Combinatorial Organocatalyst Development and Screening of Conjugate Additions

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Dekan

Für meine Eltern, Sascha, Jakub und Nora

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Table of Contents

CHAPTER 1

Introduction

1 Introduction

Organocatalysis is currently one of the fastest growing fields of research in organic chemistry.[1] Catalysis by metal-free organic molecules has been known in organic chemistry for more than 100 years, but its full potential was not recognized until the 21st century.

Today, the most applications of organocatalysis are asymmetric reactions. Development of new chiral catalysts is based on the structural tuning of known catalysts and on the synthesis of catalyst libraries. Many of the known organocatalysts are readily prepared and easily modified, making it possible to synthesize large catalyst libraries in a reasonable time frame. Therefore, considerable efforts have been made to develop efficient screening methods for organocatalyst development and optimization.[2]

Conventional screening methods are based on product analysis. Due to background reactions or catalytically active impurities, the enantiomeric excess obtained by these methods does not always reflect the intrinsic selectivity of the catalyst. In the PFALTZ group, MARKERT recently developed a new screening method for chiral catalysts, based on mass-labeled quasienantiomeric substrates and electrospray ionization-mass spectrometry (ESI-MS).[3, 4] This method allowed for determination of the intrinsic enantioselectivity of catalysts in the kinetic resolution of allylic esters by mass spectrometric monitoring of catalytic intermediates. In contrast to conventional screening methods, simultaneous screening of catalyst mixtures in a homogeneous solution was possible. Based on the concept of back-reaction screening, the methodology was extended by MÜLLER to palladium-catalyzed allylic substitutions[4, 5] and by TEICHERT to copper- and organo-catalyzed Diels-Alder reactions.[4, 6]

In catalyst discovery, mechanistic studies and the modular structure of catalysts are also very important. The aim of this thesis was the utilization of these tools for the development of new organocatalysts and the fine-tuning of their structure. A further goal was to extend the application range of ESI-MS screening to other organocatalytic reactions.

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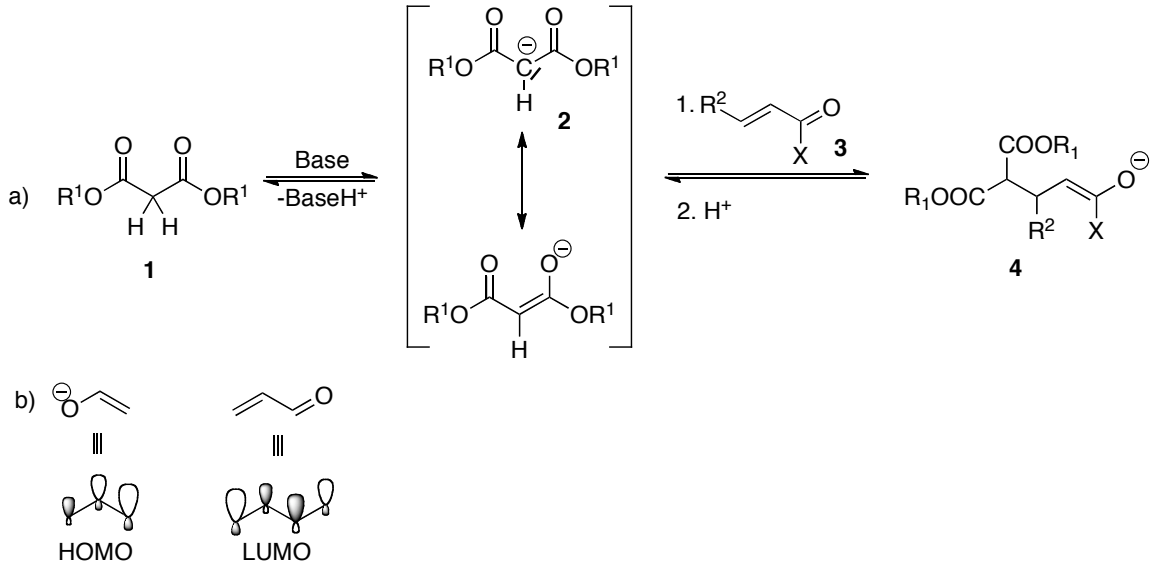
CHAPTER 2

1,4-Addition of Active Methylene Compounds to α,β-Unsaturated Aldehydes, ESI-MS Screening

2 1,4-Addition of Active Methylene Compounds to α,β-Unsaturated Aldehydes, ESI-MS Screening

2.1 Introduction: 1,4-Additions to α,β-Unsaturated Aldehydes

An important application for organocatalysts is the Michael addition, named after A. MICHAEL, who investigated 1,4-additions of resonance-stabilized carbanions to activated double and triple bonds.[1-3] Such resonance-stabilized carbanions are formed by deprotonation of active methylene compounds, such as 1,3-dicarbonyl compounds **1** or nitroalkanes (Scheme 2.1a). The regioselectivity of the attack can be explained by frontier molecular orbitals (Scheme 2.1b). The highest orbital coefficient of the enolate's HOMO is on the central carbon and the highest LUMO coefficient of the unsaturated system is on the β-carbon. According to the HSAB (hard and soft acids and bases) principle, the soft nucleophile attacks the soft electrophilic center at the 4-position.



Scheme 2.1. a) The mechanism of the 1,4-addition of malonate to α,β-unsaturated carbonyl compound; b) frontier molecular orbitals of an enolate and an enal.

Much effort has been put into the development of stereoselective Michael additions. Besides the diastereoselective approach via chiral auxiliaries,[4] metal-catalyzed enantioselective reactions have also been developed.[5] In the last decade, organocatalyzed reactions have received much attention and numerous applications of organic molecules as catalysts for 1,4-additions have been reported.[6]

2.1.1 Organocatalyzed 1,4-Additions

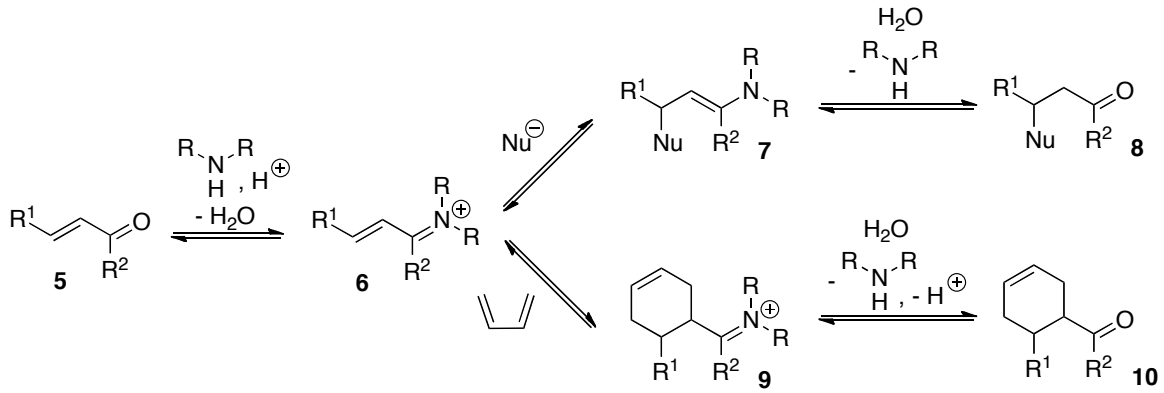
The scope of the activation models of organocatalysts in 1,4-additions is very broad.[7] Most reactions proceed via formation of covalent bonds between the catalyst and substrate. Amines (primary or secondary) are frequently used as covalent catalysts, since they can activate carbonyl compounds via formation of enamine [8] or iminium[9] intermediates. These types of activation, summarized as aminocatalysis,[10] will be thoroughly discussed in the following chapter (iminium) and chapter 3 (enamine), respectively.

Furthermore, 1,4-additions can be catalyzed by weak interactions between the catalyst and substrate. Examples of noncovalent organocatalysts are the chiral quarternary ammonium salts employed by MARUOKA,[11] cinchona alkaloids[12] and chiral thiourea derivatives.[13]

A great advantage of organocatalysis is the possibility to combine different activation modes in one catalyst to enhance its activity and selectivity. Thus, an effective activation of nucleophile and electrophile by bifunctional catalysts can be achieved.

2.1.2 Iminium Catalysis and 1,4-Additions

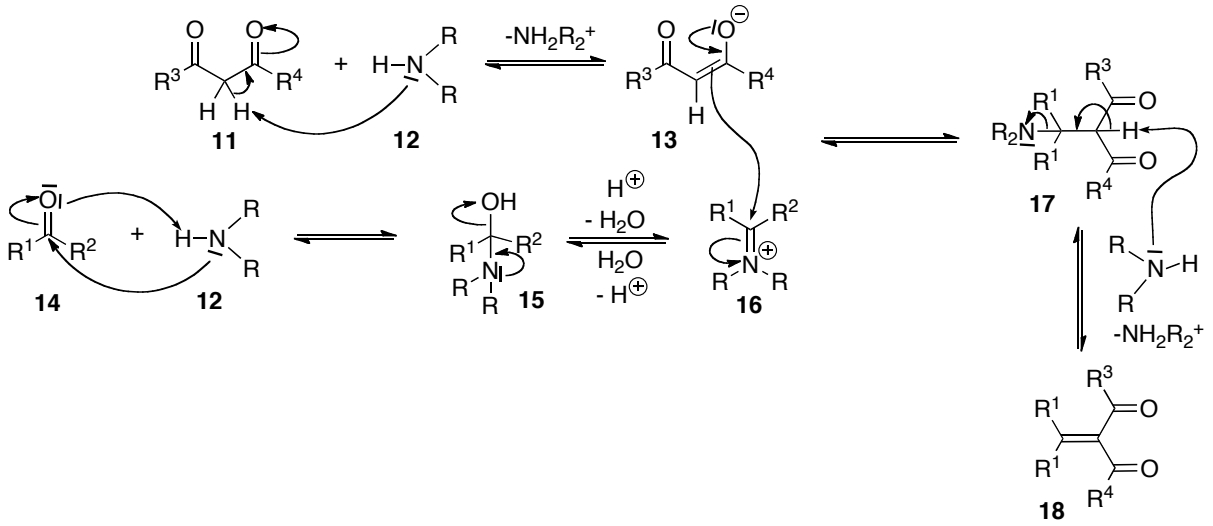
Iminium catalysis is based on the reversible reaction of a carbonyl compound (usually α,β-unsaturated) with a primary or secondary amine to form an iminium intermediate (Scheme 2.2).[9b] The iminium ion is more electrophilic than the corresponding carbonyl compound, and, thus activated towards the attack of a nucleophile or a diene. The catalytic turnover is assured by the lability of the formed iminium intermediate (**7** and **9**).



Scheme 2.2. The principle of, and common reaction types, in iminium catalysis.

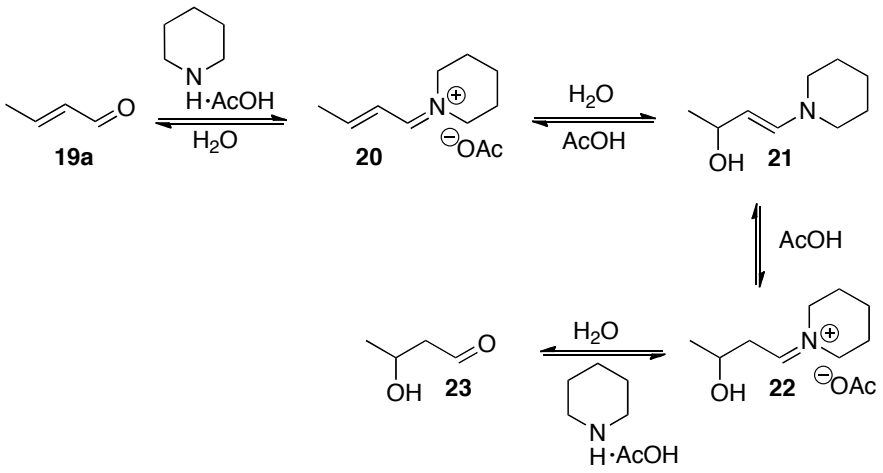
2.1.2.1 Historical Overview[9b, 14]

Probably the first example of amine catalysis is the reaction of aldehydes or ketones with active methylene compounds in the presence of a weak base, known as the KNOEVENAGEL condensation (Scheme 2.3).[15] When a primary or secondary amine **12** is used as a catalyst, it has a double activation role. It forms an iminium ion **16** with the carbonyl compound **14** and deprotonates the nucleophile **11**. The product of the reaction **18**, a highly substituted α,β-unsaturated dicarbonyl compound, can undergo a Michael reaction with the enolate, if this is present in excess. If $R^3 = R^4 = OH$, the reaction might be followed by decarboxylation.



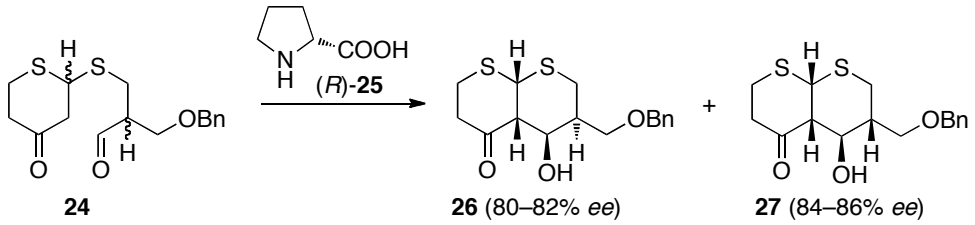
Scheme 2.3. The mechanism of the Knoevenagel condensation catalyzed by a primary or secondary amine.[16]

The first iminium catalyzed conjugate addition was discovered by LANGENBECK in 1937 (Scheme 2.4).[17] A 1,4-addition of water to crotonaldehyde was catalyzed by piperidinium acetate and proceeded via iminium intermediate **20**. An equilibrium between the product and starting material was observed.



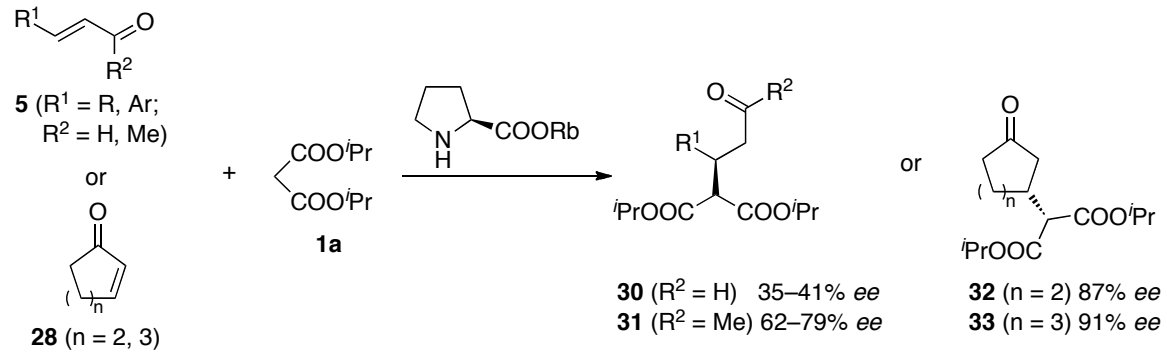
Scheme 2.4. Piperidine-catalyzed Michael addition.

In 1981, WOODWARD and co-workers reported a *D*-proline-catalyzed *retro*-Michael reaction of erythromycin core intermediate **24**, which was followed by Michael re-addition and subsequent aldol reaction, thus resulting in deracemization of **24** (Scheme 2.5).[18] Both diastereomers, **26** and **27**, were obtained in good *ee*.



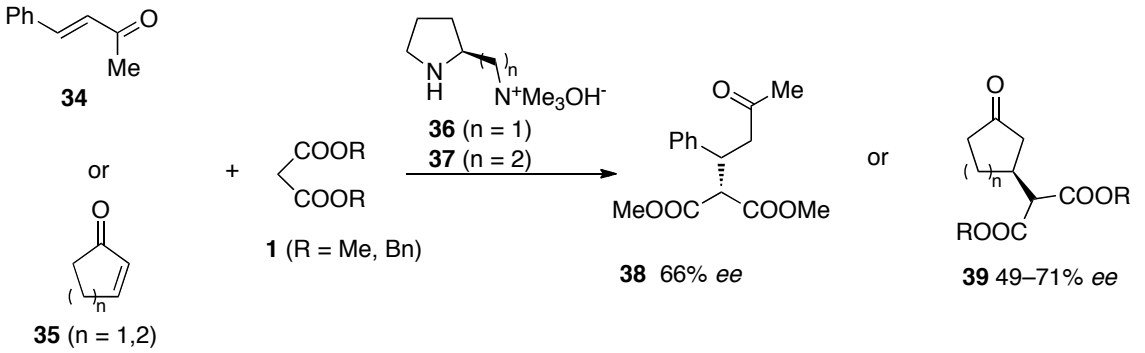
Scheme 2.5. *D*-Proline-catalyzed deracemization of **24**.

The first asymmetric secondary amine-catalyzed Michael addition of malonates to α,β-unsaturated aldehydes was reported by YAMAGUCHI and co-workers.[19] In 1991 they found that lithium prolinate can effectively catalyze the reaction of dimethyl malonate and unsaturated aldehydes, but no enantioselectivities were reported.[19a] They proposed an activation model where the catalyst activates both the Michael donor and the acceptor. In their later studies, rubidium prolinate was used as a more efficient catalyst for the addition of diisopropyl malonate to diverse cyclic and acyclic unsaturated ketones and aldehydes (Scheme 2.6).[19b]



Scheme 2.6. The first asymmetric Michael addition of malonates to α,β-unsaturated carbonyl compounds.

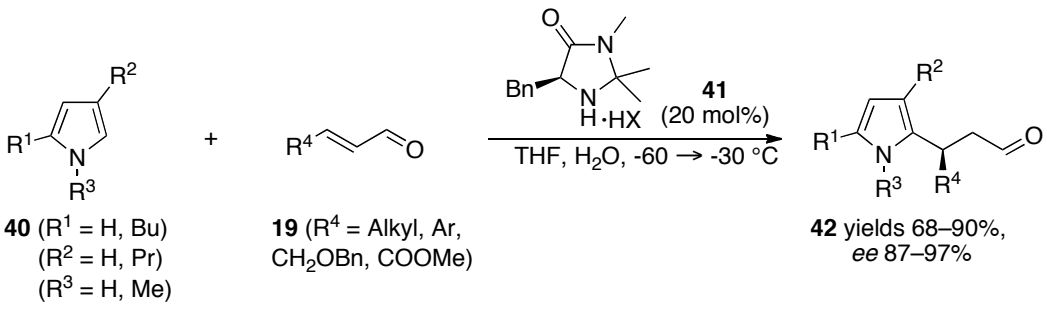
Literally the first organic catalyst without any metal ion for the asymmetric Michael addition to α,β-unsaturated carbonyl compounds was published by KAWARA and TAGUCHI (Scheme 2.7).[20] Depending on the structures of electrophiles and nucleophiles, low to moderate enantiomeric excess was obtained. Interestingly, the opposite enantioselectivity was observed than that obtained by YAMAGUCHI. It was explained by interaction between the approaching nucleophile and the quarternary ammonium salt of the catalyst.[19c]



Scheme 2.7. Michael addition of malonates to unsaturated ketones catalyzed by **36** and **37**.

In 2000, a new age of iminium catalysis started with MACMILLAN's discovery of a highly enantioselective iminium catalyzed Diels-Alder reaction.[21] The first application of his first-generation catalyst **41** in a 1,4-addition was the reaction of pyrroles and unsaturated aldehydes, which gave the products in high yields and good *ee* (Scheme 2.8).[22] Since then, the field of iminium catalysis has expanded and now, numerous highly selective organocatalysts and useful transformations are known, all of which are based on iminium activation. The reaction scope has also been expanded to include a range of different nucleophiles (C-, N-, O-, S-).[6] Furthermore, these reactions are often a part of cascade (domino) reactions, which lead to complex products in a one-pot reaction sequence.[23]

1,4-Additions of active methylene compounds, especially malonates to α,β-unsaturated aldehydes are the subject of this chapter and will be closely discussed in following section.

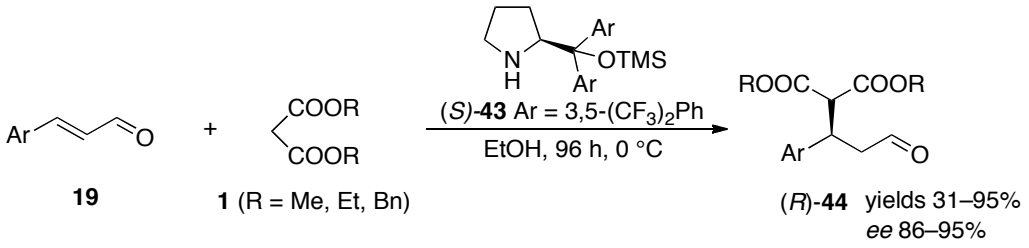


Scheme 2.8. Organocatalyzed 1,4-addition of pyrroles to α,β-unsaturated aldehydes.

2.1.2.2 Reactions of α,β-Unsaturated Aldehydes with Malonates

Although highly selective organocatalytic 1,4-additions of malonates to enones were known,[24] there was no effective catalyst for α,β-unsaturated aldehydes. KOCHETKOV reported attempts to optimize YAMAGUCHI's catalyst, but low enantioselectivities were obtained in the reaction of crotonaldehyde and diethyl malonate.[25] 3-, 4- or 5-substituted prolinate salts served as catalysts.

In 2006, JØRGENSEN and co-workers successfully applied their prolinol-derived catalyst **43** in the Michael addition of malonates to enals (Scheme 2.9).[26] The reactions were performed at 0 °C in EtOH and required long reaction times (4 d). Aromatic enals were converted to the products in moderate to good yields and good to high enantioselectivities.

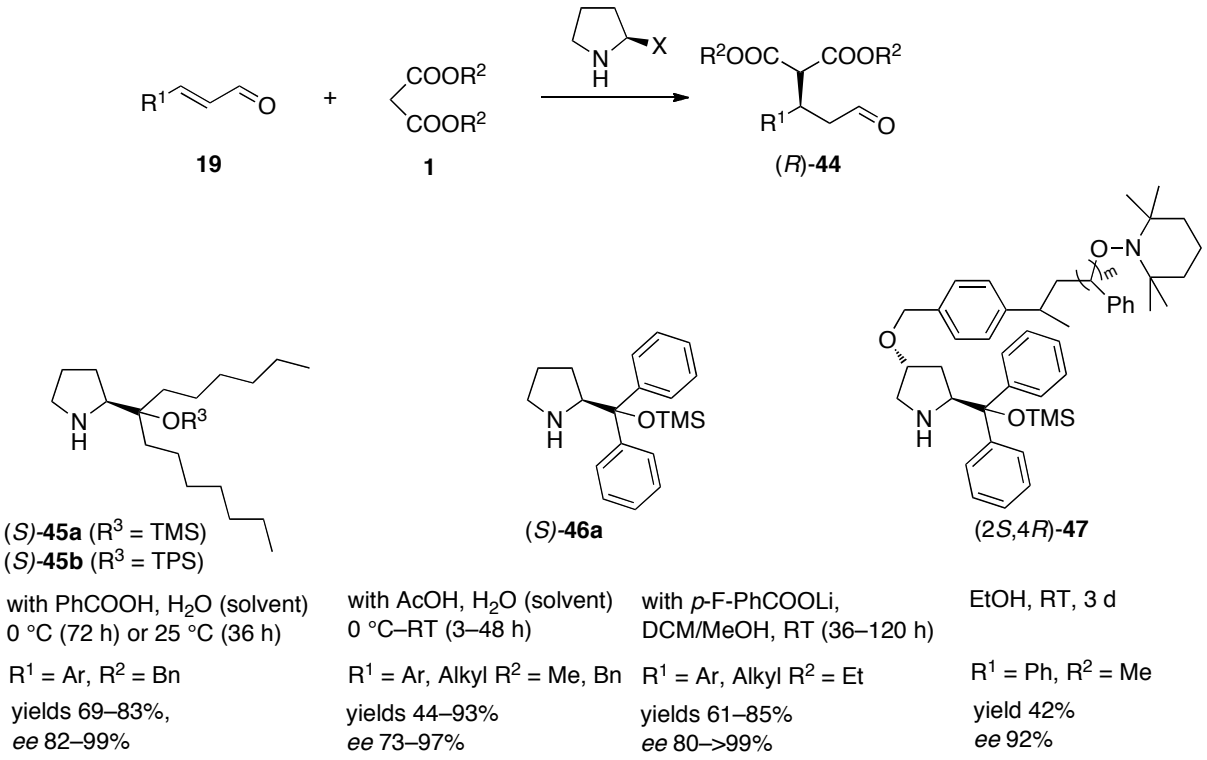


Scheme 2.9. First highly selective Michael addition of malonates to enals.

Further development in this field was based on modification of catalyst structure and optimization of reaction conditions. PALOMO introduced a water-compatible catalyst with hydrophobic alkyl chains and bulky silyl groups (*S*)-**45**, which gave good yields and good to

high enantioselectivities (Scheme 2.10).[27] The reactions were performed in water with benzoic acid as an additive.

MA and co-workers showed, that the TMS-substituted catalyst (*S*)-**46a** produces high yields and enantioselectivities when the reaction is performed in water with acetic acid as an additive (Scheme 2.10).[28] Also alkyl- and alkenyl-substituted enals gave the product in moderate yields and moderate to high *ee*, when a substoichiometric amount of acetic acid was used.



Scheme 2.10. Organocatalyzed asymmetric Michael addition of malonates to α,β-unsaturated aldehydes.

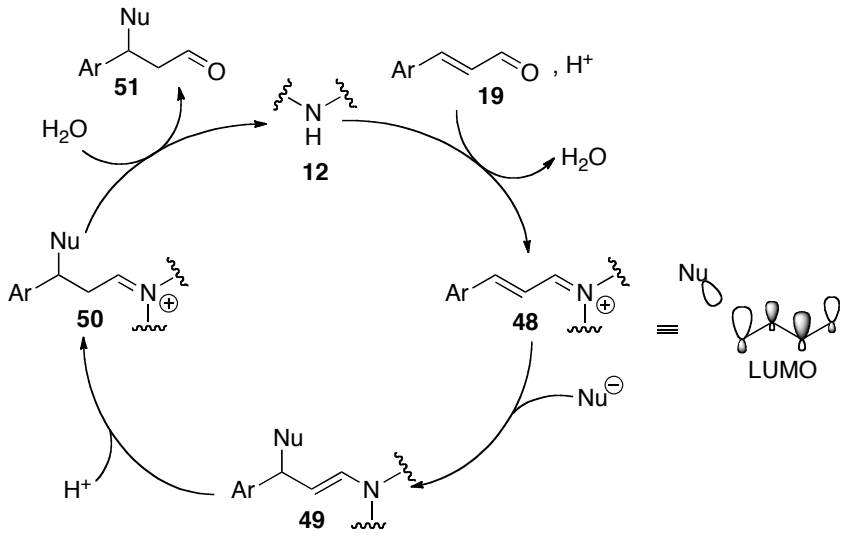
WENDORFF and STUDER investigated the possibility of catalyst immobilization.[29] They synthesized a prolinol derivative bound to oligostyrene (2*S*,4*R*)-**47**, which was then immobilized onto a polystyrene matrix to give fibre systems. Moderate yield and good enantioselectivity was observed in the model reaction of dimethyl malonate addition to cinnamaldehyde (Scheme 2.10). However, the activity of the catalyst decreased during the third run in recycling experiments.

LIANG and YE found, that addition of a base had beneficial effect on the reaction.[30] Only 1 mol% of catalyst (*S*)-**46a** and 2 mol% of base were needed to yield the products in moderate

to good yields and good to high enantioselectivities (Scheme 2.10). Alkyl-substituted enals required higher catalyst loadings and longer reaction times.

2.1.2.3 Mechanism of Iminium-catalyzed Michael Addition

Despite many publications dealing with iminium-catalyzed Michael additions, its mechanism has not been studied in detail. The generally accepted catalytic cycle starts with the formation of the iminium intermediate **48** from aldehyde **19** and catalyst **12** (Scheme 2.11).[6] The reactivity of the iminium intermediates can be explained by a lower energy of the LUMO when compared to the corresponding unsaturated carbonyl compound. Iminium ions are ambident electrophiles, but, in analogy to the carbonyl compound, the largest coefficient of the LUMO is at the 4-position, which is then attacked by the nucleophile. The enamine intermediate **49** is protonated to give iminium **50** before being hydrolyzed to product **51** and regenerating the catalyst.



Scheme 2.11. The catalytic cycle of an iminium-catalyzed Michael addition.

PLATTS and TOMKINSON reported kinetic and theoretical investigations into the iminium ion catalyzed Diels-Alder reaction.[31] They showed that C-C bond formation is the rate-determining step, whereas the formation and hydrolysis of iminium intermediates are fast.

MAYR and co-workers investigated electrophilic reactivities of α,β-unsaturated iminium ions.[32] They could isolate triflate salts of iminium ions **52** derived from MACMILLAN's catalyst **41**, and **53**, derived from silyl prolinol (*S*)-**46a**. NOE experiments were performed on

iminium ions to determine the structure of the main stereoisomers (Figure 2.1). Their findings were in line with recent calculations, meaning that (*E*)-**52** and (*E*)-**53** were the preferred conformers.[33]

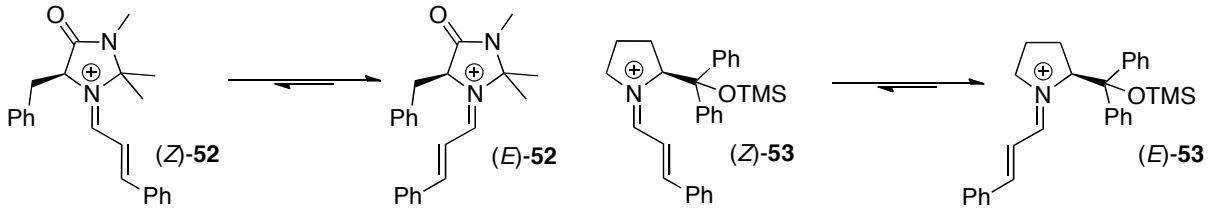
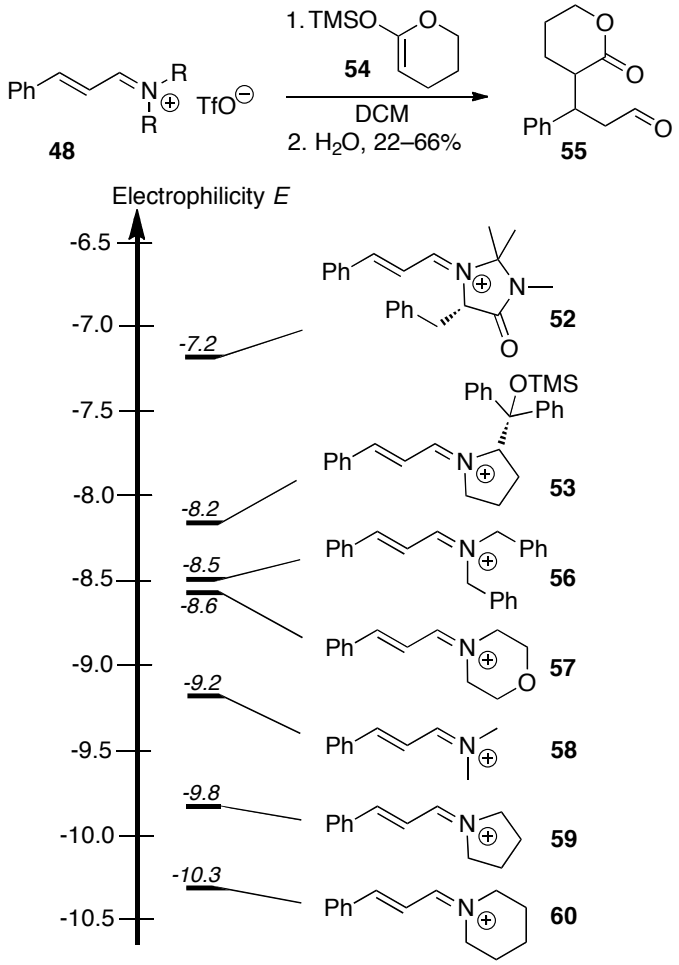


Figure 2.1. Conformations of iminium ions **52** and **53**.

Based on the kinetic studies of the Michael addition of ketene acetal **54** to iminium triflates **48**, the electrophilicity parameters of iminium ions were determined and compared (Scheme 2.12).[32] Among the tested iminium ions, **52** was the most electrophilic one, followed by **53**. MAYR also claims that the rate of the overall process is controlled not only by the reactivity of iminium ions, but also by the rates of their formation and their equilibrium concentrations.



Scheme 2.12. Determination of the electrophilicity of iminium ions in 1,4-addition.

The structures of iminium ions derived from **41** were further studied by X-Ray, NMR and DFT-calculations by PLATTS, TOMKINSON[34] and SEEBACH.[35a, b] SEEBACH and UCHIMARU also reported a comprehensive study on the structure and reactivity of iminium ions derived from diarylsilyl prolinol catalysts.[35c] They confirmed the generally accepted rationale for the high stereoselectivity in reactions proceeding via iminium intermediates. The large $Ar_2(OR)C$-group blocks one face of the π-system, so that nucleophile approaches from the opposite face. Furthermore, the bulky group causes a preference for the (*E*)-configuration of the iminium ion (Figure 2.2). However, as their own and MAYR's NMR experiments already showed, the (*Z*)-conformer is present in solution as well (about 10%). But if the (*Z*)-conformer is present in reactions and has similar reactivity, it will lead to lower enantioselectivities. More investigations are necessary to interpret these findings.

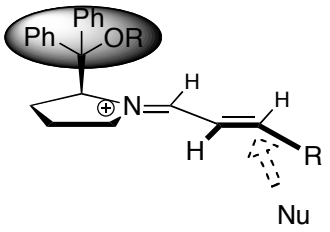


Figure 2.2. Attack of nucleophile on the (*E*)-conformer of iminium ion.

SEEBACH and UCHIMARU further explained the shielding caused by the large $Ar_2(OR)C$-group. It is believed that one of the aryl groups is aligned above the π-system and constrains the nucleophile from the attack on this side.[33c, d] However, calculations and crystal structures suggested that the bond between the pyrrolidine ring and the $Ar_2(OR)C$- group is arranged in a *sc-exo* conformation, in which the RO- group is aligned above the π-system (Figure 2.3).

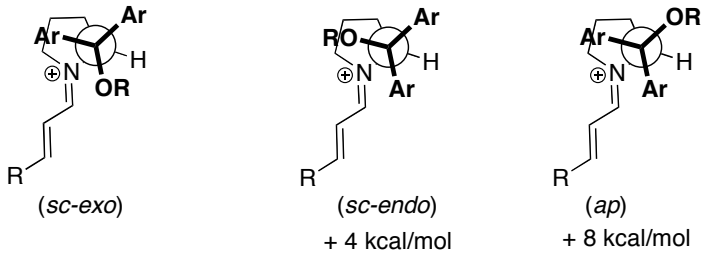


Figure 2.3. Conformations around the C-C bond between pyrrolidine and $Ar_2(OR)C$-group and the calculated difference in energy in the gas phase.

2.2 Introduction: Electrospray Ionization Mass Spectrometry

The goal of this project was to develop an efficient ESI-MS (electrospray ionization mass spectrometry) screening system for organocatalytic 1,4-additions.

Electrospray ionization is a mild ionization method, which allows for the transfer of molecular ions from solution directly into the gas phase without fragmentation. Electrospray originates in industry. In 1968 DOLE showed that gas-phase ions could be generated by spraying a polystyrene solution into an evaporation chamber.[36] Based on these achievements, Fenn coupled the electrospray source to a quadrupole mass analyzer.[37] His findings enabled the analysis of biomolecules,[38] which are often thermally labile and too large to be analyzed by classical methods. In the present day, electrospray ionization mass spectrometry (ESI-MS) and its tandem version ESI-MS/MS are well-established tools, not only for analyses of biomolecules, but also for non-volatile organometallic complexes[39] as well as for the detection of reaction intermediates[40] and for high-throughput screening of catalysts.[41]

2.2.1 Principle of Electrospray Ionization[42]

The electrospray process can be divided into three stages: droplet formation, shrinkage of charged droplets and production of gas-phase ions. The diluted analyte solution is pumped through an electrospray capillary. The high voltage on the capillary provides an electric-field gradient, which causes a charge separation at the liquid surface. The liquid forms a so-called Taylor cone at the capillary tip.[43] If the applied field is high enough, a fine jet is formed, which breaks into droplets.[44]

The droplets shrink due to solvent evaporation. The repulsion between the charges increases at the surface until it overcomes the surface tension. It results in so-called Coulomb fission into smaller droplets.[45] This process repeats until very small and highly charged droplets are formed. The formation of desolvated gas-phase ions can be explained by two models. According to the "charged residue model" (CRI) the evaporation of solvent and droplet fission continues until droplets containing single ions are formed.[36] Evaporation of residual solvent leads to non-solvatated ions. The "ion evaporation model" (IEM) predicts direct emission of ions from the droplets if they reach a certain radius.[46]

2.2.2 ESI-MS Detection of Reaction Intermediates in Organocatalysis

ESI-MS is suitable for investigation of reaction intermediates due to its mildness and to the possibility of directly analyzing solutions. The study of catalyzed reactions with ESI-MS is possible due to its high sensitivity, which requires only a low concentration of analyte (10^{-5}-10^{-2} M). Since many intermediates of organocatalytic reactions are charged or can be protonated in solution, they are amenable to detection by ESI-MS.

EBERLIN and co-workers reported the first application of ESI-MS(/MS) in organocatalysis.[47] They detected and characterized key intermediates of the 1,4-diazabicyclo[2,2,2]octane (DABCO) catalyzed Morita-Baylis-Hillman (MBH) reaction. More recently, the same group reinvestigated the same reaction and provided evidence for the accepted mechanism by the detection of new intermediates.[48] These studies are examples of on-line monitoring, which utilizes a reactor coupled to the ion source.[40b] This setup allows for the screening of the reaction in the real time and the detection of transient species. MASERAS, EBERLIN and COELHO extended the studies on the MBH reaction to thiourea catalysis.[49]

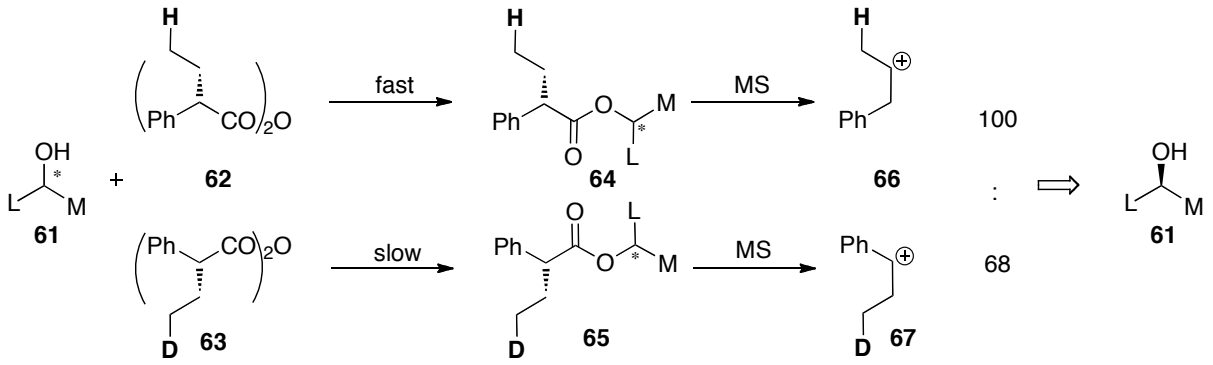
METZGER reported ESI-MS study of the (*S*)-proline catalyzed aldol reaction of acetone to aromatic and aliphatic aldehydes.[50] The presumed intermediates were characterized by high-resolution measurement and MS/MS experiments. The same group performed a mechanistic study on organocatalyzed α-halogenation of butanal by ESI-MS.[51] Dual ESI-MS methodology, which is based on spraying of two reagents by separate capillaries into the microreactor, allowed for the detection of intermediates milliseconds after the initiation of the reaction.

SCHRADER and GLORIUS used ESI-MS for the investigation of a carbene catalyzed *umpolung* reaction of cinnamaldehyde and 4-chlorobenzaldehyde.[52] SCHRADER and LIST succeeded in intercepting and characterizing important intermediates of a chiral Brønsted acid catalyzed cascade reaction.[53] Furthermore, ESI-MS was used to support mechanistic investigations of the thiourea catalyzed nitro-Michael addition[54] and in the prolinamide catalyzed aldol reaction.[55]

2.2.3 Quasienantiomers in Mass Spectrometry

A significant limitation of mass spectrometry is its inability to distinguish enantiomeric and diastereomeric compounds, as they have the same mass. Several methods for the introduction

of chiral information into mass-spectrometric measurements were developed.[56] Most of them are based on the formation of diastereomers or diastereomeric interactions. HOREAU reported a much simpler approach.[57] By introduction of mass labels, a method for the determination of absolute configuration of secondary alcohols was developed (Scheme 2.13). An alcohol with unknown configuration **61** was treated with anhydrides **62** and **63** (1:1 mixture) that behaved like enantiomers but differed in mass. A kinetic resolution gave esters **64** and **65**, which were subjected to electron impact mass spectrometry (EI-MS). The relative peak intensities of formed fragments **66** and **67** were compared and, based on the most abundant species, the absolute configuration of the alcohol was determined.



Scheme 2.13. Horeau's method for determination of absolute configuration of chiral alcohols.

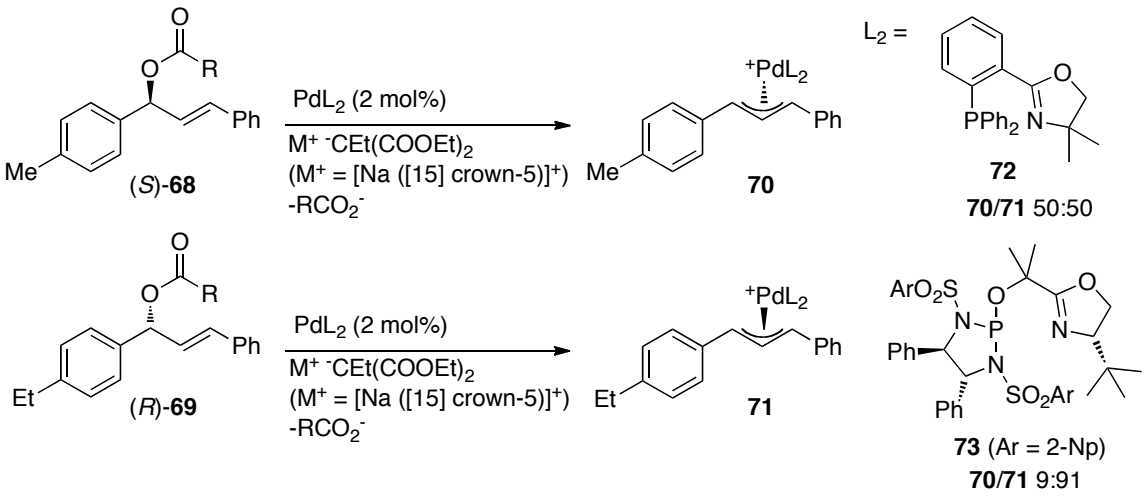
Pairs of compounds such as **62**/**63** or **64**/**65** are called quasienantiomers. By definition, quasienantiomers are any pair of compounds that can be turned into enantiomers by slightly changing the composition of substituents.[58] They have found applications in identification, analysis, separation and synthesis of enantiomers.

SUIZDAK and FINN extended HOREAU's method to the determination of enantiomeric excess of chiral alcohols and amines[59] and employed this approach later to screen chiral ligands in the Rh-catalyzed hydrosilylation of ketones.[60] A similar application to lipase-catalyzed kinetic resolution was reported by REETZ.[61]

2.2.4 ESI-MS Screening

MARKERT and PFALTZ recently reported the application of ESI-MS to the palladium-catalyzed kinetic resolutions of allylic esters (Scheme 2.14). [62, 63] They developed a new screening method for chiral catalysts based on mass-labeled quasienantiomeric substrates and mass spectrometric monitoring of catalytic intermediates. An equimolar mixture of

quasienantiomeric allylic esters (*S*)-**68**/(*R*)-**69** was subjected to kinetic resolution with a palladium-catalyst. The charged intermediates were monitored by ESI-MS and from the ratio of signal intensities the selectivity of the catalyst was determined. With achiral ligand **72**, the observed ratio was 50:50. The reaction with chiral ligand **73** showed a ratio of 9:91 that directly reflected the selectivity of the catalyst in kinetic resolution. The methodology was also extended to the simultaneous screening of catalyst libraries, which were prepared in one batch.[64]



Scheme 2.14. ESI-MS Screening of the palladium-catalyzed kinetic resolution of the mixture of quasienantiomers (*S*)-**68**/(*R*)-**69**.

The previous work showed that the selectivity in the kinetic resolution did not always correlate with the enantioselectivity of the nucleophilic addition. This problem was overcome by screening of the *retro*-reaction of quasienantiomeric products of the allylic alkylation and amination, as shown by MÜLLER.[65] According to the principle of microscopic reversibility,[66] the *retro*-reaction proceeds *via* the same mechanism as the forward reaction, thus the selectivity should be the same in both directions (Figure 2.4). This methodology is also generally applicable to the reactions of prochiral substrates that lead to chiral products, as shown by TEICHERT in copper- and organocatalyzed Diels-Alder reactions.[67]

a) kinetic resolution: b) prochiral substrate: c) *retro* reaction:

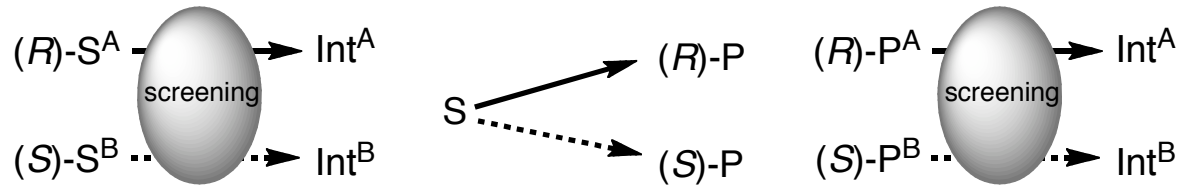
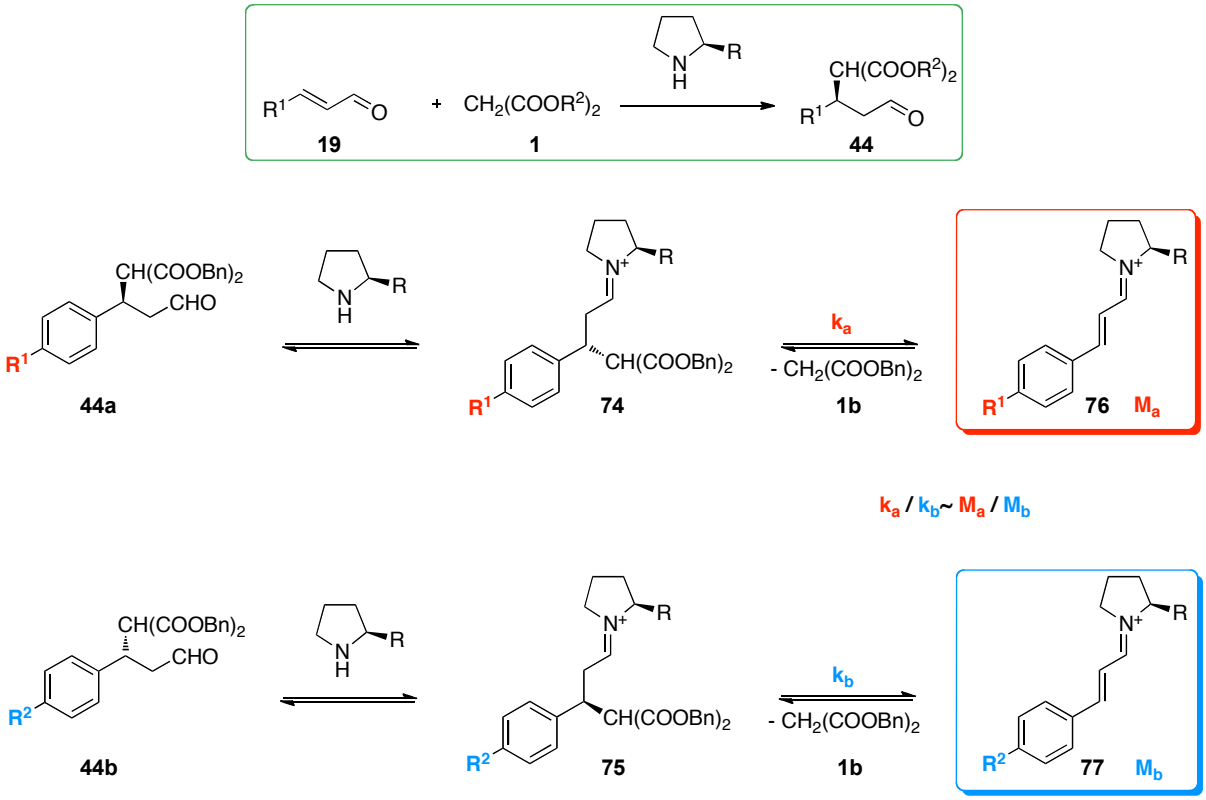


Figure 2.4. Mass-spectrometric approaches to the screening: a) The screening of kinetic resolution with chiral substrates (*R*)-S^A/(*S*)-S^B bearing mass-labels A/B; mass-labeled intermediates (Int) are observed in mass spectrum; b) The reaction with prochiral substrate S, screening is not applicable; c) The screening of the *retro*-reaction with chiral mass-labeled products (*R*)-P^A/(*S*)-P^B, mass-labeled intermediates (Int) are observed in mass spectrum.

2.2.5 Objectives

The aim of this project was the development of a screening method for the organocatalyzed Michael reaction of malonates **1** to α,β-unsaturated aldehydes **19** (Scheme 2.15). Based on the principle of microscopic reversibility, it should be possible to determine the enantioselectivity of a catalyst by screening the intermediates in the *retro*-Michael reaction of a pair of quasienantiomeric Michael adducts **44a** and **44b**. Because the transition states of the forward and back reaction are identical, the ratio of the signal intensities of intermediates **76** and **77** with masses M_a and M_b should reflect the enantioselectivity of the catalyst. An extension of this methodology to the screening of catalyst mixtures was planned.

Furthermore, optimization and mechanistic studies of the forward Michael reaction were anticipated.



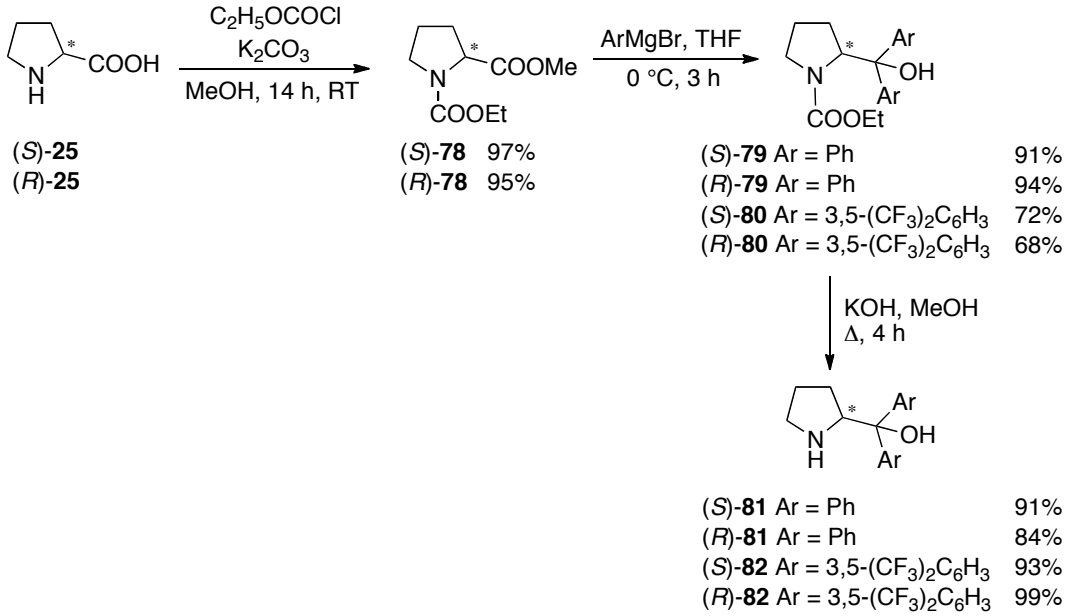
Scheme 2.15. The principle of mass-spectrometric screening of the *retro*-Michael addition.

2.3 Synthesis of Catalysts and Quasienantiomers

2.3.1 Synthesis of Catalysts

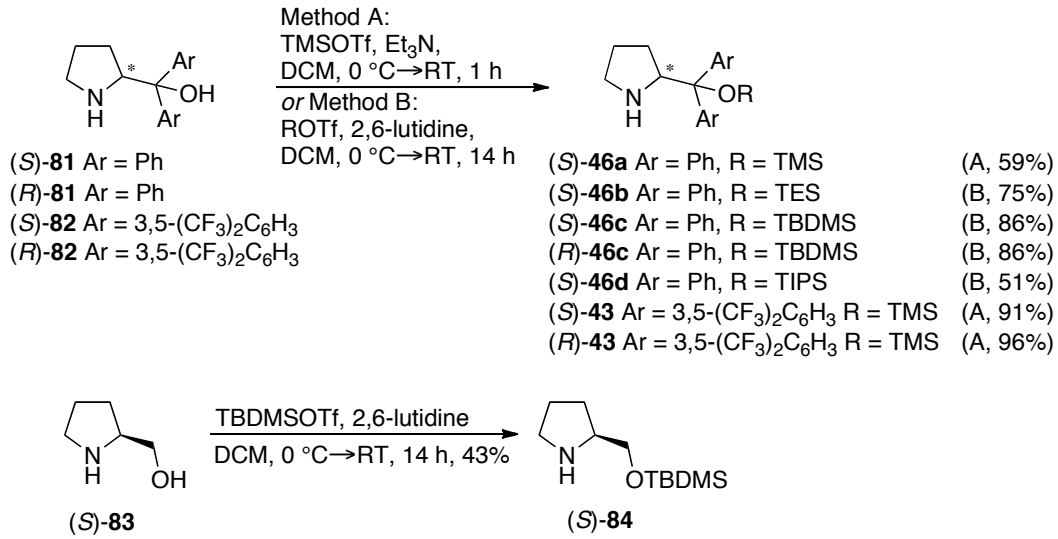
Prolinol-derived organocatalysts **43** and **46** were introduced in 2005 by JØRGENSEN[68] and HAYASHI.[69] They were applied in numerous organocatalytic reactions involving iminium and enamine activation as very selective and effective catalysts.[70]

Amino alcohols **81** and **82** were synthesized according to a protocol previously reported by PERIASAMY (Scheme 2.16).[71] Protection and esterification of (*S*)- and (*R*)-proline were accomplished in one step in high yield. Grignard addition to *N*-ethyl carbamates **78** was followed by deprotection. Diarylprolinol derivatives **81** and **82** were obtained in good to excellent overall yields.



Scheme 2.16. Synthesis of catalysts **81** and **82**.

The silylation of aminoalcohols **81**–**83** was accomplished following the procedures of JØRGENSEN (Scheme 2.17, method A)[68] and HAYASHI (Scheme 2.17, method B).[69] Amino alcohols **81**–**83** were treated with trialkylsilyl triflates in the presence of base (NEt_3 or 2,6-lutidine) to give catalysts **43** and **46a**–**d** in moderate to good yields. The less bulky catalyst (*S*)-**84** was synthesized in moderate yield from (*S*)-prolinol using the same method.



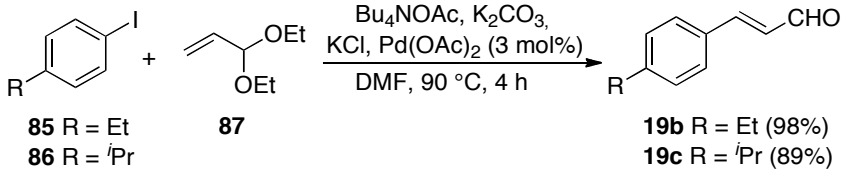
Scheme 2.17. Synthesis of catalysts **43**, **46a-d** and **84**.

In this manner a small library of organocatalysts was synthesized in moderate to good overall yields.

2.3.2 Synthesis of Quasienantiomeric Michael Addition Adducts

Quasienantiomers for ESI-MS screening should be prepared as single enantiomers (*ee* > 99%). The mass labels must not affect the reactivity of quasienantiomers. Based on the initial studies of C. HUMPHREY in our group, Et- and ^{i}Pr-groups were chosen as candidates for appropriate mass labels.

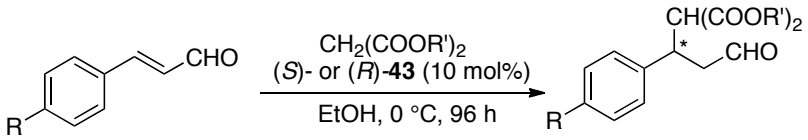
The quasienantiomers were prepared in a two-step synthesis. Et- And ^{i}Pr-substituted cinnamaldehydes **19b** and **19c** were obtained by Heck coupling from corresponding aryl iodides **85** and **86** and ethyl acrolein acetal (**87**) in good yields (Scheme 2.18).[72]



Scheme 2.18. Synthesis of substituted cinnamaldehydes **19b** and **19c**.

Cinnamaldehydes **19b** and **19c** were subjected to a Michael reaction with dibenzyl malonate in the presence of catalyst (*S*)- or (*R*)-**43** (10 mol%) following a procedure reported by JØRGENSEN.[26] All quasienantiomeric adducts **44c**–**e** were obtained in moderate to good

yields and good *ee* (Scheme 2.19). Two recrystallizations were necessary to achieve virtually enantiopure material. Methyl malonate adduct (*R*)-**44c** was prepared with slightly higher enantiomeric excess, but it was isolated as an oil, preventing further purification by recrystallization. During later investigations, optimized conditions for Michael addition had been found (see experimental part and section 2.7.2) and quasienantiomers **44d** and **44e** were prepared in higher yields and almost enantiomerically pure.



19b R = Et (98%)
19c R = ^{i}Pr (89%)

(*R*)-**44c** R = Et R' = Me (55%, 93% *ee*)
(*R*)-**44d** R = Et R' = Bn (83%, 91% *ee*)
(*S*)-**44d** R = Et R' = Bn (70%, 91% *ee*)
(*R*)-**44e** R = ^{i}Pr R' = Bn (82%, 91% *ee*)
(*S*)-**44e** R = ^{i}Pr R' = Bn (47%, 91% *ee*)

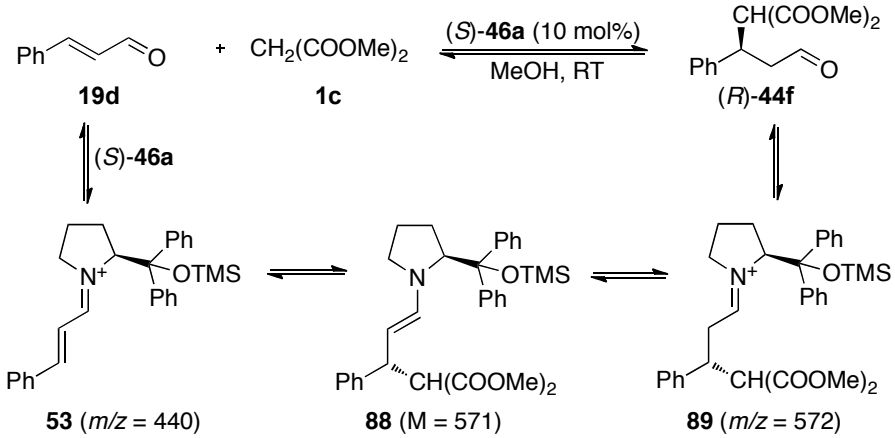
Scheme 2.19. Synthesis of Michael adducts **44c-e**.

The four enantiopure quasienantiomers were synthesized *via* two-step procedure in moderate to good overall yields.

2.4 ESI-MS Screening of Single Catalysts

2.4.1 Preliminary Test Experiments

In order to find conditions for the monitoring of reaction intermediates with ESI-MS, the Michael addition of dimethyl malonate to cinnamaldehyde catalyzed by (*S*)-**46a** was followed by ESI-MS (Scheme 2.20). The best solvent for the detection of intermediates was found to be acetonitrile. After 15 minutes, the signal of iminium ion **53** (*m/z* = 440) was observed to be the most intense (Figure 2.5). The signal of iminium species **89** (*m/z* = 572) and the sodium adduct of enamine **88** (*m/z* = 594) were detected, as well. Several small signals could not be assigned.



Scheme 2.20. Michael addition of dimethyl malonate to cinnamaldehyde with (*S*)-**46a**.

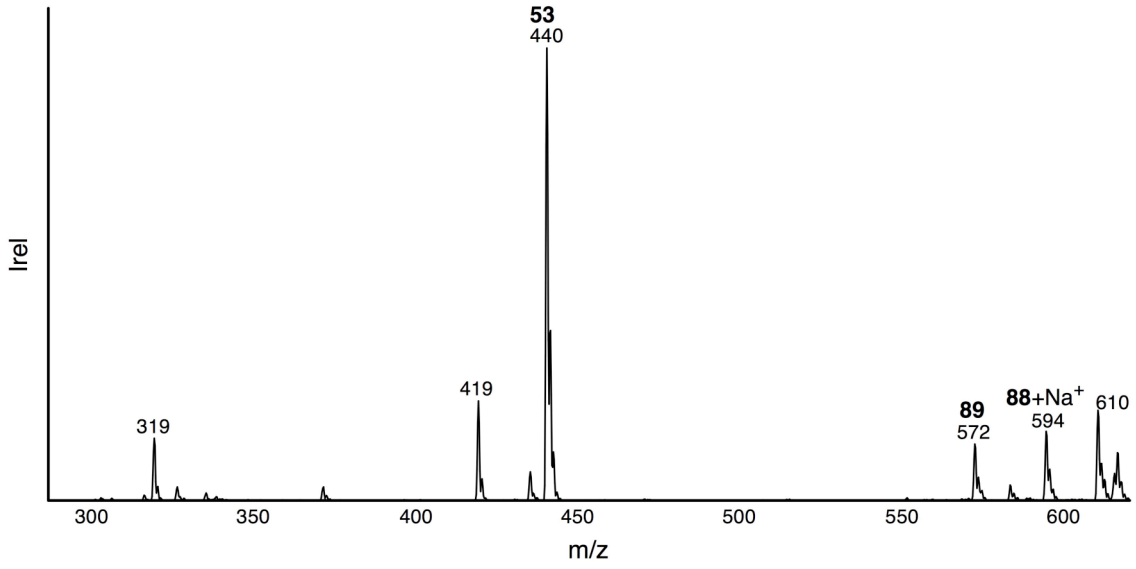
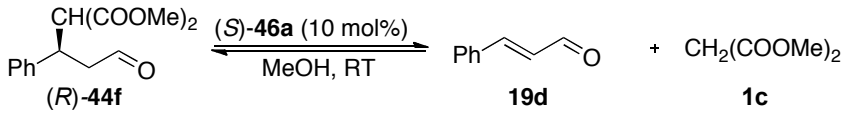


Figure 2.5. ESI-MS spectrum of Michael addition of dimethyl malonate to cinnamaldehyde catalyzed by (*S*)-**46a**.

The *retro*-Michael reaction was performed under the same conditions as the forward reaction (Scheme 2.21). Catalyst (*S*)-**46a** was added to a stirred solution of Michael adduct (*R*)-**44f** in MeOH, and the reaction was followed by ESI-MS. An exceptionally clean spectrum was observed after 15 minutes with the iminium ion **53** signal (*m/z* = 440) being the most prominent one (Figure 2.6). Only two other signals of high intensity appeared in the spectrum, which were assigned to the Michael adduct iminium ion **89** (*m/z* = 572) and the protonated catalyst **46a** (*m/z* = 326).



Scheme 2.21. *Retro*-Michael reaction of (*R*)-**44f** with catalyst (*S*)-**46a**.

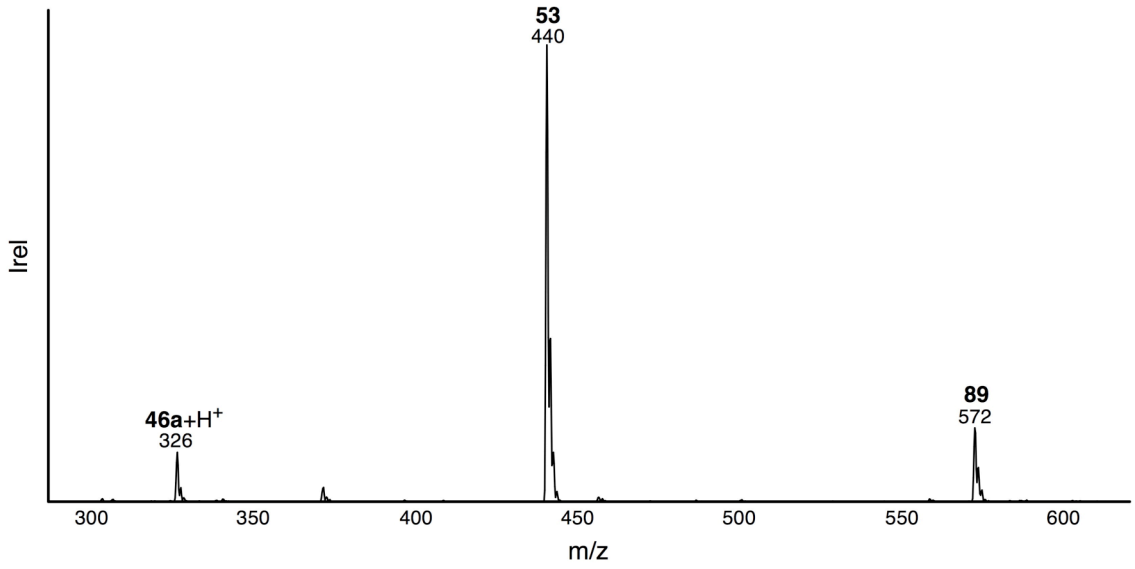
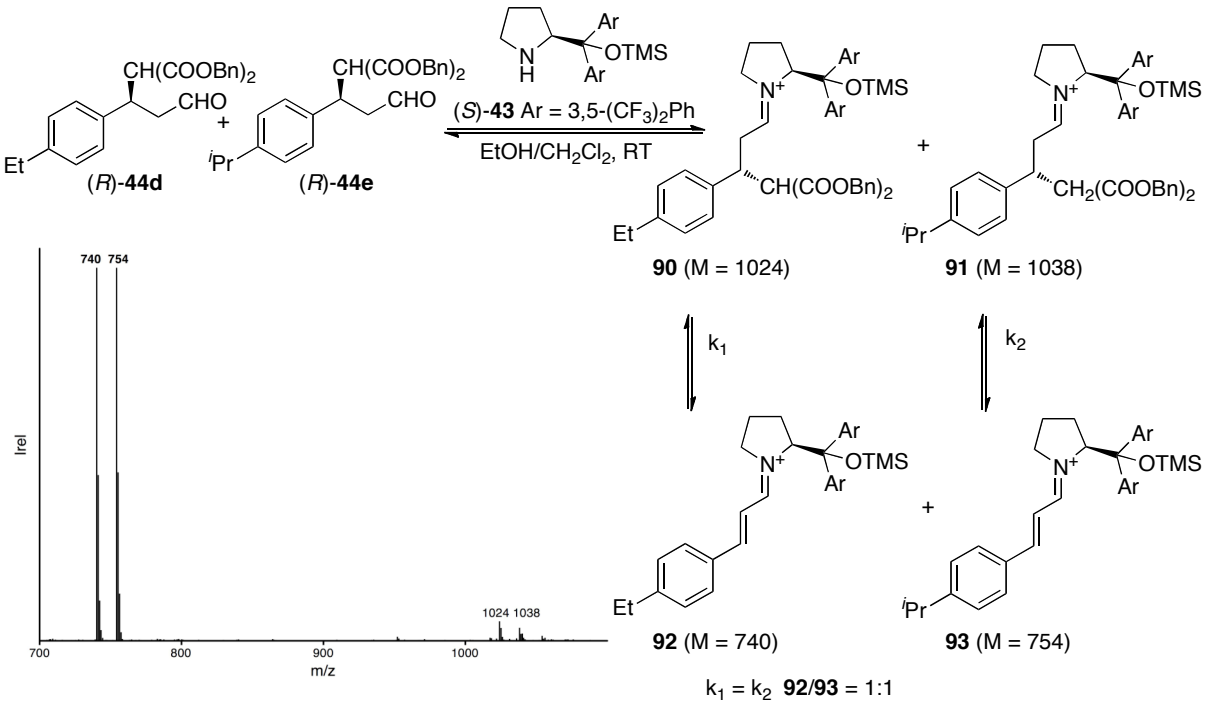


Figure 2.6. ESI-MS spectrum of the *retro*-Michael addition of Michael adduct (*R*)-**44f** catalyzed by (*S*)-**46a**.

2.4.2 Validation of the Method, General Screening Protocol

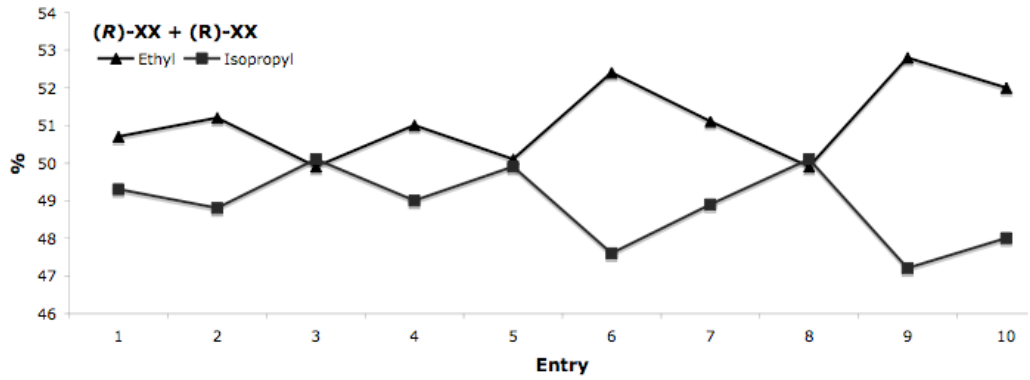
To examine the suitability of the mass labels, quasienantiomers (*R*)-**44d** and (*R*)-**44e** were subjected to a *retro*-Michael reaction with catalyst (*S*)-**43** (Scheme 2.22**)**. The measurement was repeated 10 times. The average ratio of intensities of the intermediates **92** and **93** was (51±1)/(49±1), which confirms that the effect of mass labels on the reactivity of quasienantiomeric Michael adducts is negligible (Figure 2.7a). The same experiment was

performed with (*S*)-**44d**, (*S*)-**44e** and catalyst (*R*)-**43** to give an average ratio of (50±1)/(50±1) (Figure 2.7b).



Scheme 2.22. *Retro*-Michael reaction of (*R*)-**44d** and (*R*)-**44e**.

a)



b)

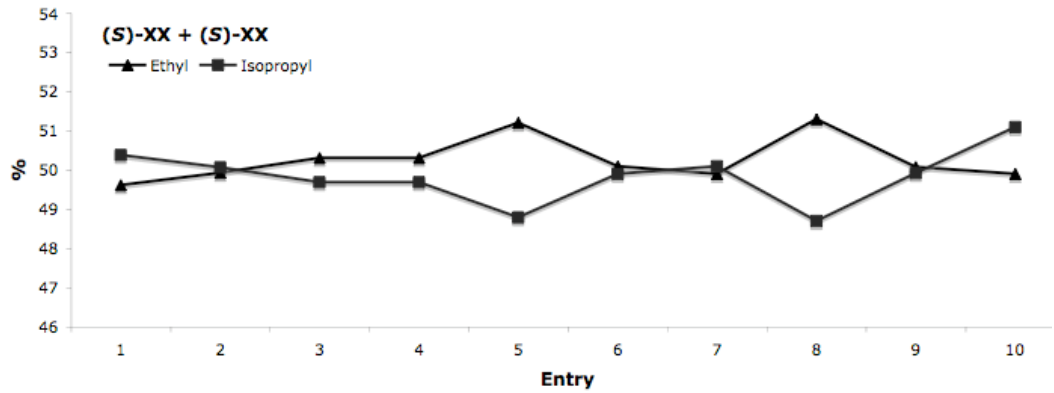
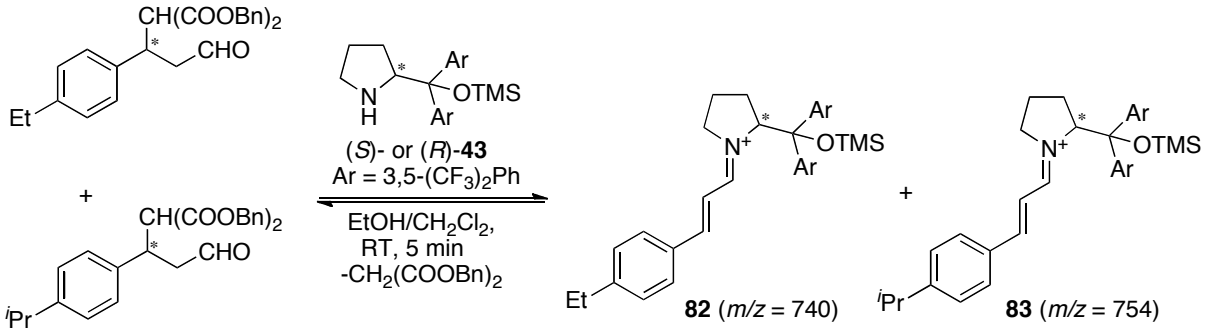


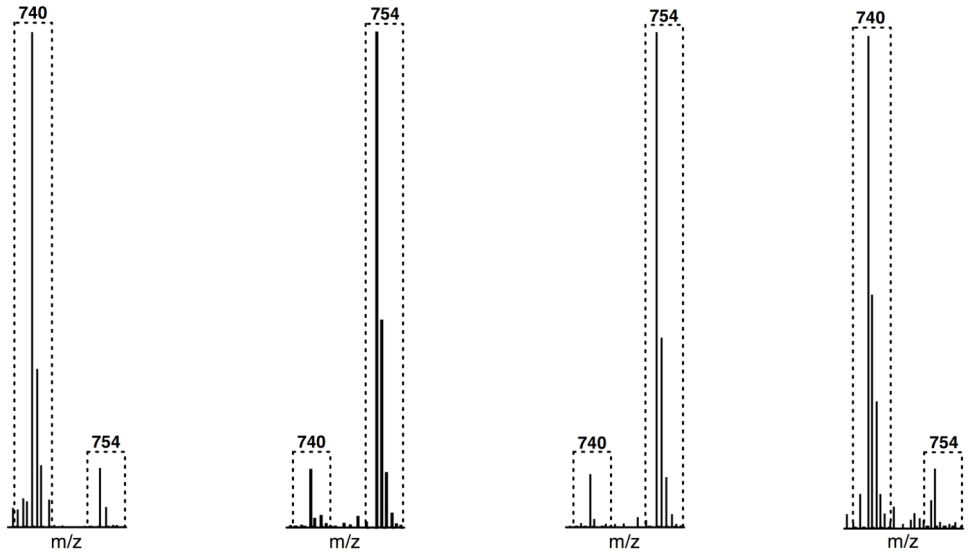
Figure 2.7. Relative signal intensities in 10 measurements of the *retro*-Michael reaction of: a) (*R*)-**44d**/(*R*)-**44e** with catalyst (*S*)-**43**; b) (*S*)-**44d**/(*S*)-**44e** with catalyst (*R*)-**43**.

Another proof of the method's validity was provided by the reactions of quasienantiomeric pairs (*R*)-**44d**/(*S*)-**44e** and (*S*)-**44d**/(*R*)-**44e** with both enantiomers of catalyst **43**. The reactions of one quasienantiomeric pair with 2 enantiomers of **43** should give the inverted ratio of signal intensities. Furthermore, the inversely labeled quasienantiomers should result in the same but inverted ratio with the same enantiomer of **43**.



(*R*)-**44d**/(*S*)-**44e** or (*S*)-**44d**/(*R*)-**44e**

Scheme 2.13. *Retro*-Michael reaction catalyzed by **43**.



90:10	10:90	11:89	89:11
(*R*)-**44d**/(*S*)-**44e**	(*S*)-**44d**/(*R*)-**44e**	(*R*)-**44d**/(*S*)-**44e**	(*S*)-**44d**/(*R*)-**44e**
(*S*)-**43**	(*S*)-**43**	(*R*)-**43**	(*R*)-**43**

Figure 2.8. *Retro*-Michael reaction of 4 combinations of quasienantiomeric pairs (*R*)-**44d**/(*S*)-**44e**, (*S*)-**44d**/(*R*)-**44e** and (*R*)- and (*S*)-**43**.

As expected, all four experiments gave identical results within the margin of error (Figure 2.8). The reaction setup followed the general screening protocol (Scheme 2.13). A 1:1 mixture of Et- and ^{i}Pr-substituted quasienantiomers **44d** and **44e** and a catalyst (10 mol%) in a

1:9 CH_2Cl_2/EtOH mixture was stirred for 5 minutes at room temperature, then diluted with MeCN catalyst concentration of *ca*. 10^{-5} M and analyzed by ESI-MS. The spectra were collected as centroids. The signals of the iminium derivatives of the Michael adducts **90** and **91** and the *retro*-Michael products **92** (*m/z* = 740) and **93** (*m/z* = 754) were clearly visible in the spectra (Figure 2.8, only **92** and **93** are shown).

Due to the fact that the reaction is reversible, it is important to take samples after a short time, as longer reaction times result in racemization of the quasienantiomeric Michael adducts. In the *retro*-Michael reaction of quasienantiomers (*R*)-**44d**/(*S*)-**44e** and catalyst (*S*)-**46c**, the detected ratio of intermediates **94**/**95** after 5 minutes was 97:3, but after 17 h a ratio of 90:10 was observed (Figure 2.9).

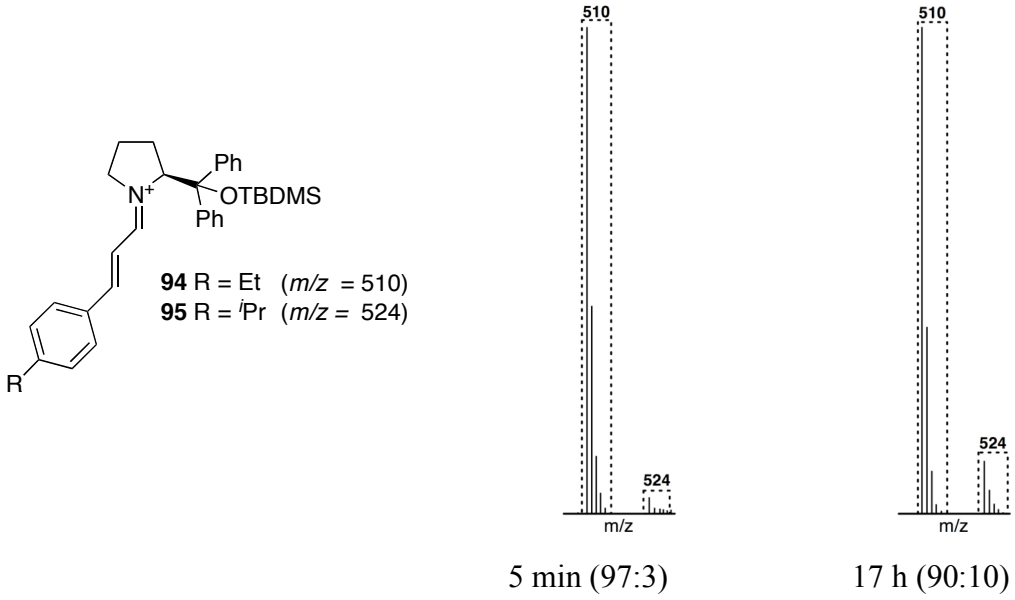
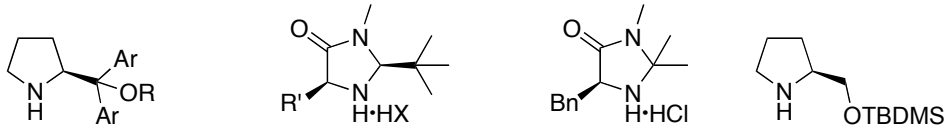


Figure 2.9. ESI-MS spectra of the *retro*-Michael addition of (*R*)-**44d**/(*S*)-**44e** with catalyst (*S*)-**46c** after 5 minutes and 17 hours.

2.4.3 Results of ESI-MS Screening

Following the general screening protocol, different either synthesized or commercially available catalysts (Figure 2.10) were subjected to ESI-MS screening with both quasienantiomeric pairs. The results were further validated by comparison with the preparative forward reaction under the same conditions (Table 2.1, column A). The enantioselectivity in the forward reaction was determined by HPLC. It was important to perform the reaction at RT, in an EtOH/DCM 9:1 mixture with equimolar amounts of

aldehyde and malonate. The reaction was interrupted after 2 hours to avoid racemization of the product. Preparative reactions were also carried out at 0 °C (Table 2.1, column B), and under these conditions, enantiomeric ratios of ≥99:1 were obtained with catalysts **46c** and **46d**[69], which were also identified as the most selective catalysts in the ESI-MS screening. Once again, both enantiomers of catalysts **46c** were tested, and, as expected, similar results were obtained. No intermediates were observed in the reaction with catalysts **81** and (*S*)-proline, possibly due to the formation of an inactive charge-neutral cyclic species. The spectra obtained from the imidazolidinone catalyst class (**96a**, **96b** and **41a**)[20, 73] were very complex, and the signals of intermediates were either low or not observed. Possibly, the strong acid was responsible for their low activity.



43 Ar = 3,5-$(CF_3)_2C_6H_3$ R = TMS
46a Ar = Ph R = TMS
46b Ar = Ph R = TES
46c Ar = Ph R = TBDMS
46d Ar = Ph R = TIPS
81 Ar = Ph R = H

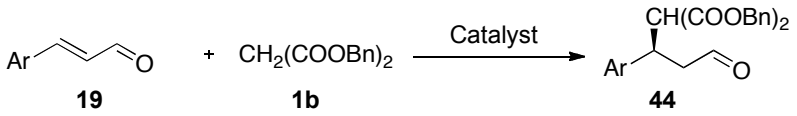
96a X = Cl R' = Bn
96b X = CF_3COO R' = H

41a

84

Figure 2.10. Organocatalysts for ESI-MS screening.

Table 2.1. Screening of organocatalysts.



19 **1b** **44**

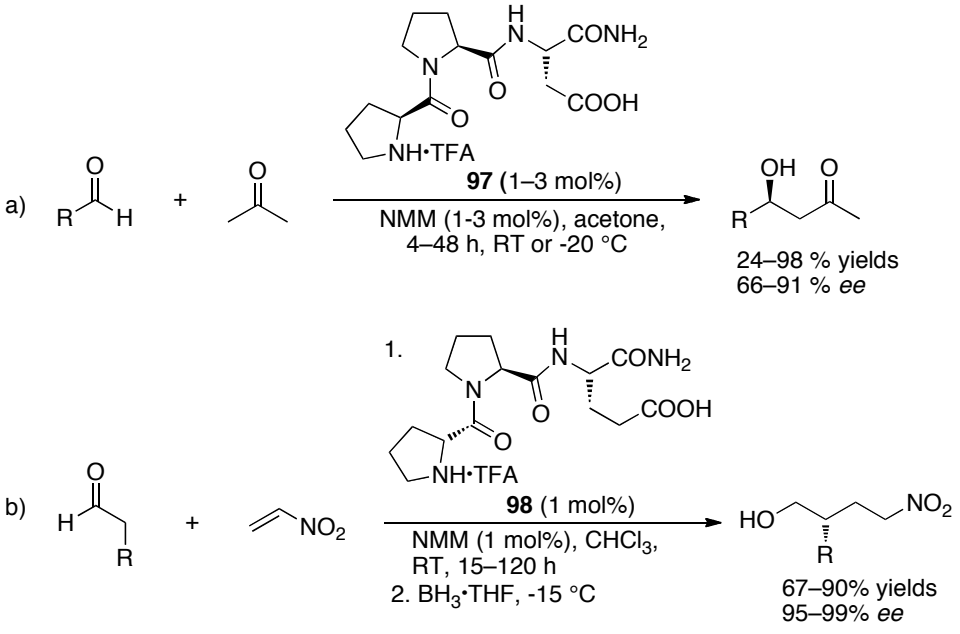
Entry	Catalyst	ESI-MS Screening		*e.r.* (prep. reaction)	
		(*R*)-44d/(*S*)-44e	(*S*)-44d/(*R*)-44e	A[a,f]	B[b,f]
1	(*S*)-**43**	90:10	10:90	90:10	95:5
2	(*R*)-**43**	11:89	89:11	nd[g]	95:5
3	(*S*)-**46a**	93:7	7:93	93:7	96:4
4	(*S*)-**46b**	94:6	6:94	95:5	96:4
5	(*S*)-**46c**	97:3	4:96	97:3	99:1
6	(*R*)-**46c**	3:97	97:3	nd[g]	1:99
7	(*S*)-**46d**	96:4	3:97	97:3	99.5:0.5
8	(*S*)-**84**	59:41	40:60	62:38	nd[g]
9	(*S*)-**81**	nr[c,d]	nr[c,d]	nr[c]	nd[g]

Entry	Catalyst	ESI-MS Screening		*e.r.* (prep. reaction)	
		(*R*)-44d/(*S*)-44e	(*S*)-44d/(*R*)-44e	A[a,f]	B[b,f]
10	(*S*)-proline	nr[c,d]	nd[g]	nd[g]	nd[g]
11	(2*S*,5*S*)-**96a**	66:34[e]	nd[g]	nd[g]	nd[g]
12	(*S*)-**41a**	68:32[e]	nd[g]	nd[g]	nd[g]
13	(*S*)-**96b**	nr[c,d]	nd[g]	nd[g]	nd[g]

[a]Performed with **19b** (Ar = 4-Et-Ph) and **19c** in EtOH/DCM 9:1 at RT, stopped after 2 h. [b]Performed with **19b** (Ar = 4-Et-Ph) and **19c** in EtOH at 0 °C. [c]No reaction. [d]No intermediates observed. [e]Very low intensity. [f]Determined by chiral-stationary-phase HPLC. [g]Not determined.

2.4.4 Screening of Small Oligopeptides

Oligopeptides represent an important class of organocatalysts[74, 75], which have found widespread use, particulary in reactions proceeding *via* enamine activation. The group of H. WENNEMERS has found very efficient applications of tripeptides (**97a** and **97b**) in aldol reactions and 1,4-additions of aldehydes to nitroolefins (Scheme 2.24).[75] With these catalysts, only low loading (0.1–1 mol%) is necessary to achieve high yields and selectivites.

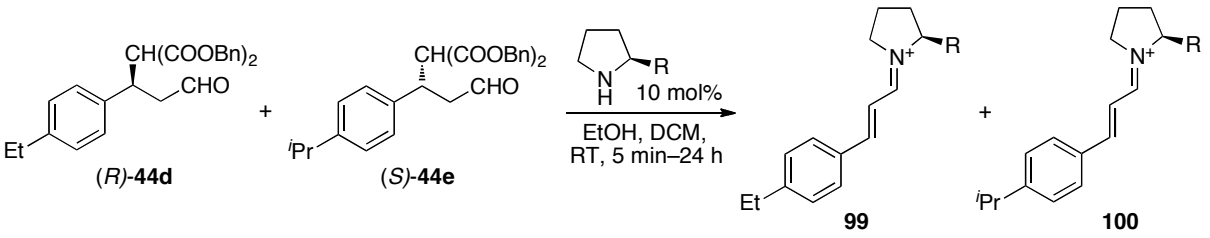


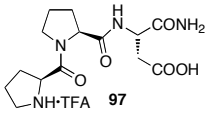
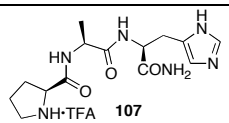
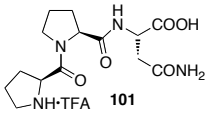
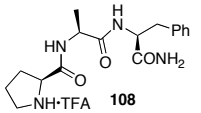
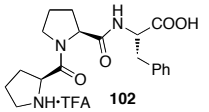
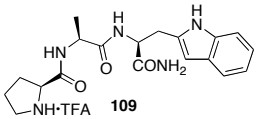
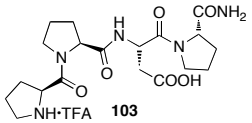
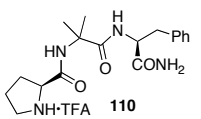
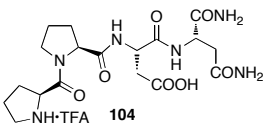
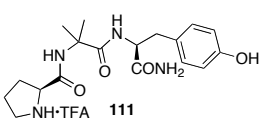
Scheme 2.24. Selected examples for the use of small tripeptides in organocatalysis: a) In an aldol reaction; b) In a 1,4-addition of aldehydes to nitroethene.[75]

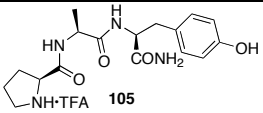
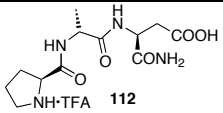
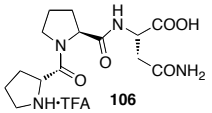
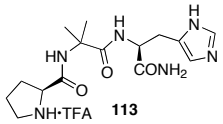
Due to the presence of a pyrrolidine moiety, it should be possible to use these tripeptides in the Michael addition of malonates to unsaturated aldehydes. ESI-MS screening could be a very useful tool for finding a selective catalyst out of the oligopeptide library that can be synthesized in a straightforward fashion. The ESI-MS screening of tripeptides in Diels-Alder reactions has already been successfully performed by A. TEICHERT.[76]

Following the general screening protocol, 14 tri- and tetrapeptides were subjected to an ESI-MS screen with (*S*)-**44d**/(*R*)-**44e** (Table 2.2). All catalysts were used as HCl or TFA salts. Most catalysts demonstrated low activity in the *retro*-Michael addition. The signals of iminium intermediates **99** and **100** were either very low or absent after 5 minutes. After 24 h, the intensity rose slightly, but the measured ratio of intermediates was different from that measured after 5 minutes, possibly due to racemization.

Table 2.2. ESI-MS screening of tripeptides.[a]



Catalyst	ESI-MS (*R*)-44d/(*S*)-44e	Catalyst	ESI-MS (*R*)-44d/(*S*)-44e
 **97**	25:75[b] 38:62[d]	 **107**	nr[c]
 **101**	39:61[b] 43:57[d]	 **108**	23:77
 **102**	83:17	 **109**	nr[c]
 **103**	53:47[c,d]	 **110**	23:77
 **104**	49:51[c,d]	 **111**	26:74[b]

Catalyst	ESI-MS (*R*)-44d/(*S*)-44e	Catalyst	ESI-MS (*R*)-44d/(*S*)-44e
 **105**	27:73[b]	 **112**	33:67[b]
 **106**	nr[c]	 **113**	nr[c]

[a]Performed with (*R*)-**44d,** (*S*)-**44e** and catalyst (10 mol%) in EtOH/DCM 9:1 at RT. [b]Very low intensity after 5 minutes. [c]No reaction; no intermediates after 5 minutes. [d]After 24 hours.

Only peptides bearing a phenylalanine unit (**102**, **108** and **110**) showed significant activity. The intermediates of these catalysts could be detected after 5 minutes, and the signals had satisfactory intensity, although they were not as high as those obtained from silyl prolinol-derived catalysts. In the ESI-MS spectrum of the *retro*-Michael reaction catalyzed by **102** the iminium intermediate **114** (*m/z* = 502, *m/z* (**115**) = 516) signal was the most intense (Figure 2.11). The signals of protonated catalyst **102** (*m/z* = 360) and its sodium adduct (*m/z* = 382) appeared in the spectrum as well, together with several signals assigned to quasienantiomers (*m/z* = 467/481, 513/527). The appearance of the signals of these species is an indicator for lower catalytic activity.

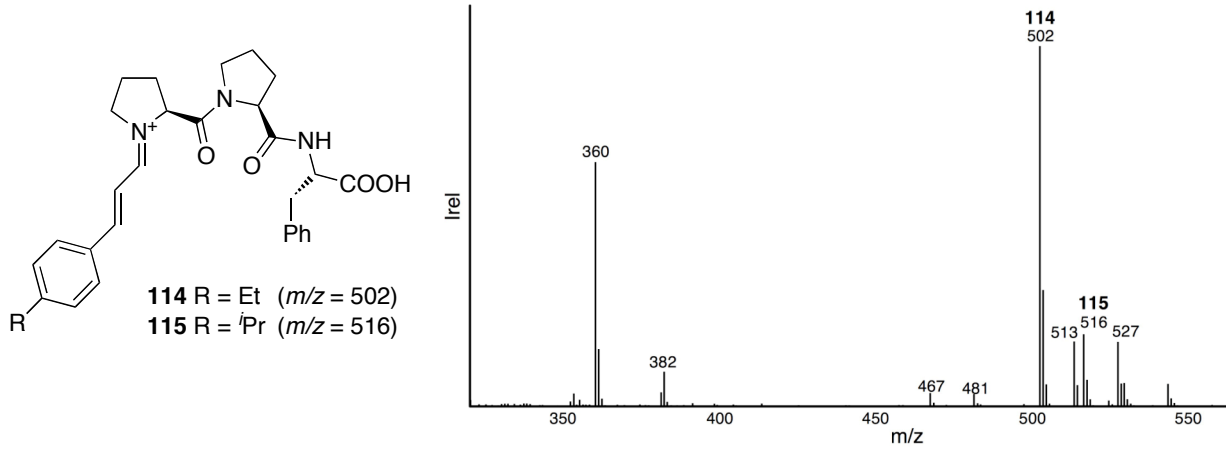


Figure 2.11. ESI-MS spectrum of the *retro*-Michael reaction of quasienantiomeric pair (*R*)-**44d**/(*S*)-**44e** with catalyst **102**.

Interestingly, the central amino acid of the tripeptide seems to have a strong impact on the selectivity. Catalyst **102** with (*S*)-proline as the central amino acid gave the opposite ratio of intermediate intensities than **108** with (S)-alanine and **110** with 2-methylalanine. Another structural difference is the terminal acid in **102** and amide in **108** and **110**.

The selectivity of 14 tripeptides could be expeditiously examined by ESI-MS. Although the activity and selectivity of these catalysts were lower compared to silyl prolinol derived catalysts, it was shown that the ESI-MS screening method is, in principle, applicable to this catalyst class.

2.4.5 Conclusions

A convenient screening method for enantioselective organocatalysts based on the monitoring of reaction intermediates in the *retro*-Michael addition was developed. We could show, that Et- and ^{i}Pr- are appropriate mass labels for quasienantiomers. A validation using four combinations of quasienantiomeric Michael adducts and both catalyst enantiomers was conducted.

Using this method, several catalysts were subjected to ESI-MS screening. The most selective catalysts could be easily identified without time-consuming analysis and purification of reaction products.

The methodology was extented to a library of peptidic organocatalysts from the group of H. WENNEMERS. In the screening it was found that only tripeptides bearing a phenylalanine unit show sufficient activity in the *retro*-Michael addition. The selectivity of these catalysts demonstrated an interesting structural dependence, which should be closer investigated in the future.

In conlusion, the experiments demonstrated that this screening method is applicable to different kinds of catalysts and organocatalyzed reactions. The extension of this methodology to enamine catalysis should be possible and is currently being investigated in our group.

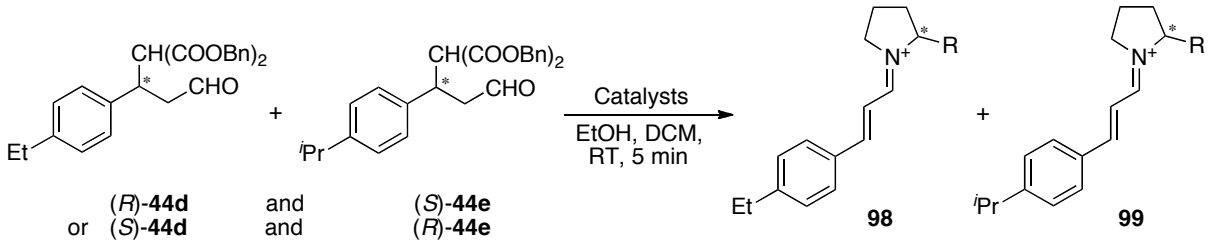
2.5 Screening of Catalyst Mixtures

2.5.1 Preliminary Results

An advantage of the screening of catalyst mixtures is the possibility to determine the selectivity of several catalysts at once by performing just one reaction and one analysis. The requirements for multi-catalyst screening are:

1. The catalysts in the mixture should have similar activity in the *retro*-reaction.
2. The main isotope signals of catalysts and intermediates must not overlap.

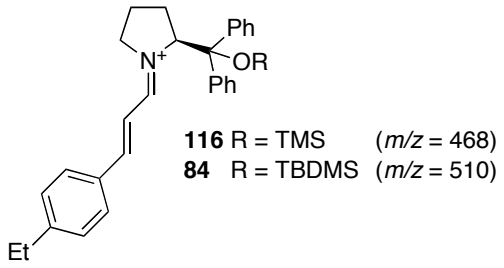
The same screening protocol as for the single catalysts was applied. In a screening of y (y = 1, 2, 3…) catalysts, 10/y mol% of each catalyst were used (Scheme 2.25). In some cases it was necessary to use more concentrated samples for the clean detection of all intermediates.



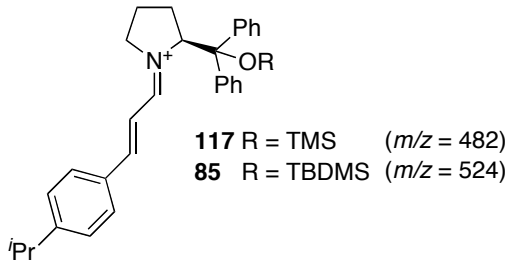
Scheme 2.25. Screening of catalyst mixtures with both pairs of quasienantiomers.

The first test experiments were carried out with catalysts (*S*)-**46a** and (*S*)-**46c**, which have similar selectivity. All iminium intermediates were detected (Figure 2.12a) and the selectivity of each catalyst was determined. These results corresponded to those from the single catalyst screening (values in parentheses). Inversely labeled quasienantiomers gave inverted ratios of intermediates (Figure 2.12b).

Next, catalysts (*S*)-**46c** and (*S*)-**84** with different selectivities were subjected to the screening with both quasienantiomeric pairs (Figure 2.13). Again, good agreement with the results from the single catalyst screens was obtained.



a) (*R*)-**44d**/(*S*)-**44e**



b) (*S*)-**44d**/(*R*)-**44e**

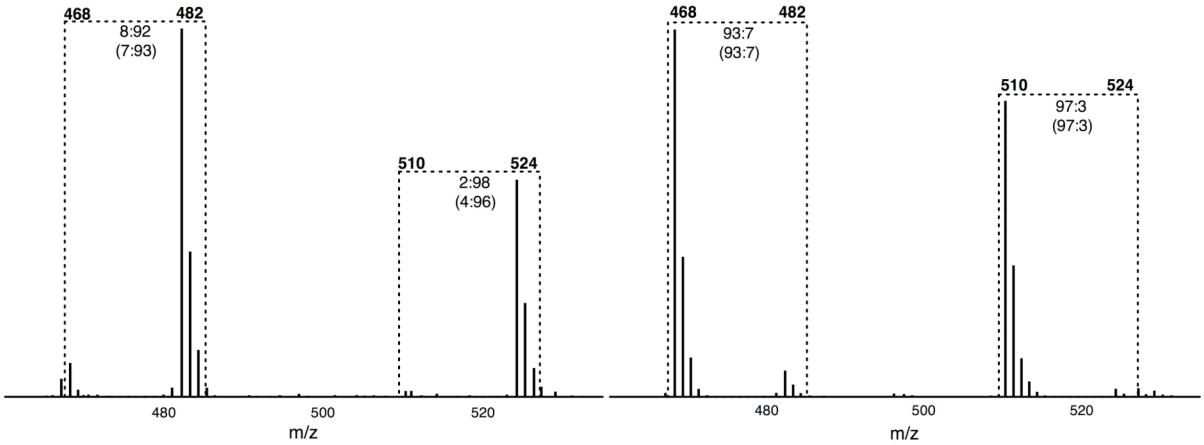
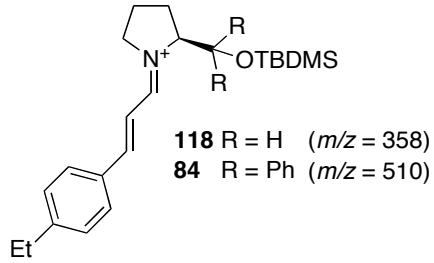
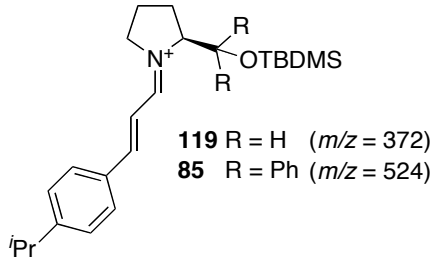


Figure 2.12. ESI-MS screening of organocatalysts (*S*)-**46a**, (*S*)-**46c** with: a) (*R*)-**44d**/(*S*)-**44e**; b) (*S*)-**44d**/(*R*)-**44d**. The ratios for single catalyst screenings are given in parentheses.



a) (*R*)-**44d**/(*S*)-**44e**



b) (*S*)-**44d**/(*R*)-**44e**

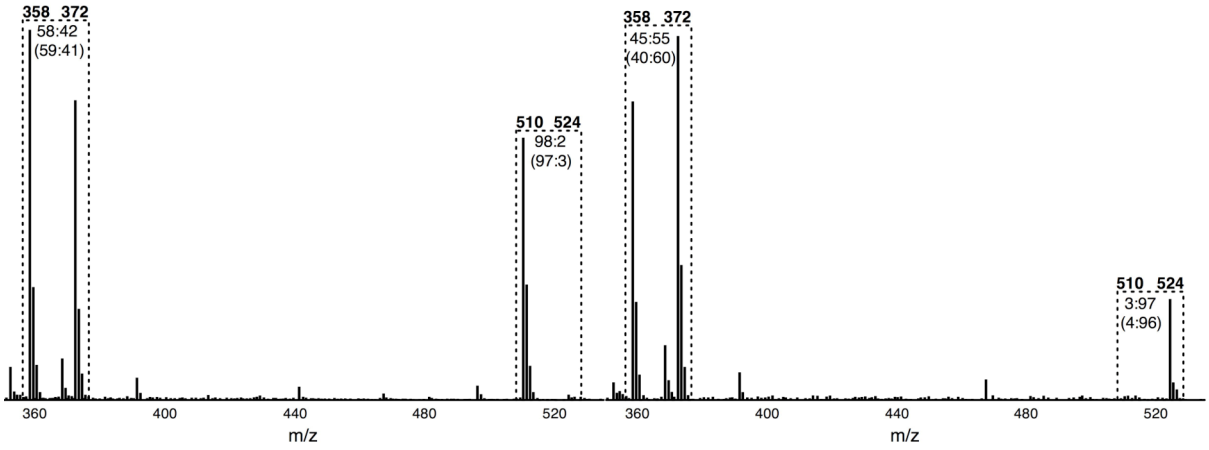
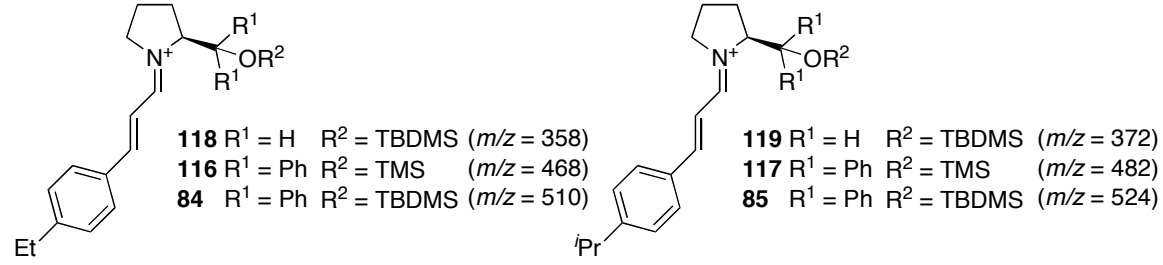


Figure 2.13. ESI-MS screening of organocatalysts (*S*)-**46c**, (*S*)-**84** with: a) (*R*)-**44d**/(*S*)-**44e**; b) (*S*)-**44d**/(*R*)-**44d**. The ratios for single catalyst screenings are given in parentheses.

2.5.2 Screening of Mixtures of Three and Four Catalysts

With promising preliminary results in hand, simultaneous screening of three catalysts was conducted. As anticipated, the results from screening with quasienantiomers (*R*)-**44d**/(*S*)-**44e** were comparable to those from the single catalyst screens (Figure 2.14a), whereas screening with (*S*)-**44d**/(*R*)-**44e** deviated slightly from the single catalyst screens. The signal ratios of intermediates of catalysts (*S*)-**46a** and (*S*)-**46c** matched to those of single catalyst screening. However, catalyst (*S*)-**84** gave with quasienantiomers (*S*)-**44d**/(*R*)-**44e** ratio inverted to the expected one.



(*R*)-**44d**/(*S*)-**44e** b) (*S*)-**44d**/(*R*)-**44e**

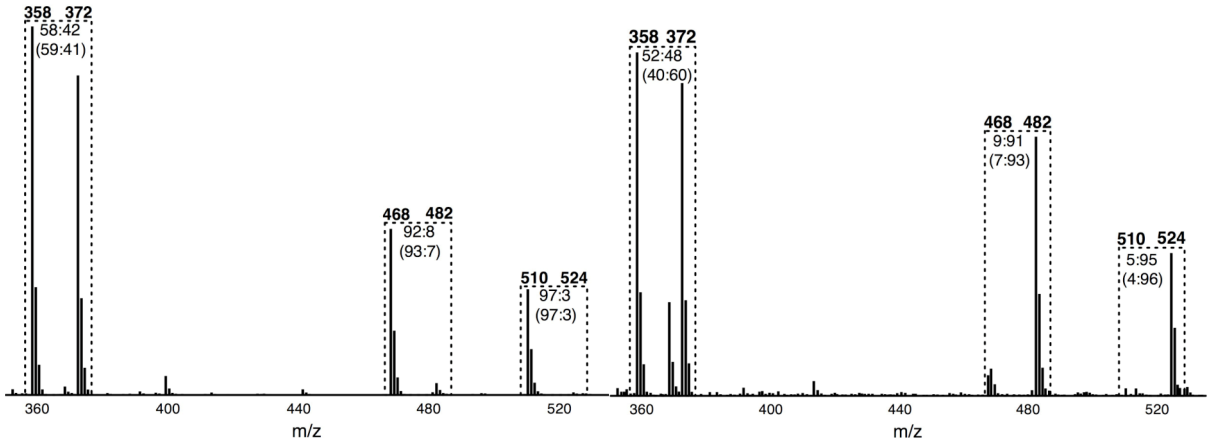
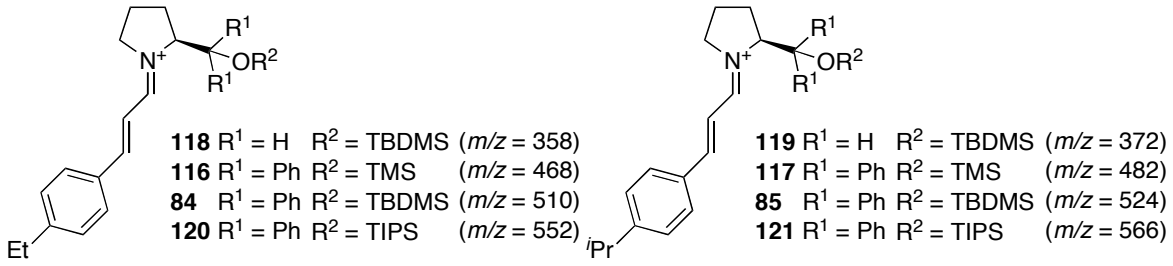
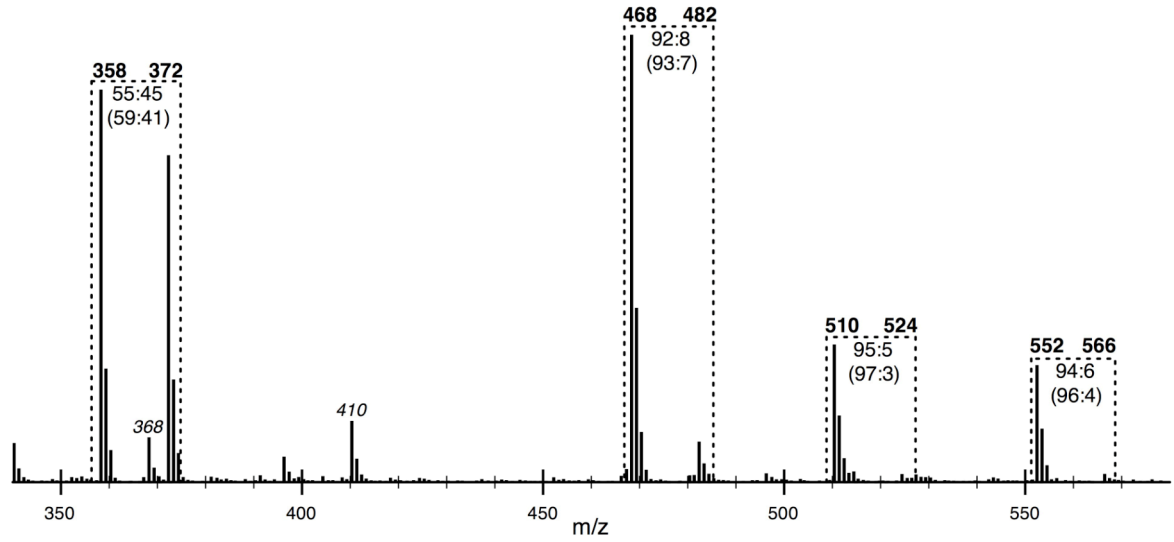


Figure 2.14. ESI-MS screening of three organocatalysts (*S*)-**46a**, (*S*)-**46c** and (*S*)-**84** with: a) (*R*)-**44d**/(*S*)-**44e**; b) (*S*)-**44d**/(*R*)-**44e**. The ratios for single catalyst screenings are given in parentheses.

A similar situation was observed in the screening of four catalysts (Figure 2.15). The ratios of intermediate signals did not perfectly match the results from the single catalyst screens, but nevertheless, the most and least selective catalysts could be easily identified. The signal at *m/z* = 368 corresponds to the mass of protonated (*S*)-**46c**, the signal at *m/z* = 410 to the protonated (*S*)-**46d**.



a) (*R*)-**44d**/(*S*)-**44e**



b) (*S*)-**44d**/(*R*)-**44e**

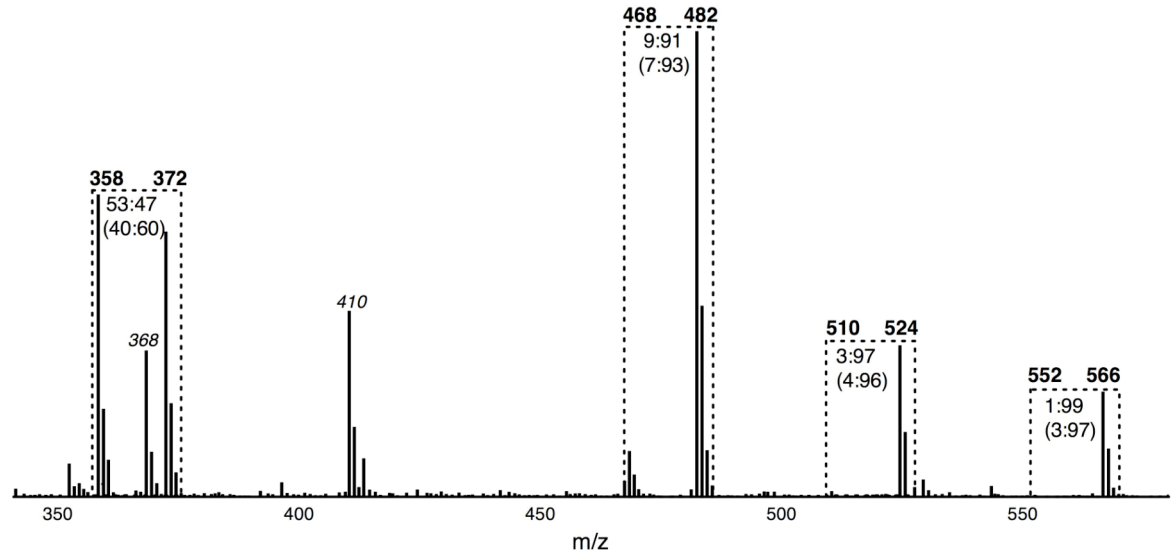
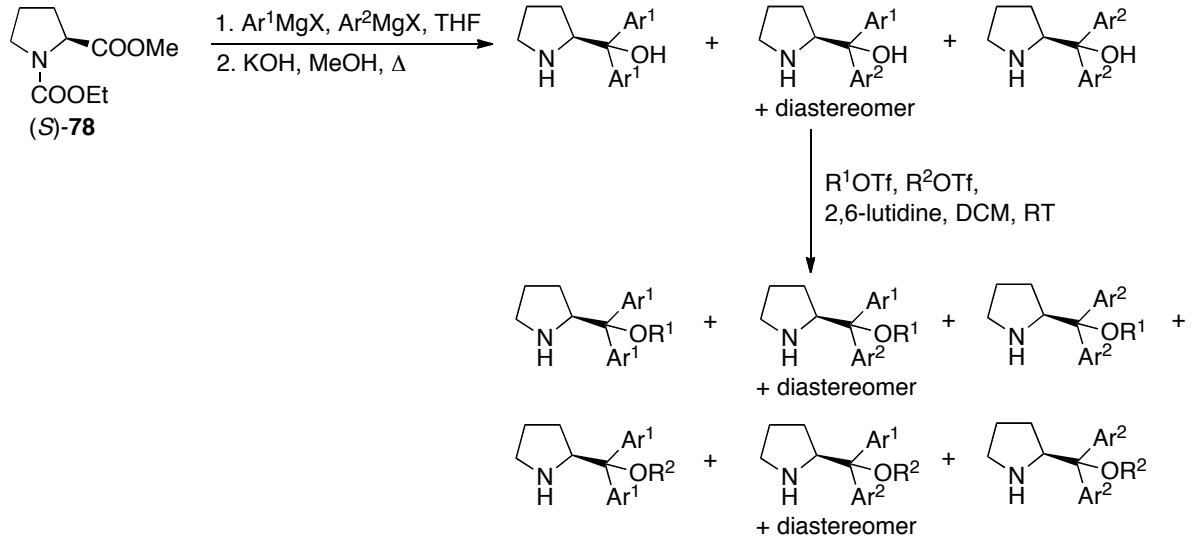


Figure 2.15. ESI-MS screening of four organocatalysts (*S*)-**46a**, **(***S*)-**46c**, (*S*)-**46d** and (*S*)-**84** with: a) (*R*)-**44d**/(*S*)-**44e**; b) (*S*)-**44d**/(*R*)-**44e**. The ratios for single catalyst screenings are given in parentheses.

2.5.3 Screening of One-Batch Catalyst Mixtures

It could be shown in previous experiments that the screening and analysis of multiple catalysts in one reaction is possible. However, every catalyst must be synthesized individually. Much more efficient would be the screening of a catalyst mixture that has been prepared in one batch, as recently shown by MARKERT and RÖSEL.[64]

A simple and well established synthetic route for the preparation of a small library of diarylprolinol silyl ethers was envisioned (Scheme 2.26).[69, 71] Such a synthesis, with two Grignard reagents and two silylation agents, would lead to a mixture of six catalysts, two of them being diastereomeric mixtures. The reagents must have similar reactivity and different mass, so that intermediate signals do not overlap.

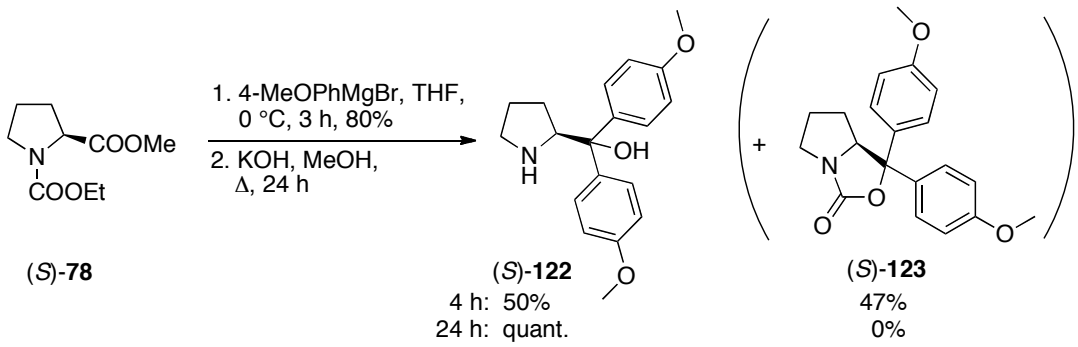


Scheme 2.26. Envisioned synthesis of a mixture of catalysts.

F. HOFMANN investigated the possible use of either two silylating agents or two Grignard reagents during her *Wahlpraktikum.*

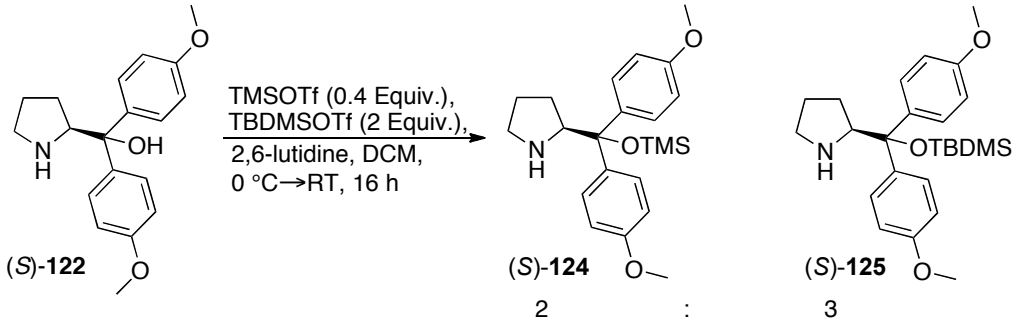
2.5.3.1 In situ Synthesis of a Catalyst Mixture with Two Different Silylating Reagents

TMSOTf and TBDMSOTf were chosen as test silylating agents due to their adequate difference in mass and steric bulk. Amino alcohol (*S*)-**122** was prepared from protected prolinate (*S*)-**78** by a known reaction sequence in high overall yield (Scheme 2.27).[71] The second step required a long reaction time (24 h), to avoid a mixture of amino alcohol (*S*)-**122** and bicylic compound (*S*)-**123** (4 h).



Scheme 2.27. Synthesis of aminoalcohol (*S*)-**122**.

Amino alcohol (*S*)-**122** was treated with an excess of TMSOTf (2.5 Equiv.) and TBDMSOTf (2.5 Equiv.). Only TMS-silylated product (*S*)-**124** was formed, due to the higher reactivity of TMSOTf. The use of an equimolar amount of TMSOTf (1 Equiv.) and an excess of TBDMSOTf (4 Equiv.) led to 96:4 mixture of (*S*)-**124**/(*S*)-**125**, which was not suitable for the screening. Finally, both catalysts could be synthesized as a 2:3 mixture when using only 0.4 equivalents of TMSOTf and excess of TBDMSOTf (2 Equiv., Scheme 2.28). The crude mixture was directly used in the screening.



Scheme 2.28. Synthesis of catalyst mixture (*S*)-**124**/(*S*)-**125**.

The mixture (*S*)-**124**/(*S*)-**125** was subjected to the *retro*-Michael reaction with quasienantiomeric pair (*R*)-**44d**/(*S*)-**44e**. Despite impurities present in the catalyst mixture, the intermediates could be detected and the selectivity of both catalysts determined (Figure 2.16). As expected, the catalyst with the more bulky silyl group (*S*)-**125** was more selective in the screening.

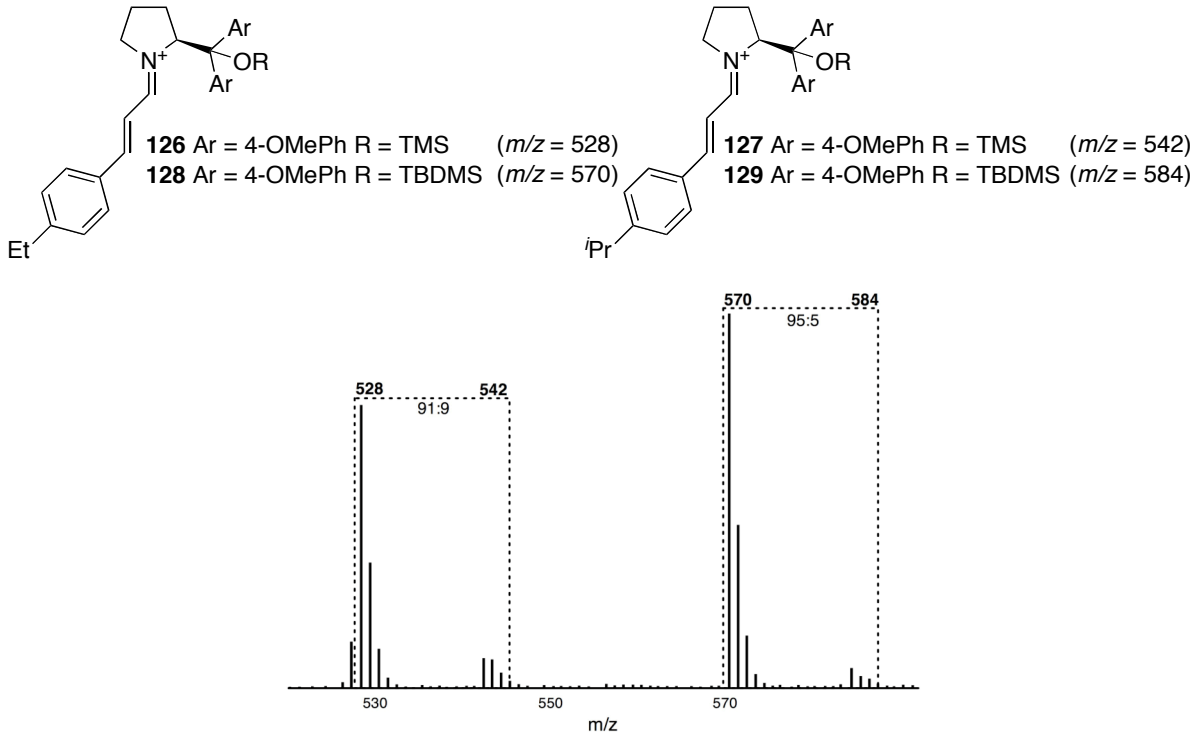
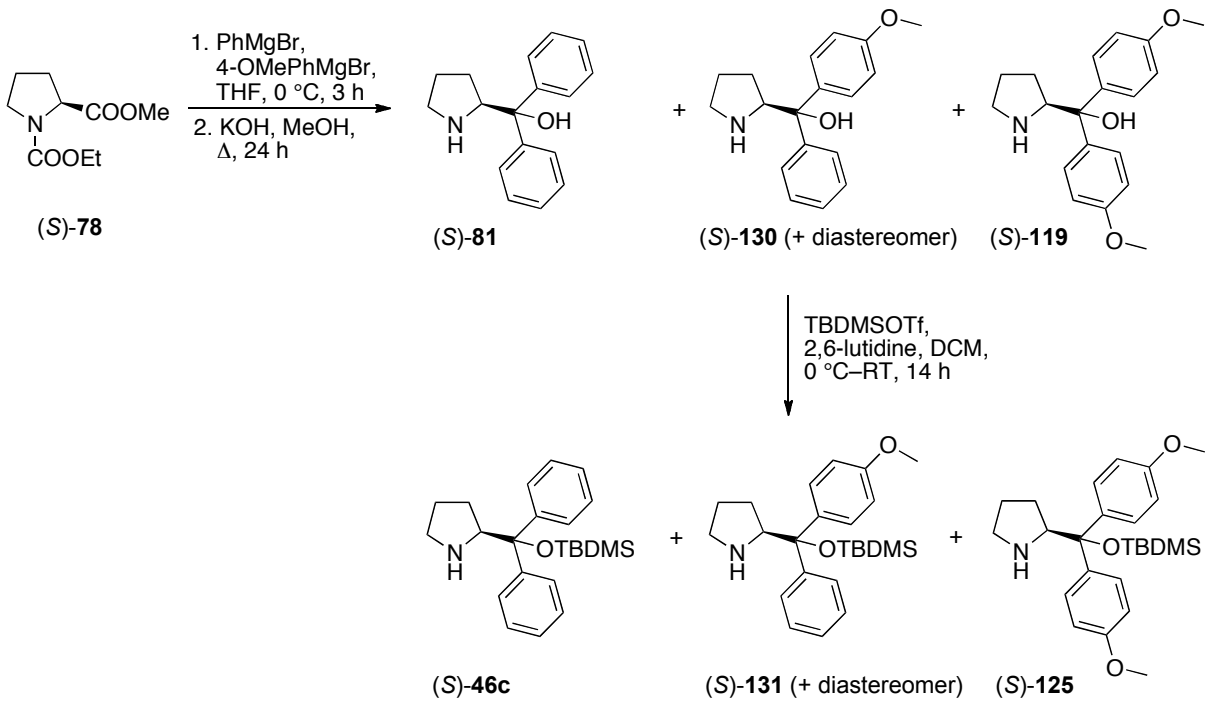


Figure 2.16. ESI-MS screening of catalyst mixture (*S*)-**124**/(*S*)-**125** with quasienantiomeric adducts (*R*)-**44d**/(*S*)-**44e.**

2.5.3.2 In situ Synthesis of a Catalyst Mixture with Two Different Grignard Reagents

Similar reactivity of phenyl- and *p*-methoxyphenyl magnesium bromide in the Grignard addition was expected. Moreover, the difference in the mass of the reagents is 30, which is sufficient and not too high for the screening. Reaction with a 1:1 mixture of Grignard reagents led to a mixture of alcohols, which was subjected to hydrolysis in refluxing KOH solution to remove the *N*-protecting group (Scheme 2.29). It was important to mix the Grignard reagents in an addition funnel, as only a small amount of the mixed alcohol (*S*)-**130** was otherwise formed. The resulting crude mixture of pyrrolidine derivatives was treated with TBDMSOTf to give the mixture (*S*)-**46c**/(*S*)-**131**/(*S*)-**125**. (*S*)-**131** was probably obtained as a diastereomeric mixture. The stereogenic centre at the quartenary carbon should not have much impact on the selectivity of the catalyst.

ESI-MS screening was directly performed on the crude mixture of catalysts (Figure 2.17). All intermediates were readily identified and the selectivity of each catalyst was determined. It appears that all three catalysts have similar selectivity.



Scheme 2.29. Synthesis of catalyst mixture (*S*)-**46c**/(*S*)-**131**/(*S*)-**125**.

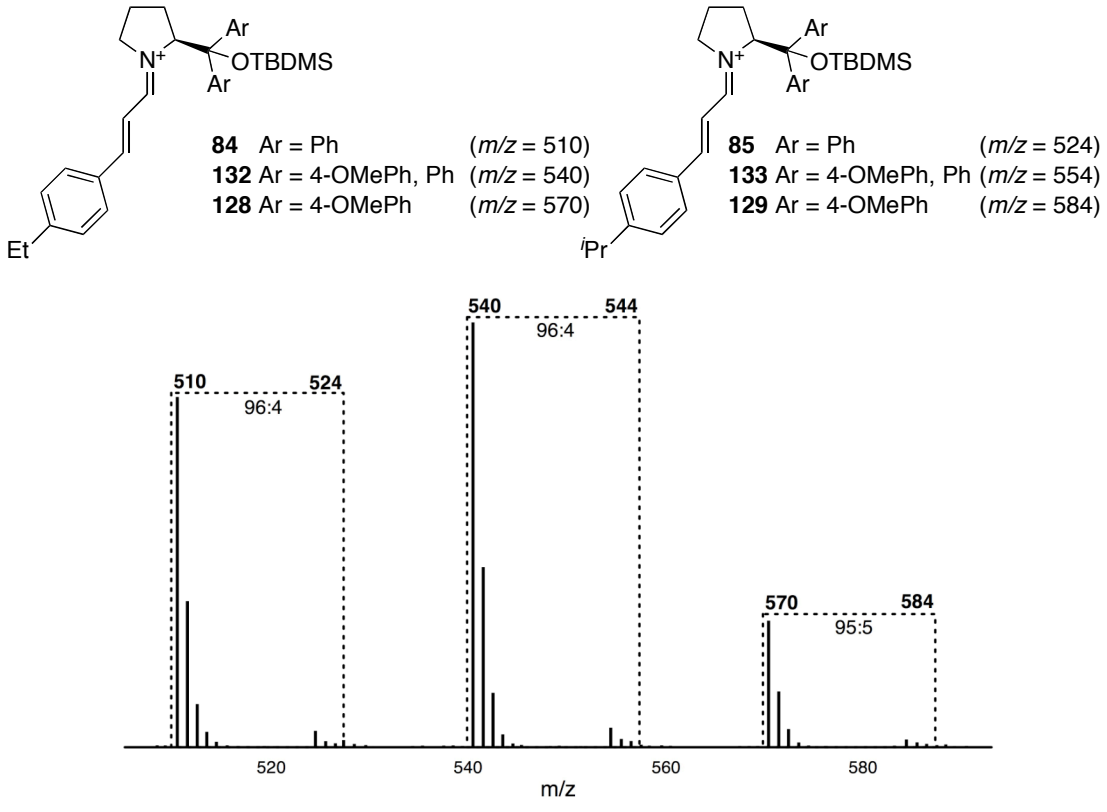
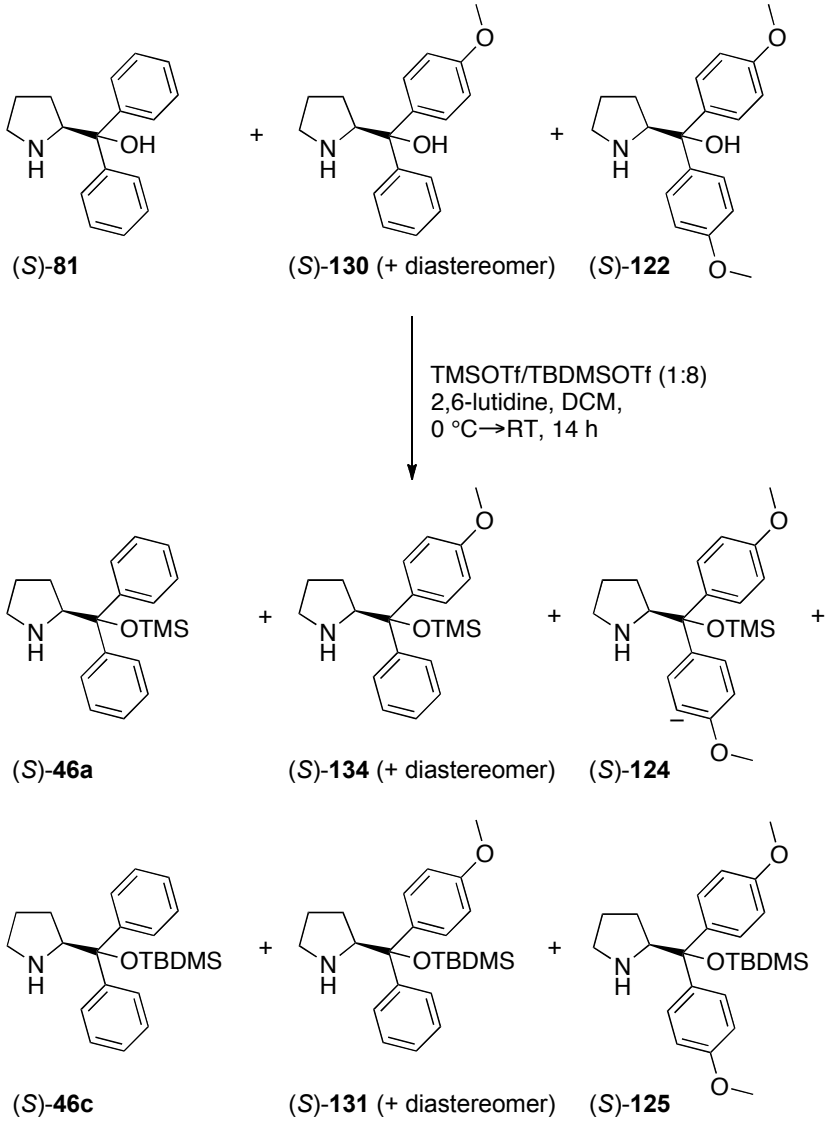


Figure 2.17. ESI-MS screening of catalyst mixture (*S*)-**46c**/(*S*)-**131**/(*S*)-**125** with quasienantiomeric adducts (*R*)-**44d**/(*S*)-**44e.**

2.5.3.3 Synthesis and Screening of Mixture of Six Catalysts

Having found appropriate conditions for Grignard addition and silylation with two reagents, a small library of six catalysts was synthesized. The crude mixture of amino alcohols (*S*)-**81**/(*S*)-**130**/(*S*)-**122** was treated with a 1:8 mixture of TMSOTf and TBDMSOTf. The latter was used in excess to account for its lower reactivity (Scheme 2.30). Several trials were necessary to find the appropriate ratio of silylating agents because the amount of amino alcohols (*S*)-**81**/(*S*)-**130**/(*S*)-**122** in the crude mixture was only estimated. A mixture of only TMS-substituted catalysts (*S*)-**46a**/(*S*)-**134**/(*S*)-**124** was obtained with 1:8 mixture of TMSOTf and TBDMSOTf. After aqueous workup, ESI-MS screening was performed directly on both crude catalysts mixtures.



Scheme 2.30. Synthesis of catalyst mixture (*S*)-**46a**/(2*S*)-**134**/(*S*)-**124**/(*S*)-**46c**/(2*S*)-**131**/(*S*)-**125**.

The ESI-MS screening of the mixture (*S*)-**46a**/(2*S*)-**134**/(*S*)-**124** has revealed (2*S*)-**134**, as a mixture of diastereomers, to be the most selective catalyst (Figure 2.18).

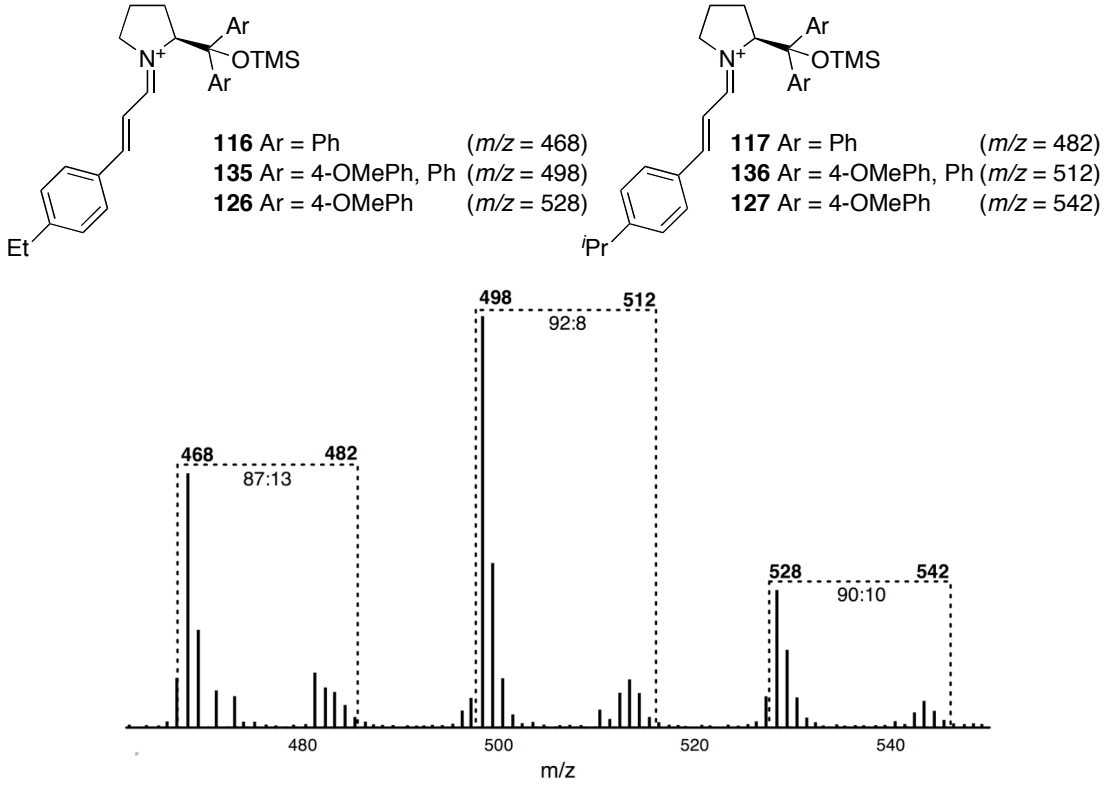
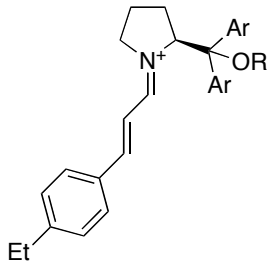
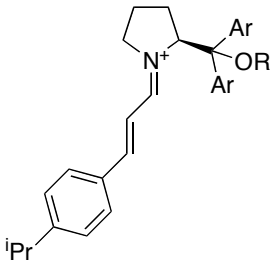


Figure 2.18. ESI-MS screening of catalyst mixture (*S*)-**46a**/(2*S*)-**134**/(*S*)-**124** with quasienantiomeric adducts (*R*)-**44d**/(*S*)-**44e.**

The intermediates derived from the six catalysts were all readily identified in the spectrum (Figure 2.19). Although the accuracy was somewhat lower than in single catalyst screens due to signal overlap and interfering signals from impurities, the selectivity order of the six catalysts could be unambigously established. The most selective catalyst in this series was (*S*)-**46c** with an enantiomeric ratio of 97:3, which was identical to the value determined in the single catalyst screen.





116 Ar = Ph R = TMS (*m/z* = 468)
135 Ar = 4-OMePh, Ph R = TMS (*m/z* = 498)
84 Ar = Ph R = TBDMS (*m/z* = 510)
126 Ar = 4-OMePh R = TMS (*m/z* = 528)
132 Ar = 4-OMePh, Ph R = TBDMS (*m/z* = 540)
128 Ar = 4-OMePh R = TBDMS (*m/z* = 570)

117 Ar = Ph R = TMS (*m/z* = 482)
136 Ar = 4-OMePh, Ph R = TMS (*m/z* = 512)
85 Ar = Ph R = TBDMS (*m/z* = 524)
127 Ar = 4-OMePh R = TMS (*m/z* = 542)
133 Ar = 4-OMePh, Ph R = TBDMS (*m/z* = 554)
129 Ar = 4-OMePh R = TBDMS (*m/z* = 584)

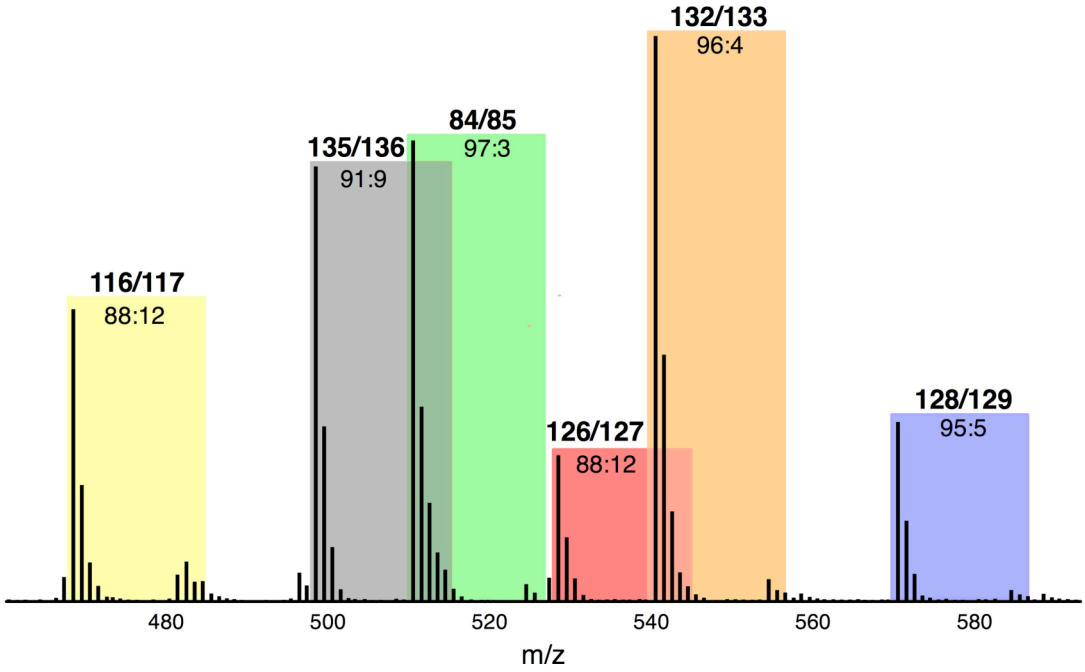
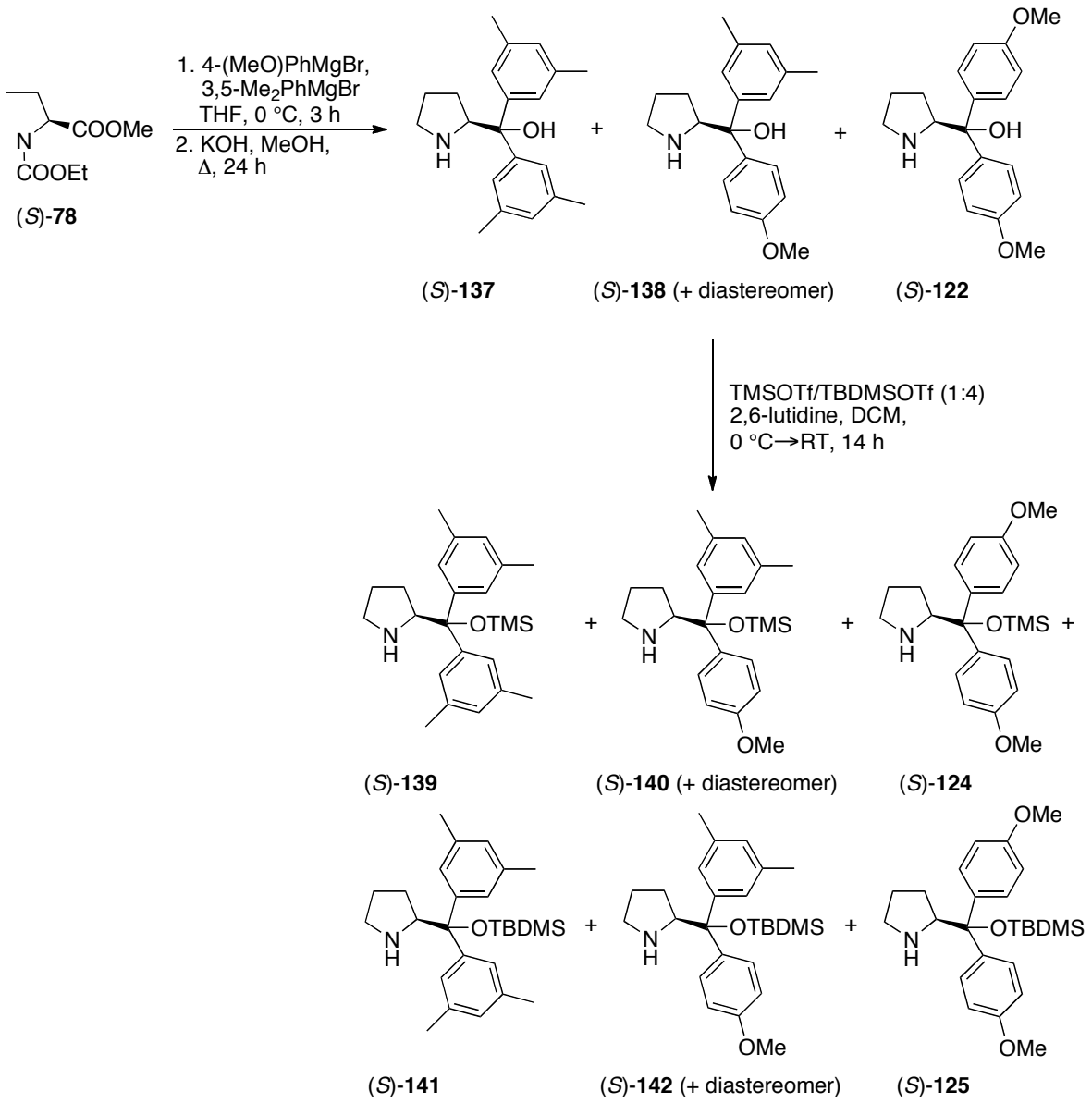


Figure 2.19. ESI-MS screening of catalyst mixture (*S*)-**46a**/(2*S*)-**134**/(*S*)-**124**/(*S*)-**46c**/(2*S*)-**131**/(*S*)-**125**. with quasienantiomeric adducts (*R*)-**44d**/(*S*)-**44e**.

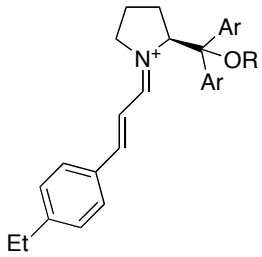
2.5.3.4 Synthesis and Screening of Catalyst Mixture with Small Difference in Mass

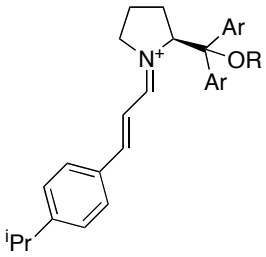
To apply the new methodology to the synthesis of different catalyst mixtures, another mixture of six catalysts (*S*)-**139**/(*S*)-**140**/(*S*)-**124**/(*S*)-**141**/(*S*)-**142**/(*S*)-**125** was synthesized in one batch without purification in any of the three steps (Scheme 2.31).



Scheme 2.31. Synthesis of catalyst mixture (*S*)-**139**/(*S*)-**140**/(*S*)-**124**/(*S*)-**141**/(*S*)-**142**/(*S*)-**125**.

The mixture was subjected to the mass spectrometric screening of the *retro*-Michael reaction. The resulting spectrum was more complicated due to the large overlap in the signals of the intermediates (Figure 2.20). The selectivity of several catalysts was calculated by subtraction of the calculated isotopic pattern from the measured intensity of the signal. The most selective catalysts from the screen are TBDMS-derivatives (*S*)-**141** and (*S*)-**142**. Their selectivity can be compared to the selectivity of catalysts bearing phenyl groups. However, the accuracy of the screening with this mixture is lower due to signal overlap.





143	Ar = 3,5-Me_2Ph	R = TMS	(*m/z* = 524)	**144**	Ar = 3,5-Me_2Ph	R = TMS	(*m/z* = 538)
145	Ar = 4-OMePh, 3,5-Me_2Ph	R = TMS	(*m/z* = 526)	**146**	Ar = 4-OMePh, 3,5-Me_2Ph	R = TMS	(*m/z* = 540)
126	Ar = 4-OMePh	R = TMS	(*m/z* = 528)	**127**	Ar = 4-OMePh	R = TMS	(*m/z* = 542)
147	Ar = 3,5-Me_2Ph	R = TBDMS	(*m/z* = 566)	**148**	Ar = 3,5-Me_2Ph	R = TBDMS	(*m/z* = 580)
149	Ar = 4-OMePh, 3,5-Me_2Ph	R = TBDMS	(*m/z* = 568)	**150**	Ar = 4-OMePh, 3,5-Me_2Ph	R = TBDMS	(*m/z* = 582)
128	Ar = 4-OMePh	R = TBDMS	(*m/z* = 570)	**129**	Ar = 4-OMePh	R = TBDMS	(*m/z* = 584)

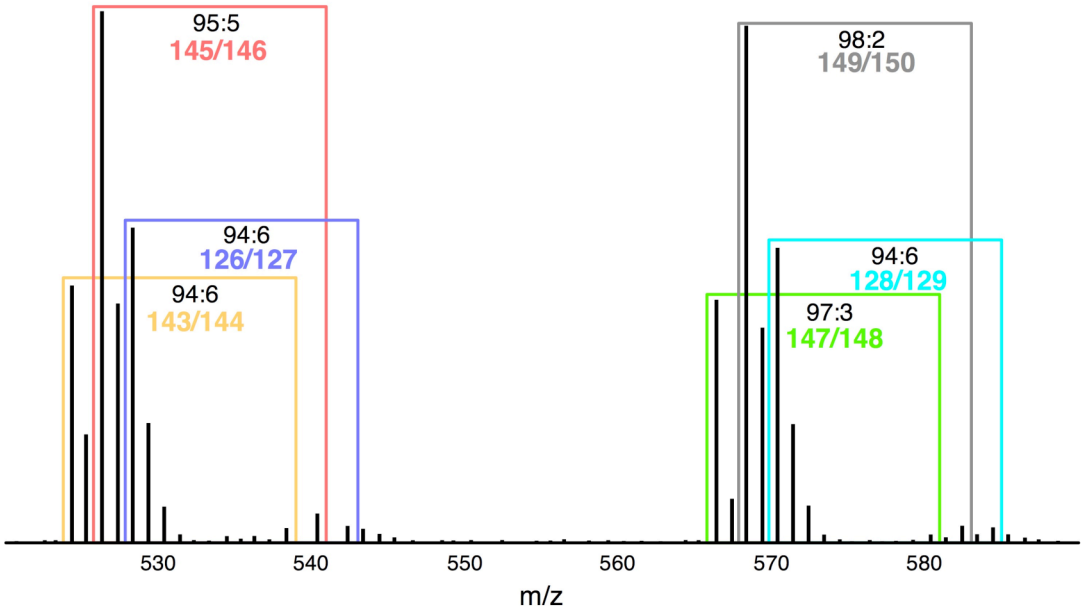
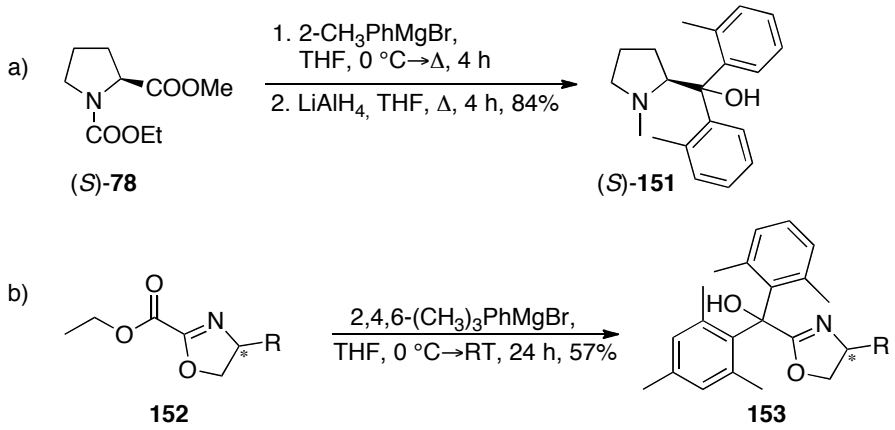


Figure 2.20. ESI-MS screening of catalyst mixture (*S*)-**139**/(*S*)-**140**/(*S*)-**124**/(*S*)-**141**/(*S*)-**142**/(*S*)-**125** with quasienantiomeric adducts (*R*)-**44d**/(*S*)-**44e**.

2.5.3.5 Synthesis and screening of catalyst mixture with bulky aryl groups

To apply the new methodology to the synthesis of different catalyst mixtures, we wanted to test bulky Grignard reagents. Several attempts to prepare a mixture from protected proline and *o*-tolyl- and 2,4,6-trimethylphenylmagnesium bromides using the procedure developed by PERIASAMY[71] were unsuccessful, since very complex mixtures were obtained after Grignard reaction. According to literature, *o*-tolylmagnesium bromide should react with the protected proline methyl ester (*S*)-**78** in refluxing THF (Scheme 2.32a).[77] BOLM successfully applied

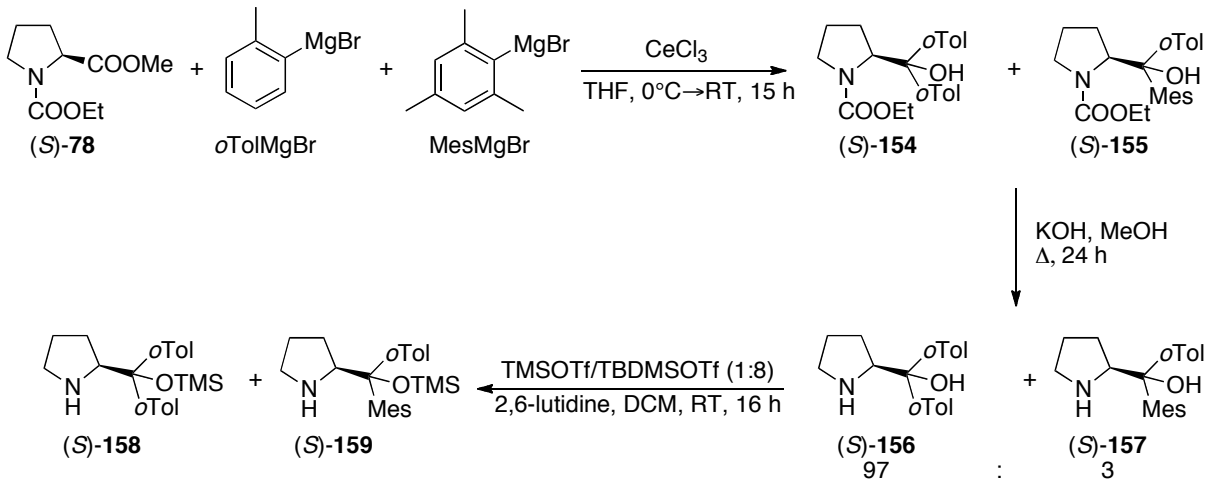
mesitylmagnesium bromide to the synthesis of new oxazoline derivatives in a reaction with ester **152** (Scheme 2.32b).[78]



Scheme 2.32. Literature examples for the use of bulky Grignard reagents for the synthesis of tertiary alcohols: a) Addition of *o*-tolylmagnesium bromide to protected proline (*S*)-**78**.[77] b) Addition of Mesitylmagnesium bromide to oxazoline **152**.[78]

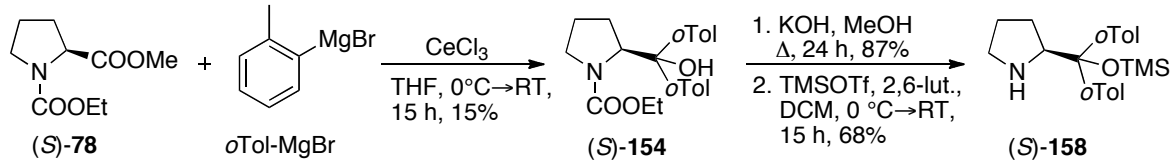
The reaction of protected proline methyl ester (*S*)-**78** and mixtures of Grignard reagents was repeated, following the method of ZHAO.[77] After removal of the protecting group, the ESI-MS analysis showed, that only very low conversion was achieved. Further derivatization and screening were not successful. IMAMOTO has shown, that $CeCl_3$ can accelerate Grignard additions.[79] Indeed, the addition of $CeCl_3$ to the Grignard reagents promoted the reaction, although in low yield, as seen in the reaction with only *o*-tolylmagnesium bromide (15% yield of pure product, monoaddition observed as well). Deprotection afforded the mixture of amino alcohols (*S*)-**156** and (*S*)-**157** (97:3, Scheme 2.33). The dimesityl-substituted product was not detected. The mixture was treated with TMSOTf/TBDMSOTf (1:8), but only TMS-substituted products were obtained (*S*)-**158** and (*S*)-**159**. No product was formed in the reaction with TBDMSOTf, even in high excess.

The crude mixture (*S*)-**158**/(*S*)-**159** was subjected to the mass spectrometric screening of the *retro*-Michael addition, but no intermediates were observed. The reason might be the steric bulk of the catalysts or the high amount of impurities in the mixture.



Scheme 2.33. Synthesis of a catalyst mixture (*S*)-**158**/(*S*)-**159**.

To prove if the catalyst with bulky aryl groups is able to form the intermediates, catalyst (*S*)-**158** was prepared from (*S*)-**78** (Scheme 2.34). In the reaction with *o*TolMgBr, the product of monoaddition (ketone) was identified in the crude reaction mixture as the main product. The tertiary alcohol (*S*)-**156** was isolated in *ca*. 15% yield, and was not entirely pure. The following two steps led to catalyst (*S*)-**158**, which could not be isolated pure. Nevertheless, (*S*)-**158** was used in the Michael addition of dibenzyl malonate to cinnamaldehyde. With 7 mol% of (*S*)-**158**, the Michael addition took place (65% conversion after 5 h at 0 °C, 98% ee). Furthermore, the ESI-MS screening of the *retro*-Michael reaction was carried out. The intermediates were observed, and the obtained enantiomeric ratio was 98:2. Thus, the failure of the *retro*-Michael addition with the mixture was probably caused by impurities present in the crude mixture.



Scheme 2.34. Synthesis of catalyst (*S*)-**158.**

2.5.4 Conclusions

Based on the ESI-MS screening method, an efficient combinatorial strategy for the development and structural optimization of organocatalysts for the Michael addition to α,β-unsaturated aldehydes was developed.

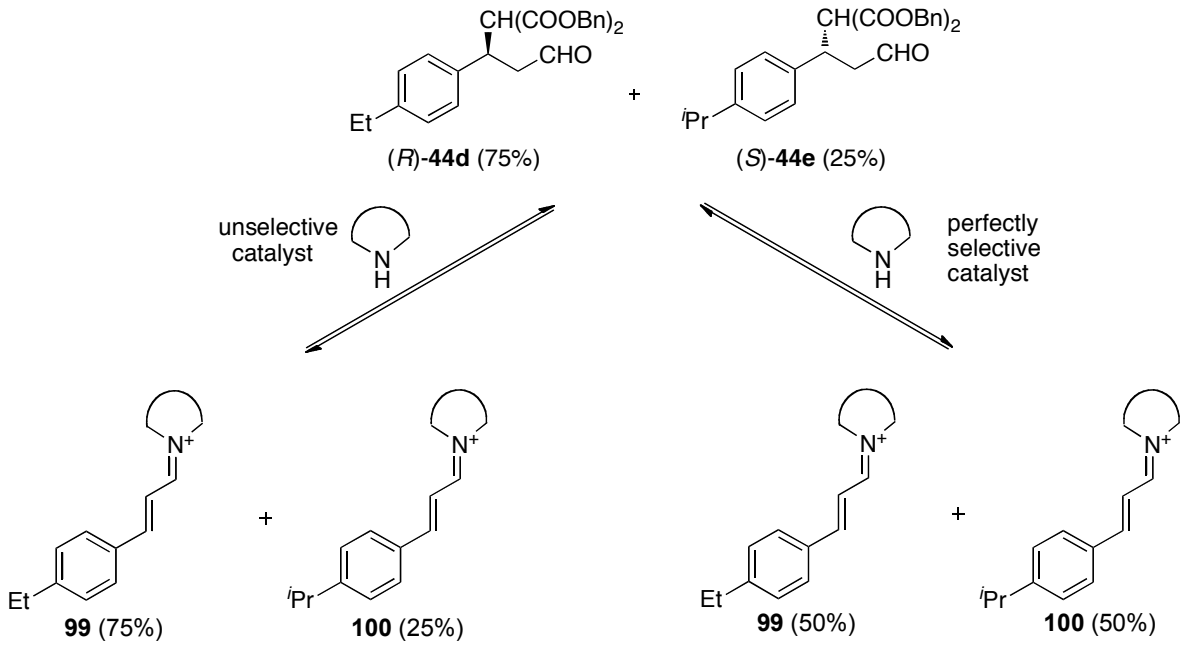
It was possible to determine the selectivity of up to four catalysts in one mixture. Moreover, the use of two different Grignard reagents and two silylating agents in the catalyst synthesis provided a crude mixture of 6 catalysts (*S*)-**46a**/(2*S*)-**134**/(*S*)-**124**/(*S*)-**46c**/ (2*S*)-**131**/(*S*)-**125** in one batch. This mixture was subjected to ESI-MS screening, which revealed the most selective catalyst from the mixture.

This combinatorial library synthesis combined with ESI-MS screening allows for rapid and reliable structural optimization of a catalyst. In contrast to conventional parallel screening methods, simultaneous evaluation of a mixture of catalysts is possible without the need to isolate and purify the individual catalysts.

This methodology could be applied to other classes of catalysts and substrates. Its limitations lie in mass differences between the catalysts and in the synthesis of the catalyst mixture, which must provide products in good to high yield in every step.

2.6 Screening of Racemic Catalysts

The screening of racemic organocatalysts would be a useful extension of our method, especially for catalysts that cannot be synthesized from the chiral pool. For these species, the screening would provide a fast and effective tool for the determination of selectivity. As recently demonstrated by MARKERT, MÜLLER and EBNER, the selectivity of racemic catalysts in kinetic resolutions of allylic esters can be determined in this way.[80] The extension of this principle to the *retro*-Michael reaction was examined. When a scalemic mixture of quasienantiomers is used, the ratio of observed intermediates depends on the selectivity of catalyst. For example, with a 75:25 mixture of quasienantiomers, an achiral or unselective catalyst should give a 75:25 ratio of intermediates (Scheme 2.35) since it cannot distinguish the two quasienantiomers. Each enantiomer of a perfectly selective catalyst reacts with only one quasienantiomer, thus a ratio of 50:50 should be observed.



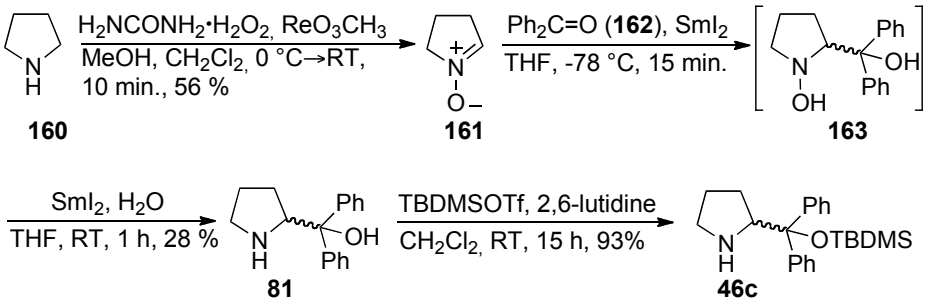
Scheme 2.35. The principle of ESI-MS screening of racemic catalysts.

Under pseudo zero-order conditions, the expected ratio of intermediates for a catalyst of known selectivity can be calculated from Equation **[1]**, where s is the selectivity factor of the catalyst ($s = k_{fast}/k_{slow}$ = [%(major intermediate)/%(minor intermediate)], k is the rate constant of the rate-limiting and enantioselectivity-determining step in the *retro*-Michael reaction).

$$\mathbf{XX}:\mathbf{XX} = 50\left(\frac{3}{s+3}+\frac{3s}{3s+1}\right):50\left(\frac{s}{s+3}+\frac{1}{3s+1}\right) \qquad \textbf{[1]}$$

2.6.1 Synthesis of Racemic Catalyst 46c

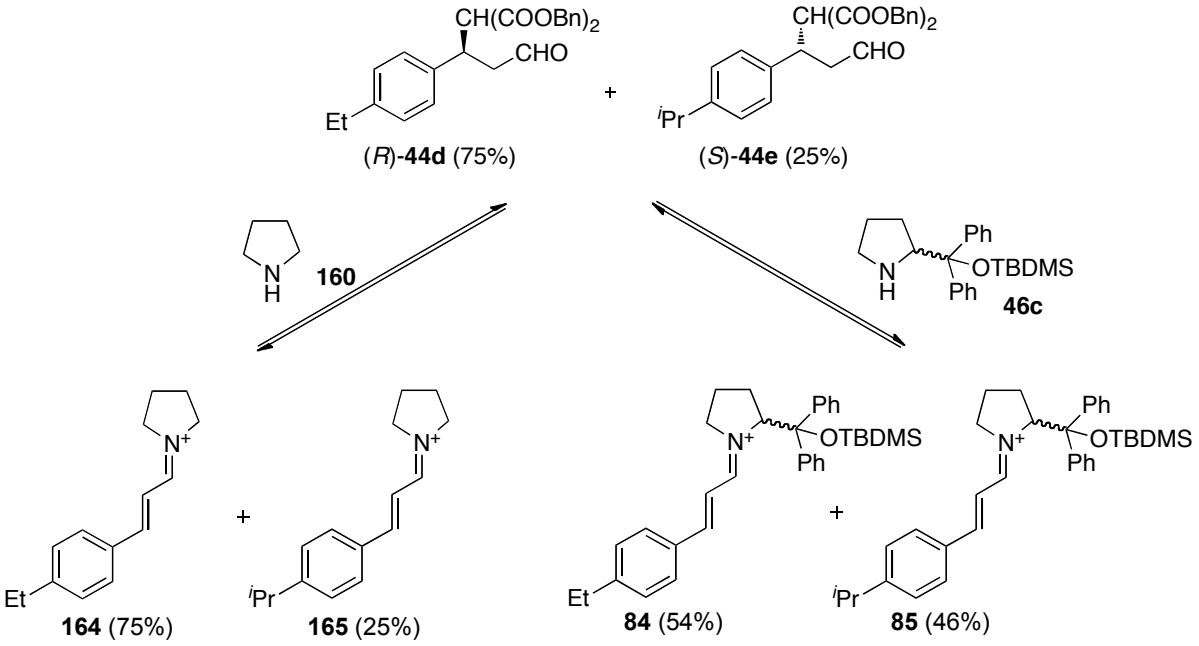
To test the methodology in the screening of organocatalysts, a simple synthesis of known racemic catalysts should be applied. Pyrrolidine (**160**) was chosen as an achiral catalyst. Recently, CHAVANT has reported a SmI_2-mediated reaction of 1-pyrroline-*N*-oxide (**161**) with benzophenone (**162**) for the synthesis of racemic amino alcohol **81** (Scheme 2.36).[81] Following this methodology, pyrrolidine (**160**) was oxidized by urea-hydrogen peroxide and methyltrioxorhenium to give *N*-oxide **161** in moderate yield. SmI_2-mediated cross-coupling of *N*-oxide **161** and ketone **162** gave *N*-hydroxyamino alcohol **163**, which was reduced to amino alcohol **81** in low yield, as a result of te poor stability of *N*-oxide **163** in solution. Amino alcohol **81** was treated with TBDMSOTf to give racemic catalyst **46c**. Catalyst **46c** was already found to be very selective in the ESI-MS screening for the Michael addition of malonates to cinnamaldehyde (ratio of intermediates 97:3).



Scheme 2.36. Synthesis of racemic catalyst **46c**.

2.6.2 Attempts to Screen Racemic Catalysts

The *retro*-Michael reaction of a scalemic mixture of quasienantiomers (*R*)-**44d**/(*S*)-**44e** (75:25, 9.38 µmol/3.12 µmol) with pyrrolidine (**160**) and **46c** was carried out, following the general screening protocol from chapter 2.4. From Equation **[1]**, the expected ratio of intermediates is 75:25 for **160**, and 54:46 for **46c** (Scheme 2.37). However, in both cases the observed ratio was 74:26. This ratio showed no dependence on reaction time (10 seconds, 5 minutes, 30 minutes, 2 h, 24 h).

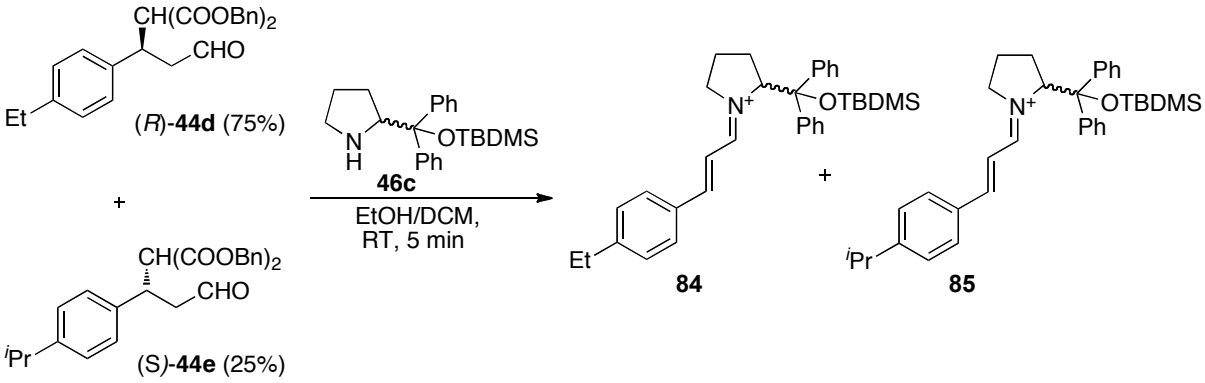


Scheme 2.37. *Retro*-Michael reaction of (*R*)-**44d**/(*S*)-**44e** (75:25) with **160** and **46c** and the expected ratios of intermediates.

The screening of racemic catalyst requires, that the reaction order is zero with regards to the substrate.[82] Possibly, the rate of the *retro*-Michael reaction depends on the concentration of the quasienantiomers (*R*)-**44d**/(*S*)-**44e**, and is, therefore, not zero order referring to the substrate. Unfortunately, it was not possible to investigate the kinetics of the reaction with ReactIR due to the overlap of IR signals.

If the rate dependence on the concentration of (*R*)-**44d**/(*S*)-**44e** is the reason, lowering the concentration of the catalyst and thus keeping the concentration of the quasienantiomers effectively constant, should lead to improved results. Indeed, with only 1 mol% of catalyst, the detected ratio of intermediates (*m/z* = 510/524) was 70:30 (Table 2.3). Further improvement was achieved with a catalyst loading of 0.5 mol% (65:35, Figure 2.21). With a 0.25 mol%, the ratio of intermediates was 66:34, but due to the very low concentration of the intermediates, the intensity of the signals was very low. Another difficulty was the presence of the signals of (*R*)-**44d**/(*S*)-**44e** (*m/z* = 467, 481, 483, 497, 513, 527, 529, 543). In the experiments with low catalyst loading, a more concentrated reaction mixture was used (30.0 µmol/10.0 µmol (*R*)-**44d**/(*S*)-**44e** in 50 µL DCM. 50 µL EtOH). Unfortunately, no further improvement could be achieved. Concentration and reaction temperature did not have any impact on the observed ratio of intermediates. Freezing of intermediates (-78 °C) was also attempted without any success.

Table 2.3. ESI-MS screening of the *retro*-Michael reaction with racemic catalyst **46c**.



Entry	Catalyst loading [mol%]	(*R*)-44d/(*S*)-44e [µmol]	DCM/EtOH [µL]	ESI-MS 84/85
1	10	9.38/3.12	90/10	74:26
2	1	30.0/10.0	50/50	70:30
3	0.5	30.0/10.0	50/50	65:35
4	0.25	30.0/10.0	50/50	66:34

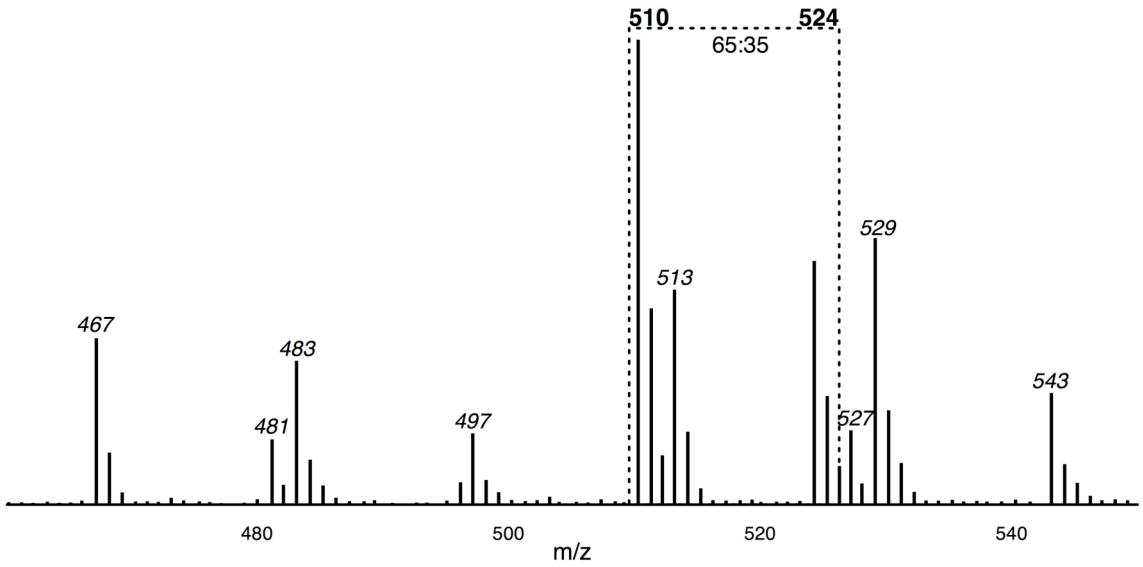


Figure 2.21. ESI-MS spectrum of the *retro*-Michael addition of (*R*)-**44d**/(*S*)-**44e** with catalyst **46c** (0.5 mol%).

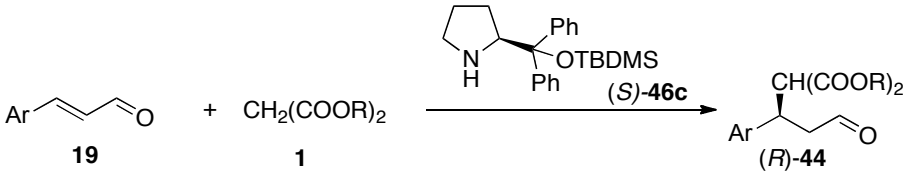
2.6.3 Conclusion

The viability of performing an ESI-MS screening of racemic catalysts based on the work of LLOYD-JONES was examined.[82] A racemic catalyst **46c** was synthesized following the procedure of CHAVANT.[81] The screening of **46c** as a highly selective catalyst and **160** as an achiral catalyst was performed using scalemic mixture of quasienantiomers (*R*)-**44d**/(*S*)-**44e** (75:25).

Due to the rate dependence on the concentration of (*R*)-**44d**/(*S*)-**44e**, a straightforward application of the methodology was not possible in this case. An improvement was achieved by applying a low catalyst loading, but the expected ratio of intermediates was not observed. Thus, further investigations will be necessary to evaluate the scope of this approach.

2.7 Optimization and Mechanistic Studies of the Preparative Reaction

After identification of the most selective catalysts, further investigation into the preparative Michael addition of malonates to enals with catalyst (*S*)-**46c** (Scheme 2.37) was desired. It is known that additives such as acids, bases or water can accelerate organocatalytic reactions.[83] Furthermore, mechanistic studies were intended.

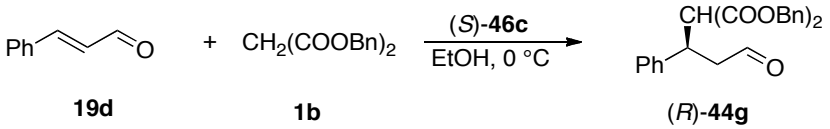


Scheme 2.37. Michael addition of malonates to enals.

2.7.1 Optimization of Reaction Conditions

In their first report on the enantioselective Michael addition of malonates to enals, JØRGENSEN *et. al.* did not describe the use of any additives.[26] Despite good to high enantioselectivities, the reaction was not practical due to the long reaction times. Furthermore, the reaction was performed under inert atmosphere, which is often unnecessary in organocatalysis. Therefore, we examined the reaction in air with catalyst (*S*)-**46c** (Table 2.4). Apparently, not only is air tolerated in this reaction, the catalyst loading can be reduced to 5 mol%.

Table 2.4. Optimization of catalyst loading in the Michael addition with catalyst (*S*)-**46c**.[a]

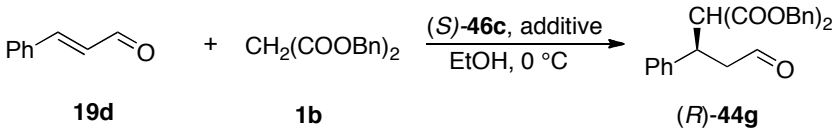


Entry	Conditions	Catalyst [mol%]	Time [h]	Conversion [%][b]	Yield [%][c]	*ee* [%][d]
1	Ar	10	74	94	92	98
2	air	10	74	95	92	98
3	air	7	84	99	97	99
4	air	5	84	95	90	99
5	air	3	84	76	73	99
6	air	1	84	31	28	93

[a]Performed with **19d** (0.19 mmol), **1b** (0.13 mmol), (*S*)-**46c** (0.0088 mmol, 7 mol%), in ethanol (0.5 mL) at 0 °C. [b]Determined by ^{1}H-NMR. [c]Isolated yield. [d]Determined by chiral-stationary-phase HPLC.

Further optimization was performed with 7 mol% of catalyst (*S*)-**46c**. In iminium-catalyzed reactions, acids can accelerate the formation of the iminium intermediate from the catalyst and enal as well as conversion of the product enamine to the corresponding iminium salt, which then undergoes hydrolysis to the final product (Figure 2.23).[83] Indeed, the addition of a catalytic amount of a weak acid such as $PhCO_2H$ (7–20 mol% with respect to malonate) resulted in a strong rate enhancement (Table 2.5 and Figure 2.22). The reaction slowed down with 40 mol% benzoic acid. In contrast to the reaction without additives, this reaction can be performed at room temperature without racemization. However, stronger acids, such as CF_3CO_2H, completely inhibited the reaction. The addition of sodium benzoate or hydrogencarbonate gave inferior results, in contrast to a recent report on the beneficial effect of carboxylate salts in this reaction.[30]

Table 2.5. Effect of additives on the Michael addition of malonates to α,β-unsaturated aldehydes.[a]



19d **1b** (*R*)-**44g**

Entry	Additive	pKa (H_2O)	Time [h]	Conv. [%][c]	*ee* [%][d]
1	none	-	84	99	99
		-	15	30	99
		-	24	48	99
		-	48	68	99
2	PhCOOH (7 mol%)	4.2	15	97	99
3	PhCOOH (7 mol%)[b]	4.2	6	95	97
4	PhCOOH (3.5 mol%)	4.2	15	98	99
5	PhCOOH (20 mol%)	4.2	15	97	99
6	PhCOOH (40 mol%)	4.2	15	92	99
7	PhCOONa (7 mol%)	4.2[e]	15	63	96
8	4-$NO_2(C_6H_4)$COOH (7 mol%)	3.4	15	97	99
9	4-OMe(C_6H_4)COOH (7 mol%)	4.5	15	98	99
10	CH_3COOH (7 mo%)	4.8	15	93	94
11	CH_3COOH (solvent)	4.8	24	52	95
12	CH_3COONa (7 mol%)	4.8[e]	15	77	89

Entry	Additive	pKa (H_2O)	Time [h]	Conv. [%][c]	*ee* [%][d]
13	CF_3COOH (7 mol%)	-0.25	24	0	nd[f]
14	*p*-$CH_3(C_6H_4)SO_3H$ (7 mol%)	-2.8	24	0	nd[f]
15	$NaHCO_3$ (7 mol%)	3.6[e]	24	38	94

[a]Performed with **19d** (0.19 mmol), **1b** (0.13 mmol), (*S*)-**44c** (0.0088 mmol, 7 mol%), additive in ethanol (0.5 mL) at 0 °C. [b]RT. [c]Conversion determined by ^{1}H-NMR. [d]Determined by chiral-stationary-phase HPLC. [e]pKa of conjugate acid. [f]Not determined.

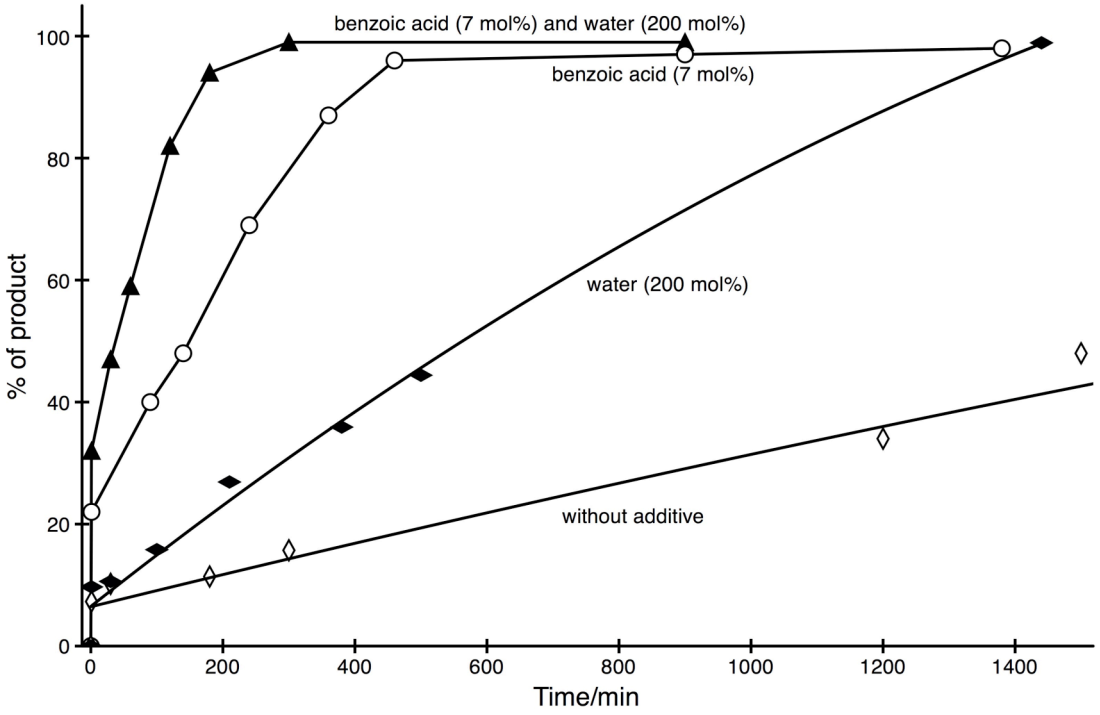


Figure 2.22. The dependence of product formation on time in the presence of additives at 0 °C.

The dependence of conversion on time was measured by ^{1}H-NMR and compared to the reactions carried out with or without benzoic acid and water additives (Figure 2.22).[84] When no acid was present, the formation of the iminium intermediate was slower. In the presence of benzoic acid, the formation of the iminium ion was accelerated and the reaction showed a high initial rate. ESI-MS spectra of cinnamaldehyde and catalyst showed that benzoic acid strongly accelerates the conversion of the aldehyde to the iminium ion (Figure 2.24). In the absence of the acid in stoichiometric reactions no iminium ion was observed after 30 min at 0 °C in ethanol.

The addition of water (2 equiv. relative to malonate) resulted in a further rate increase, whereas water alone had a weaker effect (Figure 2.22). The effects of water on organocataly-

tic reactions have been discussed in the literature.[85] In this case water accelerates the hydrolysis of the iminium species (Figure 2.23). It was also found, that the reaction will even proceed when water is used as a solvent.[27] Increasing the amount of water up to 20 equiv relative to malonate did not affect the rate of the reaction.

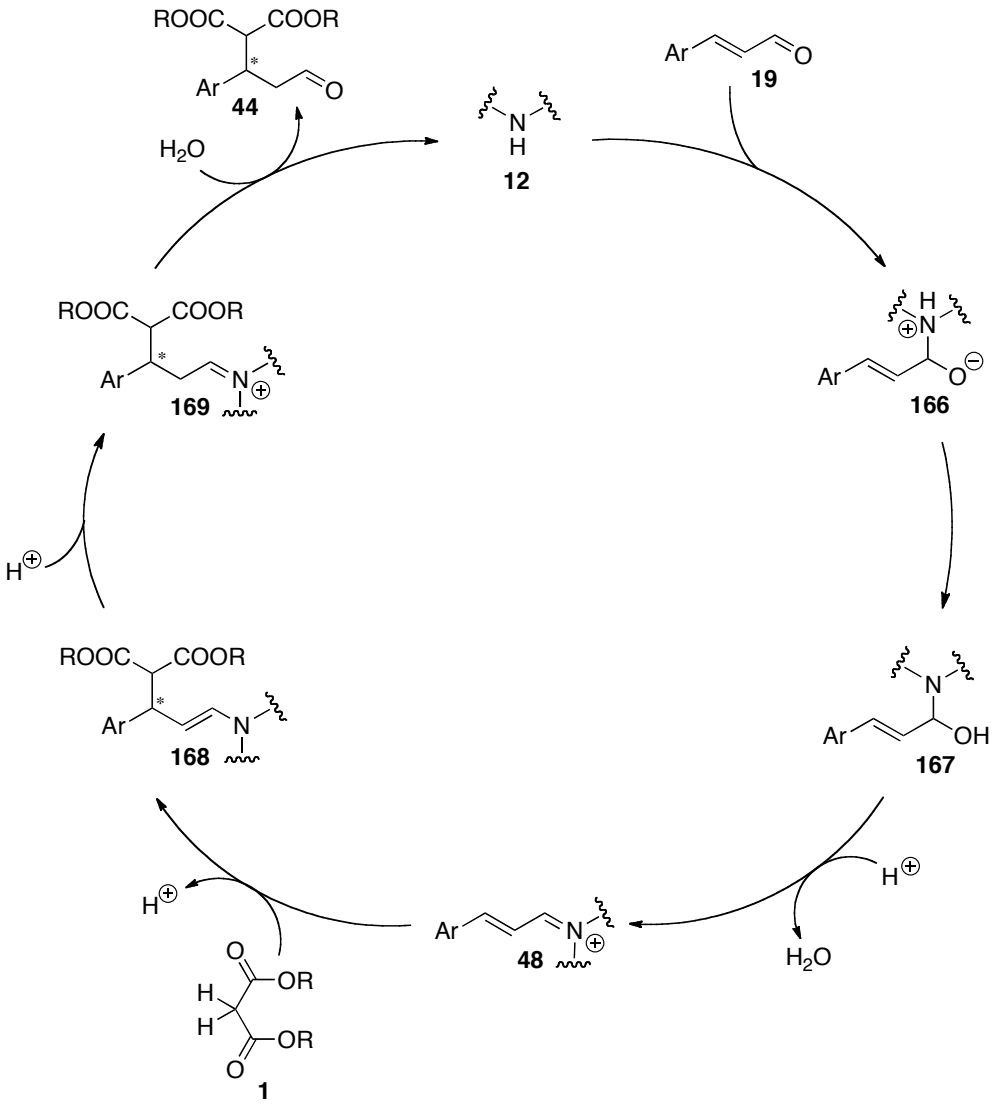


Figure 2.23. The catalytic cycle of secondary amine-catalyzed Michael addition of malonates to α,β-unsaturated aldehydes. The equilibrium arrows have been replaced by one-way arrows for clarity.

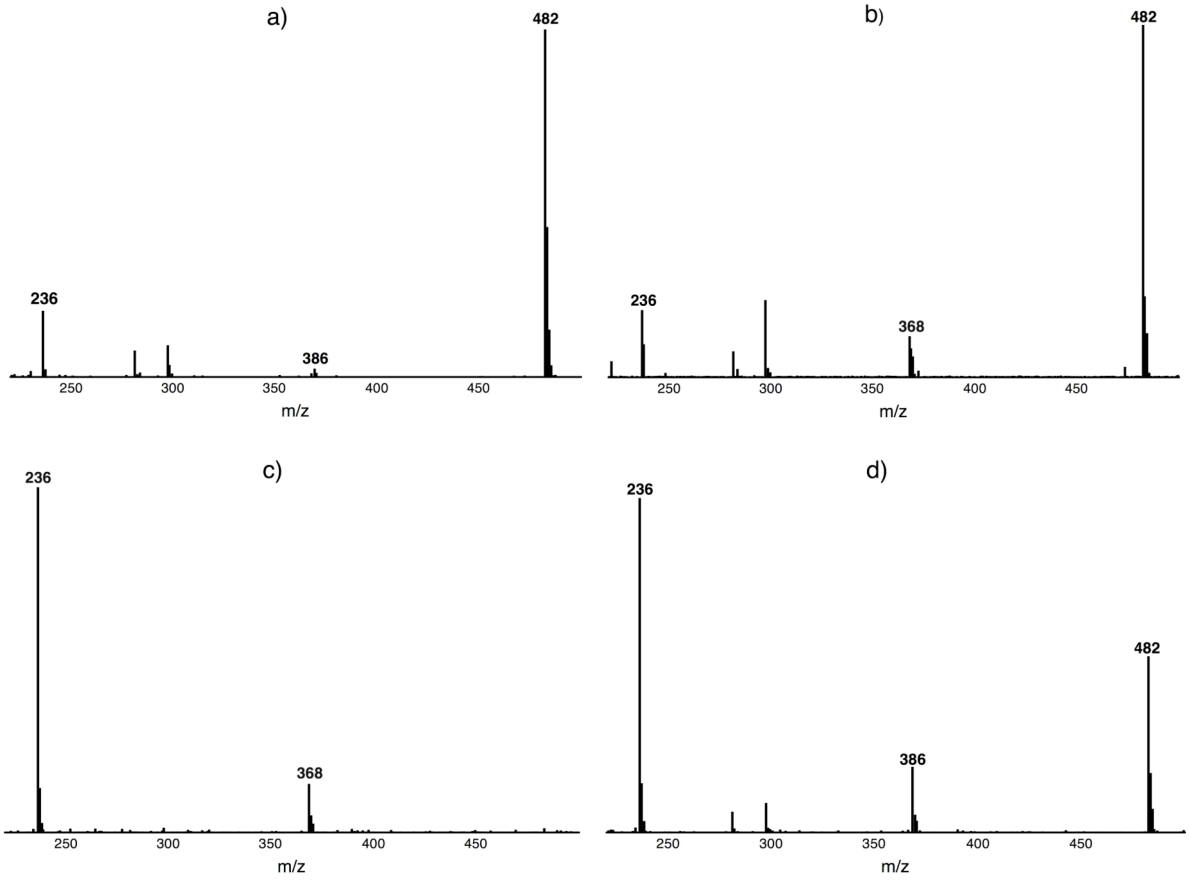
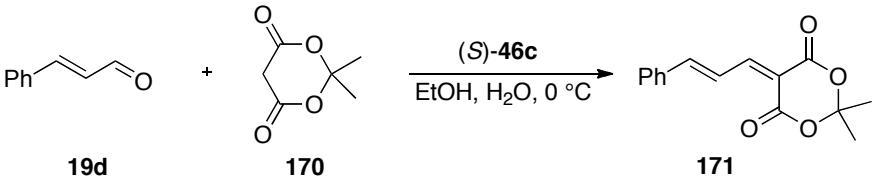


Figure 2.24. ESI-MS spectra of cinnamaldehyde, PhCOOH and (*S*)-**46c**: a) 5 mol% (*S*)-**46c**, 0 mol% PhCOOH; b) 5 mol% (*S*)-**46c**, 5 mol% PhCOOH; c) 65 mol% (*S*)-**46c**, 0 mol% PhCOOH; d) 65 mol% (*S*)-**46c**, 65 mol% PhCOOH.

2.7.2 Substrate Scope

With optimized conditions in hand, the substrate scope was explored (Table 2.6). The reaction was found to be general for the malonates tested. However, Meldrum's acid gave 1,2- instead of 1,4-addition, followed by elimination of water (48% yield, Scheme 2.38). High yields and enantioselectivities were obtained with a range of aromatic unsaturated aldehydes. The reaction of the aliphatic unsaturated aldehyde **19h** yielded several unidentified by-products resulting from the self-condensation of the aldehyde.[86, 87] To suppress this side-reaction, the aldehyde was added slowly to the mixture of catalyst and malonate. Under these conditions, product **44l** was formed in high enantiomeric purity but only moderate yield (Table 2.6, entry 9). Isolated **44l** was contaminated with dibenzyl malonate, as it underwent *retro*-Michael addition on silica gel.

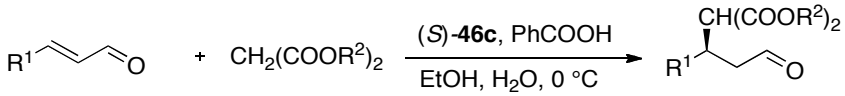
The reaction of dibenzyl malonate and cinnamaldehyde was also conducted on a gram scale with only 2 mol% of catalyst (Table 2.6, entry 10) in wet ethanol (> 5% H_2O) at room temperature. After 8 hours and one recrystallization, the pure product was obtained in 90% yield and >99% *ee*.



19d **170** **171**

Scheme 2.38. Reaction of (*E*)-cinnamaldehyde and Meldrum's acid.

Table 2.6. Michael addition of malonates to α,β-unsaturated aldehydes.[a]



19 **1** (*R*)-**44**

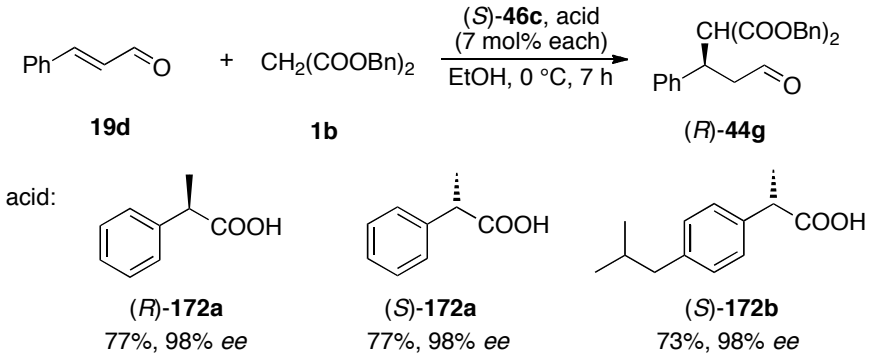
Entry	R^1	R^2	Product	Time [h]	Yield [%]	*ee*[e] [%]
1[b]	4-Et-(C_6H_4) (**19b**)	Bn (**1b**)	**44d**	6	90	>99
2[b]	4-^{i}Pr-(C_6H_4) (**19c**)	Bn (**1b**)	**44e**	6	89	>99
3	Ph (**19d**)	Bn (**1b**)	**44g**	5	97	99
4	Ph (**19d**)	Me (**1c**)	**44f**	5	92	>99
5	Ph (**19d**)	Et (**1d**)	**44h**	5	95	>99
6	4-MeO-(C_6H_4) (**19e**)	Me (**1c**)	**44i**	8	95	99
7	4-NO_2-(C_6H_4) (**19f**)	Me (**1c**)	**44j**	8	96	99
8	2-Furyl (**19g**)	Me (**1c**)	**44k**	6	92	99
9[c]	^{n}Bu (**19h**)	Bn (**1b**)	**44l**	24	55[f]	96
10[d]	Ph (**19d**)	Bn (**1b**)	**44g**	8	90	>99

[a]Performed with **19** (0.19 mmol), **1** (0.13 mmol), (*S*)-**46c** (0.0088 mmol), PhCOOH (0.0088 mmol) and water (0.25 mmol) in ethanol (0.5 mL) at 0 °C. [b]Performed with **19b** or **19c** (1.00 mmol), **1b** (0.67 mmol), (*S*)-**46c** (0.047 mmol), PhCOOH (0.047 mmol) and water (1.34 mmol) in ethanol (2.5 mL) at 0°C. [c]**19h** was added to **1b** and (*S*)-**46c** during 3 hours. [d]Performed at RT, with 2.50 mmol **19d**, 2 mol% (*S*)-**46c** and benzoic acid, in technical EtOH, yield and *ee* after 1 recrystallization. [e]Determined by chiral-stationary-phase HPLC. [f]Isolated product contained 10% of **1b**.

2.7.3 Chiral Acids as Additives

If the benzoate anion forms a tight ion pair with the iminium intermediate, the effect of a chiral acid on the selectivity might be observed. Therefore, the Michael addition of dibenzyl malonate to (*E*)-cinnamaldehyde with chiral acids **172** was conducted (Scheme 2.39). The reactions were slightly slower than the reaction with benzoic acid (70–80% conversion after 7 h), but the enantiomeric excess did not change (98%).

In contrast to these results, in 2009 XU reported a tandem oxa-Michael reaction catalyzed by (*S*)-**46a** and (*S*)-Mosher's acid (α-methoxy-α-trifluoromethylphenylacetic acid).[88] (*S*)-Mosher's acid improved both yield and enantioselectivity (94% yield, 80% *ee*) when compared to benzoic acid (65% yield, 36% *ee*) or its enantiomer (90% yield, 71% *ee*). Under optimized conditions, *ee* values of up to 99% were obtained. As a rationale for the observed improvement, a tight ion pair was proposed.



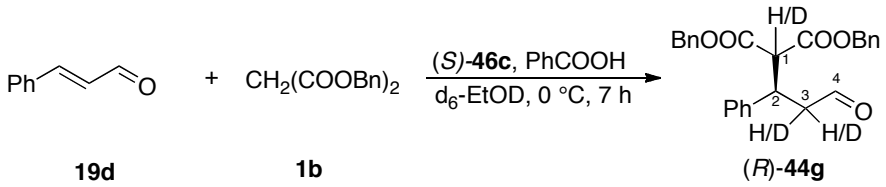
Scheme 2.39. Michael addition of **19d** to **1b** in the presence of chiral acids.

2.7.4 Solvent Isotope Effect

Isotope effects are very useful tools for mechanistic studies.[89] Solvent isotope effects are changes in rates or equilibria that are observed in deuterated solvents when compared to unlabeled solvents. They occur when solvent molecules are involved in the mechanism of the reaction or when the transition state is solvated differently by labeled and unlabeled solvent. Furthermore, an isotope exchange between a solvent molecule and reactants can lead to an isotope effect. Solvent isotope effects can be either kinetic or thermodynamic.

The Michael addition of dibenzyl malonate to (*E*)-cinnamaldehyde was carried out in d_6-EtOD containing 5 mol% D_2O (Scheme 2.40). The progress of the reaction was followed by ^{1}H-NMR (Figure 2.25). A small positive isotope effect was observed, with

k_H(rel)/k_D(rel) ≈ 1.5. It is not clear if the observed effect is kinetic or thermodynamic, because the isotope distribution in the product was different in each of the runs performed. In the first run, 77% of product was obtained after column chromatography and recrystallization, with 20% ^{2}H at CH_2(CHO) and 20% ^{2}H at CH(COOBn)$_2$. Upon repetition, 98% product was obtained after column chromatography, with 50% ^{2}H at CH_2(CHO). ^{2}H-NMR experiments confirmed the presence of deuterium.



Scheme 2.40. Malonate addition to cinnamaldehyde in d_6-EtOD.

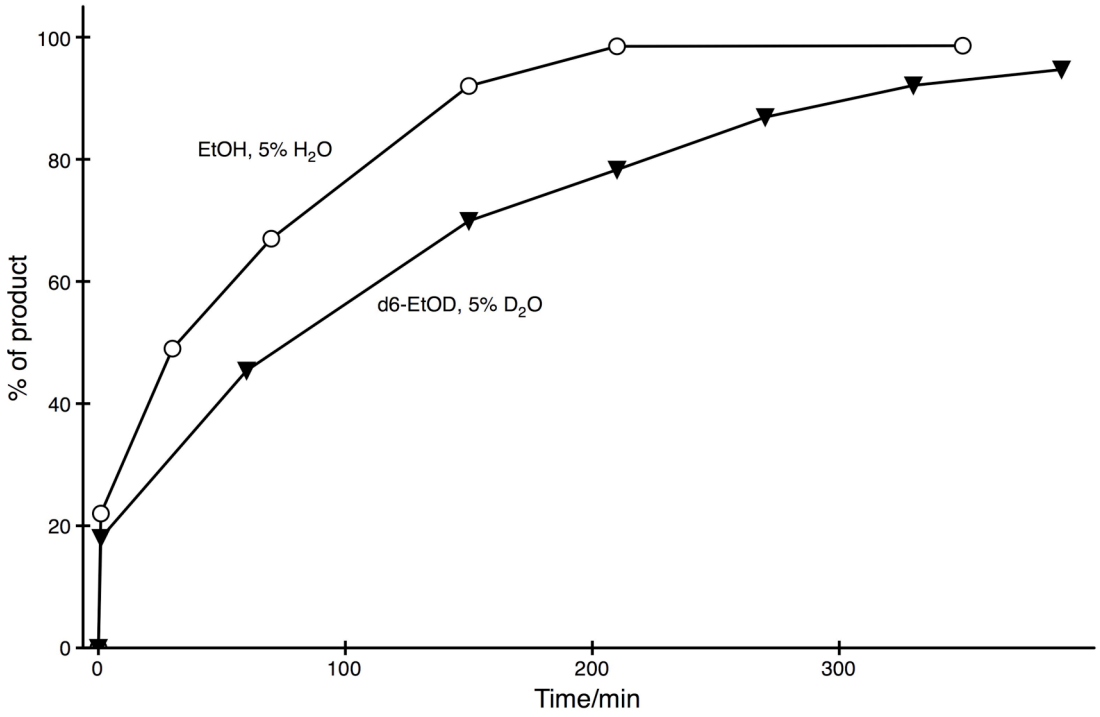


Figure 2.25. Solvent isotope effect in Michael addition of malonate **1b** to **19d**.

Moreover, the reaction was monitored by ESI-MS. Before the addition of the malonate, a signal at *m/z* = 486 corresponding to **173** was observed (Figure 2.26a). 30 minutes after the addition of malonate, a more complicated isotopic pattern occurred. Due to the fast H/D exchange and reversibility of the reaction, deuterated iminium **173-d** was formed (Figure 2.26b). The H/D exchange can occur at two acidic positions in the intermediate **174** (*m/z* = 766), thus leading to the species **174-d** and **174-d'** (*m/z* = 767) and **174-d$_2$** (*m/z* = 768). Signals at *m/z* = 782, 783 and 784 correspond to the hemiaminals of **174-d**, **174-d'**and **174-d$_2$**.

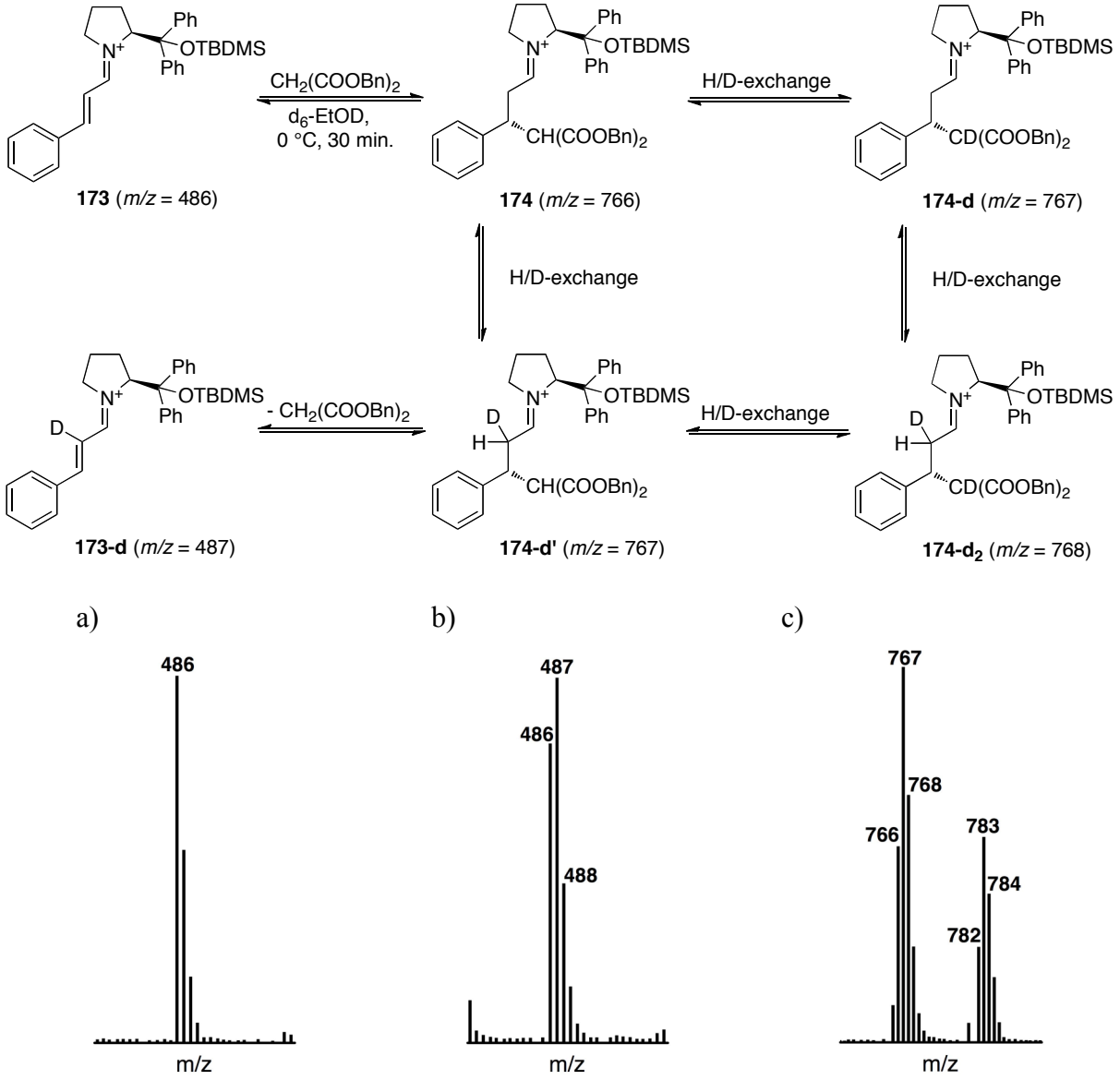


Figure 2.26. The signals of intermediates in the Michael addition of **1b** to **19d** in d_6-EtOH: a) **173** before the addition of malonate; b) **173** after the addition of malonate; c) **174**.

A solvent isotope effect was observed. It seems to have been caused by fast proton/deuterium exchange, which can happen at two acidic positions in the product or intermediate.

2.7.5 Nonlinear Effect

The reaction was examined for nonlinear effects.[90] As demonstrated in Figure 2.27, the experiments with samples of catalyst **46c** of varying enantiomeric purity showed a clear negative nonlinear effect. As a possible explanation, the involvement of two catalyst

molecules in the enantioselective step was considered. One molecule forms the iminium intermediate, the other forms a chiral nucleophilic species by hydrogen bonding to the enol form of malonate.

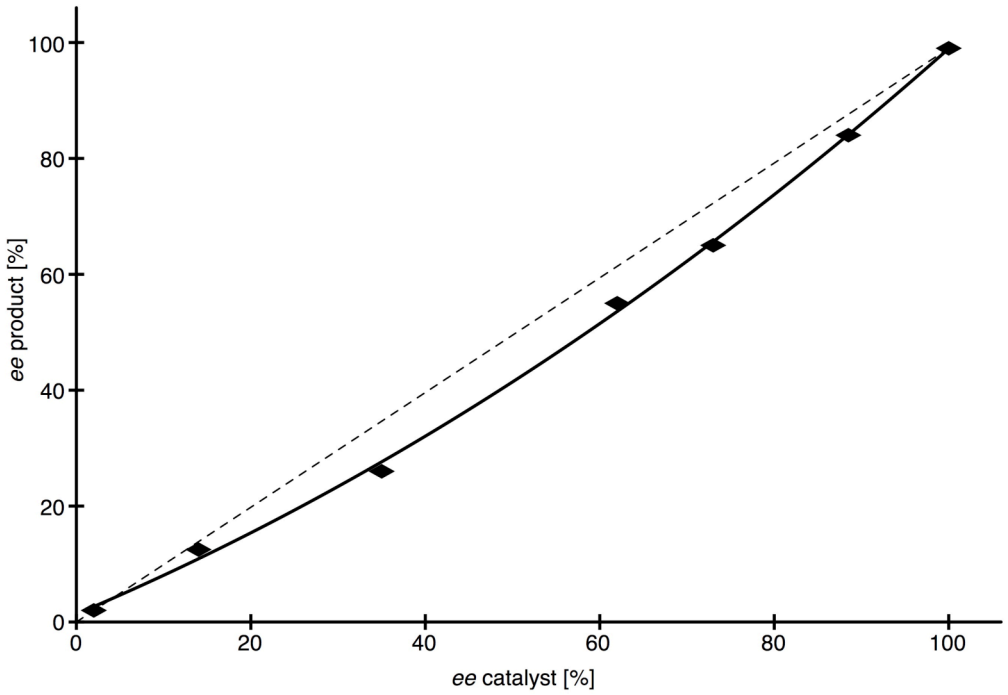


Figure 2.27. The nonlinear effect in the Michael addition of malonate **1b** to aldehyde **19d** catalyzed by **46c**.

These findings were supported by ESI-MS and ^{1}H-NMR experiments. The mass spectrum of malonate in the negative ionization mode is of low intensity (Figure 2.28a). However, in the presence of catalyst (*S*)-**46c**, the signal at *m/z* = 283 appears as the most prominent (Figure 2.28b). This signal corresponds to deprotonated malonate and was also observed in the catalytic reaction in the presence of (*S*)-**46c** and PhCOOH. The signal of benzoate at *m/z* = 121 was present as well.

Similarly, the ^{1}H-NMR spectrum of dibenzyl malonate in d_6-EtOD changed after the addition of (*S*)-**46c** (Figure 2.29**)**. The signal at 3.46 ppm related to the acidic CH_2-group of malonate completely disappeared in the presence of the catalyst (equimolar amount). The same phenomenon was previously mentioned by YAMAGUCHI.[19a]

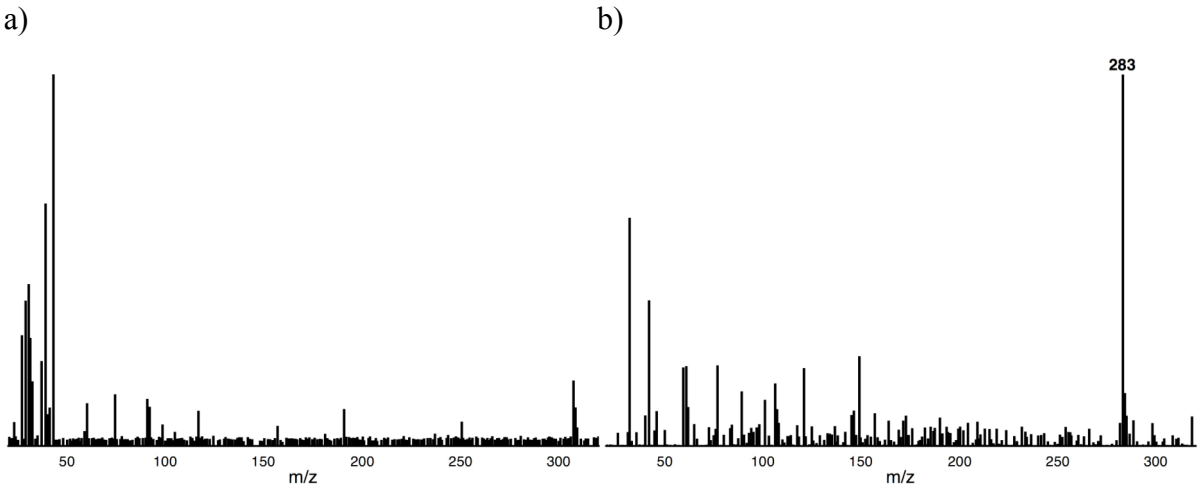


Figure 2.28. ESI-MS spectra in the negative ionization mode of: a) malonate **1b**; b) malonate **1b** and (*S*)-**46c**.

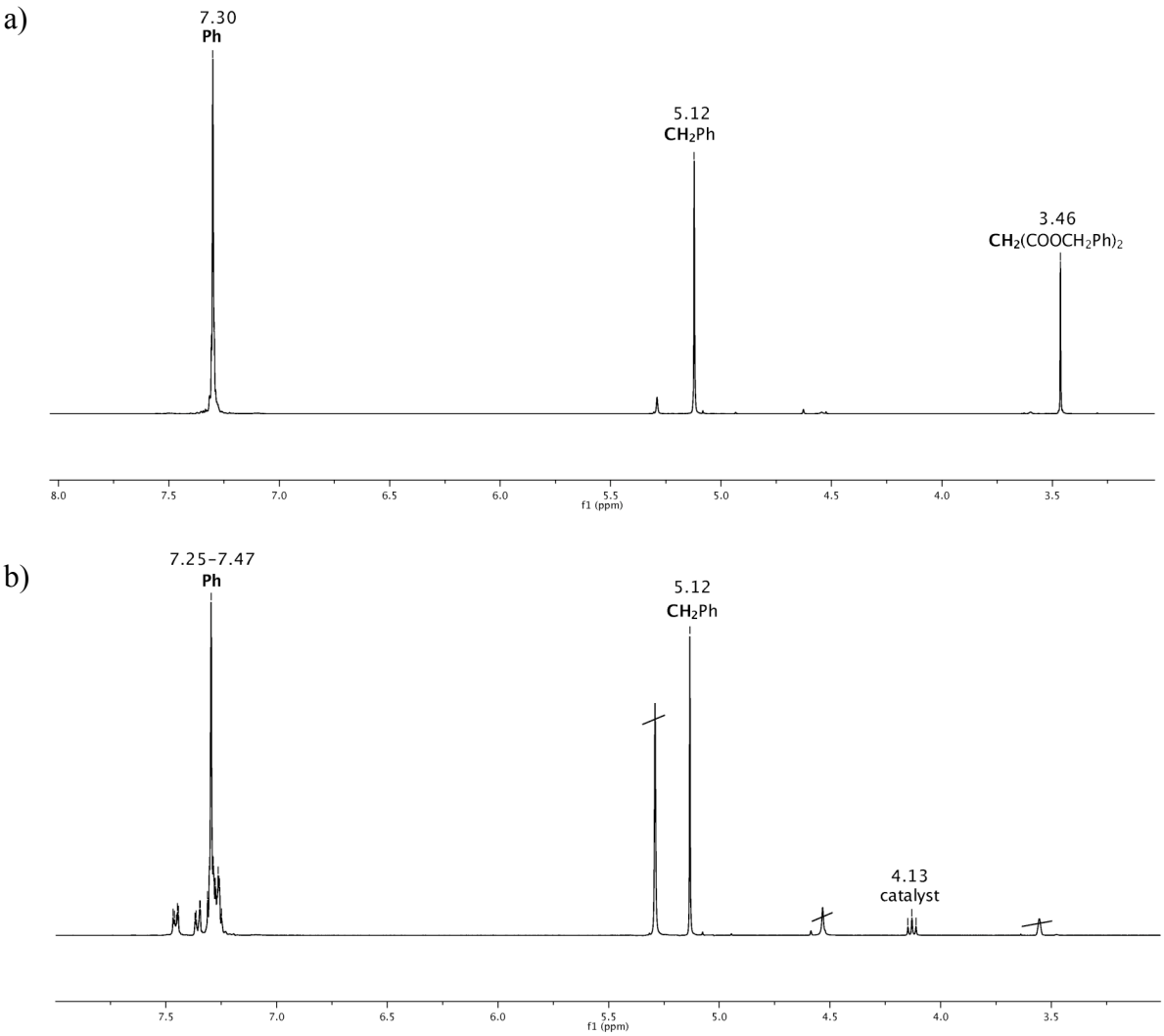
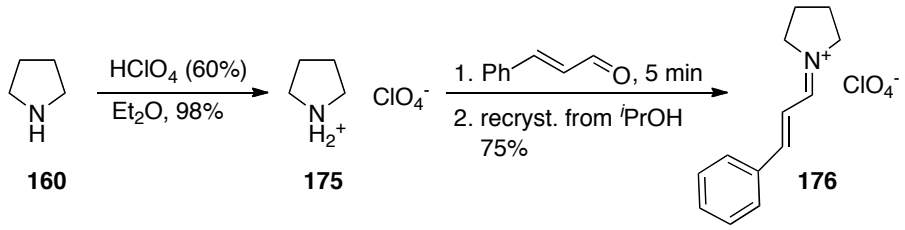
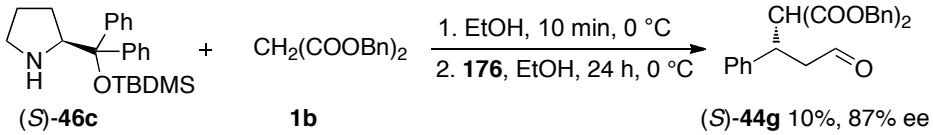


Figure 2.29. ^{1}H-NMR spectra in d_6-EtOD of: a) dibenzyl malonate; b) dibenzyl malonate and (*S*)-**46c**; the solvent signals are crossed-out.

To test the double activation hypothesis, the iminium salt **176** was prepared according to a known procedure (Scheme 2.41)[91] and reacted with equimolar amounts of dibenzyl malonate and catalyst (*S*)-**46c** (Scheme 2.42). After 24 h at 0 °C, the Michael adduct **44g** was obtained as the (*S*)-enantiomer in 87% *ee*, as opposed to the (*R*)-enantiomer formed in the catalytic reaction with (*S*)-**46c** (Table 3, Entry 3).



Scheme 2.41. Synthesis of iminium perchlorate **176**.



Scheme 2.42. Effect of (*S*)-**46c** in the addition of malonate **1b** to iminium salt **176**.

Thus, there appears to be a mismatch between the chiral induction by the chiral iminium group and that of the chiral catalyst-malonate adduct. However, control by the iminium group strongly dominates, such that high enantioselectivities are still possible. This mismatch between the actions of the two catalyst molecules explains the observed negative nonlinear effect. If a non-enantiopure catalyst is used, four pairs of activated species are involved in the enantioselective step: two mismatched and, accordingly, less reactive homochiral combinations and two matched and therefore, more reactive heterochiral combinations (Figure 2.30). The two heterochiral pairs [(*R*)-iminium/(*S*)-malonate and (*S*)-iminium/(*R*)-malonate] are present in equal amounts and so, produce racemic product. Because these heterochiral pairs are more reactive, formation of racemic product will be faster than the corresponding enantioselective process and, as a consequence, the proportion of racemate in the product will be higher than in the catalyst.

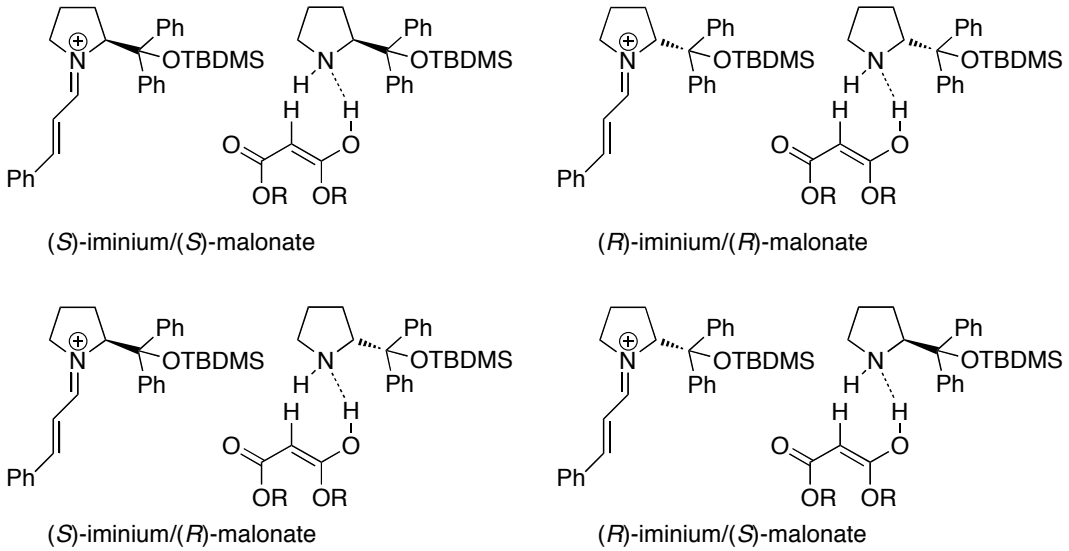


Figure 2.30. The four possible combinations of chiral active species in a reaction with a non-enantiopure catalyst.

A nonlinear effect in the Michael addition was demonstrated. As shown by the experiments discussed above, the involvement of two catalyst molecules in the catalytic cycle accounts for the observed effect.

2.7.6 The Catalytic Cycle

To summarize the findings from previous experiments, a catalytic cycle for the Michael addition of malonates to enals was proposed (Figure 2.31). The secondary amine **12** reacts with the aldehyde **19** to form the iminium intermediate **48** *via* **166** and **167**. In this process, a proton accelerates the formation of the iminium ion from **167**. Since water is formed in the latter step, the formation of an iminium intermediate is suppressed by the presence of water.

Simultaneously, the amine **12** activates the nucleophile, probably via hydrogen bonding with the enol form of malonate **1**. The activated nucleophile **177** attacks the iminium intermediate **48** at the 4-position to give enamine **168**. The enamine is protonated, generating iminium intermediate **169**, which is then hydrolyzed to amine **12** and product **44**. Both water and weak acids accelerate the overall process.

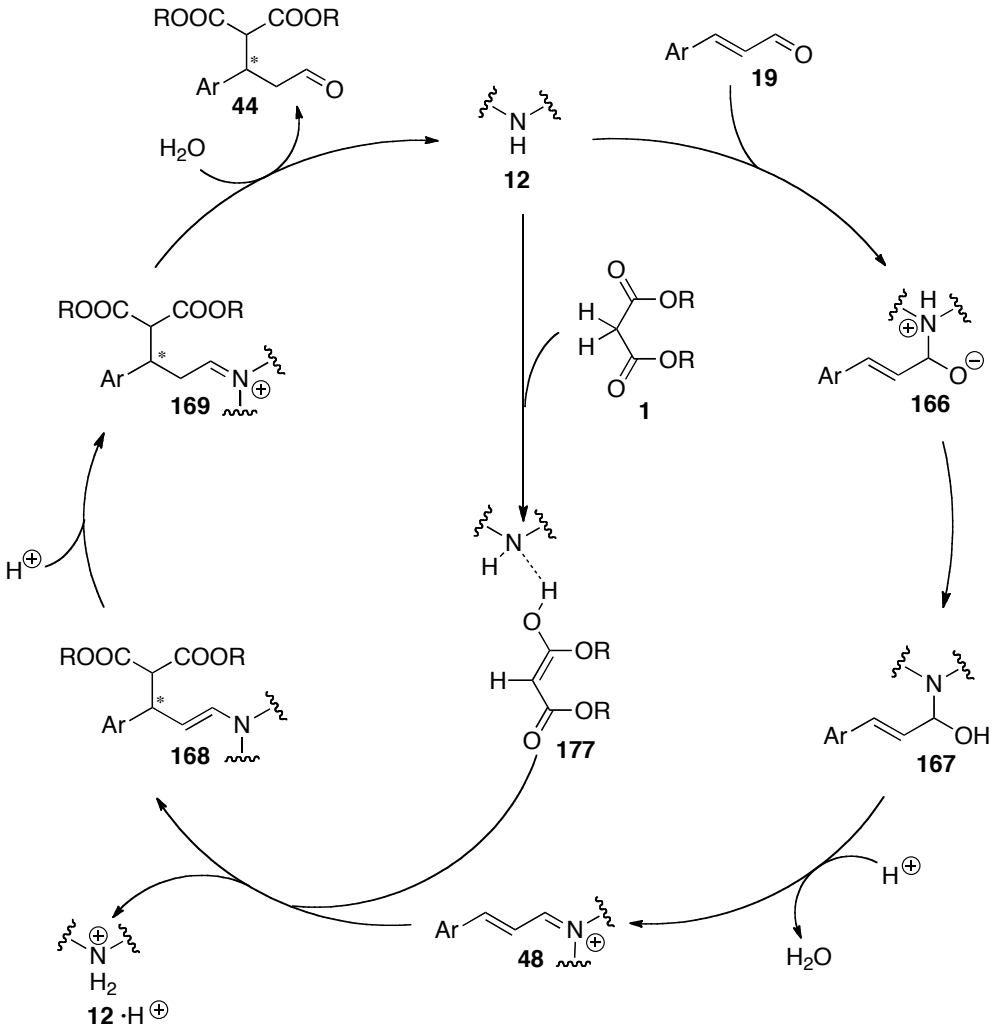
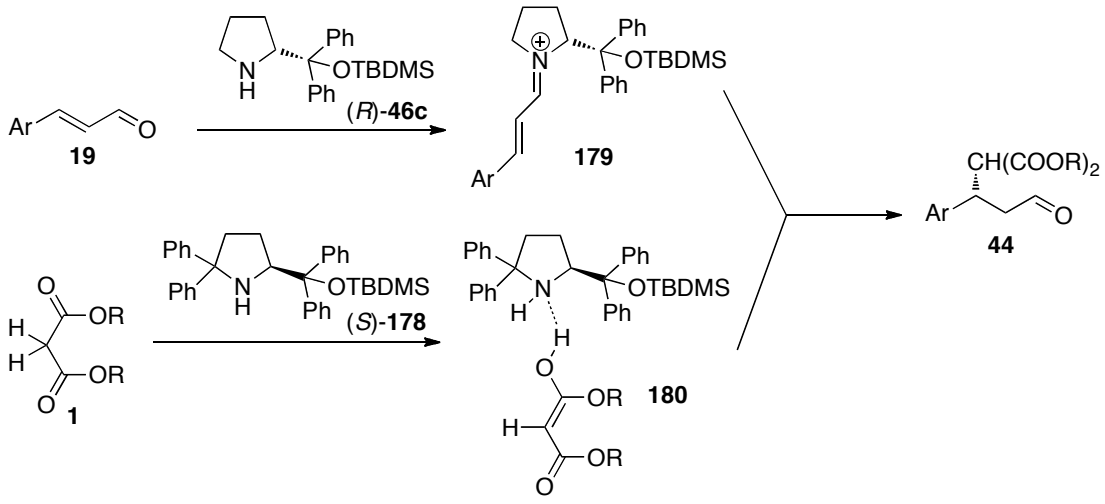


Figure 2.31. The catalytic cycle of secondary amine-catalyzed Michael addition of malonates to α,β-unsaturated aldehydes. The equilibrium arrows have been replaced by one-way arrows for clarity.

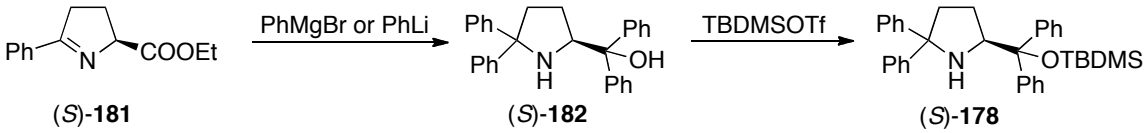
2.7.7 Synthesis of Bulky Co-catalysts for Nucleophile Activation

The mechanical observations would be especially valuable if they led to new more efficient catalysts. A bulky co-catalyst, (*S*)-**178**, was envisioned as a model. **178** should not be able to form an iminium intermediate with the aldehyde and would thus only activate the nucleophile in a Michael addition with catalyst (*R*)-**46c** (Scheme 2.43).

The synthesis of (*S*)-**178** by addition of PhMgBr or PhLi to ketimine (*S*)-**181** (Scheme 2.44) and subsequent silylation was planned. Ketimines are difficult substrates for the addition of organometallic reagents due to the low electrophilicity of the imine carbon and side reactions such as enolization.[92] However, several literature examples for such additions are known.



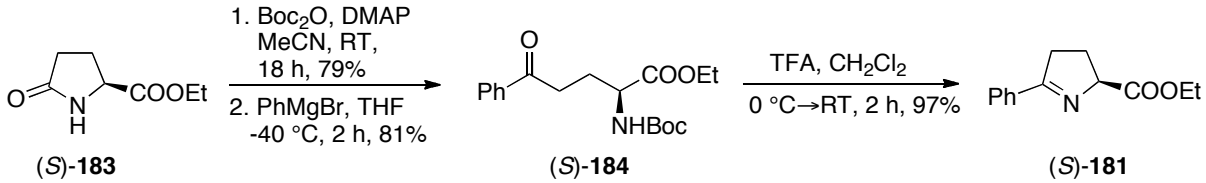
Scheme 2.43. Envisioned Michael addition of malonates to enals with the catalyst/co-catalyst system.



Scheme 2.44. Proposed synthesis of (*S*)-**178**.

*2.7.7.1 Attempted Synthesis of (S)-**178***

The ketimine (*S*)-**181** was prepared in good overall yield (62%) following the procedure of YOKOYAMA (Scheme 2.45).[93] (*S*)-Ethyl pyroglutamate ((*S*)-**183**) was *N*-protected with a *Boc*-group followed by the addition of PhMgBr (1.2 Equiv) to give the ketone (*S*)-**184** (64% yield over two steps). The *Boc*-group removal and following cyclization were achieved by treatment with TFA to yield the ketimine (*S*)-**181** (97%).



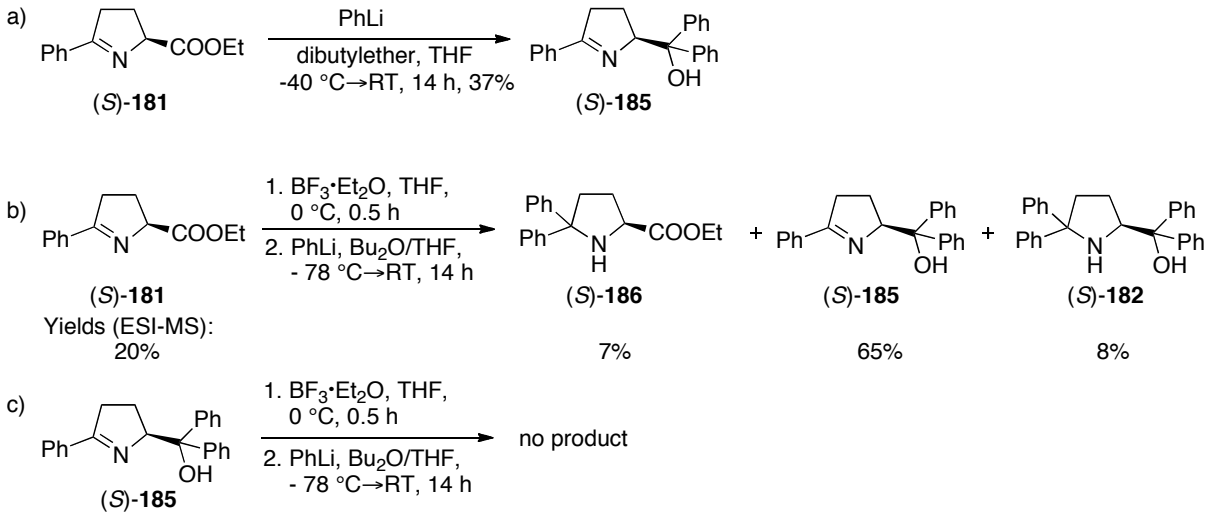
Scheme 2.45. Synthesis of ketimine (*S*)-**181**.

The addition of PhMgBr (6 Equiv) to ketimine (*S*)-**181** led to a very complex mixture of the starting material, biphenyl, the enolization product and the product of the addition to the ester group. Several precedents for this reaction can be found in the literature. One of the most

important is the report from SAINSBURY *et. al.* on organolithium reagents to arylimines derived from 3*H*-indole.[94] The addition of PhLi gave the product in 74% yield, whereas addition of the alkyllithium reagents gave multiple products, including the substitution product on the phenyl group. They assumed that addition of PhLi proceeds via conventional nucleophilic addition.

Following the procedure of SAINSBURY, the reaction of PhLi (4.8 Equiv) with ketimine (*S*)-**181** was carried out (Scheme 2.46a). Unfortunately, only the starting material and tertiary alcohol (*S*)-**185** were isolated from the reaction mixture. No desired product, (*S*)-**182**, was detected by ESI-MS in the crude mixture.

COLLUM showed that BF_3 activates ketimines towards the addition of organolithium reagents.[95] Hindered *tert*-alkylamines were prepared in moderate to good yields. Based on these results, the PhLi addition to (*S*)-**181** in the presence of $BF_3{\cdot}Et_2O$ was performed (Scheme 2.46b). For the first time, the imine addition products (*S*)-**182** and (*S*)-**186** were detected by ESI-MS, but their isolation was not successful due to the complexity of the mixture. No conversion was achieved in the addition of PhLi to (*S*)-**185** (Scheme 2.46c).

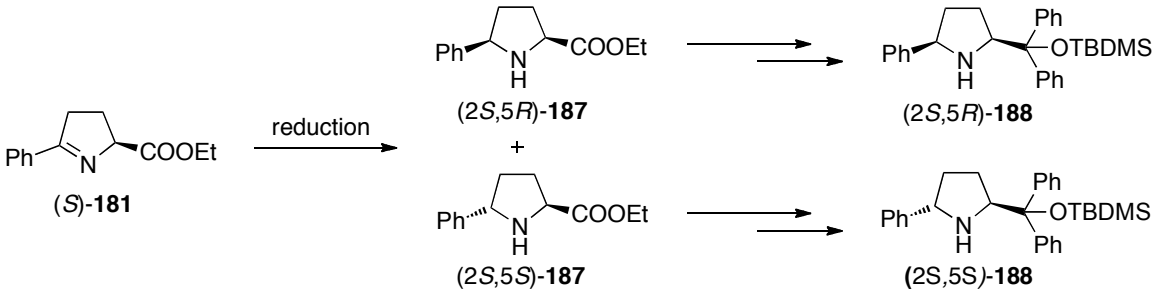


Scheme 2.46. Attempts to the synthesis of (*S*)-**182**.

The addition of organometallic reagents to the ketimine (*S*)-**181** could only be accomplished in the presence of $BF_3{\cdot}Et_2O$, and led to a complex mixture since the reactivity of the ester group was higher. Therefore, we focused on alternative approaches to the bulky co-catalysts.

*2.7.7.2 Synthesis of Bulky Co-catalysts (2S,5S)- and (2S,5R)-**188***

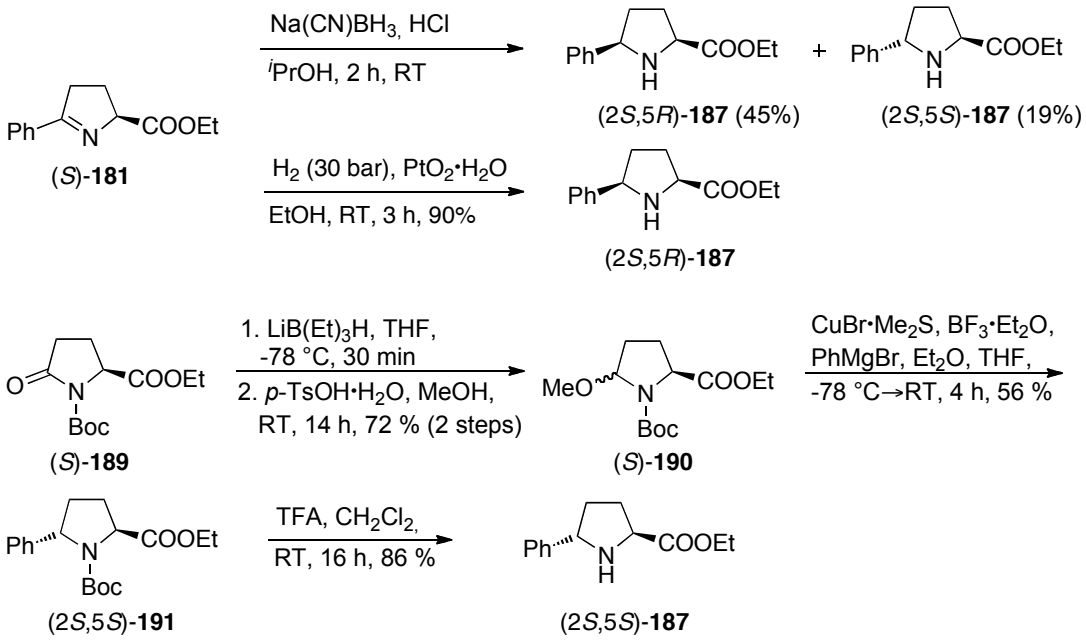
The reduction of ketimine (*S*)-**181** would provide 2 diastereomeric esters (2*S*,5*S*)- and (2*S*,5*R*)-**187**, which could be further transformed to diphenylsilyl ethers (2*S*,5*S*)- and (2*S*,5*R*)-**188** (Scheme 2.47). These ethers were expected to be hindered enough to not form iminium intermediates with the aldehyde.



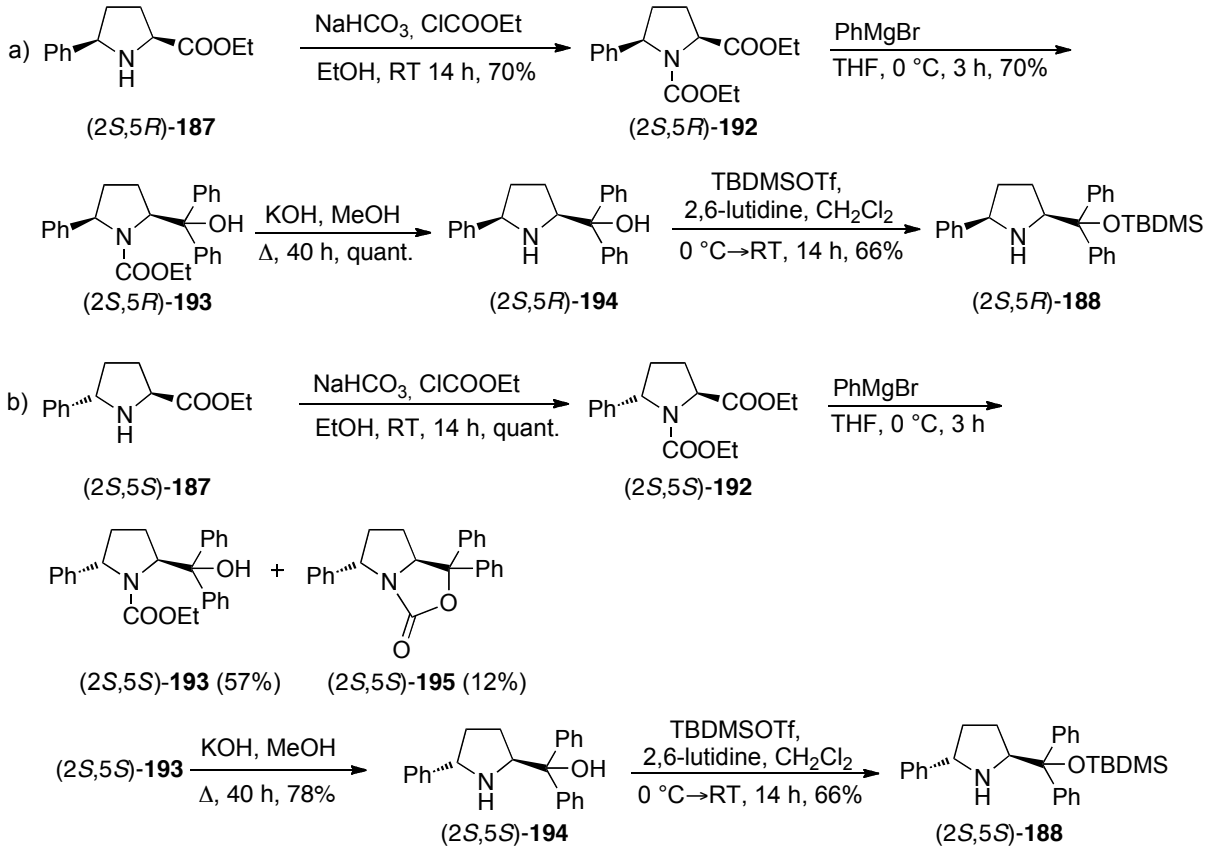
Scheme 2.47. Proposed synthesis of catalysts (2*S*,5*S*)- and (2*S*,5*R*)-**188**.

N. HOSTETTLER performed the non-selective reduction of (*S*)-**181** with $Na(CN)BH_3$ according to YAMAMOTO during his *Schlussversuch* (Scheme 2.48a). The diastereomers were separated by column chromatography and isolated in 45% ((2*S*,5*R*)-**187**) and 19% yield ((2*S*,5*S*)-**187**), respectively. The *cis*-selective reduction of (*S*)-**181** was performed by hydrogenation (30 bar) with $PtO_2 \cdot H_2O$ as a catalyst (Scheme 2.47b).[93] The selective synthesis of (2*S*,5*S*)-**187** was achieved in a 4-step sequence from (*S*)-**189** following the procedure of PEDREGAL (Scheme 2.48c).[96] A selective reduction of the amidic carbonyl group with $LiBEt_3H$ followed by methylation of the hemiaminal gave (5*S*)-**190** in ca 72% yield and 80% purity. (5*S*)-**190** was used directly in the reaction with an organocopper reagent that was generated *in situ* from PhMgBr and copper bromide-dimethyl sulfide complex. It was not possible to determine the diastereomeric ratio, since the product was contamined by an unknown impurity. PEDREGAL reported a diastereomeric ratio of ≥98.5 : ≤1.5. However, the deprotection afforded (2*S*,5*S*)-**187** as a single diastereomer in an 86% yield.

The diastereomeric esters were further transformed following the procedure for the synthesis of diarylprolinols (Scheme 2.49).[71] Protected esters (2*S*,5*R*)- and (2*S*,5*S*)-**192** were obtained in good to high yields. They were further treated with PhMgBr to give (2*S*,5*R*)-**193** in 70% yield and (2*S*,5*S*)-**193** in 57% yield along with bicyclic (2*S*,5*S*)-**195**. The formation of bicyclic product was not observed in the reaction with (2*S*,5*R*)-**192**. The deprotection required long reaction times and repeated addition of the base. In the final step, the amino alcohols were silylated in good yields.



Scheme 2.48. Synthesis of diastereomeric esters (2*S*,5*R*)- and (2*S*,5*S*)-**187**.



Scheme 2.49. Synthesis of co-catalysts (2*S*,5*S*)- and (2*S*,5*R*)-**188**.

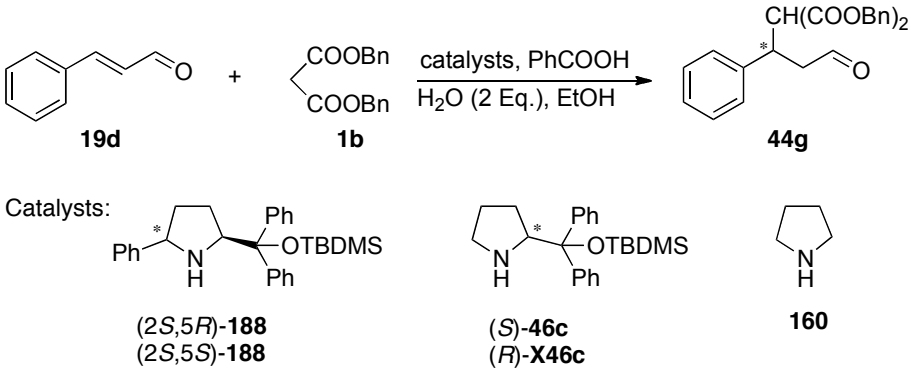
The bulky co-catalysts (2*S*,5*S*)- and (2*S*,5*R*)-**188** could be prepared stereoselectively in good overall yields from ketimine (*S*)-**181**.

*2.7.7.3 Co-catalysts (2S,5S)- and (2S,5R)-**188** in the Michael Addition*

In order to evaluate if catalysts (2*S*,5*S*)- and (2*S*,5*R*)-**188** are able to form iminium intermediates, they were tested in the *retro*-Michael reaction. No intermediates were detected by ESI-MS. The intensity of intermediate signals in the addition of dibenzyl malonate to cinnamaldehyde was very low. With catalyst (2*S*,5*S*)-**188**, the detected catalyst/intermediate ratio was 98:2. The conversion determined by ^{1}H-NMR was 13% after 24 h at 0 °C, and 32% after 48 h at RT, *ee* 70–71% (Table 2.7, entries 1–4). Catalyst (2*S*,5*R*)-**188** showed a promising 0.2% of intermediate, however, the reaction was faster than with the *trans*-catalyst (conversion 34% after 24 h at 0 °C and 69% after 48 h at RT). The *cis*-diastereomer gave higher *ee* (92–93% depending on the temperature).

Next, (2*S*,5*S*)-**188** and (2*S*,5*R*)-**188** were tested as potential basic co-catalysts in the Michael reaction (Table 2.7). The reactions were carried out with 5 mol% of catalyst (*S*)- and (*R*)- **46c**, and achiral **160** at either 0 or 25 °C. Unfortunately, no improvements in enantioselectivity were observed, neither under these conditions, nor in the absence of benzoic acid and water, nor with the catalyst (*S*)-**46a**.

Table 2.7. Michael addition of dibenzyl malonate to cinnamaldehyde with (2*S*,5*S*)-**188** and (2*S*,5*R*)-**188** as co-catalysts.[a]



Entry	Catalyst/Cocatalyst	T [°C]	Time [h]	Conversion [%][c]	ee [%][d]
1[b]	(2*S*,5*R*)-**188**	0	24	34	93
2[b]	(2*S*,5*S*)-**188**	0	24	13	70
3	(2*S*,5*R*)-**188**	25	48	69	92
4	(2*S*,5*S*)-**188**	25	48	32	71
5	(*S*)-**46c**	0	6	92	99
6	(2*S*,5*R*)-**188**/(*S*)-**46c**	0	6	93	99

Entry	Catalyst/Cocatalyst	T [°C]	Time [h]	Conversion [%][c]	ee [%][d]
7	(2*S*,5*S*)-**188**/(*S*)-**46c**	0	6	91	99
8	(*S*)-**46c**	25	6	97	98
9	(2*S*,5*R*)-**188**/(*S*)-**46c**	25	6	97	98
10	(2*S*,5*S*)-**188**/(*S*)-**46c**	25	6	97	97
11	(*R*)-**46c**	25	4.5	96	-98
12	(2*S*,5*R*)-**188**/(*R*)-**46c**	25	4.5	96	-96
13	(2*S*,5*S*)-**188**/(*R*)-**46c**	25	4.5	96	-97
14	**160**	25	6	96	0
15	(2*S*,5*R*)-**188**/**160**	25	6	99	1
16	(2*S*,5*S*)-**188**/**160**	25	6	98	2

[a]Performed with **19d** (0.188 mmol), **1b** (0.125 mmol), catalyst (6.25 µmol), cocatalyst (6.25 µmol), PhCOOH (6.25 µmol) and H_2O (4.5 µL) in ethanol (0.5 mL). [b] [a]Performed with cocatalyst (8.75 µmol). [c]Determined by ^{1}H-NMR. [d]Determined by chiral-stationary-phase HPLC.

According to the ESI-MS, the ratio of intermediates formed from the catalysts and the cocatalysts was between 90:10 and 99:1. It seems that the less hindered catalysts better activate both the electrophile and the nucleophile.

2.7.8 Conclusions

The most selective catalyst determined by the initial screen was used in the Michael addition of malonates to unsaturated aldehydes. The conditions for the Michael addition were optimized. A strong accelerating effect of carboxylic acids was observed, which allows for considerably shorter reaction times and much lower catalyst loadings. Further improvement was achieved by addition of water into the reaction mixture. The reaction was general for aromatic aldehydes and methyl, ethyl and benzyl malonate.

A distinct nonlinear effect was observed that was rationalized by a double nucleophilic-electrophilic activation mechanism involving two catalyst molecules. This hypothesis was supported by further mechanistic studies, including ESI-MS and NMR studies. An enhanced catalytic cycle for the Michael addition based on mechanistic studies was proposed.

Sterically hindered catalysts (2*S*,5*R*)- and (2*S*,5*S*)-**188** were synthesized in moderate overall yields and tested in the Michael addition as potential co-catalysts for nucleophile activation.

Unfortunately, no improvements in enantioselectivity were observed under the conditions tested.

Altogether, ESI-MS was not only helpful in identifying the most selective catalyst, but could also be used to optimize the reaction conditions and in mechanistic investigations.

2.8 References

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CHAPTER 3

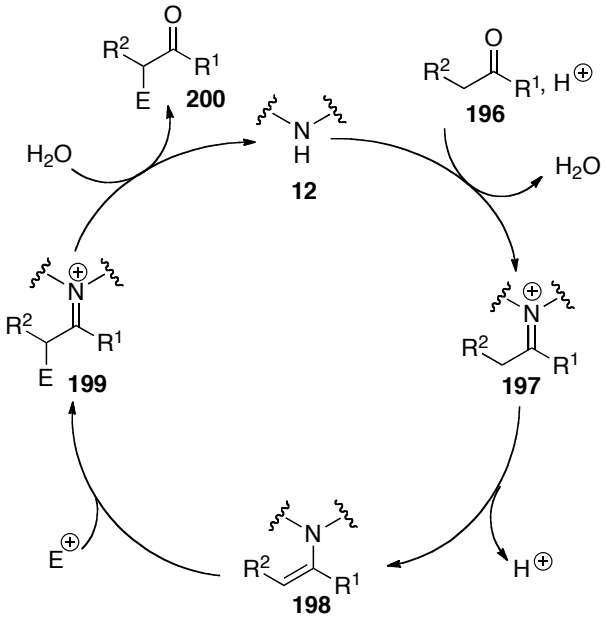
Towards Self-Assembling Organocatalysts

3 Towards Self-Assembling Organocatalysts

3.1 Introduction

3.1.1 Enamine Catalysis[1]

There are several different modes of substrate activation by organocatalysts.[2] For example, the use of chiral amines for iminium catalysis was discussed in Chapter 2. Additionally, numerous reactions with amine catalysts proceed via enamine catalysis, whose general mechanism is depicted in Scheme 3.1. An iminium intermediate **197** is formed from a carbonyl compound **196** and a primary or secondary amine **12**. **197** is converted to enamine **198** that is activated towards reaction with electrophiles. After the reaction with an electrophile, the iminium intermediate **199** is formed, which is then hydrolyzed to give the product **200** and the amine **12** is recovered.

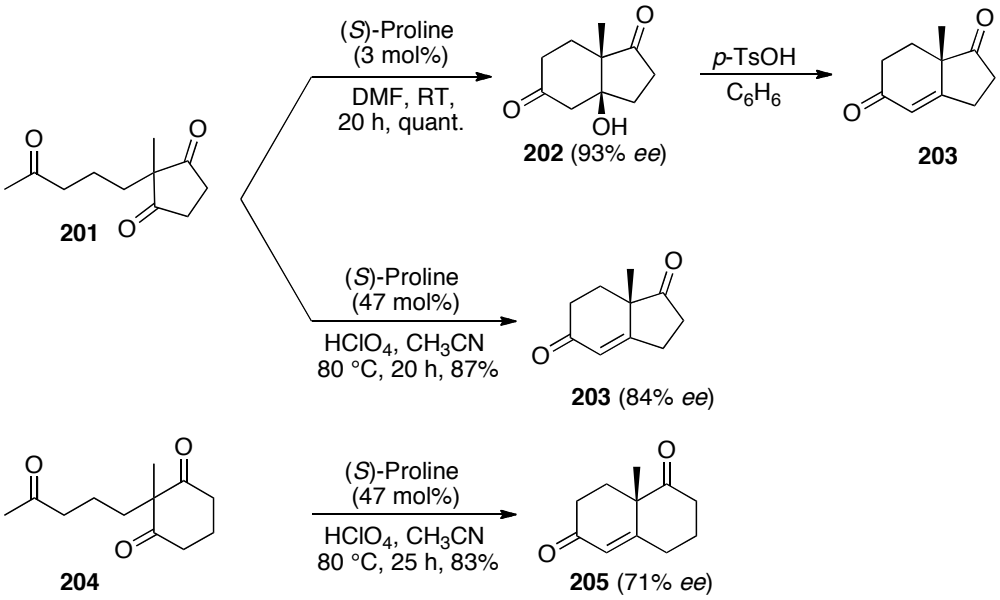


Scheme 3.1. The principle of enamine catalysis.

First reports on amine-catalyzed aldol reactions appeared 80 years ago.[3] One of the most frequently used catalysts was piperidinium acetate, which was also employed in intramolecular aldol reactions by WIELAND and MIESCHER[4] and later by WOODWARD.[5]

The first highly enantioselective enamine-catalyzed reactions were discovered in the early 1970s by two groups. HAJOS and PARRISH reported proline-catalyzed intramolecular aldol reactions of triketone **201** to aldol product **202** in good yield and high *ee* (Scheme 3.2).[6]

Aldol **202** was converted to condensation product **203** by treatment with *p*-TsOH. They proposed that the aldol reaction proceeds via a hemiaminal formed from the ketone and proline, although SPENCER had confirmed the enamine mechanism in piperidinium acetate-catalyzed reactions before.[7] EDER, SAUER and WIECHERT[8] demonstrated that ketones **201** and **204** directly yielded the condensation products **203** and **205** in the reaction with (*S*)-proline (10–200 mol%) in the presence of a strong acid.



Scheme 3.2. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

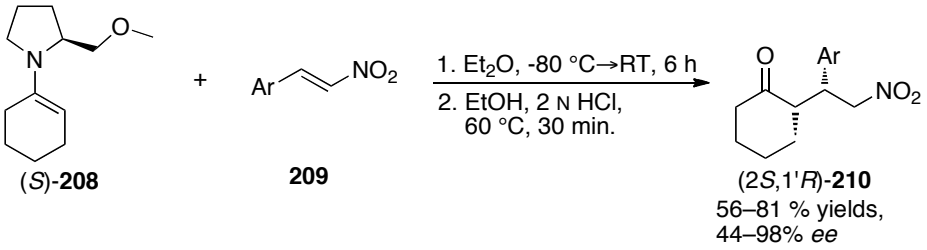
Although several contributions in this field appeared later,[9] no methodology was developed until 2000, when LIST and BARBAS reported a (*S*)-proline catalyzed intermolecular aldol reaction (Scheme 3.3)[10]. With 30 mol% of catalyst, acetone (**196a**), aromatic and aliphatic aldehydes **206**, the aldol products **207** were obtained in good yields and enantioselectivities.

Scheme 3.3. Proline-catalyzed aldol reaction reported by LIST and BARBAS.

Since this discovery, the field of enamine-catalysis has expanded. Proline and its derivatives are considered a privileged catalyst class, as they have proved efficient not only for aldol reactions, but also for Mannich reactions, 1,4-additions and α-functionalizations.

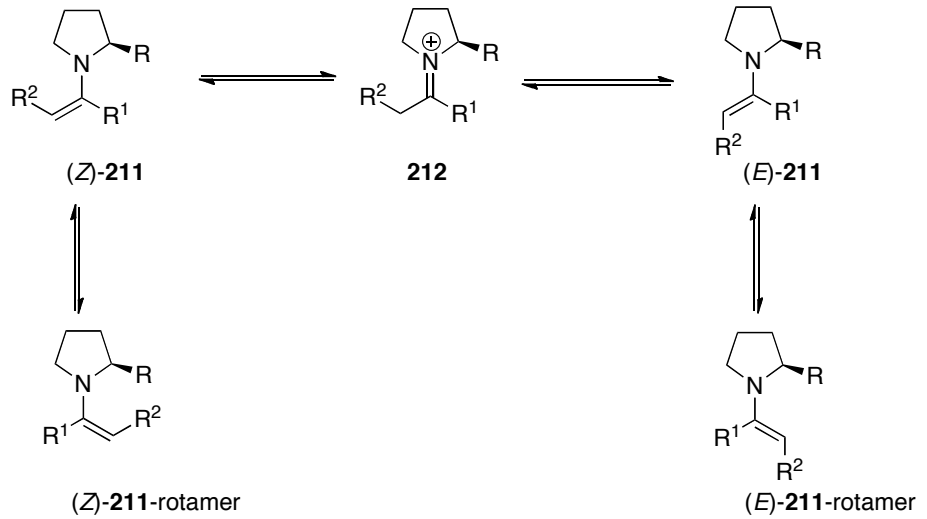
3.1.1.1 1,4-Additions of Ketones to Nitroolefins

Enamines had been used in 1,4-additions stoichiometrically since the report of STORK on alkylation and acylation of carbonyl compounds.[11] 1,4-Additions of chiral enamine (*S*)-**208** to nitrostyrenes were investigated by SEEBACH (Scheme 3.4).[12] This work is of particular interest, because the explanation of the stereoselective outcome of this reaction can also be employed in catalytic reactions.



Scheme 3.4. Stoichiometric 1,4-addition of enamine (*S*)-**208** to nitroolefins **209**.

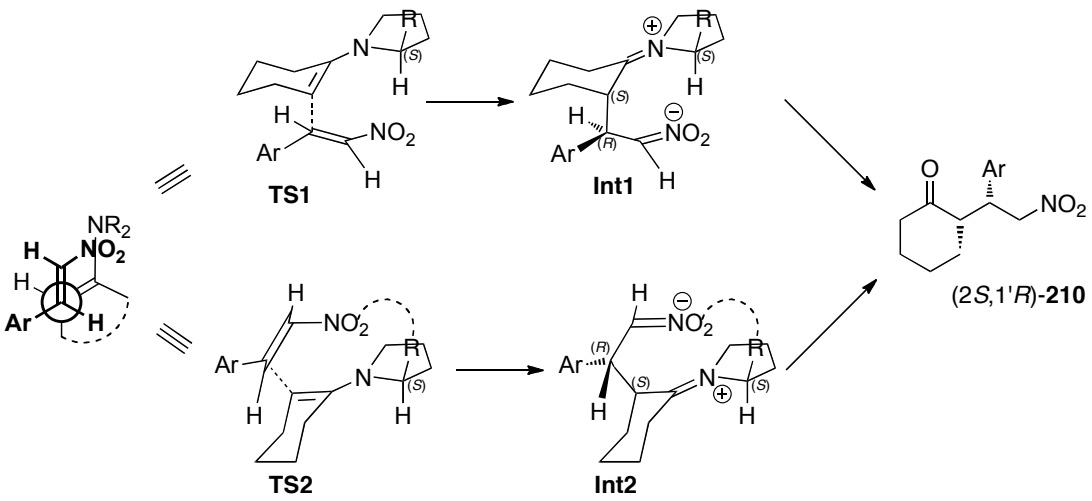
The stereoselectivity of enamine-catalyzed reactions is influenced by the geometry of the enamine intermediate **211**, which can form *E* or *Z* isomers (Scheme 3.5).[1] The geometric preference depends on both the catalyst and the substrate. For example, cyclic ketones, such as cyclohexanone, form *E*-isomers. Moreover, enamines can exist as two rotamers (Scheme 3.5).



Scheme 3.5. Dynamic equilibria between *E* and *Z* isomers and two rotamers of an enamine.

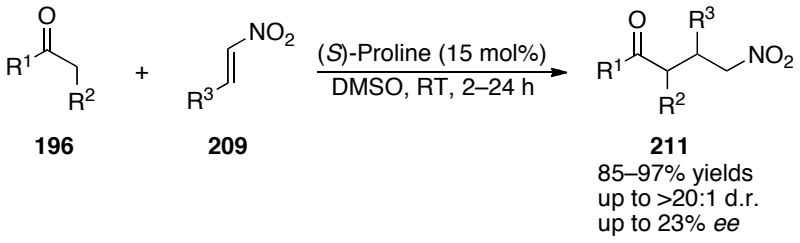
Based on the SEEBACH's model, it is generally accepted that enamine-catalyzed 1,4-additions proceed via acyclic synclinal transition state (Scheme 3.6). The enamine- and nitroolefin-double bonds are situated *gauche* to each other. The partially positive enamine nitrogen and the partially negative nitro group are electrostatically attracted. An example with an

(*S*)-enantiomer of a proline-derived catalyst and cyclohexanone is presented in Scheme 3.6. The R-group either provides steric shielding (**TS1**) or interacts with the nitro group to form the more constrained transition state **TS2**. Both transition states lead to the same stereoisomer. No experimental or computational results are available to rule out one of these pathways.



Scheme 3.6. Transition states **TS1**, **TS2** and iminium intermediates **Int1**, **Int2** in the 1,4-addition of cyclohexanone to an (*E*)-nitroolefin.

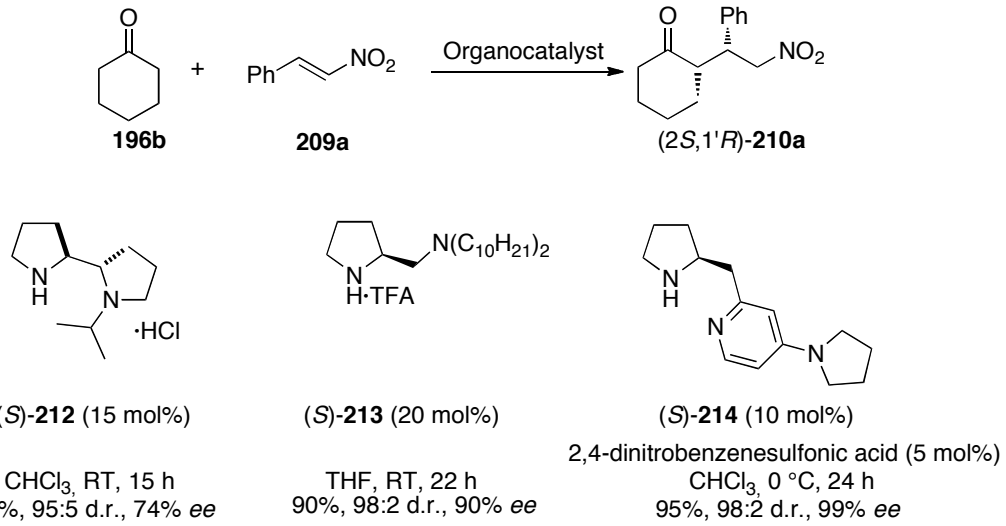
A plethora of highly selective and effective catalysts for 1,4-additions of ketones to nitroolefins has been reported to date.[13] The first enamine-catalyzed addition of ketones to nitrostyrene was investigated by LIST (Scheme 3.7).[14] Using (*S*)-proline as catalyst provided the products in high yield and with good diastereoselectivity, albeit with low enantioselectivity. ENDERS demonstrated that the enantioselectivity can be improved by using methanol as the solvent (*ee* up to 76%).[15]



Scheme 3.7. The first organocatalyzed 1,4-addition of ketones to nitroolefins.

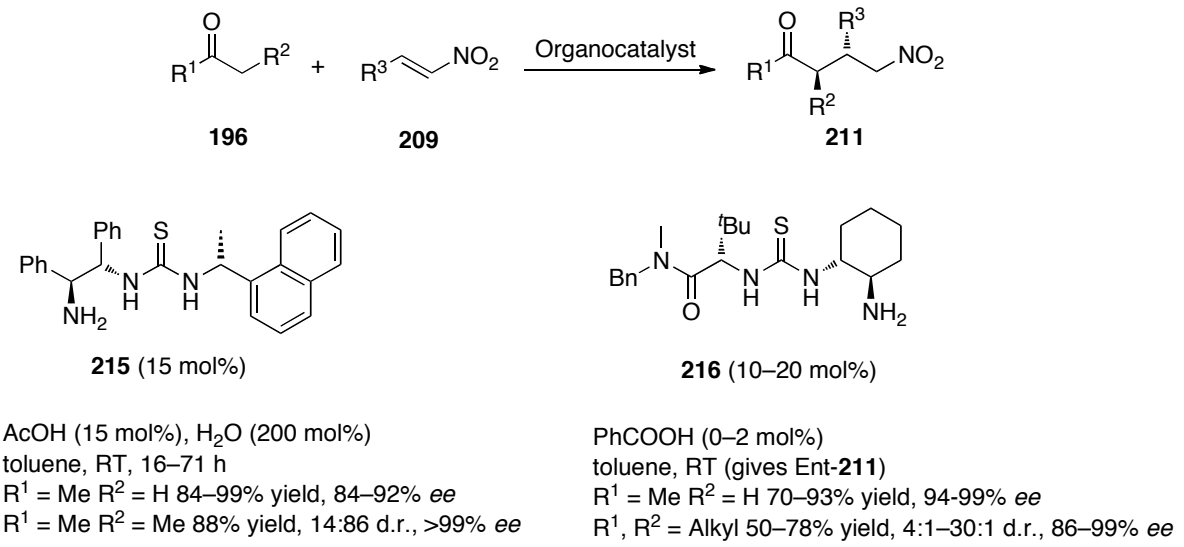
Modified proline-derived catalysts were found to be more selective. In particular, catalysts with an additional nitrogen atom showed exceptional selectivity in the reactions of cyclic ketones. In general, acyclic ketones were converted to the products with lower selectivity. ALEXAKIS introduced the bipyrrolidine catalyst (*S*)-**212**, which afforded the product

(2*S*,1'*R*)-**210a** in good yield and with good dia- and enantioselectivity (Scheme 3.8).[16] BARBAS investigated structural features of diverse diamine catalysts and found that the reaction proceeded in high yield and selectivity with (*S*)-**213** as a catalyst (Scheme 3.8).[17] Even higher selectivities were achieved by KOTSUKI with pyrrolidine-pyridine catalyst (*S*)-**214** (Scheme 3.8).[18]



Scheme 3.8. Examples of effective diamine organocatalysts for the 1,4-addition of cyclohexanone to β-nitrostyrene.

Acyclic ketones remained challenging until 2006, when TSOGOEVA[19] (catalyst **215**) and JACOBSEN[20] (catalyst **216**) developed bifunctional thiourea-based catalysts for this transformation (Scheme 3.9). Both catalysts are based on the same activation mode. The primary amine activates the ketone by formation of a *Z*-enamine in contrast to pyrrolidine-based secondary amines that afford *E*-enamines. The interaction between the nitroolefin and the thiourea moiety of the catalyst accounts for the appropriate orientation of reactants in the transition state. Catalyst **215** converts cyclic and acyclic ketones to γ-nitroketones in good to high yields and enantioselectivities in the presence of acetic acid and water. Even higher diastereoselectivity was obtained with **216**.



Scheme 3.9. Highly selective 1,4-additions of acyclic ketones to nitroolefins.

3.1.2 Self-assembling Catalysts via Hydrogen Bonding

Catalyst development is a time-consuming and complex process. The prediction of catalyst properties, such as selectivity and activity is very difficult and the substrate scope of any given catalyst is usually narrow. Combinatorial synthesis of catalyst libraries has become an important strategy in catalyst research.[21]

A new approach to catalyst libraries in homogeneous catalysis is based on the use of supramolecular ligands that are formed by self-assembly of building blocks.[22] The aim is to use two monodentate ligands that are complementarily bound together, thus mimicking a bidentate ligand (Figure 3.1). The self-assembly relies on the formation of non-covalent interactions such as hydrogen bonds, metal-ligand or Coulomb interactions. In this text the focus is placed on self-assembling catalysts *via* hydrogen bonding.

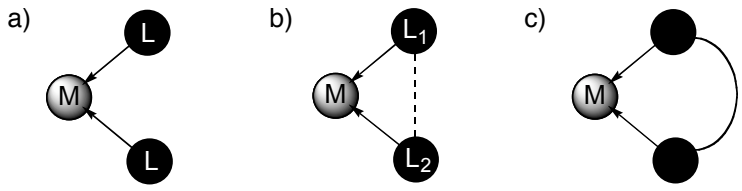
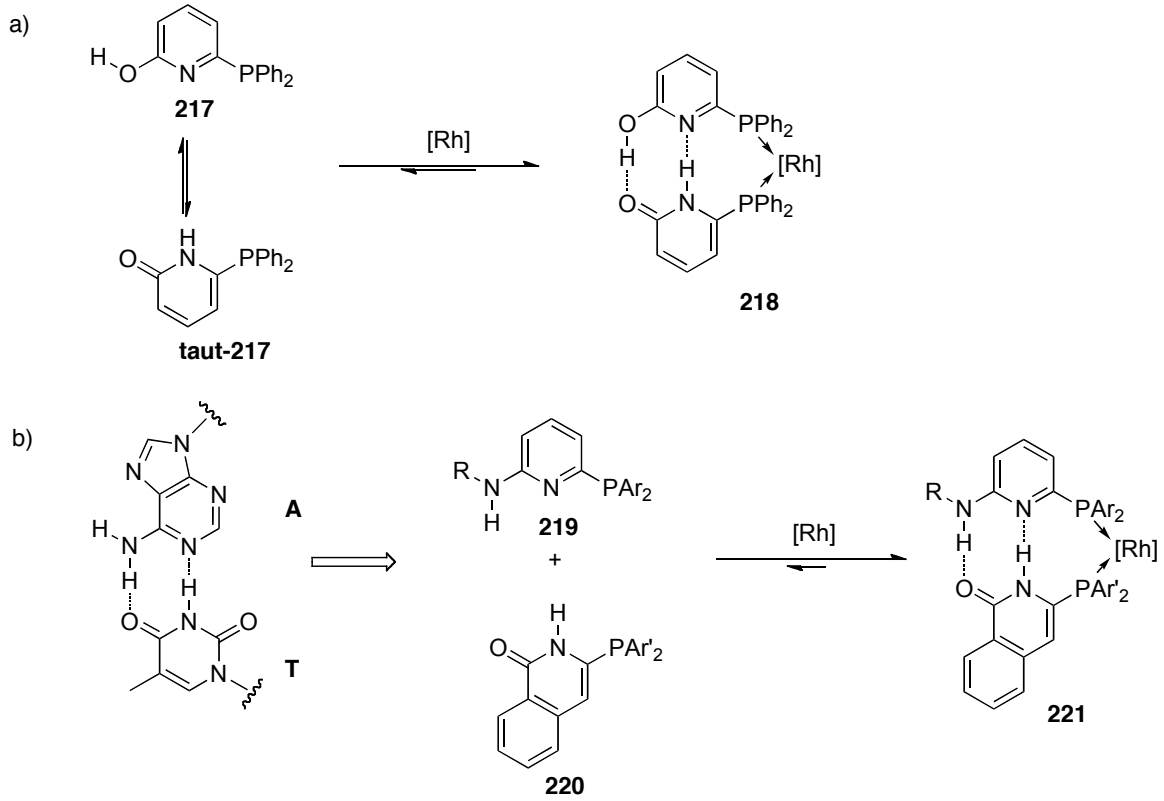


Figure 3.1. Types of metal complexes: a) with two monodentate ligands; b) with two monodentate ligands interacting non-covalently; c) with a bidentate ligand.[22]

A novel concept for the construction of self-assembled ligands was described by BREIT (Scheme 3.10a).[23] The self-assembly of functionalized 2-pyridone **217** and its tautomer **taut-217** was employed in a highly regioselective, rhodium-catalyzed hydroformylation of olefins. This approach did not allow for the use of two different ligands due to the possible competing formation of homodimeric species. Therefore, a new system based on the adenine (A)-thymine (T) base pair was developed (Scheme 3.10b).[24] Catalysts containing functionalized aminopyridine **219** and isoquinolone **220** were employed in the hydroformylation of terminal alkenes. Based on this principle, a small library containing 16 catalysts was prepared and tested. The methodology was extended to libraries of heterocycle-containing phosphine ligands.[25] Applications in enantioselective reactions were also developed.[26]

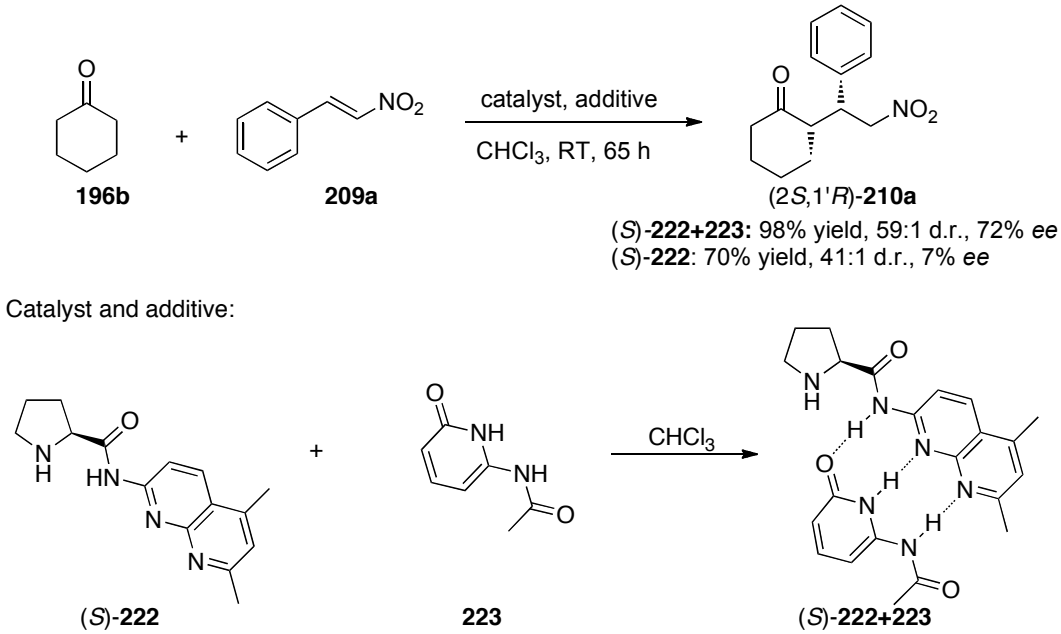


Scheme 3.10. Self-assembly of monodentate to bidentate ligands: a) Based on the tautomers of hydroxypyridine **217**; b) As analogy to adenine-thymine base pair.

3.1.1.2 Self-assembling Organocatalyst Based on Hydrogen Bonds

An application of hydrogen bond assembled organocatalysts was reported by CLARKE and FUENTES.[27] Their approach is based on complementary hydrogen bonding between a chiral

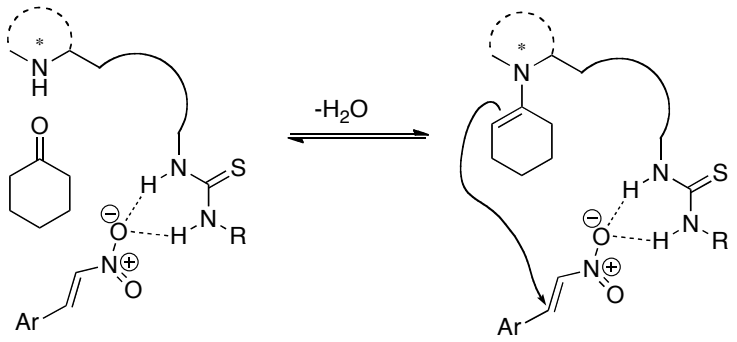
precatalyst and an achiral additive that influences the steric environment of the catalyst. In contrast to BREIT's system, the self-assembly was based on three hydrogen bonds. The catalysts were tested in the 1,4-addition of cyclohexanone to *β*-nitrostyrene (Scheme 3.11). Catalyst (*S*)-**222** turned out to be highly diastereoselective, but the product obtained was almost racemic. Out of the tested additives, the pyridone derivative **223** provided the best enhancement of catalyst activity and selectivity. Using a 1:1 mixture of (*S*)-**222** and **223**, the product was obtained with 59:1 d.r. and 72% *ee*. The complementary binding was confirmed by ^{1}H-NMR studies.



Scheme 3.11. 1,4-Addition of cyclohexanone to *β*-nitrostyrene catalyzed by the self-assembly of catalyst (*S*)-**222** and additive **223**.

3.3.2 Objectives

The activation of both reactants is possible in the 1,4-addition of ketones to nitroolefins. Either a primary or secondary amine can form an enamine with the ketone and a thiourea moiety can activate the nitroolefin by the formation of hydrogen bonds (Scheme 3.12). TSOGOEVA[19] and JACOBSEN[20] showed that a connection of both functionalities in one molecule produces highly selective catalysts.



Scheme 3.12. The principle of a bifunctional catalyst in 1,4-additions of ketones to nitroolefins.[19]

The aim of this project was to develop a new concept for organocatalysts (Figure 3.2). Based on the work of CLARKE,[27] the new catalyst would consist of two parts connected by hydrogen bonds. In addition, each part would be able to activate one reactant in an organocatalyzed reaction. Two basic structural motifs for bifunctional, self-assembled catalysts were envisioned. The first generation catalyst is a simplified CLARKE's catalyst (*S*)-**222**+**223** with only two hydrogen bonds. The R-group represents the additional functionality, e.g. for the 1,4-addition of ketones to nitroolefins a thiourea moiety. The second generation catalyst is based on a proline-pyridine derivatives (*S*)-**227** and (*S*)-**229** that should be able to form hydrogen bonds to simple pyridine-derived additives **225** and **228**.

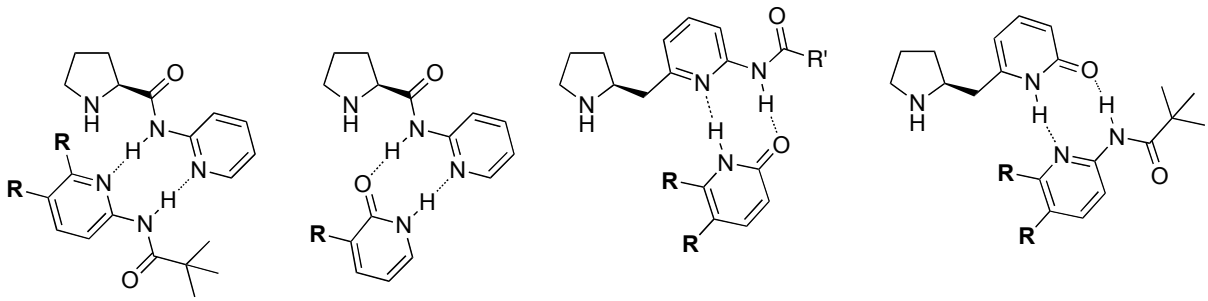


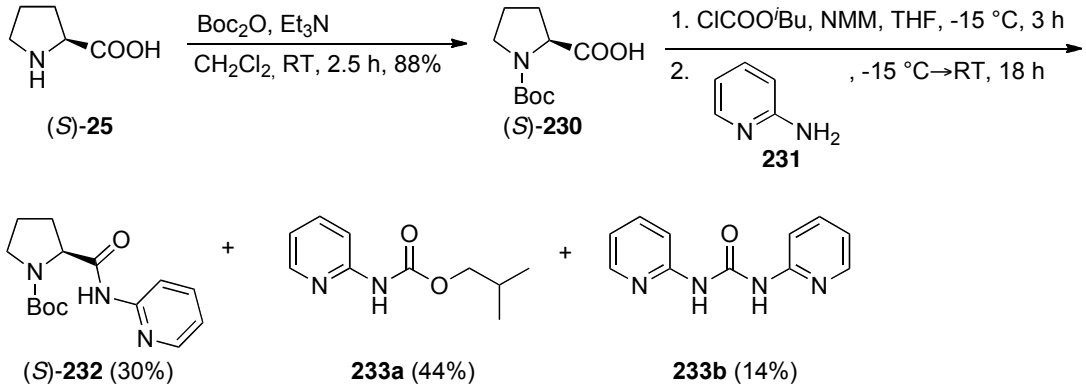
Figure 3.2. The structures of new organocatalysts envisioned within this work.

3.2 First Generation Catalyst

3.2.1 Synthesis of Catalyst

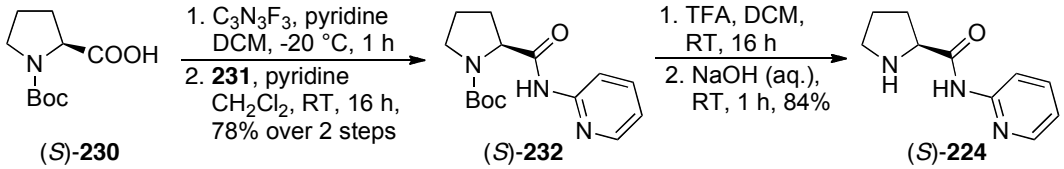
The pyrrolidine-part of the first generation catalyst (*S*)-**224** was reported as catalyst in aldol reactions of ketones with α-keto acids.[28] It can be prepared from protected proline by coupling with 2-aminopyridine followed by deprotection.

Following a reported procedure, the coupling of *Boc*-protected (*S*)-proline ((*S*)-**230**) with amine **231** was performed with isobutyl chloroformate and *N*-methylmorpholine (Scheme 3.13).[29] The product (*S*)-**232** was obtained in 30% yield, together with two by-products **233a** (44%) and **233b** (14%) resulting from incomplete formation of the mixed anhydride from the acid and the chloroformate.



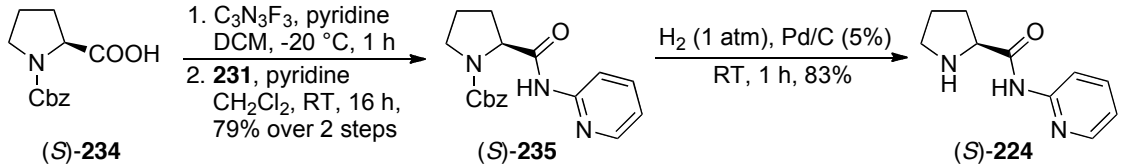
Scheme 3.13. Synthesis of protected amide (*S*)-**232** by coupling *via* isobutyl chloroformate activation.

Acid fluorides are known to be highly efficient acylating reagents. CARPINO reported the synthesis of amino acid-derived fluorides with cyanuric fluoride and their employment in peptide coupling.[30] No racemization was observed during the whole process. By a modification of CLARKE's procedure, the protected proline (*S*)-**230** was treated with cyanuric fluoride in the presence of a base (Scheme 3.14).[31] The acid fluoride was isolated and used directly in the reaction with amine **231** to give the product (*S*)-**232** in good yield. The deprotection was achieved in good yield by treatment with TFA. It was found that partial hydrolysis of the amide bond took place (up to 10%).



Scheme 3.14. Synthesis of amide (*S*)-**224** via coupling of acid fluoride and amine **231**.

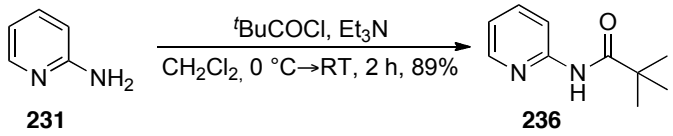
In order to avoid the cleavage of the amide during the acidic deprotection, the *Cbz*-protecting group was used (Scheme 3.15). As with the previous synthesis, the protected amide (*S*)-**235** was obtained in good yield. Subsequent hydrogenolytic deprotection provided the amide (*S*)-**224** in good yield without any side reactions. This synthesis can be performed without the utilization of column chromatography.



Scheme 3.15. Synthesis of amide (*S*)-**224** from (*S*)-**234**

3.2.2 Synthesis of Additives

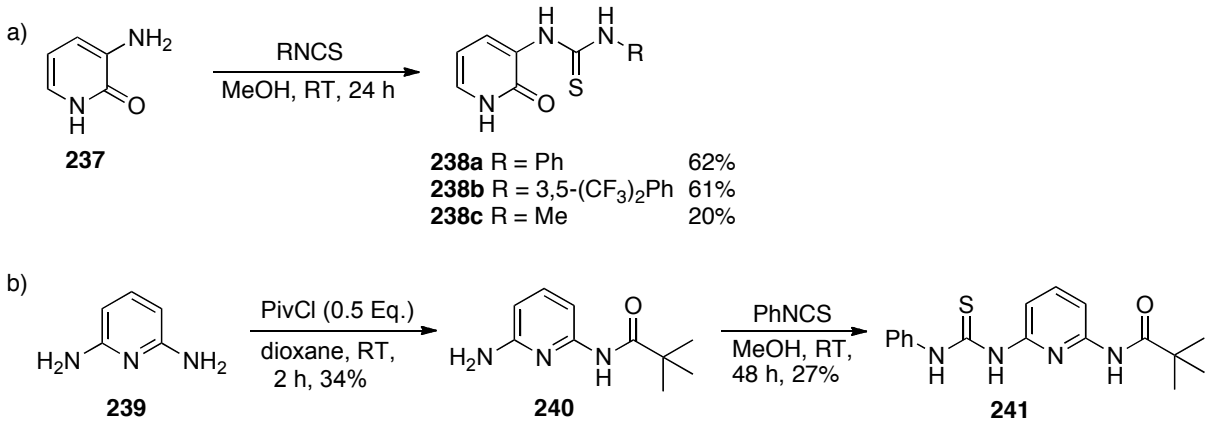
The additives for the self-assembled catalyst could be derived from 2-aminopyridine and 2-pyridone. For this purpose, 2-aminopyridine (**231**) was transformed to amide **236** in good yield (Scheme 3.16).



Scheme 3.16. Synthesis of amide **236**.

The thiourea functionality can be introduced by the reaction of amines with thioisocyanates. The thiourea **238a** was prepared from 3-amino-2-pyridone (**237**) and phenyl thioisocyanate in moderate yield following a published method (Scheme 3.17a).[32] By the same method, thioureas **238b** and **238c** were obtained in low to moderate yields.

2,6-Aminopyridine (**239**) was treated with pivaloyl chloride to provide the monoacylated product **240** in low yield (Scheme 3.17b). The following reaction with phenyl isothiocyanate gave the additive **241** in low yield. This reaction sequence was not optimized.



Scheme 3.17. The synthesis of thiourea additives.

3.2.3 1,4-Addition of Cyclohexanone to Nitrostyrene with (*S*)-224 and Additives

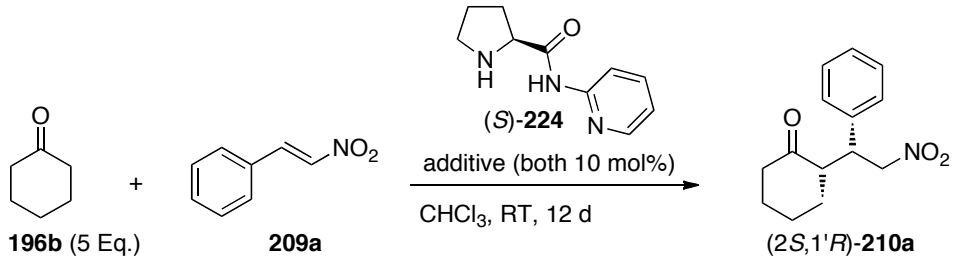
The 1,4-addition of cyclohexanone to *β*-nitrostyrene was carried out under the conditions reported by CLARKE (Table 3.1).[26] The reaction mixture was stirred at room temperature with 10 mol% of catalyst (*S*)-**224** and 10 mol% of additives.

In contrast to CLARKE's results, the reaction was not complete after 12 days. In the absence of any additives, the product was obtained in 61% yield, 93:7 d.r. and 11% *ee*. In general, additives with a free amine function (**231** and **239**) inhibit the reaction and do not influence the enantiomeric excess. Unsubstituted 2-pyridone (**242**) showed a small acceleration and an improvement in *ee* (Table 3.1, Entry 3). Although additives **238a-c** were insoluble in chloroform, **238a** and **b** provided the opposite enantiomer, albeit with low *ee* (Table 3.1, Entries 8, 9, 13). Under neat conditions, catalyst (*S*)-**224** was even less active than in chloroform and nearly unselective. The addition of thiourea **238a**, which was soluble under these conditions, enhanced the activity and selectivity (Table 3.1, Entry 11). No conversion was obtained when DMSO and CF_3CH_2OH were used as solvents.

The results indicate that some additives have an effect on the reactions. The formation of self-assembly from catalyst (*S*)-**224** and additives **236** and **242** was examined by ESI-MS (Figures 3.3 and 3.4). In both cases, the signals assigned to catalyst (*S*)-**224** (protonated (*S*)-**224** *m/z* = 192; its sodium adduct *m/z* = 214; sodium adduct of the dimer of (*S*)-**224** *m/z* = 405) were the most intense ones. The signals of the additives were also detected; additive **236** in its protonated form (*m/z* = 179), sodium adduct (*m/z* = 210) and the sodium adduct of the dimer (*m/z* = 379). The molecular ion (*m/z* = 95) and sodium adduct (*m/z* = 118) of the additive **242** were also observed. The signals of self-assembled species (*S*)-**224**+**236** (sodium adduct

m/z = 392) and (*S*)-**224**+**242** (*m/z* = 286; sodium adduct *m/z* = 392) were visible in the spectra, though of lower intensity.

Table 3.1. 1,4-addition of cyclohexanone to *β*-nitrostyrene catalyzed by (*S*)-**224** in the presence of additives.[a]



Entry	Additive	Conv. [%][b]	Yield [%]	d.r.[b]	*ee* [%][c]
1	–	74	61	93:7	11
2	**236**	63	58	94:6	12
3	2-pyridone (**242**)	90	83	95:5	24
4	**231**	36	16	94:6	12
5	**239**	54	45	91:9	6
6	**237**	63	55	90:10	14
7	*N*,*N*'-dimethylthiourea (**243**)	33	19	92:8	12
8	**238a**	73	63	94:6	-9
9[d]	**238a**	79	68	95:5	-12
10[e]	–	14	13	nd[f]	-3
11[e]	**238a**	68	61	92:8	-25
12	**241**	88	81	94:6	5
13	**238b**	61	57	92:8	-11
14	**238c**	44	37	94:6	7

[a]Performed with *β*-nitrostyrene (0.250 mmol), cyclohexanone (1.20 mmol), (*S*)-**224** (25 µmol) and additive (25 µmol) in $CHCl_3$ (2 mL) at RT. [b]Determined by ^{1}H-NMR. [c]Determined by HPLC on chiral stationary phase. [d]Cyclohexanone (5.00 mmol). [e]Performed neat in cyclohexanone (19.2 mmol). [f]Not determined.

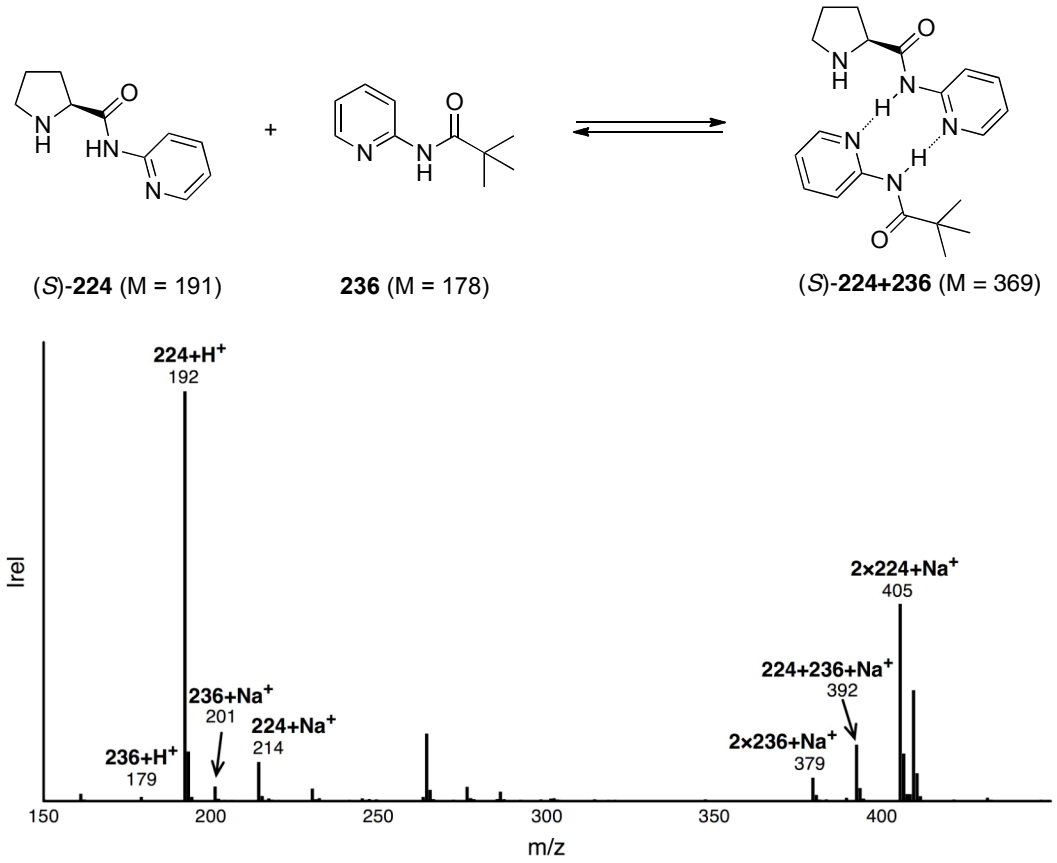


Figure 3.3. ESI-MS spectrum of the mixture of catalyst (*S*)-**224** and additive **236**.

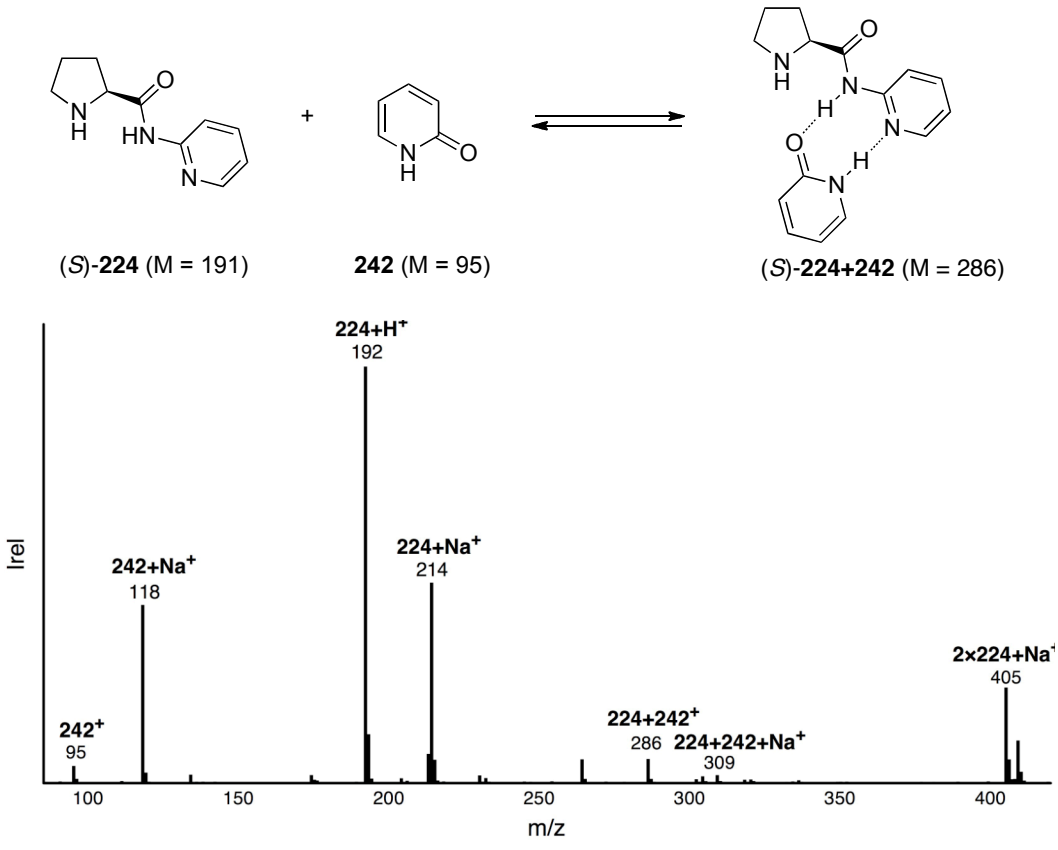


Figure 3.4. ESI-MS spectrum of the mixture of catalyst (*S*)-**224** and additive **242**.

In the ESI-MS spectrum corresponding to the 1,4-addition of cyclohexanone to *β*-nitrostyrene, the mass peak at *m/z* = 272, representing the protonated enamine intermediate **244**, was the most prominent one (Figure 3.5). The signals of the free, protonated catalyst (*m/z* = 192) and the sodium adduct of the additive **242** (*m/z* = 118) were also visible in the spectrum. The signal at *m/z* = 421 was identified as iminium intermediate **245**, and the small signal at *m/z* = 389 could be assigned to the sodium adduct of enamine **246**.

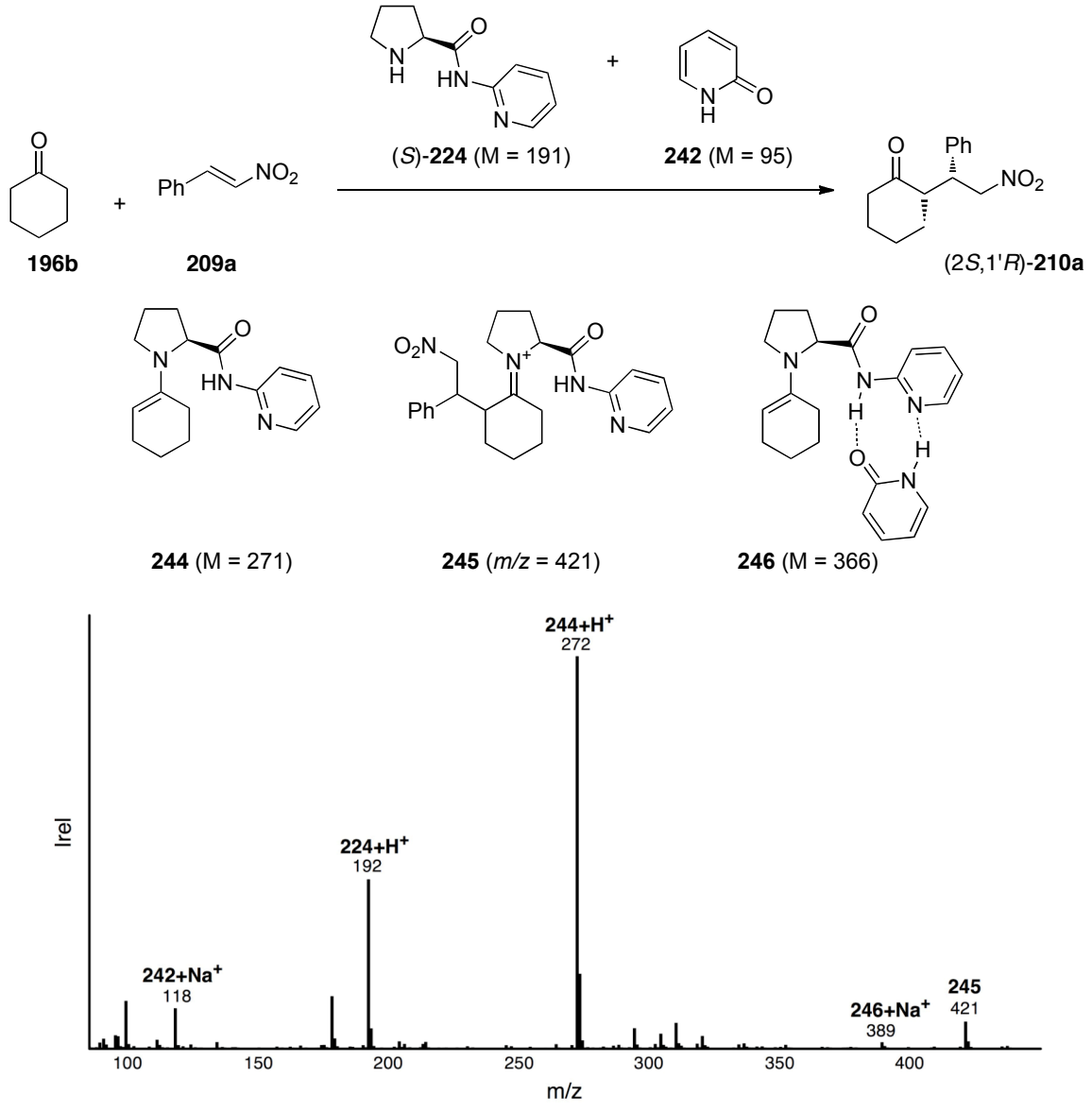


Figure 3.5. The ESI-MS spectrum of 1,4-addition of cyclohexanone to nitrostyrene catalyzed by (*S*)-**224** and **242**.

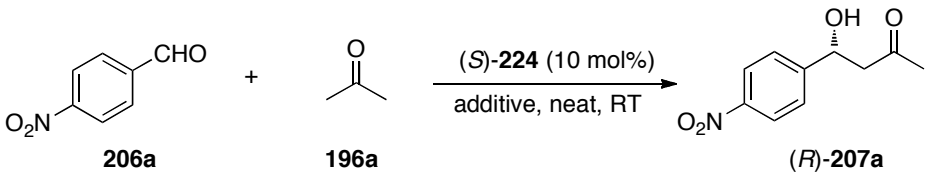
It is not clear how the electrospray conditions and those in the mass spectrometer affect the formation of the self-assembled species and whether the observed spectra reflect the actual situation during the reaction.

3.2.4 Organocatalyzed Aldol Reaction

The proline amide (*S*)-**224** was shown to be an inactive and unselective catalyst in the enamine-catalyzed 1,4-additions. However, proline amides represent a commonly used catalyst class in direct aldol reactions.[1, 33] An important structural feature of proline amides is the acidic proton of the amide that activates the electrophile.

Therefore, the catalyst (*S*)-**224** was tested in the aldol reaction of *p*-nitrobenzaldehyde and acetone (Table 3.2). The reactions were performed with acetone as solvent, because very low conversion was obtained in chloroform. Full conversions were obtained in 3 days. The reaction required only 2 days in the presence of additive **241**. As expected, the effects of the additives on enantiomeric excess were small, because acetone is not suitable for the formation of hydrogen bonds. The most significant difference in *ee* was achieved with additive **238b** (29% *ee*, Table 3.2, Entry 5).

Table 3.2. Aldol reaction catalyzed by (*S*)-**224** and additives.[a]



206a **196a** (*R*)-**207a**

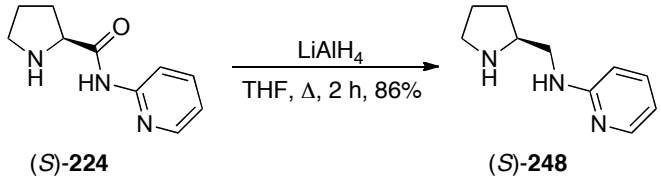
Entry	Additive	Time [h]	Conversion [%][b]	Yield [%]	*ee* [%][c]
1	–	65	99	86	41
2	**236**	65	99	86	42
3	**238a**[d]	65	quant.	88	38
4	**238c**[d]	68	quant.	84	44
5	**238b**	68	quant.	86	29
6	**241**	48	quant.	92	37
7	**242**	72	quant.	90	44
8	1-isoquinolinol (**247**)	72	quant.	88	44

[a]Catalyst (*S*)-**224** (25 µmol) and additive (25 µmol) were dissolved in dry acetone (6.8 mmol) and after 15 minutes, 4-nitrobenzaldehyde (250 µmol) was added. [b]Determined by ^{1}H-NMR. [c]Determined by HPLC on chiral stationary phase. [d]The additive not completely dissolved.

The tested conditions were not suitable for the formation of the self-assembled species. Moreover, a different functional group than a thiourea should be utilized in order to improve the activity and selectivity of the catalyst in the aldol reaction.

3.2.5 Reduced Catalyst (*S*)-248

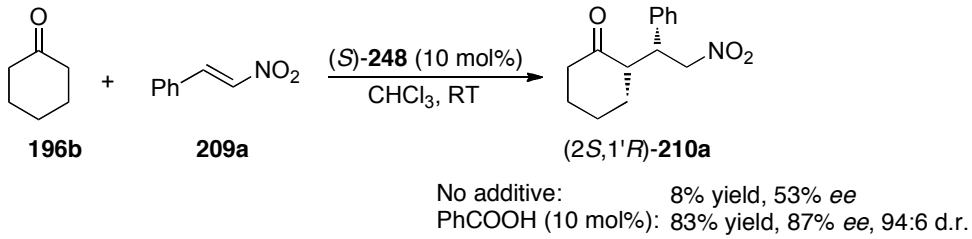
As mentioned above, the amide functionality is likely responsible for the low activity of the catalyst (*S*)-**224** in the 1,4-addition. Therefore, (*S*)-**224** was reduced with $LiAlH_4$ to give the diamine (*S*)-**248** in good yield (Scheme 3.18).



Scheme 3.18. Reduction of the catalyst (*S*)-**248**.

*3.2.5.1 (S)-**248** in 1,4-Addition of Cyclohexanone to β-Nitrostyrene*

Following the same reaction setup as for catalyst (*S*)-**224**, the 1,4-addition of cyclohexanone to *β*-nitrostyrene was carried out (Scheme 3.19). Very low conversion and moderate *ee* was obtained after 12 days. However, addition of benzoic acid (10 mol%) accelerated the reaction. The product was obtained in good diastereomeric and enantiomeric excess.



Scheme 3.19. 1,4-Addition of cyclohexanone to *β*-nitrostyrene with catalyst (*S*)-**248**.

It was found that a problem with the reproducibility of the enatiomeric excess occured. This problem was caused during preparation of the sample for HPLC (Figure 3.6). The product **210a** tends to crystallize out of many solvents. Several samples for HPLC were directly prepared after evaporation of cyclohexane/ethyl acetate after the column. Other samples were prepared after transferring of the product into smaller flask as a solution in DCM. The samples resulting from the material obtained by evaporation of cyclohexane/ethyl acetate gave irreproducible results, because **210a** crystallized out as an enantiomerically enriched material. The samples prepared after the evaporation of DCM led to reproducible results as a result of the good solubility of the product in DCM.

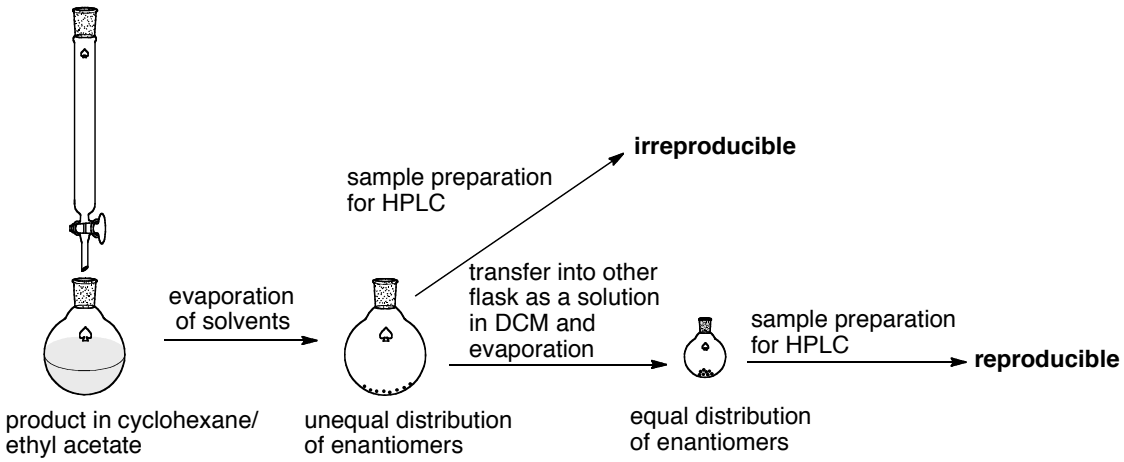
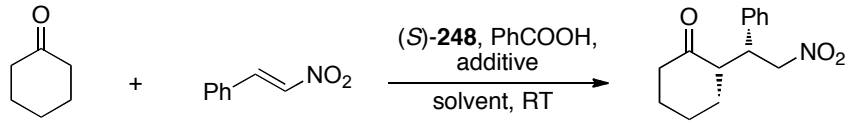


Figure 3.6. The preparation of the samples for HPLC and the reproducibility of the results.

In order to optimize the promising result obtained in chloroform in the presence of benzoic acid, a solvent screening was carried out (Table 3.3). The best results were obtained in toluene and under neat conditions. Longer reaction time was necessary when water (2 Equiv) was added to the reaction performed in toluene, but the product was obtained with higher enantiomeric excess.

Table 3.3. Screening of solvents in 1,4-addition of cyclohexanone to *β*-nitrostyrene.[a]



196b **209a** (2*S*,1'*R*)-**210a**

Entry	Additive	Solvent	Time [h]	Conv. [%][b]	Yield [%]	d.r.[b]	*ee* [%][c]
1	-	$CHCl_3$	72	91	83	94:6	87
2	H_2O (2 Eq.)	$CHCl_3$	72	90	84	95:5	88
3	-	Water	72	38	19	n.d.[d]	91
4	-	Neat	24	97	89	93:7	94
5	H_2O (2 Eq.)	Neat	24	97	87	96:4	94
6	-	Toluene	41	94	83	94:6	91
7	H_2O (2 Eq.)	Toluene	72	93	84	94:6	93
8	-	*n*-Hexane	72	70	63	93:7	90
9	H_2O (2 Eq.)	*n*-Hexane	72	49	42	94:6	91

[a]Performed with cyclohexanone (1.20 mmol), *β*-nitrostyrene (250 µmol), catalyst (*S*)-**248** (25 µmol), PhCOOH (25 µmol) and water (500 µmol) in solvent (2 mL) at RT. [b]Determined by ^{1}H-NMR. [c]Determined by HPLC on chiral stationary phase. [d]Not determined.

*3.2.5.2 Structural Modifications of Catalyst (S)-**248***

In order to investigate the catalytic activity of (*S*)-**248**, structural analogs **224**, **249-251** were envisioned (Figure 3.7). These analogs should be applied to the 1,4-addition of cyclohexanone to *β*-nitrostyrene and the results compared to those obtained with (*S*)-**248**.

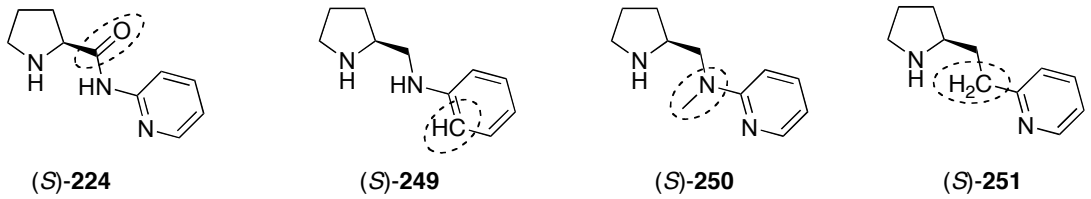
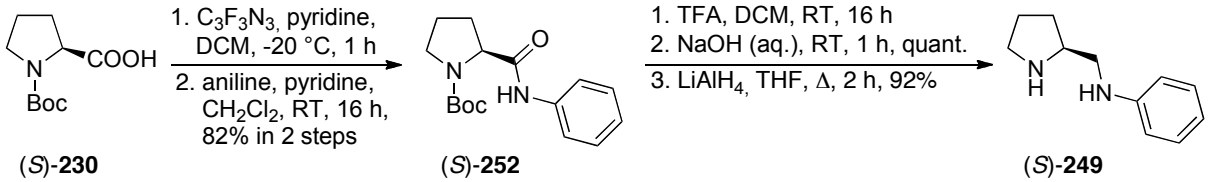


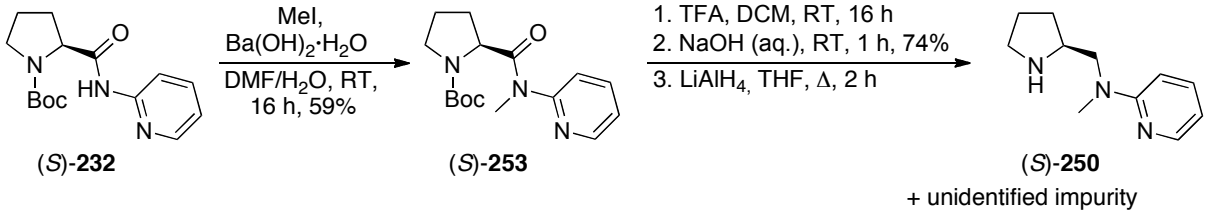
Figure 3.7. Modifications of catalyst (*S*)-**248**.

Diamine (*S*)-**249** was recently employed in the 1,4-addition of cyclohexanone to *β*-nitrostyrene.[34] Using 20 mol% of catalyst, the product was obtained in 80% yield, 17:1 d.r. and 77% *ee*. As this catalyst should be tested under exactly the same conditions, it was prepared from protected (*S*)-proline in good overall yield (Scheme 3.20).



Scheme 3.20. Synthesis of diamine (*S*)-**249**.

The synthesis of diamine (*S*)-**250** was examined by D. RÖSCH during his *Schlussversuch* (Scheme 3.21). The protected amide (*S*)-**232** was methylated with methyl iodide in the presence of a base in moderate yield. Deprotection provided the amide in good yield, although an unknown inseparable impurity was present. This impurity remained inseparable after the reduction to diamine (*S*)-**250**.



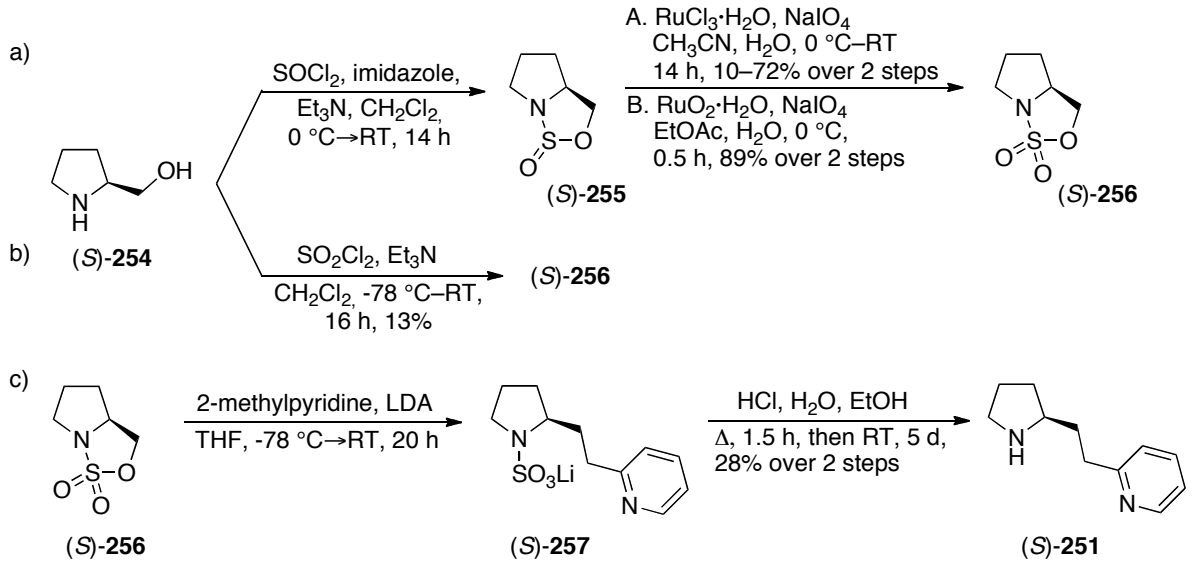
Scheme 3.21. The attempted synthesis of (*S*)-**250**.

As the diamine (*S*)-**250** could not be prepared in a pure form, the literature-known catalyst (*S*)-**251** was prepared from (*S*)-prolinol.[35] It was reported that (*S*)-**251** provided the product

of 1,4-addition of cyclohexanone to *β*-nitrostyrene in 55% yield, 92:8 d.r. and 55% *ee*. The reaction was performed in chloroform.

Following the reported procedure, (*S*)-prolinol was converted to sulphamidite (*S*)-**255** that was oxidized to sulphamidate (*S*)-**256** (Scheme 3.22a).[36] Oxidation with ruthenium(III) chloride was not reproducible due to the high hydrophilicity of the oxidant.[36a] Oxidation with ruthenium(IV) oxide provided product (*S*)-**256** in 89% yield over two steps.[36b] Low yield was obtained in the direct cyclization of (*S*)-prolinol with sulfuryl chloride (Scheme 3.22b).[36a]

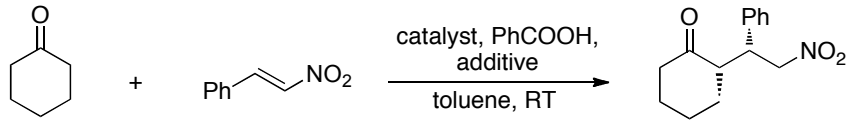
D. ROESCH performed the reaction of the sulfamidate (*S*)-**256** with lithiated 2-methylpyridine (Scheme 3.22c). After the deprotection of (*S*)-**257**, the product (*S*)-**251** was obtained in low yield.



Scheme 3.22. The synthesis of catalyst (*S*)-**251**: a) Two-step synthesis of catalyst precursor (*S*)-**256**; b) Direct synthesis of catalyst precursor (*S*)-**256**; c) Reaction of catalyst precursor (*S*)-**256** with lithiated 2-methylpyridine and deprotection.

With the catalyst (*S*)-**248** analogs in hand, the 1,4-addition of cyclohexanone to *β*-nitrostyrene was carried out (Table 3.4). It seems that both the amino and the pyridine moiety are responsible for the action of catalyst (*S*)-**248**. All catalysts tested required longer reaction times and were less selective. A positive effect of water on the selectivity was observed only with catalyst (*S*)-**248**. The amide (*S*)-**224** provided the product with small enantiomeric excess and moreover, needed six days to achieve high conversion.

Table 3.4. 1,4-Addition of cyclohexanone to *β*-nitrostyrene with analogs of catalyst (*S*)-**248**.[a]



196b **209a** (2*S*,1'*R*)-**210a**

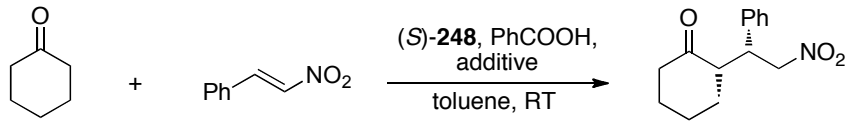
Entry	Catalyst	Additive	Time [h]	Conv. [%][b]	Yield [%]	d.r.[b]	*ee* [%][c]
1	(*S*)-**248**	-	41	94	83	94:6	91
2	(*S*)-**248**	H_2O (2 Eq.)	72	93	84	94:6	93
3	(*S*)-**224**	-	144	98	91	91:9	38
4	(*S*)-**224**	H_2O (2 Eq.)	144	89	79	93:7	25
5	(*S*)-**249**	-	72	quant.	94	93:7	87
6	(*S*)-**249**	H_2O (2 Eq.)	72	92	87	95:5	87
7	(*S*)-**251**	-	72	99	91	94:6	89
8	(*S*)-**251**	H_2O (2 Eq.)	72	39	32	95:5	89

[a]Performed with cyclohexanone (1.20 mmol), *β*-nitrostyrene (250 µmol), catalyst (25 µmol), PhCOOH (25 µmol) and water (500 µmol) in toluene (2 mL) at RT. [b]Determined by ^{1}H-NMR. [c]Determined by HPLC on chiral stationary phase.

*3.2.5.3 Optimization of the Reaction Conditions with Catalyst (S)-**248***

It was found that the reaction is faster when a lower amount of solvent is used (Table 3.5). The reaction was completed in less than 1 day in a more concentrated reaction mixture. The product precipitates from such concentrated reaction mixtures. When this reaction mixture was cooled to -18 °C for 1 h, the precipitated product was obtained in moderate yield with high d.r and *ee* (Table 3.5, Entry 4). The higher concentration allowed for the reaction to be performed at 0 °C, which led to improved *ee* and d.r. (Table 3.5, Entries 8 and 9).

Table 3.5. Optimization of the concentration of the catalyst (*S*)-**248**.[a]



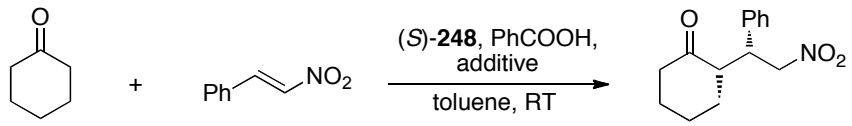
196b **209a** (2*S*,1'*R*)-**210a**

Entry	Additive	T [°C]	Conc. [mM][b]	Time [h]	Conv. [%][c]	Yield [%]	d.r.[c]	*ee* [%][d]
1	-	25	12	41	94	83	94:6	91
2	H_2O (2 Eq.)	25	12	72	93	84	94:6	93
3	-	25	40	23	quant.	90	93:7	92
4[e]	-	25	40	23	quant.	65	98:2	>99
5	H_2O (2 Eq.)	25	40	23	98	87	94:6	93
6	-	0	12	72	74	63	97:3	94
7	H_2O (2 Eq.)	0	12	72	35	29	97:3	95
8	-	0	40	48	99	94	98:2	95
9	H_2O (2 Eq.)	0	40	48	72	65	99:1	96

[a]Performed with cyclohexanone (1.20 mmol), *β*-nitrostyrene (250 µmol), catalyst (*S*)-**248** (25 µmol), PhCOOH (25 µmol) and water (500 µmol) in toluene. [b]Catalyst concentration. [c]Determined by ^{1}H-NMR. [d]Determined by HPLC on a chiral stationary phase. [e]Work up: the crude reaction mixture was cooled to -18 °C for 1 h and the precipitated product was filtered off.

The catalyst loading can be reduced to 5 mol% at a catalyst concentration of 40 mM, but no effect on either d.r. or on *ee* was observed (Table 3.6). Reduction of the catalyst loading to 2.5 mol% led to a very sluggish reaction (under the best conditions, 58% conversion after 90 h).

Table 3.6. Optimization of the catalyst loading.[a]



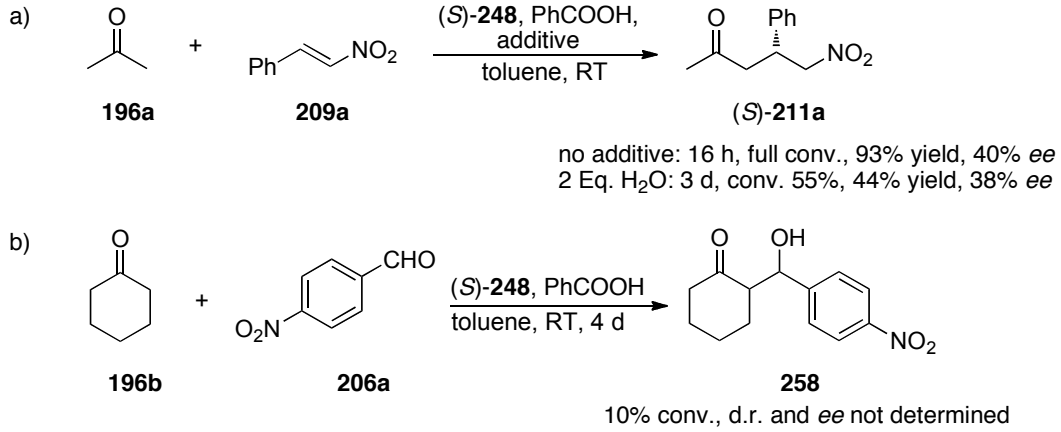
196b **209a** (2*S*,1'*R*)-**210a**

Entry	Catalyst loading [mol%]	Conc. [mM][b]	Time [h]	Conv. [%][c]	Yield [%]	d.r.[c]	*ee* [%][d]
1	10	40	23	quant.	90	93:7	92
2	5	40	16	98	86	94:6	93
3	2.5	40	90	40	n.i.[e]	90:10	n.d.[f]
4	2.5	30	90	35	n.i.[e]	93:7	n.d.[f]
5[e]	2.5	40	90	58	49	93:7	93

[a]Performed with cyclohexanone (1.20 mmol), *β*-nitrostyrene (250 µmol), catalyst (*S*)-**248** (25 µmol), PhCOOH (25 µmol) and water (500 µmol) in toluene. [b]Catalyst concentration. [c]Determined by ^{1}H-NMR. [d]Determined by HPLC on a chiral stationary phase. [e]Performed with 750 µmol cyclohexanone.

As mentioned above, acyclic ketones are more challenging substrates. Therefore, the reaction of acetone and *β*-nitrostyrene was carried out under the optimized conditions (Scheme 3.23a, 10 mol% (*S*)-**248**, 40 mM catalyst concentration, RT). The reaction was completed in 16 hours

and the product was obtained in 93% yield with 40% *ee*. The addition of water led to a slightly lower enantiomeric excess. As expected, the aldol reaction was sluggish under the same conditions (Scheme 3.23b).



Scheme 3.23. Catalyst (*S*)-**248** in: a) 1,4-Addition of acetone to *β*-nitrostyrene; b) Aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde.

3.2.6 Conclusions

The catalyst (*S*)-**224** was prepared starting from either *Boc*- or *Cbz*-protected (*S*)-proline in good overall yield. It was employed in the 1,4-addition of cyclohexanone to *β*-nitrostyrene. Under the conditions tested, (*S*)-**224** was shown to be unselective and ineffective.

The possibility of forming self-assemblies with 2-functionalized pyridine derivatives was examined. Among the additives tested, several showed small effects on the activity and selectivity of (*S*)-**224**. Unfunctionalized 2-pyridone (**242**) provided a small enhancement in selectivity. Thiourea-derived additives **238a-b** led to the formation of the opposite enantiomer, albeit with low *ee*. The formation of self-assemblies between (*S*)-**224** and **236** and **242** was detected by ESI-MS.

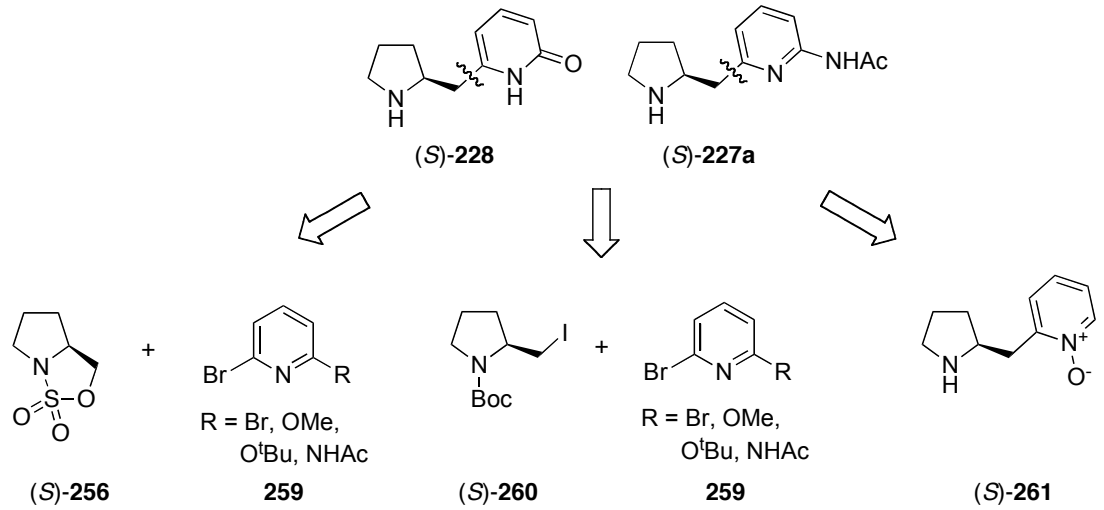
Only small effects of additives were observed in the (*S*)-**224**-catalyzed aldol reaction between *p*-nitrobenzaldehyde and acetone. The aldol product was obtained in high yield and low enantiomeric excess.

A reduction of the carbonyl bond of (*S*)-**224** furnished diamine (*S*)-**248**. (*S*)-**248** was tested in the 1,4-addition of cyclohexanone to *β*-nitrostyrene. The activity of (*S*)-**248** in the absence of additives was low, however, addition of benzoic acid accelerated the reaction. A small enhancement in enantioselectivity was observed in the presence of 2 equivalents of water. After optimization of the reaction conditions (solvent, concentration, temperature, catalyst

loading), the product was formed in high yield and with good diastereo- and enantiomeric excess. The screening of catalyst (*S*)-**248** analogues revealed that the secondary amine-pyridine moiety is necessary for the effective performance of the catalyst.

3.3 Second Generation Catalyst

It seems that the carbonyl group of catalyst (*S*)-**224** is responsible for its low effectiveness. Therefore, catalysts (*S*)-**227a** and (*S*)-**228** were expected to be more active. They might be prepared from sulfamidate (*S*)-**256** or iodide (*S*)-**260** by reaction with pyridine derivatives **259** (Scheme 3.24) or from *N*-oxide (*S*)-**261** .

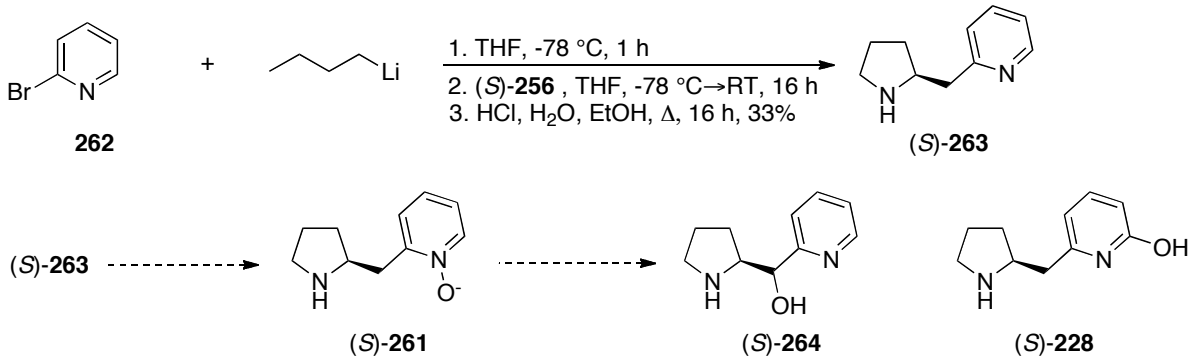


Scheme 3.24. Proposed synthesis of catalysts (*S*)-**227a** and (*S*)-**228**.

3.3.1 Synthesis of Catalyst (*S*)-227a

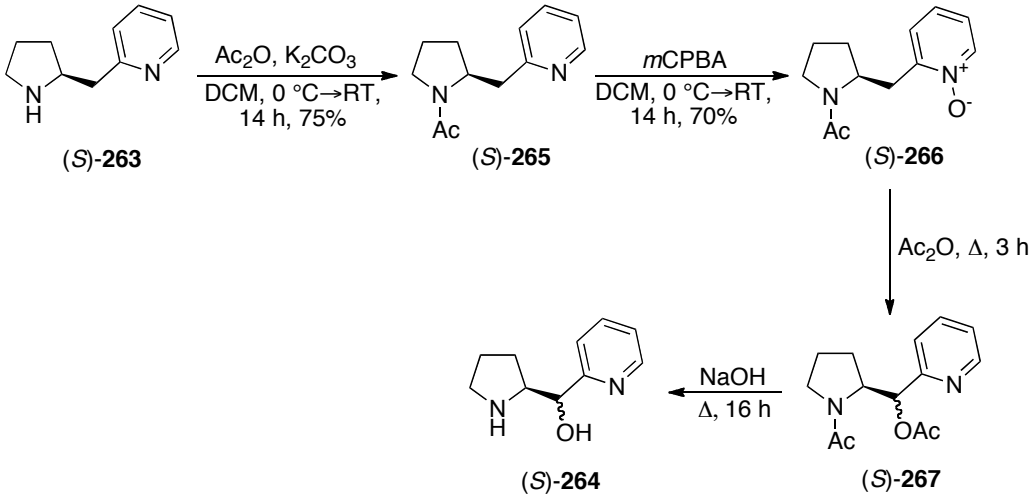
3.3.1.1 Rearrangement of the N-Oxide

Amine (*S*)-**263** was prepared in low yield by a reported procedure from sulfamidate (*S*)-**256** (Scheme 3.25).[35] The amine should be transformed to an *N*-oxide, which can undergo a rearrangement either to the methylene group or the 6-pyridine position.



Scheme 3.25. Synthesis of (*S*)-**256** and proposed following transformations.

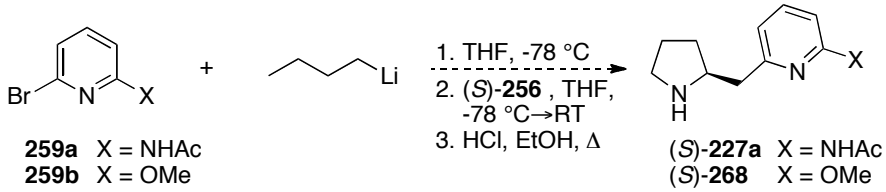
Direct oxidation of (*S*)-**263** with *m*CPBA led to a complex mixture. Therefore, the nitrogen of the pyrrolidine was protected as the acetamide (Scheme 3.26). Oxidation with *m*CPBA provided *N*-oxide (*S*)-**266** in good yield, but not entirely pure. The rearrangement was achieved by treatment with Ac_2O followed by deprotection. Analysis of the crude material showed that alcohol (*S*)-**264** was formed. Due to its high solubility in water, the purification attempts were unsuccessful.



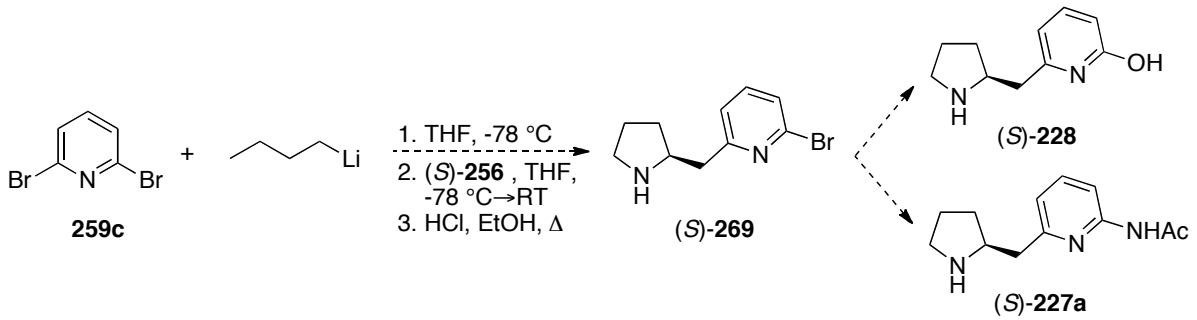
Scheme 3.26. Synthesis of *N*-oxide (*S*)-**266**, its rearrangement and subsequent deprotection

*3.3.1.2 Addition of Organolithium Reagents to Sulfamidate (S)-**256***

In analogy to the reaction of the 2-pyridine-derived organolithium reagent, 2,6-disubstituted pyridine derivatives might be employed in the substitution to sulfamidate (*S*)-**256**. Reaction with amine **259** would directly lead to catalyst (*S*)-**227a** (Scheme 3.27). The methyl group of (*S*)-**268** could then be removed to give catalyst (*S*)-**228**. Alternatively, the bromine in (*S*)-**269** could be substituted by a hydroxide or amide to give catalysts (*S*)-**227a** and (*S*)-**228** (Scheme 3.28). Unfortunately, all three reaction mixtures were very complex. The desired product was neither isolated nor detected in any of the mixtures.



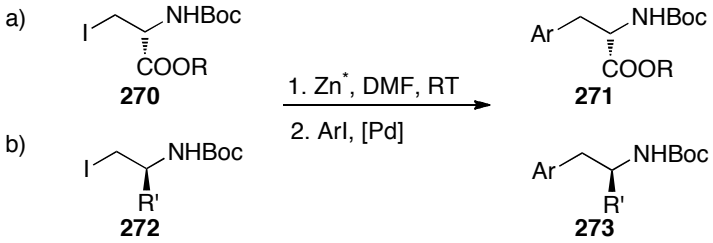
Scheme 3.27. Proposed reactions of functionalized 2-bromopyridines with sulfamidate (*S*)-**256**.



Scheme 3.28. Proposed reaction of 2,6-dibromopyridine with sulfamidate (*S*)-**256** and following transformations.

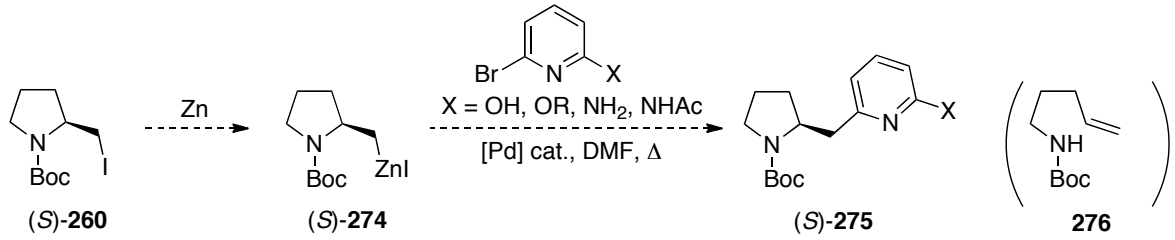
*3.3.1.3 Negishi Coupling of Iodide (S)-**260***

A new synthetic approach was based on the work of JACKSON, who reported the synthesis of non-natural amino acids **271** from corresponding iodides **270** by palladium-catalyzed Negishi coupling (Scheme 3.29a).[37, 38] The method was further extended to the synthesis of protected *β*-aryl-*α*-alkylethylamines **273** (Scheme 3.29b).[39] The organozinc reagents derived from iodides **270** and **272** exhibited sufficient stability to avoid the elimination.



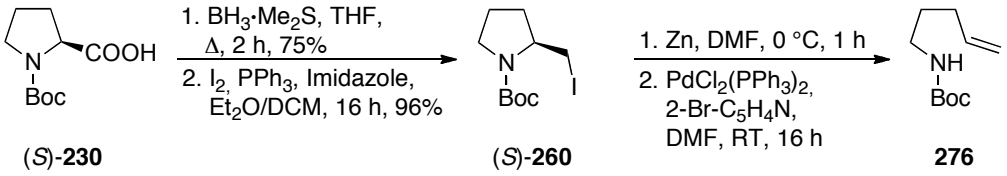
Scheme 3.29. Synthesis of: a) Non-natural amino acids **271**; b) Chiral amines **273**.

Analogously, the proline-derived iodide (*S*)-**260** might react in a similar way with pyridine-derived bromides to provide the precursors of desired catalysts (Scheme 3.30). The stability of proline-derived organozinc reagent **274** in dimethylacetamide was recently investigated.[40] In this solvent, only the elimination product **276** was formed after the zinc insertion and aqueous workup.



Scheme 3.30. Proposed synthesis of catalysts (*S*)-**275** *via* Negishi coupling.

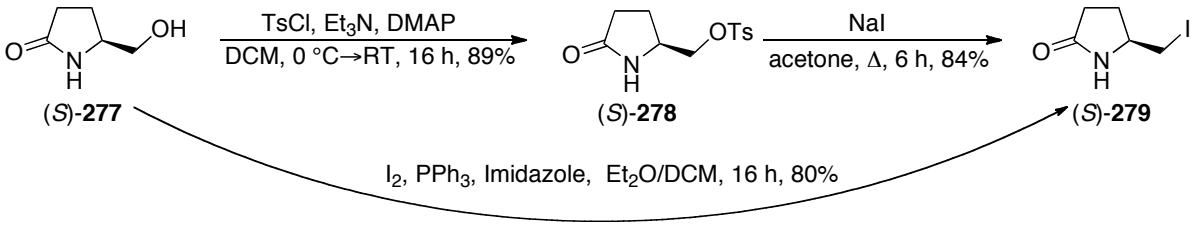
The synthesis of iodide (*S*)-**260** was achieved in two steps from protected proline (*S*)-**230** (Scheme 3.31).[40] The acid (*S*)-**230** was reduced with $BH_3 \cdot Me_2S$ in 75% yield. The resulting alcohol was converted to iodide (*S*)-**260** by reaction with iodine and triphenylphosphine in 96% yield. Iodide (*S*)-**260** was treated with activated zinc dust in DMF for 1 h. To test its reactivity, 2-bromopyridine was used as an electrophile and $PdCl_2(PPh_3)_2$ as a catalyst. Unfortunately, after work up only elimination product **276** was obtained. Other electrophiles or catalysts ($Pd_2(dba)_3$, PAr_3) did not improve the result. It was thus confirmed that the organozinc reagent is very unstable in DMF.



Scheme 3.31. Synthesis of the iodide (*S*)-**260**, its reaction with zinc and subsequent elimination.

3.3.1.4 Negishi coupling of Pyroglutamic Acid-Derived Iodide

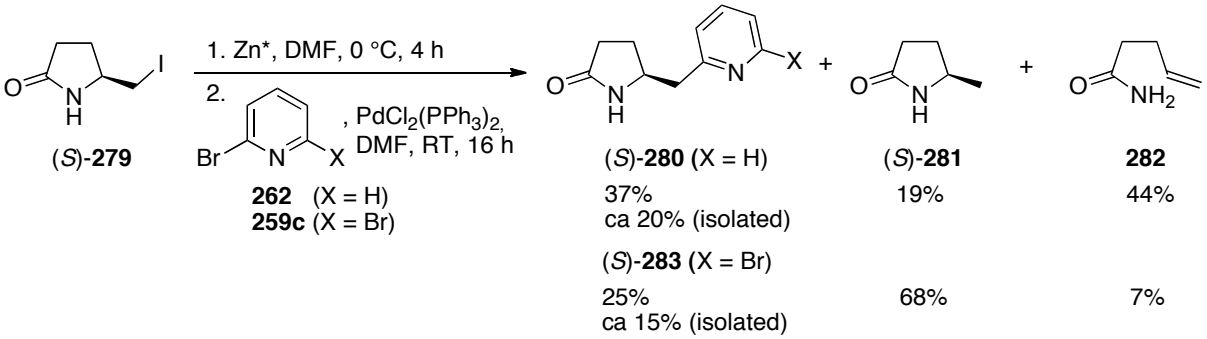
The use of the organozinc reagent derived from iodide (*S*)-**279** in copper-catalyzed or mediated reactions has been described in the literature.[40, 41] (*S*)-**279** was prepared from commercially available alcohol (*S*)-**277** by two different methods (Scheme 3.32). The direct Appel-type iodination provided (*S*)-**279** in 80% yield. The second synthesis included tosylation and nucleophilic substitution. Tosylate (*S*)-**278** was obtained in 89% yield and was further transformed to the iodide (*S*)-**279** in 84% yield (75% overall yield). The second method did not require purification by column chromatography.



Scheme 3.32. Synthesis of iodide (*S*)-**279**.

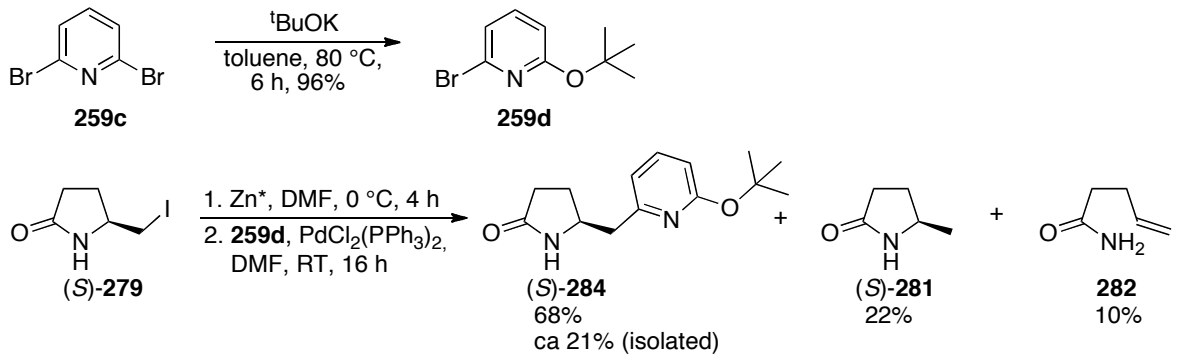
The organozinc reagent was generated from iodide (*S*)-**279** and activated zinc (Scheme 3.33).[42] The Negishi coupling was first performed with 2-bromopyridine to give the product

(*S*)-**280** as a mixture with (*S*)-**281** and elimination-byproduct **282**. (*S*)-**281** resulted from the protodemetallation of the unreacted organozinc reagent during work-up. The product recovered was contaminated with the reaction by-products. With 2,6-dibromopyridine as an electrophile, the product (*S*)-**283** was obtained in 15% yield as a mixture with (*S*)-**281**.



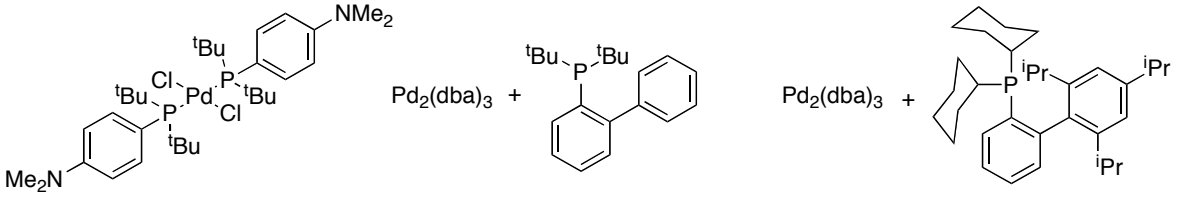
Scheme 3.33. Negishi coupling between iodide (*S*)-**279** and 2-bromo- and 2,6-dibromopyridine.

Furthermore, the possibility of using a functionalized pyridine as an electrophile in the Negishi coupling was investigated. Pyridine derivative **259d** was prepared in good yield from 2,6-dibromopyridine (Scheme 3.34).[43] The coupling was carried out with 5 mol% of $PdCl_2(PPh_3)_2$ and with an excess (1.3 Equiv.) of the electrophile. The product (*S*)-**284** was obtained in 13% yield as a mixture with **282** ((*S*)-**284**/**282** 77:23). The amount of the elimination product **282** was reduced when the organozinc reagent was transferred into another flask to separate it from the unreacted zinc (ratio ((*S*)-**284**/(*S*)-**281**/**282** 56:38:6, 13% yield of (*S*)-**284**). This ratio of the product and by-products was obtained after aqueous work-up, which led to loss of the material. Finally, the yield of (*S*)-**284** was improved to 21% by changing the extraction solvent to DCM (ratio ((*S*)-**284**/(*S*)-**281**/**282** 68:22:10). However, it is necessary to improve the purification procedure to minimize the loss of the material.



Scheme 3.34. Synthesis of the pyridine derivative **259d** and its application in the Negishi coupling with iodide (*S*)-**279**.

Improvement was also not observed when performing the reaction at 40 °C or by using other catalysts and ligands (Figure 3.8). Recently, LIPSHUTZ reported a zinc-mediated palladium-catalyzed cross-coupling in water containing a surfactant. In the absence of a stoichiometrically preformed organozinc reagent, catalyst **285**, in the presence of Zn-powder, diamine and a surfactant provided coupling products in good to high yields. Thus, the coupling of (*S*)-**279** with **259d** was carried out following the reported conditions. Unfortunately, only the reduction product (*S*)-**281** was recovered.



285 (*S*)-**284**/(*S*)-**281**/**282** 54:51:5

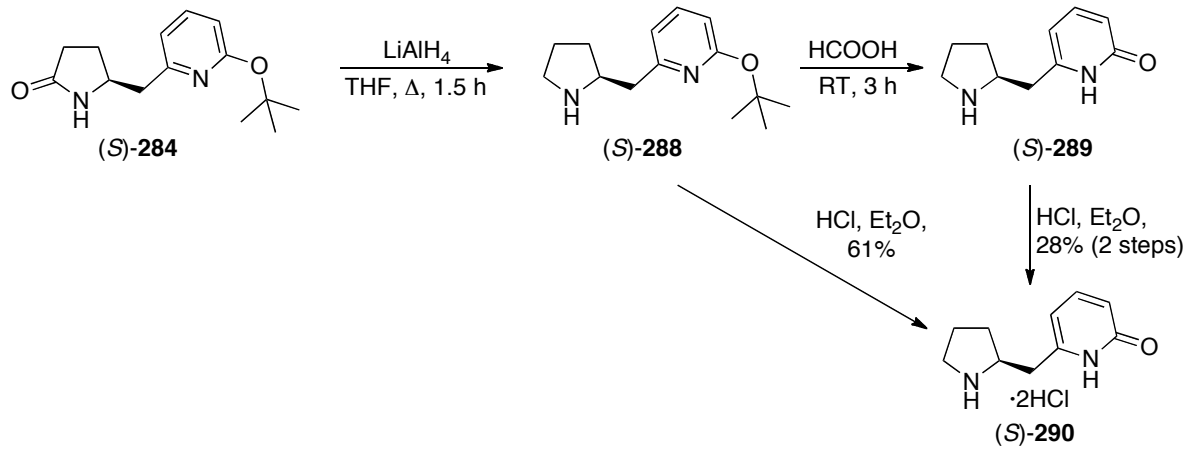
286 51:39:10

287 12:67:21

Figure 3.8. Catalysts used in the Negishi coupling and the obtained results.

3.3.1.5 Reduction and Deprotection of (S)-284

The amide carbonyl of (*S*)-**284** was reduced with $LiAlH_4$ to give the amine (*S*)-**288** (Scheme 3.35). The purification of (*S*)-**288** by *kugelrohr* distillation failed, therefore, the next step was performed with the crude mixture. The removal of the *tert*-butyl-group was achieved by treatment of (*S*)-**288** with formic acid to give the desired catalyst (*S*)-**289** as a mixture with the unknown by-product. The purification of (*S*)-**289** was accomplished by isolation as a hydrochloride (*S*)-**290** and its recrystallization from MeOH/Et_2O mixture. The purification of (*S*)-**288** as hydrochloride was also attempted. (*S*)-**288** was dissolved in Et_2O and 2 M solution of HCl in Et_2O was added dropwise. A colorless solid was formed immediately. ^{1}H-NMR showed that the precipitated solid was the deprotected catalyst (*S*)-**290**.



Scheme 3.35. Reduction and deprotection of (*S*)-**284** to give the desired catalyst (*S*)-**289**.

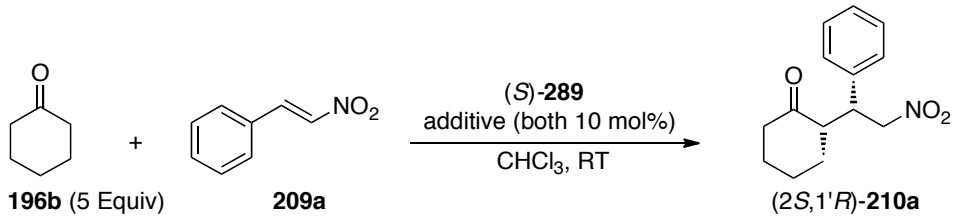
Ultimately, catalyst (*S*)-**289** was prepared in a low overall yield. Further optimization of reaction conditions is necessary to reduce the amount of side-products and improve the reactivity of the coupling partners.

3.3.2 Catalyst (*S*)-289 in 1,4-Addition of Cyclohexanone to *β*-Nitrostyrene

(*S*)-**290** was tested in the 1,4-addition of cyclohexanone to *β*-nitrostyrene, but no conversion was observed after 10 days. Neutralization with organic and inorganic bases was associated with loss of the material. Successful neutralization was accomplished by passing the catalyst solution through a VariPure ion exchange filter prior to catalysis.

Catalysis with (*S*)-**289** was performed in more concentrated solutions than with catalyst (*S*)-**224** (Table 3.7). The new catalyst (*S*)-**289** was found to be more active and selective than (*S*)-**224**. Among the additives tested, 1-isoquinolinol **247** accelerated the reaction. However, no effect on selectivity was observed. The thiourea-derived additives reduced the *ee* slightly. The reaction was faster in the presence of benzoic acid.

Table 3.7. 1,4-addition of cyclohexanone to *β*-nitrostyrene catalyzed by (*S*)-**289** in the presence of additives.[a]



Entry	Additive	Time [h]	Conv. [%][b]	Yield [%]	d.r.[b]	*ee* [%][c]
1	–	90	72	57	94:6	88
2	**236**	90	68	58	94:6	88
3	**242**	90	81	71	94:6	88
4	**247**	48	96	85	94:6	87
5	**238a**	90	79	70	93:7	77
6	**241**	90	88	79	93:7	81
7	PhCOOH	21	91	83	94:6	89
8	**242**, PhCOOH	21	95	86	95:5	90
9	**247**, PhCOOH	21	99	89	94:6	90

[a]Performed with *β*-nitrostyrene (0.250 mmol), cyclohexanone (1.20 mmol), (*S*)-**289** (25 µmol) and additive (25 µmol) in $CHCl_3$ (0.5 mL) at RT. [b]Determined by ^{1}H-NMR. [c]Determined by HPLC on chiral stationary phase.

3.3.3 Conclusions

The aim of this project was the synthesis of modular organocatalysts based on the self-assembly of two parts bearing different activating functionalities. One part of the self-assembly should be a proline-derived secondary amine that can form an enamine intermediate with a ketone in its 1,4-addition to a nitroolefin. The nitroolefin could be activated by a thiourea moiety that would be bound to the second part of the self-assembly (the additive).

The first-generation catalyst was derived from a proline amide. The additives showed effects on the activity and selectivity of the catalyst. However, the catalyst (*S*)-**224** was rather inactive. Therefore, catalyst (*S*)-**289** was designed. (*S*)-**289** was expected to be more active in 1,4-additions of ketones to nitroolefins.

Several synthetic pathways towards catalyst (*S*)-**289** were investigated. The reactions of sulfamidate (*S*)-**256** with different pyridine-derived organolithium reagents were unsuccessful. The organozinc reagent formed from iodide (*S*)-**260** was very unstable and led to the elimination product **276**. Finally, it appeared that the organozinc reagent formed from iodide (*S*)-**279** was stable enough to be used in the Negishi coupling with different pyridine-derived electrophiles. The pyridine derivative **259d** provided the catalyst precursor (*S*)-**284** in low yield. (*S*)-**284** was converted to the catalyst (*S*)-**289** by reduction and deprotection in good yield. An optimization of the Negishi coupling is still necessary.

Catalyst (*S*)-**289** was shown to be an active and selective catalyst in the 1,4-addition of cyclohexanone to *β*-nitrostyrene. The additives displayed only a small impact on the outcome of the reaction. Additive **247** accelerated the reaction, but the selectivity remained the same. Since the thiourea functionality neither affect the activity nor the selectivity of the catalyst, other additives should be designed, e.g. ones bearing a carboxylic acid. Moreover, the self-assembling catalyst should be tested in other organocatalyzed reactions. That would allow for different modifications of the additives.

3.4 References

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CHAPTER 4

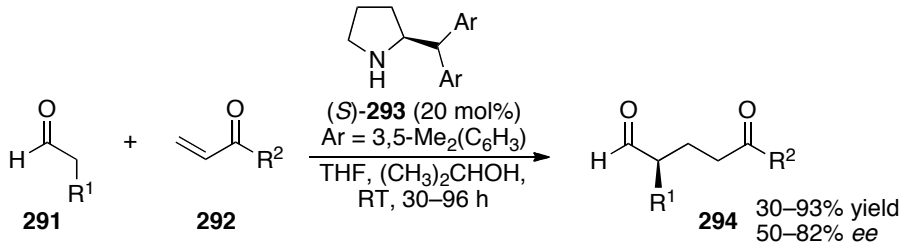
Detection of Catalytic Intermediates as Mechanistical Tool

4 Detection of Catalytic Intermediates as Mechanistical Tool

4.1 Organocatalyzed 1,4-Addition of Aldehydes to Enones

4.1.1 Introduction

The direct 1,4-addition of nucleophiles to simple unsaturated carbonyl compounds represents an important field of research in organocatalysis. The first stereoselective Michael addition of aldehydes to enones was reported by JØRGENSEN (Scheme 4.1).[1] The catalyst (*S*)-**293** provided the product **294** in good yields and with moderate to good enantioselectivities. The sterically hindered *tert*-butyl vinyl ketone required a longer reaction time and afforded the product in low yield.



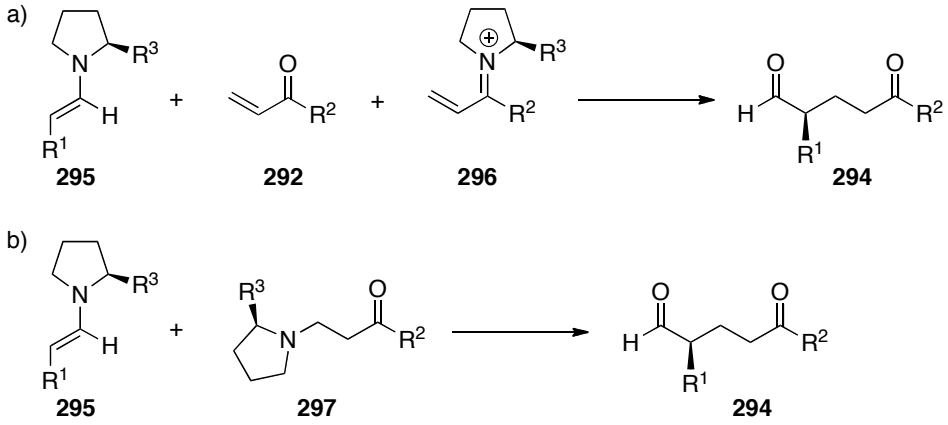
Scheme 4.1. Enantioselective Michael addition of aldehydes to enones.

Several mechanistic pathways were proposed (Scheme 4.2). Based on the observed negative nonlinear effect, the participation of more than one catalyst molecule in the transition state was assumed.[1] Scheme 4.2a shows the generally accepted scenario, where aldehyde **291** forms an enamine intermediate **295** with the catalyst. **295** attacks either the ketone **292** or the iminium intermediate **296**, which is more reactive but present only in low concentration. Sterically hindered ketones probably do not form the iminium species, which would explain the lack of a nonlinear effect.

It was observed that the catalyst can attack the ketone at the 4-position (Scheme 4.2b). It was speculated that the 1,4-adduct played a role in the catalytic cycle, but this was not confirmed in the experiments with the preformed 1,4-adduct.

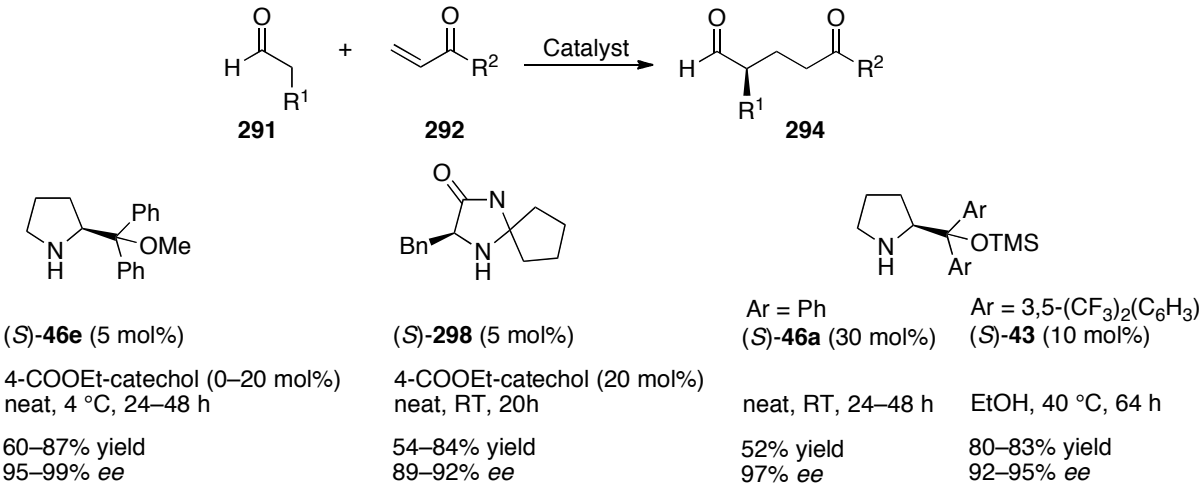
Recently, based on theoretical calculations, WONG suggested that this reaction might instead proceed via a hydrogen bond stabilized enol-form of the aldehyde than via enamine intermediates.[2] A more comprehensive computational study compared the preferences for

the formation of enol tautomer, enamine and iminium intermediates.[3] It was found that the reaction most likely proceeds *via* addition of the enamine **295** to the ketone **292**.



Scheme 4.2. Two possible mechanistic pathways in the Michael addition of aldehydes to enones.

CHI and GELLMAN introduced pyrrolidine derivative (*S*)-**46e** as a highly selective catalyst for the Michael addition of aldehydes to enones (Scheme 4.3).[4] They found that a lower catalyst loading improved the selectivity. Ethyl vinyl ketone required the presence of an acidic additive in order to increase its activity. Another highly selective and active catalyst reported by GELLMAN was imidazolidinone (*S*)-**298**.[5] NMR-studies presented in this report confirmed the formation of the enamine intermediate and its role in the catalytic cycle. Diarylprolinol silyl ethers (*S*)-**46a** and (*S*)-**43** were employed by JØRGENSEN[6] and HAYASHI.[7]

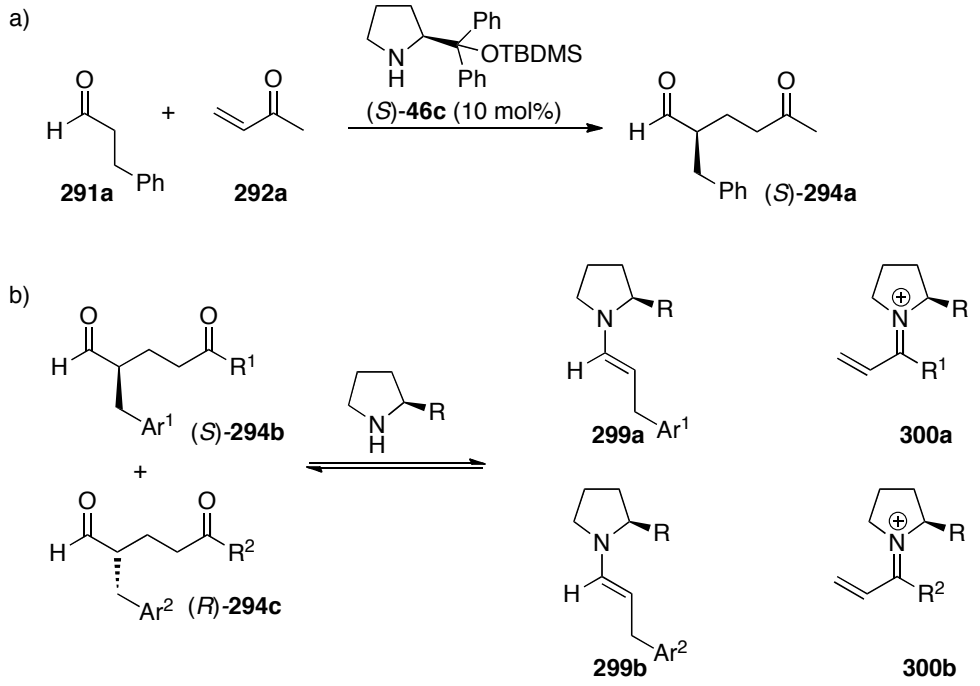


Scheme 4.3. Michael addition of aldehydes to enones.

The usefulness of this reaction was demonstrated in the total synthesis of natural products.[8] Furthermore, its intramolecular version was reported,[9] as well as its application in a desymmetrization reaction.[9c, 10]

4.1.1.1 Objectives

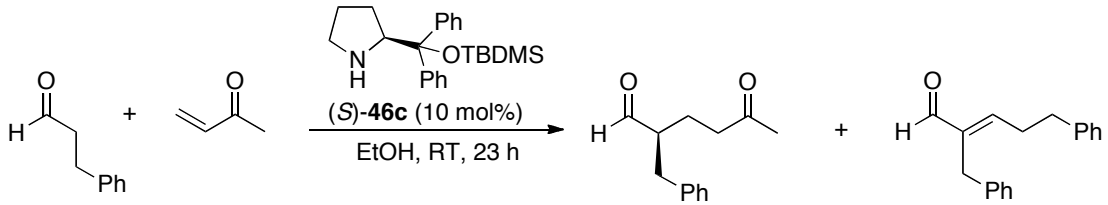
The aim of this project was to investigate the possibility of extending the ESI-MS screening method to enamine-catalyzed reactions, such as the Michael addition of aldehydes to enones (Scheme 4.4). Since there are only a few efficient catalysts for this reaction, such a screening would provide a valuable tool for the investigation of new catalyst libraries. Moreover, ESI-MS could be applied to the forward reaction in order to provide evidence for the existence of intermediates proposed by JØRGENSEN.[1]



Scheme 4.4. a) The 1,4-addition of aldehyde **291a** to ketone **292a**; b) The principle of the screening of the *retro*-reaction of the quasienantiomers (*S*)-**294b**/(*R*)-**294c**.

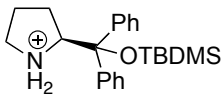
4.1.2 ESI-MS Monitoring of the Forward Reaction

The 1,4-addition of hydrocinnamaldehyde to methyl vinyl ketone was carried out with the catalyst (*S*)-**46c** applying the conditions reported by by JØRGENSEN (Scheme 4.5).[6] The ketone was consumed after 1 day, however, four aldehyde species were observed in the ^{1}H-NMR spectrum. Three of them were assigned as hydrocinnamaldehyde, product (*S*)-**294a** and the by-product **301** resulting from the self-condensation of the aldehyde. One signal could not be identified. The product was isolated in 64% yield and 60% enantiomeric excess. The isolated yield of the by-product **301** was 10%.

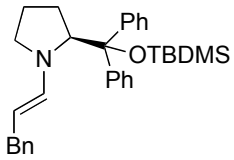


Scheme 4.5. 1,4-Addition of aldehyde **291a** to ketone **291b** catalyzed by (*S*)-**46c**.

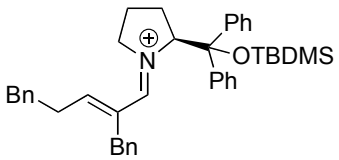
The reaction was studied by ESI-MS after dilution of aliquots in acetonitrile. In the spectum of the aldehyde and catalyst, only a very small signal of protonated enamine **302** (*m/z* = 484) was detected (Figure 4.1). The most intense signals were those of the catalyst [**46c**+H$^+$] (*m/z* = 368) and [**46c**-OTBDMS] (*m/z* = 236). The signal at *m/z* = 600 can be assigned to the iminium ion with the self-condensation product **303**. Signals at *m/z* = 616 and 632 could not be assigned.



46c+H$^+$
m/z = 368



302
M = 483



303
m/z = 600

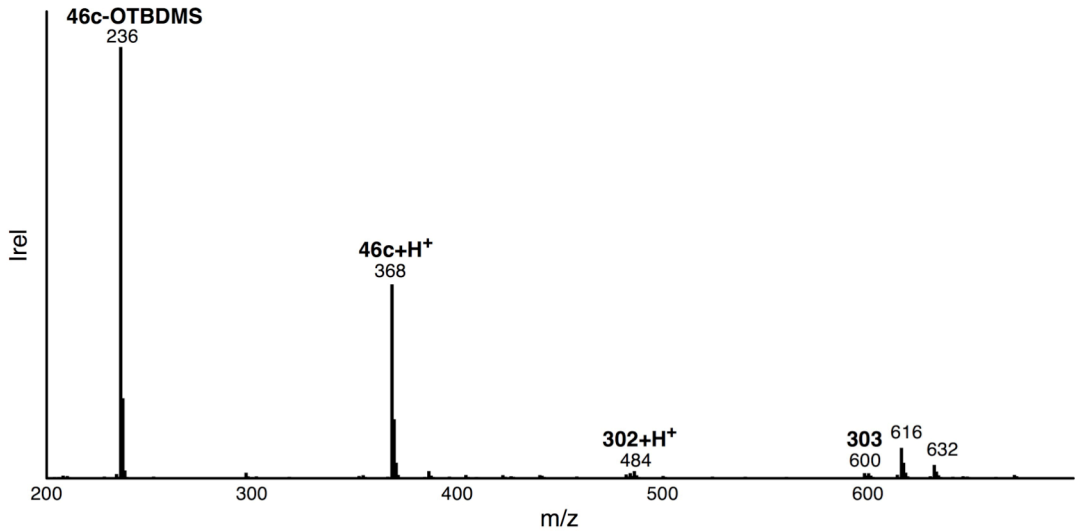
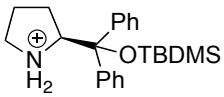
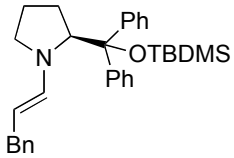


Figure 4.1. ESI-MS spectrum of aldehyde **291a** and catalyst (*S*)-**46c**.

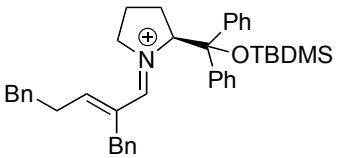
A more complex spectrum was obtained 5 minutes after the addition of the ketone **292b** (Figure 4.2a). The signal of the expected iminium ion **304** was not observed. Instead, two highly intense signals appeared, which were assigned to the protonated catalyst-ketone 1,4-adduct **305** (*m/z* = 438) and [**305**-OTBDMS] (*m/z* = 306). The intensity of the protonated enamine **302** (*m/z* = 484) was higher. A very small peak of the product iminium intermediate **554** (*m/z* = 554) was also detected. After 1 hour, the signals of the intermediates either became very small or disappeared entirely (Figure 4.2b). Several signals could not be assigned. The signals of the 1,4-adduct **305** were the most prominent.



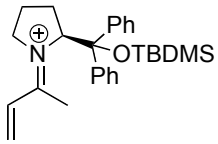
46c+H+
m/z = 368



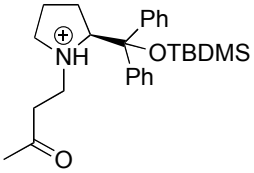
302
M = 484



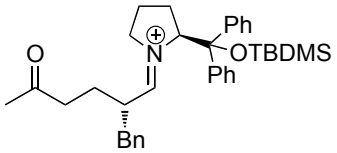
303
m/z = 600



304
m/z = 420



305+H+
m/z = 438



306
m/z = 554

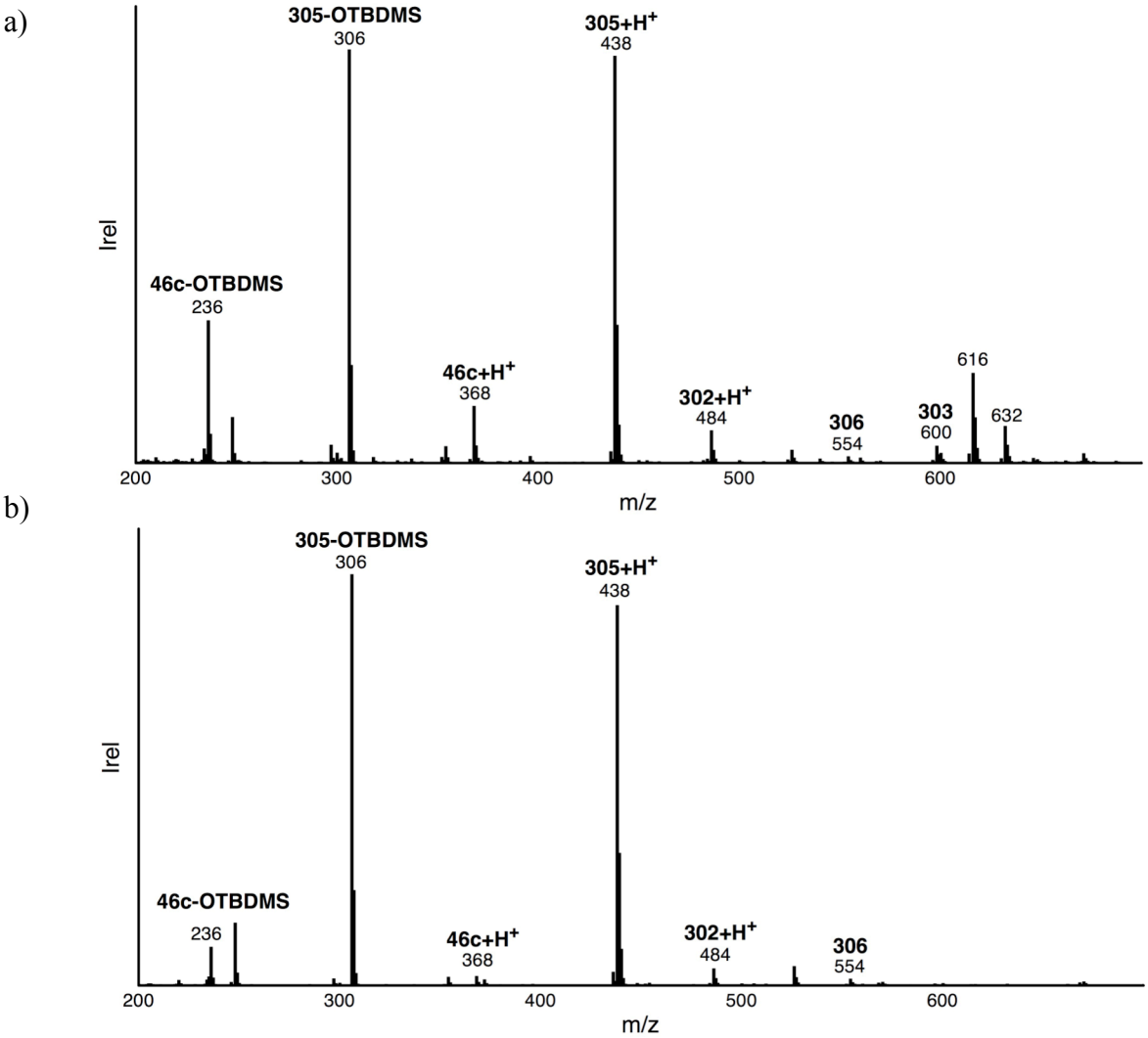
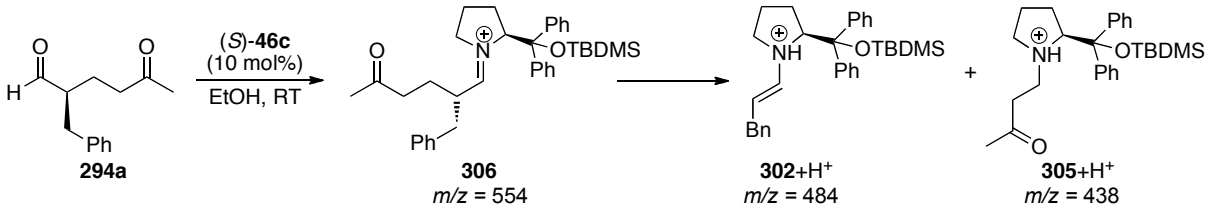


Figure 4.2. ESI-MS spectra of the 1,4-addition of aldehyde **291a** to ketone **292a** after: a) 5 minutes; b) 60 minutes.

The formation of the 1,4-adduct **305** was confirmed by ^{1}H-NMR. In a 1:1 mixture of ketone **212a** and the catalyst (*S*)-**46c** in d_6-EtOD, 9% adduct **305** was detected after 30 minutes. The amount of **305** increased after 1 hour to 30% and after 14 h to 87%, respectively. **305** was stable in solution after 4 days.

4.1.3 *Retro*-1,4-addition attempts

The *retro*-1,4-addition of the product **294a** and catalyst (*S*)-**46c** was carried out under the same conditions as the forward reaction (Scheme 4.6). The reaction was followed by ESI-MS (Figure 4.3). After 5 minutes, only the catalyst and iminium intermediate **306** signals were observed. No other relevant signals could be detected with longer reaction times. ^{1}H-NMR analysis of the crude reaction mixture after one day showed only the starting material.



Scheme 4.6. Attempted *retro*-Michael addition.

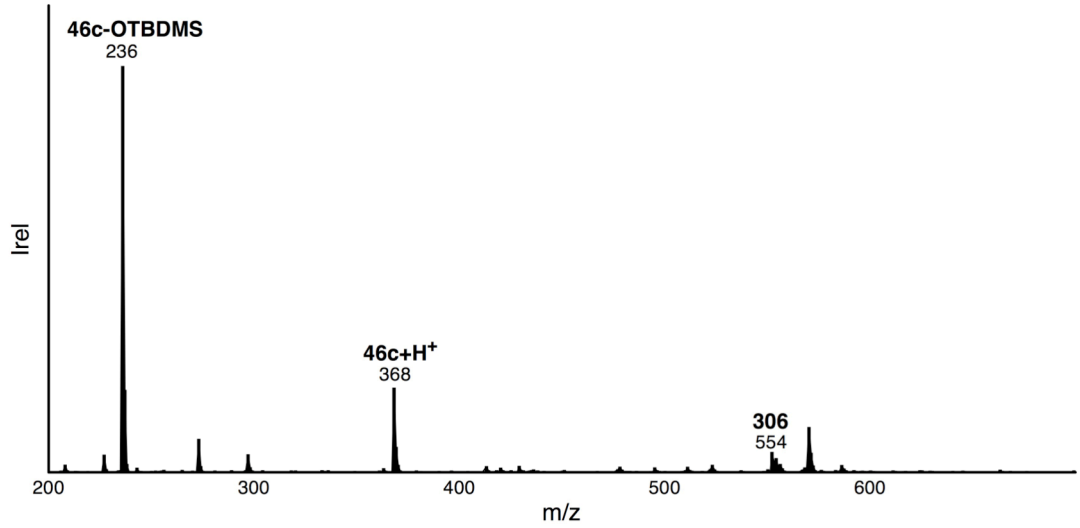


Figure 4.3. ESI-MS spectrum of the *retro*-Michael addition.

4.1.4 Conclusions

The catalyst (*S*)-**46c** provided the product of the 1,4-addition of hydrocinnamaldehyde to methyl vinyl ketone in moderate yield and with modest enantiomeric excess. In order to intercept the reaction intermediates, the reaction was monitored by ESI-MS. Unexpectedly, the most abundant species in the spectrum was the 1,4-adduct of the catalyst to the ketone. The iminium intermediate proposed by JØRGENSEN was not detected.[1] The enamine intermediate **302** and iminium ions **303** and **306** were observed as well, although with low intensities.

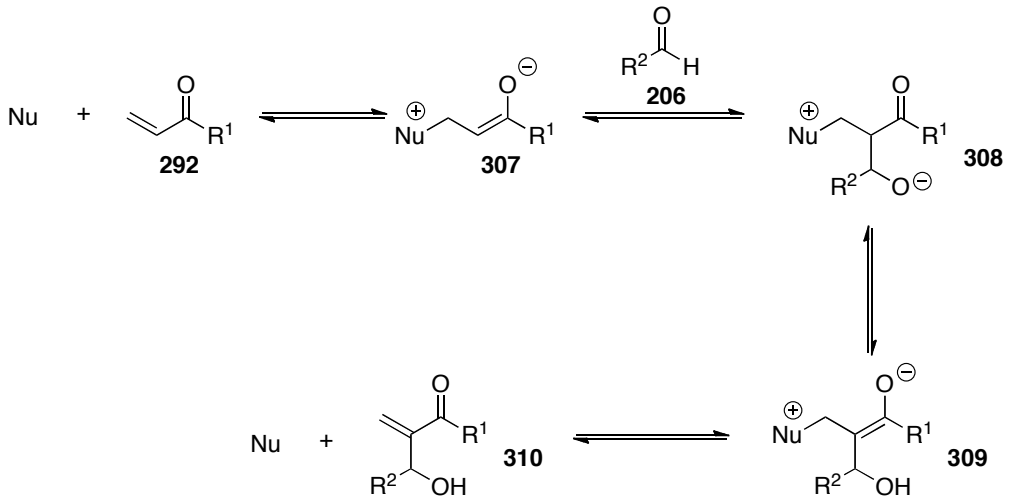
The *retro*-reaction could not be performed under the tested conditions. Only the iminium intermediate **306** was detected in the ESI-MS spectrum.

The formation of the 1,4-adduct **305** was confirmed by ^{1}H-NMR. It was very surprising that **305** was detected as the main component of the reaction mixture. Such intermediates are a part of the catalytic cycle of the Morita-Baylis-Hillman reaction and will be investigated further in the next section.

4.2 Morita-Baylis-Hillman Reaction

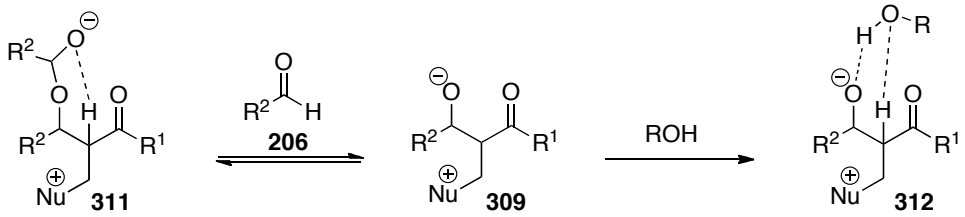
4.2.1 Introduction

The Morita-Baylis-Hillman (MBH) reaction is a coupling reaction of an electron-deficient olefin and a carbonyl compound (Scheme 4.7).[11] The reaction was discovered by MORITA in 1968, who used a phosphine as a nucleophilic catalyst.[12] BAYLIS and HILLMAN discovered that the reaction can be catalyzed by a tertiary amine.[13] The simplified mechanism of the MBH reaction is shown in the Scheme 4.7.[14] The nucleophilic catalyst attacks the unsaturated carbonyl compound at the 4-position. The zwitterionic intermediate **307** undergoes an aldol reaction with the carbonyl compound **206** to give the intermediate **308**. A proton transfer leads to **309**, which undergoes a *retro*-Michael reaction to provide the free catalyst and product **310**.



Scheme 4.7. The original mechanism of the Morita-Baylis-Hillman reaction.

The aldol reaction was assumed to be the rate-determining step of the reaction. However, it was later discovered that the proton shift leading to intermediate **309** or its keto-form is the rate-determining step. Two different mechanisms were proposed for this step (Scheme 4.8). MCQUADE suggested that a second aldehyde molecule, bound as a hemiacetal, is involved in the proton shift.[15] AGGARWAL and LLOYD-JONES investigated the MBH reaction in the presence of a proton source and proposed **312** as the intermediate.[16] An ESI-MS study of the reaction verified the dualistic character of this step by the interception of key intermediates.[17]

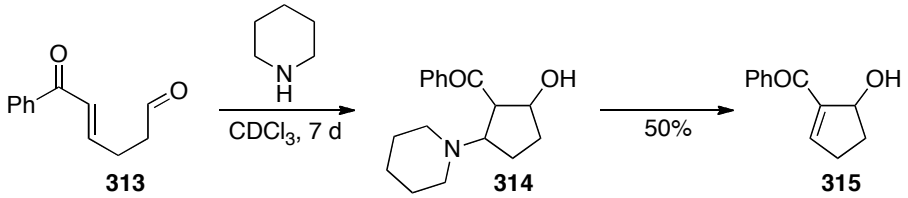


Scheme 4.8. Proposals for the intermediates in the MBH reaction.

Numerous metal and organic catalysts were developed for the enantioselective MBH reaction.[11d-f] Most catalysts are bifunctional, having both a nucleophilic part and an integrated Brönsted acid. Alternatively, acidic co-catalysts are used. In the following section, reactions in the presence of secondary amines will be discussed.

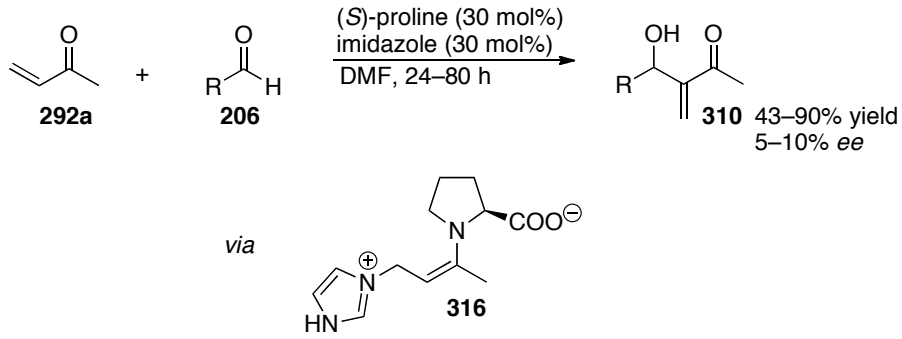
4.2.1.1 Secondary Amines in the Morita-Baylis-Hilman Reaction

Secondary amines are underrepresented as catalysts or co-catalysts for the MBH reaction. MURPHY investigated intramolecular MBH reaction with secondary amines as catalysts (Scheme 4.9).[18] Piperidine provided the product in moderate yield after 7 days.



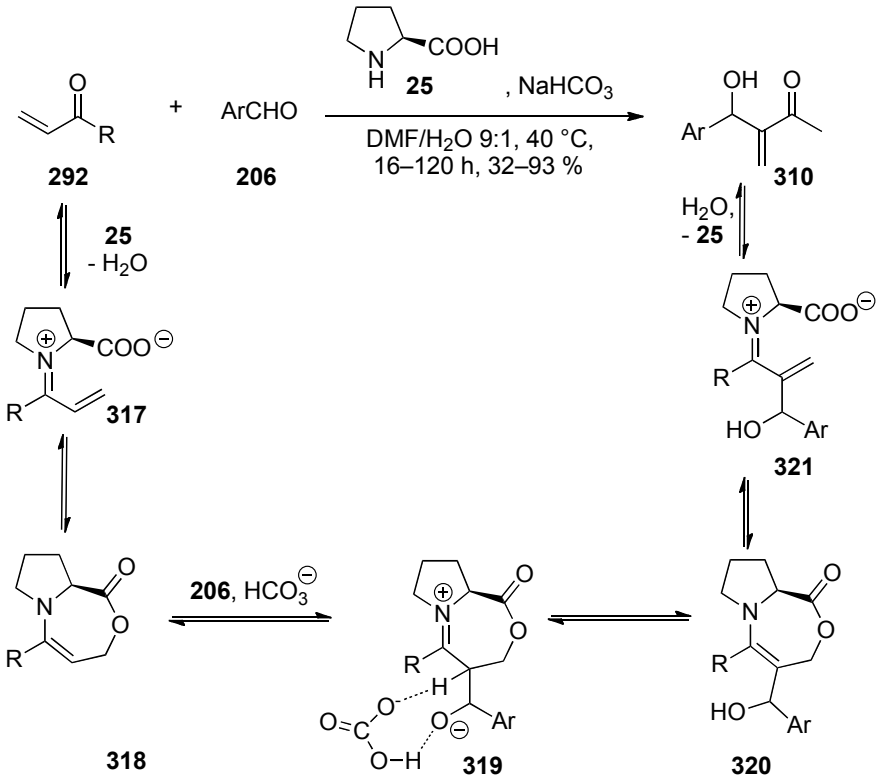
Scheme 4.9. Piperidine-catalyzed intramolecular MBH reaction.

SHI reported a (*S*)-proline/imidazole catalyzed intermolecular MBH reaction (Scheme 4.10).[19] The adduct **310** was obtained in good yield, but very low enantiomeric excess. No conversion was achieved when only (*S*)-proline or imidazole were used. It was proposed that proline forms an iminium intermediate with the ketone. This intermediate is then attacked by imidazole to give the double activated intermediate **316**. Improvements in the enantiomeric excess were achieved by other researchers through the use of other nucleophiles as catalysts. For example, chiral teriary amino alcohols,[20] small peptides[21] and *N*-methylimidazole[22] have all been employed.



Scheme 4.10. Proline/imidazole catalyzed MBH reaction.

Only few reports on the use of secondary amines as single catalysts in the MBH reaction are known. HONG could demonstrate for the first time that proline itself can catalyze intramolecular MBH reactions.[23] JØRGENSEN reported a tandem Michael/MBH reaction catalyzed by diarylprolinol silyl ether (*S*)-**43**.[24] DRUTTADAURIA discovered, that proline can efficiently catalyze the reaction between aryl aldehydes **206** and alkyl vinyl ketones **292** in the presence of $NaHCO_3$ (Scheme 4.11).[25] The products were formed in good to high yields, but as racemates. A detailed mechanism based on quantum-mechanical calculations was proposed. The iminium intermediate **317** is formed from ketone **292** and proline. **317** is converted to cyclic enamine **318**, which then reacts with the aldehyde to give **319**. The hydrogencarbonate anion seems to stabilize the zwitterionic intermediate **319** that is transformed to cyclic enamine **320**. The *retro*-Michael reaction and a subsequent hydrolysis provide the product. No intermediates could be detected by ^{1}H-NMR.



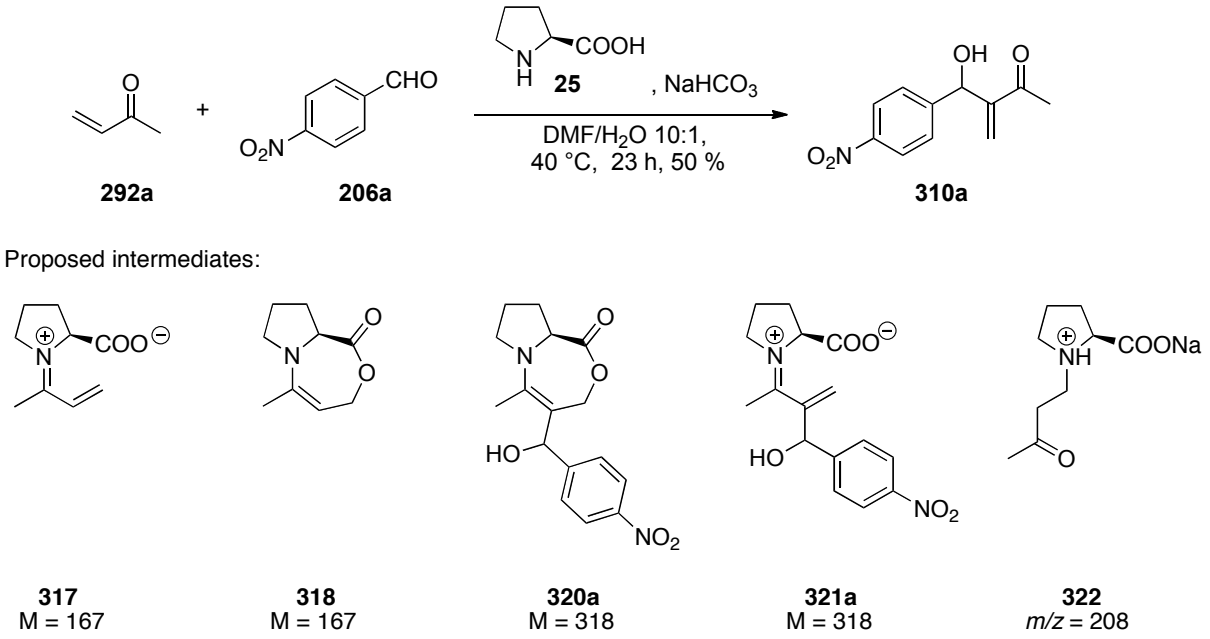
Scheme 4.11. Proposed mechanism of the proline-catalyzed MBH reaction.

4.2.1.2 Objectives

The observed 1,4-addition of the catalyst to the enone is the first step of the MBH reaction. Therefore, the possibility of performing the MBH reaction with secondary amines as catalysts should be tested.

4.3.2 ESI-MS Monitoring of the Morita-Baylis-Hillman Reaction

The MBH reaction was carried out with (*S*)-proline following the reported method (Scheme 4.12).[25] The reaction was monitored by ESI-MS (Figure 4.4). The spectrum was very complex, but out of the proposed intermediates, only a small peak belonging to **320a** (*m/z* = 318) was detected. Instead, one of the most intense signals could be assigned to the 1,4-adduct **322** (*m/z* = 208).



Scheme 4.12. MBH reaction catalyzed by (*S*)-proline and the proposed intermediates.

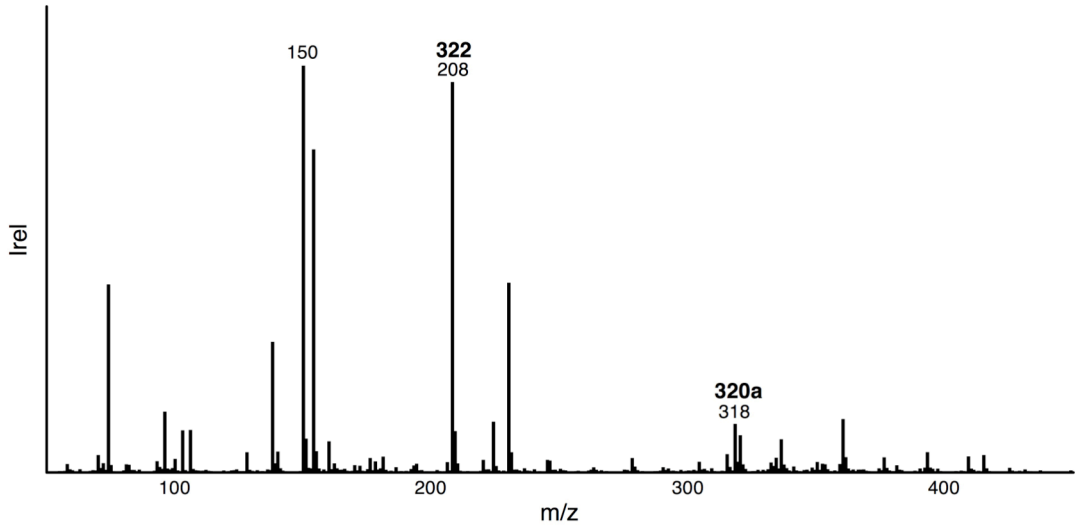
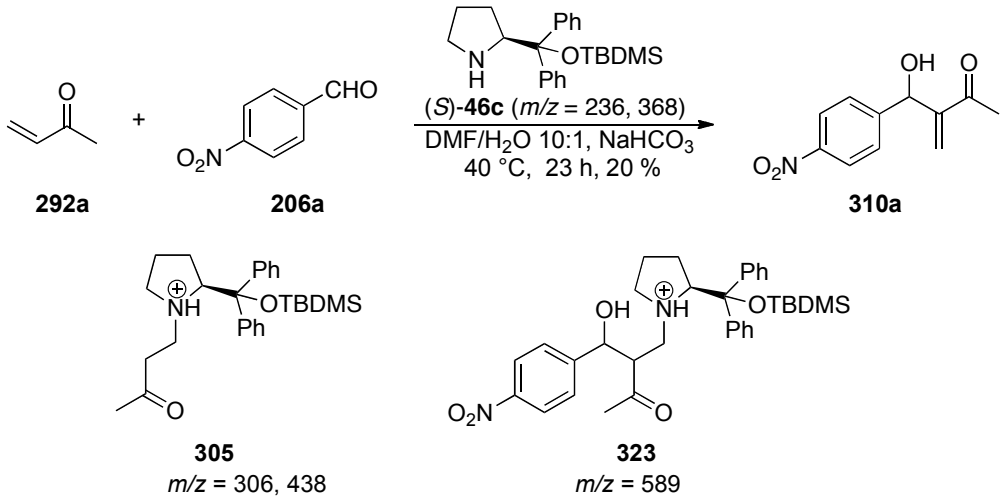


Figure 4.4. ESI-MS spectrum of the MBH reaction catalyzed by (*S*)-proline.

Under the same conditions, the reaction with the catalyst (*S*)-**46c** was carried out (Scheme 4.13). The product was obtained as a racemate in 20% yield. The ESI-MS spectrum of this reaction was less complex than with proline (Figure 4.5). Besides the catalyst signals (*m/z* = 236 and 368), the peaks of the intermediates **305** (*m/z* = 306 and 438) and **323** (*m/z* = 589) were detected. Both intermediates are part of the catalytic cycle of the MBH reaction.



Scheme 4.13. The MBH reaction catalyzed by (*S*)-**46c**.

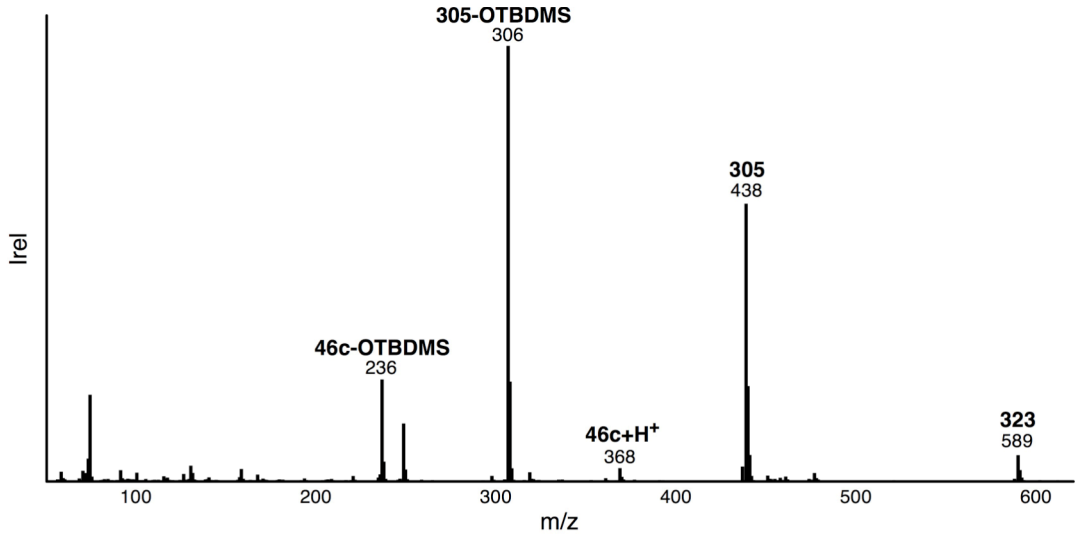


Figure 4.5. The ESI-MS spectrum of the MBH reaction catalyzed by (*S*)-**46c**.

4.3.3 Conclusions

The formation of the 1,4-adduct **305** between an enone and secondary amine was observed during the investigations of the 1,4-addition of aldehydes to methyl vinyl ketone. **305** is an important intermediate in the Morita-Baylis-Hillman reaction. Therefore, the possibility of using a secondary amine as a catalyst for this reaction was investigated.

The Morita-Baylis-Hillman reaction was carried out with (*S*)-proline and (*S*)-**46c** as catalyst. The reactions were monitored by ESI-MS. In the reaction with (*S*)-proline, no significant

peaks of the proposed intermediates were detected. Instead, the sodium salt of 1,4-adduct **322** was one of the species that gave the most intense signals.

The catalyst (*S*)-**46c** was less efficient than proline under the same conditions. However, two intermediates **305** and **323** could be identified in a clean ESI-MS spectrum. More investigations are necessary to find optimized conditions for this reaction using a secondary amine as a catalyst.

4.3 References

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CHAPTER 5

Experimental

5 Experimental

5.1 Analytical Methods

NMR-Spectroscopy: NMR spectra were recorded on a Bruker Avance 400 (400 MHz, BBO probe head) or Bruker Avance DRX 500 (500 MHz, BBO or BBI probe heads) NMR spectrometers. Chemical shifts δ (ppm) are given relative to solvent: references for $CDCl_3$ were 7.26 ppm (^{1}H-NMR) and 77.16 ppm (^{13}C-NMR), for d_6-DMSO 2.50 ppm (^{1}H-NMR) and 39.51 ppm (^{13}C-NMR), for d_4-MeOD 3.31 ppm (^{1}H-NMR) and 49.00 ppm (^{13}C-NMR), for d_6-EtOD 1.11 ppm and 3.56 ppm (^{1}H-NMR) and 17.31 ppm and 56.96 ppm (^{13}C-NMR). ^{13}C-NMR spectra were acquired on a broad band decoupled mode. The assignment of ^{1}H- and ^{13}C-signals was partly made using 2D-NMR experiments (COSY, HMQC, HMBC). Multiplets were assigned as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet), m_c (centred multiplet) and br s (broad singlet).

Mass Spectrometry (MS): EI (Electron ionization) and FAB (fast atom bombardment) mass spectra were measured by Dr. H. Nadig (Department of Chemistry, University of Basel) on VG70-250 (EI) and Finnigan MAT312 (FAB) mass spectrometers. The ions were generated by EI (70 eV) or FAB using 3-nitrobenzyl alcohol (NBA) as matrix and, when necessary, KCl as additive. Electron spray ionization (ESI) was measured on Varian 1200L Triple Quad MS/MS mass spectrometer in acetonitrile (septum sealed bottle under argon and over 4 Å MS) solution at concentrations between 10^{-4} and 10^{-5} M (40 psi nebulizing gas, 4.9 kV spray voltage, 18 psi drying gas at 200 °C, 38 V capillary voltage, 1300 V detector voltage). The data are given as mass units per charge (*m/z*) and relative intensities of signals are given in brackets.

Infrared Spectroscopy (IR): Infrared spectra were measured on a Perkin Elmer 1600 series FTIR spectrometer, where solid samples were prepared as KBr wafers, liquid samples were measured between NaCl plates; or on a Shimadzu FTIR-8400S spectrometer with neat substances using a Golden Gate ATR accessory. Absorption bands are given in wave numbers $\tilde{\nu}$ [cm^{-1}]. The peak intensity is assigned with s (strong), m (medium) and w (weak). The index br stands for broad.

Melting Point (m.p.): The melting points were measured on a Büchi 535 melting point apparatus. The values are not corrected.

Optical Rotation ($[\alpha]_D^{20}$): $[\alpha]_D^{20}$-values were measured on a Perkin Elmer Polarimeter 341 in a cuvette (l = 1 dm) at 20 °C at 589 nm (sodium lamp). Concentration *c* is given in g/100 mL.

Thin Layer Chromatography (TLC): TLC plates were obtained from Macherey-Nagel (Polygram® SIL G/UV254, 0.2 mm silica with fluorescence indicator, 40 × 80 mm). For visualization UV light (254 nm, 366 nm), basic permanganate solution (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% (w/w) aqueous NaOH, 300 mL H_2O) and ceric sulphate solution (15% (w/w) H_2SO_4 saturated with ceric sulphate) were used.

High Performance Liquid Chromatography (HPLC): For HPLC analysis Shimadzu systems with SCL-10A System Controller, CTO-10AC column oven, LC10-AD pump system, DGU-14A degasser, and SPD-M10A Diode Array- or UV-vis detector were used. Chiralcel column AD-H and Chiralpak columns AS-H and OD-H (4.6 × 250 mm) from Daicel Chemical Industries Ltd. were used.

Gas Chromatography (GC): The gas chromatographs in use were Carlo Erba HRGC Mega2 Series 800 (HRGC Mega 2). Achiral separations were performed with Macherey-Nagel Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm). For chiral separations Chiraldex γ-cyclodextrine G-TA column (30 m × 0.25 mm × 0.25 μm) was used.

Elemental Analysis (EA): Elemental analyses were carried out by Mr. W. Kirsch at the Department of Chemistry at the University of Basel, on Leco CHN-900 (C-, H-, N-detection) and Leco RO-478 (O-detection) analyzers. The data are indicated in mass percent.

5.2 Reagents and Working Techniques

Commercially available reagents and starting material were ordered from Acros Organics, Alfa Aesar, Aldrich, Fluka, Merck or Strem Chemicals.

Dry solvents were prepared according to standard procedures,[1] dried by passage over activated alumina under nitrogen atmosphere (PureSolv, Innovative Technology Inc)[2] or purchased from Fluka or Aldrich in septum-sealed bottles and kept under inert atmosphere over molecular sieves. If necessary, solvents were degassed by three freeze-pump-thaw cycles.

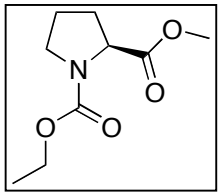
Air- and moisture-sensitive syntheses were performed under argon atmosphere in heating gun vacuum dried glassware using standard Schlenk techniques or in a glove box (MBRAUN

labmaster 130, N_2). Organocatalytic reactions were performed in culture tubes with screw-cap under air.

Column chromatography was carried out on silica gel 60 (0.040-0.063 mm) obtained from Fluka or Merck. Generally, the *flash column chromatography* according to Still[3] was performed. Solvents were technical grade and were purified by distillation prior to use.

5.3 Towards Self-Assembling Organocatalysts

5.3.1 Synthesis of Catalysts



(*S*)-1-(Ethoxycarbonyl)proline methyl ester ((*S*)-78)[4]

General method I:

(*S*)-Proline (1.15 g, 10.0 mmol) was dissolved in dry methanol (20 mL). Anhydrous K_2CO_3 (1.38 g, 10.0 mmol) was added followed by ethyl chloroformate (2.1 mL, 2.4 g, 22 mmol) during 5 minutes at 0 °C. The reaction mixture was further stirred for 14 h at RT. Methanol was evaporated and water (10 mL) was added. The residue was extracted with chloroform (3 × 15 mL), combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product (1.96 g, 97%) as colorless oil. The crude product was used without further purification in the next step.

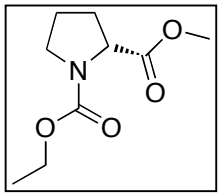
$C_9H_{15}NO_4$ (201.22 g/mol)

$\boldsymbol{R_f}$ = 0.32 (SiO_2, EA/pentane 20:80).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.19 and 1.26 (2 × t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3, rotamers), 1.84–2.03 (m, 3H, 4-*H*, 3-H_A), 2.04–2.29 (m, 1H, 3-H_B), 3.40–3.63 (m, 2H, 5-*H*), 3.72 and 3.74 (2 × s, 3H, $COOCH_3$, rotamers), 4.03–4.19 (m, 2H, CH_2CH_3), 4.30 and 4.36 (2 × dd, $^3J_{HH}$ = 4.0 Hz and 8.8 Hz, 1H, 2-*H*, rotamers).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 15.0 (CH_2CH_3), 23.9 and 24.7 (*C*-4, rotamers), 30.3 and 31.3 (*C*-3, rotamers), 46.7 and 47.1 (*C*-5, rotamers), 52.5 (*C*-2), 59.2 and 59.4 (CH_2CH_3, rotamers), 61.6 ($COOCH_3$), 155.0 and 155.5 (*C*OOEt, rotamers), 173.7 (*C*OOMe).

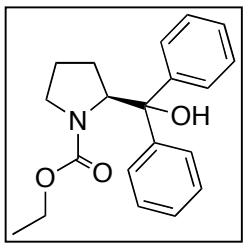
MS (FAB, NBA) *m/z* (%): 202 ($[M+H]^+$, 100), 142 ($[M-COOMe]^+$, 56), 128 ($[M-OCOOEt]^+$, 51), 70 ($C_4H_7N^+$, 27).
$[\alpha]_D^{20}$ = -58.2 (c = 0.50, $CHCl_3$) (Lit.[5] $[\alpha]_D^{20}$ = -75.1 (c = 1.03, $CHCl_3$)).



(R)-1-(Ethoxycarbonyl)proline methyl ester ((*R*)-78)[4]

By general method **I**, (*R*)-proline (576 mg, 5.00 mmol), K_2CO_3 (692 mg, 5.00 mmol) and ethyl chloroformate (1.0 mL, 1.2 g, 11 mmol) gave the crude product (856 mg, 95%), which was obtained as colorless oil and was directly used in the next step.

$C_9H_{15}NO_4$ (201.22 g/mol)
$[\alpha]_D^{20}$ = 60.3 (c = 0.50, $CHCl_3$).



(*S*)-Ethyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate ((*S*)-79)[4]

General Method II:
(*S*)-*N*-(Ethyoxycarbonyl)proline methyl ester (1.95 g, 9.7 mmol) was dissolved in THF (20 mL). Phenylmagnesium bromide (19.4 mL of 2.0 M solution in THF, 38.8 mmol) was added at 0 °C during 30 minutes. The mixture was stirred for 3 hours at 0 °C and 0.5 h at RT. The reaction was quenched with sat. NH_4Cl (20 mL) and a white precipitate was formed. The supernatant liquid was decanted and the precipitate was washed with chloroform (2 × 15 mL). Organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of solvent afforded a colorless solid (3.19 g). The crude product was purified by column chromatography (SiO_2, EA/pentane 10/90) to give (*S*)-**79** as colorless oil that solidified on standing (2.86 g, 91%).

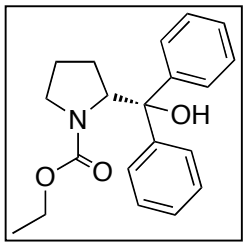
$C_{20}H_{23}NO_3$ (325.40 g/mol)
R_f = 0.53 (SiO_2, EA/pentane 20:80).
m. p. 112–113 °C (Lit.[5] 115–117 °C).
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 0.75–0.81 (m, 1H, 4-H_A), 1.23 (t, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3), 1.46–1.51 (m, 1H, 4-H_B), 1.91–1.96 (m, 1H, 3-H_A), 2.07–2.13 (m, 1H, 3-H_B),

2.93–2.98 (m, 1H, 5-H_A), 3.38–3.42 (m, 1H, 5-H_B), 4.07–4.15 (m, 2H, CH_2CH$_3$), 4.93 (dd, $^3J_{HH}$ = 3.6 and 8.8 Hz, 1H, 2-*H*), 6.10 (br s, 1H, O*H*), 7.29–7.32 (m, 10H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 15.1 (CH_2CH_3), 23.3 (*C*-4), 30.1 (*C*-3), 48.1 (*C*-5), 62.3 (CH_2CH_3), 66.3 (*C*-2), 82.0 (CPh_2OH), 127.5 (*Ph*H), 127.6 (*Ph*H), 127.8 (*Ph*H), 128.0 (*Ph*H), 144.1 (*Ph*C) 158.2 (*C*OOEt).

MS (FAB, NBA) *m/z* (%): 326 ($M+H^+$, 11), 308 $[M-OH]^+$, 59), 236 ($[M-COOEt-OH+H]^+$, 7), 142 ($C_7H_{12}NO_2^+$, 100), 70 ($C_4H_7N^+$, 24).

$[\alpha]_D^{20}$ = -145.5 (c = 1.00, $CHCl_3$) (Lit.[5] $[\alpha]_D^{20}$ = -146 (c = 1.04, $CHCl_3$)).

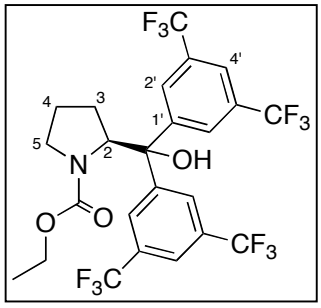


(*R*)-1-Ethyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate ((*R*)-79)

By general method **II**, the Grignard reagent (10 mL of 1.0 M solution in THF, 10 mmol) and (*R*)-*N*-(ethyoxycarbonyl)proline methyl ester (503 mg, 2.50 mmol) in 5 mL THF gave the crude product, which was purified by column chromatography (SiO_2, EA/pentane 5:95–20:80) to give the protected amino alcohol (*R*)-**79** (765 mg, 94%) as colorless oil that solidified on standing.

$C_{20}H_{23}NO_3$ (325.40 g/mol)

$[\alpha]_D^{20}$ = 146.0 (c = 1.00, $CHCl_3$).



(*S*)-1-Ethyl 2-[bis-(3,5-bis(trifluoromethyl)phenyl)-hydroxymethyl]pyrrolidine-1-carboxylate ((*S*)-80)

General method III:

Magnesium turnings (0.486 g, 20.0 mmol) were placed in an oven tried two-necked flask with a condenser. The flask was cooled to RT by flushing with Ar. Dry THF (8 mL) was added, followed by 3,5-bis(trifluoromethyl)-bromobenzene (1.7 mL, 2.9 g, 10 mmol) was added dropwise during 30 minutes. The contents were further stirred for 30 minutes. The solution turned brown.

By general method **II**, this Grignard reagent solution and (*S*)-*N*-(ethyoxycarbo-nyl)proline methyl ester (503 mg, 2.50 mmol) in 5 mL THF gave the crude product, which was purified

by column chromatography (SiO_2, EA/pentane 20/80) to give the protected amino alcohol (*S*)-**80** (1.08 g, 72%) as pale yellow solid.

$C_{24}H_{19}F_{12}NO_3$ (597.39 g/mol)

R_f = 0.50 (SiO_2, EA/pentane 10:90).

m. p. 144–145 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 0.97–1.02 (m, 1H, 4-H_A), 1.22 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3), 1.63–1.69 (m, 1H, 4-H_B), 1.75–1.82 (m, 1H, 3-H_A), 2.08–2.13 (m, 1H, 3-H_B), 2.90–2.96 (m, 1H, 5-H_A), 3.51–3.57 (m, 1H, 5-H_B), 4.09–4.21 (m, 2H, CH_2CH_3), 4.86 (dd, $^3J_{HH}$ = 5.3 Hz and 8.6 Hz, 1H, 2-*H*), 7.00 (br s, 1H, O*H*), 7.82 (s, 2H, Ar*H*), 7.86 (s, 2H, Ar*H*), 7.89 (s, 2H, Ar*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 14.5 (CH_2CH_3), 23.3 (*C*-4), 30.4 (*C*-3), 48.1 (*C*-5), 62.8 (CH_2CH_3), 66.7 (*C*-2), 82.8 (CAr_2OH), 122.0 (hept., $^3J_{CF}$ = 3.8 Hz, *C*-4'), 122.2 (hept., $^3J_{CF}$ = 3.8 Hz, *C*-4'), 123.3 (q, $^1J_{CF}$ = 273 Hz, CF_3), 123.4 (q, $^1J_{CF}$ = 273 Hz, CF_3), 127.7 (q, $^3J_{CF}$ = 3.1 Hz, *C*-2'), 128.1 (q, $^3J_{CF}$ = 3.1 Hz, *C*-2'), 131.6 (q, $^2J_{CF}$ = 33.4 Hz, CCF_3), 131.9 (q, $^2J_{CF}$ = 33.4 Hz, CCF_3), 145.3 (*C*-1'), 147.3 (*C*-1'), 158.9 (*C*OOEt).

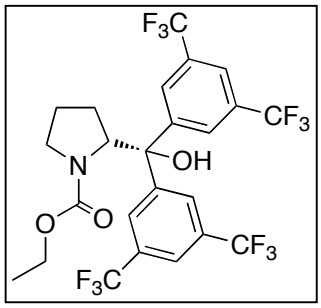
^{19}F-NMR ($CDCl_3$, 376 MHz) δ/ppm: -64.2 (CF_3), -63.9 (CF_3).

MS (FAB, NBA) *m/z* (%): 598 ($[M+H]^+$, 12), 580 ($[M-OH]^+$, 20), 142 ($[M-Ar_2COH]^+$, 100), 70 ($C_4H_8N^+$, 33).

IR (ATR): $\tilde{\nu}$ = 3446m; 2990w; 1674s; 1417m; 1340m; 1205m; 1163w; 1104m; 1046w; 993w; 710m; 675s.

EA: calc. for $C_{24}H_{19}F_{12}NO_3$: C, 48.25; H, 3.21; N, 2.34; F, 38.16; O, 8.03. Found: C, 48.22; H, 3.17; N, 2.29.

$[\alpha]_D^{20}$ = -45.1 (c = 1.0, $CHCl_3$).



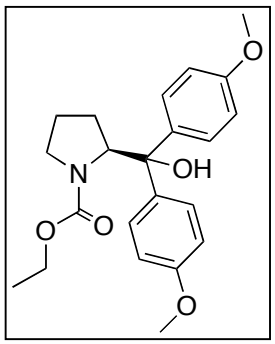
(*R*)-1-Ethyl 2-[bis-(3,5-bis(trifluoromethyl)phenyl)-hydroxymethyl]pyrrolidine-1-carboxylate ((*R*)-80)

(*R*)-*N*-(Ethyoxycarbonyl)proline methyl ester (478 mg, 2.37 mmol) was treated with 3,5-bis(trifluoromethyl)-phenyl magnesium bromide (8.0 mL of 1.25 M solution in THF, 10 mmol)) following the general method **III**. Crude product was purified by column chromatography (SiO_2, EA/pentane 10:90) to give (*R*)-**80** (961 mg, 68%) as colorless solid.

$C_{24}H_{19}F_{12}NO_3$ (597.39 g/mol)

EA: calc. for $C_{24}H_{19}F_{12}NO_3$: C, 48.25; H, 3.21; N, 2.34; F, 38.16; O, 8.03. Found: C, 48.22; H, 3.18; N, 2.29.

$[\alpha]_D^{20}$ = + 45.4 (c = 1.0, $CHCl_3$).



(*S*)-1-Ethyl 2-[bis(4-methoxyphenyl)hydroxymethyl]-pyrrolidine-1-carboxylate ((*S*)-324)

By general method **II**, the Grignard reagent (20 mL of 1.0 M solution in THF, 20 mmol) and (*S*)-*N*-(ethyoxycarbonyl)-proline methyl ester (805 mg, 4.00 mmol) in 5 mL THF gave the crude product, which was purified by column chromatography (SiO_2, EA/pentane 10:90–30:70) to give (*S*)-**324** (1.23 g, 80%) as pale yellow solid.

$C_{22}H_{27}NO_5$ (385.45 g/mol)

R_f = 0.23 (silica, EA/pentane 20:80).

m.p. 45–47 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 0.73–0.85 (m, 1H, 4-H_A), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 1.44–1.51 (m, 1H, 4-H_B), 1.85–1.92 (m, 1H, 3-H_A), 2.02–2.12 (m, 1H, 3-H_B), 2.89–2.96 (m, 1H, 5-H_A), 3.36–3.44 (m, 1H, 5-H_B), 3.80 (s, 6H, OCH_3), 4.06–4.19 (m, 2H, CH_2CH_3), 4.87 (dd, $^3J_{HH}$ = 3.3 and 8.8 Hz, 1H, 2-*H*), 5.96 (br s, 1H, O*H*), 6.79–6.86 (m, 4H, Ar*H*), 7.25–7.33 (m, 4H, Ar*H*).

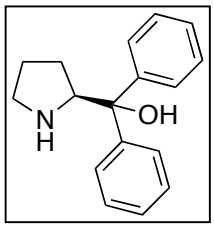
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 14.8 (CH_2CH_3), 23.1 (*C*-4), 29.7 (*C*-3), 47.8 (*C*-5), 55.3 (OCH_3), 62.0 (CH_2CH_3), 77.1 (*C*-2), 81.0 (CAr_2OH), 112.8 (*Ar*H), 113.0 (*Ar*H), 128.9 (*Ar*H), 129.4 (*Ar*H), 136.0 (*Ar*C), 139.0 (*Ar*OMe) 158.7 (*C*OOEt).

MS (FAB, NBA) *m/z* (%): 386 ($M+H^+$, 4), 368 $[M-OH]^+$, 100), 243 ($[M-C_7H_{12}NO_2^+$, 62), 142 ($C_7H_{12}NO_2^+$, 85), 70 ($C_4H_7N^+$, 35).

IR (ATR): $\tilde{\nu}$ = 3337br w (O-H); 3002w; 1665s (C=O); 1609s; 1510s; 1423s; 1339s; 1297s; 1248s (ν_{C-N}); 1121s; 1037m; 987m; 830s (Ar); 762m.

EA: calc. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63; O, 20.75. Found: C, 68.37; H, 7.02; N, 3.60.

$[\alpha]_D^{20}$ = -113.2 (c = 1.00, $CHCl_3$).



(*S*)-Diphenyl(pyrrolidin-2-yl)methanol ((*S*)-81)[4]

General Method IV:

The protected amino alcohol (*S*)-**79** (2.86 g, 8.79 mmol) was partly dissolved in dry methanol (20 mL) and KOH (4.94 g, 88.0 mmol) was added. The mixture was heated on reflux for 4 h. Methanol was evaporated and water (20 mL) was added. The product was extracted with $CHCl_3$ (3 × 20 mL), dried over $MgSO_4$. Evaporation of the solvent afforded the product (2.02 g, 91%) as colorless solid. Crude product was directly used in the next step. An analytical sample was obtained by recrystallization from hexane.

$C_{17}H_{19}NO$ (253.34 g/mol)

R_f = 0.08 (SiO_2, EA/pentane 40:60).

m. p. 74-75 °C (Lit.[6] 76.5–77.5 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.55–1.78 (m, 5H, NH, 3-*H*, 4-*H*), 2.91–2.98 (m, 1H, 5-H_A), 3.01-3.05 (m, 1H, 5-H_B), 4.25 (t, $^3J_{HH}$ = 7.6 Hz, 1H, 2-*H*), 4.55 (br s, 1H, O*H*), 7.14–7.19 (m, 2H, PhH_{para}), 7.26–7.31 (m, 4H, PhH_{orto}), 7.48–7.51 (m, 2H, PhH_{meta}), 7.55–7.57 (m, 2H, PhH_{meta}).

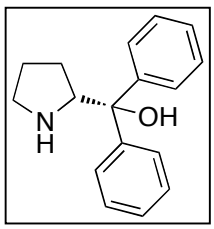
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 25.5 (*C*-4), 26.3 (*C*-3), 46.8 (*C*-5), 64.5 (*C*-2), 77.1 (*C*Ph_2OH), 125.6 (*Ph*H_{orto}), 125.9 (*Ph*H_{orto}), 126.4 (*Ph*H_{para}), 126.5 (*Ph*H_{para}), 128.0 (*Ph*H_{meta}), 128.3 (*Ph*H_{meta}), 145.4 (*Ph*C), 148.2 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 254 ($M+H^+$, 32), 236 ($[M-OH]^+$, 19), 70 ($C_4H_7N^+$, 100).

IR (ATR): $\tilde{\nu}$ = 3345w; 2966w; 2834w; 1489m; 1448m; 1184w; 1064m; 986m; 751m; 707s; 694s; 636m.

EA: calc. for $C_{17}H_{19}NO$: C, 80.60, H, 7.56; N, 5.53; O, 37.76. Found: C, 80.45; H, 7.49; N, 5.43.

$[\alpha]_D^{20}$ = -59.1 (c = 3.00, MeOH) (Lit.[6] $[\alpha]_D^{20}$ = -58.8 (c = 3.00, MeOH)).

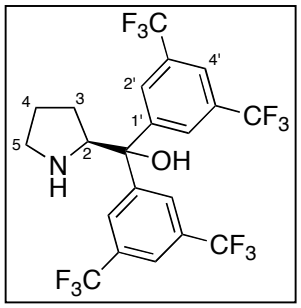


(*R*)-Diphenyl(pyrrolidin-2-yl)methanol ((*R*)-81)[4]

The deprotection of (*R*)-**79** (650 mg, 2.00 mmol) was accomplished following the general method **IV** by using KOH (1.12 g, 20.0 mmol) in MeOH (5 mL). Crude product was obtained as pale yellow solid and was

purified by recrystallization from hexane (425 mg, 84%, colorless solid).

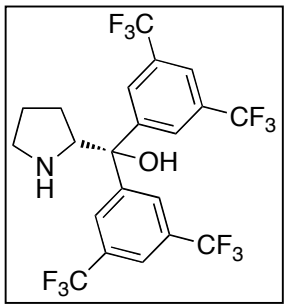
$C_{17}H_{19}NO$ (253.34 g/mol)
$[\alpha]_D^{20}$ = 60.2 (c = 3.10, MeOH).



(*S*)-Bis[3,5-bis(trifluoromethyl)phenyl](pyrrolidin-2-yl)methanol ((*S*)-82)

The deprotection of (*S*)-**80** (740 mg, 1.24 mmol) was accomplished following the general method **IV** by using KOH (670 mg, 11.9 mmol) in MeOH (4 mL). Crude product was obtained as pale yellow solid (588 mg, 93%) and was used directly in the next step. An analytical sample was prepared by recrystallization from hexane.

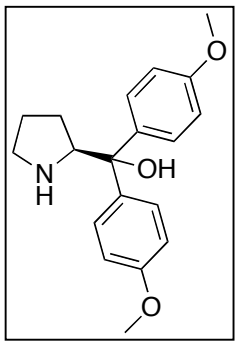
$C_{21}H_{15}F_{12}NO$ (525.33 g/mol)
R_f = 0.10 (SiO_2, EA/pentane 5:95).
m. p. 109–110 °C (Lit.[7] 117–118 °C).
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.50–1.55 (m, 2H, 4-*H*), 1.68 (s, 1H, N*H*), 1.76–1.83 (m, 2H, 3-*H*), 3.02-3.11 (m, 1H, 5-*H*), 4.35 (t, 1H, $^3J_{HH}$ = 7.8 Hz, 2-*H*), 5.08 (br s, 1H, O*H*), 7.76 (s, 2H, Ar*H*), 7.96 (s, 2H, Ar*H*), 8.04 (s, 2H, Ar*H*).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 25.5 (*C*-4), 26.7 (*C*-3), 46.9 (*C*-5), 64.2 (*C*-2), 76.6 (*C*Ar$_2$OH), 121.4 (hept., $^3J_{CF}$ = 3.7 Hz, *C*-4'), 121.6 (hept., $^3J_{CF}$ = 3.7 Hz, *C*-4'), 123.5 (q, $^1J_{CF}$ = 243 Hz, *C*F$_3$), 125.8 (q, $^3J_{CF}$ = 2.7 Hz, *C*-2'), 126.3 (q, $^3J_{CF}$ = 2.7 Hz, *C*-2'), 132.0 (q, $^2J_{CF}$ = 33.4 Hz, *C*CF$_3$), 132.2 (q, $^2J_{CF}$ = 33.4 Hz, *C*CF$_3$), 146.6 (*C*-1'), 149.6 (*C*-1').
^{19}F-NMR ($CDCl_3$, 376 MHz) δ/ppm: -64.0 (C*F*$_3$), -63.9 (C*F*$_3$).
MS (FAB, NBA) *m/z* (%): 526 ([M+H]$^+$, 100), 508 ([M-OH]$^+$, 17), 70 ($C_4H_7N^+$, 93), 43 ($C_2H_5N^+$, 29).
IR (ATR): $\tilde{\nu}$ = 3419w; 2973w; 2864w; 1369m; 1274s; 1122s; 1101m; 991w; 890m; 843m; 704m; 681s.
EA: calc. for $C_{21}H_{15}F_{12}NO$: C, 48.01; H, 2.88; N, 2.67; F, 43.3; O, 3.05. Found: C, 47.98; H, 2.95; N, 2.57.
$[\alpha]_D^{20}$ = -19.5 (c = 3.1, MeOH) (Lit.[7] $[\alpha]_D^{26}$ = -51 (c = 1.1, $CHCl_3$).



(*R*)-Bis[3,5-bis(trifluoromethyl)phenyl](pyrrolidin-2-yl)methanol ((*R*)-82)

The deprotection of (*R*)-**80** (930 mg, 1.56 mmol) was accomplished following the general method **IV** by using KOH (898 mg, 16.0 mmol) in MeOH (5 mL). Crude product was obtained as pale yellow solid (831 mg, 99%) and was purified by recrystallization from hexane (631 mg, 77%).

$C_{21}H_{15}F_{12}NO$ (525.33 g/mol)
$[\alpha]_D^{20}$ = 19.7 (c = 3.1, MeOH).



(*S*)-2-Bis(4-methoxyphenyl)(pyrrolidin-2-yl)methanol ((*S*)-122)

The deprotection of (*S*)-**324** (200 mg, 0.519 mmol) was accomplished following the general method **IV** by using KOH (292 mg, 5.20 mmol) in MeOH (3 mL). The starting material was consumed due to TLC after 3 h. The isolated crude mixture consisted of product (*S*)-**122** and by-product ((*S*)-**123**) in 1:1 ratio. The mixture was purified by column chromatography (SiO_2, EA/pentane 30:70, then acetone). (*S*)-**122** was obtained as colorless solid (81 mg, 47%) and (*S*)-**123** as colorless oil (81 mg, 50%). When the reaction time was prolonged (24 h), the crude product was obtained as colorless oil (165 mg, quant.) and was used directly in the next step. An analytical sample was prepared by recrystallization from hexane.

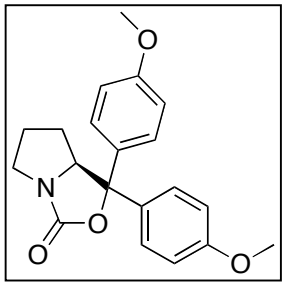
$C_{19}H_{23}NO_3$ (253.34 g/mol)
m. p. 62–63 °C.
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.53–1.75 (m, 5H, N*H*, 3-*H*, 4-*H*), 2.90–2.99 (m, 1H, 5-H_A), 3.00–3.04 (m, 1H, 5-H_B), 3.76 (s, 6H, OCH_3), 4.16 (t, $^3J_{HH}$ = 7.6 Hz, 1H, 2-*H*), 6.80 (d, $^3J_{HH}$ = 6.8 Hz, 2H, Ar*H*), 6.82 (d, $^3J_{HH}$ = 6.8 Hz, 2H, Ar*H*), 7.37 (d, $^3J_{HH}$ = 9.1 Hz, 2H, Ar*H*), 7.44 (d, $^3J_{HH}$ = 9.1 Hz, 2H, Ar*H*).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 25.7 (*C*-4), 26.4 (*C*-3), 46.9 (*C*-5), 55.3 (O*C*H$_3$), 55.4 (O*C*H$_3$), 64.8 (*C*-2), 77.1 (*C*Ar$_2$OH), 113.4 (*Ar*H), 113.7 (*Ar*H), 126.7 (*Ar*H), 127.1 (*Ar*H), 128.0 (*Ar*H), 128.3 (*Ar*H), 138.2 (*Ar*O), 140.8 (*Ar*C).

MS (FAB) *m/z* (%): 314 ([M]$^+$, 100), 296 ([M-H_2O]$^+$, 57), 188 ([M-H_2O-PhOMe]$^+$, 17).

IR (ATR): $\tilde{\nu}$ = 3430br w; 3369w; 2962m; 2941m; 2874m; 2838m; 1604m; 1581m; 1507s; 1443m; 1313s; 1298m; 1166s (C-O-C); 1097m; 1025s (C-O-C); 836s (arom.); 821s (arom.).

EA: calc. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47; O, 15.32. Found: C, 72.66; H, 7.36; N, 4.30.

$[\alpha]_D^{20}$ = - 86.2 (c = 0.50, $CHCl_3$) (Lit.[8] $[\alpha]_D^{20}$ = - 44.1 (c = 0.61, MeOH).



By-product: (*S*)-1,1-bis(4-methoxyphenyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one ((*S*)-**123**):

$C_{20}H_{21}NO_4$ (253.34 g/mol)

R_f = 0.55 (SiO_2, EA/pentane 50:50).

m. p. 80 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.08–1.16 (m, 1H, 3-H_A),1.61–1.69 (m, 1H, 3-H_B), 1.80–1.90 (m, 1H, 4-H_A), 1.94–2.00 (m, 1H, 4-H_B), 3.22–3.27 (m, 1H, 5-H_A), 3.69–3.75 (m, 1H, 5-H_B), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.48 (dd, $^3J_{HH}$ = 5.6 and 10.4 Hz, 1H, 2-*H*), 6.85–6.87 (m, 4H, Ar*H*), 7.25 (d, $^3J_{HH}$ = 9.1 Hz, 2H, Ar*H*), 7.40 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar*H*).

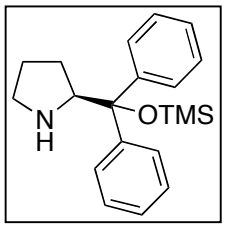
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 25.0 (*C*-4), 29.1 (*C*-3), 46.1 (*C*-5), 55.3 (O*C*H_3), 69.4 (*C*-2), 85.8 (*C*Ar_2O), 113.6 (*Ar*H), 113.8 (*Ar*H), 126.8 (*Ar*H), 127.6 (*Ar*H), 132.7 (*Ar*O), 135.8 (*Ar*O), 158.8 (*Ar*C), 159.5 (*Ar*C), 160.7 (COO).

MS (FAB) *m/z* (%): 314 ([M+H]$^+$, 100), 296 ([M-COOH]$^+$, 43), 188 ([M-COOH-PhOMe]$^+$, 33), 135 (37).

IR (ATR): $\tilde{\nu}$ = 3475br w; 2962s; 2839m; 1743s (C=O); 1610s; 1510s; 1463s; 1361s; 1302s; 1181s (C-O-C); 1026m; 988m; 958m; 822s (arom.); 774m.

EA: calc. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; O, 18.86. Found: C, 70.74; H, 6.25; N, 3.96.

$[\alpha]_D^{20}$ = -214.3 (c = 0.95, $CHCl_3$) (Lit.[8] $[\alpha]_D^{20}$ = - 44.1 (c = 0.61, MeOH).



(*S*)-2-[Diphenyl((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-46a)[9]

General method V:

TMSOTf (0.47 mL, 0.58g, 2.6 mmol) was added at 0 °C to a solution of amino alcohol (*S*)-**81** (507 mg, 2.00 mmol) and triethylamine (0.34 mL, 0.26 g, 2.6 mmol) in dichloromethane (10 mL). The reaction was allowed to reach ambient temperature and was stirred for 1 h. The reaction was quenched with water (10 mL) and product was extracted with DCM (3 × 10 mL) and organic extracts were dried over $MgSO_4$. Evaporation of solvent afforded green-yellow oil (773 mg), which was further purified by column chromatography (SiO_2, EA/pentane 40:60) to give the product (381 mg, 59%) as pale yellow oil.

$C_{20}H_{27}NOSi$ (325.52 g/mol)

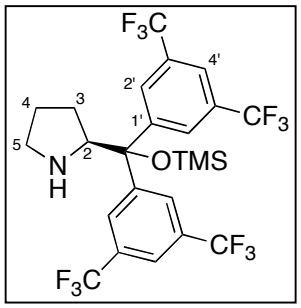
R_f = 0.35 (SiO_2, EA).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 0.09 (s, 9H, Si(CH_3)$_3$), 1.36–1.39 (m, 1H, 4-H_A), 1.55–1.58 (m, 3H, 3-H_2, 4-H_B), 1.68 (s, 1H, N*H*), 2.76–2.88 (m, 2H, 5-*H*), 4.03 (t, $^3J_{HH}$ = 7.0 Hz, 1H, 2-*H*), 7.18–7.29 (m, 6H, Ph*H*), 7.34–7.37 (m, 2H, Ph*H*), 7.45–7.47 (m, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 2.1 (Si(*C*H_3)$_3$), 25.0 (*C*-4), 27.4 (*C*-3), 47.1 (*C*-5), 65.3 (*C*-2), 83.1 (*C*Ph_2OR), 126.7 (*Ph*H_{orto}), 126.8 (*Ph*H_{orto}), 127.5 (*Ph*H_{para}), 127.6 (*Ph*H_{para}), 128.4 (*Ph*H_{meta}), 128.6 (*Ph*H_{meta}), 145.7 (*Ph*C), 146.8 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 326 ([M+H]$^+$, 91), 255 ([M-C_4H_8N]$^+$, 24), 236 ([M-OTMS]$^+$, 100), 70 ($C_4H_7N^+$, 52).

$[\alpha]_D^{20}$ = -43.8 (c = 1.00, $CHCl_3$) (Lit.[9] $[\alpha]_D^{20}$ = -30 (c = 1.00, CH_2Cl_2)).



(*S*)-2-[(Bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-43)

By general method **V**, the amino alcohol (*S*)-**82** (443 mg, 0.842 mmol) was treated with TMSOTf (0.20 mL, 0.24 g, 1.1 mmol) in the presence of triethylamine (0.11 g, 0.15 mL, 1.1 mmol). The crude product was purified by column chromatography (SiO_2, EA/pentane 10:90) to give the product (450 mg, 90 %) as an off-white solid.

$C_{24}H_{23}F_{12}NOSi$ (597.51 g/mol)

R_f = 0.55 (SiO_2, EA/pentane 5:95).

m. p. 54–56 °C.

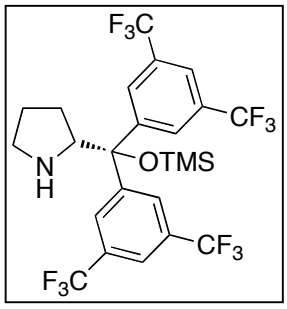
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: -0.08 (s, 9H, CH_3), 1.06–1.15 (m, 1H, 4-H_A), 1.40–1.58 (m, 2H, 4-H_B, 3-H_A), 1.65–1.74 (m, 2H, NH, 3-H_B), 2.61 (dt, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, 5-H_A), 2.97 (dt, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 6.6 Hz, 1H, 5-H_B), 4.27 (t, $^3J_{HH}$ = 7.3 Hz, 1H, 2-H), 7.82 (s, 2H, ArH), 7.89 (s, 2H, ArH), 8.06 (s, 2H, ArH).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 1.9 (CH$_3$), 25.2 (C-4), 27.5 (C-3), 47.2 (C-5), 64.3 (C-2), 82.3 (CAr$_2$OR), 121.5 (hept., $^3J_{CF}$ = 3.8 Hz, C-4'), 121.7 (hept., $^3J_{CF}$ = 3.8 Hz, C-4'), 123.1 (q, $^1J_{CF}$ = 272 Hz, CF$_3$), 123.3 (q, $^1J_{CF}$ = 272 Hz, CF$_3$), 128.1 (q, $^3J_{CF}$ = 3.1 Hz, C-2'), 128.6 (q, $^3J_{CF}$ = 3.1 Hz, C-2'), 130.8 (q, $^2J_{CF}$ = 33.4 Hz, CCF$_3$), 131.5 (q, $^2J_{CF}$ = 33.4 Hz, CCF$_3$), 146.4 (C-1'), 148.1 (C-1').

^{19}F-NMR ($CDCl_3$, 376 MHz) δ/ppm: -63.96 (CF$_3$), -64.04 (CF$_3$).

MS (FAB, NBA) *m/z* (%): 598 ([M+H]$^+$, 71), 526 ([M-C_4H_9N]$^+$, 71), 508 ([M-OTMS]$^+$, 36), 70 ($C_4H_7N^+$, 100).

$[\alpha]_D^{20}$ = -6.6 (c = 1.18, CH_2Cl_2) (Lit.[9] $[\alpha]_D^{20}$ = -6.8 (c = 1.20, CH_2Cl_2)).

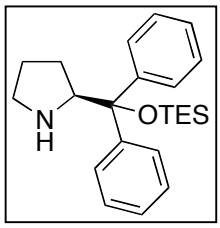


(*R*)-2-[(Bis(3,5-bis(trifluoromethyl)phenyl)-((trimethylsilyl)oxy)methyl]pyrrolidine ((*R*)-43)

By general method **V**, the aminoalcohol (*R*)-**82** (260 mg, 0.495 mmol) was treated with TMSOTf (0.12 mL, 0.14 g, 0.64 mmol) in the presence of triethylamine (90 µL, 65 mg, 0.64 mmol). The crude product was purified by column chromatography (SiO_2, EA/pentane 10:90) to give the (*R*)-**43** (280 mg, 96 %) as an off-white solid.

$C_{24}H_{23}F_{12}NOSi$ (597.51 g/mol)

$[\alpha]_D^{20}$ = 6.8 (c = 1.15, CH_2Cl_2).



(*S*)-2-[Diphenyl((triethylsilyl)oxy)methyl]pyrrolidine ((*S*)-46b)[10]

General method VI:

To a dichloromethane (0.6 mL) solution of amino alcohol (*S*)-**81** (152 mg, 600 µmol) was added 2,6-lutidine (0.49 mL, 0.45 g, 4.2 mmol) and TESOTf (0.68 mL, 0.79 g, 3.0 mmol) at 0 °C. The reaction mixture was stirred for 14 h at RT and quenched with sat. NH_4Cl (2 mL). The organic materials were extracted with chloroform (3 × 3 mL) and washed with 1 M KOH (2 mL) and water (2 mL). Organic materials were dried over $MgSO_4$, filtered and concentrated in vacuo. Crude product was purified by column chromatography (SiO_2, EA/pentane 1:99–30:70) to give the product (165 mg, 75 %) as colorless oil.

$C_{23}H_{33}NOSi$ (367.60 g/mol)

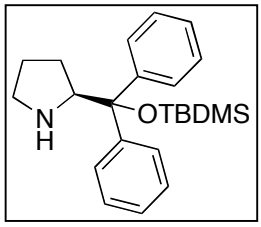
R_f = 0.12 (SiO_2, EA/pentane 20:80).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 0.35 (q, $^3J_{HH}$ = 7.9 Hz, 6H, CH_2CH_3), 0.86 (t, $^3J_{HH}$ = 7.9 Hz, 9H, CH_2CH_3), 1.22–1.28 (m, 1H, 4-H_A), 1.50–1.61 (m, 4H, 3-*H*, 4-H_B, N*H*), 2.67–2.72 (m, 1H, 5-H_A), 2.78–2.84 (m, 1H, 5-H_B), 4.01 (t, $^3J_{HH}$ = 7.2 Hz, 1H, 2-*H*), 7.21–7.29 (m, 6H, Ph*H*), 7.34–7.37 (m, 2H, Ph*H*), 7.46–7.48 (m, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 6.7 (CH_2CH_3), 7.4 (CH_2CH_3), 25.3 (*C*-4), 27.9 (*C*-3), 47.4 (*C*-5), 65.8 (*C*-2), 83.0 (CPh_2OR), 127.0 (*Ph*H), 127.1 (*Ph*H), 127.4 (*Ph*H), 127.7 (*Ph*H), 128.2 (*Ph*H), 129.0 (*Ph*H), 145.7 (*Ph*C), 146.8 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 368 ($M+H^+$, 74), 297 ($[M-C_4H_8N]^+$, 10), 236 ($[M-OTES]^+$, 100), 70 ($C_4H_7N^+$, 44).

$[\alpha]_D^{20}$ = -47.5 (c = 1.00, $CHCl_3$) (Lit.[10] $[\alpha]_D^{33}$ = -48.4 (c = 0.097, $CHCl_3$)).



(*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl]-pyrrolidine ((*S*)-46c)[10]

By general method **VI** amino alcohol (*S*)-**81** (300 mg, 1.18 mmol), 2,6-lutidine (0.98 mL, 0.90 g, 8.4 mmol) and TBDMSOTf (1.3 mL, 1.6 g, 5.9 mmol) gave the crude mixture, which was purified by column chromatography (SiO_2, EA/pentane 1:99–30:70). (*S*)-**46c** (380 mg, 86%) was obtained as colorless solid.

$C_{23}H_{33}NOSi$ (367.60 g/mol)

R_f = 0.12 (SiO_2, EA/pentane 20/80).

m.p. 67-68 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: -0.46 (s, 3H, SiCH_3), -0.21 (s, 3H, SiCH_3), 0.95 (s, 9H, C(CH_3)$_3$), 1.18–1.26 (m, 1H, 4-H_A), 1.50–1.63 (m, 3H, 3-*H*, 4-H_B), 1.81 (s, 1H, N*H*), 2.65–2.70 (m, 1H, 5-H_A), 2.80–2.86 (m, 1H, 5-H_B), 4.02 (t, $^3J_{HH}$ = 7.2 Hz, 1H, 2-*H*), 7.23–7.28 (m, 6H, Ph*H*), 7.35–7.37 (m, 2H, Ph*H*), 7.50–7.52 (m, 2H, Ph*H*).

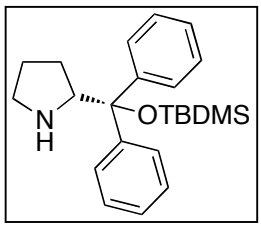
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: -3.2 (*C*H$_3$), -2.5 (*C*(CH$_3$)$_3$), 25.1 (*C*-4), 26.5 (C(*C*H$_3$)$_3$), 28.0 (*C*-3), 47.3 (*C*-5), 65.8 (*C*-2), 83.2 (*C*Ph$_2$OR), 127.07 (*Ph*H), 127.14 (*Ph*H), 127.4 (*Ph*H), 127.7 (*Ph*H), 128.4 (*Ph*H), 129.4 (*Ph*H), 145.4 (*Ph*C), 146.6 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 368 (M+H$^+$, 51), 297 ([M-C$_4$H$_8$N]$^+$, 11), 236 ([M-OTBDMS]$^+$, 100), 70 (C$_4$H$_7$N$^+$, 37).

IR (KBr): $\tilde{\nu}$ = 3056m, 2870s, 1466s, 1419s, 1355m, 1252s (Si-C), 1119s (C-O), 1063s, 964w, 770s (Ph), 699s (Ph).

EA: calc. for $C_{23}H_{33}NOSi$: C, 75.15; H, 9.05; N, 3.81; O, 4.35; Si, 7.64. Found: C, 75.23; H, 8.86; N, 3.64.

$[\alpha]_D^{20}$ = -34.2 (c = 1.00, $CHCl_3$) (Lit.[10] $[\alpha]_D^{32}$ = -34.4 (c = 0.198, $CHCl_3$)).

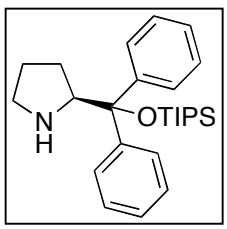


(*R*)-2-[((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl]-pyrrolidine ((*R*)-46c)

By general method **VI** amino alcohol (*R*)-**81** (152 mg, 0.598 mmol), 2,6-lutidine (0.49 mL, 0.45 g, 4.2 mmol) and TBDMSOTf (0.69 mL, 0.82 g, 3.1 mmol) gave the crude mixture, which was purified by column chromatography (SiO_2, EA/pentane 1:99-30:70). (*R*)-**46c** (190 mg, 86 %) was obtained as colorless solid.

$C_{23}H_{33}NOSi$ (367.60 g/mol)

$[\alpha]_D^{20}$ = 34.5 (c = 1.10, $CHCl_3$).



(*S*)-2-[Diphenyl((triisopropylsilyl)oxy)methyl]pyrrolidine ((*S*)-46d)

By general method **VI** amino alcohol (*S*)-**81** (253 mg, 1.00 mmol), 2,6-lutidine (0.82 mL, 0.75 g, 7.0 mmol,) and TIPSOTf (1.3 mL, 1.5 g,

4.8 mmol) gave the crude mixture, which was purified by column chromatography (SiO_2, EA/cyclohexane 1:99-30:70). (*S*)-**46d** (210 mg, 51%) was obtained as colorless oil. An analytical sample was obtained by bulb-to-bulb distillation (190–200 °C at 0.15 mbar).

$C_{26}H_{39}NOSi$ (409.68 g/mol)

$\boldsymbol{R_f}$ = 0.12 (SiO_2, EA/ cyclohexane 20/80).

b.p. 190–200 °C (0.15 mbar).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 0.80–0.86 (m, 3H, SiC*H*$(CH_3)_2$), 0.92 (d, $^3J_{HH}$ = 4.1 Hz, 9H, SiCH(C*H*$_3)_2$), 0.94 (d, $^3J_{HH}$ = 4.1 Hz, 9H, SiCH(C*H*$_3)_2$), 1.05–1.09 (m, 1H, 4-H_A), 1.44–1.55 (m, 1H, 4-H_B), 1.59–1.68 (m, 1H, 3-H_A), 1.73–1.82 (m, 1H, 3-H_B), 1.87 (br s, 1H, N*H*), 2.47–2.53 (m, 1H, 5-H_A), 2.73–2.79 (m, 1H, 5-H_B), 4.16 (t, $^3J_{HH}$ = 7.4 Hz, 1H, 2-*H*), 7.23–7.29 (m, 6H, Ph*H*), 7.40–7.42 (m, 2H, PhH_{ortho}), 7.48–7.50 (m, 2H, PhH_{ortho}).

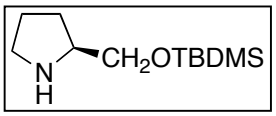
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 13.9 (Si*C*H$(CH_3)_2$), 18.6 (SiCH(*C*H$_3)_2$), 18.7 (SiCH(*C*H$_3)_2$), 25.3 (*C*-4), 28.0 (*C*-3), 47.2 (*C*-5), 65.7 (*C*-2), 83.7 (*C*Ph$_2$OR), 127.2 (*Ph*H), 127.5 (*Ph*H), 127.6 (*Ph*H), 129.2 (*Ph*H), 129.5 (*Ph*H), 144.9 (*Ph*C), 146.0 (*Ph*C).

MS (ESI, 200 °C, 30 V) *m/z* (%): 410 (M+H$^+$, 100), 236 ([M-OTIPS]$^+$, 13).

IR (ATR): $\tilde{\nu}$ = 3058w, 2924s, 2864s, 1491m, 1444m, 1388m, 1250w, 1059s, 997w, 918w, 881s; 840m; 700s, 669m.

EA: calc. for $C_{26}H_{39}NOSi$: C, 76.23; H, 9.59; N, 3.42; O, 3.91; Si, 6.86. Found: C, 76.22; H, 9.62; N, 3.56.

$[\alpha]_D^{20}$ = -3.6 (c = 0.89, $CHCl_3$).



(*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-84)

By general method **VI** (*S*)-prolinol (0.10 g, 98 µL, 1.0 mmol), 2,6-lutidine (0.81 mL, 0.75 g, 7.0 mmol) and TBDMSOTf (1.1 mL, 1.3 g, 5.0 mmol) gave the crude product, which was purified by column chromatography (SiO_2, EA/pentane 1:99–30:70). (*S*)-**84** (92 mg, 43%) was obtained as light orange oil.

$C_{11}H_{25}NOSi$ (215.17 g/mol)

$\boldsymbol{R_f}$ = 0.15 (SiO_2, EA/pentane 20/80).

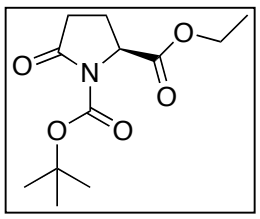
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 0.04 (s, 6H, Si*C*H$_3$), 0.88 (s, 9H, *C*$(CH_3)_3$), 1.40–1.46 (m, 1H, 4-H_A), 1.67–1.78 (m, 3H, 3-*H*, 4-H_B), 2.14 (s, 1H, N*H*), 2.79–2.85 (m, 1H, 5-H_A),

2.94–3.00 (m, 1H, 5-H_B), 3.11–3.16 (m, 1H, 2-*H*), 3.50 (dd, $^2J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, CH_AH$_B$OTBDMS), 3.57 (dd, $^2J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, CH$_A$$H_B$OTBDMS).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: -5.3 (Si*C*H$_3$), 18.4 (*C*(CH$_3$)$_3$), 25.5 (*C*-4), 26.0 (C(*C*H$_3$)$_3$), 29.8 (*C*-3), 46.6 (*C*-5), 60.1 (*C*-2), 67.0 (*C*H$_2$OR).

MS (ESI, 200 °C, 30 V) *m/z* (%): 215 ($M+H^+$, 100).

$[\alpha]_D^{20}$ = -7.3 (c = 1.00, $CHCl_3$) (Lit. [11] $[\alpha]_D^{20}$ = -6.6 (c = 0.8, $CHCl_3$)).



(*S*)-1-(*tert*-Butyloxycarbonyl)pyroglutamic acid ethyl ester ((*S*)-189)[12]

To the solution of (*S*)-Ethyl pyroglutamate (1.00 g, 6.36 mmol) and DMAP (78 mg, 0.64 mmol) in acetonitrile (12 mL) was added Boc_2O (1.53 g, 7.00 mmol). The solution was stirred at RT for 18 h, concentrated in vacuo and purified by chromatography (SiO_2, cyclohexane/EA 80:20–65:35) to give a thick oil, which was recrystallized from pentane/Et_2O to give the product as colorless solid (1.29 g, 79%).

$C_{12}H_{19}NO_5$ (257.28 g/mol)

R_f = 0.08 (silica, EA/ cyclohexane 35:65).

m.p. 51–52 °C (Lit.[12] 53–54 °C, hexane).

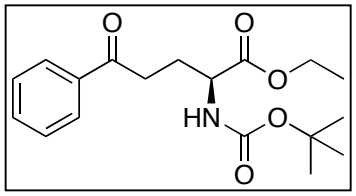
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.48 (s, 9H, C(C*H*$_3$)$_3$), 1.99–2.05 (m, 1H, 4-H_A), 2.25–2.36 (m, 1H, 4-H_B), 2.43–2.51 (m, 1H, 3-H_A), 2.57–2.66 (m, 1H, 3-H_B), 4.22 (q, $^3J_{HH}$ = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 4.58 (dd, $^3J_{HH}$ = 2.8 Hz and 9.4 Hz, 5-*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 8.7 (*C*H$_3$), 16.1 (*C*-4), 22.4 (C(*C*H$_3$)$_3$) 25.7 (*C*-3), 53.5 (*C*-5), 56.2 (*C*H$_2$CH$_3$), 78.1 (*C*(CH$_3$)$_3$), 143.8 (*C*O^{t}Bu), 165.9 (*C*OOEt), 167.9 (N*C*OR).

MS (FAB, NBA) *m/z* (%): 258 ($[M+H]^+$, 18), 202 ($[M-C_4H_7]^+$, 40), 158 ([M-COOtBu]$^+$, 100), 84 ([M-COOtBu-COOEt]$^+$, 21], 57 ($C_3H_7N^+$, 42).

IR (ATR): $\tilde{\nu}$ = 2980w, 2930w, 1772s, 1736s, 1701m, 1458w, 1364m, 1306s, 1273s, 1209m, 1095s, 1045s, 1026s, 852m, 842m, 777m.

$[\alpha]_D^{20}$ = -49.5 (c = 0.50, MeOH) (Lit. [12] $[\alpha]_D^{20}$ = -39.8 (c = 0.50, MeOH)).



(*S*)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-5-oxo-5-phenyl-pentanoate ((*S*)-184)[13, 14]

Phenylmagnesium bromide (8.4 mL of 1 M solution in THF, 8.4 mmol) was added to the lactam (*S*)-**189** (1.80 g, 7.00 mmol) dissolved in dry THF (40 mL) at -40 °C under Ar. After 2 h of stirring at -40 °C, the reaction mixture was quenched with AcOH/MeOH (30 mL, 1:1) and diluted with Et_2O (30 mL). The organic layer was washed with water (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by recrystallization from Et_2O/pentane to give (*S*)-**184** as colorless solid (1.91 g, 81%).

$C_{18}H_{25}NO_5$ (335.39 g/mol)

R_f = 0.40 (SiO_2, EA/ cyclohexane 25:75, 254 nm).

m.p. 82–83 °C (Lit.[14] 82–83 °C).

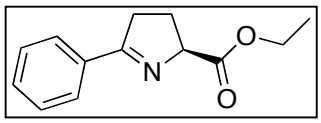
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.26 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 1.41 (s, 9H, $C(CH_3)_3$), 2.04–2.11 (m, 1H, 3-H_A), 2.28–2.34 (m, 1H, 3-H_B), 3.00–3.16 (m, 2H, 4-*H*), 4.18 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2CH_3), 4.35–4.36 (m, 1H, 2-*H*), 5.18 (d, $^3J_{HH}$ = 7.6 Hz, 1H, N*H*), 7.43–7.46 (m, 2H, Ph*H*), 7.53–7.57 (m, 1H, Ph*H*), 7.93-7.95 (m, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 14.3 (CH_2CH_3), 27.2 (*C*-3), 28.4 ($C(CH_3)_3$), 34.7 (*C*-4), 53.2 (*C*-2), 61.6 (CH_2CH_3), 80.0 ($C(CH_3)_3$), 128.1 (*Ph*H), 128.7 (*Ph*H), 133.3 (*Ph*H), 136.8 (*Ph*C), 155.6 (*C*O^{t}Bu), 172.5 (*C*OOEt), 199.0 (*C*OPh).

MS (FAB) *m/z* (%): 336 ($[M+H]^+$, 39), 280 ($[M-C_4H_7]^+$, 58), 218 ($[M-NCOO^tBu]^+$, 100), 162 ($[M-COOtBu-COOEt]^+$, 21], 57 ($C_4H_9^+$, 41).

IR (ATR): $\tilde{\nu}$ = 3366w, 2984w, 1740m, 1684s, 1514m, 1448m, 1373m, 1283m, 1254m, 1217m, 1169s, 1157s, 1018s, 858m, 740s, 690m.

$[\alpha]_D^{20}$ = -14.5 (c = 0.50, MeOH).



(*S*)-2-Ethyl 5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate ((*S*)-181)[14]

To a solution of *Boc*-amine (*S*)-**184** (1.01 g, 3.00 mmol) in dichloromethane (45 mL) was added TFA (3.3 mL, 5.1 g, 45 mmol) at 0 °C and the resulting solution was allowed to warm to RT and stirred for 2 h. The mixture was neutralized with triethylamine (7.3 mL, 5.4 g,

53 mmol). Water was added to the mixture and the organic phase was separated. The water layer was extracted with dichloromethane (2 × 40 mL). Collected organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, cyclohexane/EA 80:20) to afford (*S*)-**181** as colorless oil (632 mg, 97%).

$C_{13}H_{15}NO_3$ (217.26 g/mol)

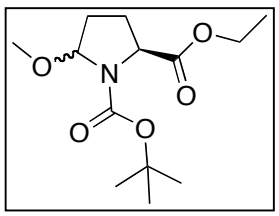
R_f = 0.25 (silica, EA/CH 20:80).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 2.17–2.23 (m, 1H, 4-H_A), 2.24–2.37 (m, 1H, 4-H_B), 2.91–3.00 (m, 1H, 3-H_A), 3.09–3.18 (m, 1H, 3-H_B), 4.22 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH_3), 4.88 (dd, $^3J_{HH}$ = 6.4 Hz and 8.4 Hz, 1H, 5-*H*), 7.36–7.45 (m, 3H, Ph*H*), 7.85–7.87 (m, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 14.3 (CH_2CH_3), 26.5 (*C*-4), 35.5 (*C*-3), 61.1 (CH_2CH_3), 74.7 (*C*-5), 128.1 (*Ph*H), 128.5 (*Ph*H), 131.0 (*Ph*H), 133.9 (*Ph*C), 173.0 (*C*=N), 176.1 (*C*OOEt).

MS (FAB) *m/z* (%): 217 (M^+, 7), 144 ([M-COOEt]$^+$, 100), 91 ($C_7H_7^+$, 14), 41 ($C_2H_3N^+$, 6).

$[\alpha]_D^{20}$ = 99.3 (c = 1.00, CH_2Cl_2).



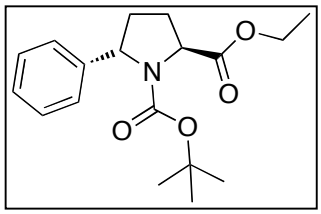
(2*S*,5*R*)/(2*S*,5*S*)- 1-(*tert*-Butoxycarbonyl)-5-methoxypyrrolidine-2-carboxylic acid ethyl ester ((2*S*,5*R*)/(2*S*,5*S*)-190)[15]

A solution of protected (*S*)-ethyl pyroglutamate (*S*)-**189** (2.00 g, 12.7 mmol) in dry THF (100 mL) was cooled to -78 °C. Then $LiEt_3BH$ (15.3 mL of 1 M solution in THF, 15.3 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 minutes. Sat. $NaHCO_3$ was added (35 mL) and the mixture was allowed to warm to 0 °C. 80 drops of H_2O_2 (33%) were added and the mixture was stirred for additional 30 minutes. After warming to RT, the organic phase was separated and water layer was washed with Et_2O (3 × 50 mL). The collected organic extracts were dried over $MgSO_4$, filtrated and concentrated in vacuo.

The crude product was dissolved in MeOH (40 mL) and *p*-TsOH·H_2O (243 mg, 1.28 mmol) was added. The solution was stirred at RT overnight, then sat. $NaHCO_3$ (10 mL) was added and MeOH was evaporated. The residue was extracted with Et_2O (3 × 20 mL), the organic extracts were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The crude

product (1.95 g, ca 72%, ca 80% pure by ^{1}H-NMR) was obtained as colorless oil and was directly used in the next step.

$C_{13}H_{23}NO_5$ (273.33 g/mol)
R_f = 0.22 (silica, EA/cyclohexane 20:80).



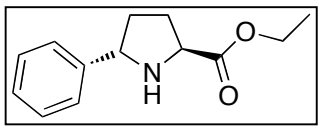
(2*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid ethyl ester ((2*S*,5*S*)-191)[14]

To a stirred suspension of CuBr·Me_2S (3.00 g, 14.6 mmol) in dry Et_2O (30 mL) was at -40 °C slowly added PhMgBr (14.6 mL of 1 M solution in THF, 14.6 mmol). The mixture was stirred at this temperature for 45 min, cooled to -78 °C and BF_3·Et_2O (1.8 mL, 2.1 g, 15 mmol) was added dropwise. The reaction mixture was stirred for 30 min and then the crude ethyl ester (2*S*,5*R*)/(2*S*,5*S*)-**190** (1.25 g, 80% pure, 3.66 mmol) in Et_2O (6 mL) was added dropwise. The mixture was allowed to warm to RT during 3 h and was stirred for an additional hour. A 1:1 mixture of NH_4Cl and conc. NH_3 (20 mL) was added and the mixture was stirred overnight. The organic layer was separated and water layer was extracted with Et_2O (2 × 30 mL). Collected organic extracts were washed with sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography (SiO_2, EA/cyclohexane 5:95–20:80). The obtained product (colorless oil) was contaminated with unknown impurity (1.03 g, 65 % purity, 56% yield) and was used directly in the next step.

$C_{18}H_{25}NO_4$ (319.40 g/mol)
R_f = 0.45 (silica, EA/cyclohexane 20:80).
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.20 and 1.42 (2 × s, 9H, C(CH_3)$_3$, rotamers), 1.27 and 1.32 (2 × t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3CH$_2$, rotamers), 1.75–1.84 (m, 1H, 3-H_A), 1.92–1.98 (m, 1H, 4-H_A), 2.26–2.34 (m, 1H, 4-H_B), 2.41–2.52 (m, 1H, 3-H_B), 4.14–4.28 (m, 2H, CH$_3$CH_2), 4.51 and 4.64 (2 × dd, $^3J_{HH}$ = 1.5 Hz and 8.8 Hz, 1H, 5-*H*, rotamers), 5.03 and 5.21 (2 × dd, $^3J_{HH}$ = 1.3 Hz and 8.4 Hz, 1H, 2-*H* rotamers), 6.81 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ph*H*), 7.14–7.32 (m, 4H, Ph*H*).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 14.3 and 14.4 (CH$_2$CH_3, rotamers), 27.4 and 28.2 (*C*-4, rotamers), 28.1 and 28.4 (C(CH_3)$_3$, rotamers), 32.6 and 33.6 (*C*-3, rotamers), 60.1 and

60.5 (*C*-5, rotamers), 61.2 and 61.3 CH_2CH_3, rotamers), 61.4 and 61.8 (*C*-2, rotamers), 80.3 and 80.5 ($C(CH_3)_3$, rotamers), 125.3 (*Ph*H), 125.5 (*Ph*H), 126.8 (*Ph*H), 126.9 (*Ph*H), 128.3 (*Ph*H), 128.6 (*Ph*H), 129.9 (*Ph*H), 143.4 and 144.5 (*Ph*C, rotamers), 153.8 and 154.6 (*C*OO^{t}Bu, rotamers), 172.9 and 173.2 (*C*OOEt, rotamers).

MS (FAB, NBA) *m/z* (%): 329 ($M+H^+$, 22), 264 ($[M-C_4H_9]^+$, 100), 246 (([M-COOEt]$^+$, 26), 190 (([M-C_4H_9-COOEt]$^+$, 34), 146 ([M-COOEt-COO^{t}Bu]$^+$, 58).



(2*S*,5*S*)-Ethyl 5-phenylpyrrolidine-2-carboxylate ((2*S*,5*S*)-187)[15]

The *Boc*-protected ester (2*S*,5*S*)-**191** (900 mg of 64% pure compound, 1.80 mmol) was dissolved in DCM (60 mL), TFA was added (2.1 mL, 3.2 g, 28.2 mmol) and the mixture was stirred overnight. The mixture was washed with sat. $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Crude product (650 mg, orange oil) was purified by column chromatography (SiO_2, cyclohexane/EA 95:5–90:10). The product was obtained as colorless oil (340 mg, 86%).

$C_{13}H_{17}NO_2$ (219.28 g/mol)

R_f = 0.44 (silica, EA/cyclohexane 20:80).

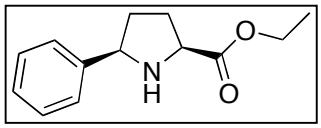
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.29 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_2CH_3), 1.72–1.77 (m, 1H, 4-H_A), 1.95–2.02 (m, 1H, 3-H_A), 2.17–2.23 (m, 1H, 4-H_B), 2.33–2.38 (m, 2H, 3-H_B), 2.58 (br s, 1H, N*H*), 4.03 (dd, $^3J_{HH}$ = 5.5 Hz and 8.5 Hz, 1H, 2-*H*), 4.21 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2CH_3), 4.37 (dd, $^3J_{HH}$ = 7.0 Hz, and 8.5 Hz, 1H, 5-*H*), 7.23 (t, $^3J_{HH}$ = 7.0 Hz, 1H, Ph*H*), 7.32 (t, $^3J_{HH}$ = 8.0 Hz, 2H, Ph*H*), 7.38 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 14.4 (CH_3), 29.9 (*C*-3), 34.8 (*C*-4), 59.7 (*C*-2), 61.1 (CH_2CH_3), 61.8 (*C*-5), 126.5 (*Ph*H), 127.0 (*Ph*H), 128.4 (*Ph*H), 144.6 (*Ph*C), 176.0 (*C*OOEt).

MS (EI, 70 eV, RT) *m/z* (%): 219 (M^+, 2), 146 ([M-COOEt]$^+$, 100), 129 ([M-PhCH]$^+$, 40), 91 ($PhCH_2^+$, 6).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3348w, 2964w, 2928w, 1730s, 1452w, 1367w, 1205m, 1121w, 1030w, 820w, 756w, 702m, 631w.

$[\alpha]_D^{20}$ = -84.5 (c = 1.00, $CHCl_3$) (Lit.[15] $[\alpha]_D^{25}$ = -86.7 (c = 0.7, $CHCl_3$)).



(2*S*,5*R*)-Ethyl 5-phenylpyrrolidine-1-carboxylate ((2*S*,5*R*)-187)[14]

Ketimine (*S*)-**181** (217 mg, 1.00 mmol) was dissolved in EtOH (3 mL) and PtO_2 (3.0 mg, 13 µmol) was added. The mixture was hydrogenated (30 bars) in an autoclave at RT. After 3 h, the solution was filtered through celite (0.5 × 3 cm), the solvent was removed in vacuo and the crude product (colorless oil, 198 mg, 90%) was directly used in the next step.

$C_{13}H_{17}NO_2$ (219.28 g/mol)

R_f = 0.31 (silica, EA/cyclohexane 20:80).

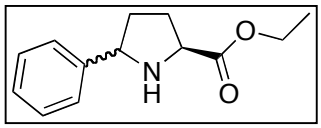
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.32 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 1.67–1.79 (m, 1H, 4-H_A), 2.12–2.24 (m, 1H, 3-*H*, 4-H_B), 2.57 (br s, 1H, N*H*), 3.92 (dd, $^3J_{HH}$ = 4.9 Hz and 8.7 Hz, 1H, 2-*H*), 4.19–4.26 (m, 3H, CH_2CH_3, 5-*H*), 7.24–7.28 (m, 1H, Ph*H*), 7.33–7.37 (m, 2H, Ph*H*), 7.45–7.47 (m, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 14.4 (CH_3), 30.8 (*C*-3), 34.3 (*C*-4), 60.3 (*C*-2), 61.3 (CH_2CH_3), 63.8 (*C*-5), 126.9 (*Ph*H), 127.3 (*Ph*H), 128.6 (*Ph*H), 143.4 (*Ph*C), 175.3 (*C*OOEt).

MS (EI, 70 eV, RT) *m/z* (%): 219 (M^+, 5), 146 ([M-COOEt]$^+$, 100), 129 ([M-PhCH]$^+$, 36), 91 ($PhCH_2^+$, 12).

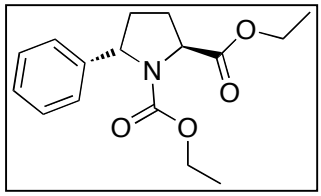
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2920s, 2851m, 1731m, 1456w, 1377w, 1204w, 1028w, 826bw, 700w.

$[\alpha]_D^{20}$ = 12.5 (c = 1.00, $CHCl_3$) (Lit.[15] $[\alpha]_D^{25}$ = 9.7 (c = 0.9, $CHCl_3$)).



(2*S*,5*R*)/(2*S*,5*S*)-Ethyl 5-phenylpyrrolidine-1-carboxylate ((2*S*,5*R*)/(2*S*,5*S*)-187)[14]

Ketimine (*S*)-**181** (1.09 g, 5.02 mmol) was dissolved in 1:11 mixture of conc. HCl and ^{i}PrOH (55 mL). $NaBH_3CN$ (1.59 g, 25.3 mmol) was added and the mixture was stirred for 2 h at RT. Sat. $NaHCO_3$ (50 mL) was added, followed by water (50 mL). The mixture was extracted with EA (3 × 40 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, cyclohexane/EA 80:20), which provided the products (2*S*,5*S*)-**187** (211 mg, 19%) and (2*S*,5*R*)-**187** (501 mg, 45%) as colorless oils. The analytical data of both compounds were identical to those prepared by alternative selective methods.



(2*S*,5*S*)-1-(Ethoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid ethyl ester ((2*S*, 5*S*)-192)

By general method **I** ester (2*S*,5*S*)-**187** (320 mg, 1.46 mmol), ethylchloroformate (140 µL, 158 mg, 1.46 mmol) and $NaHCO_3$ (123 mg, 1.46 mmol) gave the crude product as colorless oil (425 mg, quant.), which was directly used in the next step.

$C_{16}H_{21}NO_4$ (291.34 g/mol)

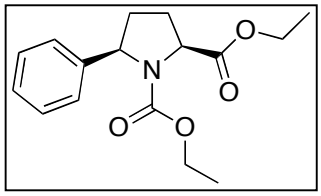
R_f = 0.43 (SiO_2, EA/cyclohexane 20:80).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 0.98 and 1.20 (2 × t, $^3J_{HH}$ = 7.5 Hz, 3H, NCOOCH$_2$C*H*$_3$, rotamers), 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CHCOOCH$_2$C*H*$_3$), 1.78–1.84 (m, 1H, 4-*H*$_A$), 1.92–2.01 (m, 1H, 3-*H*$_A$), 2.17–2.37 (m, 1H, 3-*H*$_B$), 2.43–2.54 (m, 2H, 4-*H*$_B$), 3.98–4.06 (m, 2H, NCOOC*H*$_2$CH$_3$), 4.13–4.25 (m, 2H, CHCOOC*H*$_2$CH$_3$), 4.60 (dd, $^3J_{HH}$ = 3.5 Hz and 8.5 Hz, 1H, 2-*H*), 5.17 (dd, $^3J_{HH}$ = 8.5 Hz, and 10.0 Hz, 1H, 5-*H*), 7.13–7.38 (m, 5H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 14.3 and 14.4 (*C*H$_3$, rotamers), 14.5 and 14.7 (*C*H$_3$, rotamers), 27.2 and 28.3 (*C*-3, rotamers), 32.5 and 33.6 (*C*-4, rotamers), 60.2 and 60.3 (*C*-2, rotamers), 61.1 and 61.2 (*C*H$_2$CH$_3$, rotamers), 61.3 and 61.4 (*C*H$_2$CH$_3$, rotamers), 61.5 and 61.6 (*C*-5, rotamers), 125.3 (*Ph*H), 125.4 (*Ph*H), 126.5 (*Ph*H), 126.8 (*Ph*H), 216.9 (*Ph*H), 128.4 (*Ph*H), 128.6 (*Ph*H), 143.3 and 143.8 (*Ph*C, rotamers), 154.5 and 155.3 (N*C*OOEt, rotamers), 172.6 and 172.8 (*C*OOEt, rotamers).

MS (FAB, NBA) *m/z* (%): 292 ([M+H$^+$], 100), 246 ([M-OEt]$^+$, 26), 218 ([M-COOEt]$^+$, 92), 77 ($C_6H_5^+$, 18).

$[\alpha]_D^{20}$ = -99.9 (c = 1.08, $CHCl_3$).



(2*S*,5*R*)-1-(Ethoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid ethyl ester ((2*S*,5*R*)-192)

By general method **I** ester (2*S*,5*R*)-**187** (190 mg, 0.87 mmol), ethylchloroformate (83 µL, 94 mg, 0.87 mmol) and $NaHCO_3$ (83 mg, 0.87 mmol) gave the crude product, which was purified by column chromatography (SiO_2, cyclohexane/EA 80:20). (2*S*,5*R*)-**192** was obtained as colorless oil (177 mg, 70%).

$C_{16}H_{21}NO_4$ (291.34 g/mol)

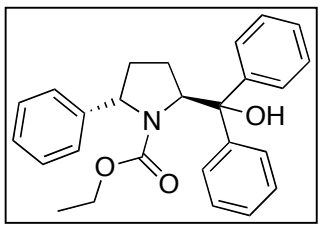
R_f = 0.31 (silica, EA/cyclohexane 20:80).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 0.95 and 1.21 (2 × t, $^3J_{HH}$ = 7.1 Hz, 3H, NCOOCH$_2$C*H*$_3$, rotamers), 1.33 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CHCOOCH$_2$C*H*$_3$), 1.95–2.09 (m, 2H, 4-*H*), 2.19–2.36 (m, 2H, 3-*H*), 3.95–4.11 (m, 2H, NCOOC*H*$_2$CH$_3$), 4.23–4.32 (m, 2H, CHCOOC*H*$_2$CH$_3$), 4.40–4.50 (m, 1H, 2-*H*), 4.88 and 4.98 (2 × t, $^3J_{HH}$ = 5.8 Hz, 1H, 5-*H*), 7.22 (t, $^3J_{HH}$ = 7.6 Hz, 1H, PhH_{para}), 7.32 (t, $^3J_{HH}$ = 7.8 Hz, 2H, PhH_{meta}), 7.55 (t, $^3J_{HH}$ = 7.6 Hz, 2H, PhH_{ortho}).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 14.3 (*C*H$_3$), 14.6 (*C*H$_3$), 28.6 and 29.4 (*C*-3, rotamers), 34.5 and 35.5 (*C*-4, rotamers), 60.7 and 61.0 (*C*-2, rotamers), 61.2 (*C*H$_2$CH$_3$), 61.4 (*C*H$_2$CH$_3$), 62.6 and 63.0 (*C*-5, rotamers), 126.3 (*Ph*H), 126.8 (*Ph*H), 126.9 (*Ph*H), 128.2 (*Ph*H), 128.4 (*Ph*H), 142.8 and 143.5 (*Ph*C, rotamers), 154.9 and 155.7 (N*C*OOEt, rotamers), 172.8 and 173.0 (*C*OOEt, rotamers).

MS (EI, 70 eV, 50 °C) *m/z* (%): 291 (M^+, 3), 218 ([M-COOEt]$^+$, 100), 146 ([M-2COOEt]$^+$, 13).

$[\alpha]_D^{20}$ = 23.3 (c = 0.95, $CHCl_3$).



(2*S*,5*S*)-Ethyl 2-(hydroxydiphenylmethyl)-5-phenyl-pyrrolidine-1-carboxylate ((2*S*,5*S*)-193)

By general method **II** protected ester (2*S*,5*S*)-**192** (400 mg, 1.37 mmol) and PhMgBr (5.5 mL of 1 M solution in THF, 5.5 mmol) in THF (3 mL) gave the crude product in 3 h at 0 °C. It was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 95:5-90:10) to give product as colorless solid (315 mg, 57%) and the by-product (2*S*,5*S*)-**195** was isolated as a 70:30 mixture with main product (210 mg). Analytical sample of (2*S*,5*S*)-**195** was obtained after recrystallization from Et_2O (colorless solid, 67 mg, 12%).

Product ((2*S*,5*S*)-**192**):

$C_{26}H_{27}NO_3$ (401.50 g/mol)

R_f = 0.57 (SiO_2, EA/cyclohexane 20:80)

m.p. 112–114 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 0.71–0.83 (m, 4H, CH_3, 4-H_A), 1.18–1.24 (m, 1H, 4-H_B), 1.90–1.95 (m, 1H, 3-H_A), 2.32–2.43 (m, 1H, 3-H_B), 3.87–3.95 (m, 2H, CH_2CH$_3$), 4.60 (m_c, 1H, 5-*H*), 5.35 (m_c, 1H, 2-*H*), 6.06 (br s, 1H, O*H*), 7.02 (d, $^3J_{HH}$ = 7.3 Hz, 2H, Ph*H*), 7.19 (t, $^3J_{HH}$ = 7.0 Hz, 1H, Ph*H*), 7.26–7.39 (m, 10H, Ph*H*), 7.49 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ph*H*).

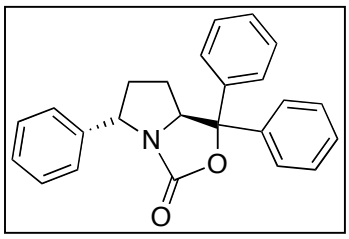
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 14.1 (CH_2CH_3), 27.2 (*C*-3), 32.4 (*C*-4), 61.8 (CH_2CH_3), 63.7 (*C*-5), 66.2 (*C*-2), 82.3 (CPh_2OH), 124.7 (*Ph*H), 126.6 (*Ph*H), 127.4 (*Ph*H), 127.6 (*Ph*H), 127.9 (*Ph*H), 128.1 (*Ph*H), 128.5 (*Ph*H), 128.6 (*Ph*H), 143.8 (*Ph*C), 145.7 (*Ph*C), 147.0 (*Ph*C), 159.3 (*C*OOEt).

MS (FAB, NBA) *m/z* (%): 402 ($M+H^+$, 7), 384 ($[M-OH]^+$, 60), 218 ($[M-Ph_2COH]^+$, 100), 129 (14), 117 (18).

IR (ATR): $\tilde{\nu}$ = 3489w; 2957w; 1676s (C=O); 1446m; 1400m; 1375m; 1335m; 1126m; 1014m; 764s; 750s; 694s.

EA: calc. for $C_{22}H_{27}NO_5$: C, 77.78; H, 6.78; N, 3.49; O, 11.95. Found: C, 77.85; H, 6.81; N, 3.35.

$[\alpha]_D^{20}$ = -131.0 (c = 0.48, $CHCl_3$).



By-product: (5*S*,7a*S*)-1,1,5-Triphenyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one ((2*S*,5*S*)-**195**)

$C_{24}H_{21}NO_2$ (355.43 g/mol)

R_f = 0.46 (SiO_2, EA/cyclohexane 20:80).

m.p. 124–125 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.31–1.40 (m, 1H, 3-H_A), 1.83–1.88 (m, 1H, 3-H_B), 1.95–2.02 (m, 1H, 4-H_A), 2.60–2.66 (m, 1H, 4-H_B), 4.85 (dd, $^3J_{HH}$ = 5.0 Hz and 10.5 Hz, 1H, 2-*H*), 5.13 (t, $^3J_{HH}$ = 8.0 Hz, 1H, 5-*H*), 7.13–7.47 (m, 13H, Ph*H*), 7.61 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ph*H*).

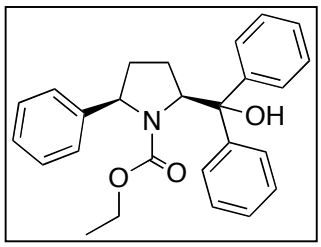
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 30.7 (*C*-3), 35.2 (*C*-4), 62.3 (*C*-5), 69.3 (*C*-2), 86.2 (CPh_2OR), 125.6 (*Ph*H), 125.7 (*Ph*H), 126.2 (*Ph*H), 127.3 (*Ph*H), 127.4 (*Ph*H), 128.5 (*Ph*H), 128.6 (*Ph*H), 128.7 (*Ph*H), 128.8 (*Ph*H), 140.3 (*Ph*C), 142.6 (*Ph*C), 143.3 (*Ph*C), 160.6 (*C*OO).

MS (EI, 70 eV, 150 °C) *m/z* (%): 355 (M^+, 36), 183 (Ph_2COH^+, 30), 145 ([M-Ph_2C-O-C(=O)]$^+$, 76), 104 ($C_8H_8^+$, 100), 77 ($C_6H_5^+$, 8).

IR (ATR): $\tilde{\nu}$ = 3055w; 2918w; 1749s (C=O); 1493m; 1445m; 1340m; 1236s; 1180m; 1055m; 989m; 8ssm; 768s; 748s; 698s.

EA: calc. for $C_{22}H_{27}NO_5$: C, 81.10; H, 5.95; N, 3.94; O, 9.00. Found: C, 80.85; H, 6.05; N, 3.77.

$[\alpha]_D^{20}$ = -224.9 (c = 1.00, $CHCl_3$).



(2*S*,5*R*)-Ethyl 2-(hydroxydiphenylmethyl)-5-phenyl-pyrrolidine-1-carboxylate ((2*S*,5*R*)-193)

By general method **II** protected ester (2*S*,5*R*)-**193** (150 mg, 0.515 mmol) and PhMgBr (2.1 mL of 1 M solution in THF, 2.1 mmol) in THF (1.5 mL) gave the crude product in 3 h at 0 °C. It was purified by column chromatography (SiO_2, cyclohexane/EA 95:5–90:10) to give a colorless solid (143 mg, 70%).

$C_{26}H_{27}NO_3$ (401.50 g/mol)

R_f = 0.47 (SiO_2, EA/cyclohexane 20:80).

m.p. 139–140 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.01 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.56–1.63 (m, 1H, 4-H_A), 2.12–2.34 (m, 3H, 4-H_B, 3-*H*), 3.88–3.94 (m, 1H, CH_AH$_B$CH$_3$), 4.01–4.07 (m, 1H, CH$_A$$H_BCH_3$), 4.86 (t, $^3J_{HH}$ = 8.5 Hz, 1H, 5-*H*), 5.22 (m_c, 1H, 2-*H*), 5.41(br s, 1H, O*H*), 7.02 (d, $^3J_{HH}$ = 6.8 Hz, 2H, Ph*H*), 7.22–7.37 (m, 9H, Ph*H*), 7.50 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph*H*), 7.58 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph*H*).

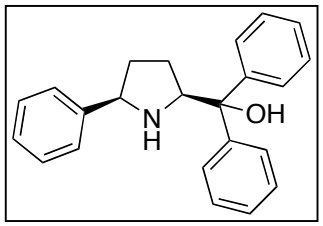
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 14.2 (CH_2*C*H$_3$), 29.1 (*C*-3), 33.7 (*C*-4), 62.2 (CH_2CH$_3$), 64.5 (*C*-5), 68.2 (*C*-2), 81.3 (*C*Ph$_2$OH), 126.3 (*Ph*H), 126.7 (*Ph*H), 127.1 (*Ph*H), 127.2 (*Ph*H), 127.4 (*Ph*H), 127.8 (*Ph*H), 127.9 (*Ph*H), 128.1 (*Ph*H), 128.2 (*Ph*H), 143.0 (*Ph*C), 144.0 (*Ph*C), 146.9 (*Ph*C), 159.8 (*C*OOEt).

MS (FAB, NBA) *m/z* (%): 402 (M+H$^+$, 8), 384 [M-OH]$^+$, 55), 218 ([M-Ph_2COH]$^+$, 100), 129 (14), 117 (20).

IR (ATR): $\tilde{\nu}$ = 3240m; 2984w; 1665s (C=O); 1439m; 1410m; 1379m; 1326s; 1126m; 1034m; 764s; 702s.

EA: calc. for $C_{22}H_{27}NO_5$: C, 77.78; H, 6.78; N, 3.49; O, 11.95. Found: C, 77.40; H, 6.80; N, 3.30.

$[\alpha]_D^{20}$ = -45.3 (c = 0.49, $CHCl_3$).



(2*S*, 5*R*)-Diphenyl[5-(phenylpyrrolidin-2-yl)]methanol ((2*S*,5*R*)-194)

The deprotection of (2*S*,5*R*)-**193** (120 mg, 299 µmol) was accomplished following the general method **IV** by using KOH (336 mg, 6.00 mmol), which was added in two portions (second one after 24 h). The mixture was heated on reflux in MeOH (3.5 mL) for 40 h. Crude product was obtained as colorless solid (101 mg, quant.). No further purification was necessary.

$C_{23}H_{23}NO$ (329.43 g/mol)

R_f = 0.61 (SiO_2, EA/cyclohexane 10:90, 254 nm).

m.p. 134–135 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.57 (bs, 1H, N*H*), 1.63–1.79 (m, 2H, 3-H_A, 4−H_A), 1.83–1.92 (m, 1H, 3-H_B), 2.07–2.16 (m, 1H, 4-H_B), 4.25 (dd, $^3J_{HH}$ = 6.6 and 8.8 Hz, 1H, 5-*H*), 4.45 (dd, $^3J_{HH}$ = 6.6 and 8.6 Hz, 1H, 2-*H*), 4.75 (s, 1H, O*H*), 7.14−7.35 (m, 11H, Ph*H*), 7.54 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ph*H*), 7.61 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph*H*).

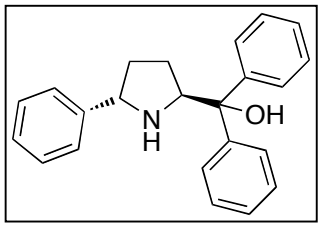
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 26.0 (*C*-3), 34.8 (*C*-4), 62.4 (*C*-5), 64.2 (*C*−2), 77.2 (*C*Ph_2OH), 125.6 (*Ph*H), 125.9 (*Ph*H), 126.6 (*Ph*H), 126.7 (*Ph*H), 127.3 (*Ph*H), 128.2 (*Ph*H), 128.4 (*Ph*H), 128.5 (*Ph*H), 144.0 (*Ph*C), 145.3 (*Ph*C), 148.0 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 330 ($[M+H]^+$, 61), 312 $[M\text{-}OH]^+$, 13), 146 ($[M-Ph_2COH]^+$, 100), 105 ($C_7H_5O^+$, 14), 91 ($C_7H_7^+$, 12), 77 ($C_6H_5^+$, 13).

IR (ATR): $\tilde{\nu}$ = 3361w; 3024w; 2925w; 1493m; 1448m; 1393m; 1252s; 1186w; 1055w; 1027w; 750s; 696s; 640m.

EA: calc. for $C_{23}H_{23}NO$: C, 83.86; H, 7.04; N, 4.25; O, 4.86. Found: C, 83.77; H, 7.19; N, 4.24.

$[\alpha]_D^{20}$ = -9.3 (c = 0.65, $CHCl_3$).



(2*S*,5*S*)-Diphenyl[5-(phenylpyrrolidin-2-yl)]methanol ((2*S*,5*S*)-194)

The deprotection of (2*S*,5*S*)-**193** (250 mg, 0.623 mmol) was accomplished following the general method **IV** by using KOH (336 mg, 6.00 mmol) 700 mg, 12.5 mmol) which was added in two portions (second one after 20 h). The mixture was heated on reflux in MeOH (3.5 mL) for 40 h. Crude product was obtained as colorless solid (160 mg, 78%). No further purification was necessary.

$C_{23}H_{23}NO$ (329.43 g/mol)

R_f = 0.51 (silica, EA/cyclohexane 10:90, 254 nm).

m.p. 125–126 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.67–1.74 (m, 1H, 3-H_A), 1.82–1.91 (m, 2H, 3-H_B, 4-H_A), 2.22–2.29 (m, 1H, 4-H_B), 4.38 (t, $^3J_{HH}$ = 6.8 Hz, 1H, 5-*H*), 4.69 (t, $^3J_{HH}$ = 8.1 Hz, 1H, 2-*H*), 5.29 (s, 1H, O*H*), 7.15−7.21 (m, 2H, Ph*H*), 7.25−7.37 (m, 9H, Ph*H*), 7.54 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph*H*), 7.62 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph*H*).

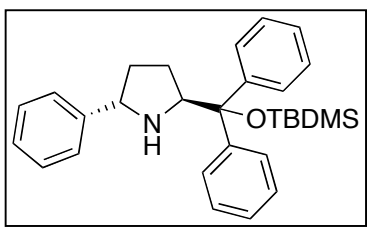
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 27.6 (*C*-3), 35.0 (*C*-4), 62.7 (*C*-5), 65.1 (*C*−2), 77.3 (*C*Ph_2OH), 125.7 (*Ph*H), 126.1 (*Ph*H), 126.2 (*Ph*H), 126.5 (*Ph*H), 126.7 (*Ph*H), 127.2 (*Ph*H), 128.1 (*Ph*H), 128.4 (*Ph*H), 128.8 (*Ph*H), 145.3 (*Ph*C), 145.7 (*Ph*C), 148.1 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 330 ($[M+H]^+$, 82), 312 ($[M\text{-}OH]^+$, 20), 146 ($[M-Ph_2COH]^+$, 100), 117 (22), 77 ($C_7H_5^+$, 18).

IR (ATR): $\tilde{\nu}$ = 3259w; 3024w; 2929w; 1491m; 1446m; 1400w; 1188m; 1093w; 983m; 756s; 696s; 665m.

EA: calc. for $C_{23}H_{23}NO$: C, 83.86; H, 7.04; N, 4.25; O, 4.86. Found: C, 83.56; H, 7.20; N, 4.14.

$[\alpha]_D^{20}$ = -125.6 (c = 0.69, $CHCl_3$).



(2*S*,5*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)diphenyl-methyl]-5-phenylpyrrolidine ((2*S*,5*S*)-188)

By general method **VI**, amino alcohol (2*S*,5*S*)-**194** (80.0 mg,

0.243 mmol), TBDMSOTf (280 µL, 321 mg, 1.21 mmol) and 2,6-lutidine (200 µL, 182 mg, 1.70 mmol) gave yellow oil, which was purified by column chromatography (SiO_2, cyclohexane/EA 99:1). (2*S*,5*S*)-**188** was obtained as colorless oil (88 mg, 82%).

$C_{29}H_{37}NOSi$ (443.70 g/mol)

R_f = 0.75 (SiO_2, EA/cyclohexane 10:90).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: -0.43 (s, 3H, SiC*H*$_3$), -0.20 (s, 3H, SiC*H*$_3$), 0.97 (s, 9H, C(C*H*$_3$)$_3$), 1.49–1.57 (m, 1H, 4-*H*$_A$), 1.69–1.77 (m, 1H, 4-*H*$_B$), 1.78–1.94 (m, 2H, 3-*H*), 1.95 (br s, 1H, N*H*), 3.71 (t, $^3J_{HH}$ = 7.0 Hz, 1H, 5-*H*), 4.41 (t, $^3J_{HH}$ = 7.5 Hz, 1H, 2-*H*), 7.19–7.22 (m, 1H, Ph*H*), 7.25–7.33 (m, 10H, Ph*H*), 7.40 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, 2H, Ph*H*), 7.57 (dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.5 Hz, 2H, Ph*H*).

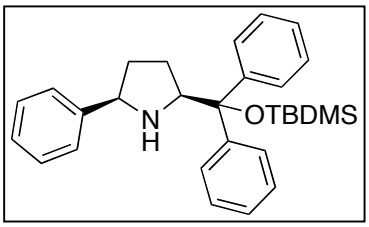
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: -3.2 (Si*C*H$_3$), -2.5 (Si*C*H$_3$), 19.1 (*C*(CH$_3$)$_3$), 26.5 (C(*C*H$_3$)$_3$), 28.6 (*C*-3), 34.8 (*C*-4), 62.1 (*C*-5), 65.4 (*C*-2), 83.8 (*C*Ph$_2$OR), 126.4 (*Ph*H), 126.6 (*Ph*H), 127.3 (*Ph*H), 127.4 (*Ph*H), 127.8 (*Ph*H), 128.4 (*Ph*H), 128.7 (*Ph*H), 129.5 (*Ph*H), 145.3 (*Ph*C), 146.2 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 444 ([M+H]$^+$, 60), 312 [M-OTBDMS]$^+$, 64), 146 ([M-Ph$_2$COTBDMS]$^+$, 100), 39 ($C_3H_3^+$, 8).

IR (ATR): $\tilde{\nu}$ = 1950w; 1491m; 1443m; 1358w; 1242s; 1064m; 1034w; 833s; 773m; 762m; 698s.

EA: calc. for $C_{29}H_{37}NOSi$: C, 78.50; H, 8.40; N, 3.16; O, 3.61; Si, 6.33. Found: C, 78.04; H, 8.70; N, 3.23.

$[\alpha]_D^{20}$ = -93.0 (c = 0.56, $CHCl_3$).



(2*S*,5*R*)-2-[((*tert*-Butyldimethylsilyl)oxy)diphenyl-methyl]-5-phenylpyrrolidine ((2*S*,5*R*)-188)

By general method **VI**, amino alcohol (2*S*,5*R*)-**194** (80.0 mg, 0.243 mmol), TBDMSOTf (280 µL, 321 mg, 1.21 mmol) and 2,6-lutidine (200 µL, 182 mg, 1.70 mmol) gave a yellow oil, which was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 99:1–95:5). (2*S*,5*R*)-**188** was obtained as colorless oil (71 mg, 66%).

$C_{29}H_{37}NOSi$ (443.70 g/mol)

$\boldsymbol{R_f}$ = 0.70 (SiO_2, EA/cyclohexane 10:90).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: -0.42 (s, 3H, SiCH_3), -0.27 (s, 3H, SiCH_3), 0.71–0.81 (m, 1H, 4-H_A), 0.94 (s, 9H, C(CH_3)$_3$), 1.74–1.90 (m, 4H, 4-H_B, 3-*H*, N*H*), 4.15 (dd, $^3J_{HH}$ = 6.8 Hz and 10.4 Hz, 1H, 5-*H*), 4.31 (t, $^3J_{HH}$ = 6.4 Hz, 1H, 2-*H*), 7.13–7.32 (m, 11H, Ph*H*), 7.40 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.6 Hz, 2H, Ph*H*), 7.61 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.6 Hz, 2H, Ph*H*).

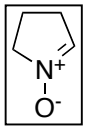
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: -3.1 (Si*C*H$_3$), -2.7 (Si*C*H$_3$), 19.1 (*C*(CH$_3$)$_3$), 26.4 (C(*C*H$_3$)$_3$), 27.4 (*C*-3), 34.0 (*C*-4), 63.2 (*C*-5), 64.0 (*C*-2), 83.4 (*C*Ph$_2$OR), 126.7 (*Ph*H), 126.8 (*Ph*H), 126.9 (*Ph*H), 127.4 (*Ph*H), 127.7 (*Ph*H), 128.1 (*Ph*H), 129.3 (*Ph*H), 129.9 (*Ph*H), 144.5 (*Ph*C), 145.8 (*Ph*C), 148.0 (*Ph*C).

MS (FAB, NBA) *m/z* (%): 444 ([M+H]$^+$, 100), 312 [M-OTBDMS]$^+$, 93), 146 ([M-Ph$_2$COTBDMS]$^+$, 45), 39 ($C_3H_3^+$, 14).

IR (ATR): $\tilde{\nu}$ = 1994w; 1491m; 1443m; 1340m; 1242s; 1064m; 1034w; 958w; 833s; 773m; 760m; 696s.

EA: calc. for $C_{23}H_{23}NO$: C, 78.50; H, 8.40; N, 3.16; O, 3.61; Si, 6.33. Found: C, 78.11; H, 8.56; N, 3.26.

$[\alpha]_D^{20}$ = -30.2 (c = 0.68, $CHCl_3$).



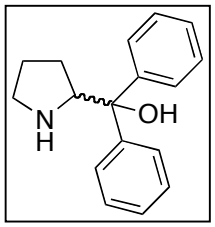
3,4-dihydro-2*H*-pyrrole-1-oxide (161)[17]

Methyltrioxorhenium (6.2 mg, 25 μmol) and urea hydrogen peroxide (3.29 g, 35.0 mmol) were suspended in dry CH_2Cl_2 (100 mL). Methanol (2.5 mL) was added and after 15 min the suspension turned yellow. The reaction mixture was cooled to 0 °C and pyrrolidine (420 μL, 356 mg, 5.00 mmol) was added. After warming up to room temperature, MTO was added (6.2 mg, 25 μmol) in one portion. The solution turned pale yellow. The solvent was removed in vacuo and the crude product (yellow oil) was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 90:10). The product was obtained as colorless oil (240 mg, 56%), which was directly used in the next step.

C_4H_7NO (85.10 g/mol)

$\boldsymbol{R_f}$ = 0.38 (SiO_2, CH_2Cl_2/MeOH 90:10).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.12–2.19 (m, 2H, 4-*H*), 2.61–2.67 (m, 2H, 3-*H*), 3.83–3.89 (m, 2H, 5-*H*), 6.77–6.79 (m, 1H, 2-*H*).

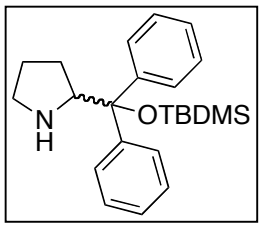


(±)-Diphenyl(pyrrolidin-2-yl)methanol (81)[17]

N-oxide **161** (75.0 mg, 0.881 mmol) in THF (1.7 mL) was added to the solution of benzophenone (115 mg, 0.629 mmol) in THF (4.3 mL) and the mixture was cooled to -78 °C. Samarium iodide in THF (14 mL of 0.1 M solution, 1.4 mmol) was added dropwise and the violet mixture was stirred for 15 minutes. Then, degassed water (0.45 mg, 45 µL, 2.5 mmol) was added, followed by samarium iodide in THF (18 mL of 0.1 M solution, 1.8 mmol). The reaction mixture was allowed to warm to room temperature, where upon it turned yellow. The mixture was stirred at RT for 1 h. Then sat. $Na_2S_2O_3$ (6 mL), 1 M NaOH (19 mL) and EA (25 mL) were added. The organic phase was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo.

The crude orange product was purified by column chromatography (SiO_2, cyclohexane/EA 70:30 then CH_2Cl_2/MeOH 90:10). The product was obtained as colorless solid (45 mg, 28%). The spectroscopic data were in agreement with those of single enantiomers previously prepared by other methods.

$C_{17}H_{19}NO$ (253.34 g/mol)
***R**$_f$* = 0.08 (silica, EA/pentane 40:60).
m. p. 74–75 °C (Lit.[6] 76.5–77.5 °C).
MS (ESI, 200 °C, 38 V) *m/z* (%): 254 ($M+H^+$, 21), 236 ($[M-OH]^+$, 100).



(±)-2-[((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl]pyrrolidine (46c)

By general method **VI** racemic aminoalcohol **81** (40.0 mg, 0.158 mmol), TBDMSOTf (180 µL, 0.21 g, 0.79 mmol) and 2,6-lutidine (130 µL, 120 mg, 1.12 mmol) gave the crude product, which was purified by column chromatography (SiO_2, cyclohexane/EA 5:95-30:70). The product was obtained as colorless oil, which solidified on standing (55 mg, 93%). The spectroscopic data were in agreement to those of single enantiomers previously prepared by another method.

$C_{23}H_{33}NOSi$ (367.60 g/mol)

R_f = 0.12 (silica, EA/pentane 20/80).

m.p. 67–68 °C.

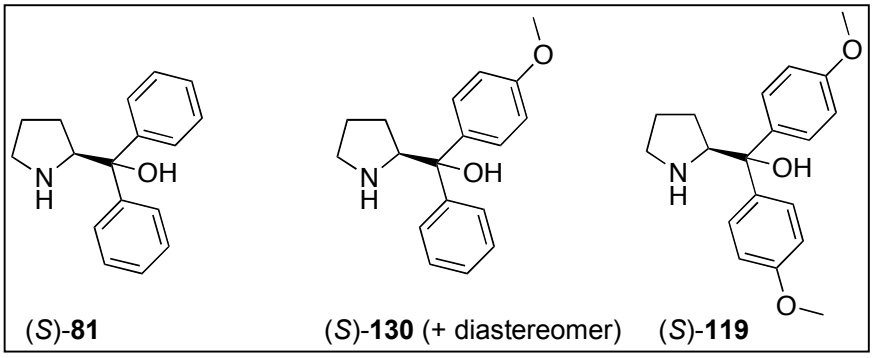
MS (ESI, 200 °C, 38 V) *m/z* (%): 368 ($M+H^+$, 16), 236 ($[M\text{-OTBDMS}]^+$, 100).

5.3.2 Synthesis of Catalyst Mixtures

(*S*)-Diphenyl(pyrrolidin-2-yl)methanol ((*S*)-81)

(*S*)-(4-Methoxyphenyl)(phenyl)(pyrrolidin-2-yl)methanol ((*S*)-130)

(*S*)-Bis(4-methoxyphenyl)(pyrrolidin-2-yl)methanol ((*S*)-119)



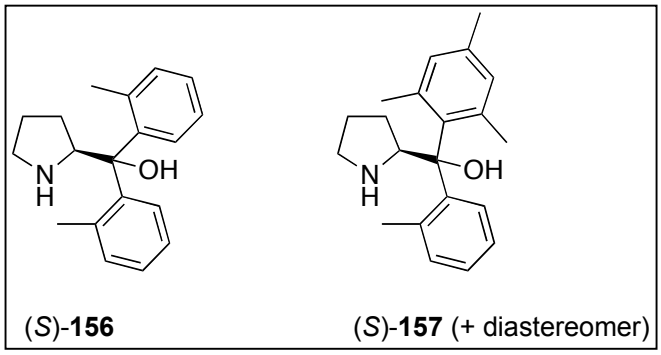
By general method **IV** protected proline methyl ester (*S*)-**78** (450 mg, 2.24 mmol), phenylmagnesium bromide (4.5 mmol, 4.5 mL of 1 M solution in THF) and 4-methoxyphenylmagnesium bromide (4.5 mmol, 4.5 mL of 1 M solution in THF) gave at 0 °C in 3 hours the crude mixture (2.0 g) of protected amino alcohols. The Grignard reagents were premixed in addition funnel.

The crude product mixture was dissolved in methanol (15 mL) and KOH (1.26 g, 22.4 mmol) was added. The mixture was refluxed for 24 h. Methanol was evaporated and water (10 mL) was added. The product was extracted with $CHCl_3$ (3 × 10 mL). Collected organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product mixture (1.6 g) was obtained as colorless oil.

(*S*)-**81** $C_{17}H_{19}NO$ (253.34 g/mol)
(*S*)-**130** $C_{18}H_{21}NO_2$ (283.36 g/mol)
(*S*)-**119** $C_{19}H_{23}NO_3$ (313.39 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 314 ($[M+H]^+$((*S*)-**119**), 47), 296 ($[M-OH]^+$((*S*)-**119**), 69), 284 ($[M+H]^+$((*S*)-**130**), 48), 266 ($[M-OH]^+$((*S*)-**130**), 100), 254 ($[M+H]^+$((*S*)-**81**), 43), 236 ($[M-OH]^+$((*S*)-**81**), 17).

(*S*)-(Pyrrolidin-2-yl)di-*o*-tolylmethanol ((*S*)-156)
(*S*)-Mesityl(pyrrolidin-2-yl)(*o*-tolyl)methanol ((*S*)-157)



(*S*)-**156** (*S*)-**157** (+ diastereomer)

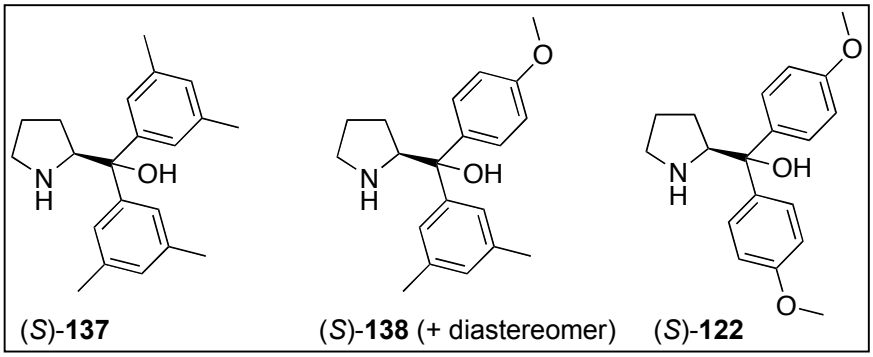
$CeCl_3 \cdot 7H_2O$ (5.01 g, 13.4 mmol) was heated at 140 °C under high vacuum (0.08 mbar) overnight. The white powder was suspended in dry THF (35 mL) at 0 °C under Ar and stirred for 30 minutes before a mixture of *o*-tolylmagnesium chloride (6.7 mL of 1 M solution in THF, 6.7 mmol) and mesitylmagnesium bromide (6.7 mL of 1 M solution in THF, 6.7 mmol) was added dropwise. The mixture was stirred at 0 °C for 2 h, then protected proline ester (*S*)-**78** (450 mg, 2.24 mmol) was added. The mixture was stirred overnight at RT, then sat. NH_4Cl (30 mL) was added. Organic material was extracted with Et_2O (3 × 30 mL), collected organic extracts were dried over $MgSO_4$ and concentrated in vacuo.

The crude product mixture (935 mg) was dissolved in methanol (3 mL) and KOH (1.00 g, 17.7 mmol) was added. The mixture was refluxed for 24 h. The methanol was evaporated and water (5 mL) was added. The product was extracted with $CHCl_3$ (3 × 5 mL). Collected organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product mixture (850 mg) was obtained as colorless oil.

(*S*)-**156** $C_{19}H_{23}NO$ (281.39 g/mol)
(*S*)-**157** $C_{21}H_{27}NO$ (309.45 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 310 ($[M+H]^+$((*S*)-**157**), 2), 292 ($[M-OH]^+$((*S*)-**157**), 2), 282 ($[M+H]^+$((*S*)-**156**), 84), 264 ($[M-OH]^+$((*S*)-**156**), 100).

(*S*)-Bis(3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol ((*S*)-137)
(*S*)-(3,5-Dimethylphenyl)(4-methoxyphenyl)(pyrrolidin-2-yl)methanol ((*S*)-138)
(*S*)-Bis(4-methoxyphenyl)(pyrrolidin-2-yl)methanol ((*S*)-122)



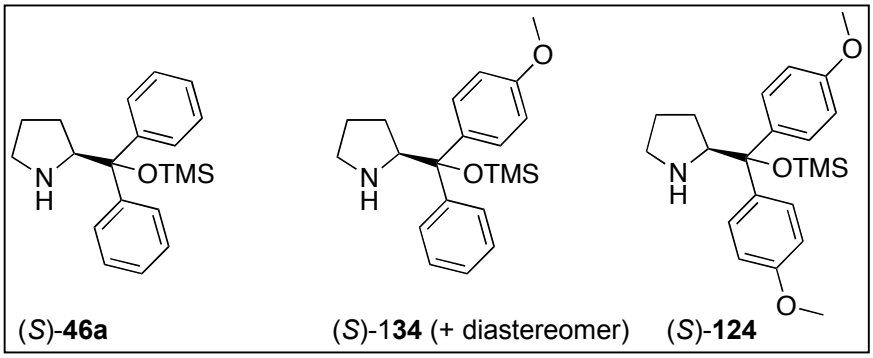
By general method **IV** protected proline methyl ester (*S*)-**78** (450 mg, 2.24 mmol), 3,5-dimethylphenylmagnesium bromide (4.5 mmol, 9.0 mL of 0.5 M solution in THF) and 4-methoxyphenylmagnesium bromide (4.5 mmol, 4.5 mL of 1 M solution in THF) gave at 0 °C in 3 hours the crude mixture of protected amino alcohols (1.01 g). The Grignard reagents were premixed in addition funnel.

The crude product mixture was dissolved in methanol (15 mL) and KOH (1.26 g, 22.4 mmol) was added. The mixture was refluxed for 24 h. Methanol was evaporated and water (10 mL) was added. The product was extracted with $CHCl_3$ (3 × 10 mL). Collected organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product mixture (900 mg) was obtained as colorless oil.

(*S*)-**137** $C_{21}H_{27}NO$ (309.45 g/mol)
(*S*)-**138** $C_{20}H_{25}NO_2$ (311.42 g/mol)
(*S*)-**122** $C_{19}H_{23}NO_3$ (313.39 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 314 ([M+H]$^+$((*S*)-**122**), 58), 312 ([M+H]$^+$((*S*)-**138**), 100), 310 ([M+H]$^+$((*S*)-**137**), 69), 296 ([M-OH]$^+$((*S*)-**122**), 60), 294 ([M-OH]$^+$((*S*)-**138**), 90), 292 ([M-OH]$^+$((*S*)-**137**), 54).

(*S*)-2-[Diphenyl((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-46a)
(2*S*)-2-[(4-Methoxyphenyl)(phenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((2*S*)-134)
(*S*)-2-[Bis(4-methoxyphenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-124)



By general method **VI**, the mixture of products was prepared from mixture of amino alcohols (*S*)-**81**, (*S*)-**119** and (*S*)-**130** (500 mg), 2,6-lutidine (0.57 mL, 0.52 g, 4.9 mmol), TMSOTf (0.13 mL, 0.16 g, 0.70 mmol) in dichloromethane (0.4 mL) at 0 °C–RT overnight. The crude product mixture was obtained as yellow oil (600 mg) and directly used in the screening.

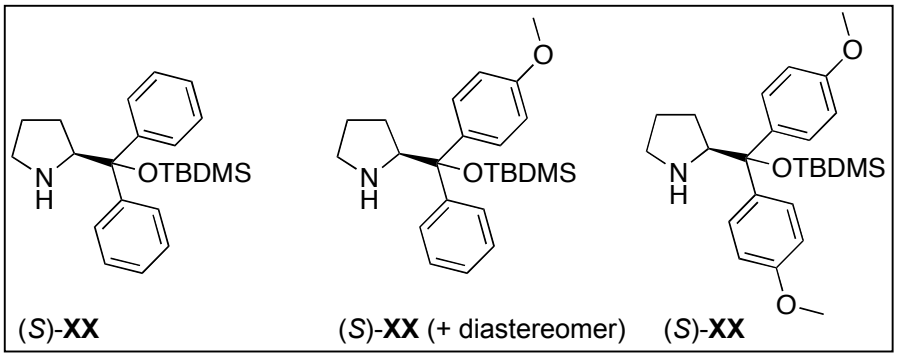
(*S*)-**46a** $C_{20}H_{27}NOSi$ (325.52 g/mol)
(*S*)-**134** $C_{21}H_{29}NO_2Si$ (355.55 g/mol)
(*S*)-**124** $C_{22}H_{31}NO_3Si$ (385.57 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 386 ([M+H]$^+$((*S*)-**124**), 10), 356 ([M+H]$^+$((*S*)-**134**), 21), 326 ([M+H]$^+$((*S*)-**46a**), 11), 296 ([M-OTMS]$^+$((*S*)-**124**), 58), 266 ([M-OTMS]$^+$((*S*)-**134**), 100), 236 ([M-OTMS]$^+$((*S*)-**46a**), 49).

((*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl]pyrrolidine ((*S*)-46c)

(2*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)(4-methoxyphenyl)(phenyl)methyl]-pyrrolidine ((2*S*)-131)

(*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)bis(4-methoxyphenyl)methyl]pyrrolidine ((*S*)-125)



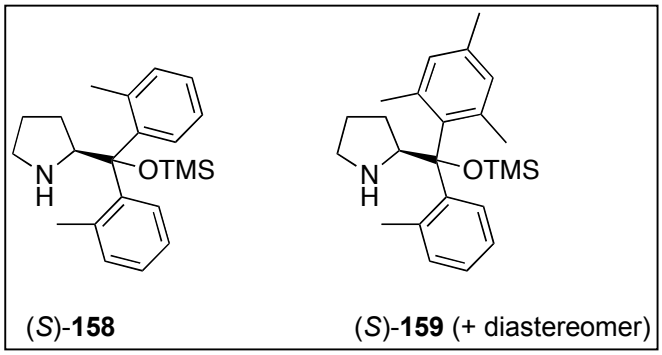
By general method **VI**, the mixture of products was prepared from mixture of amino alcohols (*S*)-**81**, (*S*)-**119** and (*S*)-**130** (500 mg), 2,6-lutidine (0.57 mL, 0.52 g, 4.9 mmol), TBDMSOTf (0.64 mL, 0.74 g, 2.8 mmol) in dichloromethane (0.4 mL) at 0 °C–RT overnight. The crude product mixture was obtained as yellow oil (600 mg) and directly used in the screening.

(*S*)-**46c** $C_{23}H_{33}NOSi$ (367.60 g/mol)
(*S*)-**131** $C_{24}H_{35}NO_2Si$ (397.63 g/mol)
(*S*)-**125** $C_{25}H_{37}NO_3Si$ (427.65 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 428 ($[M+H]^+$((*S*)-**125**), 2), 398 ($[M+H]^+$((*S*)-**131**), 14), 368 ($[M+H]^+$((*S*)-**46c**), 16), 296 ($[M-OTBDMS]^+$((*S*)-**125**), 49), 266 ($[M-OTBDMS]^+$ ((*S*)-**131**), 2), 236 ($[M-OTBDMS]^+$((*S*)-**46c**), 100).

(*S*)-2-[Di-*o*-tolyl((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-158)

(2*S*)-2-[Mesityl(*o*-tolyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-159)



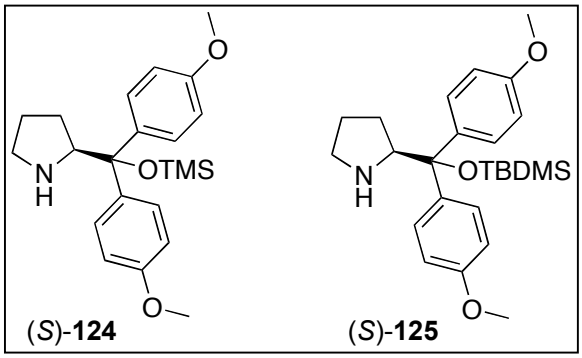
By general method **VI**, the mixture of products was prepared from mixture of amino alcohols (*S*)-**156** and (*S*)-**157** (100 mg), 2,6-lutidine (0.15 mL, 0.14 g, 1.3 mmol), TMSOTf (18 µL, 20 µg, 91 µmol) in dichloromethane (0.5 mL) at 0 °C–RT overnight. The crude product mixture was obtained as yellow oil (150 mg) and directly used in the screening.

(*S*)-**158** $C_{22}H_{31}NOSi$ (353.57 g/mol)
(*S*)-**159** $C_{24}H_{35}NOSi$ (381.63 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 382 ($[M+H]^+$((*S*)-**159**), 1), 354 ($[M+H]^+$((*S*)-**158**), 21), 292 ($[M-OTMS]^+$((*S*)-**159**), 1), 264 ($[M-OTMS]^+$((*S*)-**158**), 100).

(*S*)-2-[Bis(4-methoxyphenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-124)

(*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)bis(4-methoxyphenyl)methyl]pyrrolidine ((*S*)-125)



By general method **VI**, the mixture of products was prepared from amino alcohol (*S*)-**122** (100 mg, 0.32 mmol), 2,6-lutidine (0.26 mL, 0.24 g, 2.2 mmol), TMSOTf (23 µL, 29 µg, 0.13 mmol) and TBDMSOTf (0.17 g, 0.15 mL, 0.64 mmol) at 0 °C–RT in dichloromethane (0.6 mL). Crude product mixture was analyzed by ESI-MS and directly used in the screening.

(*S*)-**124** $C_{22}H_{31}NO_3Si$ (385.57 g/mol)
(*S*)-**125** $C_{25}H_{37}NO_3Si$ (427.65 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 428 ($[M+H]^+$((*S*)-**125**), 8), 386 ($[M+H]^+$((*S*)-**124**), 11), 296 ($[M-OR]^+$((*S*)-**124**, (*S*)-**125**), 100).

(*S*)-2-[Diphenyl((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-46a)

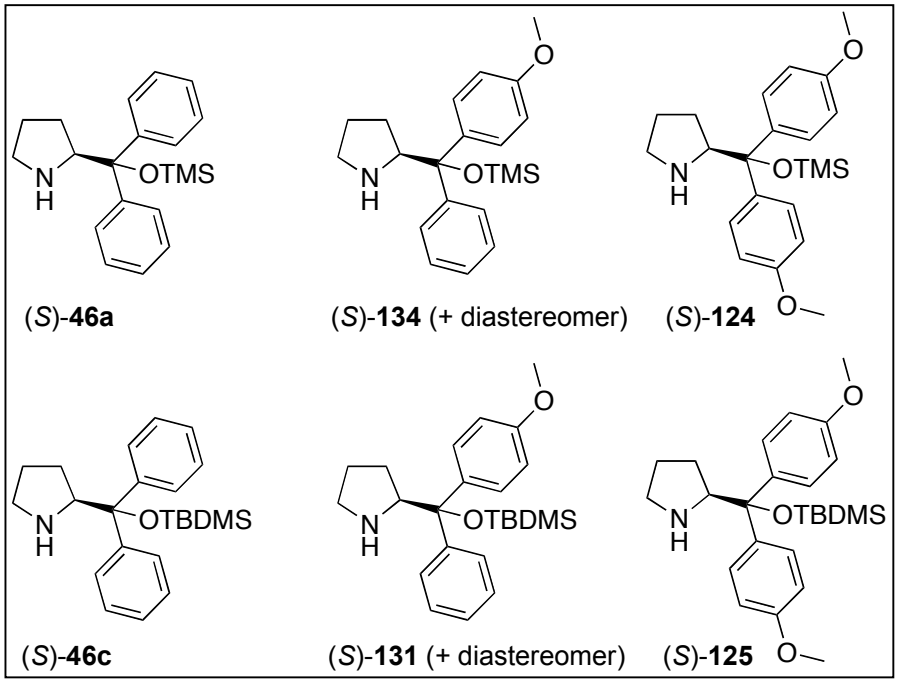
(2*S*)-2-[(4-Methoxyphenyl)(phenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((2*S*)-134)

(*S*)-2-[Bis(4-methoxyphenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-124)

((*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl]pyrrolidine ((*S*)-46c)

(2*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)(4-methoxyphenyl)(phenyl)methyl]-pyrrolidine ((2*S*)-131)

(*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)bis(4-methoxyphenyl)methyl]pyrrolidine ((*S*)-125)



By general method **VI**, the mixture of products was prepared from mixture of amino alcohols (*S*)-**81**, (*S*)-**119** and (*S*)-**130** (500 mg), 2,6-lutidine (0.57 mL, 0.52 g, 4.9 mmol), TMSOTf (67 µL, 78 µg, 0.35 mmol) and TBDMSOTf (0.64 mL, 0.74 g, 2.8 mmol) in DCM (0.4 mL) at 0 °C–RT overnight. The crude product mixture was obtained as yellow oil (650 mg) and directly used in the screening.

(*S*)-**46a** $C_{20}H_{27}NOSi$ (325.52 g/mol)

(*S*)-**134** $C_{21}H_{29}NO_2Si$ (355.55 g/mol)

(*S*)-**124** $C_{22}H_{31}NO_3Si$ (385.57 g/mol)

(*S*)-**46c** $C_{23}H_{33}NOSi$ (367.60 g/mol)

(*S*)-**131** $C_{24}H_{35}NO_2Si$ (397.63 g/mol)

(*S*)-**125** $C_{25}H_{37}NO_3Si$ (427.65 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 428 ([M+H]$^+$((*S*)-**125**), 2), 398 ([M+H]$^+$((*S*)-**131**), 14), 386 ([M+H]$^+$((*S*)-**124**), 1), 368 ([M+H]$^+$((*S*)-**46c**), 16), 356 ([M+H]$^+$((*S*)-**134**), 4), 326 ([M+H]$^+$((*S*)-**46a**), 3), 296 ([M-OR]$^+$((*S*)-**124**, (*S*)-**125**), 49), 266 ([M-OR]$^+$((*S*)-**131**, (*S*)-**134**), 2), 236 ([M-OR]$^+$((*S*)-**46a**, (*S*)-**46c**), 100).

(*S*)-2-[Bis(3,5-dimethylphenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-139)

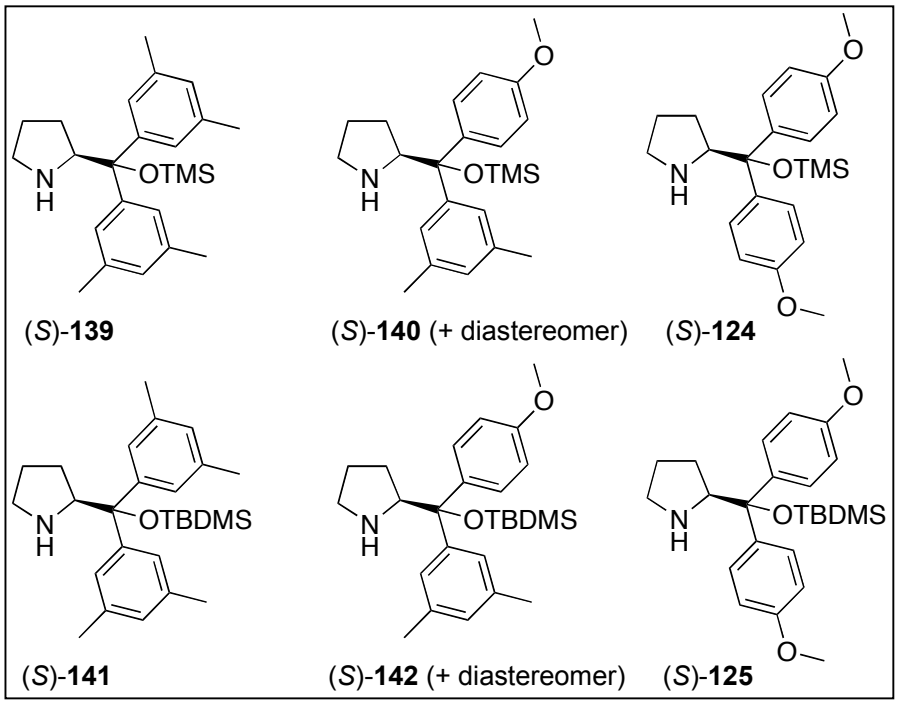
(2*S*)-2-[(3,5-Dimethylphenyl)(4-methoxyphenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((2*S*)-140)

(*S*)-2-[Bis(4-methoxyphenyl)((trimethylsilyl)oxy)methyl]pyrrolidine ((*S*)-124)

(*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)bis(3,5-dimethylphenyl)methyl]pyrrolidine ((*S*)-141)

(2*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)(3,5-dimethylphenyl)(4-methoxyphenyl)-methyl]pyrrolidine ((2*S*)-142)

(*S*)-2-[((*tert*-Butyldimethylsilyl)oxy)bis(4-methoxyphenyl)methyl]pyrrolidine ((*S*)-125)



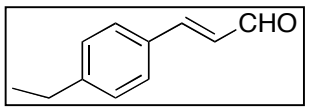
By general method **VI**, the mixture of products was prepared from mixture of amino alcohols (*S*)-**122**, (*S*)-**137** and (*S*)-**138** (500 mg), 2,6-lutidine (0.79 mL, 0.73 g, 6.8 mmol), TMSOTf (97 μL, 0.11 g, 0.50 mmol) and TBDMSOTf (0.89 mL, 1.0 g, 3.9 mmol) in DCM (1 mL) at

0 °C–RT overnight. The crude product mixture was obtained as yellow oil and directly used in the screening.

(*S*)-**139** $C_{24}H_{35}NOSi$ (381.63 g/mol)
(*S*)-**140** $C_{23}H_{33}NO_2Si$ (383.60 g/mol)
(*S*)-**124** $C_{22}H_{31}NO_3Si$ (385.57 g/mol)
(*S*)-**141** $C_{27}H_{41}NOSi$ (423.71 g/mol)
(*S*)-**142** $C_{26}H_{39}NO_2Si$ (425.68 g/mol)
(*S*)-**125** $C_{25}H_{37}NO_3Si$ (427.65 g/mol)

MS (ESI, 200 °C, 38 V) *m/z* (%): 428 ($[M+H]^+$((*S*)-**125**), 3), 426 ($[M+H]^+$((*S*)-**142**), 10), 424 ($[M+H]^+$((*S*)-**141**), 10), 386 ($[M+H]^+$((*S*)-**124**), 4), 384 ($[M+H]^+$((*S*)-**140**), 11), 382 ($[M+H]^+$((*S*)-**139**), 10), 296 ($[M-OR]^+$((*S*)-**124**, (*S*)-**125**), 36), 294 ($[M-OR]^+$((*S*)-**140**, (*S*)-**142**), 100), 292 ($[M-OR]^+$((*S*)-**139**, (*S*)-**141**), 74).

5.3.3 Synthesis of Quasienantiomeric Michael Adducts



(*E*)-3-(4-Ethylphenyl)acrylaldehyde (19b)[18]

General method VII:

4-Ethyl-1-iodobenzene (0.67 mL, 1.1 g, 4.6 mmol) was dissolved in DMF (18 mL) and Bu_4NOAc (2.77 g, 9.18 mmol), K_2CO_3 (0.952 g, 6.89 mmol), KCl (0.342 g, 4.59 mmol) were added to the solution stirred under Ar at RT. Then acrolein diacetal (2.10 mL, 1.79 g, 13.8 mmol) was added followed by palladium diacetate (31.4 mg, 140 µmol). The resultant yellow solution was stirred at 90 °C for 3 h to give a dark brown solution. The reaction mixture was cooled to RT and 2 M HCl (7 mL) was added followed by stirring at RT for 15 minutes. The mixture was diluted with Et_2O (50 mL) and washed with water (50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL). Combined ether layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo to give 1.52 g of crude product as pale brown oil. The crude product was purified by column chromatography (SiO_2, EA/pentane 10:90) to give **19b** as pale yellow oil (720 mg, 98%).

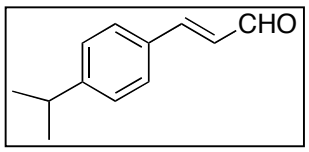
$C_{11}H_{12}O$ (169.21 g/mol)

R_f = 0.47 (SiO_2, EA/pentane 10:90).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, C*H*$_3$), 2.69 (q, $^3J_{HH}$ = 7.6 Hz, 3H, C*H*$_2$), 6.69 (dd, $^3J_{HH}$ = 7.8 Hz and 15.7 Hz, 1H, C*H*CHO), 7.26 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ar*H*), 7.44–7.50 (m, 3H, C*H*Ar, Ar*H*), 9.68 (d, $^3J_{HH}$ = 7.8 Hz, 1H, C*H*O).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 15.1 (*C*H$_3$), 28.7 (*C*H$_2$), 127.6 (*C*HCHO), 128.5 (*Ar*H), 131.4 (Ar*C*H), 148.1 (*Ar*CH$_2$), 152.9 (*Ar*CH), 193.7 (*C*HO).

MS (EI, 70 eV) *m/z* (%): 160 (M^+, 12), 131 ([M-C_2H_5]$^+$, 100), 91 ($C_7H_7^+$, 12).



(*E*)-3-(4-Isopropylphenyl)acrylaldehyde (19c)[18]

By general method **VII** 4-isopropyl-1-iodobenzene (0.74 mL, 1.1 g, 4.6 mmol), Bu_4NOAc (2.77 g, 9.18 mmol), K_2CO_3 (0.952 g, 6.89 mmol), KCl (0.342 g, 4.59 mmol), acrolein diacetal (2.10 mL, 1.79 g, 13.8 mmol) and $Pd(OAc)_2$ (31.4 mg, 140 μmol) in DMF (18 mL) gave the crude product. It was purified by column chromatography (SiO_2, EA/pentane 10:90) to give **19c** (711 mg, 89 %) as pale yellow oil.

$C_{12}H_{14}O$ (174.24 g/mol)

R_f = 0.51 (SiO_2, EA/pentane 10:90).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.26 (d, $^3J_{HH}$ = 6.8 Hz, 6H, C*H*$_3$), 2.94 (hept, $^3J_{HH}$ = 6.8 Hz, 1H, C*H*(CH$_3$)$_2$), 6.69 (dd, $^3J_{HH}$ = 7.8 Hz and 15.9 Hz, 1H, C*H*CHO), 7.27 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ar*H*), 7.46 (d, $^3J_{HH}$ = 15.9 Hz, 1H, ArC*H*), 7.50 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ar*H*), 9.68 (d, $^3J_{HH}$ = 7.8 Hz, 1H, C*H*O).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 23.8 (*C*H$_3$), 34.3 (*C*H(CH$_3$)$_2$), 127.3 (*Ar*H), 127.9 (*C*HCHO), 128.8 (*A*rH), 148.1 (*Ar*CH(CH$_3$)$_3$), 152.9 (*Ar*CH), 193.7 (*C*HO).

MS (EI, 70 eV) *m/z* (%): 174 (M^+, 15), 131 ([M-C_3H_7]$^+$, 100).

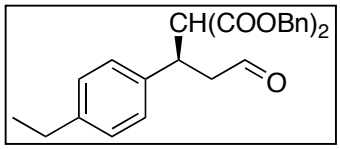
General method VIII for Michael addition (optimized conditions)

Aldehyde (188 μmol), catalyst (*S*)-**46c** (3.3 mg, 8.8 μmol) and benzoic acid (1.1 mg, 8.8 μmol) were dissolved in ethanol (0.5 mL) with water (4.5 μL) and cooled to 0 °C. Malonate (125 μmol) was added to the yellow solution, which was stirred at 0 °C. The reaction progress was controlled by TLC. When all malonate was consumed, the reaction

mixture was filtered through 1.5 × 1 cm column of silica gel and the silica gel was washed with dichloromethane. After evaporation of solvent, the crude mixture was purified by flash column chromatography (SiO_2, Et_2O/pentane 1:10–3:10).

General procedure for the synthesis of quasienantiomers

The quasienantiomers **44d** and **44e** were prepared according to the general method **VIII** from aldehydce **19b-c** (1.01 mmol) and dibenzyl malonate (95% pure, 175 μL, 201 mg, 670 μmol), with catalyst **46c** (17.2 mg, 46.9 μmol) and benzoic acid (5.7 mg, 47 μmol). The quasienantiomers can be purified by recrystallization from Et_2O/pentane.



(*R*)-Dibenzyl 2-[1-(4-ethylphenyl)-3-oxopropyl]-malonate ((*R*)-44d)

(*R*)-**44d** was prepared from (*E*)-3-(4-ethylphenyl)acrylaldehyde and dibenzyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 6 h as colorless solid (268 mg, conversion 97%, yield 90%, >99% *ee*).

$C_{28}H_{28}O_5$ (444.52 g/mol)

R_f = 0.60 (SiO_2, EA/pentane 30:70).

m. p. 70–71 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3), 2.59 (q, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2CH$_3$), 2.83–2.86 (m, 2H, CH_2CHO), 3.82 (d, $^3J_{HH}$ = 9.8 Hz, 1H, CH(COOBn)$_2$), 3.99–4.05 (m, 1H, ArCH), 4.86/4.92 (AB, $^2J_{AB}$ = 12.0 Hz, 2H, CH_AH_BPh), 5.14 (s, 2H, CH_2Ph), 7.05–7.12 (m, 4H, ArH), 7.24–7.38 (m, 10H, ArH), 9.53 (t, $^3J_{HH}$ =1.8 Hz, 1H, CHO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 15.4 (*C*H$_3$), 28.5 (*C*H$_2$CH$_3$), 39.3 (Ar*C*H), 47.4 (*C*H$_2$CHO), 57.7 (*C*H(COOBn)$_2$), 67.3 (*C*H$_2$Ph), 67.6 (*C*H$_2$Ph), 128.1 (*Ar*H), 128.3 (*Ar*H), 128.4 (*Ar*H), 128.5 (*Ar*H), 128.6 (*Ar*H), 128.7 (*Ar*H), 135.1 (*Ar*C), 135.2 (*Ar*C), 136.8 (*Ar*C), 143.5 (*Ar*C), 167.4 (*C*OOBn), 167.9 (*C*OOMe), 200.3 (*C*HO).

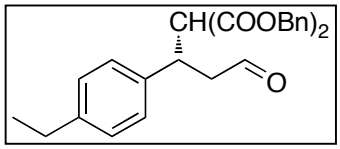
MS (FAB, NBA) *m/z* (%): 445 ([M+H]$^+$, 7), 251 (11), 91 ([PhCH$_2$]$^+$, 100).

IR (ATR): $\tilde{\nu}$ = 2970w, 1742s (C=O), 1710s (C=O), 1456m, 1380m, 1310m, 1248s, 1171s, 1142s, 1075m, 991m, 906m, 833m, 752s, 696s.

EA calc. for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35; O 18.00. Found: C, 75.52; H, 6.22.

$[\alpha]_D^{20}$ = -14.7 (c = 0.97, $CHCl_3$).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 24.8 min (minor), t_R = 31.1 min (major).



(*S*)-Dibenzyl 2-[1-(4-ethylphenyl)-3-oxopropyl]-malonate ((*S*)-44d)

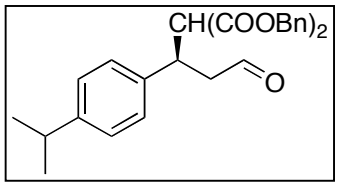
(*S*)-**44d** was prepared from (*E*)-3-(4-ethylphenyl)acrylaldehyde and dibenzyl malonate with catalyst (*R*)-**46c** according to general method **VIII** in 5 h as colorless solid (259 mg, conversion 95%, yield 87%, >99% *ee*).

$C_{28}H_{28}O_5$ (444.52 g/mol)

EA calc. for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35; O 18.00. Found: C, 75.51; H, 6.40.

$[\alpha]_D^{20}$ = 14.5 (c = 0.95, $CHCl_3$).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 24.8 min (major), t_R = 31.1 min (minor).



(*R*)-Dibenzyl 2-[1-(4-isopropylphenyl)-3-oxopropyl]-malonate ((*R*)-44e)

(*R*)-**44e** was prepared from (*E*)-3-(4-isopropylphenyl)-acrylaldehyde and dibenzyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 6 h as colorless solid (273 mg, conversion 97%, yield 89%, >99% *ee*).

$C_{29}H_{30}O_5$ (458.55 g/mol)

R_f = 0.60 (SiO_2, EA/pentane 30:70).

m. p. 52–53 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.21 (d, $^3J_{HH}$ = 4.3 Hz, 6H, CH_3), 281–2.88 (m, 3H, CH_2CHO+CH(CH_3)$_2$), 3.82 (d, $^3J_{HH}$ = 9.6 Hz, 1H, CH(COOBn)$_2$), 3.99–4.06 (m, 1H, ArCH), 4.81/4.96 (AB, $^2J_{AB}$ = 12.0 2H, CH_ACH_BPh), 5.14 (s, 2H, CH_2Ph), 7.06–7.10 (m, 4H, ArH), 7.26–7.37 (m, 10H, ArH), 9.53 (t, $^3J_{HH}$ =1.6 Hz, 1H, CHO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 24.0 (CH_3), 33.8 (CH(CH_3)$_2$), 39.3 (ArCH), 47.3 (CH_2CHO), 57.6 (CH(COOBn)$_2$), 67.4 (CH_2Ph), 67.6 (CH_2Ph), 126.9 (*Ar*H), 128.0 (*Ar*H),

128.3 (*Ar*H), 128.4 (*Ar*H), 128.5 (*Ar*H), 128.6 (*Ar*H), 128.7 (*Ar*H), 135.1 (*Ar*C), 135.2 (*Ar*C), 136.9 (*Ar*C), 148.1 (*Ar*C), 167.4 (*C*OOBn), 167.9 (*C*OOMe), 200.3 (*C*HO).

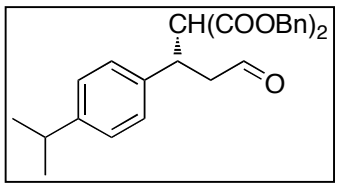
MS (FAB, NBA) *m/z* (%): 459 ($[M+H]^+$, 6), 265 (6), 91 ($[PhCH_2]^+$, 100).

IR (ATR): $\tilde{\nu}$ = 2967w, 1739s, 1708s, 1456m, 1379m, 1311m, 1245s, 1073s, 985m, 903m, 830m, 737s, 695s.

EA calc. for $C_{28}H_{28}O_5$: C, 75.96; H, 6.59; O, 17.45. Found: C, 75.84; H, 6.53.

$[\alpha]_D^{20}$ = -13.7 (c = 0.99, $CHCl_3$).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 17.9 min (minor), t_R = 25.7 min (major).



(*S*)-Dibenzyl 2-[1-(4-isopropylphenyl)-3-oxopropyl-]malonate ((*S*)-44e)

(*S*)-**44e** was prepared from (*E*)-3-(4-isopropylphenyl)-acrylaldehyde and dibenzyl malonate with catalyst (*R*)-**46c** according to general method **VIII** in 5 h as colorless solid (270 mg, conversion 96%, yield 88%, >99% *ee*).

$C_{29}H_{30}O_5$ (458.55 g/mol)

EA calc. for $C_{28}H_{28}O_5$: C, 75.96; H, 6.59; O, 17.45. Found: C, 75.93; H, 6.68.

$[\alpha]_D^{20}$ = 13.8 (c = 0.98, $CHCl_3$).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 17.9 min (major), t_R = 25.7 min (minor).

5.3.4 ESI-MS Screening

General procedure for the organocatalyzed retro-Michael addition

The organocatalyst (1.25 µmol) was added to a solution of quasienantiomers **44d** and **44e** (6.25 µmol each) in ethanol (90 µL) and dichloromethane (10 µL) and the mixture (12.5 mM solution of catalyst) was stirred for 5 minutes at room temperature. An aliquot of the reaction mixture was diluted with acetonitrile to approximately 0.01 mM with respect to catalyst concentration and analyzed by ESI MS. The spectra were recorded in the centroid mode and the selectivity of the catalyst was determined by integration of the peaks of the major isotopes

for both adduct intermediates **76** and **77**. When screening mixtures of more catalysts, (1.25/amount of catalysts) μmol of each catalyst was used. When screening a synthesized catalyst mixtures, the crude mixture (ca 0.5 mg) was used.
In the screening of racemic catalysts, 75:25 mixture of quasienantiomers **44d** and **44e** was subjected to the screening.

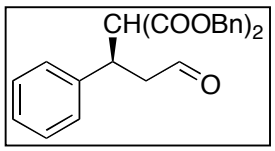
General procedure for Michael addition (for validation of screening, Table 2.1, Chapter 2, conditions A)

(*E*)-3-(4-Ethylphenyl)acrylaldehyde (20.0 mg, 125 μmol) and catalyst (12.5 μmol) were dissolved in ethanol (0.90 mL) and dichloromethane (0.10 mL). Dibenzyl malonate (95% pure, 33 μL, 37.4 mg, 125 μmol) was added to the yellow solution, which was then stirred at room temperature for 2 h. The reaction mixture was filtered through 1.5 × 1 cm column of silica gel and the silica gel was washed with dichloromethane. After evaporation of solvent, the crude mixture was purified by flash column chromatography (SiO_2, Et_2O/pentane 1:10–3:10).

General procedure for Michael addition (Table 2.1, Chapter 2, conditions B)

(*E*)-3-(4-Ethylphenyl)acrylaldehyde (30.0 mg, 188 μmol) and catalyst (12.5 μmol) were dissolved in ethanol (0.5 mL) and cooled to 0 °C. Dibenzyl malonate (95% pure, 33 μL, 37.4 mg, 125 μmol) was added to the yellow solution, which was then stirred at 0 °C for 3 d. The reaction mixture was filtered through 1.5 × 1 cm column of silica gel and the silica gel was washed with dichloromethane. After evaporation of solvent, the crude mixture was purified by flash column chromatography (SiO_2, Et_2O/pentane 1:10-3:10).

5.3.5 Michael Addition Products



(*R*)-Dibenzyl 2-(3-oxo-1-phenylpropyl)malonate ((*R*)-44g)[19]

(*R*)-**44g** was prepared from (*E*)-cinnamaldehyde and dibenzyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 5 h as colorless solid (50.5 mg, conversion 99%, yield 97%, 99% *ee*).

$C_{26}H_{24}O_5$ (416.17 g/mol)

R_f = 0.45 (SiO_2, EA/pentane 20:80).

m. p. 68–69 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.87 (dd, $^3J_{HH}$ = 1.8 Hz and 8.2 Hz, 2H, CH_2CHO), 3.83 (d, $^3J_{HH}$ = 9.8 Hz, 1H, C*H*(COOBn)$_2$), 4.02–4.08 (m, 1H, PhC*H*), 4.86/4.92 (AB, $^2J_{AB}$ = 12.2 Hz, 2H, CH_AH_BPh), 5.13/5.16 (AB, $^2J_{HH}$ = 12.4 Hz, 2H, CH_AH_BPh), 7.20–7.33 (m, 15H, Ph*H*), 9.54 (t, $^3J_{HH}$ = 1.8 Hz, 1H, C*H*O).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 39.6 (Ph*C*H), 47.4 (*C*H_2CHO), 57.6 (*C*H(COOBn)$_2$), 67.4 (COO*C*H_2Ph), 67.6 (COO*C*H_2Ph),127.7 (*Ph*H), 128.2 (*Ph*H), 128.3 (*Ph*H), 128.4 (*Ph*H), 128.6 (*Ph*H), 128.7 (*Ph*H), 128.9 (*Ph*H), 135.0 (*Ph*C), 135.1 (*Ph*C), 139.7 (*Ph*C), 167.3 (*C*OOBn), 167.8 (*C*OOBn), 200.0 (*C*HO).

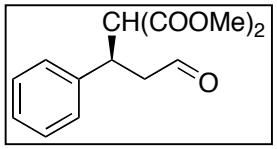
MS (FAB, NBA) *m/z* (%): 417 ([M+H]$^+$, 14), 91 ([PhCH_2]$^+$, 100), 39 ($C_3H_3^+$, 14).

$[\alpha]_D^{20}$ = -18.2 (c = 1.00, $CHCl_3$) (Lit.[19] $[\alpha]_D^{23}$ = -15.7 (c = 1.03, $CHCl_3$, 84% *ee*).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 31.3 min (minor), t_R = 44.1 min (major).

Alternative synthesis: Cinnamaldehyde (0.47 mL, 496 mg, 3.75 mmol), catalyst (*S*)-**46c** (18.4 mg, 50.0 µmol) and benzoic acid (6.1 mg, 50.0 µmol) were dissolved in ethanol (90%, 3.0 mL). Dibenzyl malonate (95% purity, 0.65 mL, 748 mg, 2.50 mmol) was added to the yellow solution, which was then stirred at room temperature. The reaction progress was controlled by TLC and ^{1}H-NMR. Conversion after 8 h was 97%. The solvent was removed in vacuo and pentane (4 mL) was added to precipitate the crude product, which was filtered off (yellow solid, 1.05 g, contained <10% of starting material). The crude product was recrystallized from Et_2O/pentane (3:1) to afford pure (*R*)-**44g** as colorless crystalline solid (0.94 g, 90%, >99% *ee*).

EA calc. for $C_{26}H_{24}O_5$: C, 74.98; H, 5.81; O 19.21. Found: C, 75.28; H, 5.90.



(*R*)-Dimethyl 2-(3-oxo-1-phenylpropyl)malonate ((*R*)-44f)[19]

(*R*)-**44f** was prepared from (*E*)-cinnamaldehyde and dimethyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 5 h as colorless oil, which crystallized at 4 °C overnight (30.5 mg, conversion 99%, yield 92%, >99% *ee*).

$C_{14}H_{16}O_5$ (264.27 g/mol)

R_f = 0.40 (SiO_2, EA/pentane 20:80).

m. p. 42–43 °C.

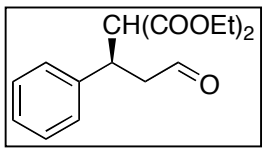
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.90–2.93 (m, 2H, CH_2), 3.50 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.74 (d, $^3J_{HH}$ = 9.9 Hz, 1H, CH(COOMe)$_2$), 3.99–4.05 (m, 1H, PhCH), 7.22–7.29 (m, 5H, PhH), 9.59 (t, $^3J_{HH}$ = 1.5 Hz, 1H, CHO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 39.6 (PhCH), 47.3 (CH$_2$), 52.6 (CH$_3$), 52.9 (CH$_3$), 57.4 (CH(COOMe)$_2$), 127.7 (PhH), 128.1 (PhH), 128.9 (PhH), 139.8 (PhC), 168.0 (COOMe), 168.5 (COOMe), 200.1 (CHO).

MS (FAB, NBA) *m/z* (%): 265 ([M+H]$^+$, 26), 133 ([PhCHCHCHO]$^+$, 100), 73 ([CH_2COOCH_3]$^+$, 40).

$[\alpha]_D^{20}$ = -35.8 (c = 0.70, $CHCl_3$) (Lit. [19] $[\alpha]_D^{23}$ = -29.8 (c = 0.56, $CHCl_3$, 93% *ee*).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.5 mL/min, 210 nm, t_R = 19.4 min (minor), t_R = 20.4 min (major).



(*R*)-Diethyl 2-(3-oxo-1-phenylpropyl)malonate ((*R*)-44h)[19]

(*R*)-**44h** was prepared from (*E*)-cinnamaldehyde and diethyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 5 h as colorless oil, which crystallized at 4 °C overnight (34.8 mg, conversion 100%, yield 95%, >99% *ee*).

$C_{16}H_{20}O_5$ (292.33 g/mol)

R_f = 0.36 (SiO_2, EA/pentane 20:80).

m. p. 42–43 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.00 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3), 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 2.84–2.96 (m, 2H, CH_2CHO), 3.70 (d, $^3J_{HH}$ = 10.1 Hz, 1H, CH(COOEt$_2$)), 3.94 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH$_3$), 3.99–4.05 (m, 1H, PhCH), 4.20 (q, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2CH$_3$), 7.23–7.27 (m, 5H, PhH), 9.60 (t, $^3J_{HH}$ = 1.5 Hz, 1H, CHO).

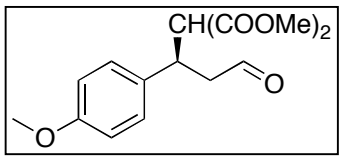
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 13.9 (CH_2CH_3), 14.1 (CH_2CH_3), 39.7 (PhCH), 47.6 (CH$_2$CHO), 57.7 (CH(COOEt)$_2$), 61.6 (CH$_2$CH$_3$), 61.9 (CH$_2$CH$_3$), 127.6 (*Ph*H), 128.3 (*Ph*H), 128.8 (*Ph*H), 139.9 (*Ph*C), 167.6 (*C*OOEt), 168.1 (*C*OOEt), 200.3 (*C*HO).

MS (FAB, NBA) *m/z* (%): 293 ([M+H]$^+$, 50), 201 ([M-COOEt-H$_2$O]$^+$, 17), 161 ([M-PhCHCHCHO+H]$^+$, 100), 133 ([PhCHCHCHO]$^+$, 40), 105 ([PhCHCH]$^+$, 25), 77 ($C_6H_5^+$, 24).

MS (EI, 70 eV, 100 °C) *m/z* (%): 292 (M$^+$, 0.4), 219 ([M-COOEt]$^+$, 6), 201 ([M-COOEt-H$_2$O]$^+$, 25), 173 ([M-COOEt-EtO]$^+$, 31), 160 ([M-PhCHCHCHO]$^+$, 100), 133 ([PhCHCHCHO]$^+$, 34), 105 ([PhCHCH]$^+$, 23), 77 ($C_6H_5^+$, 7).

$[\alpha]_D^{20}$ = -33.2 (c = 0.70, $CHCl_3$) (Lit.[19] $[\alpha]_D^{23}$ = -25.8 (c = 1.02, $CHCl_3$, 89% *ee*)).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.5 mL/min, 210 nm, t_R = 20.6 min (major), t_R = 27.6 min (minor).



(*R*)-Dimethyl 2-(1-(4-methoxyphenyl)-3-oxopropyl)-malonate ((*R*)-44i)[19]

(*R*)-**44i** was prepared from (*E*)-3-(4-methoxyphenyl)-acrylaldehyde and dimethyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 8 h as yellow oil, which crystallized at 4 °C overnight (35.0 g, conversion 98%, yield 95%, 99% *ee*).

$C_{15}H_{18}O_6$ (294.30 g/mol)

R_f = 0.14 (SiO_2, EA/pentane 20:80).

m. p. 59–60 °C.

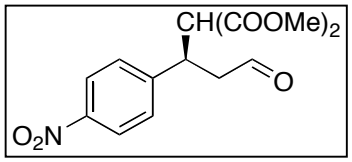
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 2.82–2.92 (m, 2H, CH_2), 3.51 (s, 3H, OCH_3), 3.69 (d, $^3J_{HH}$ = 9.8 Hz, 1H, CH(COOMe)$_2$), 3.73 (s, 3H, COOCH_3), 3.76 (s, 3H, COOCH_3), 3.97 (dt, $^3J_{HH}$ = 5.0 Hz and 9.8 Hz, 1H, ArCH), 6.81 (d, $^3J_{HH}$ = 8.5 Hz, 2H, ArH), 7.14 (d, $^3J_{HH}$ = 8.5 Hz, 2H, ArH), 9.57 (s, 1H, CHO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 38.9 (ArCH), 47.4 (CH$_2$), 52.6 (COOCH$_3$), 52.8 (COOCH$_3$), 55.3 (CH(COOMe)$_2$), 57.6 (OCH$_3$), 114.2 (*Ar*H), 129.2 (*Ar*H), 131.7 (*Ar*C), 158.9 (*Ar*O), 168.0 (*C*OOMe), 168.6 (*C*OOMe), 200.3 (*C*HO).

MS (EI, 70 eV, 100 °C) *m/z* (%): 294 (M^+, 27), 163 ($[ArCHCHCHO]^+$, 100), 151 (22), 135 (70).

$[\alpha]_D^{20}$ = -30.4 (c = 0.76, $CHCl_3$) (Lit.[19] $[\alpha]_D^{23}$ = -22.3 (c = 0.65, $CHCl_3$, 92% *ee*).

HPLC: Chiralcel AD-H, heptane/isopropanol 90:10, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 28.4 min (major), t_R = 33.1 min (minor).



(*R*)-Dimethyl 2-(1-(4-nitrophenyl)-3-oxopropyl)-malonate ((*R*)-44j)

(*R*)-**44j** was prepared from (*E*)-3-(4-nitrophenyl)-acrylaldehyde and dimethyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 8 h as yellow oil, which crystallized at 4 °C overnight (37 g, conversion 100%, yield 96%, 99% *ee*).

$C_{14}H_{15}NO_7$ (309.27 g/mol)

R_f = 0.08 (SiO_2, EA/pentane 20:80).

m. p. 63–64 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 2.97–3.09 (m, 2H, CH_2), 3.09 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.78 (d, $^3J_{HH}$ = 9.5 Hz, 1H, CH(COOMe)$_2$), 4.14 (dt, $^3J_{HH}$ = 4.7 Hz and 9.5 Hz, 1H, ArCH), 7.45 (d, $^3J_{HH}$ = 8.5 Hz, 2H, ArH), 8.15 (d, $^3J_{HH}$ = 8.5 Hz, 2H, ArH), 9.62 (s, 1H, CHO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 38.9 (ArCH), 47.1 (CH$_2$), 52.9 (OCH$_3$), 53.1 (OCH$_3$), 56.4 (CH(COOMe)$_2$), 124.0 (ArH), 129.3 (ArH), 147.3 (ArN), 147.8 (ArC), 167.6 (COOMe), 168.0 (COOMe), 298.6 (CHO).

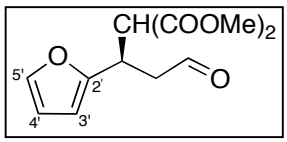
MS (FAB, NBA) *m/z* (%): 319 ($[M+H]^+$, 25), 133 (68), 57 (100).

IR (ATR): $\tilde{\nu}$ = 1744s (COOMe), 1730s (COOMe), 1720s (CHO), 1516m, 1438m, 1347s, 1236s, 1168m, 1004s, 859s, 699s.

EA: calc. for $C_{14}H_{15}NO_7$: C, 54.37; H, 4.89; N, 4.53; O, 36.21. Found: C, 54.43; H, 4.94; N, 4.30.

$[\alpha]_D^{20}$ = -17.5 (c = 0.56, $CHCl_3$).

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 28.6 min (major), t_R = 35.4 min (minor).



(*R*)-Dimethyl 2-(1-(furan-2-yl)-3-oxopropyl)malonate ((*R*)-44k)

(*R*)-**44k** was prepared from (*E*)-3-(2-furyl)acrylaldehyde and dimethyl malonate with catalyst (*S*)-**46c** according to general method **VIII** in 6 h as yellow oil (29.2 g, conversion 96%, yield 92%, 99% *ee*).

$C_{12}H_{14}O_6$ (254.24 g/mol)

R_f = 0.24 (SiO_2, EA/pentane 20:80)

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 2.81–2.93 (m, 2H, CH_2), 3.58 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.76 (d, $^3J_{HH}$ = 8.2 Hz, 1H, CH(COOMe)$_2$), 4.08 (dt, $^3J_{HH}$ = 5.1 Hz and 8.8 Hz, 1H, ArCH), 6.06 (d, $^3J_{HH}$ = 3.0 Hz, 2H, 3'-*H*), 6.20 (dd, $^3J_{HH}$ = 1.5 Hz and 3.0 Hz, 1H, 4'-*H*), 7.24 (d, $^3J_{HH}$ = 1.5 Hz, 1H, 5'-*H*), 9.61 (s, 1H, CHO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 33.1 (Ar*C*H), 44.7 (*C*H$_2$), 52.8 (O*C*H$_3$), 52.9 (O*C*H$_3$), 54.8 (*C*H(COOMe)$_2$), 107.4 (*Ar*H), 110.4 (*Ar*H), 142.2 (*Ar*H), 152.8 (*Ar*C), 167.99 (*C*OOMe), 168.12 (*C*OOMe), 199.6 (*C*HO).

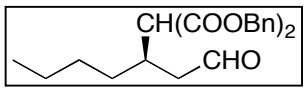
MS (EI, 70 eV, 50 °C) *m/z* (%): 254 (M^+, 15), 194 ([M-COOMe]$^+$, 38), 166 ([M-COOMe-CO]$^+$, 68), 123 ([M-CH(COOMe)$_2$]$^+$, 100), 95 ([M-CH(COOMe)$_2$-CO]$^+$, 71), (67 ($C_4H_3O^+$, 29).

IR (ATR): $\tilde{\nu}$ = 2955w, 2920w, 1724s (C=O), 1435m, 1256m, 1194m, 1146s, 918w, 739s.

EA: calc. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55; O, 37.76. Found: C, 56.86; H, 5.65.

$[\alpha]_D^{20}$ = -21.0 (c = 1.02, $CHCl_3$).

HPLC: Chiralcel AD-H, heptane/isopropanol 97:3, 20 °C, 5 µL, 1.0 mL/min, 210 nm, t_R = 20.8 min (minor), t_R = 22.7 min (major).



(*R*)-Dibenzyl 2-(1-oxoheptan-3-yl)malonate ((*R*)-44l)

Dibenzyl malonate (95% pure, 65 µL, 75 mg, 0.25 mmol,), catalyst (*S*)-**46c** (6.4 mg, 17 µmol,) and benzoic acid (2.1 mg, 17 µmol) were dissolved in ethanol (1.0 mL) and water (9 µL) and the mixture was cooled to 0 °C. 2-Heptenal (49 µL, 45.9 mg, 0.375 mmol) was added dropwise during 3 h and the mixture was stirred for additional 21 hours. TLC still showed starting material, ^{1}H-NMR 65% conversion. The mixture was filtered through 3 × 1 cm column of silica gel, the solvent was evaporated and the mixture was purified by column chromatography (SiO_2, Et_2O/pentane/CH_2Cl_2 1:10:0.1-2:10:0). The product was

obtained as colorless oil and contained 10% of dibenzyl malonate (61 mg, 55% of pure product, 96% *ee*).

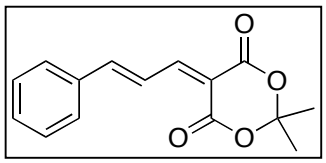
$C_{24}H_{28}O_5$ (396.18 g/mol)

$\boldsymbol{R_f}$ = 0.33 (silica, Et_2O/pentane 2:10).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 0.89 (t, $^3J_{HH}$ = 6.3 Hz, CH_3), 1.27–1.29 (m, 4H, CH_2CH_2CH$_3$), 1.37–1.45 (m, CH_2CH$_2$CH$_2$CH$_3$), 2.52 (dd, $^3J_{HH}$ = 7.0 Hz, $^2J_{HH}$ = 17.6 Hz, 1H, CH_AH$_B$CHO), 2.72 (dd, $^3J_{HH}$ = 5.0 Hz, $^2J_{HH}$ = 17.6 Hz, 1H, CH$_A$$H_B$CHO), 2.78–2.85 (m, 1H, CHCH$_2$CHO), 3.70 (d, $^3J_{HH}$ = 6.0 Hz, CH(COOBn)$_2$), 5.20 (s, 4H, CH_2Ph), 7.34–7.40 (m, 10H, PhH), 9.72 (s, 1H, CHO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 13.9 (*C*H$_3$), 22.6 (*C*H$_2$CH$_3$), 29.0 (*C*H$_2$CH$_2$CH$_3$), 32.7 (*C*H$_2$CH$_2$CH$_2$CH$_3$), 32.8 (*C*HCH$_2$CHO), 45.9 (*C*H$_2$CHO), 54.4 (*C*H(COOBn)$_2$), 67.2 (O*C*H$_2$Ph), 67.3 (O*C*H$_2$Ph), 128.4 (*Ph*H), 128.5 (*Ph*H), 128.6 (*Ph*H), 128.7 (*Ph*H), 135.3 (*Ph*C), 168.2 (*C*OOBn), 168.5 (*C*OOBn), 201.1 (*C*HO).

HPLC: Chiralcel AD-H, heptane/isopropanol 97:3, 20 °C, 5 µL, 0.5 mL/min, 210 nm, t_R = 25.1 min (minor), t_R = 27.2 min (major).



(*E*)-2,2-Dimethyl-5-(3-phenyl-2-propen-1-ylidene)-1,3-dioxane-4,6-dione (171)

The cinnamaldehyde (23 µL, 25 mg, 0.19 mmol) was dissolved in ethanol (0.5 mL) and water (4.5 µL). Then, catalyst was added (3.2 mg, 8.8 µmol, 7 mol%) and the mixture was cooled to 0 °C. Meldrum's acid (18.0 mg, 0.125 mmol) was added in one portion and the mixture was stirred for 24 hours. TLC showed incomplete reaction. The mixture was filtered through 3 × 1 cm column of silica gel, the solvent was evaporated and the mixture was purified by column chromatography (SiO_2, Et_2O/pentane/CH_2Cl_2 1:10:0.1–3:10). Product was obtained as yellow solid (15.5 mg, 48%). An analytical sample was recrystallized from Et_2O.

$C_{15}H_{14}O_4$ (258.27)

$\boldsymbol{R_f}$ = 0.42 (silica, EA/pentane 20:80).

m. p. 100–101 °C (Lit. [20] 100–102 °C).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.77 (s, 6H, C*H*$_3$), 7.41–7.45 (m, 4H, Ph*H*+PhC*H*), 7.66–7.68 (m, 2H, Ph*H*), 8.18 (d, $^3J_{HH}$ = 12.0 Hz, 1H, (C*H*C(COOR)$_2$), 8.32 (dd, $^3J_{HH}$ = 12.0 Hz and 15.0 Hz, 1H, PhCH=C*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 27.7 (*C*H$_3$), 104.8 (*C*(CH$_3$)$_2$), 111.5 (*C*(COOR)$_2$), 124.6 (PhCH=*C*H), 129.2 (*Ph*H), 129.3 (*Ph*H), 131.8 (*Ph*H), 135.0 (*Ph*C), 154.5 (Ph*C*H), 158.0 (*C*HC(COOR)$_2$), 160.8 (*C*OO), 163.0 (*C*OO).

MS (EI, 70 eV, 100 °C) *m/z* (%): 258 (M^+, 19), 200 ([M-C_3H_6O]$^+$, 100), 172 ([M-$C_4H_6O_2$]$^+$, 34), 155 ([M-PhCHCH]$^+$, 21), 128 ([M-$C_5H_6O_4$]$^+$, 88), 102 ([PhCHCH]$^+$, 24), 77 ($C_6H_5^+$, 11).

IR (ATR): $\tilde{\nu}$ = 1709s (C=O), 1562s (C=C), 1448m (C-H), 1369m, 1283s, 1199s, 999s, 921s, 856m, 793s, 750s, 711s.

EA: calc. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46; O, 24.78. Found: C, 69.41; H, 5.38.

5.3.6 Mechanistic Studies

Determination of reaction progress

(*E*)-Cinnamaldehyde (49.6 mg, 375 μmol) and catalyst (*S*)-**46c** (6.43 mg, 17.5 μmol) were dissolved in ethanol (1.0 mL) and cooled to 0 °C. In the runs with additives benzoic acid (2.14 mg, 17.5 μmol) and water (9.0 μL, 9.0 μg, 500 μmol) were added before cooling. Dibenzyl malonate (95% pure, 66 μL, 75 mg, 250 μmol) was added to the yellow solution, which was then stirred at 0 °C. Samples (100 μL) were taken from the reaction mixture after certain time intervals, dissolved in heptane (1 mL) and concentrated in vacuo. The conversion was determined by ^{1}H-NMR.

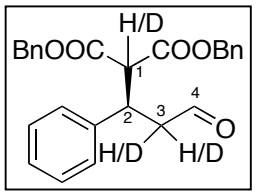
ESI-MS of 1,4-addition of malonates to α,β-unsaturated aldehydes

For catalytic reaction, (*E*)-cinnamaldehyde (24 μL, 25 mg, 0.19 mmol), catalyst (*S*)-**46c** (3.2 mg, 8.7 μmol) and, if necessary PhCOOH (1.1 mg, 8.7 μmol) were dissolved in EtOH (0.5 mL) and stirred at RT. An aliquot of the reaction mixture was diluted with acetonitrile to approximately 0.01 mM with respect to catalyst concentration and analyzed by ESI-MS. The spectra were recorded as centroid, in both positive and negative mode. After 30 minutes, dibenzyl malonate (95% pure, 33 μL, 37 mg, 125 μmol) was added to the reaction mixture.

Aliquots of the reaction mixture were diluted after indicated time periods with acetonitrile to approximately 0.01 mM with respect to catalyst concentration and analyzed by ESI MS.
For stoichiometric reaction, different amounts of cinnamadehyde (1.7 μL, 1.7 mg, 13 μmol) and dibenzyl malonate (95% pure, 2.2 μL, 2.6 mg, 8.7 μmol) were used.

^{1}H-NMR of 1,4-addition of malonates to α,β-unsaturated aldehydes

(*E*)-Cinnamaldehyde (1.5 μL, 1.6 mg, 12 μmol), catalyst (*S*)-**46c** (4.6 mg, 12 μmol) and, if necessary PhCOOH (1.5 mg, 12 μmol) were dissolved in d_6-EtOD (0.5 mL) in NMR tube and analyzed by ^{1}H-NMR (500 MHz). Dibenzyl malonate (95% pure, 3.2 μL, 3.6 mg, 12 μmol) was added to the reaction mixture, which was analyzed by ^{1}H-NMR (500 MHz) after indicated time periods.



1,4-addition of dibenzyl malonates to cinnamaldehyde in d_6-EtOD

By general method **VIII**, (*E*)-cinnamaldehyde (47 μL, 48.9 mg, 0.37 mmol), dibenzyl malonate (95% pure, 65 μL, 75 mg, 0.25 mmol), catalyst (*S*)-**46c** (6.4 mg, 17 μmol) and PhCOOH (2.1 mg, 17 μmol) in d_6-EtOD (1 mL, <5% D_2O) gave crude product in 6.5 h at 0 °C, which was purified by column chromatography (SiO_2, Et_2O/pentane 1:10-3:10) and recrystallization from Et_2O/pentane. (*S*)-**44g** was obtained as colorless solid (95% conversion, 80 mg, 77% yield, 20% incorporated ^{2}H at 1-*H*, 20% at 3-*H*).[1]

^{2}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 2.8 (br s, 3-*D*), 3.8 (br s, 1-*D*).

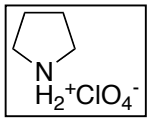
Measurement of nonlinear effect

Six mixtures of (*S*)- and (*R*)-**46c** were prepared by dissolving the enantiomers of the catalyst in different ratios in dichloromethane and concentration in vacuo. The *ee* values of the

[1] In a repeated run, 98% yield was obtained after column chromatography with 0% ^{2}H at 1-*H*, 50% at 3-*H*. **^{2}H-NMR** ($CDCl_3$, 500 MHz) δ/ppm: 2.8 (br s, 3-*D*).

mixtures were measured by HPLC (Chiralpak OD-H, heptane/isopropanol 100:0, 20 °C, 4 µL, 0.8 mL/min, 210 nm, t_R = 9.4 min (*S*), t_R = 12.5 min (*R*).

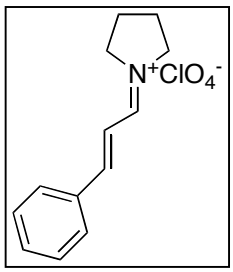
The catalytic reactions were performed according to general method **VIII** with (*E*)-cinnamaldehyde (188 µmol), catalyst **46c** (8.8 µmol), benzoic acid (8.8 µmol) and malonate (125 µmol) in ethanol (0.5 mL) with water (4.5 µL) at 0 °C.



Pyrrolidine perchlorate (175) [21, 22]

To pyrrolidine (1.0 mL, 0.85 g, 12 mmol) in diethylether (6 mL) was added perchloric acid (60% solution in water) dropwise until the mixture was just acidic (indicator paper). One additional drop of pyrrolidine was added and solvent was removed under vacuum. The crude product was recrystallized from isopropanol giving orange needles of **175** (2.09 g, 98%), which were dried under vacuum.

$C_4H_{10}ClNO_4$ (171.58 g/mol)
m. p. 238–240 °C (Lit.[21] 240–242 °C).
^{1}H-NMR (DMSO, 400 MHz) δ/ppm: 1.81 (t, $^3J_{HH}$ = 6.8 Hz, 4H, 3-*H*), 3.07 (t, $^3J_{HH}$ = 6.8 Hz, 4H, 2-*H*), 8.21 (br s, 2H, NH_2^+).
^{13}C{^{1}H}-NMR (DMSO, 101 MHz) δ/ppm: 23.7 (*C*-3), 45.1 (*C*-2).



***N*-cinnamylidene pyrrolidinium perchlorate (176)**[21, 22]

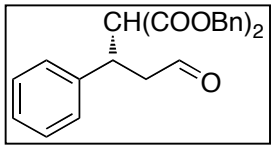
To pyrrolidine perchlorate (500 mg, 2.91 mmol) was added (*E*)-cinnamaldehyde (1.5 mL, 1.6 g, 12 mmol). The stirred solution warmed slightly. Then, TBME was added and the product precipitated as yellow solid. The crude product was filtered off and recrystallized from isopropanol to give **176** as yellow needles (623 mg, 75%).

$C_{13}H_{16}ClNO_4$ (285.72)
m. p. 149–150.5 °C (Lit.[21] 156–157 °C).
^{1}H-NMR (DMSO, 400 MHz) δ/ppm: 1.99–2.13 (m, 4H, 3-*H*), 4.03–4.10 (m, 4H, 2-*H*), 7.43 (dd, $^3J_{HH}$ = 10.4 Hz and 15.4 Hz, 1H, C*H*CH=N), 7.52–7.58 (m, 3H, Ph*H*), 7.89–7.92 (m, 3H, Ph*H*, PhC*H*), 8.80 (d, $^3J_{HH}$ = 10.4 Hz, 1H, C*H*=N).

$^{13}C\{^1H\}$-NMR (DMSO, 101 MHz) δ/ppm: 24.0 (*C*-3), 51.8 (*C*-2), 56.7 (*C*-5), 119.0 (C*H*CH=N), 129.4 (*Ph*H), 130.1 (*Ph*H), 133.0 (*Ph*H), 133.8 (*Ph*C), 157.7 (Ph*C*H), 165.6 (*C*H=N).

MS (FAB, NBA) *m/z* (%): 186 (M^+, 100), 115 ($[M-C_4H_7N]^+$, 5), 77 ($C_6H_5^+$, 5).

IR (ATR): $\tilde{\nu}$ = 1650w (C=N), 1624m, 1066s, 1001s, 954m, 865m, 840m, 754s, 686s, 597s (Cl=O), 584s.



(*R*)-Dibenzyl 2-(3-oxo-1-phenylpropyl)malonate ((*S*)-44g)

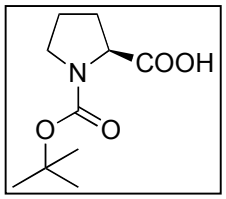
Dibenzyl malonate (95% purity, 36 μL, 41 mg, 136 μmol) and catalyst (*S*)-**46c** (50.0 mg, 136 μmol) were dissolved in ethanol (0.5 mL) and the mixture was stirred for 10 minutes at 0 °C. The iminium perchlorate salt **176** (38.9 mg, 136 μmol) was added and the mixture was stirred for 24 h at 0 °C. Solvent was removed in vacuo and water (1 mL) was added. The organic material was extracted with chloroform (3 × 1 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (SiO_2, Et_2O/pentane 1:10-3:10). The product was obtained as colorless oil, which contained ca 40% impurities (12 mg, 10 % of pure product, 87% *ee*).

$C_{26}H_{24}O_5$ (416.17 g/mol)

HPLC: Chiralcel AD-H, heptane/isopropanol 80:20, 20 °C, 5 μL, 0.8 mL/min, 210 nm, t_R = 31.3 min (major), t_R = 44.1 min (minor).

5.4 Towards Self-Assembling Organocatalysts

5.4.1 Synthesis of Catalysts and Additives

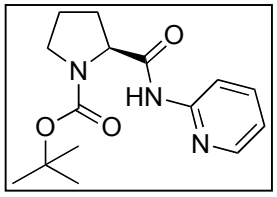


(*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxylic acid ((*S*)-230)[23]

(*S*)-Proline (5.76 g, 50.0 mmol) was suspended in DCM (100 mL). Triethylamine (9.1 mL, 6.6 g, 65 mmol) was added in one portion and the mixture was cooled to 0 °C. A solution of Boc_2O (16.4 g, 75.0 mL) in DCM (5 mL) was added dropwise and after 10 minutes, a clear solution was formed. The reaction mixture was stirred for 2.5 h, and then a

saturated solution of citric acid in water (30 mL) was added. The organic phase was separated, washed with brine (2 × 25 mL) and water (25 mL), and dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was obtained as colorless oil. Hexane (10 mL) was added and colorless precipitate was formed, which was filtered off and recrystallized from ethyl acetate/hexane. (*S*)-**230** was obtained as colorless crystalline solid (8.79 g, 82%).

$C_{10}H_{17}NO_4$ (215.25 g/mol)
R_f = 0.29 (SiO_2, EA/cyclohexane 30:70).
m.p. 130–132 °C (Lit.[24] 136–137 °C).
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.39 and 1.44 (2 × s, 9H, C(C*H*$_3$)$_3$, rotamers), 1.83–2.27 (m, 4H, 3-*H*, 4-*H*), 3.33–3.53 (m, 2H, 5-*H*), 4.19–4.34 (m, 1H, 2-*H*), 11.06 (br s, 1H, COO*H*).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 23.7 and 24.7 (*C*-4, rotamers), 28.3 (C(*C*H$_3$)$_3$), 29.1 and 30.9 (*C*-3, rotamers), 46.7 and 47.0 (*C*-5, rotamers), 59.0 (*C*-2), 80.4 and 81.1 (*C*(CH$_3$)$_3$, rotamers), 154.0 and 156.0 (*C*OO^{t}Bu, rotamers), 176.2 and 178.9 (*C*OOH, rotamers).
MS (FAB, NBA) *m/z* (%): 216 (M+H$^+$, 31), 160 ([M-C$_4$H$_9$]$^+$, 100), 114 ([M-COO^{t}Bu]$^+$, 63), 70 (C$_4$H$_8$N$^+$, 39), 57 (C$_4$H$_9^+$, 63).
$[\alpha]_D^{20}$ = - 70.5 (c = 1.03, $CHCl_3$) (Lit.[24] $[\alpha]_D^{20}$ = - 60.2 (c = 2.0, AcOH)).



(*S*)-*tert*-Butyl 2-(pyridin-2-ylcarbamoyl)pyrrolidine-1-carboxylate ((*S*)-232)

Method A.[25] (*S*)-*N*-Boc-proline (2.15 g, 10.0 mmol) was dissolved under Ar in dry THF (11 mL) and cooled to -15 °C. *N*-Methylmorpholine (1.2 mL, 1.1 g, 11 mmol) was added and subsequently very slowly isobutylchloroformate (1.4 mL, 1.5 g, 11 mmol), whereupon a precipitate formed. The mixture was stirred at -15 °C for 3 h, then 2-aminopyridine (941 mg, 10.0 mmol) was added as a solution in dry THF (2 mL). The mixture was allowed to warm to RT and stirred at this temperature for 18 h. The reaction mixture was filtered through a short silica column (10 × 3 cm) and washed with ethyl acetate (300 mL). The solvent was removed in vacuo and the crude product was purified by column chromatography. The product was obtained as colorless solid (886 mg, 30 %) and two side-

products were isolated: 2-(isobutoxycarbonylamino)pyridine (**233a**, 854 mg, 44%) and 1,3-di(pyridin-2-yl)urea (**233b**, 300 mg, 14%).

Method B (general method IX):

(*S*)-*N*-Boc-proline (2.15 g, 10.0 mmol) was dissolved in dry acetonitrile (25 mL), dry pyridine (890 µL, 870 mg, 11.0 mmol) was added and the mixture was cooled to -15 °C. Cyanuric fluoride (515 µL, 810 mg, 6.00 mmol) was carefully added. A colorless precipitate appeared after 5 minutes. The mixture was stirred at -15 °C for 1 h and CH_2Cl_2 (25 mL) and brine (50 mL) were added. The organic layer was separated, dried over $MgSO_4$ and concentrated. The obtained colorless oil was directly used in the next step and dissolved in dry CH_2Cl_2 under Ar. Dry pyridine (810 µL, 791 mg, 10.0 mmol) and 2-aminopyridine (941 mg, 10.0 mmol) were added and the mixture was stirred at RT for 16 h. The reaction mixture was filtered and the obtained solid washed with CH_2Cl_2. The solvent was removed in vacuo and the crude product purified by column chromatography (SiO_2, cyclohexane/EA 60:40). (*S*)-**232** was obtained as colorless solid (2.26 g, 78%). Alternatively, the product can be purified by washing of the solid with water and drying under high vacuum (75%).

(*S*)-**232**:

$C_{15}H_{21}N_3O_3$ (291.35 g/mol)

R_f = 0.23 (SiO_2, EA/cyclohexane 30:70).

m.p. 149–151 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.40 and 1.48 (2×s, 9H, C(C*H*$_3$)$_3$, rotamers), 1.88–2.28 (m, 4H, 3-*H*, 4-*H*), 3.36–3.55 (m, 2H, 5-*H*), 4.27–4.45 (m, 1H, 2-*H*), 7.05 (m$_c$, 1H, Ar*H*), 7.73 (m$_c$, 1H, Ar*H*), 8.23–8.28 (m, 2H, Ar*H*), 9.04–9.58 (2×br s, 1H, N*H*).

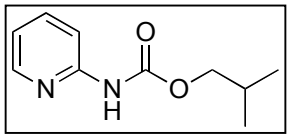
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 23.9 and 24.0 (*C*-4, rotamers), 28.4 (C(*C*H$_3$)$_3$), 31.3 (*C*-3), 47.3 (*C*-5), 61.2 and 62.1 (*C*-2, rotamers), 80.9 (*C*(CH$_3$)$_3$), 113.9 (*Ar*H), 119.9 (*Ar*H), 138.4 (*Ar*H), 148.0 (*Ar*H), 151.2 (*Ar*C), 154.5 (*C*O*O*^{t}Bu), 170.9 and 171.6 (*C*ON, rotamers).

MS (EI, 70 eV, 100 °C) *m/z* (%): 291 (M^+, 4), 218 ([M-OC_4H_9]$^+$, 7), 191 (([M-COO^{t}Bu]$^+$, 9), 170 (C_4H_7NBoc$^+$, 21), 114 ($C_4H_7NCO_2^+$, 93), 70 ($C_4H_8N^+$, 100), 57 ($C_4H_9^+$, 60).

IR (ATR): $\tilde{\nu}$ = 3213w; 2978m; 2878m; 1709s (C=O); 1684s (C=O); 1582m; 1435m; 1389m; 1377m; 1294s; 1151s; 798s.

EA: calc. for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.26; N 14.42; O, 16.47. Found: C, 61.57; H, 7.09; N, 14.20.

$[\alpha]_D^{20}$ = -90.5 (c = 1.05, MeOH).



2-(Isobutoxycarbonylamino)pyridine (**233a**):

$C_{15}H_{21}N_3O_3$ (291.35 g/mol)

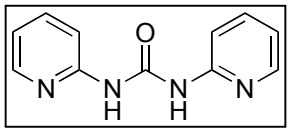
R_f = 0.23 (SiO_2, EA/cyclohexane 30:70).

m.p. 71–73 °C (Lit.[26] 74–76 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 0.96 (d, $^3J_{HH}$ = 6.6 Hz, 6H, CH_3), 1.96–2.06 (m, 1H, CH(CH_3)$_2$), 3.99 (d, $^3J_{HH}$ = 6.8 Hz, 2H, CH_2), 6.95–6.98 (m, 1H, 5-*H*), 7.66–7.71 (m, 1H, 4-*H*), 8.04 (d, $^3J_{HH}$ = 8.6 Hz, 1H, 3-*H*), 8.37 (dd, $^3J_{HH}$ = 5.1 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, 6-*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 19.2 (*C*H_3), 28.1 (*C*H(CH_3)$_2$), 71.5 (*C*H_2), 112.8 (*C*-3), 118.4 (*C*-5), 138.6 (*C*-4), 147.6 (*C*-6), 152.7 (*C*-2), 154.0 (*C*=O).

MS (EI, 70 eV, RT) *m/z* (%): 194 (M^+, 41), 137 ([M-C_4H_9]$^+$, 7), 121 ([M-O^{i}Bu]$^+$, 9), 94 ([M-COO^{i}Bu]$^+$, 100), 78 ($C_5H_4N^+$, 31), 57 ($C_4H_9^+$, 37).



1,3-Di(pyridin-2-yl)urea (**233b**):

$C_{11}H_{10}N_4O$ (214.22 g/mol)

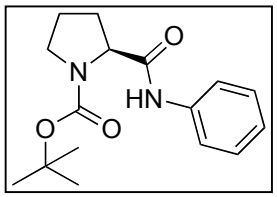
R_f = 0.10 (SiO_2, EA/cyclohexane 30:70).

m.p. 174–176 °C (Lit.[27] 177–178 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 6.99–7.02 (m, 2H, 5-*H*), 7.67–7.80 (m, 4H, 3-*H*, 4-*H*), 8.32 (dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.0 Hz, 2H, 6-*H*), 10.7 (br. s, 2H, N*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 112.5 (*C*-3), 117.4 (*C*-5), 137.6 (*C*-4), 146.6 (*C*-6), 152.2 (*C*-2), 152.3 (*C*=O).

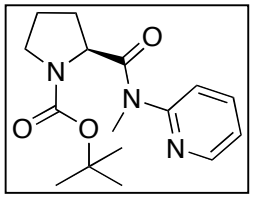
MS (EI, 70 eV, 150 °C) *m/z* (%): 214 (M^+, 11), 121 (PyrNHCO$^+$, 33), 94 (PyrNH$_2^+$, 100), 78 ($C_5H_4N^+$, 19).



(*S*)-*tert*-Butyl 2-(phenylcarbamoyl)pyrrolidine-1-carboxylate ((*S*)-252)

By general method **IX**, acid fluoride (4.15 mmol) was prepared from (*S*)-*N*-*Boc*-proline (893 mg, 4.15 mmol), pyridine (370 µL, 0.36 g, 4.6 mmol) and cyanuric fluoride (215 µL, 0.34 g, 2.5 mmol). Afterwards, the acid fluoride was treated with pyridine (335 µL, 328 mg, 4.14 mmol) and aniline (375 µL, 411 mg, 4.15 mmol) at RT for 16 h. The solid was filtered off and washed with CH_2Cl_2. The solvent was removed in vacuo and the crude product (colorless solid) purified by washing with water and drying under high vacuum (0.99 g, 82%).

$C_{16}H_{22}N_3O_3$ (290.36 g/mol)
R_f = 0.43 (SiO_2, cyclohexane/EA 70:30).
m.p. 181–183 °C (Lit.[28] 185–188 °C).
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.84–2.46 (m, 4H, 3-*H*, 4-*H*), 3.27–3.48 (m, 2H, 5-*H*), 4.24–4.42 (m, 1H, 2-*H*), 6.98–7.07 (m, 1H, PhH_{para}), 7.19–7.21 (m, 2H, PhH_{meta}), 7.44 (d, $^3J_{HH}$ = 7.9 Hz, 2H, PhH_{ortho}), 7.76 and 9.44 (2 × br s, 1H, N*H*, rotamers).
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 24.7 (*C*-4), 27.2 (*C*-3), 28.5 (C(*C*H$_3$)$_3$), 47.3 (*C*-5), 60.6 (*C*-2), 81.0 (*C*(CH$_3$)$_3$), 119.7 (*Ph*H$_{ortho}$), 123.9 (*Ph*H$_{para}$), 129.0 (*Ph*H$_{meta}$), 138.5 (*Ar*C), 156.7 (*C*OO^{t}Bu), 170.0 (*C*ON).
MS (EI, 70 eV, 150 °C) *m/z* (%): 290 (M^+, 11), 217 ([M-OC$_4$H$_9$]$^+$, 8), 170 ($C_4H_7NBoc^+$, 36), 114 ($C_4H_7NCO_2^+$, 100), 70 ($C_4H_8N^+$, 92), 57 ($C_4H_9^+$, 52).
$[\alpha]_D^{20}$ = -146.9 (c = 1.00, $CHCl_3$) (Lit.[28] $[\alpha]_D^{20}$ = -138.3 (c = 0.24, $CHCl_3$)).



(*S*)-*tert* Butyl-2-(methyl(pyridin-2-yl)carbamoyl)pyrrolidine-1-carboxylate ((*S*)-253)

Amide (*S*)-**232** (862 mg, 2.96 mmol) and $Ba(OH)_2 \cdot H_2O$ (3.36 g, 17.7 mmol) were suspended in a DMF/H_2O mixture (55 mL, 3/1). Methyl iodide (6.6 mL, 16 g, 110 mmol) was added and the mixture was stirred at RT for 16 h. The solid was filtered off and the filtrate was extracted with DCM (6 × 50 mL). Collected organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Crude product was purified by column

chromatography (SiO_2, EA/cyclohexane 1:1). (*S*)-**253** was obtained as off-white solid (0.53 g, 59 %).

$C_{16}H_{23}N_3O_3$ (305.38 g/mol)

R_f = 0.47 (SiO_2, EA).

m.p. 96–97 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.34 and 1.38 (2 x s, 9H, C(C*H*$_3$)$_3$), rotamers), 1.64–2.14 (m, 4H, 3-*H*, 4-*H*), 3.32 and 3.33 (2 x s, 3H, C*H*$_3$, rotamers), 3.27–3.58 (m, 2H, 5-*H*), 4.27–4.42 (m, 1H, 2-*H*), 7.09–7.16 (m, 1H, Ar*H*), 7.50 (d, $^3J_{HH}$ = 7.5 Hz, 1H, Ar*H*), 7.69 (dd, $^3J_{HH}$ = 6.7 Hz and 13.5 Hz, 1H, Ar*H*), 8.41 (d, $^3J_{HH}$ = 4.2 Hz, 1H, Ar*H*).

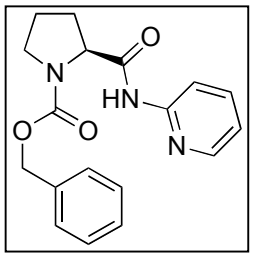
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 23.5 and 24.1 (*C*-4, rotamers), 28.5 (C(*C*H$_3$)$_3$), 30.5 and 31.7 (*C*-3, rotamers), 35.5 and 35.6 (*C*H$_3$, rotamers), 47.1 and 47.3 (*C*-5, rotamers), 57.9 and 58.2 (*C*-2, rotamers), 79.4 and 79.5 (*C*(CH$_3$)$_3$, rotamers), 121.3 (*Ar*H), 121.8 (*Ar*H), 138.3 and 138.4 (*Ar*H, rotamers), 148.8 (*Ar*H), 153.8 and 154.5 (*C*O^{t}Bu, rotamers), 155.7 and 155.9 (*Ar*C, rotamers), 173.1 and 173.5 (*C*ON, rotamers).

MS (EI 70 eV) *m/z* (%): 305 ([M]$^+$, 6), 232 ([M - OC(CH$_3$)$_3$]$^+$, 10), 205 ([M-Boc]$^+$, 20), 170 (C$_4$H$_7$NBoc$^+$, 10), 135 ([CON(CH$_3$)-Pyridine]$^+$, 13), 114 (C$_4$H$_7$NCO$_2^+$, 65), 70 (C$_4$H$_8$N$^+$, 100), 57 (C$_4$H$_9^+$, 63).

IR (KBr) $\tilde{\nu}$ = 3055w; 2978s; 2885m; 1698s (C=O); 1665s (C=O); 1588s (N-C); 1477s; 1439s (Ar); 1397s (-C(CH$_3$)$_3$); 1348s; 1331m; 1259m; 1160s; 1117s; 1086m; 992m, 873m; 795m; 773m; 752m.

EA: calc. for $C_{16}H_{23}N_3O_3$: C, 62.93; H, 7.59; N 13.76; O, 15.72. Found: C, 62.90; H, 7.53; N, 13.71.

$[\alpha]_D^{20}$ = 4.7 (c = 1.00, $CHCl_3$).



(*S*)-Benzyl 2-(pyridin-2-ylcarbamoyl)pyrrolidine-1-carboxylate ((*S*)-235)[29]

By general method **IX**, the acid fluoride (5.00 mmol) was prepared from (*S*)-*N*-*Cbz*-proline (1.25 g, 5.00 mmol), pyridine (440 µL, 435 mg, 5.5 mmol) and cyanuric fluoride (260 µL, 405 mg, 3.0 mmol). Crude acid fluoride was treated with pyridine (400 µL, 395 mg, 5.0 mmol) and 2-aminopyridine (471 mg, 5.00 mmol) at RT for 16 h. The crude product was filtered and washed with CH_2Cl_2. The solvent was removed

in vacuo and water was added to the crude product, which solidified. The colorless solid was filtered, washed with water and dried under high vacuum (1.29 g, 79%). (*S*)-**235** was directly used in the next step.

$C_{18}H_{19}N_3O_3$ (325.36 g/mol)

R_f = 0.68 (SiO_2, EA).

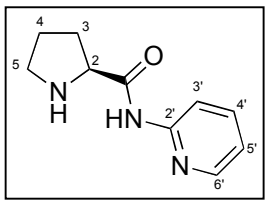
m.p. 105–107 °C.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.92–2.37 (m, 4H, 3-*H*, 4-*H*), 3.47–3.62 (m, 2H, 5-*H*), 4.38–4.53 (m, 1H, 2-*H*), 5.08–5.25 (m, 2H, C*H*$_2$Ph), 7.01–7.36 (m, 6H, Ar*H*), 7.67 (m$_c$, 1H, Ar*H*), 8.18–8.26 (m, 2H, Ar*H*), 8.56 and 9.34 (2 × bs, 1H, N*H*, rotamers).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 23.9 and 24.7 (*C*-4, rotamers), 28.6 and 31.4 (*C*-3, rotamers), 47.3 and 47.7 (*C*-5, rotamers), 61.6 (*C*-2), 67.6 and 67.7 (*C*H$_2$Ph, rotamers), 114.1 (*Ar*H), 119.9 (*Ar*H), 128.1 (*Ar*H), 128.6 (*Ar*H), 136.3 (*Ar*H), 138.3 (*Ar*H), 147.9 (*Ar*H), 151.0 (*Ar*C), 151.4 (*Ar*C), 155.0 and 156.4 (*C*OOCH$_2$Ph, rotamers), 170.4 and 171.2 (*C*ONHAr, rotamers).

MS (EI, 70 eV, 200 °C) *m/z* (%): 325 (M^+, 12), 204 ([M-CONHAr]$^+$, 18), 160 (29), 91 ($C_7H_7^+$, 100).

$[\alpha]_D^{20}$ = -116.5 (c = 1.00, $CHCl_3$).



(*S*)-*N*-(Pyridin-2-yl)pyrrolidine-2-carboxamide ((*S*)-224)

Method A (**general method X**):

Boc-protected amide (*S*)-**232** (1.00 g, 3.43 mmol) was dissolved in CH_2Cl_2 (60 mL) and TFA (3.3 mL, 4.9 g. 43 mmol) was added. The mixture was stirred at RT for 16 h. A solution of NaOH (4.7 g, 117 mmol) in H_2O (115 mL) was added and the reaction mixture was stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL) and Et_2O (4 × 150 mL). Collected organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product can be purified by column chromatography (SiO_2, ethyl acetate) or recrystallization from Et_2O/pentanes. Product was obtained as colorless solid (520 mg, 79% after column).

Method B.[33] *Cbz*-protected amide (*S*)-**235** (2.00 g, 6.15 mmol) was dissolved in MeOH (60 mL) and 5% Pd/C (200 mg) was added. The flask was purged with hydrogen two times. The mixture was stirred under 1 bar hydrogen for 1 h. The reaction mixture was filtered

through a pad of celite (3 × 1 cm), and washed with methanol. The solvent was removed in vacuo and the crude product was obtained as colorless oil, which crystallized on standing (1.18 g, quantitative) and was purified by bulb-to-bulb distillation 110–115 °C, 0.06 mbar (976 mg, 83%).

$C_{10}H_{13}N_3O$ (191.20 g/mol)

R_f = 0.12 (SiO_2, EA).

m.p. 43–45 °C (Lit.[29] 45–50 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.65–1.76 (m, 2H, 4-*H*), 1.93–2.02 (m, 1H, 3-H_A), 2.12–2.21 (m, 1H, 3-H_B), 2.62 (br. s, 1H, N*H*-pyrrolidine), 2.94–3.05 (m, 2H, 5-*H*), 3.85 (dd, $^3J_{HH}$ = 5.1 Hz and 9.4 Hz, 1H, 2-*H*), 6.94–6.97 (m, 1H, 5'-*H*), 7.60–7.65 (m, 1H, 4'-*H*), 8.17–8.24 (m, 2H, 3'-*H*, 6'-*H*), 10.2 (br s, 1H, N*H*CO).

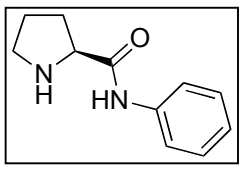
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 26.2 (*C*-4), 30.93 (*C*-3), 47.3 (*C*-5), 61.0 (*C*-2), 113.6 (*Ar*H), 119.6 (*Ar*H), 138.2 (*Ar*H), 148.0 (*Ar*H), 151.2 (*Ar*C), 174.3 (*C*ON).

MS (EI, 70 eV, 50 °C) *m/z* (%): 191 (M^+, 5), 94 ($C_5H_4NNH_2^+$, 6), 70 ($C_4H_8N^+$, 100), 43 ($C_2H_5N^+$, 5).

IR (ATR): $\tilde{\nu}$ = 3344w; 3244m; 2962m; 2872m; 1677s (C=O); 1495s; 1431s; 1298s; 1150m; 781s.

EA: calc. for $C_{15}H_{21}N_3O_3$: C, 62.81; H, 6.85; N 21.97; O, 8.37. Found: C, 62.73; H, 6.87; N, 22.04.

$[\alpha]_D^{20}$ = -55.8 (c = 1.0, MeOH) (Lit.[30] $[\alpha]_D^{20}$ = -56.0 (c = 1.0, MeOH)).



(*S*)-*N*-Phenylpyrrolidine-2-carboxamide ((*S*)-325)[31]

By general method **X** amide (*S*)-**252** (726 mg, 2.50 mmol) and TFA (2.4 mL, 3.6 g, 32 mmol) gave the crude product, which was obtained as colorless solid (478 mg, quant.) and was directly used in the next step.

$C_{11}H_{14}N_2O$ (190.24 g/mol)

R_f = 0.07 (SiO_2, cyclohexane/EA 70:30).

m.p. 76–77 °C (Lit.[31] 76–77 °C).

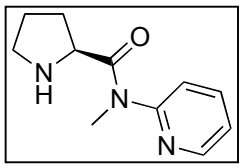
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.71–1.80 (m, 2H, 4-*H*), 2.01–2.25 (m, 3H, N*H*-pyrrolidine, 3-*H*), 2.96–3.01 (m, 1H, 5-H_A), 3.06–3.11 (m, 1H, 5-H_B), 3.86 (dd,

$^{3}J_{HH}$ = 5.1 Hz and 9.2 Hz, 1H, 2-*H*), 7.08 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H, PhH_{para}), 7.32 (t, $^{3}J_{HH}$ = 7.9 Hz, 2H, PhH_{meta}), 7.60 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H, PhH_{ortho}), 9.73 (s, 1H, N*H*CO).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 26.4 (*C*-4), 30.9 (*C*-3), 47.4 (*C*-5), 61.1 (*C*-2), 119.3 (*Ph*H_{ortho}), 124.0 (*Ph*H_{para}), 129.0 (*Ph*H_{meta}), 139.7 (*Ar*C), 173.5 (*C*ON).

MS (EI, 70 eV, 100 °C) *m/z* (%): 190 (M^+, 2), 93 ($C_6H_7N^+$, 6), 70 ($C_4H_8N^+$, 100).

$[\alpha]_D^{20}$ = -75.0 (c = 1.0, $CHCl_3$) (Lit.[31] $[\alpha]_D^{27}$ = -71.0 (c = 1.025, EtOH)).



(*S*)-*N*-Methyl-*N*-(pyridin-2-yl)pyrrolidine-2-carboxamide ((*S*)-326)

By general method **X** protected amide (*S*)-**253** (500 mg, 1.64 mmol) and TFA (1.6 mL, 2.4 g, 21 mmol) gave the crude product, which was purified by recrystallization from Et_2O and was isolated as colorless solid (250 mg, 74 %), which contained an unknown inseparable impurity.

$C_{11}H_{15}N_3O$ (205.26 g/mol)

R_f = 0.12 (SiO_2, EA).

m.p. 113–114 °C.

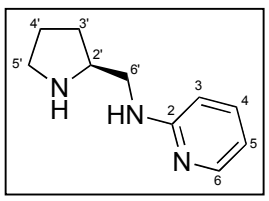
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.02–2.12 (m, 3H, 3-*H*, 4-H_A), 2.36–2.41 (m, 1H, 4-H_B), 2,27 (d, $^{3}J_{HH}$ = 4.9 Hz, 3H, CH_3), 3.31–3.35 (m, 1H, 5-H_A), 3.60–3.64 (m, 1H, 5-H_B), 4.44 (m_c, 1H, 2-*H*), 6.41 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H, 3'-*H*), 6.64 41 (d, $^{3}J_{HH}$ = 6.8 Hz, 1H, 5'-*H*), 6.94 (bs, 1H, N*H*) 7.47 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, 4'-*H*), 8.16 (d, $^{3}J_{HH}$ = 4.8 Hz, 1H, 6'-*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 24.6 (*C*-4), 26.2 (*C*H_3), 30.0 (*C*-3), 48.5 (*C*-5), 62.0 (*C*-2), 107.4 (*C*-3'), 113.4 (*C*-5'), 137.7 (*C*-4'), 148.1 (*C*-6'), 157.7 (*Ar*C), 173.9 (*C*ON).

MS (EI, 70 eV, 100 °C) *m/z* (%): 205 (M^+, 7), 147 ([M-C_3H_8N]$^+$, 100), 78 ($C_5H_4N^+$, 13).

IR (ATR): $\tilde{\nu}$ = 3315s; 3281s; 2934m; 2848m; 1647s (C=O); 1602s (C-N); 1484s; 1440s; 1403m; 1307m; 995m; 941w; 770s; 738m; 718m.

$[\alpha]_D^{20}$ = -203 (c = 0.27, $CHCl_3$).



(*S*)-*N*-(Pyrrolidin-2-ylmethyl)pyridin-2-amine ((*S*)-248)[32]

General method XI:

A 1 M solution of lithium aluminium hydride in THF (16 mL, 16 mmol) under Ar was cooled to 0 °C and the amide (*S*)-**224** (1.00 g, 5.23 mmol) was added

slowly. The reaction mixture was then heated to reflux for 2 h. After cooling to room temperature, $Na_2SO_4 \cdot 10H_2O$ was carefully added and the mixture was stirred for 1 h. The grey suspension was filtered through celite, washed wit Et_2O and the solvent was removed in vacuo. The obtained oily residue was purified by bulb-to-bulb distillation. (*S*)-**248** was obtained as colorless oil at 90–105 °C (0.06 mbar) (802 mg, 86%).

$C_{10}H_{15}N_3$ (177.25 g/mol)

R_f = 0.05 (SiO_2, EA/MeOH 10:1).

b.p. 90–105 °C (0.06 mbar) (Lit.[32] **b.p.** 102–106 °C (0.03 mbar)).

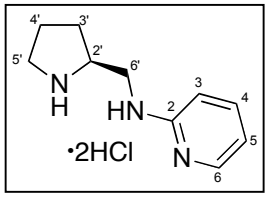
^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.32–1.41 (m, 1H, 4'-H_A), 1.56–1.85 (m, 3H, 3'-*H*, 4'-H_B), 2.32 (br s, 1H, N*H*-pyrrolidine), 2.78–2.89 (m, 2H, 5'-*H*), 3.03–3.09 (m, 1H, CH_AH$_B$NHAr), 3.26–3.35 (m, 2H, CH$_A$$H_B$NHAr, 2-*H*), 5.09 (s, 1H, N*H*Ar), 6.31 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, 3-*H*), 6.43–6.46 (m, 1H, 5-*H*), 7.26–7.30 (m, 1H, 4-*H*), 7.98 (dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, 6-*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 25.7 (*C*-3'), 29.3 (*C*-4'), 46.4 (*C*-5'), 46.5 (*C*H$_2$NHAr), 57.8 (*C*-2'), 107.4 (*C*-3), 112.5 (*C*-5), 137.1 (*C*-4), 147.9 (*C*-6), 158.9 (*C*-2).

MS (FAB, NBA) *m/z* (%): 178 ([M+H]$^+$, 100), 70 ($C_4H_8N^+$, 19).

IR (ATR): $\tilde{\nu}$ = 3270wb (NH); 2958w; 2866w; 1599s; 1507m; 1487m; 1416m; 1288m; 1148w; 767s; 734m.

$[\alpha]_D^{20}$ = 35.3 (c = 0.96, $CHCl_3$) (Lit. [32] $[\alpha]_D^{24}$ = 21.3 (c = 1.16, EtOH).



(*S*)-*N*-(Pyrrolidin-2-ylmethyl)pyridin-2-amine dihydrochloride ((*S*)-327)

Diamine (*S*)-**248** (60 mg, 0.34 mmol) was dissolved in Et_2O (2 mL) and HCl (0.51 mL of 2 M solution in Et_2O, 1.0 mmol) was added dropwise. The solvent was removed and the sticky solid was recrystallized from ^{i}PrOH (20 mL).

$C_{10}H_{17}Cl_2N_3$ (250.17 g/mol)

m.p. 192–194 °C.

^{1}H-NMR (DMSO, 500 MHz) δ/ppm: 1.62–1.77 (m, 1H, 3'-H_A), 1.83–1.91 (m, 1H, 4'-H_A), 1.94–2.02 (m, 1H, 4'-H_B), 2.13–2.20 (m, 1H, 3'-H_B), 3.11–3.18 (m, 1H, 5'-H_A), 3.20–3.27 (m, 1H, 5'-H_B), 3.72–3.89 (m, 3H, CH_2NHAr, 2-*H*), 6.91 (t, $^3J_{HH}$ = 6.6 Hz, 1H, 5-*H*), 7.19 (d,

$^{3}J_{HH}$ = 9.1 Hz, 1H, 3-*H*), 7.91–7.95 (m, 2H, 4-*H*, 6-*H*), 9.33 (bs, 1H, N*H*Ar), 9.53 (bs, 1H, N*H*–pyrrolidine), 9.75 (bs, 1H, N*H*–pyrrolidine), 14.71 (bs, 1H, N*H*Ar).

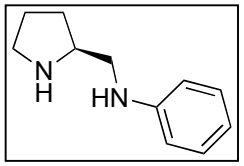
^{13}C{^{1}H}-NMR (DMSO, 126 MHz) δ/ppm: 22.8 (*C*-4'), 27.4 (*C*-3'), 42.6 (*C*H$_2$NHAr), 44.4 (*C*-5'), 57.7 (*C*-2'), 112.6 (*C*-5), 113.6 (*C*-3), 135.8 (*Ar*H), 143.1 (*Ar*H), 152.6 (*Ar*H).

MS (FAB, NBA) *m/z* (%): 178 ([M+H]$^+$, 100), 70 ($C_4H_8N^+$, 6).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3270wb (NH); 2958w; 2866w; 1599s; 1507m; 1487m; 1416m; 1288m; 1148w; 767s; 734m.

$[\alpha]_D^{20}$ = 36.9 (c = 0.50, MeOH).

EA: calc. for $C_{10}H_{17}Cl_2N_3$: C, 48.01; H, 6.85; N, 16.80. Found: C, 47.70; H, 6.75; N, 16.91.



(*S*)-*N*-(Pyrrolidin-2-ylmethyl)aniline ((*S*)-249)[33]

According to general method **XI** amide (*S*)-**325** (400 mg, 2.10 mmol) and $LiAlH_4$ (6.3 mL of 1 M solution in THF, 6.3 mmol) gave crude product in 2 h under refluxing conditions. Product was purified by bulb-to-bulb distillation (90-100 °C at 0.06 Torr) and was obtained as colorless oil, which solidified upon standing at 4 °C (342 mg, 92 %).

$C_{11}H_{16}N_2$ (177.25 g/mol)

R_f = 0.03 (SiO_2, EA).

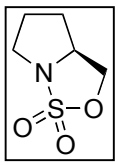
b.p. 90–100 °C (0.1 mbar) (Lit.[33] 111–112 °C (0.55 Torr)).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.42–1.49 (m, 1H, 3-H_A), 1.69–1.78 (m, 3H, 4-*H*), 1.82–1.95 (m, 1H, 3-H_B), 2.03 (br. s, 1H, N*H*-pyrrolidine), 2.89–2.97 (m, 3H, 5'-*H*, CH_AH$_B$NHPh), 3.17 (dd, $^{2}J_{HH}$ = 12.5 Hz, $^{3}J_{HH}$ = 5.0 Hz, 1H, CH$_A$$H_B$NHPh), 3.34–3.40 (m, 1H, 2-*H*), 4.15 (s, 1H, N*H*Ph), 6.64 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, PhH_{ortho}), 6.70 (t, $^{3}J_{HH}$ = 7.5 Hz, 1H, PhH_{para}), 7.18 (7, $^{3}J_{HH}$ = 8.0 Hz, 1H, PhH_{meta}).

^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 25.8 (*C*-4), 29.6 (*C*-3), 46.5 (*C*-5), 48.6 (*C*H$_2$NHPh), 57.7 (*C*-2), 113.0 (*Ph*H$_{ortho}$), 117.2 (*Ph*H$_{para}$), 129.2 (*Ph*H$_{meta}$), 148.6 (*Ph*C).

MS (EI, 70 eV, RT) *m/z* (%): 176 (M$^+$, 3), 107 (PhNHCH$_3$+, 45), 70 ($C_4H_8N^+$, 100).

$[\alpha]_D^{20}$ = 34.0 (c = 1.01, $CHCl_3$) (Lit.[33] $[\alpha]_D^{24}$ = 18.5 (c = 1.09, EtOH).



(*S*)-1,1-Dioxo-3a,4,5,6-tetrahydropyrrolo[1,2-*c*][1,2,3]oxathiazoline ((*S*)-256)[34]

1st step:

Imidazole (2.64 g, 40.0 mmol) was dissolved in CH_2Cl_2 (100 mL) and triethylamine (3.1 mL, 2.2 g, 22 mmol) was added, followed by (*S*)-prolinol (1.01 g, 10.0 mmol). The mixture was cooled to 0 °C and thionyl chloride (0.76 mL, 1.3 g, 11 mmol) was added dropwise. The reaction mixture was then allowed to warm to RT and was stirred for 16 h. Then, water (50 mL) was added, organic phase was separated and water phase was extracted with CH_2Cl_2 (2 × 20 mL). Collected organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude yellow oil (1.85g, 21:56:23 mixture of (*R,S*)/(*S,S*)-**255**/imidazole) was used in the next step.

2nd step: Method A:[34a]

The crude sulfamidite (*R,S*)/(*S,S*)-**255** (10 mmol) was dissolved in MeCN (60 mL) and cooled to 0 °C. Ruthenium trichloride monohydrate (22.5 mg, 100 μmol) and sodium metaiodate (3.21g, 15.0 mmol) were added, followed by water (50 mL). The heterogeneous mixture was stirred at RT for 16 h. Et_2O (60 mL) was added and organic phase was separated. Water phase was filtered and washed again with Et_2O (60 mL). Collected organic extracts were washed with $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. Recrystallization from Et_2O/pentane furnished product as light yellow solid (1.18 g, 72%, two steps).

Method B:[34b]

Sodium metaiodate (7.91 g, 37.0 mmol) was dissolved in H_2O (45 mL) and ruthenium oxide monohydrate (75.5 mg, 500 μmol) was added. The black suspension turned after few minutes to a green-yellow solution, which was cooled to 0 °C. Crude sulfamidite (*R,S*)/(*S,S*)-**255** (10.0 mmol) was added as a solution in EtOAc (35 mL). Two-phase system was stirred at 0 °C for 30 minutes (TLC control). The deep yellow organic phase was separated and the water phase was extracted with EtOAc (2×50 mL). Isopropanol (15 mL) was added to collected organic extracts, the black solid was filtered off, the filtrate was dried over $MgSO_4$ and concentrated in vacuo. Crude product was purified by filtration through a short column of silica (3 × 10 cm), with cyclohexane/ethyl acetate 90:10-60:40. Subsequent recrystallization from Et_2O afforded the product as colorless solid (1.54 g, 94%, two steps).

$C_5H_9NO_3S$ (163.19 g/mol)

R_f = 0.31 (SiO_2, EA/cyclohexane 40:60).

m.p. 47–48 °C (Lit. [34b] 47–48 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.77–1.85 (m, 1H, 4-H_A), 1.90–1.98 (m, 2H, 3-*H*), 2.13–2.21 (m, 1H, 4-H_B), 3.25 (dt, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, 5-H_A), 3.66 (dt, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 6.3 Hz, 1H, 5-H_B), 4.03 (dd, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.1Hz, 1H, CH_AH$_B$OSO$_2$), 4.23–4.29 (m, 1H, 2-*H*), 4.54 (dd, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8Hz, 1H, CH$_A$$H_BOSO_2$).

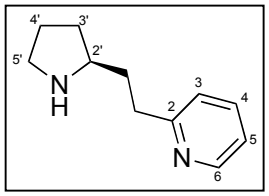
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 25.2 (*C*-4), 28.4 (C(*C*H$_3$)$_3$), 31.3 (*C*-3), 51.5 (*C*-5), 62.6 (*C*-2), 71.9 (*C*H$_2$OSO$_2$).

MS (EI, 70 eV, RT) *m/z* (%): 163 (M^+, 7), 133 ([M-OCH$_2$]$^+$, 16), 69 ($C_4H_7N^+$, 100), 41 (CH_3CN^+, 39).

IR (ATR): $\tilde{\nu}$ = 2997w; 2879w; 1708m; 1687m; 1582m; 1457w; 1333s (SO_2); 1197s; 1167s (SO_2); 1032m; 991m; 874w; 833w, 787s.

EA: calc. for $C_5H_9NO_3S$: C, 36.80; H, 5.56; N 8.58; O, 29.41; S, 19.65. Found: C, 36.96; H, 5.45; N, 8.54.

$[\alpha]_D^{20}$ = 40.3 (c = 0.95, $CHCl_3$) (Lit. [34b] $[\alpha]_D^{20}$ = 43.2 (c = 1.02, $CHCl_3$)).



(*S*)-2-(2-(Pyrrolidin-2-yl)ethyl)pyridine ((*S*)-251)[35]

To a solution of ^{i}Pr$_2$NH (0.22 mL, 0.16 g, 1.6 mmol) in dry THF (5 mL) was added *n*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.6 mmol) at -78 °C. 2-Methylpyridine (140 µL, 0.13 g, 1.4 mmol) was added dropwise. The mixture was allowed to warm to 0 °C and stirred for 1 h. The mixture was cooled again to -78 °C and sulfamidate **256** (0.80 g, 4.9 mmol) was added slowly as a solution in THF (6 mL). The mixture was allowed to reach RT and stirred overnight. The solvent was removed in vacuo and 2 N HCl (10 mL) und ethanol (10 mL) were added and heated to reflux for 1.5 h and stirred at room temperature for 5 d. Afterwards, 2 M NaOH (2 mL) was added and the mixture was extracted with DCM (5 × 20 mL). The collected organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. Crude product was purified by column chromatography (SiO_2, chloroform/*n*-propylamine (49:1)) to give the (*S*)-**251** as yellow oil (69 mg, 28 %).

$C_{11}H_{16}N_2$ (176,26 g/mol)

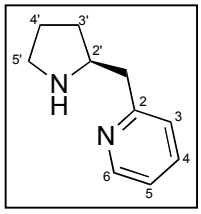
R_f = 0.25 (SiO_2, $CHCl_3$/*n*-propylamine 49:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 1.32–1.35 (m, 1H, 4'-H_A), 1.60–1.93 (m, 6H, 4'-H_B, 3'-*H*, N*H*, CH_2CH_2Ar), 2.73–2.91 (m, 3H, 2'-*H*, 5'-*H*), 2.92–3.07 (m, 2H, CH_2CH_2Ar), 7.05 (dd, $^3J_{HH}$ = 6.9 Hz and 5.1 Hz, 1H, 5-H), 7.12 (d, $^3J_{HH}$ = 7.7 Hz, 3-H), 7.57–7.47 (m, 1H, 4-H); 8.42-8.46 (m, 1H, 6-H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 25.4 (*C*-4'), 31.9 (*C*-3'), 36.1 and 36.2 (CH_2CH_2Ar), 46.5 (*C*-5'), 59.0 (*C*-2'), 121.2 and 122.6 (*C*-3, *C*-5), 136.6 (*C*-4), 149.2 (*C*-6), 161.9 (*C*-2).

MS (ESI, 30 V, 200 °C) *m/z* (%): 177 ($[M+H]^+$, 100).

$[\alpha]_D^{20}$ = -5.5 (c = 0.95, $CHCl_3$) (Lit. [35] $[\alpha]_D^{25}$ = -4.1 (c = 0.96, $CHCl_3$)).



(*S*)-2-(Pyrrolidin-2-ylmethyl)pyridine ((*S*)-263)[35]

n-BuLi (3.7 mL of 1.6 M solution in hexanes, 5.9 mmol) was added at -78 °C to solution of 2-bromopyridine (924 mg, 5.85 mmol) in dry THF (6 mL). The mixture was stirred at this temperature for 1 h. Then, sulfamidate (*S*)-**256** (734 mg, 4.50 mmol) was added as a solution in THF (6 mL). The mixture was allowed to warm to RT and stirred overnight. The solvent was removed and the orange solid residue was heated on reflux in a mixture of 2 N HCl (9 mL) and EtOH (9 mL) for 14 h. The reaction mixture was neutralized with 50% NaOH and extracted with DCM (4 × 30 mL). Collected organic extracts were dried over $MgSO_4$, the solvent was removed in vacuo and the crude product (orange oil) was purified by column chromatography (SiO_2, $CHCl_3$/ *n*-propylamine 49:1). (*S*)-**263** was obtained as yellow oil (277 mg, 38%).

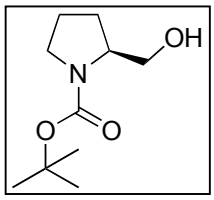
$C_{10}H_{14}N_2$ (162.23 g/mol)

R_f = 0.16 (SiO_2, $CHCl_3$/^{n}PrNH$_2$ 49:1).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.32–1.41 (m, 1H, 4'-H_A), 1.62–1.85 (m, 3H, 3'-*H*, 4'-H_B), 2.27 (br. s, 1H, N*H*), 2.75–2.99 (m, 4H, 5'-*H*, CH_2Ar), 3.37–3.44 (m, 1H, 2'-*H*), 7.02–7.05 (m, 1H, 5-*H*), 7.11 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.6 Hz, 1H, 3-*H*), 7.52 (dt, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, 4-*H*), 8.45 (dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, 6-*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 25.0 (*C*-3'), 31.4 (*C*-4'), 44.5 (*C*H$_2$Ar), 46.3 (*C*-5'), 58.9 (*C*-2'), 121.2 (*C*-5), 123.5 (*C*-3), 136.3 (*C*-4), 149.3 (*C*-6), 160.3 (*C*-2).

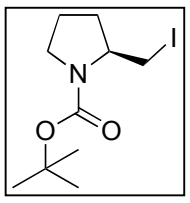
MS (FAB, NBA) *m/z* (%): 163 ([M+H]$^+$, 100), 94 ($ArCH_2^+$, 30), 70 ($C_4H_8N^+$, 26).
$[\alpha]_D^{20}$ = 13.7 (c = 1.03, $CHCl_3$) (Lit. [35] $[\alpha]_D^{24}$ = 15.5 (c = 0.90, MeOH).



(*S*)-*tert*-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate ((*S*)-328)[36]

(*S*)-*N*-Boc-Proline (1.72 g, 8.00 mmol) was dissolved in dry THF (12 mL) and $BH_3{\cdot}Me_2S$ (0.90 mL of 10 M solution in Me_2S, 9.0 mmol) was added via syringe during 15 minutes. The mixture was heated to reflux for 2 h and quenched with ice (ca 10 g). The organic material was extracted with DCM (2 × 30 mL), filtered over celite (3 × 1 cm) and the solvent was removed in vacuo. The product was purified by column chromatography (SiO_2, cyclohexane/EA 80:20). (*S*)-**328** was obtained as colorless solid (1.20 g, 75%).

$C_{10}H_{19}NO_3$ (201.26 g/mol)
R_f = 0.33 (silica, EA/cyclohexane 20:80).
m.p. 57–58 °C (Lit.[40] 60–62 °C).
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: (s, 9H, C(CH_3)$_3$), 1.50–1.54 (m, 1H, 3-H_A), 1.71–1.82 (m, 2H, 4-*H*), 1.94–2.02 (m, 1H, 3-H_B), 3.25–3.31 (m, 1H, 5-H_A), 3.39–3.45 (m, 1H, 5-H_B), 3.55–3.59 (m, 2H, CH_2OH), 3.91–3.95 (m_c, 1H, 2-*H*), 4.75 (bs, 1H, O*H*).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 24.2 (*C*-4), 28.6 (C(*C*H$_3$)$_3$), 28.8 (*C*-3), 47.6 (*C*-5), 60.3 (*C*-2), 67.7 (*C*H$_2$OH) 80.3 (*C*(CH$_3$)$_3$), 157.2 (*C*OO^{t}Bu).
MS (FAB, NBA) *m/z* (%): 202 (M+H$^+$, 48), 170 ([M-CH_2OH]$^+$, 12), 146 ([M-C_4H_9]$^+$, 100), 102 ([M-COO^{t}Bu]$^+$, 27), 57 ($C_4H_9^+$, 30).
$[\alpha]_D^{20}$ = - 49.7 (c = 1.06, $CHCl_3$) (Lit.[36] $[\alpha]_D^{24}$ = - 48.8 (c = 1.2, $CHCl_3$)).



(*S*)-2-*tert*-Butyl 2-(iodomethyl)pyrrolidine-1-carboxylic acid ((*S*)-260)[37]

General method XII:

Imidazole (749 mg, 11.0 mmol) and triphenylphosphine (2.16 g, 8.25 mmol) were dissolved in dry Et_2O under Ar and cooled to 0 °C. Iodine (2.09 g, 8.25 mmol) was added in 3 portions over 40 minutes and the brown mixture was stirred for additional 10 minutes. (*S*)-*N*-Boc-prolinol (1.11 g, 5.50 mmol) was added as a solution in Et_2O (6 mL) and DCM

(10 mL) was added. A yellow suspension was formed, which was stirred at room temperature overnight. The solid was filtered off, washed with Et_2O and the solvent was removed in vacuo. Crude product was purified by column chromatography (SiO_2, cyclohexane/EA 90:10) and recrystallization from pentane. (*S*)-**260** was obtained as colorless solid (1.65 g, 96%).

$C_{10}H_{18}INO_2$ (311.16 g/mol)

R_f = 0.61 (SiO_2, EA/cyclohexane 20:80).

m.p. 41–43 °C (Lit.[37] 38–41 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz, 295 K) δ/ppm: 1.46 (s, 9H, C(C*H*$_3$)$_3$), 1.78–2.04 (m, 4H, 3-*H*, 4-*H*), 3.11–3.50 (m, 4H, 5-*H*, C*H*$_2$I), 3.81-3.89 (m$_c$, 1H, 2-*H*).

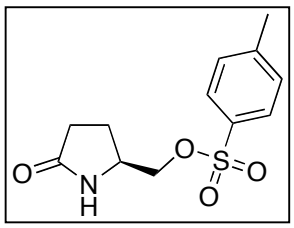
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 10.8 and 11.1 (*C*-3, rotamers), 22.9 and 23.6 (*C*-4, rotamers), 28.6 (C(*C*H$_3$)$_3$), 31.2 and 31.7 (*C*H$_2$I, rotamers), 47.2 and 47.6 (*C*-5, rotamers), 58.0 and 58.3 (*C*-2, rotamers), 79.7 and 80.0 (*C*(CH$_3$)$_3$, rotamers), 154.2 and 154.5 (*C*O*O*^{t}Bu, rotamers).

MS (FAB, NBA) *m/z* (%): 312 ($M+H^+$, 25), 256 ($[M-C_4H_7]^+$, 100), 238 ($[M-O^tBu]^+$, 11), 128 (HI^+, 19), 57 ($C_4H_9^+$, 42).

IR (ATR): $\tilde{\nu}$ = 2972m; 2868w; 1678s (C=O); 1391s; 1364s; 1306w; 1165s; 1111s; 918m; 766s.

EA: calc. for $C_{10}H_{18}INO_2$: C, 38.60; H, 5.83; I, 40.78; N, 4.50; O, 10.28. Found: C, 38.81; H, 5.67; N, 4.49.

$[\alpha]_D^{20}$ = - 35.5 (c = 0.99, $CHCl_3$) (Lit.[37] $[\alpha]_D^{20}$ = - 33.1 (c = 0.98, $CHCl_3$)).



(*S*)-(5-Oxopyrrolidin-2-yl)methyl *p*-toluenesulfonate ((*S*)-278)[38]

(*S*)-Pyroglutaminol (2.44 g, 21.2 mmol) was suspended in DCM (15 mL), triethylamine (5.0 mL, 3.6 g, 36 mmol) and DMAP (77.7 mg, 0.636 mmol) were added and the suspension was cooled to 0 °C. TsCl (3.98 g, 23.3 mmol) was added and the mixture was stirred at RT for 16 h. The reaction mixture was washed with 2 M HCl (2 × 15 mL), H_2O (15 mL), sat. $NaHCO_3$ (2 × 15 mL), brine (15 mL), the organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. Crude product was purified by recrystallization from EA/hexane to give (*S*)-**278** as colorless solid (4.71 g, 83%).

$C_{12}H_{15}NO_4S$ (269.32 g/mol)

$\boldsymbol{R_f}$ = 0.13 (SiO_2, EA).

m.p. 125–126 °C (Lit.[38] 125–126 °C)

^{1}H-NMR ($CDCl_3$, 500 MHz) δ/ppm: 1.72–1.80 (m, 1H, 4-H_A), 2.17–2.25 (m, 1H, 4-H_B), 2.27–2.35 (m, 2H, 3-*H*), 2.43 (s, 3H, CH_3), 3.85–3.92 (m, 2H, 5-*H*, CH_AH$_B$OTs), 4.01 (dd, $^2J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, CH$_A$$H_B$OTs), 6.56 (bs, 1H, N*H*), 7.34 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar*H*), 7.77 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar*H*).

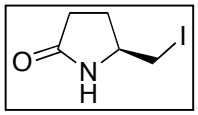
^{13}C{^{1}H}-NMR ($CDCl_3$, 126 MHz) δ/ppm: 21.7 (*C*H$_3$), 22.9 (*C*-4), 29.4 (*C*-3), 52.7 (*C*-5), 72.0 (*C*H$_2$OTs), 128.0 (*Ar*H), 130.1 (*Ar*H), 132.4 (*Ar*C), 145.4 (*Ar*S), 178.0 (*C*=O).

MS (FAB, NBA) *m/z* (%): 270 ($M+H^+$, 100), 98 ([M-OTs]$^+$, 21).

IR (ATR): $\tilde{\nu}$ = 3290m (NH); 1697s (C=O); 1647m; 1463w; 1352m (SO_2); 1165s (SO_2); 943s; 877s; 817s (Ar).

EA: calc. for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; O, 23.76; S, 11.91. Found: C, 53.13; H, 5.58; N, 5.22.

$[\alpha]_D^{20}$ = 20.5 (c = 1.01, $CHCl_3$) (Lit. [38] $[\alpha]_D^{25}$ = 20.4 (c = 1.05, $CHCl_3$)).



(*S*)-5-(Iodomethyl)pyrrolidin-2-one ((*S*)-279)

Method A:[39]

Tosylate (*S*)-**278** (4.71 g, 17.5 mmol) and NaI (7.86 g, 52.5 mmol) were dissolved in acetone (50 mL, HPLC quality) and heated to reflux on air for 6 h. The solvent was removed, water (30 mL) was added and the mixture was extracted with DCM (4 × 30 mL). Collected organic extracts were dried over $MgSO_4$, the solvent was removed in vacuo and the residue recrystallized from acetone/pentane. The product was obtained as off-white solid (3.28 g, 83%).

Method B: By general method **XII** (*S*)-pyroglutaminol (1.15 g, 10.0 mmol), iodine (3.81 g, 15.0 mmol), imidazole (1.36 g, 20.0 mmol) and triphenylphosphine (3.93 g, 15.0 mmol) gave the crude product, which was purified by column chromatography (SiO_2, EA/MeOH 10:0-10:1) and recrystallization from acetone/pentane. (*S*)-**279** was obtained as colorless solid (1.79g, 80%).

C_5H_8INO (225.03 g/mol)

$\boldsymbol{R_f}$ = 0.60 (SiO_2, EA/MeOH 10:1).

m.p. 83–84 °C (Lit.[39] 78 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.76–1.86 (m, 1H, 4-H_A), 2.26–2.50 (m, 3H, 3-*H*, 4-H_B), 3.20 (d, $^3J_{HH}$ = 5.8 Hz, 2H, CH_2I), 3.79–3.85 (m, 1H, 5-*H*), 7.12 (bs, 1H, N*H*).

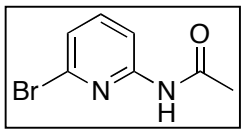
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 11.5 (*C*H_2I), 27.5 (*C*-4), 30.4 (*C*-3), 55.3 (*C*-5), 178.2 (*C*=O).

MS (EI, 70 eV, 150 °C) *m/z* (%): 225 (M^+, 2), 98 ([M-I]$^+$, 10), 84 ([M-CH_2I]$^+$, 100).

IR (ATR): $\tilde{\nu}$ = 3171w (NH); 3091w (NH); 1682s (C=O); 1666s; 1411m; 1296m; 1272s; 1202m; 980w; 950w; 764m; 663m.

EA: calc. for C_5H_8INO: C, 26.69; H, 3.58; N, 6.22; O, 56.40; O, 7.11. Found: C, 26.56; H, 3.46; N, 6.24.

$[\alpha]_D^{20}$ = -20.1 (c = 1.13, $CHCl_3$) (Lit. [39] $[\alpha]_D^{20}$ = 11.6 (c = 1.08, $CHCl_3$)).



***N*-[6-Bromo(pyridin-2-yl)]acetamide (259a)[40]**

2-Amino-6-bromopyridine (1.00 g, 5.78 mmol) was dissolved in THF (5 mL) and Et_3N (1.2 mL, 0.89 g, 8.8 mmol) was added. The mixture was cooled to 0 °C and acetyl chloride (1.0 mL, 14 mmol) was added as a solution in THF (0.5 mL). The mixture was allowed to reach room temperature and stirred for 16 h. Water (30 mL) was added, the product was filtered and dried on high vacuum (colorless solid, 1.08 g, 87%). An analytical sample was obtained after recrystallization from Et_2O.

$C_7H_7BrN_2O$ (215.05 g/mol)

$\boldsymbol{R_f}$ = 0.60 (silica, MeOH/CH_2Cl_2 10:90)

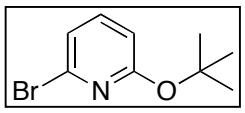
m.p. 155–156 °C (Lit.[40] 157 °C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.19 (s, 3H, CH_3), 7.18 (d, $^3J_{HH}$ = 7.8 Hz, 1H, 5-*H*), 7.53 (t, $^3J_{HH}$ = 6.6 Hz, 1H, 4–*H*), 8.15 (d, $^3J_{HH}$ = 8.1 Hz, 1H, 3-*H*), 8.25 (br s, 1H, N*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 24.7 (*C*H_3), 112.4 (*C*-3), 123.6 (*C*-5), 139.2 (*C*-6), 140.8 (*C*-4), 151.5 (*C*-2), 168.9 (*C*=O).

MS (EI, 70 eV, 150 °C) *m/z* (%): 216 (M^+, 18), 214 (M^+, 18), 174 ([M-C_2H_2O]$^+$, 97), 172 ([M-C_2H_2O]$^+$, 100), 93 ([M-C_2H_2O-Br]$^+$, 82), 43 ($C_2H_3O^+$, 36).

EA: calc. for $C_7H_7BrN_2O$: C, 39.10; H, 3.28; N, 13.03; Br, 37.16; O, 7.44. Found: C, 38.92; H, 3.19; N, 12.86.



2-Bromo-6-*tert*-Butyloxypyridine (259d)[41]

2,6-Dibromopyridine (2.00 g, 8.44 mmol) was dissolved in toluene (20 mL) and KO^{t}Bu (1.14 g, 10.1 mmol) was added. The mixture was heated to 80 °C for 6 h. The solid by-products were filtered and washed with ethyl acetate. The solvent was removed in vacuo and the crude product was purified by bulb-to-bulb distillation (70–80 °C at 0.4 mbar). The product was obtained as colorless liquid (1.66 g, 85 %).

$C_9H_{12}BrNO$ (230.10 g/mol)

R_f = 0.85 (silica, cyclohexane/EA 90:10).

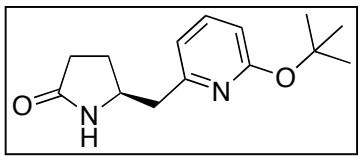
b.p. 70–80 °C (0.4 mbar).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.58 (s, 8H, C(CH_3)$_3$), 6.56 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 0.5 Hz, 1H, 5–*H*), 6.97 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.5 Hz, 1H, 3–*H*), 7.33 (dd, $^3J_{HH}$ = 7.6 and 8.1 Hz, 1H, 4-*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 28.5 (C(*C*H_3)$_3$), 81.0 (*C*(CH$_3$)$_3$), 111.6 (*C*-3), 119.6 (*C*-5), 137.7 (*C*-6), 140.1 (*C*-4), 163.1 (*C*-2).

MS (EI, 70 eV, RT) *m/z* (%): 231 (M^+, 2), 229 (M^+, 2), 175 ([M-^{t}Bu]$^+$, 96), 173 ([M- ^{t}Bu]$^+$, 96), 94 ([M- ^{t}Bu -Br]$^+$, 82), 199 ($C_4H_9^+$, 34).

EA: calc. for $C_9H_{12}BrNO$: C, 46.98; H, 5.26; N, 6.09. Found: C, 46.88; H, 5.16; N, 6.05.



(*S*)-5-[(6-(*tert*-Butyloxy)pyridin-2-yl)methyl]-pyrrolidin-2-one ((*S*)-284)

Zinc powder (843 mg, 12.9 mmol) was put into a Schlenk tube, which was heated with a heating gun and evacuated on high vacuum three times. DMF (3 mL) and TMSCl (36 µL, 32 mg, 0.26 mmol) were added and the suspension was stirred 30 minutes. The mixture was cooled to 0 °C and iodide (*S*)-**279** (968 mg, 4.30 mmol) was slowly added as a solution in DMF (3 mL). After approximately 4 hours, the formation of the zinc reagent was completed (TLC control). The excess zinc was allowed to settle and the solution was transferred via cannula to another dry Schlenk tube. Zinc was washed with DMF (1 mL). $Pd(PPh_3)_2Cl_2$

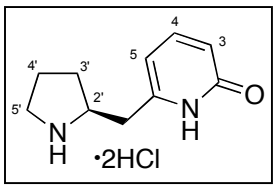
(150 mg, 214 µmol) was added, followed by bromide **259d** (1.31 g, 5.70 mmol). The mixture was stirred at RT overnight, EtOAc (100 mL) was added. The organic phase was washed with brine (50 mL), dried over $MgSO_4$ and concentrated. The resulting orange oil was purified by column chromatography (SiO_2, EA/MeOH 10:0–10:1). The product was obtained as colorless oil as a mixture with the elimination product **282** and DMF (379 mg, 68% purity, 21% yield). This mixture was directly used in the next step.

$C_{14}H_{20}N_2O_2$ (248.32 g/mol)

$\boldsymbol{R_f}$ = 0.31 (SiO_2, EA).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.57 (s, 9H, C(C*H*$_3$)$_3$), 1.82–1.92 (m, 1H, 4-*H*$_A$), 2.27–2.40 (m, 3H, 3-*H*, 4-*H*$_B$), 2.76–2.95 (m, 2H, C*H*$_2$Ar), 4.08–4.17 (m, 1H, 5-*H*), 5.98 (bs, 1H, N*H*), 6.52 (d, $^3J_{HH}$ = 8.3 Hz, 1H, ArH), 6.66 (d, $^3J_{HH}$ = 7.2 Hz, 1H, ArH), 7.45 (t, $^3J_{HH}$ = 7.7 Hz, 1H, 4'-*H*).

MS (ESI, 30 kV, 200 °C) *m/z* (%): 271 ($M+Na^+$, 18), 193 ($[M-C_4H_7]^+$, 100).



(*S*)-6-[(Pyrrolidin-2-yl)methyl]pyridin-2(1H)-one dihydrochloride ((*S*)-290)

$LiAlH_4$ (2.0 mL of 1M solution in THF) was slowly added to a solution of (*S*)-**284** (370 mg, 68% purity, 1.01 mmol) in THF (1 mL) at 0 °C. The mixture was heated to reflux for 1.5 h, $Na_2SO_4 \times 10H_2O$ was added and the mixture was stirred for 1 h at RT. The grey solid was filtered, washed with Et_2O (20 mL) and the filtrate was concentrated in vacuo. The resulting orange oil was purified by bulb-to-bulb distillation (110-120 °C at 0.08 mbar) to give colorless oil, which was dissolved in Et_2O (2 mL). HCl (2 M solution in Et_2O, ca 1 mL) was added dropwise, until no more precipitate was formed. The solvent was removed and residue was recrystallized from Et_2O/MeOH to give the pure salt (*S*)-**290** as colorless solid (148 mg, 58% in two steps).

$C_{10}H_{16}Cl_2N_2O$ (251.15 g/mol; 178.23 g/mol + HCl)

m.p. 220 °C (decomp.).

^{1}H-NMR (d_4-MeOD, 500 MHz) δ/ppm: 1.80–1.88 (m, 1H, 3'-*H*$_A$), 2.03–2.12 (m, 1H, 4'-*H*$_A$), 2.14–2.22 (m, 1H, 4'-*H*$_B$), 2.24–2.30 (m, 1H, 3'-*H*$_B$), 3.25–3.37 (m, 3H, C*H*$_2$Ar, 5'-*H*$_A$), 3.40–3.46 (m, 1H, 5'-*H*$_B$), 3.91–3.97 (m, 1H, 2'-*H*), 7.05 (d, $^3J_{HH}$ = 8.8 Hz, 1H, 3–*H*), 7.18 (d,

$^3J_{HH}$ = 7.3 Hz, 1H, 5-*H*), 8.14 (t, $^3J_{HH}$ = 8.1 Hz, 1H, 4-*H*).

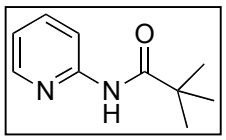
^{13}C{^{1}H}-NMR ((d$_4$-MeOD, 126 MHz) δ/ppm: 24.2 (*C*-4'), 31.0 (*C*-3'), 35.6 (*C*H$_2$Pyr), 46.6 (*C*-5'), 60.2 (*C*-2'), 114.7 (*C*-3), 116.3 (*C*-5), 148.2 (*C*-4), 148.5 (*C*-6), 163.8 (*C*=O).

MS (ESI, 30 kV, 200 °C) *m/z* (%): 357 (2M+H$^+$, 36), 179 (M+H$^+$, 100).

IR (ATR): $\tilde{\nu}$ = 2921m; 2579br s; 2435br s; 1644m; 1623m; 1541m; 1444w; 1388s; 1333s; 1166m; 1038m; 1002s; 944m; 828s; 811s; 758m; 731m.

EA: calc. for $C_{10}H_{16}Cl_2N_2O$: C, 47.82; H, 6.42; N, 11.15; Cl, 28.23; O, 6.37. Found: C, 47.79; H, 6.56; N, 10.95.

$[\alpha]_D^{20}$ = 66.3 (c = 0.50, MeOH).



N-(Pyridin-2-yl)pivalamide (236)[42]

A solution of 2-aminopyridine (0.941 g, 10.0 mmol) and triethylamine (1.7 mL, 1.2 g, 12 mmol) in dichloromethane (15 mL) was cooled to 0 °C. Pivaloylchloride (1.35 mL, 1.33 g, 11.0 mmol) in dichloromethane (2 mL) was added dropwise and the solution was stirred at 0 °C for 15 minutes and at RT for 2 h. The crude reaction mixture was poured into water (20 mL), the organic phase was separated, washed with sat. $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product (colorless oil which solidified on standing) was recrystallized from hexane. **236** was obtained as colorless solid (1.58 g, 89%).

$C_{10}H_{14}N_2O$ (178.23 g/mol)

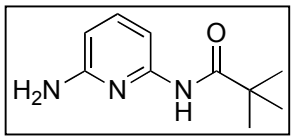
R$_f$ = 0.43 (SiO_2, EA/cyclohexane 30:70).

m.p. 61–63 °C (Lit.[46] 71–73 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.28 (s, 9H, C(C*H*$_3$)$_3$), 6.97–7.00 (m, 1H, 5-*H*), 7.63–7.67 (m, 1H, 4-*H*), 8.02 (bs, 1H, N*H*), 8.19–8.22 (m, 2H, 3-*H*, 6-*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 27.5 (C(*C*H$_3$)$_3$), 39.8 (*C*(CH$_3$)$_3$), 114.0 (*C*-3), 119.8 (*C*-5), 138.4 (*C*-4), 147.7 (*C*-6), 151.6 (*C*-2), 177.1 (*C*=O).

MS (EI, 70 eV, RT) *m/z* (%): 178 (M$^+$, 44), 121 ([M-C$_4$H$_9$]$^+$, 20), 94 ([M-CO^{t}Bu]$^+$, 100), 78 (C$_5$H$_4$N$^+$, 22), 57 (C$_4$H$_9^+$, 78).



_N_-(6-Aminopyridin-2-yl)pivalamide (240)[43]

2,6-Diaminopyridine (2.18 g, 20.0 mmol) was suspended in dioxane (10 mL). Pivaloyl chloride (1.2 mL, 1.2 g, 9.8 mmol) in dioxane (2 mL) was slowly added during 2 h. The mixture was stirred at RT for additional 2 h, the oily solid was filtered and the filtrate was concentrated to give dark yellow oil, which solidified on standing. Crude product was purified by column chromatography (SiO_2, cyclohexane/EA 80:20) to give the product as off-white solid (650 mg, 34%).

$C_{10}H_{15}N_3O$ (193.25 g/mol)

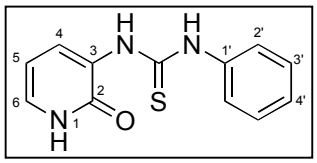
$\boldsymbol{R_f}$ = 0.70 (SiO_2, EA/cyclohexane 10:90, 254 nm)

m.p. 116–119 °C (Lit.[43] 146–148 °C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.28 (s, 9H, C(CH_3)$_3$), 4.52 (s, 2H, NH_2), 6.22 (d, $^3J_{HH}$ = 8.1 Hz, 1H, 5-*H*), 7.42 (t, $^3J_{HH}$ = 8.1 Hz, 1H, 4-*H*), 7.55 (d, $^3J_{HH}$ = 7.8 Hz, 1H, 3-*H*), 7.84 (s, 1H, N*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 27.5 (C(CH_3)$_3$), 39.9 (*C*(CH_3)$_3$), 103.2 (*C*-5), 104.4 (*C*-3), 140.5 (*C*-4), 149.9 (*C*-2), 157.1 (*C*-6), 177.0 (*C*=O).

MS (EI, 70 eV, 50 °C) *m/z* (%): 193 (M^+, 91), 136 ([M-C_4H_9]$^+$, 27), 109 ([M-CO^{t}Bu]$^+$, 100), 93 ([M-NHCO^{t}Bu]$^+$, 16), 57 ($C_4H_9^+$, 52).



1-(2-Oxo-1,2-dihydropyridin-3-yl)-3-phenylthiourea (238a)[44]

General method XIII:

2-Hydroxy-3-aminopyridine (500 mg, 4.54 mmol) was dissolved in dry methanol (50 mL) under Ar and phenyl thioisocyanate (0.54 mL, 0.61 g, 4.5 mmol) was added via syringe. The mixture was stirred at RT for 24 h. The precipitate was filtered, washed with Et_2O and the light brown solid was dried at high vacuum (693 mg, 62%).

$C_{12}H_{11}N_3OS$ (245.30 g/mol)

$\boldsymbol{R_f}$ = 0.60 (SiO_2, MeOH/CH_2Cl_2 10:90).

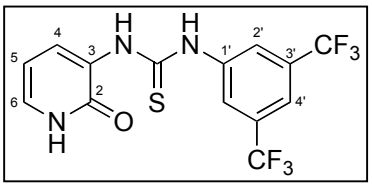
m.p. 243–245 °C (Lit.[44] 243–244 °C).

^{1}H-NMR (DMSO, 400 MHz) δ/ppm: 6.26 (t, $^3J_{HH}$ = 7.1 Hz, 1H, 5-*H*), 7.12 (dd, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, 6–*H*), 7.16 (t, $^3J_{HH}$ = 7.4 Hz, 1H, 4'-*H*), 7.36 (t,

$^{3}J_{HH}$ = 7.6 Hz, 2H, 3'-*H*), 7.54 (d, $^{3}J_{HH}$ = 7.8 Hz, 2H, 2'-*H*), 8.95 (dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.8 Hz, 1H, 4-*H*), 9.49 (s, 1H, N*H*), 10.61 (s, 1H, N*H*), 12.03 (br. s, 1H, O*H*).

^{13}C{^{1}H}-NMR (DMSO, 101 MHz) δ/ppm: 105.0 (*C*-5), 123.7 (3C, *Ph*H), 124.9 (*C*-4), 127.6 (*C*-6), 128.6 (2C, *Ph*H), 130.0 (*Ph*NH), 138.8 (*C*-3), 158.0 (*C*-2), 177.6 (*C*=S).

MS (EI, 70 eV, 250 °C) *m/z* (%): 245 (M^+, 22), 211 ($[M-SH_2]^+$, 20), 152 ($PhNH(C{=}S)NH_2^+$, 68), 135 ($PhNH(C{=}S)^+$, 95), 93 ($C_5H_3NO^+$, 100), 77 ($C_6H_5^+$, 58).



1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-oxo-1,2-dihydropyridin-3-yl)thiourea (238b)

By general method **XIII**, 2-Hydroxy-3-aminopyridine (100 mg, 0.908 mmol) and 3,5-bis(trifluoromethyl)phenyl thioisocyanate (0.17 mL, 0.25 g, 0.93 mmol) in 24 h gave crude product, which was purified by column chromatography (SiO_2, EA). The product was obtained as light brown solid (210 mg, 61%).

$C_{14}H_9F_6N_3OS$ (381.30 g/mol)

R_f = 0.52 (SiO_2, ethyl acetate).

m.p. >250 °C (decomposition).

^{1}H-NMR (DMSO, 500 MHz) δ/ppm: 6.28 (t, $^{3}J_{HH}$ = 6.6 Hz, 1H, 5-*H*), 7.19 (dd, $^{3}J_{HH}$ = 6.3 Hz, $^{4}J_{HH}$ = 1.5 Hz, 1H, 6-*H*), 7.80 (s, 1H, 4'-*H*), 8.36 (s, 2H, 2'-*H*), 8.82 (d, $^{3}J_{HH}$ = 6.3 Hz, 1H, 4-*H*), 9.79 (s, 1H, N*H*CS), 11.17 (s, 1H, N*H*CS), 12.03 (br. s, 1H, N*H*CO).

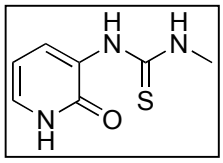
^{13}C{^{1}H}-NMR (DMSO, 126 MHz) δ/ppm: 105.0 (*C*-5), 117.0 (*C*-4'), 122.7 (*C*-2'), 123.2 (q, $^{1}J_{CF}$ = 271 Hz, *C*F_3), 125.1 (*C*-4), 128.7 (*C*-3), 129.5 (*C*-6), 130.2 (q, $^{2}J_{CF}$ = 33 Hz, *C*-3'), 141.3 (*C*-1'), 158.1 (*C*-2), 177.6 (*C*=S).

^{19}F-NMR (DMSO, 376 MHz) δ/ppm: -62.77 (CF_3).

MS (EI, 70 eV, 250 °C) *m/z* (%): 381 (M^+, 3), 347 ($[M-SH_2]^+$, 100), 271($ArNH(C{=}S)^+$, 85), 229 ($ArNH_2^+$, 35), 213 ($C_8H_3F_6^+$, 25), 110 ($C_5H_4NONH_2^+$, 58).

IR (ATR): $\tilde{\nu}$ = 3306m; 3128w; 1670m (C=O); 1600m; 1543m; 1497m; 1431s; 1385s; 1260s; 1172s; 1049s; 887s; 679s.

EA: calc. for $C_{14}H_9F_6N_3OS$: C, 44.10; H, 2.38; N 11.02; O, 4.20; F, 29.90; S, 8.41. Found: C, 44.30; H, 2.52; N, 10.99.



1-Methyl-3-(2-oxo-1,2-dihydropyridin-3-yl)thiourea (238c)

By general method **XIII**, (200 mg, 1.82 mmol) and methyl thioisocyanate (133 mg, 1.82 mmol) in 72 h gave product, which was filtered and washed with Et_2O (2 mL). The product was obtained as light brown solid (66 mg, 20%).

$C_7H_9N_3OS$ (183.23 g/mol)

$\boldsymbol{R_f}$ = 0.24 (SiO_2, EA).

m.p. 233–235 °C.

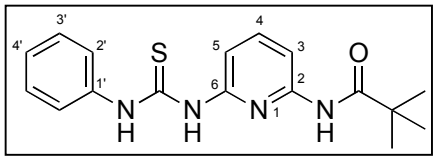
^{1}H-NMR (DMSO, 400 MHz) δ/ppm: 2.89 (s, 3H, C*H*$_3$), 6.21 (t, $^3J_{HH}$ = 6.8 Hz, 1H, 5-*H*), 7.06 (d, $^3J_{HH}$ = 5.6 Hz, 1H, 6-*H*), 8.72 (s, 1H, N*H*CS), 8.82 (d, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, 4-*H*), 9.19 (s, 1H, N*H*CS), 11.93 (s, 1H, N*H*CO).

^{13}C{^{1}H}-NMR (DMSO, 101 MHz) δ/ppm: 30.5 (*C*H$_3$), 105.0 (*C*-5), 122.8 (*C*-4), 126.8 (*C*-6), 130.4 (*C*-3), 158.0 (*C*-2), 180.4 (*C*=S).

MS (EI, 70 eV, 250 °C) *m/z* (%): 183 (M^+, 59), 152 ([M-NHMe]$^+$, 38), 110 ([M-(C=S)NHMe]$^+$, 100), 74 (MeNH(C=S)$^+$, 23).

IR (ATR): $\tilde{\nu}$ = 3259m; 3070w; 1635s ; 1550s; 1408m; 1431s; 1339s; 1234m; 1137m; 1049m; 902m, 806m; 725s; 698s.

EA: calc. for $C_7H_9N_3OS$: C, 45.89; H, 4.95; N 22.93; O, 8.73; S, 17.50. Found: C, 45.88; H, 5.00; N, 23.05.



***N*-(6-(3-Phenylthioureido)pyridin-2-yl)-pivalamide (241)**

By general method **XIII** 6-Amino-2-(pivaloylamino)-pyridine (193 mg, 1.00 mmol) and phenylthioisocyanate (0.24 mL, 0.27 g, 2.0 mmol), which was added twice (after 24 h). Only a small amount of product precipitated out of the reaction mixture after 48 h and due to TLC, the reaction was not completed. The precipitate (54 mg) was filtered and the filtrate was concentrated. Dichloromethane (2 mL) was added to the yellow residue and the unsolved solid was filtered off (36 mg). **241** was obtained as colorless solid (90 mg, 27%).

$C_{17}H_{20}N_4OS$ (328.43 g/mol)

$\mathbf{R_f}$ = 0.39 (SiO_2, cyclohexane/ethyl acetate 70:30, 254 nm).

m.p. 213–215 °C.

^{1}H-NMR (DMSO, 500 MHz) δ/ppm: 1.22 (s, 9H, C(C*H*$_3$)$_3$), 6.91 (d, $^3J_{HH}$ = 8.1 Hz, 1H, 5-*H*), 7.20 (t, $^3J_{HH}$ = 7.6 Hz, 1H, 4'-*H*), 7.29 (d, $^3J_{HH}$ = 8.1 Hz, 1H, 3-*H*), 7.37 (t, $^3J_{HH}$ = 7.8 Hz, 2H, 3'-*H*), 7.69 (d, $^3J_{HH}$ = 7.6 Hz, 2H, 2'-*H*), 7.76 (t, $^3J_{HH}$ = 8.1 Hz, 1H, 4–*H*), 9.79 (s, 1H, N*H*CS), 10.76 (s, 1H, N*H*CS), 13.24 (s, 1H, N*H*Piv).

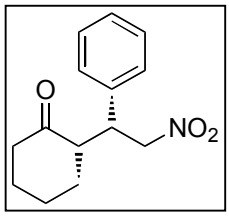
^{13}C{^{1}H}-NMR (DMSO, 126 MHz) δ/ppm: 26.9 (C(*C*H$_3$)$_3$), 107.1 (*C*-5), 107.8 (*C*-3), 125.3 (*C*-2'), 125.4 (*C*-4'), 128.0 (*C*-3'), 139.4 (*C*-4), 140.5 (*C*-1'), 149.0 (*C*-2), 151.4 (*C*-6), 176.6 (*C*=O), 178.1 (*C*=S).

MS (EI, 70 eV, 150 °C) *m/z* (%): 328 (M^+, 73), 294 ([M-SH_2]$^+$, 8), 236 ([M-PhNH]$^+$, 34), 193 ([M-PhNHCS]$^+$, 89), 151 (PhNH(C=S)NH^+, 41), 109 ($C_5H_3N(NH_2)_2^+$, 51), 57 ($C_4H_9^+$, 100).

IR (ATR): $\tilde{\nu}$ = 3375m; 3234m; 2966m; 1674s (C=O); 1618m; 1516s; 1435s; 1259s; 1186m; 995m; 791s; 764s; 688s.

EA: calc. for $C_{17}H_{20}N_4OS$: C, 62.17; H, 6.14; N, 17.06; O, 4.87; S, 9.76. Found: C, 62.20; H, 5.93; N, 16.91.

5.4.2 Organocatalyzed Reactions



(*S*)-2-((*R*)- 2-Nitro-1-phenylethyl)cyclohexanone ((2*S*,1'*R*)-210a)

General method XIV:

Catalyst (25 μmol)[2] and additives (different amounts, see Tables 3.1, 3.4, 3.7, Chapter 3) were dissolved in the solvent (see Table 3.3, Chapter 3) and stirred for 15 min. Cyclohexanone (124 μL, 118 mg, 1.20 mmol) and *β*-nitrostyrene (37.3 mg, 0.250 mmol) were added and the mixture was stirred at RT and monitored by TLC or NMR. The work up was dependent on the solvent used.

Halogenated solvents: water (1 mL) was added to the reaction mixture and organic phase was separated with Whatman 1PS phase separator (high-grade filter paper impregnated with a stabilized silicone, ∅ 7 cm). The aqueous layer was washed with the solvent (3 × 1–2 mL) and collected organic extracts were concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, cyclohexane/EA 90:10). Product was obtained as colorless solid. An analytical sample was obtained by recrystallization from Et_2O.

[2] In the runs with catalyst (*S*)-**290** the HCl was removed with VariPure™.

Neat: dichloromethane (1 mL) and water (1 mL) were added to reaction mixture and the procedure for halogenated solvents was followed.

Non-halogenated solvents: water (1 mL) was added to the reaction mixture and the organic phase was separated with Pasteur pipette. The aqueous layer was washed with ethyl acetate (3 × 1–2 mL), the collected organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Product was purified by column chromatography (SiO_2, cyclohexane/EA 90:10).

$C_{14}H_{17}NO_3$ (247.29 g/mol)

$\boldsymbol{R_f}$ = 0.33 (SiO_2, EA/cyclohexane 20:80).

m.p. 131–132 °C (99% *ee*) (Lit.[45] 133–135 °C, MeOH).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.18–1.29 (m, 1H, CH_2), 1.51–1.81 (m, 4H, CH_2), 2.04–2.12 (m, 1H, CH_2), 2.34–2.43 (m, 1H, CH_AH$_B$CO), 2.45–2.52 (m, 1H, CH$_A$$H_B$CO), 2.68 (dt, $^3J_{HH}$ = 5.0 Hz and 11.8 Hz, 1H, C*H*CO), 3.76 (dt, $^3J_{HH}$ = 4.6 Hz and 10.1 Hz, 1H, C*H*Ph), 4.63 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 9.8 Hz, 1H, CH_AH$_B$NO$_2$), 4.94 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, CH$_A$$H_BNO_2$), 7.15–7.18 (m, 2H, Ph*H*), 7.24–7.32 (m, 3H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 25.1 (*C*H$_2$), 28.6 (*C*H$_2$), 33.3 (*C*H$_2$), 42.8 (*C*H$_2$C=O), 44.0 (*C*HC=O), 52.6 (*C*HPh), 79.0 (*C*H$_2$NO$_2$), 127.8 (*Ph*H), 128.3 (*Ph*H), 129.0 (*Ph*H), 137.9 (*Ph*C), 212.1 (*C*=O).

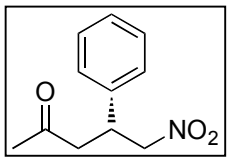
MS (FAB, NBA) *m/z* (%): 248 ([M+H]$^+$, 100), 201 ([M-NO$_2$]$^+$, 78), 137 (44), 91 ($C_7H_7^+$, 41).

IR (ATR): $\tilde{\nu}$ = 2954w; 2874w; 1693s (C=O); 1550s (NO$_2$); 1385m; 1130m; 1010w; 744m (Ar); 604m (Ar).

EA: calc. for $C_{23}H_{23}NO$: C, 68.00; H, 6.93; N, 5.66; O 19.41. Found: C, 67.79; H, 6.99; N, 5.59.

$[\alpha]_D^{20}$ = -27.9 (c = 0.75, $CHCl_3$, 99% *ee*) (Lit.[45] $[\alpha]_D^{20}$ = -27.9 (c = 1.00, $CHCl_3$).

HPLC: Chiralcel AS-H, heptane/isopropanol 70:30, 20 °C, 5 µL, 0.7 mL/min, 210 nm, t_R = 13.4 min (minor), t_R = 19.6 min (major).



(*R*)-5-Nitro-4-phenyl-pentan-2-one ((*R*)-211a)

By general method **XIV** *β*-nitrostyrene (37.3 mg, 250 µmol), acetone (88 µL, 70 mg, 1.2 mmol) in toluene (0.5 mL) in the presence of catalyst (*S*)-**248** (4.43 mg, 25.0 µmol) and benzoic acid (3.05 mg, 25.0 µmol) gave the crude product in 16 h. Product

was purified by column chromatography (SiO_2, cyclohexane/EA 90:10) and was obtained as colorless solid (>99% conv., 48 mg, 93% yield, 41% *ee*).

$C_{11}H_{13}NO_3$ (207.23 g/mol)

$\boldsymbol{R_f}$ = 0.25 (SiO_2, EA/cyclohexane 20:80).

m.p. 93–94 °C (Lit.[46] 97–98 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.10 (s, 3H, CH_3), 2.91 (d, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2CO), 4.00 (quint, $^3J_{HH}$ = 7.0 Hz, 1H, C*H*), 4.59 (dd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, CH_AH$_B$NO$_2$), 4.69 (dd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH$_A$$H_BNO_2$), 7.20–7.34 (m, 5H, Ph*H*).

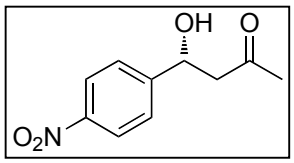
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 30.5 (*C*H$_3$), 39.1 (*C*H), 46.2 (*C*H$_2$CO), 79.6 (*C*H$_2$NO$_2$), 127.5 (*Ph*H), 128.0 (*Ph*H), 129.2 (*Ph*H), 138.9 (*Ph*C), 205.5 (*C*=O).

MS (FAB, NBA) *m/z* (%): 208 ([M+H]$^+$, 100), 161 ([M-NO$_2$]$^+$, 66), 43 ($C_2H_3O^+$, 83).

IR (ATR): $\tilde{\nu}$ = 2999w; 1713s (C=O); 1545s (NO$_2$); 1439m; 1359m; 1325w; 1202w; 1161w; 916w; 758s (Ar); 696s (Ar).

$[\alpha]_D^{20}$ = -1.5 (c = 1.00, $CHCl_3$, 40% *ee*) (Lit.[47] $[\alpha]_D^{20}$ = -4.7 (c = 1.00, $CHCl_3$, 90% *ee*).

HPLC: Chiralcel AS-H, heptane/isopropanol 75:25, 20 °C, 5 µL, 0.7 mL/min, 210 nm, t_R = 20.8 min (minor), t_R = 28.6 min (major).



(*R*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one ((*R*)-207a)

Catalyst (*S*)-**224** (4.78 mg, 25.0 µmol) and additive (25.0 µmol, see Table 3.2, Chapter 3) were dissolved or suspended in acetone (500 µL, 0.29 g, 6.8 mmol,) and stirred 15 minutes. Aldehyde **206a** (37.9 mg, 250 µmol) was added and the mixture was stirred at RT and monitored by TLC. Water (0.5 mL) was added and the mixture was extracted with EtOAc (3 × 2 mL). Collected organic extracts were dried over $MgSO_4$, concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, cyclohexane/EA 80:20–60:40) to yield the product as a yellow solid. An analytical sample (colorless solid) was obtained by recrystallization from Et_2O/pentane.

$C_{10}H_{11}NO_4$ (209.20 g/mol)

$\boldsymbol{R_f}$ = 0.25 (SiO_2, EA/cyclohexane 20:80).

m.p. 61–63 °C (Lit.[48] 63 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.22 (s, 3H, CH_3), 2.79–2.90 (m, 2H, CH_2), 3.57 (br s, 1H, OH), 5.26 (dd, $^3J_{HH}$ = 4.1 and 7.8 Hz, 1H, C*H*OH), 7.54 (d, $^3J_{HH}$ = 8.5 Hz, 2H, Ph*H*), 8.21 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 30.9 (*C*H_3), 51.6 (*C*H_2), 69.1 (*C*H), 123.9 (*Ph*H), 126.6 (*Ph*H), 147.5 (*Ph*N), 150.0 (*Ph*C), 208.6 (*C*=O).

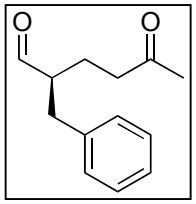
MS (EI, 70 eV, 150 °C) *m/z* (%): 209 (M^+, 14), 191 ([M-H_2O]$^+$, 35), 174 (36), 151 ([M-C_3H_6O]$^+$, 78), 77 ($C_6H_5^+$, 41), 58 ($C_3H_6O^+$, 53), 43 ($C_2H_3O^+$, 100).

IR (ATR): $\tilde{\nu}$ = 3439 br w (OH), 1713s (C=O); 1599m; 1518s (NO_2); 1339s (NO_2); 1290w; 1240w; 1163m; 1076m; 856m; 746s (Ar).

$[\alpha]_D^{20}$ = 29.1 (c = 1.00, $CHCl_3$, 42% *ee*) (Lit.[49] $[\alpha]_D^{24}$ = 69.9 (c = 0.42, $CHCl_3$, 95% *ee*).

HPLC: Chiralcel AS-H, heptane/isopropanol 70:30, 20 °C, 5 µL, 0.7 mL/min, 210 nm, t_R = 24.0 min (major), t_R = 29.1 min (minor).

5.5 Detection of Catalytic Intermediates as Mechanistical Tool



(*S*)-2-Benzyl-5-oxohexanal ((*S*)-294a)[50]

3-Phenylpropanal (**291a**) (265 µL, 268 mg, 2.00 mmol) and catalyst (*S*)-**46c** (36.8 mg, 100 µmol) were solved in EtOH (0.5 mL). Methyl vinyl ketone (83 µL, 70.1 mg, 1.0 mmol) was added and the mixture was stirred at room temperature until the disappearance of the ketone was observed by TLC. After 23 h the solvent was removed in vacuo and the crude mixture purified by column chromatography (SiO_2, Et_2O/pentane/CH_2Cl_2 1:10:0.1–5:10:0). The main product, (*S*)-2-Benzyl-5-oxo-hexanal was obtained as colorless oil (130 mg, 64%, 60% *ee*). The by-product **301** (51 mg, 10%) was obtained as yellow oil.

Main product ((*S*)-**294a**):

$C_{13}H_{16}O_2$ (204.26 g/mol)

R_f = 0.23 (SiO_2, EA/cyclohexane 20:80).

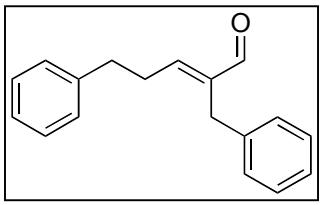
^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 1.71–1.79 (m, 1H, 3-H_A), 1.84–1.92 (m, 1H, 3-H_B), 2.07 (s, 3H, CH_3), 2.35–2.52 (m, 2H, 4-H_AH_B), 2.59–2.66 (m, 1H, 2-*H*), 2.71 (dd, $^3J_{HH}$ = 7.1 Hz and 13.9 Hz, 1H, PhCH_ACH_B), 3.01 (dd, $^3J_{HH}$ = 7.1 Hz and 13.9 Hz, 1H, PhCH_ACH_B), 7.10–7.40 (m, 5H, Ph*H*), 9.63 (d, $^3J_{HH}$ = 2.5 Hz, 1H, C*H*O).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 22.2 (*C*-3), 30.0 (*C*H_3), 35.4 (*C*H_2Ph), 40.6 (*C*-4), 52.5 (*C*-2), 126.6 (*Ph*H), 128.7 (*Ph*H), 129.0 (*Ph*H), 138.3 (*Ph*C), 204.1 (*C*HO), 207.8 (R_2C=O).

MS (EI, 70 eV, 50 °C) *m/z* (%): 204 (M^+, 6), 176 ([M-CO]$^+$, 11), 146 ([M-CH_3COCH_2]$^+$, 23), 91 ($C_7H_7^+$, 100), 43 ($C_2H_3O^+$, 54).

$[\alpha]_D^{20}$ = - 1.9 (c = 0.55, $CHCl_3$, 60% *ee*) (Lit.[50c]: $[\alpha]_D^{20}$ = -3.4 (c = 0.77, $CHCl_3$, 58% *ee*).

Chiral GC: Chiraldex G-TA column, 130 °C/45min/2 °C/min/150 °C/10 min, t_R = 57.7 min (major), t_R = 59.6 min (minor).



By-product: (*E*)-2-benzyl-5-phenylpent-2-enal (**301**):

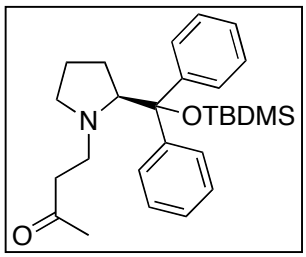
$C_{18}H_{18}O$ (250.33 g/mol)

R_f = 0.61 (SiO_2, EA/cyclohexane 20:80).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.74–2.80 (m, 4H, 4-*H*, 5-*H*), 3.60 (m, 2H, PhCH_2), 6.64 (t, $^3J_{HH}$ = 8.4 Hz 1H, 3-*H*), 7.12–7.34 (m, 10H, Ph*H*), 9.46 (s, 1H, C*H*O).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 29.7 (*C*-4), 31.1 (*C*H_2Ph), 34.5 (*C*-5), 126.2 (*Ph*H), 126.5 (*Ph*H), 128.4 (*Ph*H), 128.5 (*Ph*H), 128.6 (*Ph*H), 128.7 (*Ph*H), 139.1 (*Ph*C), 140.5 (HC=*C*), 142.9 (*Ph*C), 154.9 (H*C*=C), 194.7 (*C*HO).

MS (EI, 70 eV, RT) *m/z* (%): 250 (M^+, 6), 159 ([M-C_7H_7]$^+$, 25), 145 ([M-C_8H_9]$^+$, 34), 91 ($C_7H_7^+$, 100).



(*S*)-5-[2-(((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl)-pyrrolidin-1-yl]butan-2-one ((*S*)-305)

Stoichiometric formation: Methyl vinyl ketone (8.3 µL, 7.0 g, 0.10 mmol) was added to a solution of catalyst (*S*)-**46c** (36.8 mg, 0.100 mmol) in d^6-EtOD (0.5 mL) in NMR tube. Reaction progress was followed by ^{1}H-NMR. New species (*S*)-**305** was observed after 30 minutes ((*S*)-**46c**:(*S*)-**305** 91:9), after 1.5 h 70:30, 14 h 13:87. (*S*)-**305** was stable in solution after 4 days in NMR tube at room

temperature. Several signals in ^{1}H-NMR could not be found or assigned, due to fast H/D exchange and equilibrium with methyl vinyl ketone and (*S*)-**305**.

Catalytic formation: Methyl vinyl ketone (8.3 µL, 7.0 g, 0.10 mmol) was dissolved in EtOH (100 µL), catalyst (3.68 mg, 10.0 µmol) and PhCOOH (1.22 mg, 10.0 µmol) were added. The mixture was stirred for 5 minutes, then a sample of 10 µL was diluted in CH_3CN (to 1 mL) and 100 µL of this solution were diluted with CH_3CN to 1 mL. This solution was then injected to ESI-mass spectrometer.

$C_{27}H_{39}NO_2Si$ (437.69 g/mol)

^{1}H-NMR (d^6-EtOD, 500 MHz) δ/ppm: -0.52 (s, 6H, Si(CH_3)$_2$), 0.17–0.22 (m, 1H), 0.82 (s, 9H, C(CH_3)$_3$), 1.10–1.16 (m, 1H, 3-H_A), 1.66–1.69 (m, 3H), 1.74–1.78 (m, 2H), 2.04–2.10 (m, 1H), 2.21–2.24 (m, 1H, 4-H_A), 2.42–2.46 (m, 1H), 2.59–2.64 (m, 1H, 5-H_A), 3.24–3.28 (m, 1H, 5-H_B), 3.84 (t, $^3J_{HH}$ = 6.5 Hz, 1H, 2-*H*), 7.14–7.21 (m, 6H, Ph*H*), 7.38–7.40 (m, 2H, Ph*H*), 7.45–7.47 (m, 2H, Ph*H*).

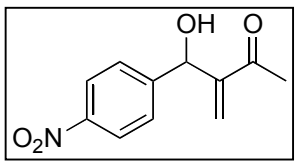
^{13}C{^{1}H}-NMR (d^6-EtOD, 126 MHz) δ/ppm: -3.7 (Si*C*H$_3$), -3.4 (Si*C*H$_3$), 18.6 (*C*(CH$_3$)$_3$), 23.3 (CH$_2$), 25.77 (CH$_2$), 25.83 (C(*C*H$_3$)$_3$), 28.3 (*C*H$_3$CO), 52.7 (*C*-5), 54.3 (CH$_2$), 71.4 (*C*-2), 83.8 (*C*Ph$_2$OR), 126.2 (*Ph*H), 126.6 (*Ph*H), 127.2 (*Ph*H), 127.4 (*Ph*H), 127.6 (*Ph*H), 128.5 (*Ph*H), 128.8 (*Ph*H), 129.7 (*Ph*H), 130.1 (*Ph*H), 142.4 (*Ph*C), 143.8 (*Ph*C), 209.8 (*C*=O).

Several signals could not be found or assigned, due to fast H/D exchange.

MS (ESI, 200 °C, 38 V) *m/z* (%): 438 ([M+H]$^+$(**305**), 41), 368 ([M+H]$^+$(**46c**), 1), 306 ([M-OTBDMS]$^+$(**305**), 100), 236 ([M-OTBDMS]$^+$(**46c**), 36).

Retro 1,4-addition of (*S*)-294a

(*S*)-**294a** (51.1 mg, 250 µmol) was dissolved in EtOH (0.25 mL) and catalyst (*S*)-**46c** (9.19 mg, 25.0 µmol) was added. The mixture (12.5 mM solution of catalyst) was stirred at room temperature. An aliquot of the reaction mixture (after 5 minutes and 24 h) was diluted with acetonitrile to approximately 0.01 mM with respect to catalyst concentration and analyzed by ESI MS. The spectra were recorded in the centroid mode.



(±)-3-[Hydroxy(4-nitrophenyl)methyl]but-3-en-2-one (310a)[51]

p-Nitrobenzaldehyde (52.9 mg, 0.350 mmol) and methyl vinyl

ketone (86 µL, 70 mg, 1.0 mmol) were solved in DMF (300 µL) and water (30 µL), (*S*)-proline (4.03 mg, 3.50 µmol) and $NaHCO_3$ (7.35 mg, 87.5 µmol) were added and the mixture was stirred at 40–46 °C for 23 h. Then, water (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 1 mL). Collected organic extracts were washed with brine (1 mL), dried over $MgSO_4$ and solvent was removed in vacuo. Crude product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 80:20) and the product was obtained as colorless oil (39 mg, 50%, 4% *ee* (*S*)).

$C_{11}H_{11}NO_4$ (221.21 g/mol)

R_f = 0.38 (silica, EA/cyclohexane 30:70).

m.p. 72–73 °C (Lit.[51] 76–77 °C).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ/ppm: 2.35 (s, 3H, CH_3), 3.44 (d, $^3J_{HH}$ = 3.8 Hz, 1H, O*H*), 5.66 (d, $^3J_{HH}$ = 3.8 Hz, 1H, C*H*OH), 6.04 (d, $^2J_{HH}$ = 1.2 Hz, 1H, CH_AH_B), 6.26 (d, $^2J_{HH}$ = 1.2 Hz, 1H, CH_AH_B), 7.53 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ph*H*), 8.15 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ph*H*).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz) δ/ppm: 26.5 (*C*H_3), 72.2 (*C*HOH), 123.7 (*Ar*H), 127.4 (*Ar*H), 127.9 (*C*H_2), 147.4 (*Ar*C), 149.1 (H_2C=*C* or *Ar*C), 149.1 (H_2C=*C* or *Ar*C), 200.2 (*C*=O).

MS (FAB, NBA) *m/z* (%): 222 ($[M+H]^+$, 31), 204 ($[M-OH]^+$, 34), 158 (35), 43 ($C_2H_3O^+$, 100).

[α]$_D^{20}$ = - 2.2 (c = 1.04, $CHCl_3$, 4% *ee*) (Lit.[53] **[α]$_D^{20}$** = 16.0 (c = 0.5, $CHCl_3$, 94% *ee* (*R*)-**XX**)).

HPLC: Chiralcel OD-H, heptane/isopropanol 95:5, 20 °C, 5 µL, 0.8 mL/min, 210 nm, t_R = 33.9 min (major), t_R = 36.7 min (minor).

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CHAPTER 6

Appendix: List of Abbreviations

6 Appendix: List of Abbreviations

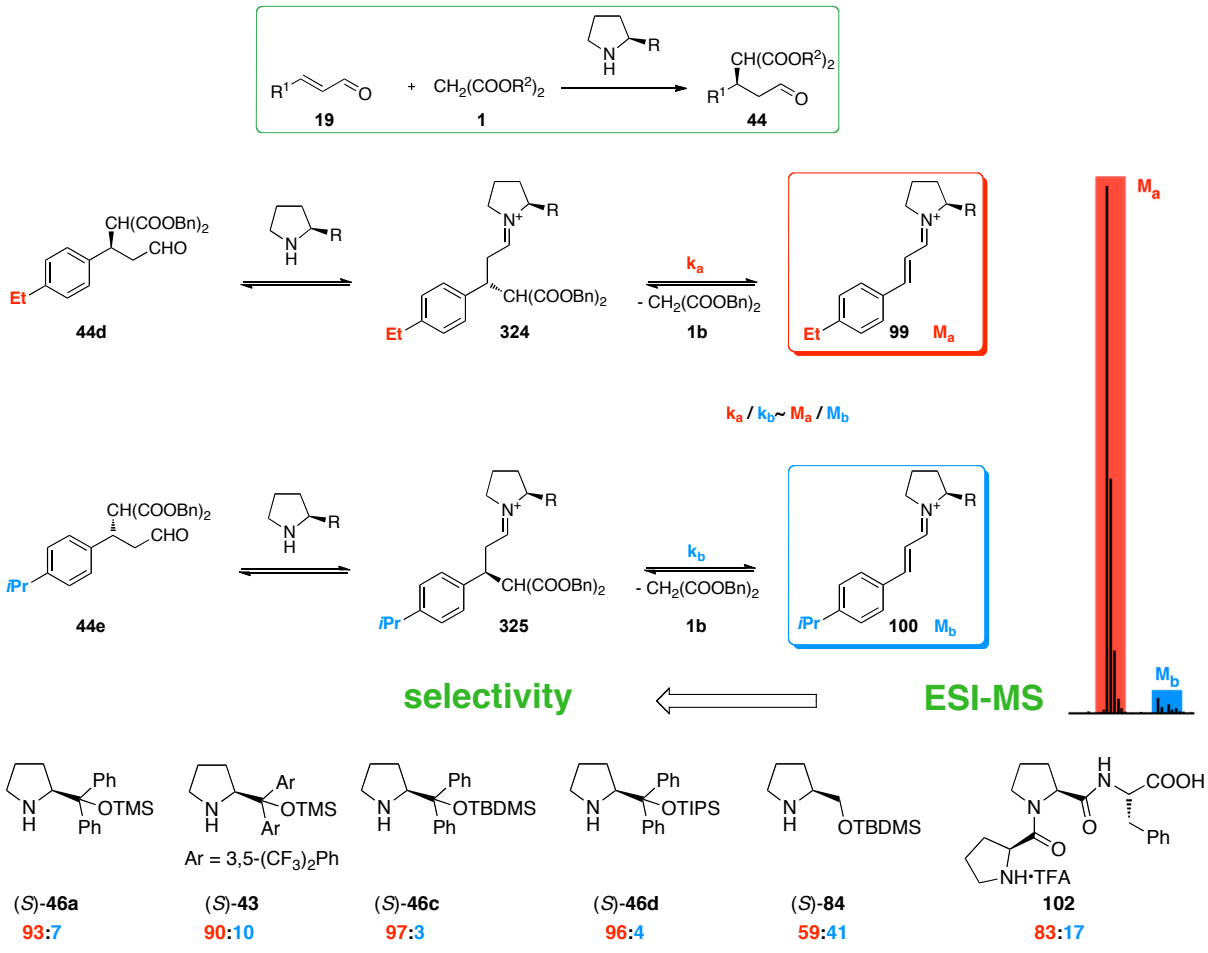
2,6-lut.	2,6-lutidine
A	adenine
Å	Ångström (10^{-10} m)
Ac	acetyl
ap	antiperiplanar
Ar	aryl
ATR	attenuated total reflection (IR)
b.p.	boiling point
BBI	broadband inverse (NMR)
BBO	broadband observe (NMR)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
c	concentration
cal	calorie
Cbz	benzyloxycarbonyl
conv.	conversion
COSY	homonuclear correlation spectroscopy (NMR)
d	day(s); doublet (NMR)
δ	chemical shift
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2,2,2]octane
dba	dibenzylideneacetone
DCM	dichloromethane
decomp.	decomposition
DFT	density functional theory
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
E	electrophile
e.r.	enantiomeric ratio
EA	elemental analysis; ethyl acetate
ee	enantiomeric excess
EI	electron impact ionization (MS)
equiv.	equivalent
ent	enantiomer
ESI	electrospray ionization (MS)
Et	ethyl
eV	electron volt
FAB	fast atom bombardment (MS)
FT	furrier transformation
GC	gas chromatography
h	hour(s)
hept.	heptet
HMBC	heteronuclear multiple bond correlation (NMR)
HMQC	heteronuclear multiple quantum coherence (NMR)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HSAB	hard and soft acids and bases
Hz	Hertz
i	*iso*
IR	infrared spectroscopy
J	coupling constant
k	rate constant
L	ligand
LDA	lithium di-*iso*-propylamide
LUMO	lowest occupied molecular orbital
m	multiplet (NMR); medium (IR)
M	molarity (mol/L)
M	metal
m.p.	melting point
m/z	mass to charge ratio (MS)
MBH	Morita-Baylis-Hillman
m_c	centered multiplet
***m*CPBA**	3-chloroperoxybenzoic acid
Me	methyl
Mes	3,5-mesityl
min.	minute(s)
MS	mass spectrometry; molecular sieve
N	normality
nd	not determined
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOE	nuclear overhauser enhancement (NMR)
Np	naphtyl
nr	no reaction
Nu	nucleophile
Ph	phenyl
Piv	pivaloyl; trimethylacetyl
pKa	negative common logarithm of the acid dissociation constant
ppm	parts per million
Pr	propyl
prep.	preparative
psi	pound per square inch
q	quartet

quant.	quantitative
R_f	retention factor
RT	room temperature
s	selectivity factor
s	singlet (NMR); strong (IR)
sc	synclinal
t	triplet
T	tymine; temperature
taut	tautomer
TBDMS	*tert*-butyldimethylsilyl
TBME	*tert*-butylmethylether
tert	tertiary
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
t_R	retention time
Ts	4-toluenesulfonyl
UV	ultra violet
$\tilde{\nu}$	wave number (IR)
w	weak (IR)

Summary

Diverse approaches to the discovery of new organocatalysts were examined. A novel screening method based on mass-spectrometric detection of catalytic intermediates was applied to the organocatalyzed Michael reaction of malonates **1** to α,β-unsaturated aldehydes **19** (Scheme S1). Based on the principle of microscopic reversibility, it is possible to determine the enantioselectivity of a catalyst by screening the intermediates in the *retro*-Michael reaction of a pair of quasienantiomeric Michael adducts **44d** and **44e**.

After establishing the appropriate conditions for the *retro*-reaction and for the mass-spectrometric measurement, the ESI-MS screening of different organocatalysts was conducted. The selectivity of the catalysts was determined without time-consuming purification and analysis of the products. The results obtained by the screening correlated to the enantioselectivities in the preparative reaction.



Scheme S1. ESI-MS screening of the *retro*-Michael reaction.

The method was successfully extended to the screening of catalyst mixtures (Figure S1). A crude mixture of six catalysts synthesized in one batch was subjected to mass-spectrometric screening. The most selective catalyst was easily identified.

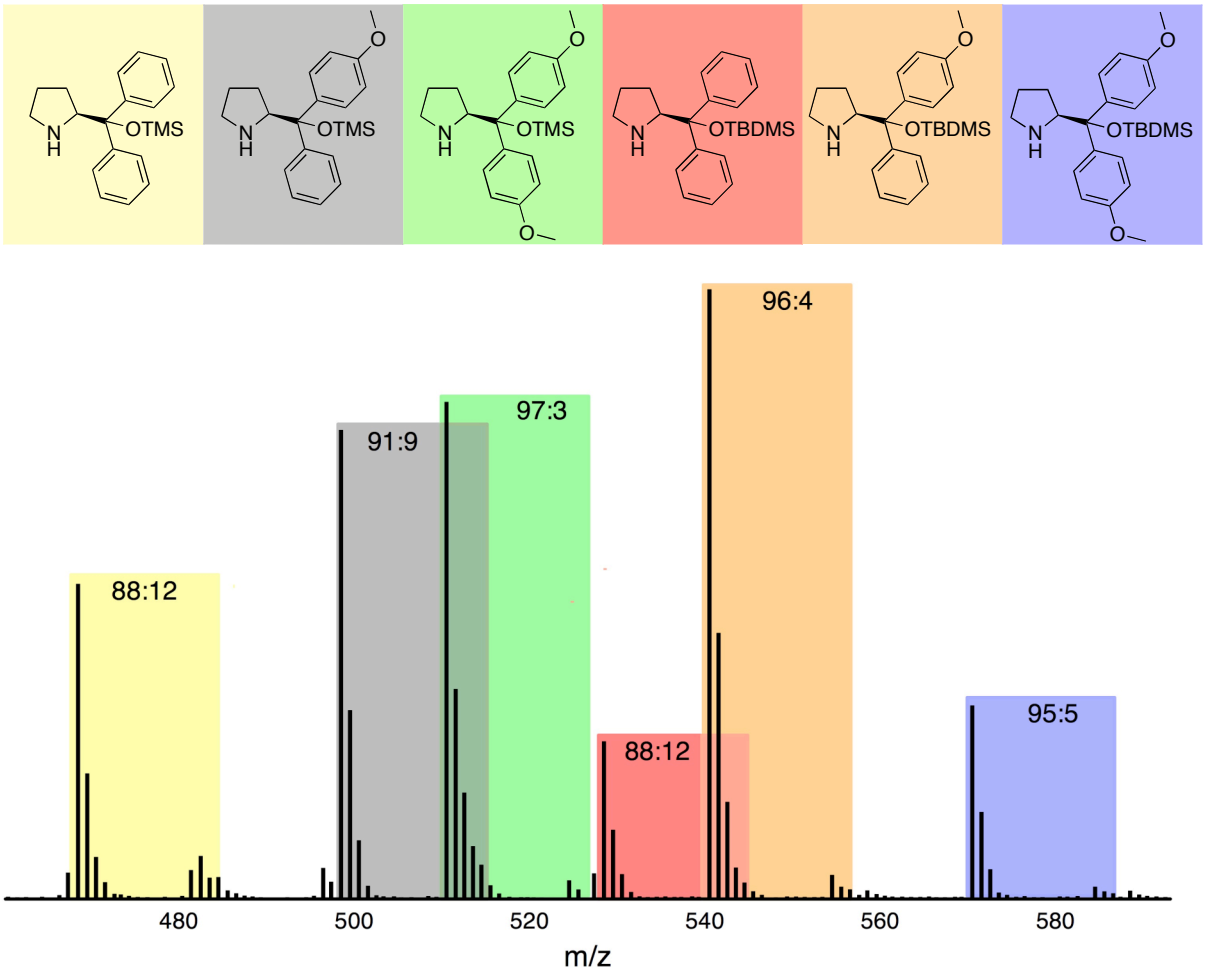
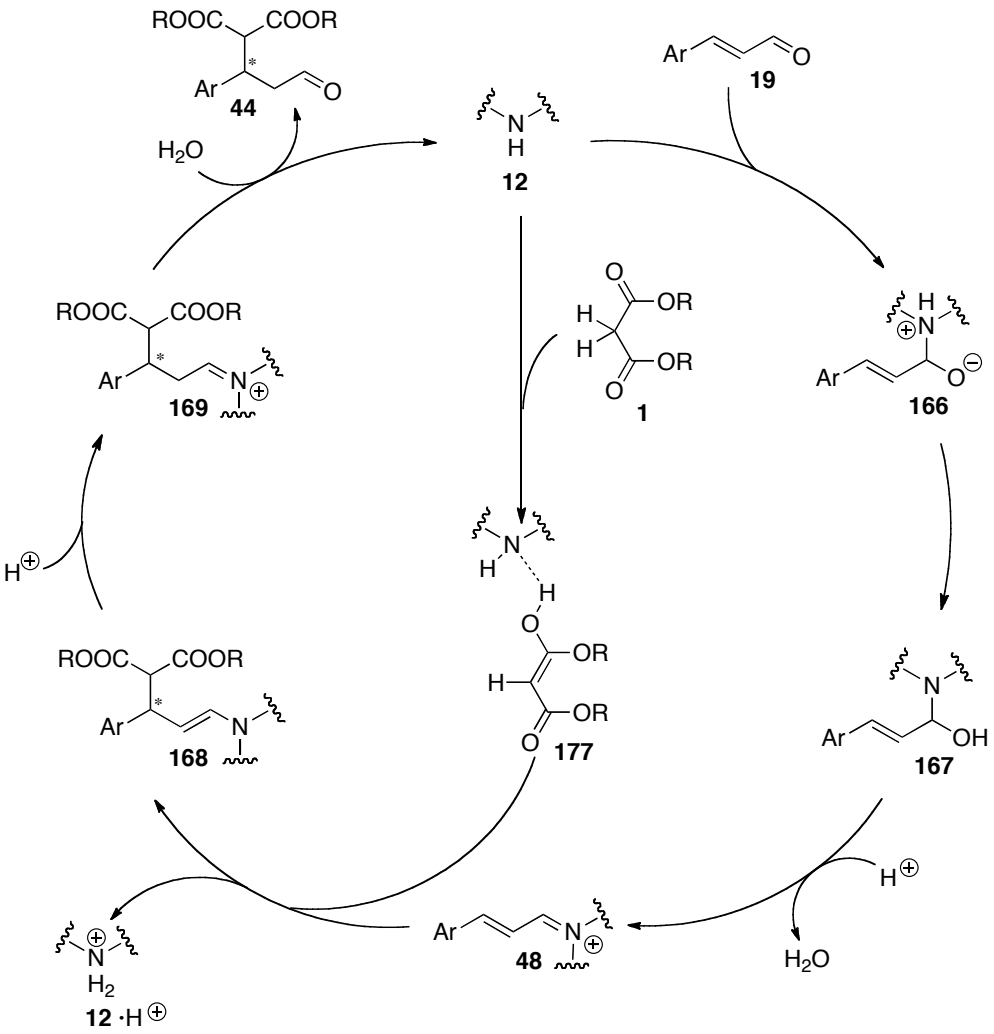


Figure S1. The ESI-MS spectrum of the *retro*-Michael reaction screening with a catalyst mixture.

Catalyst (*S*)-**46c** was applied to the preparative Michael addition. The optimization provided a highly effective and selective method for the synthesis of chiral 2-substituted malonates. A strong accelerating effect of weak carboxylic acids and water as additives was observed. The optimization led to shorter reaction times and lower catalyst loading.

In addition, mechanistic studies of the reaction were carried out. The observation of a significant negative nonlinear effect led to the assumption that the catalyst activates both reaction partners in the Michael addition. NMR and ESI-MS studies confirmed this hypothesis. Based on these discoveries, a more detailed catalytic cycle for the Michael addition of malonates to enals was proposed (Scheme S2).

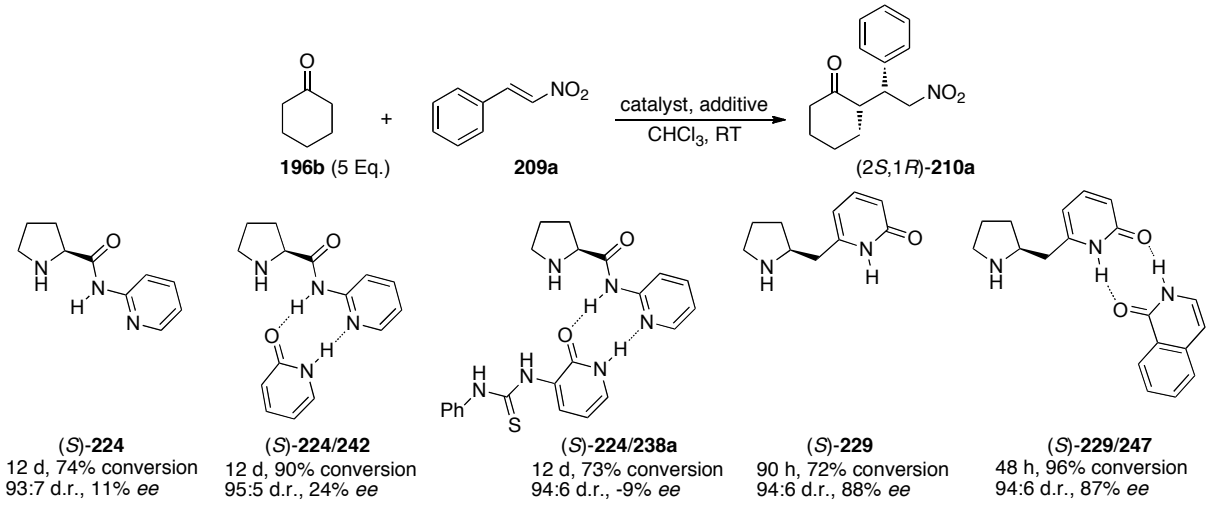


Scheme S2. The catalytic cycle of secondary amine-catalyzed Michael addition of malonates to α,β-unsaturated aldehydes.

In conclusion, an efficient combinatorial strategy for the development and structural optimization of organocatalysts for the Michael addition to α,β-unsaturated aldehydes was developed. In contrast to conventional parallel screening methods, simultaneous evaluation of a mixture of catalysts is possible without the need to isolate and purify the individual catalysts. Thus, this method should greatly facilitate the search for more efficient catalysts for substrates that give unsatisfactory results with known catalysts. An optimization of the preparative Michael addition was carried out. In addition, mechanistic studies provided insights into the action mode of secondary amines as catalysts.

An alternative approach towards the development of new catalysts was based on self-assembled catalyst constituting of two parts connected by hydrogen bonds. The structure comprised a proline-derived unit for the activation of a carbonyl compound and a pyridine

derivative as an additive, which can provide steric hindrance or activate the other reaction partner. The enamine-catalyzed 1,4-addition of ketones to nitroolefins was chosen as a test reaction (Scheme S3). Catalyst (*S*)-**224** displayed poor activity and selectivity. However, the formation of self-assembled species was indicated by enhanced or reversed selectivity and by their detection with ESI-MS. Improvements in both activity and selectivity were achieved with catalyst (*S*)-**229**. The additive **247** accelerated the reaction. In principle, it was shown that the additives affect the outcome of the reaction.



Scheme S3. 1,4-Addition of cyclohexanone to β-nitrostyrene with self-assembling catalysts.

The possibility of extending the ESI-MS screening of the Michael addition of aldehydes to enones was investigated. Unfortunately, the *retro*-Michael reaction did not take place under the conditions tested. ESI-MS was also used for mechanistic investigations of the forward reaction. Interestingly, the 1,4-adduct of the catalyst and methyl vinyl ketone was observed as the most abundant species in the mass spectrum. Since such species are important intermediates in the Morita-Baylis-Hillman reaction, the possibility to use catalyst (*S*)-**46c** in the reaction of methyl vinyl ketone and an aromatic aldehyde was investigated. Indeed, catalyst (*S*)-**46c** was able to catalyze the reaction, although in low yield. Moreover, the catalytic intermediates could be identified in this reaction.

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