# Stereoselective Mannich Reactions of Mono Thiomalonates

# &

# Screening for Peptidic Triazolium Salt Based Catalysts

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von

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Prof. Dr. Andreas Pfaltz

Basel, den 15.10.2013

Prof. Dr. Jörg Schibler

Dekan

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# Part I

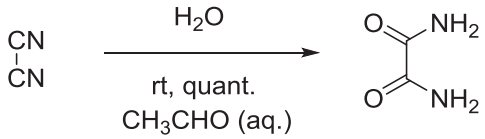
# Stereoselective Mannich Reactions of Mono Thiomalonates

# 1 Introduction

## 1.1 Asymmetric Organocatalysis

Catalytic asymmetric synthesis, or the ability of controlling the three dimensional structure of a molecule by just a small amount of chiral catalyst has emerged as a widely researched field in the last decades.[1] Besides transition metal and enzyme catalysis, organocatalysis has evolved as an additional approach to the production of enantiomerically enriched organic compounds.[2] Organocatalysts are small molecules composed of mainly carbon, hydrogen, nitrogen, oxygen, sulphur and phosphorus atoms that function as catalysts in the absence of metal centres. These molecules have several advantages. They are usually robust, readily available and not as expensive and toxic as metal based catalysts.[2] In most instances organocatalysts show enhanced stability against oxygen and water, allowing for reactions to proceed and demanding reaction conditions like inert atmosphere, dry solvents etc. can typically be avoided. Organocatalytical methods are especially interesting for the synthesis of pharmaceuticals and other compounds that do not tolerate metal contamination.[3-6]

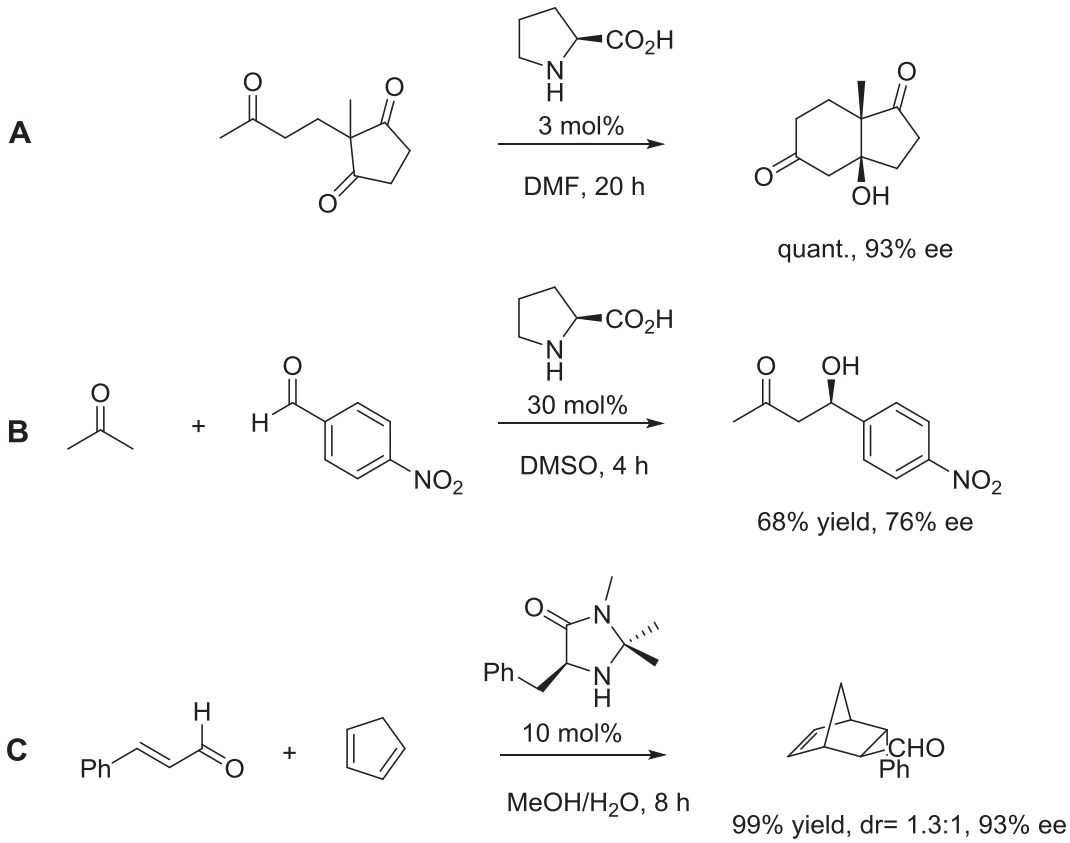
The history of organocatalysis began already in 1895 with Justus von Liebig, who discovered the transformation of dicyan into oxamide in the presence of aqueous acetaldehyde which he later on identified as catalyst (Scheme 1).[7]




*Scheme 1. Justus von Liebig´s synthesis of oxamide from dicyan and water.*[7]

After decades of focusing on transition metal catalysis, two milestones in the history of organocatalytic reactions were discovered in the second half of the last century. In 1960 Pracejus reported the cinchona alkaloid catalyzed addition of methanol to methyl phenyl ketene affording the addition product in an enantioselectivity of 74% ee. In the 1970´s Hajos and Parrish[8] at Hoffmann La Roche (Switzerland) and independently at the same time Eder, Sauer and Wiechert[9] at Schering (Germany) discovered the intramolecular asymmetric Robinson annulation of a triketone catalyzed by L-proline (Scheme 2). The corresponding annulated product was obtained in an enantioselectivity of 93% ee, which was a remarkably

high level of selectivity at that time. In the last decade, asymmetric organocatalysis has grown to an immensely researched field. Various types of organocatalysts have been developed that promote reactions as diverse as cycloadditions, Michael additions, aldol reactions, Mannich type reactions and many other types of reactions with excellent enantioselectivities (Scheme 2).[3-6]

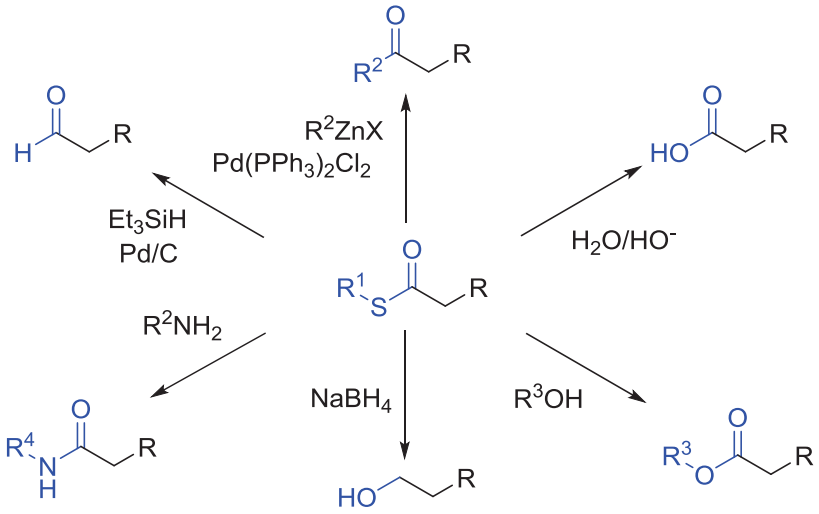



*Scheme 2. Examples of organocatalytic reactions:* ***A****: Intramolecular asymmetric Robinson annulation catalyzed by* L*-proline; Hajos, Parrish,[8] Eder, Sauer, Wiechert.[9]* ***B:*** *Aldol reaction catalyzed by* L*-proline; List, Lerner, Barbas.[10]* ***C****: Diels Alder reaction catalyzed by oxazolidone; MacMillan.[11]*

# 1.2 Thioesters

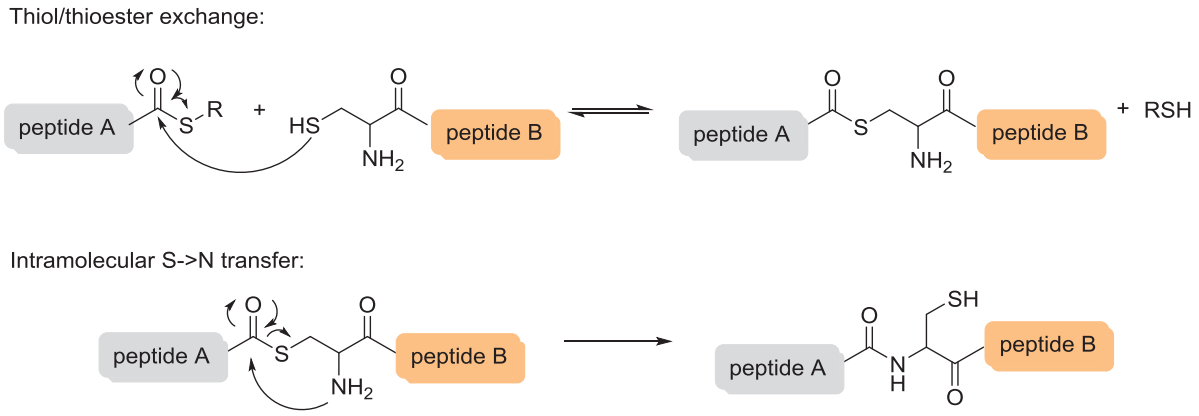
## 1.2.1 Versatility and Properties of Thioesters

Thioesters are important structural motifs in biochemistry and organic synthesis. They are extensively used as activated esters and allow for easy functionalization and conversion into a variety of other functional groups such as esters, ketones,[12] aldehydes[13] or amides (Scheme 3).




*Scheme 3. Versatility of transformations of thioesters*

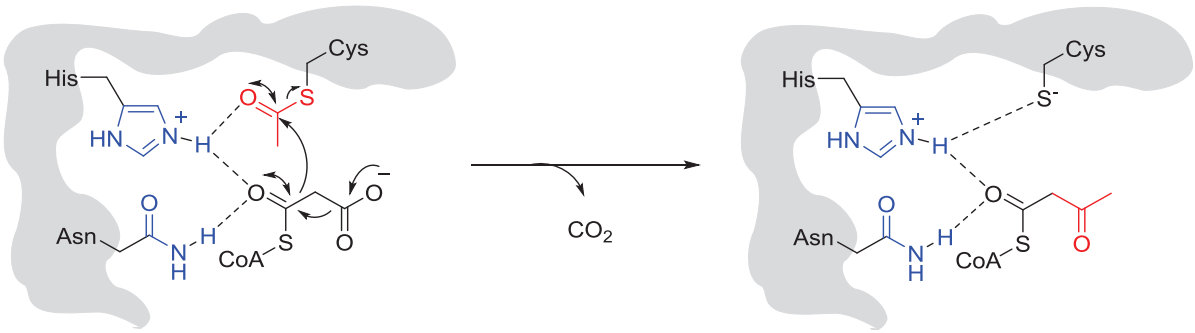
An important approach that utilizes the reactivity of thioesters is native chemical ligation (NCL) allowing for the generation of long and difficult peptides.[14-16] This concept is based on a linkage of peptidic segments that contain a *C*-terminal thioester and a *N*-terminal cysteine. The linkage takes place due to a kinetically favored but reversible thiol/thioester exchange, followed by a highly thermodynamically favored intramolecular and irreversible S -> N acyl shift (Scheme 4). Hence, an amide linkage is formed out of a thioester intermediate. NCL allows for the synthesis of various peptides with a size of up to 300 amino acids, however with the limitation, that the final peptide has to contain cysteine residues.[14-16]




*Scheme 4. Concept of native chemical ligation (NCL)*[14-16]

In nature, thioesters are also important molecules. They are used as activated building blocks or intermediates for the synthesis of various cellular components including peptides, polyketides and fatty acids.[17-18] Besides the possibility of transforming thioesters *via* nucleophilic attack of an alcohol or an amine to esters and amides respectively, thioesters can

also be converted to their enolates and act themselves as nucleophiles in C-X bond forming reactions. However, due to the low acidity of the $\alpha$-protons of thioesters,[19] thioester enolate generation requires special activation (*e.g.* hydrogen bonding) available in several enzymes. A group of enzymes that possess this ability to generate thioester enolates in the active site are polyketide synthases (PKSs), which are present in *e.g.* bacteria, plants and fungi.[17-18, 20-22] In their active site, the amino acids cysteine, histidine and asparagine are involved in the reaction of the thioester building blocks acetyl-CoA and malonyl-CoA (Scheme 5). In a mechanism that was reported by Noel *et al.* it is postulated that CoA bound malonic acid half thioester is activated for decarboxylation through hydrogen bonding by asparagine and protonated histidine.[21] Upon decarboxylation, a thioester enolate is generated, which is still coordinated to histidine and asparagine. The coordinated thioester enolate is then attacking an acetylated cysteine which is placed in proximity in the active site.[18] This initial Claisen condensation is then followed by a cascade of enzyme catalyzed transformations, which finally lead to the synthesis of various polyketides. The resulting polyketides possess a broad structural diversity and are involved in a variety of biological and pharmacological activities, including antibiotic, anticancer, antifungal and immunosuppressive properties.[18]

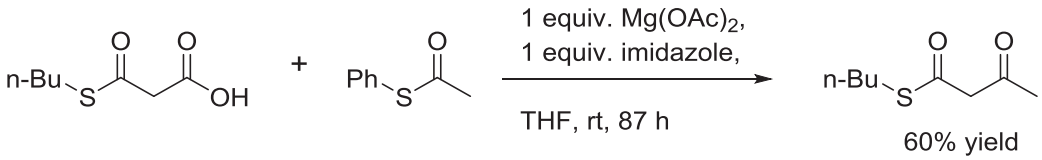



*Scheme 5. Claisen Condensation in the active site of PKS*[21]

## 1.2.2. Thioester Enolates in Organic Chemistry

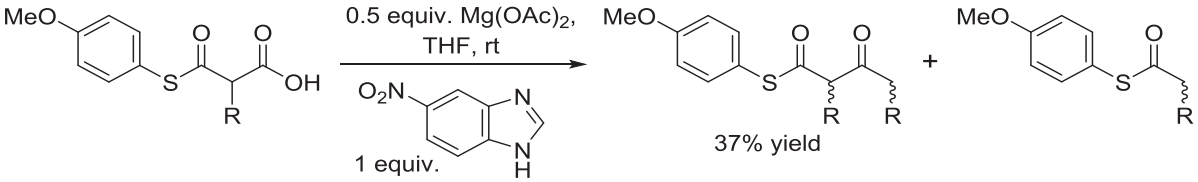
Inspired by nature, synthetic chemists have used malonic acid half thioesters (MAHTs) as thioester enolate equivalents and several decarboxylative addition reactions to different electrophiles have been developed.[23-35] However, due to the low acidity of MAHTs $\alpha$-protons, [19] typically bases or metal-based Lewis acids are necessary to generate thioester enolates in a synthetic environment.[19, 36] Several metal based approaches towards the addition reaction of MAHTs to electropiles have been developed. Kobuke and Yoshida presented in 1978 the first example of an addition reaction of MAHTs, being an

intramolecular Claisen condensation with thioacetate (Scheme 6).[37] The reaction was accomplished using equimolar amounts of a magnesium salt and imidazole, yielding *β*-keto thioesters in yields of 60%.



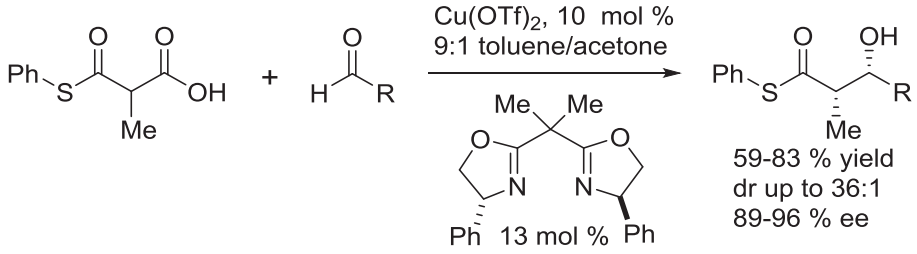

*Scheme 6. Claisen condensation of MAHTs and thioacetate*[37]

Inspired by these results, the group of Matile reported in 2001 the self-condensation of MAHTs towards the synthesis of *β*-keto thioesters (Scheme 7).[38] As in the report of Kobuke and Yoshida, a magnesium salt as well as a benzimidazole was used to promote the reaction. An intensive and precise fine tuning of all reaction parameters allowed for the synthesis of the thiomalonate dimer in yields of up to 37%. However, they stated that the applicability of this approach towards biomimetic polyketide synthesis remains problematic.



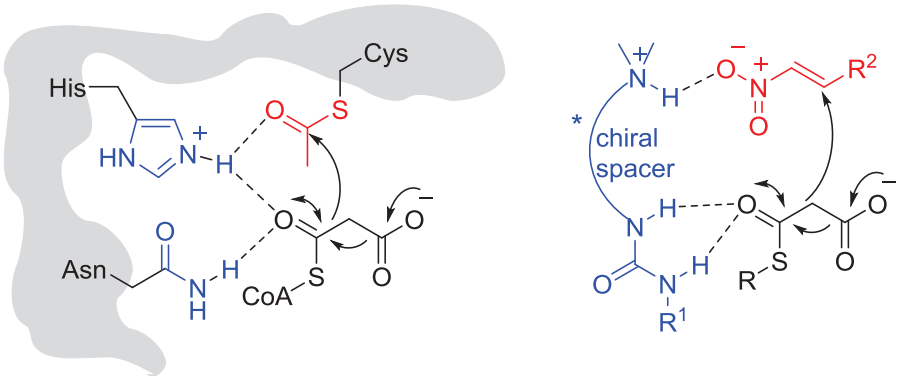

*Scheme 7. Self-condensation of MAHTs*[38]

The first catalytic addition reaction of MAHTs to aldehydes was reported by Shair *et. al* in 2003. In the presence of a Cu(II) catalyst and an imidazole derivative, yields of up to 97% have been achieved.[24] Additionally, in 2005, an asymmetric variant of this aldol reaction was achieved by the same group (Scheme 8). With a copper-Phbox catalyst, enantioselectivities of up to 86% ee were obtained, using methyl-substituted MAHT as substrate.[23]



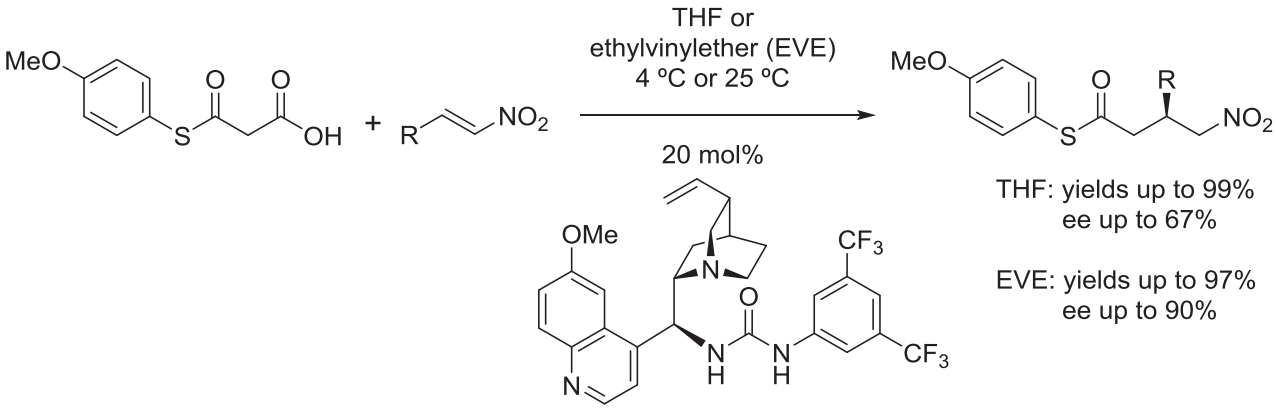

*Scheme 8. Diastereoselective addition reaction of MAHTs to aldehydes*[24]

Besides other metal catalyzed examples for the decarboxylative addition reactions of MAHTs to electrophiles,[34, 39] the first asymmetric organocatalytic addition reaction of MAHTs to nitroolefins was developed in 2007 by Wennemers and Lubkoll.[26] Inspired by nature, where MAHTs are activated by coordination through asparagine and protonated histidine residues, they speculated that a bifunctional organocatalyst, providing both, a hydrogen bonding and a basic moiety, could be a key for efficient catalysis (Scheme 9). As the hydrogen bonding side they chose a urea moiety that activates the MAHT towards deprotonation by the nearby basic tertiary amine. The protonated tertiary amine as well as the urea offer then hydrogen bonding sites for the deprotonated MAHT as well as its reaction partner and provide a defined stereochemical environment for the C-C bond forming event.




*Scheme 9. Design of an active site of PKS imitating organocatalyst*[26]

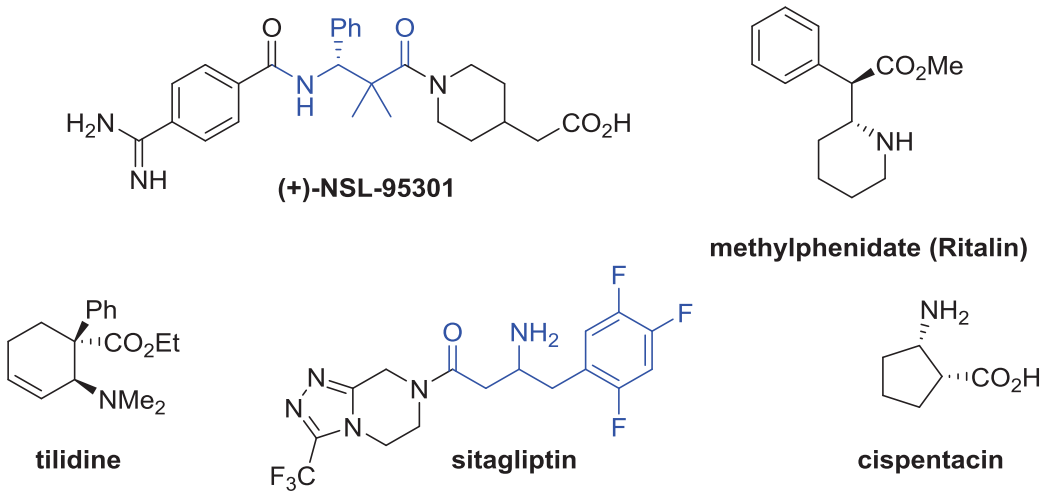
For that purpose, cinchona alkaloid urea and thioureas where tested as catalyst and an *epi*-quinine urea derivative turned out to be the optimal catalyst (Scheme 10). After optimization of the reaction conditions, *γ*-nitrothioesters were obtained in high yields and enantioselectivities of up to 90% in the presence of 20 mol% of the catalyst.[26]



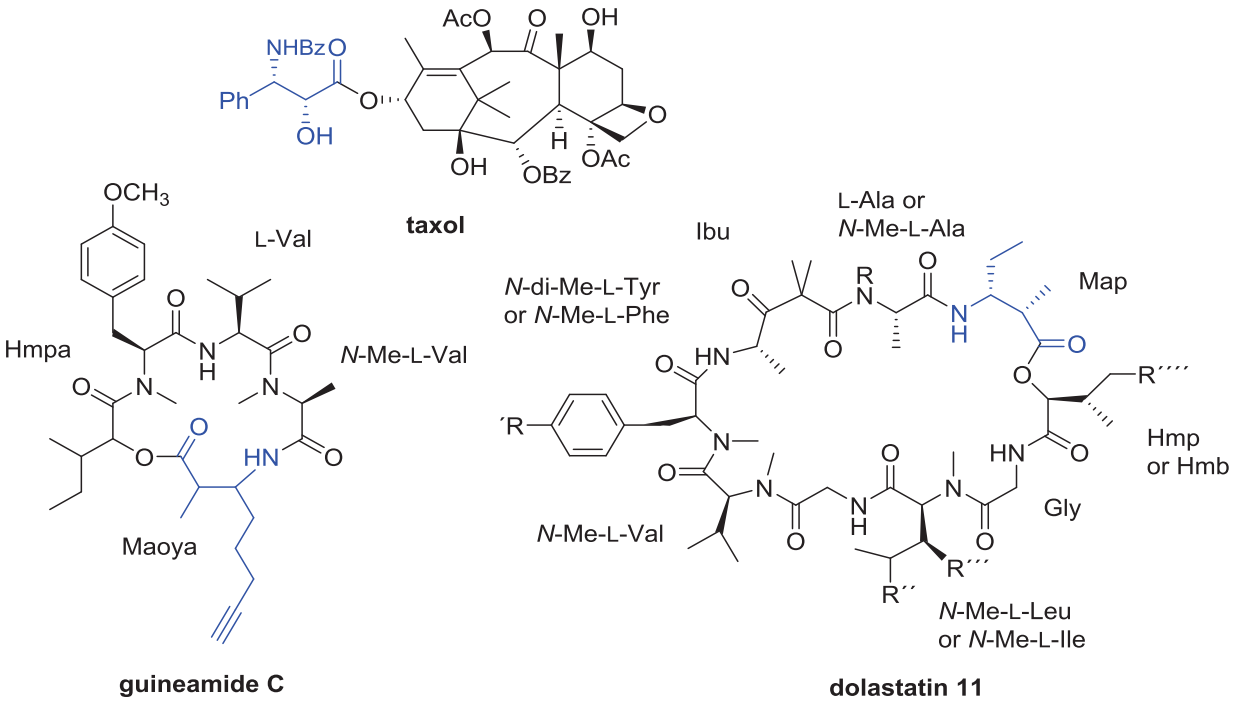

*Scheme 10. Decarboxylative addition reaction of MAHTs to nitroolefins*[26]

## 1.3 Organocatalytic Mannich Type Reactions

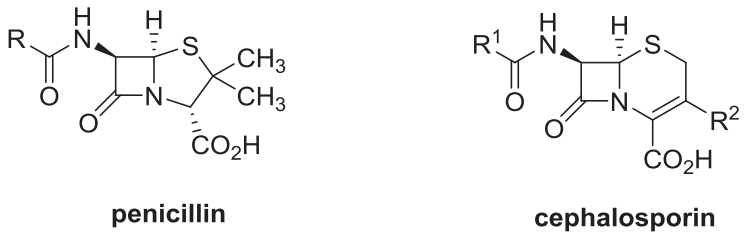
The Mannich reaction is among the most important C-C bond forming reactions in organic synthesis allowing for the generation of one or two stereogenic centres in one single bond forming event.[36, 40-41] Asymmetric organocatalytic variants offer practical access to enantiomerically enriched *β*-amino carbonyl compounds including *β*-amino thioesters which are direct precursors of *β*-amino acids.[42] *β*-Amino acids are important key components of biologically active pharmaceuticals and peptides (Scheme 11). Several small pharmaceutical products such as the antithrombotic agent (+)-NSL-95301 or Ritalin which is known to treat the ADHS syndrome embody a *β*-amino acid substructure (Scheme 11). Also analgesic tilidine, antihyperglycemic sitagliptin and the antifungal and antibiotic cispentacin contain *β*-amino acids as a core structure (Scheme 11). In natural products, *β*-amino acids occur for example in taxol, one of the most potent antitumor agents, as well as in guineamide C and dolastatine 11 (Scheme 12).[42] In addition, biologically relevant peptides with *β*-amino acids in their sequence often show interesting features such as enhanced activity and increased enzymatic stability. Furthermore, *β*-amino acids are important precursors for lactams which are potentially biologically active and often key structures of antibiotics (Scheme 13).




*Scheme 11. β-Amino acids as core structures in small pharmaceutical compounds*




*Scheme 12. β-Amino acids in natural products*

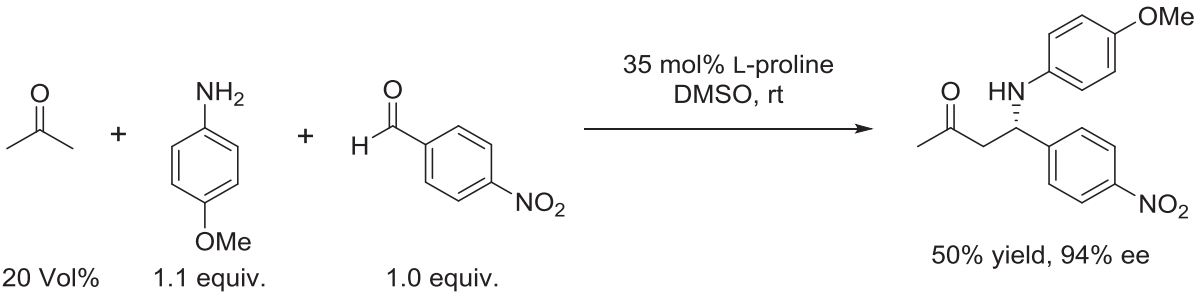



*Scheme 13. β-Lactams as antibiotics*

The known catalytic asymmetric Mannich approaches differ with respect to the strategy for the formation or activation of nucleophile and electrophile. In the first and simplest approach preformed enolates are used as nucleophiles in combination with chiral Lewis or Brønsted acids for the activation of the imine moiety (indirect Mannich reaction). Several examples of indirect Mannich reaction have been reported by the groups of Kobayashi,[43-45] Sodeoka,[46-47] Lectka[48-49] and Jacobsen.[50] In the work of Kobayashi chiral zirconium/BINOL complexes were successfully used as catalysts, representing the first catalytic enantioselective direct Mannich type reaction. The catalytic enantioselective Mannich type reactions of silyl enol ethers and $\alpha$-imino esters were published in two similar reports by Sodeoka *et al.* and Lectka *et al.* in 1998, where palladium(II)/BINAP and copper(I)/BINAP complexes respectively, were applied as the catalyst. However, disadvantages of these reactions are the need for the preparation and the instability of the preformed enolates which are typically silylketene acetals and silylenol ethers.

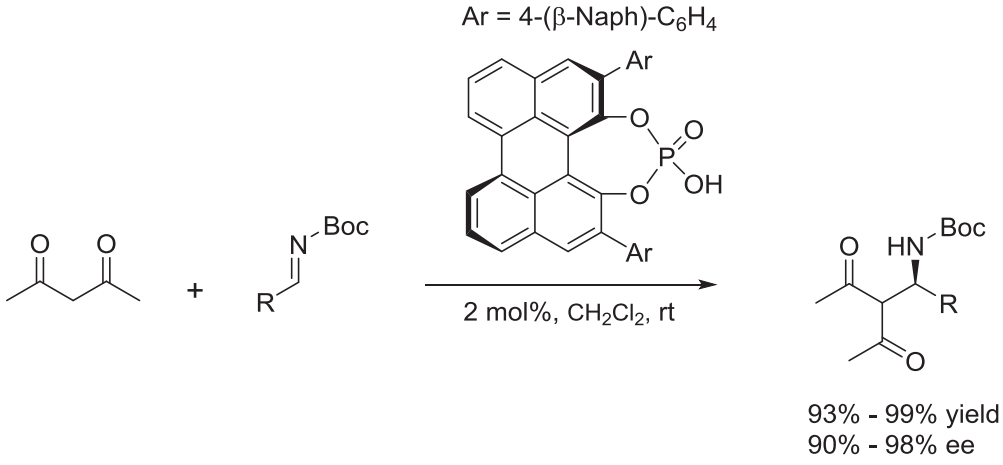
A newer concept represents the direct Mannich type reaction. Within this approach unmodified carbonyl compounds are used directly as nucleophiles, avoiding prior preparation of the enolate. In direct catalytic asymmetric Mannich type reactions the enolate is generated within the catalytic cycle. [36, 40-41] The transformations are catalyzed by chiral metal catalysts[51-56] as well as organocatalysts[28, 57-67] yielding steroselectively $\beta$-amino carbonyl compounds.

The first organocatalyzed direct Mannich type reaction was reported by the group of List in 2000 using L-proline for enamine activation of unmodified ketones.[68-69] Although a high catalyst loading of 35 mol% was necessary to obtain moderate yields, the enantioselectivity of the product was 94% ee (Scheme 14).



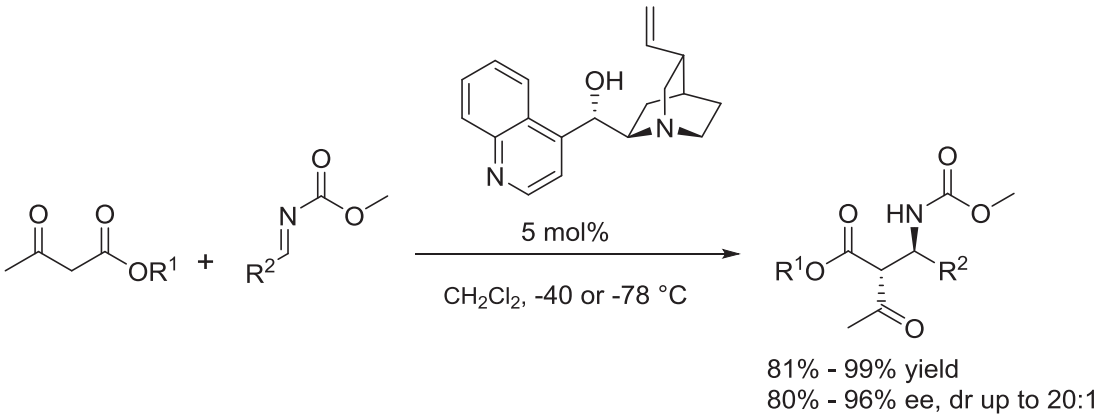

*Scheme 14. L-proline catalyzed direct Mannich type reaction*[68-69]

Organocatalysts such as chiral Brønsted acids have also been shown to efficiently catalyze the direct Mannich reaction. The group of Terada reported in 2004 the successful application of phosphoric acid catalyst in the reaction of a 1,3-diketone and a preformed imine (Scheme 15).[66] They showed that Brønsted acids promote the direct Mannich reaction enantioselectively *via* hydrogen bonding of an imine substrate. Finally, $\alpha$-amino ketones were obtained in the presence of as little as 2 mol% of the phosphoric acid catalyst in excellent yields (93 - 99%) and enantioselectivities (90% ee - 98% ee).




*Scheme 15. Brønsted acid catalyzed direct Mannich type reaction of 1,3-dicarbonyl compounds*[66]

Alternatively, tertiary amines have also been successfully applied to asymmetric direct Mannich type reactions. In 2005, Schaus *et al.* reported the diasteroselective addition of $\beta$-keto esters to preformed aryl methyl carbamate imines catalyzed by cinchona alkaloid cinchonine (Scheme 16).[61] The nucleophilic enolate equivalent is formed through deprotonation of the $\alpha$-proton of the $\beta$-ketoester. Then protonated catalyst and the enolate form a chiral ion pair which is stereoselectively attacking the electrophilic imine. The products were obtained in good yields (81 - 99%) and excellent stereoselectivities (ee up to 96%, dr up to 20:1).

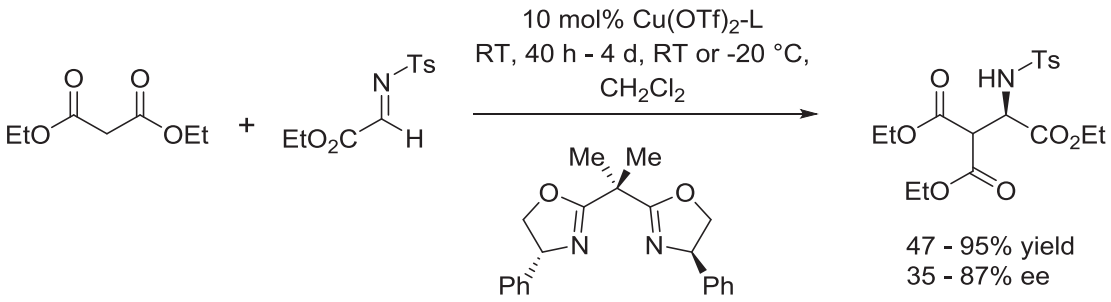



*Scheme 16. Diastereoselective Cinchonine catalyzed Mannich type reaction of β-keto esters*[61]

## 1.3.1 Addition Reactions of Malonates to Imines

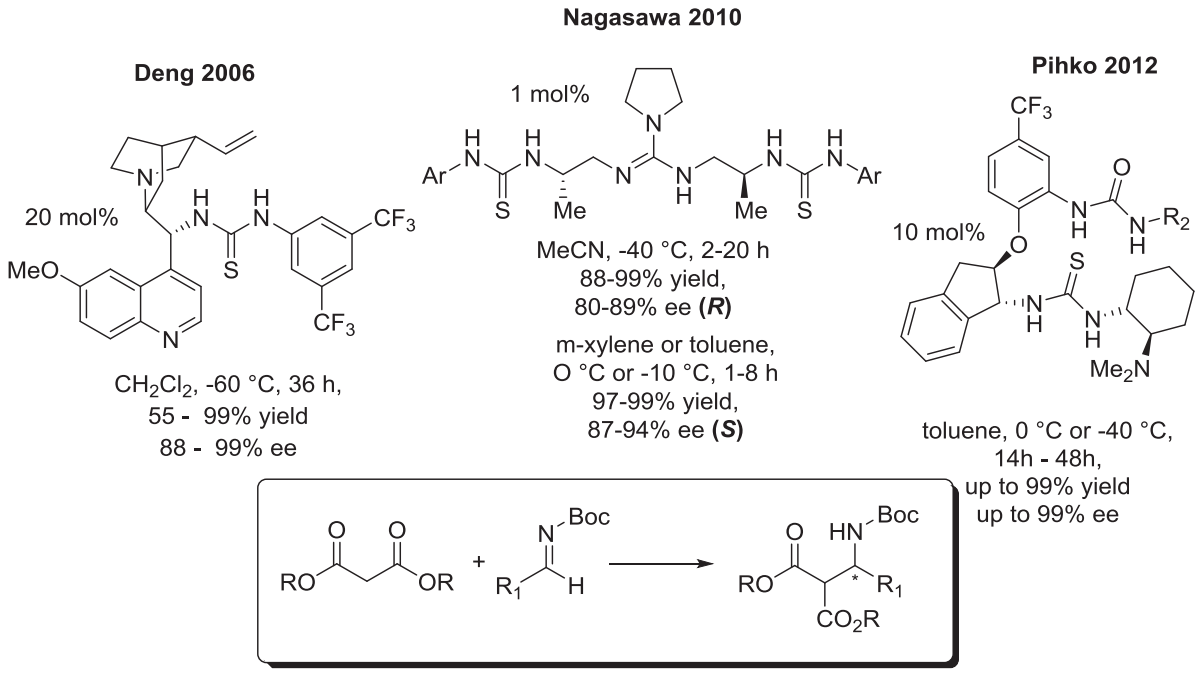
Amongst 1,3-dicarbonyl compounds, the addition of malonates to imines is of special interest since the addition products provide direct access to $\beta^3$-amino acids. However the organocatalytic direct Mannich type reaction of malonates and especially thiomalonates is more difficult. Malonates are harder to enolize than 1,3-diketones and $\beta$-ketoesters, due to the weaker acidity of their $\alpha$-protons.[70] Therefore the generation of enolates from malonates requires typically higher catalyst loadings of 10 - 20 mol% while leading to only low yields. In addition, the reaction with unsymmetrical malonates allows the generation of two stereogenic centers, however, the control of both, the enantio- as well as the diastereoselectivity is a challenging task.

A first metal catalyzed approach towards the direct Mannich type reaction with malonates was reported by the group of Jørgensen who applied chiral Lewis acids such as copper(II)/bisoxazoline complexes to the addition reaction of malonates to activated $\alpha$-imino esters (Scheme 17).[54]



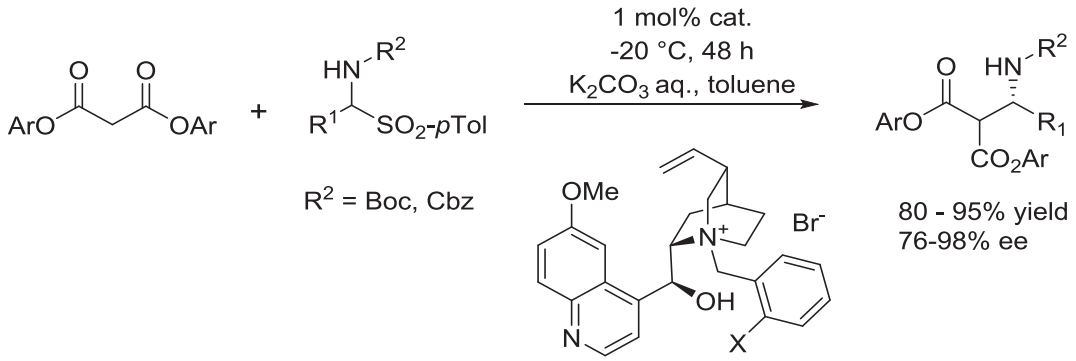

*Scheme 17. Chiral Lewis acid catalyzed direct Mannich type reaction of malonates*[54]

The first organocatalyzed direct Mannich type reaction of malonates to simple imines was reported in 2006 by Deng *et al.* (Scheme 18). A bifunctional catalyst was chosen, providing a thiourea moiety as chiral hydrogen bond donor to activate the imine and a cinchona alkaloid as a chiral hydrogen bond acceptor activating the malonate (Scheme 18).[63] The addition products were obtained in high yields (up to 99%) and enatioselectivities of 88% - 99% ee. However, high catalyst loadings of 20 mol% and a long reaction time was required. Since this first organocatalytic example, several contributions have been made to the organocatalyzed direct Mannich type reaction of malonates to simple imines using typically cinchona alkaloid catalysts.[57, 62, 65, 67, 71-75]




*Scheme 18. Organocatalytic direct Mannich type reaction of malonates: Cinchona alkaloid derivatives*[63] *Conformationally flexible guanidine/bisthiourea organocatalyst*[73-74] *Internally activated urea and thiourea organocatalyst*[75]

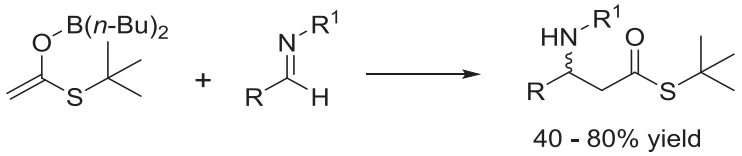
Recently, other classes of catalysts have been developed. For example the group of Nagasawa has developed a conformationally flexible guanidine/bisthiourea organocatalyst which provides both enantiomers of the $\beta$-amino carbonyl compound depending on the solvent used (Scheme 18).[73-74] In 2012, Pihko *et al.* reported an internally activated bifunctional catalyst (Scheme 18).[75] The catalyst includes a urea and a thiourea moiety, which form a rigid scaffold through intramolecular hydrogen bonding. The catalyst was applied in the addition reaction of symmetrical malonates to *N*-Boc protected imines and the addition products were obtained in high enantioselectivities (ee up to 99%). In addition to imines, $\alpha$-amido sulfones have also been successfully applied to direct Mannich type reactions with malonates. This strategy involves *N*-carbamoyl imine generation *in situ* from $\alpha$-amido sulfones which allows the use of often unstable and moisture sensitive imines derived from acyclic aldehydes.[57, 71] For example Ricci *et al.* described the phase transfer catalyzed addition reaction of malonates to $\alpha$-amido sulfones, generating the *N*-carbamoyl imine *in situ* (Scheme 19).[71] In addition, the groups of Deng[62] and Schaus[72] showed that $\alpha$-amido sulfone precursors can also be applied using a bifunctional organocatalyst, not based on phase transfer catalysis.




*Scheme 19. Phase transfer catalysis for the direct Mannich type reaction with in situ generated imines[71]*

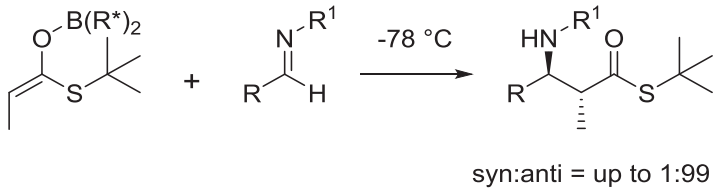
## 1.3.2 Addition Reactions of Thioesters to Imines

Utilizing thioesters for the organocatalyzed asymmetric direct Mannich type reaction results in the direct generation of $\beta$-amino thioesters. Thioesters have a distinctly higher acidity of their $\alpha$-protons compared to regular esters ($pk_a$ difference of 2 units), however thioester enolate generation requires special activation. In 1981, the first thioester enolate condensation with imines was developed by Ohno *et al.* (Scheme 20).[76] A vinyloxyboran was used as thioester enolate, which then reacted smoothly with the imine to form $\beta$-amino thioesters in reasonable yields (40 - 80%).



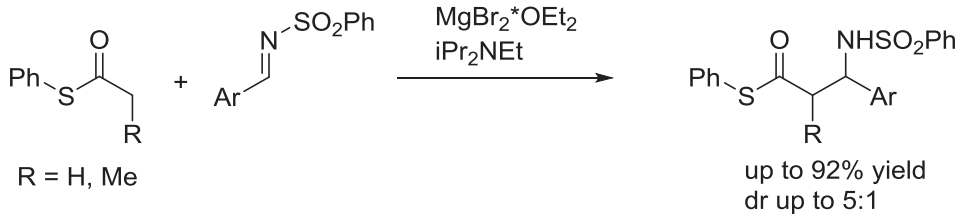

*Scheme 20. Addition of boron ketene acetals to imines*[76]

One decade later, the group of Corey reported the first method for the asymmetric synthesis of chiral $\beta$-amino thioester from achiral imines and esters using chiral organoborone reagents (Scheme 21).[77] The reaction was developed in the course of exploring stereoselective synthesis strategies towards chiral $\beta$-lactams using achiral starting materials. Use of a chiral boron ligand as selectivity inducer, yielded the addition product in excellent stereoselectivity thus providing a useful route to several $\beta$-lactams.



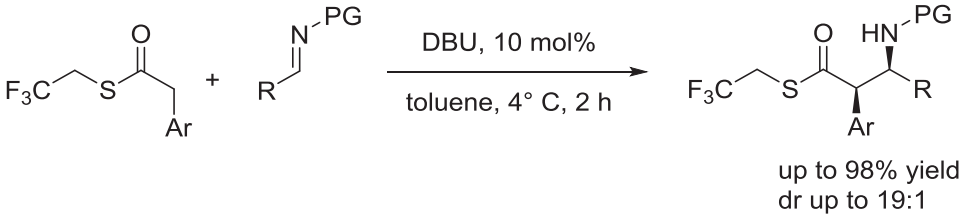

*Scheme 21. Addition of chiral organoborone thioester enolate to imines*[77]

In contrast to the approach of using strong bases to generate the thioester enolate, soft enolization appeared as an attractive new methodology.[78-80] Within this concept, weak bases in combination with Lewis acids lead to reversible deprotonation at the $\alpha$-position of the thioester. The deprotonation by weak bases, such as tertiary amines, is facilitated by polarization of the carbonyl moiety due to Lewis acid interactions. The advantages are that less harsh reaction conditions are required and that the method is less labour intensive since the thioester enolate is generated *in situ*. Coltart *et al.* reported the first direct Mannich type reaction based on soft enolization of thioesters in 2008 (Scheme 22).[81] In the presence of excess amount of magnesium bromid ethyl etherate, thioesters reacted smoothly with sulfinylimines to afford the addition products in up to 92% yield and moderate diastereoselectivity favoring the *syn*-isomer.



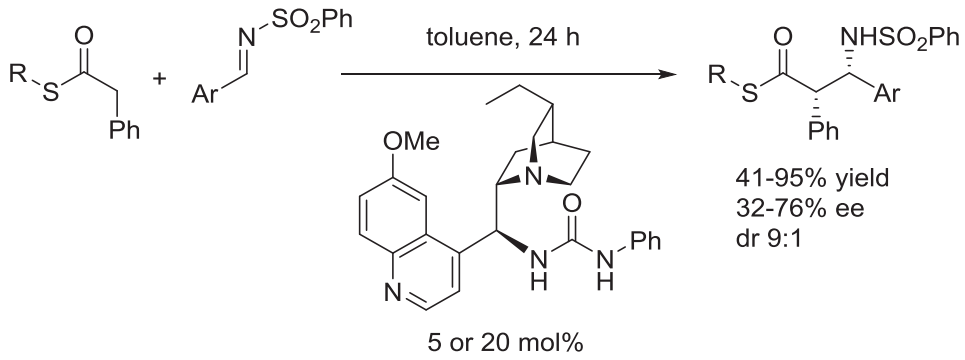

*Scheme 22. Soft enolization of thioesters with magnesium bromide ethyl etherate and diisopropylamide*[81]

Soft enolization with purely organic catalysts has been achieved using either activated thioesters as nucleophiles, or malonic acid half thioesters in the decarboxylative Mannich type reaction. In 2008 Barbas *et al.* explored the diastereoselective direct Mannich type reaction using electronically activated trifluoroethyl thioester which provides a sufficient ester donor reactivity for a non decarboxylative approach (Scheme 23).[82] The group found that catalytic amounts of the tertiary base diazabicycloundecene DBU (10 mol%) were effectively catalyzing the first *syn*-selective direct Mannich type reaction. The resulting *β*-amino thioesters were obtained in up to 98% yield and diastereoselectivities of up to 19:1.



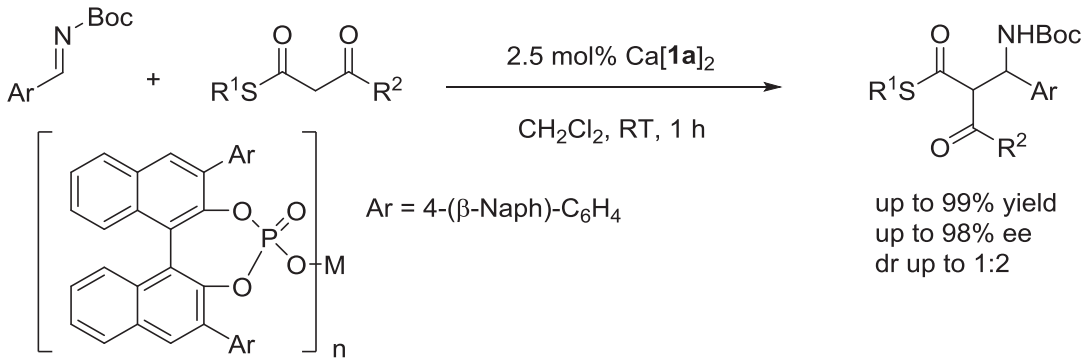

*Scheme 23. First syn-selective non-decarboxylative direct Mannich type reaction*[82]

Later in 2010, Coltart *et al.* showed that the concept of soft enolization can also be applied in a biomimetic catalytic asymmetric Mannich reaction of activated thioesters such as phenyl acetic acid thioesters (Scheme 24).[83] The development of the catalyst was inspired by the citrate synthase where thioester activation is achieved by hydrogen bonding interactions. Due to proximity effects, inherent to the system as a result of the close spatial arrangement of the base and the *α*-proton of the thioester, deprotonation by a weaker base such as a carboxylate group is allowed, resulting in the addition reaction. Cinchona alkaloid ureas proved to provide an environment similar to the catalytic pocket of the citrate synthase thus providing a hydrogen bonding as well as a basic moiety for proximity-assisted intracomplex soft enolization (Scheme 24). The system was *syn*-selective, however stereoselectivities were just in a moderate range of 32 - 76% ee and 9:1 dr.




*Scheme 24. Organocatalytic soft enolization with cinchona alkaloid urea derivatives*[83]

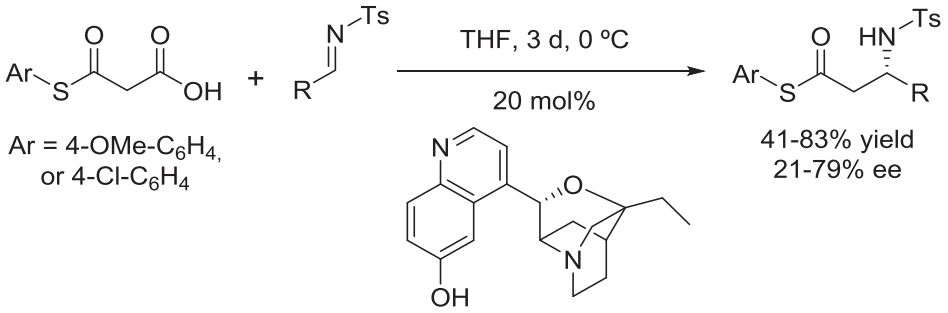
In the same year, the group of Ishihara successfully applied for the first time *β*-keto thioesters and thiomalonates to the direct Mannich type reaction using Brønsted bases such as Ca(II) salts of phosphoric acids as catalysts (Scheme 25).[53] Whereas the addition of *β*-keto thioesters was catalyzed by both, the protonated phosphoric acid as well as the Ca(II)-complex, the reaction with thiomalonates was only accomplished when the more strongly basic Ca(II)-complex was used (Scheme 25).[84-85]




*Scheme 25. Brønsted base catalysed direct Mannich type reaction of β-keto thioesters and thiomalonates*[53]

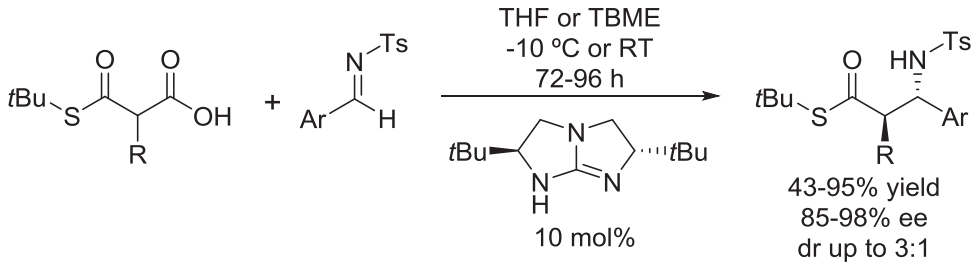
In contrast to electronically tuned thioesters which are suitable for soft enolization addition reactions, malonic acid half thioesters (MAHTs), which base on the concept of addition and decarboxylation, have also emerged as thioester enolate equivalents, as introduced in chapter 1.2.[26] In 2007, Ricci *et al.* reported the first biomimetic decarboxylative enantioselective addition reaction of MAHTs to *N*-tosyl imines (Scheme 26).[29] A quinidine derivative served as catalyst, possessing a basic tertiary amine and a hydrogen bond donor (phenolic OH). The addition products were obtained in good yields of 41 - 83% and moderate enantioselectivities of 21 - 79 % ee. However, rather high catalyst loading (20 mol%) and long reaction times (3 days) were required. The authors claimed that the decarboxylation step is crucial for the

occurrence of the reaction to proceed. This was demonstrated by the observation that in the presence of methyl protected MAHT, where the decarboxylation is not possible, no conversion to the $\beta$-amino thioester was observed.




*Scheme 26. Cinchona alkaloid catalyzed decarboxylative Mannich type reaction with N-Ts imines*[29]

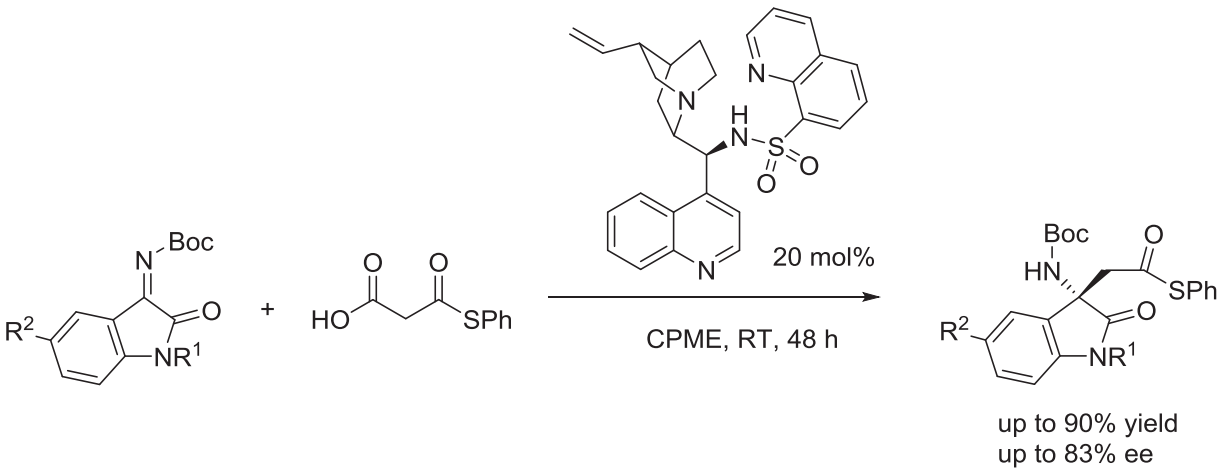
Later, in 2011, Tan *et al.* developed a chiral bicyclic guanidine catalyst for a proximity-assisted decarboxylative strategy (Scheme 27).[28] This new type of catalyst led to improved results regarding reactivity and stereoselectivity in the decarboxylative Mannich type reaction of MAHTs and additionally allowed for the use of MAHTs bearing an alkyl substituent at the $\alpha$-position. DFT calculations supported the concept of an initial addition reaction followed by decarboxylation.




*Scheme 27. Guanidine derived bifunctional catalyst for the decarboxylative Mannich type reaction of $\alpha$-methyl substituted MAHTs with N-Ts imines*[28]

Besides aldimines, also ketimines proved to be accessible electrophiles for the organocatalytic decarboxylative Mannich type reaction. Ketimines are typically less reactive than aldimines but their use as electrophiles leads to the generation of all-carbon quaternary stereogenic centers at the $\alpha$-position to the nitrogen. The group of Shibata reported in 2012, that ketimines, derived from isatin were successfully transformed to $\beta$-amino thioesters in the presence of MAHTs and 20 mol% of 8-quinolin sulfonylated organocatalysts (Scheme 28).[32] The products were obtained in high yields of up to 90% and steroselectivities of up to 83% ee and could directly be transformed into a gastrin/cholecyctokinin B receptor antagonist. With the help of X-ray crystallographic analysis they showed that hydrogen bonding occurs

between the sulfonimide proton and the 8-quinolyl nitrogen resultimg in a constraint structure of the catalyst which is important for the induction of enantioselectivity. Mechanistically, they claimed, that the MAHT is activated by the sulfonamid moiety *via* hydrogen bonding. In contrast to previous mechanistic proposals, [28] decarboxylation of the MAHT is proposed prior to the C-C bond forming event, at the basic site of the cinchona alkaloid moiety. The resulting thioester enolate adds to the ketimine which coordinates to the protonated basic site, leading to the addition reaction.

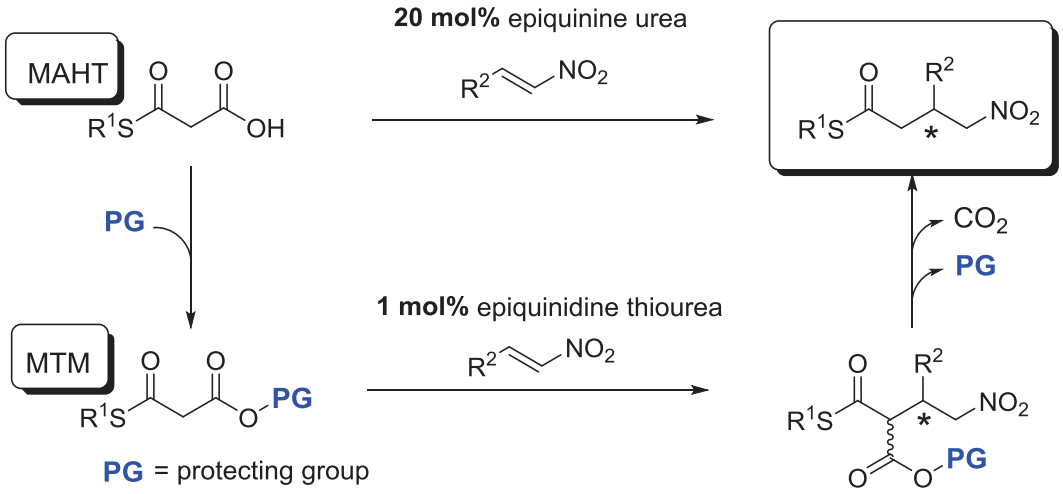



*Scheme 28. Decarboxylative organocatalyzed addition reaction of MAHTs to ketimines - Generation of quaternary stereogenic center*[32]

In all of these reported examples $\beta$-amino thioesters have been generated using thioester enolates within mild organocatalytic approaches. However, either MAHTs, which suffer from low reactivity due to their tendency to partially decarboxylate without a simultaneous C-C bond formation, or electronically activated thioesters have been used. The reactions with these pro-nucleophiles typically require high catalyst loading and long reaction times of several days. Examples with simple thiomalonates are limited to symmetrical thiomalonates and only one example is reported utilizing strong basic Brønsted base catalysis.[53] The organotcatalytic synthesis of $\beta$-amino thioesters bearing quaternary stereogenic centers is also limited to only one example were ketimines were used as electrophiles. However, to the best of our knowledge no examples of the asymmetric organocatalyzed direct Mannich type reaction affording $\beta$-amino thioester bearing an all-quaternary stereogenic center at the $\alpha$-position to the thioester are reported.

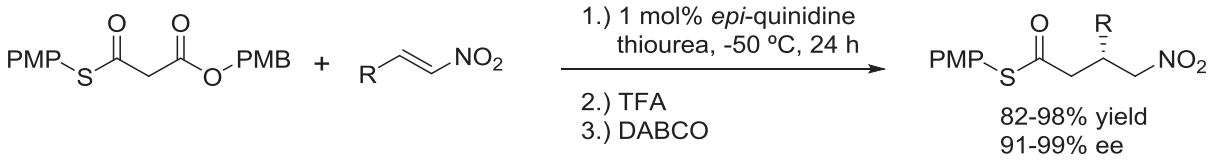
These results suggest that there is still space to optimize the asymmetric organocatalyzed synthesis of $\beta$-amino thioester by exploring new thioester enolate equivalents that allow for more efficient addition reactions to imines. As a contribution to this issue, our

group recently designed mono thiomalonates (MTMs) as thioester enolate equivalents (Scheme 29).[86] Those pro nucleophiles bear a cleavable ester moiety and proved to be more stable and efficient than MAHTs in the mild organocatalytic 1,4-addition reaction to nitroolefins.[86]




*Scheme 29. Addition reaction of MAHTs vs MTMs to nitroolefins*[26, 86]

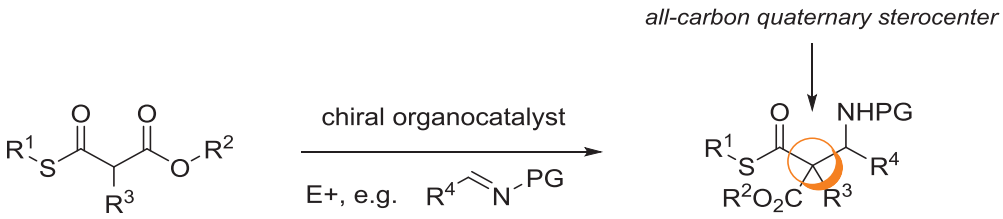
In comparison to the analogous reaction using MAHT as nucleophile only 1/20 of the original catalyst loading was required to obtain the same yields (Scheme 29).[26, 86] The initially formed addition products were deprotected and decarboxylated *in situ* affording γ-nitrothioesters in high overall yields of up to 95% and excellent enantioselectivities of up to 98% ee (Scheme 30).[86]




*Scheme 30. MTMs as new thioester enolate equivalents in the organocatalyzed addition reaction to nitroolefins*[86]

Due to these advantages of MTMs over MAHTs in the organocatalyzed 1,4-addition reaction to nitroolefins, we decided to investigate these new thioester enolate equivalents in the direct Mannich type reaction with imines. If the reactivity of MTMs is also enhanced towards other electrophiles than nitroolefins, we envisioned to overcome the drawbacks of thioester enolate based organocatalytic direct Mannich type reactions which are high catalyst loading (10 – 20 mol%) and long reaction times (3 – 4 days). Furthermore, α-substituted MTMs might allow

for the generation of $\beta$-amino thioesters bearing an all-carbon quaternary stereogenic center at the $\alpha$-position, hence giving access to the facile synthesis of direct precursors of $\beta^{2,2,3}$-amino acids (Scheme 31).[87-90]

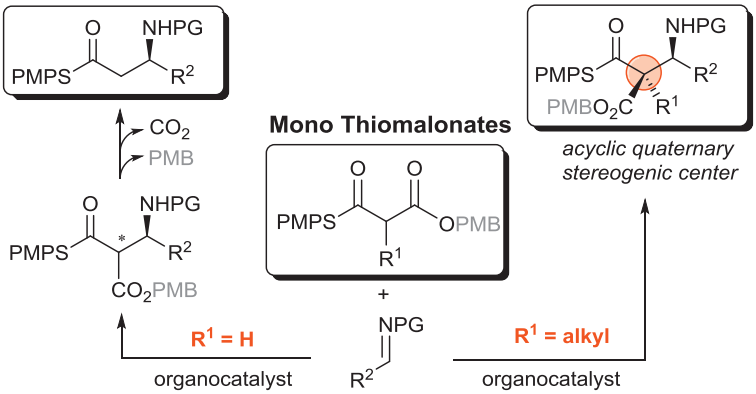



*Scheme 31. α-Substitutet MTMs for the generation of an all-carbon α quaternary stereogenic center in β-amino thioesters*

# 2 Objective

The stereoselective synthesis of $\beta$-amino thioesters is of high interest since they are versatile and common building blocks for a variety of pharmaceutical important compounds.[4, 36, 91] Besides, $\beta$-amino thioesters are important $\beta$-amino acid precursors that give access to $\beta$-peptides. In particular, $\beta$-amino thioesters bearing linear all-carbon $\alpha$-quaternary stereogenic centers are hence of great value but successful approaches for their direct stereoselective generation are not available up to date. Organocatalytic asymmetric transformations of thiomalonates with imines offer an attractive way to generate $\beta$-amino thioesters. However, due to the low acidity of the $\alpha$-protons of thioesters, enolate generation typically requires high catalyst loadings (10-20 mol%) and long reaction times (days).

The objective of this part of the thesis was to develop new and efficient stereoselective syntheses of $\beta$-amino thioesters using mono thiomalonates (MTMs) as thioester enolate equivalents (Scheme 32).




*Scheme 32. Mono thiomalonates as thioester enolate equivalents in Mannich type reactions*

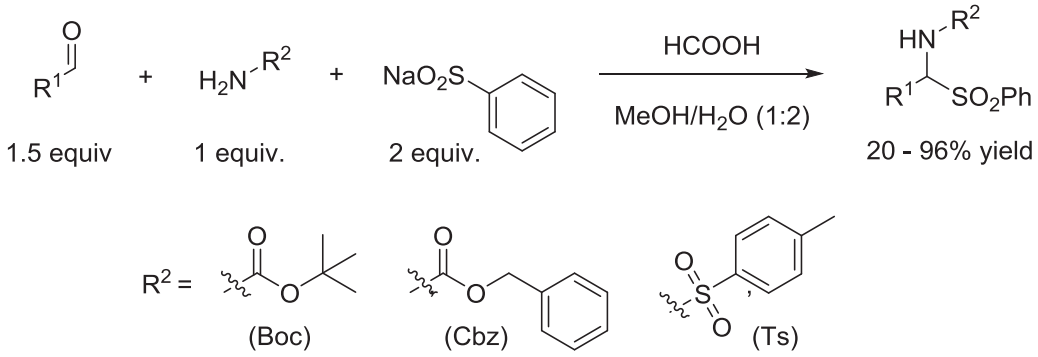
In addition, as a second aim, we evaluated $\alpha$-substituted MTMs for the direct Mannich type reaction in order to obtain $\beta$-amino thioesters bearing linear all-carbon $\alpha$-quaternary stereogenic centers (Scheme 32). The third aim was to explore the synthetic value of $\beta$-amino thioesters in peptide synthesis. Thioesters are activated carboxylic acids, thus $\beta$-amino thioesters should be applicable as building blocks for coupling agent free liquid phase as well as solid phase peptide synthesis.

# 3 Investigations on the Addition Reaction of Mono Thiomalonates to Imines

## 3.1. Synthesis of the Imines

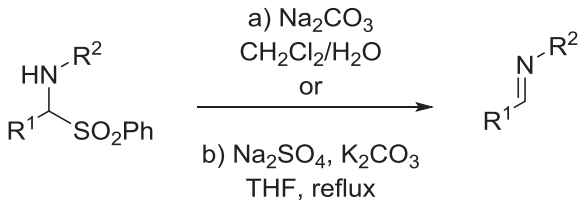
We started this work with the synthesis of different protected imines for the organocatalyzed addition reaction of mono thiomalonates (MTMs). Protective groups on the amine of the $\beta$-amino thioesters are crucial to the further synthetic utility of the Mannich products. Additionally, the reactivity of imines is lower than that of the parent aldehyde, and an activating group on the nitrogen has been shown to enhance this reactivity.[92] The *p*-methoxyphenyl group (PMP) is the most commonly used protective group in imine chemistry.[93-95] Especially in proline-catalyzed Mannich reactions, the PMP group appeared to be crucial to obtain high enantioselectivities.[40, 96] However, its removal requires harsh oxidative conditions, limiting the synthetic potential of the Mannich products. Also frequently used is the tosyl group (Ts). It has been found to be a highly electronically activating protecting group and is typically used in decarboxylative Mannich reactions using MAHTs as nucleophiles.[28-29] Additionally, benzyloxycarbonyl (Cbz) and *tert*-butoxycarbonyl (Boc), due to their easy removability under mild conditions, are of great interest for the direct Mannich reaction.[82, 97-108] Amongst those examples we chose tosyl, Boc-carbamate and Cbz-carbamate as protecting groups for our studies and prepared *N*-Ts imines, *N*-Boc imines and *N*-Cbz imines.

The imines were synthesized following a two-step protocol that was introduced by the group of Green.[109] In a first step $\alpha$-amido sulfones were prepared in a condensation reaction of an aldehyde, an arene-sulfinate and, in the case of Boc- and Cbz-$\alpha$-amido sulfones a carbamate, whereas for Ts-$\alpha$-amido sulfones *para*-toluylsulfonamide was used (Scheme 33). All reaction components were dissolved in a mixture of 1:2 methanol and water followed by addition of formic acid. After 48 – 72 h at room temperature, $\alpha$-amido sulfones precipitated from the reaction mixture and were easily purified by filtration and washing with water and diethylether. These imine precursors are neither air nor moisture sensitive and can be stored for several years (> 5 years).




*Scheme 33. Synthesis of α-amido sulfones*

The corresponding imines were formed in a second step from $\alpha$-amido sulfones by elimination with base under aqueous or water free conditions (Scheme 34).[92, 109]

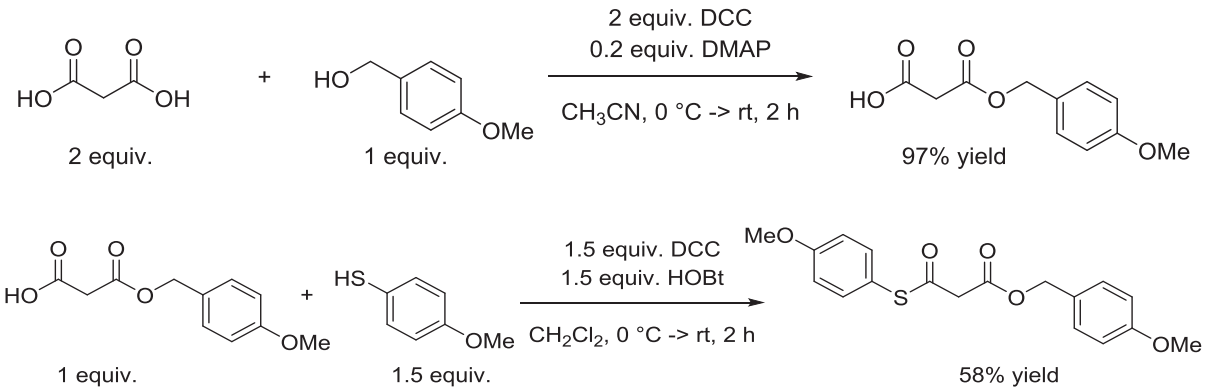



*Scheme 34. Synthesis of imines under aqueous (a) or waterfree (b) conditions*

Imines are less stable than their $\alpha$-amido sulfone precursors due to their tendency to hydrolyze when they are not stored under dry conditions. Hence, they were freshly prepared from the corresponding $\alpha$-amido sulfone precursors for all asymmetric reactions within this thesis.

## 3.2 Synthesis of Mono Thiomalonates (MTMs)

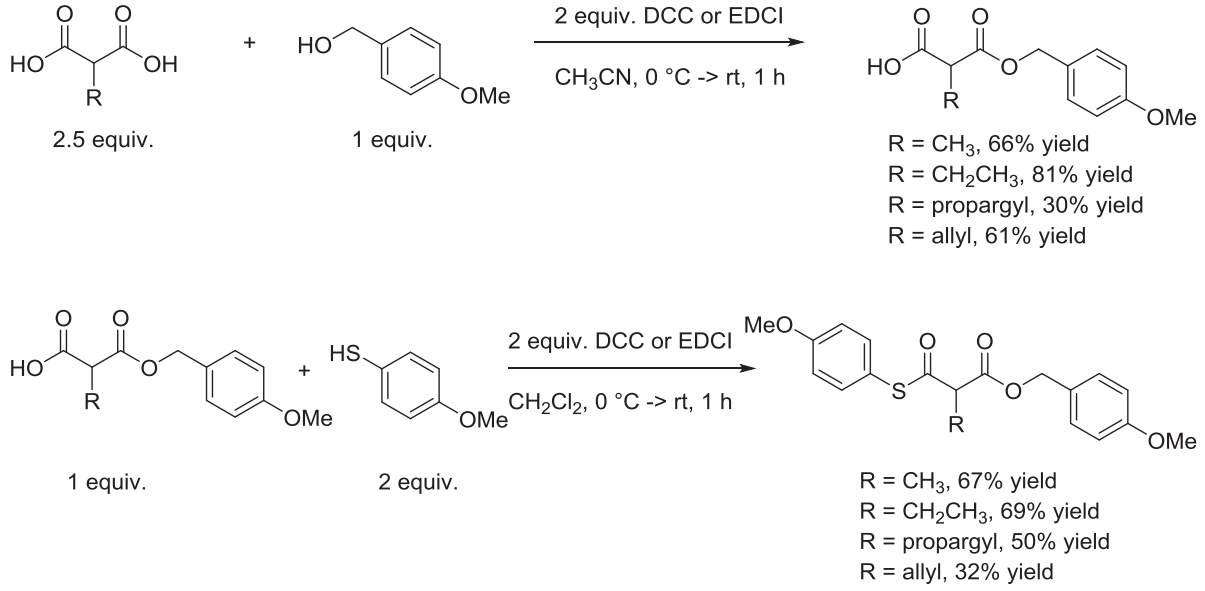
Mono thiomalonates are protected malonic acid half thioesters and therefore asymmetric malonic acid derivatives. Our group has developed a convenient protocol for the synthesis of mono thiomalonates.[86] In a first step a regular malonic acid halfoxoester (MAHO) was formed in a DCC mediated coupling with *para*-methoxybenzyl-alcohol (PMB-OH) and an excess of malonic acid. After isolation of the MAHO by extraction, DCC coupling with *para*-methoxyphenyl-thiol (PMP-SH) resulted in the desired MTM (Scheme 35).




*Scheme 35. Synthesis of MTMs*

This strategy gave access to a variety of asymmetric malonic acid derivatives. Since initial addition reactions of PMB-O/PMP-S MTM with imines resulted in already good conversions (> 90%) and stereoselectivities (> 70% ee) (chapter 3.4.2 and 3.4.3), this mono thiomalonate was chosen for our studies also with regard to results obtained in the addition reaction with nitroolefins, where PMB-O/PMP-S MTM performed most successful.[86]

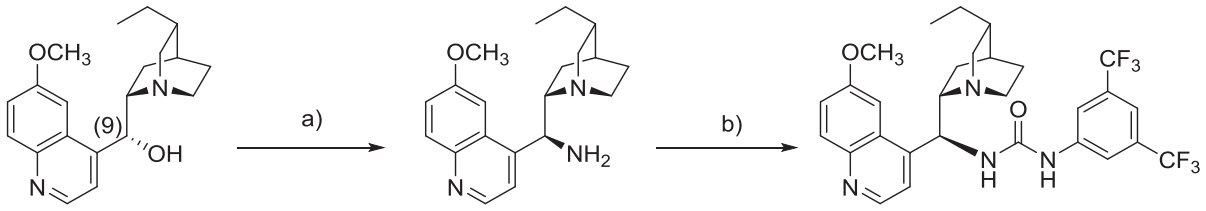
This synthesis protocol was also used for the generation of MTMs bearing small substituents at the $\alpha$-position, *e.g.* methyl, ethyl, allyl or propargyl substituents (Scheme 36). $\alpha$-Substituted malonic acid substrates were either commercially available or were prepared out of malonates by hydrolyses of the ester, prior to the coupling reaction. The resulting $\alpha$-substituted PMB-O/PMP-S MTMs were used in Mannich type transformations yielding products with linear all-carbon quaternary stereogenic centers.




*Scheme 36. Synthesis of α-substituted MTMs*

## 3.3 Organocatalysts

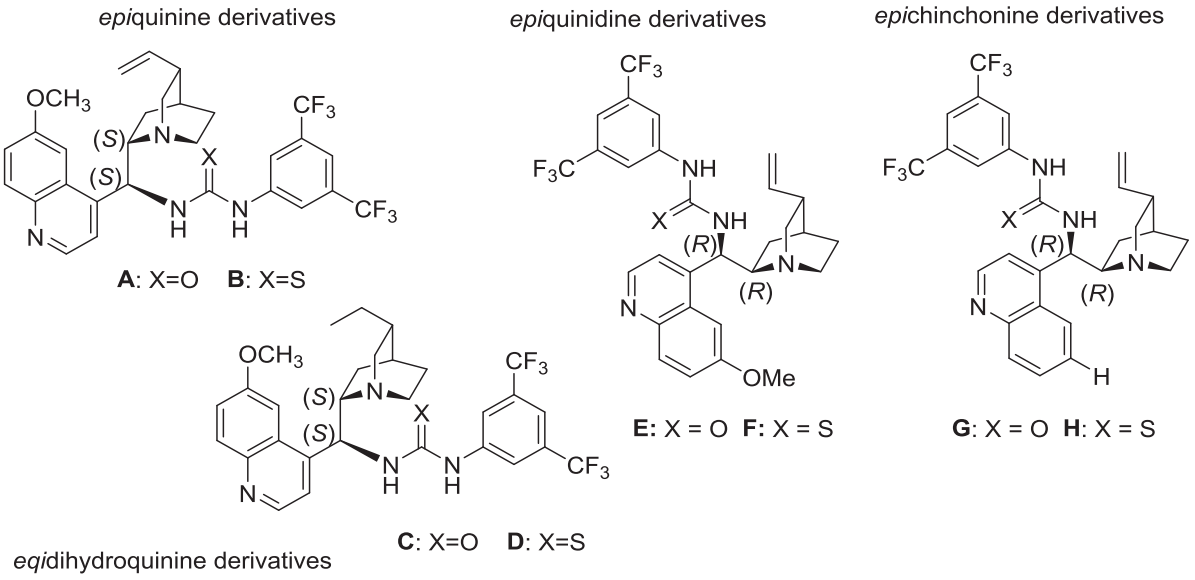
As mentioned in the introduction, bifunctional catalysts have proven to efficiently catalyze addition reactions of MAHTs, malonates and MTMs to electrophiles.[28, 32, 62-63, 72, 75, 83, 86] Cinchona alkaloid urea or thioureas are among the most widely used catalysts. Cinchona alkaloids are commercially available and easily transformed into urea or thiourea derivatives in a two-step protocol (Scheme 37). As a first step, an azide is introduced under Mitsunobu conditions at C9 of the cinchona alkaloid resulting in the inversion of its configuration. The azide gets then reduced to an amine *via* Staudinger reduction, which is transformed in a second step into a urea or thiourea moiety in the presence of isocyanates or thioisocyanates respectively. Due to the structurally diverse family of Cinchona alkaloids, a collection of several potential catalysts is readily generated.[110-113] The catalysts offer first, a basic moiety (tertiary amine) for deprotonation of thioesters $\alpha$-proton (thioester enolate generation) and second the protonated basic moiety as well as the urea/thiourea moiety for hydrogen bonding, thus activating both substrates and providing a defined stereochemical environment




*Scheme 37. Synthesis of epiquinine urea derivative: a) i: $PPh_3$, THF, DIAD, DPPA, 0 °C, 12 h; ii: $PPh_3$, 50 °C, 2 h, $H_2O$; b) i: 3,5-bis(trifluoromethyl)phenylisocyanate, THF, 0 °C, 12 h, 91%*

The Cinchona alkaloid derived catalysts that were tested within this study are shown in Scheme 38. The set of catalysts contains quinine **A** and **B** as well as quinidine derivatives **E** and **F** (*pseudo* enantiomers) to explore the influence of the stereochemistry at C8 and C9 of the cinchona alkaloid moiety on the outcome of the addition reaction. Additionally, the influence of the presence or absence of the methoxy group at the quinoline system was explored by comparing quinidine **E** and **F** and cinchonine derivatives **G** and **H**. Also the influence of the ethyl *vs.* vinyl substituent at the quinuclidine moiety was investigated by comparing quinine **A** and **B** with dihydroquinine **C** and **D** derivatives in the catalyst set. Finally, also the influence of the hydrogen bonding moiety was explored by comparing

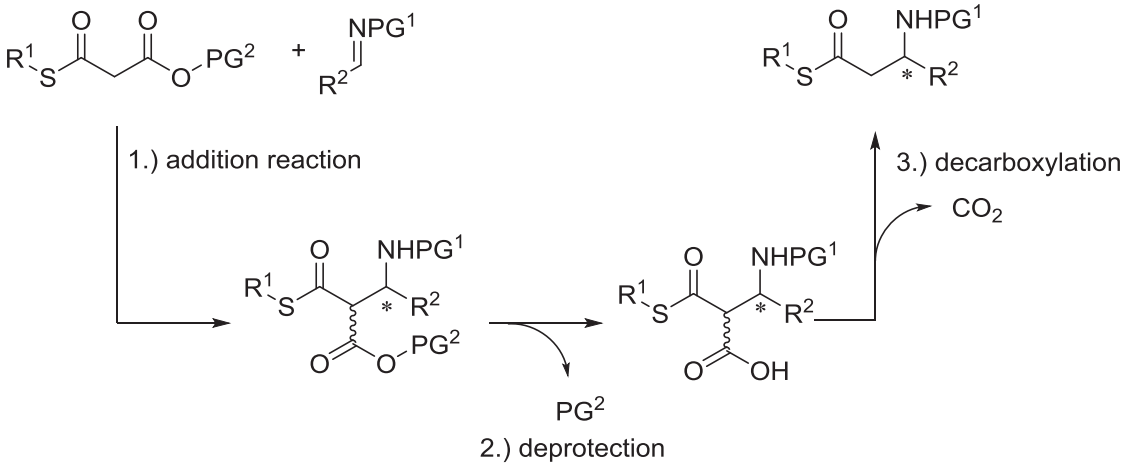
catalysts containing a urea functionality **A**, **C**, **E** and **G** with catalyst having a thiourea functionality **B**, **D**, **F** and **H**.




*Scheme 38. Cinchona alkaloid urea/thiourea derived catalysts that were tested for the addition reaction of MTMs to imines*

## 3.4 Addition Reactions of $\alpha$-Unsubstituted MTMs to Imines

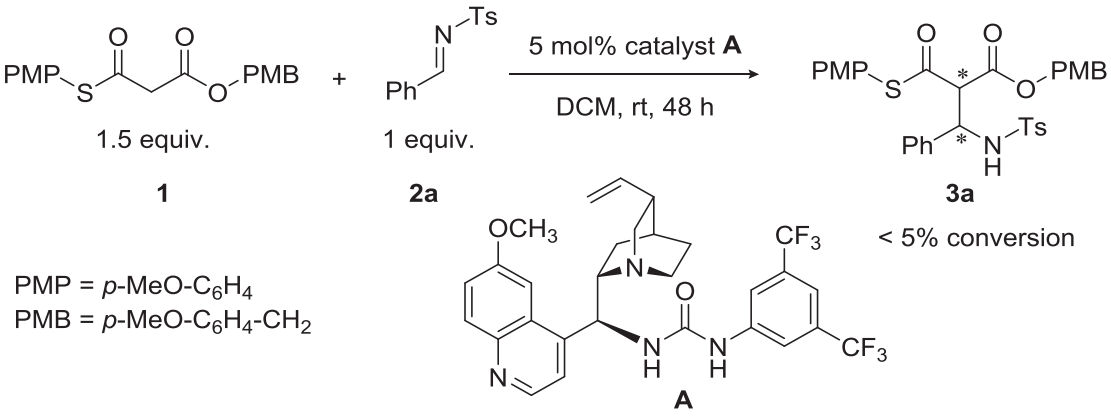
The strategy for the direct Mannich type reaction between $\alpha$-unsubstituted MTMs and imines includes three steps. In the first step the C-C bond forming event takes place. Within this addition reaction, two new stereogenic centers are formed. One stereogenic center, which is in the $\beta$-position to the thioester, is formed enantioselectively. The other stereogenic center which is in the $\alpha$-position to the thioester is formed without enantiocontrol. The reason for that is given by the basic environment of the reaction, provided by the catalyst. This results in easy de- and reprotonation at the $\alpha$-position of the $\beta$-amino thioester, thus leading to the racemization of this stereogenic center. However, upon cleavage of the acid labile PMB ester, $\beta$-amino thioester bearing a free carboxylic acid is generated which in a next step is decarboxylated under basic conditions resulting in erasing the non enantioselectively formed stereo center (Scheme 39).




*Scheme 39. Strategy for the use of MTMs as electrophile in Mannich type reactions*

## 3.4.1 *N*-Ts Protected Imines

We started to investigate *N*-Ts-imines as electrophiles with a model reaction between arylaldimine **2a**, generated according to the described method (Scheme 34a), and MTM **1** using 5 mol% of *epi*quininethiourea catalyst **A**, which was identified as optimal catalyst in the 1,4 addition reaction of MTMs and nitroolefins (Scheme 40).[86, 92, 109]

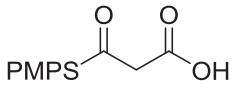
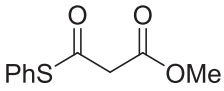


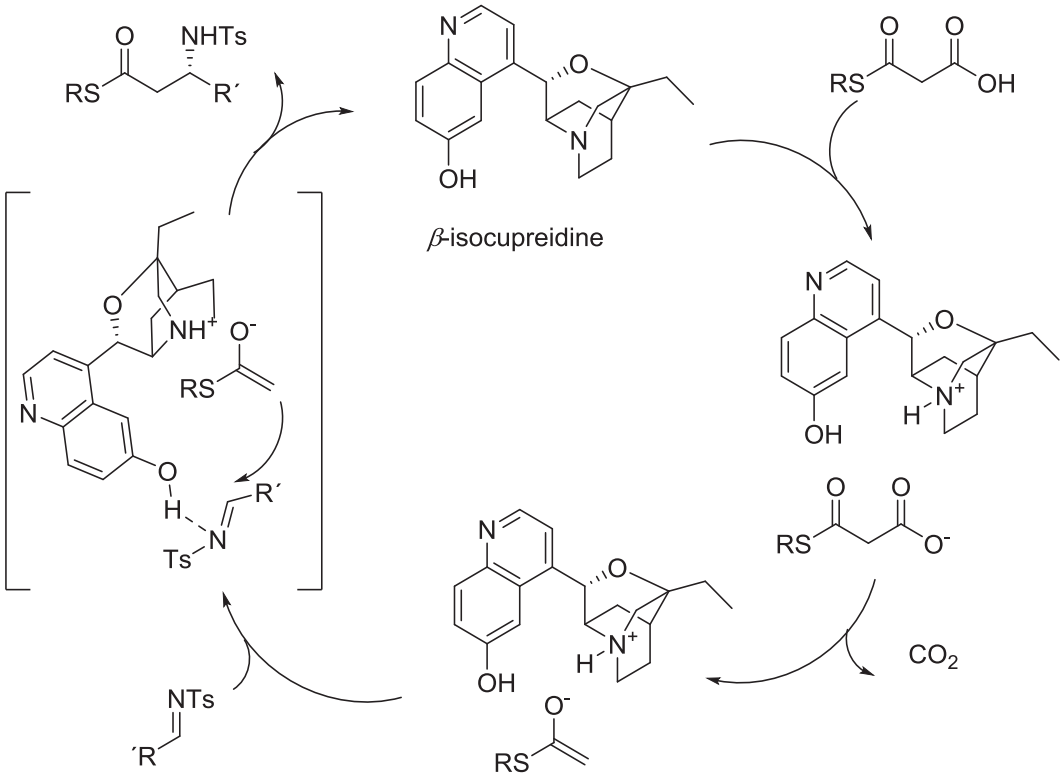

*Scheme 40. Mannich type reaction between MTM and N-Ts aryl aldimine*

Although *N*-Ts protected imines served as suitable electrophiles in the decarboxylative addition reactions of MAHTs,[28-29] in the model reaction between *N*-Ts imine **2a** and MTM **1** the substrates proved to be not very reactive. The reaction was conducted in methylene chloride and analyzed after 48 hours. Less than 5% conversion of the MTM **1** was observed and additionally no other side products were formed. Also in the presence of different other cinchona alkaloid urea and thiourea derivatives (catalysts **A**-**G**, see chapter 3.3) only traces of

addition product **3a** were obtained. In contrast, Ricci *et al.* investigated the decarboxylative Mannich reaction between MAHTs and *N*-Ts imines obtaining yields of 41 - 48%.[29] However, to strengthen the theory that the decarboxylation plays a crucial role for the occurrence of the reaction, mechanistic experiments with a methyl protected MAHT were conducted by the Ricci group (Scheme 41).[29] Indeed, when a methyl protected MAHT was used as substrate only slow and sluggish addition to *N*-Ts imines were observed after 48 hours in the presence of the cinchona alkaloid derived catalyst *β*-isocupreidine (Table 1, entry 2).

*Table 1. Different reactivities of MAHT and protected MAHT towards N-Ts imines*[29]

| entry | substrate | yield [%] |
|---|---|---|
| 1 |  | 41-48 |
| 2 |  | traces |

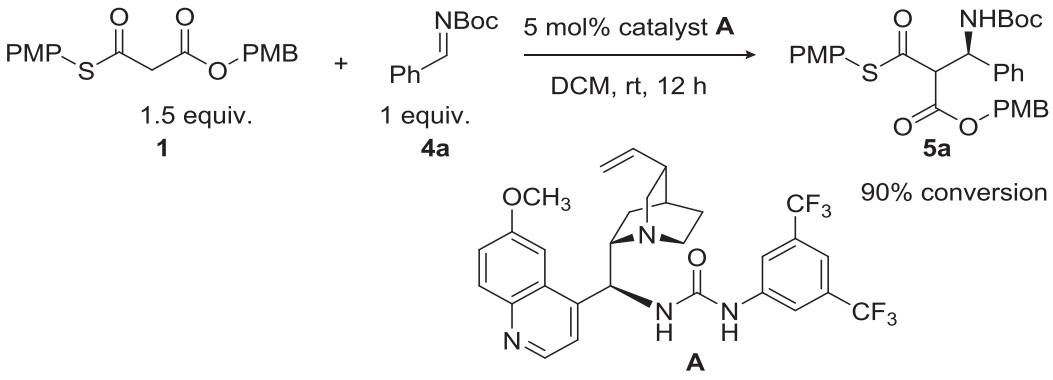



*Scheme 41. Ricci´s proposed catalytic cycle for the decarboxylative addition reaction of MAHT to N-Ts-imines*[29]

Those findings are in agreement with our results revealing *N*-Ts imines as unsuitable electrophiles for the Mannich type reaction with protected MAHTs (MTMs).

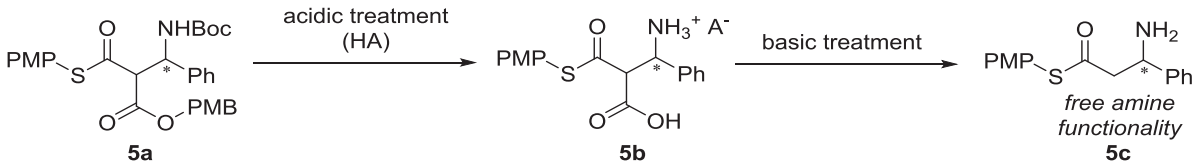
### 3.4.2 *N*-Boc Protected Imines

Next we tested *N*-Boc protected imines as electrophiles. In contrast to *N*-Ts protected imines, *N*-Boc protected imine **4a** reacted readily with 1.5 equivalents of MTM **1** in a first model reaction catalyzed by 5 mol% *epi*quinine urea catalyst **A** (Scheme 42). Addition product **5a** was observed in 90% conversion after 12 hours reaction time in methylene chloride at room temperature.



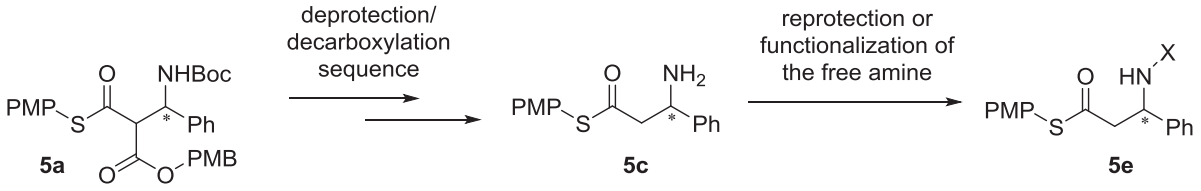

*Scheme 42. Mannich type reaction between MTM **1** and N-Boc aryl aldimine **4a***

The *tert*-butoxycarbonyl (Boc) group is of synthetic interest since it can easily be removed from the addition product upon acidic treatment, thus providing the product for further functionalization. However, one limitation of using *N*-Boc protected imines for the addition reaction with PMB-O/PMP-S MTM **1** lies in the fact that the *para*-methoxy group of product **5a** is not orthogonal to the *tert*-butoxycarbonyl group of its amine. This means that acidic treatment of the addition product **5a** leads to the deprotection of both, the ester and amine protecting groups resulting in deprotected *β*-amino thioester **5c** (Scheme 43).



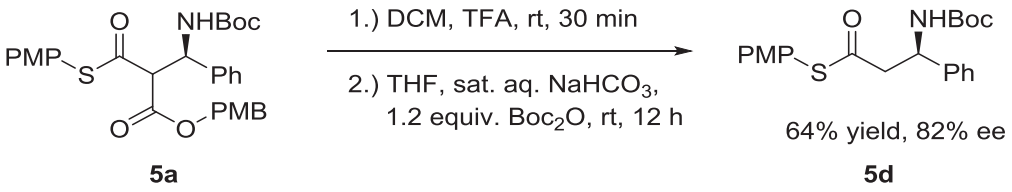

*Scheme 43. Acidic deprotection and basic decarboxylation sequence of N-Boc β-amino thioester **5a***

On the one hand, this gives direct access to *β*-amino thioesters with a free amine functionality (**5c**), on the other hand this rises difficulties in the chromatographic determination of the final products´ (**5c**) stereoselectivitiy. To overcome this problem we considered the following strategy. We thought to determine the stereoselectivity of the addition product **5a** before the deprotection/decarboxylation sequence and prove that the enantioselectivity of the stereocenter at the *β*-position remains unaffected after the deprotection and decarboxylation sequence (Scheme 44). This should be possible by reprotecting or functionalize decarboxylated product **5c** and compare both determined enantioselectivities (**5a** and **5e**) (Scheme 44). In that manner a rapid screening for stereoselectivity should be possible directly after the addition reaction.




*Scheme 44. Acidic deprotection and basic decarboxylation sequence followed by functionalization of β-amino thioester **5c***

However, the determination of the enantiomeric ratio of addition product **5a** was found to be difficult. Several attempts to separate the four diastereomers of **5a** by analytical HPLC analysis failed. Therefore, we concentrated on a second strategy. In order to shorten the sequence to obtain a product suitable for chiral chromatographic analysis of the stereoselectivity, we developed a decarboxylation sequence in which a *N*-Boc reprotection step is incorporated (Scheme 45). To our delight we found the following reaction sequence to work. First, addition product **5a** was treated with a 1:1 mixture of trifluoroacetic acid (TFA) in methylene chloride for 30 minutes. After evaporation of all volatiles, a mixture of 1.2 equivalents of $Boc_2O$ in THF and saturated aqueous $NaHCO_3$ solution was added to the crude mixture which was then vigorously stirred at room temperature for 12 hours. Extraction and chromatographic purification then yielded *N*-Boc protected *β*-amino thioester **5d** in 64% yield over two steps (Scheme 45). The stereoselectivity of product **5d** was now possible to be determined by chiral chromatographic analysis and an enantiomeric excess of 82% ee was determined for this first model reaction.




*Scheme 45. Deprotection and decarboxylation of N-Boc Mannich addition product*

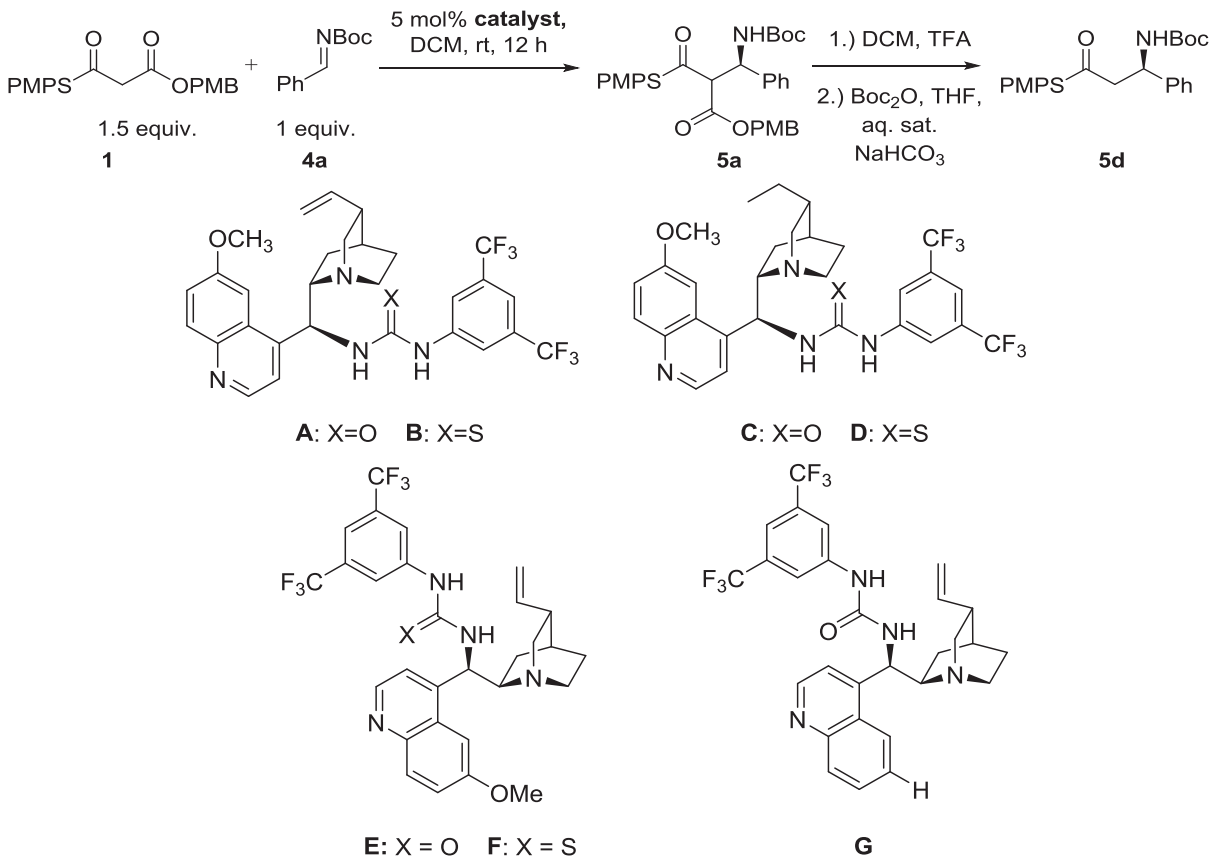
### 3.4.2.1 Optimization of the Reaction Conditions

With the analytical issue resolved, we continued the studies with a catalyst screening for the addition reaction of MTM **1** and *N*-Boc protected imine **4a**. Several cinchona alkaloid urea and thiourea derivatives **A-G** were tested for their catalytic activity in methylene chloride at room temperature (Table 2). The set of catalysts that was tested contained *epi*quinine **A** and **B** as well as *epi*quinidine derivatives **E** and **F** (*pseudo* enantiomers) to explore the influence of the stereochemistry at the C9 position of the cinchona alkaloid moiety (see chapter 3.3). Additionally, the influence of the presence or absence of the methoxy group at the quinoline system was explored by comparing *epi*quinidine **E** and *epi*cinchonine derivatives **G**. Also the influence of the ethyl *vs.* vinyl substituent at the quinuclidine moiety was investigated by comparing *epi*quinine **A** and **B** and *epi*dihydroquinine **C** and **D** derivatives in the catalyst set. Finally, also the influence of the hydrogen bonding moiety was explored by comparing catalysts containing an urea functionality, **A** and **C** with catalyst having a thiourea functionality **B** and **D**. The reactions of the catalyst screening were conducted with 1.5 equivalents of MTM **1**, 1 equivalent of *N*-Boc imine **4a** and 5 mol% of catalyst. The reactions were performed in methylene chloride at room temperature and were analyzed after 12 hours of reaction time.

With all catalysts tested, moderate to good yields of the addition product **5a** were obtained (Table 2). Higher yields were obtained when the catalyst contained a urea moiety instead of a thiourea moiety. For example with *epi*quinine urea derivative **A** 87% yield was determined whereas with *epi*quinine thiourea catalyst **B** 64% yield were obtained (Table 2, entries 1 and 2). Also with the dihydroanalog of quinine and the quinindine derived catalysts higher yields were observed with the urea derivative (90 % yield for **C** *vs.* 87 % yield for **D**; 81% yield for **E** *vs.* 76% yield for **F**). Additionally, an ethyl substituent at the quinuclidine moiety of the catalyst led to higher yields than a vinyl substituent. With *epi*dihydroquinine urea derivative **C**, 90% yield were obtained, whereas the reaction with *epi*quinine urea **A**

resulted in a slightly lower yield of 87% (Table 2, entries 1 and 3). The same trend was even more pronounced for the mentioned thiourea derivatives. For *epi*dihydroquinine thiourea derivative **D** 87% yield were obtained, whereas with *epi*quinine thiourea **B** only 64% of the addition product **5a** were formed (Table 2, entries 2 and 4).

*Table 2. Organocatalyst screening for the addition reaction of MTM 1 and N-Boc protected imine **4a***




| entry | catalyst | yield[a] of 5a [%] | ee [b] of 5d [%] |
|---|---|---|---|
| 1 | **A** | 87 | 82 (*R*) |
| 2 | **B** | 64 | 74 (*R*) |
| 3 | **C** | 90 | 83 (*R*) |
| 4 | **D** | 87 | 80 (*R*) |
| 5 | **E** | 81 | 80 (*S*) |
| 6 | **F** | 76 | 70 (*S*) |
| 7 | **G** | 92 | 65 (*S*) |

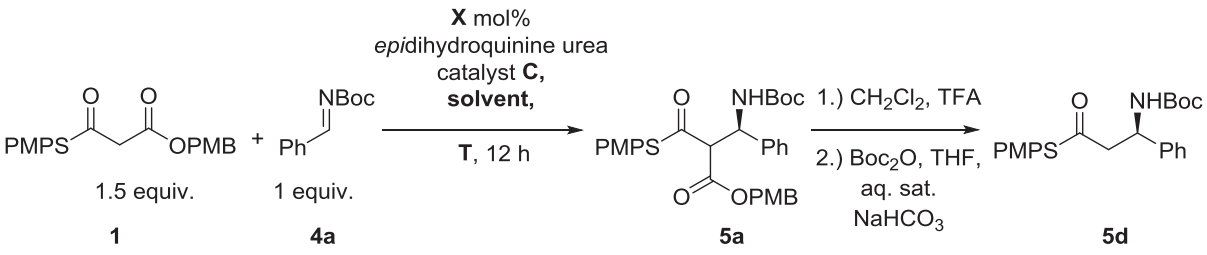
[a]Isolated yield. [b]Determined by chiral-phase HPLC analysis.

With the *pseudo* enantiomers of the quinine derivatives *epi*quinidine urea derivative **E** and *epi*quinidine thiourea derivative **F** lower yields were observed for the urea derivative (81% yield for **E** *vs.* 87% yield for **A**) and higher yields for the thiourea derivatives (76% yield for **F** *vs.* 64% yield for **B**) (Table 2, entries 1,2,5,6). When the methoxy group at the quinoline was replaced by a simple proton, such as in *epi*cinchonine urea **G**, the highest yield of 92% was obtained (Tabel 2, entry 7). The enantioselectivities were obtained from *β*-amino thioester **5d** after a deprotection, decarboxylation and Boc-reprotection sequence, since, as already mentioned, no suitable conditions were found to analyze the enantiomeric excess of addition product **5a**.

For the enantioselectivities similar trends were observed. As for the observed yields, higher values of enantiomeric excess were obtained in the presence of urea derived catalysts compared to thiourea catalysts. For example with with *epi*quinine urea derivative **A** 82% ee was obtained whereas with *epi*quinine thiourea catalyst **B** 74% ee were obtained (Table 2, entries 1 and 2). The same is true for the dihydroanalog of quinine and the quinindine derived catalysts and higher values of enantiomeric excess were observed with the urea derivative (83 % ee for **C** *vs.* 80 % ee for **D**; 80% ee for **E** *vs.* 70% ee for **F**). Comparing quinine derived catalysts and its dihydroanalogs, better enantioselectivities were obtained with the catalyst of the dihydroanalogs. Although more or less the same results were obtained for the urea derivatives (83% ee for *epi*dihydroquinine urea derivative **C**, 82% ee for *epi*quinine urea derivative **A**, table 2, entries 1 and 3), the trend was more pronounced for the comparable thiourea derivatives. For *epi*dihydroquinine thiourea derivative **D** 80% ee was obtained, whereas with *epi*quinine thiourea **B** only 74% ee were obtained (Table 2, entries 2 and 4). Catalysts with inverted stereochemistry at the C9 position provided the opposite enantiomer of *β*-amino thioester **5d** with ee´s of 80% ee for *epi*quinidine urea derivative **E** and 70% ee for *epi*quinidine thiourea derivative **F** (Table 2, entries 5 and 6). The results for *epi*cinchonine urea **G** (65% ee) clearly showed that the presence of the methoxy group at the quinoline moiety is necessary to obtain high enantioselectivity (Table 2, entry 7). In summary, *epi*dihydroquinine urea catalyst **C** performed best in terms of reactivity and stereoselectivity by providing addition product **5a** in 90% yield and *β*-amino thioester **5d** in 83% ee (Table 2, entry 3). Therefore we chose *epi*dihydroquinine urea catalyst **C** as optimal catalyst and used it for further optimization studies.

Next, we investigated the influence of different parameters on the reaction outcome (Table 3). Besides the solvent, also the temperature and the catalyst loading was varied.

*Table 3. Influence of the reaction parameters catalyst loading, solvent and temperature*




| entry | mol% | solvent | T [ °C] | yield[a] of 5a [%] | ee[b] of 5b [%] |
|---|---|---|---|---|---|
| 1 | 5 | $CH_2Cl_2$ | RT | 90 | 80 (*R*) |
| 2 | 1 | $CH_2Cl_2$ | RT | 91 | 80 (*R*) |
| 3 | 1 | $CHCl_3$ | RT | quant. | 79 (*R*) |
| 4 | 1 | toluene | RT | quant. | 76 (*R*) |
| 5 | 1 | benzene | RT | quant. | 76 (*R*) |
| 6 | 1 | THF | RT | 95 | 74 (*R*) |
| 7 | 1 | EtOAc | RT | 82 | 69 (*R*) |
| 8 | 1 | acetone | RT | 99 | 68 (*R*) |
| 9 | 1 | $CH_3CN$ | RT | 85 | 64 (*R*) |
| 10 | 1 | $CH_2Cl_2$ | -50 | 89 | 90 (*R*) |
| 11 | 1 | $CH_2Cl_2$ | -80 | 98 | 94 (*R*) |

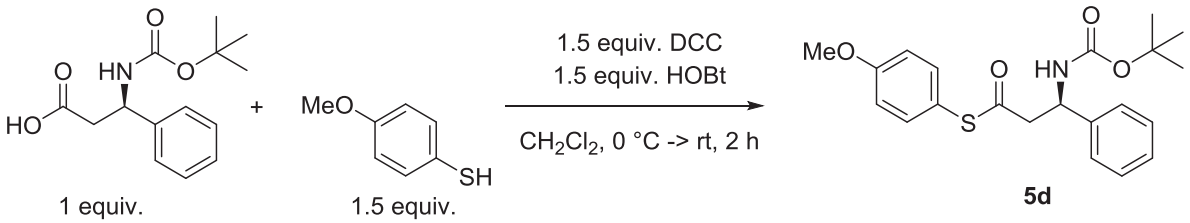
[a]Isolated yield [b]Determined by chiral-phase HPLC analysis.

Encouraged by the high yields obtained with 5 mol% *epi*dihydroquinine urea catalyst **C** (90% yield), we explored the reaction with a lower catalyst loading such as 1 mol%, in methylene chloride at room temperature. We were pleased to obtain similarly good results for the yield of addition product **5a** (91% yield) as well as for the enatiomeric excess of *β*-amino thioester **5d** (80% ee) (Table 3, entry 2). Next, a solvent screening was conducted at room temperature with 1 mol% of *epi*dihydroquinine urea catalyst **C**. The reaction proceeded sufficiently well in a range of different polar and apolar solvents. Best results for the yield of addition product **5a** and for the enantiomeric excess of *β*-amino thioester **5d** were obtained in chloroform and dichloromethane, however, due to environmental reasons, methylenechloride was chosen for further optimization reactions (Table 3, entries 2 and 3). Lowering the temperature had a

positive effect on the enantioselectivity. At -50 °C the enantiomeric excess of *β*-amino thioester **5d** increased to 90% and at -80 °C, 94% ee were achieved (Table 3, entries 10 and 11). Finally we were pleased to obtain the addition product **5a** under the optimized reaction conditions in a yield of 98% and an enantiomeric excess of *β*-amino thioester **5d** of 94% with as little as 1 mol% of *epi*dihydroquinine urea catalyst **C** (Table 3, entry 11).

### 3.4.2.2 Determination of the Absolute Configuration

To determine the absolute configuration of *N*-Boc *β*-amino thioester **5d** we compared its HPLC retention time with that of the same thioester that was synthesized from commercially available (*R*)-Boc protected $\beta^3$-phenylalanine in a DCC mediated coupling reaction with *p*-methoxy thiophenol (Scheme 46).




*Scheme 46. Synthesis of β-amino thioesters from Boc protected D-$\beta^3$-phenyl alanine*

Thioester **5d** was purified *via* preparative TLC and the retention time of the pure enantiomer was determined by HPLC ananlysis ($t_R$ = 20.5 minutes) (Figure 1). The major enantiomer of asymmetrically synthesized **5d** eluted as well at 20.5 minutes, whereas the minor enantiomer has a retention time of 18.5 minutes. By comparison of both HPLC chromatograms we were able to determine the configuration of the major enantiomer of **5d** to be (*R*).

**reference** **asymmetrically synthesized 5d**

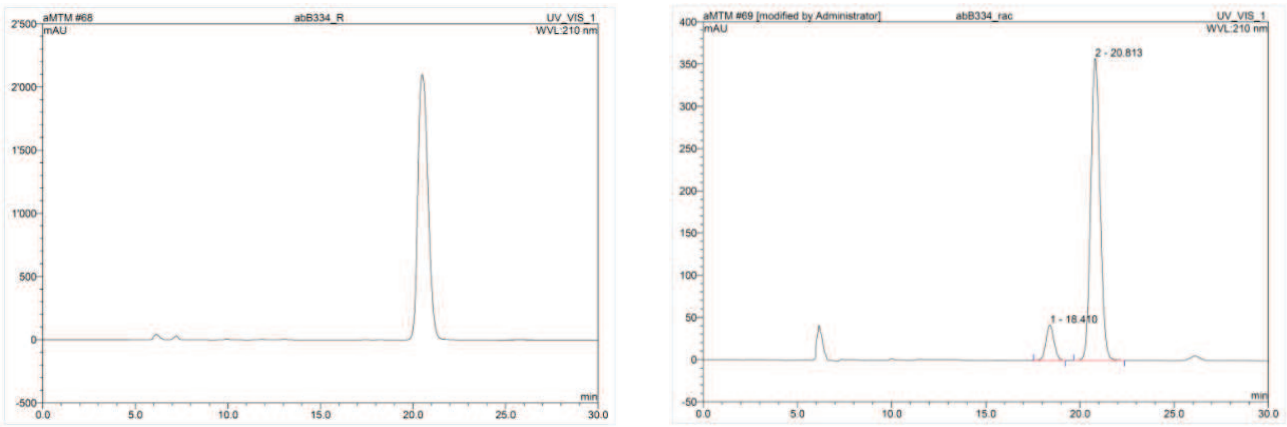
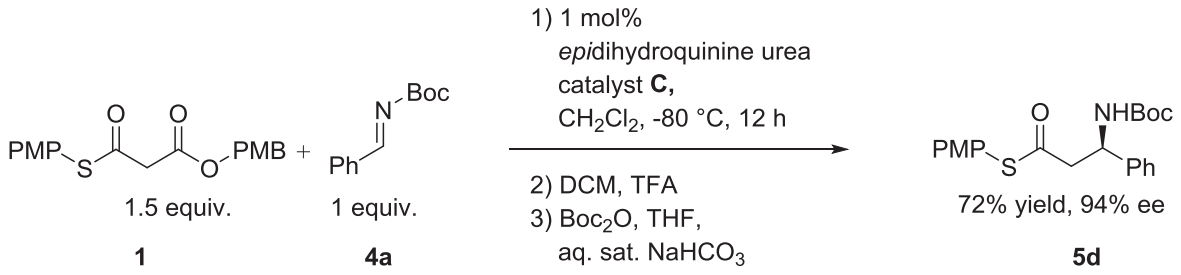



*Figure 1. Determination of the absolute configuration of β-amino thioester **5d** by HPLC analysis*

In summary we have shown that as little as 1 mol% of *epi*dihydroquinine urea catalyst **C** is sufficient to achieve good conversion (98% yield) within a reaction time of 12 hours in the direct Mannich type reaction between MTM **1** and *N*-Boc aryl imine **4a**. The corresponding *β*-amino thioester **5d** was obtained with a high enantioselectivity of 94% ee. A drawback of this reaction is the additional step of reprotecting the amine of the *β*-amino thioester **5c**, obtained after the deprotection decarboxylation sequence (Scheme 44). However we achieved to combine the Boc reprotection step with the decarboxylation step and obtained *β*-amino thioester **5d** in an overall yield of 72% after three steps (Scheme 47).

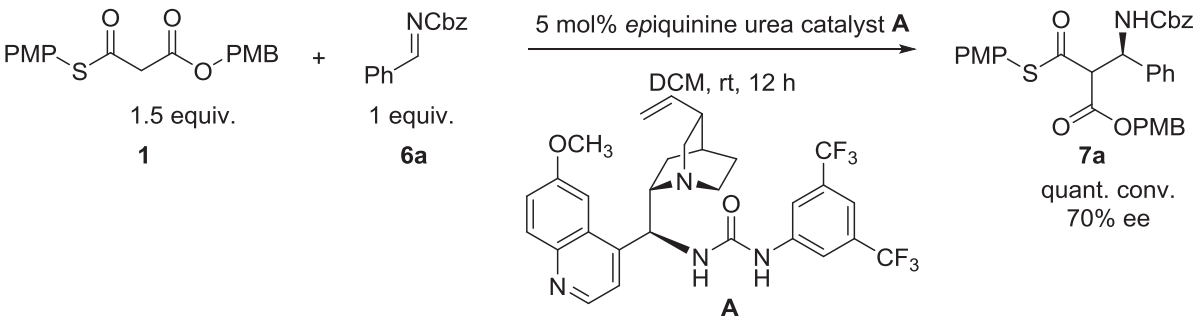



*Scheme 47. Optimized reaction conditions for the Mannich type reaction of MTM and N-Boc imine **4a***

## 3.4.3 *N*-Cbz Protected Imines

*N*-Cbz protected imines, as mentioned in chapter 3.1, are also widely used electrophiles for the direct Mannich type reaction. The Cbz group is orthogonal to the PMB group of the MTM and offers therefore advantages for our strategy towards the synthesis of *β*-amino thioesters which includes an acidic deprotection step (Scheme 39).

In a first model reaction in methylene chloride with 1.5 equivalents of MTM **1** and *N*-Cbz arylaldimine **6a**, addition product **7a** was quantitatively formed with an enantiomeric excess of 70% in the presence of 5 mol% of *epi*quinine urea derivative **A** after 2 hours of reaction time (Scheme 48).



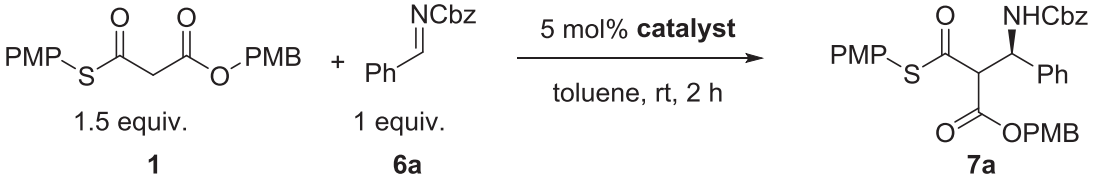

*Scheme 48. First model reaction with N-Cbz imines as electrophiles.*

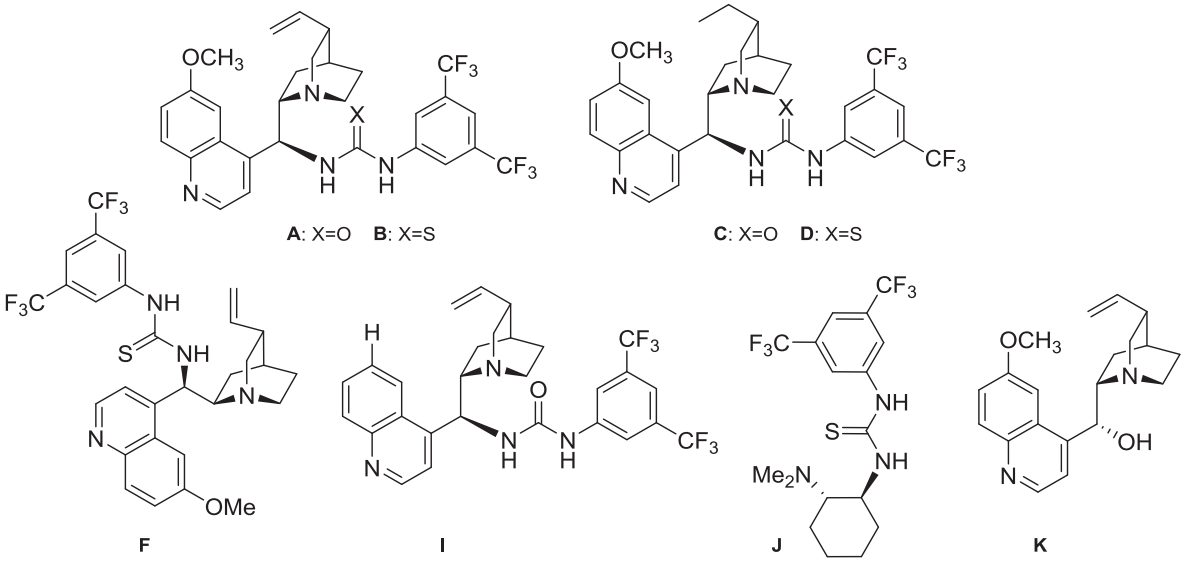
Encouraged by these initial results we continued the study with a screening of catalysts. The set of catalysts tested included cinchona alkaloid urea and thiourea derivatives **A** - **D** and **F**, that where introduced in chapter 3.3. To enlarge the structural diversity of the catalyst set, additionally, *epi*cinchonidine urea catalyst **I**, as well as Takemotos catalyst **J**, bearing a thiourea moiety and a tertiary amine in a different spatial arrangement, and simple quinine **K**, lacking a urea or thiourea moiety, were tested. The reactions of the catalyst screening were conducted with 1.5 equivalents of MTM **1**, 1 equivalent of *N*-Cbz imine **6a** and 5 mol% of catalyst (Table 4). The reactions were performed in toluene at room temperature and were analyzed after 2 hours of reaction time.

Amongst the catalysts tested all urea- and thiourea derivatives (catalysts **A** – **J**) showed nearly the same catalytic efficiency and quantitative conversion was observed for catalysts **A-J** (Table 4, entries 1-7). Only simple quinine **K** was less efficient, and 60% conversion to addition product **7a** was observed after 2 hours in the presence of 5 mol% catalyst (Table 4, entry 8). In terms of stereoselectivity bigger differences were observed. *Epi*quinine urea catalyst **A** provided the addition product with an enantiomeric excess of 70% and slightly lower values (66% ee) were obtained for the corresponding thiourea catalyst **B** (Table 4, entries 1 and 2). In the presence of the dihydroanalogs no differences where observed for the urea or thiourea derivative. For both *epi*dihydroquinine urea catalyst **C** and *epi*dihydroquinine thiourea catalyst **D** 75% ee were obtained for addition product **7a** (Table 4, entries 3 and 4). Comparing the results obtained with catalyst **A** and **C** (**B** and **D** respectively) clearly shows that an ethyl group at the quinuclidine moiety, as in *epi*dihydroquinine urea catalyst **C**, leads to a higher enantioselectivity (75% ee) than a vinyl group (70% ee for *epi*quinine urea catalyst **A**) (Table 4, entries 1 and 3). This trend was even more pronounced with the thiourea derivatives since 75% ee were obtained for *epi*dihydroquinine thiourea catalyst **D** and 60% ee for *epi*quinine thiourea catalyst **B** (Table 4, entries 2 and 4). No significant influence had the presence or absence of a methoxy group at the quinoline moiety since 70% ee were observed with *epi*quinine urea catalyst **A** and 69% ee for *epi*cinchonidine urea catalyst **I**, lacking this methoxy group (Table 4, entries 1 and 6). To investigate the importance of the stereochemistry at C9 of the cinchona alkaloid structure, *epi*quinidine thiourea catalyst **F** and *epi*quinine thiourea catalyst **B** were compared (Table 4 , entries 2 and 5). *Epi*quinidine thiourea catalyst **F** provided addition product **7a** with the opposite stereochemistry, however with a significantly lower enantioselectivity. Only 41% ee were obtained with *epi*quinidine thiourea catalyst **F** whereas 70% ee were obtained with *epi*quinine thiourea catalyst **B** (Table 4, entries 2 and 5). Takemotos catalyst **J**, possessing a different

spatial arrangement of the two crucial functionalities (tertiary amine and urea/thiourea moiety) was found to be less enantioselective. Although MTM **1** reacted quantitatively with *N*-Cbz arylaldimine **6a** in the presence of 5 mol% of catalyst **J**, the product was obtained in poor enantioselectivity of 54% (Table 4, entry 7).

*Table 4. Catalyst screening for the addition reaction of MTM **1** to N-Cbz-arylaldimine **6a***




| entry | catalyst | conv. [a] [%] | ee [b] [%] |
|---|---|---|---|
| 1 | **A** | quant. | 70 (*R*) |
| 2 | **B** | quant. | 66 (*R*) |
| 3 | **C** | quant. | 75 (*R*) |
| 4 | **D** | quant. | 75 (*R*) |
| 5 | **F** | quant. | 41 (*S*) |
| 6 | **I** | quant. | 69 (*R*) |
| 7 | **J** | quant. | 54 (*S*) |
| 8 | **K** | 60 | 12 (*S*) |

[a]Estimated by TLC and 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

Quinine **K** itself, lacking a urea or thiourea moiety, did also promote the reaction but was the least efficient catalyst in terms of stereoselectivity. Only 12% ee was obtained with quinine

**K**, clearly demonstrating the importance of the urea or thiourea moiety for the enantioselectivity of the catalyst (Table 4, entry 8). These results clearly show that not only the presence of the correct functional groups but also their relative orientation is important to obtain the addition products in good enantioselectivities. Cinchona alkaloid urea and thiourea derivatives with (*R*) configuration at C9 (**A** – **D** and **I**) possess the best orientation amongst all catalysts tested. Most enantioselectively (75% ee) performed the catalysts derived from *epi*dihydroquinine **C** and **D** and *epi*dihydroquinine urea catalyst **C** was chosen for further optimization studies (Table 4, entry 3).

### 3.4.3.1 Optimization of the Reaction Conditions

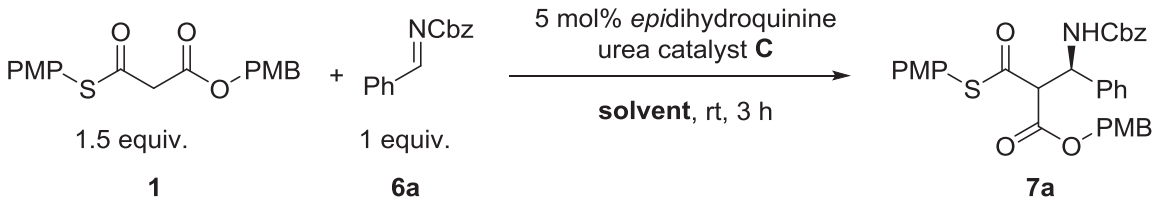
Having found *epi*dihydroquinine urea catalyst **C** as the optimal catalyst, we investigated the influence of different reaction parameters like solvent, temperature and catalyst loading on the outcome of the reaction. We started with a solvent screening at room temperature using 5 mol% of *epi*dihydroquinine urea catalyst **C**, *N*-Cbz imine **6a** and a slight excess of 1.5 equivalents of MTM **1**. We tested a variety of different protic, aprotic and aromatic solvents (Table 5). Diminished solubility of the starting materials were observed when linear ethers like diethylether and ethylvinylether (Table 5, entries 5 and 6) were used as solvents. Solubility problems were also observed in ethanol (Table 5, entry 12).

Methylene chloride and chloroform allowed for a good combination of high reactivity and high enantioselectivity (Table 5, entry 1 and 2). Also reactions in aromatic solvents provided the addition product **7a** in good yields, however in benzene a low enantiomeric excess of 54% was obtained (Table 5, entry 3 and 4). Reactions in polar aprotic solvents, such as tetrahydrofurane, ethyl acetate, acetone and acetonitrile, proceeded with different rates, however provided for lower enantioselectivities (< 50% ee) than in apolar solvents (Table 5, entry 7-10). Finally, in the polar protic solvent ethanol, as well as in DMF, the reaction did not proceed at all.

As the results show, big differences on the outcome of the reaction were observed in all solvents tested. Different solvents were tolerated however *epi*dihydroquinine urea catalyst **C** performed best in apolar solvents and the highest enantioselectivities were achieved in methylene chloride, chloroform or toluene (Table 5, entries 1-3).. One conclusion that can be drawn out of these results is that in polar solvents, which can possibly interact with the

substrates for example through H-bonding, lower stereoselectivities are obtained due to the fact that non-bonding interactions with the catalyst and the substrate are disrupted.

*Table 5. Solvent screening for the addition reaction of MTM **1** to N-Cbz arylaldimine **6a***



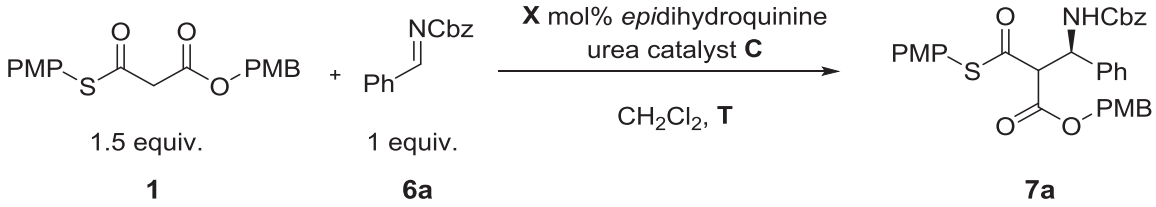

| entry | solvent | yield[a] [%] | ee[b] [%] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 90 | 73 (*R*) |
| 2 | $CHCl_3$ | 86 | 69 (*R*) |
| 3 | toluene | 86 | 72 (*R*) |
| 4 | benzene | 83 | 54 (*R*) |
| 5 | $Et_2O$ | 88 | 65 (*R*) |
| 6 | EVE | 41 | 35 (*R*) |
| 7 | THF | 94 | 27 (*R*) |
| 8 | EtOAc | 49 | 36 (*R*) |
| 9 | acetone | 50 | 45 (*R*) |
| 10 | $CH_3CN$ | 81 | 48 (*R*) |
| 11 | DMF | traces | - |
| 12 | EtOH | traces | - |

[a]Isolated yields. [b]Determined by chiral-phase HPLC analysis.

Since methylene chloride allowed for the best combination of reactivity and stereoselectivity of *epi*dihydroquinine urea catalyst **C**, we chose it as solvent for further optimization studies.

Next, we explored the influence of the catalyst loading and the temperature on the reaction outcome (Table 6). First, we set up a reaction with 1.5 equivalents of MTM **1** and *N*-Cbz-imine **6a** at room temperature using as little as 1 mol% of *epi*dihydroquinine urea catalyst **C**. Indeed, as little as 1 mol% of of *epi*dihydroquinine urea catalyst **C** was sufficient to obtain full conversion to the addition product **7a** within 3 hours in the same enantiomeric excess as with 5 mol% catalyst (73% ee) (Table 6, entries 1 and 2).

*Table 6. Optimization of the parameters catalyst loading and temperature for the addition reaction of MTM **1** to N-Cbz-arylaldimine **6a***



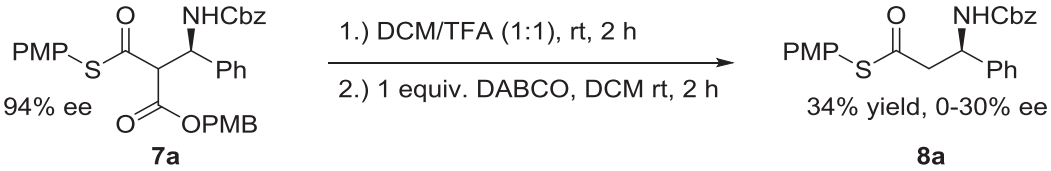

| entry | mol % | time [h] | T [°C] | conversion[a] [%] | ee[b] [%] |
|---|---|---|---|---|---|
| 1 | 5 | 2 | RT | quant. | 73 (*R*) |
| 2 | 1 | 3 | RT | quant. | 73 (*R*) |
| 3 | 1 | 3 | -10 | quant. | 86 (*R*) |
| 4 | 1 | 3 | -50 | 98[c] | 85 (*R*) |
| 5 | 1 | 4 | -78 | 98[c] | 94 (*R*) |
| 6 | 0.5 | 18 | -78 | 95 | 94 (*R*) |
| 7 | 0.3 | 18 | -78 | 95 | 91 (*R*) |
| 8 | 0.1 | 30 | -78 | 69 | 93 (*R*) |
| 9 | 0.01 | 30 | -78 | < 10 | - |

[a]Estimated by TLC and 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis. [c]Isolated yield

Since we obtained already good conversions in very short reaction times, our focus was now directed to optimize the stereoselectivity of the addition product **7a**. We conducted a temperature screening and were pleased to find that decreasing the temperature to -78 °C resulted in an increase in the stereoselectivity from 73% ee to 94% ee (Table 6, entries 2-5). The catalyst loading could also be decreased to as little as 0.1 mol% without loss of stereoselectivity (93% ee) but the reaction rate decreased as well and a reaction time of 30 hours was required to obtain 69% conversion (Table 6, entries 5-8). Therefore we decided to stay with 1 mol% as catalyst loading, allowing for 98% yield and 94% ee of the addition product **7a** in the presence of 1.5 equivalents of MTM **1**, within a short reaction time of 4 hours at -78°C in methylene chloride (Table 6, entry 5).

### 3.4.3.2 Deprotection and Decarboxylation Studies

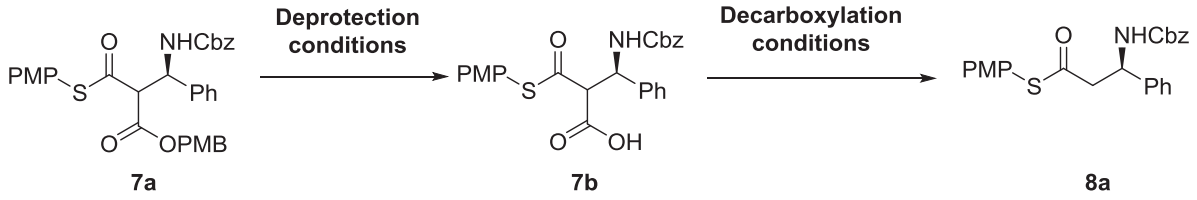
Within the addition reaction of MTMs to imines, two new stereogenic centers are formed. The stereocenter in the $\beta$-position to the thioester, is formed enantioselectively, whereas the center in the $\alpha$-position to the thioester is formed without enantiocontrol, due to the basic environment of the reaction, provided by the catalyst. In order to obtain optically pure $\beta$-amino thioesters it is therefore important to deprotect and decarboxylate the Mannich addition product to remove the stereocenter that was not formed enantioselectively. In the case of $\gamma$-nitro thioesters, deprotection with TFA followed by decarboxylation with DABCO in methylene chloride yielded the desired product in good yields and unaffected enantioselectivity.[86] However, when we applied these conditions to $\beta$-amino thioesters, we observed poor yields and racemization of the Mannich adduct **8a** (Scheme 49).




*Scheme 49. Deprotection and decarboxylation of the Mannich addition adduct **7a***

Crude NMR analysis revealed that the acidic deprotection yielded a complex mixture of deprotected addition product **7b** and numerous other fragments upon one was identified to be benzaldehyde (Table 7). We assumed that due to the strong acidic conditions a retro-Mannich reaction takes places, yielding again the imine, which upon acidic conditions decomposes into the aldehyde (benzaldehyde) and possibly the carbamate. A careful screening of deprotection conditions with TFA finally revealed that 20 equivalents of neat TFA are the balanced amount for complete PMB deprotection of **7a** without destroying the product, which is indicated by the formation of benzaldehyde (Table 7). Next to the amount of TFA the time of acid treatment is important. On a reaction scale of 0.2 mmol with respect to the amount of imine, 1 – 2 minutes of TFA treatment are sufficient for the deprotection. Longer treatment led again to the decomposition of **7a**, therefore a rapid quenching of the reaction mixture is required after the time period set (Table 7).

*Table 7. Acidic deprotection conditions*




| entry | deprotection conditions | complete deprotection after time [min] | benzaldehyd formation after time [min] |
|---|---|---|---|
| 1 | TFA neat (20 equiv.) | 40 sec. | 7.30 |
| 2 | TFA/$CH_2Cl_2$ 1:1 (20 equiv.) | 2 | 5 |

Next, we explored whether racemization occurs in the course of the basic decarboxylation step and how it can be prevented. Therefore the influence of different organic and inorganic bases such as DABCO, Hünigs´ base, pyridine, NMM and $NaHCO_3$, were investigated (Table 8).

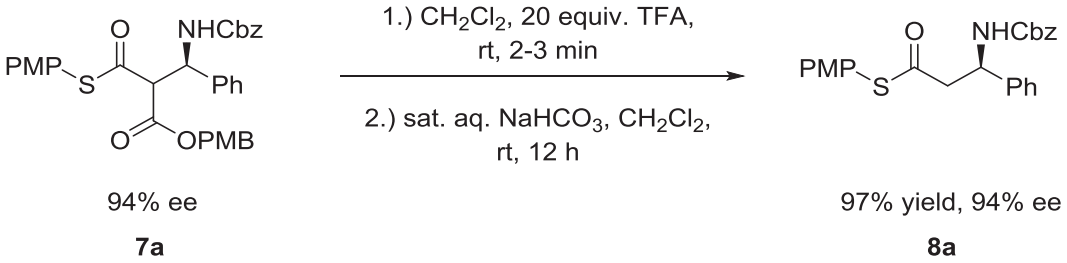
*Table 8. Evaluation of decarboxylation conditions*

| entry | base | solvent | time [h] | conversion[a] [%] | ee of 7a[b] [%] | ee of 8a[b] [%] |
|---|---|---|---|---|---|---|
| 1 | 2 equiv. DABCO | $CH_2Cl_2$ | 12 | quant. | 71 | 0 |
| 2 | 2 equiv. DABCO | $CH_2Cl_2$ | 2 | 36[c] | 71 | 0 |
| 3 | 1 equiv. DABCO | $CH_2Cl_2$ | 20 min | n.d. | 40 | 24 |
| 4 | 1 equiv. DABCO | toluene | 35 min | n.d. | 76 | 64 |
| 5 | 1 equiv. Hünigs´ base | toluene | 15 min | n.d. | 71 | 25 |
| 6 | 3 equiv. pyridine | $CH_2Cl_2$ | 6 | ≤ 50 % | n.d. | n.d. |
| 7 | 3 equiv. NMM | $CH_2Cl_2$ | 2 | 48[c] | n.d. | n.d. |
| 8 | sat. aq. $NaHCO_3$ | $CH_2Cl_2$ | 12 | quant. | 70 | 71 |

[a]Estimated by TLC and 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis. [c]Isolated yield. n.d. = not determined

The results revealed that treatment with strong organic bases such as DABCO or Hünigs´ base resulted in complete or partial racemization of *β*-amino thioester **8a** depending on the reaction time and the solvent that was used (Table 8, entries 1-5). However, weaker organic bases such as pyridine and NMM led to incomplete decarboxylation (Table 8, entries 6-7). To our delight, in a biphasic mixture of $CH_2Cl_2$ and saturated aqueous $NaHCO_3$ solution, the decarboxylation proceeded quantitatively after 12 hours and the enantioselectivity of **8a** remained unaffected (Table 8, entry 8).

In summary, we found that small amounts of saturated aqueous $NaHCO_3$ solution (ca. 30 eq. of base) are sufficient to quench unreacted TFA and decarboxylate the deprotected acid **7b**. We also found that it is important to have a biphasic mixture in the decarboxylation step to allow the resulting *β*-amino thioester **8a** to dissolve in the organic phase. Decarboxylation in the biphasic mixture of saturated aqueous $NaHCO_3$ and methylene chloride needed 12 hours for completion and yielded product **8a** in high amounts (97% yield) and most important without loss of stereoselectivity (94% ee) (Scheme 50).



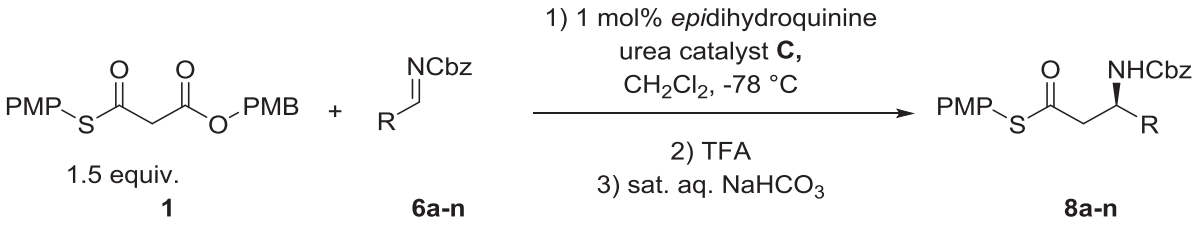

*Scheme 50. Optimized deprotection and decarboxylation conditions of the Mannich addition adduct.*

The investigations on the reaction conditions revealed, that as little as 1 mol% of *epi*dihydroquinine urea catalyst **C** is sufficient to promote the Mannich type reaction of MTM **1** and *N*-Cbz aryl aldimine **6a**. We found methylene chloride to perform as best solvent and -78 °C as optimal temperature. Under the optimized conditions addition product **7a** was obtained in 4 hours in high yield (98%) and excellent enantioselectivity (94% ee) (Table 6, entry 5). *In situ* deprotection of the PMB ester of **7a** with TFA and decarboxylation with saturated aqueous $NaHCO_3$ solution finally afforded *β*-amino thioester **8a** with an unaffected enantioselectivity of 94% and an overall yield over two steps of 86% (Table 9, entry 1).

### 3.4.3.3 Substrate Scope

Next, we investigated the generality of the catalytic enantioselective addition reaction of MTM **1** to *N*-Cbz imines **6a-n** by varying the substituent of the imine starting material (Table 9). All reactions were conducted in methylene chloride at -78 °C with an excess of 1.5 equivalents of MTM **1** and 1 mol% *epi*dihydroquinine urea catalyst **C**. *N*-Cbz imines **6a-l** and **6n** reacted readily with MTM **1** and yielded the corresponding *β*-amino thioesters **8a-l** and **8n** in high enantioselectivities (Table 9). Electron poor aromatic imines were best tolerated and the position of the substituent at the aromatic ring had no significant influence on the outcome of the reaction (Table 9, entries 2-7). Electron rich aromatic imines were slightly less reactive, nevertheless good overall yields (68 – 82% yield) were obtained and enantioselectivities were in a comparable range to that of electron poor *β*-amino thioesters (up to 98% ee) (Table 9, entries 8-11). The scope of reactions was further extended to heterocyclic imines. *N*-Cbz-thiophenyl imine **6e** reacted with MTM **1** and the corresponding *β*-amino thioester was isolated in a moderate yield of 59% and excellent enantioselectivity of 94% ee (Table 9, entry 12). The most challenging substrates proved to be aliphatic imines. Due to its intrinsic instability compared with the low reactivity towards MTM **1** in the reaction with *N*-Cbz-pentyl imine **6m** only traces of the addition product were detected by crude NMR analysis after 30 hours of reaction time (Table 9, entry 13). *N*-Cbz-cyclohexyl imine **6n** proved to be more stable and more reactive. Although a longer reaction time (18 hours) and higher catalyst loading (5 mol%) was necessary, aliphatic *β*-amino thioester was obtained in an overall yield of 62% and excellent enantioselectivity of 96% ee (Table 9, entry 14). These results show that even less reactive imines were transformed into chiral *β*-amino thioesters with high stereoselectivities. In comparison to previously reported methods for the synthesis of *β*-amino thioesters, these conditions are significantly more effective since a s little as 1 mol% of catalyst was needed (≥10 mol% for previous reported methods) and the reaction proceeded in a much faster fashion (4 h compared to 3-4 days) (see chapter 3.4.3.5).

*Table 9. Substrate scope of the addition reaction of MTM **1** to various N-Cbz-arylaldimins*




1.5 equiv. **1** | **6a-n** | **8a-n**

| entry | R | product | time [h] | yield [%] | ee[a] [%] |
|---|---|---|---|---|---|
| 1 | Ph | **8a** | 4 | 86 | 94 |
| 2 | 2-Br-$C_6H_4$ | **8b** | 4 | 86 | 96 |
| 3 | 3-Br-$C_6H_4$ | **8c** | 4 | 90 | 96 |
| 4 | 4-Br-$C_6H_4$ | **8d** | 4 | 85 | 96 |
| 5 | 4-Cl-$C_6H_4$ | **8e** | 4 | 81 | 98 |
| 6 | 4-F-$C_6H_4$ | **8f** | 4 | 93 | 96 |
| 7 | 4-$NO_2$-$C_6H_4$ | **8g** | 4 | 82 | 98 |
| 8 | 2-naphthyl | **8h** | 4 | 80 | 96 |
| 9 | 4-$CH_3$-$C_6H_4$ | **8i** | 4 | 68 | 88 |
| 10 | 2-$CF_3$-$C_6H_4$ | **8j** | 4 | 74 | 98 |
| 11 | 4-$CH_3O$-$C_6H_4$ | **8k** | 4 | 60 | 82 |
| 12 | 2-thienyl | **8l** | 4 | 59 | 94 |
| 13 | $C_4H_9$[b] | **8m** | 30 | < 5%[c] | n.d.[d] |
| 14 | $C_6H_{11}$[b] | **8n** | 18 | 62 | 96 |

[a]Determined by chiral-phase HPLC analysis. [b]Reaction was performed with 5 mol% of catalyst **C** for 18 h.
[c]Conversion determined by 1H NMR analysis. [d]not determined.

### 3.4.3.4 Determination of the Absolute Configuration

The absolute configuration of *N*-Cbz protected *β*-amino thioester **8b**, bearing an *o*-bromophenyl substituent, was determined by X-ray crystallography. This thioester crystallized from a solution in methylene chloride by slow diffusion of diethylether into the solution of thioester in methylene chloride. The bromine atom allowed the determination of the stereogenic centre to be (*R*). These results are in agreement with the results obtained for *N*-Boc protected *β*-amino thioester as reported in chapter 3.3.2.2. The major enantiomer of *N*-Boc protected *β*-amino thioester **5d** was also determined to be (*R*) by comparing its retention time with that of the same *β*-amino thioester that was synthesized from commercially available (*R*)-Boc protected $\beta^3$-phenylalanine in a DCC mediated coupling reaction.

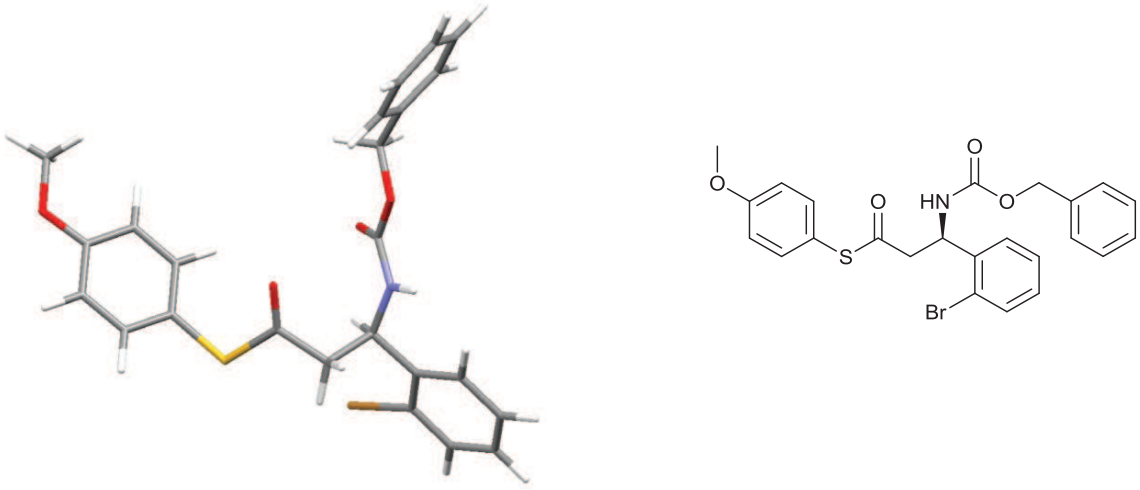
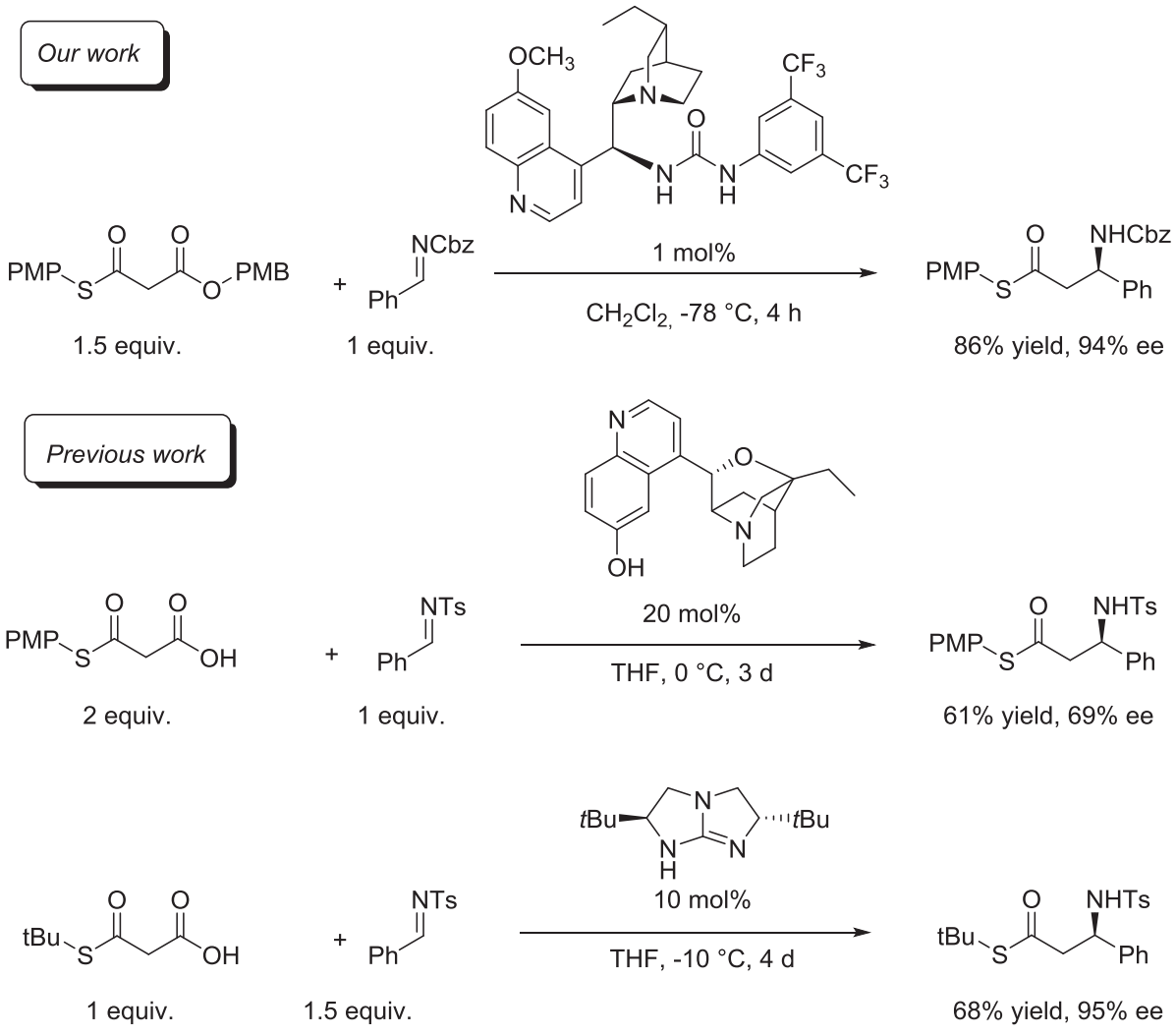



*Figure 2.Determination of the absolute configuration of **8b** by crystal structure analysis of (3R)-4-methoxyphenyl-3-(2-bromophenyl)-3-(benzyloxycarbonylamino)-propanethioate*

## 3.4.4 Summary and Comparison between MAHTs and MTMs

In summary these results show the remarkable advantages of MTMs in comparison to MAHTs in organocatalyzed Mannich reactions (Scheme 51).[28-29] We achieved a decrease of the catalyst loading from 10 – 20 mol% to as little as 1 mol%. Additionally, full conversion was achieved in very short reaction times (4 hours) even at low temperatures like -78°C (24 times shorter than in previous examples). No side products were observed utilizing MTMs and the strategy was applied for a broad variety of different imines. After a deprotection and decarboxylation sequence the products were obtained in higher yields and enantioselectivities than in approaches using MAHTs as thioester enolates (Scheme 51).




*Scheme 51. Comparison between MAHTs and MTMs in organocatalyzed Mannich reactions*[28-29]

# 3.5 Addition Reaction of $\alpha$-Substituted MTMs with Imines – Construction of Acyclic All-Carbon Quaternary Stereogenic Centers

In the previous chapter we have shown that $\alpha$-unsubstituted MTM **1** was successfully applied as activated thioester enolate equivalent for the addition reactions with imines. We were now interested in using $\alpha$-substituted MTMs for the direct Mannich type reaction with imines (Scheme 52). The products thus formed would bear an acyclic all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter, and would provide an entry to various important pharmaceutical products including $\beta^{2,2,3}$-amino amides and $\beta^{2,2,3}$-amino acids.[87-90]


*Scheme 52. Generation of acyclic all-carbon quaternary stereogenic centers by using $\alpha$-substituted MTMs in direct Mannich type reactions*

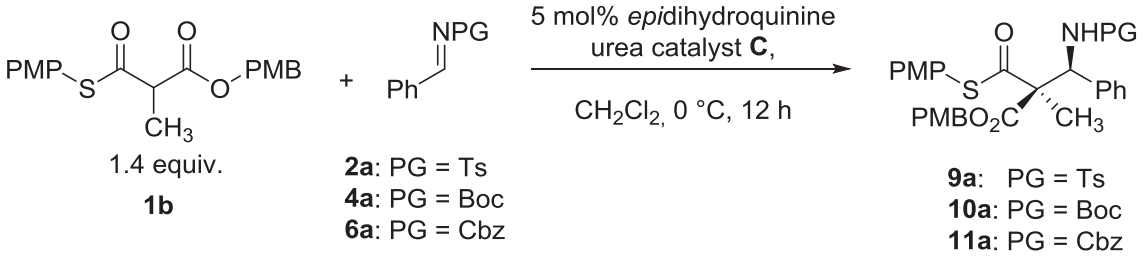
## 3.5.1 Screening of Imines

We first evaluated the addition reaction of $\alpha$-$CH_3$ substituted MTM **1b** to different protected arylimines in the presence of 5 mol% of *epi*dihydroquinine urea catalyst **C**, the optimal catalyst for the addition reaction of $\alpha$-unsubstituted MTM **1** to *N*-Boc and *N*-Cbz imines. We started with the reaction between *N*-Ts protected imine **2a** and $\alpha$-$CH_3$ substituted MTM **1b** in methylene chloride at 0 °C in the presence of 5 mol% of **C**. After 12 hours of reaction time only traces of the addition product **9a** were observed (Table 10, entry 1), demonstrating *N*-Ts imines to be unsuitable electrophiles for the reaction conditions set.

Next, *N*-carbamate protected imines were investigated. *N*-Boc and *N*-Cbz protected imines **4a** and **6a** reacted readily with $\alpha$-$CH_3$ substituted MTM **1b**, in methylene chloride in the presence of 5 mol% of *epi*dihydroquinine urea catalyst **C** at 0 °C in methylene chloride.

Considerable differences in their reactivity were observed (Table 10, entry 2-3). In the presence of *N*-Boc imine **4a** a conversion of $\alpha$-$CH_3$ substituted MTM **1b** of only 24% was detected after a reaction time of 12 hours (Table 10, entry 2). *N*-Cbz imine **6a** proved to be more reactive and we observed a significantly higher conversion of 83% under the same conditions as used for *N*-Boc imine (Table 10, entry 3). The diastereoselectivity of the catalyst is also clearly dependent on the protecting group of the imine. In the reaction with *N*-Cbz imine **6a** the addition product was obtained with an already good diastereoselectivity of 7:1 whereas in the reaction with *N*-Boc-imine **4a** a lower diastereoselectivity of 4:1 was observed (Table 10, entries 2 and 3).

*Table 10. Screening of N-protecting group for the addition reaction of $\alpha$-$CH_3$-substituted MTM **1b** to arylaldimines*




| entry | PG | conv.[a] [%] | dr[a] | ee[b] [%] |
|---|---|---|---|---|
| 1 | **Ts** | < 5 | n.d.[c] | n.d.[c] |
| 2 | **Boc** | 24 | 4:1 | n.d.[c] |
| 3 | **Cbz** | 83 | 7:1 | 82 |

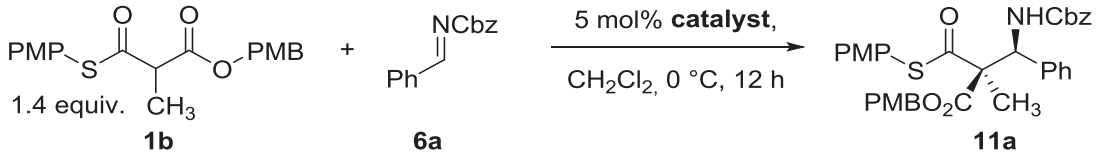
[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis. [c]not determined.

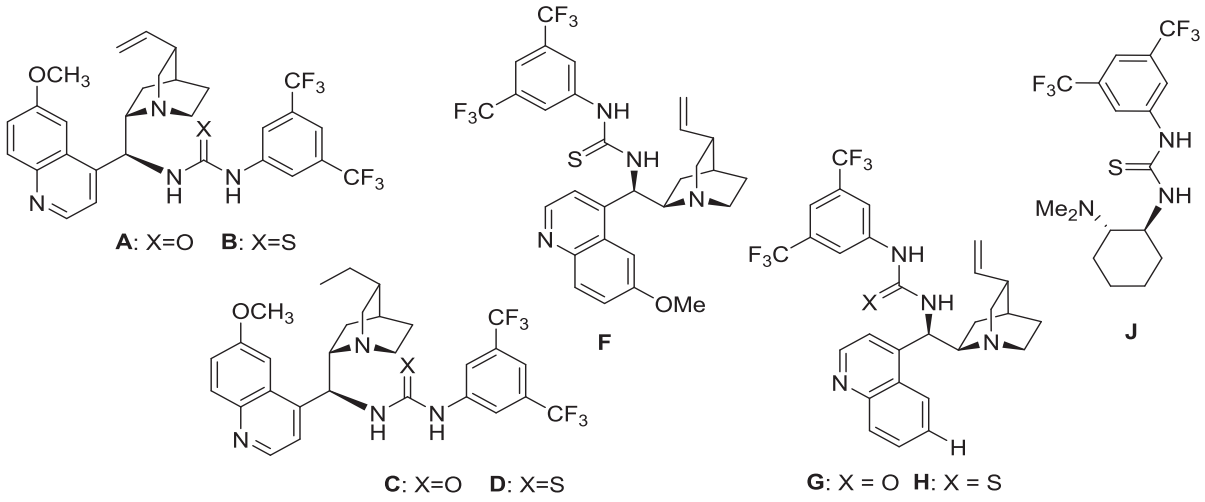
## 3.5.2 Optimization of the Reaction Conditions

With *N*-Cbz protected imine **6a** the best results in terms of reactivity (83% conversion of $\alpha$-$CH_3$ substituted MTM **1b** within 12 hours) and stereoselectivities (82% ee, dr = 7:1) were obtained. Therefore we concentrated on optimization studies for the addition reaction of $\alpha$-$CH_3$ substituted MTM **1b** to *N*-Cbz protected imine **6a** and investigated the catalytic efficiency of different cinchona alkaloid derived urea and thiourea catalysts, previously introduced in chapter 3.3 (Table 11). Addition product **11a** was obtained with high conversions with all catalysts tested, using 1.4 equivalents $\alpha$-$CH_3$ substituted MTM **1b**,

5 mol% of catalyst, a reaction temperature of 0°C, methylene chloride as solvent and a reaction time of 12 hours (Table 11).

*Table 11. Catalyst screening for the addition reaction of α-$CH_3$-substituted MTM **1b** to arylaldimine **6a***




| entry | catalyst | conversion[a] [%] | dr[a] | ee[b] [%] |
|---|---|---|---|---|
| 1 | **A** | 87 | 11:1 | 97 (53) (*2S,3S*) |
| 2 | **B** | 90 | 7:1 | 95 (78) (*2S,3S*) |
| 3 | **C** | 95 | 8:1 | 96 (65) (*2S,3S*) |
| 4 | **D** | quant. | 7:1 | 95 (62) (*2S,3S*) |
| 5 | **F** | 89 | 3:1 | 72 (75) (*2R,3R*) |
| 6 | **G** | 94 | 6:1 | 86 (69) (*2R,3R*) |
| 7 | **H** | quant. | 4:1 | 72 (76) (*2R,3R*) |
| 8 | **J** | 95 | 2:1 | 79 (78) (*2R,3R*) |

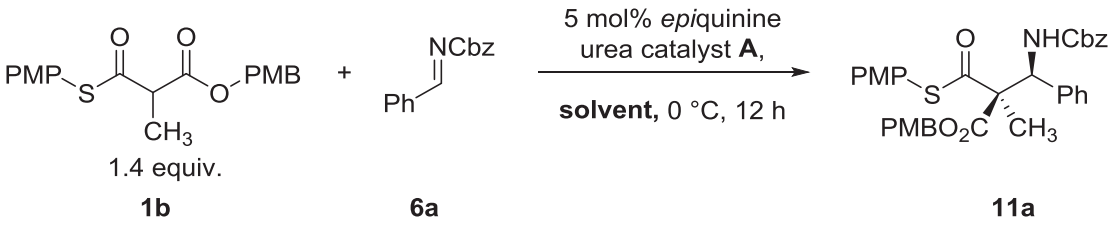
[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

Significant differences were observed in the stereoselectivity of the reaction outcome. Catalysts derived from quinine and dihydroquinine (**A-D**) provided the addition product **11a** with best stereoselectivities (Table 11, entries 1-4). Comparable to the observations made for unsubstituted MTM **1**, urea derived catalysts performed more stereoselective than their

corresponding thiourea derivatives. For example, with *epi*quinine urea catalyst **A** a diastereoselctivity of 11:1 and an enantiomeric excess of the main diastereoisomer of 97% was obtained, whereas with *epi*quinine thiourea catalyst **B** a diastereoselctivity of 7:1 and an enantiomeric excess of the main diastereoisomer of 95% was determined (Table 11, entries 1 and 2). The same trend, however not as significant, was seen for the dihydroquinine derivatives: With *epi*dihydroquinine urea catalyst **C** a diastereoselectivity of 8:1 and an enantiomeric excess of 96% was observed, whereas with *epi*dihydroquinine thiourea catalyst **D** a diastereoselctivity of 7:1 and an enantiomeric excess of the main diastereoisomer of 95% was obtained (Table 11, entries 3 and 4). For *epi*cinchonine urea catalyst **G** and *epi*cinchonine thiourea catalyst **H**, lacking a methoxy group at the quinoline moiety and having opposite configuration at C8 and C9 than the quinine and dihydroquinine derived catalysts **A**, **B**, **C** and **D**, the urea **G** derivative also performed more stereoselectively (Table 11, entries 7 and 8). With *epi*cinchonine urea catalyst **G** a diastereoselctivity of 6:1 and an enantiomeric excess of the opposite enantiomer (2*R*,3*R*) of 86% was observed, whereas with *epi*cinchonine thiourea catalyst **H** a diastereoselctivity of 4:1 and an enantiomeric excess of the main diastereoisomer of 72% was determined (Table 11, entries 6 and 7). With Takemoto´s catalyst **J** a diastereoselectivitv of 2:1 and an enantioselectivity in favour of the (2*R*,3*R*)-enantiomer of 79 % was obtained (Table 11, entry 6). *Epi*quinine urea catalyst **A** was identified as optimal catalyst since it provided for best values in terms of stereoselectivity (dr of 11:1, 97% ee) at 0 °C in methylene chloride with a catalyst loading of 5 mol%. Next, we investigated the influence of the reaction medium on reactivity and stereoselectivity (Table 12).

We tested the reaction at 0 °C in a range of different solvents. Several apolar and polar aprotic solvents turned out to be suitable for the reaction, and high conversions of $\alpha$-$CH_3$ substituted MTM **1b** to the desired addition product **11a** (> 86%) were obtained (Table 12, entries 1-8). More differences were observed in the stereoselectivities. In general, the reaction proceeded more stereoselectively in apolar solvents such as methylene chloride, toluene, benzene and diethyl ether (Table 12, entries 1-4) than in polar solvents such as tetrahydrofuran, ethyl acetate, acetone and acetonitrile (Table 12, entry 5-8). As observed for reactions with the unsubstituted MTMs (chapter 3.4.3.1), polar protic solvents such as ethanol turned out to be not suitable yielding the product in traces only (Table 12, entry 9). *Epi*quinine urea catalyst **A** performed most enantioselectively and diastereoselectively in methylene chloride which was chosen as solvent for further optimization studies (Table 12, entry 1).

*Table 12. Solvent screening for the addition reaction of α-$CH_3$-substituted MTM **1b** to arylaldimine **6a***

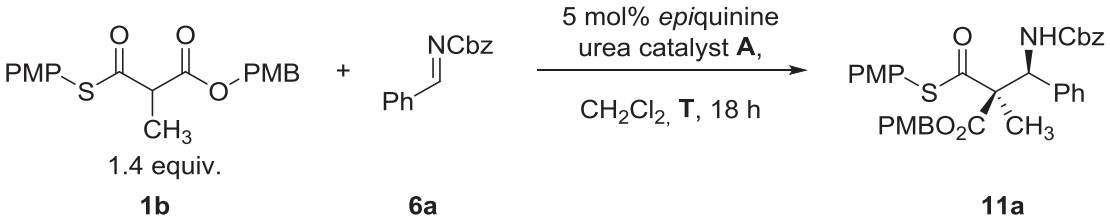



| entry | solvent | conversion[a] [%] | dr[a] | ee[b] [%] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 87 | 11:1 | 95 (58) (*2S,3S*) |
| 2 | toluene | 97 | 5:1 | 81 (67) (*2S,3S*) |
| 3 | benzene | quant. | 6:1 | 81 (54) (*2S,3S*) |
| 4 | $Et_2O$ | 94 | 8:1 | 88 (46) (*2S,3S*) |
| 5 | THF | 92 | 3:1 | 52 (15) (*2S,3S*) |
| 6 | EtOAc | 99 | 3:1 | 62 (22) (*2S,3S*) |
| 7 | acetone | quant. | 5:1 | 72 (29) (*2S,3S*) |
| 8 | $CH_3CN$ | 97 | 5:1 | 81 (32) (*2S,3S*) |
| 9 | EtOH | traces | - | - |

[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

Finally we tested the influence of the temperature on the reactivity and stereoselectivity of *epi*quinine urea catalyst **A** (Table 13). Although at 0 °C, the product was obtained in an already excellent stereoselectivity of 97% ee and with a high dr of 11:1 we were curious if lowering the temperature would lead to an increase of diastereoselectivity. To our delight, the reaction proceeded well at lower temperature. Good conversion to addition product **11a** was observed within a reaction time of 12 hours for all reactions from 0 °C down to -78 °C (Table 13). Pleasingly, the diastereoselectivity was increased to a value of 32:1 at a temperature of -78 °C (Table 13, entry 4).

*Table 13. Temperature screening for the addition reaction of α-$CH_3$-substituted MTM **1b** to arylaldimine.*



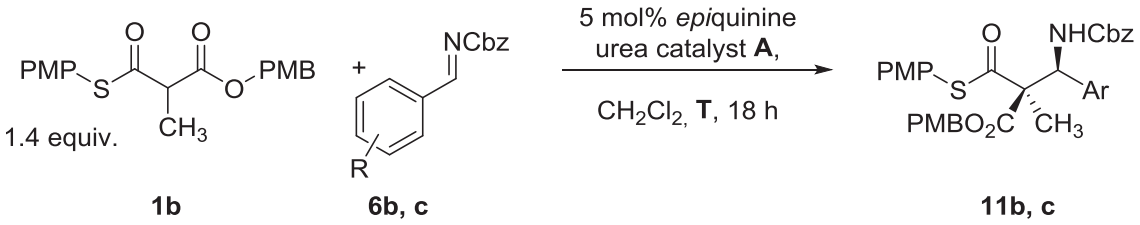

| entry | T [°C] | conversion[a] [%] | dr[a] | ee[b] [%] |
|---|---|---|---|---|
| 1 | 0 | 87 | 11:1 | 97 (53) (*2S,3S*) |
| 2 | -20 | 89 | 15:1 | 97 (61) (*2S,3S*) |
| 3 | -40 | 92 | 20:1 | 98 (63) (*2S,3S*) |
| 4 | -78 | quant. | 32:1 | 99 (66) (*2S,3S*) |

[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

## 3.5.3 Substrate Scope

The optimization investigations revealed that for the reaction of α- $CH_3$-substituted MTM **1b** with *N*-Cbz-imines **6a** as little as 5 mol% of *epi*quinine urea catalyst **A** is sufficient to obtain β-amino thioester **11a** bearing a linear all-carbon quaternary stereogenic center adjacent to a tertiary stereogenic center in a conversion of α-$CH_3$ substituted MTM **1b** of 87% and excellent stereoselectivity (dr = 32:1, ee = 99 %). With those optimized conditions in hand we set out to investigate the substrate scope. α- $CH_3$-substituted MTMs were used in a little excess of 1.4 equivalents and reactions were performed in methylene chloride at -78 °C in the presence of 5 mol% of *epi*quinine urea catalyst **A**. Surprisingly when we tested bromine substituted aromatic imines under the reaction conditions, we observed only slow reaction rates and conversions of only 35% for **6b** and 56% for **6c** respectively (Table14, entries 1 and 2). Therefore, a conversion-temperature screening was conducted for substituted aromatic *N*-Cbz imines **6b** and **6c**, revealing a reaction temperature of -60 °C to provide for the best compromise between conversion and stereoselectivity (Table 14).

*Table 14. Diastereoselectivity-time profile for the addition reaction of α-substituted MTM **1b** to arylaldimine*




**1b** **6b, c** **11b, c**

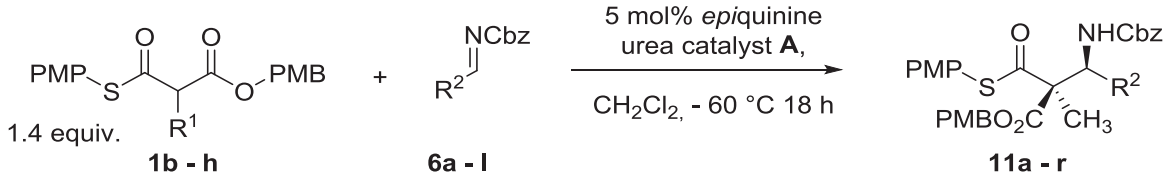
| entry | R | product | T [°C] | conversion[a] [%] | dr[a] | ee[b] [%] |
|---|---|---|---|---|---|---|
| 1 | 2-Br | **11b** | -78 | 35 | 32:1 | 99 (71) |
| 2 | 4-Br | **11c** | -78 | 56 | 19:1 | 95 (63) |
| 3 | 2-Br | **11b** | 0 | 91 | 7:1 | 96 (66) |
| 4 | 4-Br | **11c** | 0 | 95 | 10:1 | 97 (59) |
| 5 | 2-Br | **11b** | -40 | 99 | 23:1 | 98 (76) |
| 6 | 4-Br | **11c** | -40 | 77 | 35:1 | 99 (70) |
| 7 | 2-Br | **11b** | -60 | 95 | 35:1 | 99 (79) |
| 8 | 4-Br | **11c** | -60 | 83 | 26:1 | 99 (70) |

[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

Having defined -60 °C as the optimal reaction temperature, we tested a broad range of *α*-substituted MTM and *N*-Cbz-imine combinations. Best results were obtained with imines bearing electron-poor aromatic substituents (95 - 99 % yield, dr = 20:1 - 99:1, 96% - 99% ee; Table 15, entries 1-5). Although we obtained *β*-amino thioesters derived from imines with electron rich aromatic substituents in a little bit lower yields, the products were still formed with equally excellent stereoselectivities like the products derived from imines bearing electron-poor aromatic substituents (79% - 84% yield, dr = 20:1 - 36:1, 96% - 99% ee; Table 15, entries 6-8). Interestingly, *N*-Cbz-3,5-(dimethoxy)benzylimine **6i** (Table 13, entry 9) with two electron donating substituents in the meta position of the benzene ring, reacted with good conversion and high enantioselectivity (99% ee) however, with a lower diastereoselectivity of 6:1 dr. Also heteroaromatic 2-thiophenyl imine **6j** was reactive (78% yield) and the product was obtained in excellent diastereo- and enantioselectivity (dr = 99:1, 97% ee, table 15,

entry 10). Reactions with less reactive aliphatic imines needed longer reaction times and higher catalyst loading of 10 mol% (Table 15, entry 11).

*Table 15. Substrate scope for the addition reaction of α-substituted MTMs to arylaldimine.*




| entry | $R^1$ | $R^2$ | product | yield [%] | dr[a,b] | ee[b] [%] |
|---|---|---|---|---|---|---|
| 1 | $CH_3$ | Ph[c] | **11a** | 99 | 31:1 | 99 |
| 2 | $CH_3$ | 2-Br-$C_6H_4$ | **11b** | 99 | 35:1 | 99 |
| 3 | $CH_3$ | 4-Br-$C_6H_4$ | **11c** | 99 | 26:1 | 99 |
| 4 | $CH_3$ | 4-Cl-$C_6H_4$ | **11d** | 99 | 99:1 | 99 |
| 5 | $CH_3$ | 4-F-$C_6H_4$ | **11e** | 95 | 34:1 | 99 |
| 6 | $CH_3$ | 4-$CH_3$-$C_6H_4$ | **11f** | 81 | 25:1 | 99 |
| 7 | $CH_3$ | 2-$CF_3$-$C_6H_4$ | **11g** | 84 | 36:1 | 96 |
| 8 | $CH_3$ | 4-$CH_3O$-$C_6H_4$ | **11h** | 79 | 20:1 | 98 |
| 9 | $CH_3$ | 3,5-$CH_3O$-$C_6H_3$ | **11i** | 97 | 6:1 | 99 |
| 10 | $CH_3$ | 2-thienyl | **11j** | 78 | 99:1 | 97 |
| 11 | $CH_3$ | $C_6H_{11}$[d] | **11k** | 44 | 3:1 | 87 |
| 12 | $CH_3$ | $C_4H_9$[d] | **11l** | 45 | n.d. [f] | n.d.[f] |
| 13 | Et | Ph | **11m** | 63[e] | 7:1 | 97 |
| 14 | $^i$Pr | Ph | **11n** | 0 | - | - |
| 15 | cyclopentyl | Ph | **11o** | 0 | - | - |
| 16 | Bn | Ph | **11p** | 94 | 6:1 | 99 |
| 17 | allyl | Ph | **11q** | 60 | 21:1 | 99 |
| 18 | propargyl | Ph | **11r** | 90 | 20:1 | 98 |

[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis. [c]-78 °C, [d]0 °C, 10 mol% A, 48 h. [e]0 °C. [f]not determined

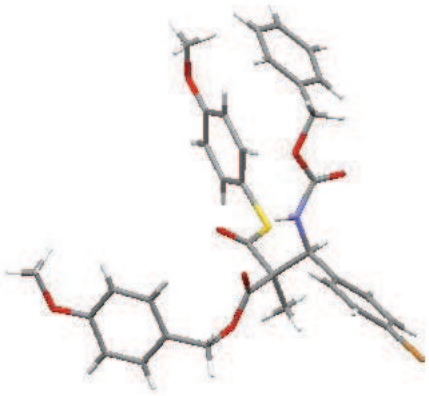
The product derived from cyclohexyl imine **6k** was obtained in moderate yield of 45% and good enantioselectivitiy of 87% ee, but for the product derived from pentyl imine **6l**, which we isolated in a yield of 44% no suitable conditions were found to determine the stereoselectivty (Table 15, entries 11-12). However, it needs to be mentioned that those aliphatic *β*-amino thioesters **11k-l** are less stable and decomposed to a mixture of unknown compounds at room temperature within a few hours.

MTMs bearing ethyl, benzyl or synthetically valuable allyl or propargyl substituents at the *α*-position were also tolerated and addition products were obtained in good yields and stereoselectivities using 5 mol% of *epi*quinine urea catalyst **A** (60% - 94% yield, dr = 3:1 - 21:1, 97% - 99% ee; Table 15, entries 13, 16-18). Limitations of the reaction are MTMs with bulky aliphatic substituents which turned out to be unreactive under the reaction conditions. No product formation was observed at 0 °C when *α*-isopropyl **1d** and *α*-cyclopentyl **1e** substituted MTMs were used as nucleophiles (Table 13, entries 14 and 15). Similar results were obtained when an aromatic MTM such as *α*-phenyl MTM was used. Although the MTM was transformed to a species that could not be identified, no addition reaction to the imine was observed.

Overall, these results demonstrate that *α*-substituted MTMs are useful substrates for cinchona alkaloid catalyzed Mannich reaction with a broad range of imines. 5 mol% of catalyst and 1.4 equivalents of MTM are typically sufficient to provide the products in high yields of up to 99% and excellent stereoselectivities of up to 99% ee and dr of up to 99:1.

## 3.5.4 Determination of the Absolute Configuration

The absolute configuration of *N*-Cbz protected *α*-$CH_3$-substituted *β*-amino thioester **11c**, bearing an *p*-bromophenyl substituent, was determined by X-ray crystallography. The thioester crystallized from a solution in methylene chloride by slow diffusion of diethylether into the solution of thioester in methylene chloride. The bromine atom allowed for the determination of the two stereogenic centres to be (*S*)-configurated. These results are in agreement with the results obtained for *N*-Boc protected *α*-unsubstituted *β*-amino thioester as reported in chapter 3.3.2.2. as well as for *N*-Cbz protected *α*-unsubstituted *β*-amino thioester (see chapter 3.3.3.4).



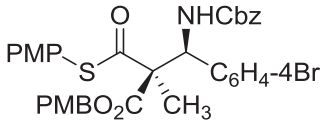
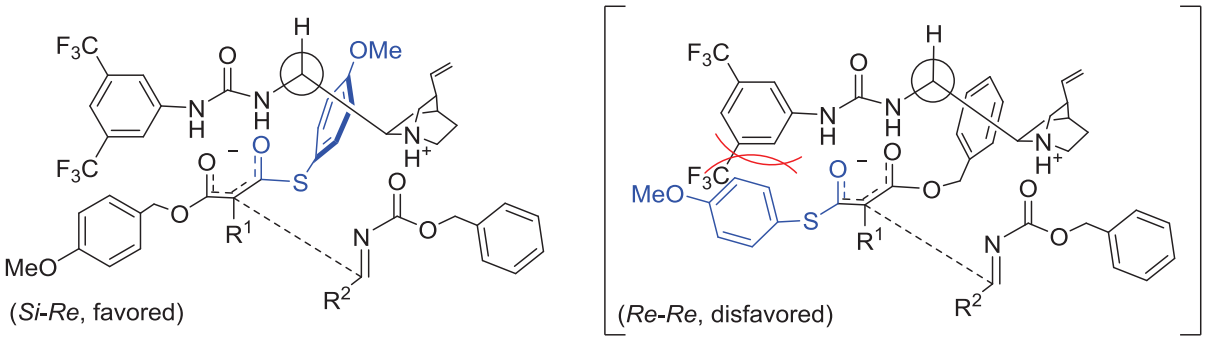



*Figure 2.Determination of the absolute configuration of* ***11c*** *by crystal structure analysis of (2S,3S)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-bromo)phenyl-3-(benzyloxycarbonylamino)-propanethioate*

A plausible transition state for the reaction is shown in Scheme 53. Such a transition state was previously postulated for the addition reaction of $\alpha$-$CH_3$-substituted MTM **1b** to nitroolefins by our group, based on mechanistic experiments.[114] The combination of a flexible oxoester and a rigid thioester directs the interactions between the MTM and the catalyst in such a way that the benzyl moiety is on the same side as the 3,5-di(trifluoromethyl)phenyl group of the catalyst. Interactions were the phenyl moiety is on the same side as the 3,5-di(trifluoromethyl) phenyl group of the catalyst are unlikely due to their steric repulsion. Assuming the interaction introduced first, this leads then to the addition of the MTM enolate from the *Si* face to the *Re* face of the imine. The orientation of the imine will be favoured by hydrogen bonding between the protonated nitrogen at the quinuclidine moiety and the carbamate. A *Re-Re* face approach is disvavored due to the mentioned steric interactions.

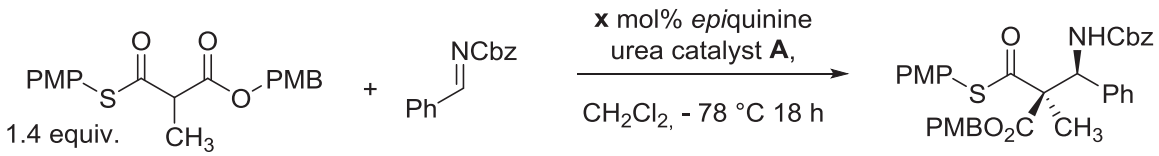



*Scheme 53 .Possible transition state for the cinchona alkaloid catalyzed addition reaction of MTM* ***1b*** *and N-Cbz imine* ***6a***

## 3.5.5 Investigations on the Stereoselectivity

As reported in the previous chapter, with 5 mol% of *epi*quinine urea catalyst **A** high values of enantioselectivity (up to 99% ee) and diastereoselectivity (dr up to 32:1) were obtained in the addition reaction between $\alpha$-$CH_3$ substituted MTM **1b** and arylimine **6a**. However, when we lowered the catalyst loading to 1 mol% a drop of the diastereoselectivity to 14:1, was observed while the enantioselectivity remained the same (Table 16, entry 2). To find out the reason for this observation we conducted several experiments. First, we wondered if the different concentration of the catalyst with respect to the reaction medium had caused the loss of diastereoselectivity. However, in an experiment with 1 mol% of catalyst **A** with a concentration of 0.01 mol/l a similar value of diastereoselectivity (dr = 16:1) was observed (Table16, entry 3).

*Table 16. Concentration screening for the addition reaction of $\alpha$-$CH_3$-substituted MTM **1b** to arylaldimine **6a***




**1b** **6a** **11a**

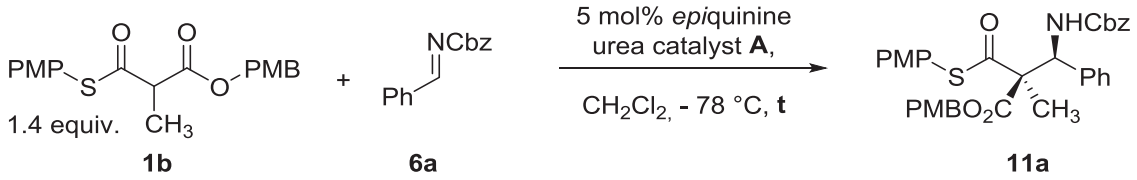
| entry | mol% | [Cat] | conversion[a] [%] | dr[a] | ee[b] [%] |
|---|---|---|---|---|---|
| 1 | 5 | 0.01 M | quant. | 32:1 | 99 (66) |
| 2 | 1 | 0.002 M | 94 | 14:1 | 98 (68) |
| 3 | 1 | 0.01 M | 83 | 16:1 | 97 (52) |

[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

Next, we documented the diastereocontrol over the reaction time and conducted a diastereoselectivity/time profile for the reaction with 5 mol% of *epi*quinine urea catalyst **A** (Table 17). We set up the reaction under the optimized conditions at -78 °C and took samples after 2 h, 4 h, 6 h, 8 h and 21 h and immediately determined conversions and diastereoselectivities. Within the first two hours already 59% of addition product **11a** was formed however only in a moderate diastereoselectivity of 8:1. In the next 2 hours additional 20% of product was formed with an overall diastereoselectivity of 13:1. After 21 hours, when

the reaction is completed, the diastereoselectivity of product **11a** had risen to its maximum of 32:1 (Table 17).

*Table 17. Diastereoselectivity-time profile for the addition reaction of α-$CH_3$-substituted MTM **1b** to arylaldimine 6a*




**1b** **6a** **11a**

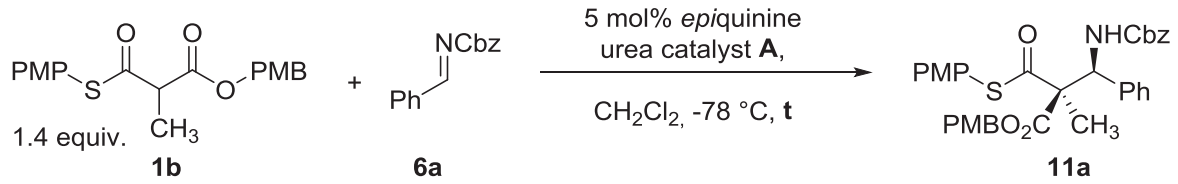
| entry | rct. time [h] | conversion[a] [%] | dr[a] | ee[b] [%] |
|---|---|---|---|---|
| 1 | 2 | 59 | 8:1 | 93 (63) |
| 2 | 4 | 79 | 13:1 | 96 (63) |
| 3 | 6 | 83 | 15:1 | 98 (64) |
| 4 | 8 | 82 | 17:1 | 97 (62) |
| 6 | 21 | 88 | 29:1 | 99 (66) |

[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

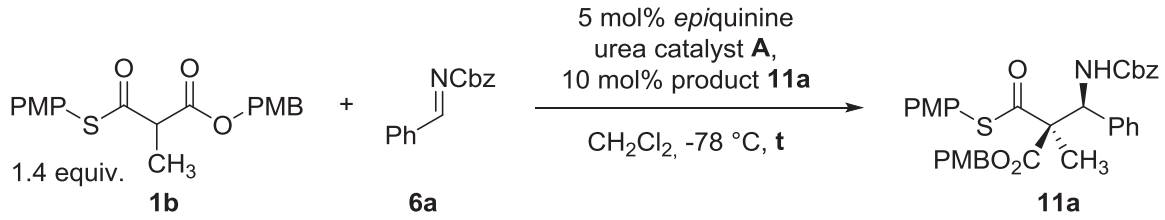
We reasoned that either a defined ratio of educts to product to catalyst is important to form the product in high diastereoselectivity, or that the product itself is involved in the catalytic pathway that induces diastereoselectivity. To strengthen this hypothesis we wondered if we could tune the diastereoselectivity-time profile by adding diastereomeric pure product at the beginning of the reaction. We compared two experiments. In the first experiment we set up the typical reaction with 1.4 equivalents of α-$CH_3$-MTM **1b**, 1 equivalent imine **6a** and 5 mol% *epi*quinine urea catalyst **A** in dichloromethane at -78 °C (reaction setup I). In a second experiment we additionally added 10% of the diastereomeric pure product at the beginning of the reaction (reaction setup II) (Scheme 54). We documented a diastereoselectivity-time profile in the same way as described before and compared the results (Table 18). The results show, that the addition of diastereomeric pure product as "co-catalyst" had no significant influence on the evolution of diastereoselectivity during the course of the reaction (Figure 4).

After 2 hours of reaction time, a higher diastereoselectivity was observed for **setup II**. However, this is due to the fact that at that stage, the reaction contains a mixture of added diastereomeric pure product and newly formed product. This effect gets smaller as soon as more diastereomerically enriched product is formed in **setup I**. The data suggests that the product itself is not involved in the catalytic pathway that induces diastereoselectivity.

**Reaction setup I:**




**Reaction setup II:**




*Scheme 54. Experiment setup to investigate self catalysis of the product.*

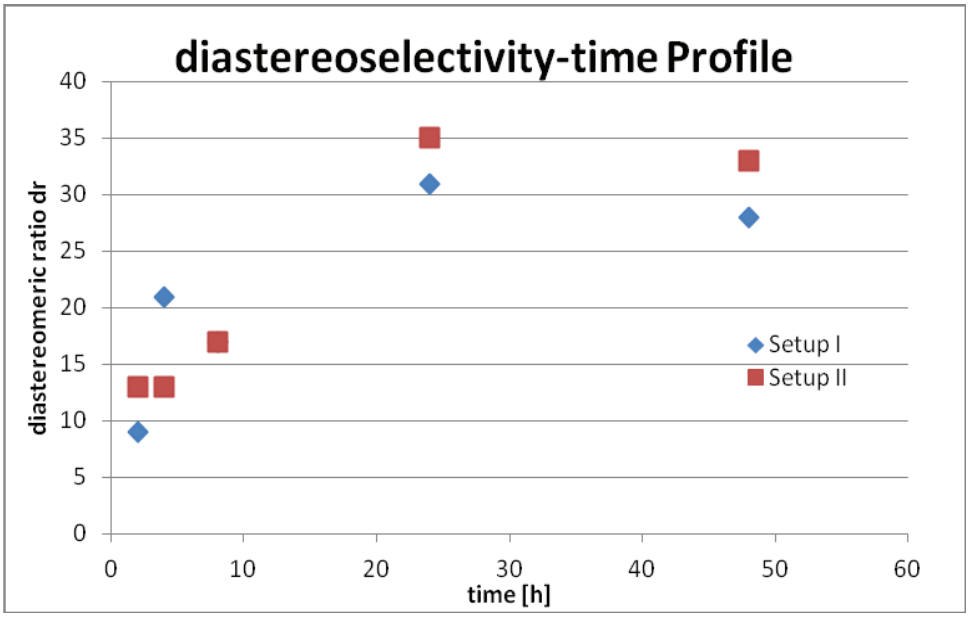



*Figure 4. Diastereoselectivity-time profile.*

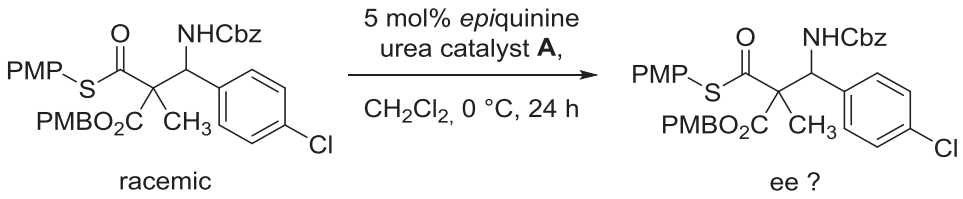
*Table 18. Diastereoselectivity-time profile for the addition reaction of α-$CH_3$-substituted MTM **1b** to arylaldimine **6a***

| entry | reaction setup | rct. time[h] | dr[a] | ee[b] [%] |
|---|---|---|---|---|
| 1 | I | 2 | 9:1 | 97 (66) |
| 2 | II | 2 | 13:1 | 97 (65) |
| 3 | I | 4 | 21:1 | 98 (60) |
| 4 | II | 4 | 13:1 | 98 (67) |
| 5 | I | 8 | 17:1 | 98 (62) |
| 6 | II | 8 | 17:1 | 98 (62) |
| 7 | I | 24 | 31:1 | 99 (70) |
| 8 | II | 24 | 35:1 | 99 (67) |
| 9 | I | 48 | 28:1 | 99 (65) |
| 10 | II | 48 | 33:1 | 99 (65) |

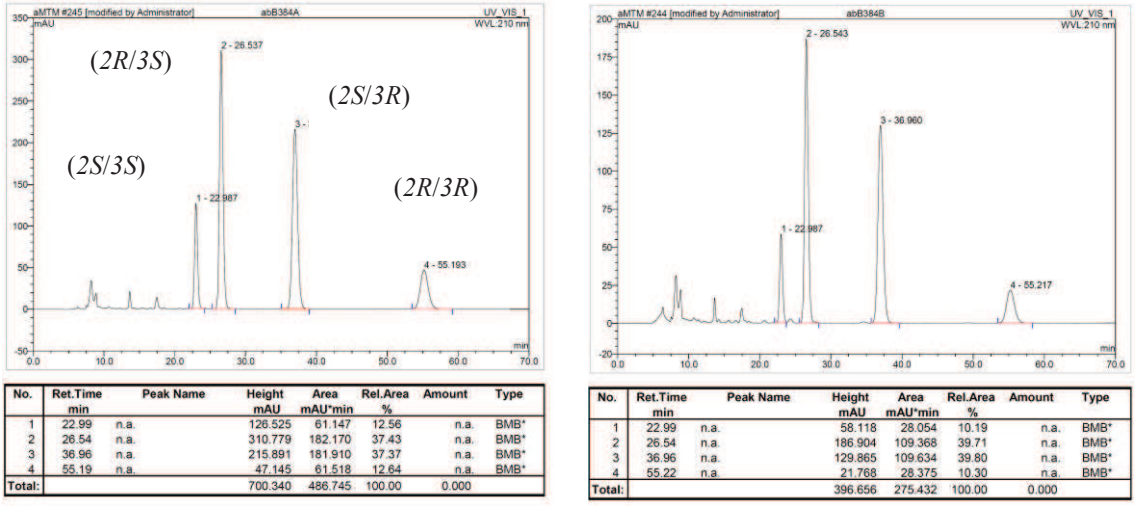
[a]Determined by 1H NMR analysis. [b]Determined by chiral-phase HPLC analysis.

Next, we investigated if a retro-Mannich reaction occurs during the catalytic process, which could be an explanation for the increasing diastereoselectivity. We dissolved racemic addition product **11d** with a dr of 1:3 (previously synthesized using an excess of DABCO as base) in dichloromethane and added 5 mol% of *epi*quinine urea catalyst **A** at 0 °C (Scheme 55). Notably in the reaction with DABCO the main diastereoisomer is the opposite of that, which is predominantly formed in the cinchona alkaloid catalyzed reaction. The reaction mixture was cooled to 0 °C and 5 mol% of *epi*quinine urea catalyst **A** were added (Scheme 55). The mixture was then stirred at 0 °C for 24 hours followed by analyzing the stereoselectivity of the product by HPLC analysis. We observed no changes, neither in the enantioselectivity nor in the diastereoselectivity, which means that we can exclude retro reaction under the conditions used (Figure 5). In order to manifest the thesis that no retro-Mannich reaction occurs in the presence of *epi*quinine urea catalyst **A**, one could think about mixing racemic *β*-amino thioester with the catalyst and additional substrates such as another imine (e.g. *N*-Boc protected imine or more reactive *N*-Cbz protected imine) or an MTM with another

substitution at the $\alpha$-position. If the retro-Mannich reaction would occur, we should detect those possible mixed $\beta$-amino thioesters.




*Scheme 55. Investigations on the retro-Mannich reaction.*




| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 22.99 | n.a. | 126.525 | 61.147 | 12.56 | n.a. | BMB* |
| 2 | 26.54 | n.a. | 310.779 | 182.170 | 37.43 | n.a. | BMB* |
| 3 | 36.96 | n.a. | 215.891 | 181.910 | 37.37 | n.a. | BMB* |
| 4 | 55.19 | n.a. | 47.145 | 61.518 | 12.64 | n.a. | BMB* |
| Total: | | | 700.340 | 486.745 | 100.00 | 0.000 | |

| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 22.99 | n.a. | 58.118 | 28.054 | 10.19 | n.a. | BMB* |
| 2 | 26.54 | n.a. | 186.904 | 109.368 | 39.71 | n.a. | BMB* |
| 3 | 36.96 | n.a. | 129.865 | 109.634 | 39.80 | n.a. | BMB* |
| 4 | 55.22 | n.a. | 21.768 | 28.375 | 10.30 | n.a. | BMB* |
| Total: | | | 396.656 | 275.432 | 100.00 | 0.000 | |

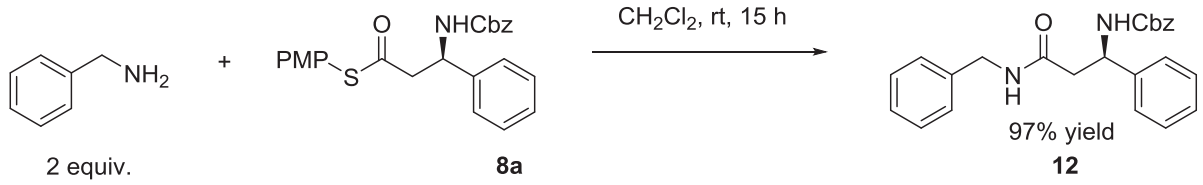
*Figure 5. Investigations on the retro-Mannich reaction*

## 3.6 Transformation of the Thioester

The thioester moiety is an important and synthetically versatile functional group because it allows for easy transformations into a variety of other functional groups (see chapter 1.2). Amongst these transformations, the generation of amides are of interest since their formation out of amines and carboxylic acids typically requires coupling reagents for the activation of the carboxylic acid. Since $\beta$-amino thioesters are directly related to $\beta$-amino acids we envisioned to utilize our catalysis products as "pre activated" $\beta$-amino acid equivalents for peptide couplings omitting additional activating reagents.

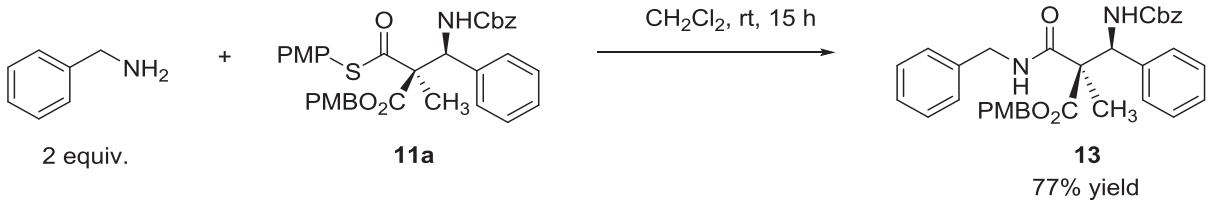
## 3.6.1 Amide Bond Formation in Solution

To investigate the general reactivity of the PMP ester towards amines we started with a reaction between *N*-Cbz protected *β*-amino thioester **8a** and an excess of benzylamine (2 equiv.). Amide product **12** was isolated in a yield of 97%, after a reaction time of 15 hours at room temperature in methylene chloride (Scheme 56).




*Scheme 56. Amidation reaction between N-Cbz β-amino thioester **8a** and benzylamine.*

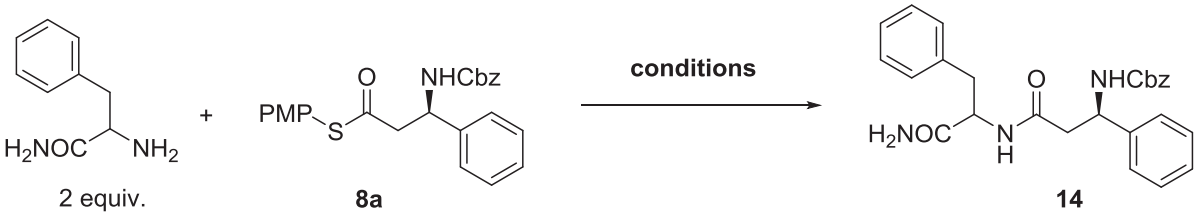
Also sterically hindered $\beta^{2,2,3}$-amino thioester **11a** was successfully transformed into the corresponding amide **13** under the same conditions (Scheme 57).




*Scheme 57. Amidation reaction between N-Cbz β-amino thioester **11a** and benzylamine.*

The transformation with less reactive amines like amino acid H-Phe-$NH_2$ was more difficult. In the reaction with two equivalents of *β* - amino thioester **8a** only traces of amide product **14** were observed after 18 hours reaction time at room temperature (Table 19, entry 1). We tried to optimize the reaction conditions but several attempts failed. Neither the addition of base, nor addition of catalytic amounts of activating agent DMAP led to considerable conversion (Table 19, entries 2-3). For example *β*-amino amide **14** was obtained in 7% yield after 72 hours of reaction time when 2 equivalents of Hünigs´base were added to the reaction mixture in methylene chloride (Table 19, entry 3). When we used pyridine as an activating solvent the product formation was increased and we isolated *β*-amino amide **14** in a yield of 16% after a reaction time of 18 hours (Table 19, entry 4). To our delight, microwave irradiation (1 h at 80 °C (MW) then 18 h at room temperature) promoted the reaction in pyridine and the corresponding dipeptide **14** was isolated in 89% yield (Table 19, entry 5).

*Table 19. Optimization of the amidation reaction between β-amino thioester **8a** and H-Phe-$NH_2$*



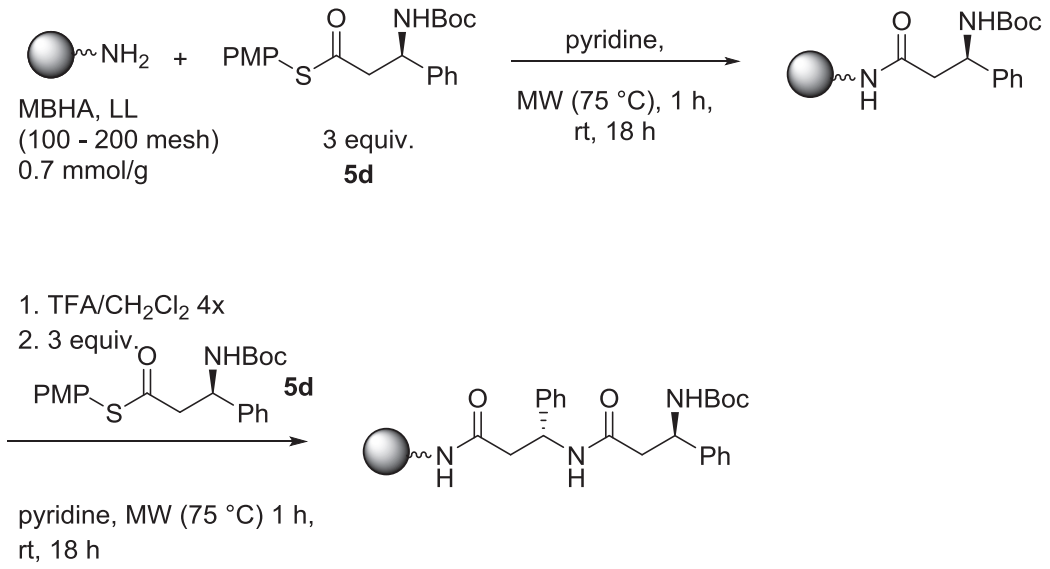

| entry | solvent | additive | conc. [M] | temp [°C] | time [h] | yield [%] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | - | 0.1 | rt | 18 | traces |
| 2 | $CH_2Cl_2$ | DMAP | 0.1 | rt | 18 | traces |
| 3 | $CH_2Cl_2$ | 2 equiv. Hünigs base | 0.1 | rt | 72 | 7 |
| 4 | pyridine | - | 0.5 | rt | 18 | 16 |
| 5 | pyridine | - | 0.5 | MW 80 °C 1 h | 18 | 89 |

When we investigated the microwave assisted amidation reaction in more detail we observed that directly after microwave irradiation 10-20% of the *β*-amino thioesters are converted to the amide **14**. After an additional reaction time of 18 hours at room temperature the product is formed in 89% yield. This demonstrates that the microwave irradiation forces the reaction and that PMP thioesters can be used as an activated carboxylic acid analogues for direct amidation reaction with less reactive amines such as amino acids. We found that a concentrated reaction mixture (0.5 M) and microwave activation of 1 hour is important to force the reaction to occur.

### 3.6.2 Amide Bond Formation on Solid Support

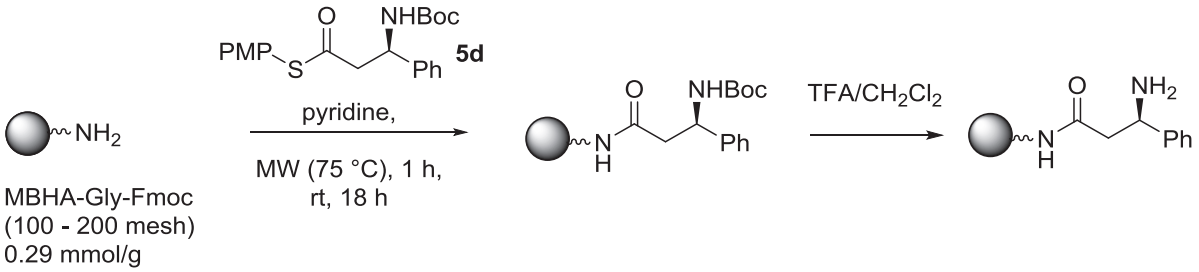
Having established suitable conditions for coupling agent free liquid phase peptide synthesis we were interested in using *β*-amino thioesters as pre activated *β*-amino acids analogues for peptide couplings on solid support. Solid phase peptide synthesis (SPPS), since its introduction by Merrifield in 1963,[115] is arguably the easiest and most effective way to synthesize peptides. The synthesis of *β*-peptides on solid support is typically more difficult than the synthesis of *α*-peptides.[116-119] Difficulties are typically observed in both, the removal of the protecting group and the carboxamide bond forming reaction due to on resin self-association of the growing peptide chain.[116-118] To overcome these difficulties microwave irradiation has successfully been applied for the synthesis of *β*-peptides, yielding the products in higher efficiency and purity.[120-121]

In our first attempts we envisioned the synthesis of a *β*-peptide on solid support utilizing *β*-amino thioester building blocks. For that purpose we chose *N*-Boc protected *β*-amino thioesters **5d** which would enable us to apply the Boc SPPS strategy. We chose MBHA resin LL (100 -200 mesh)*HCl, a convenient solid support for Boc based SPPS, and started the coupling reactions with the neutralized resin. In the first coupling step we added 3 equivalents of *N*-Boc *β*-amino thioester **5d** in 0.2 ml pyridine (0.25M) to the resin and exposed the reaction mixture to microwave irradiation (75 °C, 1 h) (Scheme 58). Afterwards, the mixture was allowed to stand at room temperature for another 18 hours, followed by intensive washing with DMF and dichloromethane. Since a qualitative test (a TNBS test[122] is indicating the presence or absence of primary amines due to colouration) revealed incomplete coupling, the procedure was repeated under the same conditions. After an intensive washing protocol with DMF and dichloromethane, a colourless TNBS test finally indicated complete coupling. We continued with the Boc deprotection following a standard Boc deprotection protocol (50% TFA in dichloromethane).[122] In the second coupling step 3 equivalents of *N*-Boc *β*-amino thioester **5d** in 0.2 ml pyridine (0.25M) were added and the coupling was repeated until the TNBS test revealed complete reaction (1 time). Surprisingly at this stage different attempts of deprotecting the *N*-terminal Boc group failed. From existing literature about solid phase *β*-peptide synthesis it is known that coupling and deprotection steps become more difficult as the chain length of the peptide reaches ca. six residues.[116-118] However, we observed those difficulties already after the second residue.



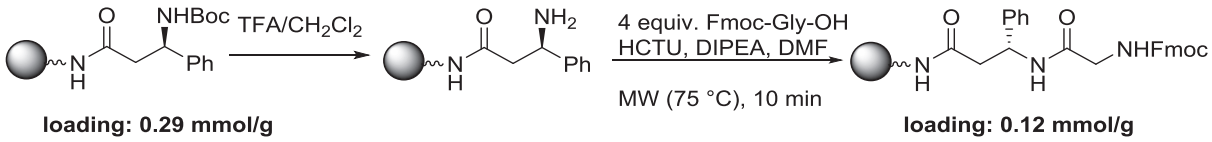

*Scheme 58. SPPS with N-Boc β-amino thioester **5d** on MBHA resin.*

We assumed that the loading of the resin could also play an important role and therefore repeated the reactions on a MBHA resin with a lower loading. The loading was reduced from 0.7 mmol/g to 0.29 mmol/g by coupling 1.5 equivalents of Fmoc-Gly-OH followed by acetylation of the remaining free amines (Scheme 58). The loading of the resin was determined by a quantitative Fmoc test,[123] to be 0.29 mmol/g. This resin was directly used for the following coupling reactions (Scheme 58). After Fmoc deprotection, visualized by the red coloured beads in the TNBS test, a solution of 3 equivalents of *N*-Boc *β*-amino thioester **5d** in 0.2 ml pyridine was added to the resin. The reaction mixture was exposed to microwave irradiation (75°C, 1 h) followed by 18 hours of reaction at room temperature. A TNBS test revealed complete coupling visualized by colourless beads however deprotection of the *N*-terminal Boc proved to be difficult again. In accordance with the reaction on MBHA resin with a higher loading, qualitative tests revealed incomplete deprotection after treating the resin with a 1:1 mixture of TFA in dichloromethane.



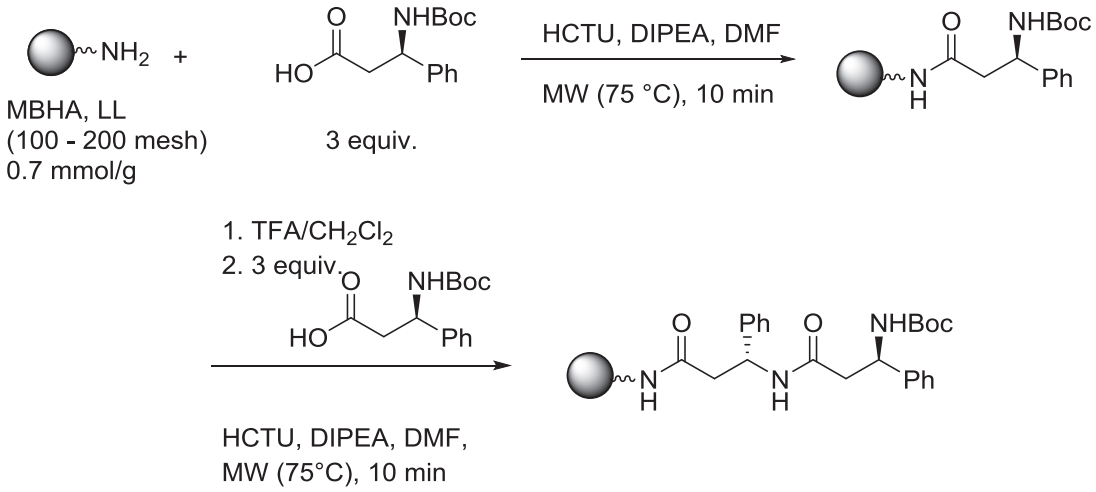

*Scheme 59. SPPS with N-Boc β-amino thioester **5d** on MBHA resin with lower loading*

To achieve a quantitative determination of the deprotection efficiency, we coupled Fmoc-Gly-OH to the peptide using standard coupling reagents and protocols (Scheme 60). The amount of coupled glycine was then determined with a photometric Fmoc test that revealed a loading of 0.12 mmol/g. Assuming that the glycine coupling was quantitative, which we checked through a TNBS test, these results show that during the previous Boc deprotection only approximately half of the Boc protected amines were definitely deprotected.




*Scheme 60. Quantitative Fmoc test*

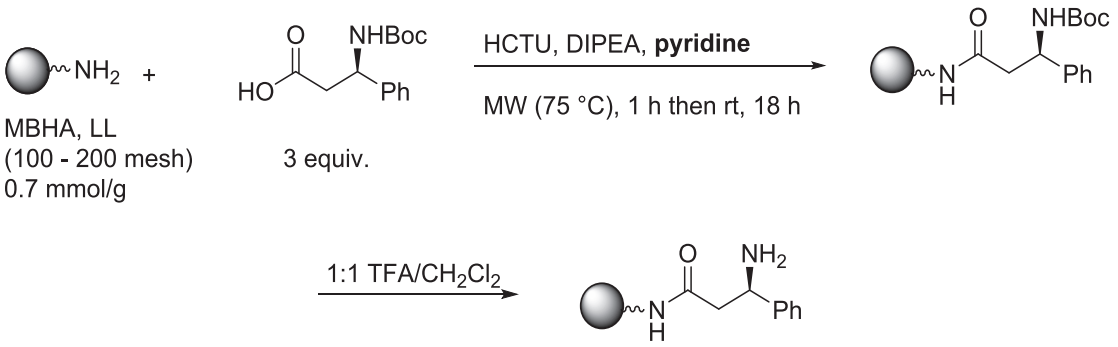
In a comparison experiment we synthesized the same model peptide with commercially available Boc-(*R*)-3-amino-phenyl propionic acid using standard coupling reagents and protocols (Scheme 61) and a quantitative photometric Fmoc test revealed complete coupling and Boc deprotection.




*Scheme 61. SPPS with commercially available Boc-(R)-3-amino-phenyl propionic acid on MBHA resin*

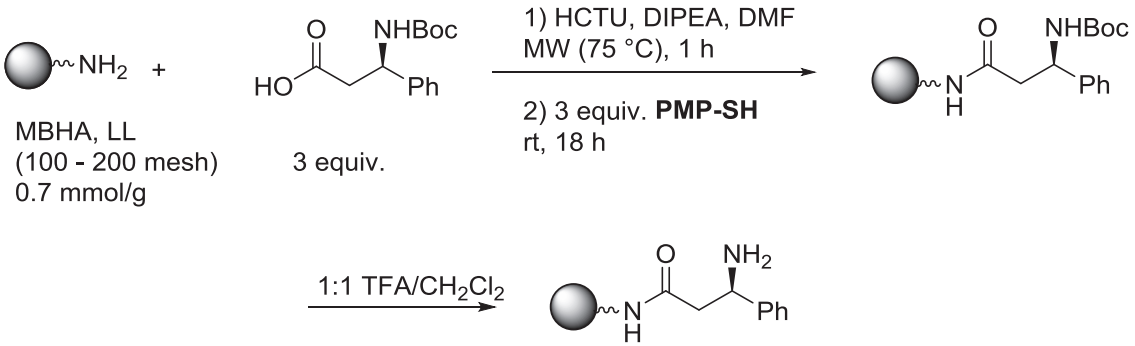
The only differences in the reaction setup of these two comparable reactions were the solvent and the released PMP thiol. Thus we were able to test the influences on the Boc deprotection in the peptide synthesis with commercially available Boc-(*R*)-3-amino-phenyl propionic acid. To investigate the influence of the solvent we conducted the microwave assisted coupling

reaction in pyridine with 3 equivalents of Boc-(*R*)-3-amino-phenyl propionic acid, 1.5 equivalents HCTU and 4.5 equivalents DIPEA, using the same temperature and time parameters as in the reaction with *N*-Boc protected *β*-amino thioesters. The completeness of the coupling was determined by a TNBS test followed by Boc deprotection with a 1:1 mixture of TFA in methylene chloride (Scheme 62). The TNBS test revealed complete deprotection, demonstrating that traces of pyridine, that could still be in the resin had no influence on the Boc deprotection.




*Scheme 62. SPPS with commercially available Boc-(R)-3-amino-phenyl propionic acid in pyridine*

In the next experiment we added 3 equivalents of PMP thiol after coupling of the commercially available amino acid (Scheme 63). The mixture was allowed to stand overnight, followed by a washing procedure and Boc deprotection.




*Scheme 63. SPPS with commercially available Boc-(R)-3-amino-phenyl propionic acid in pyridine; Addition of PMP-SH*

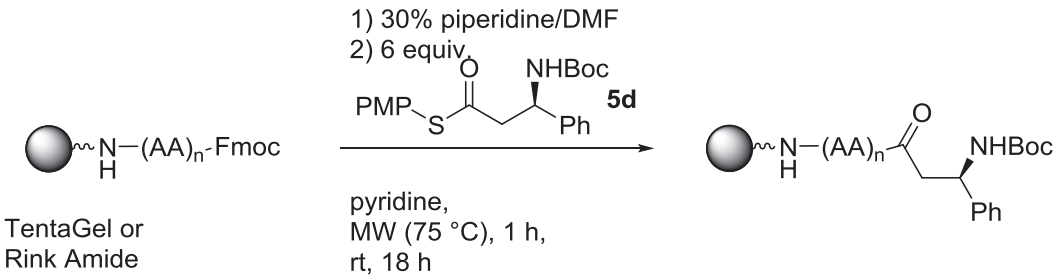
Surprisingly, after Boc deprotection, the TNBS test was clearly not as intensively coloured as in the syntheses lacking PMP thiol (Scheme 61 and 62). This result demonstrates that in the

synthesis with *N*-Boc β-amino thioester **5d**, the released PMP-thiol is possibly interfering with the *N*-Boc protecting group leading to incomplete Boc deprotections under the deprotection conditions tested. To utilize *N*-Boc *β*-amino thioesters as building blocks for solid phase peptide synthesis, better washing conditions, than simple washes with DMF and methylene chloride need to be evaluated to remove the released thiol completely. For example complexating agents like Ni salts could help to remove the thiol.

### 3.6.2.1 Coupling of Thioester Building Blocks as *N*-Terminal Amino Acids to Peptides

Peptides bearing *N*-terminal *β*-amino acids are of high interest since a single *β*-amino acid, positioned at the *N*-terminus can lead to enhanced stability of the peptide against biodegradability.[124] Additionally, *N*-terminal *β*-amino acids can influence the turn of peptides therefore offering great advantages for example in foldamer research.[125] In the previous chapter we have shown that *β*-amino thioesters can be utilized for peptide synthesis omitting additional coupling reagents. Next we explored whether we can couple Boc protected $\beta^3$- amino thioester **5d** using microwave irradiation (1 h, MW 75 °C, then 18 h, room temperature) to several $\alpha$ - and $\beta$ -peptides of different length Table 20).

*Table 20. N-terminal coupling of β-amino thioester **5b** to various α- and β-peptides.*




| entry | H-(AA)$_n$-TG | Main peak in LC-MS (m/z) |
|---|---|---|
| 1 | $(Gly)_5$ | 450.2 $(M+1)^+$ |
| 2 | Ala-Gly-Gly | 350.1 $(M+1)^+$ |
| 3 | $(\beta^3\text{-Phe})_2$-Gly | 531.3 $(M+1)^+$ |

The couplings were conducted on TentaGel as solid support and we used a less sterically demanding glycine pentamer as well as a tripeptide with more sterically demanding *N*-terminal alanine and also a $\beta^3$-phenylalaninetrimer to evaluate the coupling on to $\beta$-peptides. The outcome of the reaction was judged after test cleavages under acidic (TFA) or methanolysis condition (10% $Et_3N$ in MeOH, 12 h). LC-MS analysis revealed that $\beta$-amino thioester **5d** was successfully coupled to all peptides but no conclusions about the final purity can be drawn. From LC-MS analytics we saw that the coupling worked in the same purity as model peptides that were synthesized using the corresponding $\beta$ -amino acid under HCTU/DIPEA coupling conditions (Table 20).

## 3.7 Summary and Conclusion

In summary we have developed a mild organocatalyzed approach for the synthesis of *β*-amino thioesters through Mannich type reactions of mono thiomalonates (MTMs). Those nucleophiles proved to be highly reactive in the addition reaction with *N*-carbamate protected imines providing for *β*-amino thioesters in high yields and excellent enantioselectivities. In the presence of as little as 1 mol% of cinchona alkaloid urea derivatives a broad substrate scope was explored. Different *N*-Cbz protected imines including electron poor and electron rich aromatic, as well as less reactive aliphatic imines reacted readily with MTMs, demonstrating the generality of the developed protocol. In comparison to organocatalytic decarboxylative Mannich approaches, utilizing MAHTs as nucleophiles, we showed that MTMs react in a more efficient way. We achieved to decrease the catalyst loading from 10-20 mol% to as little as 1 mol% and the reaction time from 3-4 days to 4 hours. For reactions with *N*-Boc protected imines we showed that *β*-amino thioesters bearing a free amino functionality are readily accessible using our approach thus giving a synthetically valuable entry for direct further functionalization.

The direct generation of acyclic all-carbon quaternary stereogenic centers is still a synthetic challenge since the steric hindrance is limiting the substrates reactivity due to the crowded environment for the nucleophilic attack. As a contribution to this challenge we showed that various *α*-functionalized MTMs react readily with *N*-Cbz-protected imines. The addition reaction resulted in the highly stereoselective generation of an all-carbon quaternary stereogenic center adjacent to a tertiary stereogenic center in the presence of 5 mol% of a cinchona alkaloid urea catalyst. Various different substrate combinations of *N*-Cbz protected imines and alkyl substituted MTMs (methyl, ethyl, propargyl, ally, benzyl) were tolerated and the addition products were obtained in excellent yields and stereoselectivities. Additionally, *β*[2,2,3]-amino thioesters bearing allyl or propargyl substituents offer the possibility for further functionalization at the quaternary stereogenic center.

Furthermore, we showed the synthetic value of *β*-amino thioesters as building blocks for coupling agent free liquid phase, as well as solid phase peptide synthesis. *β*-Amino thioesters are activated *β*-amino acids and we developed a coupling agent free approach for the synthesis of dipeptides in solution as well as for the *N*-terminal coupling on solid support.

The Wennemers group is currently extending the applicability of $\alpha$-substituted and $\alpha$-unsubstituted MTMs to ketimines which would allow for the generation of quaternary sterogenic centers at the $\beta$-position and two adjacent all-carbon quaternary stereogenic centers respectively.

Mechanistic studies of reactions of $\alpha$-substituted MTMs with nitroolefins have revealed that the rigid substituent at the thioester and the flexible substituent at the regular ester of MTMs are important to direct the interactions with the catalyst in such a way that the addition of the MTM enolate occurs from its *Si* face to the *Re* face of the nitroolefins. This transition state model can also be applied for the addition reaction to imines since the major diastereoisomer is (2*S*,3*S*) configured. Further detailed mechanistic studies could additionally provide insight into the observation of an increasing diastereoselectivity during the course of the reaction and allow for a deeper understanding of the diastereoselective pathway of the reaction.

These studies demonstrate the high value of MTMs in Mannich type addition reactions. The resulting products, whose synthesis was optimized using the MTM approach, are of high potential and building blocks for pharmaceutically important molecules such as $\beta$-lactams or antihyperglycemic sitagliptin.

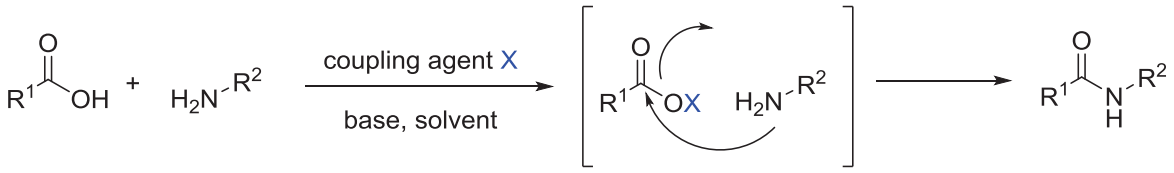
# Part II

# Screening for Peptidic Triazolium Salt Based Catalysts

# 4 Introduction

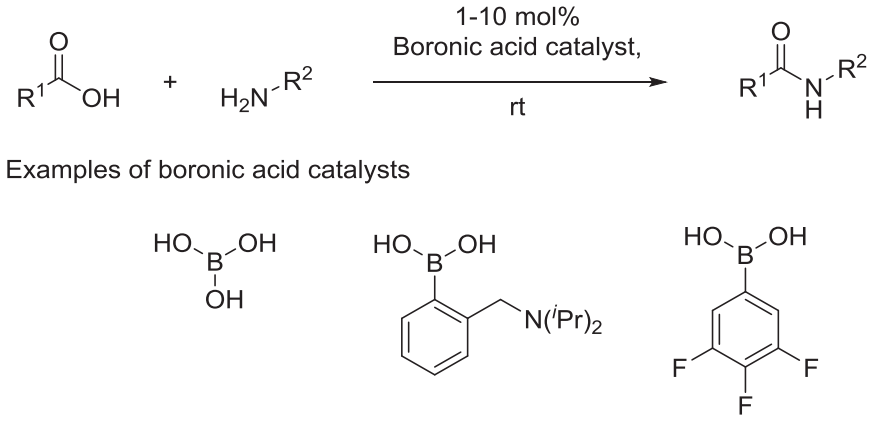
## 4.1 Catalytic Amide Bond Formation

Carboxylic acid amides are among the most essential functional groups in organic chemistry.[126] In addition to being the key chemical connection of proteins, they are the basis for some of the most widely used polymers and drugs.[127] In nature, amide bonds are formed within cells in ribosomes. These machineries generate long proteins at extremely high reaction rates by assembling the amino acids step by step using active esters of amino acid building blocks and RNA.[128] In organic chemistry, carboxylic acid amide synthesis requires also activating agents. However, in contrast to nature, the activation of the carboxylic is not performed catalytically but typically with stoichiometric amounts of coupling reagents (Scheme 64).[129] Such processes require extensive protection of other functional groups and numerous byproducts are typically generated that need to be separated from the reaction mixture.



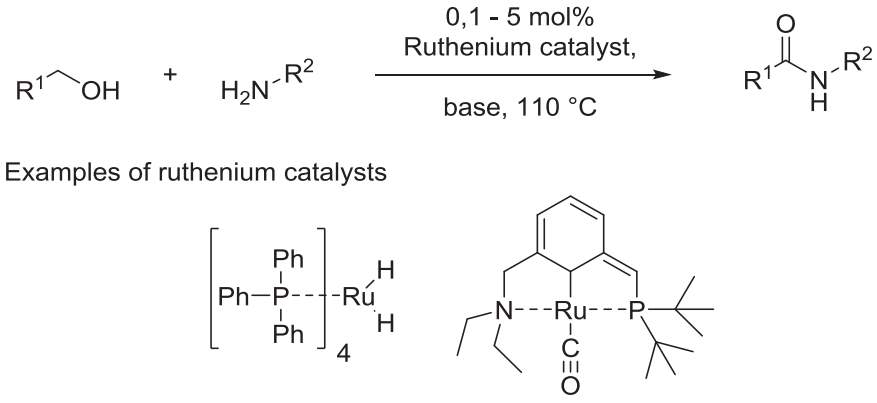

*Scheme 64. Convenient amide bond formation out of carboxylic acids and amines using stoichiometric amounts of activating agent*

These drawbacks make the most common amide bond forming reactions uneconomical and wasteful, and improved methods are of great interest. Catalytic approaches for their preparation from simple starting materials such as carboxylic acids or aldehydes and amines are rare.[130-132] Amongst the existing approaches boronic acid catalysts are the most prominent (Scheme 65).[133-137]




*Scheme 65. Boronic acid catalyzed direct condensation of carboxylic acids and amines*[133-137]

The boronic acid catalysts, which are typically used in 1 - 10 mol% generate an active ester, suitably activated for the nucleophilic attack of simple amines. In that manner, waste free amidation reactions are accomplished. In addition to carboxylic acids, alcohols can be used for oxidative amidation reactions with amines catalyzed by ruthenium catalysts (Scheme 66). These reactions work without the need of any additives and only molecular hydrogen is formed as by-product. However, typically high temperatures are required for the reactions, which limits their applicability.[131]

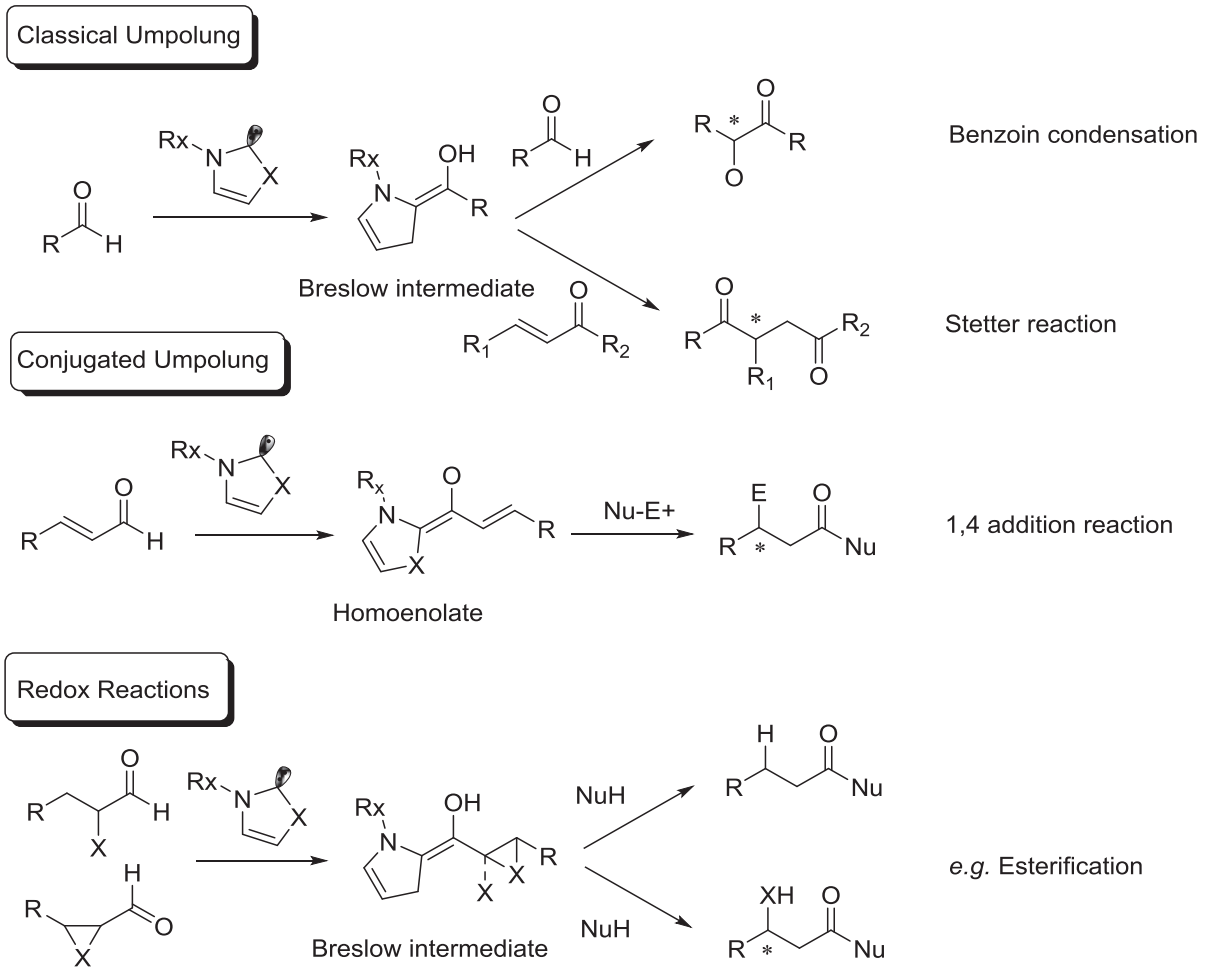



*Scheme 66. Ruthenium catalyzed direct condensation of alcohols and amines*[131]

## 4.1.2 *N*-Heterocyclic Carbenes

*N*-heterocyclic carbenes are very reactive neutral nucleophilic species that possess a divalent carbon with only six valence electrons.[138-139] Nucleophilic carbenes are found in nature for example as catalytically active species in the coenzyme thiamine.[140] The active site embeds a thiazolium salt which is involved in catalytic nucleophilic acylation reactions. Since the discovery of carbenes by Wanzlick *et al.* in the 1960´s,[141-142] they were considered for

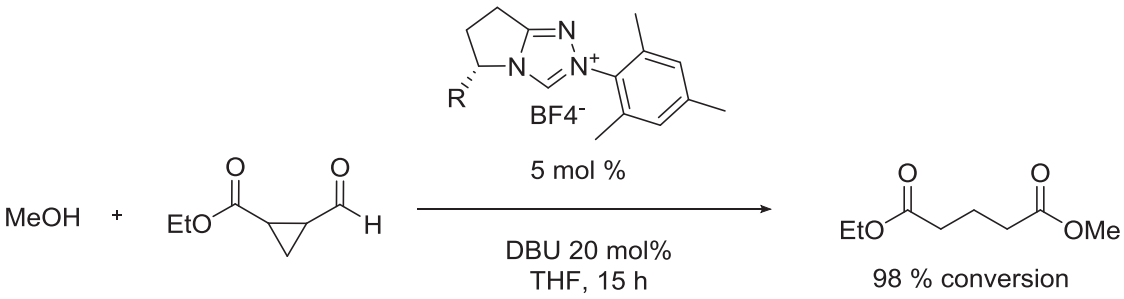
several years as highly reactive intermediates. In 1991, the first bench stable carbene compound was isolated and characterized by Arduenga *et al.*.[143-144] *N*-heterocyclic carbenes are typically synthesized by deprotonation of their corresponding salts and have been used in a variety of transformations.[138-139] Besides their ability to act as ligands in organometallic chemistry, they are also used as organocatalysts.[139] Their unique properties include classical Umpolung reactivity by transforming normally electrophilic aldehydes into nucleophilic species (*e.g.* in Benzoin and Stetter reactions), conjugated Umpolung reactivity, allowing for 1,4 addition reactions of $\alpha,\beta$ unsaturated aldehydes and nucleophilic addition reactivity accomplishing redox reactions (Scheme 67).[139]




*Scheme 67. Reactivity of NHCs*

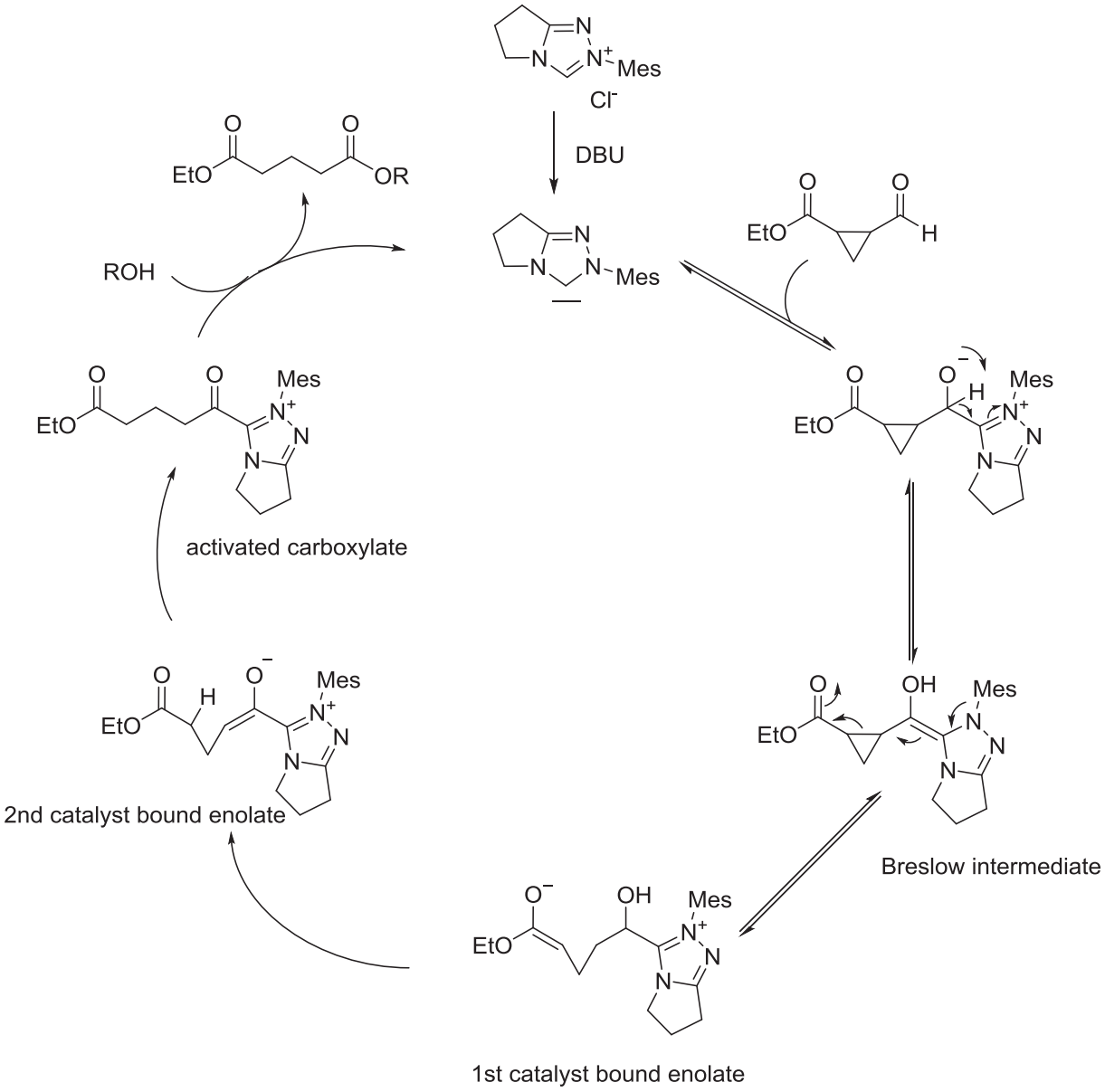
### 4.1.3 *N*-Heterocyclic Carbenes as Catalysts for Redox Reactions

NHC-catalyzed redox reactions allow for the synthesis of esters, thioesters, carboxylic acids, carbamoylazides and many more utilizing $\alpha$-functionalized aldehydes and the corresponding nucleophiles as substrates. [145-152] An example of redox esterification has been reported by Bode *et al.* in 2006.[149] The reaction was mediated by 5 mol% of *N*-heterocyclic carbene *via* catalytically generated activated carboxylates (Scheme 68) and besides DBU, which is needed to deprotonate the NHC salt, no other additives were required. The ester product was obtained in 98% yield after 15 hours reaction time at room temperature in THF.




*Scheme 68. N-heterocyclic carbene catalyzed redox esterification between alcohols and $\alpha$-functionalized aldehydes*[149]

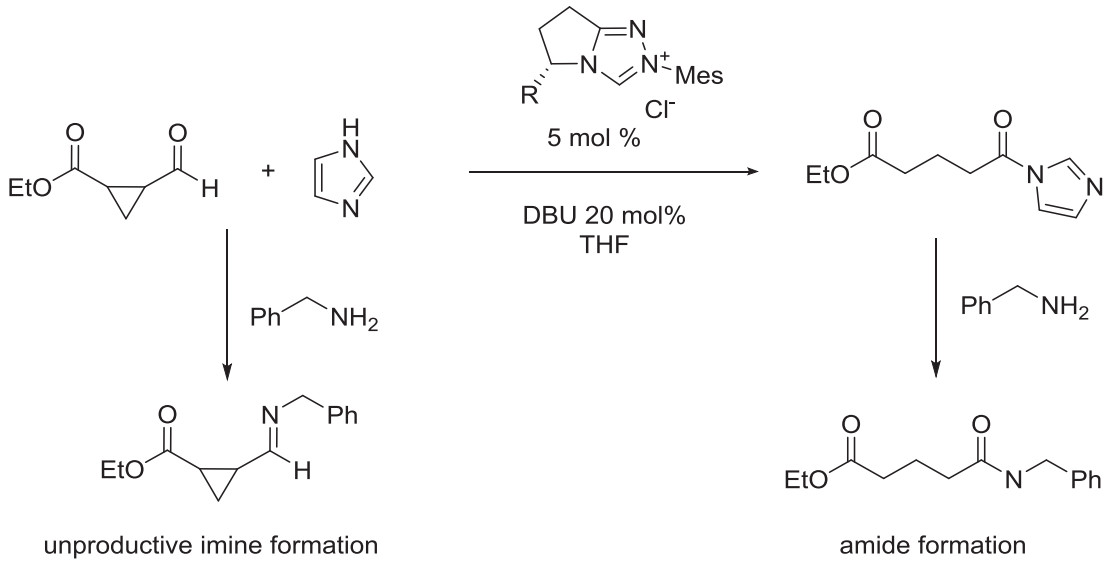
Based on deuterium exchange experiments, the following reaction pathway was proposed (Scheme 69). Upon addition of deprotonated catalyst to the formylcyclopropane aldehyde, a Breslow intermediate is formed which is reversably transformed into the first catalyst bound enolate. This enolate is rapidly quenched to a more stable second enolate which further undergoes protonation and tautomerization to form an activated carboxylate suitably activated for nucleophilic attack of an alcohol.




*Scheme 69. Reaction pathway of N-heterocyclic carbene catalyzed redox esterification reaction*[149]

Besides, alcohols, also thiols were well tolerated as nucleophiles providing the thioesters in yields of up to 95%. However, in the presence of amines less than 5% of the amide product was isolated. NMR studies of the crude mixture revealed that most of the aldehyde starting material was converted into the corresponding imine (Scheme 70). After a screening of nucleophilic co-catalysts, which are known to be involved in acylation reactions, imidazole was found to be optimal to completely suppress imine formation thus leading to full conversion of the amide product.[153] NMR studies suggested a tandem catalysis approach. As a first step the NHC is forming an activated carboxylate (Scheme 70) followed by an

intermolecular acyl transfer from the NHC to the additive. This second generated acyl azolium is also an activated acyl azolium species which can react with amines to form amide products.

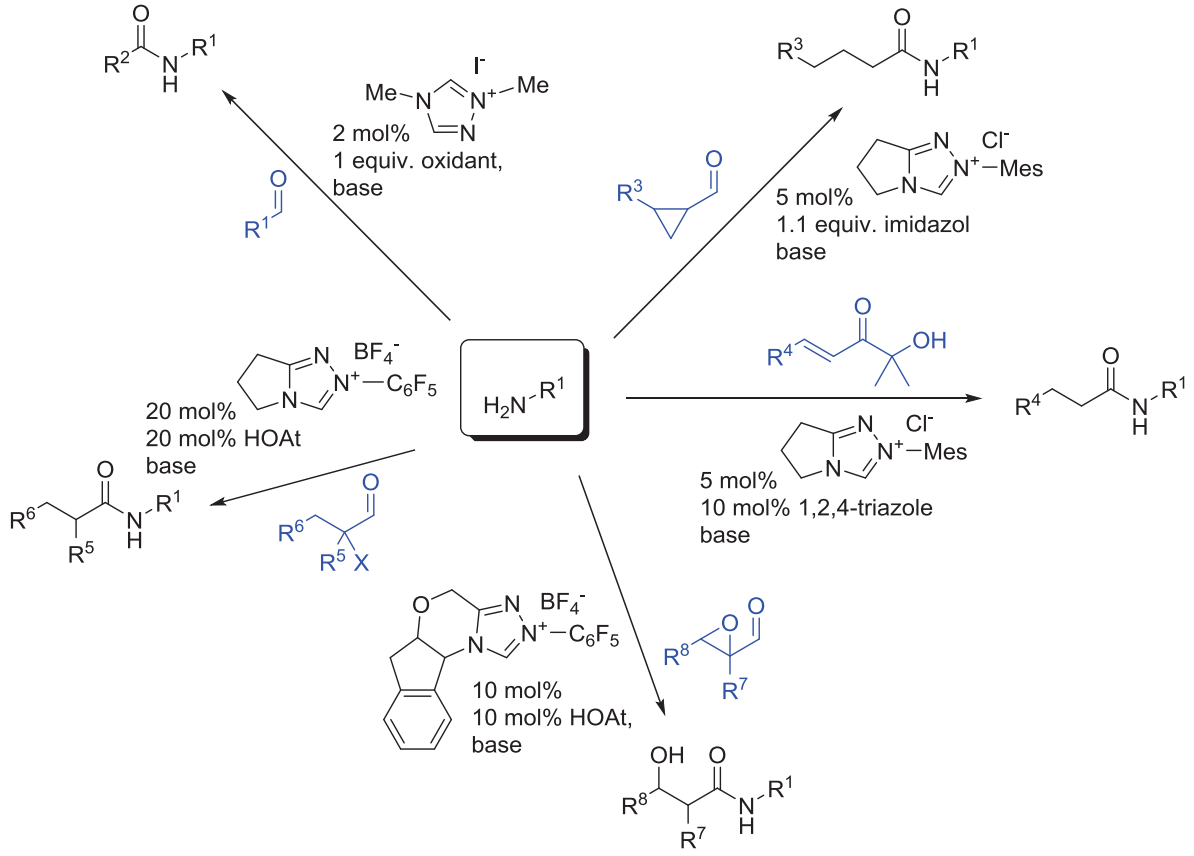



*Scheme 70. Redox Amidation reaction catalyzed by NHC with co-catalyst imidazole; An inter molecular acyl transfer is necessary to facilitate the amide bond formation*[153]

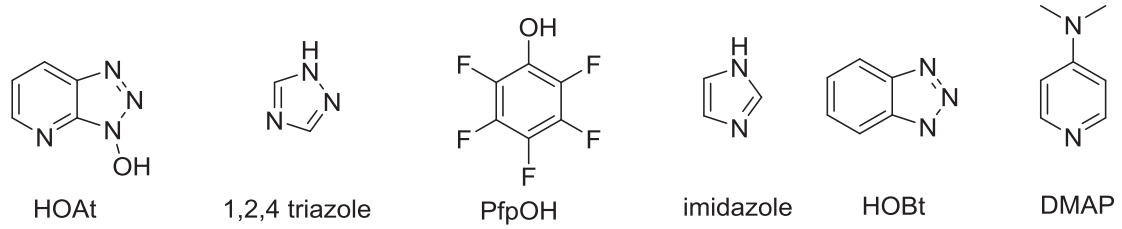
## 4.1.4 *N*-Heterocyclic Carbenes as Catalysts for Redox Amidation Reactions

Due to their unique reactivity, *N*-heterocyclic carbenes (NHC) have shown to be potential candidates for catalytic amidation reactions (Scheme 71).[153-155] NHCs and co-catalysts, catalytically generate activated carboxylates from $\alpha$-functionalized aldehydes such as formylcyclopropanes[153] $\alpha,\beta$ unsaturated aldehydes,[153] $\alpha$-halo aldehydes,[156] epoxyaldehydes[156] and $\alpha$-hydroxyenones.[157] The activated carboxylate is transformed to an amide by reaction with amines in the presence of a co-catalyst thus resulting in a redox amidation reaction. In recent years, several additives have been identified to promote the NHC-catalyzed redox amidation. Examples thereof are shown in Scheme 72. For example HOAt was successfully used as additive in NHC catalyzed redox amidation reactions of $\alpha$-halo aldehydes,[156] epoxyaldehydes[156] and $\alpha,\beta$-unsaturated aldehydes.[158] 1,2,4, Triazole served as optimal co-catalyst in the amidation of $\alpha$-hydroxyenones.[157] The redox amidation reaction with formylcyclopropanes,[153] was furnished by imidazole. In addition, HOBt, DMAP and PfpOH were found to provide for good yields in the amidation reaction of $\alpha$-halo aldehydes.[156] Recently hydroxamic acids were identified as good co-catalysts in reactions

with $\alpha$-hydroxyenones.[159-160] Furthermore, the transformation of $\alpha$-unfunctionalized aldehydes into amides with simple amines has also been accomplished using *N*-heterocyclic carbenes as catalysts and besides a co-catalyst, stoichiometric amounts of an oxidant were required (Scheme 71).[161]




*Scheme 71. NHC catalyzed amidation reaction with $\alpha$-functionalized aldehyds*



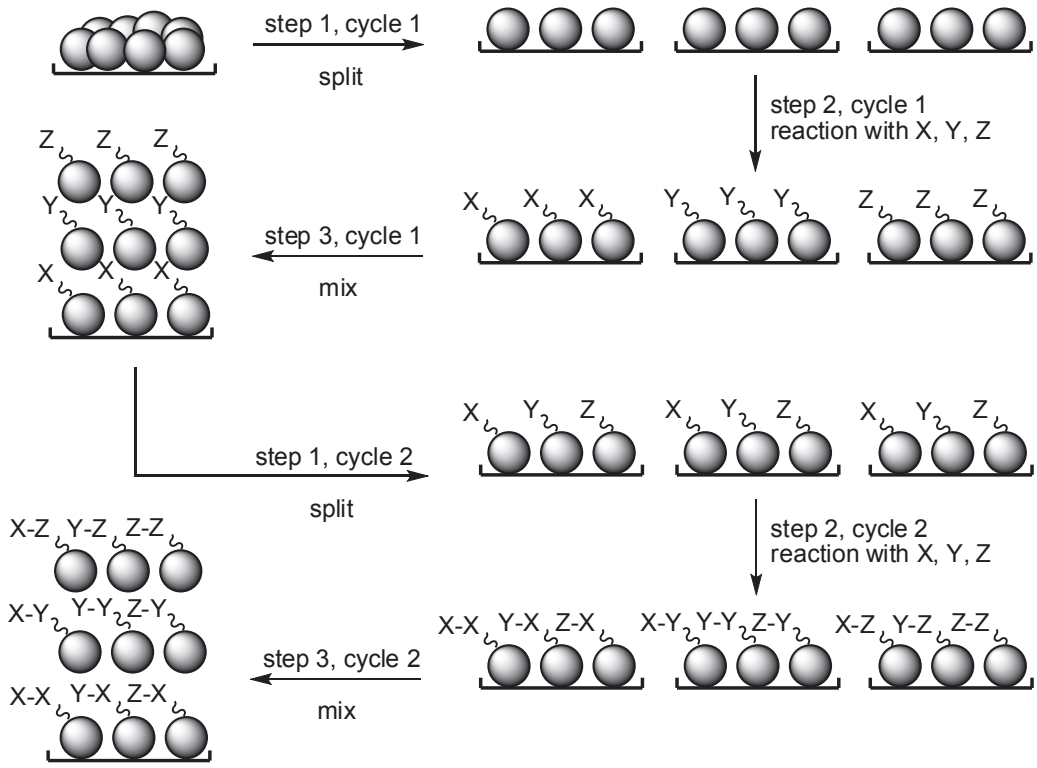

*Scheme 72. Co-catalysts for NHC catalyzed redox amidation reactions*

## 4.2 Combinatorial Chemistry

The prediction of the catalytic activity and selectivity in the development of peptidic organocatalysts is a great challenge. Even small peptides, due to their multitude of rotational freedom degrees, adopt so many conformational states that a purely rational design is difficult. Although computational methods can help to achieve this goal, rational design is still very time consuming and labour-intensive because of the synthesis and testing of a variety of potential ligands. Very elegant and effective tools for the discovery of catalysts in general are therefore smart combinatorial screening methods.[162-164] Combinatorial chemistry is an empirical approach to the evolutionary development of natures´ catalysts by the combined process of mutations and selection for the fittest.[163] The methods involved allow the selection and simultaneous screening for a catalytically active compound in a variety of diverse compounds. Chemical approaches for the generation of molecular diversity include parallel libraries, one-bead-one-compound libraries,[165-167] or dynamic combinatorial libraries.[164]

### 4.2.1. Split-and-mix Libraries

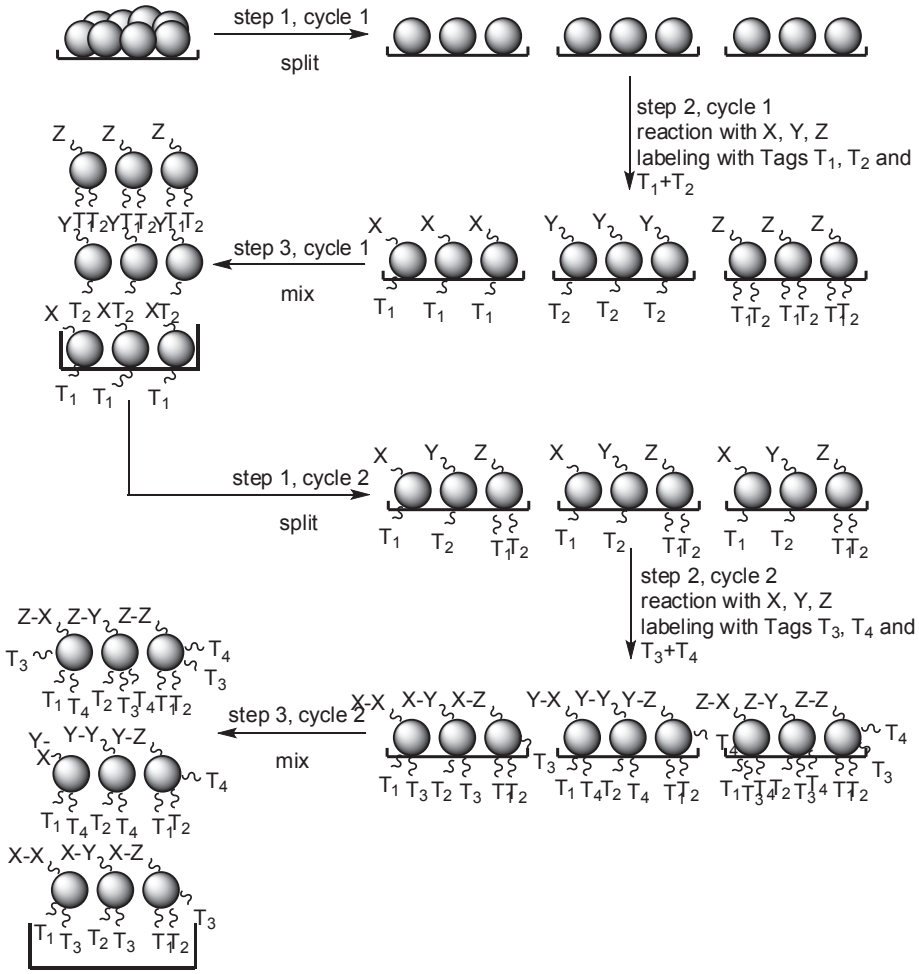
Split-and-mix synthesis is arguably the most elegant strategy in building up a combinatorial library of a large molecular diversity.[168-171] The strategy is suitable for the synthesis of compounds of which building blocks can be connected in high yields. The synthesis of so called “one-bead-one-compound” libraries consists of three steps. In the first step, the resin is divided in equal portions. Each portion is then functionalized with a different building block. The beads are then combined, mixed and divided in equal portions again, ready for the next reaction with another set of building blocks (Scheme 73).[168] The cycle can be repeated as often as necessary to obtain a library of the desired size. In this way, a library with 20 building blocks (*e.g.* amino acids) can after 3 cycles of split-and-mix synthesis contain $20^3$ = 8000 different members.[164]




*Scheme 73. Split-and-mix synthesis of a library of 9 compounds*

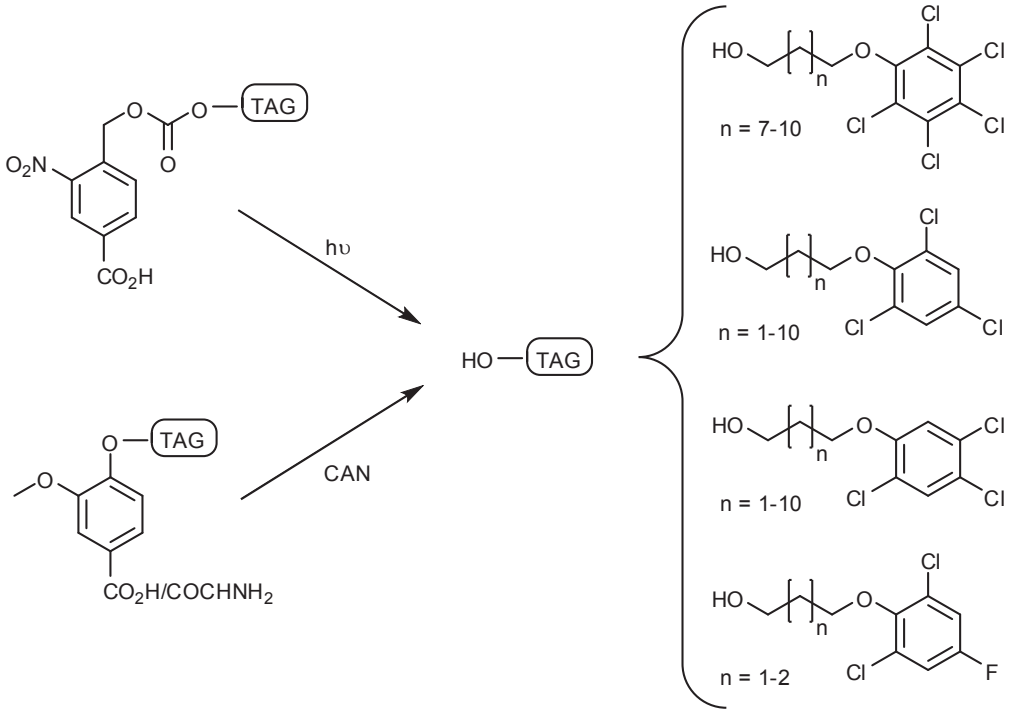
## 4.2.2 Chemical Encoding

The identification of the compound that is attached to a bead is as essential as the screening of a library itself. Since one bead contains typically only 100 pmol of functionalisable groups, compound analysis is difficult. A very elegant method to circumvent the direct analysis of the attached compounds is chemical encoding.[172-174] The principle of chemical encoding encompasses the attachment of easily analyzable and inert chemical tags to 1-5% of the functionalities of the bead during each reaction cycle (Scheme 74).




*Scheme 74. Example of a synthesis of a chemical encoded library of 9 dipeptid*

The tags are used as a binary code and record the synthetic history of each bead. For each different compound and each different reaction step a unique combination of tags is needed. In general, with a set of 4 different tags per synthesis step, $2^4$-1 = 15 positions e.g. 15 different amino acids can be encoded. Thus 12 (3x4) tags can encode a library of $15^3$=3375 different compounds. In Scheme 75 a set of suitable tags is shown. These molecules are mixed ethers of long alkyl chained alcohols and polyhalogenated aromatics.[172-173]

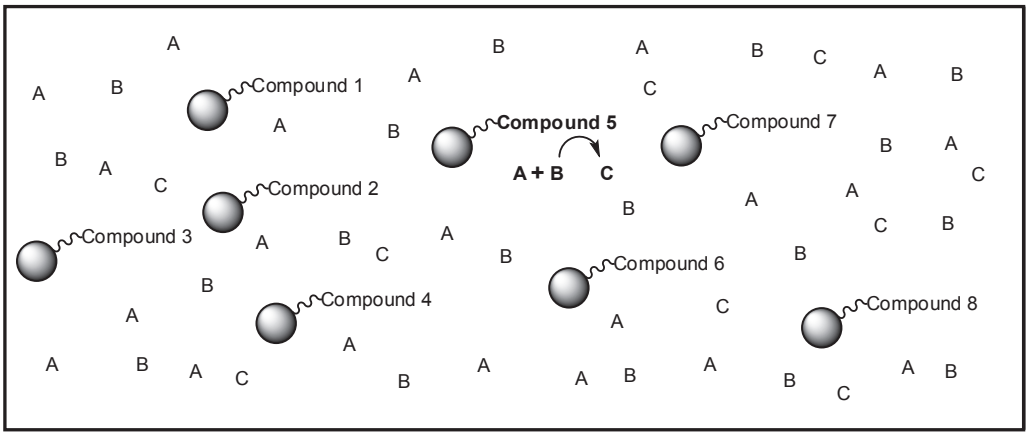



*Scheme 75. Photocleavable and oxidative cleavable tags*[173]

These tags have several advantages. They can easily be separated by gas chromatography (GC) because of their structural diversity and be identified due to their different retention time. They are detectable by electron capture detectors (ECD) even in amounts of as little as 1pM and they can be attached to the resin *via* oxidative or photocleavable linker. The photocleavable linker is based on *o*-nitrobenzylcarbonate,[172] and the oxidative cleavable linker on vanillinic acid.[173] The latter can be cleaved by cerium ammonium nitrate (CAN). Both linkers can be coupled to the bead *via* their carboxylic acid function to form esters or amides depending on the resin material.

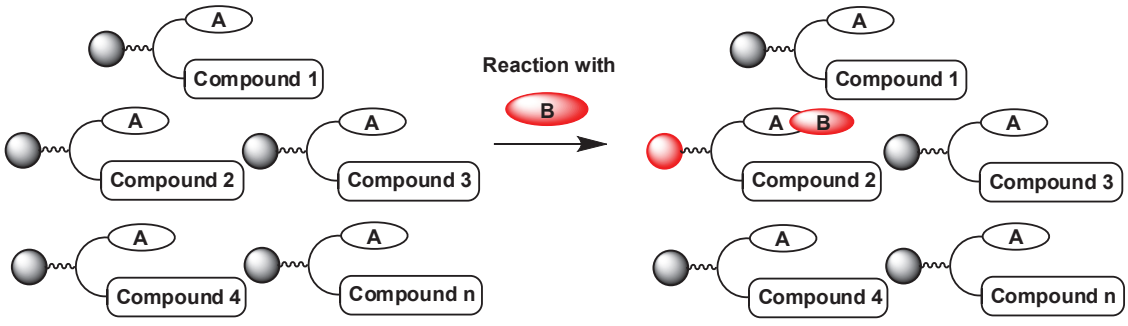
## 4.2.3 Catalyst Substrate Co-Immobilisation

Identifying catalytically active library members is challenging thus requires general and reliable screening methods.[164] In case of monomolecular as well as bimolecular reactions having starting materials and products in solution the identification of the catalytic active compound is either very difficult or impossible because of the rapid diffusion of the products (Scheme 76).




*Scheme 76. Effects of free diffusion: Only compound 5 is catalytically active but the product C is distributed in the whole assay*

Solutions to this challenge are reactions in gels,[175-176] where the diffusion is slowed down, the generation of insoluble coloured reaction products[177] or IR-thermography[178] monitoring changes in the reaction heat $\Delta H°_r$. An alternative more general tool for the identification of catalysts for bimolecular reactions is the concept of catalyst-substrate co-immobilisation (Scheme 77).[179] The basis of this concept is that both, the library member, the potential catalyst, and one of the substrates are immobilized on the same bead through a bifunctional linker. The second substrate is free in solution and labelled with for example a dye, fluorophor or radioactivity. If a library member is able to catalyze the reaction between the two substrates, the labelled substrate will be covalently bound to the resin. The labelled bead can then be separated and the catalyst identified.[164]




*Scheme 77. Principle of the catalyst substrate co-immobilisation[164]*

The principle of catalyst substrate co-immobilisation is especially suitable for the identification of catalytically active peptides. An encoded peptide library can be easily synthesized on one end of *e.g.* a lysine based linker. The second end can be functionalized with the desired substrate through an amide bond. The free substrate in solution is typically

labelled by a dye and after the reaction and an intensive washing are ideally 1% of the beads coloured what reflects a selective catalysis. With this concept, our group identified peptides of the type Pro-Pro-Xaa as excellent catalysts for aldol reaction between aldehydes and ketones, demonstrating that the catalyst-substrate co-immobilisation method is as powerful tool for the development of catalytically active peptides.[179-180]

# 5 Objective

## 5.1 Preface

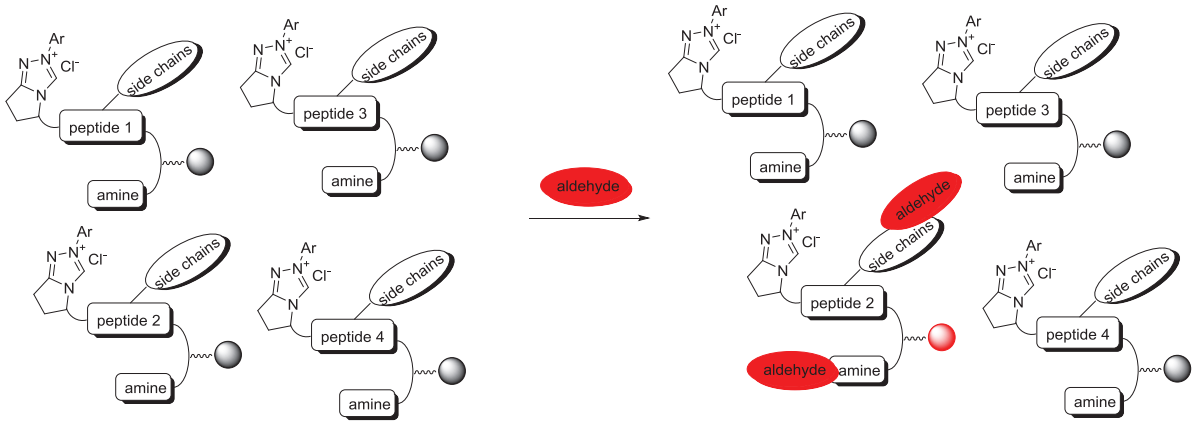
The studies described in this part of the thesis were conducted in collaboration with Chenaimwoyo A. Gondo and Prof. Jeffrey W. Bode at the ETH Zürich.

## 5.2 Objective

Catalytic redox amidations of simple aldehydes and amines are of great synthetic value since they allow for facile amide bond formation omitting the typically required stoichiometric amounts of activating agents. *N*-heterocyclic carbenes (NHCs) are potential catalysts for these transformations since they catalytically form transient activated carboxylates with $\alpha$-functionalized aldehydes. Those NHC-activated carboxylates proved to be readily transformed into esters, thioesters, carboxylic acids, carbamoyl azides and many more in the presence of the corresponding nucleophile.[181] In contrast, similar reactions with amines as nucleophiles are often unsuccesfull due the tendency of amines to form imines in the presence of aldehydes and their low reactivity towards acyl azolium compounds.[149, 182-183] However, when a nucleophilic co-catalyst is additionally present in the reaction mixture, amide formation is achieved (see chapter 4.1.4). The co-catalyst undergoes first a reaction with the acyl azolium resulting in the generation of a second traditional activated carboxylate which reacts readily with amines to form amides. This intermolecular acyl transfer from the NHC to the co-catalyst was identified as a key step to promote redox amidations between $\alpha$-functionalized aldehydes and amines.[153, 156-160]

The objective of this part of the thesis was to develop a catalytic system for the redox amidation reaction between $\alpha$-functionalized aldehydes and amines, proving for both functionalities (triazolium salt as NHC precursor and a co-catalyst) assembled on one single molecule. We hypothesized that a peptidic triazolium salt bearing nucleophilic amino acids *e.g.* histidine, lysine, tyrosine or serine could fulfill the requirements for a catalytic intramolecular acyl transfer and thus being a potent redox amidation promoter. We aimed to develop such a catalytic system using a combinatorial approach (Scheme 78). Therefore we planned to prepare a triazolium salt functionalized peptidic library and envisioned to use it for

a combinatorial screening in order to identify possible promoters for intramolecular acyl transfers and redox amidation reactions of $\alpha$-functionalized aldehydes and amines in the absence of an external co-catalyst.

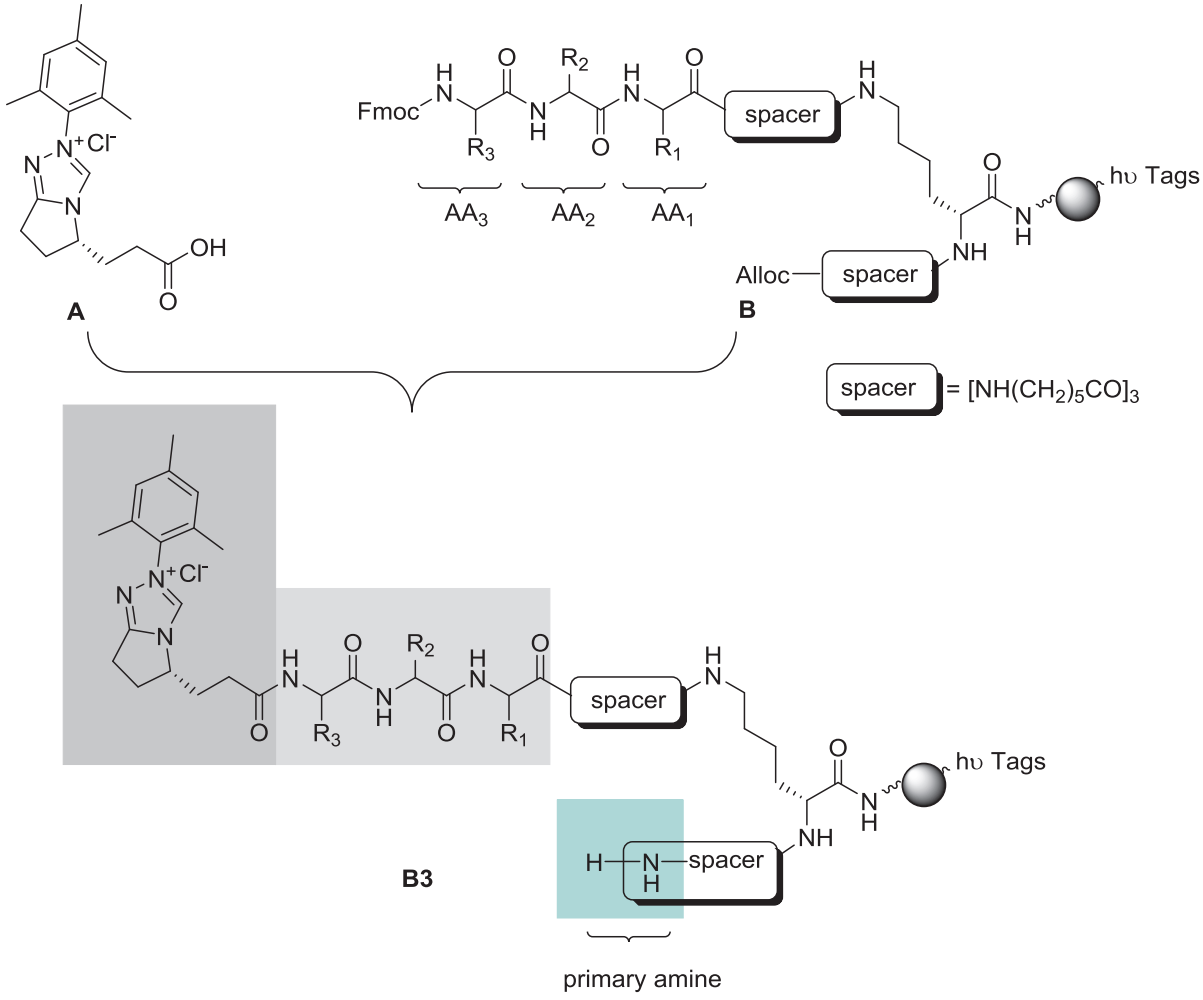



*Scheme 78. Combinatorial screening approach to identify peptidic triazolium salts that promote the redox amidation reaction between α-reducible aldehydes and amines in the absence of an external co-catalyst*

# 6 Combinatorial Screening of Tripeptidic Triazolium Salt Catalysts for Redox Amidation Reactions

## 6.1 Design of the Library

We started our investigations on the identification of a catalytic system for the redox amidation of $\alpha$-functionalized aldehydes and amines with the preparation of a structurally diverse triazolium salt functionalized tripeptidic library (Scheme 79).



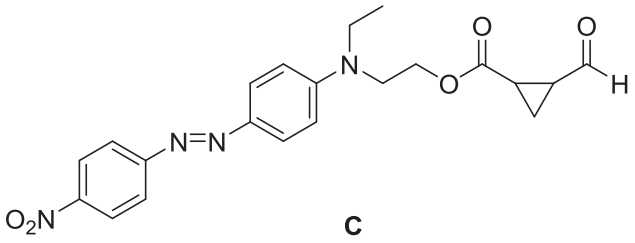

*Scheme 79. Encoded triazolium salt functionalized tripeptidic library with amine functionality co-immobilized on TentaGel (AA1 and AA3 = L-Pro, D-Pro, L-Ala, L-Val, L-Ser, L-Thr, L-Asp, L-Glu, L-Asn, L-Gln, L-His, L-Arg, L-Phe, L-Tyr; AA2 = L-Pro, D-Pro, D-Ala, D-Val, D-Ser, D-Thr, D-Asp, D-Glu, D-Asn, D-Gln, D-His, D-Arg, D-Phe, D-Tyr.)*

We decided to use tripeptide library **B** that had previously been prepared in our group using the split and mix approach (see chapter 4.2.1). It contained a set of structural diverse amino acids such as histidine, tyrosine and serine which could potentially act as co-catalyst. The

tripetidic library was prepared at one end of a bifunctional lysine linker on TentaGel resin whereas the second end of the linker bore a protected amine functionality (co-immobilized substrate, see chapter 4.2.3). The library contained fifteen different D- and L-amino acids in each of the three positions; hence consisted of a maximum of $15^3$= 3375 different tripeptides (Scheme 79).[184]

As a NHC precursor we used carboxylic acid functionalized triazolium salt **A**, recently synthesized by the group of Bode, and envisioned to couple it *via* its carboxylic acid moiety to the *N*-terminus of the encoded tripeptide library **B** (Scheme 79).[185] The triazolium salt core of structure **A** is one of the most general NHC precursors and was chosen as nucleophilic catalyst since it had proved to be suitable for promoting the redox amidation reaction of $\alpha$-functionalized aldehydes and amines in the presence of a co-catalyst.[153]

As the second substrate which is free in solution and dye labeled, Disperse Red labeled 2-formylcyclopropanecarboxylate **C** was chosen (Scheme 80). This substrate contains an $\alpha$-reducible aldehyde moiety and the dye, allowing for the separation and identification of those beads that have the substrate covalently attached.

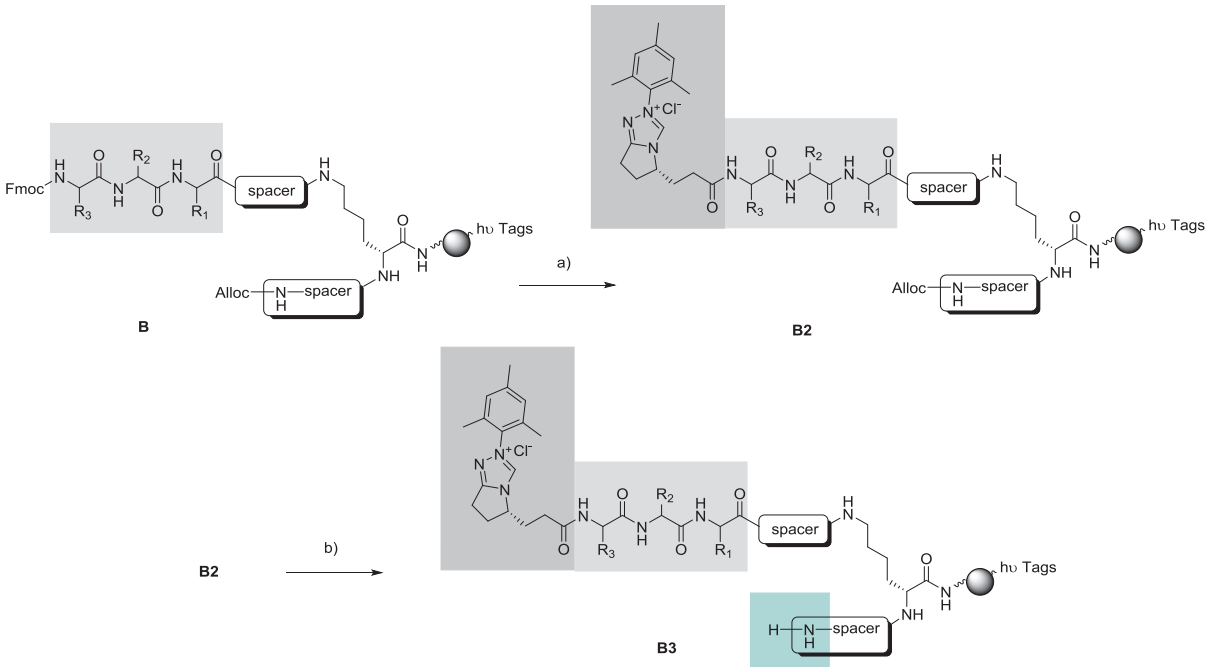



**C**

*Scheme 80. Structure of Disperse Red labeled α-functionalized aldehyde **C***

## 6.2 Preparation and Functionalization of the Library

The libraries for the different combinatorial assays were prepared as follows (Scheme 81). After Fmoc deprotection of unfunctionalized and orthogonally protected library **B**, carboxylic acid functionalized triazolium salt **A** was coupled to the library using DIC and Oxyma as coupling reagents.[185] The resulting library **B2** was treated with $[PPh_3]_4$ and diethylamine (DEA) which led to Alloc deprotection of the second arm of the lysine linker.



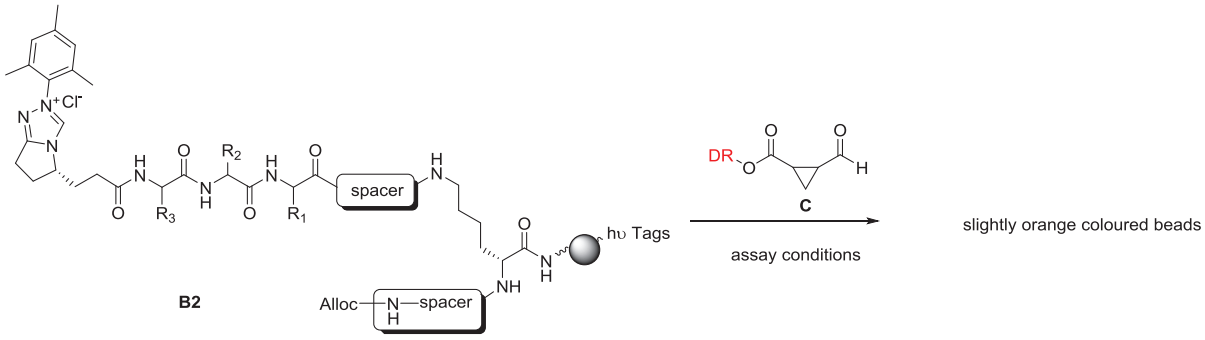

*Scheme 81. Preparation and functionalization of the tripeptide triazolium salt libraries; a) i:20% piperidine/DMF: ii:* **A** *(2 equiv.), DIC (2 equiv.), Oxyma (2 equiv.), DMF, 3h, rt b) Pd[PPh$_3$]$_4$ (0.1 equiv.), DEA (20 equiv.), DMF:DCM (1:1), 2h, rt.*

## 6.3 Combinatorial Assays

The combinatorial assays were each conducted with 4 mg of the particular library which corresponds to two to three copies of each library member. Disperse Red labelled 2-formylcyclopropanecarboxylate **C** was added to the resin in a concentration of 2.5 M in methylene chloride (2.5 equiv.) followed by the addition of diazabicycloundecene (DBU, 4 equiv.) resulting in the deprotonation of the triazolium salt. The assays were shaken for 18 hours at 35 °C followed by an intensive washing of the beads to remove all non-covalently bound dye labeled substrate (including NHC-substrate that was not transferred to either the sidechains of the peptide or the amine at the second arm of the linker). The most intensively coloured beads were identified by visual inspection under a low-power microscope and individually transferred into capillaries. The tags were then cleaved by UV-light and analyzed by GC-ECD in order to analyze the sequence of the tripeptide.

## 6.3.1 Negative Control

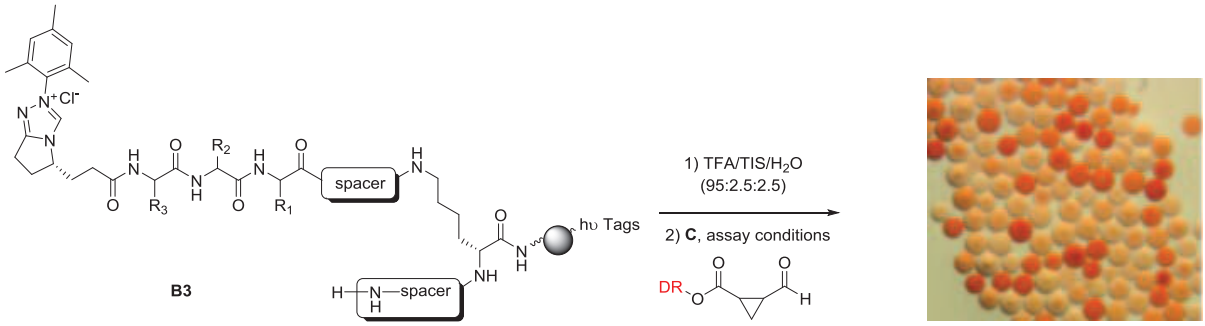
We started the combinatorial screening with a negative control assay to ensure no false positive results of our approach. For the negative control we subjected library **B2** to the screening conditions stated in 6.3 (Scheme 82). Since no free functionalities were present besides the triazolium salt, we expected to observe no coloured beads, meaning no covalently bound dye labelled substrate **C**. Surprisingly all beads of the assay were slightly orange coloured. However, since there are no possibilities of a covalent attachment of the dye marked substrate we assigned the colouration as background, possibly resulting from partially decomposed NHC. This observation was useful to distinguish real positive from false positive hits in the other assays.




*Scheme 82. Negative control of combinatorial screening*

## 6.3.2 Amidation Assay

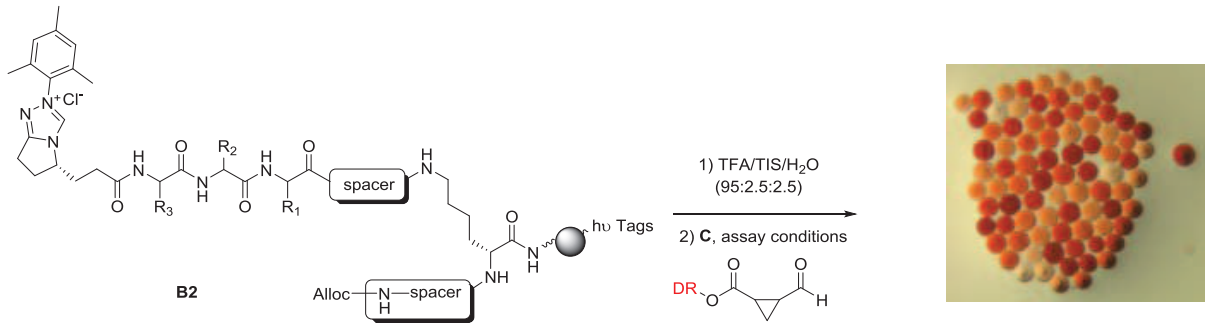
In the second type of assays (amidation assay) we screened for promoters of the redox amidation reaction, thus used library **B3** with the free amine functionality on the resin (Scheme 83). In a first step we deprotected the peptidic side chains of library **B3** and exposed the resin then to the general screening conditions. We observed that about one of three beads turned red which were easy to distinguish from the orange background colouration of the other beads. The colour was indicating that the triazolium salt peptides on these beads had been able to mediate the redox amidation reaction between the resin bound amine and the dye-marked aldehyde derivative **C**.




*Scheme 83. Amidation assay: About 1 of 3 beads remained coloured after intensive washing*

## 6.3.3 Intramolecular Acyl Transfer Assay

In the third type of assay (intramolecular acyl transfer assay) we investigated the hypothesis of an intramolecular acyl transfer of the NHC-adduct to the peptidic backbone. We used library **B2** with the Alloc protected amine functionality at the resin and deprotected the side chains of the peptidic backbone with TFA/TIS/$H_2O$ (95:2.5:2.5). The resin was then mixed with the dye labelled aldehyde **C** under the general screening conditions (Scheme 84). About one of two beads were red coloured and interestingly one of four beads had even more intense red colour as we observed it in the amidation assay. The red coloured beads indicated that within these triazolium salt peptides an intramolecular acyl transfer of NHC bound dye-marked aldehyde derivative **C** to the side chains of the peptide had occurred.




*Scheme 84. Intramolecular acyl transfer assay: About 1 of 2 beads remained coloured after intensive washing*

## 6.4 Results of Combinatorial Assays

### 6.4.1 Amidation Assay

*Table 21. Identified peptide sequences of the amidation assay*

| TS-AA3 | AA2 | AA1-TG |
|---|---|---|
| D-Pro | L-Pro | L-His |
| D-Pro | D-Tyr | D-Gln |
| D-Pro | D-Tyr | L-Pro |
| D-Pro | D-Val | L-Tyr |
| L-Pro | D-Val | L-His |
| L-Pro | D-His | Gly |
| L-Pro | D-Tyr | Gly |
| L-Pro | D-Tyr | L-Ser |
| L-Pro | D-Tyr | L-Tyr |
| L-Pro | D-Phe | L-Tyr |
| L-Pro | D-Phe | L-Tyr |
| L-Pro | D-Phe | L-Tyr |
| L-Pro | Gly | L-Tyr |
| L-Pro | D-Val | L-Tyr |
| L-Arg | D-Val | L-Tyr |
| L-Asn | D-Ala | L-Tyr |
| L-Asn | L-Pro | L-Tyr |

| TS-AA3 | AA2 | AA1-TG |
|---|---|---|
| L-Asp | D-Ala | L-Tyr |
| L-Asp | D-His | Gly |
| L-Asp | D-His | L-Val |
| L-Asp | D-Tyr | L-Asp |
| L-Ala | D-Tyr | L-Arg |
| L-Tyr | D-Tyr | L-Arg |
| L-Tyr | D-Tyr | L-Val |
| L-Tyr | D-Tyr | L-Ala |
| L-Tyr | L-Pro | L-Ala |
| L-Tyr | L-Pro | L-Val |
| L-Tyr | D-Ala | L-Val |
| L-Tyr | D-Asp | L-Ser |
| L-Tyr | D-Ala | L-Thr |
| L-Tyr | D-Arg | Gly |
| L-Tyr | Gly | L-Tyr |
| L-Val | D-Tyr | L-Tyr |
| L-Val | D-His | L-Glu |

Analyses of the peptide sequences showed interesting selectivity (Table 21). In the amidation assay proline and tyrosine were predominantly found at the *N*-terminus. In the second position again tyrosine was the most common amino acid besides histidine and hydrophobic amino acids like valine and alanine. At the *C*-terminus, tyrosine was also the most abundant amino acid and again hydrophobic amino acids like valine and glycine were found. Additionally, nearly each amino acid appeared at least once in the middle and *C*-terminal position with the exception of proline. In summary, Pro-Tyr-Aaa, Pro–Aaa–Tyr and Tyr-Tyr-Aaa (Aaa = arbitrary amino acid) motives were most frequently observed, and sequence L-Pro-D-Phe-L-Tyr was found three times.

## 6.4.2 Intramolecular Acyl Transfer Assay

*Table 22. Identified peptide sequences of the intramolecular acyl transfer assay*

| TS-AA3 | AA2 | AA1-TG |
|---|---|---|
| D-Pro | D-Arg | L-Thr |
| L-Pro | D-His | L-Thr |
| L-Pro | D-His | L-Tyr |
| D-Pro | D-His | L-Arg |
| D-Pro | D-His | L-Val |
| D-Pro | D-Val | L-His |
| D-Pro | D-Gln | L-Ser |
| D-Pro | D-Phe | L-Ser |
| D-Pro | L-Pro | L-Ser |
| L-Pro | Gly | L-Ser |
| D-Pro | D-Tyr | Gly |
| L-Phe | D-Ala | Gly |
| L-Tyr | D-Ala | Gly |
| L-Tyr | D-His | L-Ala |
| L-Tyr | D-His | L-Tyr |

| TS-AA3 | AA2 | AA1-TG |
|---|---|---|
| L-Tyr | D-Ser | L-Arg |
| L-Tyr | D-Ser | L-Ser |
| L-Tyr | L-Pro | L-Val |
| L-His | D-Arg | L-Asn |
| L-His | L-Pro | L-Asn |
| L-His | Gly | L-Asp |
| L-Asp | D-Val | L-Arg |
| L-Asp | D-Gln | L-Tyr |
| L-Ser | D-Tyr | L-Ala |
| Gly | D-Tyr | L-Thr |
| L-Arg | D-Tyr | L-Val |
| L-Gln | D-Ala | L-His |
| L-Val | D-Arg | L-Ser |
| L-Ala | D-Phe | L-Ser |

The intramolecular acyl transfer assay represents an assay lacking an external nucleophile. However, the coloured beads indicated a covalent attachment of the aldehyde to the backbone of the peptide and therefore an acyl transfer from the NHC-adduct to nucleophilic side chains of the peptide backbone. In this assay again proline and tyrosine were predominantly found at the *N*-terminus. Interestingly histidine was found to be significantly more abundant, predominantly at the *N*-terminus or in the second position (AA2). In the second position (AA2) histidine was the most common amino acid besides tyrosine, representing an opposite distribution as in the amidation assay. At the *C*-terminus, interestingly, serine, which was rarely found in the amidation assay, was the most abundant amino acid. Again proline was predominately found at the *N*-terminus but not at the *C*-terminus and only twice in the middle. Thus this time Pro-His-Aaa and Pro–Aaa–Ser (Aaa = arbitrary amino acid) motives were most frequently observed.

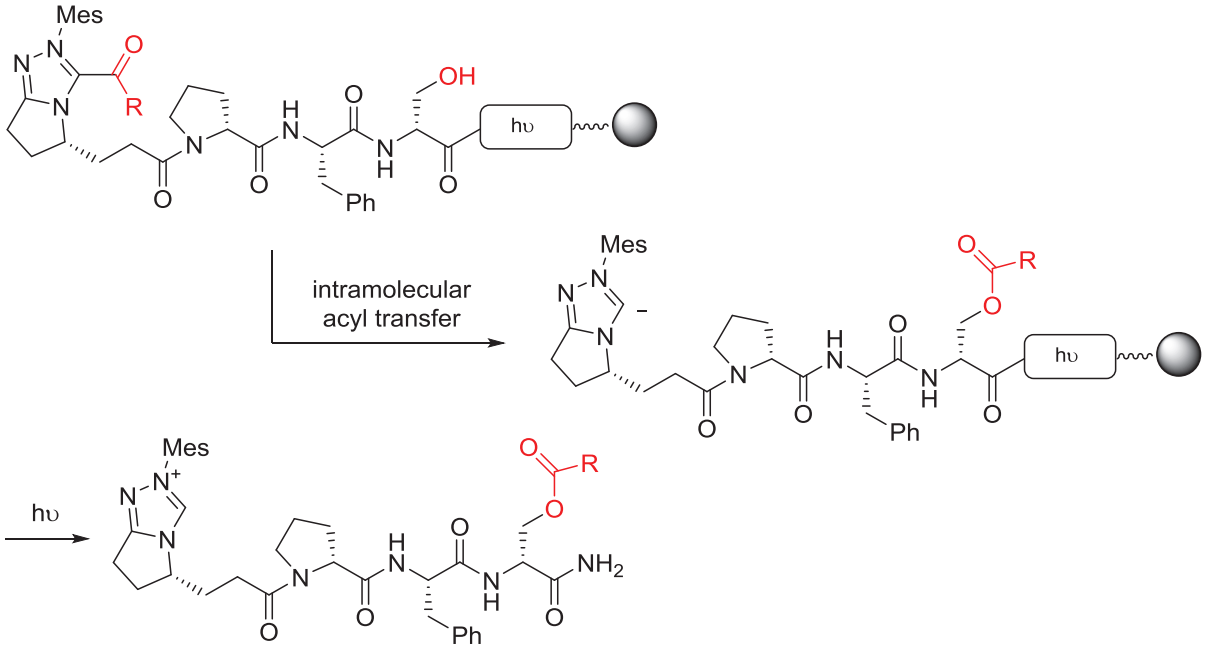
## 6.5 Investigations on the Identified Sequences

### 4.6.1 Intramolecular Acyl Transfer Studies

The results from the combinatorial screening suggested that an intramolecular acyl transfer from the *N*-heterocyclic carbene to the backbone of the peptide had occurred. To probe this hypothesis we resynthesized hit sequences of the assays *via* a photolabile linker on TentaGel and removed the side chain protecting groups with TFA. We chose sequences with the most frequently found Pro-His-Aaa and Pro-Aaa-Ser motive and additionally a sequence with a C-terminal histidine (see chapter 6.4.2) and prepared triazolium salt (TS)-D-Pro-D-Val-L-His-TG **D**, TS-D-Pro-D-His-L-Val-TG **E** and TS-D-Pro-D-Phe-L-Ser-TG **F**. Ethyl 2-formylcyclopropanecarboxylate was added to the resin bound sequences in a concentration of 2.5 M in methylene chloride (2.5 equiv.) followed by the addition of 4 equiv. DBU. After 2 hours of reaction we separated the resin from the reaction mixture and cleaved the triazolium salt peptide from the resin *via* UV light. We analyzed the cleaved compounds by LCMS and MALDI and assumed to determine the mass of the triazolium salt peptide plus the additional mass of the aldehyde to strengthen the hypothesis that the aldehyde is covalently bound to the peptidic backbone (Scheme 85). Indeed, the studies on sequences **D**-**F** revealed that the triazolium salt peptides were partially acylated, meaning that the aldehyde was covalently bound to the backbone in some of the catalysts (Scheme 85). However significant differences in the amounts of acylated catalyst were found when we compared histidine- (**D** and **E**) and serine-containing peptides. In the case of serine-containing sequence **F**, high amounts (~95% conversion) of acylated catalyst were detected, whereas the histidine-containing sequences **D** and **F** were acylated to a lower extent of approximately 5% (Table 23, entries 1-3).

Since cysteine was not implemented in the tripeptidic library **B**, we also tested cysteine-containing sequence and replaced in sequence **F** L-Ser by L-Cys resulting in sequence **G (**TS-D-Pro-D-Phe-L-Cys-TG). The results showed that replacing serine by cysteine results in a lower amount of acylation (~ 50 % conversion) (Table 23, entries 3 and 4). We were also interested if the position of the amino acid bearing the nucleophilic side chain matters. Therefore we synthesized sequence variations of TS-D-Pro-D-Phe-L-Ser **F** by testing a sequence with L-Ser at the AA2 position (TS-D-Pro-L-Ser-D-Phe **H**) and a sequence with L-Ser at the AA3 position (TS-L-Ser-D-Pro-D-Phe **I**) (Table 23, entries 4-6). The results showed that the position of the nucleophilic side chain had an impact on the amount of

acylation. We observed ~ 50 % conversion with NHC-D-Pro-L-Ser-D-Phe **H** having serine at the AA2 position and a higher amount of ~ 95% conversion with the sequences having serine at the AA1 and AA3 position (NHC-L-Ser-D-Pro-D-Phe **I** and NHC-D-Pro-D-Phe-L-Ser **F)** (Table 23, entries 3, 5, 6).




*Scheme 85. Intramolecular acyl transfer on the example of TS-D-Pro-D-Phe-L-Ser-hυ-TG*

*Table 23. Identification of amount of acylation of peptide sequences.*

| entry | assignment | peptide sequence in TS-$AA_3$-$AA_2$-$AA_1$-hυ-TG | conversion of acylation[a] [%] |
|---|---|---|---|
| 1 | **D** | D-Pro-D-Val-**L-His** | ~ 5% |
| 2 | **E** | D-Pro-**D-His**-L-Val | ~ 5% |
| 3 | **F** | D-Pro-D-Phe-**L-Ser** | ~ 95% |
| 4 | **G** | D-Pro-D-Phe-**L-Cys** | ~ 50% |
| 5 | **H** | D-Pro-**L-Ser**-D-Phe | ~ 50% |
| 6 | **I** | **L-Ser**-D-Pro-D-Phe | ~ 95% |

[a]Estimated by LCMS and MALDI analysis.

Due to the high amounts of acylation for serine- and cysteine-containing sequences we hypothesized that this ester or thioester formed at serine and cysteine respectively is strongly bound and possibly too unreactive towards external nucleophiles such as an amine. However histidine-containing catalysts could act as an acyl shuttler, due to their weaker bound acyl residues indicated by the lower amount of acylation.

## 6.5.2 Redox Amidation

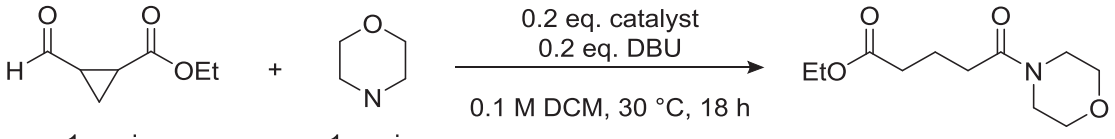
### 6.5.2.1 Model Reaction

Next we examined the catalytic efficiency of tripeptidic triazolium salts for the redox amidation reaction of $\alpha$-functionalized aldehydes and amines. Based on the results of the screening of the amidation assay and the results of the intramolecular acyl transfer studies we chose peptidic triazolium salt sequences **J**-**L** for our investigations. TS-L-Pro-D-Phe-L-Tyr-TG **J** was the lead hit in the combinatorial screening of the amidation assay since it occurred three times on collected beads. TS-L-Pro-D-Val-L-His-TG **K** was also found in the amidation assay and contains and histidine which we assumed to be important based on the results of the intramolecular acyl transfer studies. TS-L-His-D-Pro-D-Phe-TG **L** is a rationally designed sequence bearing a histine at the AA3 position of the peptidic backbone. We used resin bound trazolium salt peptides for the amidation reactions allowing for easy removement from the reaction mixture and hence fast determination of the conversion by 1H NMR analysis.

The first redox amidation reactions were peformed in methylene chloride with equimolar amounts of ethyl 2-formylcyclopropane carboxylate **15** and morpholine **16** in the presence of 20 mol% resin bound catalyst and 20 mol% of DBU. The reaction mixture was stirred at 35 °C for 18 hours followed by filtration of the resin bound catalyst and analysis of the crude reaction mixture. All reactions were compared with a control experiment, where additionally one equivalent of imidazole was added. Resin bound triazolium salt peptides **J**-**L** were tested and significant differences were observed. The control experiments revealed that in the presence of one equivalent of imidazole with all catalysts tested, full conversion was achieved (Table 24). However, in the reaction mixture with peptide **J** (TS-L-Pro-D-Phe-L-Tyr-TG) the most frequently found hit sequence of the redox amidation assay no amidation product **17** was observed in the absence of imidazole. In contrast, sequences **K** and **L**, containing a histidine either in the AA1 or AA2 position, performed better in the absence of imidazole. For TS-L-Pro-D-Val-L-His-TG (**K**) a yield of 59% yield was observed and for

TS-L-His-D-Pro-D-Phe-TG (**L**), 48% yield was determined (Table 24, entries 2 and 3). To probe the importance of histidine in the peptidic structure we additionally tested a rationally designed triazolium salt peptide that was not found in the screening and bore no nucleophilic amino acids (TS-Gly-D-Asn-L-Phe-TG **M**). The results clearly showed that an imidazole moiety in the peptidic structure is essential to allow for the acylation of an amine Table 24, entry 4). Neither peptide **J** containing tyrosine nor peptide **M**, containing no nucleophilic amino acids, promoted the redox amidation reaction between ethyl 2-formylcyclopropane carboxylate **15** and morpholine **16**. Only histidine containing peptides catalytically promoted the formation of the amide in the absence of an external co-catalyst and peptide **K** (TS-L-Pro-D-Val-L-His-TG) providing for the best conversion to the amidated product **17** was chosen for further optimization studies.

*Table 24. Model redox amidation reaction*




1 equiv. **15** | 1 equiv. **16** | **17**

| entry | assignment | peptide sequence in TS-AA3-AA2-AA1-TG | conv.[a] [%] | Control conv.[b] [%] |
|---|---|---|---|---|
| 1 | **J** | L-Pro-D-Phe-D-Tyr | 0 | 100 |
| 2 | **K** | D-Pro-D-Val-L-His | 59 | 100 |
| 3 | **L** | L-His-D-Pro-D-Phe | 48 | 100 |
| 4 | **M** | Gly-D-Asn-L-Phe | 0 | 100 |

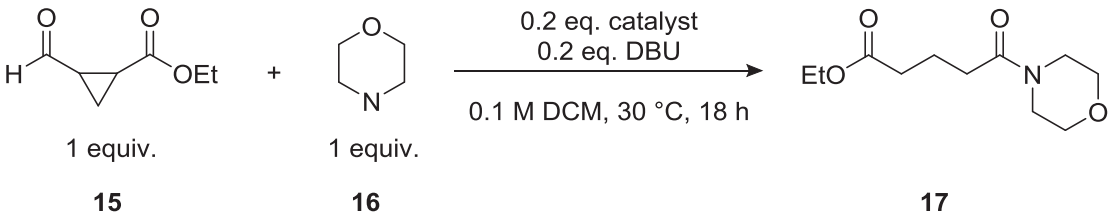
[a]Determined by 1H NMR analysis.[b]Reaction was performed with 1 equivalent of imidazol

### 6.5.2.2 Optimization Studies

In order to determine the importance of the structural aspects of the peptidic triazolium salts, analogs of TS-L-Pro-D-Val-L-His-TG **K** were prepared and tested in the model redox amidation reaction (Table 25). With all stereoisomers **K1**-**K8** similar result regarding the

conversion to the amide product **17** were obtained (Table 25). Catalysts with a D-amino acid at the AA1 or AA3 position proved to be little more reactive and the highest conversion was obtained with **K6** and **K7** (63% and 64% conversion, Table 25, entries 5-6).

*Table 25. Model redox amidation reaction with diasteroisomers of sequence **K***




**15** **16** **17**

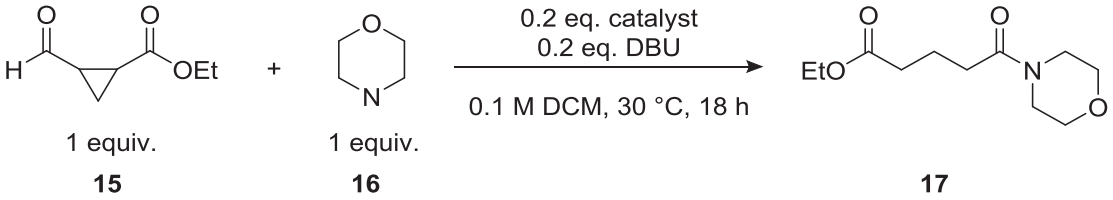
| entry | assignment | peptide sequence in TS-AA3-AA2-AA1-TG | conv.[a] [%] |
|---|---|---|---|
| 1 | **K1** | **L**-Pro-**L**-Val-**L**-His | 58 |
| 2 | **K2** | **D**-Pro-**L**-Val-**L**-His | 55 |
| 3 | **K3** | **L**-Pro-**L**-Val-**D**-His | 49 |
| 4 | **K4** | **L**-Pro-**D**-Val-**D**-His | 53 |
| 5 | **K5** | **D**-Pro-**L**-Val-**D**-His | 63 |
| 6 | **K6** | **D**-Pro-**D**-Val-**D**-His | 64 |
| 7 | **K7** | **D**-Pro-**D**-Val-**L**-His | 59 |
| 8 | **K8** | **L**-Pro-**D**-Val-**L**-His | 51 |

[a]Determined by 1H NMR analysis.

To investigate the influence of amino acids besides histidine on the ability to promote the redox amidation reaction, we synthetized dipeptidic **N** (TS-D-Pro-D-His-TG) lacking valine and compared the results obtained with peptide **K6** (TS-D-Pro-D-Val-D-His-TG) (Table 26). Although dipeptidic **N** (TS-D-Pro-D-His-TG) showed up to be little less reactive (60% conversion compared to 64% conversion for **K6**), the results show that the influence of valine in the structure of the catalyst might not play that important role on promoting the amidation reaction to product **17**. As a control experiment and to strengthen the value of histidine we evaluated the reactivity of peptides **O** (TS-L-Pro-Gly-TG) and **P** (TS-L-Pro-L-Phe-TG)

lacking a histidine in their structure. Once again no conversion to amidation product **17** was observed which revealed that histidine is the most important part of the peptidic structure to promote the redox amidation reaction (Table 26, entries 3 and 4). Finally, catalysts consisting of only one histidine moiety besides the triazolium salt were tested. We obtained 51% conversion with sequence **Q** TS-D-His-TG and 62 % conversion with sequence **R** TS-D-His-TG (Table 26, entries 5 and 6).

*Table 26: Model redox amidation reaction with rationally designed peptidic triazolium salts*



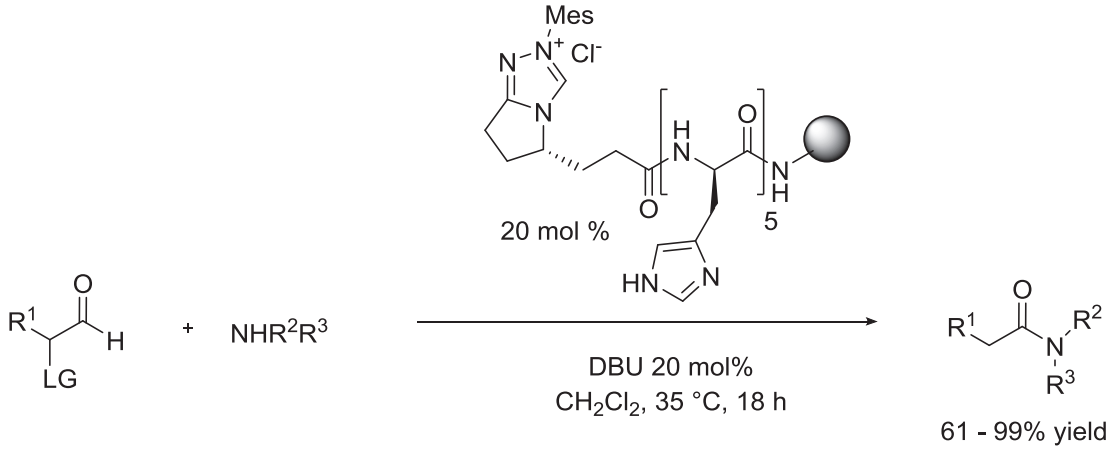

| entry | assignment | peptide sequence in TS-AA3-AA2-AA1-TG | conv.[a] [%] |
|---|---|---|---|
| 1 | **K6** | D-Pro-D-Val-D-His | 64 |
| 2 | **N** | D-Pro-D-His | 60 |
| 3 | **O** | L-Pro-Gly | 0 |
| 4 | **P** | L-Pro-L-Phe | 0 |
| 5 | **Q** | L-His | 51 |
| 6 | **R** | D-His | 62 |

[a]Determined by 1H NMR analysis.

## 6.6 Conclusion and Outlook

In summary we have shown that combinatorial chemistry is a useful tool to identify bifunctional peptidic *N*-heterocyclic carbene catalysts for transformations that utilize the additional functionality provided by the peptidic moiety to perform reactions not catalyzed by NHCs alone (*e.g.* redox amidation). Several sequences were identified that promote an intramolecular acyl transfer from the NHC-adduct to the side chains of the peptidic triazolium salt. Within the combinatorial screening histidine containing peptidic sequences were identified to successfully promote the redox amidation reaction between 2-formylcyclopropane carboxylate and morpholine in the absence of an external co-catalyst. Further rational modifications revealed that a catalyst consisting of a triazolium salt and only one histidine moiety sufficiently catalyzed the redox amidation reaction between 2-formylcyclopropane carboxylate and morpholine without the need of an external co-catalyst. Additional non-nucleopilic amino acids in the catalyst seem not to be involved in promoting the redox amidation, however for future goals, which include the kinetic resolution of amines, the stereochemical environment, given by tripeptidic sequences can play a more important role.

In a continuation of this work, Gondo and Bode have recently introduced a solid supported triazolium bound pentapetide containing five histidine units (Scheme 86).[185] The resin bound triazolium salt catalyzed the redox amidation reaction of various $\alpha$-functionalized aldehydes and amines and yields of up to 61 – 99% were achieved in the presence of 20 mol% of the solid supported catalyst after 18 hours reaction time. Aside from base, which is needed to generate the carbene, no other additives were needed.




*Scheme 86. Redox Amidation reaction catalyzed by solid supported triazolium bound pentapetide containing five histidine units*[185]

# 7 Experimental

## 7.1 General Aspects and Materials

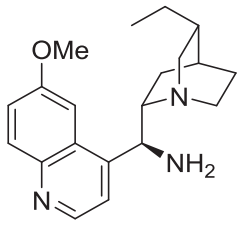
Materials and reagents were of the highest commercially available grade and used without further purification. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F254 plates. Compounds were visualized by UV and $KMnO_4$. Flash chromatography was performed using Merck silica gel, high purity grade, pore size 60 Å, particle size 40-63 μm. $^{1}H$- and $^{13}C$-NMR spectra were recorded on Bruker NMR spectrometers (Avance 250, Avance 400 or DPX 400). Chemical shifts are reported in ppm and were calibrated against the solvent or internal standard (TMS) signals. Electrospry (ESI) mass spectra were recorded on a Bruker Esquire 3000 Plus or. High resolution mass spectroscopy (HRMS) was carried out on a Bruker Daltonics maXis apparatus. Normal phase HPLC analyses were performed on an analytical HPLC with a diode array detector SPD-M10A from Shimadzu or on an Dionex UltiMate 3000 HPLC system (Thermo-Fisher) using Chiracel columns (AD-H, AS-H) (250 mm x 4.6 mm) from Daicel.GC-ECD measurements were performed using an Agilent 7890A Series GC system with electron capture detection from Agilent Technologies with a GC capillary of the type 19091A-102E HP_Ultra 1 (25 m x 0.200 mm x 0.33 μm) from J&W Scientific.

## 7.2 General Protocol for the Synthesis of Urea or Thiourea Functionalized Cinchona Alkaloids

### 7.2.1 General Protocol for the Synthesis of *epi*Cinchona Alkaloids

Cinchona alkaloid (14.7 mmol, 1 equiv.) and triphenyl phosphine (4.63 g, 17.6 mmol, 1.2 equiv.) were dissolved in 60 ml of dry THF and the solution was cooled to 0˚C. Diisopropylazodicarboxylate (3.57 g, 17.6 mmol, 1.2 equiv.) was added in one portion. A solution of diphenylphosphorylazide (4.85 g, 17.6 mmol, 1.2 equiv.) in 20 ml of dry THF was added drop wise at 0 ˚C. The reaction was stirred overnight at 0 °C followed by heating at 50 ˚C for 2 hours. Triphenyl phosphine (5.01 g, 19.1 mmol, 1.3 equiv.) was added and the reaction mixture was stirred at 50 ˚C until the evolution of gas had ceased. The mixture was cooled to RT and 1.5 ml of distilled water was added. The reaction was kept under vigorous stirring for additional 3 hours. All volatiles were evaporated under reduced pressure and 120 ml of a 1:1 mixture of $CH_2Cl_2$ and 10 % HCl in water were added. The aqueous phase was washed four times with 50 ml of $CH_2Cl_2$. The pH of the aqueous phase was increased to 10 with a 25 % solution of $NH_4OH$ in water and was washed 4 times with 50 ml of $CH_2Cl_2$. The combined organic phases were dried with $Na_2SO_4$, filtrated and the volatiles were evaporated under reduced pressure. The crude mixture was purified with column chromatography (EtOAc/MeOH/aqueous $NH_4OH$, 50/50/1).

**9-*epi*dihydroquinine-$NH_2$**



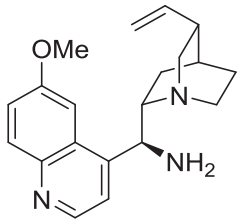

Yield: 43%, yellow oil

$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.69 (d, $J$ = 4 Hz, 1H), 7.97 (d, $J$ = 12 Hz, 1H), 7.68 (br, s, 1H), 7.61 (d, $J$ = 4 Hz, 1H), 7.47 (dd, $J$ = 8 Hz, 4Hz, 1H), 4.74 (d, $J$ = 12 Hz, 1H), 4.01 (s, 3H), 3.32 (m, 3H), 2.85 (m, 1H), 2.61 (m, 1H), 1.59 (m, 4H), 1.30 (m, 3H), 0.87 (t, $J$ = 8 Hz, 3H), 0.73 (q, $J$ = 8 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 158.0, 148.3, 145.2, 132.2, 129.2, 121.6, 58.4, 55.9, 41.5, 37.9, 29.3, 28.0, 26.2, 25.7, 12.5.

MS (ESI) *m/z*: 326 $[M+H]^+$, M= 325.2 calculated for $C_{20}H_{27}N_3O$.

**9-*epi*quinine-$NH_2$**




Yield: 91%, yellow oil

$^1$H-NMR (400 MHz, $CDCl_3$, 25 ˚C): $\delta$ = 8.76 (d, $J$ = 4.7 Hz, 1H), 8.05 (d, $J$ = 9.3 Hz, 1H), 7.69-7.67 (br, 1H), 7.45 (d, $J$=4.5 Hz, 1H), 7.40 (dd, $J$ = 9.3 Hz, 2.8 Hz, 1H), 5.89-5.75 (m, 1H), 5.06-4.96 (m, 2H), 4.61 (d, $J$ = 10.0 Hz, 1H), 3.98 (s, 3H), 3.34-3.09 (m, 3H), 2.86-2.78 (m, 2H) 1.65-0.74 (m, 6H).

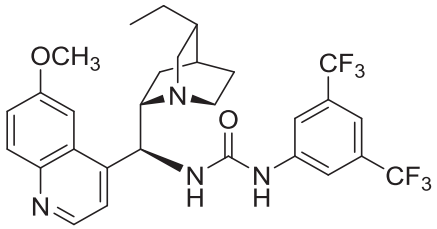
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 ˚C): $\delta$ = 157.5, 147.7, 146.8, 144.5, 141.5, 131.6, 128.6, 121.2, 114.3, 77.2, 57.9, 56.1, 55.4, 40.8, 39.6, 37.9, 27.4, 25.9, 18.3.

MS (ESI) *m/z*: 324 $[M^+H]$, M= 323.2 calculated for $C_{20}H_{25}N_3O$.

### 7.2.2 General Protocol for the Synthesis of (Thio)Urea functionalized Cinchona Alkaloids

To a mixture of 9-*epi*cinchona alkaloid-$NH_2$ (6.14 mmol, 1 equiv.) in 20 ml of dry THF, a solution of 3,5-bis(trifluoromethyl)phenyliso(thio)cyanate (1.67 g, 6.14 mmol, 1 equi.) in 10 ml dry THF was added at 0 °C. The reaction mixture was kept at 0 °C for 10 minutes followed by warming up to room temperature and vigorous stirring overnight. All volatiles were evaporated under reduced pressure and the crude mixture was purified by column chromatography ($CH_2Cl_2$/MeOH from 97:3 to 90:10). The desired (thio)urea derivative was isolated as a white amorphous solid.

**9-*epi*dihydroquinine-urea**




Yield: 91%, white solid

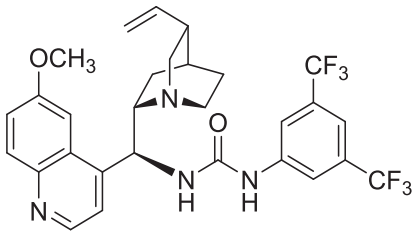
$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.82 (d, $J$ = 4 Hz, 1H), 8.40 (br, s, 1H), 8.07 (d, $J$ = 8 Hz, 1H), 7.82 (d, $J$ = 4 Hz, 1H), 7.73 (s, 2H), 7.44 (dd, $J$ = 8 Hz, 4Hz, 1H), 7.37 (d, $J$ = 8 Hz, 1H), 7.31 (s, 1H), 6.41 (br, s, 1H), 5.71 (br, s, 1H), 4.05 (s, 3H), 3.63 (br, s, 1H), 3.37-3.06 (m, 3H), 2.96 (t, $J$ = 8 Hz, 1H), 2.70 (m, 1H), 1.99 (m, 1H), 1.71 (m, 3H), 1.58 (m, 1H), 1.44 (m, 1H), 1.28 (m, 1H), 1.11 (m, 2H), 0.95 (dd, $J$ = 12 Hz, 8Hz, 1H), 0.73 (t, $J$ = 8 Hz, 3H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 158.6, 154.6, 147.2, 145.0, 140.6, 132.0, 131.7, 131.6, 131.3 (q, $J$= 23.3 Hz), 124.5, 121.7, 118.1, 118.07, 115.3, 101.9, 59.5, 57.2, 55.8, 41.6, 36.3, 27.6, 27.3, 26.7, 24.8, 11.8.

$^{19}$F-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = -75.5

MS (ESI): m/z: 581 $[M+H]^+$, M= 580.2 calculated for $C_{29}H_{30}F_6N_4O_2$.

**9-*epi*quinine-urea**




Yield: 80% ($CH_2Cl_2$/MeOH from 95:5 to 80:20), white solid

$^1$H-NMR (400 MHz, $CDCl_3$, 25 ˚C): $\delta$ = 8.81 (d, $J$ = 4 Hz, 1H), 8.42 (br, s, 1H), 8.07 (d, $J$ = 8 Hz, 1H), 7.81 (d, $J$ = 4 Hz, 1H), 7.72 (s, 2H), 7.45 (dd, $J$ = 8 Hz, 4Hz, 1H), 7.36 (d, $J$ = 8 Hz, 1H), 7.34 (s, 1H), 6.32 (m, 1H), 5.65 (ddd, $J$ = 20 Hz, 10 Hz, 4 Hz, 2H), 5.00 (d, $J$ = 12 Hz, 1H), 4.85 (d, $J$ = 16 Hz, 1H), 4.03 (s, 3H), 3.53 (m, 1H), 3.19 (m, 1H), 3.06 (m, 1H), 2.93 (q, $J$ = 8 Hz, 1H), 2.67 (m, 1H), 2.24 (m, 1H), 1.73-1.60 (m, 4H), 0.95 (dd, $J$ = 16 Hz, 8 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 ˚C): $\delta$ = 158.5, 154.7, 147.2, 144.9, 140.6, 140.5, 132.4, 132.0, 131.7, 131.4, (q, $J$ = 33.0 Hz), 131.6, 127.1, 124.5, 121.7, 118.2, 115.4, 115.0, 101.9, 59.9, 55.8, 55.4, 41.4, 38.6, 27.4, 26.9.

$^{19}$F-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = -63.2

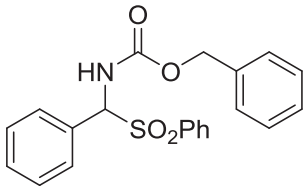
MS (ESI): m/z: 579 $[M+H]^+$, M= 578.2 calculated for $C_{29}H_{28}F_6N_4O_2$.

## 7.3 General Protocol for the Synthesis of *N*-Protected Imines

### 7.3.1 General Protocol for the Synthesis of $\alpha$-Amido Sulfones

A 100 ml flask was charged with benzylcarbamate (0.30 g, 2.0 mmol, 1 equiv.) and benzene sulfonic acid sodium salt (0.66 g, 4.0 mmol, 2 equiv.). The solids were suspended in a mixture of methanol and water 1:2 (9 ml). The aldehyde (3.0 mmol, 1.5 equiv.) was added in one portion followed by the addition of formic acid (98%, 2.5 ml). The reaction mixture was stirred at room temperature for 48 – 96 hours. The resulting white precipitate was isolated *via* a Büchner funnel and washed with water (3 x 5 ml) and cold diethylether (2 x 5 ml). The resulting residue was dried *in vacuo* to afford the product as a white solid.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)benzylamine**

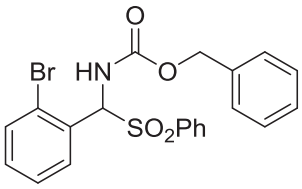



Yield: 80%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.17 (d, $J$ = 10 Hz, 1H), 7.85 (d, $J$ = 7 Hz, 2H), 7.76 (t, $J$ = 6 Hz, 1H), 7.65-7.35 (m, 4H), 7.44-7.35 (m, 6H), 7.22-7.20 (m, 2H), 6.12 (d, $J$ = 12 Hz, 1H), 4.88 (q, $J$ = 12 Hz, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ =155.7, 137.1, 136.8, 134.6, 130.7, 130.1, 129.9, 129.6, 129.5, 128.8, 128.6, 128.4, 128.2, 75.4, 66.5.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-2-bromobenzylamine**

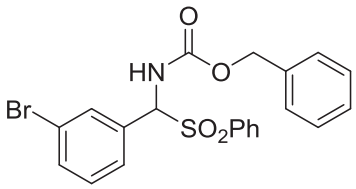



Yield: 74%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.16 (d, $J$ = 12 Hz, 1H), 7.92 (d, $J$ = 8 Hz, 1H), 7.78 (m, 3H), 7.68 (d, $J$ = 8 Hz, 1H), 7.62 (t, $J$ = 8 Hz, 2H), 7.50 (t, $J$ = 8 Hz, 1H), 7.38 (m, 4H), 7.23 (d, $J$ = 8 Hz, 2H), 6.58 (d, $J$ = 12 Hz, 1H), 4.90 (q, $J$ = 13 Hz, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 155.7, 137.1, 136.6, 135.0, 133.1, 132.1, 131.5, 131.0, 129.9, 129.3, 128.9, 128.5, 128.3, 125.7, 73.9, 66.8.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-3-bromobenzylamine**

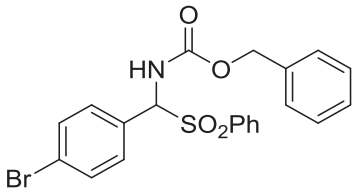



Yield: 84%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.18 (d, $J$ = 8 Hz, 1H), 7.95 (m, 1H), 7.87 (d, $J$ = 8 Hz, 2H), 7.77 (m, 1H), 7.68-7.60 (m, 4H), 7.40-7.34 (m, 4H), 7.21 (d, $J$ = 4 Hz, 1H), 6.21 (d, $J$ = 12 Hz, 1H), 4.88 (q, $J$ = 11 Hz, 1H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 155.6, 136.9, 136.7, 134.8, 133.3, 132.7, 132.6, 130.7, 129.6, 129.5, 129.4, 128.9, 128.4, 128.1, 121.9, 74.4, 66.6.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-4-bromobenzylamine**

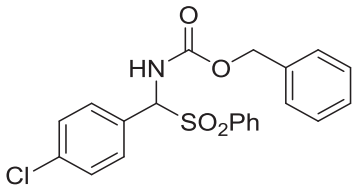



Yield: 68%

$^{1}$H-NMR (300 MHz, DMSO, 25 °C): $\delta$ = 9.18 (d, $J$ = 12 Hz, 1H), 7.64 (d, $J$ = 8 Hz, 2H), 7.77 (t, $J$ = 6 Hz, 1H), 7.63-7.59 (m, 6H), 7.36-7.34 (m, 3H), 7.21-7.19 (m, 2H), 6.17 (d, $J$ = 12 Hz, 1H), 4.87 (q, $J$ = 12 Hz, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): 155.6, 136.9, 136.7, 134.8, 132.2, 131.6, 130.1, 129.6, 129.6, 128.8, 128.4, 128.2, 123.6, 74.6, 66.6.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-4-chlorobenzylamine**

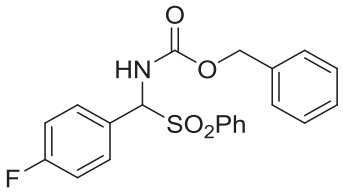



Yield: 41%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.17 (d, $J$ = 12 Hz, 1H), 7.85-7.20 (m, 13H), 6.18 (d, $J$ = 12 Hz, 1H), 4.87 (m, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 155.6, 136.9, 136.7, 134.9, 134.7, 132.0, 129.7, 129.6, 129.6, 128.8, 128.7, 128.4, 128.2, 74.5, 66.6.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-4-fluorobenzylamine**



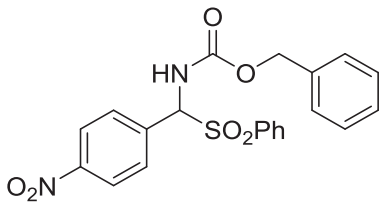

Yield: 83%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.16 (d, *J* = 10.8 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.78-7.79 (m, 3H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.36-7.35 (m, 3H), 7.28-7.20 (m, 4H), 6.17 (d, *J* = 10.4 Hz, 1H), 4.87 (q, *J* = 10.9 Hz, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 164.5, 162.0, 155.6, 136.9, 136.7, 132.5, 132.4, 129.6, 129.5, 128.8, 128.4, 128.2, 127.1, 127.0, 115.7, 115.5, 74.5, 66.6.

$^{19}$F-NMR (100 MHz, DMSO, 25 °C): $\delta$ = -111.9

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-4-nitrobenzylamine**

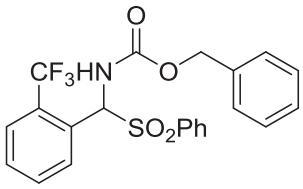



Yield: 96%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.34 (d, *J* = 10 Hz, 1H), 8.20 (m, 2H), 8.00 (m, 2H), 7.90 (m, 2H), 7.79 (m, 1H), 7.63 (m, 2H), 7.35 (m, 3H), 7.21 (m, 2H), 6.42(d, *J* = 10 Hz, 1H), 4.88 (m, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 156.0, 149.0, 137.9, 136.7, 135.0, 131.5, 129.7, 129.7, 128.8, 128.5, 128.2, 123.6, 74.4, 66.7.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-2-(trifluoromethyl)benzylamine**



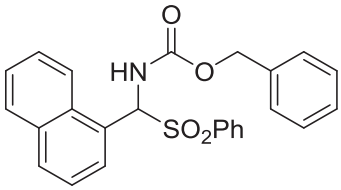

After stirring the reaction mixture for 48 h, a phase appeared at the bottom of the flask. $CH_2Cl_2$ (5 ml) was added and the phases were separated. The organic phase was dried over MgSO4, filtrated and all volatiles were removed at reduced pressure. The resulting colorless oil crystallized within 12 h. The white solid was washed with water (3 x 5ml) and cold diethyl ether (2 x 5 ml). The resulting residue was dried *in vacuo* to afford the product as a white solid

Yield: 70%

$^1$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.35 (d, $J$ = 8 Hz, 1H), 8.17 (d, $J$ = 8 Hz, 1H), 7.83-7.76 (m, 5H), 7.70 (t, $J$ = 8 Hz, 1H), 7.62 (t, $J$ = 8 Hz, 2H), 7.39-7.33 (m, 3H), 7.22 (d, $J$ = 8 Hz, 2H), 6.36 (d, $J$ = 12 Hz, 1H), 4.87 (q, $J$ = 13 Hz, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 154.9, 136.7, 136.1, 134.6, 132.7, 131.4, 130.3, 129.4, 128.8, 128.4, 128.0, 127.9, 70.2, 66.3.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-2- (naphthyl)benzylamine**

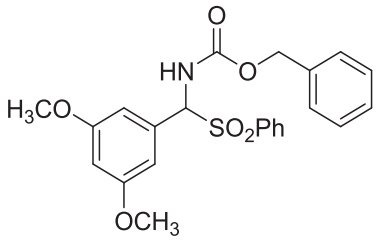



Yield: 52%

$^1$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.37 (d, $J$ = 12 Hz, 1H), 8.23 (d, $J$ = 8 Hz, 1H), 8.05 (d, $J$ = 8 Hz, 2H), 8.00 (d, $J$ = 8 Hz, 1H), 7.95 (d, $J$ = 8 Hz, 2H), 7.76 (t, $J$ = 8 Hz, 1H), 7.63 (m, 5H), 7.34 (m, 3H), 7.19 (d, $J$ = 8 Hz, 2H), 6.92 (d, $J$ = 8 Hz, 1H), 4.87 (q, $J$ = 13 Hz, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 155.4, 136.8, 136.2, 134.2, 133.0, 131.3, 130.1, 129.2, 129.1, 128.7, 128.3, 128.1, 127.9, 127.7, 127.1, 126.8, 126.0, 125.1, 123.1.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-3,5-(dimethoxy)benzylamine**

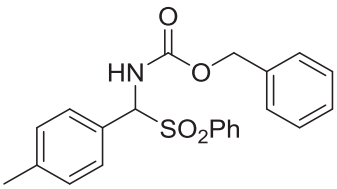



Yield: 36%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.09 (d, *J* = 10.8 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.75 (t, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.37-7.33 (m, 3H), 7.23 (d, *J* = 10.8 Hz, 2H), 6.81 (s, 2H), 6.53 (s, 1H), 6.04 (d, *J* = 10.8 Hz, 1H), 4.90 (q, *J* = 10.3 Hz, 2H), 3.72 (s, 6H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 160.5, 155.7, 137.2, 136.8, 134.6, 132.7, 129.6, 129.5, 128.8, 128.4, 128.2, 108.3, 101.8, 75.6, 66.6, 55.8.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-4-methylbenzylamine**

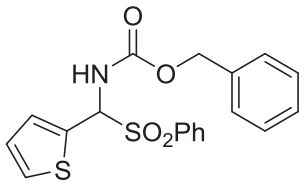



Yield: 59%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.11 (d, *J* = 10.8 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.75 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H), 7.38-7.30 (m, 3H), 7.22-7.20 (m, 4H), 6.04 (d, *J* = 10.8 Hz, 1H), 4.87 (q, *J* = 10.9 Hz, 2H), 2.33 (s, 3H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = $\delta$ = 155.7, 139.4, 137.2, 136.8, 134.5, 130.0, 129.6, 129.5, 129.2, 128.8, 128.4, 128.2, 127.6, 75.2, 66.5, 21.3.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-2-thiophenylamine**

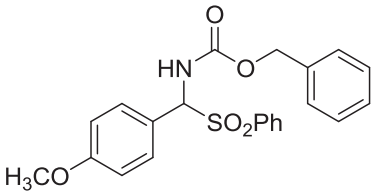



Yield: 73%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.06 (d, *J* = 8 Hz, 1H), 7.76 (m, 4H), 7.57 (m, 3H), 7.34 (m, 4H), 7.22 (d, *J* = 8 Hz, 2H), 6.21 (d, *J* = 12 Hz, 1H), 4.88 (q, *J* = 9 Hz, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 155.6, 137.0, 136.8, 134.6, 131.1, 129.6, 129.5, 128.9, 128.8, 128.5, 128.3, 127.9, 126.7, 71.9, 66.6.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-4-methylbenzylamine**

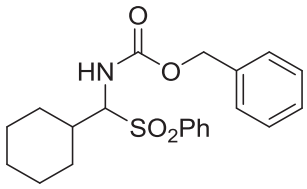



Yield: 20%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.08 (d, *J* = 12 Hz, 1H), 7.82 (d, *J* = 4 Hz, 2H), 7.75 (t, *J* = 6 Hz, 1H), 7.58 (m, 4H), 7.34 (m, 3H), 7.20 (d, *J* = 8 Hz, 2H), 6.96 (d, *J* = 8 Hz, 2H), 6.03 (d, *J* = 8 Hz, 1H), 4.87 (q, *J* = 11 Hz, 2H), 3.78 (s, 3H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 160.1, 155.2, 136.8, 136.3, 134.0, 131.0, 129.0, 128.9, 128.3, 127.9, 127.7, 121.9, 113.6, 74.5, 66.0, 55.2.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-cyclohexylamine**

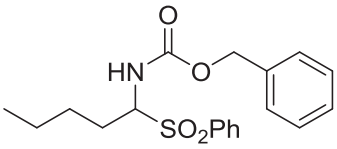



Yield: 56%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 8.36 (d, *J* = 10.4 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.37-7.32 (m, 3H), 7.14 (d, *J* = 6.4 Hz, 2H), 4.82-4.72 (m, 3H), 2.19 (m, 1H), 1.89-1.86 (m, 2H), 1.76-1.68 (m, 2H), 1.62-1.59 (m, 1H), 1.32-1.07 (m, 5H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 156.1, 138.4, 136.9, 134.3, 129.4, 129.2, 128.8, 128.3, 128.0, 76.0, 66.2, 36.7, 30.3, 28.1, 25.9, 25.8, 25.7.

***N*-(benzyloxycarbonyl)-α-(phenylsulfonyl)-pentylamine**

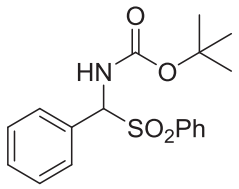



Yield: 64%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 8.36 (d, *J* = 9.6 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.38-7.32 (m, 3H), 7.19 (d, *J* = 6.4 Hz, 2H), 4.87 (q, *J* = 10.1 Hz, 2H), 4.82-4.77 (m, 1H), 2.01-1.95 (m, 1H), 1.74-1.65 (m, 1H), 1.39-1.19 (m, 4H), 0.84 (t, *J* = 6.8 Hz, 3H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 156.0, 137.2, 137.0, 134.5, 129.6, 129.4, 128.8, 128.3, 128.0, 72.3, 66.2, 27.5, 25.7, 21.9, 14.1.

***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)benzylamine**

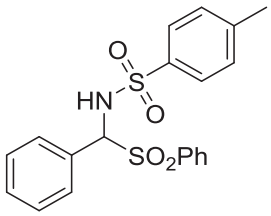



Yield: 71%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 8.73 (d, $J$ = 12 Hz, 1H), 7.87 (d, $J$ = 8 Hz, 2H), 7.73 (t, $J$ = 8 Hz, 1H), 7.64 (m, 4H), 7.41 (m, 3H), 6.02 (d, $J$ = 8 Hz, 1H), 1.18 (s, 9H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 154.9, 137.9, 134.8, 131.1, 130.8, 130.2, 130.0, 129.9, 129.0, 80.2, 75.2, 28.7.

***N*-tosyl-α-(phenylsulfonyl)benzylamine**



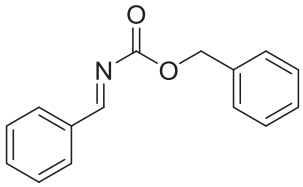

Yield: 67%

$^{1}$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 9.15 (s, 1H), 8.03 (d, $J$ = 8 Hz, 2H), 7.85 (d, $J$ = 8 Hz, 2H), 7.72 (t, $J$ = 8 Hz, 1H), 7.68 (m, 2H), 7.62 (m, 5H), 7.45 (d, $J$ = 8 Hz, 2H), 2.22 (s, 3H).

### 7.3.2 General Protocol for the Synthesis of Imines from $\alpha$-Amido Sulfones

A mixture of α-amido sulfone (0.2 mmol) in $CH_2Cl_2$ (2 ml) and aqueous $Na_2CO_3$ (10%, saturated with NaCl, 2 ml) was vigorously stirred at room temperature for 12 hours. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 0.5 ml). The combined organic phases were washed with brine and dried with MgSO4. After filtration, all volatiles were removed and the residue was dried *in vacuo* to yield a colourless oil.

**Benzaldehyde-*N*-(benzyloxycarbonyl)imine**

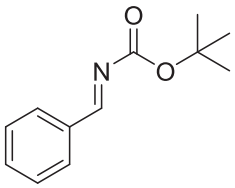


Yield: 98%

$^1$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 8.97 (s, 1H), 7.96 (d, $J$ = 8 Hz, 2H), 7.68 (t, $J$ = 8 Hz, 1H), 7.56 (t, $J$ = 8 Hz, 2H), 7.42 (m, 5H), 5.27 (s, 2H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 171.0, 164.0, 136.6, 130.8, 130.0, 129.4, 129.2, 68.9.

**Benzaldehyde-*N*-(*tert*-butoxycarbonyl)imine**

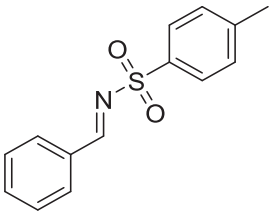


Yield: 96%

$^1$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 8.82 (s, 1H), 7.91 (d, $J$ = 8 Hz, 2H), 7.60 (t, $J$ = 8 Hz, 1H), 7.51 (t, $J$ = 8 Hz, 2H), 1.49 (s, 9H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ = 168.9, 163.1, 134.9, 134.3, 130.4, 129.9, 82.3, 28.4.

**Benzaldehyde-*N*-tosylimine**

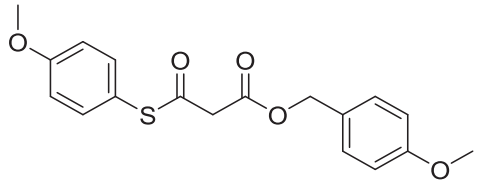



Yield: 92%

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 9.03 (s, 1H), 7.91 (m, 4H), 7.62 (t, $J$ = 8 Hz, 1H), 7.49 (t, $J$ = 8 Hz, 2H), 7.35 (d, $J$ = 8 Hz, 2H), 2.44 (s, 3H).

## 7.4 Synthesis of Mono Thiomalonates

### 4-Methoxybenzyl-3-((4-methoxyphenyl)thio)-3-oxopropanoate (1a)



To a solution of malonic acid (12.5 g, 120 mmol, 2 equiv.) in dry acetonitrile (120 ml) was added under inert argon atmosphere, DMAP (1.47 g, 12.0 mmol, 0.2 equiv.) and 4-methoxybenzyl alcohol (8.29 g, 60.0 mmol, 1 equiv.). The mixture was cooled to 0 °C and a solution of DCC (24.8 g, 120 mmol, 2 equiv.) in dry $CH_3CN$ (50 ml) was added drop wise over a period of 30 minutes. After stirring the mixture for another 30 minutes at 0 °C, the flask was removed from the icebath and allowed to warm to room temperature. The reaction mixture was stirred at room temperature for another 2 hours followed by filtration of DCU. All volatiles were removed at reduced pressure and the crude mixture was re-dissolved in a mixture of $CH_2Cl_2$ (40 ml) and EtOAc (160 ml). The organic phase was extracted with saturated aqueous $NaHCO_3$ solution (3x 50 ml). The pH of the combined aqueous phase was then carefully decreased to pH 3 by addition of an aqueous solution of HCl (10%). The aqueous phase was re-extracted with $CH_2Cl_2$ (3 times 70 ml each) and the combined organic phases were dried with $MgSO_4$. After filtration all volatiles were removed at reduced pressure to yield a red solid (13.1 g, 97% yield) that was used without further purification. To the solid, dissolved in dry $CH_2Cl_2$ (90 ml), was added HOBt (12.2 g, 90.0 mmol, 1.5 equiv.) and 4-methoxythiophenol (12.6 g, 90.0 mmol, 1.5 equiv.) under nitrogen atmosphere. The solution was cooled to 0 °C and a solution of DCC (18.6 g, 90.0 mmol, 1.5 equiv.) in $CH_2Cl_2$ (60 ml) was added dropwise within 30 minutes. The reaction mixture was stirred for 15 minutes at 0 °C and then at room temperature for two hours. DCU was removed by filtration and all volatiles were removed at reduced pressure. The crude compound was then purified by column chromatography using $CH_2Cl_2$:pentane with a gradient of 7:3 to pure $CH_2Cl_2$. After removal of all the volatiles at reduced pressure, 12.0 g (58%) of a white solid was isolated.

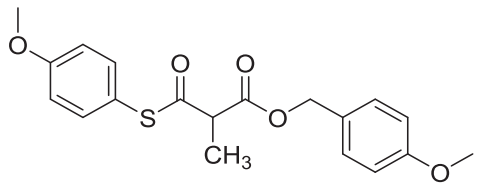
$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.36-7.33 (m, 4H), 6.98-6.90 (m, 4H), 5.16 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (s, 2H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 191.6, 165.8, 161.0, 159.8, 136.2, 130.3, 127.3, 117.6, 115.0, 114.0, 67.3, 55.7, 55.4, 48.9.

$\nu_{max}$ (neat)/cm$^{-1}$: 3021, 1729, 1680, 1251.

HRMS (ESI) *m/z*: calculated for $C_{18}H_{18}NaO_5S$ $[M+Na]^+$ 369.0767; found, 369.0771.

**4-Methoxybenzyl-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (1b)**



To a solution of methyl malonic acid (8.86 g, 75 mmol, 2.5 equiv.) in dry $CH_2Cl_2$ (60 ml) was added under inert argon atmosphere, 4-methoxybenzyl alcohol (4.14 g, 30.0 mmol, 1 equiv.). The mixture was cooled to 0 °C and EDCI (11.5 g, 60 mmol, 2 equiv.) was added portion wise over a period of 10 minutes. The mixture was stirred at room temperature for 30 minutes, then washed with 40 ml of water and extracted with saturated aqueous $NaHCO_3$ solution (2 x 25 ml). The pH of the combined aqueous phase was carefully decreased to pH 3 by addition of an aqueous solution of HCl (4 %). The aqueous phase was re-extracted with $CH_2Cl_2$ (3x 20 ml), and the combined organic phases were dried over $MgSO_4$. After filtration, all volatiles were removed at reduced pressure to yield a colorless oil (4.7 g, 66% yield) that was used without further purification. To the oil, dissolved in dry $CH_2Cl_2$ (20 ml) was added 4-methoxythiophenol (1.72 ml, 14.0 mmol, 2 equiv.) at 0 °C under a nitrogen atmosphere. EDCI (2.68 g, 14.0 mmol, 2equiv.) was added portion wise and the resulting mixture was stirred for 1h at room temperature. The reaction mixture was washed with 10 ml of water and the organic phase was extracted with brine (2 x 20 ml), dried with MgSO4 and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography on silica gel using a gradient of a mixture of hexane:EtOAc from 10:1 to 3:1 as eluent to afford 1.70 g (67%) of a colourless oil.

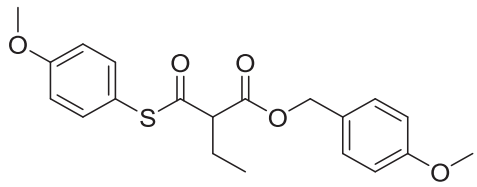
$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.36-7.25 (m, 4H), 6.96-6.88 (m, 4H), 5.18 (s, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 3.80 (q, $J$ = 7 Hz, 1H), 1.53 (d, $J$ = 7 Hz, 3H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 194.9, 169.2, 160.9, 159.8, 136.2, 130.1, 127.6, 117.6, 115.0, 114.0, 67.2, 55.4, 55.3, 53.5, 14.2.

$\nu_{max}$ (neat)/cm$^{-1}$: 3066, 2981, 1731, 1684, 1243.

HRMS (ESI) *m/z*: calculated for $C_{19}H_{24}NO_5S$ $[M+NH_4]^+$ 378.1370; found, 378.1376.

**4-Methoxybenzyl-2-ethyl-3-((4-methoxyphenyl)thio)-3-oxopropanoate (1c)**



To a solution of ethyl malonic acid (2.8 g, 21.2 mmol, 2 equiv.) in dry $CH_3CN$ (15 ml) was added under inert argon atmosphere, 4-methoxybenzyl alcohol (1.46 g, 10.6 mmol, 1 equiv.) and DMAP (0.26 g, 2.12 mmol, 0.2 equiv.). The mixture was cooled to 0 °C and a solution of DCC (4.37 g, 21.2 mmol, 2 equiv. in $CH_3CN$ (5 ml) was added drop wise within a period of 10 minutes. The mixture was stirred at room temperature for 1 hour followed by filtration of DCU. All volatiles were removed at reduced pressure and the crude mixture was re-dissolved in a mixture of $CH_2Cl_2$ (10 ml). The organic phase was extracted with saturated aqueous $NaHCO_3$ solution (2 x 10 ml). The pH of the combined aqueous phase was then carefully decreased to pH 3 by addition of an aqueous solution of HCl (4%). The aqueous phase was re-extracted with $CH_2Cl_2$ (3x 10 ml), and the combined organic phases were dried with $MgSO_4$. After filtration, all volatiles were removed at reduced pressure to yield a colorless oil (2.16 g, 81%). To the oil, dissolved in dry $CH_2Cl_2$ (15 ml) was added 4-methoxythiophenol (2.10 ml, 17.1 mmol, 1.6 equiv.) and HOBt (2.31 g, 17.1 mmol, 1.6 equiv.) at 0 °C under a nitrogen atmosphere. A solution of DCC (3.53 g, 17.1 mmol, 1.6 equiv.) in $CH_2Cl_2$ (5 ml) was added drop wise within a period of 10 minutes followed by stirring the mixture at room temperature for 2.5 hours. The reaction mixture was filtrated and the filtrate was concentrated at reduced pressure. The resulting crude product was purified by flash chromatography on silica gel using a gradient of a mixture of hexane:EtOAc from 10:1 to 3:1 as eluent to afford 2.11 g (69%) of a white solid.

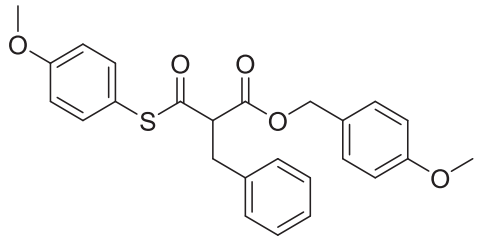
$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.35-7.28 (m, 4H), 6.96-6.91 (m, 4H), 5.18 (s, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.63 (t, $J$ = 7 Hz, 1H), 2.09-2.01 (m, 2H), 1.02 (t, $J$ = 7.5 Hz, 3H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 194.1, 168.5, 160.9, 159.7, 136.1, 130.1, 127.6, 117.7, 114.9, 114.0, 67.1, 61.0, 55.4, 55.3, 23.0, 11.8.

$\nu_{max}$ (neat)/cm$^{-1}$: 3019, 2923, 1764, 1678, 1200.

HRMS (ESI) *m/z*: calculated for $C_{20}H_{22}NaO_5S$ $[M+Na]^+$ 397.1080; found, 397.1087.

**4-Methoxybenzyl-2-benzyl-3-((4-methoxyphenyl)thio)-3-oxopropanoate (1f)**



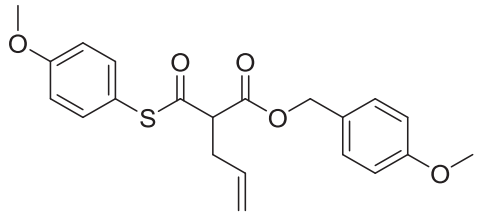
$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.33-7.25 (m, 5H), 7.22-7.19 (m, 4H), 6.94-6.89 (m, 4H), 5.14 (s, 2H), 4.01 (t, $J$ = 7.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.31 (m, 2H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 193.6, 167.9, 160.9, 159.7, 137.4, 136.1, 130.1, 129.0, 128.6, 126.9, 117.5, 114.9, 113.9, 67.3, 60.9, 55.3, 35.3.

$\nu_{max}$ (neat)/cm$^{-1}$: 3009, 1730, 1686, 1255.

HRMS (ESI) *m/z*: calculated for $C_{25}H_{28}NO_5S$ $[M+NH_4]^+$ 454.1683; found, 454.1690.

**4-Methoxybenzyl-2-allyl-3-((4-methoxyphenyl)thio)-3-oxopropanoate (1g)**



To a solution of allyl malonic acid (1.0 g, 6.94 mmol, 2.5 equiv.) in dry $CH_3CN$ (6 ml) was added under inert argon atmosphere, 4-methoxybenzyl alcohol (0.38 g, 2.78 mmol, 1 equiv.) at 0 °C. EDCI (1.07 g, 5.56 mmol, 2 equiv.) was added portionwise and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with 10 ml of water and the organic phase was extracted with saturated aqueous $NaHCO_3$ solution (2 x 10 ml). The pH of the combined aqueous phase was then carefully decreased to pH 3 by addition of an aqueous solution of HCl (4%) at 0 °C. The aqueous phase was re-extracted with $CH_2Cl_2$ (3 x 10 ml), and the combined organic phases were dried with $MgSO_4$. After filtration, all volatiles were removed at reduced pressure to yield a colorless oil (0.45 g, 1.70 mmol). To the oil, dissolved in dry $CH_2Cl_2$ (4 ml) was added 4-methoxythiophenol (0.42 ml, 3.4 mmol, 2 equiv.) and the reaction mixture was put to at 0 °C under a nitrogen atmosphere. EDCI (0.65 g, 3.4 mmol, 2 equiv.) was added portion wise and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with 10 ml of water and the organic phase was extracted with brine (2 x 10 ml), dried over MgSO4 and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography on silica gel using a gradient of a mixture of hexane:EtOAc from 10:1 to 3:1 as eluent to afford 0.21 g (32%) of a colorless oil.

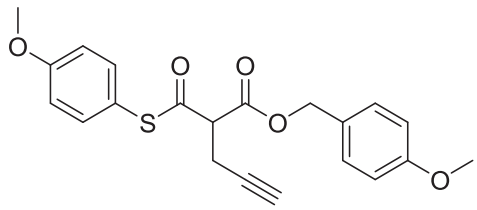
$^1$H-NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 7.36-7.34 (m, 2H), 7.30-7.28 (m, 2H), 6.92-6.87 (m, 4H), 5.81 (ddt, *J* = 17 Hz, 10 Hz, 7 Hz, 1H), 5.18 (s, br, 2H), 5.17 (dq, *J* = 17 Hz, 1.5 Hz, 1H), 5.12 (dq, *J* = 10 Hz, 1.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (t, *J* = 7.5 Hz, 1H), 2.78-2.74 (m, 2H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 193.4, 167.9, 160.9, 159.8, 136.1, 133.6, 130.2, 127.5, 118.1, 117.5, 115.0, 114.0, 67.3, 58.9, 55.4, 55.3, 33.4.

$\nu_{max}$ (neat)/cm$^{-1}$: 3020, 2956, 1737, 1695, 1592, 1249.

HRMS (ESI) *m/z*: calculated for $C_{21}H_{26}NO_5S$ $[M+NH_4]^+$ 404.1526; found, 404.1519.

**4-Methoxybenzyl-3-((4-methoxyphenyl)thio)-2-methyl-3-propargylpropanoate (1h)**



To a solution of propargyl malonic acid (3.2 g, 22.5 mmol, 1 equiv.) in dry $CH_3CN$ (113 ml) was added under inert argon atmosphere, 4-methoxybenzyl alcohol (3.1 g, 22.5 mmol, 1 equiv.). The mixture was cooled to -15 °C and a solution of DCC (7.0 g, 33.8 mmol, 1.5 equiv.) in $CH_3CN$ (56 ml) was added dropwise within a period of 10 minutes. The mixture was stirred at room temperature for 1 hour followed by filtration of DCU. All volatiles were removed at reduced pressure and the crude mixture was re-dissolved in a mixture of $CH_2Cl_2$ (20 ml). The organic phase was extracted with saturated aqueous $NaHCO_3$ solution (2 x 20 ml). The pH of the combined aqueous phase was then carefully decreased to pH 3 by addition of an aqueous solution of HCl (4%) at 0 °C. The aqueous phase was re-extracted with $CH_2Cl_2$ (3 x 20 ml), and the combined organic phases were dried over $MgSO_4$. After filtration, all volatiles were removed at reduced pressure to yield a white solid (1.76 g, 6.7 mmol). To the solid, dissolved in dry $CH_2Cl_2$ (34 ml) was added 4-methoxythiophenol (1.88 g, 13.4 mmol, 2 equiv.) and the reaction mixture was put to at -15 °C under a nitrogen atmosphere. EDCI (2.57 g, 13.4 mmol, 2 equiv.) was added portion wise and the resulting mixture was stirred at room temperature for 2.5 hours. The reaction mixture was washed with 10 ml of water and the organic phase was extracted with brine (2 x 20 ml), dried with MgSO4 and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography on silica gel using a gradient of a mixture of $CH_2Cl_2$:pentane from 6:4 to 10:1 as eluent to afford 1.27 g (50%) of a yellow oil.

$^1$H-NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.36-7.34 (m, 2H), 7.30-7.28 (m, 2H), 6.96-6.92 (m, 4H), 5.21 (s, 2H), 3.94 (t, $J$ = 7.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.90 (ddd, $J$ = 14 Hz, 7.5 Hz, 2.5 Hz, 1H), 2.84 (ddd, $J$ = 14 Hz, 7.5 Hz, 2.5 Hz, 1H), 2.09 (t, $J$ = 2.5 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 192.5, 167.0, 161.0, 159.8, 136.1, 130.2, 127.3, 117.2, 115.0, 114.0, 79.7, 70.9, 67.6, 57.9, 55.4, 55.3, 18.8.

$\nu_{max}$ (neat)/cm$^{-1}$: 3026, 2913, 1741, 1699, 1495, 1250.

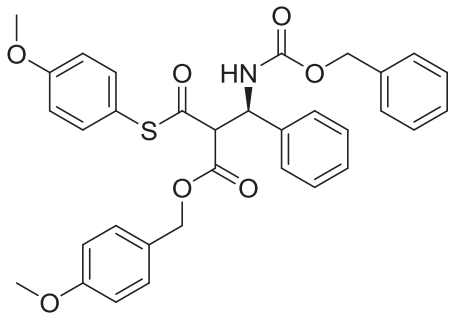
HRMS (ESI) *m/z*: calculated for $C_{21}H_{24}NO_5S$ $[M+NH_4]^+$ 402.1370; found, 402.1365.

## 7.5 General Protocol for the Organocatalyzed Mannich Reaction of Imines and $\alpha$-unsubstituted Mono Thiomalonates

### 7.5.1 General Protocol for the Addition reaction

To a suspension of α-amido sulfone (76.2 mg, 0.2 mmol, 1 equiv.) in $CH_2Cl_2$ (2 ml) was added 2 ml of an aqueous solution of $Na_2CO_3$ (10% $Na_2CO_3$, saturated with NaCl). The mixture was vigorously stirred for 12 hours at room temperature. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 0.5 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ followed by filtration. All volatiles were removed and the residue was dried *in vacuo*. The freshly prepared imine was dissolved in dry $CH_2Cl_2$ (1 ml) and MTM (109.2 mg, 0.3 mmol, 1.5 equiv.) was added. The reaction mixture was cooled to the defined temperature followed by addition of catalyst (1.16 mg, 0.002 mmol, 1 mol%). The reaction mixture was stirred at the temperature for the time stated followed by removal of all volatiles at reduced pressure. The crude product was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$: (pentane:EtOAc 7:1) of 9:1.

**(*3R*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-3-phenyl-3-(benzyloxy-carbonylamino)-propanethioate (7a)**



Yield: 98%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.37-7.23 (m, 12H), 7.17-7.10 (m 2H), 6.94-6.38 (m, 4H), 6.49-6.38 (m, 1H), 5.69-5.64 (m, 1H), 5.19-5.02 (m, 4H), 4.27-4.25 (m, 1H), 3.85-3.82 (m, 6H). (major diastereoisomer)

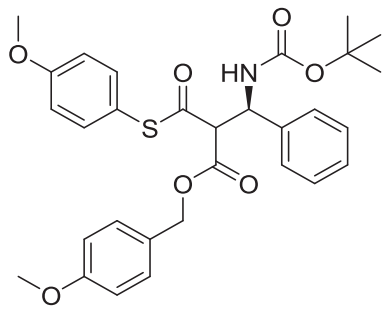
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 194.5, 191.6, 167.1, 166.0, 161.1, 161.0, 159.8, 159.9, 155.7, 155.5, 138.8, 138.7, 136.4, 136.4, 136.3, 136.0, 130.3, 130.2, 128.7, 128.7, 128.5, 128.4, 128.0, 128.0, 127.9, 127.9, 127.1, 126.9, 126.5, 126.5, 117.1, 117.1, 116.9 116.9, 115.0, 115.0, 114.0, 113.9, 67.7, 67.5, 66.9, 66.8, 63.5, 62.5, 55.4, 55.4, 55.3, 55.3, 55.2, 54.9. (both diastereoisomers)

$\nu_{max}$ (neat)/cm$^{-1}$: 1741, 1703, 1690, 1590, 1494, 1454, 1286, 1245, 1155.

HRMS (ESI) *m/z*: calculated for $C_{33}H_{35}N_2O_7S$ $[M+NH_4]^+$ 603.2159; found, 603.2151.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (R) = (25.8 min), 27.0 min, (S) = (30.9 min), 32.5 min (94% ee).

**(*3R*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-3-phenyl-3-(*tert*-butoxycarbonylamino)-propanethioate (5a)**



Yield: 98%

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.33-7.25 (m, 7H), 7.14 (m, 2H), 6.91-6.85 (m, 4H), 6.20 (br, s, 1H), 5.61 (br, s, 1H), 5.14 (s, br, 2H), 4.29 (br, s, 1H), 3.78 (s, 6H), 1.45 (s, 9H). (main diastereoisomer)

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 194.3, 191.7, 167.1, 166.2, 161.1, 161.0, 159.9, 159.8, 155.2, 155.0, 139.3, 139.3, 136.3, 136.1, 130.3, 130.1, 128.7, 128.7, 127.8, 127.8, 127.2, 127.1, 126.6, 126.6, 117.3, 117.1, 115.0, 115.0, 114.0, 114.0, 79.8, 79.7, 67.6, 67.4, 63.8, 62.8, 55.4, 55.4, 55.3, 55.3, 54.8, 54.5, 28.4, 28.4). (both diastereoisomers)

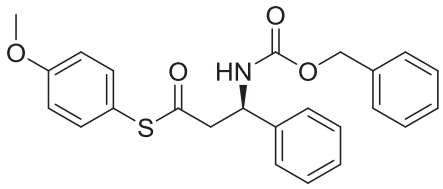
$\nu_{max}$ (neat)/cm$^{-1}$: 3383, 1738, 1686, 1680, 1594, 1512, 1495, 1458, 1291, 1245, 1156.

HRMS (ESI) *m/z*: calculated for $C_{30}H_{34}NO_7S$ $[M+H]^+$ 552.2050; found, 552.2051.

### 7.5.2 General Protocol for the Organocatalyzed Synthesis of α-unfunctionalized $\beta^3$-amino thioesters:

To a suspension of $\alpha$-amido sulfone (76.2 mg, 0.2 mmol, 1 equiv.) in $CH_2Cl_2$ (2 ml) was added 2 ml of an aqueous solution of $Na_2CO_3$ (10% $Na_2CO_3$, saturated with NaCl). The mixture was vigorously stirred for 12 hours at room temperature. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 0.5 ml). The combined organic phases were washed with brine, dried with $MgSO_4$ and fitered. All volatiles were removed and the residue was dried *in vacuo*. The freshly prepared imine was dissolved in dry $CH_2Cl_2$ (1 ml) and MTM (109.2 mg, 0.3 mmol, 1.5 eq) was added. The reaction mixture was cooled to the defined temperature followed by addition of catalyst (1.16 mg, 0.002 mmol, 1 mol%). The reaction mixture was stirred at the temperature for the time stated followed by removal of all volatiles at reduced pressure. The crude mixture was treated with TFA (0.25 ml, 3.25 mmol, 16 equiv.) for 3 minutes followed by the immediate addition of 4 ml of saturated aqueous $NaHCO_3$ solution (4.8 mmol, 24 equiv.) and $CH_2Cl_2$ (2 ml). The mixture was vigorously stirred overnight. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 1 ml) and EtOAc (2 x 1 ml) if the crude did not dissolve well in pure $CH_2Cl_2$. The combined organic phases were washed with brine and dried with $MgSO_4$. Filtration and removal of all volatiles yielded a crude product that was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$: (pentane:EtOAc 7:1) of 9:1.

**(*3R*)-4-methoxyphenyl-3-phenyl-3-(benzyloxycarbonylamino)propanethioate (8a)**




Yield: 86%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.41-7.31 (m, 10H), 7.24-7.22 (m, 2H), 6.95-6.93 (m, 2H), 5.85 (br, s, 1H), 5.20 (m, 1H), 5.16 (d, $J$ = 12.5 Hz, 1H), 5.12 (d, $J$ = 12.5 Hz, 1H), 3.84 (s, 3H), 3.26 (dd, $J$ = 14.5 Hz, 4.8 Hz, 1H), 3.14 (dd, $J$ = 14.5 Hz, 5.6 Hz, 1H).

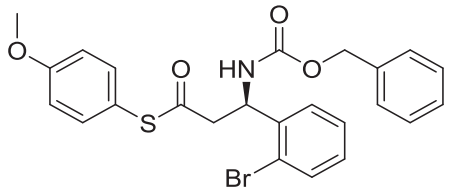
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 196.6, 160.8, 155.5, 140.4, 136.4, 136.1, 128.8, 128.5, 128.4, 128.1, 127.8, 126.3, 117.8, 114.9, 66.9, 55.4, 52.5, 48.6.

$\nu_{max}$ (neat)/cm$^{-1}$: 3306, 1710, 1685, 1534, 1495, 1251, 1176.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{24}NO_4S$ $[M+H]^+$ 422.1421; found, 422.1424.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (R) = 22.1 min, (S) = 32.8 min (94% ee).

**(*3R*)-4-methoxyphenyl-3-(2-bromophenyl)-3-(benzyloxycarbonylamino)propanethioate (8b)**




Yield: 86%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.57 (d, $J$ = 12 Hz, 1H), 7.31 (m, 7H), 7.16 (m, 3H), 6.90 (d, $J$ = 8 Hz, 2H), 6.15 (br, d, $J$ = 8 Hz, 1H), 5.49 (ddd, $J$ = 8 Hz, 5.5 Hz, 5.0 Hz, 1H), 5.09 (d, $J$ = 12.5 Hz, 1H), 5.03 (d, $J$ = 12.5 Hz, 1H), 3.80 (s, 3H), 3.22 (dd, $J$ = 15 Hz, 5.5 Hz, 1H), 3.12 (dd, $J$ = 15 Hz, 5.0 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.2, 160.9, 155.3, 139.2, 136.3, 136.0, 133.3, 129.3, 128.5, 128.1, 127.9, 127.7, 122.6, 117.6, 115.0, 66.9, 55.4, 52.4, 46.3.

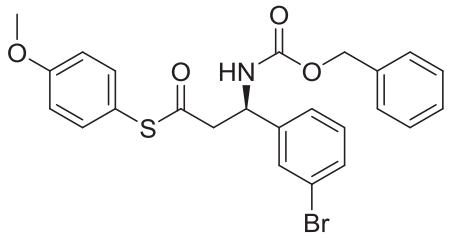
$\nu_{max}$ (neat)/cm$^{-1}$: 3325, 1694, 1532, 1494, 1246, 1174.

MS (ESI): m/z (%): 524.1 $[M+H+Na]^+$ (100), 522.1 (98) M= 500.4 calculated for $C_{24}H_{22}BrNO_4S$.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{23}BrNO_4S$ $[M+H]^+$ 500.0526; found, 500.0516.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (6:4, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (R) = 17.2 min, (S) = 21.4 min (96% ee); Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (R) = 13.96 min, (S) = 16.5 min.

**(*3R*)-4-methoxyphenyl-3-(3-bromophenyl)-3-(benzyloxycarbonylamino)propanethioate (8c)**




Yield: 90%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.42-7.38 (m, 2H), 7.33-7.30 (m, 5H), 7.20-7.16 (m, 4H), 6.91 (d, *J* = 8 Hz, 2H), 5.85-5.83 (m, 1H), 5.16-5.14 (m, 1H), 5.10 (d, *J* = 12 Hz, 1H), 5.06 (d, *J* = 12 Hz, 1H), 3.81 (s, 3H), 3.16 (dd, *J* = 15 Hz, 5 Hz, 1H), 3.07 (dd, *J* = 15 Hz, 4.5 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 196.7, 160.9, 155.4, 136.1, 130.9, 130.3, 129.4, 128.6, 128.3, 128.2, 128.13, 128.11, 125.0, 122.9, 117.5, 115.0, 67.0, 55.4, 52.0, 48.2.

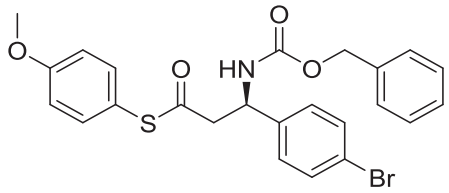
$\nu_{max}$ (neat)/cm$^{-1}$: 3304, 1690, 1684, 1531, 1494, 1245, 1183.

MS (ESI): m/z (%): 524.1 $[M+H+Na]^+$ (100), 522.1 (98) M= 500.4 calculated for $C_{24}H_{22}BrNO_4S$.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{23}BrNO_4S$ $[M+H]^+$ 500.0526; found, 500.0535.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (8:2, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (R) = 16.9 min, (S) = 34.0 min (96% ee).

**(*3R*)-4-methoxyphenyl-3-(4-bromophenyl)-3-(benzyloxycarbonylamino)propanethioate (8d)**




Yield: 85%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.50-7.28 (m, 2H), 7.36-7.30 (m, 5H), 7.23-7.19 (m, 4H), 6.95-6.93 (m, 2H), 5.86 (m, 1H), 5.18 (m, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 3.84 (s, 3H), 3.21 (dd, *J* = 15.0 Hz, 4.5 Hz, 1H), 3.11 (dd, *J* = 15.0 Hz, 5.0 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 196.7, 160.9, 155.5, 139.5, 136.2, 136.0, 131.8, 128.6, 128.5, 128.2, 128.1, 121.7, 117.5, 115.0, 67.0, 55.4, 52.0, 48.2.

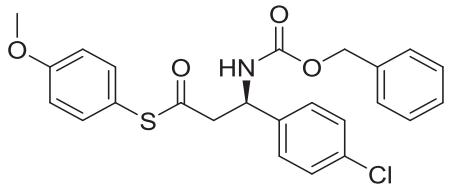
$\nu_{max}$ (neat)/cm$^{-1}$: 3306, 1715, 1685, 1539, 1494, 1248, 1172.

MS (ESI): m/z (%): 524.1 $[M+H+Na]^+$ (100), 522.1 (98) M= 500.4 calculated for $C_{24}H_{22}BrNO_4S$.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{23}BrNO_4S$ $[M+H]^+$ 500.0526; found, 500.0526.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (R) = 22.7 min, (S) = 31.2 min (96% ee).

**(*3R*)-4-methoxyphenyl-3-(4-chlorophenyl)-3-(benzyloxycarbonylamino)propanethioate (8e)**




Yield: 81%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.42-7.21 (m, 11H), 6.91 (d, $J$ = 8 Hz, 2H), 5.81 (br, s, 1H), 5.17-5.13 (m, 1H), 5.13 (d, $J$ = 12.0 Hz, 1H), 5.08 (d, $J$ = 12.0 Hz, 1H), 3.81 (s, 3H), 3.21 (dd, $J$ = 15.0 Hz, 4.5 Hz, 1H), 3.11 (dd, $J$ = 15.0 Hz, 5.0 Hz, 1H).

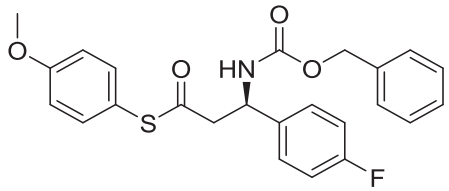
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 196.9, 160.9, 155.5, 144.0, 139.1, 136.0, 133.5, 128.9, 128.5, 128.2, 128.1, 127.7, 117.5, 115.0, 67.0, 55.4, 52.0, 48.3.

$\nu_{max}$ (neat)/cm$^{-1}$: 1704, 1684, 1526, 1494, 1235, 1173.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{23}ClNO_4S$ $[M+H]^+$ 456.1031; found, 465.1027.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 14.8 min, (S) = 18.5 min (98% ee).

**(*3R*)-4-methoxyphenyl-3-(4-fluorophenyl)-3-(benzyloxycarbonylamino)propanethioate (8f)**




Yield: 93%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.35-7.28 (m, 7H), 7.21 (d, $J$ = 8.0 Hz 2H), 7.06 (t, $J$ = 9.0 Hz, 2H), 6.94 (d, $J$ = 8.0 Hz 2H), 5.81 (br, s, 1H), 5.20 (br, s, 1H), 5.14 (d, $J$ = 12.0 Hz, 1H), 5.09 (d, $J$ = 12.0 Hz, 1H), 3.84 (s, 3H), 3.22 (dd, $J$ = 15.0 Hz, 5.0 Hz, 1H), 3.11 (dd, $J$ = 15.0 Hz, 5.0 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.4, 162.0 (d, $^{1}J_{C\text{-}F}$ = 245 Hz), 160.9, 155.5, 143.4, 136.2, 136.0, 128.5, 128.1, 128.0 (d, $^{2}J_{C\text{-}F}$ = 10.0 Hz), 117.5, 115.7, 115.5, 115.0, 67.0, 55.4, 51.9, 48.4.

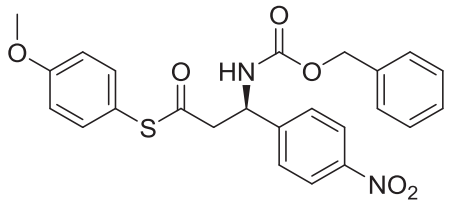
$^{19}$F-NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = -114.6.

$\nu_{max}$ (neat)/cm$^{-1}$: 1704, 1685, 1531, 1495, 1246, 1178.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{22}FNNaO_4S$ $[M+Na]^+$ 462.1146; found, 462.1152.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7.5:2.5, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 14.5 min, (S) = 18.7 min (96% ee).

**(*3R*)-4-methoxyphenyl-3-(4-nitrophenyl)-3-(benzyloxycarbonylamino)propanethioate (8g)**




Yield: 82%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.18 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 7.32 (m, 5H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.03 (br, s, 1H), 5.26 (m, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.25 (dd, *J* = 15.5 Hz, 5.5 Hz, 1H), 3.17 (dd, *J* = 15.5 Hz, 5.0 Hz, 1H).

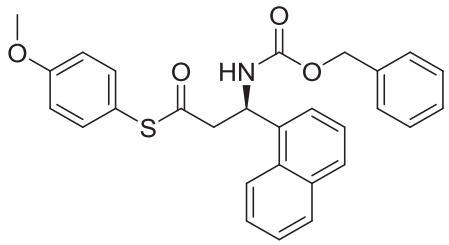
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 198.9, 161.1, 147.4, 136.0, 129.9, 128.6, 128.3, 128.2, 128.1, 127.2, 124.0, 118.8, 117.0, 115.1, 67.2, 55.4, 52.0, 47.7.

$\nu_{max}$ (neat)/cm$^{-1}$: 3315, 1703, 1683, 1511, 1490, 1343, 1245, 1172.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{23}N_2O_6S$ $[M+H]^+$ 467.1271; found, 467.1268.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 28.2 min, (S) = 38.7 min (98% ee).

**(*3R*)-4-methoxyphenyl-3-(2-naphthyl)-3-(benzyloxycarbonylamino)-propanethioate (8h)**



Yield: 80%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.16 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.62-7.53 (m, 2H), 7.51-7.46 (m, 2H), 7.37-7.29 (m, 5H), 7.20 (m, 2H), 6.92 (m, 2H), 6.13-6.08 (m, 1H), 5.92 (s, br, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 3.83 (s, 3H), 3.36 (dd, *J* = 15 Hz, 5 Hz, 1H), 3.30 (dd, *J* = 15 Hz, 5 Hz, 1H).

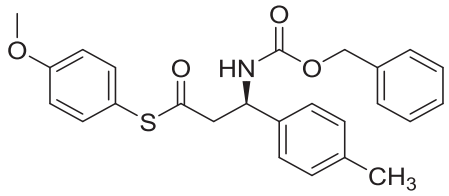
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 196.6, 160.8, 155.5, 136.0, 134.0, 129.1, 128.6, 128.5, 128.1, 126.8, 125.9, 125.2, 123.2, 122.7, 117.8, 114.9, 66.9, 55.4, 49.0, 48.0.

$\nu_{max}$ (neat)/cm$^{-1}$: 3324, 1685, 1540, 1494, 1245, 1172.

HRMS (ESI) *m/z*: calculated for $C_{28}H_{25}NNaO_4S$ $[M+Na]^+$ 494.1396; found, 494.1394.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 26.0 min, (S) = 31.1 min (96% ee).

**(*3R*)-4-methoxyphenyl-3-(4-methylphenyl)-3-(benzyloxycarbonylamino)-propanethioate (8i)**



Yield: 68%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.36 (m, 5H), 7.25-7.17 (m, 6H), 6.95-6.93 (m, 2H) 5.76 (br, s, 1H), 5.23-5.18 (m, 1H), 5.15 (d, *J* = 12.5 Hz, 1H), 5.09 (d, *J* = 12.5 Hz, 1H), 3.84 (s, 3H), 3.24 (dd, *J* = 15.0 Hz, 5.0 Hz, 1H), 3.12 (dd, *J* = 15.0 Hz, 5.5 Hz, 1H), 2.37 (s, 3H).

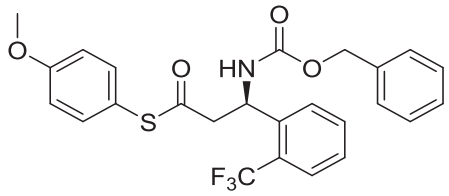
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 196.6, 160.8, 155.5, 137.5, 136.4, 136.1, 129.4, 128.5, 128.1, 127.7, 126.2, 120.2, 117.9, 114.9, 66.8, 55.4, 52.3, 48.7, 21.1.

$\nu_{max}$ (neat)/cm$^{-1}$: 1686, 1531, 1496, 1252, 1174.

HRMS (ESI) *m/z*: calculated for $C_{25}H_{26}NO_4S$ $[M+H]^+$ 436.1577; found, 436.1583.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 23.7 min, (S) = 39.5 min (88% ee).

**(*3R*)-4-methoxyphenyl-3-(2-(trifluormethyl)phenyl)-3-(benzyloxycarbonylamino)-propanethioate (8j)**




Yield: 74%, colourless oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.72 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 4.0 Hz, 2H), 7.44 (quin, *J* = 4.1 Hz, 1H), 7.34 (m, 5H), 7.25-7.24 (d, *J* = 8.5 Hz, 2H), 6.97-6.94 (d, *J* = 8.5 Hz, 2H), 6.19 (s, br, 1H), 5.60-5.54 (m, 1H), 5.11 (d, *J* = 11.9 Hz, 1H), 5.05 (d, *J* = 11.9 Hz, 1H), 3.85 (s, 3H), 3.13-3.06 (m, 2H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.0, 160.9, 155.2, 139.9, 136.0, 132.3, 128.5, 128.1 (q, *J* = 4.0 Hz), 127.9, 127.6, 126.4, 126.3 (q, *J* = 4.0 Hz), 126.2, 124.4 (q, *J* = 273 Hz, $CF_3$), 117.5, 115.0, 113,7 (q, *J* = 32 Hz), 66.9, 55.4, 49.2, 48.1.

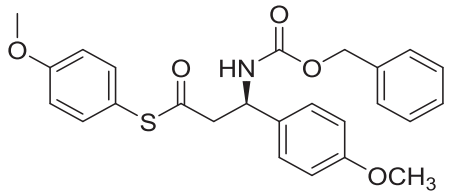
$^{19}$F-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = -58.5.

$\nu_{max}$ (neat)/$cm^{-1}$: 1703, 1699, 1495, 1311, 1249, 1121.

HRMS (ESI) *m/z*: calculated for $C_{25}H_{23}F_3NO_4S$ $[M+H]^+$ 490.1294; found, 490.1295.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 15.3 min, (S) = 18.9 min (98% ee).

**(*3R*)-4-methoxyphenyl-3-(4-methoxyphenyl)-3-(benzyloxycarbonylamino)-propanethioate (8k)**




Yield: 60%, colourless oil

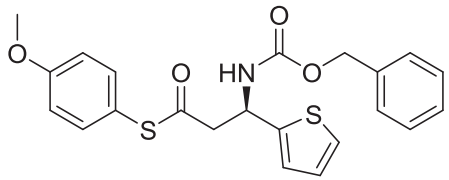
$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.41-7.29 (m, 9H), 6.90 -6.88 (m, 2H), 6.84-6.81 (m, 2H), 6.13 (s, br, 1H), 5.40-5.38 (m, 1H), 5.07 (d, *J* = 12 Hz, 1H), 4.98 (d, *J* = 12 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 160.2, 159.4, 154.8, 136.5, 131.2, 128.5, 128.2, 128.1, 127.7, 122.9, 114.5, 114.0, 67.0, 62.3, 55.3, 52.0.

$\nu_{max}$ (neat)/cm$^{-1}$: 3297, 1689, 1508, 1239, 1171.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 45.1 min, (S) = 54.0 min (82% ee).

**(*3R*)-4-methoxyphenyl-3-(thiophen-2-yl)-3-(benzyloxycarbonylamino)-propanethioate (8l)**




Yield: 59%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.39-7.32 (m, 6H), 7.25-7.23 (m, 2H), 7.18 (m, 1H), 7.05 (d, *J* = 4 Hz, 1H), 6.95-6.93 (m, 2H), 5.75 (s, br, 1H), 5.33 (m, 1H), 5.16 (d, *J* = 12 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 3.84 (s, 3H), 3.28 (dd, *J* = 16.0 Hz, 4 Hz, 1H), 3.16 (dd, *J* = 15.0 Hz, 4 Hz, 1H).

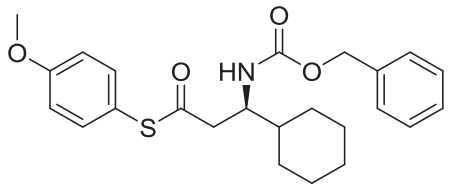
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 196.8, 160.8, 155.5, 141.4, 136.3, 136.1, 128.5, 128.1, 128.0, 126.5, 126.1, 121.5, 117.7, 115.0, 66.9, 55.4, 48.7, 48.1.

$\nu_{max}$ (neat)/cm$^{-1}$: 1673, 1525, 1493, 1281, 1245, 1172.

HRMS (ESI) *m/z*: calculated for $C_{22}H_{22}NO_4S_2$ $[M+H]^+$ 428.0985; found, 428.0980.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 33.4 min, (S) = 47.8 min (94% ee).

**(*3R*)-4-methoxyphenyl-3-cyclohexyl-3-(benzyloxycarbonylamino)-propanethioate (8n)**




Yield: 62%, colourless oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.39-7.29 (m, 7H), 6.97-6.94 (m, 2H), 5.19 (br, d, 1H), 5.14 (d, $J$ = 12.5 Hz, 1H), 5.09 (d, $J$ = 12.5 Hz, 1H), 3.89 (m, 1H), 3.85 (s, 3H), 2.94 (dd, $J$ = 15.5 Hz, 6.0 Hz, 1H), 2.88 (dd, $J$ = 15.5 Hz, 5.0 Hz, 1H), 1.84-1.55 (m, 6H), 1.29-0.93 (m, 5H).

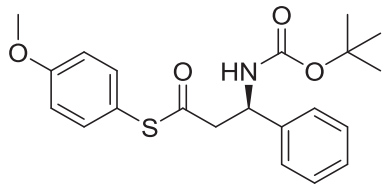
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.5, 160.8, 156.0, 136.6, 136.1, 128.5, 128.0, 128.0, 118.1, 114.9, 66.6, 55.4, 53.8, 45.0, 41.1, 30.0, 29.1, 26.2, 26.0, 25.9.

$\nu_{max}$ (neat)/cm$^{-1}$: 3316, 2917, 2849, 1695, 1684, 1536, 1493, 1243, 1173.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{30}NO_4S$ $[M+H]^+$ 428.1890; found, 428.1886.

HPLC: Chiracel AS-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$: (R) = 26.2 min, (S) = 19.3 min (96% ee).

**(*3R*)-4-methoxyphenyl-3-phenyl-3-(*tert*-butoxycarbonylamino)propanethioate (5d)**



To a solution of (*3R*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-3-phenyl-3-(*tert*-butoxycarbonylamino)-propanethioate in $CH_2Cl_2$ (0.5 ml) was added TFA (0.5 ml) and the mixture was stirred for 30 minutes at room temperature. After removal of all volatiles at reduced pressure, the residue was dissolved in THF (0.5 ml) and saturated aqueous solution of $NaHCO_3$ (1 ml) was added. A solution of $Boc_2O$ (26.2 mg, 0.12 mmol, 1.2 equiv.) in THF (0.5 ml) was added dropwise and the mixture was vigorously stirred at room temperature for 12 hours. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 1 ml).The combined organic phases were washed with brine and dried over MgSO4. Filtration and removal of all volatiles yielded a crude product that was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$: (pentane:EtOAc 7:1) of 9:1. Purification afforded a white solid (25.5 mg, 72% yield).

$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.41-7.34 (m, 2H), 7.33-7.26 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 5.53 (br, s, 1H), 5.16 (br, s, 1H), 3.84 (s, 3H), 3.21 (dd, *J* = 15.0 Hz, 5.0 Hz, 1H), 3.11 (dd, *J* = 15.0 Hz, 5.5 Hz, 1H), 1.44 (s, 9H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 204.3, 160.8, 155.0, 140.6, 136.0, 128.6, 127.6, 126.3, 117.9, 114.9, 55.4, 52.1, 49.0, 28.4.

$\nu_{max}$ (neat)/cm$^{-1}$: 3398, 1710, 1683, 1590, 1513, 1490, 1367, 1242, 1170.

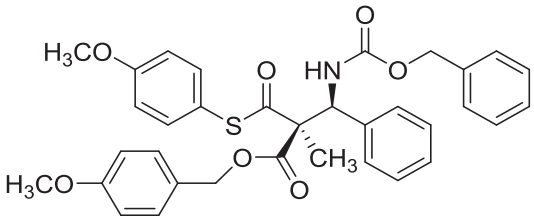
HRMS (ESI) *m/z*: calculated for $C_{21}H_{26}NO_4S$ $[M+H]^+$ 388.1577; found, 388.1577.

HPLC: Chiracel OD-H column, n-hexane/i-PrOH (9:1, 40 °C), 0.5 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (R) = 20.8 min, (S) = 18.4 min (94% ee).

### 7.6 General Protocol for the Organocatalyzed Mannich Reaction of Imines and $\alpha$-substituted Mono Thiomalonates

To a suspension of $\alpha$-amido sulfone (76.2 mg, 0.2 mmol, 1 equiv.) in $CH_2Cl_2$ (2 ml) was added 2 ml of an aqueous solution of $Na_2CO_3$ (10%, saturated with NaCl). The mixture was vigorously stirred for 12 hours at room temperature. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 0.5 ml). The combined organic phases were washed with brine, dried with MgSO4 followed by filtration. All volatiles were removed and the residue was dried *in vacuo*. The freshly prepared imine was dissolved in dry $CH_2Cl_2$ (1 ml) and MTM (100.8 mg, 0.28 mmol, 1.4 equiv.) was added. The reaction mixture was cooled to the temperature stated followed by addition of catalyst (0.01 mmol, 5 mol%). The reaction mixture was stirred at the temperature set for 18 hours followed by removal of all volatiles at reduced pressure. The crude product was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$: methanol of 95.5:0.5.

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-phenyl-3-(benzyloxycarbonylamino)-propanethioate (11a)**




Yield: 99%, colourless oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.38-7.25 (m, 13H), 6.99-6.89 (m, 5H), 5.40 (d, *J* = 10 Hz, 1H), 5.22 (d, *J* = 12.5 Hz, 1H), 5.20-5.13 (m, 2H), 5.03 (d, *J* = 12 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 1.55 (s, 3H).

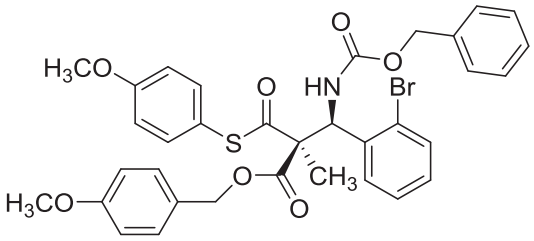
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.9, 170.4, 161.0, 159.9, 155.4, 137.6, 136.6, 130.3, 128.50, 128.47, 128.4, 128.14, 128.10, 128.0, 126.9, 116.8, 115.0, 114.0, 67.7, 66.7, 65.2, 60.3, 55.4, 55.3, 21.1.

$\nu_{max}$ (neat)/cm$^{-1}$: 1725, 1592, 1505, 1494, 1247, 1215, 1208, 1175.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{37}N_2O_7S$ $[M+NH_4]^+$ 617.2316; found, 617.2311.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.4 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 21.5 min, (minor enantiomer) = 36.9 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(2-bromo)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11b)**




Yield: 99%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.62-7.59 (m, 1H), 7.37 (m, 4H), 7.30-7.21 (m, 6H), 7.14 (m, 2H), 7.05-6.87 (m, 4H), 6.17 (d, *J* = 8.5 Hz, 1H), 5.22 (d, *J* = 12.5 Hz, 1H), 5.22-5.21 (m, 2H), 5.01 (d, *J* = 12.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 1.60 (s, 3H).

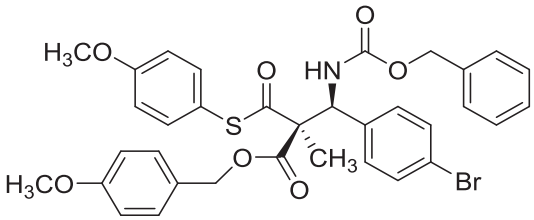
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 198.0, 170.7, 161.0, 160.0, 155.4, 138.0, 136.7, 133.2, 130.7, 130.4, 130.0, 129.5, 128.9, 128.5, 128.1, 128.0, 126.9, 125.7, 116.7, 115.1, 114.0, 67.9, 66.8, 65.8, 57.8, 55.4, 20.0.

$\nu_{max}$ (neat)/cm$^{-1}$: 1723, 1680, 1592, 1510, 1494, 1246, 1217, 1174.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{36}BrN_2O_7S$ $[M+NH_4]^+$ 695.1421; found, 695.1417.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.4 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 18.8 min, (minor enantiomer) = 22.7 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-bromo)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11c)**




Yield: 99%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.35 (m, 6H), 7.25-7.20 (m, 4H), 7.16-7.10 (m, 2H), 6.95-6.80 (m, 5H), 5.29 (d, *J* = 12 Hz, 1H), 5.18-5.08 (m, 3H), 5.01 (d, *J* = 12 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 1.50 (s, 3H).

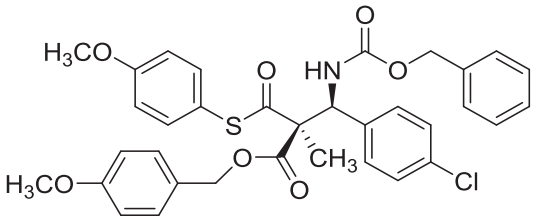
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.7, 170.2, 161.0, 159.9, 155.4, 136.62, 136.56, 136.4, 131.4, 130.4, 130.1, 128.5, 128.11, 128.09, 126.8, 122.2, 116.6, 115.0, 114.0, 67.8, 66.9, 64.9, 59.8, 55.4, 21.1.

$\nu_{max}$ (neat)/cm$^{-1}$: 3421, 1712, 1684, 1591, 1515, 1491, 1447, 1247, 1212, 1176, 1115.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{32}BrNNaO_7S$ $[M+Na]^+$ 700.0975; found, 700.0982.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.40 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 24.2 min, (minor enantiomer) = 62.4 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-chloro)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11d)**




Yield: 99%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.35 (m, 4H), 7.23-7.20 (m, 8H), 6.93-6.87 (m, 5H), 5.30 (d, *J* = 9.5 Hz, 1H), 5.19-5.08 (m, 3H), 5.00 (d, *J* = 12.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 1.50 (s, 3H).

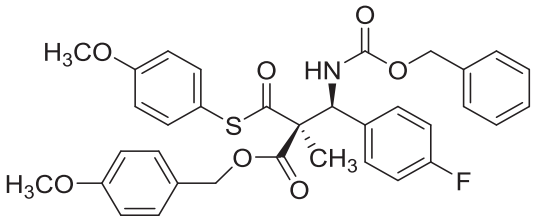
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.7, 170.2, 161.0, 159.9, 155.4, 136.6, 136.4, 136.13, 136.12, 134.0, 130.4, 129.8, 128.5, 128.11, 128.09, 126.8, 116.6, 115.0, 114.0, 67.8, 66.9, 65.0, 60.0, 55.4, 55.3, 21.1.

$\nu_{max}$ (neat)/$cm^{-1}$: 3422, 1717, 1684, 1591, 1513, 1491, 1448, 1247, 1212, 1177, 1115.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{36}ClN_2O_7S$ $[M+NH_4]^+$ 651.1926; found, 651.1940.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.40 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 23.3 min, (minor enantiomer) = 55.6 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-fluoro)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11e)**



Yield: 95%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.37 (m, 4H), 7.29-7.24 (m, 6H), 6.97-6.89 (m, 7H), 5.37 (d, *J* = 9.5 Hz, 1H), 5.22-5.12 (m, 3H), 5.02 (d, *J* = 12.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 1.54 (s, 3H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.7, 170.3, 162.5 (d, $^{1}J_{C\text{-}F}$ = 245), 161.0, 159.9, 155.4, 136.6, 136.5, 133.5, 130.4, 130.2 (d, $^{2}J_{C\text{-}F}$ = 9), 128.5, 128.1, 126.9, 116.7, 115.4, 115.14, 115.06, 114.0, 67.8, 66.8, 65.2, 59.7, 55.4, 55.3, 21.1.

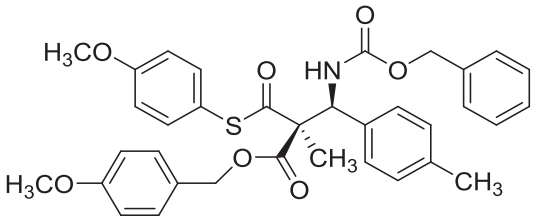
$^{19}$F-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = -113.9.

$\nu_{max}$ (neat)/cm$^{-1}$: 3307, 1741, 1707, 1680, 1535, 1509, 1490, 1455, 1247, 1215, 1177, 1106.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{32}FNNaO_7S$ $[M+Na]^+$ 640.1776; found, 640.1766.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.40 ml/min, UV detection λ = 254 nm: $t_R$ : (major enantiomer) = 21.0 min, (minor enantiomer) = 36.3 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-methyl)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11f)**




Yield: 81%, white solid

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.36-7.32 (m, 4H), 7.29-7.20 (m, 4H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.93-6.87 (m, 5H), 5.32 (d, *J* = 9.5 Hz, 1H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.14 (s, 2H), 5.00 (d, *J* = 12.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.34 (s, 3H), 1.51 (s, 3H).

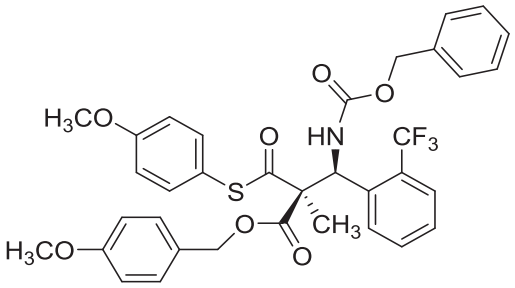
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.9, 170.4, 160.9, 159.8, 155.4, 137.8, 136.6, 134.6, 130.3, 129.0, 128.5, 128.3, 128.1, 128.02, 127.97, 127.0, 116.9, 115.0, 114.0, 67.6, 66.7, 65.3, 60.1, 55.4, 55.3, 21.14, 21.10.

$\nu_{max}$ (neat)/$cm^{-1}$: 3420, 1717, 1684, 1591, 1518, 1495, 1448, 1302, 1247, 1209, 1177, 1122.

HRMS (ESI) *m/z*: calculated for $C_{35}H_{35}NNaO_7S$ $[M+Na]^+$ 636.2026; found, 636.2024.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (4:6, 40 °C), 0.40 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 21.7 min, (minor enantiomer) = 47.8 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(2-triflouromethyl)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11g)**




Yield: 84%, viscous oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.70 (d, *J* = 4 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.42-7.26 (m, 10H), 7.15 (d, *J* = 12 Hz, 1H), 6.99-6.89 (m, 4H), 6.03 (d, *J* = 12 Hz, 1H), 5.28 (d, *J* = 12 Hz, 1H), 5.26-5.13 (m, 2H), 5.02 (d, *J* = 12 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 1.46 (s, 3H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.9, 171.0, 170.0, 161.0, 160.0, 155.0, 137.3, 136.7, 132.4, 130.5, 130.0, 128.9, 128.5, 128.3, 128.0, 126.8, 116.7, 115.0, 114.0, 114.0, 68.0, 66.7, 65.5, 55.4, 54.5, 46.3, 20.4, 13.6.

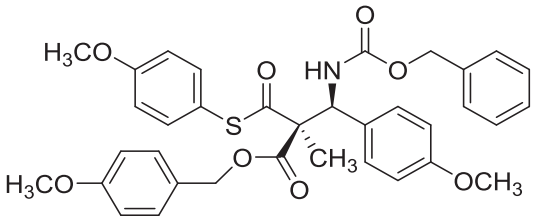
$^{19}$F-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = -55.4.

$\nu_{max}$ (neat)/$cm^{-1}$: 3614, 1731, 1496, 1307, 1249, 1173, 1124.

HRMS (ESI) *m/z*: calculated for $C_{35}H_{32}F_3NNaO_7S_2$ $[M+Na]^+$ 690.1744; found, 690.1734.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (7:3, 40 °C), 0.37 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 17.4 min, (minor enantiomer) = 19.9 min (96% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-methoxy)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11h)**




Yield: 79%, viscous colourless oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.41-7.33 (m, 5H), 7.29-7.20 (m, 6H), 6.93-6.88 (m, 4H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.30 (d, *J* = 9.0 Hz, 1H), 5.21-5.15 (m, 2H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.01 (d, *J* = 12.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 1.52 (s, 3H).

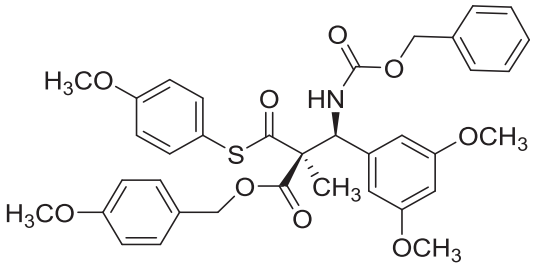
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.9, 170.4, 160.9, 159.8, 159.3, 155.4, 136.6, 130.4, 129.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.0, 116.9, 115.0, 114.0, 113.7, 67.6, 66.7, 65.4, 59.9, 55.4, 55.3, 55.2, 21.1.

$\nu_{max}$ (neat)/cm$^{-1}$: 3406, 1727, 1717, 1683, 1510, 1492, 1455, 1247, 1218, 1181, 1124.

HRMS (ESI) *m/z*: calculated for $C_{35}H_{35}NNaO_8S$ $[M+Na]^+$ 652.1976; found, 652.1987.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.37 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 24.8 min, (minor enantiomer) = 46.1 min (98% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(3,5-dimethoxy)phenyl-3-(benzyloxycarbonylamino)-propanethioate (11i)**




Yield: 97%, viscous colourless oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.36-7.31 (m, 4H), 7.26-7.22 (m, 4H), 6.95-6.86 (m, 5H), 6.50 (s, br, 2H), 6.41 (t, *J* = 2 Hz. 1H), 5.30 (d, *J* = 9.5 Hz, 1H), 5.19 (d, *J* = 12 Hz, 1H), 5.18-5.11 (m, 2H), 5.02 (d, *J* = 12 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.76 (s, 6H), 1.54 (s, 3H).

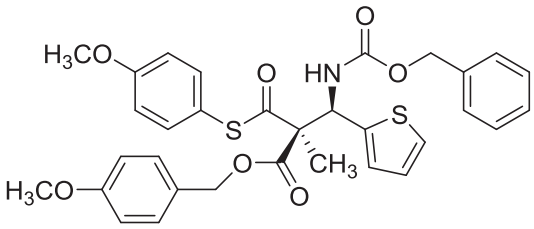
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.8, 170.5, 160.9, 160.7, 159.8, 155.4, 139.9, 136.6, 130.0, 128.5, 128.1, 128.0, 126.9, 116.8, 115.0, 114.0, 106.7, 100.1, 67.7, 66.7, 65.1, 60.5, 55.4, 55.32, 55.27, 21.1.

$\nu_{max}$ (neat)/cm$^{-1}$: 1724, 1593, 1494, 1455, 1297, 1246, 1203, 1154, 1106.

HRMS (ESI) *m/z*: calculated for $C_{36}H_{37}NNaO_9S$ $[M+Na]^+$ 682.2081; found, 682.2074.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (2:8, 40 °C), 0.30 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 41.5 min, (minor enantiomer) = 45.2 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(thiophen-2-yl)-3-(benzyloxycarbonylamino)-propanethioate (11j)**




Yield: 78%, colourless viscous oil

$^{1}$H-NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.33-7.15 (m, 10H), 6.96 (d, *J* = 5 Hz, 1H), 6.90-6.85 (m, 4H), 6.70 (d, *J* = 10 Hz, 1H), 5.49 (d, *J* = 10 Hz, 1H), 5.19-4.98 (m, 4H), 3.82 (s, 3H), 3.80 (s, 3H), 1.53 (s, 3H).

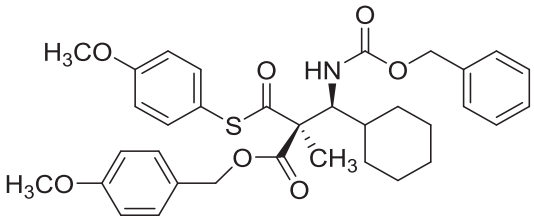
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.7, 170.6, 160.9, 159.9, 155.5, 138.4, 136.6, 130.3, 128.5, 128.10, 128.08, 128.0, 127.5, 127.0, 125.7, 124.0, 116.8, 115.0, 114.0, 67.7, 66.8, 65.2, 56.2, 55.4, 55.3, 20.7.

$\nu_{max}$ (neat)/$cm^{-1}$: 2950, 1723, 1700, 1592, 1510, 1493, 1454, 1301, 1244, 1215, 1173, 1104.

HRMS (ESI) *m/z*: calculated for $C_{32}H_{31}NNaO_7S_2$ $[M+Na]^+$ 628.1434; found, 628.1422.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.30 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 28.1 min, (minor enantiomer) = 46.9 min (97% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-cyclohexyl-3-(benzyloxycarbonylamino)-propanethioate (11k)**




Yield: 44% (0 °C, 10 mol% catalyst, 24 h), colourless viscous oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.40-7.28 (m, 7H), 7.21-7.17 (m, 2H), 6.94-6.87 (m, 4H), 5.92 (d, *J* = 10.5 Hz, 1H), 5.23-5.16 (m, 2H), 5.10-5.80 (m, 2H), 4.26 (dd, *J* = 10.5 Hz, 4 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 1.79-1.51 (m, 6H), 1.42-0.90 (m, 7H).

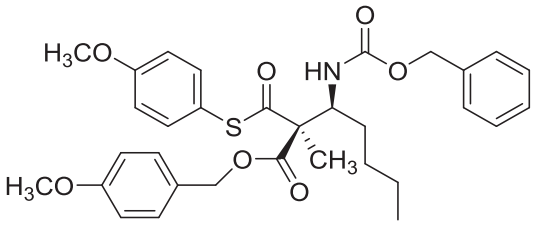
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 198.3, 171.0, 160.8, 159.8, 156.3, 136.5, 130.4, 130.3, 128.5, 127.9, 127.9, 127.1, 117.3, 115.0, 114.9, 114.0, 67.5, 66.6, 64.5, 60.1, 55.4, 55.3, 40.2, 32.5, 26.5, 25.9, 20.2.

$\nu_{max}$ (neat)/$cm^{-1}$: 2829, 2853, 1730, 1712, 1699, 1592, 1511, 1495, 1456, 1245, 1214, 1173, 1110.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{39}NNaO_7S$ $[M+Na]^+$ 628.2339; found, 628.2338.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (2:8, 40 °C), 0.30 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 27.5 min, (minor enantiomer) = 25.3 min (87% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-cyclohexyl-3-(benzyloxycarbonylamino)-propanethioate (11l)**



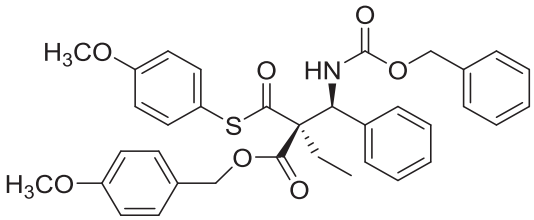

Yield: 45% (0 °C, 10 mol% catalyst, 24 h), colourless viscous oil

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 199.0, 170.5, 160.9, 159.7, 156.2, 154.8, 136.6, 136.5, 136.4, 134.0, 130.3, 130.2, 129.2, 129.0, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 127.9, 115.0, 114.9, 114.0, 113.9, 71.3, 67.4, 66.6, 55.4, 27.4, 26.2, 22.4, 22.1, 14.0, 13.8.

HRMS (ESI) *m/z*: calculated for $C_{32}H_{37}NNaO_7S$ $[M+Na]^+$ 602.2183; found, 602.2174.

HPLC: no suitable HPLC conditions developed.

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-ethyl-3-phenyl-3-(benzyloxycarbonylamino)-propanethioate (11n)**



Yield: 63% (0 °C), colourless viscous oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.37-7.07 (m, 13H), 7.00-6.89 (m, 5H), 5.39 (d, $J$ = 9 Hz, 1H), 5.26-4.99 (m, 4H), 3.86 (s, 3H), 3.84 (s, 3H), 2.02-1.86 (m, 2H), 1.00 (t, $J$ = 7.5 Hz, 3H).

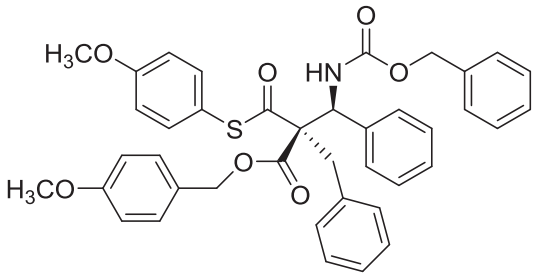
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 197.7, 170.1, 160.9, 159.9, 155.4, 137.8, 136.6 130.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 126.8, 117.2, 115.0, 114.0, 69.1, 67.6, 66.7, 59.6, 55.4, 55.3, 28.8, 9.6.

$\nu_{max}$ (neat)/cm$^{-1}$: 1724, 1592, 1493, 1247, 1215, 1173.

HRMS (ESI) *m/z*: calculated for $C_{35}H_{36}NO_7S$ $[M+H]^+$ 614.2207 found, 614.2208.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (1:1, 40 °C), 0.39 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 20.8 min, (minor enantiomer) = 68.1 min (97% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-benzyl-3-phenyl-3-(benzyloxycarbonylamino)-propanethioate (11p)**




Yield: 94 % (0 °C), colourless viscous oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.41-7.00 (m, 18H), 6.95 – 6.93 (m, 4H), 6.81 (d, *J* = 9.5 Hz, 1H), 5.52 (d, *J* = 9.5 Hz, 1H), 5.22 (d, *J* = 11.5 Hz, 1H), 5.17 (d, *J* = 12.5 Hz, 1H), 5.15 (d, *J* = 11.5 Hz, 1H), 5.03 (d, *J* = 12.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.38 (d, *J* = 13.5 Hz, 2H), 3.32 (d, *J* = 13.5 Hz, 1H).

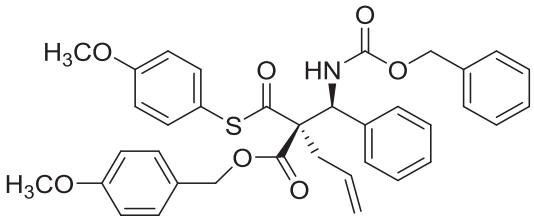
$^{13}$C-NMR (100 MHz, $CDCl_3$, 2 5°C): δ = 200.0, 169.7, 160.9, 160.1, 155.5, 137.8, 136.5, 136.3, 135.1, 130.2, 130.5, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.8, 127.2, 126.4, 118.2, 114.9, 114.1, 69.2, 67.8, 66.8, 60.3, 55.4, 55.3, 42.0.

$\nu_{max}$ (neat)/$cm^{-1}$: 3120, 2976, 1713, 1687, 1263.

HRMS (ESI) *m/z*: calculated for $C_{40}H_{37}NNaO_7S$ $[M+Na]^+$ 698.2183; found, 698.2184.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (1:1, 40 °C), 0.35 ml/min, UV detection λ = 254 nm: $t_R$ : (major enantiomer) = 25.3 min, (minor enantiomer) = 23.0 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-allyl-3-phenyl-3-(benzyloxycarbonylamino)-propanethioate (11q)**



Yield: 60%, viscous colourless oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): 7.49-7.18 (m, 14H), 6.99-6.89 (m, 4H), 5.80 (dddd, *J* = 17 Hz, 10 Hz, 8.8 Hz, 6.0 Hz, 1H), 5.39 (d, *J* = 9.5 Hz, 1H), 5.23 (d, *J* = 12 Hz, 1H), 5.25-5.12 (m, 5H), 4.99 (d, *J* = 12 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.70 (dd, *J* = 14 Hz, 6 Hz, 1H), 2.59 (dd, *J* = 14 Hz, 8.5 Hz, 1H).

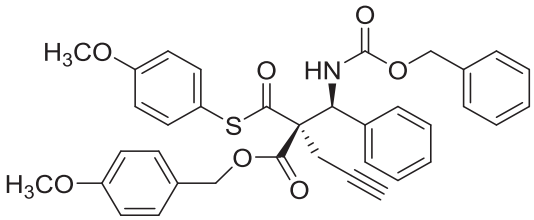
$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): 197.1, 169.8, 160.9, 160.0, 155.3, 137.5, 136.5, 132.1, 130.7, 128.6, 128.5, 128.2, 128.2, 128.1, 128.0, 128.0, 126.6, 119.7, 117.1, 115.0, 114.0, 68.5, 67.8, 66.7, 59.4, 55.4, 55.3, 40.0.

$\nu_{max}$ (neat)/$cm^{-1}$: 2985, 1720, 1718, 1592, 1493, 1247, 1214, 1173.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{35}NNaO_7S$ $[M+Na]^+$ 648.2026; found, 648.2025.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.37 ml/min, UV detection λ = 254 nm: $t_R$ : (major enantiomer) = 19.2 min, (minor enantiomer) = 67.6 min (99% ee).

**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-propargyl-3-phenyl-3-(benzyloxycarbonylamino)-propanethioate (11r)**



Yield: 90%, viscous colourless oil

$^{1}$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.41-7.27 (m, 14 H), 6.97-6.88 (m, 4H), 5.63 (d, *J* = 9 Hz, 1H), 5.27-5.16 (m, 3H), 5.03 (d, *J* = 12 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.89 (dd, *J* = 16.5 Hz, 2.5 Hz, 1H), 2.67 (dd, *J* = 16.5 Hz, 2.5 Hz, 1H), 2.25 (t, *J* = 2.5 Hz, 1H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 195.1, 168.8, 161.0, 160.0, 155.3, 137.2, 136.5, 130.7, 128.54, 128.46, 128.4, 128.2, 128.2, 128.1, 128.0, 127.9, 126.5, 116.9, 115.0, 114.0, 78.5, 73.5, 68.2, 67.3, 66.8, 66.8, 57.7, 55.4, 55.3, 25.0.

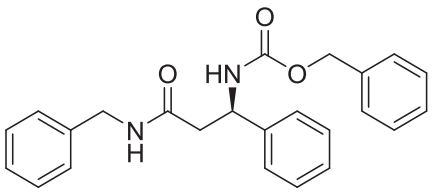
$\nu_{max}$ (neat)/cm$^{-1}$: 3289, 2849, 1716, 1592, 1493, 1246, 1213, 1173.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{33}NNaO_7S$ $[M+Na]^+$ 646.1870; found, 646.1868.

HPLC: Chiracel AD-H column, n-hexane/i-PrOH (3:7, 40 °C), 0.39 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ : (major enantiomer) = 20.9 min, (minor enantiomer) = 74.9 min (98% ee).

## 7.7 Transformations of β-Amino Thioesters

Preparation of **benzyl (*R*)-(3-(benzylamino)-3-oxo-1-phenylpropyl)carbamate (12)**



To a solution of β-amino thioester **8a** (100 mg, 0.24 mmol, 1 equiv.) in $CH_2Cl_2$ (0.5 ml) was added benzylamine (50.7 mg, 0.474 mmol, 2 equiv.) and the reaction was stirred at room temperature for 15 hours. All volatiles were removed and the crude product that was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$:MeOH of 98:2. Purification afforded a white solid (89.3 mg, 97% yield) that forms a gel in $CH_2Cl_2$.

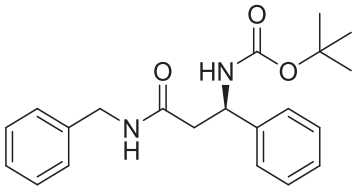
$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.32-7.21 (m, 13H), 7.03-6.97 (m, 2H), 6.57 (s, br, 1H), 5.87 (s, br, 1H), 5.14 (t, *J* = 5.5 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 4.37 (dd, *J* = 15 Hz, 6 Hz, 1H), 4.27 (dd, *J* = 15 Hz, 5.5 Hz, 1H), 2.82 (dd, *J* = 14.5 Hz, 5.5 Hz, 1H), 2.68 (dd, *J* = 14.5 Hz, 5.5 Hz, 1H).

$^{13}$C-NMR (100 MHz, MeOD, 25 °C): $\delta$ = 171.0, 156.5, 141.9, 139.2, 138.2, 128.2, 128.0, 127.6, 127.2, 127.04, 126.98, 126.7, 126.1, 66.1, 52.7, 42.59, 42.58.

$\nu_{max}$ (neat)/cm$^{-1}$: 3307, 3062, 1680, 1634, 1495, 1453, 1343, 1264, 1156.

HRMS (ESI) *m/z*: calculated for $C_{24}H_{25}N_2O_3$ $[M+H]^+$ 389.1860; found, 389.1860.

Preparation of ***tert*-butyl (*R*)-(3-(benzylamino)-3-oxo-1-phenylpropyl)carbamate**



To a solution of *β*-amino thioester **5d** (48 mg, 0.124 mmol, 1 equiv.) in $CH_2Cl_2$ (0.5 ml) was added benzylamine (26.6 mg, 0.248 mmol, 2 equiv.) and the reaction was stirred at room temperature for 15 hours. All volatiles were removed and the crude product that was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$: MeOH of 98:2. Purification afforded a white solid (43.5 mg, 99% yield) that forms a gel in $CH_2Cl_2$.

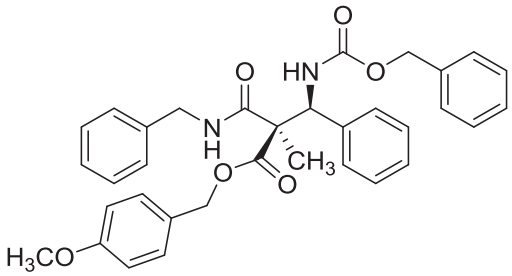
$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.33-7.23 (m, 8H), 7.02-7.00 (m, 2H), 6.20 (s, br, 1H), 5.85 (s, br, 1H), 5.03 (m, 1H), 4.34 (dd, *J* = 15 Hz, 6 Hz, 1H), 4.28 (dd, *J* = 15 Hz, 6 Hz, 1H), 2.74 (dd, *J* = 15 Hz, 5 Hz, 1H), 2.67 (dd, *J* = 15 Hz, 5 Hz, 1H), 1.40 (s, 9H).

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): 170.3, 155.4, 137.8, 128.7, 128.6, 127.5, 127.4, 127.3, 126.1, 79.5, 51.9, 43.4, 42.8, 28.4.

$\nu_{max}$ (neat)/cm$^{-1}$: 3383, 1737, 1686, 1495, 1343, 1245, 1155.

HRMS (ESI) *m/z*: calculated for $C_{21}H_{27}N_2O_3$ $[M+H]^+$ 355.2016; found, 355.2018.

Preparation of **4-methoxybenzyl (*R*)-(3-(benzylamino)-2-((S)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)-2-methyl-3-oxopropanoate (13)**



To a solution of *β*-amino thioester **11a** (63 mg, 0.105 mmol, 1 equiv.) in $CH_2Cl_2$ (0.1 ml) was added benzylamine (22.5 mg, 0.21 mmol, 2 equiv.) and the reaction was stirred at room temperature for 15 hours. All volatiles were removed and the crude product that was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$:MeOH of 99.5:0.5. Purification afforded a white solid (46.0 mg, 77% yield).

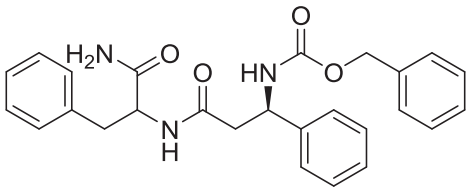
$^1$H-NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.25 (s, br, 1H), 7.36-7.23 (m, 11H), 7.19-7.13 (m, 2H), 7.13 (d, $J$ = 8.5 Hz, 2H), 7.07 (d, $J$ = 8.5 Hz, 2H), 6.92 (d, $J$ = 8.5 Hz, 2H), 5.31 (d, $J$ = 9.5 Hz, 1H), 5.14-5.03 (m, 4H), 4.43-4.31 (m, 2H), 3.86 (s, 3H), 1.67 (s, 3H). (major diastereoisomer)

$^{13}$C-NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 173.8, 170.9, 160.0, 156.1, 138.7, 137.6, 136.6, 130.7, 130.3, 128.6, 128.5, 128.3, 128.0, 127.9, 127.6, 127.4, 127.3, 126.6, 114.1, 67.7, 66.8, 60.0, 56.6, 55.4, 43.5, 22.4. (major diastereoisomer)

$\nu_{max}$ (neat)/cm$^{-1}$: 1716, 1652, 1515, 1496, 1241, 1175, 1108.

HRMS (ESI) *m/z*: calculated for $C_{34}H_{35}N_2O_6$ $[M+H]^+$ 567.2490; found, 567.2488.

Preparation of **benzyl ((1*R*)-3-((1-amino-1-oxo-3-phenylpropan-2-yl)amino)-3-oxo-1-phenylpropyl)-carbamate (14)**



A 0.5 ml microwave vial was charged with a solution of *β*-amino thioester **8a** (42.1 mg, 0.1 mmol, 2 equiv.) in pyridine (0.2 ml). H-Phe-$NH_2$ (8.2 mg, 0.05 mmol, 1 equiv.) was added and the sealed vial was heated to 80 °C for 1 hour in a microwave apparatus. The reaction was further stirred at room temperature for 18 hours. The crude mixture was dissolved in $CH_2Cl_2$ and was extracted with 1M HCl solution to remove pyridine. The organic phase was washed with brine, dried with $MgSO_4$ and all volatiles were removed at reduced pressure. The crude product was purified by flash column chromatography on silica gel using a mixture of $CH_2Cl_2$:MeOH of 95:5 and toluene as co-solvent. Purification afforded a white solid (39.7 mg, 89% yield) that forms a gel in a $CH_2Cl_2$.

$^1$H-NMR (400 MHz, DMSO, 25 °C): $\delta$ = 8.03 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.37-7.09 (m, 15 H), 5.02-4.91 (m, 3H), 4.43 (td, *J* = 8.5 Hz, 5 Hz, 1H), 2.93 (dd, *J* = 14 Hz, 5 Hz, 1H), 2.72 (dd, *J* = 14 Hz, 8.5 Hz, 1H), 2.58 (dd, *J* = 14.5 Hz, 8.0 Hz, 1H), 2.49 (dd, *J* = 14.5 Hz, 7 Hz, 1H).

$^{13}$C-NMR (100 MHz, DMSO, 25 °C): $\delta$ =173.3, 169.4, 155.7, 143.6, 138.3, 137.5, 129.5, 128.8, 128.6, 128.5, 128.20, 128.15, 127.3, 126.7, 126.6, 65.7, 54.0, 52.2, 42.8, 38.0.

$\nu_{max}$ (neat)/cm$^{-1}$: 3312, 3021, 1717, 1683.

MS (MALDI) *m/z*: calculated for: $C_{26}H_{28}N_3O_4$ $[M+H]^+$ 446.2074, found: 446.2074; $C_{26}H_{27}N_3NaO_4$ $[M+Na]^+$ 448.1894, found: 468.1894; $C_{26}H_{27}N_3KO_4$ $[M+K]^+$ 484.1633, found: 484.1633.

## 7.7.1 Solid Phase Peptide Synthesis with β-Amino Thioester Building Blocks

### 7.7.1.1 General Protocol for Solid Phase Peptide Synthesis

**Protocol A: Fmoc deprotection**

1 ml of a solution of 20% piperidine in DMF was added to the resin and the mixture was shaken for 10 minutes. After the removal of the solvent by filtration the procedure was repeated a second time for another 10 minutes. The solvent was removed and the resin was washed with DMF (3 x ca. 1.5 ml, 1-2 min) and $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min). The deprotection was checked by TNBS-test.[122]

**Protocol B1: Microwave assisted coupling with HCTU**

Boc protected amino acid (3 equiv.), $^{i}Pr_2NEt$ (3 equiv.) and HCTU (3 equiv.) were dissolved in DMF (4ml/g) and added to the pre swollen resin in a reaction vessel. The mixture was shaken for 10 minutes at 75 °C under microwave irradiation. After the solution was removed, the resin was washed with DMF (3 x ca. 1 ml, 1 - 2 min) and $CH_2Cl_2$ (5 x ca. 1 ml, 1 - 2 min). The completeness of the coupling was checked by TNBS-test.[122] The coupling protocol was repeated in cases where incomplete functionalization of the resin was observed.

**Protocol B2: Coupling with HCTU**

Fmoc protected amino acid (1.5 equiv.), $^{i}Pr_2NEt$ (4.5 equiv.) and HCTU (1.5 equiv.) were dissolved in DMF (4ml/g) and added to the pre swollen resin in a syringe equipped with a filter. The mixture was shaken for 2 h. After the solution was removed, the resin was washed with DMF (3 x ca. 1.5 ml, 1 - 2 min) and $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min). The completeness of the coupling was checked by TNBS-test.[122] The protocol was repeated in cases of incomplete coupling.

**Protocol C: Boc deprotection**

1 ml of a solution of 50% TFA in $CH_2Cl_2$ was added to the resin in a syringe equipped with a filter and the mixture was shaken for 5 minutes. After removal of the solvent by filtration the procedure was repeated a second time for 20 minutes. The solvent was removed and the resin was washed with $CH_2Cl_2$ (2 x ca. 1 ml, 1 - 2 min), IPA (2 x ca. 1 ml, 1 - 2 min) and $CH_2Cl_2$

(2 x ca. 1 ml, 1 - 2 min). The TFA salt was neutralized with 10% TEA in $CH_2Cl_2$ (2 x ca. 1 ml, 10 min) and washed with $CH_2Cl_2$ (2 x ca. 1 ml, 1 - 2 min), IPA (2 x ca. 1 ml, 1 - 2 min), $CH_2Cl_2$ (2 x ca. 1 ml, 1 - 2 min), IPA (2 x ca. 1 ml, 1 - 2 min), $CH_2Cl_2$ (2 x ca. 1 ml, 1 - 2 min), IPA (2 x ca. 1 ml, 1 - 2 min) and DMF (3 x ca. 1 ml, 1 - 2 min). The deprotection was checked by TNBS-test.[122]

**Protocol D1: Cleavage from TentaGel S-NH2 resin via methanolysis[186]**

The resin was washed with MeOH (2 x ca. 1ml, 1-2 min) and was transferred to a round bottom flask equipped with a magnetic stirrer. The resin was treated with 0.5 ml of 10% $Et_3N$ in MeOH anhydrous overnight. The suspension was filtrated and the filtrate was concentrated under reduced pressure.

**Protocol D2: Cleavage from Rink Amide AM resin with TFA**

The resin was washed with $CH_2Cl_2$ (2 x ca. 1.5ml, 1-2 min) and mixed with a solution of TFA in $CH_2Cl_2$ (2:1) for 2.5 h. After the solution was filtered, another quantity of TFA in $CH_2Cl_2$ (2:1) was added and the mixture was stirred for 30 min. The collected filtrates were evaporated under reduced pressure and $Et_2O$ was added to the residual oil upon peptide precipitation. The suspension was filtered and washed with $Et_2O$, and the solid was dried at high vacuum.

**Protocol E: Peptide synthesis by the Peptide synthesizer**

Rink Amide AM resin (200-400 mesh) (250 mg, 0.62 mmol/g) was placed into the reaction vessel. The calculated quantity of Fmoc protected amino acid was dissolved in DMF (0.5 M) and placed in the corresponding vessel. HCTU/DMF (0.5 M), $^{i}Pr_2NEt$/NMP (3 M) and 40% piperidine/DMF were also placed into the corresponding vessels.

**Protocol E1: Fmoc deprotection**

3 ml DMF were added to the resin, the vessel was shaken for 12 min and emptied in 1 min and 45 sec. 2.4 ml 40% piperidine in DMF were added, the vessel was shaken for 5 min and emptied in 1 min and 45 sec. 1.2 ml 40% piperidine in DMF and 1.2 ml DMF were added, the vessel was shaken for 10 min and emptied in 1 min and 45 sec. Finally, 3.6 ml DMF were

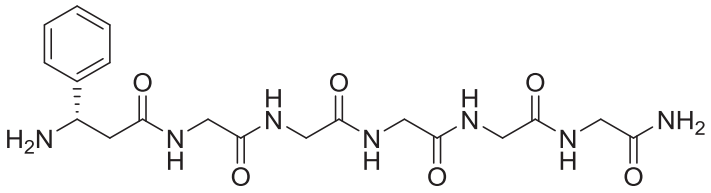
added, the vessel was shaken for 1 min and emptied in 1 min and 45 sec. The last step was repeated 4 times.

**Protocol E2: Coupling cycle**

1.2 ml (4eq) Fmoc-amino acid solution and 0.6 ml $^{i}Pr_2NEt$/NMP were added, the vessel was shaken for 1 h and emptied in 1 min and 45 sec. 3.6 ml DMF were added, the vessel was shaken for 1 min and emptied in 1 min and 45 sec. The last step was repeated 2 times and the amino acid was deprotected following protocol E1.

### 7.7.1.2 Coupling of thioester building blocks as *N*-terminal amino acids

Preparation of **H-$\beta^3$-Phe-[Gly]$_5$-NH$_2$**

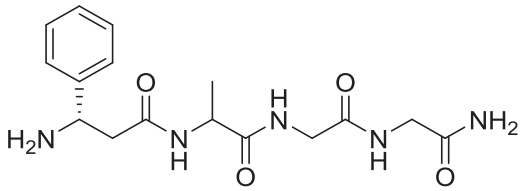


The peptide was synthesized on 25 mg Rink amide AM resin (200 – 400 mesh) resin (0.71 mmol/g, 17.7 μmol). The first five amino acids were assembled by the Peptidesynthesizer (protocol E) by coupling Fmoc-Gly-OH five times according protocols E1 and E2. The sixth coupling was performed with Boc-$\beta^3$-Phe-SPMP **5d** (41.2 mg, 106.5 μmol, 6 equiv.) and $^{i}Pr_2NEt$ (18.5 ml, 106.5 μmol, 6 equiv.) dissolved in pyridine (0.3 ml). The reaction mixture was added to the deprotected resin and the mixture was shaken for 1 hour at 75 °C under microwave irradiation followed by 18 hours at room temperature. After the solution was removed, the resin was washed with DMF (3 x ca. 1 ml, 1-2 min) and $CH_2Cl_2$ (5 x ca. 1 ml, 1-2 min). The peptide was cleaved from the resin (protocol D2) and the analysed by LC-MS.

MS (ESI) *m/z*: 450.2 $[M+H]^+$, M= 449.2 calculated for $C_{19}H_{27}N_7O_6$.

HPLC: Phenomenex 1.8 μm, gradient: $CH_3CN/H_2O$ 90% to 10% in 20 min, 50 °C, 1 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ = 1.6 min.

Preparation of **H-$\beta^3$-Phe-Ala-[Gly]$_2$-NH$_2$**

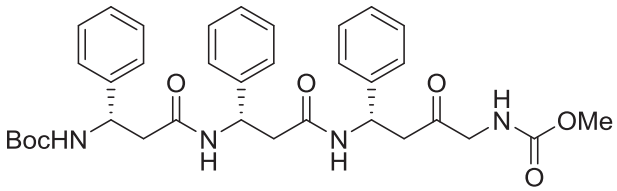


The peptide was synthesized on 25 mg Rink amide AM resin (200 – 400 mesh) resin (0.71 mmol/g, 17.7 μmol). The first three amino acids were assembled by the Peptidesynthesizer (protocol E) by coupling two times Fmoc-Gly-OH and once Fmoc-L-Ala-OH according protocols E1 – E2. The fourth coupling was performed with Boc-$\beta^3$-Phe-SPMP **5d** (41.2 mg, 106.5 μmol, 6 equiv.) and $^i$Pr$_2$NEt (18.5 ml, 106.5 μmol, 6 equiv.) dissolved in pyridine (0.3 ml). The reaction mixture was added to the deprotected resin and the mixture was shaken for 1 hour at 75 °C under microwave irradiation followed by 18 hours at room temperature. After the solution was removed, the resin was washed with DMF (3 x ca. 1 ml, 1 - 2 min) and $CH_2Cl_2$ (5 x ca. 1 ml, 1 - 2 min). The peptide was cleaved from the resin (protocol D2) and was analysed by LC-MS.

MS (ESI) *m/z*: 350.1 $[M+H]^+$, M= 349.2 calculated for $C_{16}H_{23}N_5O_4$.

HPLC: Phenomenex 1.8 μm, gradient: $CH_3CN/H_2O$ 90% to 10% in 8 min, 50 °C, 1 ml/min, UV detection $\lambda$ = 254 nm: $t_R$ = 0.5 min.

Preparation of **Boc-[$\beta^3$-Phe]$_3$-Gly-OMe**




The peptide was synthesized on 25 mg TentaGel-Gly-Fmoc resin (0.286 mmol/g, 7.15 μmol). After Fmoc deprotection (protocol A) the first and the second coupling cycles were performed with Boc-β$^3$-Phe-OH (5.07 mg, 21.5 μmol, 3 equiv.), HCTU (8.85 mg, 21.5 μmol, 3 equiv.) and $^i$Pr$_2$NEt (3.8 μl, 21.5 μmol, 3 equiv.) according protocol B1. the third coupling was performed with Boc-$\beta^3$-Phe-SPMP **5d** (16.6 mg, 42.9 μmol, 6 equiv.) and $^i$Pr$_2$NEt (7.5 μl, 42.9 μmol, 6 equiv.) dissolved in pyridine (0.2 ml). The reaction mixture was added to the deprotected resin (protocol C) and the mixture was shaken for 1 hour at 75 °C under microwave irradiation followed by 18 hours at room temperature. After the solution was removed, the resin was washed with DMF (3 x ca. 1 ml, 1 - 2 min) and $CH_2Cl_2$ (5 x ca. 1 ml, 1 - 2 min). The peptide was cleaved from the resin (protocol D1) and was analysed by LC-MS.

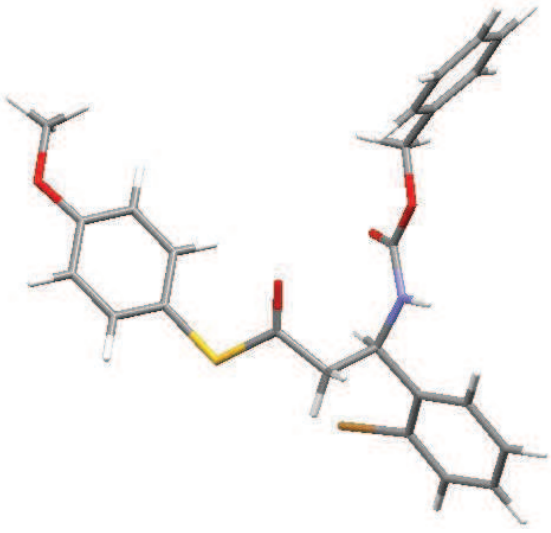
MS (ESI) *m/z*: 531.3 $[M\text{-Boc}+H]^+$, M= 630.3 calculated for $C_{35}H_{42}N_4O_7$; M-Boc= 530.3 calculated for $C_{30}H_{34}N_4O_5$.

HPLC: Phenomenex 1.8 μm, gradient: $CH_3CN/H_2O$ 90% to 10% in 20 min, 50 °C, 1 ml/min, UV detection λ = 254 nm: $t_R$ = 3.8 min.

## 7.8 X-Ray Crystallography

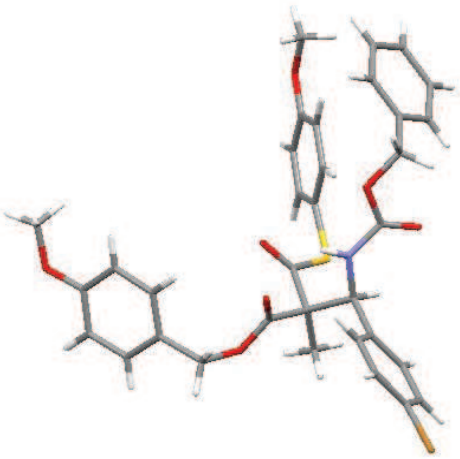
### (*3R*)-4-methoxyphenyl-3-(2-bromophenyl)-3-(benzyloxycarbonylamino)propanethioate (8b)

Crystal data for (*3R*)-4-methoxyphenyl-3-(2-bromophenyl)-3-(benzyloxycarbonylamino) propanethioate: formula $C_{24}H_{22}BrNO_4S$, M = 500.40, F(000) = 1024, colourless plate, size 0.020 x 0.160 x 0.160 $mm^3$, orthorhombic, spacegroup P 21 21 21, Z = 4, a = 5.0279(12) Å, b = 11.150(3) Å, c = 39.167(2) Å, α = 90°, β = 90°, γ = 90°, V = 2195.7(10) $Å^3$, $D_{calc.}$ = 1.514 $g/cm^3$. The crystal was measured on a Bruker Kappa Apex-II Duo diffractometer at 293(2)K using graphite-monochromated MoKα-radiation with λ = 0.71073 Å, Θmax = 27.56°. Minimal/maximal transmission 0.74/0.97, μ = 1.999 $mm^{-1}$. The Apex2 suite has been used for data collection and integration. From a total of 35672 reflections, 5080 were independent (merging r = 0.0734). From these, 4642 were considered as observed (I>2.0σ(I)) and were used to refine 281 parameters. The structure was solved by direct methods using the program SHELXS-97 (Sheldrick, 2008). Least-squares refinement against F was carried out on all non-hydrogen atoms using the program SHELXL-97 (Sheldrick, 2008). R = 0.0502 (observed data), wR = 0.0803 (all data), GOF = 1.727. Minimal/maximal residual electron density = -0.70/0.86 $eÅ^{-3}$.



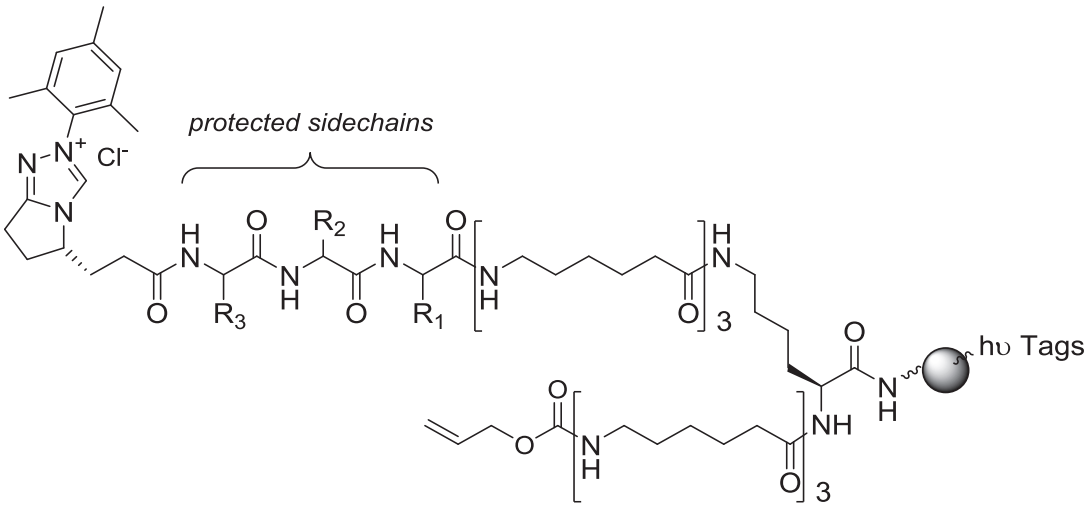
**(*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-bromo)phenyl-3-(benzyloxycarbonylamino)-propanethioat (11d)**

Crystal data for (*2S*,*3S*)-4-methoxyphenyl-2-(4-methoxy-benzyloxycarbonyl)-2-methyl-3-(4-bromo)phenyl-3-(benzyloxycarbonylamino)-propanethioat: formula $C_{34}H_{32}NO_7SBr$, M = 678.58, F(000) = 1400, colourless plate, size 0.16 x 0.025 x 0.005 $mm^3$, orthorhombic, spacegroup $P2_12_12_1$, Z = 4, a = 6.3038(3) Å, b = 21.1154(7) Å, c = 23.4035(8) Å, α = 90°, β = 90°, γ = 90°, V = 3115.2(2) $Å^3$, $D_{calc.}$ = 1.447 $mg/cm^3$. The crystal was measured on a Bruker Kappa Apex-II Duo diffractometer at 100.02 K using graphite-monochromated MoKα-radiation with λ = 0.71073 Å, Θmax = 27.56°. Minimal/maximal transmission 0.74/0.97, μ = 2.844 $mm^{-1}$. The Apex2 suite has been used for data collection and integration. From a total of 11811 reflections, 5316 were independent (merging r = 0.0339). From these, 5316 were considered as observed (I>2.0σ(I)) and were used to refine 400 parameters. The structure was solved by direct methods using the program SHELXS-97 (Sheldrick, 2008). Least-squares refinement against F was carried out on all non-hydrogen atoms using the program SHELXL-97 (Sheldrick, 2008). R = 0.0277 (observed data), wR = 0.0626 (all data), GOF = 1.008. Minimal/maximal residual electron density = -0.24/0.32 $eÅ^{-3}$.



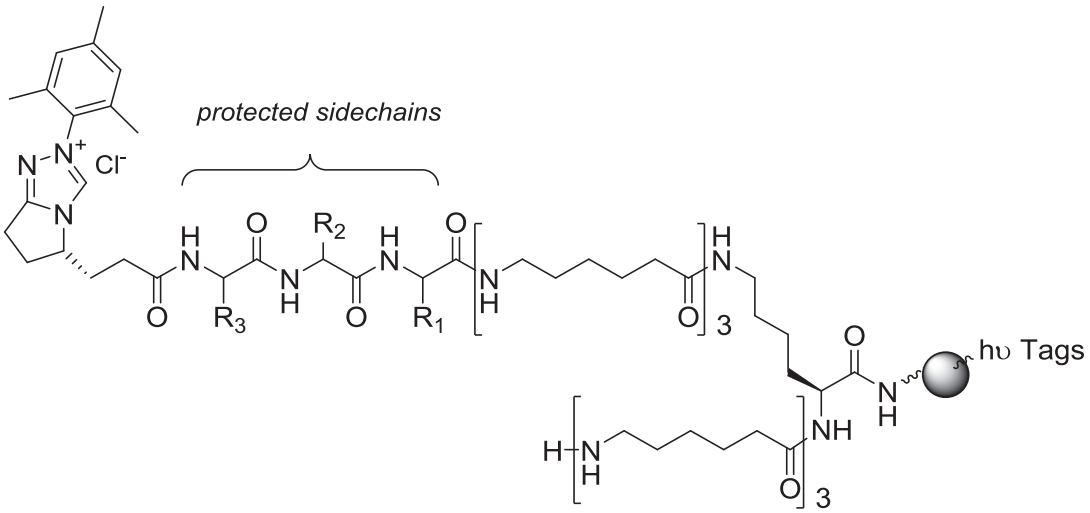
## 7.9 Preparation of the Tripeptidic Triazolium Salt Libraries

Tripeptidic triazolium salt library **B2**



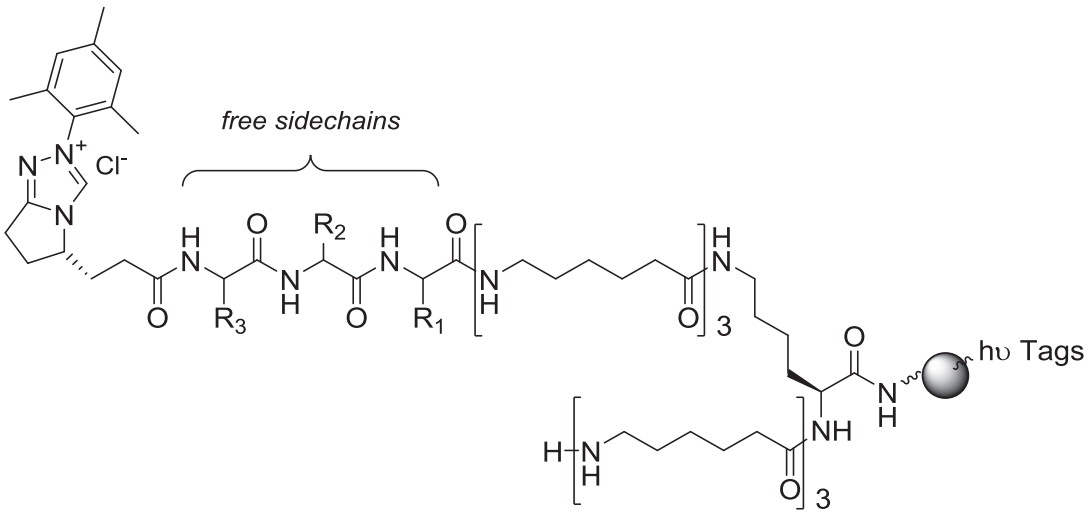

100 mg (0.26 mmol/g, 26 μmol, 1 equiv.) unfunctionalized tripeptide library **B** were placed into a 5 ml syringe equipped with a filter and were Fmoc deprotected (protocol A). Carboxylic acid functionalized triazolium salt **A** (52 μmol, 2 equiv.) was preactivated with DIC (52 μmol, 2 equiv.) and Oxyma (52 μmol, 2 equiv.) in DMF for 10 minutes. The solution was added to the resin and was shaken at room temperature for 2 hours. The reactants were removed and another 2 equiv. of activated A was added and the resin was shaken at room temperature over night. The resin was washed with DMF (5 x ca. 1.5 ml, 1-2 min), and $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min). The completeness of the deprotection was checked by TNBS- test.[122] The resin was dried *in vacuo* for 4 hours and was used without further purification.

Tripeptidic triazolium salt library **B3**



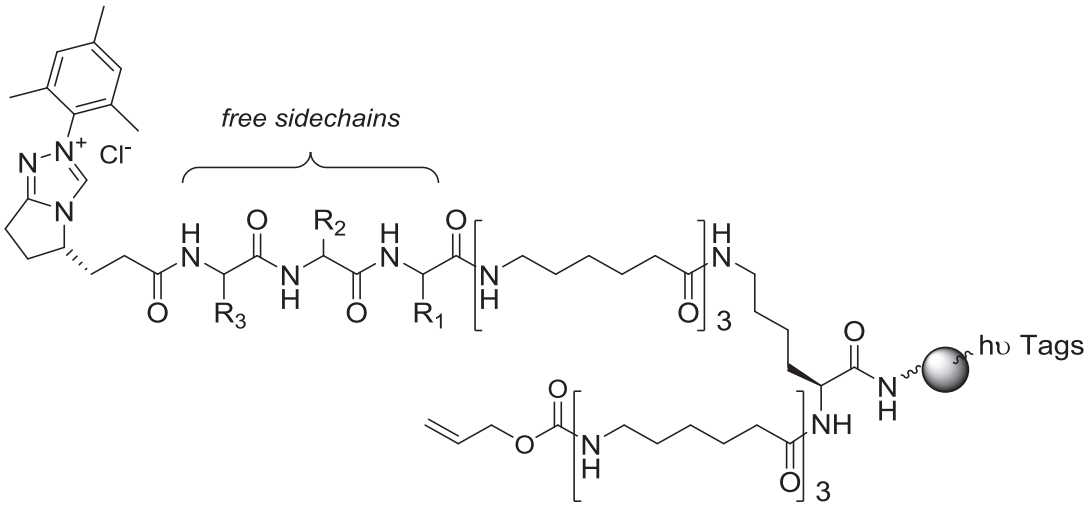
50 mg (0.26 mmol/g, 13 μmol, 1 equiv.) triazolium salt functionalized tripeptide library **B2** were placed into a 10 ml syringe equipped with a filter. The resin was washed with $CH_2Cl_2$ (3 x 5 ml, 1-2 min) followed by addition of 0.7 ml of a 1:1 mixture of abs. $CH_2Cl_2$ and DMF. The syringe was flushed with argon for 10 min. Diethylamine (2.7 μl, 260 μmol, 20 equiv.) and $Pd(PPh_3)_4$ (1.5 mg, 10 mol%) were added and the mixture was shaken for 2 h under argon. The solvent was removed and the resin was washed with DMF (3 x 5 ml, 1-2 min), a 0.5% solution of diethyldithiocarbamate trihydrate in DMF (5 x 5 ml, 1-2 min) and $CH_2Cl_2$ (5 x 5 ml, 1-2 min). The completeness of the deprotection was checked by TNBS- test.[122]

Tripeptidic triazolium salt library **B4**




4 mg (0.26 mmol/g, 1 μmol, 1 equiv.) triazolium salt functionalized tripeptide library **B3** were placed into a 2 ml syringe equipped with a filter. The resin was washed with $CH_2Cl_2$ (3 x 5 ml, 1-2 min) followed by addition of a 95:0.25:0.25 mixture of TFA:TIPS:$H_2O$ (3 x 1 ml, 5 min, 10 min, 2 h). The reaction mixture was shaken at room temperature. The solvent was removed and the resin was washed with $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min), 9:1 $CH_2Cl_2$/$NEt_3$ (5 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min) and DMF (3 x ca. 1.5 ml, 1-2 min). The resin was directly used for the combinatorial assays.

Tripeptidic triazolium salt library **B5**



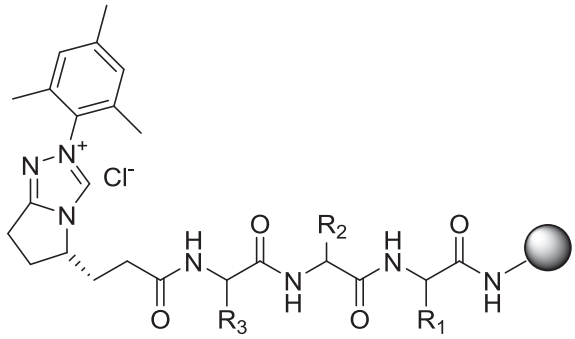

4 mg (0.26 mmol/g, 1 μmol, 1 equiv.) triazolium salt functionalized tripeptide library **B2** were placed into a 2 ml syringe equipped with a filter. The resin was washed with $CH_2Cl_2$ (3 x 5 ml, 1-2 min) followed by addition of a 95:0.25:0.25 mixture of TFA:TIPS:$H_2O$ (3 x 1 ml, 5 min, 10 min, 2 h). The reaction mixture was shaken at room temperature. The solvent was removed and the resin was washed with $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min), 9:1 $CH_2Cl_2$/$NEt_3$ (5 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min) and DMF (3 x ca. 1.5 ml, 1-2 min). The resin was directly used for the combinatorial assays.

## 7.10 Protocol for the Combinatorial Assays

Ca. 4 mg of the library **B2**, **B4** or **B5** (1 μmol, 1.0 eq.) were weighed in a 2 ml syringe equipped with a filter and were pre swollen in methylene chloride. The pre swollen resin was transferred to a 2 ml Eppendorf vial followed by addition of 1 ml of a solution of dye marked 2-formylcyclopropanecarboxylate **C** (2.5 mM, 2.5 eq.) in methylene chloride and 0.6 μl DBU (4 μmol, 4.0 equiv.). After shaking the mixture at 35 °C for 18 h, the solvent was removed and the beads were intensively washed according to the following protocol: $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min), triethylamine/$CH_2Cl_2$ (1:9) (5 x ca. 1.5 ml, 1-2 min), MeOH (5 x ca. 1.5 ml, 1-2 min), $NH_2OH$*HCl (1.5 mg in 1 ml DMF) (3 x ca. 1 ml, 1 x 20 min, 2 x 10 min), DMF (3 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (2 x ca. 1.5 ml, 1-2 min), TFA/ $CH_2Cl_2$ (1:3) (2 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (3 x ca. 1.5 ml, 1-2 min), MeOH (3 x ca. 1.5 ml, 1-2 min), DMF (3 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (3 x ca. 1.5 ml, 1-2 min). The beads were transferred to a microscope slide and a drop of decane was added. Red coloured beads were separated under the microscope and transferred to another slide in order to compare them with each other. The most intensively coloured beads were placed in single 20 μl capillaries which were melted on one end afterwards. The beads were centrifuged to the closed end of the capillary and were washed with DMF (3 x 3 μl) whereas the washing liquid was removed after each centrifugation step with a syringe. After the addition of 3 μl DMF the capillaries were melted on the other end and placed in UV light for 2 h to liberate the tags. The alcohol groups in the tag solution were silylated *in situ* with 1 μl BSA and the solutions were analysed with GC-ECD (temperature gradient: 200-320°C in 11 min).

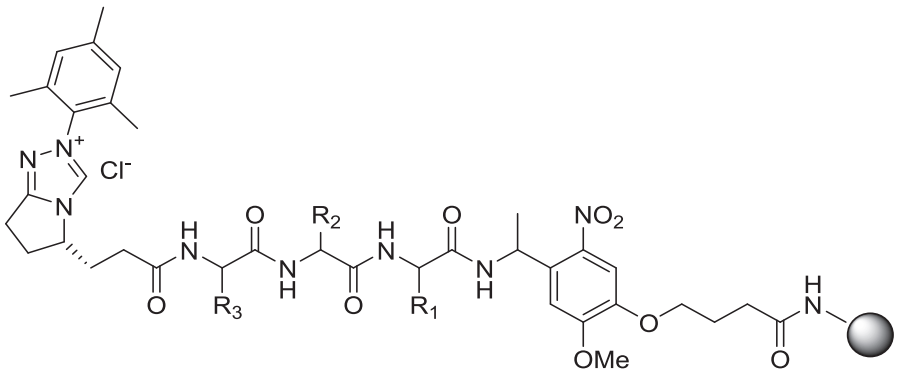
## 7.11 Protocol for the Synthesis of Solid Supported Peptidic Triazolium Salts

### 7.11.1 Synthesis on TentaGel S-$NH_2$ resin



The solid supported peptidic triazolium salt was synthesized on Tentagel S-$NH_2$. The solid supported tripeptides were first prepared by the Peptidesynthesizer (protocol D) with 20 mg Tentagel S-$NH_2$ resin (0.29 mmol/g; 5.8 μmol, 1 eq.). Fmoc deprotections were performed according protocol D1 and amino acid coupling cycles according protocol D2. Carboxylic acid functionalized triazolium salt **A** was preactivated with DIC (11.6 μmol, 1.5 equiv.) and Oxyma (11.6 μmol, 1.5 equiv.) in DMF for 10 minutes. The solution was added to the resin and was shaken at room temperature over night. If a TNBS test revealed incomplete coupling, another 1.5 equiv. of activated **A** was added and the resin was shaken at room temperature for 3 h. The resin was washed with DMF (5 x ca. 1.5 ml, 1-2 min), and $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min). The side chains protecting groups were removed upon addition of TFA:TIPS:$H_2O$ (95:2.5:2.5) (3 x 3 ml, 5 min, 2 h). The resin was washed with $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min), 9:1 $CH_2Cl_2$/$NEt_3$ (5 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min) and MeOH (3 x ca. 1.5 ml, 1-2 min). The resin was dried *in vacuo* over night and was used without further purification.

### 7.11.2 Synthesis on TentaGel S-$NH_2$ resin with photolabile linker



The solid supported peptidic triazolium salt was synthesized on 20 mg Tentagel S-$NH_2$ (0.29 mmol/g; 5.8 μmol, 1 eq.) in a photoresist syringe. After Fmoc deprotection (protocol A) the first coupling cycle (protocol B2) was performed with 4-[4-[1-(Fmoc)ethyl]-2-methoxy-5-nitrophenoxy]butanoic acid (4.5 mg, 8.7 μmol), HCTU (10.8 mg, 26.1 μmol) and $^{i}Pr_2NEt$ (1.5 μl, 8.7 μmol). The tripeptides were then coupled by the Peptidesynthesizer (protocol D). Fmoc deprotections were performed according protocol D1 and amino acid coupling cycles according protocol D2. Carboxylic acid functionalized triazolium salt **A** was preactivated with DIC (11.6 μmol, 1.5 eq.) and Oxyma (11.6 μmol, 1.5 eq.) in DMF for 10 minutes. The solution was added to the resin and was shaken at room temperature over night. If a TNBS test revealed incomplete coupling, another 1.5 equiv. of activated **A** was added and the resin was shaken at room temperature for 3 h. The resin was washed with DMF (5 x ca. 1.5 ml, 1-2 min), and $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min). The side chains protecting groups were removed upon addition of TFA:TIPS:$H_2O$ (95:2.5:2.5) (3 x 3 ml, 5 min, 2 h) The resin was washed with $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min), 9:1 $CH_2Cl_2$/$NEt_3$ (5 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min) and MeOH (3 x ca. 1.5 ml, 1-2 min). The resin was dried *in vacuo* over night and was used without further purification.

## 7.12 Protocol for Redox Amidation Reactions

The solid supported tripeptidic triazolium salt (10 mg, 2.9 μmol, 0.2 equiv) was placed into a 2 ml Eppendorf vial and methylene chloride (0.075 M), ethyl-2-formylcyclopropane-carboxylate (15 μmol, 1 equiv.) and DBU (2.9 μmol, 0.2 equiv.) were added. The mixture was shaken at 35 °C for 30 minutes followed by addition of morpholine (15 μmol, 1 equiv.). The mixture was shaken at 35 °C for 18 hours. The solution was filtered from the resin and the filtrate was concentrated *in vacuo*. The conversion in the crude mixture was analysed by $^{1}$HNMR by our collaborators.

## 7.13 Protocol for the Intramolecular Acyl Transfer Reactions

Tripeptidic triazolium salt via photocleavable linker bound to resin (10 mg, 2.9 μmol, 0.2 equiv.) was placed into a photoresist 2 ml Eppendorf vial and methylene chloride (0.075 M), ethyl-2-formylcyclopropanecarboxylate (15 μmol, 1 equiv.) and DBU (2.9 μmol, 0.2 equiv.) were added. The mixture was shaken at 35 °C for 2 hours. The solvent was removed and the beads were intensively washed according to the following protocol: $CH_2Cl_2$ (5 x ca. 1.5 ml, 1-2 min), triethylamine/$CH_2Cl_2$ (1:9) (5 x ca. 1.5 ml, 1-2 min), MeOH (5 x ca. 1.5 ml, 1-2 min), $NH_2OH$*HCl (1.5 mg in 1 ml DMF) (3 x ca. 1 ml, 1 x 20 min, 2 x 10 min), DMF (3 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (2 x ca. 1.5 ml, 1-2 min), TFA/ $CH_2Cl_2$ (1:3) (2 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (3 x ca. 1.5 ml, 1-2 min), MeOH (3 x ca. 1.5 ml, 1-2 min), DMF (3 x ca. 1.5 ml, 1-2 min), $CH_2Cl_2$ (3 x ca. 1.5 ml, 1-2 min). The resin was transferred to a capped vial and acetonitrile was added. The vial was placed in UV light for 2 h. The solution was filtered from the resin and was analysed by our collaborators by LCMS and MALDI to determine the amount of acylation.

# 8 Abbreviations

| | |
|---|---|
| AA | amino acid |
| Aaa | arbitrary amino acid |
| Alloc | Allyloxycarbonyl |
| Bn | benzyl |
| Boc | *tert.*-butyloxycarbonyl |
| $Boc_2O$ | *di-tert*.-butyl dicarbonate |
| BSA | *N,O*-Bistrimethylsilylacetamide |
| CAN | cerium ammonium nitrate |
| Cbz | benzyloxycarbonyl |
| $CDCl_3$ | deuterated chloroform |
| $CH_2Cl_2$ | dichlormethane |
| $CH_3CN$ | acetonitrile |
| $CHCl_3$ | chloroform |
| CoA | coenzyme A |
| conv. | conversion |
| d | doublet |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-Diazabicycloundec-7-ene |
| DCC | (*N,N*)-Dicyclohexylcarbodiimide |
| DCU | dicyclohexylurea |
| DIAD | Diisopropyl azodicarboxylate |
| DIC | (*N,N*)-Diisopropylcarbodiimide |
| DMAP | 4-Dimethylaminopyridine |
| DMF | (*N,N*)-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DPPA | diphenyl phosphorazidate |
| dr | diastereomeric ratio |
| E | electrophile |
| ECD | electron capture detection |
| EDCI | *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide |
| ee | enantiomeric excess |
| equiv. | equivalents |

| | |
|---|---|
| ESI | electron spray ionisation |
| Et | ethyl |
| $Et_3N$ | triethyl amine |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| EVE | ethyl vinylether |
| EWG | electron withdrawing group |
| Fmoc | 9-fluorenylmethoxycarbonyl |
| GC | gas chromatography |
| H | proton |
| HCl | hydrochloric acid |
| HCTU | 2-(6-Chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate |
| $H_2O$ | water |
| HOAt | *N*-Hydroxy 7-azabenzotriazole |
| HOBt | *N*-Hydroxy benzotriazole |
| HPLC | high performance liquid chromatography |
| IPA | *iso*-propanol |
| $^{i}Pr_2NEt$ | *N*-Ethyldiisopropylamine |
| $^{i}PrOH$ | *iso*-propanol |
| IR | infra red |
| J | coupling constant |
| m | multiplet |
| M | molar |
| $[M]^+$ | molecule cation |
| MAHO | malonic acid halfoxoester |
| MAHT | malonic acid halfthioester |
| Me | methyl |
| MeOH | methanol |
| MHz | megahertz |
| mol% | molar ratio in percent |
| MS | mass spectrometry |
| MTM | mono thiomalonate |
| $NaHCO_3$ | sodium hydrogen carbonate |

| | |
|---|---|
| NCL | native chemical ligation |
| NHC | *N*-heterocyclic carbene |
| NMM | *N*-methylmorpholine |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| Oxyma | ethyl 2-cyano-2-(hydroxyimino)acetate |
| PfpOH | pentafluorophenol |
| Ph | phenyl |
| p$K_a$ | acid dissociation constant |
| PKS | polyketide synthase |
| ppm | part per million |
| PhBox | 2,2-isopropylidenebis(4-phenyl-2-oxazoline) |
| PMB | *para*-methoxy benzyl |
| PMP | *para*-methoxy phenyl |
| q | quartet |
| quant. | quantitative |
| $R_f$ | retention factor |
| RT | room temperature |
| s | singlet |
| SPPS | solid phase peptide synthesis |
| Ts | toluyl sulfonyl |
| TS | triazolium salt |
| t | triplet |
| $^t$Bu | *tert.*-butyl |
| $^t$BuOH | *tert.*-butanol |
| TFA | trifluoroacetic acid |
| TG | TentaGel |
| THF | tetrahydro furan |
| TLC | thin layer chromatography |
| TMS | trimethyl sillyl |
| TNBS | trinitrobenzenesulfonic acid |
| $t_R$ | retention time HPLC |
| UV | ultraviolet |

# 9 Literature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