-*anti*-**3e** as a colorless resin. TLC, R_f = 0.41 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ = +36.4 (*c* 0.58, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.93 (m, 4H, Ar), 6.59 (dd, *J* = 8.6, 1.5 Hz, 1H, Ar), 7.53 (t, *J* = 3.9 Hz, 1H, Ar), 7.49 (t, *J* = 3.5 Hz, 1H, Ar), 6.95 (dd, *J* = 6.1, 2.0 Hz, 1H, H4), 6.79 (m, 1H, H6″), 6.68 (t, *J* = 4.3 Hz, 1H, H5″), 6.32 (dd, *J* = 6.2, 1.6 Hz, 1H, H3), 6.65 (t, *J* = 3.8 Hz, 1H, H4″), 6.36 (m, 1H, H3″), 5.59 (bd, *J* = 3.4 Hz, 1H, H1′), 5.18 (ddd, *J* = 3.5, 1.8, 1.8 Hz, 1H, H5), 3.90 (s, 3H, OMe), 1.59 (s, 9H, Bu^t); 13C NMR (75 MHz, $CDCl_3$) δ 168.9 (Cq), 149.7 (Cq), 147.4 (Cq), 146.2 (CH), 137.3 (Cq), 137.0 (C), 133.6 (Cq), 133.3 (CH), 129.4 (CH), 129.0 (CH), 128.2 (CH), 127.9 (CH), 126.6 (CH), 126.3 (CH), 125.6 (CH), 124.5 (CH), 121.3 (CH), 117.8 (CH), 111.8 (CH), 109.8 (CH), 83.8 (Cq), 67.6 (CH), 57.7 (CH), 55.9 (CH_3), 28.3 (3C, CH_3). ESI-MS *m/z* 467.10 $[M+Na]^+$ (Calcd 467.19 $[M+Na]^+$). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30. Found: C, 72.88; H, 6.41; N, 6.29. HPLC: *anti*-**3e**, t_R 12.55 min (99.0%); *syn*-**3e**, t_R 17.89 min (1.0%) (CN-100, 5 μm, hexane/*i*PrOH 95:5, 1.0 mL/min, 254 nm). Chiral HPLC: (5*R*,1'*S*)-**3e**, t_R 15.16 min (75.2%); (5*S*,1'*R*)-**3e**, t_R 36.39 min (24.8%) **(**Chiralcel OD-H, hexane/anhydrous EtOH 90:10, 1.0 mL/min, 254 nm).

(*R*)-5-(*N*-*tert*-Butoxycarbonyl)-[(*R*)-(2-methoxyphenylamino)(furan-2-yl)methyl]-1*H*-pyrrol-2(5*H*)one (*anti*-3f). Lactam *anti*-**3f** was prepared according to the representative procedure described for *anti*-**3a**, utilizing *N*-[(furan-2-yl)methylene]-2-methoxybenzenamine **2f** (42.0 mg, 0.21 mmol, 1.0 equiv), and **1c** (80.0 mg, 0.31 mmol, 1.5 equiv). The diastereomeric ratio of the addition products was determined to be >99.0:1.0 by analytical HPLC (see below). The crude residue was purified by silica-gel flash chromatography (hexane/EtOAc 80:20), to yield 77 mg (90%) of (+)-*anti*-**3f** as a colorless resin. TLC, R_f = 0.22 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ = +100.1 (*c* 0.80, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H, H5′), 7.07 (m, 1H, H4), 6.66-6.80 (m, 3H, H6″, H5″, H4″), 6.58 (bd, *J* = 7.7 Hz, 1H, H3″), 6.36 (m, 1H, H4′), 6.29 (m, 2H, H3′, H3),

5.55 (m, 1H, H1′), 5.19 (m, 1H, H5), 4.30 (bs, 1H, NH), 3.82 (s, 3H, OMe), 1.54 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (Cq), 153.4 (Cq), 149.7 (Cq), 147.4 (Cq), 146.3 (CH), 142.6 (CH), 137.1 (Cq), 129.6 (CH), 121.3 (CH), 118.2 (CH), 111.6 (CH), 110.7 (CH), 110.2 (CH), 107.5 (CH), 83.5 (Cq), 65.6 (CH), 55.8 (CH_3), 52.7 (CH), 29.5 (3C, CH_3). ESI-MS *m/z* 407.45 $[M+Na]^+$ (Calcd 407.16 $[M+Na]^+$). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.68; H, 6.40; N, 7.26. HPLC: *anti*-**3f**, t_R 10.00 min (100%) (CN-100, 5 μm, hexane/*i*PrOH 90:10, 1.0 mL/min, 254 nm). Chiral HPLC: (1'*S*,5*R*)-**3f**, t_R 10.01 min (82.9 %); (1'*R*,5*S*)-**3f**, t_R 12.93 min (17.1%) **(**Chiralcel OD-H, hexane/*i*PrOH 90:10, 1.0 mL/min, 254 nm).

Representative three-component VMMn Procedure (procedure b, Table 3.4). 5-(*N*-*tert*-Butoxycarbonyl)-[(2-methoxyphenylamino)(3-methyl)butyl]-1*H*-pyrrol-2(5*H*)one (*anti*-3g). Chiral phosphine **C3** (10.0 mg, 0.02 mmol, 0.10 equiv) and AgOAc (3.4 mg, 0.02 mmol, 0.10 equiv) were dissolved in undistilled BHT-stabilized (250 ppm) THF (1.0 mL) and allowed to stir for 10 min at 22 °C. A separate vial was charged with *o*-anisidine (**18a**) (23.6 μL, 0.21 mmol, 1.0 equiv) and $MgSO_4$ (48 mg, 0.40 mmol) into which aldehyde **2g** (22.5 μL, 0.21 mmol, 1.0 equiv) was added. The resulting mixture was allowed to stir for 10 min after which the crude imine was subsequently diluted with undistilled THF (0.50 mL), and transferred to the above silver-peptide complex solution, followed by the addition of *i*-PrOH (24.0 μL, 0.31 mmol, 1.5 equiv)/H_2O (6.0 μL, 0.31 mmol, 1.5 equiv). The resulting solution was allowed to stir at 0 °C for 10 min. 2-(Trimethylsilyloxy)pyrrole **1c** (82.0 mg, 0.31 mmol, 1.5 equiv) was then added and the resulting mixture was allowed to stir at 0 °C for 16 h. The reaction was quenched upon addition of buffer solution (pH 7, 10.0 mL), followed by warming to 25 °C with vigorous stirring for 10 min. The mixture was then extracted with EtOAc (3 × 10 mL), and the organic layers were collected, dried with $MgSO_4$, filtered, and concentrated in vacuo. The diastereomeric ratio of the addition products **3g** was determined to be 99.0:1.0 by 1H NMR analysis of the crude reaction mixture. The crude residue was then purified by silica-gel flash chromatography (petroleum ether/EtOAc elution gradient from 80:20 to 65:35), to yield 62 mg (52%) of *anti*-**3g** as colorless resin: TLC, R_f = 0.28 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ = +74.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 6.2, 1.9 Hz, 1H, H4), 6.76 (m, 2H, Ar), 6.66 (m, 2H, Ar), 6.26 (dd, *J* = 6.2, 1.5 Hz, 1H, H3), 4.77 (ddd, *J* = 3.3, 1.8, 1.8 Hz, 1H, H5), 4.46 (m, 1H, H1′), 3.78 (s, 3H, OMe), 1.84 (ept, *J* = 6.7 Hz, 1H, H3′), 1.52 (m, 11H, *t*-Bu, Boc, H2′), 1.01 (dd, *J* = 6.1, 6.1 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 153.2, 151.7, 145.9, 139.2, 129.9, 121.5 (2C), 110.3 (2C), 83.2, 76.6, 66.8, 55.8, 28.3 (3C), 25.4 (2C), 23.4, 22.5. ESI-MS *m/z* 397.30 $[M+Na]^+$ (Calcd 397.20 $[M+Na]^+$). Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07; N, 7.48. Found: C, 67.38;

H, 8.50; N, 7.45. Chiral HPLC: (1′*S*,5*R*)-**3g**, t_R 13.35 min (82.3%); (1′*R*,5*S*)-**3g**, t_R 17.91 min (17.7%) (Chiralcel OD-H, hexane/anhydrous EtOH 98:2, 0.9 mL/min, 254 nm).

5-(*N*-*tert*-Butoxycarbonyl)-[(2-methoxyphenylamino)(2-methyl)propyl]-1*H*-pyrrol-2(5*H*)one (*anti*-3h). Lactam *anti*-**3h** was prepared according to the representative procedure B described for **3g**, utilizing aldehyde **2h** (20.0 μL, 0.21 mmol, 1.0 equiv), *o*-anisidine (**18a**) (23.6 μL, 0.21 mmol, 1.0 equiv), and 2-(trimethylsilyloxy)pyrrole **1c** (82.0 mg, 0.32 mmol, 1.5 equiv). The diastereomeric ratio of the addition products was determined to be 87.0:13.0 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was then purified by silica-gel flash chromatography (petroleum ether/EtOAc from 80:20 to 65:35), to yield 62 mg (36%) of the major isomer *anti*-**3h** as a colorless resin: TLC, R_f = 0.37 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ = +73.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 6.2, 2.0 Hz, 1H, H4), 6.77 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar), 6.72 (dd, *J* = 7.0, 1.2 Hz, 1H, Ar), 6.62 (m, 2H, Ar), 6.28 (dd, *J* = 6.2, 1.5 Hz, 1H, H3), 5.04 (ddd, *J* = 3.3, 1.7, 1.7 Hz, 1H, H5), 4.01 (dd, *J* = 9.6, 3.5 Hz, 1H, H1′), 3.78 (s, 3H, OMe), 1.75 (m, 1H, H3′), 1.47 (s, 9H, *t*-Bu, Boc), 1.20 (d, *J* = 6.7 Hz, 3H, CH_3), 1.09 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 149.8, 146.8, 145.3, 138.9, 130.2, 121.3, 117.2, 111.3, 110.2, 83.1, 64.8, 60.8, 55.8, 33.8, 28.2 (3C), 21.2, 20.2. ESI-MS *m/z* 383.30 $[M+Na]^+$ (Calcd 383.19 $[M+Na]^+$). Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.50; H, 7.89; N, 7.68. Chiral HPLC: (1′*S*,5*R*)-**3h**, t_R 18.38 min (82.3%); (1′*R*,5*S*)-**3h**, t_R 29.78 min (17.7%) (Chiralcel OD-H, hexane/anhydrous EtOH 98:2, 0.9 mL/min, 254 nm).

Benzyl (*S*)-[(*R*)-1-(*tert*-butoxycarbonyl)-5-oxopyrrolidin-2-yl](phenyl) methylcarbamate (13) (Scheme 3.2). To a solution of *anti*-**3a** (50 mg, 0.13 mmol) in MeOH (10 mL), cooled to 0 °C into an ice bath, $NiCl_2 \cdot 7H_2O$ (8 mg, 0.033 mmol) was added and the resulting solution was allowed to vigourously stir at the same temperature. After 10 min $NaBH_4$ (5 mg, 0.13 mmol) was added in one portion with the occurrence of a vigorous gas evolution. Stirring was continued, and the reaction was monitored by TLC. After 2 h, the reaction mixture was quenched and neutralized by adding a saturated aqueous NH_4Cl solution (10 mL) and the resulting biphasic mixture was stirred vigorously for additional 30 min. The phases were separated and the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated in vacuo. The saturated lactam **12** (49 mg, 98%), was obtained as a colorless resin which was later manipulated without any other purification. TLC, R_f = 0.40 (hexane/EtOAc 70:30); $[\alpha]^D_{20}$ = +101.0 (*c* 0.92, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.41 (m, 5H, Ph), 6.78 (bd, *J* = 7.5 Hz, 1H, H6″), 6.67 (m, 2H, H5″, H4″), 6.37 (bd, *J* = 6.8

Hz, 1H, H3″), 5.02 (d, *J* = 2.7 Hz, 1H, H1′), 4.66 (m, *J* = 1H, H5), 3.90 (s, 3H, OMe), 2.44 (m, 2H, H3α, H3β), 2.00 (m, 2H, H4α, H4β), 1.54 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (Cq), 150.6 (Cq), 147.3 (Cq), 139.4 (Cq), 136.9 (Cq), 129.0 (2C, CH), 127.8 (CH), 127.1 (2C, CH), 121.3 (CH), 117.6 (CH), 111.3 (CH), 109.8 (CH), 83.6 (Cq), 62.2 (CH), 60.0 (CH), 55.8 (CH_3), 32.0 (CH_2), 28.2 (3C, CH_3), 19.2 (CH_2). ESI-MS *m/z* 419.3 $[M+Na]^+$(Calcd 419.2 $[M+Na]^+$). Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.97; H, 7.12; N, 7.07. Found: C, 70.09; H, 7.30; N, 7.00. A solution of saturated lactam **12** (49.0 mg, 0.12 mmol) in a 1:1 MeOH:CH_2Cl_2 mixture (2.0 mL), was added to a solution of $PhI(OAc)_2$ (159.0 mg, 0.49 mmol, 4.0 equiv.) in MeOH (2.0 mL), under N_2 atmosphere and stirred at 0 °C for 30 min. Aqueous HCl (1.0M, 1.9 mL) was then added and the resulting solution was warmed to 22 °C. After 1h of vigorous stirring at the same temperature, the pH was adjusted to pH 7 by careful addition of Na_2CO_3. The resulting slurry was then diluited with CH_2Cl_2 (12.0 mL), CbzCl (71 μL, 0.49 mmol, 4.0 equiv.) was added and the resulting mixture was stirred for additional 4 h at 22 °C. The biphasic mixture was then transferred into a separatory funnel, and the two phases were separated. The acqueous phase was washed with EtOAc (3 × 15 mL) and the organic phases were collected, washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica-gel flash chromatography (hexane/EtOAc 70/30) yielding 23 mg (45% two steps) of lactam (+)-**5** as a brownish resin. TLC, R_f = 0.31 (hexane/EtOAc 70:30); $[\alpha]^D_{20}$ = +26.0 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.40 (m, 10H, Ph Bn, Ar Cbz), 6.0 (d, *J*= 7.74 Hz, 1H, NH), 5.26 (m, 1H, H1′), 5.14 (d, *J*= 12.1 Hz, 1H, H1α″), 5.06 (d, *J* = 12.5 Hz, 1H, H1β″), 4.59 (ddd, *J*= 8.4, 2.5, 2.5 Hz, 1H, H5), 2.28 (ddd, *J*= 13, 7.4, 2.8 Hz, 1H, H3), 2.16-2.01 (m, 1H, H4), 1.90-1.80 (m, 1H, H3) 1.60 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.07 (Cq), 156.10 (Cq), 151.02 (Cq) 136.42 (Cq, 2C), 129.09 (4C, CH), 128.72 (CH), 128.28 (CH), 127.04 (4C, CH), 84.03 (Cq), 77.90 (CH), 67.32 (CH_2), 61.39 (CH), 31.51 (CH_2), 28.20 (3C, CH_3), 28. 20 (CH_2). ESI-MS *m/z* 447.2 $[M+Na]^+$ (Calcd 447.1 $[M+Na]^+$). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 87.91; H, 6.65; N, 6.60. Found: C, 87.80; H, 6.71; N, 6.58.

Benzyl (*R*)-[(*S*)-1-(*tert*-butoxycarbonyl)-5-oxopyrrolidin-2-yl](phenyl)methyl carbamate (*ent*-13) Palladium (10 wt.% on activated carbon, 10 mg) was added to a solution of unsaturated lactam **14** (40 mg, 0.14 mmol) and NaOAc (10 mg) in anhydrous EtOAc (8 mL) at room temperature. The reaction vessel was degassed under vacuum and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen for 4 h, after which time the hydrogen was evacuated, the catalyst filtered off and the filtrate concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane:EtOAc, 60/40) to furnish 38 mg (95%) of saturated lactam **15** as an amorphous solid. TLC, R_f = 0.34 (hexane/EtOAc

60:40); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 4.97 (d, *J*= 5.46 Hz, 1H, H1′), 4.46-4.39 (m, 1H, H5), 3.20 (bs, 1H, OH), 2.02-1.91 (m, 3H, H3α, H3β, H4α), 1.70-1.61 (m, 1H, H4β), 1.50 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.99 (Cq), 151.00 (Cq), 140.23 (Cq), 128.72 (2C, CH), 128.3 (CH), 126.6 (2C, CH), 83.5 (Cq), 73.8 (CH), 62.23 (CH), 33.08 (CH_2), 31.55 (3C, CH_3), 19.22 (CH_2). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.91; H, 7.39; N, 4.70. To a solution of saturated lactam **15** (38 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (2.0 mL), Et_3N (54 μL, 0.39 mmol, 3 equiv) was added under N_2 atmosphere and vigorous stirring at room temperature. The reaction mixture has been cooled to 0 °C in ice bath and then MsCl (24 μL, 0.31 mmol, 1.3 equiv) was slowly added. After 30 min the reaction was warmed to 25 °C and kept under stirring for 3h. The reaction was quenched with a saturated aqueous solution of NH_4Cl until neutralization and extracted with EtOAc (3 × 10 mL). The organic phases were collected, washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica-gel flash chromatography (CH_2Cl_2/EtOAc 90:10 to 85:15) to give 39 mg (79%) of a protected lactam intermediate, as a brownish resin. To a solution of the previously prepared lactam intermediate (70 mg, 0.19 mmol) in DMF (8.0 mL), NaN_3 (99 mg, 1.52 mmol, 8.0 equiv.) was added and the resulting mixture was warmed to 80 °C under stirring for 24 h. The reaction mixture was concentrated under vacuo and the resulting residue, dissolved in CH_2Cl_2, was washed with H_2O (4 × 15 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo to give a crude product which was purified by silica-gel flash chromatography (Et_2O/EtOAc 90:10) yielding azide **16** (40 mg, 67%) as a colorless resin. TLC, R_f = 0.92 (Et_2O/EtOAc 50:50); $[\alpha]^D_{20}$ = –95.5 (*c* 1.00, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H, Ph), 5.29 (d, *J*= 2.5 Hz, 1H, H1′), 4.32 (ddd, *J*= 9.2, 2.2, 2.2 Hz, 1H, H5), 2.80 (ddd, *J*= 18, 10.2, 10.2 Hz, 1H, H3α), 2.37 (ddd, *J*= 18, 10.3, 2.6 Hz, 1H, H 3β), 1.93 (dddd, *J*= 13.5, 9.9, 2.5, 2.5 Hz, 1H, H4α), 1.72 (dddd, *J*= 13.5, 10.2, 9.2. 2.2 Hz, 1H, H 4β), 1.61 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.64 (Cq), 150.36 (Cq), 136.62 (Cq) 129.21 (2C, CH), 128.56 (CH), 126.68 (2C, CH), 83.88 (Cq), 67.34 (CH), 62.31 (CH), 32.20 (CH_2), 29.88 (CH_2), 28.34 (3C, CH_3). ESI-MS *m/z* 339.2 $[M+Na]^+$ (Calcd 339.1 $[M+Na]^+$). Anal. Calcd for $C_{16}H_{21}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.91; H, 6.42; N, 17.80. To a solution of azide **16** (40 mg, 0.13 mmol) and NaOAc (10 mg) in anhydrous EtOAc (8 mL) palladium (10 wt.% on activated carbon, 10 mg) was added at room temperature. The reaction vessel was degassed under vacuum and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen for 4 h, after which time the hydrogen was evacuated, the catalyst filtered off and the filtrate concentrated under to furnish 30 mg (82%) of an amine intermediate which was used without further purification. To a solution of CbzCl (14.8 μL, 0.10 mmol, 1 equiv) in MeCN (1.0 mL) kept at room

temperature under N_2 atmosphere, were sequentially added Et_3N (14 μL, 0.10 mmol, 1 equiv) and a solution of the previosly synthesized amine intermediate (30 mg, 0.10 mmol) in MeCN (5.0 mL). The reaction mixture was allowed to stir at room temperature until completion for 3h. The reaction was quenched with a saturated aqueous solution of NH_4Cl until neutralization and later extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were collected, washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by silica-gel flash chromatography (hexane/EtOAc 70:30) yielding compound (–)-*ent*-**13** (15 mg, 34%), whose spectroscopic data fully match those obtained for compound (+)-**13**, except for the optical rotation value ($[\alpha]^D_{20}$ = –35.7 (*c* 0.11, $CHCl_3$). Chiral HPLC: Chiralcel OD-H, hexane/EtOH 95:5, 1.0 mL/min, 254 nm (1'*S*,5*R*)-(+)-**13**, t_R 22.73 min; $[\alpha]^D_{20}$ = + 26.0 (*c* 1.00, $CHCl_3$) (1'*R*,5*S*)-(–)-*ent*-**13**, t_R 19.63 min; $[\alpha]^D_{20}$= –35.7 (*c* 0.11, $CHCl_3$).

Representative three-component VMMn Procedure (Table 3.6). (*R*)-1-(Benzyloxycarbonyl)-5-{(*S*)-1-[4-methoxy-2-(thiomethyl)phenylamino]-3-methylbutyl}-1*H*-pyrrol-2(5*H*)one (*anti*-24a). Chiral phosphine **C3** (5.3 mg, 0.01 mmol) and AgOAc (1.7 mg, 0.01 mmol) were dissolved in undistilled BHT-stabilized (250 ppm) THF (208 μL) and allowed to stir for 10 min at 22 °C. A separate vial was charged with 4-methoxy-2-(methylthio)aniline (**18c**) (35.1 mg, 0.21 mmol) and $MgSO_4$ (50 mg, 0.41 mmol) into which aldehyde **19a** (21.7 μL, 0.21 mmol) was added at room temperature. The resulting mixture was allowed to stir for 10 min; the crude imine was diluted with undistilled THF (830 μL) and transferred to the above silver-peptide complex solution, followed by the addition of a mixture of *i*-PrOH (23.7 μL, 0.31 mmol)/H_2O (5.6 μL, 0.31 mmol). The resulting mixture was allowed to stir at −30 °C for 10 min. 2-(Trimethylsilyloxy)pyrrole (**17**) (90.0 mg, 0.31 mmol) was diluted with undistilled THF (776 μL), then added in one portion and the resulting mixture was allowed to stir at −30 °C for 16 h. The reaction was quenched upon addition of buffer solution (pH 7, 1.0 mL), followed by warming to 25 °C with vigorous stirring for 10 min. The mixture was extracted with EtOAc (3 × 10 mL), and the organic layers were collected, dried with $MgSO_4$, filtered, and concentrated in vacuo. The diastereomeric ratio of the Mannich products **24a** was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc=70:30), to yield 85.9 mg (90%) of *anti*-**24a** as a light red resin: TLC, R_f=0.40 (petroleum ether/EtOAc=70:30); $[\alpha]_D^{20}$ = +174.2 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.33 (m, 5H, Cbz), 7.28 (dd, *J* = 6.2, 1.6 Hz, 1H, H4), 6.92 (d, *J* = 2.9 Hz, 1H, H3″), 6.55 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.42 (brd, *J* = 8.9 Hz, 1H, H6″), 6.30 (dd, *J* = 6.2, 1.6 Hz, 1H, H3), 5.35 (d, *J* = 12.3 Hz, 1H, Cbz), 5.21 (d, *J* = 12.4 Hz, 1H, Cbz), 4.88 (brs, 1H,

H5), 4.44 (m, 1H, H1′), 3.69 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.74 (m, 1H, H3′), 1.50 (t, *J* = 7.0 Hz, 2H, H2′), 0.96 (d, *J* = 6.6 Hz, 3H, CH_3), 0.92 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 151.7 (Cq), 151.4 (Cq), 146.7 (CH), 141.8 (Cq), 135.4 (Cq), 129.8 (CH), 128.8 (2CH), 128.6 (CH), 128.5 (2CH), 121.4 (Cq), 119.5 (CH), 115.4 (CH), 111.9 (CH), 68.2 (CH_2), 66.6 (CH), 55.9 (CH_3), 52.6 (CH), 43.3 (CH_2), 25.5 (CH), 23.0 (CH_3), 22.6 (CH_3), 18.6 (CH_3). ESI-MS *m/z* 477.30 $[M+Na]^+$ (Calcd 477.20 $[M+Na]^+$). Anal. Calcd for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65; N, 6.16. Found: C, 66.09; H, 6.70; N, 6.13. Chiral HPLC: (1′*S*,5*R*)-**24a**, t_R 21.65 min (97.9%); (1′*R*,5*S*)-**24a**, t_R 28.26 min (2.1%) (Whelk-O1, hexane/EtOH=80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-{(*S*)-[4-methoxy-2-(thiomethyl)phenylamino] (cyclohexyl)methyl}-1*H*-pyrrol-2(5*H*)one (*anti*-24b). Prepared according to the representative procedure, utilizing aldehyde **19b** (25.4 μL, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc=70:30), to yield 92.8 mg (92%) of the *anti*-**24b** as a red resin: TLC, R_f=0.39 (petroleum ether/EtOAc=70:30); $[\alpha]_D^{20}$ = +233.3 (*c*=1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.35 (m, 5H, Cbz), 7.27 (dd, *J* = 6.2, 1.8 Hz, 1H, H4), 6.91 (d, *J* = 2.8 Hz, 1H, H3″), 6.52 (dd, *J* = 8.9, 2.8 Hz, 1H, H5″), 6.33 (d, *J* = 10.4 Hz, 1H, H6″), 6.30 (dd, *J* = 6.4, 1.3 Hz, 1H, H3), 5.30 (d, *J* = 12.4 Hz, 1H, Cbz), 5.16 (d, *J* = 12.4 Hz, 1H, Cbz), 5.09 (s, 1H, H5), 4.13 (dd, *J* = 8.8, 2.3 Hz, 1H, H1′), 3.68 (s, 3H, OMe), 2.24 (s, 3H, SMe), 1.88 (m, 2H, alkyl), 1.69 (m, 2H, alkyl), 1.47 (m, 1H, alkyl), 1.28-1.21 (m, 5H, alkyl), 1.02 (m, 1H, alkyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 151.3 (2Cq), 146.5 (CH), 142.9 (Cq), 135.5 (Cq), 129.9 (CH), 128.8 (2CH), 128.5 (CH), 128.4 (2CH), 120.6 (Cq), 119.5 (CH), 115.5 (CH), 111.6 (CH), 68.1 (CH_2), 64.6 (CH), 58.8 (CH), 55.9 (CH_3), 43.0 (CH), 31.0 (CH_2), 30.5 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 18.7 (CH_3). ESI-MS *m/z* 503.30 $[M+Na]^+$ (Calcd 503.20 $[M+Na]^+$). Anal. Calcd for $C_{27}H_{32}N_2O_4S$: C, 67.47; H, 6.71; N, 5.83 Found: C, 67.22; H, 6.75; N, 5.84. Chiral HPLC: (1′*S*,5*R*)-**24b**, t_R 21.82 min (97.0%); (1′*R*,5*S*)-**24b**, t_R 29.14 min (3.0%) (Whelk-O1, hexane/EtOH=80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-{(*S*)-1-[4-methoxy-2-(thiomethyl)phenylamino]-2-methylpropyl}-1*H*-pyrrol-2(5*H*)one (*anti*-24c). Prepared according to the representative procedure, utilizing aldehyde **19c** (19.2 μL, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc=70:30),

to yield 69.4 mg (75%) of the *anti*-**24c** as a red resin: TLC, R_f=0.40 (petroleum ether/EtOAc=70:30); $[\alpha]_D^{20}$ = +202.7 (*c*=0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5H, Cbz), 7.27 (dd, *J* = 7.3, 2.0 Hz, 1H, H4), 6.91 (d, *J* = 2.8 Hz, 1H, H3″), 6.53 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.34 (d, *J* = 8.5 Hz, 1H, H6″), 6.30 (dd, *J* = 6.1, 1.4 Hz, 1H, H3), 5.30 (d, *J* = 12.4 Hz, 1H, Cbz), 5.17 (d, *J* = 12.4 Hz, 1H, Cbz), 5.09 (s, 1H, H5), 4.04 (dd, *J* = 9.1, 2.5 Hz, 1H, H1′), 3.68 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.77 (m, 1H, H2′), 1.17 (d, *J* = 6.7 Hz, 3H, CH_3), 1.03 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (Cq), 151.3 (2Cq), 146.4 (CH), 142.8 (Cq), 135.4 (Cq), 130.0 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 120.6 (Cq), 119.4 (CH), 115.5 (CH), 111.6 (CH), 68.1 (CH_2), 64.9 (CH), 60.3 (CH), 55.9 (CH_3), 33.7 (CH), 21.0 (CH_3), 20.2 (CH_3), 18.8 (CH_3). ESI-MS *m/z* 463.30 $[M+Na]^+$ (Calcd 463.18 $[M+Na]^+$). Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.41; N, 6.36. Found: C, 65.20; H, 6.49; N, 6.39. Chiral HPLC: (1′*S*,5*R*)-**24c**, t_R 22.47 min (97.7%); (1′*R*,5*S*)-**24c**, t_R 27.97 min (2.3%) (Whelk-O1, hexane/EtOH=80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-{(*S*)-1-[4-methoxy-2-(thiomethyl)phenylamino] ethyl}-1*H*-pyrrol-2(5*H*)one (*anti*-24d). Prepared according to the representative procedure, utilizing aldehyde **19d** (11.8 μL, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc=70:30-60:40), to yield 59.8 mg (69%) of the *anti*-**24d** as a red resin: TLC, R_f=0.20 (petroleum ether/EtOAc=70:30); $[\alpha]_D^{20}$ = +240.7 (*c*=0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.28 (m, 6H, Cbz, H4), 6.94 (d, *J* = 2.9 Hz, 1H, H3″), 6.61 (dd, *J* = 8.85, 3.0 Hz, 1H, H5″), 6.41 (d, *J* = 8.9 Hz, 1H, H6″), 6.33 (dd, *J* = 6.1, 1.4 Hz, 1H, H3), 5.34 (1/2 ABq, *J* = 12.4 Hz, 1H, Cbz), 5.27 (1/2 ABq, *J* = 12.4 Hz, 1H, Cbz), 4.86 (s, 1H, H5), 4.45 (m, 1H, H1′), 3.71 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.34 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (Cq), 151.8 (Cq), 151.5 (Cq), 146.7 (CH), 141.5 (Cq), 135.5 (Cq), 129.6 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2C), 122.0 (Cq), 119.3 (CH), 115.3 (CH), 112.3 (CH), 68.3 (CH_2), 67.2 (CH), 56.0 (CH_3), 49.6 (CH), 18.8 (CH_3), 18.3 (CH_3). ESI-MS *m/z* 435.20 $[M+Na]^+$ (Calcd 435.15 $[M+Na]^+$). Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 64.11; H, 5.90; N, 6.73. Chiral HPLC: (1′*S*,5*R*)-**24d**, t_R 30.01 min (97.8%); (1′*R*,5*S*)-**24d**, t_R 36.09 min (2.2%) (Whelk-O1, hexane/EtOH=80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-{(*S*)-1-[4-methoxy-2-(thiomethyl)phenylamino]-3-phenylpropyl}-1*H*-pyrrol-2(5*H*)one (*anti*-24e). Prepared according to the representative

procedure, utilizing aldehyde **19e** (27.7 μL, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc elution gradient from 80:20 to 75:25), to yield 69.7 mg (66%) of the *anti*-**24e** as a red resin: TLC, R_f=0.20 (petroleum ether/EtOAc=70:30); $[\alpha]_D^{20}$ = +154.9 (*c*=0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 10H, Cbz, Ph), 7.17 (d, *J* = 7.1 Hz, H4), 6.92 (d, *J* = 2.9 Hz, 1H, H3″), 6.50 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.30 (m, 2H, H6″ and H3), 5.27 (d, *J* = 12.4 Hz, 1H, Cbz), 5.17 (d, *J* = 12.3 Hz, 1H, Cbz), 4.87 (s, 1H, H5), 4.38 (m, 1H, H1′), 3.68 (s, 3H, OMe), 2.85 (m, 1H, H3′), 2.71 (m, 1H, H3′), 2.27 (s, 3H, SMe), 2.07 (m, 1H, H2′), 1.84 (m, 1H, H2′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (Cq), 151.4 (Cq), 151.1 (Cq), 146.2 (CH), 142.1 (Cq), 141.1 (Cq), 135.2 (Cq), 129.7 (CH), 128.6 (4CH), 128.4 (2CH), 128.3 (CH), 128.2 (2CH), 126.2 (CH), 121.1 (Cq), 119.1 (CH), 115.1 (CH), 111.8 (CH), 68.0 (CH_2), 66.5 (CH), 55.7 (CH_3), 53.9 (CH), 36.3 (CH_2), 33.0 (CH_2); 18.5 (CH_3). ESI-MS *m/z* 525.21 $[M+Na]^+$ (Calcd 525.19 $[M+Na]^+$). Anal. Calcd for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57. Found: C, 69.05; H, 6.04; N, 5.58. Chiral HPLC: (1′*S*,5*R*)-**24e**, t_R 30.03 min (96.8%); (1′*R*,5*S*)-**24e**, t_R 36.91 min (3.2%) (Whelk-O1, hexane/EtOH=80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-{(*S*)-1-[4-methoxy-2-(thiomethyl)phenylamino] octyl}-1*H*-pyrrol-2(5*H*)one (*anti*-24f). Prepared according to the representative procedure, utilizing aldehyde **19f** (32.8 μL, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc=75:25-70:30), to yield 82.4 mg (79%) of the *anti*-**24f** as a red resin: TLC, R_f=0.30 (petroleum ether/EtOAc=70:30); $[\alpha]_D^{20}$ = +151.5 (*c*=0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.33 (m, 5H, Cbz), 7.29 (dd, *J* = 6.2, 2.1 Hz, 1H, H4), 6.92 (d, *J* = 2.9 Hz, 1H, H3″), 6.56 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.39 (brd, *J* = 8.7 Hz, 1H, H6″), 6.31 (dd, *J* = 6.2, 1.6 Hz, 1H, H3), 5.32 (d, *J* = 12.4 Hz, 1H, Cbz), 5.21 (d, *J* = 12.4 Hz, 1H, Cbz), 4.91 (brs, 1H, H5), 4.33 (m, 1H, H1′), 3.69 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.68 (m, 2H, H2′), 1.50 (m, 2H, H3′), 1.28 (m, 8H, H4′, H5′, H6′, H7′), 0.89 (dd, *J* = 7.0, 6.5 Hz, 3H, H8′), ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (Cq), 151.6 (Cq), 151.4 (Cq), 146.7 (CH), 142.8 (Cq), 135.4 (Cq), 129.7 (CH), 128.8 (2CH), 128.5 (CH), 128.4 (2CH), 120.6 (Cq), 119.3 (CH), 115.4 (CH), 111.6 (CH), 68.2 (CH_2), 66.5 (CH), 55.9 (CH_3), 53.5 (CH), 33.7 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 18.6 (CH_3), 14.3 (CH_3). ESI-MS *m/z* 519.20 $[M+Na]^+$ (Calcd 519.24 $[M+Na]^+$). Anal. Calcd for $C_{28}H_{36}N_2O_4S$: C, 67.71; H, 7.31; N, 5.64.

Found: C, 67.65; H, 7.33; N, 5.62. Chiral HPLC: (1′*S*,5*R*)-**6e**, t_R 15.93 min (97.0%); (1′*R*,5*S*)-**6e**, t_R 19.38 min (3.0%) (Whelk-O1, hexane/EtOH=80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-{(*R*)-1-[4-methoxy-2-(thiomethyl)phenylamino]-2-(*tert*-butyldimethylsilyl)oxyethyl}-1*H*-pyrrol-2(5*H*)one (*anti*-24g). Prepared according to the representative procedure, utilizing aldehyde **19g** (38.8 μL, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc 70:30), to yield 58.1 mg (51%) of the *anti*-**24g** as a yellow resin: TLC, R_f=0.38 (petroleum ether/EtOAc=70:30); $[\alpha]_D^{20}$ = +106.9 (*c*=0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 6.2, 2.1 Hz, 1H, H4), 7.43-7.40 (m, 2H, Cbz), 7.38-7.30 (m, 3H, Cbz), 6.92 (d, *J* = 2.9 Hz, 1H, H3″), 6.55 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.40 (brd, *J* = 9.0 Hz, 1H, H6″), 6.21 (dd, *J* = 6.2, 1.6 Hz, 1H, H3), 5.34 (d, *J* = 12.4 Hz, 1H, Cbz), 5.26 (d, *J* = 12.4 Hz, 1H, Cbz), 5.09 (brs, 1H, H5), 4.46 (dt, *J* = 5.6, 2.8, 2.8 Hz, 1H, H1′), 3.89 (dd, *J* = 10.6, 2.2 Hz, 1H, H2′), 3.74 (dd, *J* = 10.6, 5.8 Hz, 1H, H2′) 3.70 (s, 3H, OMe), 2.23 (s, 3H, SMe), 0.92 (s, 9H, ^{t}Bu), 0.06 (s, 3H, CH_3), 0.05 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5 (Cq), 151.5 (Cq), 151.2 (Cq), 148.2 (CH), 141.3 (Cq), 135.3 (Cq), 128.6 (2CH), 128.3 (CH), 128.2 (CH), 128.1 (2CH), 121.6 (Cq), 119.4 (CH), 115.2 (CH), 111.7 (CH), 67.9 (CH_2), 65.8 (CH), 63.7 (CH_2), 55.8 (CH_3), 54.6 (CH), 25.9 (CH_3), 18.1 (Cq), 18.1 (CH_3), −5.6 ($2CH_3$). ESI-MS *m/z* 565.30 $[M+Na]^+$ (Calcd 565.23 $[M+Na]^+$). Anal. Calcd for $C_{28}H_{38}N_2O_5SSi$: C, 61.96; H, 7.06; N, 5.16. Found: C, 62.0; H, 7.10; N, 5.19. Chiral HPLC: (1′*S*,5*R*)-**24g**, t_R 15.24 min (91.0%); (1′*R*,5*S*)-**24g**, t_R 17.90 min (9.0%) (Whelk-O1, hexane/EtOH=80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-{(*R*)-[4-methoxy-2-(thiomethyl)phenylamino][(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-1*H*-pyrrol-2(5*H*)one (26) and (*S*)-(1-benzyloxycarbonyl)-5-{(*S*)-[4-methoxy-2-(thiomethyl)phenylamino][(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-1*H*-pyrrol-2(5*H*)one (*ent*-27) (Scheme3. 3, eq.1). Prepared according to the representative procedure, utilizing aldehyde (*R*)-**25** (27.3 mg, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be 89:11 (**26**:*ent*-**27**) by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc elution gradient from 80:20 to 75:25) to yield 61.5 mg (59%) of **26** and 7.6 mg (7%) of *ent*-**27** as a light yellow resin: TLC, R_f=0.30 (petroleum ether/EtOAc=70:30). Analitycally pure samples were then obtained by semipreparative HPLC (CN 100A 10μ, hexane:EtOH=98:2, 3.0 mL/min, 254nm, t_R 57.17

for **26** and t_R 63.29 for *ent*-**27**). Data for **26**: $[\alpha]_D^{20}$ = +261.6 (*c*=0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 6.2, 2.1 Hz, 1H, H4), 7.46-7.35 (m, 5H, Cbz), 6.94 (d, *J* = 2.9 Hz, 1H, H3″), 6.44 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.23 (d, *J* = 9.0 Hz, 1H, H6″), 6.19 (dd, *J* = 6.3, 1.6 Hz, H3), 5.35 (1/2 ABq, *J* = 12.4 Hz, 1H, Cbz), 5.29 (1/2 ABq, *J* = 12.4 Hz, 1H, Cbz), 4.91 (dd *J* = 4.3, 2.2 Hz, 1H, H5), 4.73 (brs, 1H, NH), 4.49 (m, 2H, H1′, H2′), 4.05 (dd, *J* = 8.0, 6.6 Hz, 1H, H3′), 3.68 (s, 3H, OMe), 3.61 (dd, *J* = 7.8, 7.7 Hz, 1H, H3′), 2.25 (s, 3H, SMe), 1.51 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 151.9 (Cq), 151.4 (Cq), 149.1 (CH), 142.2 (Cq), 135.5 (Cq), 128.8 (2CH), 128.6 (CH), 128.4 (2CH), 128.2 (CH), 120.9 (Cq), 120.0 (CH), 115.3 (CH), 110.6 (Cq), 110.4 (CH), 76.8 (CH), 68.3 (CH_2), 67.5 (CH), 66.8, (CH_2), 56.0 (CH_3), 53.3 (CH), 26.5 (CH_3), 25.7 (CH_3), 18.7 (CH_3). ESI-MS *m/z* 521.23 $[M+Na]^+$ (Calcd 521.18 $[M+Na]^+$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.51; H, 6.11; N, 5.68. Data for *ent*-**27**: $[\alpha]_D^{20}$ =−174.2 (*c*=0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.35 (m, 6H, Cbz, H4), 6.90 (d, *J* = 2.9 Hz, 1H, H3″), 6.56 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.43 (d, *J* = 8.9 Hz, 1H, H6″), 6.35 (dd, *J* = 6.2, 1.6 Hz, H3), 5.25 (d, *J* = 12.3 Hz, 1H, Cbz), 5.24 (m, 1H, H5), 5.15 (d, *J* = 12.3 Hz, 1H, Cbz), 4.47 (m, 1H, H1′), 4.07 (m, 2H, H2′, H3′), 3.91 (m, 1H, H3′), 3.69 (s, 3H, OMe), 2.27 (s, 3H, SMe), 1.54 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 152.2 (2Cq), 146.5 (CH), 141.3 (Cq), 135.3 (Cq), 130.1 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 122.0 (Cq), 119.0 (CH), 115.2 (CH), 112.4 (CH), 110.6 (Cq), 76.8 (CH), 68.2 (2C, CH_2/CH), 66.3 (CH), 57.1 (CH), 55.9 (CH_3), 27.2 (CH_3), 25.4 (CH_3), 18.9 (CH_3). ESI-MS *m/z* 521.14 $[M+Na]^+$ (Calcd 521.18 $[M+Na]^+$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.41; H, 6.11; N, 5.67.

(*R*)-1-(Benzyloxycarbonyl)-5-{(*R*)-[4-methoxy-2-(thiomethyl)phenylamino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-1*H*-pyrrol-2(5*H*)one (27) (Scheme 3, eq.2). Prepared according to the representative procedure, utilizing aldehyde (*S*)-**25** (27.3 mg, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture (no other isomers detected). The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc elution gradient from 80:20 to 75:25) to yield 65.9 mg (63%) of **27** as a light yellow resin: TLC, R_f=0.30 (petroleum ether/EtOAc=70:30). Data for **27**: $[\alpha]_D^{20}$ = +178.3 (*c*=0.18, $CHCl_3$); for ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$), see compound *ent*-**27**. ESI-MS *m/z* 521.21 $[M+Na]^+$ (Calcd 521.18 $[M+Na]^+$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.52; H, 6.06; N, 5.61.

Compounds 26 and 27 (Scheme 3.3, eq.3). Prepared according to the representative procedure, utilizing aldehyde (*R,S*)-**25** (27.3 mg, 0.21 mmol), aniline **18c** (35.5 mg, 0.21 mmol), and pyrrole **17** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be 44:56 (**26**:**27**) by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc=80:20-75:25) to yield 29.5 mg (28%) of **26** and 37.5 mg (36%) of **27** as a light yellow resin: TLC, R_f=0.30 (petroleum ether/EtOAc=70:30). Analitycally pure samples were then obtained by semipreparative HPLC (CN 100A 10μ, hexane:EtOH=98:2, 3.0 mL/min, 254nm, t_R 57.17 for **26** and t_R 63.29 for **27**). Data for **26**: $[\alpha]_D^{20}$ = +257.7 (*c*=0.8, $CHCl_3$); data for **9**: $[\alpha]_D^{20}$ = +158.5 (*c*=0.18, $CHCl_3$).

(3*S*,4*S*,5*S*)-1-(Benzyloxycarbonyl)-5-{(*S*)-1-[4-methoxy-2-(thiomethyl) phenylamino]ethyl}-3,4-dihydroxypyrrolidin-2-one (28). To a stirred solution of the lactam *anti*-**24d** (50 mg, 0.12 mmol) in dry CH_2Cl_2 (2.0 mL) were added dicyclohexano-18-crown-6 ether (22.6 mg, 0.06 mmol) and powdered $KMnO_4$ (30 mg, 0.19 mmol) at room temperature. After 2h, the reaction was quenched by the addition of saturated aqueous Na_2SO_3 and citric acid solutions to the reaction mixture until the brown color disappeared. The resulting colorless solution was extracted with EtOAc (3 × 10 mL) and the organic layers were collected, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc=40:60-30:70), to yield 21.4 mg (40%) of **28** as a red resin: TLC, R_f=0.88 (petroleum ether/EtOAc=40:60); $[\alpha]_D^{20}$ = +112.7 (*c*=0.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.38 (m, 5H, Cbz,), 6.89 (d, *J* = 2.8 Hz, 1H, H3″), 6.41 (dd, *J* = 8.8, 2.7 Hz, 1H, H5″), 6.20 (d, *J* = 8.8 Hz, 1H, H6″), 5.36 (s, 2H, Cbz), 4.70 (d, *J* = 4.9 Hz, 1H, H3), 4.52 (d, *J* = 4.9 Hz 1H, H4), 4.20 (d, *J* = 1.8 Hz, 1H, H5), 3.94 (m, 1H, H1′), 3.70-3.90 (brs, 1H, OH), 3.71 (s, 3H, OMe), 3.45 (brs, 1H, OH), 2.28 (s, 3H, SMe), 1.33 (d, *J* = 6.5 Hz, 1H, CH_3, H2′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (Cq), 152.5 (Cq), 151.9 (Cq), 140.9 (Cq), 135.5 (Cq), 128.9 (2CH), 128.7 (3CH), 123.2 (Cq), 118.5 (CH), 114.6 (CH), 112.3 (CH), 71.7 (CH), 70.5 (CH), 69.2 (CH_2), 66.6 (CH), 56.0 (CH_3), 50.6 (CH), 19.2 (CH_3), 18.4 (CH_3). ESI-MS *m/z* 469.18 $[M+Na]^+$ (Calcd 469.15 $[M+Na]^+$). Anal. Calcd for $C_{22}H_{26}N_2O_6S$: C, 59.18; H, 5.87; N, 6.27. Found: C, 59.11; H, 5.93; N, 6.24.

(*R*)-5-{(*S*)-1-[(Benzyloxycarbonyl)amino]-3-methylbutyl]}pyrrolidin-2-one (29). To a solution of *anti*-**24a** (29 mg, 0.06 mmol) in MeOH (1.0 mL), cooled to 0 °C into an ice bath, $NiCl_2 \cdot 7H_2O$ (11.4 mg, 0.05 mmol) was added and the resulting solution was allowed to vigorously stir at the same temperature. After 10 min $NaBH_4$ (6.0 mg, 0.16 mmol) was added in one portion with the occurrence of a vigorous gas evolution. Stirring was

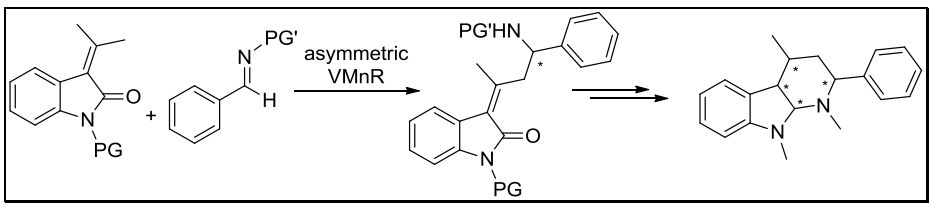
continued, and the reaction was monitored by TLC. After 6 h, the reaction mixture was quenched and neutralized by adding a saturated aqueous NH_4Cl solution (8 mL) and the resulting biphasic mixture was stirred vigorously for additional 30 min. The phases were separated and the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated in vacuo. The reaction crude was purified by silica-gel flash chromatography (Et_2O), to yield 21.5 mg (74%) of a saturated lactam intermediate as yellow resin. In a 10 mL round bottom flask containing the previously prepared lactam intermediate (21.5 mg, 0.05 mmol, 1.0 equiv), CAN (62 mg, 0.11 mmol, 2.4 equiv), MeCN (250 μL) and H_2O (40 μL) were added. The mixture was allowed to stir at 0°C for 10 min. Aqueous HCl 1N (60 μL) was added and the resulting solution was warmed to 22°C and allowed to stir at the same temperature for 1h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous HCl 1N (3 × 3 mL). Aqueous NaOH 2N was added to the collected aqueous layers until pH=10 was reached. The basified aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the organic phases were collected, dried over $MgSO_4$, filtered and concentrated in vacuo to yield 5.7 mg (40%, two steps from *anti*-**24a**) of **29** as a red resin: TLC, R_f=0.33 (EtOAc/MeOH=95:5); $[\alpha]_D^{20}$ = −33.9 (*c*=0.2, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO) δ 7.57 (s, 1H, NH), 7.39-7.28 (m, 5H, Ph), 7.11 (d, *J* = 9.4 Hz, 1H, NH), 5.04 (s, 2H, Cbz), 3.52 (m, 1H, H1′), 3.41 (m, 1H, H5), 2.11-1.93 (m, 3H, H3, H4), 1.79 (m, 1H, H3), 1.57 (m, 1H, H3′), 1.24 (m, 2H, CH_2, H2′), 0.87 (d, *J* = 6.7 Hz, 3H, CH_3), 0.84 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3 (Cq), 156.8 (Cq), 136.4 (Cq), 128.8 (2CH), 128.4 (CH), 128.3 (2CH), 67.2 (CH_2), 58.7 (CH), 52.0 (CH), 39.3 (CH), 30.1 (CH_2), 24.9 (CH), 23.7 (CH_2), 22.5 (CH_3), 21.8 (CH_3). ESI-MS *m/z* 327.5 $[M+Na]^+$ (Calcd 327.18 $[M+Na]^+$). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.95; H, 7.97; N, 9.18.

(2*S*,3*R*,3a*S*,6a*S*)-3-[4-Methoxy-2-(thiomethyl)phenylamino]-4-(benzyloxycarbonyl)-hexahydro-2-(hydroxymethyl)furo[3,2-*b*]pyrrol-5-one (30). Lactam **26** (21 mg, 0.04 mmol) was treated with 80% aq acetic acid (750 μL) and, after being stirred at 40°C for 18h, the resulting solution was concentrated under vacuo. The reaction crude was purified by silica-gel flash chromatography (petroleum ether/EtOAc 30:70), to yield 6.0 mg (30%) of a partially deprotected diol intermediate as a yellow resin. To a solution of the previously prepared lactam intermediate (6.0 mg, 0.013 mmol) in dry THF (1.7 mL), DBU (3.0 μL, 0.02 mmol) was added and the resulting solution was stirred for 19h at room temperature. The reaction mixture was then filtered through a short pad of silica gel that was washed with EtOAc (15 mL). After concentration in vacuo, the crude residue was purified by silica-gel flash chromatography (petroleum ether/EtOAc 20:80), to yield 6.0 mg (quantitative yield) of **30** as a brownish resin: TLC, R_f=0.60 (EtOAc); $[\alpha]_D^{20}$ =

+14.0 (*c*=0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.37 (m, 5H, Cbz,), 7.01 (d, *J* = 8.9 Hz, 1H, H6′), 6.98 (d, *J* = 2.9 Hz, 1H, H3′), 6.69 (dd, *J* = 8.8, 2.9 Hz, 1H, H5′), 5.39 (1/2 ABq, *J* = 12.8 Hz, 1H, Cbz), 5.35 (1/2 ABq, *J* = 13.0 Hz, 1H, Cbz), 4.87 (td, *J* = 5.1, 2.6 Hz, 1H, H6a), 4.73 (s, 1H, OH), 4.57 (dd, *J* = 5.4, 0.8 Hz, 1H, H3a), 4.36 (brd, *J* = 4.1 Hz, 1H, H3), 4.30 (q, *J* = 4.4 Hz, 1H, H2), 3.96 (1/2 ABq, *J* = 12.3, 4.4 Hz, 1H, C*H*$_2$OH), 3.91 (1/2 ABq, *J* = 12.2, 4.6 Hz, 1H, C*H*$_2$OH), 3.83 (s, 1H, NH), 3.78 (s, 3H, OMe), 2.80-2.78 (m, 2H, H6), 2.37 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (Cq), 152.7 (Cq), 151.9 (Cq), 139.8 (Cq), 136.5 (Cq), 128.9 (2CH), 128.8 (CH), 128.5 (2CH), 123.3 (Cq), 118.6 (CH), 114.2 (CH), 113.1 (CH), 79.3, (CH), 72.6 (CH), 68.8 (CH_2), 67.7 (CH), 61.5 (CH_2), 60.9 (CH), 56.0 (CH_3), 40.0 (CH_2), 17.8 (CH_3). ESI-MS *m/z* 481.3 $[M+Na]^+$ (Calcd 481.15 $[M+Na]^+$). HRMS (NSI) calcd for $C_{23}H_{27}N_2O_6S$ $[M + H]^+$: 459.1590; found: 459.1601.

Chapter 4

Investigations into the asymmetric vinylogous Mannich reaction with 3-alkylidene-2-oxindoles: synthesis of hexahydro-α-carbolines



4.1 Introduction

2-Oxindoles constitute important molecular scaffolds in relevant natural products and synthetic compounds of pharmaceutical interest.[1] In figure 4.1 a selection of compounds bearing the 2-oxindole moiety is shown. Structure **1** represents (*E*)- and (*Z*)-3-(3'-methyl-2'-butenylidene)-2-indolinones, the first naturally occurring 3-alkenyl-oxindoles to be isolated. They are two yellow pigments known for their antipyretic properties in the Chinese traditional medicine.[2] Gelsemine **2** is a naturally occurring compound isolated from *gelsemium sempervirens*; its intriguing three-dimensional structure, more than its doubtful pharmacological properties, has caught the attention of synthetic chemists since decades.[3]

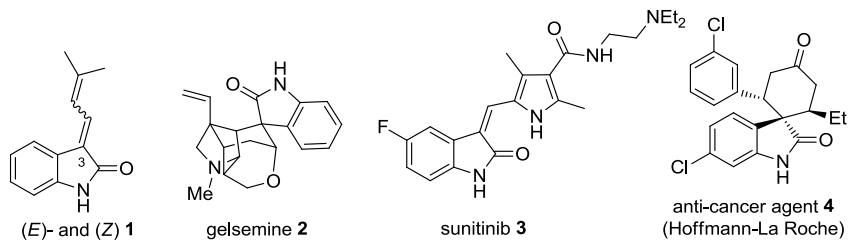


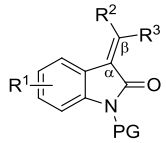
Figure 4.1. Chemical entities containing the key 2-oxindole core.

Sunitinib **3** and compound **4** are two oxindole structures belonging to the medicinal chemistry context: **3** is a multi-targeted receptor tyrosine kinase inhibitor commercialized by Pfizer as Sutent®, whereas spiro-oxindole **4** was patented by Hoffmann-La Roche for a possible anti-cancer treatment.

In the wide landscape of 2-oxindoles derivatives, we recently focused our attention on the possible vinylogous reactivity of 3-alkylidene-2-oxindoles. From a structural point of view, these scaffolds

[1] a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. b) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, 11505. c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *47*, 8748. c) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527. Wang, H.-L.; Li, Z.; Wang, G.-W.; Yang, S.-D. *Chemm. Commun.* **2011**, *47*, 11336.
[2] K. Hata, K. Baba, M. Kozawa, *Chem. Pharm. Bull.* **1978**, *26*, 2279.
[3] Lin, H.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 36.

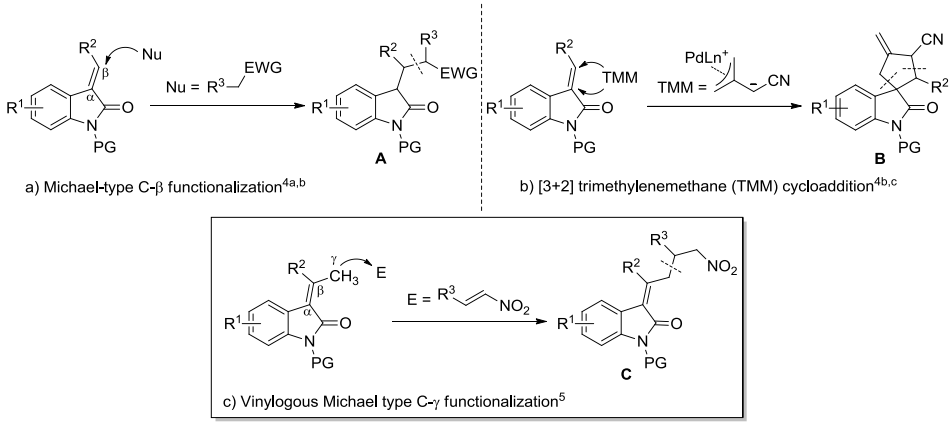
are extremely versatile synthetic entities, which bear a γ-lactam ring with an exocyclic carbon-carbon double bond at the α-position (C3 site) (figure 4.2).



3-alkylidene 2-oxindole **5**

Figure 4.2. General structure of 3-alkylidene 2-oxindoles.

Their versatility resides in their inherently multifaceted reactivity as, for examples, Michael acceptor substrates at the Cβ-position[4a,b] or substrates for synchronous[4b,c] and stepwise [4a,b] cycloaddition reactions (scheme 4.1)



Scheme 4.1. Scrutinized reactivity of 3-alkylidene-2-oxindoles.

Much less investigated, if completely neglected, was the propensity of these scaffolds to act as nucleophilic species at the enolizable exocyclic Cγ-position. Intrigued by this unexplored reactivity, Zanardi and co-workers recently launched a program where γ-enolizable-3-alkylidene-2-oxindoles could be synthesized and used as donor

[4] Selected examples: a) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Gannichi, B.; Pescaioli, S.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7200. b) Jiang, K.; Jia, Z.-J.; Chen, S.; Wu, L., Chen, Y.-C. *Chem. Eur. J.* **2010**, *16*, 2852. c) Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am. Chem. Soc.* **2007**, *129*, 3086. d) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396.

species in direct and indirect vinylogous aldol/Michael addition reactions. In particular, a direct and asymmetric organocatalytic vinylogous Michael reaction was proposed, based on the newly-discovered reactivity of such scaffolds as pro-nucleophilic donors (picture c in scheme 4.1).[5]

Aimimg at further exploring and widening the reactivity of 3-alkylidene oxindoles as skillful vinylogous pro-nucleophiles to be used in synthesis, we focused on their possible exploitation in the Mannich and vinylogous Mannich addition reaction realm. Based on previous successful findings in the Michael addition context,[5] we decided to begin our studies by firstly applying a direct, asymmetric organocatalytic approach and the results of these efforts are herein discussed.

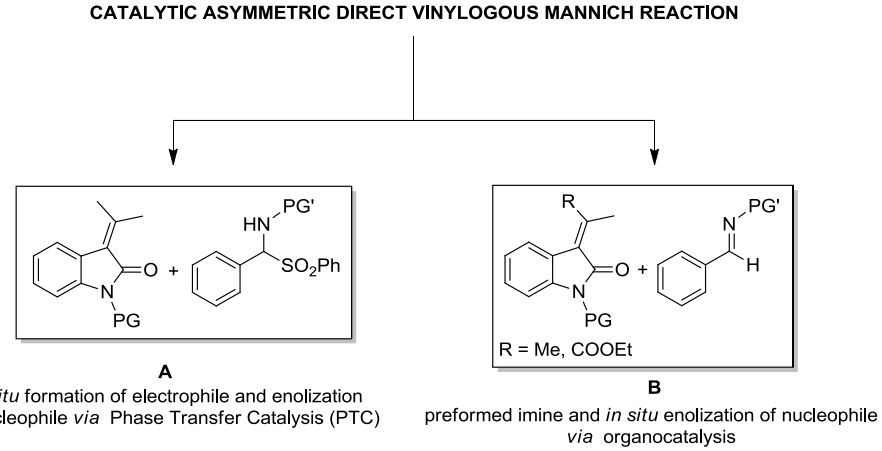


Figure 4.3. Two tested routes for catalytic asymmetric VMnR with 3-alkylidene-2-oxindole pro-nucleophiles.

Two possible routes were envisaged:

1. to apply the Phase Transfer Catalysis (PTC)[6] concept using a chiral non racemic onium salt as the catalyst component. Reactions could be carried out by exploiting the *in situ* formation of the imine

[5] Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6200.
[6] For a recent review see Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

Mannich acceptor starting from α-amido sulfones with concomitant enolization of the pro-nucleophilic indole (picture A in figure 4.3).

2. to employ *Cinchona*-derived bifunctional organocatalysts which would possibly provide the *in situ* enolization of the pro-nucleophile and concomitant activation of the preformed imine acceptor. Reactions could be possibly enhanced by the presence of a weak Brønsted acid as a co-catalyst (picture B in figure 4.3).

Clearly, the possibility of carrying the reaction in an indirect modality – that is using a preformed indole silicon dienolate and a preformed imine according to a vinylogous Mukaiyama-Mannich reaction VMMnR – remained a viable route worth to be explored [7] and indeed we decided to postpone such endeavour in a second step of the research.

In privileging the direct approach as a first chance, we took into consideration the principle of atom and step economy, and practicality of execution as well. Furthermore, the employment of organocatalysts would have put the methodology in the context of an environmentally benign chemistry.

4.2 Results and discussion

4.2.1 Phase-transfer-catalyzed asymmetric direct VMnRs

The Phase Transfer Catalysis (PTC)[6] concept could offer a unique opportunity to develop a rapid and practical vinylogous Mannich reaction, due to the possibility of forming the electrophile in situ with concomitant enolization of the indole pro-nucleophile in the same reaction environment.

[7] Rassu, G.; Zambrano, V.; Tanca, R.; Sartori, A.; Battistini, L.; Zanardi, F.; Curti, C.; Casiraghi, G. *Eur. J. Org. Chem.* **2012**, 466.

We did not dispose of many precedents in the field, since a sole example was found in the literature dealing with the asymmetric vinylogous Mannich reaction using PTC (see chapter 2).[8]

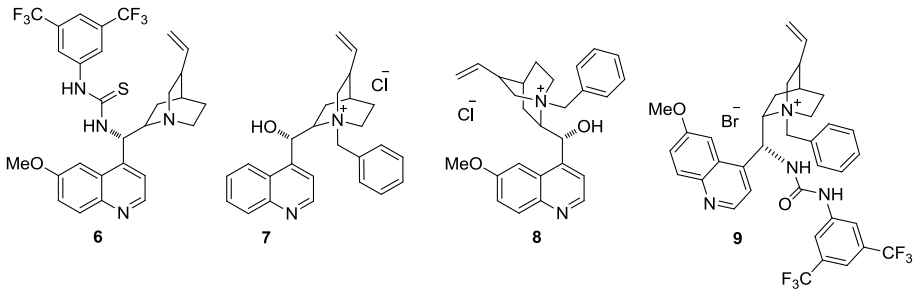


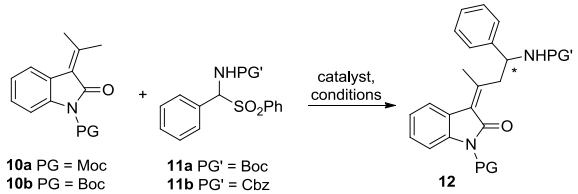
Figure 4.4. Organocatalysts scrutinized during the screening for the asymmetric direct VMnR in this work.

Thus, we began our studies taking the addition between indoles **10a**/**10b** to sulfonamides **11a**/**11b** as the model reaction (Table 4.1). Finding the right catalyst and reaction conditions were the main points of our preliminary scrutiny. Chiral quaternary ammonium salts derived from *Cinchona* alkaloids were firstly examined as the phase transfer catalysts. These organic molecules are the most currently employed catalysts in PTC and they are easy to prepare from commercially available and cheap starting materials. Furthermore, they are relatively safe and can be stored without any particular precautions.

When using phase transfer catalyst **8** with K_2CO_3 as base at high temperature,[9] the reaction did not work, returning the starting reactants almost untouched (table 4.1, entry 2). Deployment of a bifunctional organic catalyst such as 9-thiourea *Cinchona*-derived alkaloid **6**, which is not actually a phase transfer catalyst, in the presence of a basic aqueous solution,[10] failed to give the desired product **12aa** (entry 1).

[8] Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 1620.
[9] Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem. Eur. J.* **2007**, *13*, 8338.
[10] Song, J.; Shih, H.-W.; Deng, L. *Org. Lett*. **2007**, *9*, 603.

Table 4.1. Results of the PTC screening.[a]



10a PG = Moc
10b PG = Boc

11a PG' = Boc
11b PG' = Cbz

12

entry	Nu [eq]	E [eq]	catalyst [eq]	reaction conditions	yield [%][b]	dr[c] (*Z*:*E*)	ee[d] [%] (*Z*)
1	**10a** (1.0)	**11a** (1.0)	**6** (0.1)	Na_2CO_3 (0.1 M), DCM, rt, 18h	—	—	—
2	**10b** (1.0)	**11a** (1.0)	**8** (0.1)	K_2CO_3 (5.6 M), Toluene, 0 to 46 °C,))), 48h	—	—	—
3	**10b** (1.0)	**11a** (1.0)	**7** (0.2)	Na_2CO_3 (0.1 M), DCM, 0 °C to rt, 24h	—	—	—
4	**10b** (1.5)	**11a** (1.0)	**6**+**7** (0.1+0.1)	Na_2CO_3 (0.1 M), DCM, 0 °C to rt, 96h	3	99:1	15
5	**10b** (1.5)	**11a** (1.0)	**7** (0.1)	KOH (2.0 eq), DCM dry, −15 °C, 19h	27	99:1	15
6	**10b** (1.5)	**11b** (1.0)	**8** (0.2)	KOH (3.0 eq), DCM dry, −20 °C, 42h	12	—	16
7	**10b** (1.5)	**11a** (1.0)	**9** (0.1)	KOH (2.0 eq), DCM dry, −20 °C, 22h	45	99:1	47
8	**9b** (1.5)	**10a** (1.0)	**9** (0.1)	KOH (2.0 eq), DCM dry, 5−0 to −30 °C, 40h	41	99:1	40
9	**9b** (1.5)	**10a** (1.0)	**9** (0.1)	K_2CO_3 (2.0 eq), DCM dry, −20 °C to rt, 7 days	—	—	—

[a] For each catalyst, almost the same reaction conditions as those reported in the literature were adopted (see corresponding reference within the text). [b] Isolated yield after flash column chromatography. [c] Diastereomeric ratio determined by analysis of ^{1}H NMR spectra of the reaction crude [d] Enantiomeric excess determined with chiral column HPLC analysis.

The reason of the lack of activity could be ascribed to the basic medium which could prevent the generation of the alleged quaternary salt on the quinuclidine ring of the catalyst which, in turn, might be responsible for the stabilization of the indole dienolate through hydrogen bonding.[5]

In an effort to investigate the possibility of a cooperative catalysis, a mixture of organocatalysts **6** and **7** was used (entry 4). Unfortunately, the desired Mannich product was isolated in low yield as almost a racemate (15% ee). The use of a solid base, KOH, at lower temperature (–15 °C) gave the desired product in a 27% yield and still poor enantioselectivity (15% ee, entry 5). It was reasoned that the scarce enantiomeric excess detected with phase transfer catalysts **7** and **8** could be due to the absence of a strong H-bond donor group installed on the catalyst, such as a thio- or urea group, capable of activating the imine electrophile.

In the reaction carried out with ammonium salt **9**, a urea-containing phase transfer catalyst recently introduced by Dixon and co-workers,[11] the product **12ba** (PG = PG' = Boc) was isolated in a reasonable 45% yield and with a promising 47 ee% (entry 7). This result, though not brilliant *per se*, constituted a valuable cornerstone since it partially validated the hypothesis of the need of imine activation through strong H-bond donors within the catalyst. The modest enantioselectivity here observed could be derived from competitive racemic background, and this was proved by performing control experiments in achiral environments.[12]

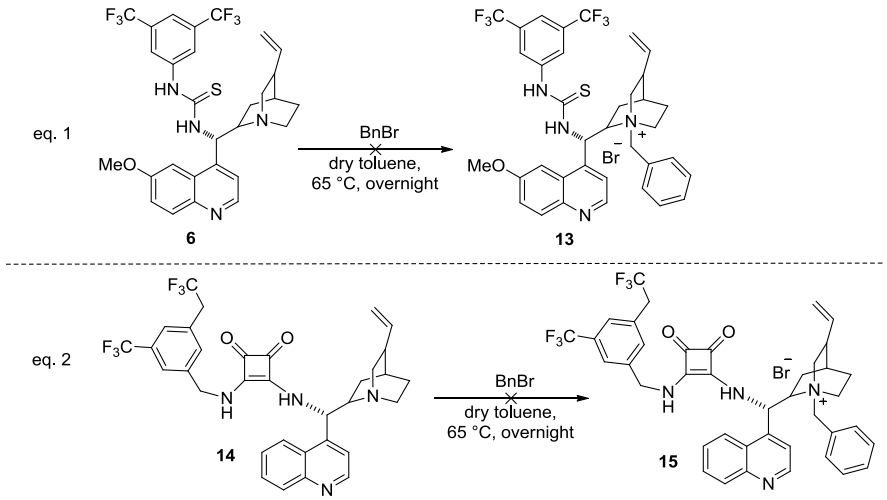
A noteworthy feature was the virtually absolute formation of the *Z*-configure Mannich product, evidence of the perfect stereocontrol dictated by the dienolate geometry in determining the relative stereochemistry.

Based on the results with catalyst **9**, attempts were made aimed at optimizing the reaction parameters: as shown in entry 8, the

[11] Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492.
[12] Control experiments carried out in identical conditions without the presence of the chiral catalysts revealed the formation of products **12** with an isolated yield ranking from 10 to 30%.

temperature was lowered to −50 °C but no reactivity was observed until the reaction was warmed to −30 °C. The use of different inorganic bases such as K_2CO_3 did not produce any significant result (entry 9).

Reasoning on possible pK_a value range of the hydrogen atoms of the thiourea/urea moiety of the catalysts together with different structural features,[13] the idea was to design and synthesize novel phase-transfer catalysts bearing protons more acidic than **9**, able to be engaged in strong H-bond interactions, in order to favor a tight transition state with both the reactants. Was it possible, a high degree of enantiocontrol could be gained and, at the same time, the rate of the chiral reaction could be enhanced as compared to the racemic background.



Scheme 4.2. Synthetic attempts to new H-bond phase-transfer catalysts.

Based on these assumptions, we designed two novel PTC compounds, namely **13** and **15** in scheme 4.2, which joined together the capabilities of a H-bond donor moiety with that of a quinuclidinium ammonium salt. Thus, commercially available thiourea organocatalyst

[13] a) Jakab, J.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724. b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890.

6 and squaramide **14** were parallely treated with benzyl bromide under standard conditions (scheme 4.2). Compound **6** failed to give the desired phase-transfer version **13**, whereas squaramide **14** was converted into the desired compound **15**, whose structure was detected by ^{1}H NMR and ESI-mass spectra analyses. Disappontingly, purification of **15** through flash column chromatography with silica gel turned out to be extremely troublesome, and we were not able to obtain it in a pure form.

These attempts cannot be considered conclusive, and more experimentation will be needed in order to obtain useful quantities of catalyst **15** to be deployed in phase trasfer catalyzed vinylogous Mannich reactions.

4.2.2 Organocatalyzed VMnR with preformed imines

As mentioned before (picture B, figure 4.3), the second approach toward the asymmetric vinylogous Mannich reaction involving 3-alkylidene-2-oxindoles entailed the pre-formation of the imine component and the *in situ* enolization of the indole pro-nucleophile promoted by a proper bifunctional organocatalyst.

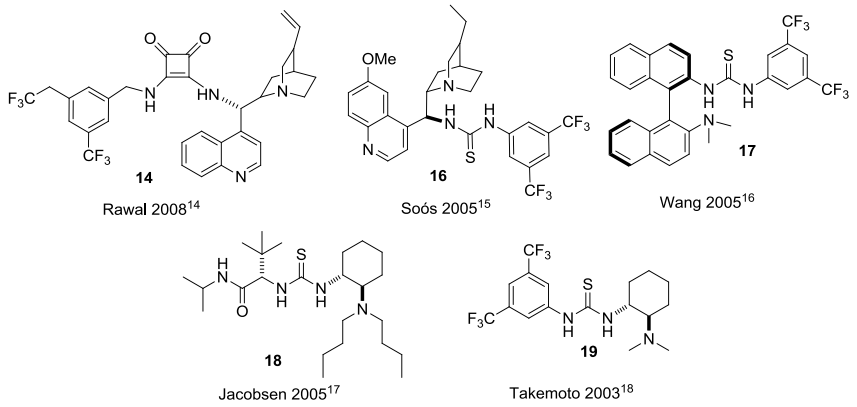
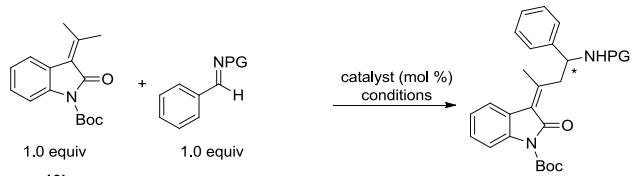


Figure 4.5. Organocatalysts scrutinized for the VMnR with preformed imines.

In figure 4.5, a list of the organocatalysts screened in our study is reported. Squaramide **14**, one of the elected organocatalysts to be

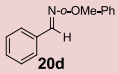
assayed, was synthesized for the first time in 2008 by Rawal and co-workers.[14] Its structure differs markedly from urea/thiourea-based organocatalysts in some key structural and functional features such as a) duality; b) rigidity; c) H-bond spacing; d) H-bond angle, and e) pK_a.[13b]

Table 4.2. Screening of the H-bond donor organocatalysts.[a]



1.0 equiv — **10b**; 1.0 equiv — **20a** PG = Boc, **20b** PG = Cbz, **20c** PG = Ts, **20d** PG = *o*-OMe-Ph

12

entry	Imine	catalyst (equiv)	reaction conditions	yield [%][b]	dr[c] (*Z*:*E*)	ee[d] [%] (*Z*)
1	 **20d**	**6** (0.1)	Toluene (0.1 M), −15 °C, 66h	—	—	—
2	 **20b**	**6** (0.1)	dry DCM (0.1 M), 0 °C, 38h	—	—	—
3	 **20a**	**6** (0.1)	Toluene (0.1 M), 40 °C, 37h	—	—	—
4	 **20a**	**19** (0.1)	Toluene (0.1 M), rt to 45 °C, 6 days	—	—	—
5	 **20c**	**6** (0.2)	PhCOOH (50 mol%), TFA (50 mol%), toluene (0.1 M), −40 to 50 °C, 6 days	—	—	—
6	 **20c**	**14** (0.1)	NEt_3 (50 mol%), toluene:$CHCl_3$ 1:1 (0.07 M), rt to 40 °C, 8 days	5	—	2
7	 **20c**	**18** (0.1)	Toluene (0.5 M), rt to 40 °C, 8 days	3	—	15
8	 **20c**	**17** (0.1)	Toluene (0.1 M), (−)-sparteine, rt to 50 °C, 51h	—	—	—

[14] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

entry	Imine	catalyst (equiv)	reaction conditions	yield [%][b]	dr[c] (*Z*:*E*)	ee[d] [%] (*Z*)
continuing from the previous page						
9	 20c	**19** (0.1)	Toluene (0.5 M), rt, 28h	24	99:1	11
10	 15d	**16** (0.1)	Toluene (0.5 M), rt, 28h	32	95:5	3

[a] For each catalyst almost the same reaction conditions as those reported in the literature were adopted (see corresponding reference within the text) [b] Isolated yield after flash column chromatography. [c] Diastereomeric ratio determined by analysis of ^{1}H NMR data of the reaction crude [d] Enantiomeric excess determined with chiral column HPLC analysis.

Squaramides may be considered as vinylogous amides, whereas thiourea derivatives are thioamides, and this feature causes both the carbonyl and amine moieties to be coplanar, making the catalyst costrained from a conformational perspective. Moreover, the squared shape of the ring induces a convergent position of the hydrogen atoms. The pK_a values of acid N-H protons in **14** have been predicted to be lower from those reported for urea/thiourea-based structures,[13b] although specific calculations have not been reported yet. *Cinchona*-derived isothiourea **16** (9-*epi*-DHQT) was firstly reported by Soós and colleagues,[15] while binaphthyl catalyst **17** was firstly reported by Wang,[16] thiourea **18** by Jacobsen,[17] and **19** by Takemoto.[18] For all but **14** and **18** the pK_a values of acid N-H protons have been calculated.[13a]

Keeping in mind these studies together with different structural properties, the catalysts were selected for the screening (table 4.2).

Employing indole **10b** and differently protected phenyl imines **20a-d** as the reactants and using thioureas **6** or **19** as the catalysts, no appreciable results were obtained, as revealed by entries 1-5 (table 4.2). These results seem to be independent from the electronic nature of the imine precursor. In fact, lowering the LUMO energy of the electrophile by swapping from imines bearing an electron-donating

[15] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.
[16] Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.
[17] Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.
[18] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

substituent, such as **20d**, to ones with electron-withdrawing groups such as Boc, Cbz and Ts in imines **20a-c**, the reaction course did not differ substantially.

The addition of weak Brønsted acid co-catalysts was also tested, since it is known that many organocatalyzed reactions may benefit from such acid species which can increase the reaction rate.[19] The employment of substoichiometric benzoic acid to thiourea **6** proved, however, unsuccessful (entry 5).

Using squaramide catalyst **14** with triethylamine delivered product **12bc** with low efficiency (5% yield) as a racemate (entry 6). Wang's catalyst **17** with the chiral sparteine as a base additive failed to give **12bc** (entry 8).

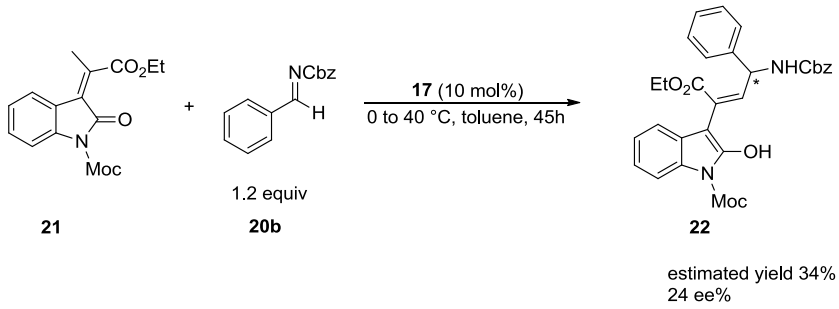
A significative change in terms of isolated yield of the products was observed with Takemoto catalyst **19** and Soos catalyst **16**[20] using a fivefold increase of reaction concentration (from 0.1 M to 0.5 M): in these instances, adduct **12bc** was isolated in 24% and 32% yields, respectively, albeit with very poor enantioinduction (entries 9 and 10).

The main problem of this reaction set was the substantial lack of reactivity of imines **20a-b** and **20d**, as judged by ^{1}H NMR analysis of the reaction crude (recovery of unaltered starting materials).

A second option in our hands was to act on the nucleophile using a more activated nucleophilic partner in order to produce a HOMO raising effect. Introducing a carboxyalkyl moiety into the alkylideneindole strucuture such as in compound **21** (scheme 4.3) would have certainly impacted both the γ-proton acidity and the reactivity of the evolving dienolate. Thus, as shown in scheme 4.3, nucleophile **21** was reacted with imine **20b** under cinchona-thiourea catalysis (10 mol% loading of catalyst **17**) delivering the expected

[19] Klausen, R. S.; Jacobsen E. N. *Org. Lett*. **2009**, *11*, 887.
[20] During the chiral HPLC analysis a spontaneous resolution was observed: after the dissolution in *i*-PrOH, a precipitate was formed and it resulted to be racemic whereas the supernatant had a 37% *ee*.

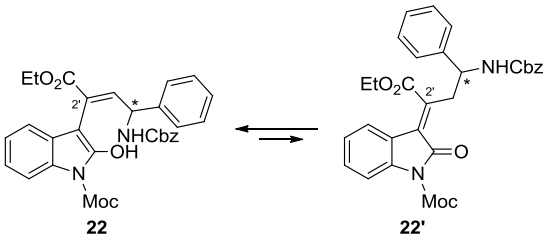
Mannich product **22** in a promising 34% yield and with a still poor 24% enantiomeric excess. This result confirmed our hypothesis and elected the activated indole **21** as a possible candidate for development of the direct VMnR.



Scheme 4.3. Asymmetric direct VMnR with activated donor **21**.

From analysis of ^{1}H, ^{13}C, COSY and HSQC NMR experiments we were convinced that the Mannich adduct **22** could be isolated in its tautomeric enolic form possibly induced by favorable intramolecular hydrogen bonding network (scheme 4.4).

For example, by examining the ^{1}H NMR spectrum of compound **22**, a singlet signal at 6.83 ppm was observed that was assigned to H2' because of its downfield chemical shift and absence of coupling multiplicity. Complete absence of the methylene protons in the corresponding tautomer **22'** was noted.



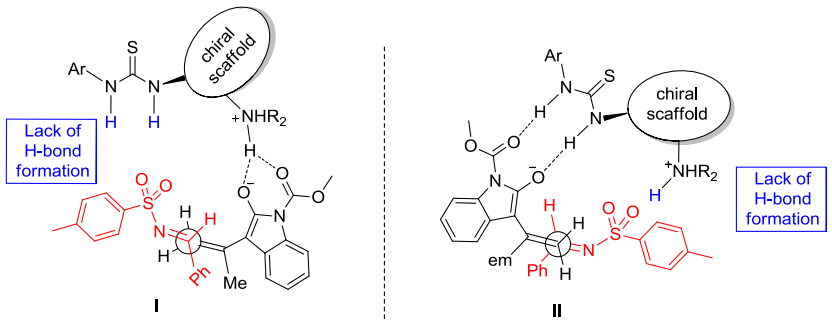
Scheme 4.4. The two possible tautomers of **22**.

Heating the molecule (variable temperature NMR up to 65 °C) did not cause any variation in the ^{1}H NMR spectrum denoting that no hydrogen bond breakage was affected at this temperature.

By inspecting the preliminary results of the catalytic asymmetric VMnR with preformed imines, we became aware that the main difficulties were connected with the induction of enantioselectivity, that is, the selected organocatalysts were scarcely able to selectively and simultaneously activating the reacting partners. Preliminary results in entries 9 and 10 of Table 4.2 and those of scheme 4.3 represent possible starting points, but finding the right catalyst system represents a key issue that is still to be pursured.

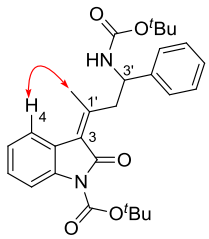
Keeping in mind the postulated and calculated activation modes of thiourea-based organocatalysts,[21] we tried to furnish a rational explanation for the poor enantioselectivity observed in our studies. We presume that in both possible transition states **I** and **II** (scheme 4.5),[22] the imine component such as *N*-tosyl imine **20c** is hardly able to engaging favorable interactions with the catalyst, with absence of H-bond interactions with either the thiourea moiety (transition state **I**)[21b] or the protonated amine within the quinuclidine ring (transition state **II**).[21a] The imine acceptor might thus be able to flip, exposing its *re* and *si* face as well during the attack from the nucleophile. The lack of this type of interaction could prevent formation of an organized and tight transition state, responsible for high level of enantiodifferentiation observed in other direct vinylogous reactions.[5,23]

[21] a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119; b) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc*. **2006**, *128*, 13151.
[22] An antiperiplanar trajectory is represented but other approaches cannot, in principle, be ruled out.
[23] The vinylogous aldol reaction performed following conditions in entry 10 table 5 with 4-nitro-benzaldehyde delivered the corresponding aldol product in 50% isolated yield and 80% *ee*.



Scheme 4.5. Postulated transition states possibly accounting for the lack of enantiocontrol during the VMnR.

4.2.3 Stereochemical assessment



(*Z*)-**12ba**

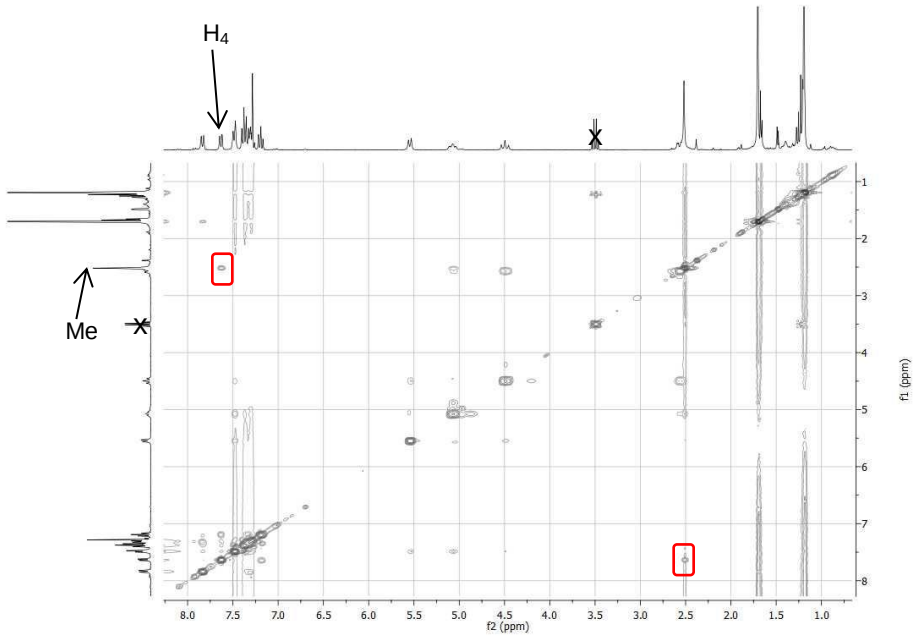


Figure 4.6. Significant NOE contacts of compound **12ba** (^{1}H-^{1}H NOESY experiment at 300 MHz in $CDCl_3$).

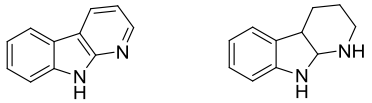
The Mannich products in this study such as compound **12ba** feature two stereogenic elements: the geometry of the exocyclic carbon-carbon double bond (*E* vs *Z*) and one stereocenter at C3'.

The geometry of the double bond in **12ba** was inequivocally established by ^{1}H-^{1}H NMR NOESY esperiments (at 300 MHz in $CDCl_3$), as shown in figure 4.6. A H_4-methyl NOE contact proved diagnostic to establish the *Z*-configuration of the exocyclic double bond. The stereochemistry of product **12bc** was determined using the same 2D NMR experiment.

The absolute configuration at the C3' stereocenter in enantioenriched compounds (entries 9 and 10 of Table 4.2 and compound **22** in scheme 4.3) was not determined due to low ee values.

4.2.4 Towards the synthesis of hexahydro α-carbolines

α-Carboline backbone **23** and its hexahydro counterpart **24** (figure 4.7) have commonly found widespread appearance in natural products.



23 **24**

Figure 4.7. General structures of α-carboline **23** and hexahydro derivative **24**.

In particular, the pyrido[2,3-*b*]indole nucleus **23** (α-carboline) is a "privileged" indole framework which is commonly found in pharmaceutical drugs and natural products.[24] In figure 4.8 a panel of carboline-containing structures is reported. The pyrido[2,3-*b*]indole

[24] (a) Bolton, D.; Forbes, I. T.; Hayward, C. J.; Piper, D. C.; Thomas, D. R.; Thompson, M.; Upton, N. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 1941; (b) Love, B. E. *Top. Heterocycl. Chem.*, **2006**, *2*, 93; (c) Somei, U.; Basha, A. *Indole Alkaloids*, Hawood Academic Publishers, Amsterdam, 1997; (d) Humphre, G. R.; Kuethe, J. T. *Chem. Rev*., **2006**, *106*, 2875; (e) Sundberg, R. J. *Indoles*, Academic Press, London, 1996; (f) Sundberg, R. J. *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Ress, E. F. V. Scriven and C. W. Bird, Pergamon Press, Oxford, U.K., 1996, vol. 2, p. 119.

backbone is present in grossularine-1 (**25**), a naturally occurring alkaloid, and mescengricin (**26**), a natural compound isolated from *Streptomyces griseoflavus*, known to be a neuronal cell protecting substance. α-Carboline **27** is a molecular entity of medicinal interest due to its action as cyclin-dependent kinase (CDK) inhibitor.

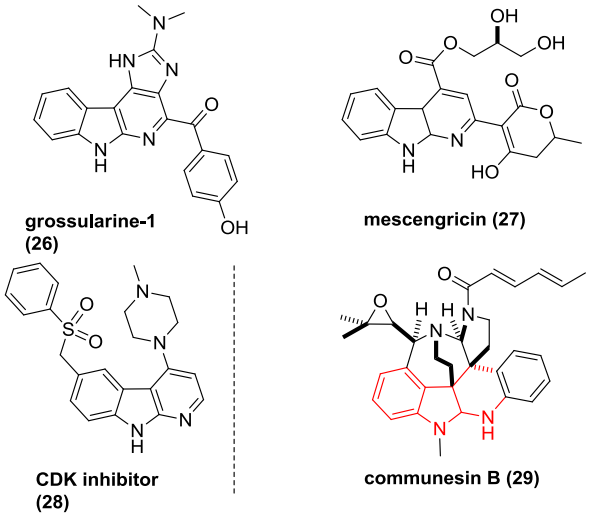


Figure 4.8. Molecules containing the α-carboline motifs **23** and **24**.

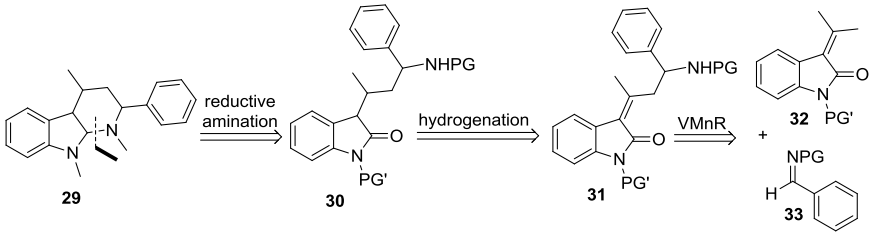
The 2,3,4,4a,9,9a-hexahydro-1H-pyrido[2,3-*b*]indole motif (**24**) (hexahydro α-carboline) is a less common moiety but it is still important and present within naturally occurring compounds such as in communesin B (**28**) and related derivatives.[25]

As it appears evident at first sight, structures **23** and **24** differ from each other for possible different conformations of the pyridine/piperidine ring, the former being rigidly planar (in α-carboline **23**) because of its aromatic nature. This feature can be clearly recognized by comparing the three-dimensional structure **28** to the other flattened compounds in figure 4.8.

[25] Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170.

Despite the continuous efforts in developing efficient protocols for the synthesis of α-carbolines,[26] catalytic asymmetric (and symmetric) methodologies towards hexahydro α-carbolines are still rare.[27]

Our strategy featuring a vinylogous Mannich reaction between 3-alkenyl-2-oxindole nucleophiles and imine electrophiles was perfectly suited for the straightforward synthesis of perhydro α-carbolines bearing variable substituents at the C2 and C4 positions.

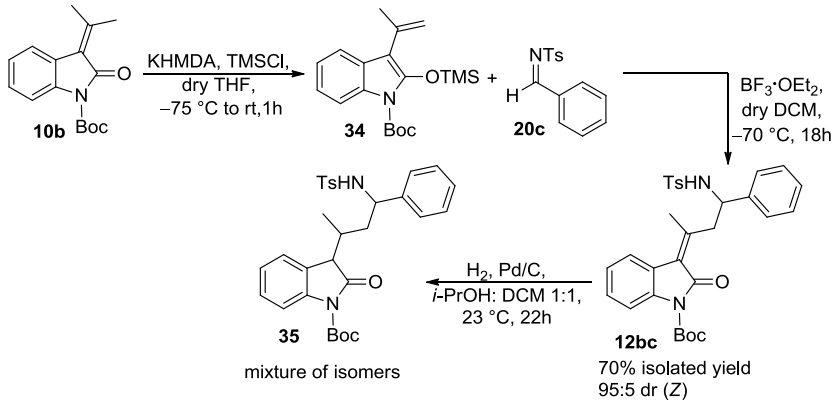


Scheme 4.6. Retrosynthetic strategy to perhydro α-carbolines **29**.

The retrosynthetic plan in scheme 4.6 is extremely straightforward: it was envisioned that the α-carboline target **29** could derive from **30** by intramolecular reductive amination. Compound **30** could be formed by reduction of the exocyclic double bond in **31** which ultimately could be the result of a VMnR between 3-alkylidene-2-oxindole **32** and imine **33**. Would it possible to perform the VMnR in an asymmetric way, chiral nonracemic carboline target compounds would be easily at hand.

We firstly applied our strategy by employing an indirect Mukaiyama-type vinylogous Mannich reaction in a symmetric format. Thus, the starting 3-alkylidene-2-oxindole **10b** was easily converted to the corresponding trimethylsilyldienolate **34**, which was reacted with tosyl imine **20c** under the agency of boron trifluoride etherate (scheme 4.7).

[26] For recent article see, a) Gupta, S.; Kumar, B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10154. b) Basavaiah, D.; Reddy, D. M. *Org. Biomol. Chem.* **2012**, *10*, 8774. c) Kumar, A. S.; Rao, P. V. A.; Nagarajan, R. *Org. Biomol. Chem.* **2012**, *10*, 5084.
[27] Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 5558.



Scheme 4.7. Preliminary investigations to aminated indole **35**.

Pleasantly, the expected Mannich adduct **12bc** was obtained in good yield (70% isolated yield, >90% conversion) and with noteworthy diastereoselection in favor of the *Z*-configured product. Subsequent reduction of the carbon-carbon double bond via catalytic hydrogenation delivered product **35** bearing two newly installed stereocenters. This compound was isolated as a mixture of four isomeric products, more than the two expected by a *syn*-selective reaction.

Because purification by silica gel flash chromatography did not provide any benefits to the analysis, we moved to semi-preparative HPLC method which allowed the isolation of a pure major compound and a collection of three peaks whose ^{1}H NMR spectrum revealed three chemical entities possibly corresponding to three different isomers in an estimated ratio of 1:0.7:0.3 (figure 4.9). At first we hypothesized that these signals could be assigned to different conformers of the two expected reduction products which could arise from strong intramolecular hydrogen bond interactions. Carrying ^{1}H NMR experiments at variable temperatures (25°C to 80 °C) did not provoke any interconversion of the signals denoting either an extreme stability of the conformers at these temperatures or defiance in this hypothesis.

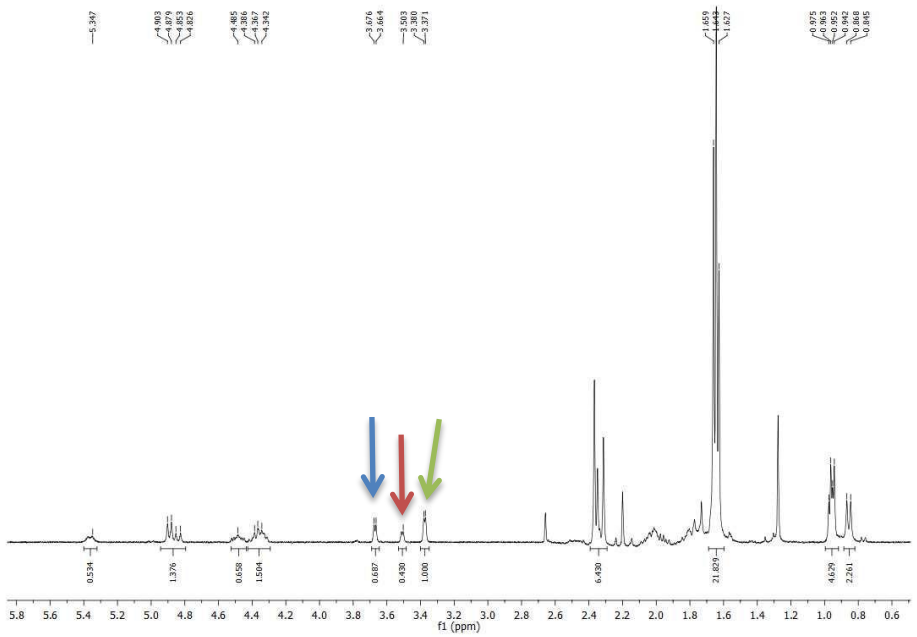
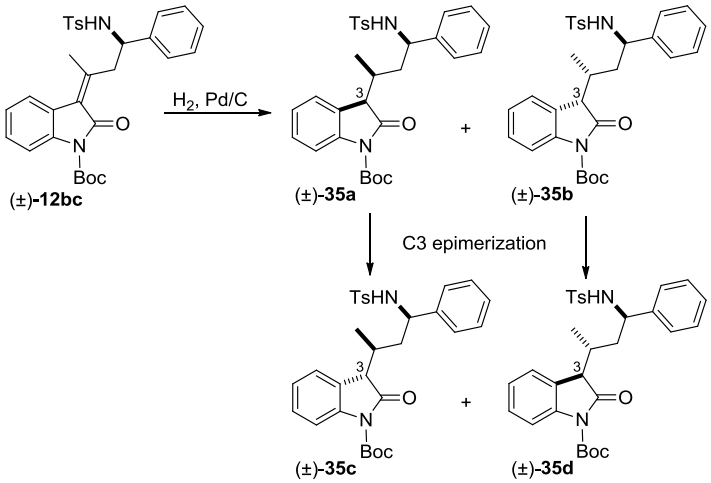


Figure 4.9. ^{1}H NMR experiment (at 300 MHz in $CDCl_3$) of compounds **35**. The sample derived from purification by semi-preparative HPLC column (CN 100A 10μ) (0.5-6.0 ppm window is shown).

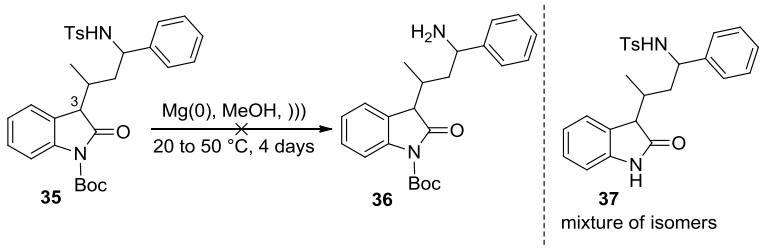
Since from NMR analyses the signals of the three unidentified products appeared similar to the major HPLC-isolated compound, we envisioned that **35** was indeed a mixture of *syn*- and *anti*-disposed configurational isomers. Despite the *syn*-selectivity of the hydrogenation reaction, a possible epimerization at the C3 position could take place, thus delivering a mixture of hydrogenated products, as shown in scheme 4.8. Epimerization of the C3 site could be feasible due to the acidic nature of the proton at the α-position of the amide moiety.



Scheme 4.8. Four different products potentially formed during the hydrogenation of (±)-**12bc**.

With milligrams quantity of one saturated isomer **35** in hands, cleavage of the tosyl group from the primary benzylic amine was attempted (scheme 4.9). The reaction was carried out with freshly crumbled Mg(0) in methanol under ultrasonic irradiation.[28] Unfortunately, the desired product **35** was not detected by analysis of the ^{1}H NMR reaction crude; instead, under the above reported conditions, the *tert*-butoxycarbonyl protecting group of oxindole **35** was cleaved, as revealed by two broad singlet signals at 8.5 ppm (^{1}H NMR spectrum at 300 MHz in $CDCl_3$) which were assigned to the lactam NH protons. Also, the splitting into two signals is evidence of the formation of an isomeric mixture of **38** due to (again!) epimerization at the C3 position.

[28] a) Wuts, P. G. M.; Greene, T. W. *Greene's protective groups in organic synthesis*, 4th edition, 2007. b) González, A. S.; Arrayás, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335.



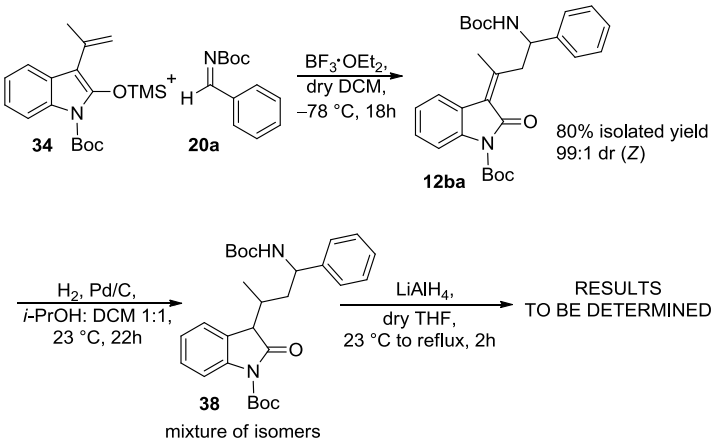
Scheme 4.9. Reaction conditions for detosylation reaction.

These initial results prompted us to think that probably the vinylogous adduct **12bc** was not the best substrate to be converted into the desired 2,4-disubstituted perhydro α-carboline of general structure **29**. The epimerization of C3 position and the extreme liability of the *N*-Boc protecting group together with the difficulty to cleave the tosyl group installed on the primary amine led us to use an alternative imine starter with an "easy-to-remove" protecting group.

As depicted in scheme 4.10, when the VMMnR was carried out with Boc-protected imine **20a**, the expected Mannich product **12ba** was obtained in high yield (89% isolated yield and >97% conversion) and with excellent diasteredifferentiation in favor of the *Z* isomer (99:1 *Z:E*).

Hydrogenation of compound **12ba** following the above reported conditions (see scheme 4.7) delivered product **38** as a mixture of isomers, which have not separated and fully characterized yet. The intermediate mixture was then subjected to hydride reduction, following conditions reported forn similar cyclization reactions[29] in order to perform the projected reductive amination. Analysis of the thin layer chromatography revealed complete conversion of **38** within two hours and work is in progress now to definitely assess the nature of the products.

[29] Buy, T.; Syed, S.; Barbas III, C. F. *J. Am. Chem. Soc.* **2009**, *131*, 8758.



Scheme 4.10. Revised strategy towards 2,4-disubstituted perhydro α-carbolines.

4.3 Conclusions and perspectives

The development of a direct asymmetric VMnR was firstly addressed. The organocatalysts were screened meticulously and attempts to rationalize the experimental results were made.

At the same time, a strategy towards the synthesis of precious 2,4-disubstituted perhydro α-carbolines was pursued, by implementing an unprecedented vinylogous Mukaiyama Mannich reaction between 3-alkylidene-2-oxindoles and activated imines. Preliminary results were successful representing good premises for the development and optimization of the work. Possible opening of the work could entail the exploitation of the above indirect VMMnR in an asymmetric format where metal-based catalytic systems could be tested. In addition, direct asymmetric VMnR versions could be assayed catalyzed by chiral ligand-metal complexes as well.

An auxiliary-based approach could also be devised, with the use of versatile chiral amine templates such as Davis *p*-toluenesulfinimines or

Ellman *N-tert*-butanesulfinimines as the acceptor components of the VMMnR.[30]

4.4 Experimental data

General experimental methods. All reactions were performed in clean, standard laboratory glassware with rubber septa. Solvents for chromatography and filtration including hexane, ethyl acetate, dichloromethane, petroleum ether, diethyl ether, anhydrous ethanol, methanol and 2-propanol were ACS or HPLC grade and used as received. Mannich reaction solvent tetrahydrofuran (BHT, 250 ppm) was purchased from Sigma-Aldrich and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} pre-coated plates with visualization under short-wavelenght UV light and by dipping the plates with molybdate reagent (aqueous H_2SO_4 solution of ceric sulphate/ammonium molybdate) followed by heating. Flash column chromatography was performed using 40-63 μm silica gel using the indicated solvent mixtures. HPLC samples were previously filtered through Whatman Anotop 10 LC membrane filters using the indicated solvent mixtures. Analytical chiral HPLC analysis was carried out using Chiralcel OD-H column and Regis (*S,S*)-Whelk-O 1 (250×4.6 mm) column. Optical rotation data were obtained on a digital polarimeter at ambient temperature using a 100 mm cell with a 1 mL capacity and are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded at 300 MHz or 400 MHz (^{1}H) and 75 MHz or 100 MHz (^{13}C). Spectra were referenced to tetramethylsilane (0.0 ppm, ^{1}H; 0.0 ppm, ^{13}C, in $CDCl_3$). Chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hertz. ^{1}H and ^{13}C NMR assignments are corroborated by 1D and 2D experiments (gCOSY, gHSQC, and DEPT sequences). ESI-mass spectra were recorded on API 150EX apparatus and are reported in the form of (*m/z*).

catalysts. Catalysts **18** and **19** were purchased from Sigma-Aldrich and used as received, catalyst **6**,[15] **7**,[31], **8**,[31] **9**,[11] **14**,[14] and **17**[16] were prepared following the published procedures. The purity of the catalysts was ascertained by close inspection of their ^{1}H and ^{13}C NMR spectra, as well as optical rotation measurements.

[30] a) Ruan, S.-T.; Luo, J.-M.; Du, Y.; Huang, P.-Q. *Org. Lett.* **2011**, *13*, 4938. b) Gu, C.-L.; Liu, L.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 5754.
[31] Wang, Y.; Sun, J.; Ding, K. *Tetrahderon* **2000**, *56*, 4447.

starting materials. 3-Alkylidene oxindoles **10a** and **10b** and compound **34**[5,7]; *tert*-butyl phenyl(phenylsulfonyl)methylcarbamate (**11a**)[32] and benzyloxycarbonyl(phenylsulfonyl)methylcarbamate (**11b**)[33]; imines **20a**,[32] **20b**,[33], **20c**[34] and **20d**[35] were synthesized according to previously published procedures.

Preparation of (*Z*)-1-*tert*-butoxycarbonyl-3-(4-*tert*-butoxycarbonylamino-4-phenylbutan-2-ylidene)indolin-2-one (12ba) (table 4.1 entry 7). Amidosulfone **11a** (25.5 mg, 0.07 mmol, 1 eq) was suspended in 1.0 mL dry DCM under an inert atmosphere. *N*-*tert*-Butoxycarbonyl-3-alkylidinene-2-oxindole **10b** (30 mg, 0.1 mmol, 1.5 eq) and catalyst **9** (5.5 mg, 7.3 μmol, 0.1 eq) were added sequentially, and the resulting mixture was cooled to –20 °C. Freshly ground KOH (8.2 mg, 0.15 mmol, 2.0 eq) was added and the resulting suspension was vigorously stirred at –20 °C. After 20 h, 100 μL 5% aq. citric acid solution was added and the solution was allowed to warm to ambient temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The diastereomeric ratio of the addition products **12ba** was determined to be 99.0:1.0 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was then purified by silica-gel flash chromatography (hexane/EtOAc 9:1), to yield 16 mg (45%) of (+)-(*Z*)-**12ba** as white amorphous solid: TLC, R_f = 0.67 (petroleum ether/EtOAc 70:30); $[\alpha]^D_{20}$ = +4.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 6 Hz, 1H, H7), 7.61 (d, *J* = 5.8 Hz, 1H, H4), 7.47 (d, *J* = 5.5 Hz, 1H, Ar), 7.38-7.25 (m, 5H, Ar), 7.18 (dd, *J* = 5.8, 5.7 Hz, 1H, H5), 5.52 (bd, *J* = 6.9 Hz, 1H, *N*H), 5.06 (m, 1H, H4'), 4.48 (dd, *J* = 8.8, 8.9 Hz, 1H, H3′α), 2.56 (d, *J* = 8.8 Hz, 1H, H3′β), 2.50 (s, 3H, Me), 1.69 (s, 9H, *t*-Bu, Boc), 1.18 (s, 9H, *t*-Bu, Boc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (Cq), 156.4 (Cq), 155.7 (Cq), 149.2 (Cq), 142.8 (Cq), 137.9 (Cq), 128.6 (2C, CH), 128.2 (CH), 127.3 (CH), 126.4 (2C, CH), 124.2 (Cq), 123.9 (3C, CH and Cq), 114.4 (CH), 84.3 (Cq), 79.0 (Cq), 54.3 (CH), 43.2 (CH), 28.2 (3C, CH_3), 28.1 (3C, CH_3), 24.5 (CH_3). ESI-MS *m/z* 464.26 $[M+H]^+$ (Calcd 464.23 $[M+H]^+$). Anal. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.81; H, 6.94; N, 6.03. Found: C, 69.86; H, 6.97; N, 6.01. HPLC: *Z*-**12ba**, Chiral HPLC: **12ba** 1st peak, t_R 18.13 min (26.0%); **12ba** 2nd peak, t_R 21.91 min (73.0%) ((*S,S*)-Whelk-O 1 (250×4.6 mm), hexane/anhydrous EtOH 90:10, 0.6 mL/min, 254 nm).

[32] Yang, J. W.; Pan, S. C.; List, B. *Org. Synth,* **2009**, *86*, 11.
[33] Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Comm.* **2006**, 1191.
[34] Cui, Z.; Yu, H.-J.; Yang, R.-F.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc.*, **2011**, *133*, 12394.
[35] Ross, N. A.; MacGregor, R. R.; Bartsch, R. A. *Tetrahedron* **2004**, *60*, 2035.

General procedure for *rac*-(*Z*)-1-*tert*-butoxycarbonyl-3-(4-*tert*-butoxycarbonylamino-4-phenylbutan-2-ylidene)indolin-2-one (12ba) (scheme 4.12). Imine **2a** (80 mg, 0.4 mmmol, 0.5 eq) was dissolved in 1.1 mL dry CH_2Cl_2 under inert atmosphere then a solution of **34** (90 mg, 0.3 mmol, 1.0 eq) in 1.1 mL of dry CH_2Cl_2 was added and the resulting solution was cooled to –78 °C. BF_3•OEt_2 (32 μL, 0.3 mmol, 1.0 eq) was added drop-wise and the reaction mixture was stirred for 18h, then quenched with solid $NaHCO_3$ (22mg) and 2.0 mL of H_2O and slowly allowed to warm to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and then the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The diastereomeric ratio of the addition products **12ba** was determined to be 99.0:1.0 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was then purified by silica-gel flash chromatography (hexane/EtOAc 9:1), to yield 94 mg (78%) of (*Z*)-**12ba** as light-yellow amorphous solid. The ^{1}H and ^{13}C NMR data matched with those reported above.

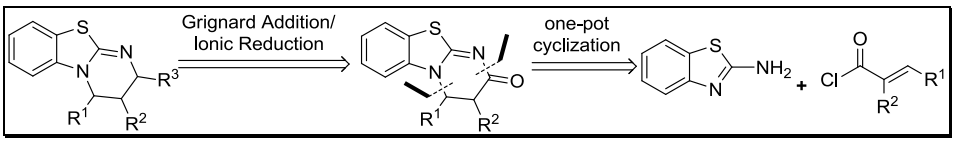
***rac*-(*Z*)-1-*tert*-butoxycarbonyl-3-(4-*p*-methylbenzensulfonylamino-4-phenylbutan-2-ylidene)indolin-2-one (12bc) (scheme 4.8):** Compound *rac*-(*Z*)-**12bc** was prepared according to procedure for *rac*-(*Z*)-**12ba** using imine **20c** (155mg, 0.6 mmol, 1.0 eq), **34** (310 mg, 0.9 mmol, 1.5 eq) and BF_3•OEt_2 (111 μL, 0.9 mmol, 1.5 eq). The diastereomeric ratio of the addition products **12bc** was determined to be 95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was then purified by silica-gel flash chromatography (gradient elution petroleum ether/EtOAc 8:2 to 7:3), to yield 222 mg (70%) of (*Z*)-**12bc** as light yellow amorphous solid: TLC, R_f = 0.36 (petroleum ether/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 1H, H7), 7.46-7.19 (m, 10H, Ar, Ts, H4, H5, H6), 6.87 (d, *J* = 8.0 Hz, 2H, Ts), 6.10 (d, *J* = 7.9 Hz, 1H, N*H*), 4.76 (ddd, *J* = 11.6, 8.0, 3,2 Hz, 1H, H4'), 4.33 (dd, *J* = 12.3, 12,3 Hz, 1H, H3′α), 2.41 (dd, *J* = 12.6, 3.3 Hz, 1H, H3′β), 2.23 (s, 3H, Me), 2.14 (s, 3H, Me) 1.73 (s, 9H, *t*-Bu, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (Cq), 154.7 (Cq), 149.2 (Cq), 142.9 (Cq), 138.3 (Cq), 138.2 (Cq), 129.9 (Cq), 129.3 (2C, CH), 128.76 (2C, CH), 128.71 (CH), 127.6 (CH), 126.6 (2C, CH), 126.5 (2C, CH), 124.9 (Cq), 124.1 (CH), 124.0 (CH), 123.7 (Cq), 114.8 (CH), 84.9 (Cq), 57.9 (CH), 44.0 (CH), 28.4 (3C, CH_3), 24.3 (CH_3), 21.5 (CH_3). ESI-MS *m/z* 455.43 $[M–Boc+Na]^+$ (Calcd 455.15 $[M–Boc+Na]^+$). Anal. Calcd for $C_{30}H_{32}N_2O_5S$: C, 67.65; H, 6.06; N, 5.26. Found: C, 67.70; H, 6.11; N, 5.29.

***rac*-1-*tert*-butoxycarbonyl-3-(4-*p*-methylbenzensulfonylamino-4-phenylbutan-2-yl)indolin-2-one (35, <u>major isomer</u>) (scheme 4.8):** Palladium (10 wt.% on

activated carbon, 10 mg) was added to a solution of unsaturated Mannich adduct **12bc** (34 mg, 0.06 mmol) in *i*-PrOH:CH_2Cl_2 1:1 (4 mL) at room temperature. The reaction vessel was degassed under vacuum and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen for 22 h, after which time the hydrogen was evacuated; the reaction mixture was filtered through a celite pad and concentrated under vacuum to give a crude residue. Analitycally pure sample of the major isomer of **35** was then obtained by semipreparative HPLC [CN 100A 10μ, hexane:anhydrous EtOH=95:5, 3.0 mL/min, 254nm, t_R 32.36 min (55.70%) for **35** major isomer and t_R 43.25 min (11.13%), 47.20 min (13.31%) and 50.31 min (15.83%) for the remaining isomers]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 1H, oxindole), 7.53 (d, *J* = 8.2 Hz, 2H, Ts), 7.31-7.03 (m, 10H, oxindole, Ph, Ts), 5.01 (d *J* = 8.5 Hz , 1H, *N*H), 4.60 (ddd, *J* = 8.9, 8,9, 5,1 Hz, 1H, H4'), 3.78 (d, *J* = 3.4 Hz, 1H, H3), 2.46-2.41 (m, 1H, H2'), 2.38-2.29 (m, 4H, Me and H3α), 1.80 (ddd, *J* = 14.2, 9.1, 5.3, 1H, H3β), 1.67 (s, 9H, Bu^t), 0.77 (d, *J* = 6.7 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (Cq), 143.3 (Cq), 140.8 (Cq), 140.5 (Cq), 137.6 (Cq), 129.5 (2C, CH), 128.7 (2C, CH), 128.1 (CH), 127.5 (2C, CH), 127.2 (2C, CH), 126.4 (2C, CH), 126.4 (2C, CH), 124.6 (CH), 124.0 (Cq), 114.8 (CH), 84.5 (Cq), 56.3 (CH), 38.1 (CH), 41.3 (CH_2), 33.3 (CH), 28.3 (3C, CH_3), 21.6 (CH_3), 15.7 (CH_3). Anal. Calcd for $C_{30}H_{34}N_2O_5S$: C, 67.39; H, 6.41; N, 5.24. Found: C, 67.43; H, 6.50; N, 5.27.

Chapter 5

A short economical and scalable synthesis of homobenzotetramisole and related organocatalysts[1]



[1] This work was made in the period October 2011-April 2012 at Texas A&M University with Prof. Daniel Romo and Dr. Omar Robles. It firstly appeared in a poster communication *Expedient Access to Homobenzotetramisole and Derivatives: Versatile Organocatalysts*; IASOC, September 22-26, 2012, Sant'Angelo, Ischia-Napoli, Italia

5.1 Introduction

During the last years, organocatalysis has become a *hot topic* in asymmetric synthesis.[2] Among the classes of organocatalysts,[3] which differ in terms of structural properties and reactivity, chiral bicyclic isothioureas represent a powerful but yet-understated category. Only recently these Lewis base catalysts have caught the attention of the synthetic chemists community due to their ability to promote different reactions such as kinetic resolution[4a-k] and dynamic kinetic resolution,[5] desymmetrization of diols,[6] determination of absolute configuration,[7] and a series of catalytic asymmetric transformations *e.g.* carboxyl or acyl [8a-d] and sulfonyl[9] group transfer, intramolecular aldol lactonizations for the formation of bi- and tricyclic β-lactones,[10] and intra- and intermolecular Michael addition-lactonization processes.[11] Furthermore, studies regarding their reactivity as Lewis Base have also been made.[12]

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[2]The importance of this branch is well witnessed by the web page http://www.wiley-vch.de/util/hottopics/organocat of WILEY-VCH publications.

[3] a) Gaunt, M. J.; Johansonn, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today*, **2007**, *12*, 8. b) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304.

[4] a) Birman, V.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. b) Birman, V.; Li, X. *Org. Lett.* **2006**, *8*, 1351. c) Birman, V.; Li, X. *Org. Lett.* **2008**, *10*, 1115. d) Zhou, H.; Xu, Q.; Chen, P. *Tetrahedron*, **2008**, *64*, 6494. e) Xu, K.; Zhou, H.; Geng, X.; Chen, P. *Tetrahedron*, **2009**, *65*, 2232. f) Yang, X.; Birman, V. *Adv. Synth. Catal.* **2009**, *351*, 2301. g) Zhang, Y.; Birman, V. *Adv. Synth. Catal.* **2009**, *351*, 2525. h) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y-S.; Itagaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11629. i) Yang, X.; Bumbu, V.; Birman, V. *Org. Lett.* **2011**, *13*, 4755. l) Belmessieri, D.; Joannesse, C.; Woods, P. A.; MacGregor, C.; Jones, C; Campbell, C. D.;. Johnston, C. P.; Duguet, N.; Concellón, C.; Bragg, R. A.; Smith, A. D. *Org. Biomol. Chem.* **2011**, *9*, 559. j) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; k) Yang, X. Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722.

[5] Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892.

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[7] Wagner, A. J.; David, J. G.; Rychnovsky, S. D. *Org. Lett*. **2011**, *13*, 4470.

[8] a)Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 8914.b) Joannesse,C.; Simal, C.; Concellón, C.; Thomson, J. E.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 2900. c) Viswambharan, B.; Okimura, T.; Suzuki, S.; Okamoto, S. *J. Org. Chem.* **2011**, *76*, 6678. d) Joannesse, C.; Johnston, C. P.; Morrill, L. C.; Woods, P. A.; Kieffer, M.; Nigst, T. A.; Mayr, H.; Lebl, T.; Philp, D.; Bragg, R. A.; Smith, A. D. *Chem. Eur. J.* **2012**, *18*, 2398.

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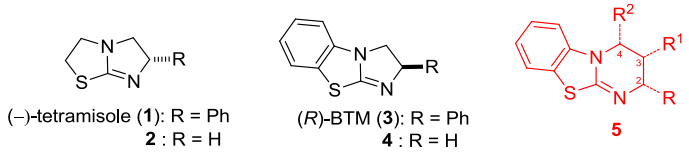


Figure 5.1. Most common chiral bicyclic isothioureas.

Due to their superior nucleophilicity and better reaction performance as compared to tetramisole (**1**), (*R*)-BTM (**3**) and the parent achiral version **2** and **4** (figure 5.1),[12a,b] the most employed compounds are those of type **5** derived from the achiral 3,4-dihydro-2*H*-pyrimido [2,1-*b*]-benzothiazole (**5a**) in figure 5.2. The first novel derivative of tetramisole that displayed superior enantioselectivity was homobenzotetramisole (HBTM) (**5b**), reported by Birman in 2008.[4c]

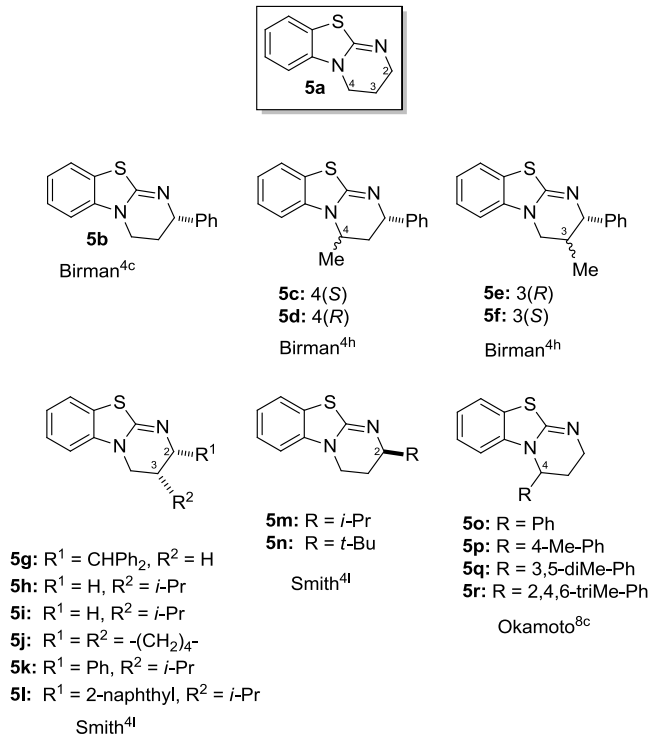


Figure 5.2. Current pyrimido-benzothiazole organocatalysts.

Subsequently, diversified chiral pyrimido-benzothiazoles were synthesized by Birman himself (**5c-f**),[4h] by Smith and co-workers (**5g-n**),[7b]

and finally by the Okamoto group (**5o-r**).[7c] The main structural motif of these compounds - the pyrimido-benzothiazole backbone - constitutes a privileged structure due to the possibility to introduce multiple chirality centers in the non-aromatic ring: the substituents are not simple embellishments since they are able to alter the ring conformation thus providing additional interactions with the substrates and ultimately leading to better catalytic activity and enantiocontrol.[4h,l]

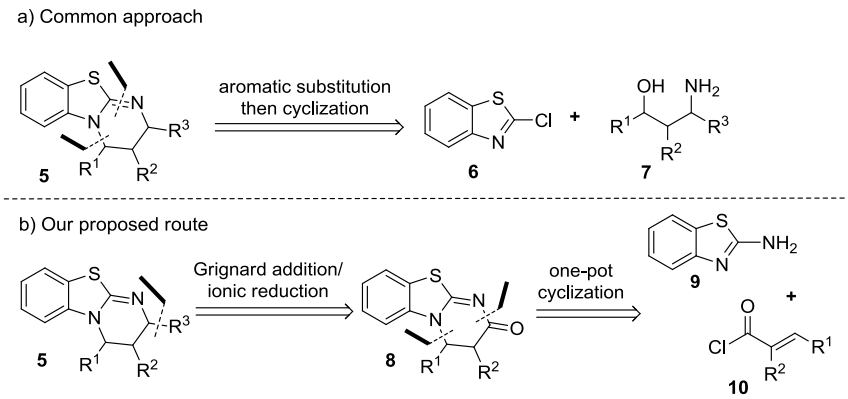
So far, the common synthetic route towards compounds **5b-n** adopted a convergent approach which required the synthesis of the corresponding enantiomerically pure γ-amino alcohols of general structure **7** (scheme 5.1). Supply of the starting chiral alcohol was the main issue of these strategies. While it could be synthesized on large scale using multiple-step procedures, the overall yields were low.[13] Conversely, only a few alcohols are commercially available, but in some cases prohibitively expensive.[14] Furthermore, the available syntheses of catalysts **5** were all carried out on the milligram scale, thus limiting of the possibility of supplying large quantities of this increasingly important nucleophilic catalyst.

Facing these limitations, and conscious of the great potential shown by chiral bicyclic isothiourea catalysts, we decided to design and execute a short and scalable synthetic route to both HBTM (**5b**) and derivatives from readily available, inexpensive starting materials.

Scheme 5.1 delineates the retrosynthetic approaches to catalysts **5**. We proposed an alternative disconnection (scheme 5.1b) starting from 2-aminobenzothiazole **9** and a general acryloyl chloride **10** (paragraph 5.2). This would constitute a complete different strategy compared to previous syntheses, which include nucleophilic aromatic substitution followed by cyclization with **6** and γ-amino alcohol **7**. We envisioned a scalable,

[13] Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta.* **2000**, *83*, 1256.
[14] Prices comparison can be make using Scifinder web. Here prices and chemical suppliers are not reported because of possible changes.

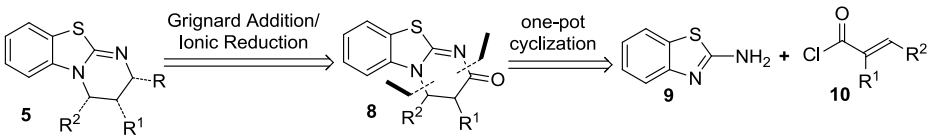
racemic synthesis initially that would enable to both enantiomers of HBTM through subsequent classical resolution or chiral chromatography separation.



Scheme 5.1. Comparison between the previous strategies and our own synthetic plan for the synthesis of pyrimido-benzothiazole organocatalysts.

5.2. Results and discussion

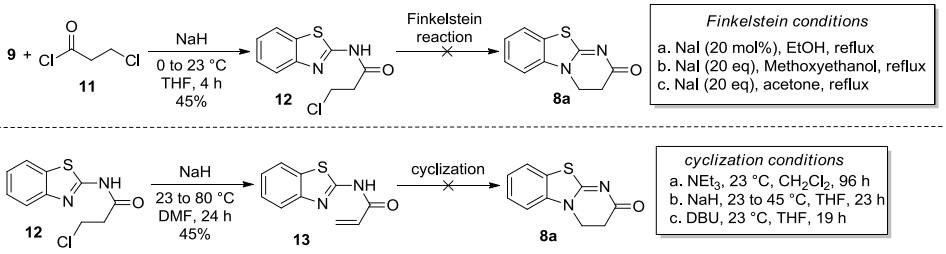
The retrosynthetic strategy, illustrated in scheme 5.2, was quite straightforward. It was envisioned that the pyrimido-benzothiazole structure **5** could derive from the 2-oxopyrimido-benzothiazole moiety **8** after Grignard addition followed by reduction of an enamine-like intermediate (not shown). Pyrimidone **8** would be prepared by one-pot cyclization from 2-aminobenzothiazole **9** and acryloyl chloride of general structure **10**, responsible for the different substitution pattern on the non-aromatic ring of the target.



Scheme 5.2. Proposed retrosynthetic plan.

Initially we embarked in the synthesis of intermediate **8**. According to a first strategy, 3-chloropropanoyl chloride (**11**) was used, which would

have led to unsubstituted **8a** (R^1 = R^2 = H). Although **8a** may be considered a trivial structure, some challenges were encountered during its preparation: available data and procedures reported in the literature were outdated and inaccurate or indeed they were completely missing.[15]



Scheme 5.3. Summary of the first attempts towards the synthesis of tricyclic moiety **8a**.

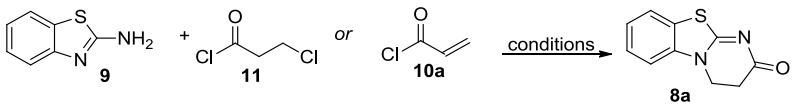
In the preliminary studies, two approaches to **8a** were pursued, as outlined in scheme 5.3: 1) formation of the uncyclized intermediate **12** and subsequent Finkelstein reaction or 2) elimination step from **12** to give Michael acceptor **13** followed by cyclization. Unfortunately, none of them proved to be successful. The Finkelstein reaction was carried out under standard or modified conditions due to the scarce solubility of compound **12** in most of the solvents.[16] It was speculated that the desired cyclization could undergo not only *via* substitution reaction of **12** but also by aza-Michael or a sort of pericyclic pathway using compound **13**, however, even using different bases failed to give compound **8a** starting from **13**.

Inspired by early reports regarding the formation of 2-oxopyrimido-benzothiazole **8a**,[15a,b] the reaction was next carried out using reactants **9** and **11** in the presence of excess Na_2CO_3, by utilizing reaction conditions which were carefully identified and established by ourselves. Using refluxing chloroform (entry 1, table 5.1), intermediate **8a** could be

[15] a) Tsatsas, G.; Costakis, E. *Chem. Comm*. **1967**, 991. b) Weinhardt, K. K.; Neumeyer, J. L. *J. org. Chem.* **1970**, *35*, 1176. c) Ambartsumova, R. F. *Chemistry of Heterocyclic Compounds* **1997**, *33*, 859.
[16] Barchéchath, S. D.; Tawatao, R. I.; Corr, M.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **2005**, *48*, 6409.

isolated, albeit in low yield. Doubling the amount of **11** and increasing the reaction time (entries 2 and 3), the reaction efficiency improved. Quite surprisingly, an increase of the reaction scale from 1 gram to 3 grams (19.8 mmol) was found to improve the yield dramatically (entry 5).

Table 5.1. Screening of reaction conditions for the synthesis of **8a**.



entry	mmol of **9**	**11** or **10a** [eq]	conditions	reaction time [h]	yield [%][a]
1	6.6	**11** (1.0)	Na_2CO_3 (5.0 eq), $CHCl_3$, reflux	8	8[b]
2	6.6	**11** (2.0)	Na_2CO_3 (5.0 eq), $CHCl_3$, reflux	19	38
3	6.6	**11** (2.0)	Na_2CO_3 (5.0 eq), $CHCl_3$, reflux	24	54
4	6.6	**11** (2.0)	Na_2CO_3 (5.0 eq), $CHCl_3$, reflux	43	42
5	19.8	**11** (2.0)	Na_2CO_3 (5.0 eq), $CHCl_3$, reflux	26	80
6[c]	19.8	**11** (2.0+2.0)	Na_2CO_3 (5.0 eq), $CHCl_3$, reflux	26	64
7[d]	39.9	**11** (2.0)	Na_2CO_3 (5.0 eq), $CHCl_3$, reflux	26	<19
8	39.9	**11** (2.0+1.0)	Na_2CO_3 (9.0 eq), $CHCl_3$, reflux	29	<40[e]
9	6.6	**11** (2.0)	Net_3 (6.0 eq), DCM	3	40
10	1.3	**11** (1.3)	DMAP (0.2 eq), DIPEA (2.0 eq), −10 to 23 °C, MeCN	20h	traces
11	1.3	**11** (1.3)	DMAP (1.0 eq), −10 to 23 °C then reflux, MeCN	21h	—
12	3.3	**11** (1.3)	DBU (1.1 eq), Na_2CO_3 (2.0 eq), 0 °C to reflux, MeCN	26h	traces
13	3.3	**11** (1.3+0.5)	DMAP (0.2 +0.05 eq), Na_2CO_3 (2.0 eq) −10 to 23 °C then reflux, MeCN	25h	61

to be continued on the next page

entry	mmol of **9**	**11** or **10a** [eq]	conditions	reaction time [h]	yield [%][a]
14	13.3	**11** (1.3+0.5)	DMAP (0.2 +0.05 eq), Na_2CO_3 (2.0 eq) –10 to 23 °C then reflux, MeCN	27h	61
15	39.9	**11** (1.3+0.5)	DMAP (0.2 +0.05 eq), Na_2CO_3 (2.0 eq) –10 to 23 °C then reflux, MeCN	24h	56
16	65.6	**11** (1.3+0.5)	DMAP (0.2 +0.05 eq), Na_2CO_3 (2.0 eq) –10 to 23 °C then reflux, MeCN	36h	54[f]
17	6.6	**10a** (1.3+0.5)	DMAP (0.2 +0.05 eq), Na_2CO_3 (2.0 eq) –10 to 23 °C then reflux, MeCN	36	67
18	66.6	**10a** (1.3+0.5)	DMAP (0.2 +0.05 eq), Na_2CO_3 (2.0 eq) –10 to 23 °C then reflux, MeCN	36	60[f,g]
19	66.6	**10a** (1.2)	Na_2CO_3 (2.2 eq) then NaI (1.0 eq), 0 °C then reflux, MeCN	8h	84[f]

[a]isolated yield after flash column chromatography on silica gel. [b]<6% yield of **13** was isolated. [c]analysis of the ^{1}H NMR crude revealed a 1:0.21:0.15 ratio of **8a**:**12**:**9**. [d]analysis of the ^{1}H NMR crude revealed a 1:0.4 ratio of **8a**:**13**. [e]estimated yield. [f]purification by recrystallization from EtOH. [g]yield estrapolated from analysis of ^{1}H NMR crude.

In spite of these promising results, the reaction reproducibility (steady final yield) remained a concern to us, and this was a pivotal point regarding the reaction scalability. Thus, when passing from 3 g to 6 gram-scale (39.9 mmoles **9** used), the yield of **8a** dropped noticeably from 80% to <19% (entry 7).

It was then decided to test the reaction in the presence of different organic bases, alone or with sodium carbonate (entries 9, 10 and 12) including the acylating agent DMAP (entry 11). In these instances, compound **8a** was obtained either in traces (entries 10-12) or in moderate yield in case of use of triethylamine (40%, entry 9); however, due to the harsh reaction conditions, these modalities were abandoned.

On a small scale, a combination of catalytic DMAP and Na_2CO_3 was attempted (entry 13) producing **8a** in a promising 61% yield. Under these

conditions, it was envisaged that intermediate **12** was generated *in situ* with the aid of DMAP, while the following cyclization was promoted by the presence of the inorganic base. According to this hypothesis, DMAP and 3-chloropropanoyl chloride (**11**) were added in two aliquots after 12 hours at low temperature whereas the inorganic base was the last reagent to be added. The protocol proved to be successful, giving compound **8a** in an appreciable yield and, most importantly, it was possible to carry out the reaction on a bigger scale (up to 10 grams of **9**), (entries 14, 15 and 16). During the scale up procedure, the purification method was improved, swapping from flash column chromatography to recrystallization.

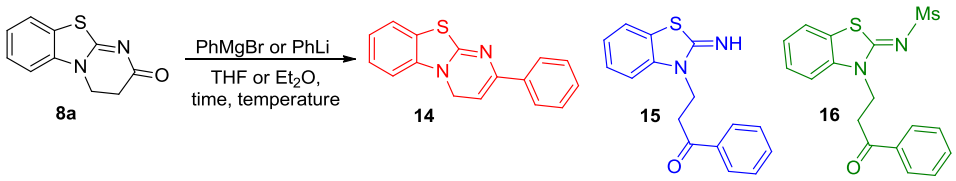
As mentioned above, we were intrigued by the plausible mechanisms of this simple reaction and, for this reason, the same conditions developed for acyl chloride **11** were applied on acryloyl chloride (**10a**), the alleged intermediate of the reaction (entry 17). Pleasantly, the desired compound **8a** was obtained in a good 67% yield and without any need of purification procedure. It was then decided to scale up the reaction with reactant **10a** due to its superior versatility: we reasoned that derivatives of compound **10a** with different substituents on the double bond might give access to a panel of diversified catalysts.

After a brief scrutiny, it was found that the use of NaI was crucial for yield's consistency, so the optimized conditions were identified, which consisted in catalytic Na_2CO_3 (2.2 eq) and NaI 91.0 eq) in acetonitrile, at 0° C to room temperature for 18 hours (entry 19), by which the cyclic intermediate **8a** was obtained in a rewarding 85% yield.[17]

The structure of 2-oxopyrimido-benzothiazole **8a** was unambiguously assigned by X-ray analysis: in this way the compound was fully characterized.

[17] Last optimized conditions were made by Dr. Omar Robles.

Table 5.2. Results of the organometallic reagent additions to **8a** under several conditions.



entry	reactant [eq]	quenching	**8a** conc [M]	temp [° C]	reaction time [h]	**14** yield [%][a]	**15** yield [%][a]	**16** yield [%][a]
1	PhMgBr (3.0)	NH_4Cl aq. sat. sol.	0.04	0 to 23	4	35	35	—
2	PhMgBr (1.2)	NH_4Cl aq. sat. sol.	0.04	0 to 23	4	30	30	—
3	PhLi (1.2)	H_2O	0.04	–70 to 23	5	10	11	—
4	PhLi (2.0)	H_2O	0.012	–70 to 23	5	11	36	—
5	PhMgBr (3.0)	MsCl	0.018	–20 to 23	4	24	—	24
6	PhLi (2.0)	MsCl	0.01	–75	7	23	—	23

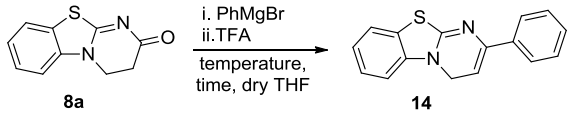
[a]isolated yield after flash column chromatography on silica gel.

As a next task, the reaction conditions of the organometallic additions to compound **8a** were scrutinized (table 5.2). First attempts gave rise to two different isolated products (entries 1-4): a sort of enamine **14** and compound **15**, both coming from the instable carbinolamine intermediate (not shown). In order to isolate the carbinolamine intermediate, a quenching procedure with mesyl chloride was tested, but in this case N-mesyl compound **16** was isolated (entries 5 and 6).

Noteworthy, the common feature of all these additions was the formation of enamine **14**, a suitable substrate for our synthesis since it could be converted into racemic HBTM (**5b**) by simple carbon-carbon double bond reduction. For this reason, the attention was next focused on the synthesis of intermediate **14** (table 5.3). The quenching procedure was modified by replacing the previously used mild aqueous conditions

with an acidic work-up (e.g. TFA), in order to promote the elimination reaction of the carbinolamine intermediate.

Table 5.3. Screening of the reaction conditions for the synthesis of **14**.



8a **14**

entry	PhMgBr [eq]	TFA [eq or mL]	temp [° C]	reaction time [h]	yield [%][a]
1	3.0	3.0 eq	0 to 23	4	38
2	3.0	3.5 mL	0 to 23	4	12
3	3.0	5.0 eq	−10 to 0	5	51
4	3.0	5.0 eq	−75	18	43
5	2.0	4.0 eq	−30 to 0	6	43
6	1.5	3.0 eq	−10	6	48
7[b]	2.0	3.0 eq	−15	4	53

[a]isolated yield after flash column chromatography on silica gel. [b]the reaction was quenched *in vacuo*.

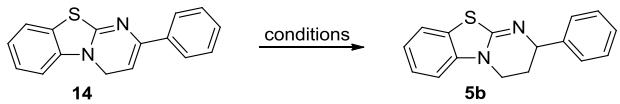
As depicted in table 5.3, a large amount of trifluoroacetic acid led to a decrease of the product isolated yield (entry 2). With stoichiometric quantities of the acid, ranging from 3.0 to 5.0 equivalents, and different reaction conditions (time, temperature and Grignard reagent equivalents) no significant improvements were obtained (entries 3-7). Finally we hypothesized that the moderate yield of enamine **14** could be ascribed to an inadequate purification system: possibly silica gel could protonate the desired compound making difficult its complete recovery from the column.

With milligrams quantities of isolated compound **14**, the conversion to HBTM (**5b**) was investigated (table 5.4). The first concern was the compatibility of the electron-rich structure with metal catalyzed hydrogenation because of the presence of sulfur, a recognized poison for some metals. As predicted, metal-based reduction failed to give the desired product (entries 1-4). Gratifyingly, ionic reduction[18] exploiting the

[18] Larson, G. L; Fry, J. L. *Ionic and Organometallic-Catalyzed Organosilane Reduction, Organic Reactions 2*, John Wiley & Sons Ed.

Et_3SiH/TFA[19] system worked well, giving racemic HBTM (**5b**) in 70% isolated yield (entry 5).

Table 5.4. Reductive protocols tested for the synthesis of *rac*-HBTM.

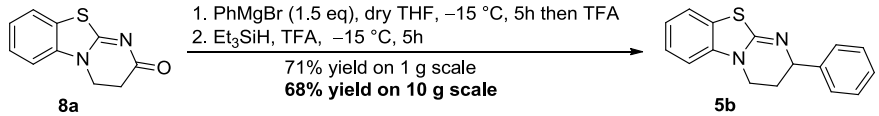


14 **5b**

entry	reagent	conditions	yield [%][a]
1	Pd/C (0.8 eq)	MeOH, 21 h, 23 °C	traces
2	Rh/Al_2O_3 (4 mol%)	300 psi, DCM:EtOH 2:1, 23 °C, 20h	—
3	Rh/C (12 mol%)	300 psi, EtOH:DCM 6:1, 23 °C, 72h	—
4	$[Ir(cod)(PCy_3)(py)]PF_6$ (5 mol%)	DCM, 23 °C, 21 h	—
5	Et_3SiH (30 eq)/TFA	−10 °C, 5 h	70
6	Et_3SiH (12 eq)/TFA	**24** (0.2M) in DCM, −10 to 23 °C, 19h	45
7	Et_3SiH (15 eq)/TFA	**24** (0.07M), −15 °C, 5h	75
8	Et_3SiH (7 eq)/TFA	**24** (0.07M), −10 °C, 5h	<50

[a]isolated yield after flash column chromatography on silica gel.

The ionic reduction conditions were then quickly optimized: the amount of triethylsilane was halved and the reaction was still efficient (entry 7). A further decrease in Et_3SiH resulted in lower yield (entries 6 and 8).



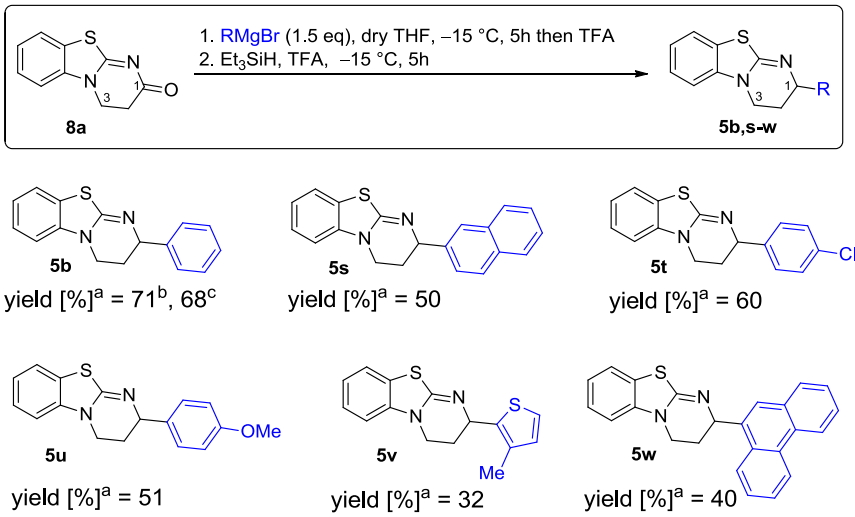
8a **5b**

Scheme 5.4. Optimized conditions of the two-steps/one sequence synthesis of *rac*-HBTM.

With these results in hand, in order to render the approach more straightforward and avoid possible loss of intermediate **14** during

[19] a) Masuno, M. N.; Molinski, T. F. *Tet. Lett.* **2001**, *42,* 8263. b) Baskaran, S.; Hanan, E.; Byun, D.; Shen, W. *Tet. Lett.* **2004**, *45*, 2107.

purification, the crude reaction mixture derived from the Grignard addition was subjected to ionic reduction conditions without previous purification (scheme 5.4).



[a]isolated yield after flash column chromatography on basic Al_2O_3.
[b]reaction carried out on 1 gram scale
[c]reaction carried out on 10 gram scale.

Scheme 5.5. Scope of the addition/reduction reaction with respect to the aromatic Grignard reagent.

This strategy proved successful, giving the desired catalyst **5b** in a notable 71% yield for the three-step sequence on a 1g scale and, indeed, the scalability of the process was confirmed up to 10 grams of **8a**.[20]

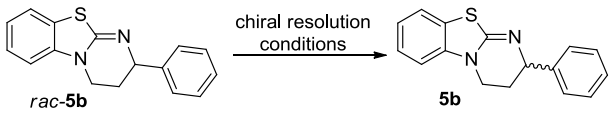
The same synthetic sequence was then applied with different Grignard reagents (scheme 5.5) obtaining a panel of catalysts, compounds **5s-w**, bearing different aromatic appendages at the C-1 carbon. The new structures were isolated in good to moderate yields.

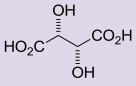
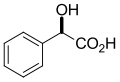
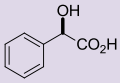
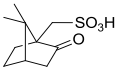
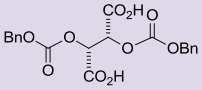
In order to maintain the synthesis as economical as possible, it was decided to resolve *rac*-HBTM (**5b**) with the aid of commercially available chiral resolving agents (table 5.5). All the trials were made on small

[20] the reaction on 10 grams was carried out by Dr. Omar Robles.

quantities of racemic **8a** but unfortunately they resulted unsuccessful. The employment of 1.0 equivalent of L-tartaric acid and D-mandelic acid in hot methanol did not succeed in the formation of the diastereomeric salt of compound **5b** (entries 1 and 2).

Table 5.5. Attempts of chiral resolution of *rac*-HBTM (**5b**).



entry	conditions	5b ee%[a]
1	 1.0 eq., MeOH, Δ	—
2	 1.0 eq., MeOH, Δ	—
3	 0.5 eq., acetone, Δ	racemic
4	 0.5 eq., acetone, Δ	25
5	 1,2-dichloroethane/water, Δ	racemic

[a]determined by chiral HPLC analysis using chiralcel OD-H column, 70:30 Hexanes:*i*-PrOH, 0.5 mL/min.

It was then decided to try the method of the "half-quantities"[21] by which only half equivalent of the resolving agent was used: with 0.5 eq of mandelic acid, racemic HBTM (**5b**) precipitated without forming any salts (entry 3), while with (–)-CSA, catalyst **5b** was recovered in 77% yield (based on the amount of the chiral resolving agent) with a promising yet insufficient 25% enantiomeric excess, as detected by HPLC analysis. Dibenzylcarbonate-protected tartaric acid was also used, but again the compound was isolated as a racemic mixture (entry 5).

[21] Brandt, J.; Gais, H.-J. *Tetrahedron:Asymmetry* **1997**, *8*, 909.

Successful separation of the catalyst **5b** on a preparative scale was obtained with supercritical fluid chromatography (SFC),[22] it offered the possibility to obtain both the enantiomers in extremely good recovered yield on multigram scale.

5.3. Conclusions and Perspectives

A straightforward, scalable and economical synthesis of HBTM and derivatives was designed and developed. The results are notable in terms of efficiency, viability, and reproducibility. Furthermore, detailed and meticulous screening of reaction conditions was made. During the development of the synthetic strategy, it was also possible to optimize the purification conditions by employing crystallization techniques and minimizing or avoiding column chromatography. Step economy was pursued by combining two steps in a one-pot sequence. Overall, the synthesis boasts two steps, one recrystallization and one filtration on basic alumina. The efficiency of the approach was subsequently demonstrated by scaling the reaction up to 10 grams. Furthermore the developed protocol was applied to the synthesis of HBTM derivatives. In conclusion, a general and efficient synthesis of a series of bicyclic isothiourea catalysts was developed. Further improvements of the procedure will entail the extension to differently substituted acryloyl chlorides[23] and resolution of the catalyst.

5.4. Experimental data

General experimental methods. All reactions were performed in flame-dried, clean, standard laboratory glassware with rubber septa. Solvents for chromatography and filtration including hexane, ethyl acetate, dichloromethane and ethanol were ACS or HPLC grade and used as received. Acetonitrile was purified by passage through activated

[22] SFC performed by Lotus Separations LLC.
[23] A little extension was made by Dr. Omar Robles. The data are not shown but were illustrated in the poster.

alumina. Tetrahydrofuran was freshly distilled over sodium and benzophenone. All commercial reagents were used as received. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} glass backed plates (Silicycle 250 µm thickness) with visualization under short-wavelenght UV light and with molybdate reagent (aqueous H_2SO_4 solution of ceric sulphate/ammonium molybdate), or on pre-coated aluminium oxide F_{254} (type E) plates without stain. Flash column chromatography was performed using 60 Å aluminium oxide basic Brockmann I (Acros, 50-200 µm) with the indicated solvent mixtures. Grignard reagents were purchased from Sigma Aldrich (phenylmagnesium bromide, 4-methoxyphenylmagnesium bromide, 9-phenanthrylmagnesium bromide), Alfa Aesar (2-naphthylmagnesium bromide, 4-Cl-phenylmagnesium bromide) and Novel Chemical Solution (3-methyl-2-thienylmagnesium bromide) and used as received. NMR spectra were recorded at 500 MHz (^{1}H) and 125 MHz (^{13}C). ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to $CDCl_3$ (7.28 ppm,) and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in hertz. Deuterated chloroform ($CDCl_3$) served as an internal standard (77.16 ppm) for all ^{13}C spectra. ^{13}C abbreviations: methane (CH), methylene (CH_2), methyl (CH_3) and quaternary carbon (Cq). High resolution mass analyses (HRMS) were conducted in the Laboratory for Biological Mass Spectrometry, Texas A&M University.

2-oxo-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (**8a**) **(procedure a)**. A round-bottomed flask was charged with 2-aminobenzothiazole (10 g, 65.6 mmol) and then dry acetonitrile (100 mL) was added with stirring, followed by addition of DMAP (1.6 g, 13.6 mmol, 0.2 equiv) under nitrogen atmosphere. The resulting suspension was cooled to 0 °C in an ice bath and a solution of 3-chloropropionyl chloride (8.4 mL, 85.5 mmol, 1.3 equiv) in dry acetonitrile (50 mL) was added gradually. The ice bath was removed and the reaction mixture was allowed to stir at 23 °C for 12 h. The flask was cooled again in an ice bath and an additional portion of DMAP (407 mg, 3.3 mmol, 0.05 equiv) and 3-chloropropionyl chloride (1.9 mL, 19.9 mmol, 0.3 equiv) was added sequentially. The ice bath was removed and the reaction was allowed to stir at room 23 °C for 1.5 h. Solid Na_2CO_3 (14.1 g, 19.9 mmol, 2.0 equiv) was then added and the reaction mixture was refluxed for 24 h. The reaction was concentrated *in vacuo*, diluted with water and extracted with dichloromethane (5 × 100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was recrystallized from ethanol (two crops from 550 mL and 250 mL sequentially) to give **8a** as a light yellow solid (7.2 g, 54%). TLC, R_f = 0.30 (CH_2Cl_2/acetone 50:50); mp = 203-211°C; IR (thin film, NaCl) 1655, 1509, 1471, 1369 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.9, 0.8, Hz 1H), 7.43 (ddd, *J* = 8.1,

7.6, 1.1 Hz, 1H), 7.26 (ddd, *J* = 7.8, 7.6, 1.0 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 4.21 (dd, *J* = 7.7, 7.7 Hz, 2H), 2.84 (dd, *J* = 7.7, 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (Cq), 173.1 (Cq), 138.4 (Cq), 127.3 (CH), 124.3 (CH), 123.4 (Cq), 122.7 (CH), 110.7 (CH), 41.0 (CH2), 28.4 (CH2); mass calcd. for $C_{10}H_8N_2OS$ 205.0436 $[M+H]^+$; HRMS (+ESI) found: 205.0442 $[M+H]^+$.

2-oxo-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (**8a**) **(procedure a)** prepared from acryloyl chloride. Compound **8a** can be prepared following the above described procedure using 2-aminobenzothiazole (1.0 g, 6.7 mmol), DMAP (163 mg, 1.3 mmol, 0.2 equiv and 41 mg, 0.3 mmol, 0.05 equiv), acryloyl chloride (700 µL, 8.6 mmol, 1.3 equiv and 162 µL, 2.0 mmol, 0.3 equiv) and Na_2CO_3 (1.4. g, 2 mmol, 2.0 equiv) . Compound **8a** was obtained as a yellow solid (916 mg, 67%) without further purification. **(procedure b).** 2-aminobenzothiazole (10g, 65.6 mmmol) and Na_2CO_3 (15.5 g, 146.5 mmol. 2.2 equiv) were suspended in dry acetonitrile (400 mL) and then cooled to 0 °C. Acryloyl chloride (6.5 mL, 80 mmol, 1.2 equiv) was added dropwise and the resulting reaction mixture was stirred at 0 °C fro 2h. NaI (10g, 66.6 mmol, 1 equiv) was added and the mixture was stirred at 80 0 °C for 8h. The crude reaction mixture was purified by recrystallization from ethanol (two crops from 550 mL and 250 mL sequentially) to afford product **8a** (11.4 g, 84%) as light yellow solid.

General Procedure for Grignard Addition/Reduction sequence

2-phenyl-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (**5b**). A flame-dried round bottomed flask was rapidly charged with **8a** (6.0 g, 29.4 mmol) as a solid and put under nitrogen atmosphere. Dry THF (780 mL) was added and the resulting suspension was cooled to −15 °C in an ethylene glycol/dry ice bath. A 1.0 M solution of phenylmagnesium bromide in THF (44 mL, 44.1 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred at −15 °C for 5 h. Trifluoroacetic acid (6.7 mL, 88.1 mmol. 3.0 equiv) was then carefully added and the reaction was stirred at −15 °C for 30 min. The mixture was concentrated under *vacuo*, diluted with water and extracted with EtOAc (4 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in *vacuo*. In a 1 L round-bottomed flask, the crude reaction mixture was charged with Et_3SiH (71 mL, 440 mmol, 15 equiv) and cooled to −15 °C. Trifluoroacetic acid (300 mL) was added and the reaction mixture was vigorously stirred under a nitrogen atmosphere −15 °C for 6 h. The reaction was concentrated in *vacuo*, washed with hexanes (3 × 50 mL) and diluted with EtOAc (mL 250). The organic phase was washed with NaOH 1.5 M (3 × 100 mL, pH of the aqueous phases 10-11), and the combined aqueous layers were washed with EtOAc (4 × 100 mL). The combined EtOAc extracts were dried over $MgSO_4$, filtered and

concentrated under *vacuo*. The crude residue was purified by aluminium oxide flash chromatography (95:5 to 6:4 hexanes/EtOAc) to give HBTM (**5b**) as a colorless solid (5.5, 70%) with spectroscopic data in accordance with the literature.

2-(naphthalene-2-yl)-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (**5s**). Naphthyl-HBTM **5s** was prepared according to the general procedure, using **8a** (500 mg, 2.4 mmol), a 0.25 M solution of 2-naphthylmagnesium bromide in Me-THF (14.7 mL, 3.7 mmol, 1.5 equiv) and Et_3SiH (5.9 mL, 36.7 mmol, 15 equiv). The crude residue was purified by aluminum oxide flash chromatography (95:5 to 60:40 hexanes/EtOAc) to give **5s** as a light yellow solid (mg 400, 50%). TLC (aluminium oxide), R_f = 0.66 (hexanes/EtOAc 6:4); IR (thin film, NaCl) 3055, 2956, 2925, 2872, 1619, 1588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (m, 4H, naphthyl), 7.48 (m, 3H, naphthyl), 7.36 (d, *J* = 7.7 Hz, 1H), 7.23 (ddd, *J* = 7.7, 7.8, 1.0 Hz, 1H), 7.05 (ddd, *J* = 7.7, 7.7, 0.8 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.91 (dd, *J* = 7.9, 4.0 Hz, 1H), 3.86 (ddd, *J* = 11.6, 8.6, 4.8 Hz, 1H), 3.71 (ddd, *J* = 11.2, 5.8, 5.4 Hz, 1H), 2.39 (m, 1H), 2.08 (dddd, *J* = 13.5, 8.4, 8.4, 5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4 (Cq), 141.7 (Cq), 140.8 (Cq), 133.5 (Cq), 132.7 (Cq), 128.3 (CH), 128.1 (CH,), 127.7 (CH), 126.1 (CH), 126.0 (CH), 125.6 (CH), 125.3 (CH), 125.1 (CH), 122.7 (CH), 122.0 (Cq), 121.9 (CH), 107.5 (CH), 58.6 (CH), 40.6 (CH_2), 27.9 (CH_2); mass calcd. for $C_20H_{16}N_2S$ 317.1112 $[M+H]^+$; HRMS (+ESI) found: 317.1106 $[M+H]^+$.

2-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (**5t**). Compound **5t** was prepared according to the general procedure for compound **5b**, using **8a** (510 mg, 2.5 mmol), a 1.0 M solution of 4-chlorophenylmagnesium bromide in THF (3.7 mL, 3.7 mmol, 1.5 equiv) and Et_3SiH (6.0 mL, 37.4 mmol, 15 equiv). The reduction was carried out at a starting temperature of 0 °C and it was gradually warmed to 23 °C over a period of 6h. The crude residue was purified by aluminum oxide flash chromatography (8:2 to 1:1 hexanes/EtOAc) to give **5t** as a light yellow solid (mg 457, 60%). TLC (aluminium oxide), R_f = 0.80 (hexanes/EtOAc 7:3); TLC (silica gel), R_f=0.48 (dichloromethane/acetone 1.1); IR (thin film on a NaCl disk) 2959, 2922, 2881, 1632, 1582 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.23 (ddd, *J* = 7.8, 7.7, 1.2 Hz, 1H), 7.04 (ddd, *J* = 7.7, 7.6, 1.1 Hz, 1H), 6.77 (dd, *J* = 7.9, 1.0 Hz, 1H), 4.69 (dd, *J* =8.4, 4.0 Hz, 1H), 3.84 (ddd, *J* = 11.6, 9.1, 4.8 Hz, 1H), 3.72 (ddd, *J* = 11.5, 5.2, 5.2 Hz, 1H), 2.31 (m, 1H), 1.94 (dddd, *J* = 13.6, 8.9, 8.9, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 158.4 (Cq), 142.9 (Cq), 140.6 (Cq), 132.5 (Cq), 128.6 (2CH), 128.1 (2CH), 126.0 (CH), 122.5 (Cq), 121.9 (2CH), 107.6 (CH), 57.9 (CH), 40.6 (CH_2), 28.0 (CH_2); mass calcd. for $C_{16}H_{13}ClN_2S$ 301.0566 $[M+H]^+$; HRMS (+ESI) found: 305.0561 $[M+H]^+$.

2-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (**5u**). Compound **5u** was prepared according to the general procedure for compound **5b**, using **8a** (55 mg, 0.27 mmol), a 0.5 M solution of 4-methoxyphenylmagnesium bromide in THF (808 µL, 0.40 mmol, 1.5 equiv) and Et_3SiH (652 µL, 4.0 mmol, 15 equiv). The Grignard reaction was carried out at a temperature from 0 °C to 23 °C over a period of 7 h. The crude residue was purified by aluminum oxide flash chromatography (7:3 to 1:1 hexanes/EtOAc) to give **5u** as a white solid (mg 40, 51%). TLC (aluminium oxide), R_f = 0.69 (hexanes/EtOAc 7:3); IR (thin film, NaCl) 2956, 2925, 1626, 1581 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.7, 0.7, 1H), 7.27 (m, 2H), 7.22 (ddd, *J* = 7.8, 7.8, 1.1 Hz, 1H), 7.01 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H), 6.88 (m, 2H), 6.74 (d, *J* = 7.9 Hz, 1H), 4.68 (dd, *J* =7.9, 3.9 Hz, 1H), 3.80 (m, 4H), 3.70 (m, 1H), 2.29 (m, 1H), 1.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6 (Cq), 158.0 (Cq), 140.8 (Cq), 136.5 (Cq), 127.7 (2CH), 125.9 (CH), 122.6 (Cq), 121.9 (CH), 121.7 (CH), 113.9 (2CH), 107.5 (CH), 57.9 (CH), 55.4 (CH_3), 40.5 (CH_2), 28.0 (CH_2); mass calcd. for $C_{17}H_{16}N_2OS$ 297.1062 $[M+H]^+$; HRMS (+ESI) found: 297.1065 $[M+H]^+$.

2-(3-methylthiophen-2-yl)-3,4-dihydro-2H-pyrimido[2,1-b]benzothiazole (**5v**). Compound **5v** was prepared according to the general procedure for compound **5b**, using **8a** (200 mg, 0.98 mmol), a 0.5 M solution of 3-methyl-2-thienylmagnesium bromide in THF (2.9 mL, 1.47 mmol, 1.5 equiv) and Et_3SiH (2.4 mL, 14.69 mmol, 15 equiv). The reduction reaction was carried out over a period of 7 h. The crude residue was purified by aluminum oxide flash chromatography (8:2 hexanes/EtOAc) to give **5v** as a light brown resin (mg 90, 32%). TLC (aluminium oxide), R_f = 0.42 (hexanes/EtOAc 8:2); IR (thin film, NaCl) 1619 cm^{-1}; 1H NMR (500 MHz, $CDCl^3$) δ 7.32 (d, *J* = 7.7, 1H), 7.21 (ddd, *J* = 7.7, 6.8, 0.9, 1H), 7.10 (d, *J* = 5.1 Hz, 1H), 7.02 (ddd, *J* = 7.6, 6.7, 0.8 Hz, 1H), 6.80 (d, *J* = 5.1 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* =8.2, 3.9 Hz, 1H), 3.83 (m, 2H), 2.33 (m, 1H), 2.27 (s, 3H), 2.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6 (Cq), 141.8 (Cq), 140.5 (Cq), 131.7 (Cq), 130.2 (CH), 125.9 (CH), 122.6 (Cq), 122.4 (CH), 121.9 (CH), 121.9 (CH), 107.7 (CH), 53.2 (CH), 40.6 (CH_2), 26.8 (CH_2), 13.9 (CH_3); mass calcd. for $C_{15}H_{14}N_2S_2$ 287.0677 $[M+H]^+$; HRMS (+ESI) found: 287.0668 $[M+H]^+$.

2-(phenanthrenyl-9-yl)-3,4-dihydro-2H-pyrimido[2,1-b]benzothiazole (**5w**). Compound **5w** was prepared according to the general procedure for compound **5b**, using **8a** (400 mg, 2.0 mmol), a 0.5 M solution of 9-phenanthrenylmagnesium bromide in THF (5.9 mL, 2.9 mmol, 1.5 equiv) and Et_3SiH (4.7 mL, 29.4 mmol, 15 equiv). The reduction reaction was carried out over a period of 14 h from 0 to 23 °C. The crude residue was

purified by aluminum oxide flash chromatography (8:2 hexanes/EtOAc) to give **5w** as a light brown resin (mg 90, 32%). TLC (aluminium oxide), Rf = 0.42 (hexanes/EtOAc 8:2); IR (thin film, NaCl) 1619 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 8.5, 1.9 Hz, 1H), 8.68 (d, *J* = 8.1 Hz, 1H), 8.11 (dd, *J* = 9.4, 1.9 Hz, 1H), 7.91 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.84 (s, 1H), 7.65 (m, 4H), 7.38 (dd, *J* = 7.7, 1.1 1H), 7.22 (ddd, *J* = 7.7, 7.8, 1.1 1H), 7.056 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.52 (dd, *J* =7.2, 4.1 Hz, 1H), 3.83 (ddd, *J* = 11.8, 8.2, 4.8 Hz, 1H), 3.60 (ddd, *J* = 11.4, 6.1, 5.1 Hz, 1H), 2.51 (m, 1H), 2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6 (Cq), 140.7 (Cq), 137.2 (Cq), 131.6 (Cq), 131 (Cq), 129.9 (Cq), 129.8 (Cq) 129.0 (CH), 126.73 (CH), 126.7 (CH), 126.5 (CH), 126.2 (CH), 126.0 (CH), 125.4 (CH), 123.6 (CH), 123.4 (CH), 122.7 (Cq), 122.4 (CH), 121.9 (CH), 121.8 (CH), 107.6 (CH), 55.1 (CH), 40.4 (CH_2), 26.6 (CH_2); mass calcd. for $C_{15}H_{14}N_2S_2$ 287.0677 $[M+H]^+$; HRMS (+ESI) found: 287.0668 $[M+H]^+$.

Chapter 6

Summary

The aim of this Doctor in Philosophy degree has been to develop valuable and solid protocols for catalytic asymmetric vinylogous Mannich reactions. The importance covered by the Mannich addition in both the "normal" version and in its vinylogous counterpart has been illustrated in the first chapters (1 and 2) and we wanted to give our contribution as well, being interested in the vinilogous reactivity.

Chapters 1 and 2 acted as a light guiding the reader through the understanding of the Mannich transformation and its evolution into vinylogous catalytic asymmetric version.

In chapter 3 a first part of research achievements are discussed. Catalytic asymmetric Vinylogous Mukaiyama Mannich reactions using pyrrole-based silicon dienolates were successfully developed. Two protocols were designed in order to fulfill the different reactivity of aromatic and aliphatic aldimines as well. The final, optimized procedure was the result of a scrupulous initial screening of different reaction parameters and reactants. The results are excellent in terms of γ-site selectivity and diastereoselectivity, whereas good isolated yields and satisfying to remarkable enantiocontrol were generally observed. In order to demonstrate the versatility of the synthesized δ-aminated structures, a further chemical elaboration was proposed. As a last point (but not less important), the absolute stereochemistry of the isolated Mannich compounds was determined following different techniques.

Chapter 4 described an ongoing project where 3-alkenyl-2-oxindole donors were the substrates for the asymmetric vinylogous Mannich reaction. Despite the lack of definitive protocols, different strategies were scrutinized and still other attempts have to be made. The Mannich scaffolds generated from this new nucleophilic progeny are extremely interesting from a synthetic point of view and for this reason a route torwards the assembly of 2,4-disubstituted perhydro α-carbolines was designed and pursued.

The research project at Texas A&M University was reported in chapter 5. Herein the studies towards an economical and efficient synthesis of homobenzotetramisole (HBTM) and its derivatives were disclosed. These pyrimido-benzothiazole organocatalysts have become increasingly popular in recent years due to their expanding utility in a variety of synthetic methods. The major drawback is the requirement of an uneconomical chiral γ-aminoalcohol for its preparation, which may not render the catalyst accessible to everyone, especially in large quantities. A short synthetic route from readily available and inexpensive starting materials and easy scaleability (up to 10 g) are the strong points of our synthetic route.

If the main objectives of this PhD program were focused on the development of the Mannich reaction in the vinylogous field intersecting the growing principles of asymmetric and organocatalysis, we may conclude that these goals have been indeed widely fulfilled.