Mono Thiomalonates as Thioester Enolate Equivalents – Organocatalytic Stereoselective Addition Reactions to Different Electrophiles

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MY FAMILY and ERICA

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Köln, 4-7 November 2009, (R)EVCAT meeting, "Organocatalysis Inspired by Polyketide Synthases".

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CONTENTS

1. Introduction

Many molecules contain one or more stereocenters. Most of the naturally occurring compounds such as amino acids and sugars are chiral and all kingdoms of life rely on the use of chiral enantiomerically pure substrates. The biological activity as well as the chemical and physical properties of different molecules are related to their stereochemistry. The activity of a biologically active compounds, for example, depends on the interaction of that active compound with cells. It is intuitive that different enantiomers would have different interactions with the chiral and enantiomerically pure components of the cells. For example, limonene, a cyclic terpene possessing one stereocenter is naturally occurring as both enantiomers. Whereas (+)-limonene induces a strong fragrance of orange upon interaction with the flavour receptors of the nose, (-)-limonene instead is responsible for the flavour of pine trees.[1]

This example shows the importance of stereochemistry and enantiopurity. Drugs with complex complex architectures, possessing many stereocenters, could originate various undesired effects when the "wrong" stereoisomer interacts with living organisms inducing a detrimental biological effect. Thus, chiral enantiomerically pure molecules need to be synthesised with a high level of stereoselection in order to avoid mixtures of stereoisomers that could be toxic or have side effects when in contact with living organisms.

Thioesters occur in nature as building blocks for the *in vivo* synthesis of biologically active compounds. Thioester-containing molecules are the equivalents of activated carboxylic acids and can undergo a wide range of modifications. One of the most well known examples is the addition reaction of malonyl-S-CoA to acetyl-S-CoA to generate polyketides or fatty acids.[2]

Synthetic chemists had a general and broad interest in thioesters for many years. The synthetic versatility of this functional group is one of the key features that attracted the attention of chemists and led to several methods for synthesising aldehydes, ketones or amides starting from thioesters that are well established and utilised on a regular basis.[3-6]

Asymmetric synthesis emerged as an important field in synthetic chemistry. Starting from achiral substrates, chiral molecules are synthesised in a catalysed chemical

transformation. Chiral enantiomerically pure catalysts contain the stereochemical information; they promote the desired reaction and induce the preferential formation of one stereoisomer over the possible others.

In the last fifteen years asymmetric organocatalysis emerged as a new field.[7] Organocatalysts do not possess metallic centres and they were proven to be able to promote a huge variety of reactions.

The objective of this thesis is to establish efficient way to promote the addition of thioester enolates with various electrophiles under mild organocatalytic reaction conditions.

Thioester enolates have typically low reactivity towards electrophiles due to the relatively low acidity of the protons in the α-position of the carbonyl group, therefore there is a need for robust thioester enolate equivalents that react readily with electrophiles in the presence of small amounts of an organocatalyst to form the addition products in high yield and stereoselectivities. In this thesis we want to demonstrate the utility of monothiomalonates (MTMs) as a new class of thioester enolates equivalents specifically designed to tackle the low reactivity of thioesters towards bases. We envisioned that the presence of both a thioester and a regular ester attached to the same methylidene would increase the acidity of this position.

The newly designed molecules were envisioned to provide the addition products with a big variety of electrophiles. The value of MTMs is demonstrated in asymmetric organocatalytic 1,4-conjugate addition reaction with nitroolefins providing chiral γ-nitrothioesters in excellent yields and stereoselectivities.

These compounds are densely functionalised and possess unique chemical properties. In fact, all of the obtained products are valuable building blocks for further transformations, thus making strategies exploiting these thioester enolates very appealing for synthetic purposes.

Finally, MTMs are tested also for their organocatalytic addition reactions to other electrophiles such as diazodicarboxylaes, α,β-unsaturated sulfones or maleimides to expand the utility of this new class of nucleophiles thereby providing synthetic protocols for the synthesis of biologically active compounds or small natural compounds.

2. Thioester Enolates in organic synthesis

2.1 Synthetic versatility of thioesters

Thioesters are interesting functional groups. They can be easily converted into a big variety of other functional groups such as ketones, aldehydes or amides using well-established synthetic procedures (Figure 1).

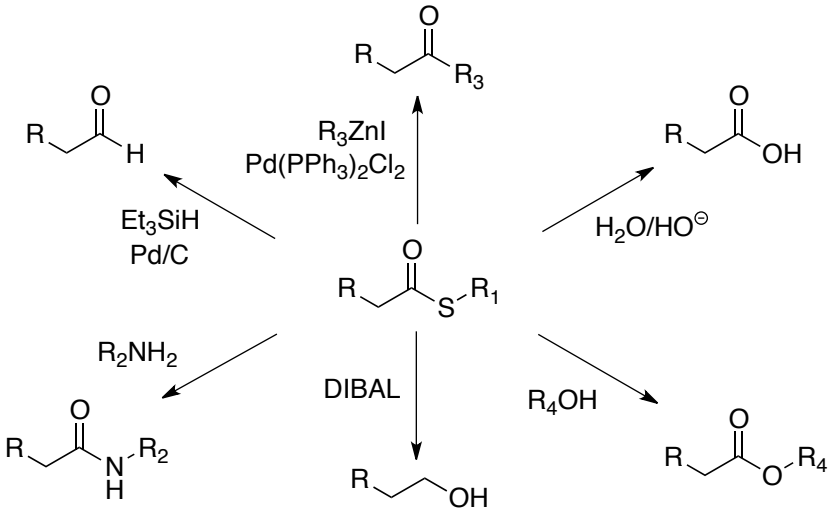
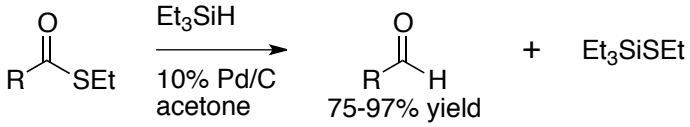


Figure 1. Transformations of thioesters in other functional groups

Fukuyama and co-workers developed synthetic procedures to synthesize, for example, aldehydes or ketones starting from thioesters.[3-6]

Aldehydes are accessible from thioester by their partial reduction using silanes in the presence of catalytic amounts of palladium under mild and neutral conditions (Scheme 1).[3]

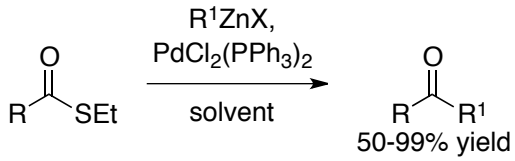


Scheme 1. Fukuyama reduction

These neutral and mild conditions resulted in a broad functional group tolerance. Esters, ethers, double bonds, amines or acetals were unreactive under the reaction conditions.

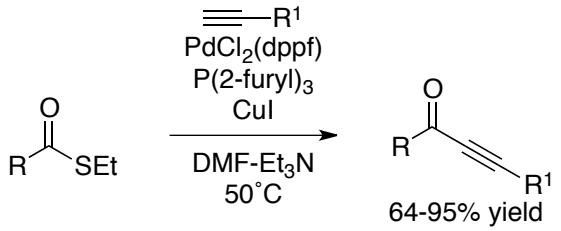
The Fukuyama coupling allows for the reduction of thioesters to ketones using organozinc reagents in the presence of a homogeneous palladium catalyst. Zinc

reagents are mild enough to only partially reduce the thioesters to the ketones without generation of tertiary alcohols.[4] These examples underline the mild conditions and the broad functional group tolerance of these transformations. A big variety of thioesters and organozinc reagents can be used to generate the desired ketones in synthetically useful yields (Scheme 2).[4]



Scheme 2. Fukuyama coupling

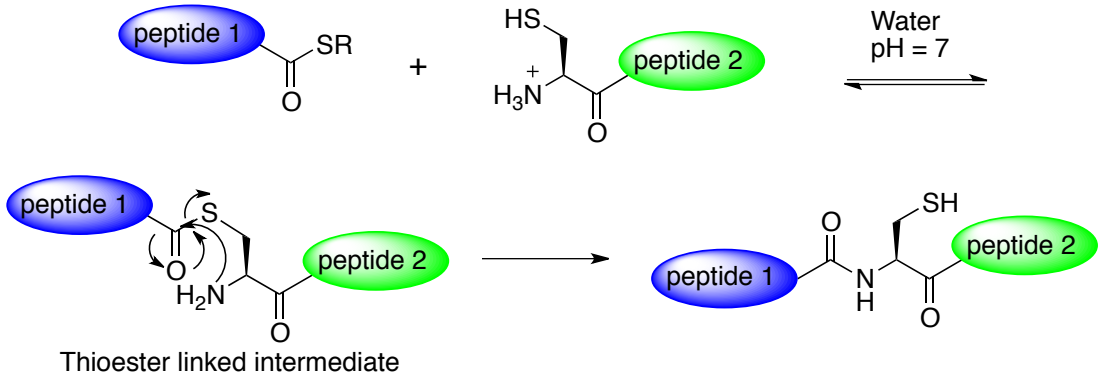
Alkynyl derivatized ketones can also be synthesised using a palladium-catalysed, copper-mediated addition of terminal alkynes to thioesters (Scheme 3).[5]



Scheme 3. Alkynylation reaction of thioesters

Native chemical ligation is an array of techniques in which the reactivity of thioesters is used for the generation of long and difficult peptides.

Two peptidic segments, containing a C-terminal thioester and a N-terminal cysteine, are reacted by means of reversible thiol/thioester exchange to yield thioester-linked products. The N-terminal cysteine is then able to undergo nucleophilic rearrangement by highly favoured, intramolecular and irreversible mechanism. Thus, the displacement of the thioester linkage with the subsequent formation of a native amide bond allows for the coupling of two long peptidic sequences. In most cases only a single product is observed since the nucleophilic displacement of the thioester linked intermediate is thermodynamically favoured only for the primary amine of the N-terminal cysteine (Scheme 4).[8]



Scheme 4. Native chemical ligation

2.2 Reactivity of thioesters towards bases and nucleophiles

Thioesters allow for reactivity at their α-position as they can be deprotonated, thus generating thioester enolates, which can be used as nucleophilic species for addition reactions with electrophiles.

In the scale of acidity of α-protons to different carbonyl-containing compounds, thioesters have pk_a values in the same range as ketones (Figure 2).[9]

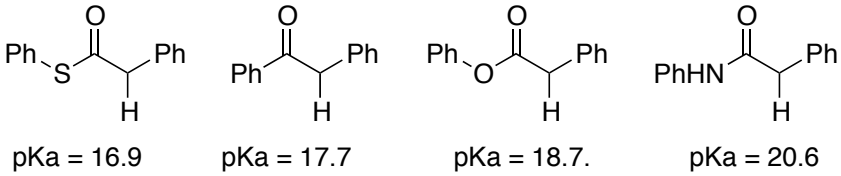


Figure 2. pKa values of the α-protons of various carbonyl compounds

The reason for this distinctly higher acidity compared to regular esters lies in the sulphur atom. Despite the lower electronegativity of sulphur compared to oxygen its ability to be engaged in resonance structures with the neighbouring C=O group is lower. This is due to the bigger atomic radius of sulphur and its possibility to access the 3d orbitals so that the electronical repulsion of the two lone pairs is lower than for oxygen resulting in a different hybridization of the valence orbitals.[10] Typically the substituents of the sulphur are arranged in angles close to 90° in contrast to the classic tetrahedral arrangements observed for the elements of the second row of the periodic table. All of these features decrease the +M effect of the sulphur, reducing then the electron density on the neighbouring carbonyl group and therefore allowing for a better charge stabilization compared to regular esters when the enolate is generated upon deprotonation.

All of the features described above, however, are responsible for the reactivity of thioesters towards nucleophiles. Lower delocalization of the lone pairs of the sulphur towards the carbonylic group increases its electrophilic character. Moreover, the negative charge, generated upon nucleophilic substitution at the acylic position, as well as the partial charges generally postulated for the transition states, can be delocalized within bigger orbitals of the atom (Figure 3).

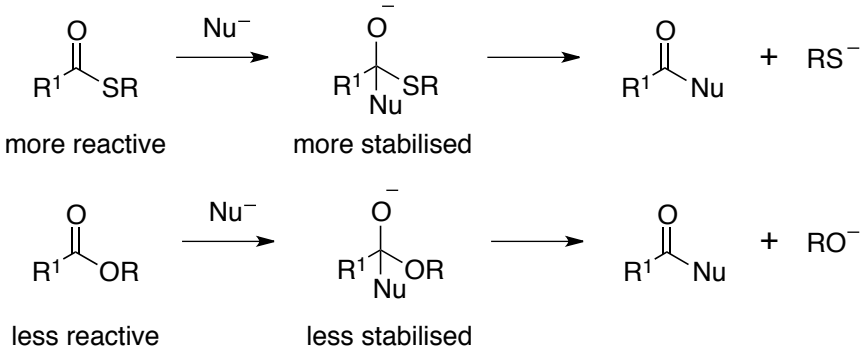


Figure 3. Relative reactivity of thioesters and regular esters towards nucleophilic acylic substitution

Further stabilization arises from the empty energetically accessible 3d orbitals that belong to the same shell as the valence electrons.[10] These features make thiols good leaving groups. It is therefore easy to convert thioesters into amides because of their higher stability. A comparison of the reactivity of carboxylic acid derivatives towards nucleophilic substitution places thioesters between regular esters and anhydrides (Figure 4).

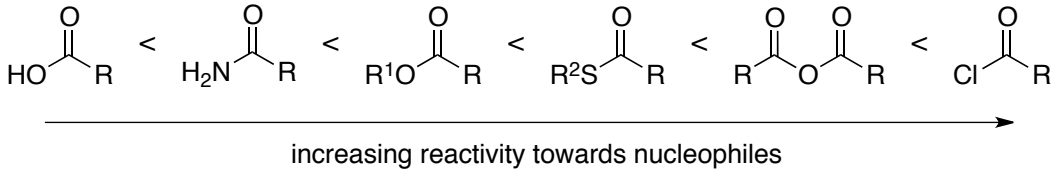
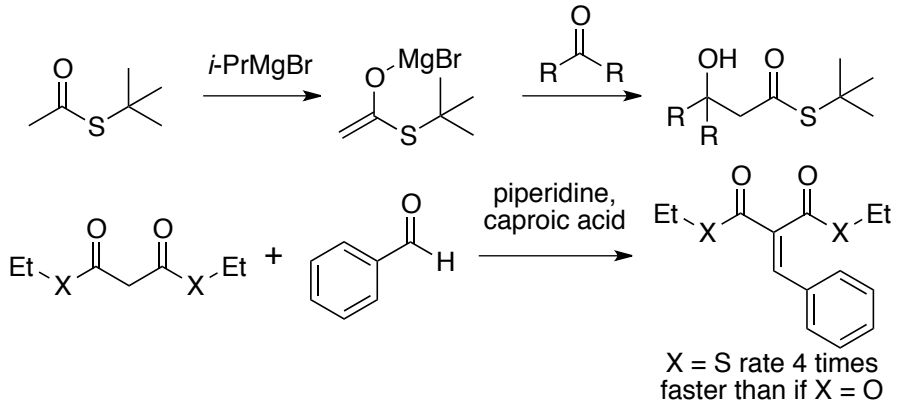


Figure 4. Relative reactivity of acyl compounds towards nucleophiles

All of the features described so far confer to thioesters a special role in organic chemistry. Their deprotonation at the α-position could be carried out using weaker bases in comparison to e.g. esters, allowing for the generation of their enolates under relatively mild conditions. However, their ability to undergo nucleophilic acylic substitution renders the generation of thioester enolates very challenging in terms of chemoselectivity and lability of the starting materials.

2.3 Lewis acid-based thioester enolate equivalents

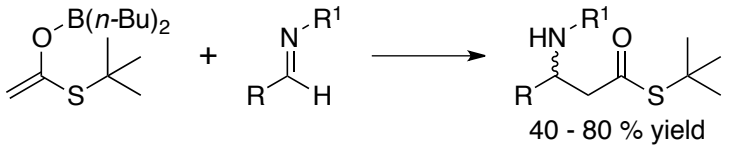
Several procedures, utilising thioester enolates as nucleophiles, have been developed over the last century. Cronyn and co-workers published a systematic study on the reactivity of thioesters in 1955.[11] They investigated the reactivity at the α-position of thioesters. The findings reported showed that S-*t*-butyl thioesters in contrast to analogous O-*t*-butyl esters form the Mg-enolate in the presence of *iso*-propyl magnesium bromide. This enolate reacted with ketones in a Reformatsky-type reaction. Additionally, the Knoevenagel condensation of di-thiomalonates was found to be four times faster compared to the same reaction using malonates as nucleophiles. This experimental evidence is consistent with the increased acidity of the proton in the α-position of thioester that allows for a fast generation of thioester enolates thereby inducing faster reaction rates compared to the case of regular esters (Scheme 5).



Scheme 5. Reactivity of thioesters in the presence of Grignard reagents and Knoevenagel condensation

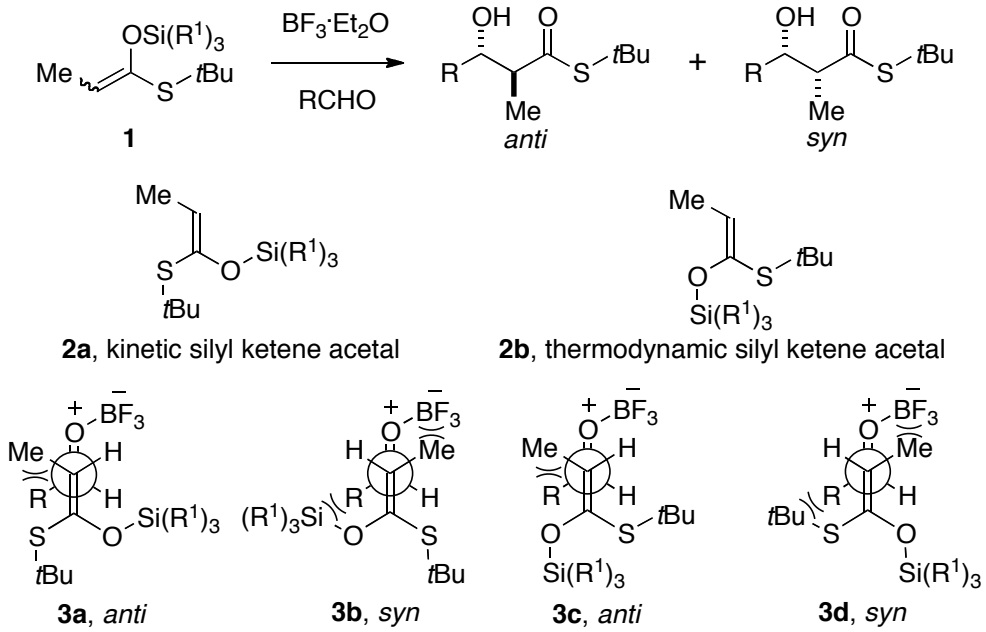
Ohno *et al.* aimed at the development of an efficient total synthesis of bleomycin and studied the addition of different enolates to imines.[12] Different ways were investigated for the generation of enolates. The enolates, generated upon decarboxylation of half esters of malonic acid, always produced large amounts of side products. The acetylated alcohol that is generated upon decarboxylation without the concomitant C-C bond formation was always recovered as the main side product. The desired adduct could only be isolated in rather low yields. The solution to the problem was achieved when vinyloxyborane was used for the generation of thioester silyl ketene acetals. The thioester enolate generated in this manner reacted smoothly with

imines to yield the desired β-amino thioesters that could then be used to perform the total synthesis (Scheme 6).



Scheme 6. Ohno's addition of boron ketene acetals to imines

Also Gennari and co-workers contributed to the investigation of thioester enolates with a series of extensive studies on the reactivity of different thioester enolates towards various electrophiles.[13] These elegant studies were aimed at the clarification of the parameters that influence the stereoselectivity of the Lewis acid mediated addition of thioester silyl ketene acetals **1** to aldehydes. They proposed a reaction mechanism involving the formation of pinwheel shaped intermediates **3a-d** between thioester silyl ketene acetals and aldehydes. The minimization of steric interactions leads to the formation of the products with high diastereomeric ratios in favour of the *anti* adduct no matter if kinetic **2a** or thermodynamic enolate **2b** was used (Scheme 7).[13a]

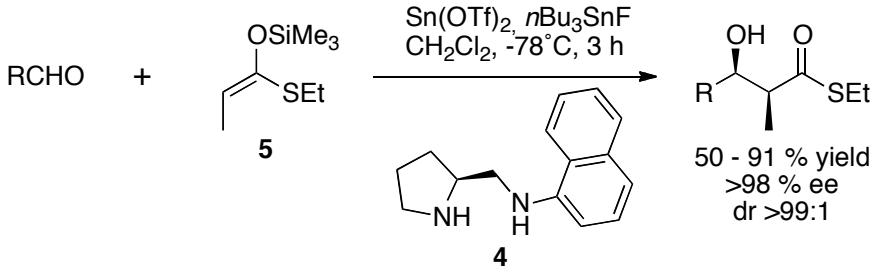


Scheme 7. Thioester ketene silyl acetals addition to aldehydes

Later, the same group demonstrated that the use of chiral Lewis acid can also induce enantioselectivity in the products.[13b] The lessons learned from these studies were

applied later in the key step of a semisynthesis of taxol[13c] and in the development of an efficient procedure for the synthesis of polyketides.[13d]

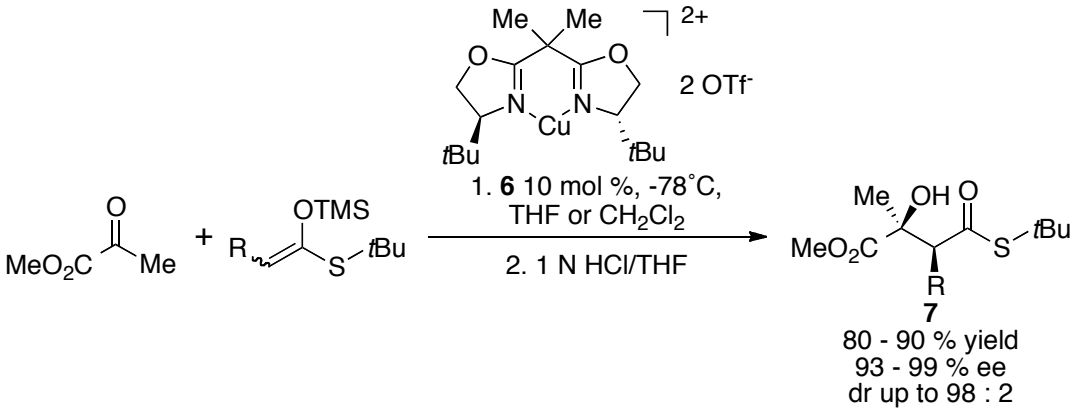
Kobayashi and co-workers played a crucial role in the development of new Lewis acid based addition reactions of thioester enolate equivalents to electrophiles. For example, his research group used E-silyl ketene acetals derived from thioesters as nucleophiles for the addition to aldehydes. Stoichiometric amounts of tin(II) triflates together with chiral diamines **4** and tributyltin fluoride promoted the addition of compound **5** to aldehydes.[14] An optimisation of the structure of the amine decreased the reaction time with higher yields and excellent stereoselectivity of the reaction. While the substrate scope for the aldehyde component is broad the methodology is only applicable to methyl substituted thioester silyl ketene acetals and large amounts of metal salts as well as diamine ligands are required to reach complete conversion of the starting materials. Additionally, Z-silyl ketene acetals proved to be poor substrates yielding the products in low yield and selectivities (Scheme 8).



Scheme 8. Tin triflate mediate addition of silyl ketene acetals to aldehydes

Evans also investigated thioester silyl ketene acetals. For example, a contribution that appeared in 1999 dealt with the copper-catalysed addition of thioester enolates to pyruvate esters. 10 mol % of the *tert*-butyl box-Cu(II) complex **6** catalysed the conversion of pyruvates to the products **7**. Optimal conditions include 10 mol % of the copper-box complex at -78˚C in THF (Scheme 9).[15] Under these conditions the obtained products had excellent levels of enantioselectivity and diastereoselectivity and sometimes a single enantiomer was isolated. It is also important to state that in the course of the reaction a quaternary stereogenic centre was formed adjacent to a tertiary stereogenic centre. Efficient catalytic procedures for the stereoselective generation of quaternary stereogenic centres are still rare due to the high steric demands of the four different substituents connected through the same C-atom. However this catalytic system was proven to be very efficient and provided an elegant

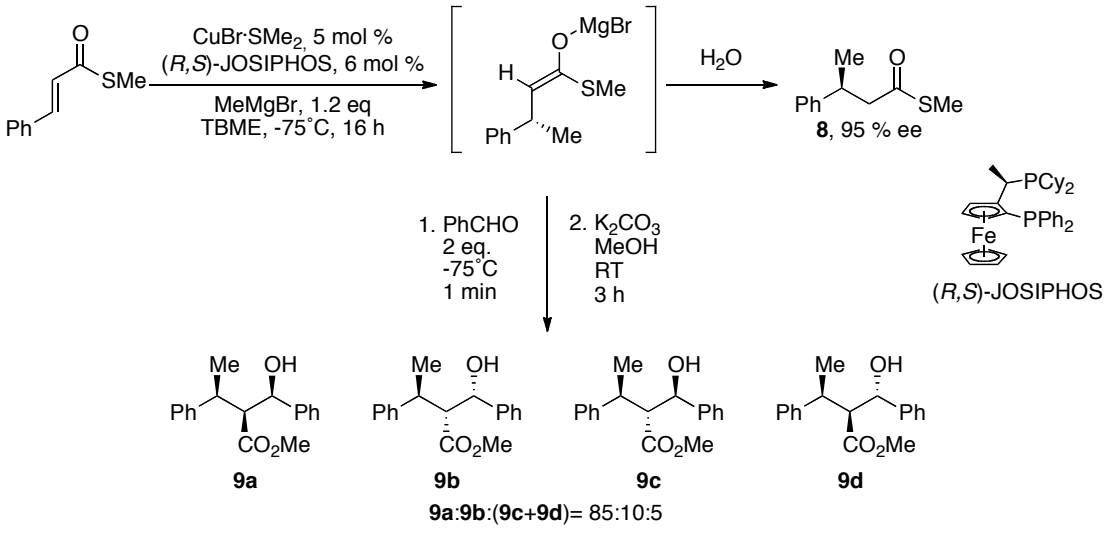
and effective solution for the stereoselective generation of quaternary stereogenic centres.



Scheme 9. Copper catalysed addition of silyl ketene acetals to pyruvates

Another way for the generation and the utilization of thioester enolates was reported by the research group of Feringa in 2006. Thioester enolates were generated upon addition of methyl magnesium bromide to α,β-unsaturated thioesters in the presence of catalytic amounts of a copper salt.[16]

While the hydrolysis of the enolates allow for the isolation of the Michael adducts **8** in good yields and 95 % ee, the addition of the thioester enolate to benzaldehyde led to the isolation of the more complex products **9a-d**, containing three consecutive stereogenic centres that were obtained in very high stereopurity. The synthetic strategy was applied in the synthesis of a series of lactones in a short and highly stereoselective route (Scheme 10).

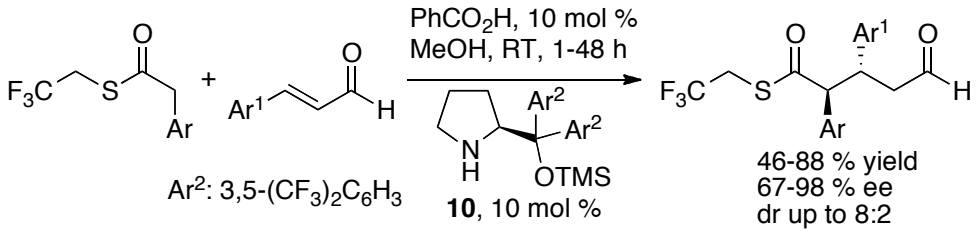


Scheme 10. The synthetic sequence developed by Feringa

2.4 Thioester enolates in organocatalysed reactions

Despite the abundance of synthetic systems published so far for the metal based addition of thioester enolate equivalents to electrophiles, there are only few organocatalytic procedures. The intrinsic challenges posed by the dual reactivity described above in dealing with thioesters, namely their low acidity of the proton at the α-position and their reactivity towards nucleophiles at the carbonyl, are arguably the reason for the lack of extensive studies on this class of compounds.

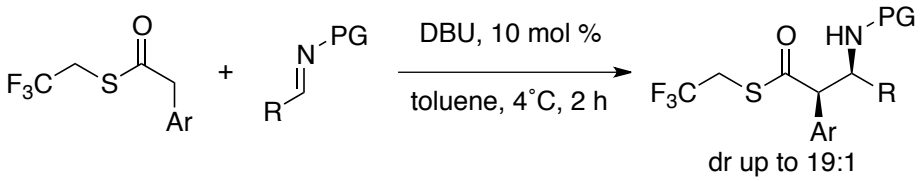
In 2008 Barbas and co-workers designed electron-poor thioesters capable of undergoing 1,4-addition reactions with α,β-unsaturated aldehydes in the presence of chiral secondary amines as catalysts and an acidic co-catalyst (Scheme 11).[17] The designed thioesters allowed for milder conditions for the generation of their enolates in comparison to electron-rich thioesters, therefore showing high stability against hydrolysis while maintaining high reactivity towards the activated electrophiles. Crucial for the reactivity of the starting materials was the nature of the thioesters and the substitution at the α-position. Only aromatic α-substituents were tolerated and the fastest rates were observed when electron-poor aromatics were employed. In addition to α,β-unsaturated aldehydes, other electrophiles were also tested. The thioesters reacted with *p*-nitrobenzaldehyde, diazodicarboxylates and nitrostyrene as well. Unfortunately the low stereochemical purity of these addition products showed that the system, albeit providing good result in the addition to α,β-unsaturated aldehydes, cannot be considered general.



Scheme 11. Organocatalysed conjugate addition reaction of thioester enolate equivalents to α,β-unsaturated aldehydes

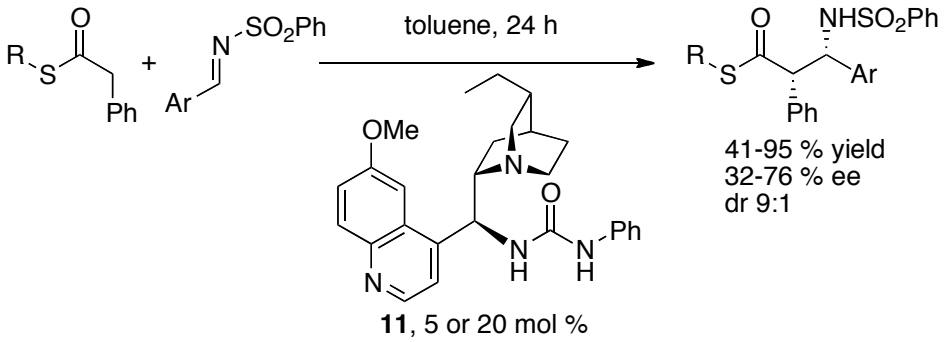
In an extension to this work, the research group of Barbas reported the addition of the same type of thioesters to imines (Scheme 12).[18] The reaction requires as little as 10 mol % of DBU as a catalyst. While no chiral catalyst was involved in the reaction and consequently racemic products were formed, high levels of diastereoselection were

observed. The diastereoselectivity of the reaction depends strongly on the reaction time. Products that were isolated and reincubated in a fresh DBU solution showed increased *syn*/*anti* ratios. Attempts to carry out the reaction in an asymmetric fashion were also made using chiral cinchonine ammonium salts as phase transfer catalyst together with KOH as a base. The enantioselectivity observed (45 % ee for the *anti* adduct) was poor and no further attempts to optimise the reaction parameters were shown.



Scheme 12. Thioester enolate equivalents addition to imines

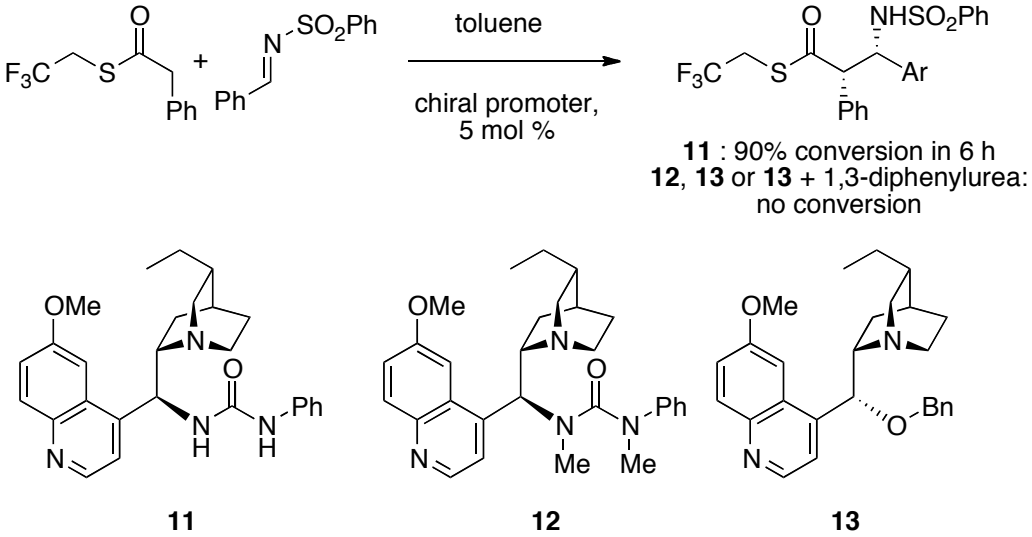
Coltart and co-workers reported the addition of thioester enolates to imines.[19] The reaction required 5 mol % of the urea derived cinchona alkaloid catalyst **11** (Scheme 13). Studies with differently substituted thioesters revealed that while trifluoro ethyl thioesters provided the highest activity, higher enantio- and diastereoselectivities were obtained when ethane thioesters were used. Thioesters derived from aromatic thiols showed no preference for the *syn* or *anti* adducts.[19]



Scheme 13. Coltart's thioester enolates addition to imines

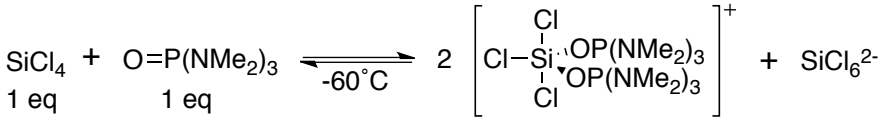
The structure of the catalyst was also examined in order to have a better understanding of the various features that govern the rate of the reaction (Scheme 14). Reactions in the presence of both methyl-substituted ureas **12** and cinchona alkaloids lacking a urea moiety, e.g. compound **13,** provided no conversion demonstrating that the ability of ureas to activate the substrates via H-bonding was crucial. In addition the covalent linkage between the basic centre of the original skeleton of the alkaloid and the electron-poor urea was found to be indispensable: the combined use of the

1,3-diphenyl urea and the basic alkaloid as catalysts resulted in no reaction and recovery of the substrates (Scheme 14).[19]



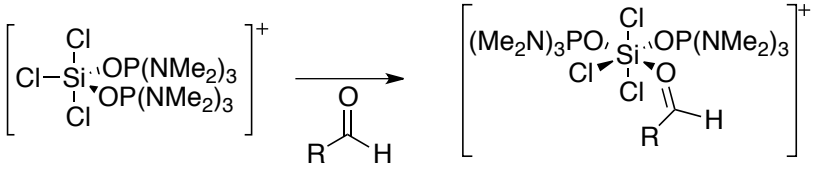
Scheme 14. Determination of the importance of the different moieties of the catalyst

Denmark reported the activation of carbonyl compounds in the presence of $SiCl_4$ and phosporamidites catalysing the direct addition of enols to e.g. aldehydes.[20] The reaction mechanism involves the nucleophilic attack of the lone pairs of the phosphoramidite at the silicon centre resulting in the expansion of the octet at the silicon centre. The following change in the geometry of the complex and the presence of the electron-donating phosphoramidite render the 3d orbitals of the silicon energetically available (Scheme 15).



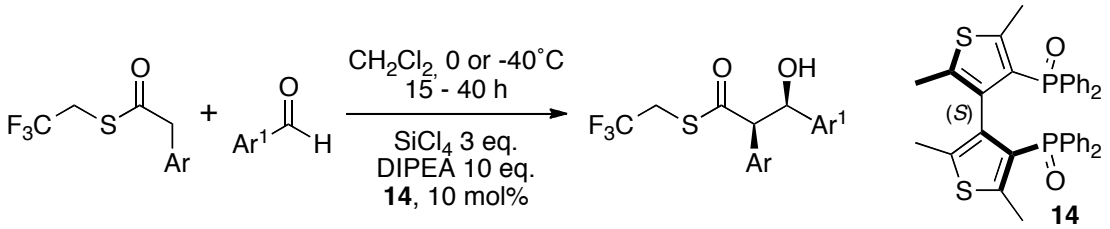
Scheme 15. Denmark's activation of aldehydes

The new species has increased affinity for aldehydes that can coordinate to the silicon. Upon coordination the aldehydes are activated and their reaction with nucleophiles can take places (Scheme 16).



Scheme 16. Complexation of aldehydes to silicon

The group of Benaglia took advantage of this activation mode and developed a direct addition of thioester enolates to aldehydes.[21] The reaction is catalysed by phosphine oxide **14** ((*S*)-tetraMe-BITIOPO) and requires large excesses of $SiCl_4$ and DIPEA (3 and 10 equivalents respectively). This example is tackling an unsolved challenge in organocatalysis: to date very few examples of direct organocatalysed addition of (thio)ester enolates to aldehydes have been reported. While the reaction is limited to aromatic aldehydes and aromatic residues at the α-position of the thioester, the levels of stereoselection are moderate to excellent (dr up to 98:2, 55-95 % ee) and synthetically useful yields were reported (35-80 % yield) (Scheme 17).

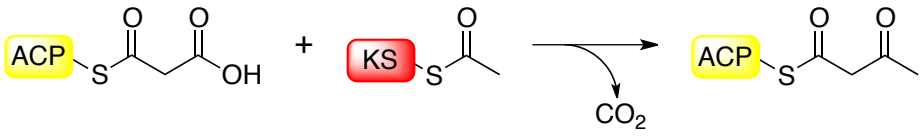


Scheme 17. Benaglia addition reaction between thioester enolate equivalents and aldehydes

2.5 Thioester enolate equivalents in enzyme-catalysed transformations

Nature utilises thioesters as building blocks for the synthesis of numerous molecules of high biological importance. Polyketides and fatty acids are originated utilising thioester-containing building blocks via their ability to generate thioester enolates.[2] Polyketides are a class of compounds that show a broad structural diversity. They are synthesised in plants, bacteria or fungi.[2,22-25] These compounds have a broad spectrum of biological and pharmacological activities as they have applications as antifungal, antibiotic and antitumoral molecules.

Polyketides are synthesised in living organisms by enzymes that belong to the family of polyketide synthases (PKAs). Malonyl CoA and acetyl CoA are activated by these enzymes and their Claisen condensation reaction begins a cascade of enzyme-catalysed transformations that lead to the synthesis of polyketides. These molecules are assembled from C_2 units by repeated head-to-tail linkage, until a chain of the required length is reached. A starter acetyl thioester unit is condensed with a malonyl unit that undergoes decarboxylation to furnish the electrons for the new carbon-carbon bond resulting in the generation of β-keto thioesters (Scheme 18).[2b]



Scheme 18. Claisen condensation between ACP-bound malonyl CoA and KS-bound acetyl CoA

Then, these β-ketoesters undergo a series of transformations that lead to the formation of biologically active compounds.

The synthesis of 6-methylsalicylic acid (6-MSA) is reported in Figure 4 as an example for the biosynthesis of polyketides.[2b]

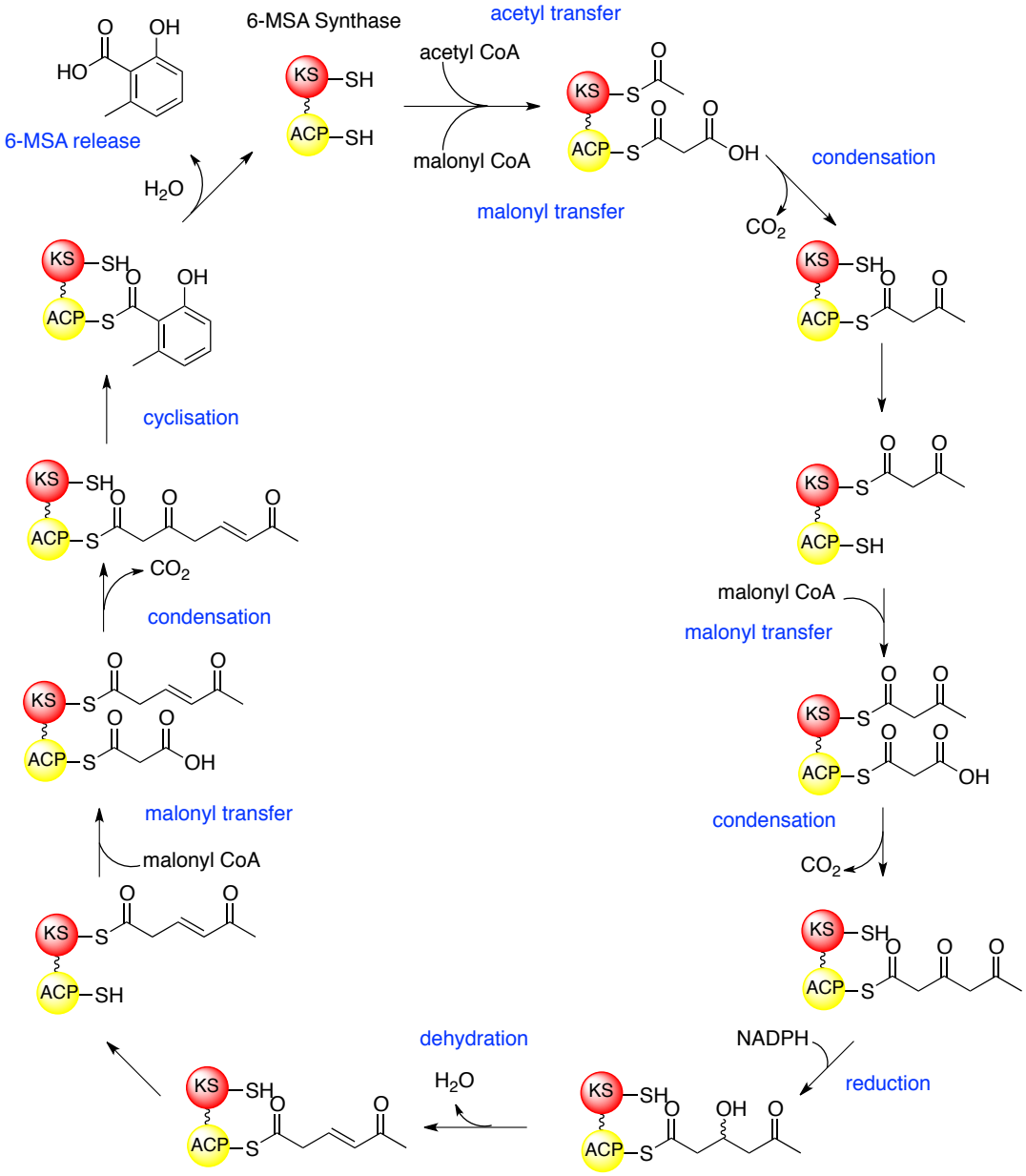


Figure 4. Biosynthesis of 6-methylsalicylic acid.[21b]

PKSs are enzymes which, in their active sites, lack metal ions and have in common the amino acids cysteine (Cys), histidine (His), and asparagine (Asn).[2] Within the catalytic triad, the His-Asn motive is responsible for activating the CoA-bound deprotonated malonic acid half thioester (MAHT) that reacts upon decarboxylation with a second Cys-bound acetyl-thioester (Figure 5).

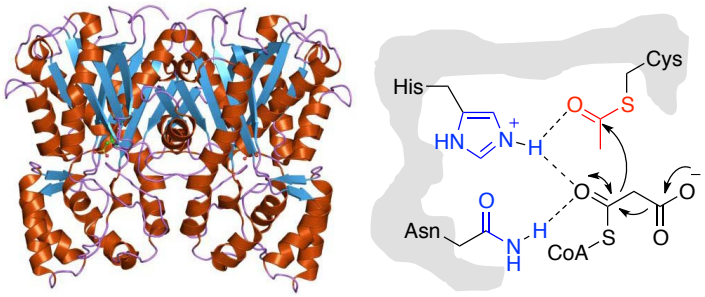
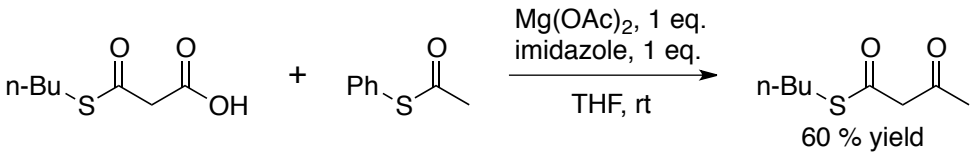


Figure 5. Type III polyketide synthase (left) and a cartoon of its active site (right)

2.6 Metal promoted decarboxylative addition of MAHTs to electrophiles

As already presented earlier in this chapter thioesters are attractive compounds due to their synthetic versatility. The ability of MAHTs to act as thioester enolate equivalents makes these compounds very appealing for the development of decarboxylative addition reactions of their nucleophilic enolates to different electrophiles. In the last decades many metal-based systems were developed for promoting the addition reaction of MAHTs to many electrophiles.

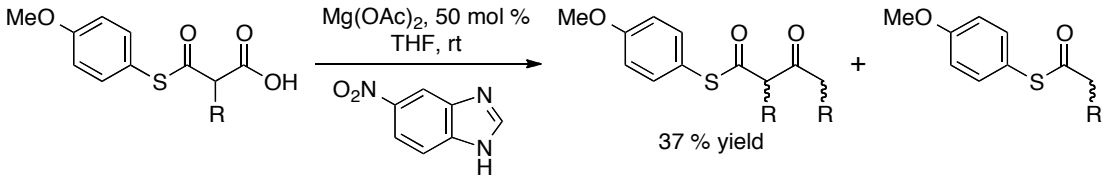
In an early example, Kobuke and Yoshida presented the intermolecular Claisen condensation between MAHTs and thioacetates providing an efficient protocol for the synthesis of β-ketothioesters.[26] The reaction is mediated by stoichiometric amounts of magnesium acetate and imidazole as base yielding the desired products in 60 % yield (Scheme 19).



Scheme 19. Claisen condensation of MAHTs to thioacetates

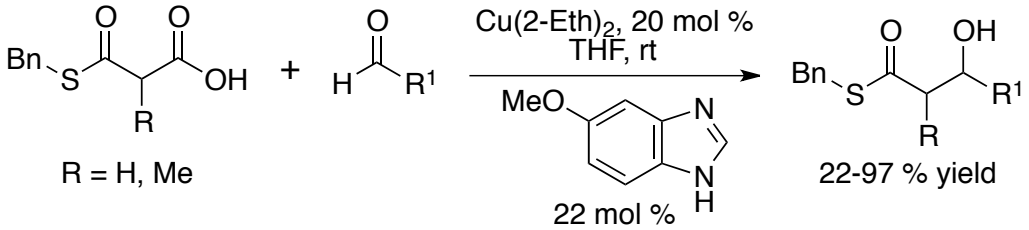
Matile and co-workers investigated the self-condensation of MAHTs for the synthesis β-ketothioesters.[27] A broad investigation on the parameters and an optimization of the reaction conditions led them to discover that a subtle balance between all of the

reaction parameters is required to promote the condensation reaction. Magnesium acetate was the best metallic promoter and could be used in substoichiometric quantities (50 mol %). Nitro-substituted benzimidazole was needed in stoichiometric amounts (1 eq.) and the best results were obtained when *p*-methoxy thioesters were used as starting materials (Scheme 20).



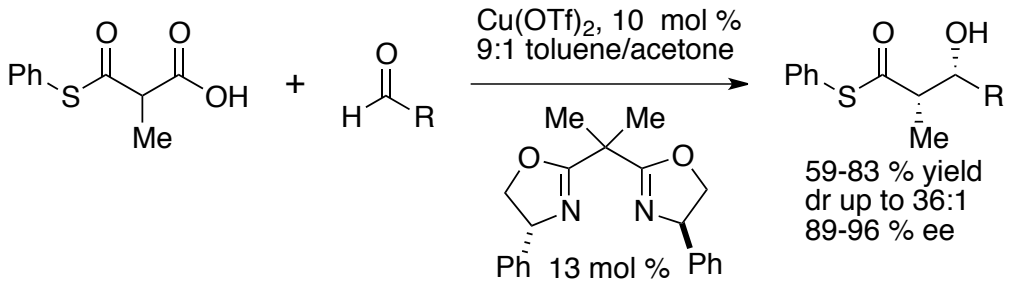
Scheme 20. Claisen self-condensation of MAHTs in the presence of Magnesium acetate

Shair and co-workers in 2003 reported the decarboxylative addition of MAHTs to aldehydes.[28] The reaction is catalysed by copper (II) salts. In addition, substoichiometric amounts of a methoxy-substituted benzimidazole were found to be crucial for the complete conversion of the reagents into the products. The addition products were isolated in moderate to good yields (22-97 % yield, Scheme 21).



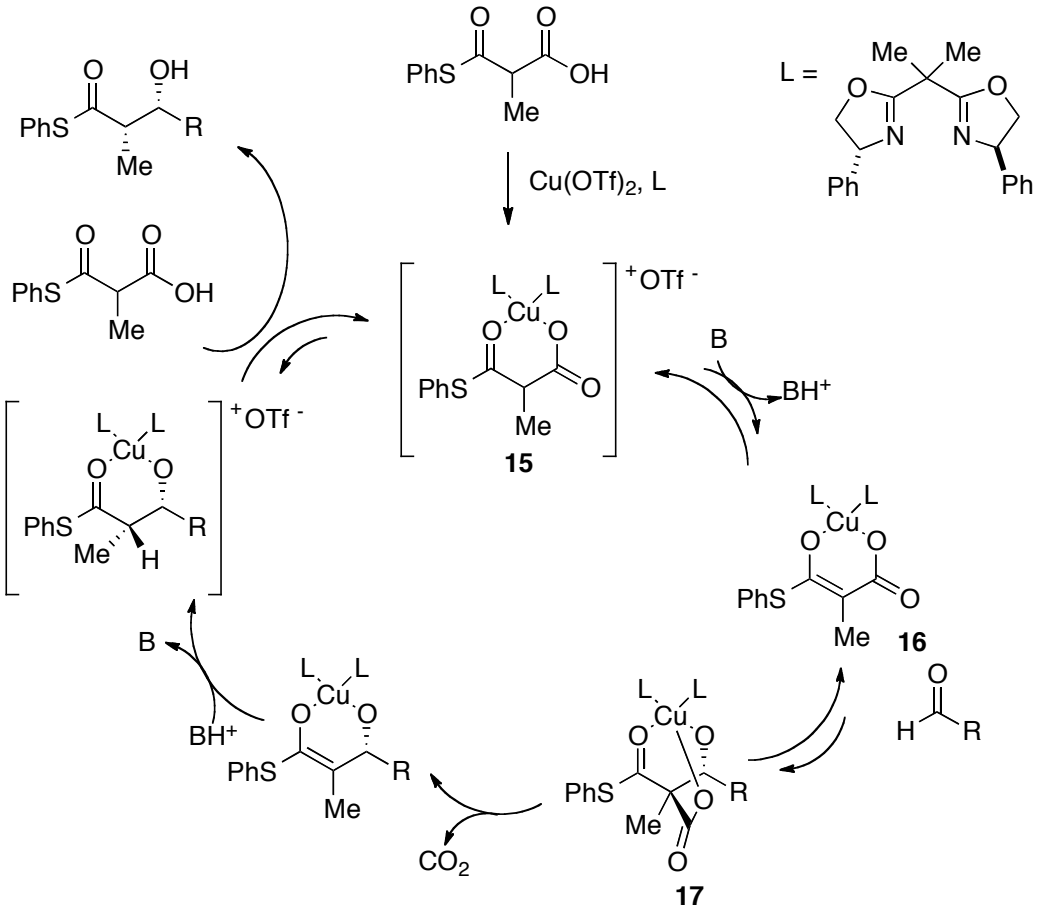
Scheme 21. Decarboxylative addition reaction of MAHTs to aldehydes

Two years later, the same research group reported the asymmetric version of the copper catalysed decarboxylative addition reaction of methyl-substituted MAHTs to aldehydes.[29] The catalyst loading was decreased to 10 mol % and the products were isolated in good yields (59-83 % yield) and stereoselectivities (dr up to 36:1, 89-96 % ee). Additionally, the reaction was proven to be very general as aromatic or aliphatic aldehydes were converted efficiently into the desired products and no protections of other functional groups were required (Scheme 22).



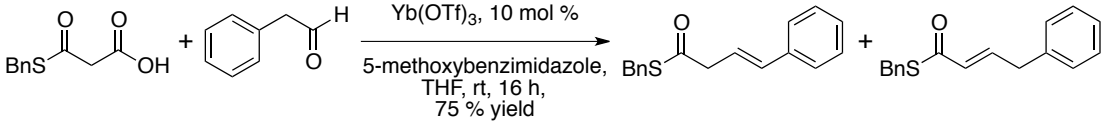
Scheme 22. Diastereoselective addition reaction of methyl-substituted MAHTs to aldehydes

A full investigation of the reaction mechanism was also reported.[30] A plausible reaction mechanism involves coordination of the MAHT to the copper catalyst to form complex **15** followed by deprotonation of the α-position to generate the enolate copper complex **16**. The new species adds to the aldehyde forming the intermediate **17**. Finally, decarboxylation, stereoselective reprotonation of the enolate and the release of the products regenerate the catalyst closing the catalytic cycle (Scheme 23).



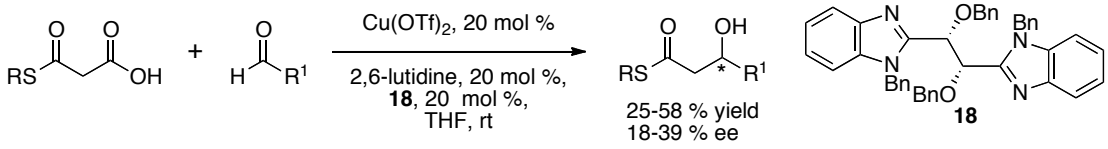
Scheme 23. The mechanism of the decarboxylative addition reaction of MAHTs to aldehydes

Other examples of metal catalysed decarboxylative addition reactions of MAHTs to aldehydes were reported. Thomas and co-workers, for example, investigated the $Yb(OTf)_3$ catalysed Doebner-Knoevenagel condensation reaction of MAHTs to aldehydes.[31] The products were obtained in good yields and the elimination of a molecule of water led to the preferential formation of the double bond conjugated to the aromatic ring (ratio of α,β:β,γ 5:95) (Scheme 24).



Scheme 24. Doebner-Knoevenagel condensation reaction between MAHTs and aldehydes

In 2003, Cozzi and co-workers reported an asymmetric version of the copper catalysed addition reaction of MAHTs to aldehydes using the chiral enantiomerically pure bis-benzimidaziole **15** as ligand and 2,6-lutidine as base.[32] However, the obtained yields and stereoselectivities were poor as the products were isolated in only 25-58 yield and 18-39 % ee (Scheme 25).



Scheme 25. Asymmetric decarboxylative addition of MAHTs to aldehydes

3. Organocatalysed decarboxylative additions of MAHTs to various electrophiles

3.1 1,4-conjugate addition reactions of MAHTs to nitroolefins

Organocatalysis emerged over the last decades with a pool of alternative tools to promote various transformations. Also decarboxylative additions of MAHTs to several electrophiles were developed in the last ten years. The driving force of this process is the development of CO_2 and the formation of the products is entropically favoured since a new gaseous molecule is formed in the course of the reaction.

The active site of polyketide synthases were the source of inspiration for the design of organocatalysts able to promote the addition reaction of MAHTs to electrophiles. As described before, three amino acids in the active site of these enzymes are mainly responsible for the catalytic activity.[2] The substrates are bound through a network of H-bonds with the crucial aminoacids. The substrates are then activated resulting in their conversion to the desired products.

The organocatalysts possess similar features to those found in the enzymes: a basic tertiary amine deprotonates the acidic starting materials and the intermediate species are bound to the catalyst and activated by H-bond donor moieties (Figure 6).

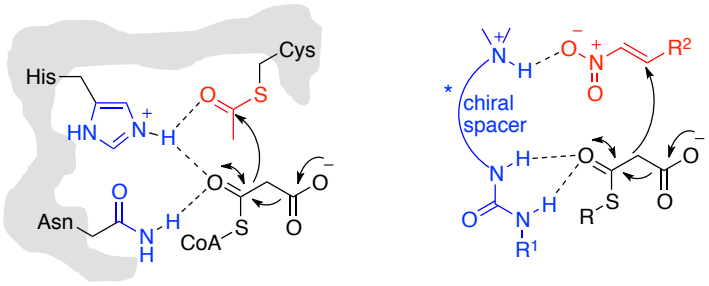
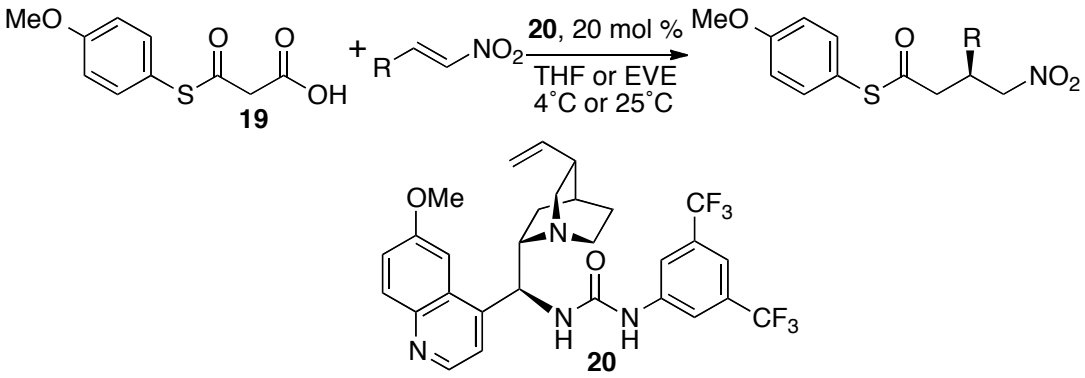
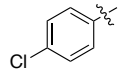
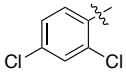
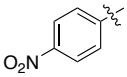
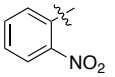
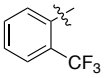
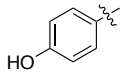
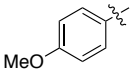
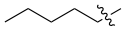


Figure 6. Analogy between the active site of PKS and organocatalysts

The Wennemers group contributed to the development of decarboxylative addition reactions of MAHTs. In 2007, Wennemers and Lubkoll presented their investigations on the conjugate addition reaction of MAHTs to nitroolefins.[33]

Table 1. Decarboxylative addition of MAHTs to nitroolefins



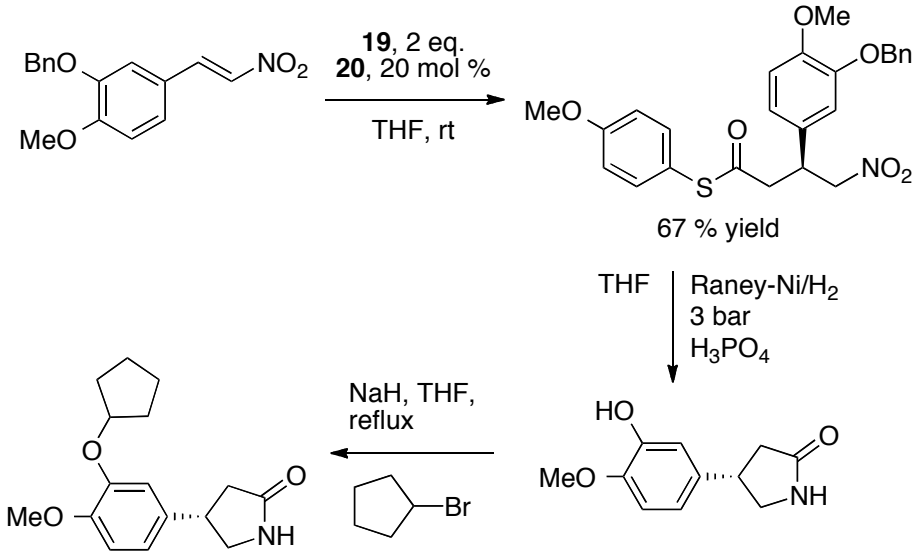
		THF[a]		EVE[b]	
Entry	R	Yield[c] [%]	ee[d] [%]	Yield[c] [%]	ee[d] [%]
1		94	63	57	88
2		96	61	41	79
3		92	56	63[e]	84[e]
4		94	55	61[e]	82[e]
5		99[e]	67[e]	51[e]	90[e]
6		89[e]	65[e]	36	86
7		93[e]	61[e]	13	73
8		78[e]	62[e]	nd[f]	nd[f]
9		78[e]	66[e]	97[e]	75[e]
10		71[e]	57[e]	43	79
11		16	63	23	78

[a] Reactions were performed at 25˚C for 24 h using 2 eq. of **19**. [b] Reactions were performed at 25˚C for 72 h using 1.2 eq. of **19**. [c] Yields of isolated products. [d] Determined by chiral-phase HPLC analysis. [e] Reaction was performed at 4˚C. [f] Not determined because of the reaction of phenolic nitroolefin with EVE.

The *epi*-quinine urea derivative **20** turned out to be the optimal catalyst. The presence of a tertiary amine and an electron deficient urea in the same molecule was found to be crucial to provide the needed activation and stabilization of the reactive intermediates via non-covalent (H-bonds) interactions. The tertiary amine of the quinine provides the basic site for the deprotonation of the MAHTs **19**, while the electron deficient urea, as well as the newly formed ammonium salt, offer binding

sites for the substrates. Indeed, 20 mol % of **20** allowed for the complete consumption of the MAHTs in 24 hours. Ethers were found to be the optimal compromise between stability and reactivity of the MAHTs. When the reaction was carried out in THF the γ-nitrothioesters was generated in good yields and selectivities. In analogy, ethylvinylether (EVE) was also discovered to be a good solvent for the addition reaction since it provided better selectivitities at the expense of reactivity and generally lower yields were observed.

Electron-deficient aromatic nitroolefins afforded products in yields up to 99 % (Table 1, entries 2–6), while electron-rich aromatic nitroolefins gave products in slightly lower yields (Table 1, entries 8 and 9). Poor conversion was observed only in the case of a sterically demanding aliphatic nitroolefin (Table 1, entry 11). It is noteworthy that no protection of the phenolic hydroxy group was necessary for the reaction to occour (Table 1, entry 8). The synthetic versatility of the resulting γ-nitrothioesters was also demonstrated by the synthesis of (*R*)-rolipram, which was accomplished in two steps from a γ-nitrothioesters obtained in the organocatalysed conjugate addition reaction (Scheme 28).



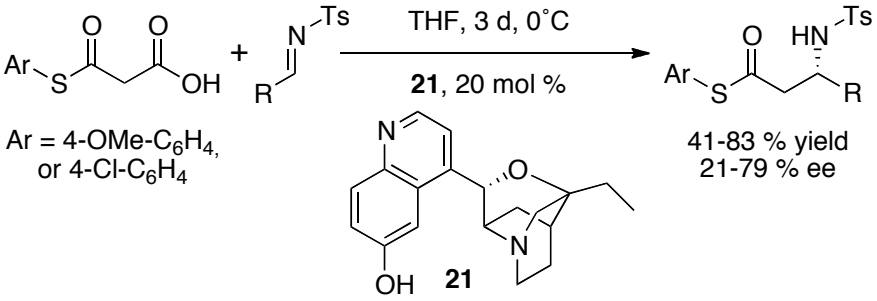
Scheme 28. Synthesis of Rolipram

These results demonstrate that organocatalysts enable the use of MAHTs as ester enolate equivalents in organic synthesis. Guided by natural PKSs, the first example of enantioselective MAHT addition reactions to nitroolefins catalyzed by a synthetic metal-free organocatalyst was reported by our research group. The 1,4-addition reactions occur under mild conditions, and tolerate both moisture and air.

Some challenges were not fully addressed as rather high catalyst loadings (20 mol % of **20**) and reaction times of days were required in order to balance the low reactivity of the starting materials. Furthermore, aliphatic-branched nitroolefins showed scarce reactivity, the corresponding products being isolated in low yields, and highly electron rich nitroolefins afforded no product at all. In addition, acetylated thiol, which forms upon decarboxylation of MAHTs was frequently recovered as the major by-product. As a result, an excess of 2 equivalents of MAHT **19** was required to completely consume the nitroolefins.

3.2 Organocatalysed decarboxylative additions of MAHTs to imines

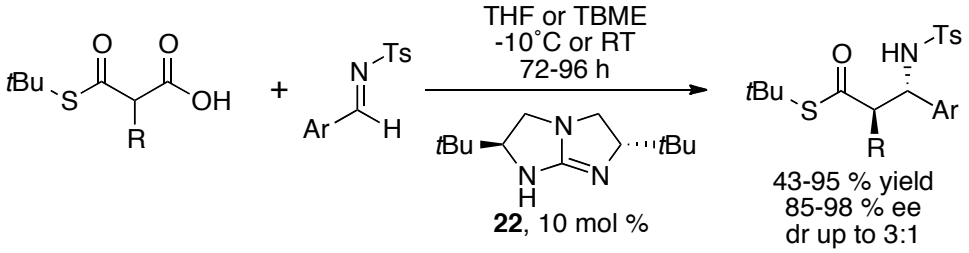
The decarboxylative addition of MAHT to imines was studied in other research groups. In 2007, Ricci and co-workers reported the decarboxylative addition of MAHTs to N-tosyl-imines.[34] The products were obtained with moderate ee values (51-79 %) and in good yields (up to 84 %). High catalyst loadings (20 mol %) and reaction times of three days are required to achieve good conversions. Best results were obtained in the presence of the quinidine derivative **21** possessing a basic tertiary amine moiety and a phenolic OH group as H-bond donor for binding of the substrates.[33] In this example the decarboxylation proved to be the crucial step to obtain the desired addition products efficiently. Molecules bearing a methyl ester, as protecting group for the carboxylic acid and therefore not being able to release CO_2 were not converted to the products (Scheme 26).



Scheme 26. Decaboxylative addition reaction of MAHTs to imines

Tan and co-workers introduced the strong organic base **22** as an organocatalyst for the decarboxylative addition of MAHTs to electrophiles.[35] Also in this case the organocatalyst combines a very strong basicity with, upon its protonation, the possibility of activating the substrates by H-bonding. These non-covalent interactions

are responsible for the catalytic rate acceleration as well as for the transfer of chirality to the products. With the help of computational studies on the reaction mechanism and minimization of the energies of the proposed intermediate species, Tan and co-workers postulated that a careful design of the substrates is required in order to increase the strength of the hydrogen bonds. On the one hand aliphatic and sterically demanding thioesters are required for an efficient shielding of one of the two faces of the prochiral enolate by the catalyst, on the other hand tosyl protected imines, offering additional lone pairs on the sulphonamide oxygens as H-bond acceptors, were shown to be crucial to provide the tightly bounded intermediates that are necessary to induce enantioselectivity. Tan *et al.* demonstrated also that MAHTs reacted with diazodicarboxylates in the presence of the same catalyst to yield highly enantioenriched β-amino thioesters (Scheme 27).



Scheme 27. Decarboxylative addition of MAHTs to imines.

All of the reported examples demonstrate that thioester enolate equivalents can be used for their addition reaction to various electrophiles under organocatalytic conditions. However, some of the features of these methodologies, as the reaction times of days, the low yields and high catalyst loadings, were not optimal. Further optimization of the structure of the catalysts as well as the substrates would allow for more efficient addition reaction of thioester enolates equivalents to electrophiles.

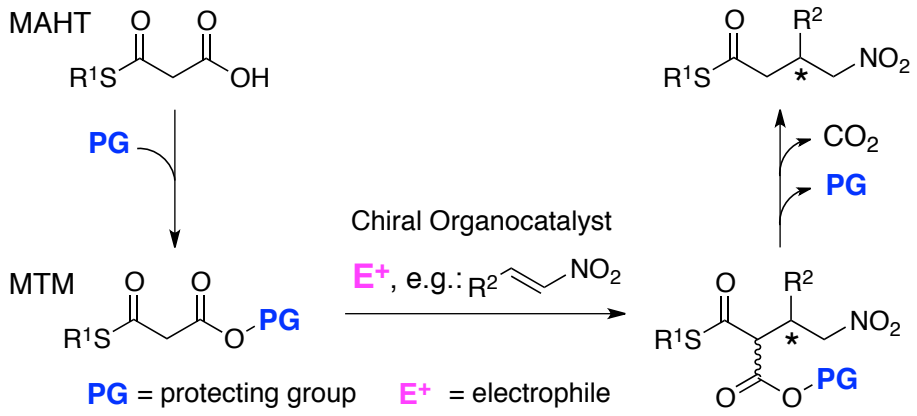
4. Objectives of this thesis

Thioester enolates, as described in the previous chapters, are important nucleophiles allowing for a large variety of chemical transformations.[3-6] The generation of a thioester enolate is still a big challenge in synthetic chemistry, due to the low acidity of the α-protons and the reactivity of the carbonyl group towards nucleophiles. Thus, harsh and dry conditions or stoichiometric reagents[11-16] have often been employed to overcome these problems. The development of new, mild and catalytic synthetic procedures for the generation of thioester enolates is of big importance. These catalytic processes would lead to the generation of less waste and the mild conditions would allow for broader functional group tolerance.

Catalytic approaches for decarboxylative additions of malonic acid hemithioester were investigated.[26-35] However, these approaches suffered from some drawbacks. Reaction times of days, high catalyst loadings and low yields are often necessary for the complete conversion of the starting materials into products.

For example, the decarboxylative addition of MAHTs to nitroolefins, published in 2007 by Lubkoll and Wennemers,[33] is an elegant example of a biomimetic catalytic approach. Taking inspiration from the mechanism of action of polyketide synthases in nature for the catalyst design and the substrates choice a new protocol for the development of conjugate Michael addition reactions of thioester enolates equivalents to nitroolefins. The main issue of this method was the formation of acetylated thiol which is obtained by the unproductive decarboxylation of the nucleophilic starting material without the C-C bond forming reaction, which is why an excess of MAHT was required. Finally, the products were obtained in moderate ee and stereoselectivities (55-67 % ee, 16-94 % yield).

To circumvent this undesired “non-productive” decarboxylation, we designed mono thiomalonates (MTMs) bearing a cleavable ester moiety as more stable thioester enolate equivalents. These substrates were envisioned to provide the addition products of thioester enolates with electrophiles in an addition, ester cleavage and decarboxylation sequence. Within this thesis the value of MTMs in asymmetric organocatalytic reactions with nitroolefins and other electrophiles was explored (Scheme 29).[36]



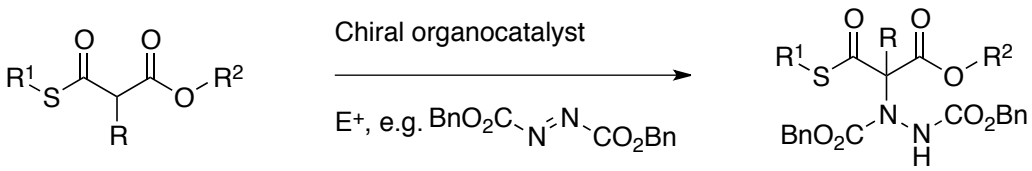
Scheme 29. The strategy for the use of MTMs

The reactivity at the α-position of MTMs was envisioned to be higher in comparison to the case of MAHTs due to the presence of the two electro-withdrawing groups, stable in basic reaction conditions, in the molecule allowing for milder reaction conditions and faster reaction rates.

The new strategy via monothiomalonates includes an additional step in the synthesis of the substrates as well as two more steps for their deprotection and decarboxylation in order to prepare the same products as in the decarboxylative addition. We thought that this increased synthetic effort might be balanced by the increased reactivity and selectivity of the reaction. Additionally, the increased stability and reactivity of the substrates could allow for their use under mild reaction conditions allowing for a broad substrates tolerance.

The MTMs resemble malonates in terms of structure but offer clear advantages. Due to the presence of the thioester moiety, the reactivity is expected to be higher than that of malonates and easily functionalizable products are obtained.

Furthermore, the use of α-substituted MTMs in reactions with other electrophiles might allow for the generation of products having quaternary stereogenic centres . We explored also the organocatalysed addition reaction of α-substituted MTMs to other electrophiles as e.g. diazodicatboxylates (Scheme 30).

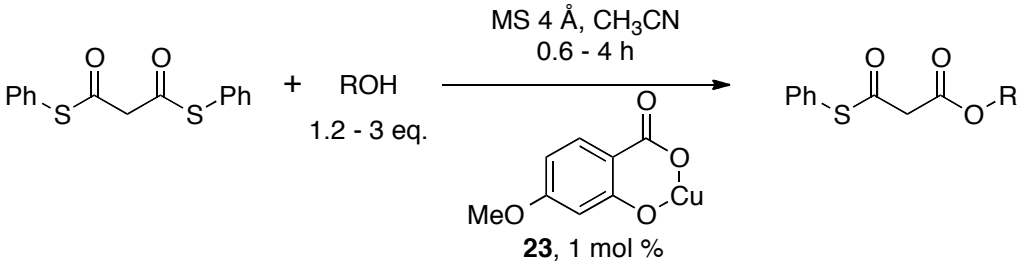


Scheme 30. Generation of quaternary stereogenic centres starting from α-substituted MTMs

5. Mono thiomalonates as thioester enolates equivalents

5.1 Synthesis of mono thiomalonates (MTMs)

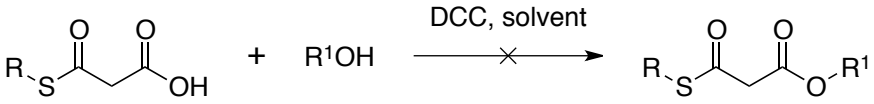
Monothiomalonates are asymmetric malonic acid derivatives. Thus, their synthesis is more challenging than the synthesis of symmetric malonates. The only example described in literature so far was reported by Matsuo and Shindo in 2011 and involved the copper(II) salicylate **23** catalysed desymmetrisation of malonic di-thiophenolesters (Scheme 31).[37] The approach relies on the alcoholysis of dithiomalonates in the presence of different alcohols. Since regular esters are thermodynamically more stable than thioesters, it is easy to substitute thioesters with alcohols allowing for a straightforward synthesis of esters. The difficulty is to control the synthesis in such a way that only one thioester is converted to the regular ester and overreaction to the dioxomalonates is prevented. The non-catalysed reaction takes place in 24 hours yielding the unsymmetrical MTMs in synthetically useful yields of 70 - >98 %. Under similar conditions, the reaction is complete in less than 5 hours when 1 mol % of a copper salt is added. The catalyst allows also for the desymmetrisation of α-substituted malonates that are more challenging to prepare due to the increased steric demands.[37]



Scheme 31. The copper catalysed desymmetrisation reaction of dithiomalonates

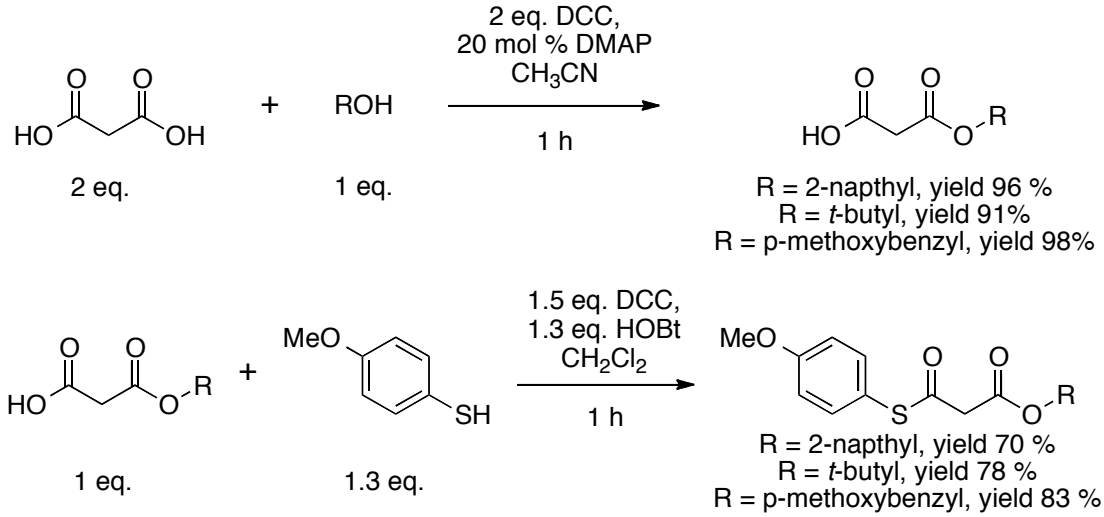
Unfortunately, when we tried to apply the same strategy for the synthesis of our target compounds, the reaction always produced large quantities of the dioxomalonate that were not separable from our target molecules by chromatographic techniques.

We next envisioned to access our target MTMs from MAHTs by coupling of the desired alcohol using *N,N'*-dicyclohexylcarbodiimide (DCC) as a dehydrating agent. This approach also failed due to the instability of the thioester under the coupling conditions (Scheme 32).



Scheme 32. DCC mediated coupling reaction between MAHTs and alcohols

Change of the coupling order finally led to a successful synthesis of MTMs. The MTMs were obtained by a DCC mediated coupling of an alcohol in the presence of an excess of malonic acid. The malonic acid hemiester was isolated by extraction and coupled with the thiol in the presence of DCC as dehydrating reagent (Scheme 33).

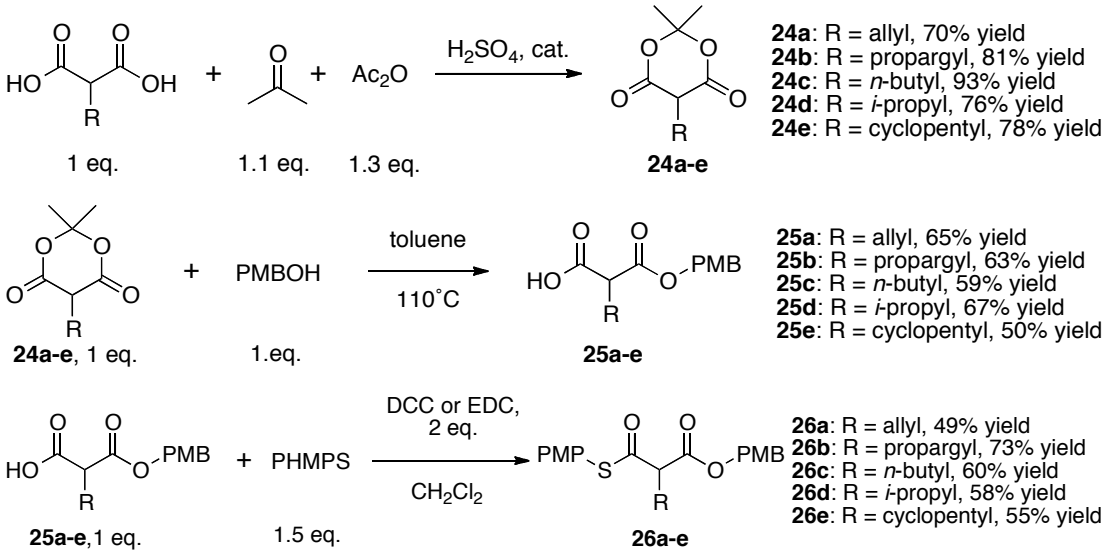


Scheme 33. The successful synthetic sequence for the synthesis of MTMs

This strategy proved to be applicable only for unsubstituted malonic acids or for malonic acid derivatives with small substituents (e.g. methyl or ethyl) in the α-position. In the case of malonic acid derivatives with larger substituents, however, the low water solubility of the starting material does not allow for purification of the malonic acid hemiester from the diacid leading to complex and difficult to separate product mixtures in the second step.

For efficient desymmetrisations of higher substituted malonic acids we decided to first synthesize the Meldrum acid derivatives **24a-e**, of various α-substituted malonic acids. Boiling Meldrum acid derivatives in toluene in the presence of the desired alcohol then cleanly provides the desired ring opened monoesters **25a-e** ready for the following coupling of the thiol with the help of DCC or EDC. This second strategy provided access to α-substituted MTMs **26a-e** in good 50-70 % yields and purities (Scheme 34). Additionally, the synthesis is easily scalable and could be carried out on

multigram scale allowing for the isolation of more than 10 grams of the desired MTMs.



Scheme 34. The synthetic sequence for the synthesis of α-substituted MTMs

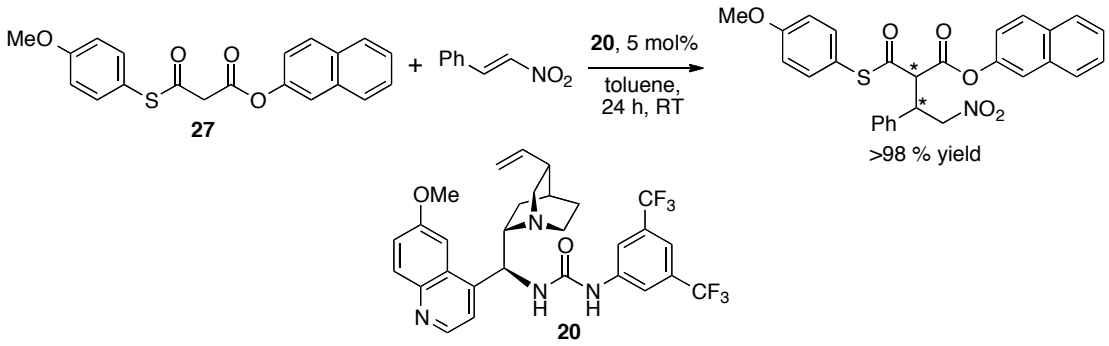
This convenient method allowed us to synthesize MTMs substituted in the α-position with a wide range of aliphatic (e.g. methyl-, *n*-butyl- or *i*-propyl substituted) or aromatic (phenyl and 3-thiophene substituted) groups.

5.2 Initial evaluation of the reactivity of MTMs

Having established a synthetic route to the MTMs, we next investigated their reactivity in the organocatalytic Michael addition reaction of MTMs to nitroolefins. Additionally, the configurational stability of the stereogenic centres of the products was investigated. Under the basic reaction conditions the stereochemistry of the stereogenic centres might be scrambled upon deprotonation of the acidic protons, so it is of crucial importance for the design of the synthetic strategies to determine whether both stereogenic centres could be obtained with high stereoselectivity.

We first examined an MTM derived from *p*-methoxy thiophenol and 2-naphthyl alcohol. The MTM **27** was tested in the 1,4-conjugate addition reaction with nitrostyrene. Pleasantly, in the presence of quinine urea catalyst **20** the starting material were completely consumed within a reaction time of 24 hours. The desired conjugate addition products were obtained in quantitative yields (>98 % yield).

Having isolated the conjugate addition product, we next explored the stereochemical integrity of the two newly formed stereogenic centres (Scheme 35).



Scheme 35. Epi-quinine urea catalysed addition reaction between MTMs and nitrostyrene

Not surprisingly, after chiral stationary phase HPLC analysis, the chromatogram showed the presence of two major and two minor species. The observed 1:1 ratio of both the two major and the two minor species supported the hypothesis that one of the two stereogenic centres was completely epimerized. Moreover the ^{1}H-NMR spectrum of the product clearly showed that the sample contained different species, therefore supporting once again the scrambling of the configuration of the stereogenic centre in the α-position. In order to further support the scrambling of the stereoselectivity we performed deuterium exchange experiments. In the presence of 5 eq. of D_2O, an exchange of the proton in the α-position was observed by ^{1}H-NMR spectroscopy after 10 minutes. The rate of this exchange is even accelerated in the presence of a cinchona alkaloid catalyst. For simplicity we show here the results obtained with the starting materials (Figure 7).

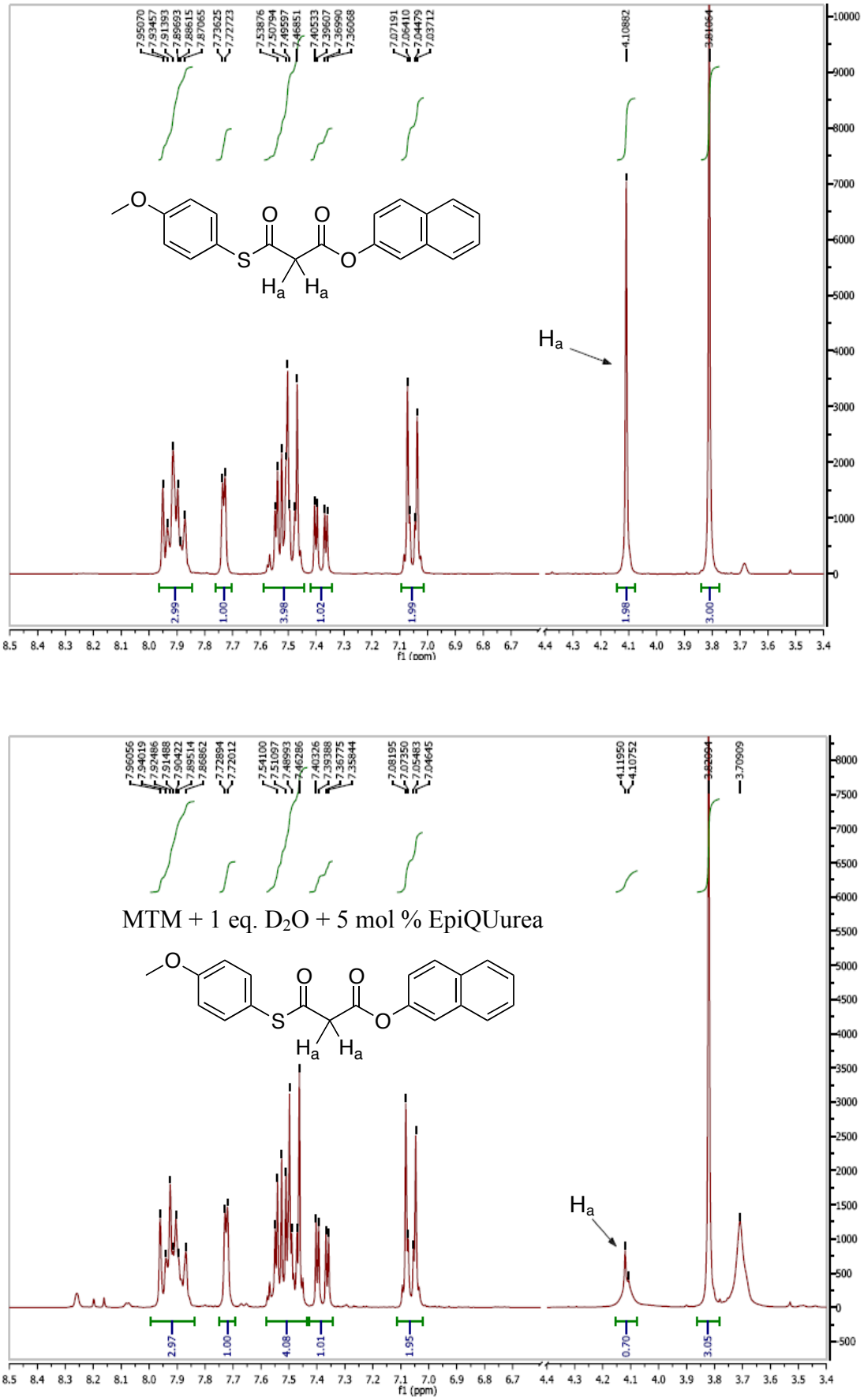
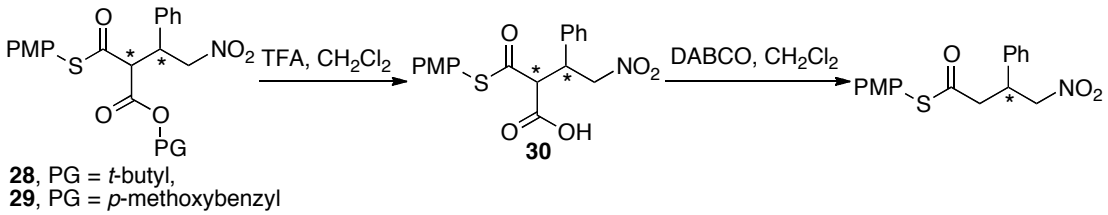


Figure 7. D_2O exchange experiments on MTMs

5.3 MTMs bearing acid labile protecting groups

Next step we sought to develop a synthetic procedure that would allow for the removal of the ester moiety and, upon decarboxylation, allow to obtain γ-nitrothioesters possessing only the stereogenic centre that is not scrambled during the reaction. Inspired by the experience of other research groups,[38] that showed that some thioesters are particularly stable under very acidic conditions, we introduced an acid labile ester as the protecting group of the carboxylic acid.

Thus, we synthesized MTMs bearing acid labile protecting groups. We started our investigation by preparing the *t*-butyl and the *p*-methoxybenzyl derivatives **28** and **29** and performed the organocatalytic conjugate addition reaction to nitrostyrene. We then treated the addition products with strong acids to see whether the deprotection as well as the decarboxylation reaction takes place under these conditions. We quickly realised that the malonic acid hemithioesters **30** do not decarboxylate even in boiling trifluoroacetic acid (TFA). We then decided to remove the acidic media and perform a base-mediated decarboxylation reaction by adding a solution of 1,4-diazabicyclo[2.2.2]octane (DABCO) in CH_2Cl_2. To our delight the reaction proceeded cleanly to yield the desired γ-nitrothioesters (Scheme 36).



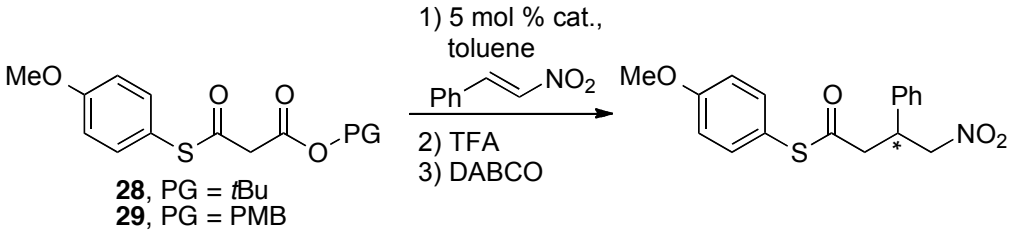
Scheme 36. The deprotection-decarboxylation procedure of γ-nitrothioesters

5.4 1,4-addition reactions of MTMs with nitroolefins

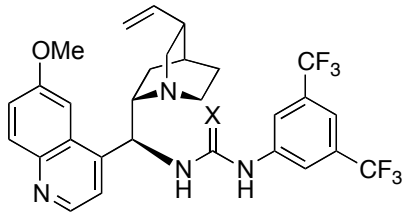
We then studied the influence of different acid labile esters for the organocatalysed 1,4-addition reactions of MTMs to nitroolefins. We decided to compare *p*-methoxy-benzyl (PMB) esters **29** with *tert*-butyl esters **28**. Thus, we examined their relative reactivity under the same reaction conditions. Additionally, we also determined the stereoselectivity by analysing the γ-nitrothioesters obtained after deprotection and decarboxylation. In terms of reactivity, both the MTMs **28** and **29** undergo the conjugate addition reaction with nitrostyrene in the presence of by the quinine urea

20. While the products were obtained in similar yields (>95% in both cases), differences were found in the enantiomeric excess observed in the products (Table 2, entry 1).

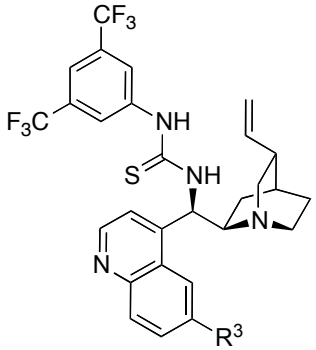
Table 2. Optimization of the structure of the organocatalyst



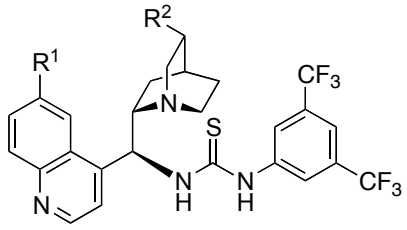
28, PG = *t*Bu
29, PG = PMB



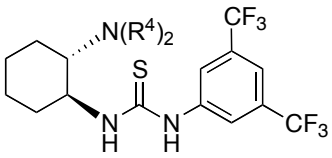
20: X = O **31**: X = S



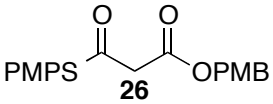
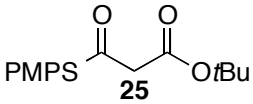
32: R^3 = OMe
33: R^3 = H



34: R^1 = H, R^2 = vinyl
35: R^1 = OMe, R^2 = ethyl



36: R^4 = H
37: R^4 = Me

			 **26**		 **25**	
entry	catalyst[a]	time (h)	Conversion (%)[b]	ee (%)[c]	Conversion (%)[b]	ee (%)[c]
1	**22**	24	quant.	86 (*S*)	quant.	77 (*S*)
2	**31**	6	quant.	85 (*S*)	quant.	78 (*S*)
3	**21**	6	quant.	84 (*S*)	quant.	79 (*S*)
4	**33**	24	50	78 (*S*)	50	75 (*S*)
5	**34**	6	quant	90 (*R*)	quant	79 (*R*)
6	**35**	6	quant.	88 (*R*)	quant.	79 (*R*)
7	**36**	24	traces	6 (*S*)	nd	nd
8	**37**	24	10	2 (*S*)	traces	10 (*S*)

[a] Reactions were performed at RT using 1.1 eq. of nitrostyrene and 5 mol % of the catalyst [b] Estimated by TLC analysis. [c] Determined by chiral-phase HPLC analysis.

While the PMB substituted MTM provided the products with 86 % ee, the *tert*-butyl analogues gave products with only 78 % ee. As these differences were rather small we decided to further study the influence of different catalyst on the levels of stereoselectivity in the reaction of both MTMs with nitrostyrene (Table 2).

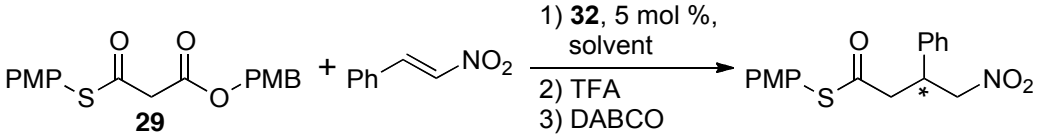
Regardless of the catalyst used, higher ee values were obtained with MTMs bearing the PMB protecting group **29** in comparison to the *tert*-butyl MTMs **28**. Moreover the levels of enantioselectivity obtained with **29** strongly depended on the catalyst structure whereas regardless of the catalyst, nearly the same ee values were obtained for the *tert*-butyl ester **28**. The *epi*-quinine urea catalyst **20** promoted the reaction with an appreciable slower rate compared to the epi-quinine thiourea **31**, while inducing the same levels of enantioselectivity (Table 2, entry 1 and 2). Amongst the cinchona alkaloid thiourea derivatives (Table 2, entries 2-6) quinidine **32** proved to be the best promoter being able to catalyse the formation of γ-nitrothioesters in 90% ee. Catalyst **36** (Table 2, entry 7), that bears a primary instead of a tertiary amine, proved to be ineffective demonstrating the importance of tertiary amines as basic centres. Finally Takemoto's catalysts **37** possessing a different spatial arrangement of the two crucial functionalities was found to be a poor promoter for 1,4-addition reactions between MTMs and nitroolefins (Table 2, entry 8) demonstrating that not only the presence of the right functional groups is required but also that their relative orientation have a strong influence on the activity of the catalyst.

5.5 Optimisation of the reaction conditions

Having found the *p*-methoxybenzyl substituted MTM **29** and the *epi*-quinidine thioureas derivative **32** as the best substrate and catalyst, we investigated different reaction conditions and their influence on the reaction outcome. Different reaction conditions were varied and the changes in conversion and selectivity were analysed.

We started our studies by investigating the influence of the solvent on the stereoselectivity induced in the conjugate addition products. Dramatic differences were observed from one solvent to another.

Table 3. Screening of different solvents



entry	solvent	time (h)	conversion (%)[a]	ee (%)[b]
1	toluene	6	quant.	90
2	CH_2Cl_2	6	quant.	84
3	Et_2O	6	quant.	83
4	THF	24	75	79
5	acetone	24	75	77
6	DMF	24	traces	nd
7	CH_3CN	24	75	75
8	benzene	6	quant.	87
9	heptane	6	quant.	75
10	EtOAc	24	75	83
11	EtOH	6	quant.	59

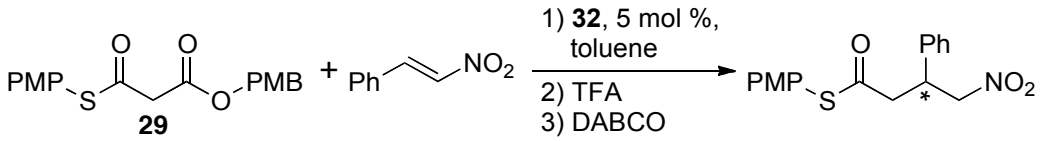
[a] Estimated by TLC analysis. [b] Determined by chiral-phase HPLC analysis.

Reactions performed in aromatic solvents provided the γ-nitrothioesters in short reaction times and high enantioselectivity (Table 3, entries 1 and 8). Polar aprotic solvents allowed for fast rates but enantioselectivity was lowered by 10-15 % ee compared to toluene (Table 3, entries 2-7 and 10). Solvents that are able to act as H-bond acceptors, therefore being bound to the thiourea moiety decreased appreciably the conversion of the starting materials into products (for example DMF, Table 3, entry 6). Additionally, lower enantioselectivities were observed confirming once again the crucial role of H-bond interactions between the catalyst and the reaction partners. The use of protic solvents such as ethanol (Table 3, entry 11) gave fast conversions but very poor enantioselectivity. The observation that protic and polars solvents as ethanol allow for high reactivity but only poor stereoselectivity suggests that the selectivity of the reaction is best when the non-bonding interactions between the catalyst and the substrates are not disrupted by interactions of the solvent with the catalyst.

The concentration is often an important parameter for reactivity and stereoselectivity. In the case of H-bond activation the probability of interaction between the donor and

the acceptor is increased if the concentration of the species is high. In order to probe the influence of concentration on this reaction we evaluated different dilutions by varying the concentration of the MTMs between 1M and 0.1 M using toluene as the reaction medium. Whereas we saw no influence on the stereochemical outcome of the reaction by varying the concentration (Table 4) the reaction rate decreased significantly at lower concentration as expected in the presence of 5 mol % of the *epi*-quinidine thiourea catalyst. We selected a concentration of 0.1 M as optimal in terms of solubility of the starting materials while maintaining good reactivity (Table 4).

*Table 4. Screening of different concentrations of MTM **29***

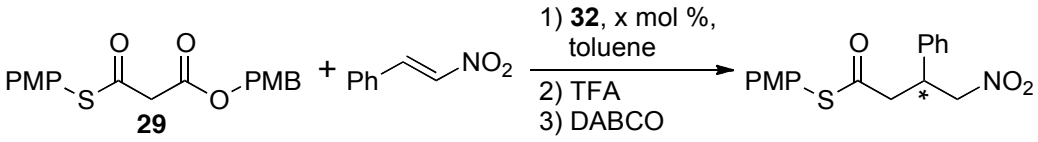


entry	[**29**], mol/l	time (h)	conversion (%)[a]	ee (%)[b]
1	1	3	quant.	90
2	0.8	6	quant.	90
3	0.6	6	quant.	90
4	0.4	8	quant.	91
5	0.3	12	quant.	91
6	0.2	12	quant.	92
7	0.1	12	quant.	92

[a] Estimated by TLC analysis. [b] Determined by chiral-phase HPLC analysis.

Catalyst loadings and different temperatures were also examined. Pleasingly, we found that decreasing the catalyst loading to 1 mol % resulted in longer reaction times of 24 hours with no effect on the enantiomeric excess of the γ-nitrothioesters (Table 5, entries 1-3). A big increase on the ee values was observed when the reaction temperature was reduced. Decreasing the temperature from RT to -50 ˚C resulted in a dramatic increase in the stereoselectivity from 90 to 98 % ee (Table 5, entries 3-6). At lower temperature the low solubility of MTMs prevented the conversion of the staring materials into products (Table 5, entry 7).

Table 5. Optimisation of the catalyst loadings and the reaction temperature



entry	mol %	time (h)	T (˚C)	conversion (%)[a]	ee (%)[b]
1	5	6	RT	quant.	90
2	3	12	RT	quant.	90
3	1	24	RT	quant.	90
4	1	24	0	quant.	91
5	1	24	-20	quant.	94
6	1	24	-50	95[c]	98
7	1	24	-60	No conversion[d]	nd

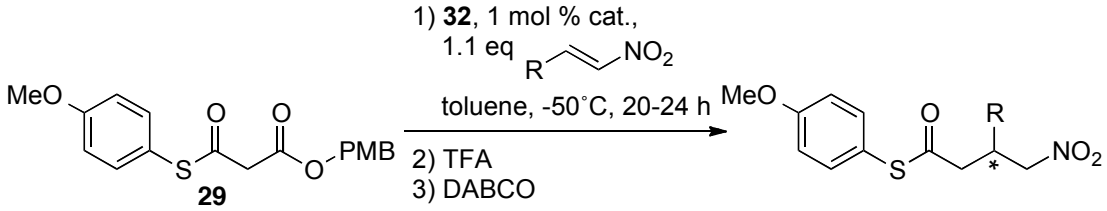
[a] Estimated by TLC analysis. [b] Determined by chiral-phase HPLC analysis. [c] Isolated yield. [d] MTM insoluble in the reaction mixture

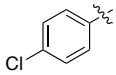
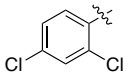
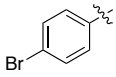
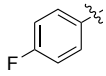
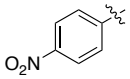
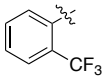
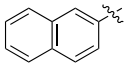
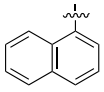
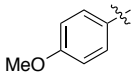
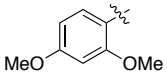
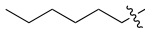
5.6 Substrate scope

Our investigations on the reaction conditions revealed that as little as 1 mol % of the epiquinidine thiourea catalyst **32** promotes the straightforward 1,4-addition reaction of MTMs **29** to nitrostyrene. Notably, only a slight excess of the nitroolefin is required to convert quantitatively the MTM **29** into the products, as 1.1 equivalent of the electrophile is added to the reaction mixtures. The best solvent was found to be toluene and at an optimal temperature of -50˚C and a concentration of the MTM **29** of 0.1 M, the g-nitrothioesters were obtained in 95 % yield and 98% ee.

Having found the best condition for the organocatalysed 1,4-addition reaction of MTM 29 to nitrostyrene, as next step we explored the substrate scope of this transformation to evaluate whether the reaction conditions are general with respect to the nitroolefin (Table 6).

Table 6. Substrate scope of the 1,4-addition reaction of MTMs to nitroolefins



entry	R	mol (%)	yield (%)[a]	ee (%)[b]
1		1	95	98
2		1	96	99
3		1	92	98
4		1	>98	99
5		1	>98	98
6		1	>98	94
7[c]		5	82	97
8		1	>98	99
9		5	>98	>99
10		3	96	97
11		1	98	98
12		3	85	98
13		5	98	91
14[d,e]		20	>98	91
15[d,e]		20	91	94

[a] Isolated yield. [b] Determined by chiral-phase HPLC analysis. [c] nitroolefin was not fully soluble. [d] Reaction took 36 h for complete conversion. [e] 2 eq. of nitroolefin with respect to MTM was used

These results demonstrate that in comparison to MAHTs that provide the same products when reacted with nitroolefins,[33] the MTMs are significantly more reactive, and thereby allow for the use of significantly lower amounts of the catalyst, near equimolar amounts of the reactants and shorter reaction times. Furthermore, the products were obtained in significantly higher stereoselectivities and fewer side

reactions occur. These features outweigh the lower atom economy of the MTMs compared to MAHTs and demonstrate their value as chemically robust yet sufficiently reactive thioester enolate equivalents.

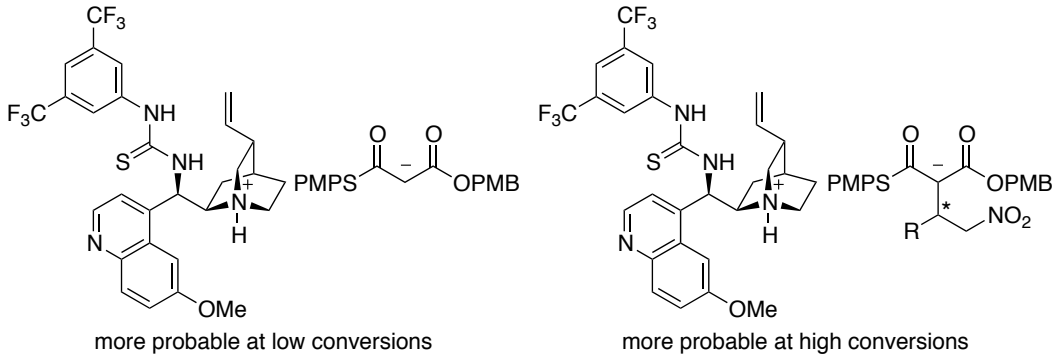
Pleasantly, all the tested nitroolefins reacted in the presence of MTM **29** originating the products in high yields and enantioselectivity (Table 6). Electron poor and electron rich aromatic nitroolefins as well as aliphatic nitroolefins undergo the organocatalytic conjugate addition reaction with MTM **29**.

As indicated in Table 6, the nature of the nitroolefin influences modestly the selectivity of the reaction. High levels of enantioselectivity were always obtained (91->99% ee). In case of less reactive electron rich nitroolefins somewhat higher catalyst loadings had to be used in order to achieve full conversion in reaction times of 24 hours. While nitrostyrene reacted in the presence of as little as 1 mol % of the alkaloid, 3 mol % and 5 mol % respectively of the *epi*-quinidine thiourea catalyst were necessary to convert the *4*-methoxyphenyl substituted nitroolefin and the 2,4-dimethoxyphenyl substituted nitroolefin to the conjugate addition products.

The most challenging substrates proved to be aliphatic nitroolefins (Table 6, entries 14-15). They required longer reaction times and higher catalyst loadings compared to the aromatic ones. The presence of sp^3 hybridized carbon substituent at the double bond renders the nitroolefins sterically less accessible for the nucleophile and render the double bond more electron rich because it is not conjugated with aromatic rings. The observed lower rate of conversion of the 4-nitrophenyl substituted nitroolefin demonstrates the importance of the concentration of the reagents in solution (Table 6, entry 7). As the nitroolefin was only partially soluble under the reaction condition, complete consumption of the starting material was only achieved when higher catalyst loadings were used.

Important for the complete transformation of the substrates into products was the low solubility of the resulting γ-nitromonothiomalonates. These molecules still possess an acidic proton (the calculated values are in the same pK_a range between 9 and 10). As a consequence acid base equilibria are still possible between the catalyst and the products, so, when most of the starting materials are converted into the products, it is more probable that the catalyst deprotonates the products rather than the MTMs, thus leading to low rates at high conversions (Scheme 37). As the product was formed it precipitated from the reaction medium avoiding its participation in acid-base

equilibria. More soluble products, as those derived from the use of aliphatic nitroolefins, typically required higher catalysts loading to complete the reaction in short reaction times. Consequently, aliphatic nitroolefins required higher catalyst loadings because of both their lower reactivity as well as the higher product inhibition of the catalyst.



Scheme 37. Acid base equilibria between catalyst and MTMs

5.7 Determination of the absolute configuration

The absolute configuration of the stereogenic centre of the 1,4-addition products was expected to be *R* in contrast to the work published by Lubkoll[33] were the *pseudo*-enantiomeric catalyst was used. The lactams accessible via the Zn mediated reduction-cyclisation crystalized when, to their solution in CH_2Cl_2, portions of pentane were added allowing us to determine the absolute configuration of the stereogenic centres by X-ray crystallography.

The lactam **38** bearing a *p*-bromophenyl substituent gave crystals that were analysed by X-ray crystallography. The heavy bromine atom allowed the unambiguous determination of the absolute configuration of the stereogenic centre that was confirmed to be *R* (Figure 8).

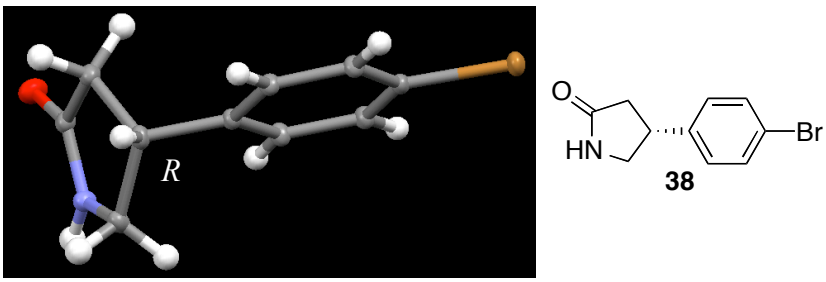
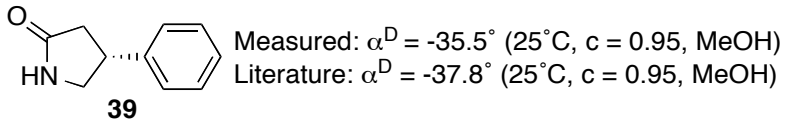


Figure 8. X-ray structure of p-bromophenyl pyrrolidinone

The phenyl lactam **39**, obtained by the already mentioned Zn mediated reduction-cyclisation reaction of the γ-nitrothioesters, was obtained and fully characterized as single (*R*)-enantiomer. A complete set of data is reported in the literature, including its optical rotation.[39] The optical rotation of the same compound synthesised with the described organocatalysed methodology, was measured. Thereby, the absolute configuration was confirmed to be *R* with a second independent technique (Figure 9).

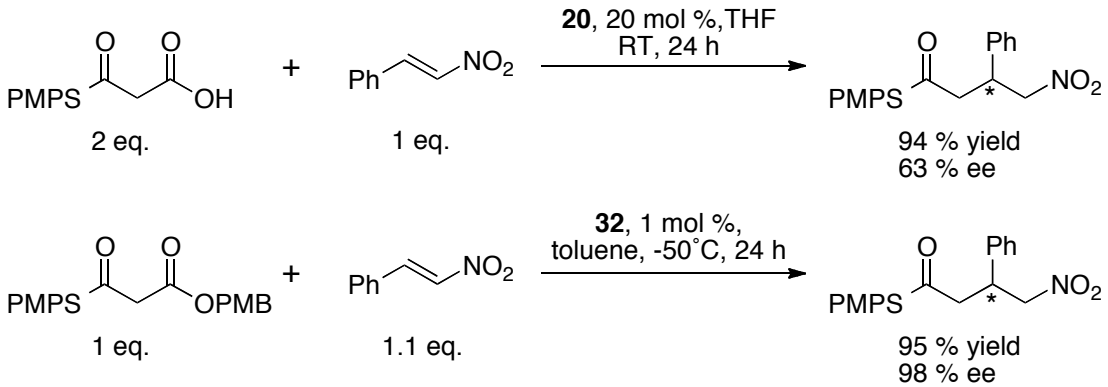


39

Figure 9. Optical rotation of phenyl-substituted pyrrolidinone

5.8 Comparison between MAHTs and MTMs

As already described at the beginning of this chapter the synthesis of MTMs requires more steps than the synthesis of MAHTs. Moreover, two additional steps are required to perform the deprotection and the decarboxylation to access the addition products.
In this chapter we described the 1,4 addition reaction of MTMs to nitroolefins as a very efficient chemical transformation where high yields and enantioselectivities were reported. To evaluate whether the use of MTMs is overall advantageous over the use of MAHTs we compare the two protocols to assess if the higher efficiency justifies the additional steps.



Scheme 38. Organocatalysed addition of MAHTs and MTS to nitrostyrene

The reactions shown in Scheme 38 reveals that some parameters are greatly improved. Comparing the addition reaction of MAHTs or MTM to nitrostyrene, the catalyst loading is decreased by a factor of 20 to as little as 1 mol %, the ratios between the substrates is almost equimolar and the stereoselectivity is increased

dramatically to 98 % ee. Furthermore, no side products were observed in the Michael addition reaction of MTMs to nitrostyrene, whereas the decarboxylative addition reaction of MAHTs always produced at least 1 eq. of acetylated thiol as a side product. An improved reactivity and selectivity was generally obtained for all of the tested nitroolefins. The less reactive the nitroolefin, the more pronounced was the positive influence of MTMs over MAHTs. For example, whereas the conjugated addition reaction of MAHT to the cyclohexyl substituted nitroolefin provided the product only in 16 % yield and 63 % ee, the same product was obtained in nearly quantitative yield and excellent enantioselectivity when MTMs were used (Table 1 and Table 6).

Other examples are the highly electron-rich nitrostyrenes such as the 2,4-dimethoxy substituted derivatives. When MAHT was used no conjugate addition reaction products were formed and the starting material together with acetylated thiol, derived from the decarboxylation of the MAHTs without forming the new C-C bond, were recovered. MTMs added smoothly to the same nitroolefin yielding with as little as 5 mol % of the catalyst the product in high yields and stereoselectivity (Table 5, entry 13). This demonstrates the broader substrate scope of the reaction using MTMs rather than MAHTs.

In conclusion MTMs not only provided the product in higher yields and stereoselectivity than MAHTs, but also allowed for the use of lower catalyst loadings and an almost equimolar ratio of the reactants. Further benefits of the use of MTMs are the lack of side products and the applicability of the strategy for a very broad variety of nitroolefins with very different properties.

5.9 Environmental factor (E factor)

Atom economy was defined by Trost as “the the maximization the number of atoms of all raw materials that end up in the products”.[40] The organocatalytic addition of MTMs to nitroolefins possess a decreased atom economy in comparison to the decarboxylative addition of MAHTs to nitroolefins due to the more complex synthesis of the starting material and the additional steps for the deprotection and decarboxylation of the product. However, we thought that efficiency is not only the number of the atoms of the reactants that are retained in the products, but is related to the whole efficiency of our process. For example, also purifications steps also

contribute to the atom economy of a given reaction and contribute largely to the economy of a process. Thus, we assumed that the Environmental Factor (E-factor) introduced by Sheldon could serve as a tool to compare the two different processes.[41] With the goal of creating tools to determine the efficiency of industrial processes, Sheldon defined the E-Factor as the ratio between the amount of waste that is generated per kg of product produced (Table 7).

The following formula is used for the determination of the E-factor:

$$\text{E-factor} = \text{total waste (kg)/product (kg)}$$

Table 7. Typical E-factor values for different branches of chemical industries

Industry sector	Annual production (t)	E-factor	Waste produced (t)
Oil refining	10^6-10^8	Ca. 0.1	10^5-10^7
Bulk chemicals	10^4-10^6	<1-5	10^4-$5*10^6$
Fine chemicals	10^2-10^4	5-50	$5*10^2$-$5*10^5$
Pharmaceuticals	10-10^3	25-100	$2.5*10^2$-10^5

According to the definition of Sheldon the waste is defined "as everything but the desired product. It takes the chemical yield into account and includes reagents, solvent losses, process aids and, in principle, even fuel".[41] So when calculating the environmental factor of an asymmetric catalysis reaction one should consider unreacted starting materials, side products, undesired stereoisomers produced, solvents, purification media (silica gel, water solutions used for extractions), catalysts and the fuel used for the production of the energy needed for the process as waste, while the denominator only represents the quantity of the desired stereoisomer.

The E-factor, taking into account the waste generated in a process, is not only measuring the efficiency of a single process but also gives an idea of the efforts needed to synthesize a desired molecule especially when multistep synthesis is required. Catalyst loadings have a dramatic influence especially if the synthesis of the catalyst is taken into account.

After having described the features of the E-factor and having evaluated the advantages of using such a parameter for the comparison of the 1,4-addition reaction

of MTMs or MAHTs to nitroolefins, we applied the concepts to these two catalytic transformations.

We calculated the E-factor of our systems at different levels in order to understand where each process has its strengths and weaknesses compared to the other.

The three chosen levels are:

Level 1. Only the 1,4-conjugate addition reaction is considered

Level 2. Also the synthesis of MTM and MAHT is considered

Level 3. Also the preparation of the catalysts is considered

We calculated the E-factor for each level comparing the conjugate addition reaction of MAHTs and MTMs with nitrostyrene. For MAHTs we considered both the reaction in THF in which good yields of the products were obtained and in EVE where high enantioselectivities were achieved (see chapter 3, Table 1), (Table 8).

Table 8. E-factor for the 1,4-addition reaction of MAHTs and MTMs to nitrostyrene

Level	MTM	MAHTs in THF	MAHTs in EVE
1	1859	2941	2764
2	3433	3888	3661
3	3492	6063	5722

Generally the determined E-factors are high, which was expected since chromatographic purifications are needed and the solvents are counted as waste whereas they are often recycled in industrial processes.

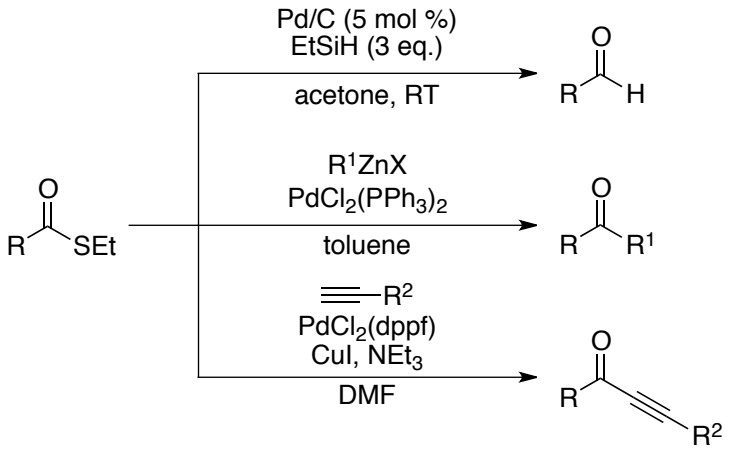
The 1,4-addition reactions (level 1) showed similar E-factors. The high yield and perfect enantioselectivity of the reaction with MTMs resulted in the highest efficiency even if the deprotection and decarboxylation steps are taken into account. The value at this level means that, considering only the step of the 1,4-addition reaction, the lower catalyst loadings, the equimolar ratio of the reactants and the high yields and selectivity greatly balance the additional steps.

At level 2, in which the synthesis of the starting materials are taken into account, the E-factors of the three processes are still in the same range. The merging of the values reflected the longer synthesis of the MTMs compared to MAHTs. But still, also at the second level, the E-factor calculated for the MTMs is the lowest.

While the synthesis of the catalyst is the same for all three processes the required catalyst loadings for the 1,4-addition reactions using MTMs as the nucleophile are dramatically lower. Thus, the impact of the preparation and purification of the catalyst is minimal on the E-factor calculated for the 1,4-conjugate addition reaction of MTMs with nitrostyrene whereas it becomes a major contributor in the case of the addition reaction of MAHTs where high catalyst loadings are required (Table 3, level 3).
In conclusion, the efficiency of these processes depends largely on the amounts of solvents and on the purification steps. Catalyst loadings have a big impact only when catalyst synthesis is taken into account. The longer synthetic procedures for the synthesis of MTMs, involving protection and deprotection steps to access the desired products, were demonstrated to be neither less economic nor less efficient. The use of the protecting *p*-methoxybenzyl group that strongly increases reactivity and selectivity of our system greatly improved the overall efficiency of the 1,4-conjugate addition reaction of MTMs to nitroolefins in comparison to the 1,4-addition reaction of MAHTs to nitroolefins.

5.10 Derivatizations of γ-nitrothioesters

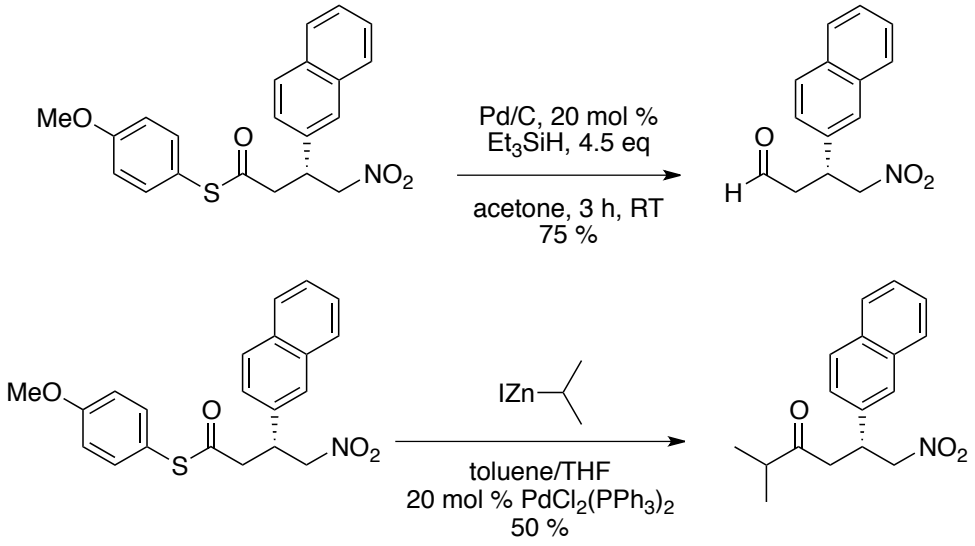
One of the appeals of using thioesters in synthesis is their synthetic versatility and the possibility to access a large variety of functional groups. Nowadays several procedures are known for the direct transformation of thioesters into different chemical entities such as amides, ketones or aldehydes.[3-6] Thioesters enolates can be added to various electrophiles for the introduction of different functionalities. Having obtained molecules of increased synthetic value, the thioesters could function as building block for the synthesis of key intermediates aiming at biologically active or natural compounds.
As described in chapter 2, an important contribution in the development of several strategies for the conversion of thioesters into various functional groups came from Fukuyama.[3-6] In his research group very efficient procedures for the reduction of thioesters into aldehydes or ketones were developed (Scheme 39).[6d]



Scheme 39. Fukuyama reduction and Fukuyama couplings of thioesters

To demonstrate that the products obtained upon addition of MTMs to nitroolefins are versatile and could serve as building blocks for the development of efficient synthesis of biologically active compounds or natural products, we explored different functionalization strategies.

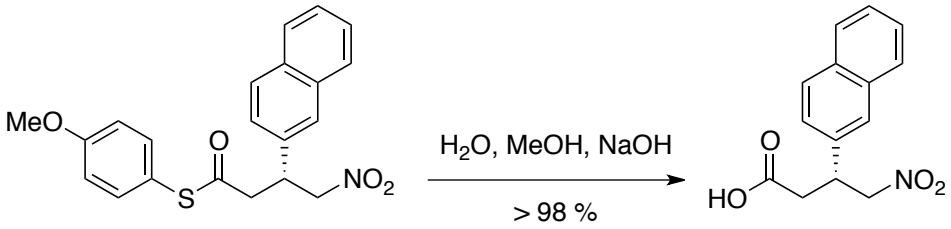
We applied the condition for the Fukuyama reduction to the γ-nitrothioesters obtained in the organocatalyzed reactions. Pleasingly we observed the clean conversion of the γ-nitrothioesters into γ-nitroaldehydes, demonstrating that the Fukuyama reduction is also feasible for these substrates. Next we applied the conditions for the Fukuyama coupling to access ketones. Also in this case clean conversion of the starting material to the new product was observed and γ-nitrothioesters were converted into their *iso*-propyl ketone analogues (Scheme 40)



Scheme 40. Fukuyama reduction and Fukuyama coupling on γ-nitrothioesters

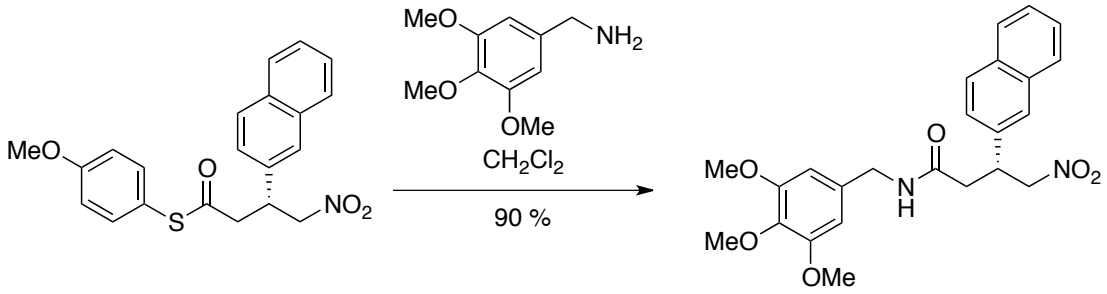
Hydrolysis and amidation reactions are also important transformations since they allow for accessing peptide chemistry or foldamer synthesis starting from thioesters.[42,43]

Thioesters were hydrolysed in the presence of aqueous bases to substitute the thiol with the hydroxyl group, and after acidic work-up the acid was isolated in nearly quantitative yields (Scheme 41).



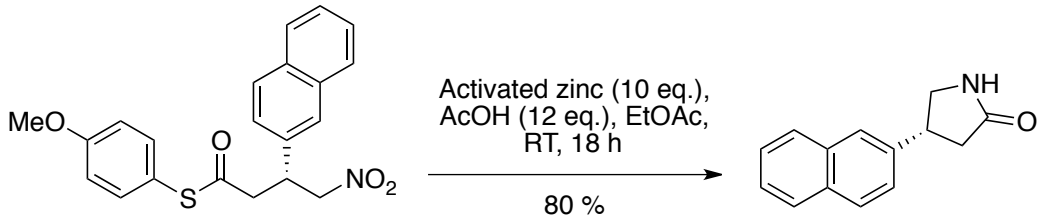
Scheme 41. Hydrolysis of γ-nitrothioesters

Next we explored the amidation reaction of thioesters. We envisioned that upon reduction of the nitro-group, γ-nitrothioesters could be used as γ-aminoacids and therefore serve as building blocks alternative to aminoacids for the synthesis of foldamers. We exposed the γ-nitrothioester to stoichiometric amounts of an amine and we observed the transformation of the thioester into the corresponding amide (Scheme 42).



Scheme 42. Amidation reaction of γ-nitrothioesters

Another interesting transformation we applied to the γ-nitrothioesters is the reduction of the nitro group with the simultaneous ring closure to generate γ-butyrolactames in quantitative yields. The zinc mediated reduction of the nitro-group in the presence of acids and the spontaneous ring closure provided lactames in 80 % yield (Scheme 43).[44]



Scheme 43. Reduction and ring closure of γ-nitrothioesters

5.11 Mechanicistic aspects

Initial mechanicistic studies revealed that MTMs are readily deprotonated by the catalyst. ^{1}H-NMR analysis of mixtures of the catalyst **32** and MTM **29** in deuterated toluene revealed that this acid-base equilibrium is a fast reaction since the catalyst is present in solution only as its salt and no free amine was detected immediately after the preparation of the solution.

To understand whether the catalyst is able to bind to the MTMs via H-bonding interactions, the chemical shift of the protons of the thiourea moiety (Figure 10, H^a and H^b) of the catalyst were analysed. By analysing and comparing with ^{1}H-NMR techniques solutions in d8-toluene containing only the catalyst **32** or a mixture of the catalyst **32** with 5 eq. of MTM **29**, it is possible to determine the presence of the H-bond interactions. These interactions are revealed by the shift of the signals of the protons of the thiourea moiety to lower fields. Indeed, in our case we observed a shift of 0.2 ppms of the signals for H^a and H^b between the solution with only the catalyst and the mixture of the catalyst with the MTM suggesting that the catalyst and substrate are bound via H-bond interactions. The non-covalent interactions can generate an array of plausible structures. Two plausible examples of these complexes are depicted in the cartoon in Figure 10. We propose a reaction mechanism in which the MTM **29** is deprotonated by the catalyst, the thioester enolate is then bound to the catalyst via H-bond interactions. The nitroolefins could react with the enolate and by reprotonation of the resulting nitronate anion the products are formed and the catalyst released (Figure 10).

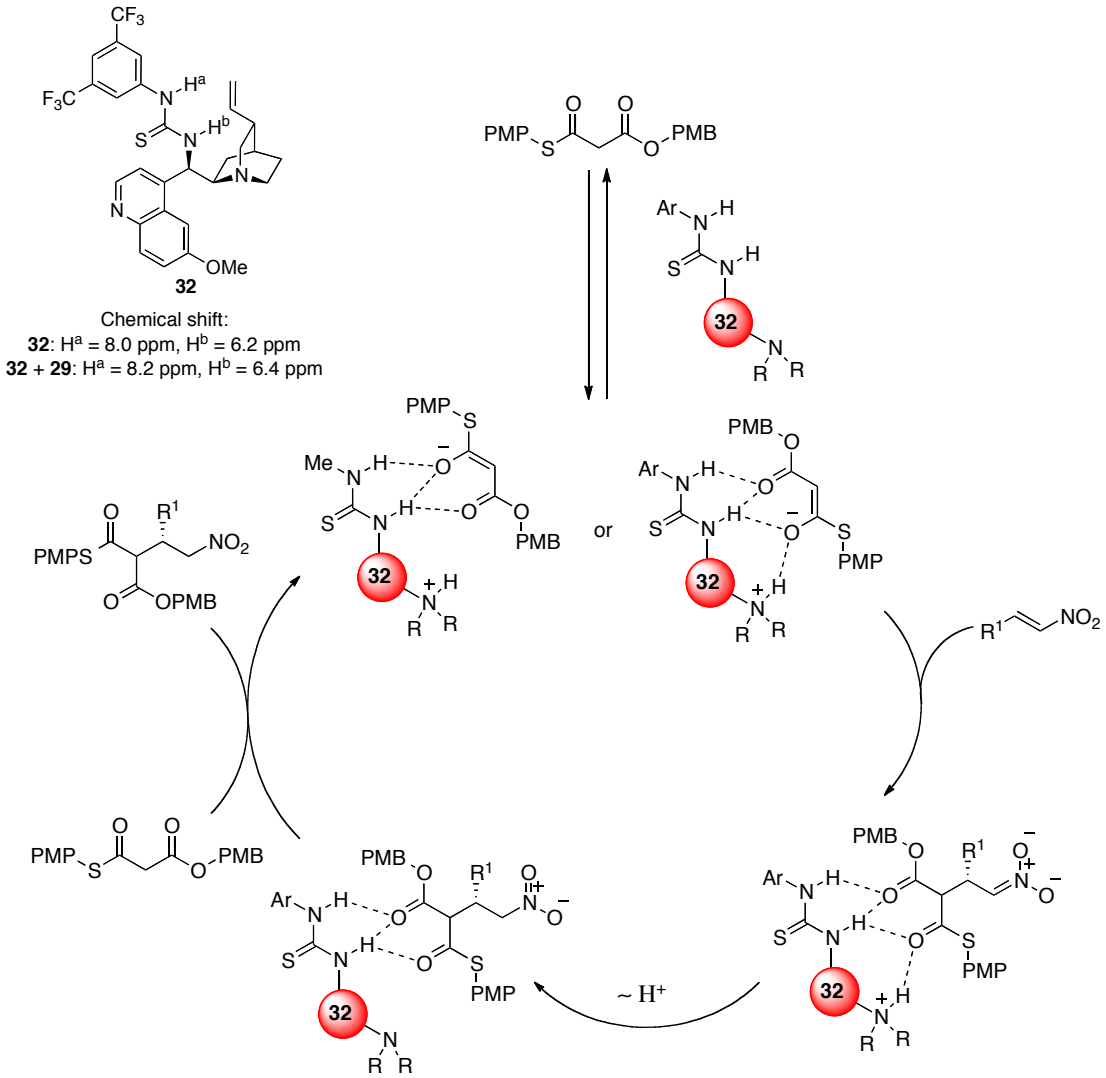


*Figure 10. 1H-NMR chemical shifts of the proton of the thiourea moiety of catalyst **32** and a cartoon of the proposed reaction mechanism,*

5.12 Conclusion

In conclusion we established mono thiomalonates as thioester enolate equivalents for the 1,4-addition reaction to nitroolefins. This transformation takes place under mild organocatalytic conditions.

The methodology has a high catalytic efficiency as the conjugate addition reaction is catalysed by as little as 1 mol % of the *epi*-quinidine thiourea derivative **29**. Additionally, the 1,4-conjugate addition products were isolated in high yields (82 ->98 %) and enantioselectivities (91->99% ee). The conjugate addition reaction has a broad substrate scope since aromatic electron rich, electron poor and aliphatic nitroolefins react in the presence of MTMs to yield the desired γ-nitrothioesters.

The versatility of γ-nitrothioesters was then evaluated and the thioester as well as the nitro group could be transformed into other functional groups. The treatment of the γ-nitrothioesters with amines allowed for the synthesis of amides therefore underlining the possibility to utilise the products of the 1,4-addition reaction for foldamers or peptides synthesis. Aldehydes and ketones were obtained by treatment of the γ-nitrothioesters in the presence of silanes and organozinc compounds, respectively. Hydrolysis of the thioester leads to the generation of the corresponding γ-nitrocarboxylic acids. Cyclic structures such as γ-butyrrolactones are synthesised by reduction of the nitro group and the subsequent spontaneous ring closure allowing for the access to heterocyclic compounds.

An evaluation of the use of MTMs or MAHTs in the 1,4-addition reaction to nitroolefins was also performed to see whether the longer and more complicated synthesis of MTMs in respect to that of MAHTs resulted in lower overall efficiency of the whole organocatalytic process. The calculation of E-factor for these organocatalytic processes allowed us to determine that the efficiency of the 1,4 addition reaction of MTMs is higher than the one of the conjugate addition reaction of MAHTs to nitroolefins. The low catalyst loadings and the increased enantioselectivities and yields, and in general the great improvements obtained when MTMs were used instead of MAHTs for their addition reaction to nitroolefins, do not affect the efficiency of the conjugate addition reaction. The design of the new substrates allowed for the identification of an improved strategy compared to the decarboxylative addition reaction of MAHTs to nitroolefins.

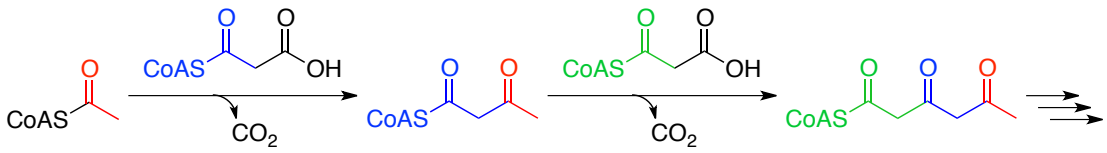
6. Organocatalytic addition reactions of MTMs to aldehydes

6.1 Introduction

As describe in the previous chapter, MTMs added to electron-deficient double bonds under mild organocatalytic condition with high efficiencies. Thus, MTMs proved to be an effective and very promising class of nucleophiles and, with the aim of expanding the scope of the organocatalysed addition reactions of MTMs, other electrophiles were considered as reaction partners. We envisioned that a valuable contribution could come from the reaction between MTMs and aldehydes. Upon addition, molecules β-hydroxythioesters would be generated. We envisioned that these molecules are an interesting building block for the development of further transformation in the aim of an efficient synthesis for target molecules such as polyketides.

6.2 Synthesis of polyketides in nature

As already mentioned in chapter 2 nature uses thioesters to produce polyketides and fatty acids (Scheme 44).[2]



Scheme 44. The decarboxylative addition reaction of malonyl CoA to thioesters for the synthesis of polyketides and fatty acids

The carbonyl groups are then reduced by reductases achieving polyalcohols as single enantiomers. These polyalcohols, polyketides and fatty acids are important classes of compounds in pharmaceutical chemistry since they show prominent activity against numerous diseases.

In Figure 11 some examples of polyketides that showed relevant activity to address different health issues are depicted.

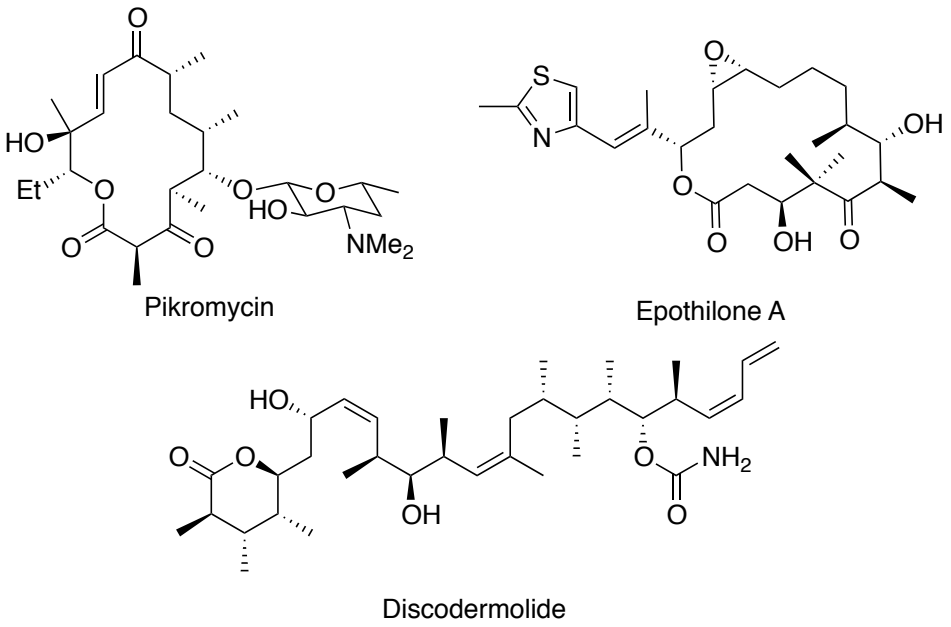


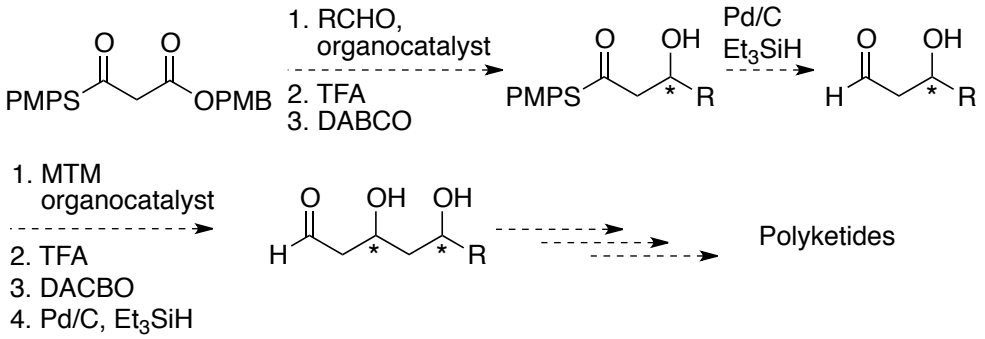
Figure 11. Examples of biologically active polyketides

Pikromycin was studied for its antibiotic properties,[45] the Epothilones attracted attention for their activity in cancer therapy.[46] Their action is explained by the inhibition of the mitotic processes of the cells by interfering with the tubulin. Discodermolide also showed a high activity against cancer. It acts by stabilising the microtubules therefore blocking the cell proliferation of unhealthy tissues.[47]

6.3 Strategy for the addition reaction of MTMs to aldehydes

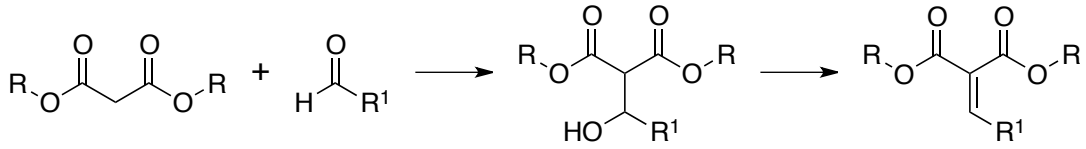
Taking inspiration by polyketide synthases, we envisioned a strategy for obtaining the access to β-hydroxythioesters by reacting MTMs with aldehydes followed by reduction of the obtained β-hydroxythioesters to the corresponding aldol-addition product. The newly generated carbonyl group could then generate β,δ-dihydroxy thioesters upon addition of another molecule of MTM. The iteration of this addition-reduction sequence would finally lead to a stereoselective synthesis of polyalcohols (Scheme 45).

Linear or cyclic polyalcohols are found in many molecules possessing biological activity (e.g. polyketides, Figure 10). Thus, an efficient organocatalytic synthesis of fragments of molecules possessing these interesting motives would provide additional synthetic tools for accessing natural products or biologically active compounds.



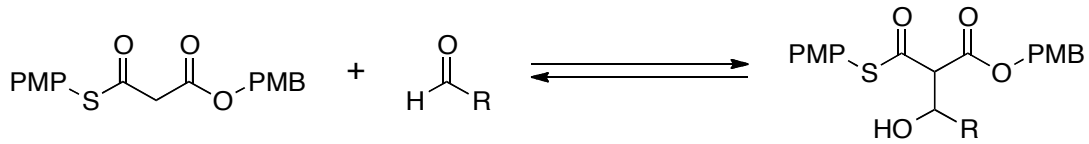
Scheme 45. The envisioned strategy to polyalcohols

The envisioned strategy requires that products, obtained by the organocatalytic addition reaction of MTMs to aldehydes, are generated in high yields and stereoselectivities. To date there are no reported examples for the organocatalysed addition of malonates to aldehydes. One of the main reasons for the lack of catalytic systems for the addition of malonates to aldehydes might be due to the difficulties in avoiding the elimination of a molecule of water that would lead to the conjugated olefins (Knoevenagel condensation, Scheme 46).



Scheme 46. Knoevenagel condensation

In addition to the elimination of a molecule of H_2O, the reversibility of the addition reaction could be another issue that needs to be solved. The β-hydroxy-MTMs can be converted back by the catalyst to the MTMs and aldehydes under the same reaction conditions (Scheme 47).

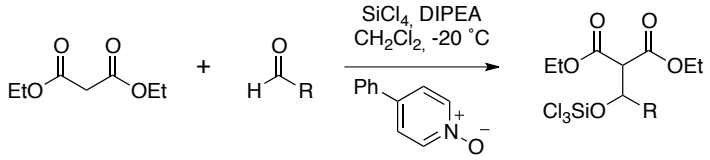


Scheme 47. Thermodynamic equilibrium for the addition reaction of MTMs to aldehydes

6.4 Addition reactions of malonates to aldehydes

The catalysed addition reaction of malonates to aldehydes seems not a widely investigated transformation.

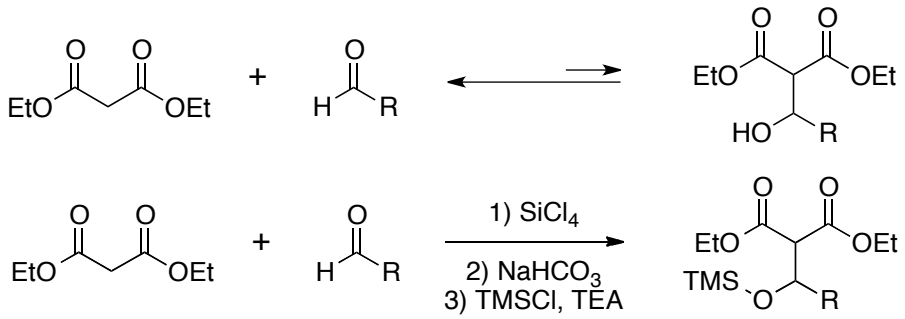
A stoichiometric approach for the addition of malonates to aldehydes was developed in the group of Massa.[48] Tetrachlorosilane, DIPEA and 4-Phenyl-pyridine-*N*-Oxyde promoted the addition of diethyl malonate or β-keto esters to aldehydes (Scheme 48).



Scheme 48. $SiCl_4$ mediated addition reaction of malonates to aldehydes

In these examples the alcohol formed upon addition is trapped by the excess amounts of the tetrachlorosilane. To prevent further decomposition the labile trichorosilane-derived product is subsequently hydrolysed with a diluted $NaHCO_3$ solution and reprotected with the more stable TMS group. The products obtained in this way are then stable enough to undergo the purification processes.

This example shows how difficult the addition of malonates to aldehydes is. Elimination of water is avoided because the alcohol is always present in solution at low temperatures or in a protected fashion (TMS or $SiCl_3$) (Scheme 49). Furthermore, the same mild conditions and the presence of the protecting groups are responsible for the irreversibility of the reaction by trapping the products in their protected form.

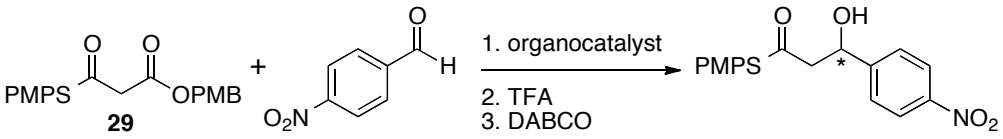


Scheme 49. Addition reaction of malonate to aldehydes in the absence or in the presence of $SiCl_4$

6.5 Addition reactions of MTMs to aldehydes

Being aware of the potential difficulties of the synthesis, we thought that the different properties of MTMs with respect to malonates alone could be enough to allow for the addition of those nucleophiles to aldehydes.

We chose the addition of our MTM **29** with electron poor aldehydes as a benchmark reaction. We explored the addition of MTMs to *p*-nitrobenzaldehyde as very activated electrophiles. We envisioned that the increased electrophilicity of the carbonyl group would allow us to find suitable reaction conditions to yield the desired β-hydroxythioester efficiently (Scheme 50).



Scheme 50. The organocatalysed addition reaction of MTMs to aldehydes

As a starting point we decided to test if the cinchona alkaloid (thio)ureas that had been proved to be excellent catalysts for the 1,4-addition reaction of MTMs to nitroolefins can promote this transformation. Since we never observed the formation of new product in the reaction mixtures, we tested other cinchona alkaloid (thio)urea derivatives. Additionally several different reaction conditions tested. Unfortunately, the desired product was never observed neither after prolonged reaction times nor using high excesses of the aldehyde (up to 10 eq.) and high catalyst loadings (50 mol % - 1 eq.).

We therefore decided to test other catalysts, possessing different moieties able to interact with the substrates. Our previous studies on the addition of MTMs to nitroolefins had revealed that H-bonding donor moieties as well as tertiary amines were crucial to provide activity and selectivity of these catalytic systems. Thus, we decided to vary the structure of the catalyst keeping these key features (Figure 12). The H-bonding modes as well as the basicity of the different candidates were varied with the aim of finding the optimal compromise that would lead to the desired transformation.

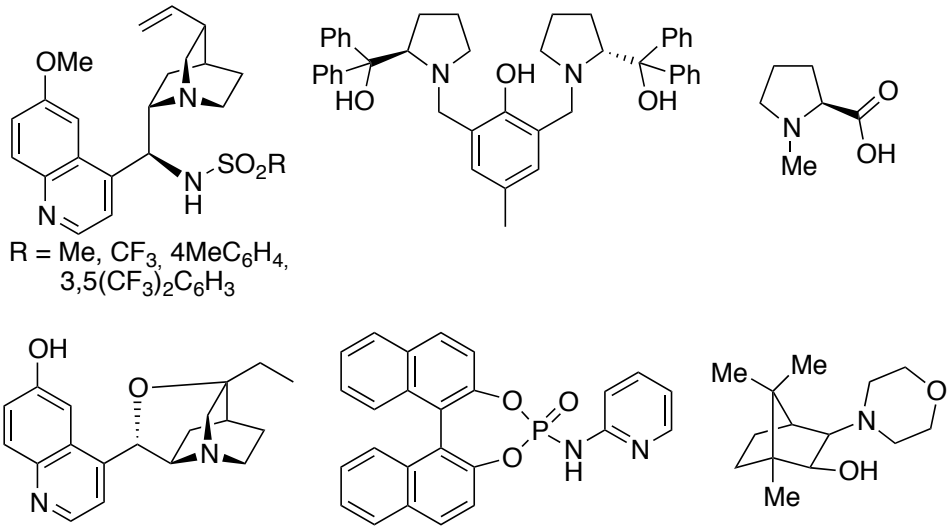
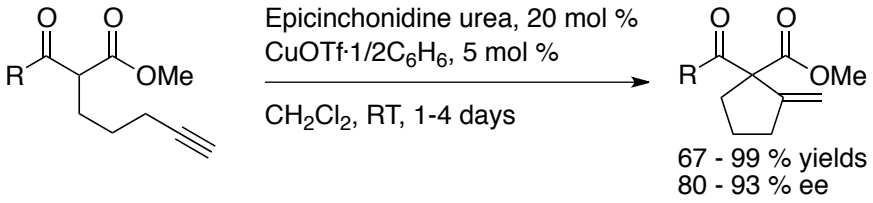


Figure 12. Some of the other organocatalysts tested

Again, in all of these cases no formation of the desired β-hydroxythioesters was observed and the reagents were recovered quantitatively.

6.6 Organo- and Lewis acid-catalysed addition reactions of MTMs to aldehydes

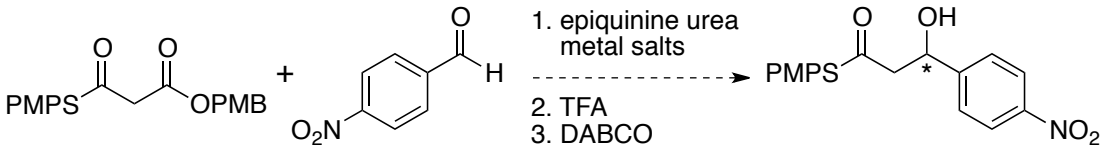
Dixon and co-workers have reported on a Conia-Ene reaction utilising a strategy involving a cinchona urea organocatalyst and a copper salt as a metallic catalyst.[49] The mixed strategy allowed for the straightforward transformation of the starting material. Dixon had shown that both the organocatalyst as well as the copper salt alone are not able to catalyse the Conia-Ene reaction (Scheme 51). Only when the activation of all the functional groups was achieved either via metal-complexation or via H-bond interactions, the conversion of substrates into products was achieved.



Scheme 51. Conia-Ene reaction of β-dicarbonyl compounds

Inspired by this mixed organo- and metal-catalysed approach, we attempted the addition of MTMs to aldehydes in the presence of quinine urea and substoichiometric amounts of metal salts. We thought that this new approach could eventually provide

even better activation of the reactants, therefore inducing efficiently the chemical transformation (Scheme 52).

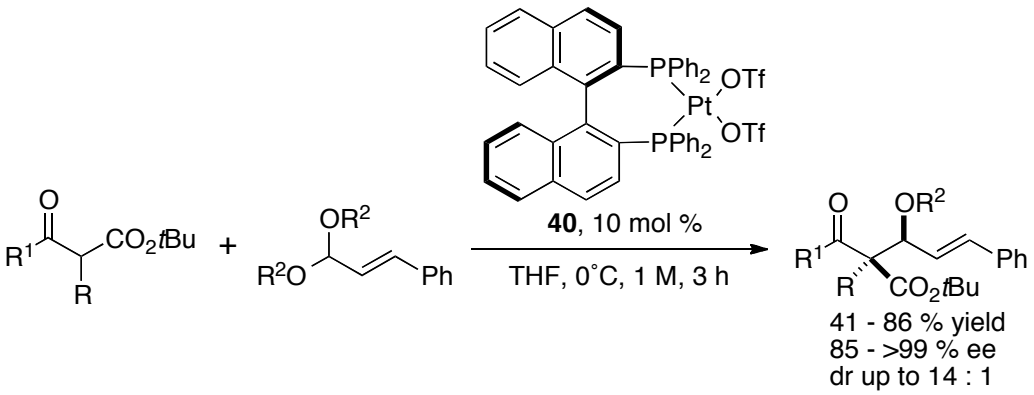


Scheme 52. Addition reaction of MTMs to aldehydes in the presence of organo and metallic catalyst

Several salts were tested. Transition metals, as $Sc(OTf)_3$, $ZnBr_2$, $NiCl_2$ $FeCl_2$ and $CuOTf\cdot1/2C_6H_6$, as well as metal salts from the first two groups of the periodic table, as LiCl, $MgBr_2\cdot OEt_2$ and KBr were tried in a series of test reactions. Once again this approach demonstrated the difficulties to find conditions for the straightforward addition of MTMs to aldehydes since no product formation was observed and complete recovery of the reactants was achieved.

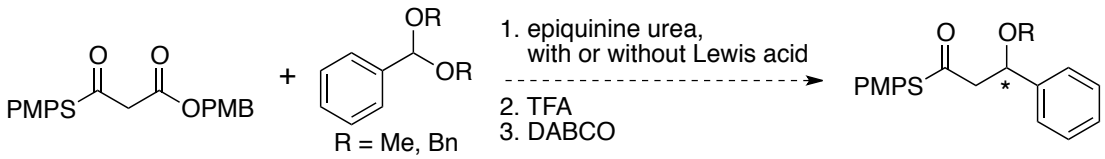
6.7 Organocatalytic addition reactions of MTMs to acetals

A different approach for the addition reaction of β-ketoesters to acetals was reported by Sodeoka and co-workers in 2008.[50] β-ketoesters were reacted with aldehydes protected as acetals in the presence of a platinum based catalyst **40**. When aldehydes were used, no product was obtained since, as discussed previously, the addition products with β-dicarbonyl compounds are in equilibrium with the reactants and the equilibrium is in favour of the reagents (Scheme 53). The use of acetals overcomes the problem of equilibria since no free hydroxyl group is present in the reaction mixture. As a consequence, the backwards reaction to the starting materials is energetically disfavoured.



Scheme 53. Pt catalysed addition reaction of β-dicarbonyl compounds to acetals

With our goal to achieve an organocatalysed reaction in mind we mixed acetals and MTMs in the presence of a cinchona alkaloid catalyst. Additionally, we tested if the addition of a Lewis acid to the reaction mixture could boost the reactivity of the substrates (Scheme 54).

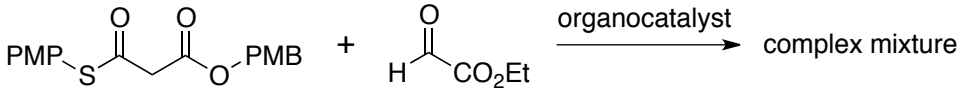


Scheme 54. Addition reaction of MTMs to acetals

Unfortunately, this approach was also not successful. The alkaloids in combination with the Lewis acids were presumably not activating the acetals enough. In order to provide for reactivity, probably complexation of the reactants to transition metals is required. MTMs are unfortunately often not compatible with many transition metals since the thioesters are poisonous for metals and no conversion was observed.

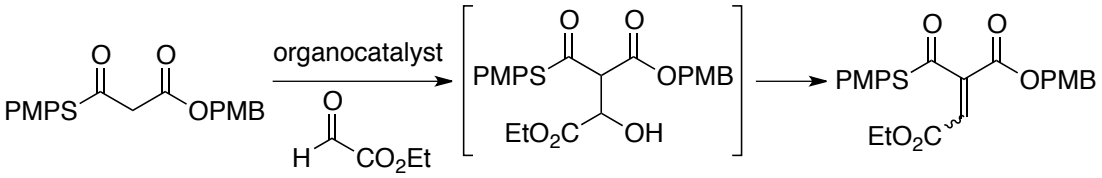
6.8 Addition reactions of MTMs to ethyl-glyoxalate

Highly reactive aldehydes were also tested. Arguably glyoxalic aldehydes are among the most electrophilic aldehydes, as the electron-withdrawing ester, is situated next to the carbonyl group of the aldehyde (Scheme 55).



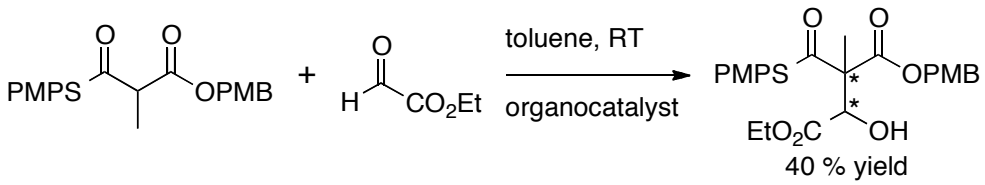
Scheme 55. Addition reaction of MTMs to glyoxalic aldehyde

In this special case we were able to observe conversion of the MTMs into new species. Unfortunately the reaction did not only produce the desired β-hydroxythioester but went further eliminating water to produce the unsaturated compounds and initialising a sequence of reactions including polymerisation (Scheme 56).



Scheme 56. Side reaction between MTMs and glyoxalic aldehyde

To prevent the elimination of water we decided to perform the same transformation using the α-methyl substituted MTM. Conversion was obtained and we could observe the formation of a new species without the generation of any of the overreaction products (Scheme 57).



Scheme 57. Addition reaction of α-substituted MTM to glyoxalic aldehyde

In this particular case the product was obtained in 40 % isolated yield. Additionally, the ^{1}H-NMR spectrum of the isolated compound showed that the product was obtained as a 1:1 mixture of diastereoisomers. Furthermore, the typical peak of aldehydes was always observed in the spectra indicating that also these products are in equilibrium with the starting materials. As soon as the isolated product was kept alone in solution the back-reaction to the reactants took place and the aldehyde and the MTM could be partially recovered (Figure 13).

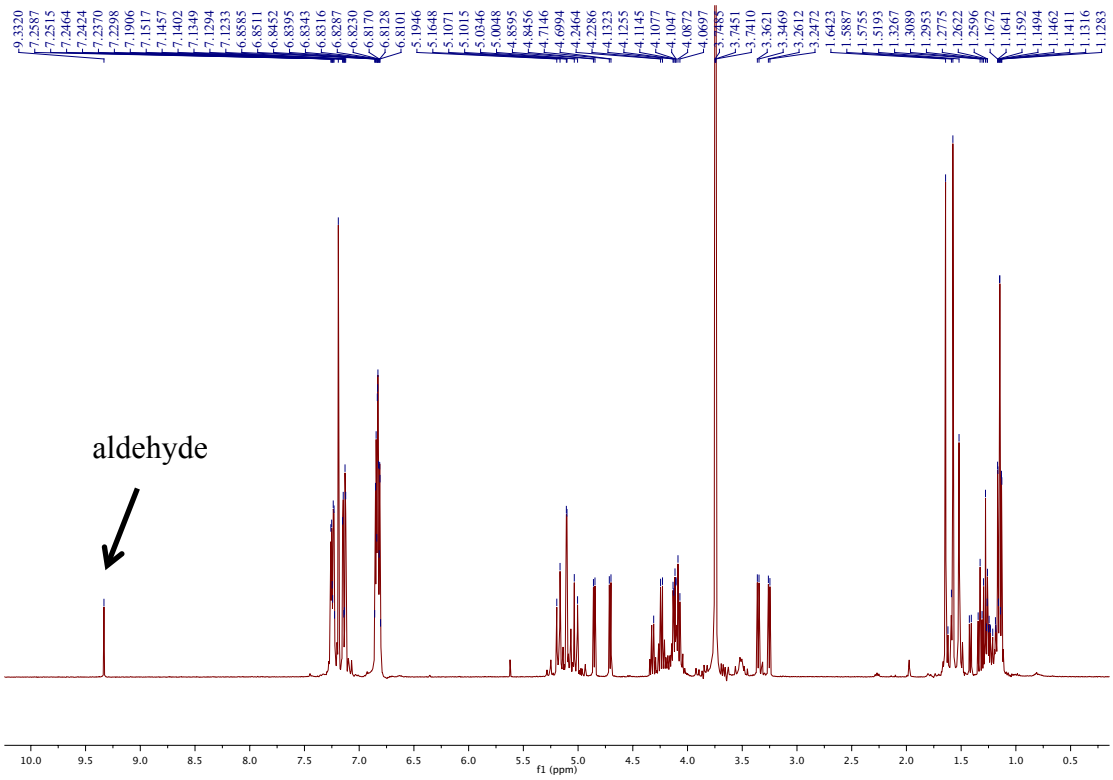


Figure 13. ^{1}H-NMR spectra of the addition product between a-methyl MTM and glyoxalic aldehyde

Other evidences for the back-reaction of the product to the reactants were obtained while analysing the isolated product with chiral-phase HPLC, together with the peaks of the diastereoisomers the Me-MTM was observed (Figure 14).

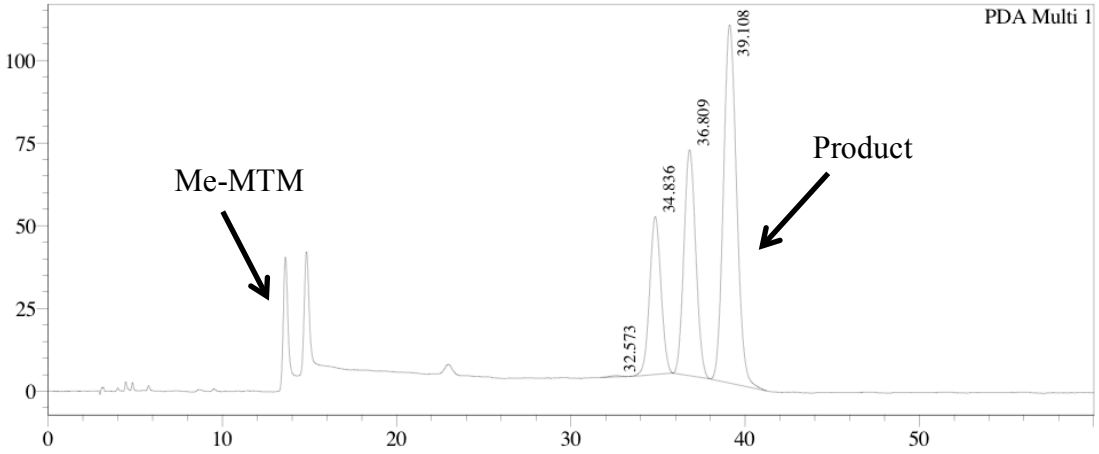


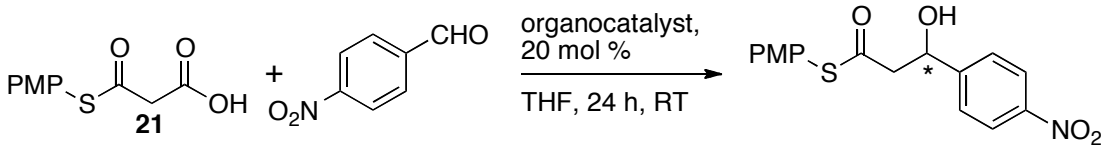
Figure 14. The chromatogram of the addition product of a-methyl MTM to glyoxalic aldehyde

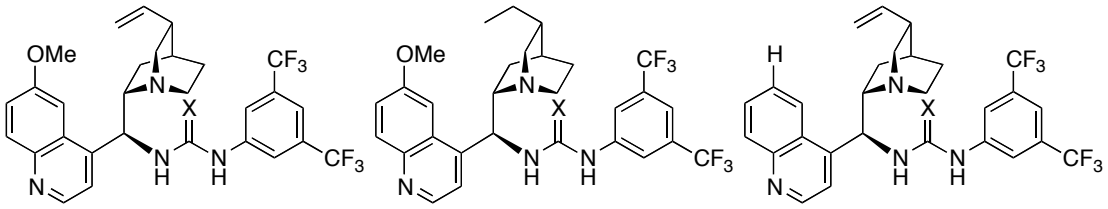
6.9Decarboxylative addition reactions of MAHTs to aldehydes

The reversibility of the reaction and the lack of stereoselectivity encouraged us to change the approach and investigate other nucleophiles.

MAHTs were envisioned to be good candidates for the decarboxylative addition reaction to aldehydes.

Table 9. Decarboxylative addition of MAHTs to p-nitrobenzaldehyde

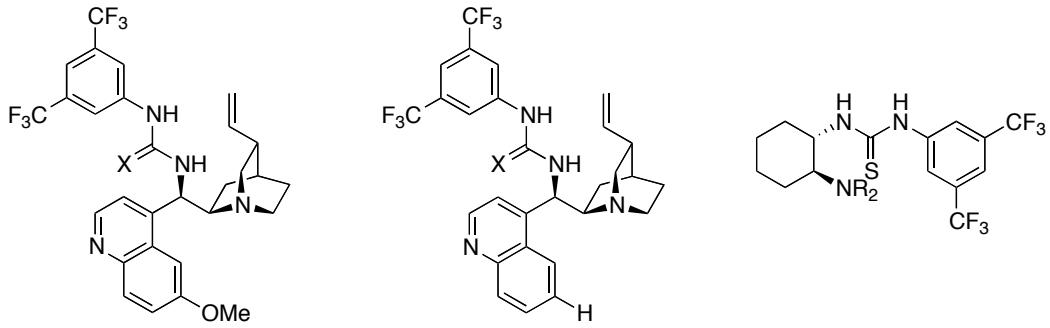




20, X = O
31, X = S

35, X = S

41, X = O
34, X = S



42, X = O
32, X = S

43, X = O
33, X = S

36, R = H
37, R = Me

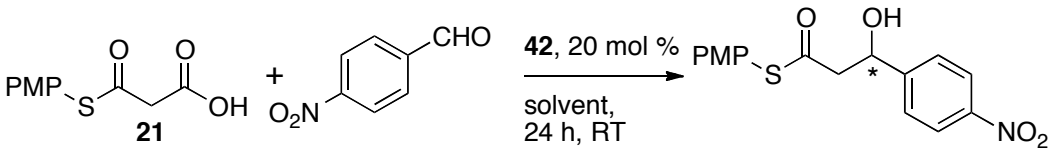
entry	catalyst	conversion (%)[a]	ee (%)[b]
1	**20**	quant.	48
2	**31**	quant.	22
3	**35**	70 %	50
4	**41**	90 %	50
5	**33**	90 %	22
6	**42**	quant.	53
7	**32**	quant.	41
8	**43**	90 %	50
9	**33**	90 %	36
10	**36**	traces	15
11	**37**	quant.	40

[a] Estimated by TLC analysis. [b] Determined by chiral-phase HPLC analysis.

In this case the backwards reaction to the starting materials is avoided by the decarboxylation. As a test reaction we investigated the addition of the previously utilised *p*-methoxythiophenol derived MAHTs **21**[33] in combination with electron poor *p*-nitrobenzaldehyde. Several catalysts were tested in THF and the results are summarised in Table 9. Pleasantly, complete conversion to the products was observed in most of the cases thus demonstrating that the reaction between these thioester enolate equivalent and aldehydes is possible. The investigation of the catalysts allowed for the identification of *epi*-quinidine urea **42** as the best catalyst giving the highest enantioselectivity of the products (Table 9, entry 6). The ees observed showed that cinchona alkaloids could act as catalysts but the reaction parameters still had to be optimised

Different solvents were tested to see whether changing the properties of the medium had an influence on the selectivity of the reaction (Table 9).

Table 10. Solvent screening for the addition reaction of MAHTs to p-nitrobenzaldehyde



entry	solvent	conversion (%)[a]	ee (%)[b]
1	THF	quant.	53
2	Et_2O	50 %	25
3	CH_3CN	50 %	19
4	DMF	traces	49
5	$CHCl_3$	25 %	2
6	CH_2Cl_2	25 %	5
7	acetone	quant.	53
8	EtOH	50 %	23
9	EtOAc	50 %	27
10	benzene	25 %	0
11	heptane	traces	5

[a] Estimated by TLC analysis. [b] Determined by chiral-phase HPLC analysis.

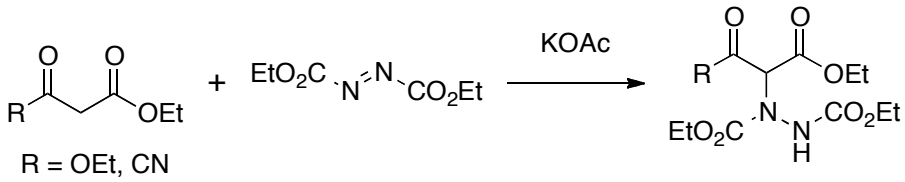
THF proved to be the best reaction medium in terms of both conversion and enantioselectivity. The influence of the temperature was also investigated. Lower temperatures decreased the reactivity to such an extent that at -40 ˚C no conversion was observed. Other aldehydes than *p*-nitrobenzalehyde proved react with MAHTs with lower reaction rates, for example electron rich aldehydes, such as *p*-anisaldehyde, provided the addition product in only 10 % yield at room temperature after 48 hours using 20 mol % of the alkaloid catalyst.

The addition of thioester enolates to aldehydes is a reaction of high importance since the products could be applied to the synthesis of interesting compounds possessing potential biological activity (e.g polyketides). Different approaches are currently under investigation in the Wennemers research group to solve this issue. Combinatorial approaches aiming at the discovery of new catalysts will be tested for the addition reaction of thioester enolate equivalents to aldehydes.

7. Organocatalytic addition reaction of MTMs to diazodicatboxylates

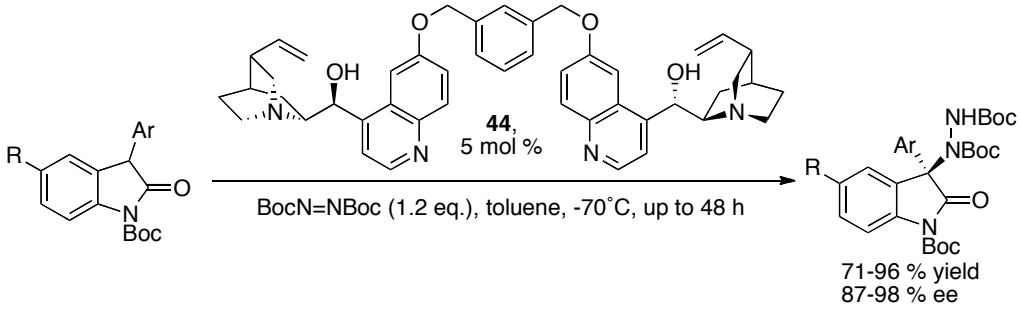
7.1 Introduction

The addition of C-nucleophiles to diazadicarboxylates is a powerful strategy to introduce nitrogen into molecular scaffolds. In 1922, Diels developed the first example for the addition reaction of β-dicarbonyl compounds to diethyl azodicarboxylates.[51] This reaction is promoted by stoichiometric amounts of weak bases such as potassium acetate (Scheme 58).



Scheme 58. The addition reaction of β-dicarbonyl compounds to diethyl azodicarboxylates

The mild and basic reaction conditions allowed for the development of different organocatalytic systems over the last decade.[52] Various research groups investigated these molecules for organocatalysed addition reaction with different nucleophiles.[53]
In 2010, Barbas and co-workers reported their investigation on the addition of 3-aryl indol-2-ones to diazodicarboxylates.[54] 5 mol % of the dimer of quinidine **44** was enough to promote the addition reaction in reasonable time. High yields and enantioselectivities were reported. The system tolerated various substitutions on both the aromatic rings of the substrates without appreciable loss in selectivity (Scheme 59).

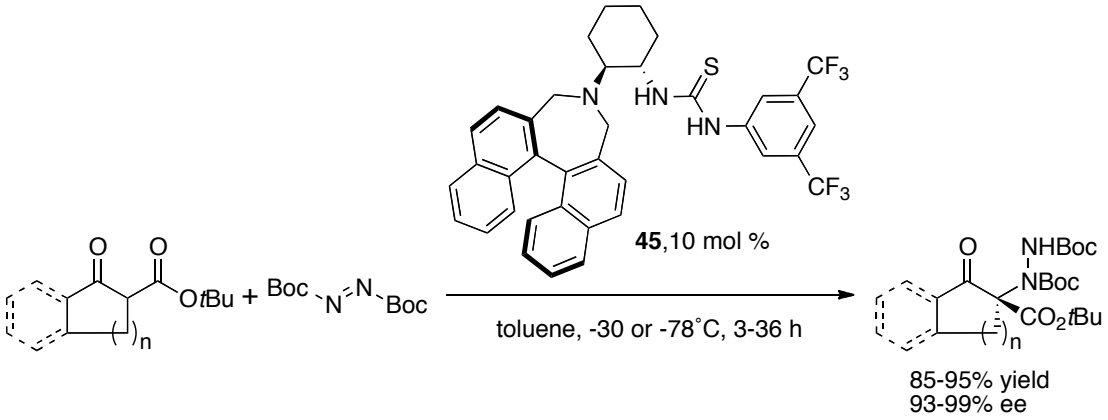


Scheme 59. Addition reaction of 3-aryl indolinones to diazodicarboxylates

7.2 Addition reactions of α-substituted β-cyanoacetates or β-ketoesters to diazodicarboxylates

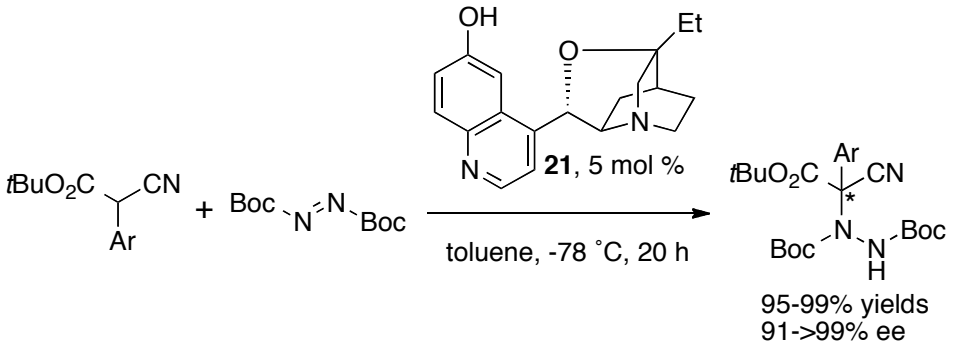
The addition reaction of α-substituted β-cyanoacetates or β-ketoesters to diazodicarboxylates is a reaction of high importance since the products possess quaternary stereogenic centres and a unique functional group density. These products could therefore be used as building blocks for the synthesis of molecules possessing biological activity.

Kim and co-workers used cyclic β-ketoesters as nucleophiles for their addition reaction with Boc protected diazodicarboxylates in the presence of catalyst **45** bearing a tertiary amine and a thiourea moiety (Scheme 60).[55] The reported enantioselectivities and yields were excellent even though long reaction times were required to complete the consumption of the reactants.



Scheme 60. Addition reaction of β-keto esters to diazodicarboxylates

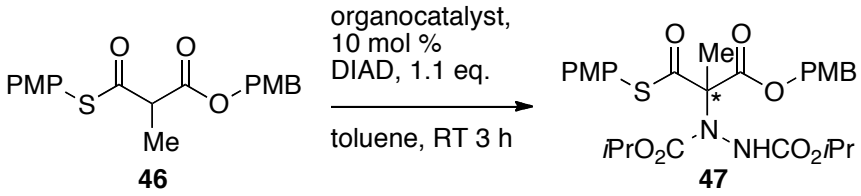
Jørgensen and co-workers reported in 2004 the organocatalysed addition of α-aryl cyanoacetates with di-*tert* butyl diazodicarboxylates.[56] β-isocupreidene **21** was used as the catalyst. As little as 5 mol % of the alkaloid promoted the transformation. Excellent enantioselectivities and yields were reported. The methodology was also extended to β-dicarbonyl compounds that reacted with lower rates and decreased levels of enantioselectivity (Scheme 61).



Scheme 61. Organocatalysed addition of α-aryl cyanoacetates with di-tert butyl diazodicarboxylates

7.3 Organocatalytic addition reactions of α-substituted MTMs to diazodicarboxylates

We decided to investigate the addition of α-substituted MTMs to azodicarboxylates. The reaction between MTMs and diazodicarboxylates would result in the Formation of a new C-N bond. The products thus formed would include a quaternary stereogenic centre; additionally, these simple transformations provide an entry into unnatural α-amino acids applicable in the synthesis of foldamers. As a benchmark reaction, we chose the addition of the *p*-methoxythiophenol-*p*-methoxybenzyl alcohol derived MTM **46** to *iso*-propyl diazodicarboxylate (DIAD) in the presence of cinchona alkaloid (thio)ureas (Scheme 62).



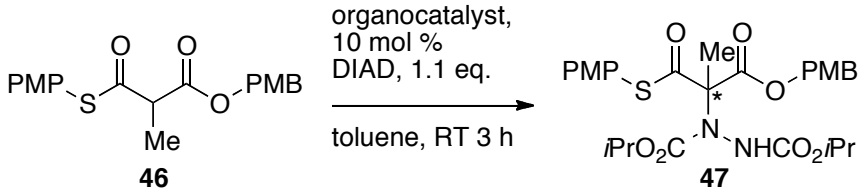
Scheme 62. Addition reaction of α-methyl MTM to DIAD

Satisfyingly, in the presence of 10 mol % of the *epi*-quinine urea derivative **22**, we observed rapid consumption of the starting material and the production of the addition product **47**.

We then tested different cinchona alkaloid (thio)ureas as catalysts in this transformation. All of the catalysts proved to be effective in promoting the addition reaction. Different levels of enantioselectivity were observed depending on the structure of the alkaloid derivatives. Most of the catalysts were catalytically active

and the formation of the product was observed with poor to moderate enantioselectivities in the range of 3-85 % ee (Table 11).

Table 11. Catalyst screening for the addition reaction of a-methyl MTM to DIAD



entry	catalyst	conversion (%)[a]	ee (%)[b]
1	**20, EpiQUU**	quant.	81
2	**31, EpiQUTU**	50 %	76
3	**41, EpiCDU**	quant.	85
4	**34, EpiCDTU**	20 %	67
5	**48, EpiH_2QUU**	quant.	77
6	**35, EpiH_2QUTU**	20 %	65
7	**37, Takemoto's cat.**	50 %	77
8	**42, EpiQDU**	quant.	73
9	**32, EpiQDTU**	20 %	47
10	**43, EpiCNU**	quant.	74
11	**33, EpiCNTU**	quant.	50
12	**Quinidine**	quant.	30
13	**Cinchonine**	quant.	3

[a] Estimated by TLC analysis. [b] Determined by chiral-phase HPLC analysis.

The best results were obtained when MTM **47** reacted with DIAD in the presence of 5 mol % of the epi-cinchonidineurea derivative **41**.

Surprisingly the Cinchonine **41** and the Cinchonidine ureas **43** differed significantly in the levels of enantioselectivity that they induced in the products. These alkaloids are known to be *pseudo*-enantiomers since they often induce the formation of opposite enantiomers with similar levels of enantiomeric enrichment (the ee values for the *pseudo*-enantiomeric catalysts differs typically by 2-3%) although they are diastereoisomers rather than enantiomers. Thus, a deviation in the enantiomeric excess of more that 5% was not expected, but we measured 11% smaller ee values when *epi*-cinchonine urea was used instead of *epi*-cinchonidine urea, possibly

indicating that the spatial orientation of the quinuclidinic ring contributes significantly to the transfer of chirality from the catalyst to the products.

7.4 Optimization of the reaction conditions

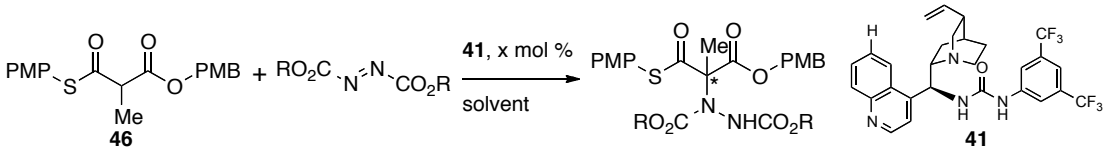
After having found epi-cinchonidine urea derivative **41** as the best organocatalyst, encouraged by the high reactivity of the electrophile and by the good enantioselectivity obtained, we investigated the influence of other reaction conditions. Solvent, catalyst loadings and temperature as well as substituent on the diazodicarboxylate were varied as reported in Table 12.

The influence of the substituent of the diazodicarboxylate was also investigated. While the di-*tert*-butyl diazodicarboxylate performed poorer than the *iso*-propyl substituted, di-benzyl diazodicarboxylate (DBAD) proved to be the most reactive and selective electrophile for the desired transformation (Table 12, entry 1, 13 and 14).

Also the solvent had a big influence on the enantioselectivity of the products. In order to induce enantioselectivity efficiently, apolar solvents gave the best results. Polar solvents, instead, were found to decrease the rates of the reaction and the originated products were obtained with reduced enantioselectivity (Table 12, entries 1-12).

Due to the high reactivity of these diazodicarboxylates the catalyst loading could be decreased to 1 mol % with only a little increase in reaction times and without losses in enantioselectivity. Finally the effect of the temperature was investigated (Table 12, entry 17, 18). Lowering the temperature resulted in lower rates without any significant benefit on the enantioselectivity. Thus, we proceeded to analyse the substrate scope of this addition reaction investigating the influence of different α-substituted MTMs in their organocatalytic addition reaction to diazodicarboxylates.

Table 12. Optimization of the reaction parameters



entry	R	solvent	**38**, mol %	time (h)	conversion (%)[a]	ee (%)[b]
1	*i*Pr	toluene	10	3	quant.	85
2	*i*Pr	CH_2Cl_2	10	24	quant.	65
3	*i*Pr	$CHCl_3$	10	24	quant.	72
4	*i*Pr	THF	10	24	quant.	58
5	*i*Pr	Et_2O	10	24	quant.	65
6	*i*Pr	EtOAc	10	24	50	60
7	*i*Pr	EtOH	10	24	quant.	5
8	*i*Pr	heptane	10	24	50	56
9	*i*Pr	CH_3CN	10	24	25	3
10	*i*Pr	DMSO	10	24	traces	rac.
11	*i*Pr	benzene	10	24	quant.	82
12	*i*Pr	acetone	10	24	75	30
13	*t*Bu	toluene	10	24	90	60
14	Bn	toluene	10	2	quant.	91
15	Bn	toluene	5	4	quant.	91
16	Bn	toluene	1	6	quant.	91
17	Bn [c]	toluene	1	24	90	90
18	Bn [d]	toluene	1	24	50	91

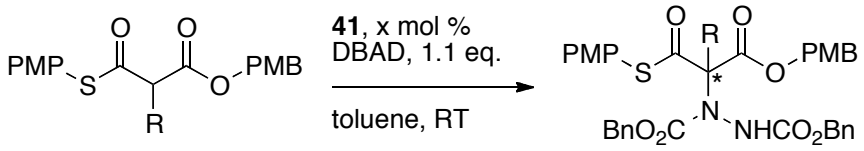
[a] Estimated by TLC analysis. [b] Determined by chiral-phase HPLC analysis. [c] Reaction performed at 0˚C. [d] Reaction performed at -50˚C

7.5 Substrate scope

α-substituted MTMs react with a slight excess of dibenzylazodicarboxylate in toluene at room temperature in the presence of as little as 1 mol % of epi-cinchonidine urea derivative **41** as catalyst originating the addition product in high yields and with 91% ee.

Having investigated these reaction parameters, we then applied the best conditions for the addition of different α-substituted MTMs to dibenzylazodicarboxylate (DBAD, Table 12).

Table 13. Substrate scope for the addition of α-substituted MTMs to DBAD



entry	R	mol %	time (h)	yield (%)[a]	ee (%)[b]
1	Methyl	1	4	> 98	91
2	Ethyl	1	12	94	91
3	Phenyl	5	24	97	90
4	3-thiophene	20	24	94	90
5	Allyl	1	24	98	91
6	Propargyl	1	12	94	90
7	Benzyl	1	24	95	90
8	*n*-Butyl	5	24	98	94
9	*i*-Propyl	20	168	30[c]	nd
10	*c*-pentyl	20	168	30[c]	nd

[a] Isolated yield. [b] Determined by chiral-phase HPLC analysis. [c] Conversion was estimated by TLC analysis

The table shows that the addition of diazodicarboxylates to various substituted MTMs proceeded efficiently in all of the tested cases. The products were isolated in good yields and enantioselectivities (94->98 % yield, 90-94 % ee). Substrates bearing aromatic groups in the α-position (Table 13, entries 3,4) proved to be less reactive and increased catalyst loadings (5 or 20 mol %) were required to consume the starting materials in 24 hours. Thus, longer reaction times and higher catalyst loadings were required to fully consume the starting materials. Longer aliphatic chains also resulted in slower rates and longer reaction times were needed (Table 13, entry 8). Substituents of the type -CH_2R were all tolerated providing the products with similar reactivity and selectivity (Table 13, entries 5-7). More sterically demanding β-branched residues were also tested (Table 13, entry 9-10). *Iso*-propyl and cyclopentyl MTMs were reacted in the presence of 20 mol % of *epi*-cinchonidine urea with

DBAD. These molecules proved to be unreactive substrates for the addition to electrophilic nitrogen-containing molecules. Only partial conversion (ca. 30-40 % estimated on TLC analysis) was observed. Presumably, steric bulk in this case plays a crucial role in shielding the nucleophile and therefore preventing the reaction to take place.

7.6 Functionalization of the products

Next we aimed at the synthesis of interesting small molecules with biological or medicinal activity and, after a screening of the literature, we selected three very promising molecules as candidates (Figure 14). L-Carbidopa[57] is a drug used clinically to treat Parkinson's disease in combination with levodopa. Myriocin or Mycestericin[58] are used as antibiotics. Those molecules are typically synthesised by metal catalysed addition of β-ketoesters to diazodicarboxylates. An alternative synthesis for the crucial polar head of the molecules would be beneficial especially if no metals are involved in the steps where the stereogenic centres are constructed.

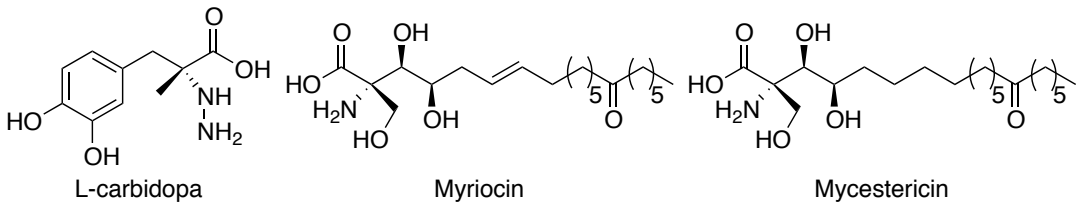
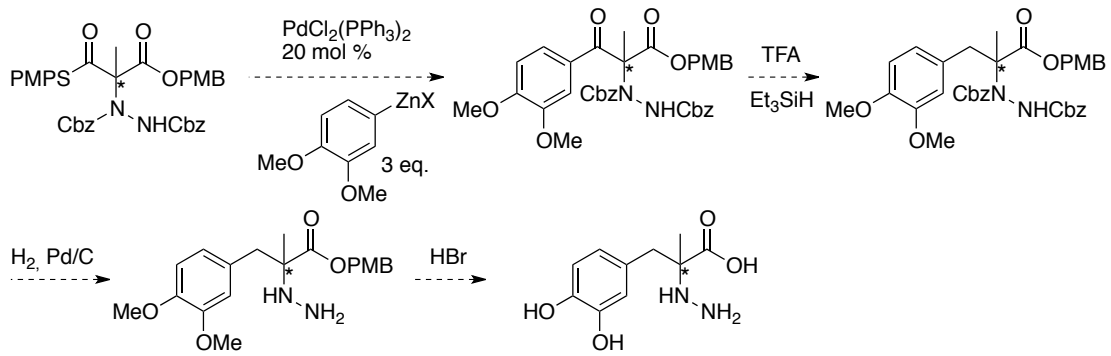


Figure 14. The target compounds

The synthesis of the target molecules depicted in Figure 14 was envisioned starting from the addition product of MTMs to azodicarboxylates. We envisioned that L-carbidopa could be accessible in only few synthetic steps (Scheme 63).

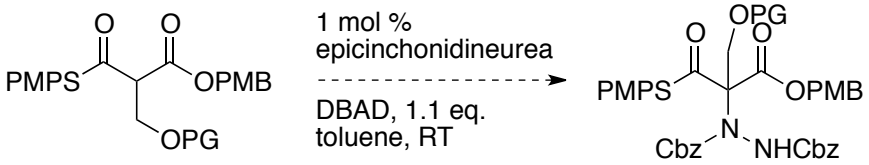


Scheme 63. The sequence to L-carbidopa

Unlike in the case of γ-nitrothioesters, the attempts to convert the addition product to the ketone, via the Fukuyama coupling, failed because the starting α-amino malonate proved to be very unreactive towards this transformation. Different batches of Pd catalyst, different catalyst loadings, differently generated zinc reagents and different reaction conditions were tested without being able to reduce the thioester to the ketone. In all cases either the complete recovery of the starting materials or the decomposition of the starting material providing steric relaxation via decarboxylation reaction of one of the two carbonyl moieties were achieved.

We then attempted to reduce the thioester to the corresponding aldehyde via the Fukuyama reaction. In this case some traces of the aldehyde were detected but it was never possible to achieve complete conversion of the substrates into the products. To boost the reactivity different silanes were tried in different quantities, different amounts of Pd/C were added to the reaction mixtures without any appreciable increase in conversions.

The synthesis of an MTM bearing the protected hydroxyl group was attempted with different strategies with the aim of developing a synthetic pathway to Myriocin or Mycestericin (Scheme 64).



Scheme 64. Addition reaction of α-methylene-β-hydroxyMTM to DBAD

Several disconnections were investigated and different synthons were tested. On the way to the desired starting material the malonate decomposed and it was not possible to isolate any trace of the intermediate products.

7.7 Conclusion

In conclusion addition reaction of α-substituted MTMs to diazodicarboxylates were investigated. All of the obtained products possess a quaternary stereogenic centre and have a high functional group density. The easy synthesis of molecules possessing quaternary stereogenic centres is often a challenge in synthetic organic chemistry. Steric demands are often decreasing the reactivity of the starting material or the

stability of the products. Our approach was designed for having α-substituted MTMs as highly acidic C-nucleophile able to undergo the desired addition reaction to diazodicarboxylates.

The addition products were obtained in 94->98 % yield and high enantioselectivity (90-94 % ee). All the tested substrates reacted under mild organocatalytic conditions and low catalyst loadings were needed for the straightforward addition reaction of α-substituted MTMs to diazodicarboxylates.

Their further functionalization could therefore lead to the synthesis of unnatural aminoacids or other interesting building blocks. Currently in the Wennemers group, different strategies for the functionalization of the products are under investigation for the synthesis of small natural products and biologically active compounds.

8. Addition reactions of MTMs to other electrophiles

Having established the organocatalytic 1,4-addition reactions of MTMs to nitroolefins and the direct addition reaction of α-substituted MTMs to diazodicarboxylates, we attempted to broaden the use of MTMs for the organocatalysed addition reaction to different electrophiles. Thus, various α,β-unsaturated compounds were tested, and the presence of two electron withdrawing groups was found to be necessary in most of the cases for the activation of the double bonds towards the addition of MTMs. Unfortunately this feature was proven to be not always sufficient since no addition reactions were observed when α,β-unsaturated di-cyanides, di-ketones or di-esters were utilised as electrophiles (Figure 15).

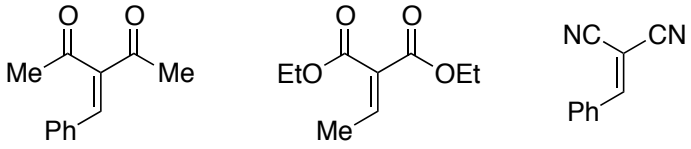
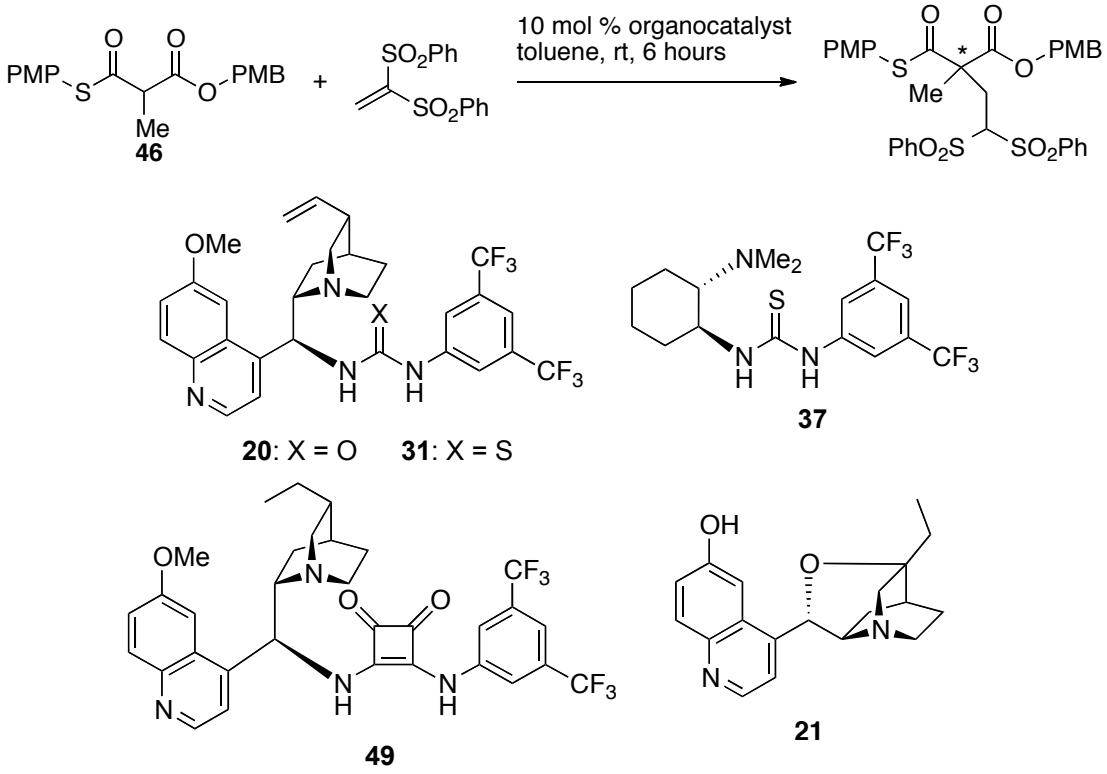


Figure 15. Electron-deficient olefins tested

On the contrary, α,β-unsaturated di-sulfones[59] showed reactivity towards MTMs and the straightforward conversion of the starting material into the addition product was observed. Initially, the addition reaction of α-methyl MTMs to unsubstituted methylidene disulfones in the presence of different organocatalysts was investigated.
In all cases full conversion to the products was observed (reaction times of up to 6 hours in the presence of 10 mol % of the organocatalysts). Unfortunately the enantioselectivity of the product proved to be very poor independently from the different classes of organocatalysts employed (Table 14).

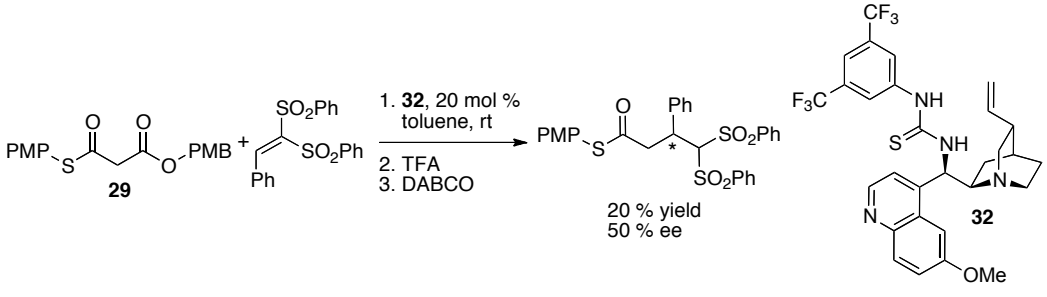
Table 14. Addition reaction of a-methyl MTMs to methylidene disulfones



entry	catalyst	conversion (%)[a]	ee (%)[b]
1	**22**	>98[c]	0
2	**31**	quant.	5
3	**37**	quant.	0
4	**49**	quant.	5
5	**19**	quant.	20

[a] determined by TLC analysis. [b] Determined by chiral phase HPLC analysis. [c] Isolated yield.

We then attempted to react unsubstituted MTMs **29** with β-substituted α,β-unsaturated bis-sulfones in the presence of epiquinidine thiourea **32**. A poor reactivity of the electrophile was observed, as the 1,4-addition product could be isolated in only 20% yield and low enantioselectivity (Scheme 66).

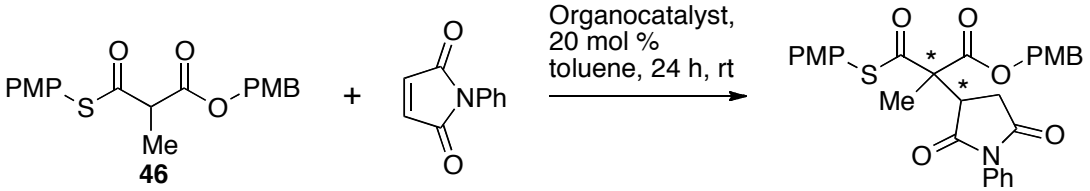


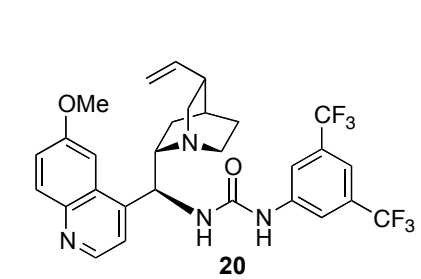
Scheme 65. Conjugate addition reaction of MTMs to β-substituted α,β-unsaturated disulfones

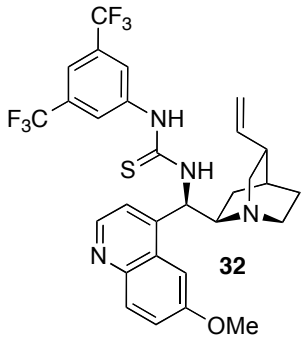
We thought that the problems of these electrophiles could be related to their structure. Indeed, these molecules possess two chemically different sulfones having very similar stereoelectronical properties. As a result the catalyst is not able to discriminate between the *si* face and the re face of the electrophile and low enantioselectivities were obtained. Moreover, the addition product possesses two very acidic protons that can compete with the starting materials for being deprotonated by the catalyst. The cinchona alkaloid-based catalysts synthesised by our group are not catalysing the addition reaction of MTMs to α,β-unsaturated di-sulfones with satisfactory stereoselectivities, so we decided to focus our attention to other targets.

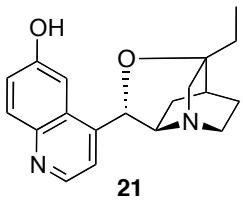
We moved our attention to maleimides that, upon addition, would generate interesting diastereoisomeric products. To our pleasure, the formation of the desired products was observed when methylsubstituted MTMs were added to phenyl-protected maleimides. The complete conversion of the starting materials, however, was never achieved even when extended reaction times and high catalyst loadings were employed. Different catalysts were then screened to try to increase the conversion rate and the stereoselectivity of the reaction.

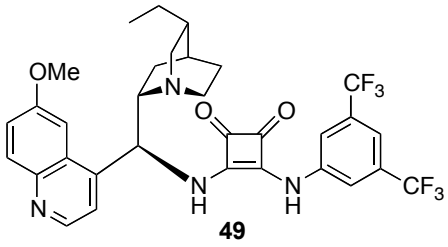
Table 15. 1,4-Addition reaction of α-substituted MTMs to N-phenyl maleimide

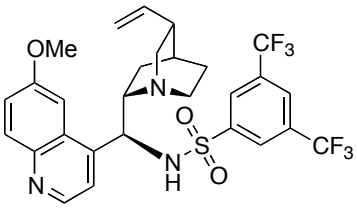


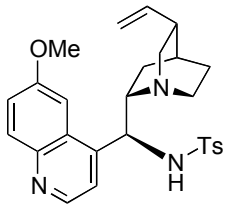


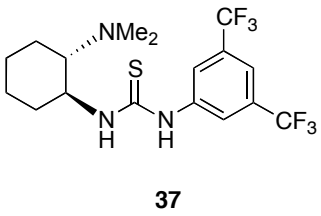


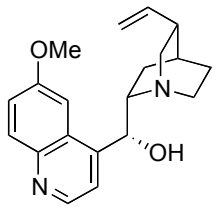


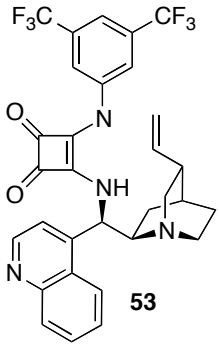












entry	catalyst	Conversion (%)[a]	dr[b]	ee (%) major[b]
1	**22**	50[c]	1.1:1	33
2	**32**	50[c]	1.7:1	83
3	**21**	50[c]	1.2:1	36
4	**49**	>95[d]	6.9:1	84
5	**50**	75[c]	1:2.0	81
6	**51**	50[c]	1:4.4	39
7	**37**	>95[d]	2.0:1	56
8	**52**	50[c]	1:2.9	46
9	**53**	50[c]	1:3.4	78

[a] Estimated by TLC analysis. [b] Determined by chiral HPLC analysis. [c] Conversion did not proceed even after extended reaction time. [d] Reaction time of 48 hours were required

Our efforts to find a suitable catalyst for the desired transformation were not very successful. Catalyst **49** was the best in our hands still providing moderate levels of enantio- and diastereoselectivity.

Additional studies are currently on-going in the Wennemers group to explore the reactivity of these classes of electrophiles and future reports will describe their behaviour in the presence of MTMs and organocatalysts under optimised reaction conditions.

9. Conclusions

In conclusion, we established MTMs as a new class of C-nucleophiles. The envisioned high reactivity of these molecules along with their stability towards basic conditions allowed for mild organocatalytic addition reactions to different electrophiles.

MTMs proved to possess a high reactivity in the Michael addition reaction to nitroolefins. Low catalyst loadings of as little as 1 mol % were suffiecient to promote the addition reaction in 24 hours. The products were obtained in >90% yield and with excellent enantioselectivities (91->99 % ee). These results demonstrate that MTMs are valuable thioester enolate equivalents for reaction with nitroolefins.

The addition reaction of MTMs to nitroolefins has a broad substrate scope. Very reactive (electron poor aromatic) and less reactive (electron rich aromatic and aliphatic) nitroolefins reacted in the presence of MTMs and the quinidine thiourea derivative **32** as catalyst demonstrating that the protocol could be applied to a vast range of nitroolefins.

The γ-nitrothioesters are versatile molecules and could be transformed into a variety of other molecules as aldehydes, ketones, amides, carboxylic acids and γ-butyrolactones. These transformations demonstrate the versatility of thioesters and the possibility for the employment of γ-nitrothioesters as building blocks for the synthesis of target molecules with interesting biological activity.

The efficiency of the organocatalysed 1,4-addition reaction of MTMs to nitroolefins was evaluated to the decarboxylative addition reaction of MAHTs to nitroolefins. The E-factor, calculated for the different processes, allowed for the direct evaluation of the efficiencies of these addition reactions.

The rather complex synthesis of MTMs is balanced by the high efficiency of the 1,4-addition reaction and the use of MTMs resulted in an improved protocol allowing for the production of the γ-nitrothioesters generating less waste compared to the use of MAHTs.

The stereoselective generation of quaternary stereogenic centres is a big challenge in organic chemistry. In order to access molecules possessing quaternary stereogenic centres, α-substituted MTMs were synthesised and evaluated in the addition reaction to diazodicarboxylates. This procedure allows for the formation of a new C-N bond.

The α-aminothioesters are interesting molecules since they resemble amino acids and could therefore be used in the synthesis of peptides containing non-natural aminoacids. Epi-cinchonidineurea **41** was found to be the best catalyst promoting the generation of the addition products between α-substituted MTMs and diazodicarboxylates in excellent 94->98 % yields and good enantioselectivities (90-94 % ee).

The methodology was applicable to a big variety of α-substituted MTMs. Aliphatic substituents such as methyl, ethyl and n-butyl, functionalised aliphatic substituents such as allyl, propargyl and benzyl and aromatic substituents such as phenyl and 3-thiophene were tolerated and the enantioselectivity of the products was ≥ 90 % in all of the cases.

These products posses a very interesting quaternary stereogenic centre. The straightforward construction of such a crowded centre is still an attractive challenge for synthetic chemists since sterical hindrance plays a crucial role limiting the reactivity of the starting material by blocking the approach of the nucleophile to the electrophile.

Finally the unique pattern and variety of functional groups offer the possibility for different functionalization startegies that could lead to the synthesis of interesting target compounds such as L-carbidopa.

Initial studies on the addition of MTMs to other electrophiles, e.g. maleimides or methylidene bis-sulphones, allowed us to determine that MTMs could serve as thioester enolate equivalents for different transformations.

The Wennemers group is currently engaged in enlarging the applicability of these nucleophiles for the addition to other electrophiles as well as in varying the structure of the MTMs and applying the reactants for the addition to various electrophilic partners.

Mannich reactions and addition reactions to electron deficient double bonds are just two of the possible examples that are currently under investigation in our group.

The products generated upon addition reaction of MTMs with imines would resemble β^2-amino acids, therefore allowing for a high yielding and highly selective synthesis of such building blocks. These molecules could show their value in foldamer synthesis or could function as chiral and highly enantiomerically enriched building blocks for the synthesis of small biologically active molecules or natural products.

Mono thiomalonate derivatives bearing cleavable esters that are not sensitive to acid but to e.g. light or hydrogenation are expected to further extend the usefulness of these thioester enolate equivalents.

Detailed mechanicistic studies would provide an insight into the role of the catalysts during the described transformations and the way the transition states are arranged for the achievement of high efficiency of stereoinduction in the addition reactions between MTMs and electrophiles.

We believe that the stereoinduction is promoted by a network of H-bonds that pre-organise the intermediates in such a way that only one stereoisomer is formed preferentially. Thus, the determination of the pattern of the non-covalent interactions together with the evaluation of charge separations and the study of the reaction intermediates is of primary importance. Computational as well as analytical tools would provide an insight in the interactions between substrates and catalyst and would allow us to get theoretical and experimental evidences of the reaction mechanism. Furthermore, experiments to determine the kinetic profile of the mechanism would give us further details on the addition reactions.

Polyketides or similar biologically occurring molecules are one of the ultimate targets. Further studies on the organocatalytic addition of thioester enolate equivalents to aldehydes under mild conditions are currently the main focus of the efforts of the group. The Fukuyama reduction of the obtained β-hydroxy thioester and the following addition of the newly synthesised aldehyde to a new molecule of thioester enolate equivalent would allow us to develop an iterative synthesis of polyalcohols that are commonly found in many natural products possessing relevant biological activities. The optimisation of this procedure would then be the one of the goals of the research in this field allowing for a significant contribution to the total synthesis of molecules such as the epothilones.

10. Experimental

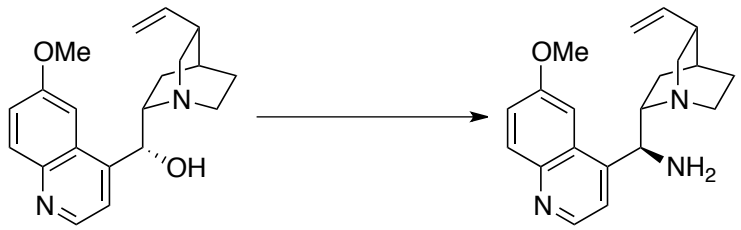
10.1 General aspects and materials

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 60, particle size 40-63 μm. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. HPLC analyses were performed on an analytical HPLC with a diode array detector from Shimadzu. Bruker Esquire 3000 Plus was used for electro spray ionisation (ESI) mass spectrometry. HPLC analyses were carried out on an analytical HPLC with a diode array detector from Shimadzu.

10.2 General synthesis of the (thio)urea-functionalized cinchona alkaloids.

Quinine (3.24 g, 10.0 mmol) and triphenyl phosphine (3.15 g, 12.0 mmol) were dissolved in 50 ml of dry THF and the solution was cooled to 0˚C. Diisopropylazodicarboxylate (2.43 g, 12.0 mmol) were added in one portion. A solution of diphenylphosphorylazide (3.30 g, 12.0 mmol) in 20 ml of dry THF was added drop wise at 0˚C. The reaction was stirred overnight at RT and then at 50˚C for 2 hours. Triphenyl phosphine (3.41 g, 13 mmol) 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 ml of distilled water was added. The reaction was kept under vigorous stirring for additional 3 hours. All the volatiles were evaporated under reduced pressure and 100 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 with 25 % solution of NH_4OH in water to 10 and washed 4 times with 50 ml of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, 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) to yield the product in 91% yield (2.96 g) as yellow oil.[60]

9-epiquinine-NH_2

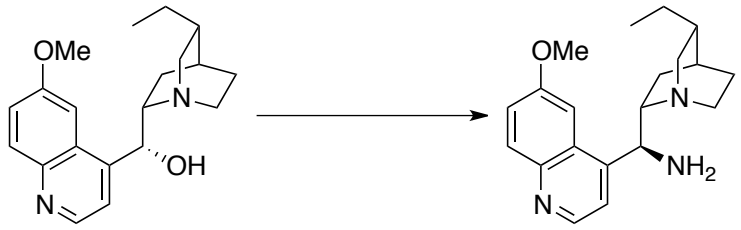


^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.76 (d, *J*=4.7 Hz, 1H), 8.05 (d, *J*=9.3 Hz, 1H), 7.69-7.67 (br, 1H), 7.45 (d, *J*=4.5 Hz, 1H), 7.40 (dd, *J*= 9.3 Hz, 2.8 Hz, 1H), 5.89-5.75 (m, 1H), 5.06-4.96 (m, 2H), 4.61 (d, *J*=10.0 Hz, 1H), 3.98 (s, 3H), 3.34-3.09 (m, 3H), 2.86-2.78 (m, 2H) 1.65-0.74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

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 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 (100) [M^++H]

9-epiDihydroquinine-NH_2

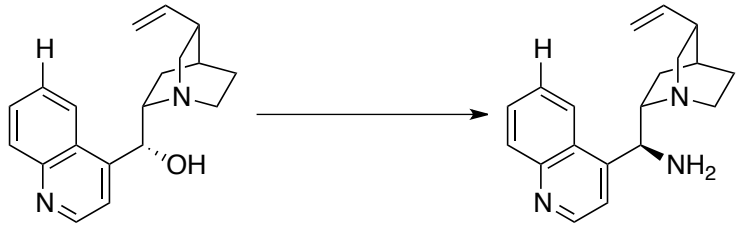


^{1}H-NMR (400 MHz, MeOD, 25˚C): δ = 8.69 (d, *J*=4.7 Hz, 1H), 7.97 (d, *J*=9.3 Hz, 1H), 7.69-7.67 (br, 1H), 7.61 (d, *J*=4.7 Hz, 1H), 7.45 (dd, *J*= 9.3 Hz, 2.6 Hz, 1H), 4.72 (d, *J*=11.0 Hz, 1H), 4.00 (s, 3H), 3.32 (ddd, *J*= 15.6 Hz, 10.5 Hz, 7.8 Hz, 1H), 3.28 (dd, *J*= 13.6 Hz, 9.9 Hz, 1H), 3.16 (q, *J*= 10.7 Hz 1H), 2.79 (ddd, *J*= 15.6 Hz, 13.8 Hz, 4.9 Hz, 1H), 2.56 (ddd, *J*= 13.6 Hz, 4.7 Hz, 2.3 Hz, 1H), 1.60 (m, 1H), 1.60 (dd, *J*= 13.3 Hz, 10.4 Hz, 1H),1.56 (bs, 1H), 1.53 (m, 1H), 1.53 (ddd, *J*= 13.3 Hz, 10.4 Hz, 2.7 Hz, 1H), 1.47 (bs, 1H), 1.35 (m, 2H), 0.85 (t, *J*= 7.3 Hz, 3H).

^{13}C-NMR (100 MHz, MeOD, 25˚C): δ = 158.8, 148.3, 147.5, 144.2, 130.6, 129.4, 122.3, 120.2, 102.1, 62.2, 57.8, 55.2, 51.9, 40.8, 37.8, 28.6, 27.6, 25.8, 25.7, 11.4

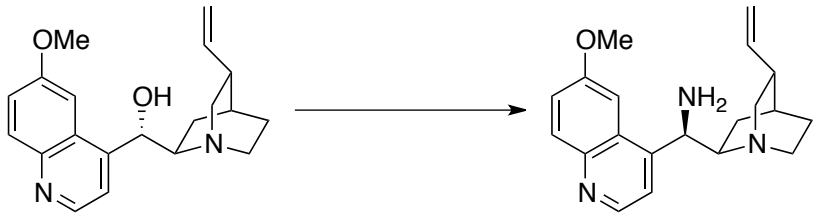
MS (ESI): m/z (%): 326 (100) [M^++H]

9-epicinchonidine-NH_2



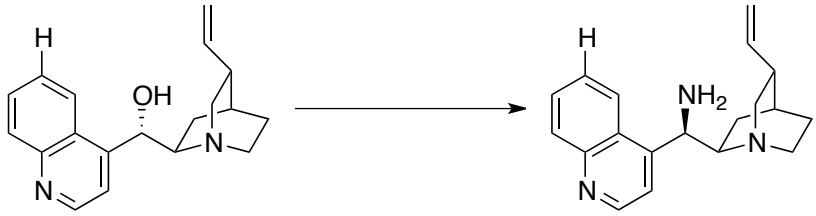
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.86 (d, *J* = 3.7 Hz; 1H), 8.32 (br s; 1H), 8.11 (d, *J* = 8.4 Hz; 1H), 7.69 (t, *J* = 7.5 Hz; 1H), 7.57 (t, *J* = 7.5 Hz; 1H), 5.81-5.72 (m, 1H), 5.00-5.93 (m, 2H), 4.70 (d, *J* = 6.6 Hz; 1H), 3.78 (br; 2H), 3.28- 2.78 (m; 5H), 2.26 (br; 1H), 1.99-1.91 (m; 1H), 1.59-1.53 (m; 3H), 1.42-1.37 (m; 1H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 150.2, 148.5, 148.4, 141.4, 130.3, 128.9, 127.6, 126.8, 126.4, 118.5, 114.3, 55.9, 40.7, 39.5, 38.1, 27.7, 27.4, 27.2, 25.8, 23.1MS (ESI): m/z (%): 294 (100) [M^++H]

9-epiquinidine-NH_2



^{1}H-NMR (400 MHz, MeOD, 25˚C): δ = 8.75 (d, J = 4.5, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.53 (br. s, 1H), 7.50 - 7.43 (m, 1H), 7.38 (dd, J = 9.1 Hz, 2.3 Hz, 1H), 5.89 (ddd, J = 17.1 Hz, 10.6 Hz, 6.5 Hz, 1H), 5.13 - 5.02 (m, 2H), 4.67 (d, J = 8.8 Hz, 1H), 3.97 (s, 3H), 3.10 - 2.88 (m, 5H), 2.28 (dd, J = 7.0 Hz, 14.9 Hz, 1H), 1.95 (br. s, 2H), 1.61 (br. s, 1H), 1.54 (t, J = 6.7 Hz, 2H), 1.19 - 1.08 (m, 1H), 1.01 - 0.90 (m, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 157.6, 147.9, 144.9, 140.9, 132.3, 132.1, 131.9, 128.9, 128.7, 128.6, 121.8, 114.6, 77.4, 55.6, 49.7, 47.6, 39.6, 27.7, 26.9, 25.2.
MS (ESI): m/z (%): 324 (100) [M^++H]

9-epicinchonine-NH_2

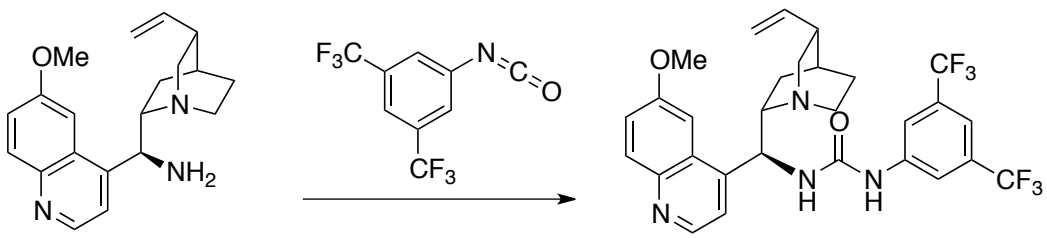


^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.85(d, *J* = 4.4 Hz, 1H), 8.29 (d, *J* = 5.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 5.84-5.76 (m, 1H), 5.06-5.01 (m, 2H), 4.74 (d, *J* = 7.4 Hz, 1H), 3.86 (br s, 2H), 3.05-2.90 (m, 5H), 2.25 (dd, *J* = 16 Hz, 7.9 Hz, 1H), 1.56-1.49 (m, 3H), 1.10-1.05 (m, 1H), 0.94-0.89 (m, 1H);
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 150.3, 148.8, 148.5, 140.3, 130.4, 129.1, 127.7, 126.5, 123.3, 119.7, 114.8, 62.3, 49.3, 47.1, 39.4, 27.6, 26.4, 24.9, 22.
MS (ESI): m/z (%): 294 (100) [M^++H]

10.3 Preparation of the (thio)urea catalyst

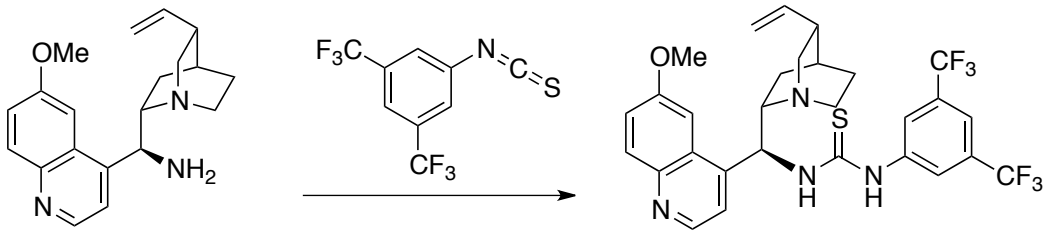
To a mixture of 9-epiquinine-NH_2 (2.96 g, 9.1 mmol, 1 eq.) in 20 ml of dry THF, a solution of 3,5-bis(trifluoromethyl)phenyliso(thio)cyanate (2.47 g, 9.1 mmol, 1 eq.) in 10 ml dry THF was added at RT. The reaction was kept under vigorous stirring overnight. The volatiles were evaporated under reduced pressure and the crude mixture was purified by column chromatography (CH_2Cl_2/MeOH from 95:5 to 80:20). The desired alkaloid was isolated in 80% yield as a white amorphous solid (3.5 g).[60]

9-epiquinine-urea



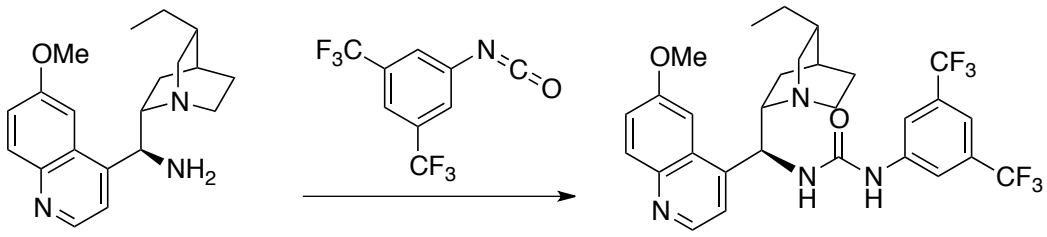
^{1}H-NMR (400 MHz, CD_3OD, 25˚C): δ = 8.68 (d, *J* = 4.7 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.93 (s, 2H), 7.84 (d, *J* = 2.6 Hz, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.45 (d, *J* = 2.7 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 5.89 (m, 1H), 5.59 (d, *J* = 9.8 Hz, 1H), 5.03 (m, 2H), 4.01 (s, 3H), 3.72 (m, 1H), 3.47 (m, 1H), 3.35 (m, 1H), 2.83 (m, 2H), 2.39 (m, 1H), 1.86 (m, 1H), 1.67 (m, 2H), 1.58 (m, 1H), 0.89 (dd, *J* = 13.5 Hz, 7.0 Hz, 1H).
^{13}C-NMR (100 MHz, CD_3OD, 25˚C): δ = 159.9, 156.7, 148.3, 147.7, 145.3, 143.2, 142.6, 133.0 (q, *J* = 33.0 Hz), 131.5, 130.0, 128.0, 123.6, 120.9, 119.1, 115.6, 115.0, 103.3, 68.8, 60.8, 57.0, 56.3, 42.2, 40.8, 28.9, 28.6, 27.5.
MS (ESI): m/z (%): 579 (100) [M^++H]

9-epiquinine-thiourea



^{1}H-NMR (400 MHz, CD_3OD, 25˚C): δ = 8.68 (d, *J*= 4.7 Hz, 1H), 8.11 (bs, 2H), 8.07 (d, *J*= 2.6 Hz, 1H), 7.95 (d, *J*= 9.3 Hz, 1H), 7.59 (bs, 1H), 7.55 (d, *J*= 4.7 Hz, 1H), 7.44 (dd, *J*= 9.3 Hz, 2.6 Hz, 1H), 6.32 (d, *J*= 11.0 Hz, 1H), 5.84 (ddd, *J*= 17.2 Hz, 10.5 Hz, 6.2 Hz, 1H), 5.02 (dt, *J*= 10.5 Hz, 1.5 Hz, 1H), 4.98 (dt, *J*= 17.2 Hz, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56 (dddd, *J*= 15.6 Hz, 10.5 Hz, 7.8 Hz, 2.3 Hz, 1H), 3.39 (bs, 1H), 3.29 (dd, *J*= 13.6 Hz, 9.9 Hz, 1H), 2.82 (ddd, *J*= 15.6 Hz, 13.8 Hz, 4.9 Hz, 1H), 2.79 (ddd, *J*= 13.6 Hz, 4.7 Hz, 2.3 Hz, 1H), 2.36 (m, 1H), 1.70 (m, 2H), 1.63 (m, 1H), 1.45 (ddd, *J*= 13.3 Hz, 10.4 Hz, 2.7 Hz, 1H), 0.89 (dd, *J*= 13.3 Hz, 10.4 Hz, 1H).
^{13}C-NMR (100 MHz, CD_3OD, 25˚C): δ = 181.6, 158.7, 147.3, 146.6, 144.2, 142.0, 141.5, 131.8 (q, *J* = 33.0 Hz), 130.3, 129.2, 123.6 (q, *J*= 272.2 Hz), 122.7, 122.6, 120.2, 116.9 (s, *J*= 3.7 Hz), 114.0, 103.3, 60.7, 55.8, 55.5, 55.4, 41.8, 39.7, 27.8, 27.7, 25.9.
MS (ESI): m/z (%): 596 (100) [M^++H]

9-epidihydroquinine-urea

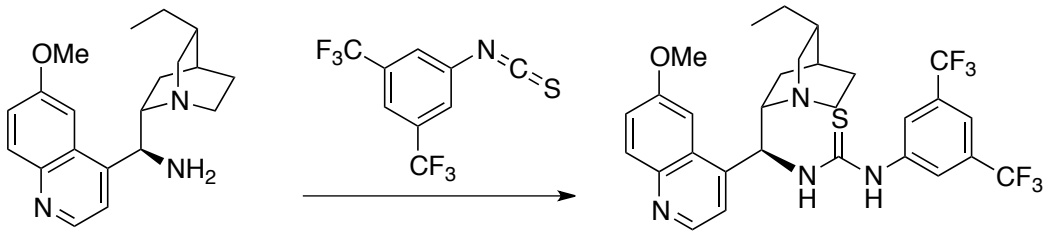


^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.83 (d, *J*= 4.5 Hz, 1H), 8.08 (d, *J*= 9.0 Hz, 1H), 7.73-7.76 (m, 3H), 7.45 (dd, J= 9.0 Hz, 2.5 Hz, 1H), 7.39-7.41 (m, 2H), 6.25 (bs, 1H), 5.56 (bs, 1H), 4.04 (s, 3H), 3.42-3.49 (m, 1H), 3.28-3.33 (m, 1H), 3.10-3.12 (m, 1H), 2.01 (m, 2H), 1.49-1.60 (m, 4H), 1.20-1.25 (m, 4H), 0.97- 1.02 (m, 1H), 0.79 (t, *J*= 7.6 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 163.1, 154.1, 146.8, 144.6, 143.0, 139.9, 131.5, 131.4, 131.3 (q, *J*= 26.3 Hz), 122.6 (q, *J*= 273.7 Hz), 121.9, 117.8, 117.75, 115.5 (bs, *J*= 2.9 Hz), 101.8, 76.8, 59.3, 56.8, 55.4, 41.1, 36.1, 27.5, 27.1, 26.5, 24.4, 11.4.

MS (ESI): m/z (%): 581 (100) [M^++H].

9-epidihydroquinine-thiourea



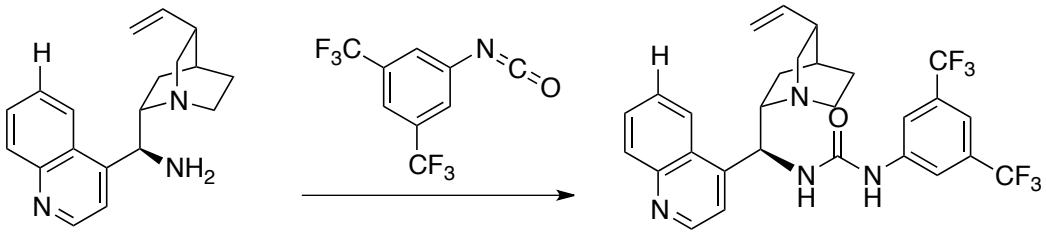
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.73 (d, *J*= 4.5 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.89 (bs, 2H), 7.70 (s, 1H), 7.45 (dd, *J*= 9.0 Hz, 2.0 Hz, 1H), 7.30-7.44 (m, 2H), 5.71 (bs, 1H), 3.99 (s, 3H), 3.21-3.33 (m, 3H), 2.81-2.87 (m, 1H), 2.59 (bs, 1H), 1.53-1.64 (m, 4H), 1.28-1.41 (m, 4H), 0.88-0.96 (m, 1H), 0.85 (t, *J*= 7.0 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 180.5, 157.7, 147.0, 144.3, 144.0, 139.5, 131.9 (q, *J*= 35.2 Hz), 131.4, 127.6, 123.1, 123.1, 122.8 (q, *J*= 272.7 Hz), 121.1,

118.3 (bs, *J*= 1.9 Hz), 101.7, 76.8, 60.8, 56.1, 53.3, 40.9, 36.4, 27.4, 26.9, 24.9, 24.3, 11.5.

MS (ESI): m/z (%): 597 (100) [M^++H].

9-epicinchonidine-urea

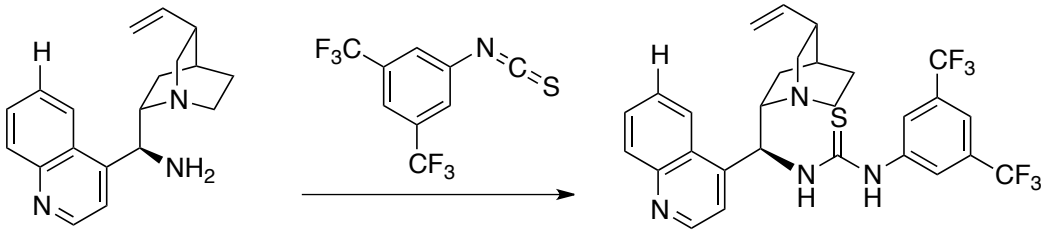


^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.90 (d, *J*= 4.8 Hz, 1H), 8.39 (d, *J*= 8.4 Hz, 1H), 8.17 (d, *J*= 8.4 Hz, 1 H), 7.78-7.65 (m, 2H), 7.63 (t, *J*= 7.6 Hz, 1H), 7.48 (d, *J*= 4.8 Hz, 1H), 7.39 (s, 1H), 6.56 (bs, 1H), 5.84 (ddd, *J*=17.1 Hz, 10.4 Hz, 6.2 Hz, 1H), 5.31 (bs, 1H), 5.12 (dd, *J*= 17.1 Hz, 10.4 Hz, 2H), 2.93 (bs, 1H), 2.84 (d, *J*= 8.8 Hz, 2H), 2.71 (t, *J*= 8.0 Hz, 2H), 2.24 (q, *J*= 6.8 Hz, 1H), 1.60 (s, 1H), 1.48-1.35 (m, 2H), 1.27 (t, *J*= 8.4 Hz, 1H), 0.91-0.86 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25˚C): δ = 156.7, 151.0, 150.0, 149.0, 143.2, 141.4, 133.0 (q, *J*= 33.3 Hz), 130.0, 128.8, 128.2, 125.0, 124.7 (q, *J*= 272.3 Hz), 120.6, 118.9, 115.5, 115.3, 61.2, 51.8, 50.2, 48.0, 40.4, 28.8, 27.3, 26.3.

MS (ESI): m/z (%): 549 (100) [M^++H]

9-epicinchonidine-thiourea



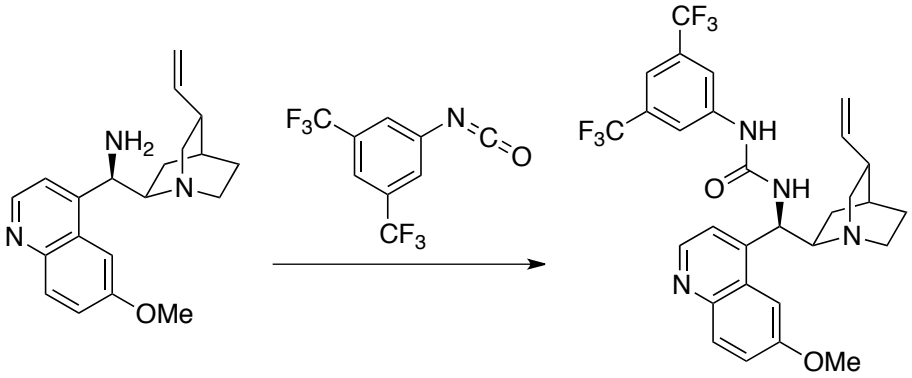
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.80 (br s, 1H), 8.35 (br s, 1H), 8.14 (d, *J*= 8.5 Hz, 1H), 7.80 (s, 2H), 7.74 (dd, *J*= 8.0 Hz, 7.5 Hz, 1H), 7.69 (s, 1H), 7.63 (dd, *J*= 8.0 Hz, 7.5 Hz, 1H), 7.27 (br s, 1H), 5.78 (br s, 1H), 5.67 (m, 1H), 4.98 (m, 2H), 3.26

(m, 1H), 3.20 (br s, 1H), 3.17 (dd, *J*= 13.5 Hz, 10.5 Hz, 1H), 2.78 (m, 2H), 2.33 (br s, 1H), 1.70 (m, 2H), 1.63 (m, 1H), 1.33 (m, 1H), 0.93 (br s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 180.9, 149.9, 148.5, 145.9, 140.7, 139.9, 132.6 (q, *J*= 33.6 Hz), 130.4, 129.5, 127.0, 123.6, 122.9 (q, *J*= 273.0 Hz), 119.1, 118.9, 115.0, 61.5, 56.5, 54.9, 41.1, 39.2, 27.5, 27.1, 25.7.

MS (ESI): m/z (%): 565 (100) [M^++H]

9-epiquinidine-urea

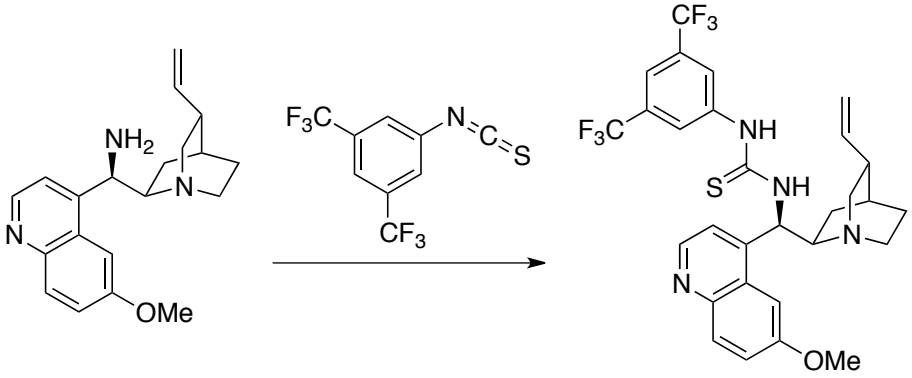


^{1}H-NMR (400 MHz, CD_3OD, 25˚C): δ = 8.64 (d, *J*= 4.7 Hz, 1H), 8.40 (bs, 1H), 7.93 (m, 1H), 7.84 (s, 2H), 7.71 (m, 1H), 7.49 (m, 1H), 7.39 (ddd, *J*= 9.2 Hz, 4.3 Hz, 2.7 Hz, 1H), 7.36 (m, 1H), 5.89 (ddd, *J*= 16.9 Hz, 10.5 Hz, 6.1 Hz, 1H), 5.55 (m, 1 H) 5.19-5.09 (m, 1H), 4.00 (s, 3H), 3.16 (m, 1H), 3.03 (m, 3H), 2.35 (m, 1H), 1.93 (s, 1H), 1.67 (bs, 1H), 1.59 (m, 3H), 1.27-1.18 (m, 1H), 1.10-1.05 (m, 1H).

^{13}C-NMR (100 MHz, CD_3OD, 25˚C): δ = 158.8, 155.8, 147.2, 144.2, 141.9, 140.4, 132.7 (q, *J* = 33.2 Hz), 130.6, 128.9, 127.8, 125.1, 122.4 (q, *J* = 272.7 Hz), 118.4 (bs, *J*= 2.1 Hz), 115.1, 114.9, 101.7, 78.1, 55.7, 49.5, 47.3, 39.2, 37.3, 27.6, 26.9, 26.5, 26.2, 25.8, 25.4, 11.8.

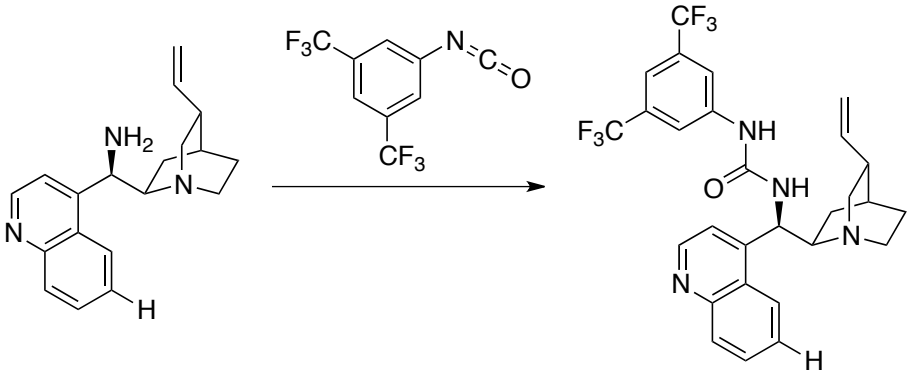
MS (ESI): m/z (%): 579 (100) [M^++H]

9-epiquinidine-thiourea



^{1}H-NMR (400 MHz, CD_3OD, 25˚C): δ = 8.67(d, *J*= 4.7 Hz, 1H), 8.11 (bs, 2H), 8.03 (d, = 2.6 Hz, 1H), 7.94 (d, *J*= 9.3 Hz, 1H), 7.59 (bs, 1H), 7.56 (d, *J*= 4.7 Hz, 1H), 7.43 (dd, *J*= 9.3 Hz, 2.6 Hz, 1H), 6.35 (d, *J*= 11.0 Hz, 1H), 5.96 (ddd, *J*= 17.2 Hz, 10.5 Hz, 6.2 Hz, 1H), 5.22 (dt, *J*= 10.5 Hz, 1.5 Hz, 1H), 5.15 (dt, *J*= 17.2 Hz, 1.5 Hz, 1H), 4.03 (s, 3H), 3.04 (dd, *J*= 13.6 Hz, 9.9 Hz, 1H), 3.34 (ddd, *J*= 13.6 Hz, 4.7 Hz, 2.3 Hz, 1H), 3.33 (m, 1H), 3.01 (m, 2H), 2.37 (m, 1H), 1.63 (m, 1H), 1.60 (m, 2H), 1.23 (ddd, *J*= 13.3 Hz, 10.4 Hz, 2.7 Hz, 1H), 1.03 (dd, *J*= 13.3 Hz, 10.4 Hz, 1H).
^{13}C-NMR (100 MHz, CD_3OD, 25˚C) δ = 181.7, 158.6, 147.3, 146.9, 144.2, 142.1, 140.8, 131.8 (q, *J*= 33.0 Hz), 130.2, 129.2, 123.7 (q, *J*= 272.2 Hz), 122.9, 122.7, 116.9 (bs, *J*= 3.7 Hz), 114.3, 103.8, 60.7, 55.5, 54.6, 49.2, 47.6, 39.2, 27.7, 26.4, 25.5.
MS (ESI): m/z (%): 597 (100) [M^++H].

9-epicinchonine-urea

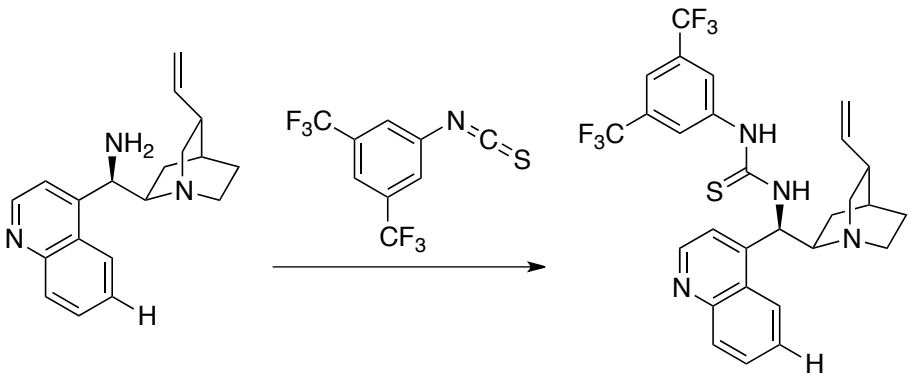


^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.90 (d, *J*= 4.8 Hz, 1H), 8.39 (d, *J*= 8.4 Hz, 1H), 8.17 (d, *J*= 8.4 Hz, 1 H), 7.78-7.65 (m, 2H), 7.63 (t, *J*= 7.6 Hz, 1H), 7.48 (d, *J*= 4.8 Hz, 1H), 7.39 (s, 1H), 6.56 (bs, 1H), 5.84 (ddd, *J*=17.1 Hz, 10.4 Hz, 6.2 Hz, 1H), 5.31 (bs, 1H), 5.12 (dd, *J*= 17.1 Hz, 10.4 Hz, 2H), 2.93 (bs, 1H), 2.84 (d, *J*= 8.8 Hz, 2H), 2.71 (t, *J*= 8.0 Hz, 2H), 2.24 (q, *J*= 6.8 Hz, 1H), 1.60 (s, 1H), 1.48-1.35 (m, 2H), 1.27 (t, *J*= 8.4 Hz, 1H), 0.91-0.86 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25˚C): δ = 156.7, 151.0, 150.0, 149.0, 143.2, 141.4, 133.0 (q, *J*= 33.3 Hz), 130.0, 128.8, 128.2, 125.0, 124.7 (q, *J*= 272.3 Hz), 120.6, 118.9, 115.5, 115.3, 61.2, 51.8, 50.2, 48.0, 40.4, 28.8, 27.3, 26.3.

MS (ESI): m/z (%): 549 (100) [M^++H]

9-epicinchonine-thiourea



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 8.83 (br s, 1H), 8.28 (br s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.85 (br s, 2H), 7.56 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.68 (s, 1H), 7.64 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.29 (br s, 1H), 5.81 (br s, 2H), 5.14 (m, 2H), 3.21 (br s, 1H), 3.00 (m, 3H), 2.92 (br s, 1H), 2.36 (m, 1H), 1.66 (s, 1H), 1.59 (m, 2H), 1.22 (br s, 1H), 0.95 (m, 1H).

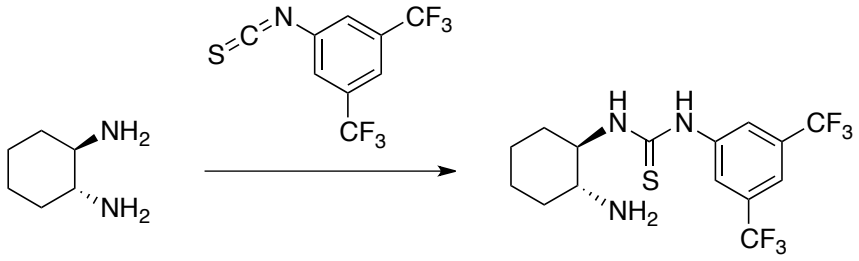
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 181.3, 150.0, 148.6, 145.8, 140.2, 139.3, 132.5 (q, *J* = 33.6 Hz), 130.5, 129.5, 127.1, 126.7, 123.4, 122.9 (q, *J* = 273.1 Hz), 122.8, 119.0, 118.7, 115.5, 61.8, 55.7, 48.5, 47.0, 38.9, 27.3, 26.0, 24.9.

MS (ESI): m/z (%): 565 (100) [M^++H]

10.4 Synthesis of diaminocyclohexyl based organocatalysts

1-((1R,2R)-2-aminocyclohexyl)-3-(3,5bis(trifluoromethyl)-phenyl)urea

In flame dried flask, in an argon atmosphere, 478 mg (3.4 mmol, 1 eq.) of 1,2-diaminocyclohexane were dissolved in 30 ml of dry THF and 0.5 ml of 3,5-bis-(trifluoromethyl)phenylisothiocyanate (3.4 mmol, 1.0 eq.) were added. The mixture was stirred at room temperature for 12 hours. The volailes were then removed under reduced pressure. The crude mixture was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N 100:5:1) to yield the product as a brown solid (yield: 79%, 2.7 mmol, 1,04 g).[61]

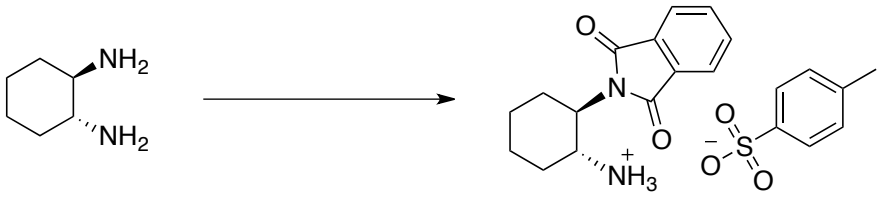


^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.81 (s, 2H), 7.38 (s, 1H), 7.89 (bs, 2H), 3.35 (m, 1H), 2.70 (bs, 2H), 2.46 (m, 1H), 1.94 (m, 2H), 1.68 (m, 2H), 1.23 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 155.8, 140.8, 131.9 (*J*= 533.2 Hz), 124.5, 118.2 (*J*= 54.1 Hz), 115.1 (*J*= 54.1 Hz), 54.4, 51.6, 32.2, 29.9, 24.3, 23.8.
MS (ESI): m/z (%): 386 (100) [M^++H].

1-((1R,2R)-2-dimethyl-aminocyclohexyl)-3-(3,5bis(trifluoromethyl)-phenyl)urea

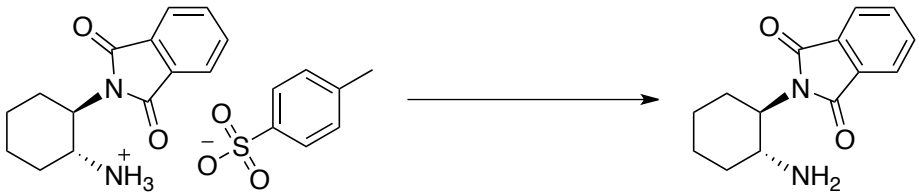
A 500 ml flask was equipped with a Dean-Stark apparatus. *p*-toluene sulfonic acid monohydrate (8.33 g, 43.8 mmol, 1 eq.) was dissolved in 220 ml of *o*-xylene. The mixture was stirred and boiled for 6 hours in order to azeotropycally distil the water and the mixture was then cooled to room temperature. 1,2-diaminocyclohexane (5 g, 43.8 mmol, 1 eq.) and phtalic anhydride (6.48 g, 43.8 mmol, 1 eq.) were added and the mixture was kept at reflux until the solution became clear and the desired product was observed as a crystalline solid. The crystals were filtered and washed with a 1:1

mixture of o-xylene and hexane. After that the crystals were dried under high vacuum, 17.7 g of pure product were isolated as white solid (42.5 mmol, yield 97 %).[61]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.57 (m, 2H), 7.43 (m, 2H), 7.24 (d, *J*= 8.1 Hz, 2H), 6.97 (d, *J*= 8.1 Hz, 2H), 4.15 (dt, *J*= 11.4Hz, 3.8 Hz, 1H), 3.88 (dt, *J*= 11.2 Hz, 3.8 Hz, 1H), 2.32 (s, 3H), 2.11-1.20 (m, 8H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 168.7, 141.0, 139.8, 133.2, 132.1, 128.6, 125.9, 123.0, 52.4, 50.6, 30.2, 28.9, 24.5, 23.6, 21.3.
MS (ESI): m/z (%): 245 (100) [M^++H] (The counter ion is not visible).

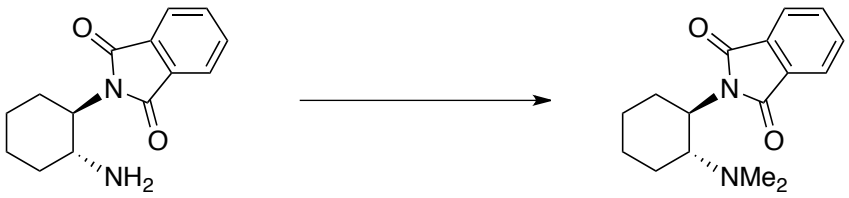
A solution of N-phtaloyl-N'-ammonium-1,2-diaminocyclohexyl-*p*-toluensulfonate (17.7 g, 42.5 mmol) in 600 ml CH_2Cl_2 is prepared in a 1 l round flask. 120 ml of a saturated solution of $NaHCO_3$ in H_2O are added and the bifasic mixture is stirred at room temperature for 12 hours. The mixture was placed in a separating funnel and the aqueous phase was washed three times with 100 ml CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated and then all the volatiles were removed under reduced pressure. 9.65 g of a crystalline colorless solid could be isolated (39.5 mmol, yield 93 %).[61]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.76 (m, 2H), 7.65 (m, 2H), 3.74 (dt, *J*= 11.5 Hz, 4.0 Hz, 1H), 3.34 (dt, *J*= 10.9 Hz, 4.0 Hz, 1H), 2.12-1.95 (m, 2H), 1.79-1.69 (m, 3H), 1.44-1.11 (m, 3H), 1.02 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 168.7, 133.7, 131.8, 123.0, 58.4, 50.3, 36.6, 29.2, 25.5, 25.1.

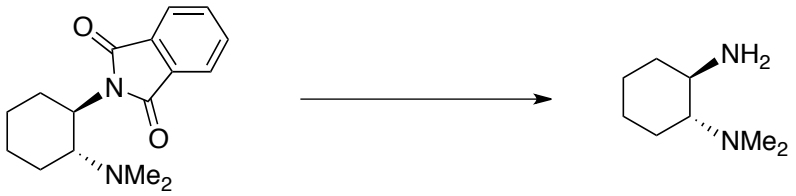
MS (ESI): m/z (%): 245 (100) [M^++H].

In a round flask 1.00 g (4.09 mmol, 1 eq.) of N-phtaloyl-1,2-diaminocyclohexane were dissolved in 25 ml of CH_3CN and stirred at room temperature. 1.66 ml of formaldehyde in water (37 % w, 20.5 mmol, 5 eq.) were added. After 15 minutes 514 mg (8.18 mmol, 2eq.) of sodium cyanoborohydride were added and the reaction was stirred for 15 more minutes. 1.30 ml of acetic acid were then added dropwise and the mixture was stirred for 2 hours. The mixture was then dilute with 30 ml of a 1:1 mixture of CH_2Cl_2 and MeOH and washed three times with 70 ml of a 1 M solution of NaOH. The organic phase was dried with $MgSO_4$, filtered and all the volatiles were evaporate under reduced pressure. The product was obtained as a pale yellow solid (686 mg, 2.52 mmol, 62 % yield).[61]



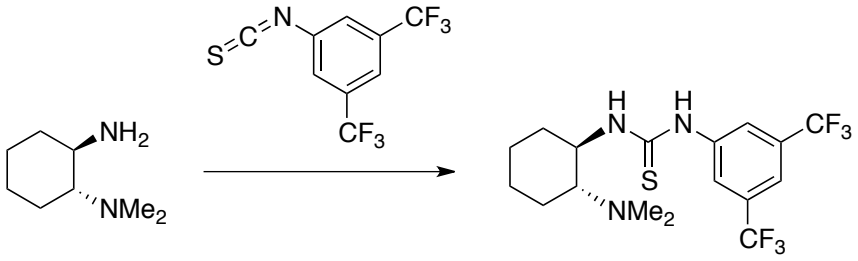
^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.79 (m, 2H), 7.65 (m, 2H), 4.04-4.13 (m, 1H), 3.33-3.24 (m, 1H), 2.12 (s, 6H), 1.93-1.77 (m, 5H), 1.35-1.10 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 168.7, 133.5, 133.2, 123.0, 62.1, 52.3, 40.3, 30.2, 25.8, 25.1, 22.6.
MS (ESI): m/z (%): 273 (100) [M^++H].

In a 25 ml flask equipped with a reflux condenser 500 mg (1.84 mmol, 1 eq) of N-phtaloyl-N'N'-dimethyl-1,2-diaminocyclohexane were dissolved in 4.5 ml of ethanol. 220 μl of hydrazine monohydrate (4.59 mmol, 2.5 eq) were added and the mixture was heated to reflux and stirred for 30 minutes. After that the mixture was cooled at room temperature, it was diluted with cold ether. The precipitate was filtered and washed with ether to remove the phtalazine generated upon reaction. The volatiles were removed under reduced pressure and the product was obtained as yellow oil (217 mg, 1.53 mmol, 83 % yield).[61]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 2.63-2.54 (m, 1H), 2.23 (s, 6H), 2.08 (s, 2H), 2.05-1.94 (m, 2H), 1.78-1.74 (m, 2H), 1.67 (m, 1H), 1.21-1.10 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 69.6, 51.5, 40.2, 35.0, 25.6, 25.1, 20.6.
MS (ESI): m/z (%): 143 (100) [M^++H].

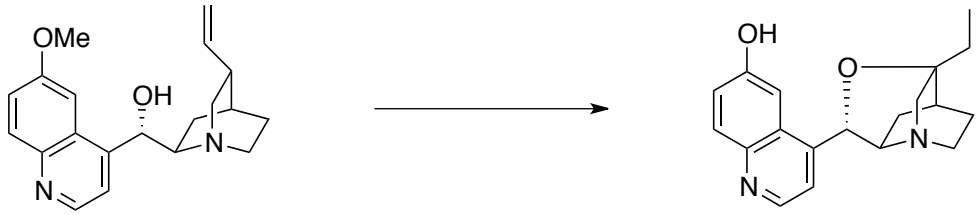
In a flame dried, two neck flask with a septum 47.8 mg (336 μmol, 1 eq) of N,N-dimethyl-1,2-diaminocyclohexane were dissolved in 3 ml THF in an argon atmosphere. 50 μl (336 μmol, 1 eq) of 3,5-bis(trifluoromethyl)phenyl isothiocyanate wera added and the mixture was stirred overnight at room temperature. The volatiles were then evaporated under reduced pressure and the product was then purified with column chromatography (CH_2Cl_2/MeOH/Et_3N 100:5:1) to yield 114 mg (276 μmol, 82 % yield) of a pale yellow amorphous solid.[61]



^{1}H-NMR (400 MHz, DMSO-d_6, 25˚C): δ = 10.0 (s, 1H), 8.21 (8.17,s 1H), 8.17 (s, 2H), 7.66 (s, 1H), 4.09 (bs, 1H), 2.54 (s, 1H), 2.21 (s, 7H), 1.82 (bs, 1H), 1.74 (bs, 1H), 1.63 (d, *J*= 11.0 Hz, 1H), 1.31-1.01 (m, 4H).
^{13}C-NMR (100 MHz, DMSO-d_6, 25˚C): δ = 178.6, 142.0, 130.8, 130.5, 130.3, 130.0, 126.5, 124.3, 122.2, 120.9, 120.0, 115.3, 65.0, 55.3, 45.7, 31.6, 24.6, 24.5, 21.0.
MS (ESI): m/z (%): 414 (100) [M^++H].

10.5 Synthesis of β-cupreidine catalyst

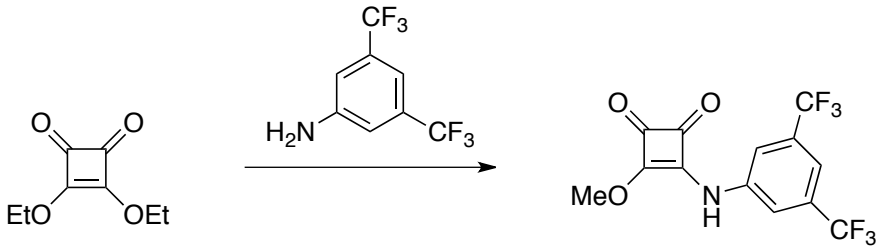
In a dry 100 mL round-bottom flask, quinidine (2 g, 6.16 mmol) and KBr (7.30 g, 61.6 mmol) were dissolved in 30 mL phosphoric acid and stirred at 100 °C for 10 days. The reaction mixture was cooled to RT and 25% KOH solution was added until pH~7-8 was reached. The mixture was extracted with CH_2Cl_2 (three times with 100 mL) and the collective organic phases were washed twice with 100 ml brine, dried over $MgSO_4$, filtrated and the volatiles were removed at reduced pressure. The crude mixture was purified by column chromatography (CH_2Cl_2/MeOH 9:1-8:2) (143 mg, 0.46 mmol; 75% yield).[56]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 9.39 (br s; 1H), 8.69 (d, *J* = 4.4 Hz; 1H), 7.95 (d, *J* = 9.2 Hz; 1H), 7.66 (d, *J* = 1.9 Hz; 1H), 7.60 (d, *J* = 4.4 Hz; 1H), 7.29 (dd, *J* = 2.3, 9.2 Hz; 1H), 5.93 (s; 1H), 3.73-3.76 (m; 2H), 3.09-3.14 (m; 1H), 2.97-3.04 (m; 1H), 2.79 (d, *J* = 13.5 Hz; 1H), 2.21-2.23 (m; 1H), 1.80-1.85 (m; 1H), 1.65-1.73 (m; 3H), 1.62-1.64 (m; 1H), 1.27-1.30 (m; 1H), 1.02 (t, *J* = 7.4 Hz; 3H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 156.7, 146.7, 143.1, 140.7, 131.4, 126.5, 122.3, 118.7, 104.9, 72.3, 56.4, 53.5, 50.1, 45.8, 32.7, 27.3, 22.9, 22.5, 7.2.
MS (ESI): m/z (%): 311 (100) [M^++H]

10.6 Synthesis of squaramide based catalyst

To a stirred solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione (4.00 g, 28.1 mmol) and zinc trifluoromethanesulfonate (0.195 g, 0.536 mmol) in methanol (20 mL) at room temperature was added 3,5-bis(trifluoromethyl)aniline (5.36g, 23.4mmol). After stirring for 48 h, a white precipitate formed, which was filtered and washed with methanol (3 X 5 mL), yielding 3-(3,5 bis(trifluoromethyl)phenylamino)-4-methoxycyclobut-3-ene-1,2-dione as a white solid (5.51g, 71 %).[62]

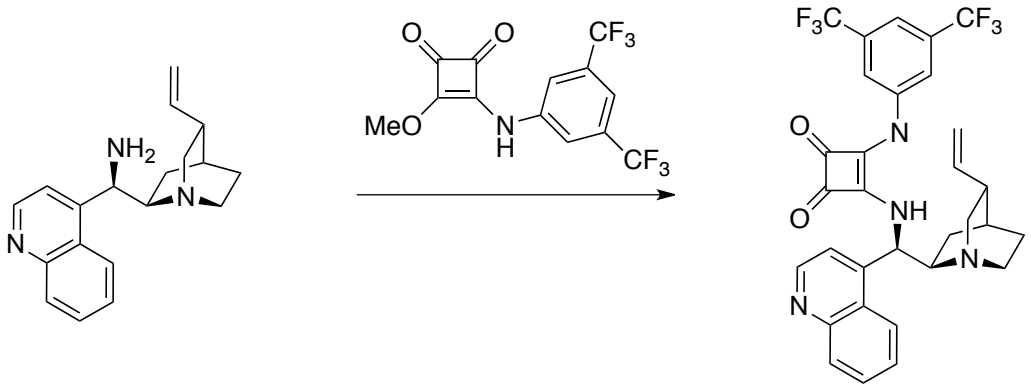


^{1}H-NMR (300 MHz, DMSO-d$_6$, 25˚C): δ = 11.20 (s, 1H), 8.04 (s, 2H), 7.79 (s, 1H), 4.41 (s,3H).

^{13}C-NMR (75 MHz, DMSO-d$_6$, 25˚C): δ = 187.3, 184.4, 179.8, 169.1, 140.4, 140.2, 131.1 (q, ^{2}J (C-C-F) = 32.9 Hz), 122.5 (q, J (C-F) = 271.3 Hz), 119.1, 115.9, 60.9.

MS (ESI): m/z (%): 362 (100) [M^{+}+Na].

To a stirred solution of 9-*epi*-aminoquinidine (1.19 g, 3.65 mmol) in methanol (40 mL) was added 3-(3,5- bis(trifluoromethyl)phenylamino)-4-methoxycyclobut-3-ene-1,2-dione (1.13 g, 3.32 mmol). After stirring for 48 h, a white precipitate formed, which was filtered and washed with methanol (3 times with 5 mL), yielding the quinidine-based squaramide catalyst (1.79 g, 85%).

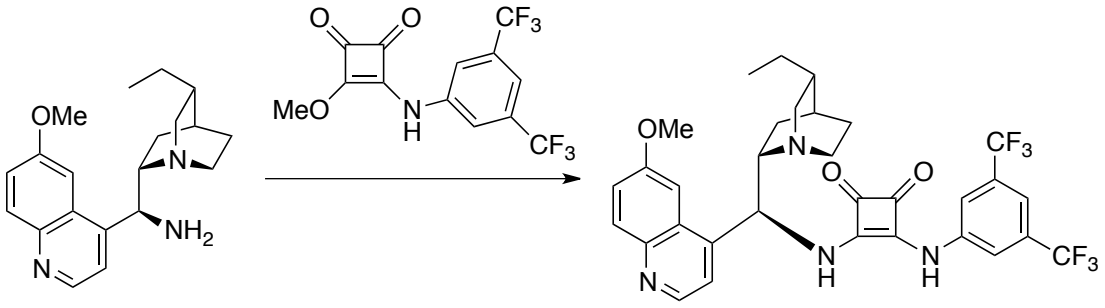


^{1}H-NMR (400 MHz, DMSO-d$_6$, 25˚C): δ = 9.02 (d, J = 4.4 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.03 (s, 2H), 7.83 (t, J = 7.6 Hz, 1H), 7.78-7.75 (m, 2H), 7.64 (s, 1H), 6.16 (bs, 1H), 5.94-5.85 (m, 1H), 5.20 (d, J = 17.2 Hz, 1H), 5.13 (d, J = 10.8 Hz, 1H), 3.18-3.13 (m, 1H), 3.03-2.95 (m, 1H), 2.93-2.83 (m, 2H), 2.30-2.24 (m, 1H), 1.60-1.51 (m, 3H), 1.02 (bs, 2H), 0.85-0.79 (m, 1H).

^{13}C-NMR (100 MHz, DMSO-d$_6$, 25˚C): δ = 184.5, 180.2, 168.9, 162.4, 150.3, 148.0, 144.8, 140.9, 140.5, 131.2 (q, J = 32.8 Hz), 129.9, 129.4, 127.1, 126.3, 123.05, 123.04

(q, *J* = 271.8 Hz), 119.4, 118.1, 114.7, 114.4, 59.3, 52.9, 48.8, 45.9, 38.6, 27.2, 25.9, 24.8.

MS (ESI): m/z (%): 602 (100) [M^++H].



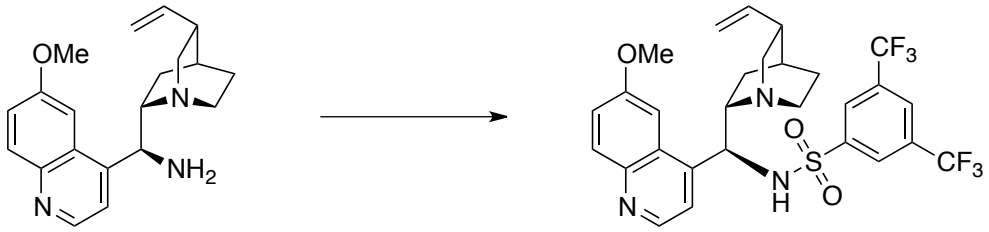
^{1}H-NMR (400 MHz, DMSO-d_6, 25˚C): δ = 10.23 (bs, 1H), 8.84 (d, *J* = 4.5 Hz, 1H), 8.36 (bs, 1H), 8.01(m, 3H), 7.78 (s, 1H), 7.71 (d, *J* = 4.5 Hz, 1H), 7.66 (s, 1H), 7.47 (dd, *J* = 9.3 Hz, 2.4 Hz, 1H), 6.07 (bs, 1H), 3.97 (s, 3H), 3.63-3.32 (m, 3H), 3.21-3.14 (m, 1H), 2.76-2.57 (m, 1H), 2.50-2.45 (m, 1H), 1.58-1.39 (m, 7H), 0.85-0.80 (m, 3H), 0.76 (br s, 1H);

^{13}C-NMR (100 MHz, DMSO-d_6, 25˚C): δ = 184.7, 180.1, 168.5, 162.7, 157.8, 147.7, 114.2, 143.0, 140.8, 131.5, 131.1 (q, *J* = 33.7 Hz), 127.4, 123.1 (q, *J* = 271.4 Hz), 121.8, 118.3, 117.6, 114.8, 101.4, 58.7, 57.1, 55.6, 36.7, 27.9, 26.8, 25.7, 24.9, 11.9.

MS (ESI): m/z (%): 634 (100) [M^++H].

10.7 Synthesis of sulphonamide-based catalysts

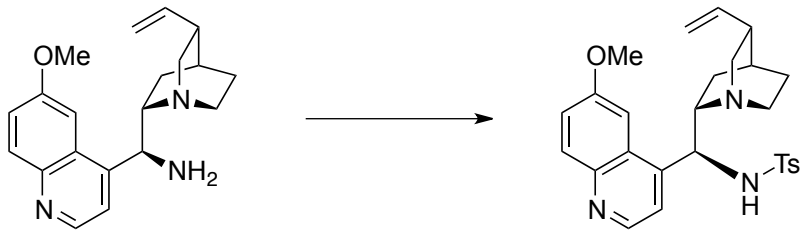
To a solution of 9-amino-9-deoxyepiquinidine (1.0 g, 3.09 mmol, 1 eq.) in anhydrous dichloromethane (15 mL) at 0˚C was added triethylamine (1.3 mL, 9.27 mmol 3 eq.) under nitrogen atmosphere, followed by 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (1.02 g, 3.25 mmol, 1.05 eq.). The reaction mixture was then stirred overnight at room temperature, and the solvent was removed *in vacuo*. The residue was purified by column chromatography to afford the sulfonamide catalyst as a white powder (1.59 g, 2.66 mmol, 86%).



^{1}H-NMR (400 MHz, CD_3OD, 25˚C): δ = 8.39 (d, *J* = 5.1 Hz, 1H), 7.64-7.78 (m, 4H), 7.36 (d, *J* = 5.1 Hz, 1H), 7.30 (m, 2H), 5.83 (m, 1H), 5.12-5.17 (m, 3H), 3.93 (s, 3H), 3.88 (m, 1H), 3.35 (m, 1H), 3.05– 3.10 (m, 3H), 2.45 (m, 1H), 1.66 (br, 3H), 1.03 (m, 1H).

^{13}C-NMR (100 MHz, CD_3OD, 25˚C): δ = 160.6, 148.0, 147.0, 146.0, 144.7, 140.7, 132.6, 132.4, 131.4, 129.4, 127.9, 125.6, 124.9, 123.9, 122.8, 121.2, 115.9, 101.6, 62.1, 56.2, 53.9, 49.9, 47.1, 38.9, 28.4, 26.2, 25.4;

MS (ESI): m/z (%): 600 (100) [M^++H].



^{1}H-NMR (400 MHz, CD_3OD, 25˚C): δ = 8.47 (d, *J* = 4.4 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 4.4 Hz, 1H), 7.36 (m, 3H), 7.23 (s, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 5.77 (m, 1H), 5.02 (d, *J* = 10.7 Hz, 1H), 4.84 (m, 2H), 3.94 (s, 3H), 2.96 (m, 3H), 2.84 (m, 1H), 2.54 (m, 1H), 2.29 (s, 3H), 2.25 (br, 1H), 1.09 (m, 3H), 0.95 (m, 1H), 0.85 (m, 1H);

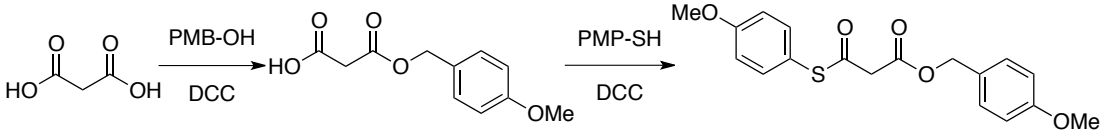
^{13}C-NMR (100 MHz, CD_3OD, 25˚C): δ = 158.3, 146.7, 145.5, 143.4, 143.3, 140.6, 136.5, 130.0, 128.8, 128.6, 127.1, 122.3, 120.3, 113.6, 100.4, 60.6, 54.9, 51.9, 48.5, 45.9, 38.2, 27.3, 25.8, 24.2, 19.9

MS (ESI): m/z (%): 479 (100) [M^++H].

10.8 Synthesis of MTMs

Malonic acid (100 mmol, 10.4 g, 2 eq) was dissolved under an inert argon atmosphere in dry acetonitrile (75 ml) and DMAP (10 mmol, 1.2 g, 0.2 eq) and 4-methoxybenzyl alcohol (50 mmol, 6.9 g, 1 eq) were added. The solution was cooled to 0°C and a solution of DCC (75 mmol, 15.5 g, 1.5 eq) in dry acetonitrile (25 ml) was added dropwise over 30 minutes. The reaction was kept at 0°C for 30 minutes and was then allowed to warm to room temperature. The reaction mixture was stirred at room temperature for other 2 hours followed by filtration of DCU and removal of all volatiles at reduced pressure. The crude mixture was re-dissolved in a mixture of CH_2Cl_2 (100 ml) and saturated aqueous $NaHCO_3$ (100 ml). The two phases were separated and the aqueous phase was washed twice with CH_2Cl_2. The pH of the aqueous phase was then decreased to pH 3 by addition of an aqueous solution of HCl (10%). The aqueous phase was reextracted with CH_2Cl_2 (3 times 80 ml each), and the combined organic phases were dried over $MgSO_4$. After filtration, all volatiles were removed at reduced pressure to yield a red solid that was used without further purification.

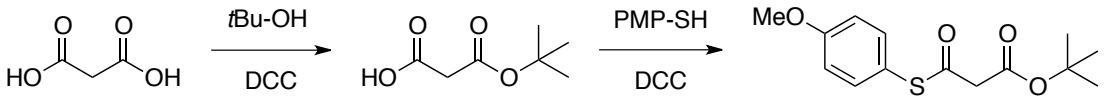
The solid was dissolved in dry CH_2Cl_2 (75 ml) and 4-methoxythiophenol (60 mmol, 8.4 g 1.2 eq) was added. The solution was cooled to 0°C and a solution of DCC (75 mmol, 15.5 g, 1.5 eq) in CH_2Cl_2 (25 ml) was added dropwise within 30 minutes. The reaction mixture was stirred for 30 minutes at 0°C and then at r.t. 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 a gradient of CH_2Cl_2/pentane (7:3) to CH_2Cl_2. After removal of all the volatiles at reduced pressure, 13.8g (80%) of MTM was isolated as white solid.



^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.32-7.29 (m, 4H), 6.95 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.13 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 (s, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 166.2, 161.4, 160.2, 136.6, 130.7, 127.7, 117.9, 115.4, 114.4, 91.0, 67.7, 55.8, 55.7, 49.3.

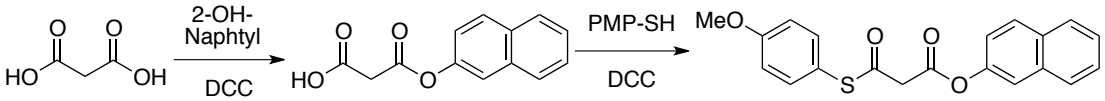
MS (ESI): m/z (%): 369 (100) [M^++Na]



^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.33 (d, *J*= 8.9 Hz 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.13 (s, 2H), 3.82 (s, 3H), 3.55 (s, 2H), 1.48 (s, 9H);

^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 191.5, 165.5, 161.3, 136.6, 118.2, 115.3, 82.9, 55.8, 50.7, 28.3.

MS (ESI): m/z (%): 305 (100) [M^++Na]



^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.87-7.79 (m, 3H), 7.60 (d, *J*= 2.2 Hz, 1H), 7.53-7.45 (m, 2H), 7.27 (dd, *J*= 8.8 Hz, 2.3 Hz, 1 H), 6.97 (m, 2 H), 3.94 (s, 2H), 3.84 (s, 3H);

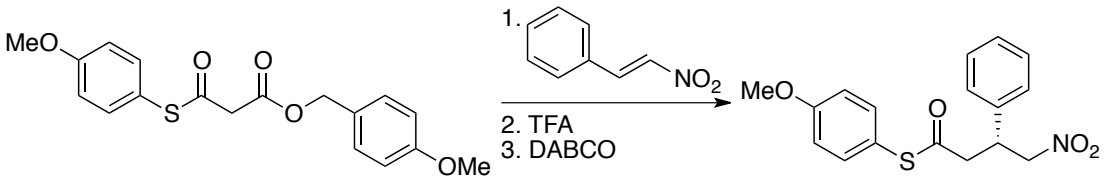
^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 190.9, 165.2, 161.5, 148.5, 136.7, 134.6, 132.7, 129.9 128.2, 128.1, 127.1, 126.4, 121.1, 118.9, 117.6, 115.5, 55.8, 49.3.

MS (ESI): m/z (%): 375 (100) [M^++Na]

10.9 General procedure for the organocatalysed 1,4 addition reaction of MTMs with nitroolefins

The nitroolefin (0.11 mmol, 1.1 equiv), MTM **1** (35 mg, 0.1 mmol), and the catalyst (0.001 mmol, 1 mol%) were dissolved in toluene (1 mL) in a capped vial at -50°C. After stirring the resulting solutions for 24 h, all volatiles were removed at reduced pressure. The oily residue was then dissolved in a solution of CH_2Cl_2 and TFA (2:1, 1 ml) and the mixture was stirred for 2 hours. After removal of all the volatiles at reduced pressure, the residue was dissolved in CH_2Cl_2 (0.5 ml) and DABCO (0.1 mol, 1 eq) was added. The mixture was stirred for 1 hour and then purified by column chromatography on silica gel (gradient of pentane/ethyl acetate 4:1 to 3:1; in the case of the aliphatic compounds the gradient was pentane/ethyl acetate 10:1 to 5:1).

(3R)-4-methoxyphenyl-4-nitro-3-phenylbutanethioate



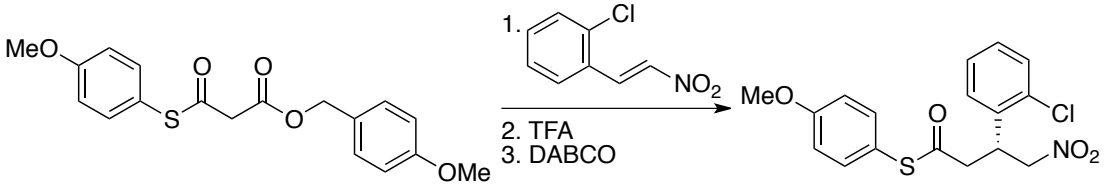
^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.33 (m, 3H), 7.22 (m, 4H), 6.91 (d, J = 8.9 Hz, 2H), 4.75 (dd, J = 6.7 Hz, 12.7 Hz, 1H), 4.66 (dd, J = 8.2 Hz, 12.7 Hz, 1H), 4.05 (m, J = 7.5 Hz, 1H), 3.81 (s, 3H), 3.07 (d, J = 7.4 Hz, 2H).

^{13}C-NMR (100 MHz, CDCl3, 25 °C): δ = 195.9, 160.7, 137.7, 135.9, 129.2, 128.0, 127.4, 117.4, 114.8, 78.9, 55.3, 45.8, 40.2.

MS (ESI): m/z (%): 332 (100) [M^++H].

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 26.5 min, (*R*) = 31.1 min (98%ee).

(3R)-4-methoxyphenyl-3-(2-chlorophenyl)4-nitrobutanethioate



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.47 – 7.42 (m, 1H), 7.31 – 7.21 (m, 5H), 6.98 – 6.91 (m, 2H), 4.86 (dd, J = 10.8, 5.1 Hz, 1H), 4.82 (dd, J = 10.8, 4.4 Hz, 1H), 4.55 (m, J = 7.0 Hz, 1H), 3.84 (s, 3H), 3.24 – 3.20 (m, 2H).

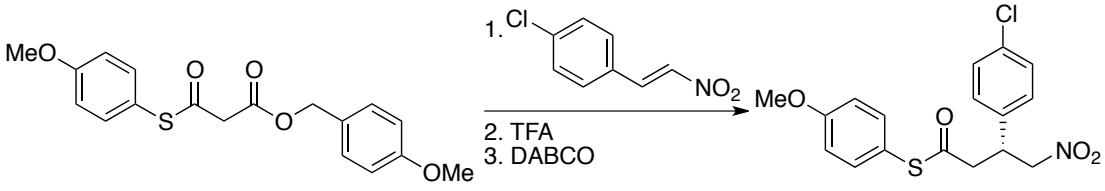
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 196.4, 161.3, 136.4, 135.4, 134.2, 130.9, 129.7, 128.8, 127.8, 117.8, 115.4, 77.5, 55.8, 44.5, 37.6.

MS (ESI): m/z (%): 366 (M^+(^{35}Cl)+H) (100), 368 (M^+(^{37}Cl)+H) (33).

Elemental analysis calcd (%) for $C_{17}H_{16}ClNO_4S$: C 55.81, H 4.41, N 3.83; found: C 55.79, H 4.34, N 3.83.

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 20.5 min, (*R*) = 22.5 min (99% ee).

(3R)-4-methoxyphenyl-3-(4-chlorophenyl)4-nitrobutanethioate



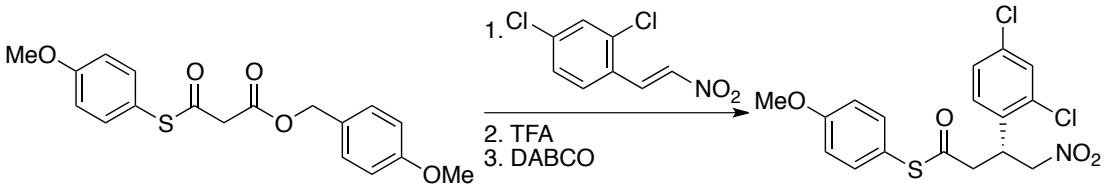
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.72 (dd, J = 6.5 Hz, 12.8 Hz, 1H), 4.61 (dd, J = 8.4 Hz, 12.8 Hz, 1H), 4.01 (m, J = 7.1 Hz, 1H), 3.81 (s, 3H), 3.04 (d, J = 7.2 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 195.7, 160.8, 136.3, 135.9, 133.9, 129.2, 128.8, 117.2, 114.9, 78.7, 55.3, 45.6, 39.8.

MS (ESI): m/z (%): 366 (M^+(^{35}Cl)+H) (100), 368 (M^+(^{37}Cl)+H) (34)

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 21.7 min, (*R*) = 30.0 min (98% ee).

(3R)-4-methoxyphenyl-3-(2,4-dichlorophenyl)4-nitrobutanethioate



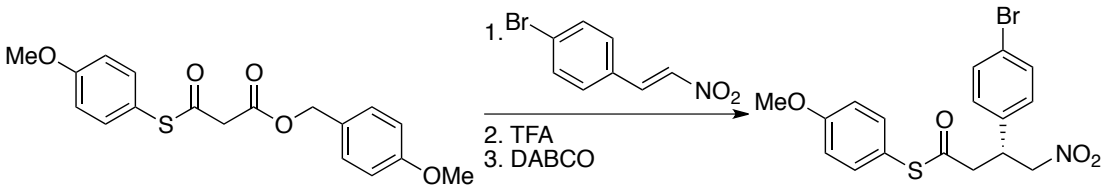
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.4 (d, J = 2.13 Hz, 1H), 7.26 (m, 1H), 7.23 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 4.81 (dd, J = 4.9 Hz, 10.8 Hz, 1H), 4.77 (dd, J = 4.2 Hz, 10.8 Hz, 1H), 4.47 (m, 1H), 3.84 (s, 3H), 3.17 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.4, 160.7, 135.7, 134.4, 134.0, 133.9, 129.6, 129.0, 127.4, 117.1, 114.6, 76.9, 54.7, 43.9, 36.3.

MS (ESI): m/z (%): 400 (M^+(^{35}Cl, ^{35}Cl)+H) (100), 402 (M^+(^{35}Cl, ^{37}Cl)+H) (67), 404 (M^+(^{37}Cl, ^{37}Cl)+H) (10).

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 22.1 min, (*R*) = 26.5 min (99% ee).

(3R)-4-methoxyphenyl-3-(4-bromophenyl)4-nitrobutanethioate



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.48 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.73 (dd, *J* = 12.8, 6.5 Hz, 1H), 4.62 (dd, *J* = 12.8, 8.4 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.82 (s, 3H), 3.05 (d, *J* = 7.2 Hz, 2H).

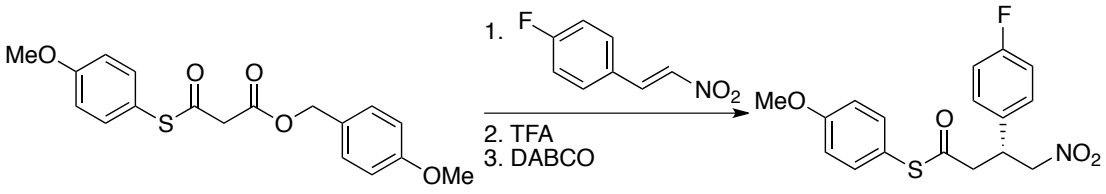
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 196.2, 161.3, 137.2, 136.4, 132.7, 129.6, 122.6, 117.7, 115.4, 79.1, 55.8, 46.0, 40.4.

MS (ESI): m/z (%): 410 (M^+(^{79}Br)+H) (100), 412 (M^+(^{81}Br)+H) (99).

Elemental analysis calcd (%) for $C_{17}H_{16}BrNO_4S$: C 55.49.77, H 3.93, N 3.41; found: C 49.79, H 3.96, N 3.48.

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 28.1 min, (*R*) = 32.1 min (98% ee).

(3R)-4-methoxyphenyl-3-(4-fluorophenyl)4-nitrobuthanethioate



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.23 - 7.18 (m, 4H), 7.08 - 7.02 (m, 2H), 6.95 - 6.90 (m, 2H), 4.74 (dd, *J* = 12.7, 6.6 Hz, 1H), 4.63 (dd, *J* = 12.7, 8.4 Hz, 1H), 4.11 - 3.98 (m, 1H), 3.82 (s, 3H), 3.05 (d, *J* = 7.2 Hz, 2H).

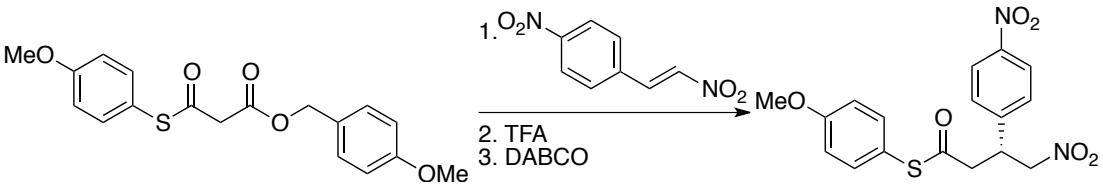
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 196.3, 164.5, 161.3, 136.4, 129.6, 129.5, 116.6, 116.4, 115.4, 79.5, 55.8, 46.3, 40.2.

MS (ESI): m/z (%): 350 (M^++H).

Elemental analysis calcd (%) for $C_{17}H_{16}FNO_4S$: C 58.44; H, 4.62; N, 4.01; found: C, 58.60; H, 4.74; N, 3.91.

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ=254 nm: t_R: (*S*)= 20.7 min, (*R*)= 29.0 min (94% ee)

(3R)-4-methoxyphenyl-3-(4-nitrophenyl)4-nitrobutanethioate



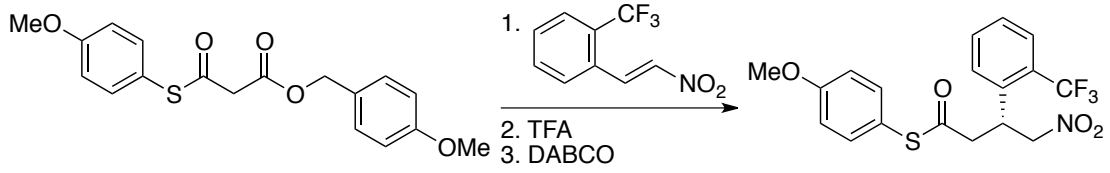
^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 8.22 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.80 (dd, *J* = 6.3Hz, 13.1 Hz, 1H), 4.70 (dd *J* = 8.6 Hz, 13.1 Hz, 1H), 4.18 (m, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 3.11 (d, *J* = 7.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 195.4, 161.0, 147.6, 145.1, 135.9, 128.6, 124.3, 116.9, 115.1, 78.2, 55.4, 45.3, 40.1.

MS (ESI): m/z (%): 377 (M^++H).

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 38.4 min, (*R*) = 54.9 min (99% ee).

(3R)-4-methoxyphenyl 3-(2-(trifluoromethyl)phenyl)4-nitrobuthanethioate



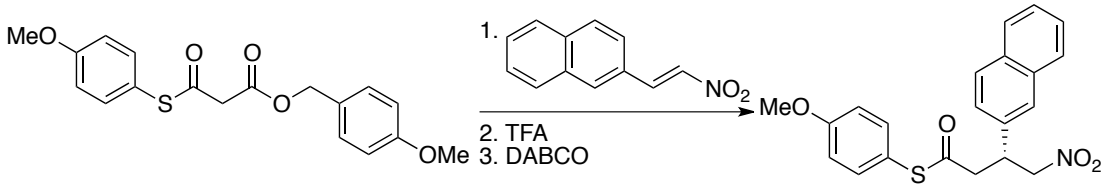
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.55 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.29 (m, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.66 (dd, *J* = 7.2 Hz, 13.9 Hz, 1H), 4.64 (dd, *J* = 7.4 Hz, 13.5 Hz, 1H), 4.32 (m, 1H), 3.66 (s, 3H), 3.98 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 195.9, 160.6, 136.4, 135.7, 131.6, 128.3, 127.8, 127.4, 126.4, 123.8, 117.0, 114.6, 77.7, 54.9, 45.4, 39.5.

MS (ESI): m/z (%): 400 (M^++H).

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 17.2 min, (*R*) = 20.8 min (99% ee)

(3R)-4-methoxyphenyl-3-(2-naphtyl)4-nitrobutanethioate



^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ = 7.91 – 7.77 (m, 3H), 7.69 (s, 1H), 7.56 – 7.47 (m, 2H), 7.34 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.18 (dd, *J* = 9.3, 2.6 Hz, 2H), 6.98 – 6.84 (m, 2H), 4.85 (dd, *J* = 12.7, 6.8 Hz, 1H), 4.77 (dd, *J* = 12.8, 8.1 Hz, 1H), 4.29 – 4.18 (m, 1H), 3.81 (s, 3H), 3.26 – 3.11 (m, 2H).

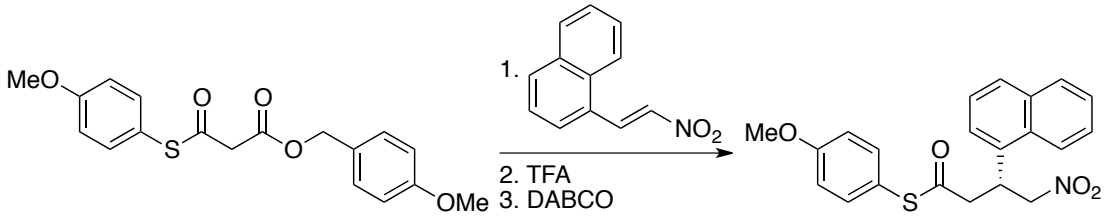
^{13}C-NMR (100 MHz, $CDCl_3$, 25°C) δ = 196.4, 161.3, 136.4, 135.6, 133.8, 133.3, 129.5, 128.3, 128.1, 127.1, 127.0, 126.8, 125.2, 117.8, 115.4, 79.4, 55.8, 46.4, 41.0.

MS (ESI): m/z (%): 382 (M^++H).

Elemental analysis calcd (%) for $C_{21}H_{19}NO_4S$: : C, 66.13; H, 5.02; N, 3.67; found: 66.27; H, 5.06; N, 3.65.

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 38.6 min, (*R*) = 49.7 min (>99% ee).

(3R)-4-methoxyphenyl-3-(1-naphtyl)4-nitrobutanethioate



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 8.17 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.61 (ddd, J = 8.5, 6.8, 1.4 Hz, 1H), 7.54 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.93 – 6.88 (m, 2H), 5.06 – 4.96 (m, 1H), 4.87 (d, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.25 (m, J = 6.8, 5.6 Hz, 2H).

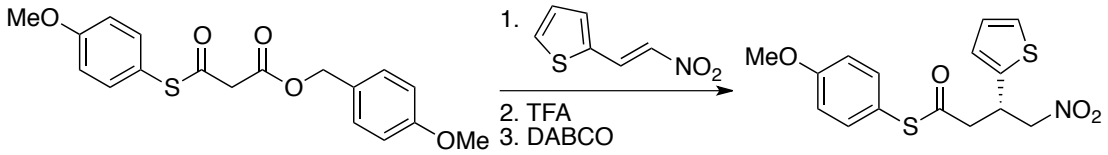
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 196.6, 161.2, 136.4, 134.6, 134.2, 133.1, 131.3, 129.7, 129.1, 127.4, 126.5, 125.7, 122.6, 117.9, 115.3, 115.0, 78.8, 55.8, 46.1.

MS (ESI): m/z (%): 382 (M^++H).

Elemental analysis calcd (%) for $C_{21}H_{19}NO_4S$: C, 66.13; H, 5.02; N, 3.67; found: C, 66.01; H, 5.18; N, 3.64.

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*R*) = 38.7 min, (*S*) = 48.3 min (97% ee).

(3S)-4-methoxyphenyl-3-(thiophen-2-yl)4-nitrobutanethioate



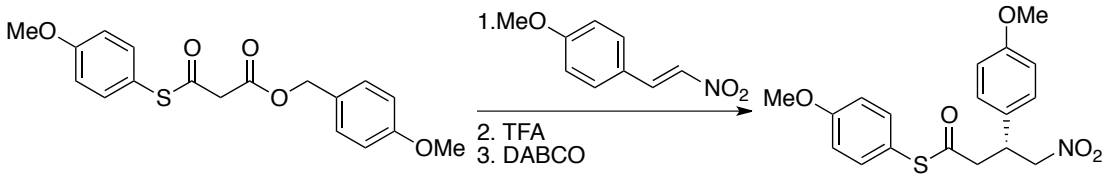
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.25-7.19 (m, 3H), 6.94-6.88 (m, 4H), 4.76 (dd, J = 6.5 Hz, 12.8 Hz, 1H), 4.66 (dd, J = 7.8 Hz, 12.8 Hz, 1H), 4.37 (m, J = 7.1 Hz, 1H), 3.82 (s, 3H), 3.14 (dd, J = 6.9 Hz, 16.1 Hz, 1H), 3.12 (dd, J = 7.5 Hz, 16.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 195.7, 160.9, 140.4, 136.0, 127.1, 125.8, 124.9, 117.3, 114.9, 79.3, 55.3, 46.5, 35.9.

MS (ESI): m/z (%): 338 (M^++H).

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*R*) = 23.4 min, (*S*) = 30.9 min (98%ee).

(3R)-4-methoxyphenyl-3-(4-methoxyphenyl)4-nitrobutanethioate



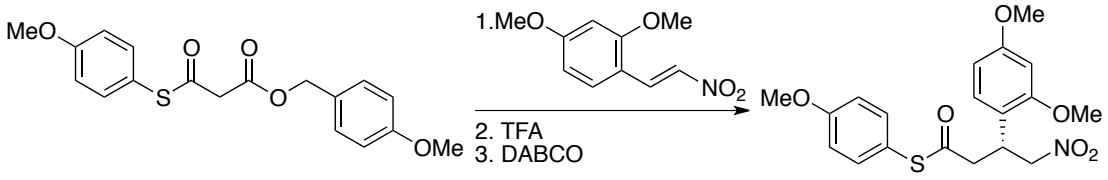
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.23 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.71 (dd, J= 12.6 Hz, 6.7 Hz, 1H), 4.61 (dd, J = 12.6 Hz, 8.3 Hz, 1H), 4.00 (m, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.04 (d, J = 7.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.0, 161.0, 159.2, 136.0, 129.6, 128.4, 117.5, 114.9, 114.3, 79.2, 55.3, 55.2, 46.0, 39.8.

MS (ESI): m/z (%): 362 (M^++H).

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 29.9 min, (*R*) = 33.8 min (98%ee).

(3R)-4-methoxyphenyl-3-(2,4-dimethoxyphenyl)4-nitrobutanethioate



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.21 – 7.16 (m, 2H), 6.94 – 6.87 (m, 3H), 6.80 (s, 1H), 6.44 (d, J = 5.5 Hz, 1H), 4.74 – 4.69 (m, 2H), 4.17 – 4.07 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.20 – 3.01 (m, 2H).

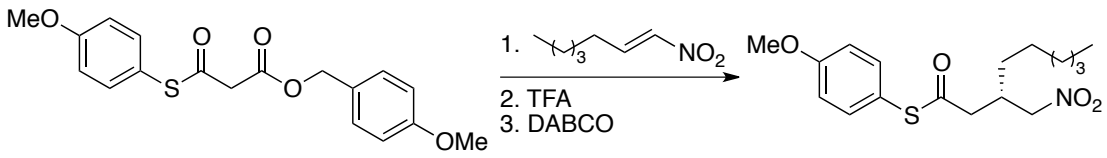
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 197.0, 161.0, 158.4, 156.9, 136.4, 131.4, 121.4, 118.5, 116.9, 115.2, 95.7, 78.2, 56.0, 55.9, 55.8, 44.8, 37.1.

MS (ESI): m/z (%): 392 (M^++H).

Elemental analysis calcd (%) for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58; found: C, 58.51; H, 5.38; N, 3.74.

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 15.1 min, (*R*) = 18.4 min (91% ee).

(3S)-4-methoxyphenyl 3-(nitromethyl) nonanethioate



^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.51 (dd, *J* = 6.3 Hz, 12.4 Hz, 1H), 4.43 (dd, *J* = 6.0 Hz, 12.4 Hz, 1H), 3.82 (s, 3H), 2.80 (dd, *J* = 7.2 Hz, 16.2 Hz, 1H), 2.77 (dd, *J* = 5.6 Hz, 16.2 Hz, 1H), 2.70 (m, 1H), 1.36 (m, 10H), 0.89 (t, *J* = 6.94 Hz, 3H).

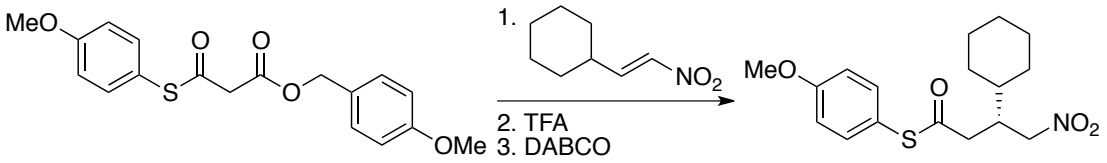
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.0, 160.8, 136.1, 117.8, 114.9, 78.3, 55.4, 44.2, 34.7, 31.5, 31.2, 29.3, 26.1, 22.4, 13.9.

MS (ESI): m/z (%): 340 (M^++H).

Elemental analysis calcd (%) for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42; N, 4.13 found: C, 60.50; H, 7.45; N, 4.34.

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (95:5, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*R*) = 31.5 min, (*S*) = 39.4 min (91% ee).

(3R)-4-methoxyphenyl 3-cyclohexyl 4-nitrobutanethioate



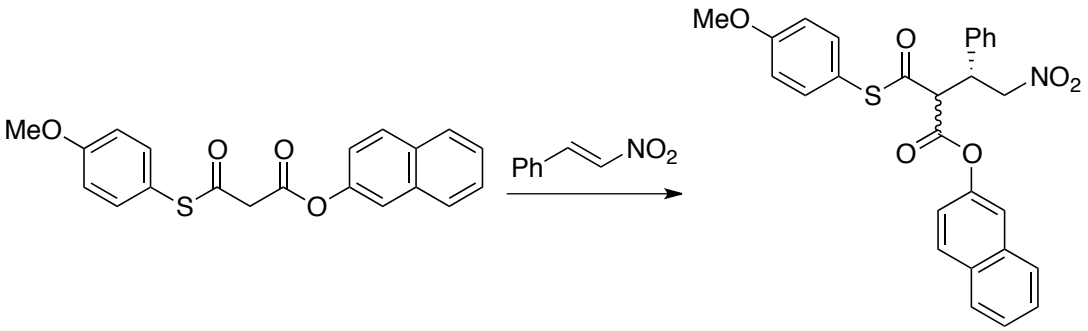
^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.31 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.49 (dd, *J* = 6.5 Hz, 12.8 Hz, 1H), 4.46 (dd, *J* = 6.3 Hz, 13.1 Hz, 1H), 3.82 (s, 3H), 2.84 (dd, *J* = 4.9 Hz, 15.7 Hz, 1H), 2.75 (m, 2H), 1.72 (m, 5H), 1.47 (m, 1H), 1.25-0.97 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 197.2, 160.8, 136.0, 117.8, 114.9, 76.7, 55.3, 41.9, 39.8, 38.8, 29.9, 26.2, 26.1.

MS (ESI): m/z (%): 338 (M^++H).

HPLC: Chiracel OD-H column with n-hexane/i-PrOH (95:5, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 38.2 min, (*R*) = 52.8 min (94% ee).

(3R)-naphthalen-2-yl 2-(((4-methoxyphenyl)thio)carbonyl)-4-nitro-3-phenylbutanoate



Mixture of diastereoisomers.

^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.89-7.71 (m, 2H), 7.51-7.34 (m, 8H), 7.22-6.80 (m, 6H), 5.11-4.85 (m, 2H), 5.53-4.38 (m, 2H), 3.86-3.81 (m, 3H).

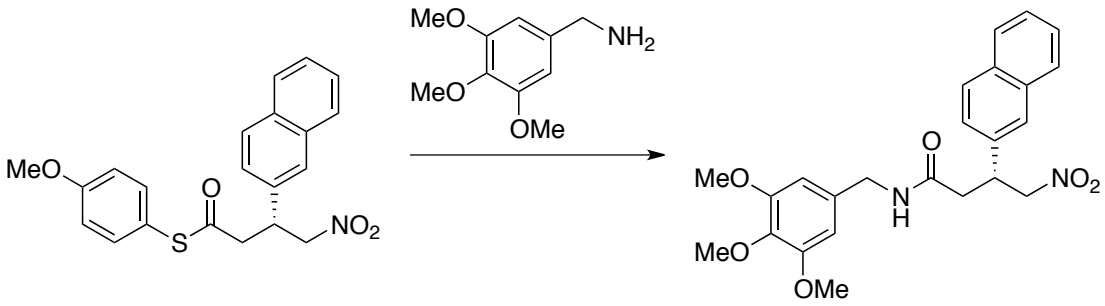
^{13}C-NMR (100 MHz, $CDCl_3$, 25°C): δ = 191.3, 191.0, 165.9, 165.2, 147.9, 147.8, 135.7, 135.6, 134.6, 134.5, 133.7, 133.6, 131.9, 131.8, 130.5, 129.9, 129.8, 129.7, 129.6, 129.3, 129.2, 128.8, 128.7, 128.5, 128.4, 128.0, 127.9, 127.9, 127.8, 127.0, 126.9, 126.3, 126.2, 126.1, 126.0, 120.8, 120.7, 118.8, 118.7, 115.7, 115.5, 76.9, 76.8 62.3, 62.0, 55.9, 55.8, 44.1, 44.0

MS (ESI): m/z (%): 503 (M^++H).

10.10 Functionalization and determination of the absolute stereochemistry of γ-nitrothioesters

Preparation of 3,4,5-(trimethoxybenzyl) 3-(2-naphthyl) 4-nitrobutanamide

The γ-nitrothioester (0.1 mmol, 38.1 mg, 1 eq) was dissolved in CH_2Cl_2, 3,4,5-trimethoxybenzylamide (0.1 mmol, 21.6 mg, 1.1 eq.) was added and the reaction was stirred for 48 hours at rt. The volatiles were evaporated at reduced pressure and the crude mixture was purified with column chromatography using as eluent EtOAc/Pentane (1:3). The amide was isolated in 90% yield (0.090 mmol, 38.4 mg).[48]



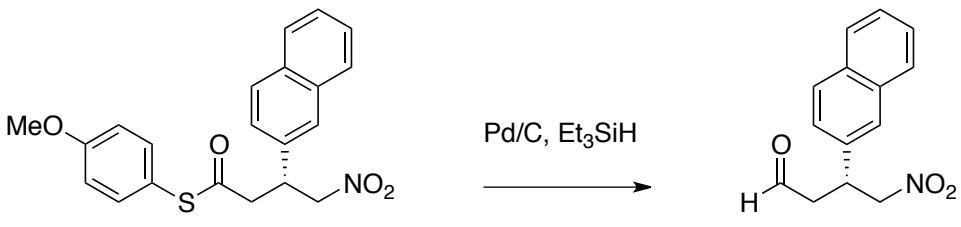
^{1}H-NMR (400 MHz, $CDCl_3$, 25°C) δ = 7.88 – 7.75 (m, 4H), 7.69 (s, 1H), 7.58 – 7.45 (m, 3H), 7.38 – 7.30 (m, 1H), 6.30 (s, 2H), 6.03 (s, 1H), 4.89 (dd, J = 12.6, 6.6 Hz, 1H), 4.79 (dd, J = 12.6, 7.9 Hz, 1H), 4.31 – 4.19 (m, 2H), 3.78 (s, 3H), 3.66 (s, 6H), 2.83 – 2.67 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25°C) δ = 169.9, 153.7, 137.5, 136.4, 133.9, 133.8, 133.2, 129.3, 128.2, 128.0, 126.94, 126.9, 126.7, 125.3, 105.1, 79.8, 61.2, 56.3, 44.4, 41.2, 40.1.

MS (ESI): m/z (%): 439 (M^++H).

Preparation of 3-(2-naphthyl) 4-nitrobutanal

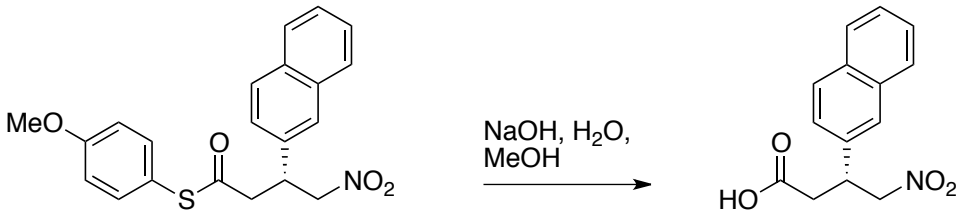
A solution made dissolving the γ-nitrothioester (0.1 mmol, 38.1 mg, 1 eq.) in dry acetone was transferred under argon in a two-necked flask. To the solution, Pd/C (10% Pd, 20 mg, 20 mol %) was added. Triethylsilane (0.3 mmol, 34 mg, 3 eq) was added dropwise over 5 minutes. The reaction was checked after 1.5 hours by TLC analysis. If the starting material was still present 1.5 more equivalents of triethylsilane should be added. The reaction was stirred at r.t. for 2 more hours. The catalyst was filtered through a pad of celite and the solvent was removed at reduced pressure. The chromatographic purification was performed with a gradient of EtOAc/Pentane from 1:10 to 1:3. The product was isolated in 76% yield (18.5 mg 0.076 mmol).[39, 46]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 9.76 (s, 1H), 7.90 – 7.80 (m, 3H), 7.72 (d, J = 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.37 (dd, J = 8.5, 1.9 Hz, 1H), 4.83 – 4.70 (m, 2H), 4.28 (m, J = 7.3 Hz, 1H), 3.15 – 2.99 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 199.1, 135.8, 133.8, 133.3, 129.6, 128.2, 128.1, 127.0, 126.8, 125.2, 79.7, 46.8, 38.5.
MS (ESI): m/z (%): 244 (M^++H).

Preparation of 3-(2-naphthyl) 4-nitrobutanoic acid

The γ-nitrothioester (0.1 mmol, 38.1 mg, 1 eq.) was dissolved in 2 ml of 2N NaOH. 10% v/v of methanol was added to ensure a clear solution. The reaction was stirred overnight. CH_2Cl_2 was added and the water phase was washed three times. The pH of the organic phase was decreased to pH 1 using concd HCl. The water phases were washed three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$. The solution was filtered and the volatiles were removed under reduced pressure. The title compound was isolated in >99% yield (26 mg, 0.1 mmol).[47]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.90 – 7.78 (m, 3H), 7.70 (s, 1H), 7.56 – 7.46 (m, 2H), 7.34 (dd, J = 8.5, 1.8 Hz, 1H), 4.80 (dd, J = 12.7, 7.1 Hz, 1H), 4.72 (dd, J = 12.7, 7.8 Hz, 1H), 4.22 – 4.09 (m, 1H), 2.92 (d, J = 7.4 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 176.4, 135.7, 133.8, 133.3, 129.5, 128.3, 128.1, 127.0, 126.8, 125.2, 115.0, 79.7, 40.4, 37.7.
MS (ESI): m/z (%): 260 (M^++H)

Preparation of 2-methyl 5-(2-naphthyl) 6-nitrohexan-3-one

Under argon these two solutions were prepared:

1. γ-nitrothioester solution:

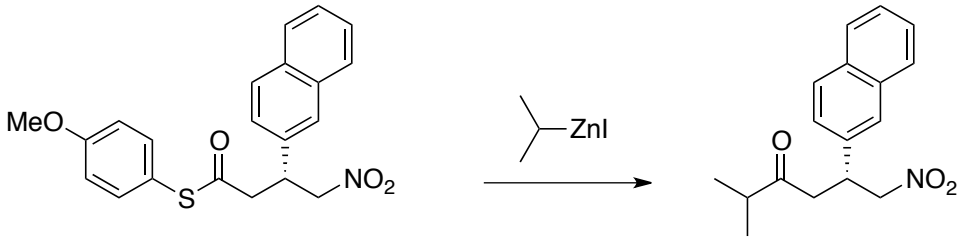
In a two-necked 10 ml flask the γ-nitrothioester (0.1 mmol, 38.1 mg, 1 eq.) was dissolved in 1 ml of dry toluene and $PdCl_2(PPh_3)_2$ was added (0.01 mmol, 7.0 mg, 10 mol %).

2. Solution of the organozinc reagent.

In a 10 ml two necked flask equipped with reflux condenser the zinc powder (0.4 mmol, 26 mg, 4 eq.) was suspended in 0.5 ml of dry THF. 1,2 dibromoethane was added (1 μl) and the solution was heated at reflux for 3 minutes. The suspension was cooled to room temperature and 1 μl of trimethylchloro silane was added and the mixture was stirred for 15 minutes. 2-iodopropane, 40 μl, was added (0.4 mmol, 4 eq.) and the mixture was stirred for 30 minutes at 60˚C.

The γ-nitrothioester solution was transferred to the organozinc solution via a cannule. The reaction was monitored by TLC and when the starting materials were consumed, the mixture was filtered through a plug of celite and washed with ether.

The filtrated solution was then washed five times with 20 ml of a saturated solution of $NaHCO_3$ and once with brine. The organic phase was dried with MgSO4, filtered and all the volatiles were removed under reduced pressure. The crude product was further purified with column chromatography (Pentane/EtOAc 3:1) and the product was isolated as colourless oil (14.2 mg, 50% yield).[39, 46]

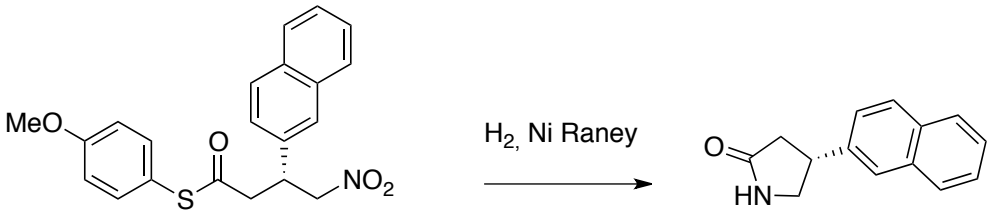


^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.88-7.78 (m, 3H), 7.78-7.64 (m, 1H), 7.56-7.44 (m, 2H), 7.44 – 7.33 (m, 1H), 4.82 (dd, J = 12.4, 6.8 Hz, 1H), 4.74 (dd, J = 12.4, 7.8 Hz, 1H), 4.23 (m, J = 7.0 Hz, 1H), 3.12-2.96 (m, 2H), 2.56 (m, J = 6.9 Hz, 1H), 1.09 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H).

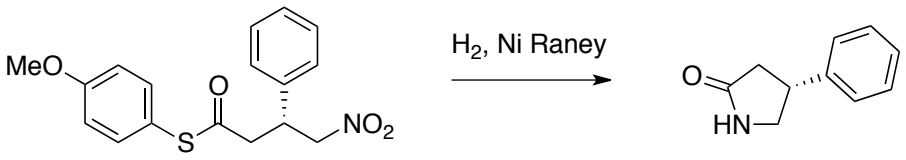
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 211.8, 136.8, 133.8, 133.2, 129.3, 128.2, 128.1, 126.9, 126.9, 126.6, 125.4, 79.8, 43.5, 41.6, 39.6, 18.4, 18.3.
MS (ESI): m/z (%): 286 (M^++H)

Preparation of 3-(2-naphthyl) cyclopentanelactam

A solution of γ-nitrothioester (355 mg, 0.76 mmol) in THF (10 ml) was placed in a hydrogenation vessel, together with H_3PO_4 (85%, 10 mol%) and Raney-Nickel (1.5 g). The hydrogenation vessel was purged three times with hydrogen and the reaction pressure was kept at a pressure of 3 bar. After 72 h the mixture was filtered under nitrogen and the residue washed with THF and acetone (50 ml each). After removal of all volatiles at reduced pressure, the residue was purified by column chromatography on silica gel (10% MeOH in $CHCl_3$) to yield the lactam (105 mg, 67%) as slightly yellowish oil.[2]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.83 (m, 3H), 7.70 (s, 1H), 7.50 (m, 2H), 7.41 (m, 1H), 4.14 (t, J = 8.4 Hz, 1H), 3.83 (ddd, J = 17.1 Hz, 14.4 Hz, 8.3 Hz, 2H), 2.97 (dd, J = 16.9, 9.1 Hz, 1H), 2.68 (dd, J = 17.0, 7.3 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 170.1, 139.3, 133.8, 133.0, 129.4, 128.1, 126.9, 126.4, 125.8, 125.0, 115.0, 56.0, 37.0, 35.2.
MS (ESI): m/z (%): 212 (M^++H)

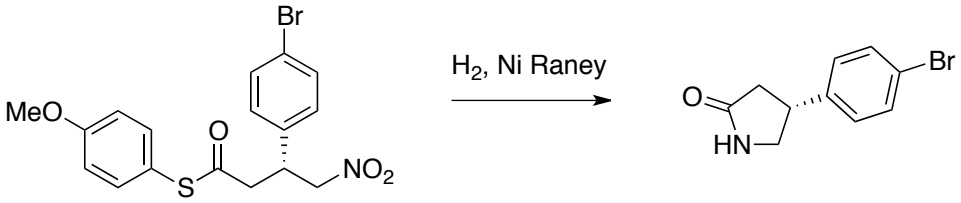


^{1}H-NMR (400 MHz, CD_3OD, 25˚C): δ = 7.58 (m, 5H), 4.17-3.93 (m, 2H), 3.65 (dd, *J*= 16.3 Hz, 8.8 Hz, 1H), 2.95 (dd, *J*= 16.5 Hz, 9.0 Hz, 1H), 2.78 (dd, *J*= 16.5 Hz, 8.7 Hz 2H).

^{13}C-NMR (100 MHz, CD_3OD, 25˚C): δ = 180.6, 143.4, 129.6, 127.8, 127.6, 50.9, 41.0, 39.2.

MS (ESI): m/z (%): 184 (M^++Na).

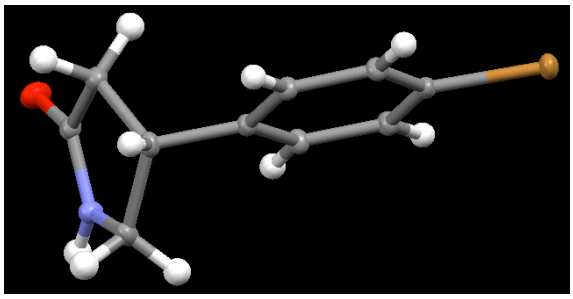
Measured α^D = -35.5˚(25˚C, c = 0.95, MeOH) Literature α^D = -37.8˚(25˚C, c = 0.95, MeOH).[49]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.43-7.38 (m, 2H), 7.09-7.04 (m, 2H), 3.72 (ddd, *J* = 9.3 Hz, 8.0 Hz, 1.0 Hz, 1H), 3.66-3.54 (m, 1H), 3.31 (dd, *J* = 9.4 Hz, 7.0 Hz, 1H), 2.67 (dd, *J* = 16.9 Hz, 8.9 Hz, 1H), 2.38 (dd, *J* = 16.9 Hz, 8.6 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 177.0, 141.1, 132.0, 128.5, 121.0, 100.0, 49.2, 39.8, 37.6.

MS (ESI): m/z (%): 263 (M^++Na).

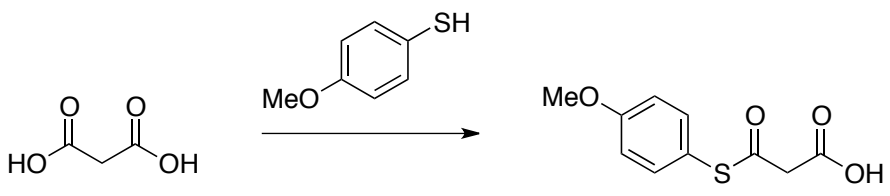


Crystal data of lactam: formula $C_{10}H_{12}Br_1N_1O_2$, M = 258.11, F(000) = 520, colourless plate, size 0.030 · 0.130 · 0.170 mm3, orthorhombic, spacegroup P 212121, Z = 4, a = 5.8120(5) Å, b = 6.7788(6) Å, c = 25.807(2) Å, α = 90°, β = 90°, γ = 90°, V = 1016.75(15) Å3, D calc. = 1.686 Mg · m-3. The crystal was measured on a Bruker Kappa Apex2 diffractometer at 123K using graphite-monochromated MoKα-radiation with λ = 0.71073 Å, Θmax = 44.202°. Minimal/maximal transmission 0.59/0.89, μ = 4.016 mm-1. The Apex2 suite has been used for data collection and integration. From

a total of 59191 reflections, 8055 were independent (merging r = 0.046). From these, 5286 were considered as observed (I>2.0σ(I)) and were used to refine 128 parameters. The structure was solved by direct methods using the program SIR92. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. R = 0.0221 (observed data), wR = 0.0381 (all data), GOF = 1.0800. Minimal/maximal residual electron density = -0.64/0.70 e Å-3. Chebychev polynomial weights were used to complete the refinement. Plots were produced using CAMERON.

10.11 Synthesis of MAHTs

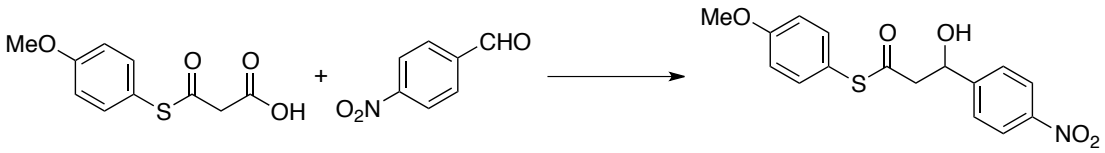
To a solution of 25 ml of trimethyl polyphosphate in 240 ml chloroform and 40 ml dry THF were added 65.3 g (628 mmol, 4 eq.) of malonic acid. After having stirred the mixture for 5 minutes, 20 ml (157 mmol, 1 eq.) of *p*-methoxy thiophenol are added dropwise to the suspension. The reaction is stirred for 96 hours at room temperature and then is diluted with 300 ml of diethyl ether. To the mixture a solution of saturated $NaHCO_3$ in water was added. The stirring was kept until the evolution of CO_2 had ceased. The phases were separated and the organic phase was washed twice with 400 ml of saturated $NaHCO_3$. The combined aqueous phases were acidified to pH=3 with a 10% solution of HCl. The acidified aqueous phase was back extracted with chloroform (5x 200 ml), the combined organic phases were dried with MgSO4, filtrated and the volatiles were evaporated at reduced pressure. The last traces of the solvents were finally evaporated with high vacuum. After having obtained a solid, the product is recrystallized. A mixture of chloroform and benzene (1:3) was added until the solid was completely dissolved. Hexane was added until a yellowish solid started to precipitate. The compound was letting standing for two hours at room temperature and then two days at 4˚C. The solid was filtrated and washed with a chilled solution of benzene and hexane (1:9). The desired product was isolated in 68% yield (24.3 g, 107 mmol) as a yellow solid.[2]



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 7.32 (d, *J*= 8.8 Hz, 2H), 6.91 (d, *J*= 8.8 Hz, 2H), 3.84 (s, 3H), 3.61 (s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 195.0, 174.5, 160.9, 136.1, 117.2, 114.9, 55.4, 52.9, 14.2.
MS (ESI): m/z (%): 249 (M^++Na)

10.12 General decarboxylative addition of MAHTs to aldehydes

45 mg of MAHT (0.2 mmol, 2 eq.) were dissolved in 1 ml THF together with 15 mg of *p*-nitrobenzaldehyde (0.1 mmol, 1 eq.). The cinchona alkaloid catalyst was added immediately (EpiQDTU, 12 mg, 0.02 mmol, 20 mol %) and the mixture was stirred for 24 hours. The volatiles were removed at reduced pressure and the mixture was purified by column chromatography. (Pentane/Et_2O 1:1).



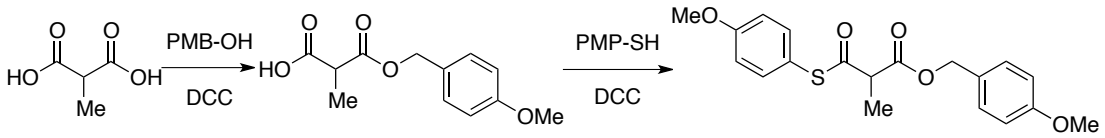
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C) δ = 8.22 (d, *J*= 8.8 Hz, 2H), 7.56 (d, *J*= 8.7 Hz, 2H), 7.29 (d, *J*= 8.8 Hz, 2H), 6.95 (d, *J*= 8.9 Hz, 2H), 5.28 (t, *J*= 6.6 Hz, 1H), 3.84 (s, 3H), 3.05 (d, *J*= 5.5 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C) δ = 198.8, 161.5, 149.7, 147.9, 147.9, 136.5, 126.9, 124.3, 117.5, 115.5, 70.3, 55.8, 51.6.
MS (ESI): m/z (%): 356 (M^++Na).

10.13 Preparation of α-substituted MTMs using the coupling strategy

Methyl malonic acid (50 mmol, 5.90 g, 1 eq.) was dissolved under an inert argon atmosphere in dry acetonitrile (250 ml) and 6.2 ml of 4-methoxybenzyl alcohol (50 mmol, 6.9 g, 1 eq) were added. The solution was cooled to -10°C and a solution of DCC (75 mmol, 15.5 g, 1.5 eq) in dry acetonitrile (60 ml) was added dropwise over 30 minutes. The reaction was kept at -10°C for 30 minutes and was then allowed to

warm to room temperature. The reaction mixture was stirred at room temperature for other 2 hours followed by filtration of DCU and removal of all volatiles at reduced pressure. The crude mixture was re-dissolved in a mixture of CH_2Cl_2 (100 ml) and saturated aqueous $NaHCO_3$ (100 ml). The two phases were separated and the aqueous phase was washed twice with CH_2Cl_2. The pH of the aqueous phase was then decreased to pH 3 by addition of an aqueous solution of HCl (10%). The aqueous phase was reextracted with CH_2Cl_2 (3 times 80 ml each), and the combined organic phases were dried over $MgSO_4$. After filtration, all volatiles were removed at reduced pressure to yield colourless oil that was used without further purification (9.53 g, 40 mmol 80 %).

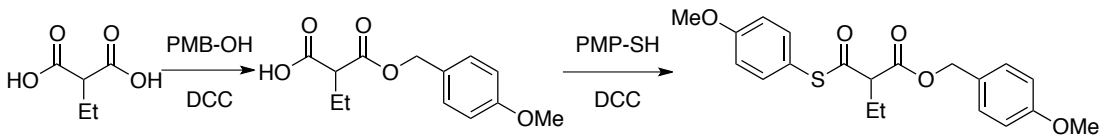
The solid was dissolved in dry CH_2Cl_2 (250 ml) and 4-methoxythiophenol (60 mmol, 8.4 g 1.2 eq) was added. The solution was cooled to -10°C and a solution of DCC (75 mmol, 15.5 g, 1.5 eq) in CH_2Cl_2 (25 ml) was added dropwise within 30 minutes. The reaction mixture was stirred for 30 minutes at -10°C and then at r.t. 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 a gradient of CH_2Cl_2/pentane (7:3) to CH_2Cl_2. After removal of all the volatiles at reduced pressure, 13.8g (80%) of MTM was isolated as colorless oil.



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.33-7.28 (m, 2H), 7.28-7.22 (m, 2H), 7.00-6.85 (m, 4H), 5.14 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.75 (q, *J* = 7.2 Hz, 1H), 1.49 (d, *J* = 7.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 194.9, 169.2, 160.8, 159.7, 136.1, 130.1, 127.5, 117.6, 114.9, 113.9, 67.2, 55.4, 55.3, 53.5, 14.1.

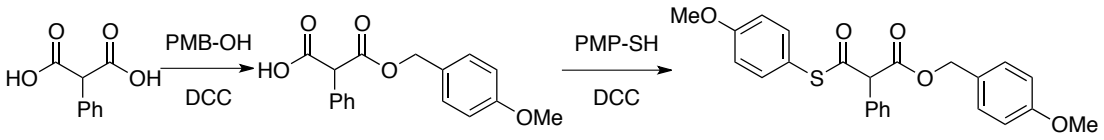
MS (ESI): m/z (%): 383 (100) [M^++Na].



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.34-7.28 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.95-6.86 (m, 4H), 5.14 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.59 (t, *J* = 7.4 Hz, 1H), 2.06 – 1.94 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 194.0, 168.4, 160.8, 159.7, 136.1, 130.1, 127.6, 117.7, 114.9, 113.9, 67.1, 60.9, 55.4, 55.3, 23.0, 11.8.

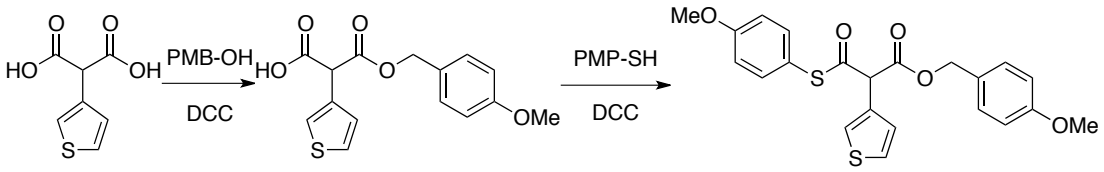
MS (ESI): m/z (%): 397 (100) [M^++Na].



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.47-7.42 (m, 1H), 7.39-7.31 (m, 4H), 7.29-7.21 (m, 2H), 7.20-7.14 (m, 2H), 6.89 (m, 2H), 6.85-6.80 (m, 2H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.06 (d, *J* = 12.0 Hz, 1H), 4.66 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 192.9, 167.9, 160.9, 159.7, 136.1, 132.6, 130.1, 129.7, 129.3, 128.7, 128.3, 127.4, 114.9, 113.9, 67.3, 64.6, 57.9, 55.3.

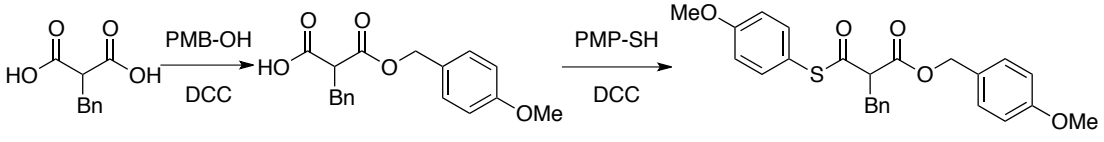
MS (ESI): m/z (%): 445 (100) [M^++Na].



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.34-7.26 (m, 3H), 7.26-7.22 (m, 2H), 7.21-7.16 (m, 2H), 6.93-6.87 (m, 2H), 6.87-6.80 (m, 2H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.70 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 192.7, 167.5, 160.9, 159.8, 136.1, 131.5, 130.1, 128.5, 127.3, 125.9, 124.5, 123.3, 117.6, 113.9, 67.6, 60.1, 55.3, 35.4.

MS (ESI): m/z (%): 451 (100) [M^++Na].

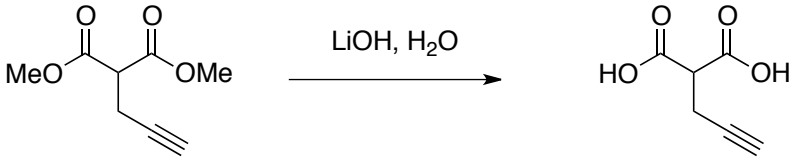


^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.33-7.14 (m, 9H), 6.97-6.83 (m, 4H), 5.12 (s, 2H), 4.00 (t, *J*= 7.6 Hz, 1H), 3.82 (s, 6H), 3.29 (dd, *J*= 7.8 Hz, 1.7 Hz 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 193.6, 167.8, 160.9, 159.7, 137.4, 136.1, 130.1, 129.0, 128.6, 127.4, 126.8, 117.5, 114.9, 114.9, 113.9, 67.2, 60.9, 55.4, 55.3, 35.2.
MS (ESI): m/z (%): 459 (100) [M^++Na].

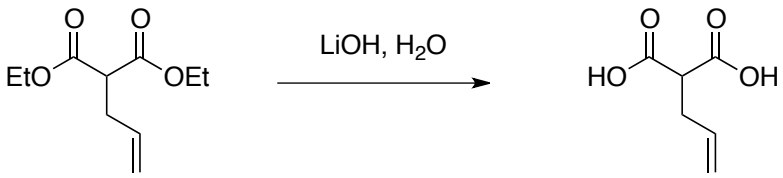
10.14 Synthesis of the α−substituted MTMs

Hydrolysis of α-substituted malonates

Propargyl di-methyl malonate 5 ml (32.88 mmol, 1eq.) was dissolved in methanol. The mixture was vigorously stirred at room temperature. Water (4.98 ml, 276.19 mmol, 8.4 eq.), and LiOH (1.65 g, 69.05 mmol, 2.1 eq.) were added and the stirring was kept for 16 hours. In an ice bath, water (7.5 ml) and concd. HCl (7.5 ml) were added to neutralise the base. The mixture was washed three times with diethyl ether (75 ml), the combined organic phases were dried over $MgSO_4$, filtrated and the volatiles were removed under reduced pressure. The α-substituted malonic acid was isolated as a white solid in 90 % yield (4.2 g, 29.6 mmol).



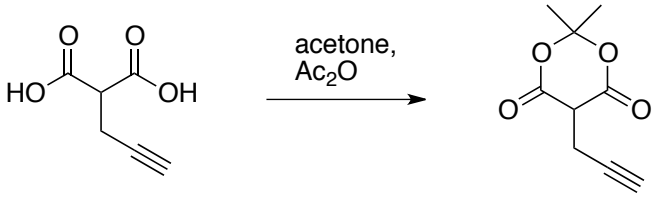
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): *δ* = 3.59 (t, *J*= 7.2 Hz, 1H), 2.6 (dd, *J*= 7.2 Hz, 2.7 Hz, 2H), 2.26 (t, *J*= 2.7 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): *δ* = 172.9, 82.7, 75.5, 58.3, 20.1.
MS (ESI): m/z (%): 165 (M^++Na)



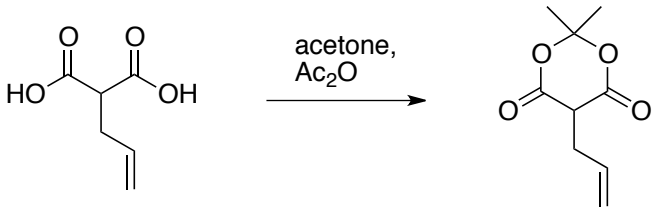
^{1}H-NMR (300 MHz, $CDCl_3$, 25˚C): δ = 5.97-5.81 (m, 1H), 5.23-5.12 (m, 2H) 3.57 (t, *J*= 5.1 Hz, 1H), 2.72-2.65 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25˚C): δ = 174.5, 129.0, 118.8, 56.9, 31.0.
MS (ESI): m/z (%): 167 (M^++Na).

Preparation of α-substituted Meldrum acids

The α-propargyl malonic acid 4 g (28.15 mmol, 1 eq.) is suspended in a mixture of acetone 2.27 ml (30.96 mmol, 1.1 eq.) and acetic anhydride 3.19 ml (33.78 mmol, 1.2 eq.). The mixture was stirred vigorously and concd. H_2SO_4 (84 μl) was added. After 2 hours the solution was placed at 4˚C and left at low temperature for 16 hours. After this time some precipitation is observed, ice-cold water (5 ml) was added to the suspension and the mixture was filtrated and washed with additional portions of ice-cold water. The filtrate was the desired α-substituted Meldrum acid isolated in 73 % yield (3.74 g, 20.55 mmol)



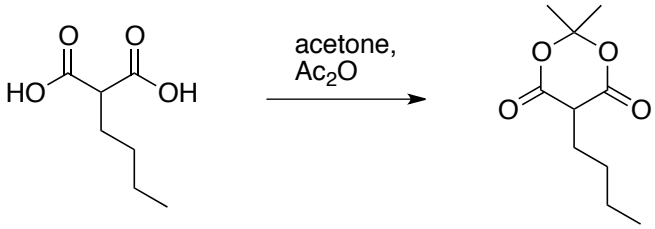
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 3.69 (t, *J*= 13.1 Hz, 1H), 3.04-3.01 (m, 2H) 2.06-2.04 (m, 1H), 1.81 (s, 3H), 1.79 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 165.9, 104.7, 82.3, 70.9, 50.7, 29.6, 27.9.
MS (ESI): m/z (%): 205 (M^++Na)



^{1}H-NMR (300 MHz, $CDCl_3$, 25˚C): δ = 5.85-5.69 (m, 1H), 5.13-5.04 (m, 2H) 3.62 (t, *J*= 5.1 Hz, 1H), 2.82-2.77 (m, 2H), 1.73 (s, 3H), 1.69 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25˚C): δ = 165.5, 127.0, 115.7, 104.5, 48.8, 32.4, 28.9, 27.9.

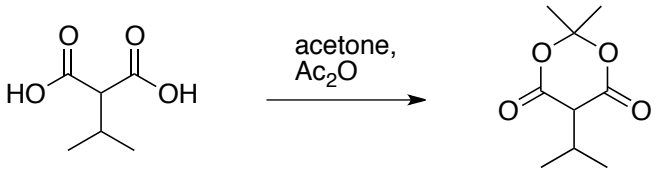
MS (ESI): m/z (%): 207 (M^++Na)



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 3.51 (t, *J*= 10.0 Hz, 1H), 2.16-2.11 (m, 2H) 1.80 (m, 3H), 1.78 (m, 3H), 1.49-1.38 (m, 4H), 0.94 (t, *J*= 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 165.7, 104.8, 46.1, 28.6, 28.4, 27.0, 26.4, 22.6, 13.7.

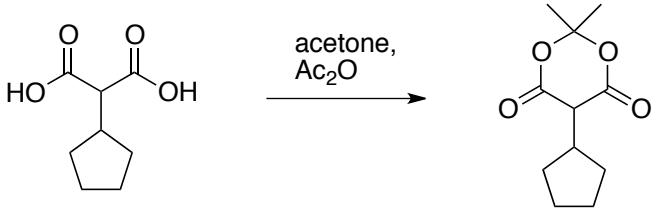
MS (ESI): m/z (%): 223 (M^++Na)



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 3.51 (t, *J*= 10.0 Hz, 1H), 2.16-2.11 (m, 2H) 1.80 (m, 3H), 1.78 (m, 3H), 2.69-1.60 (m, 1H), 1.09 (d, *J*= 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 165.0, 104.7, 48.7, 30.6, 27.9, 27.1, 20.6, 20.2.

MS (ESI): m/z (%): 209 (M^++Na)



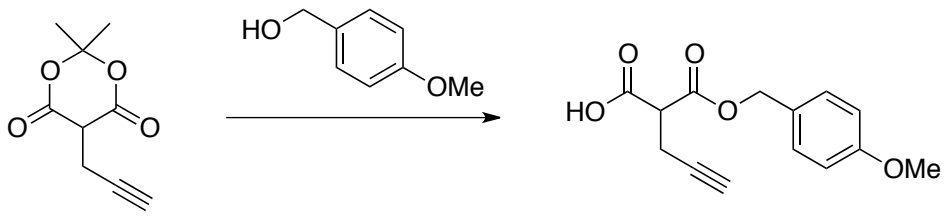
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 3.60 (d, *J*= 4.5 Hz, 1H), 2.75-2.70 (m, 1H) 1.93-1.89 (m, 2H), 1.79-1.76 (m, 7H), 1.68-1.53 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 165.2, 104.8, 49.2, 38.9, 29.6, 28.6, 27.3, 25.5.

MS (ESI): m/z (%): 235 (M^++Na)

Ring opening of Meldrum acids to synthesize malonic acid hemiesters

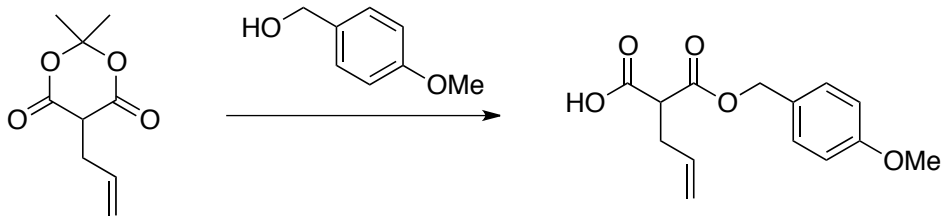
The α-propargyl meldrum acid 3 g (16.47 mmol, 1 eq.) was dissolved in toluene (5 ml) and p-methoxy benzyl alcohol was added to the mixture 2.16 ml (17.36 mmol, 1.2 eq). The solution was stirred at reflux until the starting materials were completely consumed (TLC Pentane/ethyl acetate 1:1). The mixture was cooled to room temperature and diluted with CH_2Cl_2. The solution was then washed with a saturated solution of $NaHCO_3$ (three times with 40 ml) and the combined aqueous phases were acidified using a 10 % solution of HCl. The acidified aqueous phase was then back-extracted with CH_2Cl_2 (three times with 60 ml). The combined organic phases were dried over $MgSO_4$, filtrated and the volatiles were evaporated under reduced pressure to finally yield the malonic acid emiester as a white solid in 56 % yield (2.42 g, 9.22 mmol).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.38-7.26 (m, 2H), 6.95-6.79 (m, 2H), 5.16 (d, *J* = 1.4 Hz, 2H), 3.81 (s, 3H), 3.65 (t, *J* = 7.4 Hz, 1H), 2.81 (ddd, *J* = 7.5, 2.7, 1.9 Hz, 2H), 2.01 (t, *J* = 2.6 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 179.3, 169.7, 160.4, 130.5, 129.1, 114.5, 87.8, 69.1, 65.5, 58.2, 48.5, 15.0.

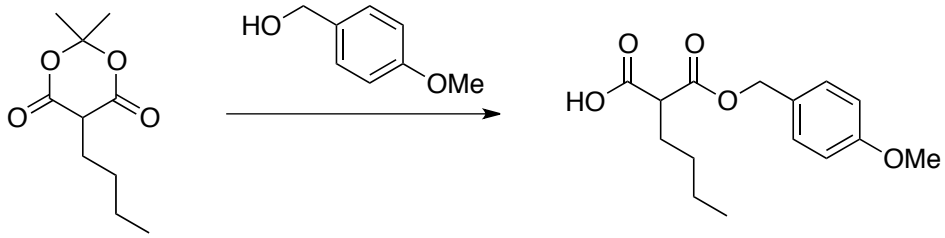
MS (ESI): m/z (%): 285 (M^++Na).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.37-7.32 (m, 2H), 6.95-6.90 (m, 2H), 5.78 (m, 1H), 5.23 (s, 2H), 5.14-5.07 (m, 2H), 3.83 (s, 3H), 3.57 (t, *J* = 7.4 Hz, 1H), 2.73 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 178.1, 167.1, 159.6, 135.4, 129.9, 127.6, 117.4, 67.4, 58.9, 55.4, 32.9.

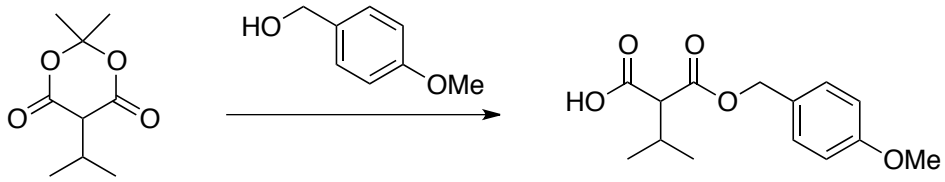
MS (ESI): m/z (%): 287 (M^++Na).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): *δ* = 7.30-7.26 (m, 2H), 6.90-6.87 (m, 2H), 5.13 (s, 2H), 3.81 (s, 3H), 3.39 (t, *J*= 7.4 Hz, 1H), 1.96-1.88 (m, 2H) 1.31-1.27 (m, 4H), 0.89-0.85 (m, 3H).

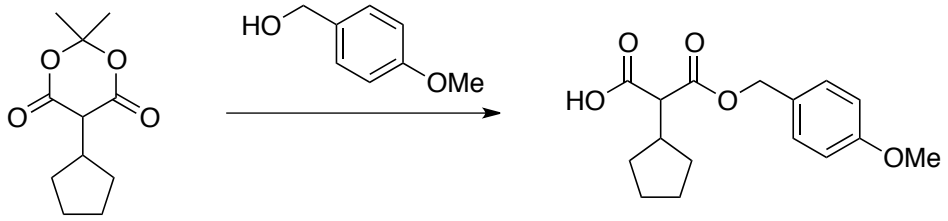
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): *δ* = 181.1, 170.2, 161.7, 130.6, 129.4, 113.9, 67.3, 57.1, 49.2, 28.4, 28.0, 22.2, 13.9.

MS (ESI): m/z (%): 303 (M^++Na).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): *δ* = 7.32-7.28 (m, 2H), 6.91-6.87 (m, 2H), 5.16 (d, *J* = 11.9 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H), 3.21 (d, *J* = 8.1 Hz, 1H), 3.04-3.01 (dhept, *J* = 8.0 Hz, 6.8 Hz, 1H) 2.06-2.04 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H).

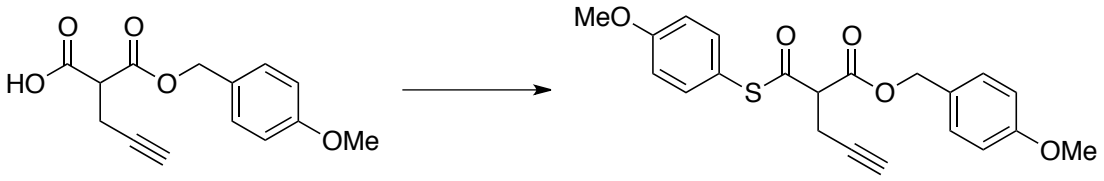
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 178.3, 165.9, 159.4, 130.5, 129.2, 113.9, 70.9, 63.4, 50.7, 29.6, 20.1, 19.8.
MS (ESI): m/z (%): 289 (M^++Na)



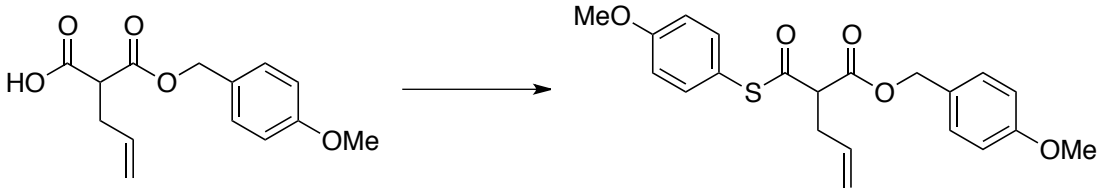
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.30-7.26 (m, 2H), 6.90-6.87 (m, 2H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H), 3.26 (d, *J* = 9.9 Hz, 1H), 2.53-2.43 (m, 1H), 1.91-1.80 (m, 2H), 1.66-1.51 (m, 4H), 1.25-1.15 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 178.0, 166.1, 158.9, 130.7, 129.1, 114.1, 70.9, 63.4, 50.7, 38.9, 32.1, 32.0, 19.8, 19.7.
MS (ESI): m/z (%): 315 (M^++Na).

Coupling of the thiol

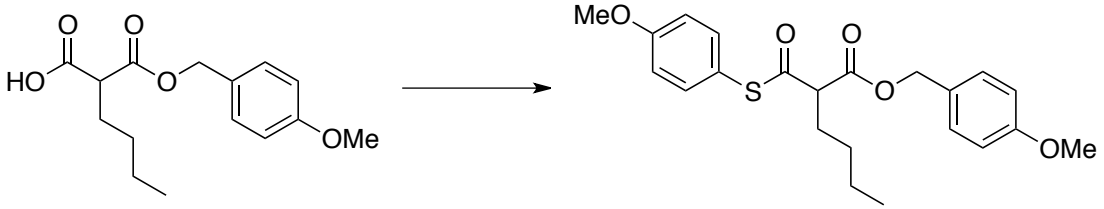
A solution of the α-propargyl malonic acid emiester 2.0 g (7.57 mmol, 1 eq.) was dissolved in dry CH_2Cl_2. After cooling the solution to 0˚C, the thiol 1.86 ml (15.14 mmol, 2 eq.) was added, the mixture was vigorously stirred and 2.90 g EDC·HCL was added (15.14 mmol, 2 eq.). The mixture was stirred for 15 minutes at 0˚C and then 1 hour at room temperature.
The mixture was then transferred in a separating funnel, 75 ml of saturated NH_4Cl solution were added and the aqueous phase was washed three times with 50 ml of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and the volatiles were evaporated at reduced pressure. The crude mixture was finally purified by column chromatography (pentane/Et_2O 2:1 to 1:1) to yield the MTM as a colorless oil (2.04 g, 5.53 mmol, yield 73%).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.36-7.31 (m, 2H), 7.30-7.26 (m, 2H), 6.98-6.89 (m, 4H), 5.20 (s, 2H), 3.92 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 4H), 2.86 (dd, *J* = 3.9, 2.7 Hz, 1H), 2.85 (dd, *J* = 4.0, 2.7 Hz, 1H), 2.06 (t, *J* = 2.7 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 192.5, 167.0, 161.0, 159.8, 136.1, 130.2, 127.3, 117.2, 115.0, 113.9, 79.6, 70.8, 67.6, 57.9, 55.4, 18.7.
MS (ESI): m/z (%): 407 (M^++Na)



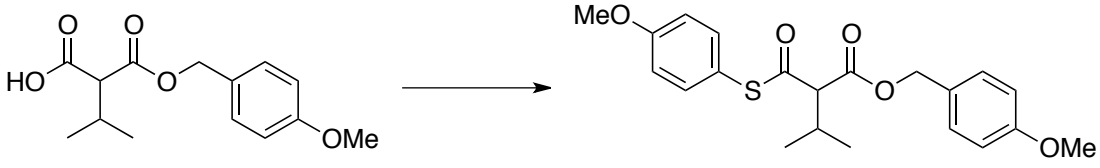
^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.36-7.31 (m, 2H), 7.29-7.25 (m, 2H), 6.97-6.91 (m, 4H), 5.78 (ddt, *J* = 17.0 Hz, 10.2 Hz, 6.8 Hz, 1H), 5.16 (s, 2H), 5.14-5.07 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78 (t, *J* = 7.4 Hz, 1H), 2.73 (dddd, *J* = 7.2 Hz, 5.8 Hz, 2.4 Hz, 1.3 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 193.4, 167.9, 160.9, 159.7, 136.1, 133.5 130.1, 127.5, 118.0, 117.5, 114.9, 113.9, 67.2, 58.9, 55.4, 55.3, 33.4.
MS (ESI): m/z (%): 409 (M^++Na).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.33-7.29 (m, 2H), 7.26-7.23 (m, 2H), 6.94-6.90 (m, 4H), 5.16 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.65 (t, *J* = 7.5 Hz, 1H), 2.05-1.90 (m, 2H), 1.38-1.22 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 192.5, 167.8, 161.2, 159.5, 132.9 130.0, 127.4, 117.6, 11489, 113.5, 66.8, 57.0, 48.5, 28.5, 27.9, 22.1, 13.9

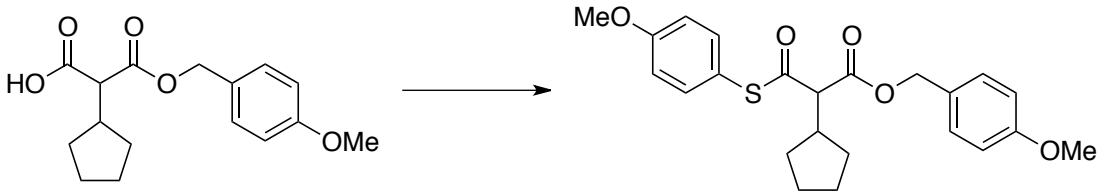
MS (ESI): m/z (%): 425 (M^++Na).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.36-7.31 (m, 2H), 7.28-7.26 (m, 2H), 6.95-6.90 (m, 4H), 5.16 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.45 (d, *J* = 9.5 Hz, 1H), 2.53 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 193.2, 167.9, 160.8, 159.7, 136.0, 130.1, 128.3, 127.6, 114.9, 113.9, 67.0, 66.7, 55.4, 55.3, 30.0, 20.5, 20.3.

MS (ESI): m/z (%): 411 (M^++Na).



^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.33-7.28 (m, 2H), 6.93-6.85 (m, 4H), 5.13 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.50 (d, *J* = 10.5 Hz, 1H), 2.65-2.53 (m, 1H), 1.87-1.77 (m, 2H), 1.62-1.54 (m, 4H), 1.30-1.15 (m, 2H).

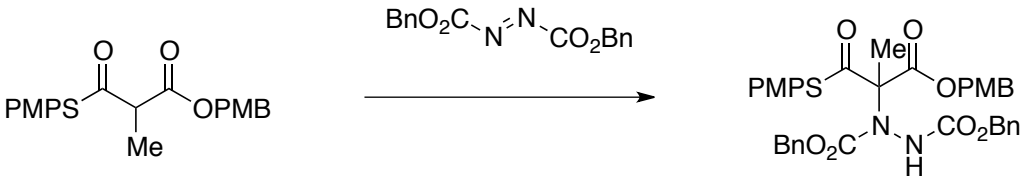
^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 193.2, 167.5, 159.9, 135.8, 130.3, 129.1, 128.2, 127.5, 114.1, 113.5, 70.9, 63.4, 50.7, 38.9, 32.1, 32.0, 19.8, 19.7.

MS (ESI): m/z (%): 437 (M^++Na).

10.15 General procedure for the organocatalytic addition of a-substituted MTMs to diazodicarboxylates

The dibenzyldiazodicarboxylate 33 mg (0.11 mmol, 1.1 equiv), methyl MTM (36 mg, 0.1 mmol), and the catalyst (0.001 mmol, 1 mol%) were dissolved in toluene (1 mL) in a capped vial. After stirring the resulting solutions for 24 h, all volatiles were

removed at reduced pressure. The oily residue purified by column chromatography on silica gel (gradient of pentane/diethyl ether acetate 3:1 to 1:1) to yield the product as a colorless solid (66 mg, 0.1 mmol, >98% yield).



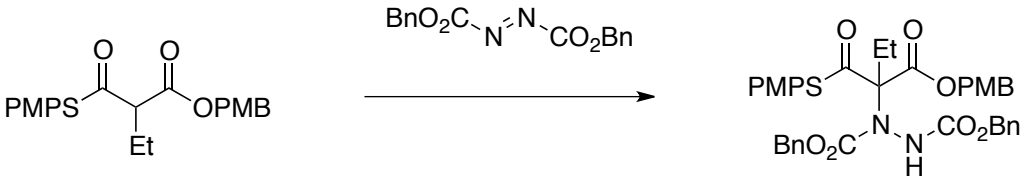
Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.46-7.12 (m, 14H), 6.98-6.63 (m, 4H), 5.36-4.97 (m, 4H), 3.82 (s, 3H), 3.81(s, 3H), 2.09-1.49 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 168.0, 160.9, 160.6, 159.8, 159.6, 155.6, 136.5, 136.4, 135.5, 135.5, 135.2, 130.2, 130.1, 128.6, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.4, 127.0, 127.0, 117.8, 117.3, 115.0, 114.8, 114.0, 113.9, 113.8, 68.8, 68.2, 68.1, 67.9, 67.7, 55.4, 55.3, 55.3.

Elemental analysis calcd (%) for $C_{35}H_{34}N_2O_9S$: C, 63.82; H, 5.20; N, 4.25 found: C, 63.95; H, 5.29; N, 4.20.

HRMS (ESI) Calcd for $[C_{35}H_{34}N_2NaO_9S]^+$: 681.1883; Found: 681.1858.



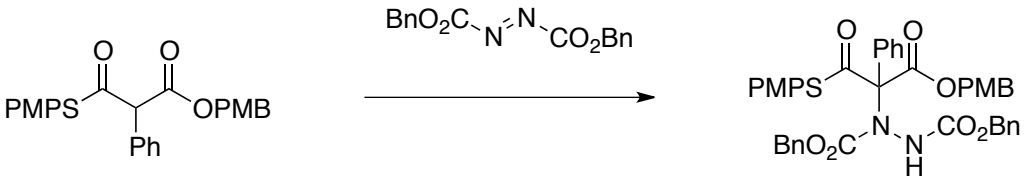
Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.46-7.11 (m, 14H), 6.97-6.78 (m, 4H), 5.43-4.87 (m, 6H), 3.82 (s, 3H), 3.80 (s, 3H), 2.33-2.04 (m, 2H), 1.11-0.89 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 167.7, 167.1, 160.8, 160.6, 159.8, 156.1, 136.6, 136.3, 135.6, 135.5, 135.2, 130.3, 130.2, 128.6, 128.5, 128.5, 128.3, 128.3, 128.0, 127.0, 118.0, 114.9, 114.7, 114.0, 113.8, 68.8, 68.0, 67.9, 67.8, 67.3, 55.4, 55.3, 55.2, 29.6, 8.8.

Elemental analysis calcd (%) for $C_{36}H_{36}N_2O_9S$: C, 64.27; H, 5.39; N, 4.16 found: C, 64.22; H, 5.57; N, 4.21.

HRMS (ESI) Calcd for $[C_{36}H_{36}N_2NaO_9S]^+$: 695.2039; Found: 695.2025.



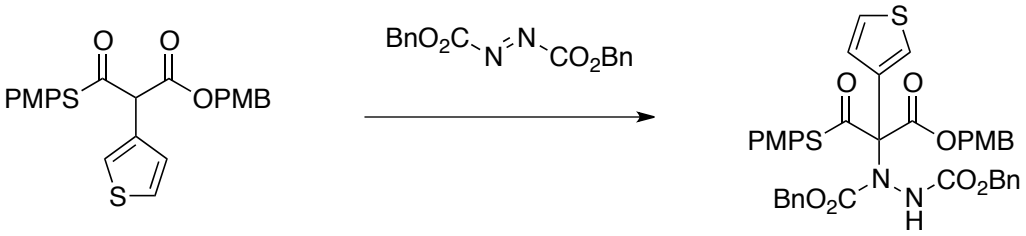
Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.84-7.06 (m, 19H), 7.06-6.48 (m, 4H), 5.45-4.77 (m, 6H), 3.94-3.66 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 168.0, 160.9, 160.6, 159.8, 159.6, 155.6, 136.5, 136.2, 130.7, 130.3, 130.1, 129.3, 128.9, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.0, 114.9, 114.7, 113.9, 113.8, 68.0, 68.0, 55.4, 55.3, 55.3, 55.2, 29.7.

Elemental analysis calcd (%) for $C_{40}H_{36}N_2O_9S$: C, 66.65; H, 5.03; N, 3.89 found: C, 66.52; H, 5.20; N, 4.09.

HRMS (ESI) Calcd for $[C_{40}H_{36}N_2NaO_9S]^+$: 743.2039; Found: 743.2062.



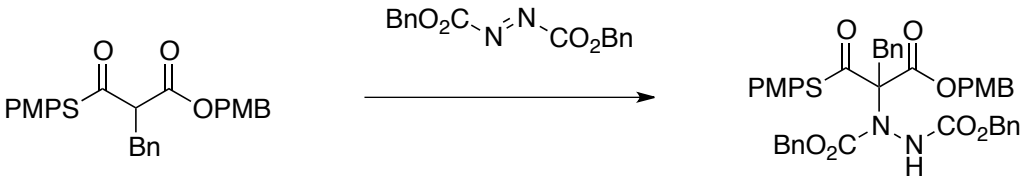
Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.48-7.10 (m, 17H), 6.96-6.77 (m, 4H), 5.33-4.91 (m, 6H), 3.94-3.72 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 160.9, 159.7, 156.4, 136.5, 136.2, 130.7, 130.4, 130.3, 130.1, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 127.8, 127.7, 127.1, 125.4, 115.0, 115.0, 114.7, 114.1, 113.9, 113.8, 68.8, 68.1, 67.9, 67.5, 55.4, 55.3, 55.2, 55.2, 29.7.

Elemental analysis calcd (%) for $C_{38}H_{34}N_2O_9S_2$: C, 62.80; H, 4.71; N, 3.85 found: C, 62.65; H, 4.92; N, 4.07.

HRMS (ESI) Calcd for $[C_{38}H_{34}N_2NaO_9S_2]^+$: 749.1603; Found: 749.1587.



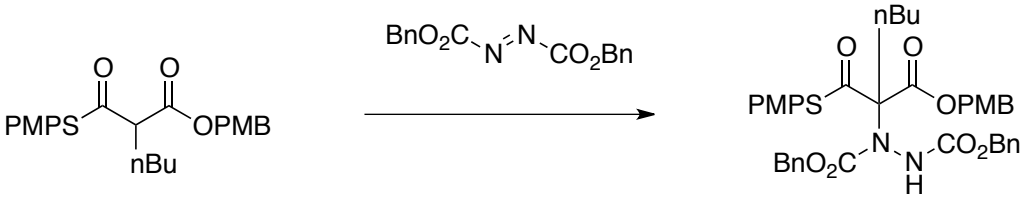
Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.67-7.14 (m, 14H), 7.06-6.61 (m, 4H), 5.48-4.82 (m, 6H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (m, 6H), 3.59 (d, J = 13.7 Hz, 1H), 3.48 (d, J = 13.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 167.4, 166.2, 160.8, 160.6, 159.8, 156.3, 155.6, 136.5, 136.2, 135.7, 135.5, 135.2, 133.3, 130.7, 130.5, 128.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.5, 126.7, 118.4, 114.8, 114.7, 114.6, 113.9, 113.8, 68.9, 68.0, 67.9, 67.8, 67.6, 55.4, 55.3, 55.2, 29.7, 29.6.

Elemental analysis calcd (%) for $C_{41}H_{38}N_2O_9S$: C, 67.02; H, 5.21; N, 3.81 found: C, 67.11; H, 5.32; N, 3.72.

HRMS (ESI) Calcd for $[C_{41}H_{38}N_2NaO_9S]^+$: 757.2196; Found: 757.2215.



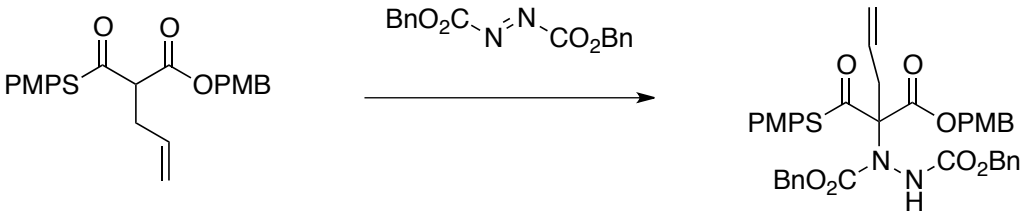
Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.45-7.14 (m, 14H), 7.03-6.64 (m, 4H), 5.35-4.93 (m, 6H), 3.83 (s, 3H), 3.80 (s, 3H), 2.20-1.94 (m, 2H), 1.56-1.05 (m, 4H), 0.81-0.77 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 167.7, 167.3, 160.8, 160.6, 159.8, 159.6, 156.5, 156.1, 136.6, 136.3, 135.6, 135.5, 135.2, 130.4, 130.3, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 127.0, 126.9, 118.4, 118.1, 114.9, 114.7, 114.0, 113.8, 68.8, 68.0, 67.9, 67.7, 67.3, 55.3, 55.3, 55.2, 35.9, 26.1, 25.9, 22.8, 22.7, 13.6, 13.5.

Elemental analysis calcd (%) for $C_{38}H_{40}N_2O_9S$: C, 65.13; H, 5.75; N, 4.00 found: C, 65.19; H, 5.68; N, 3.90.

HRMS (ESI) Calcd for $[C_{38}H_{40}N_2NaO_9S]^+$: 723.2352; Found: 700.2343.



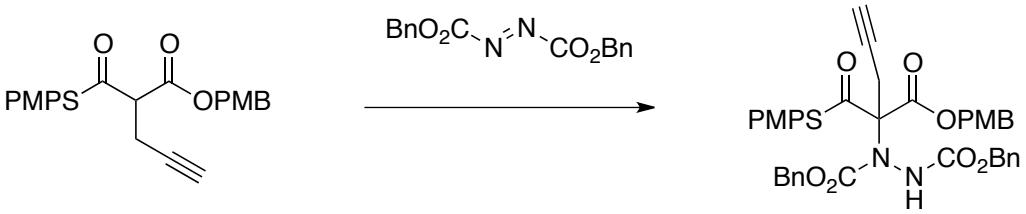
Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.62-7.08 (m, 14H), 7.01-6.31 (m, 4H), 5.77 (bs, 1H), 5.35-4.84 (m, 8H), 3.86 (s, 3H), 3.83 (s, 3H), 3.03-2.85 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 167.3, 166.7, 160.9, 160.6, 159.8, 156.4, 155.9, 136.6, 136.3, 135.6, 135.5, 130.7, 130.4, 130.2, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 120.0, 117.9, 114.9, 114.7, 113.9, 113.8, 78.4, 68.8, 68.1, 67.8, 67.5, 55.4, 55.3, 55.2, 40.2.

Elemental analysis calcd (%) for $C_{37}H_{36}N_2O_9S$: C, 64.90; H, 5.30; N, 4.09 found: C, 64.85; H, 5.20; N, 4.15.

HRMS (ESI) Calcd for $[C_{37}H_{36}N_2NaO_9S]^+$: 707.2039; Found: 707.2051.



Mixture of *cis* and *trans* isomers

^{1}H-NMR (400 MHz, $CDCl_3$, 25˚C): δ = 7.60-7.11 (m, 14H), 7.00 – 6.76 (m, 4H), 5.37-5.01 (m, 6H), 3.83 (s, 3H) 3.80 (s, 3H), 3.20 (d, J = 14.9 Hz, 2H), 2.02 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, 25˚C): δ = 166.0, 165.3, 160.9, 160.8, 159.8, 155.9, 155.5, 136.4, 136.2, 135.6, 130.5, 130.3, 128.6, 128.6, 128.5, 128.4, 128.2, 127.9, 126.8, 117.5, 114.9, 114.8, 113.8, 78.3, 72.6, 69.0, 68.5, 68.2, 67.9, 55.4, 55.3, 29.7.

Elemental analysis calcd (%) for $C_{37}H_{34}N_2O_9S$: C, 65.09; H, 5.02; N, 4.10 found: C, 65.16; H, 5.13; N, 4.01.

HRMS (ESI) Calcd for $[C_{37}H_{34}N_2NaO_9S]^+$: 705.1883; Found: 705.1869.

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