Development of new asymmetric organocatalytic domino reactions for the synthesis of (benzo-fused) five- and benzo-fused six-membered cyclic compounds

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH Aachen University zur Erlangung des akademischen Grades einer Doktorin der Naturwissenschaften genehmigte Dissertation

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Introduction

1.1. Asymmetric organocatalysis

At the beginning of the century, a large number of research groups focused their attention towards applying small organic molecules as catalysts for various processes. As a result, a broad range of asymmetric organocatalytic bond-forming reactions have been developed. Research in this area has advanced rapidly over the past decades and is now well established in the academic as well as the industrial sector.[1]

Organocatalysis offers the prospect for the chemo-, regio-, diastereo- and enantioselective synthesis of molecules that were not readily available through traditional methods. Due to the versatility, simplicity and safety of the organocatalytic reactions, organocatalysis has proved to be a powerful alternative to transition metal catalysis and biocatalysis.

Biocatalysts can be a valuable tool in industry due to their extremely high performance and ability to operate in mild conditions; nevertheless, they suffer few major drawbacks. Many enzymes show narrow substrate scope and finding the perfect fit for a given process might require laborious optimization. Another great disadvantage of biocatalysis is their insufficient stability in organic solvents.[2]

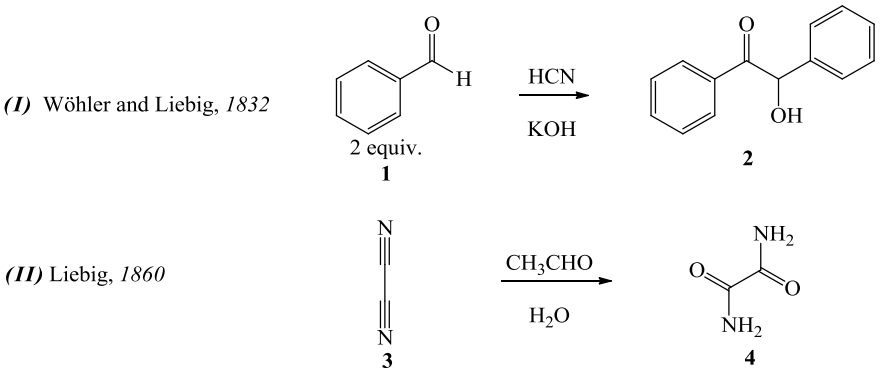
Transition metal catalysts on the other hand, show promising results concerning yields, chemo-, regio- and stereoselectivity. They offer great benefits due to their excellent performance even in very low catalyst loadings (as less as 0.01 mol%). However, their high moist and air sensitivity as well as the need of thorough purification of the obtained products from any traces of transition metals makes big scale operations quite challenging from practical point of view.[3]

In comparison, organocatalysts show just as good results in terms of selectivity, but they also tolerate wide range of functional groups and operate in mild conditions with no need of air and moist exclusion in most cases. They are readily accessible from nature's chiral pool or can be easily achieved through simple transformations. The biggest disadvantage of organocatalysts is the higher catalyst loadings necessary to promote the reactions (up to 30-40 mol%). However, many groups are focusing on overcoming this problem and manage to demonstrate excellent results with lower amounts of catalyst applied (0.2-0.5 mol%).[4]

1.2. History of organocatalysis

Nowadays organocatalysis is one of the most explored research areas in advanced organic chemistry. Although the true progress in organocatalysis started with the turn of the 21th century and since then the field expands rapidly with every day, early examples through literature can be found even 100 years ago.

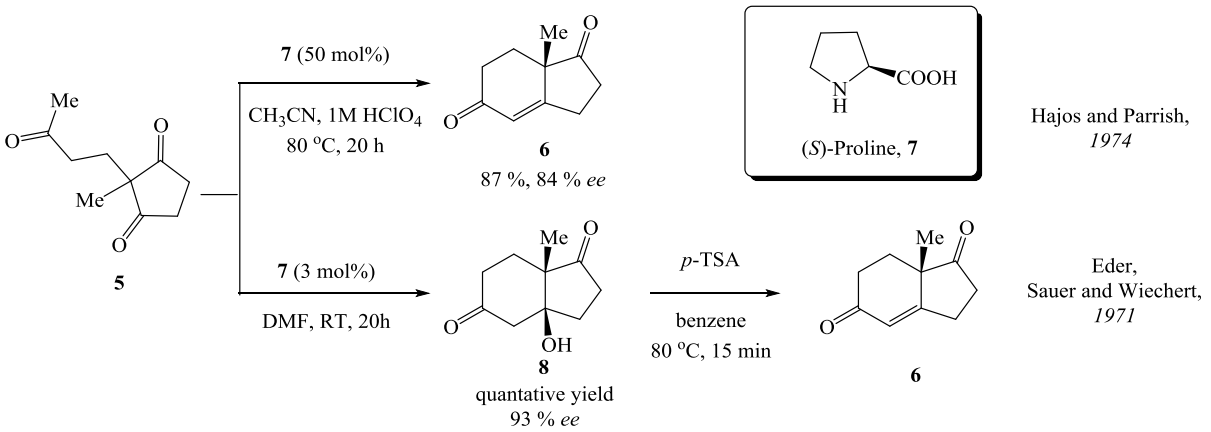
The first example of an organocatalytic reaction was reported in 1832 by Wöhler and Liebig, where two equivalents of benzaldehyde **1** react to form benzoin **2** in the presence of cyanide (Scheme 1, Eqn I).[5] Thirty years later Liebig reported the synthesis of oxamide **4** from dicyan **3** and water (Scheme 1, Eqn II).[6] The presence of acetaldehyde in this case was crucial for the reaction - it was identified to promote the process and behave as the then-named "ferment", nowadays called enzyme. In the following few decades, numerous examples of organocatalysis were published. Some of them include the studies of Knoevenagel in the field of piperidine catalyzed Knoevenagel condensation[7], the work of Dakin demonstrating that a Knoevenagel type reaction between aldehydes and carboxylic acids or esters can be mediated by amino acids[8] as well as the research of Langenbeck applying simple amino acids and small oligopeptides as catalysts for enamine type reactions.[9]



Scheme 1. First examples of organocatalytic reactions.

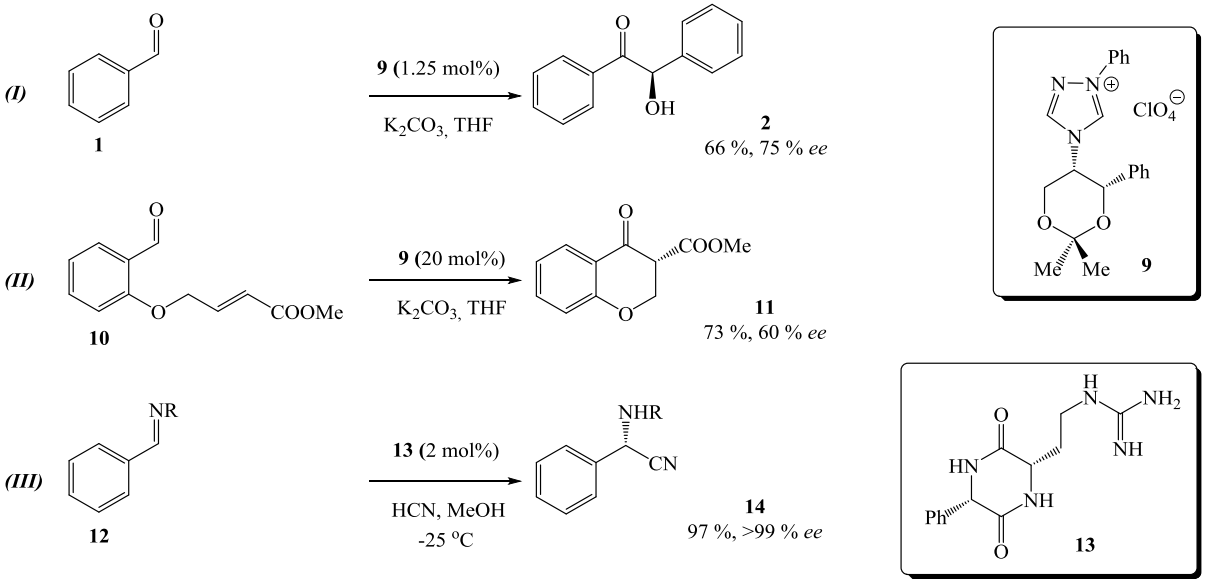
An asymmetric version of the addition of HCN to benzaldehyde was reported in 1912 by Bredig and Friske, who utilized a cinchona alkaloid as a catalyst.[10] Cinchona alkaloids were also applied for the asymmetric conversion of ketenes to (S)-methyl hydratropate by Pracejus in 1960.[11] Other important contributions to the development of asymmetric organocatalysis are the research of Yamada in applying pyrrolidine derivatives as catalysts[12], as well as the work of Sheehan in the field of *N*-heterocyclic carbene (NHC) organocatalysis.[13]

Although those examples mark the beginning of asymmetric organocatalysis, the turning point occurred in the seventies when Eder, Sauer and Wiechert[14] and Hajos and Parrish[15] reported the synthesis of the Wieland-Miescher type ketone **6** – an important intermediate in the synthesis of steroids (Scheme 2). Both research groups successfully utilized (*S*)-Proline (**7**) as a catalyst for the aldol reaction of **5** and the product **6** was achieved with excellent for the time enantioselectivities.



Scheme 2. Proline catalyzed synthesis of Wieland-Miescher type ketone **6**.

A major breakthrough in the field of NHC catalysis was achieved by Enders *et al.*, who developed the first chiral triazolium-based catalyst **9** (Scheme 3, Eqn. I).[16] The triazolium salt turned out to catalyze the benzoin reaction affording benzoin **2** in significantly improved yields and enantioselectivities utilizing a considerably reduced amount of catalyst in comparison to the already reported at the time protocols.[13, 17] The applicability of the chiral triazolium salt was further expanded to the Stetter reaction, thus the first enantioselective intramolecular Stetter reaction was developed (Scheme 3, Eqn. II).[18]

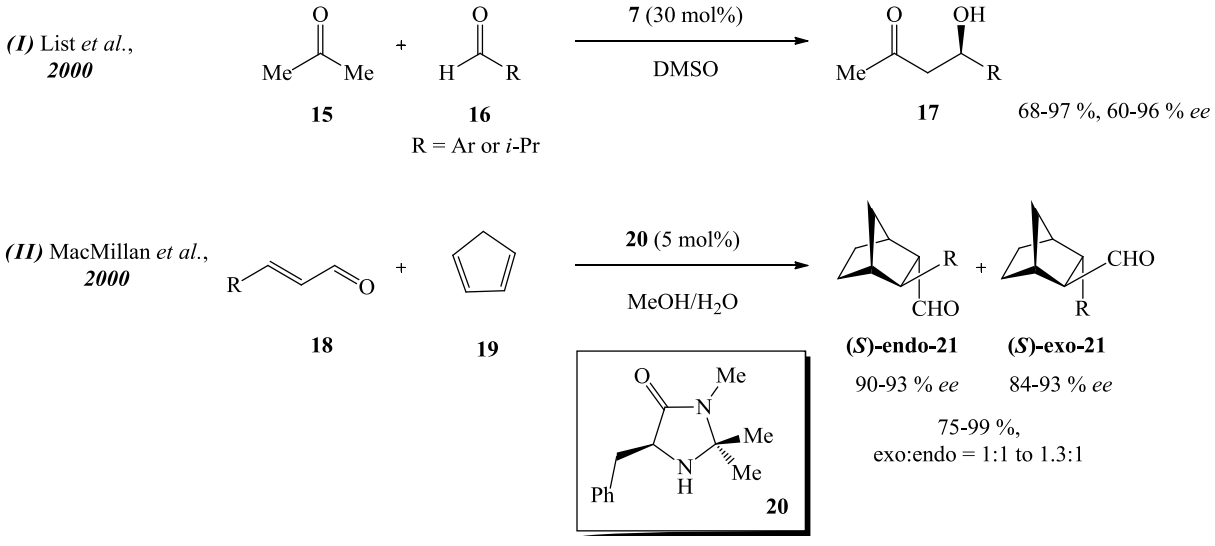


Scheme 3. (I) Asymmetric Benzoin reaction by Enders; (II) First asymmetric intramolecular Stetter reaction by Enders; (III) Asymmetric Strecker reaction by Lipton.

At the same time, significant progress in asymmetric hydrogen-bonding organocatalysis was made as well. Lipton and co-workers reported an enantioselective version of the Strecker reaction (Scheme 3, Eqn. III).[19] The cyclic dipeptide **13** catalyzed the addition of HCN to substituted imines **12** in high yields and with exceptionally high enantiomeric purity. Shortly

after that, other two types of catalysts were successfully applied in the same reaction. Jacobsen and co-workers[20] developed a thiourea catalyst, while Corey *et al.*[21] utilized a C_2-symmetric guanidine. In both cases the α-amino nitrile products **14** were achieved with excellent enantioselectivities (91 % *ee* and 86 % *ee*, respectively).

In the beginning of 21st century, List *et al.* reported the first example of applying non-metallic small-molecule catalyst for direct asymmetric intermolecular aldol reaction. After reinvestigation of the Hajos-Parrish-Eder-Sauer-Wiechert reaction, in combination with their knowledge and previous experience about the catalytic activity of aldolases, it was envisioned that (*S*)-Proline **7** could catalyze successfully the aldol reaction between acetone **15** and aromatic or branched aldehydes **16** through enamine activation (Scheme 4, Eqn I).[22] Indeed, the aldol adducts **17** were obtained in moderate to good yields and enantioselectivities. Almost simultaneously, MacMillan and co-workers published the enantioselective Diels-Alder reaction between enals **18** and cyclopentadiene **19**, achieving the corresponding *endo* and *exo* products **21** with very good enantioselectivity (Scheme 4, Eqn II).[23] The catalyst utilized in this case was the imidazolidinone **20**, which activated the enals **18** through iminium activation. Shortly after that, the first reports of asymmetric proline-catalyzed intermolecular Mannich and Michael reactions followed.[24] But the pioneering work by the groups of List and MacMillan marks the beginning of a more systematic and in-depth investigation of the asymmetric aminocatalyzed functionalization of aldehydes and ketones.



Scheme 4. Pioneering work of (I) List and (II) MacMillan.

1.3. Classification and modes of activation of organocatalysts

Since the beginning of the 21st century, tremendous progress in the field of asymmetric organocatalysis has been done. Due to the large diversity of chiral scaffolds available in nature's chiral pool, a broad range of novel organocatalysts, to be utilized in various asymmetric transformations, has been developed. A general classification based on the different modes of activation is presented in Figure 1. The organocatalysts are typically classified based on the nature of the interactions, through which the asymmetric information is transferred from the catalyst to the substrate – covalent bonding, hydrogen-bonding or ion-pairing.[25]

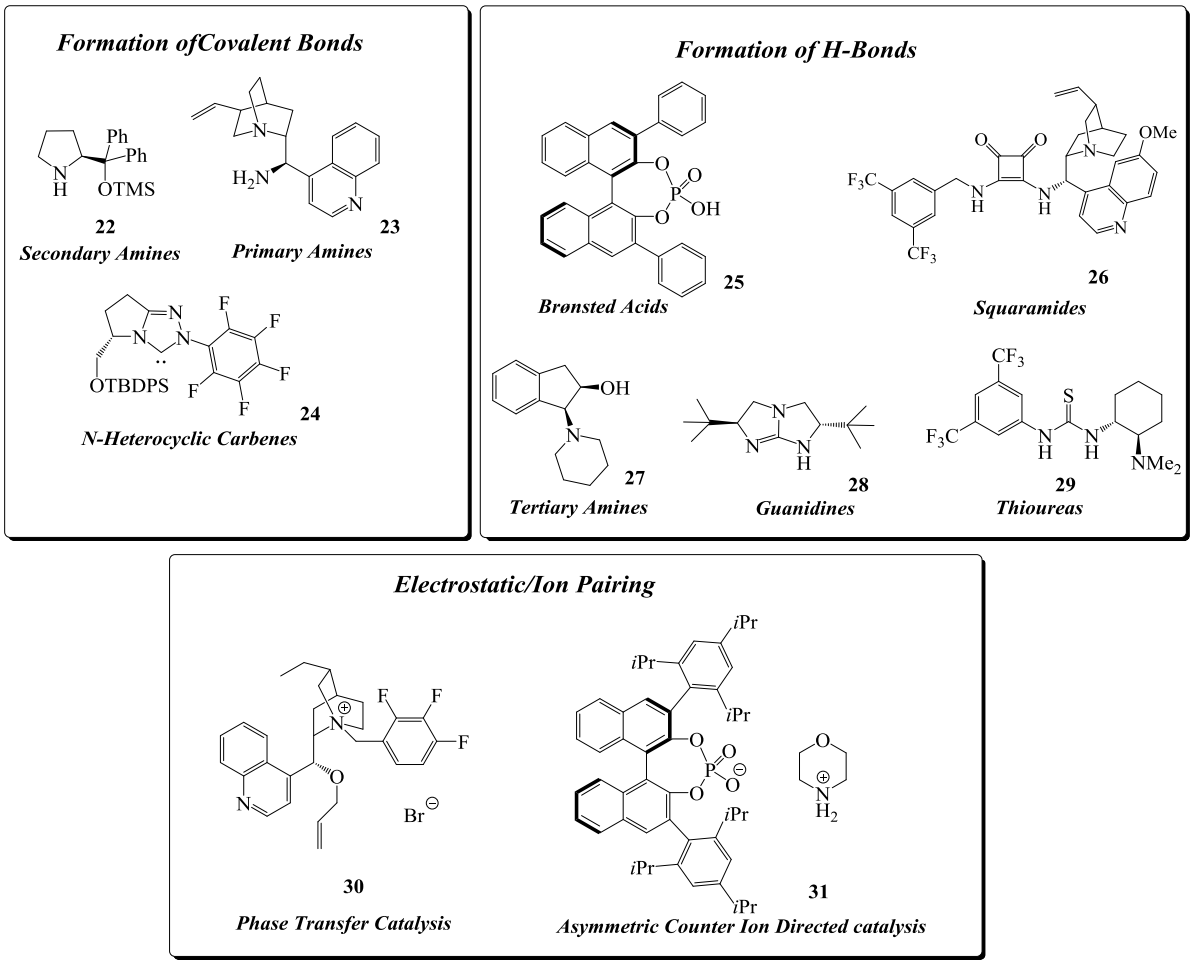
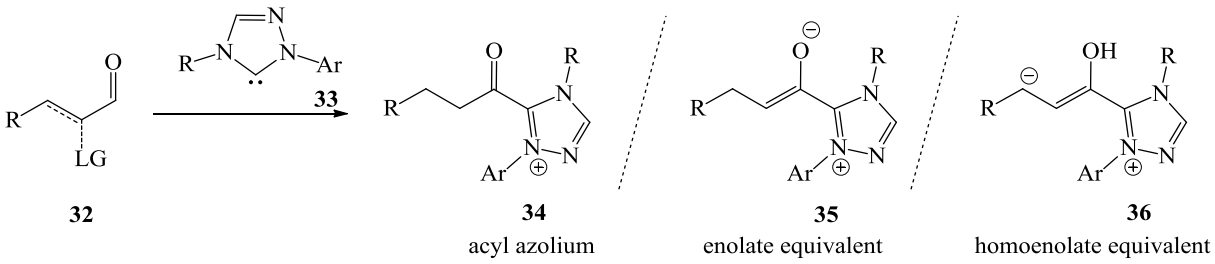


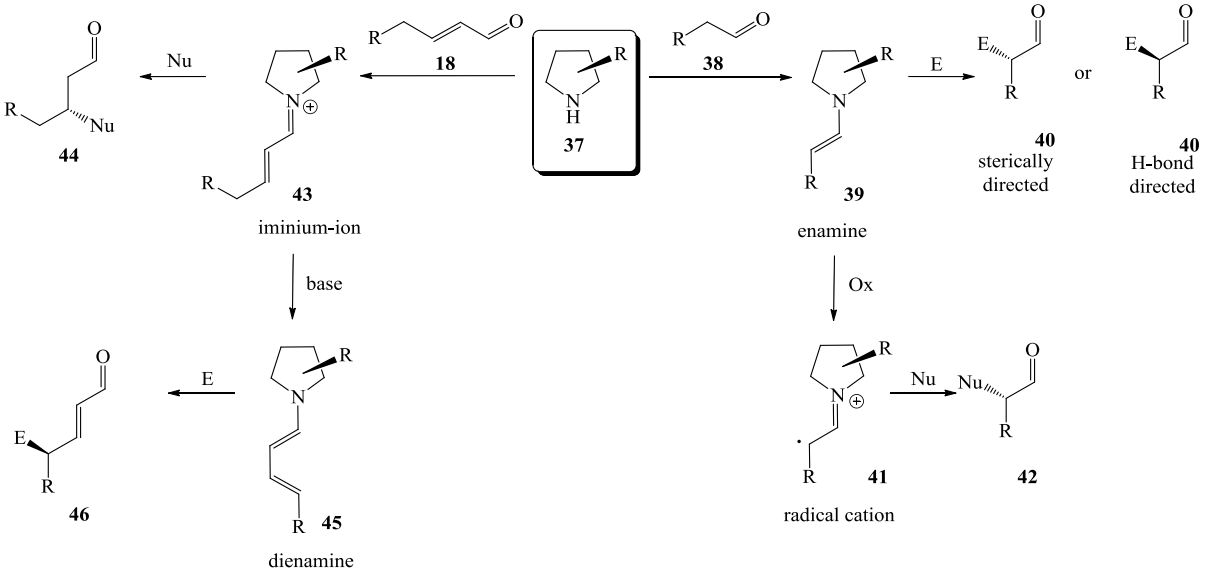
Figure 1. Classification of organocatalysts and some prominent examples.

Covalent catalyst-substrate interactions occur in the case of NHC catalysis (Scheme 5). The reaction in this case proceeds through catalytic generation of acyl anion equivalent of aldehydes, the so-called polarity reversal or "umpolung". Substrates that possess α-reducible functionality, a leaving group or unsaturation adjacent to the carbonyl group, can be transformed to the corresponding catalytic intermediate species: acyl azolium **34**, nucleophilic enol **35** and/or nucleophilic homoenolate **36**. Each of these intermediates has been exploited in various reactions, affording a variety of highly functionalized enantioenriched products.[26]



Scheme 5. Mechanism of activation of NHC catalysts.

Primary[27] and secondary[28] amines form covalent bonds with the substrates as well, thus allowing asymmetric induction in the products. In general there are four distinct types of aminocatalysed carbonyl functionalizations, two applying linear aldehydes **38** and two for α,β-unsaturated aldehydes **18** (Scheme 6). When employing a linear aldehyde **38**, as a result of its interaction with catalyst **37**, a more nucleophilic enamine intermediate **39** is formed. Since the lone-pair electrons of a nitrogen atom are higher in energy than that of an oxygen atom, the HOMO (Highest Occupied Molecular Orbital) energy of the formed enamine **39** is increased compared to the corresponding enol, thus enhancing its reactivity. The stereochemistry of the formed product **40** would depend on whether or not there are available hydrogen-bonding sites in the catalyst. In case an oxidant is present, a radical cation intermediate **41** is formed. The oxidation changes the electronic properties of the enamine into those of an electrophilic species, allowing the direct nucleophilic α-functionalization of aldehydes. This concept is known as SOMO (Single Occupied Molecular Orbital) catalysis.



Scheme 6. Mechanism of activation of aminocatalysis.

In comparison to enamine catalysis, the principle of iminium-ion **43** catalysis is decreasing the energy of the LUMO (Lowest Unoccupied Molecular Orbital) of the α,β-unsaturated aldehydes **18**, thus enhancing the electrophilic nature of the substrate and facilitating a nucleophilic attack at β-position (Scheme 6). In case of deprotonation of the iminium-ion **43**, the corresponding dienamine **45** is formed. This dienamine species can act as a nucleophile

from the α-position as well as from the γ-position of the equivalent carbonyl compound, depending on the reaction conditions and the nature of the electrophile.[29]

Formation of hydrogen-bonds between the catalyst and the electrophile as a mechanism for electrophile activation is the strategy lying behind (thio)urea[30] and squaramide[31] catalysis (Figure 2, Eqn I). The asymmetric induction occurs due to the transition state organization in accordance with the chiral moieties present in the catalyst. Although various thiourea organocatalysts have been developed and successfully applied in a wide range of reactions with excellent results, in the last few years chiral squaramides tend to show superiority under the same circumstances due to their ability to form stronger hydrogen-bonds with the substrate compared to thioureas. There are a few factors for the enhanced hydrogen-bonding ability, first of which is the more favorable geometry of the molecules: the larger distance between the two *NH*-groups as well as their better alignment allows ideal arrangement of the hydrogen-bonds themselves. Another factor is the higher acidity of the NH-protons due to their vinylogous amide nature, thus providing a polarized nitrogen moiety. These factores, in combination with the higher rigidity of the squaramide scaffold as well as the exceedingly high hydrogen-bonding acceptor capability in squaramides (driven by an increase in aromaticity upon binding with anion), promote excellent results in every case a squaramide catalyst is utilized in a reaction.

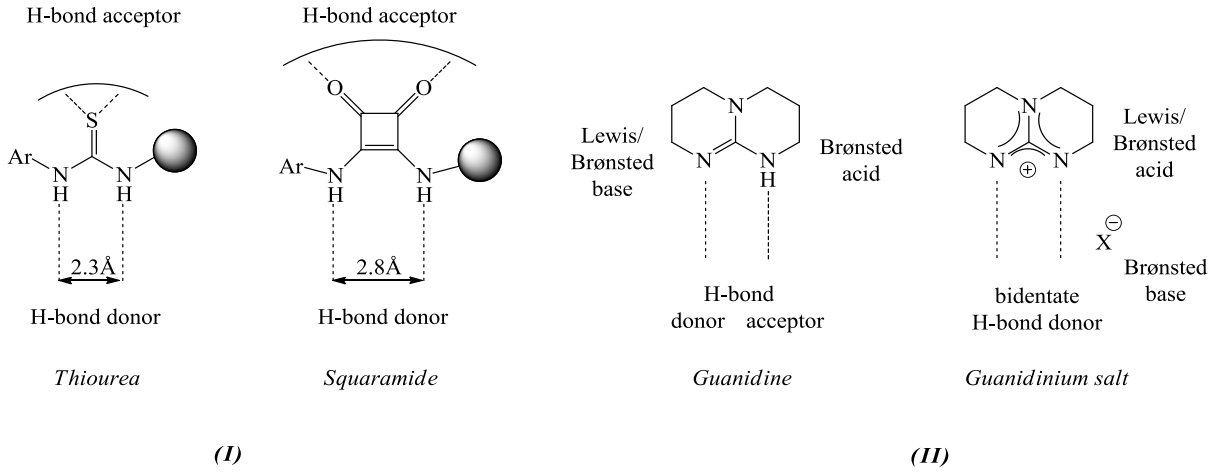


Figure 2. Modes of catalytic activation of (I) thioureas and squaramides and (II) guanidines.

Guanidines have found wide spread use as Brønsted base catalysts in asymmetric synthesis (Figure 2, Eqn II). Guanidinium salts on the other hand can be employed as weak Brønsted acids or hydrogen-bond donor catalysts and chiral counterions. The nucleophilic and Lewis basic properties of guanidines are still rarely exploited, but as of late, have been gaining increasing recognition.[32]

Another class of organocatalysts that have proven themselves to be highly efficient and versatile catalysts for an ever expanding list of synthetic transformations are the strong Brønsted acids[33], in particular the binaphtol (BINOL) derived phosphoric acids.[34] The classical strategy employed is the ability of the Brønsted acid to lower the energy of LUMO of the electrophile *via* protonation, thus activating the substrate toward reacting with

nucleophiles. Enantioselectivity is dependent on sterical factors driven by the catalyst architecture.

Brønsted base organocatalysts in contrast promote the formation of a new bond by deprotonation of a pro-nucleophile unit to render a new species with enhanced nucleophilicity.[35] The most prominent example of Brønsted base catalysts are tertiary amines with a growing focus on those derived from cinchona alkaloids.

Another successful strategy for enantioselective induction throughout a reaction is the ion-pairing.[36] The underlying idea is that ionic intermediates, formed in the course of a reaction, are necessarily accompanied by a counterion and, if this counterion is chiral and sufficient association through electrostatic interactions can be achieved, the reaction would proceed enantioselectively. A variation of the ion-pairing catalysis is the phase transfer catalysis.[37] In this case the chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and a second phase.

1.4. Organocatalyzed asymmetric domino reactions

One of the greatest goals of organic synthesis has always been the development of reactions with efficiency comparable to that seen in natural biosynthesis. Starting from simple reactants, complex structures with multiple stereocenters are highly selectively created in only a few steps. Biosynthetic processes often utilize domino reactions and their high performance makes them increasingly attractive for the organic chemistry community. As a result in the last 15 years various organocatalyzed asymmetric domino reactions have been developed.

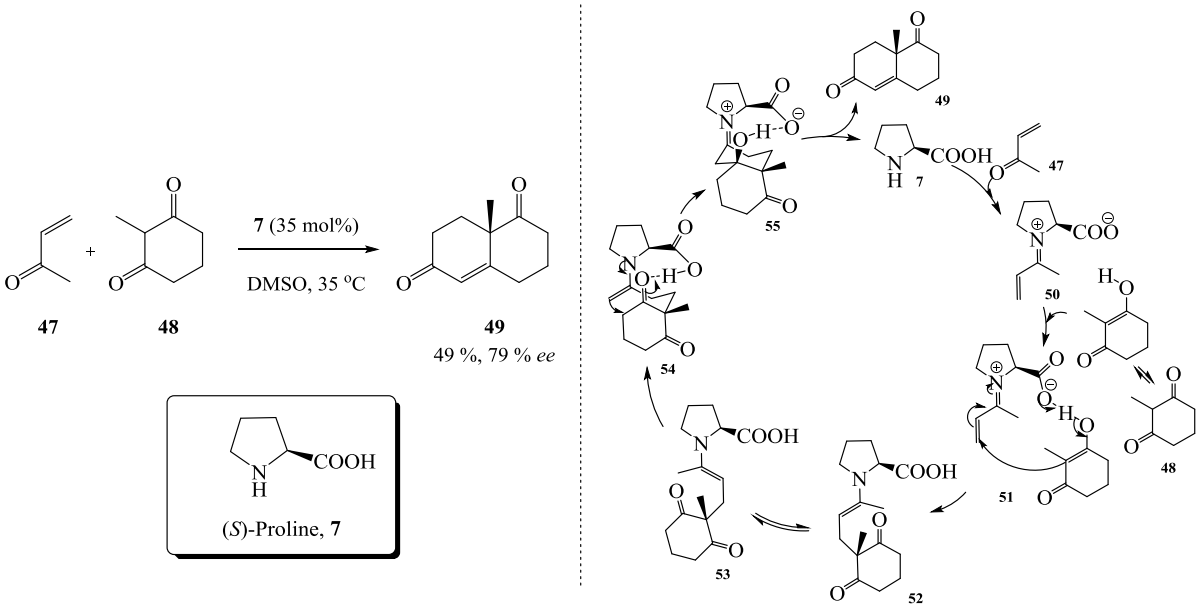
Even before the real rush has begun, in 1993 Tietze and Beifuss first defined a domino reaction as "*a process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step*".[38] According to that classification, domino reactions are seen as time-resolved processes, whereas a "tandem reaction" is space-resolved. A decade later, another classification was suggested by Fogg and dos Santos.[39] Their taxonomy is based on the number of distinct mechanisms and required catalysts. In this case "domino reaction" and its synonymic "cascade reaction" mean sequence of consecutive transformations which are all described by one kind of mechanism, while sequence of steps with different mechanisms is a "tandem reaction". Furthermore, both domino and tandem reactions are specific cases of "one-pot reactions" with all the catalysts and reactants being present from the beginning.

Domino reactions avoid time-consuming and costly protection/deprotection processes as well as purification steps. They proceed with high redox-[40], atom-[41] and step-[42] efficiency and excellent selectivities. Thus, it is not surprising they represent a flourishing area in organic synthesis with characteristic advantages over the classical synthetic methods.

1.4.1. Amine catalyzed simple domino reactions

Although proline and its derivatives were used as catalysts for the enantioselective Michael and aldol reactions in the early 1970s[12b, 14-15], their use for promoters for domino reactions was first realized three decades later. In the year 2000 Barbas and co-workers studied several chiral secondary amines as catalysts for the Robinson annulations sequence (Scheme 7).[43] With methyl vinyl ketone **47** and 2-methyl-cyclohexan-1,3-dione **48** as substrates, the condensation product **49** was obtained in 49 % yield and 76 % enantiomeric excess when the reaction was performed in the presence of *L*-proline **7** as a catalyst. Investigation of the structure/catalytic activity relationship showed that the pyrrolidine-type secondary amine group and the carboxylate functionality are both important for catalyzing the two steps of the Robinson annulations.

Regarding the mechanism of this reaction (Scheme 7), in a first step, *L*-proline **7** activates both reaction partners for the first carbon-carbon bond forming event. Methyl vinyl ketone **47** is activated through the formation of an iminium ion **50** and 2-methyl-cyclohexane-1,3-dione **48** through hydrogen bonding with the carboxylate functionality of **7**, enabling the Michael addition and affording the intermediate **52**. Izomerization of the enamine **52** provides enamine **53**, which undergoes an intramolecular aldol reaction through Zimmermann-Traxler-type transition state **54**, as proposed later through some theoretical studies by Houk and co-workers.[44] Dehydration of the intermediate **55**, followed by hydrolysis affords the bicyclic product **49** and regenerates the catalyst.

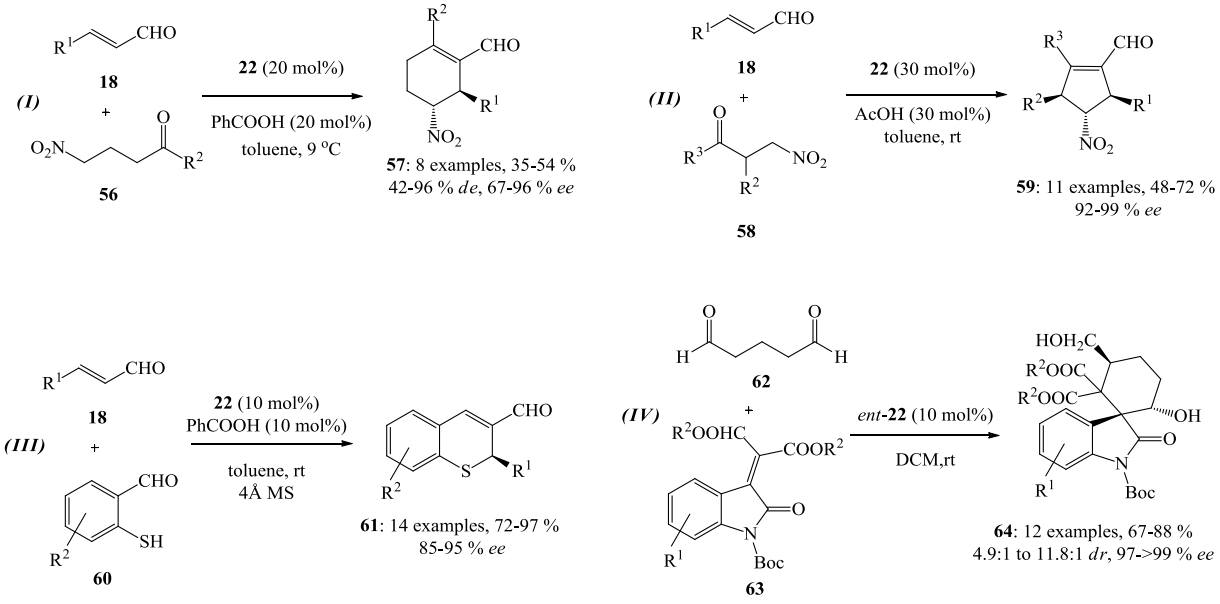


Scheme 7. First domino reaction and proposed mechanism for the Michael/Aldol sequence.

After these initial results, the field of asymmetric organocatalyzed domino reactions saw tremendous growth with development of novel cascade sequences. The Michael/Aldol pattern is now well established concerning the aminocatalyzed domino reactions of α,β-unsaturated aldehydes. Various molecules possessing a Michael donor as well as Aldol receptor moieties have been utilized as substrates in such cascade processes. In Scheme 8 are presented just few

examples, illustrating the wide diversity of molecular architectures affordable through this model. Protocols for the synthesis of chiral cyclohexenes **57** and cyclopentenes **59** were developed in the groups of Enders[45] and Hong[46]. These scaffolds were achieved through domino reactions of α,β-unsaturated aldehydes **18** with γ-nitrocarbonyl **56** and β-nitrocarbonyl **58** compounds, respectively (Scheme 8, Eqn I and II). Both reactions proceed in the presence of (*S*)-TMS-protected diphenylprolinol **22** in highly stereoselctive manner. Thiochromenes **61** can also be obtained through a reaction of α,β-unsaturated aldehydes **18** with 2-mercaptobenzaldehydes **60** (Scheme 8, Eqn III).[47]

Although α,β-unsaturated aldehydes **18** are the most common compounds utilized in such sequences, other carbonyl compounds have been exploited as well. One example is the glutaraldehyde **62**, which through a Michael/Aldol domino reaction with isatin-derived alkenes **63** affords a series of functionalized spirocyclohexane oxindoles **64** bearing three stereogenic centers (Scheme 8, Eqn IV).[48] The reaction proceeds with good yield and excellent enantioselectivities, even when the protocol was applied on gram scale.

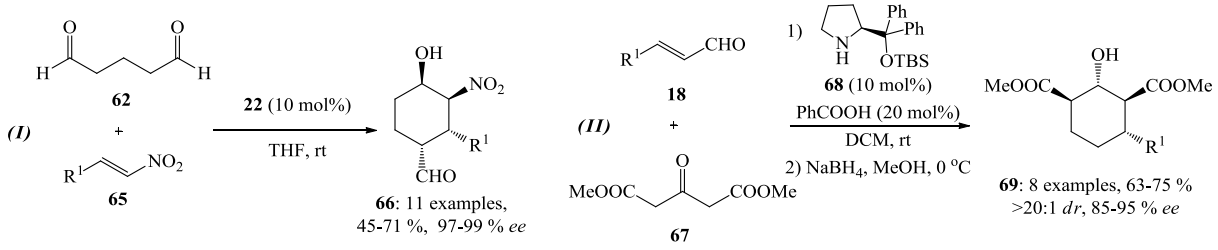


Scheme 8. Various aminocatalyzed asymmetric Michael/Aldol domino reactions.

In 2007 Hayashi *et al.* exploited glutaraldehyde **62** for a reaction with *trans*-*β*-nitrostyrene **65** in the presence of 10 mol% TMS-protected diphenylprolinol **22**, following a Michael/Henry sequence pattern (Sceme 9, Eqn I).[49] The domino reaction afforded polysubstituted cyclohexanes **66** with four new stereogenic centers. Although the product **66** was isolated as four diastereomers, the major diastereomer was obtained in good yield and excellent enantioselectivity (88 % yield, 99 % *ee*). It is worth noticing that the reaction could be performed on a large scale with just 2 mol% of the catalyst without any decrease in the selectivity.

In the same group few years later was successfully developed an organocatalytic cascade involving Michael addition, followed by Knoevenagel condensation between α,β-unsaturated aldehydes **18** and dimethyl-3-oxopentadioate **67** (Scheme 9, Eqn II).[50] The formal [3+3]-carbocycloaddition catalyzed by diphenylprolinol derivative **68** allows enantioselective access

to cyclohexenones, which are not isolated but further treated with sodium borohydride in a one-pot fashion to give the corresponding cyclohexanols **69** with excellent yields.



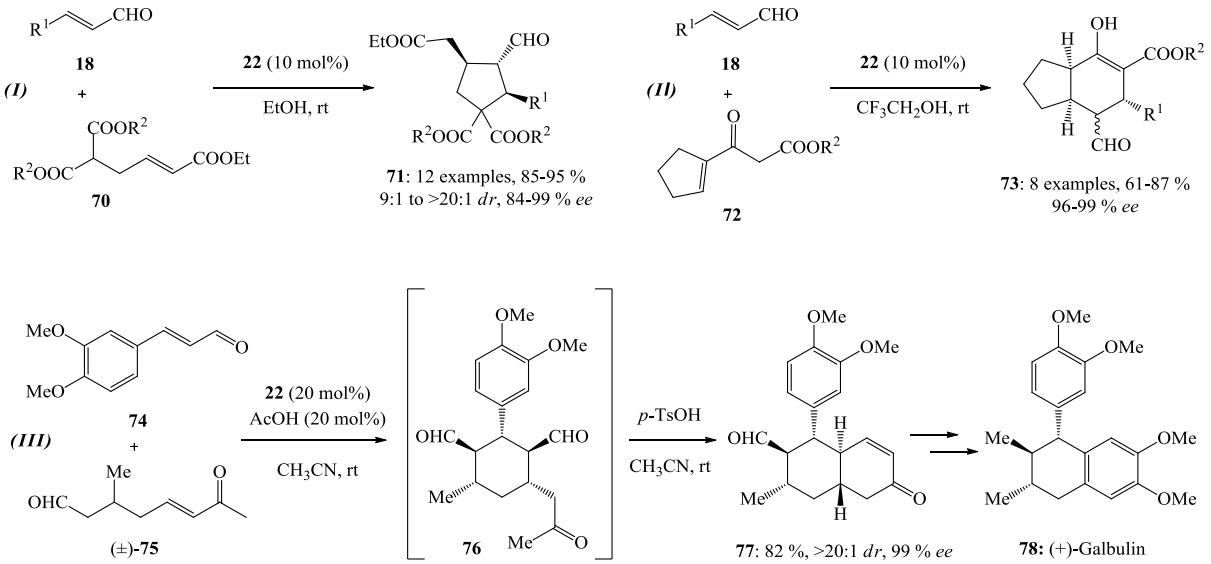
Scheme 9. Examples of (I) Michael/Henry and (II) Michael/Knoevenagel domino reactions.

Efficient asymmetric Michael/Michael domino reactions have been developed as well. These protocols require two distinct α,β-unsaturated systems with different reactivities, which would react in a sequential manner without interfering with each other. On one hand, the reactivity of one system should be lower enough not to compete with the second system for the first Michael addition, but high enough to undergo the second Michael addition. Furthermore, the existing Michael donor should participate only in the first addition. With these considerations in mind, many groups have successfully designed approaches for the Michael/Michael cascade reactions.

The first asymmetric organocatalyzed Michael/Michael domino reaction was reported by Wang and co-workers for the synthesis of polysubstituted cyclopentanes **71** (Scheme 10, Eqn I).[51] The authors designed the substrate **70** as a reaction partner with the assumption that α,β-unsaturated esters generally undergo conjugate additions at a lower rate than α,β-unsaturated aldehydes and would therefore not interfere with the secondary amine catalysis. The cyclopentane products **71** were obtained in very good yields and with excellent diastereo- and enantioselectivity.

Having in mind the fact that β-ketoesters are a very common donor in Michael additions, Brener and co-workers proposed the substrate **72** bearing a conjugated alkene as a part of a carbocyclic moiety (Scheme 10, Eqn II).[52] Upon a double Michael cascade reaction with α,β-unsaturated aldehydes, substrates of type **72** produce highly substituted fused carbocycles **73** in a single step in up to 87 % yield and 99 % *ee*.

Hong *et al.* explored the domino Michael/Michael reaction between dicarbonyl compounds and α,β-unsaturated aldehydes, obtaining cyclohexanes with two newly formed C-C bonds and four new stereogenic centers.[53] Subsequently the group successfully applied this strategy in the total synthesis of (+)-Galbulin **78** – a natural product with a tetrahydronaphthalene carbon skeleton (Scheme 10, Eqn III).[54] TMS-protected diphenylprolinol **22** catalyzed the Michael/Michael domino reaction between (*E*)-3-(3,4-dimethoxyphenyl)acrylaldehyde **74** and the racemic dicarbonyl compound **75**, affording the cyclohexane **76**. After subsequent aldol condensation performed in a one-pot fashion, the key intermediate **77** was obtained in 82 % yield and 99 % *ee* as a single diastereomer.

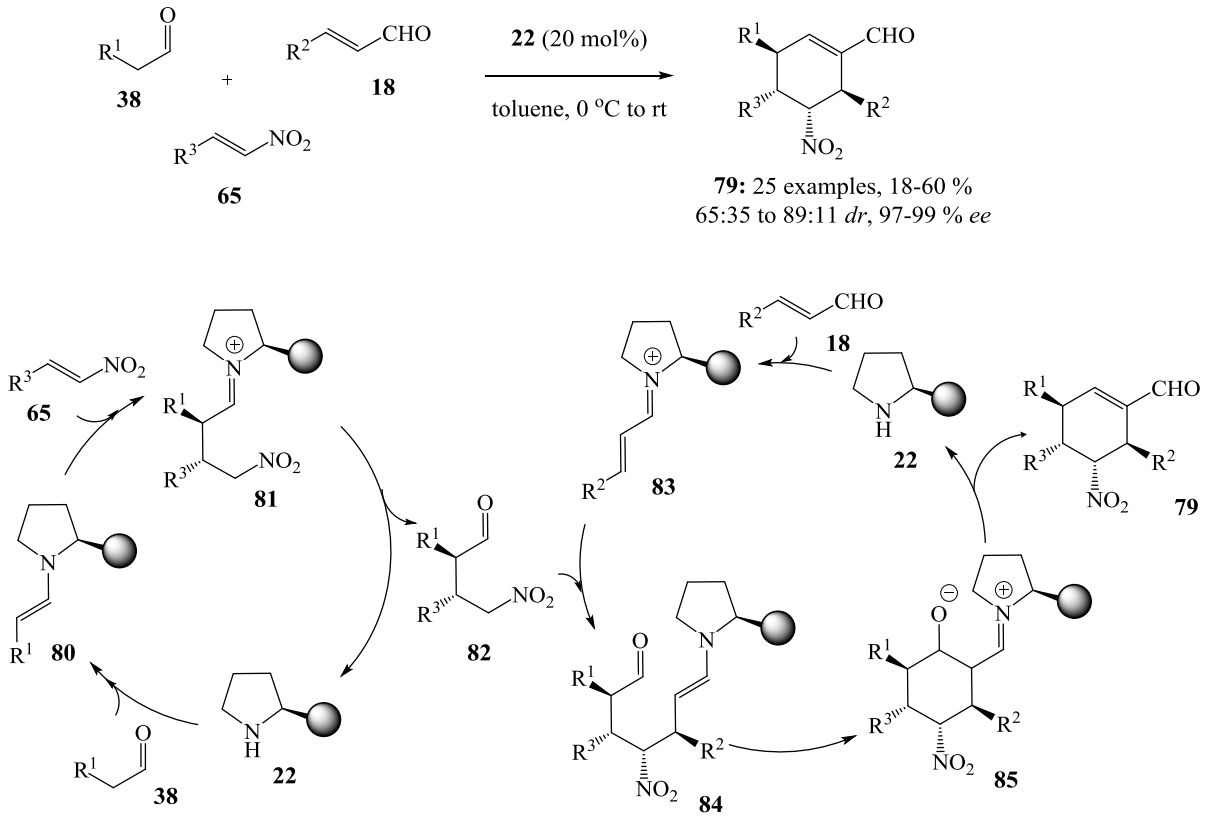


Scheme 10. Some examples of domino Michael/Michael reactions.

Many other sequences including different types of reactions have been developed through the years. Some of them include the synthesis of cyclohexenones starting from α,β-unsaturated aldehydes through Michael/Morita-Baylis-Hillman sequence with Nazarov reagents[55] or through Michael/Wittig[56] domino reactions. α,β-Unsaturated aldehydes have been also utilized in Michael/Alkylation cascade reactions for the formation of cyclopropanes upon reaction with ylides[57], chloroacetophenone[58] or bromonitromethane[59].

1.4.2. Amine catalyzed triple domino reactions

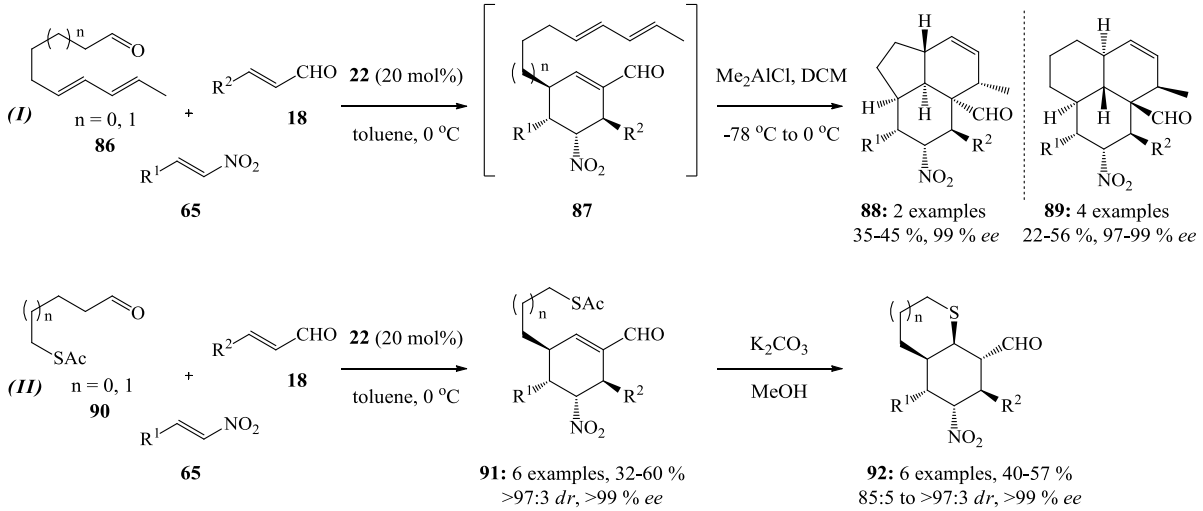
With the tremendous progress in the field of domino sequences, the next logical step was the development of new triple cascade reactions. The breakthrough came in 2006 with the development of the first three-component triple domino reaction by our group.[60] The cascade reaction consists of three consecutive C-C bond-forming steps for the creation of four stereogenic centers in a very efficient manner. Through a Michael/Michael/Aldol sequence between linear aldehydes **38**, α,β-unsaturated aldehydes **18** and nitroalkenes **65** in the presence of TMS-protected diphenylprolinol **22**, cyclohexenecarbaldehydes **79** were obtained with moderate to good yields, good diastereo- and excellent enantioselectivities (Scheme 11).



Scheme 11. First triple domino reaction and the proposed mechanism for the sequence.

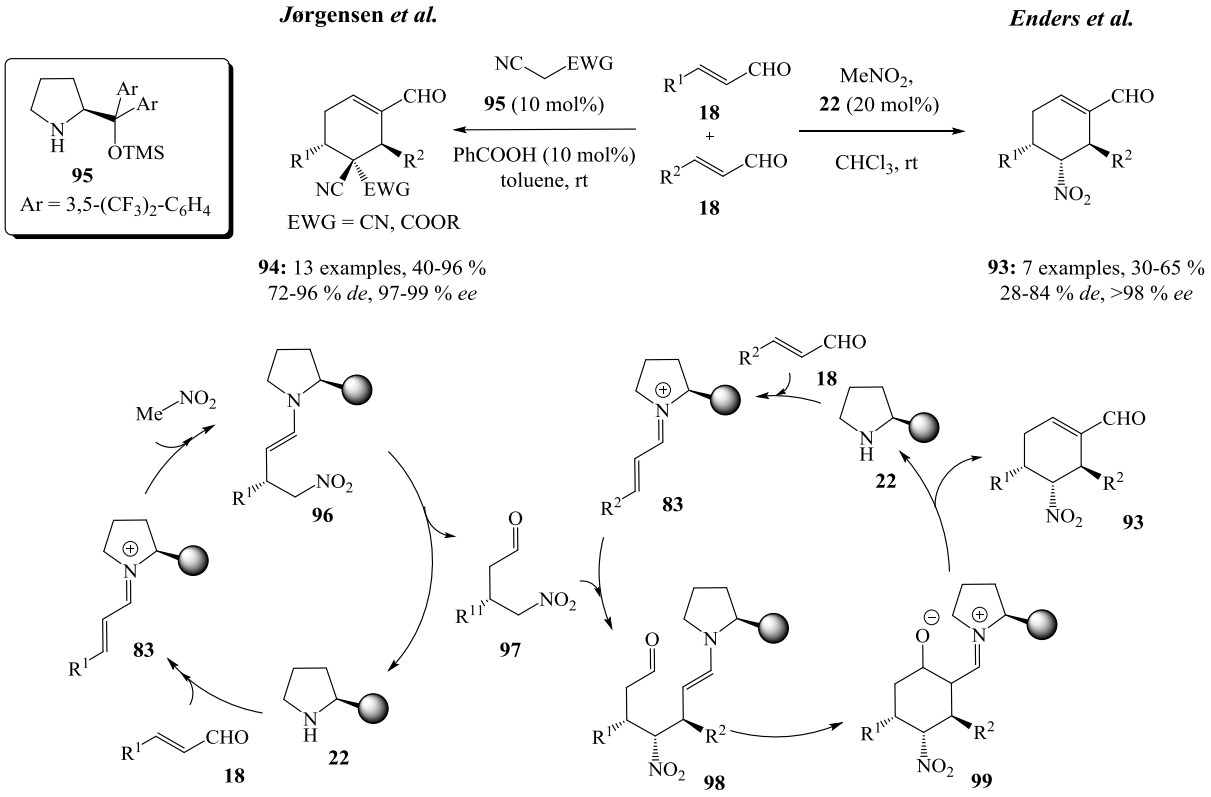
In the first step, the secondary amine catalyst **22** activates the linear aldehydes **38** *via* formation of the enamine **80** (Scheme 11). It then reacts further with the nitroalkene **65**, affording the intermediate **81**. The chemoselectivity of this first Michael addition is based on the rather higher reactivity of the nitroalkenes **65** as a Michael acceptor compared to the α,β-unsaturated aldehydes **18**. In the next step the formed nitroalkane **82** participates as a Michael donor in a reaction with the activated *via* iminium ion formation α,β-unsaturated aldehyde. The obtained addition product **84** then undergoes an intramolecular aldol condensation through enamine activation and the final product of the reaction **79** is obtained after hydrolytic return of the catalyst.

Later, the scope of the triple cascade reaction was extended to include a linear aldehyde bearing an electron-rich moiety **86** (Scheme 12, Eqn I).[61] After the products of the domino reaction **87** were obtained, a Lewis acid was added providing the tricyclic carbon frameworks **88** and **89** *via* Diels-Alder cyclization in a one-pot fashion. Remarkably, the sequence affords molecular architectures containing eight stereogenic centers with excellent selectivities. Similar approach was employed for the synthesis of highly substituted thiadecalins **92** by exploiting the triple domino reaction, followed by base-mediated sulfa-Michael addition (Scheme 12, Eqn II).[62]



Scheme 12. Further expanding the scope of the triple cascade reaction.

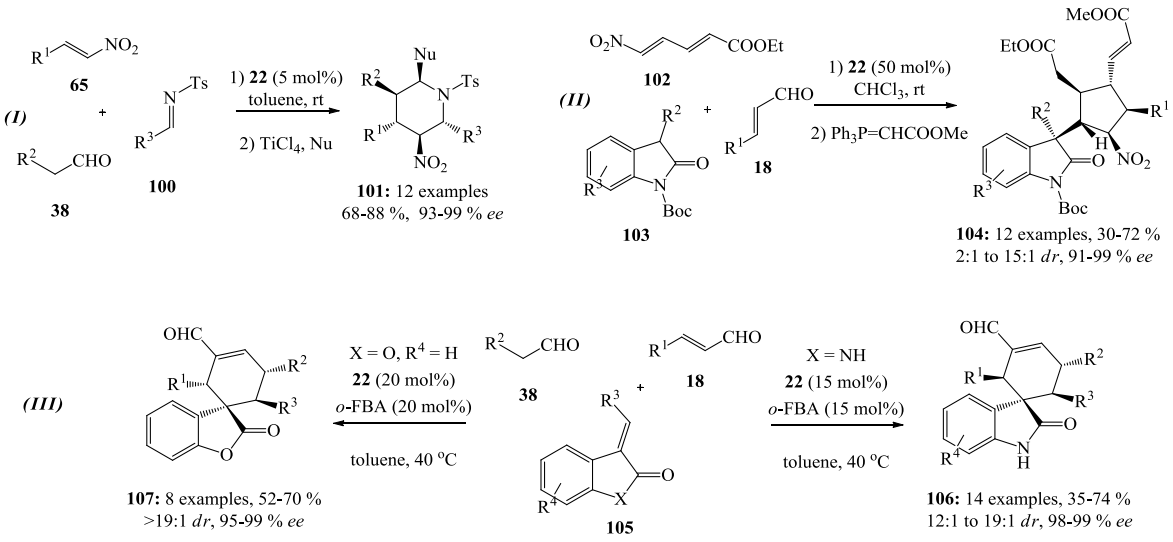
A conceptually different strategy following iminium/iminium/enamine activation mode for the synthesis of cyclohexenecarbaldehydes was reported by the groups of Jørgensen[63] and Enders[64] (Scheme 13). Utilizing α,β-unsaturated aldehydes **18** and diverse Michael donors in the presence of catalytic amounts of prolinol-based catalysts, trisubstituted cyclohexenecarbaldehydes **93-94** were obtained in moderate yields and excellent enantioselectivities. The mechanism for the triple domino reaction of α,β-unsaturated aldehydes with nitromethane is presented in Scheme 13. The first step is a Michael addition of nitromethane to the activated *via* iminium ion formation α,β-unsaturated aldehyde, affording intermediate **96**. After hydrolysis, adduct **97** is obtained. A second Michael addition of the nitroalkane **97** to an activated α,β-unsaturated aldehyde follows, generating the enamine **98**. At last, intramolecular aldol condensation takes place, furnishing the desired product **93** after hydrolysis. A triple domino reaction for the synthesis of densely substituted piperidines **101** was developed by Hayashi and co-workers (Scheme 14, Eqn I).[65] The piperidine ring is a key structural unit in organic chemistry and is present in many natural products and medicines. Through a domino Michael/aza-Henry/hemiaminalization sequence of linear aldehydes **38**, nitroalkenes **65** and imines **100**, the piperidine ring is built with high yields and excellent enantioselectivity. The product of the cascade reaction undergoes a further modification in a one-pot fashion for the Lewis-acid catalyzed substitution of the hydroxyl group at sixth position with a nucleophile, thus affording the final product **101** as a single diastereomer.



Scheme 13. Triple domino Michael/Michael/Aldol condensation sequences for the synthesis of cyclohexenecarbaldehydes **93-94** by *Enders* and *Jørgensen*.

An efficient, highly stereoselective asymmetric synthesis of fully functionalized cyclopentanes **104** bearing an oxindole moiety has been developed in our group (Scheme 14, Eqn II).[66] The triple Michael domino reaction between oxindoles **103**, unsaturated conjugated dienes **102** and α,β-unsaturated aldehydes **18**, followed by a one-pot Wittig reaction, affords three new C-C bonds and six stereocenters, including a quaternary one, in a highly efficient manner.

Oxindoles bearing a conjugated unsaturated moiety **105** (X=NH) were utilized in a domino Michael/Micahel/aldol condensation sequence for the synthesis of six-membered spirocyclic oxindole scaffolds **106** (Scheme 14, Eqn III).[67] The method relies on prolinol-catalyzed enamine/iminium/enamine activation of aldehydes, affording the products in moderate to good yields and excellent diastereo- and enantioselectivities. The same strategy was applied to olefinic benzofuranones **105** (X=O) as well, furnishing the corresponding spirocyclic benzofuranone derivatives **107** (Scheme 14, Eqn III).[68]

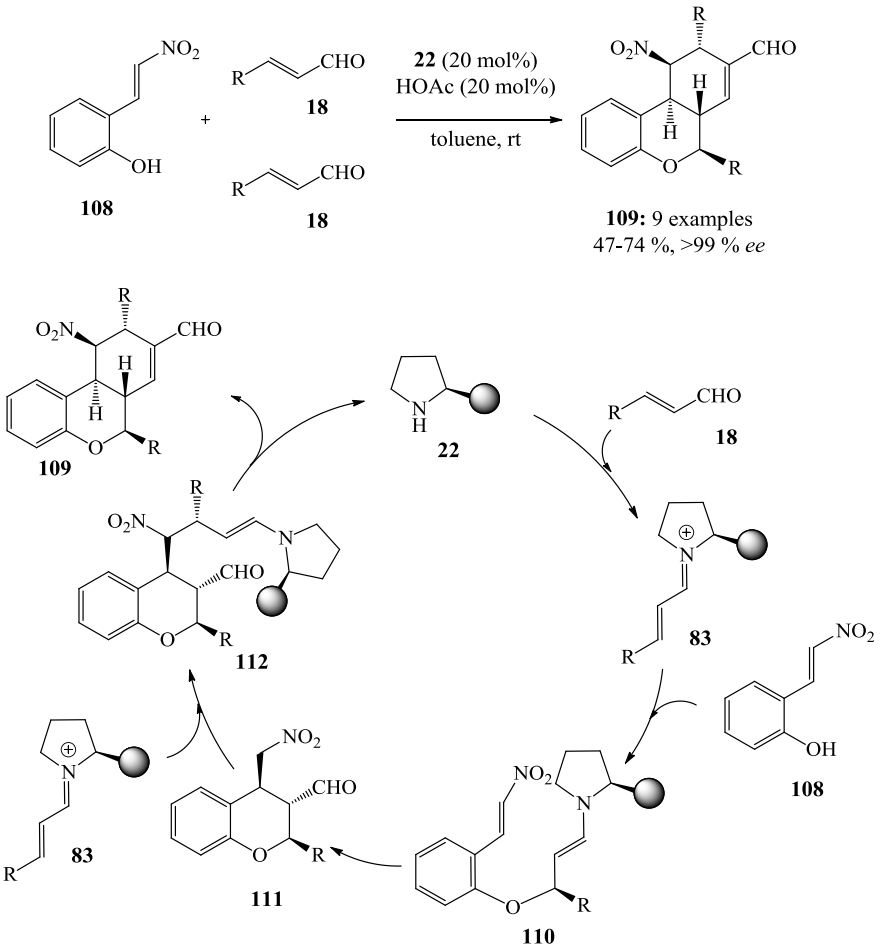


Scheme 14. Some examples of triple cascade reactions affording various molecular architectures.

1.4.3. Amine catalyzed quadruple domino reactions

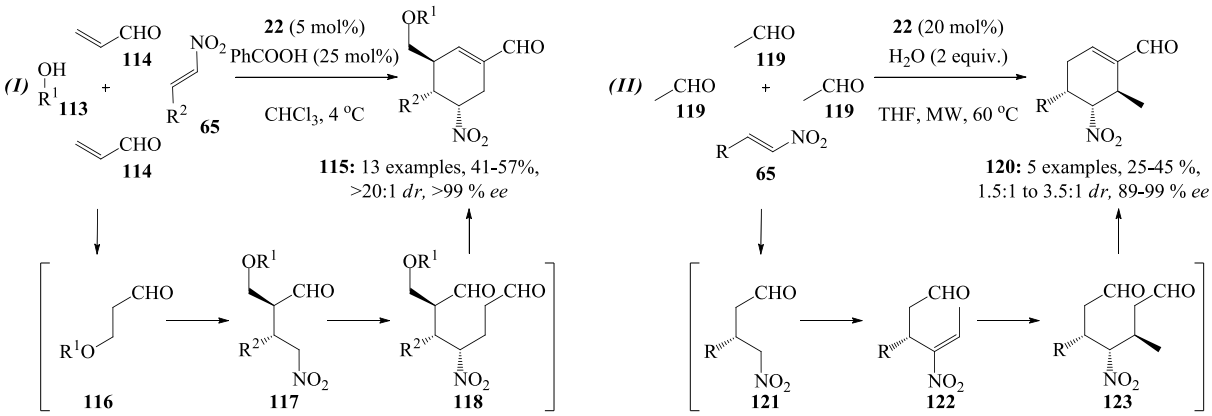
With the excellent results obtained in the field of double and triple domino reactions, chemists turned their attention towards more complex higher-order cascades. Considering matching arrangements of functional groups and design of appropriate substrates, quadruple domino sequences have been successfully achieved.

The first asymmetric quadruple domino reaction was developed by the group of Hong for the synthesis of tetrahydro-*6H*-benzo[c]chromenes **109** (Scheme 15).[69] The products are achieved through oxa-Michael/Michael/Michael/aldol condensation sequence between 2-((*E*)-2-nitrovynil)phenol **108** and α,β-unsaturated aldehydes **18** in the presence of TMS-protected diphenylprolinol **22**. The reaction begins with an oxa-Michael addition of the phenol moiety of **108** to the activated enal **83**. The formed enamine **110** subsequently reacts in an intramolecular Michael addition to the nitroalkene part of the molecule. The obtained nitroalkane **111**, which could be also isolated in some cases, is a suitable Michael donor for the third Michael addition to another molecule α,β-unsaturated aldehyde. After a final aldol condensation and hydrolysis, the product **109** with five contiguous stereogenic centers is obtained. Remarkably, from the 32 theoretically possible diastereomers, only one is formed. The authors proposed that the high stereoselectivity observed is due to the first oxa-Michael reaction, which is generally known to proceed with high selectivities. The formed first stereocenter then further controls the selective formation of the next stereocenters.



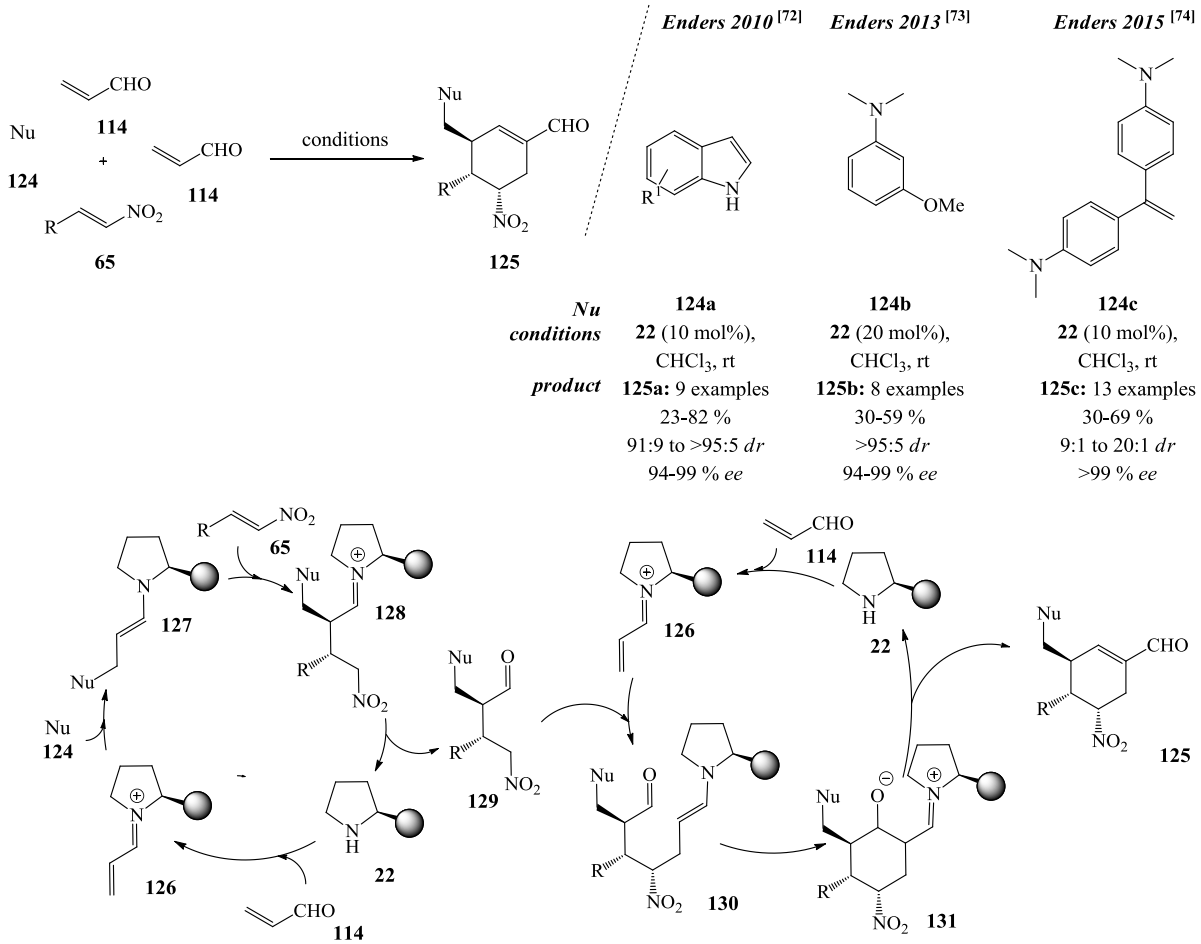
Scheme 15. First quadruple domino reaction by Hong and the proposed mechanism.

In the same year two more quadruple cascades were published by Gong[70] and Enders[71], both furnishing polysubstituted cyclohexenecarbaldehyde products (Scheme 16, Eqn I and II, respectively). In the first case, the product **115** is obtained *via* oxa-Michael/Michael/Michael/aldol condensation sequence between alcohols **113**, acrolein **114** and nitroolefins **65** (Scheme 16, Eqn I). Various alcohols such as primary, secondary and functionalized alcohols as well as phenols were successfully utilized in the reaction. Excellent selectivities were achieved with just 5 mol% of the catalyst, even when performed on a larger scale. Another quadruple cascade affording cyclohexenecarbaldehyde derivatives **120** involves a Michael/Henry/Michael/aldol condensation sequence between three equivalents of acetaldehyde **119** and one equivalent nitroalkene **65** (Scheme 16, Eqn II). The optimal conditions for the reaction in the presence of 20 mol% of the catalyst **22** require 2 equivalents of water and microwave irradiation at 60 ^{o}C. Although the diastereoselectivity is low, the major product could be easily separated through column chromatography. In contrast to the above mentioned two quadruple cascades, this reaction proceeds through enamine/iminium/enamine/enamine activation. In the first step, the enamine derived from acetaldehyde undergoes a Michael addition to the nitroalkene, affording a nitroalkane **121**. It reacts further with a second molecule of acetaldehyde and as a result a second nitroalkene **122** is formed. This nitroalkene **122** then acts as a Michael acceptor in the next Michael addition. In the last step, after an intramolecular aldol condensation, the final product of the reaction **120** is formed.



Scheme 16. Quadruple domino reactions for the synthesis of polysubstituted cyclohexenecarbaldehydes by (I) Gong and (II) Enders.

Another quadruple cascade for the synthesis of polysubstituted cyclohexene-carbaldehydes was also developed in our group (Scheme 17).

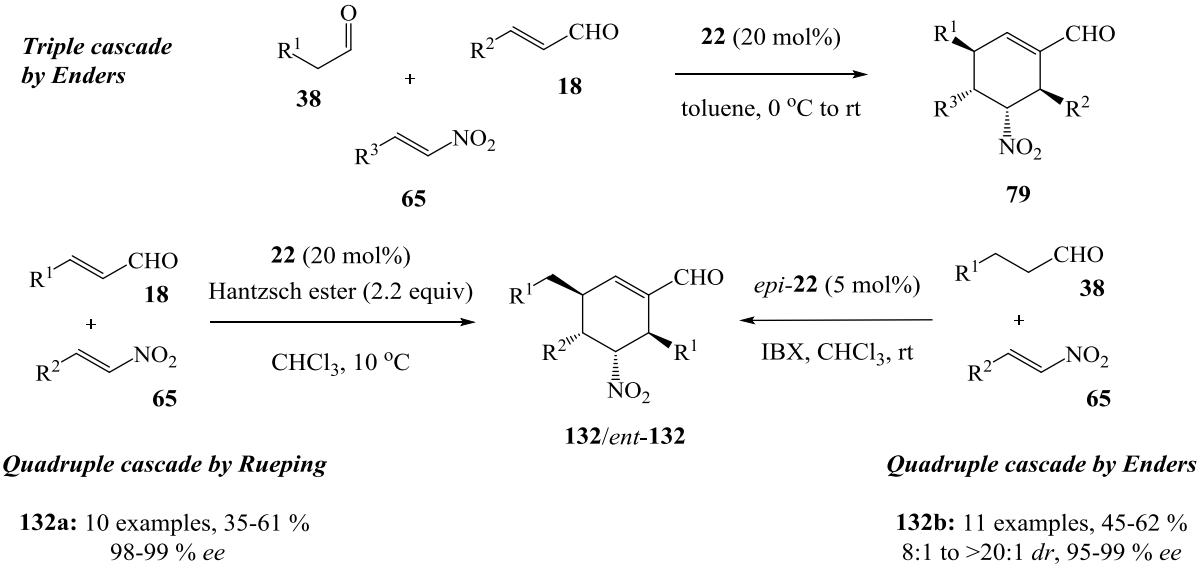


Scheme 17. Quadruple domino Friedel-Crafts/Michael/Michael/aldol condensation sequence for the synthesis of cyclohexenecarbaldehydes **125**.

Initially as a nucleophile was utilized indole **124a**, thus affording the corresponding products **125a** through a reaction with nitroalkene **65** and acrolein **114** (Scheme 17).[72] Few years later, the reaction scope was expanded to include electron-rich arenes **124b**[73] and 1,1-bis(aryl)alkenes **124c**[74] as nucleophiles. In each case, the cascade is triggered by a Friedel-

Crafts reaction of the nucleophile **124** to the activated acrolein and subsequent Michael addition to the nitroolefin **65**, affording the nitroalkane **129**. It reacts in the next Michael addition to another molecule acrolein and after an intramolecular aldol condensation, the product **125** is achieved. These multicomponent domino processes provide efficient method for the synthesis of useful scaffolds in moderate to high yields and excellent stereoselectivities.

An interesting strategy was applied by Rueping *et al.* for the synthesis of cyclohexenecarbaldehydes (Scheme 18).[75] Based on the selective reduction of α,β-unsaturated aldehydes over nitrostyrenes in the presence of secondary amine catalyst and exploiting Hantzsch ester as a reducing agent, they developed a quadruple cascade reaction consisting of hydrogenetation/Michael/Michael/aldol condensation. The reduction of the α,β-unsaturated aldehydes gives the corresponding saturated aldehydes and from that point on the domino reaction proceeds analogically to the already described in Chapter 1.4.2 triple cascade sequence developed in our group. [60] The cascade is reminiscent of enzyme-catalyzed reactions in the cells, as selective double versus quadruple cascade product could be achieved by simply varying the concentration of the substrates.

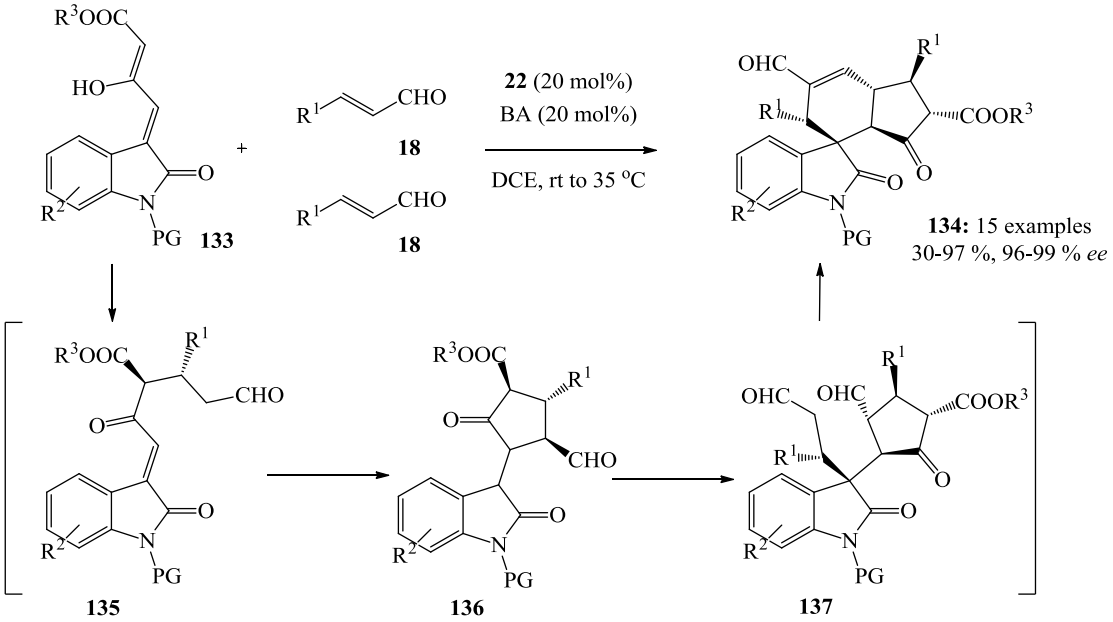


Scheme 18. Two component quadruple cascades for the synthesis of polysubstituted cyclohexenecarbaldehydes **132**.

Analogously, the opposite approach was developed in our group to trigger a quadruple domino reaction (Scheme 18).[76] The idea applied in this case is that through "oxidative enamine catalysis", *o*-iodobenzoic acid (IBX) as the oxidant converts the enamine formed from an aldehyde **38** and secondary amine catalyst into iminium ion, which would further act as a Michael acceptor. As a result a linear aldehyde was used as both the nucleophile and the electrophile in such a domino process for the formation of six-membered-ring derivatives **132**.

Interesting complex hydroindane frameworks incorporating a spirooxindole motif **134** were prepared through an asymmetric three-component quadruple cascade reaction between α,β-unsaturated aldehydes **18** and oxindole derivatives **133** (Scheme 19).[77] The reaction proceeds

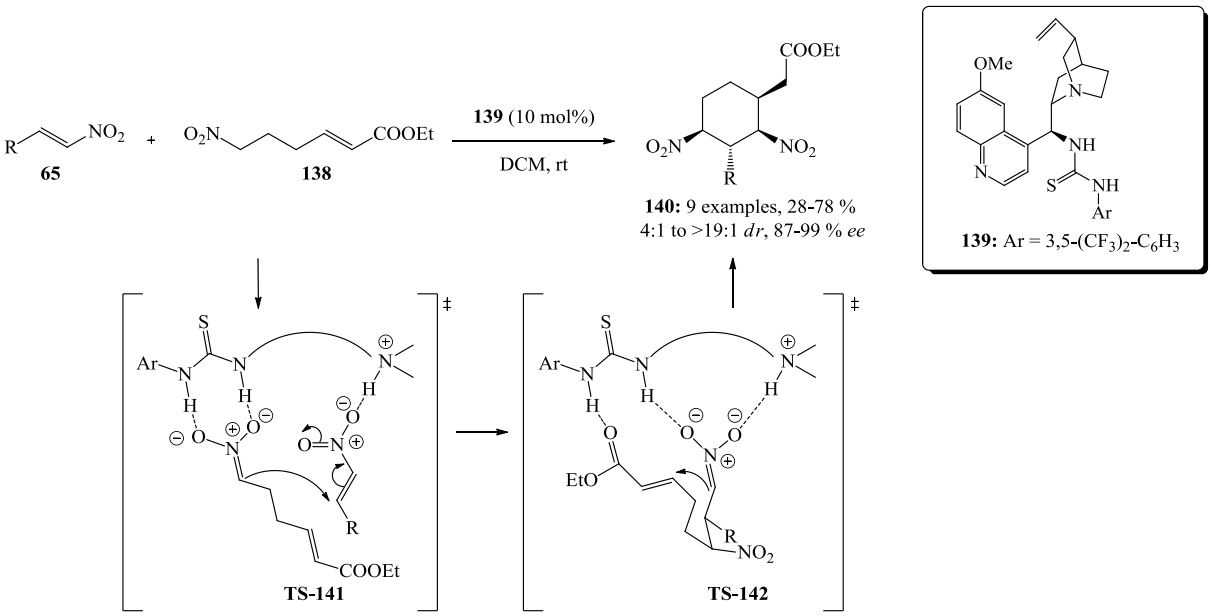
with excellent stereo control of the six contiguous stereogenic centers formed. However, the yields of the reaction were strongly dependent on the enal substitution. Whereas aromatic and heteroaromatic enals led to the corresponding products in good yields, only moderate yields were achieved when aliphatic aldehydes or two different aldehydes were employed.



Scheme 19. Synthesis of spirocyclic oxindoles **134** through a quadruple Michael/Michael/ Michael/aldol condensation sequence.

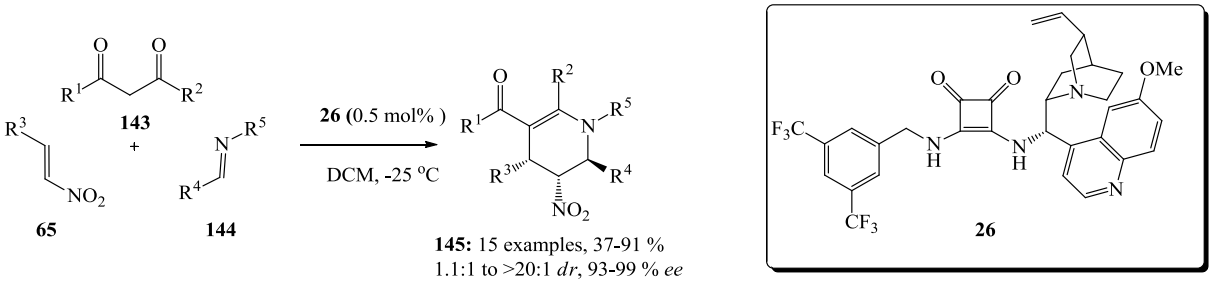
1.4.4. Domino reactions catalyzed by bifunctional catalysts

Considering previous work on the intramolecular Michael reaction, Cobb and co-workers developed a domino Michael/Michael sequence, catalyzed by the bifunctional thiourea catalyst **139** (Scheme 20).[78] They designed the cascade reaction between (*E*)-ethyl 6-nitrohex-4-enoate **138** and nitralkenes **65**, which would afford the polysubstituted cyclohexane products **140**. Indeed, the double Michael addition proceeds with the generation of four contiguous stereocenters in high enantio- and diastereoselectivities. The scope of the reaction was even further extended to utilizing 2-substituted nitroesters for the formation of five contiguous stereocenters with excellent stereocontrol. The authors proposed the transition state **141** for the first step of the domino reaction with the thiourea catalyst activating both substrates. It was assumed that the subsequent cyclization step proceeds faster than the protonation of the formed nitronate species, since no traces of the adduct of the first Michael reaction could be detected either by NMR or by thin layer chromatography. For the second Michael addition the proposed transition state **142** involves again coordination of the catalyst simultaneously to both nitronate and ester moiety.



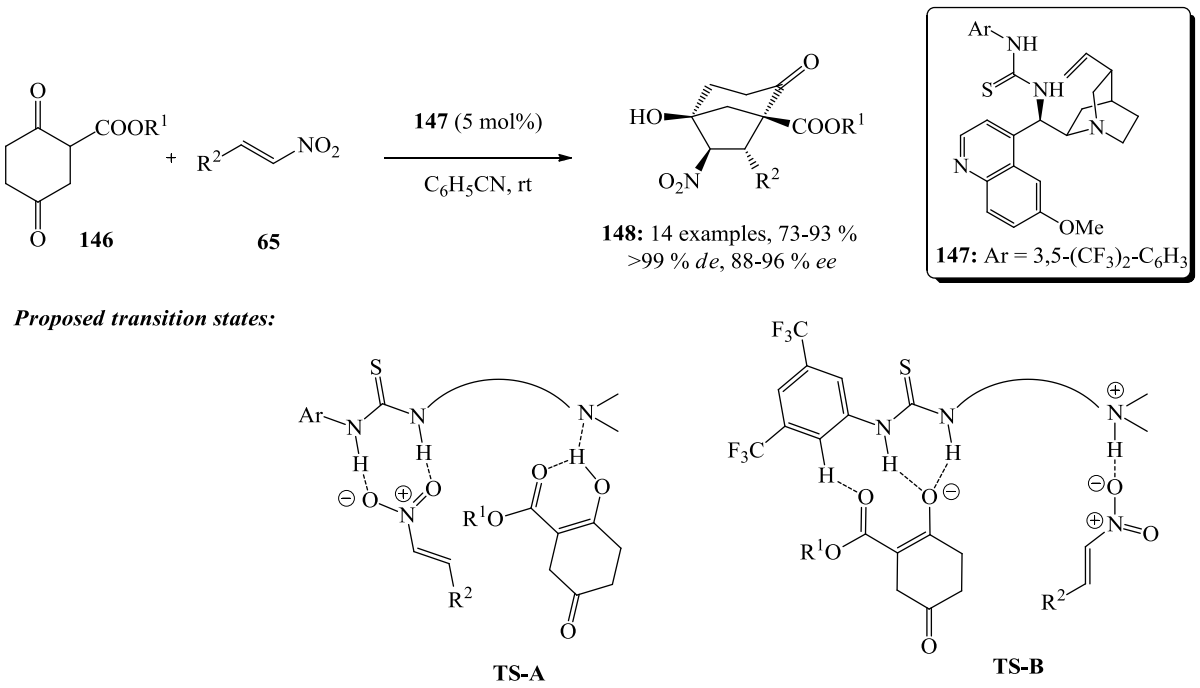
Scheme 20. Synthesis of polysubstituted cyclohexanes **140** *via* domino Michael/Michael reaction.

A triple domino Michael/aza-Henry/cyclization sequence was developed in our group for the synthesis of tetrahydropyridines **145** – a widespread substructure in various naturally occurring compounds and some synthetic bioactive molecules (Scheme 21).[79] The reaction between 1,3-dicarbonyl compounds **143**, nitroalkenes **65** and aldimines **144** is efficiently promoted by just 0.5 mol% of the quinine-derived squaramide catalyst **26**, affording the desired products in good yields, excellent enantiomeric excesses and up to >20:1 diastereomeric ratios. Furthermore, a gram-scale reaction was successfully performed without significant difference in the outcome of the reaction, thus showing the practical and preparative utility of the developed domino process.



Scheme 21. Synthesis of tetrahydropyridines **145** through Michael/aza-Henry/cyclization triple domino sequence.

A highly stereoselective domino Michael/Henry process for the synthesis of synthetically unique and medicinally important bicycle[3.2.1]octane derivatives **148** was developed, starting from nitroalkenes **65** and 2,5-dioxo-cyclohexanecarboxylate esters **146** (Scheme 22).[80] After evaluation of different catalysts, it was shown that the thiourea catalyst **147** successfully promoted the reaction with excellent stereocontrol for the formation of four stereocenters, two of which are quaternary.

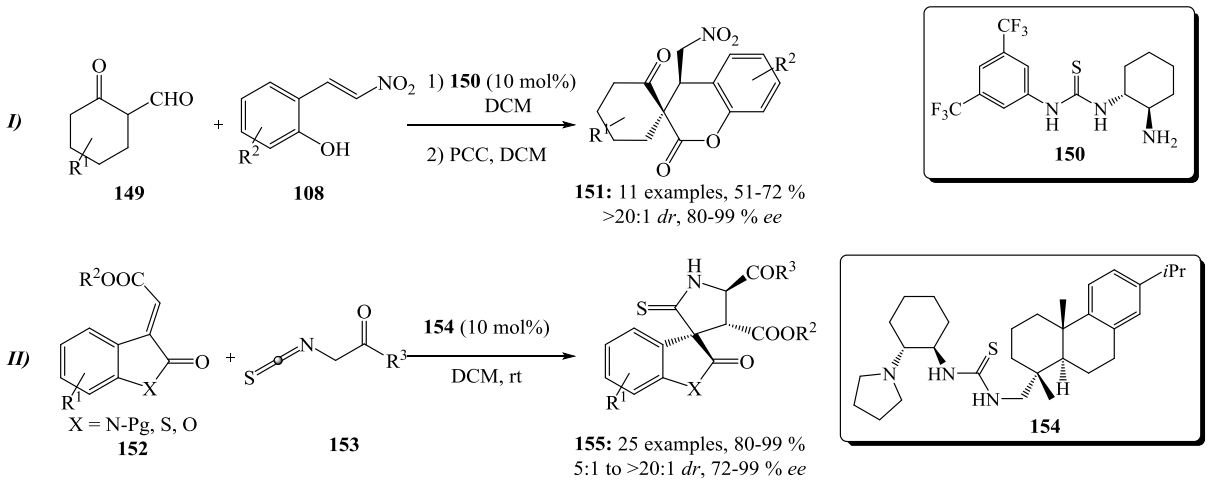


Scheme 22. Synthesis of bicyclo[3.2.1]octanes **148** through Michael/Henry sequence.

According to the general dual activation model, a transition state in which both substrates are activated simultaneously by the catalyst was proposed (Scheme 22). Nitroolefins **65** have been assumed to interact with the two nitrogen atoms of the thiourea moiety through multiple hydrogen-bonds, which results in enhancing their electrophilic nature. The enolic form of the diketoester **146** on the other hand is assumed to interact with the tertiary amine group, thus the subsequent Henry reaction results in a stereocontrolled product (Scheme 22, **TS-A**). To provide theoretical insides on the high stereoselectivity of the reaction, the authors conducted computational studies on the possible transition states of the reaction. However, the results showed that the originally proposed transition state **TS-A** was not in fact the most favourable. The calculation supported transition state **TS-B**, in which the catalyst interacts with both substrates as well but in a different pattern. After deprotonating the ketoesters **146**, the tertiary amine activates the nitrogroup of the nitrostyrene **65** by H-bonding, while the thiourea moiety interacts with the enol form of the nucleophile. The enolic ester part and the thiourea unit showed an almost coplanar structure, giving rise to a concerted hydrogen bonding network where the steric hindrance is minimized. Furthermore, the calculation indicated an additional interaction between the C-H proton from the phenyl ring of the thiourea unit and the ester group. Such interaction is enabled by the increased acidity of this proton resulting from the presence of the two CF_3-groups in the phenyl ring of the catalyst.

A new approach for obtaining 3,3-dialkylchroman-2-one **151** – a unique skeleton possessing a wide variety of pharmacological activities – was developed by Lee and co-workers (Scheme 23, Eqn I).[81] The spiro compound can be achieved through a Michael/acetalization domino sequence followed by an oxidation, starting from 2-hydroxynitrostyrene **108** and 2-oxocyclohexanecarbaldehyde **149**. Good yields, up to >20:1 diastereomeric ratio and 99 % enantiomeric excess were achieved after only 20 minutes when Takemoto catalyst **150** was utilized for the cascade process. Presumably, the amine segment of the catalyst in its role as a Brønsted base activates the nucleophile and facilitates the reaction rate while the thiourea

portion activates the electrophile through H-bonding and provides a suitable asymmetric induction medium for the reaction.

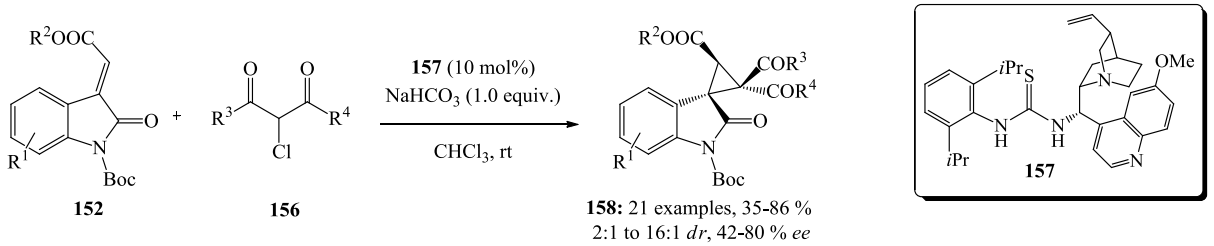


Scheme 23. Some examples of cascade reactions for the synthesis of spiro compounds.

Another complex spiro architecture, namely the densely functionalized 3,3'-thiopyrrolidonyl spirooxindole skeleton **155**, could be achieved by a simple and highly efficient cascade Michael/cyclization sequence (Scheme 23, Eqn II).[82] The authors envisioned that methyleneindolinonens **152** (X = N-Pg) could serve as the perfect electron-deficient olefin due to its high reactivity as a Michael acceptor as well as its unique structural characteristics for the construction of the product **155**. The thiourea activated Michael acceptor would undergo nucleophilic attack by α-isothiocyanato amides or esters **153**, which on the other hand are activated by deprotonation of the α-carbon atom by a Lewis base. Different bifunctional thioureas were tested in the reaction, but the rosin-derived tertiary amine thiourea catalyst **154** was found to be the most efficient. Various electronically and sterically different sunstituents in the methyleneindolinonens **152** as well as different protecting groups on the nitrogen atom proved to be compatible in the reaction conditions to provide the products in excellent yields and selectivities. Benzofuranone (**152**, X = O) and benzothiophenone (**152**, X = S) skeletons could also be applied in the domino reaction affording the corresponding products in good yields. Furthermore, to expand the application of this approach for the synthesis of more promising candidates for drug discovery, it was shown that the newly formed cycle could be easily transformed either to lactam ring through oxidation of the thiolactam group or to pyrrolidine skeleton through reduction.

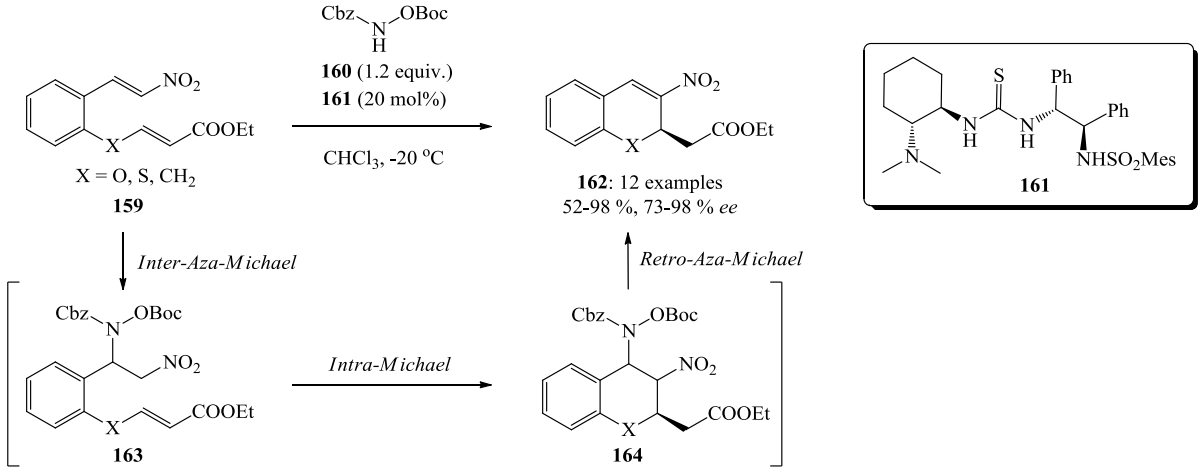
Methyleneindolinonens **152** were successfully applied for the synthesis of the corresponding spirocyclopropyl oxindole motifs **158** as well (Scheme 24).[83] As a partner for the formal [2+1] cycloaddition approach towards the products **158** with two quaternary centers, α-halo-β-dicarbonyl compounds **156** were exploited. The authors envisioned that the α-halocarbonyl compounds **156** would be an appropriate substrate for the cascade cyclopropanation due to the dual nucleophilic/electrophilic reactivity of the α-carbon atom. Some of the most common bifunctional thiourea catalysts were tested for the reaction, but neither of them gave good results in term of diastereoselectivity – two inseparable diastereomers were obtained in ratio 3:1 at best. However, a further investigation through a set of experiments showed that the diastereoselectivity was influenced by the substituents on the aromatic ring of the thiourea

catalyst and a major improvement was achieved with catalyst **157** with two bulky *i*Pr-groups occupying the two *ortho* positions. The diastereoselectivity increased to 13:1 without any loss of yield or enantioselectivity. In the optimized conditions of the reaction, various spirocyclopropyl oxindoles **158** were obtained in good yields, diastereo- and enantioselectivities.



Scheme 24. Synthesis of spirocyclopropyl oxindoles **158** through Michael/cyclization domino reaction.

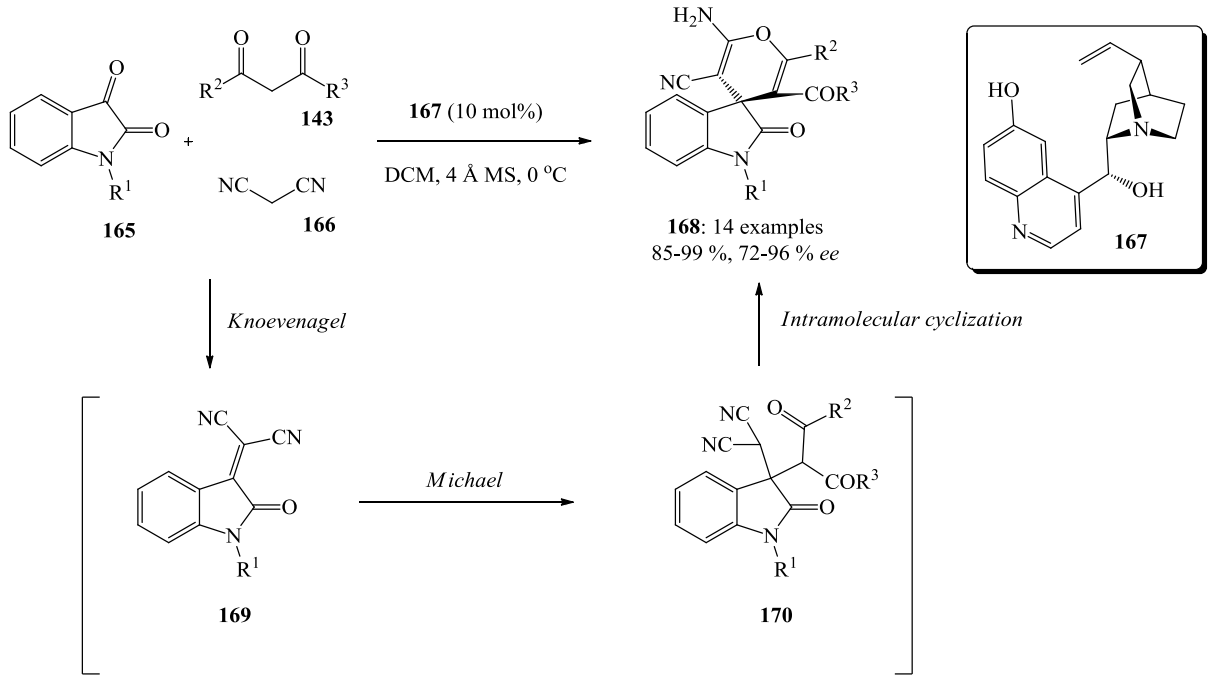
An efficient access to highly functionalized 2*H*-chromenes (**162**, X = O), 2*H*-thiochromenes (**162**, X = S) and 1,2-dihydronaphthalenes (**162**, X = CH_2) was developed by Xiao and co-workers (Scheme 25).[84]



Scheme 25. Synthesis of 2*H*-chromenes **162** (X = O), 2*H*-thiochromenes **162** (X = S) and 1,2-dihydronaphtha-lenes **162** (X = CH_2) through aza-Michael/Michael/retro aza-Michael domino sequence.

For this approach involving domino aza-Michael/Michael/retro aza-Michael sequence, benzyl *tert*-butoxycarbonyloxycarbamate **160** was exploited as the nucleophile promoter due to its ability to initiate a reversable aza-Michael addition reaction (Scheme 25). The authors utilized acrylate linked nitroolefin substrates **159** with the consideration that the nitroalkene moiety is more reactive than the α,β-unsaturated ester motif and thus the chemoselectivity of the process would not be influenced. Indeed, no side products were observed and the desired compounds **162** were achieved with excellent yield and enantioselectivity. Furthermore, the domino products were easily further converted into biologically and pharmaceutically valuable structures through simple transformations.

A domino Knoevenagel/Michael/cyclization sequence for the synthesis of heterocyclic spiroindoles **168** was developed by Yuan and co-workers (Scheme 26).[85] The reaction between isatin **165**, malononitrile **166** and 1,3-diketones **143** in the presence of cupreine **167** as a catalyst affords the desired products in very high yields and selectivities. When 3-ketoesters or malonate derivatives were utilized instead of 1,3-diketones **143** however, the enantioselectivity of the reaction dropped drastically down to <10 % *ee*. The domino process in this case starts with a Knoevenagel condensation of isatin **165** with malononitrile **166**, affording the corresponding isatylidene malononitrile derivatives **169**. Next, a Michael addition between dicarbonyl compound **143** and **169**, catalyzed by cupreine **167**, takes place. Finally, the intramolecular cycloaddition, involving the activated by the catalyst *CN*-group as the electrophile, proceeds to furnish the final spirocyclic compound **168**.

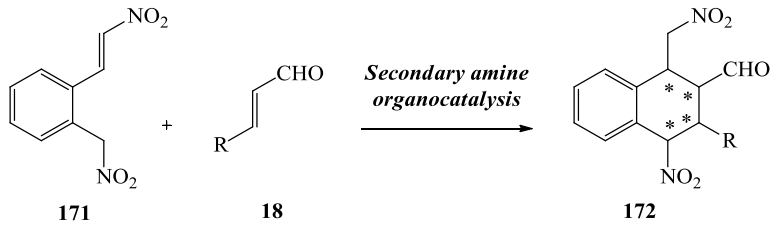


Scheme 26. Triple domino reaction for the synthesis of heterocyclic spiroindoles **168**.

2. Objectives

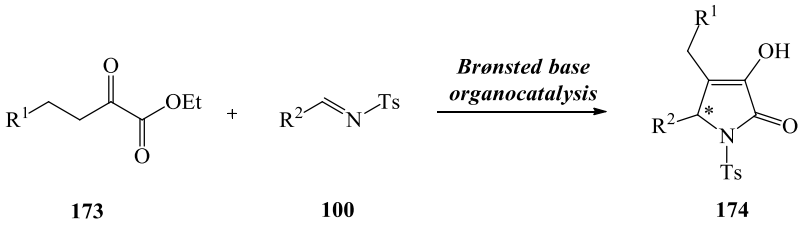
The present work can be divided into four projects.

The first project involves the development of a new Michael/Michael domino reaction for the synthesis of polysubstituted 1,2,3,4-tetrahydronaphthalenes **172** (Scheme 27). Such compounds should be obtained through a reaction of α,β-unsaturated aldehydes **18** and 2-(nitromethyl)nitrostyrene **171** under conditions of secondary amine organocatalysis.



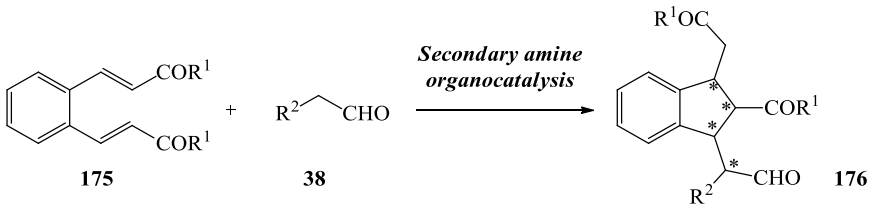
Scheme 27. Asymmetric synthesis of 1,2,3,4-tetrahydronaphthalenes **172** *via* Michael/ Michael domino reaction.

The second project includes the domino Mannich/cyclization sequence between α-ketoesters **173** and tosylimines **100** (Scheme 28). As a result of this process 4,5-disubstituted 3-hydroxy-1*H*-pyrrol-2(5H)-ones **174** should be obtained. The reaction is promoted by a Brønsted base organocatalyst.



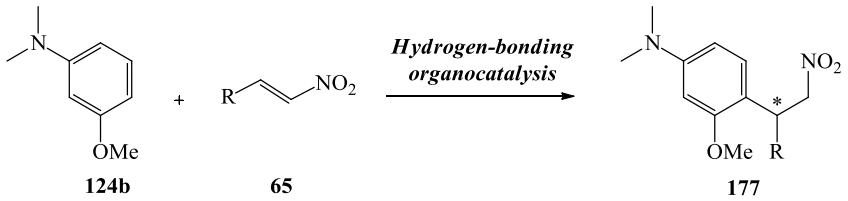
Scheme 28. Asymmetric synthesis of 4,5-disubstituted 3-hydroxy-1*H*-pyrrol-2(5H)-ones **174** through Mannich/cyclization domino reaction.

Next, the reaction between the *o*-divinylketone **175** and linear aldehydes **38** should be investigated. The Michael/Michael domino reaction for the construction of 1,2,3-polysubstituted indane **176** is promoted by secondary amine organocatalysts.



Scheme 29. Asymmetric synthesis of indanes **176** *via* Michael/Michael domino reaction.

In the last project, a study of the enantioselective organocatalytic Friedel-Crafts-type Michael addition of electron-rich alkenes **124b** to nitroolefins **65** was planned (Scheme 30). The reaction should be facilitated by bifunctional hydrogen-bonding catalysts.



Scheme 30. Enantioselective Friedel-Crafts-type Michael addition between anilines **124b** and nitroalkenes **65**.

3. Results and discussion

3.1. Asymmetric synthesis of 1,2,3,4-tetrahydronaphthalenes *via* Michael/Michael domino reaction

The 1,2,3,4-tetrahydronaphthalene moiety (also known as tetralin) is a structural unit of many natural compounds possessing various biological activities. In Figure 3 are presented some prominent examples.

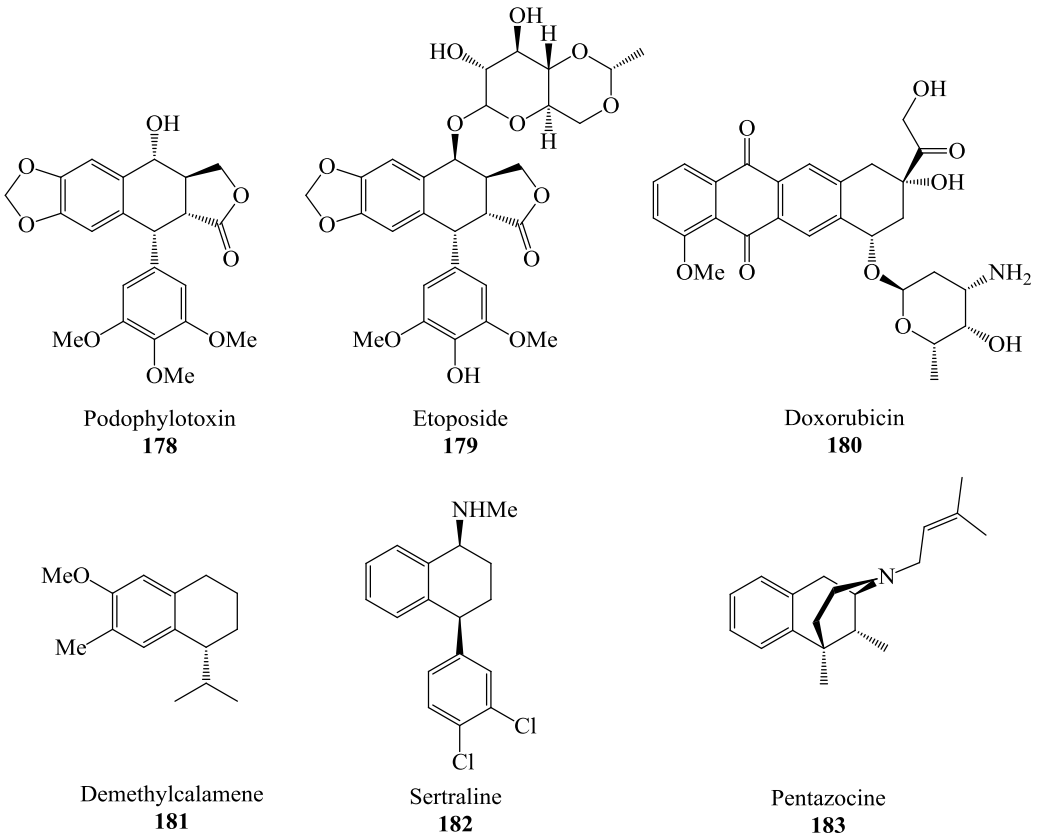


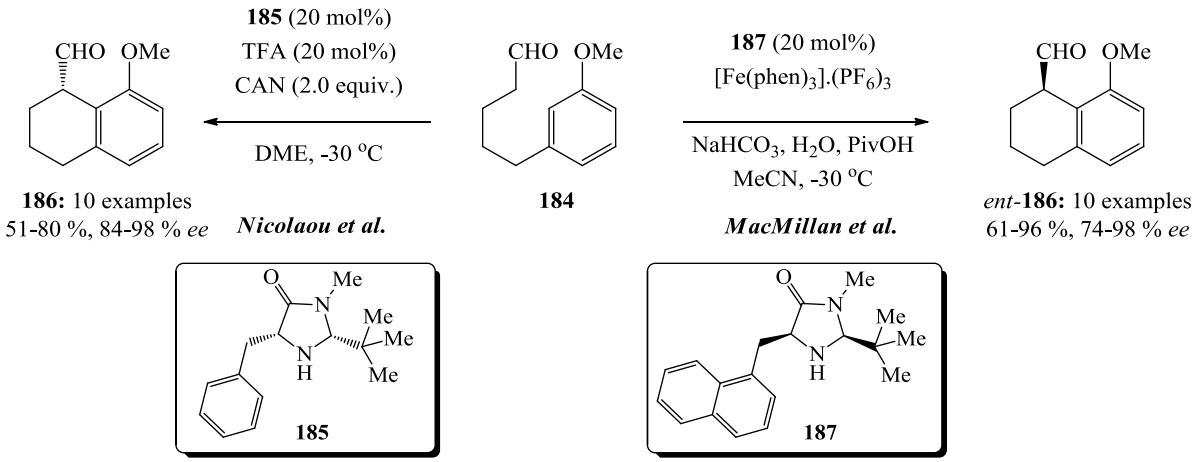
Figure 3. Some examples of bioactive compounds containing the tetrahydronaphthalene core.

Podophylotoxin **178** is a non-alkaloid toxic lignan extracted from the roots and rhizomes of *Podophyllum* species and it is the active compound in ointments for the topical treatment of some types of warts.[86] Its non-toxic derivative Etoposide **179** was synthesized in 1966 and since then its biological activity has been extendedly studied.[87] Etoposide **179** itself as well as its derivatives display high anticancer activity and is used in various chemotherapies, including lung cancer, lymphomas and genital tumors. Another anticancer agent containing tetralin architecture is Doxorubicin **180**.[88] It is often used in combination chemotherapy as a component of various chemotherapy regiments and it is sold under a number of different brand names (*Rubex*, *Adriamycin RDF*, *Doxil*, etc.). In 1979 Bohlmann *et al.* isolated the compound Demethylcalamene **181** from *Heterotheca grandiflora*, which shows great potential against Adenocarcinoma.[89] Sertraline **182** (trade names *Zoloft*, *Lustral*) on the other

hand is an antidepressant of the selective serotonin reuptake inhibitor class, prescribed for major depressive disorder as well as obsessive-compulsive disorder, panic and social anxiety.[90] Pentazocine **183** is a synthetically prepared opioid analgesic drug used to treat moderate to severe pain.[91] It is as well tolerated as morphine, but is free of any significant addiction liability.

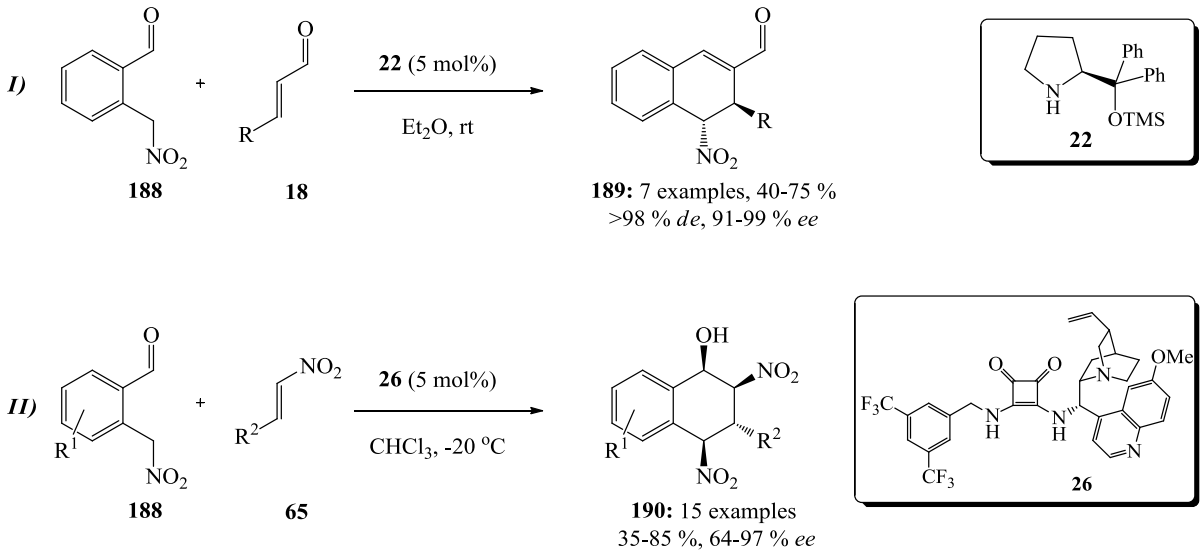
The wide range of biological activities and the great potential of compounds including a tetralin structure core have attracted the interest of many chemists over the years and as a result various synthetic methods for achieving such structures in an asymmetric fashion have been developed.[92]

An organocatalytic approach to 1,2,3,4-tetrahydronaphthalenes-1-carbaldehyde **186** was developed simultaneously by Nicolaou[93] and MacMillan[94] in 2009 (Scheme 31). Both groups independently described the enantioselective intramolecular Friedel-Crafts-type α-arylation of aldehydes *via* organo-SOMO catalysis.



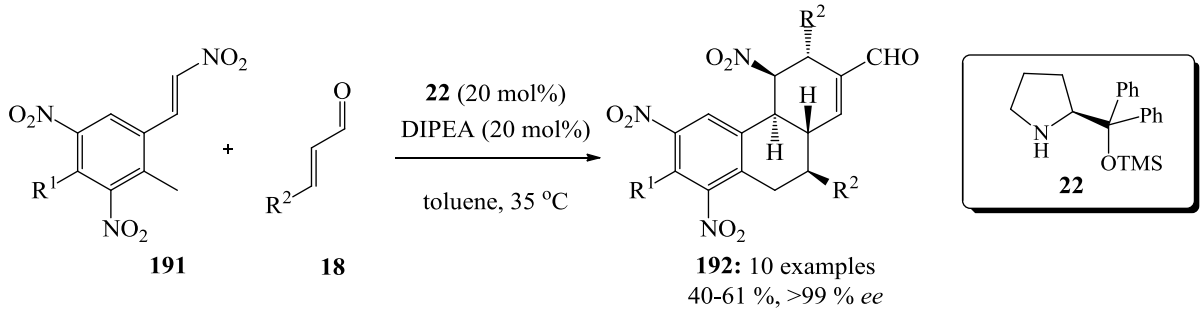
Scheme 31. Friedel-Crafts-type α-arylation of aldehydes **184** *via* organo-SOMO catalysis.

In the same year a domino Michael/Aldol condensation sequence for the synthesis of polysubstituted 3,4-dihydronaphthalenes **189** was developed in our group (Scheme 32, Eqn I).[95] The reaction between 2-(nitromethyl)benzaldehyde **188** and α,β-unsaturated aldehydes **18** is efficiently catalyzed by TMS-protected diphenylprolinol **22** to afford the corresponding products in good yields and excellent stereoselectivities. Later, the process was expanded to include the reaction between the substrate **188** with nitroalkenes **65** under hydrogen-bond catalysis (Scheme 32, Eqn II).[96] In this case elimination of water was avoided and the domino Michael/Henry reaction afforded the 1,2,3,4-tetrahydronaphthalene products **190** bearing four contiguous stereogenic centers.



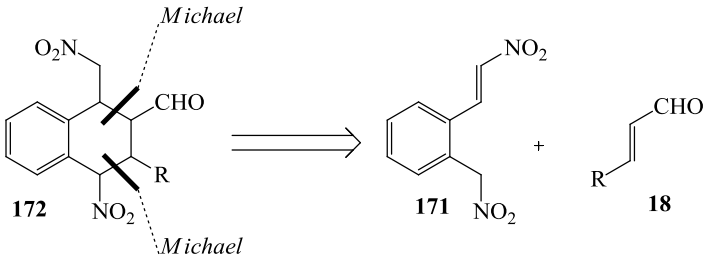
Scheme 32. Organocatalytic domino approach towards polysubstituted tetralins.

In 2014 Hong and co-workers utilized a similar substrate **191** for the synthesis of hexahydrophenanthrene structures **192** through a quadruple domino reaction (Scheme 33).[97] The authours envisioned that by introducing electron-withdrawing groups (two nitro groups) on the aromatic ring, the methyl group of the toluenyl moiety would be activated. Indeed, the toluene derivative **191** could be deprotonated by a weak base and could serve as an effective phenylogous nucleophile for the desired conjugate addition. The highly substituted hexahydrophenanthrenes **192** were obtained with excellent diastereo- (>20:1) and enantioselectivities (>99 % *ee*).



Scheme 33. Quadruple domino Michael/Michael/Michael/Aldol sequence for the synthesis of hexahydrophenanthrenes **192**.

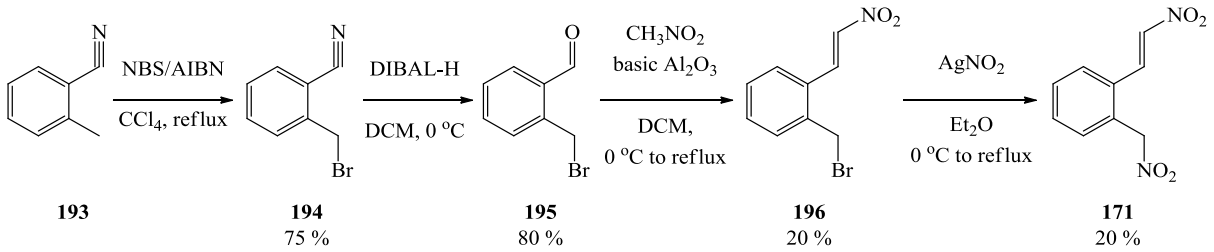
To expand the organocatalytic domino approach towards 1,2,3,4-tetrahydronaphthalene products developed in our group and presented already in Scheme 32, it was envisioned that tetralin structures of type **172** could be obtained through domino Michael/Michael sequence starting from 2-(nitromethyl)nitrostyrene **171** and α,β-unsaturated aldehydes **18** in conditions of secondary amine catalysis (Scheme 34).



Scheme 34. Retrosynthetic analysis of 1,2,3,4-tetrahydronaphthalenes **172**.

3.1.1. Synthesis of the starting materials

2-(Nitromethyl)nitrostyrene **171** could be obtained through the synthetic pathway presented in Scheme 35.



Scheme 35. Synthesis of 2-(nitromethyl)nitrostyrene **171**.

The first step is a bromination at the benzylic position of the commercially available *o*-tolunitrile **193**. Following the general conditions for the reaction with *N*-bromosuccinimide (NBS), 2-(bromomethyl)benzonitrile **194** was obtained in 75 % yield.

The next step includes the reduction of the nitrile group to an aldehyde.[98] Reduction with DIBAL-H and a subsequent acidic workup afforded the aldehyde **195** in good yield.

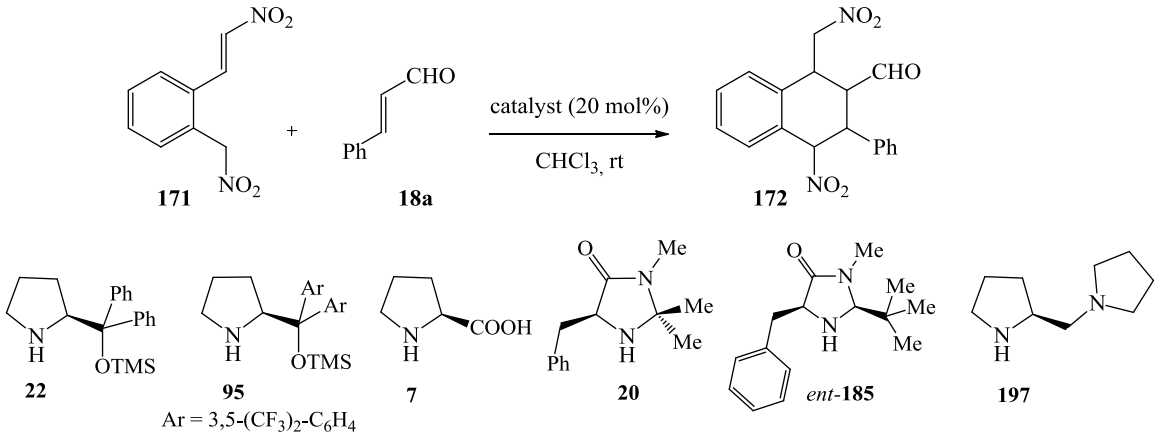
Due to certain instability of the aldehyde **195**, a mild procedure for the synthesis of the nitrostyrene **196** was required. The most common procedures for the synthesis of nitrostyrenes, involving strong basic or acidic conditions, resulted in decomposition of the starting material. However, the nitrostyrene **196** could be obtained through a reaction in the presence of basic alumina, albeit with low yields (20 %).[99]

At last, a substitution of the bromine atom at the benzylic position with a nitro group afforded the desired 2-(nitromethyl)nitrostyrene **171**. Unfortunately, this last step proceeds with low yield as well (20 %).

3.1.2. Optimization of the conditions of the domino reaction

First, a series of secondary amine organocatalysts were screened to determine which would effectively promote the domino reaction. The investigation was performed with 2-(nitromethyl)nitrostyrene **171**, cinnamaldehyde **18a** and 20 mol% of the coresponding catalyst in chloroform as solvent. With common catalysts as (*S*)-Proline **7** and the imidazolidinone catalysts **20** and *ent*-**185**, as well as with Jørgensen catalyst **95**, only traces of the product were observed (Table 1, entries 2-5). Catalyst **197** bearing a basic moiety afforded the desired product, although in low yield (Table 1, entry 6). The best catalyst for this reaction proved to be TMS-protected diphenylprolinol **22** (Table 1, entry 1), providing the product **172** in 63 % yield.

Table 1. Catalyst screening



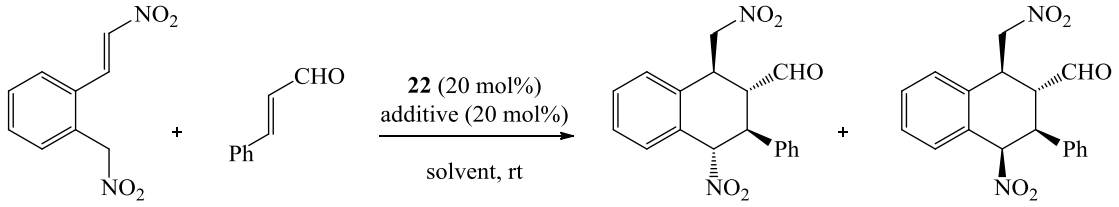
Entry[a]	Catalyst	Time [d]	Yield [%][b]	*dr*[c]
1	**22**	2	63	2:1
2	**95**	3	traces	-
3	**7**	3	traces	-
4	**20**	3	Traces	-
5	**185**	3	Traces	-
6	**197**	3	20	-

a) All reactions were performed on 0.5 mmol scale with 1.0 equiv. **171**, 1.0 equiv. **18a** and 0.2 equiv. catalyst in 1 mL of solvent at room temperature. b) Yield of isolated product **172** after flash column chromatography. c) Determined by ^{1}H-NMR of the crude product.

With the optimal catalyst determined, we proceeded to screen different solvents for the domino reaction. As previously mentioned, performing the reaction in chloroform afforded the desired tetralin **172** after 2 days with 63 % yield (table 2, entry 1). The product was acquired as two diastereomers in ratio 2:1. Comparable yield and selectivity were obtained in toluene, however longer reaction time was necessary for the reaction – 4 days (Table 2, entry 2). Performing the reaction in THF resulted in decreasing the yield (Table 2, entry 3), while with diethyl ether as a solvent the diastereomeric ratio was reduced to 1:1 (Table 2, entry 4).

In common solvents as MeOH, DCM, DMF and acetonitrile no product could be isolated due to its instability in these conditions (Table 2, entries 5-8). Considering the relative instability of the product **172**, the reaction was tested in dry solvent under argon atmosphere as well (Table 2, entry 9). However, there was no significant improvement of the outcome of the reaction. Decreasing the temperature to 0 °C on the other hand, resulted in slowing down the process and even after prolonged reaction time the yield was just 35 % (Table 2, entry 10). Further trials to improve the result of the domino sequence by applying basic or acidic additives (Table 2, entries 11-14) and by varying the ratio of the starting materials turned out to be inefficient.

Table 2. Optimisation of the conditions



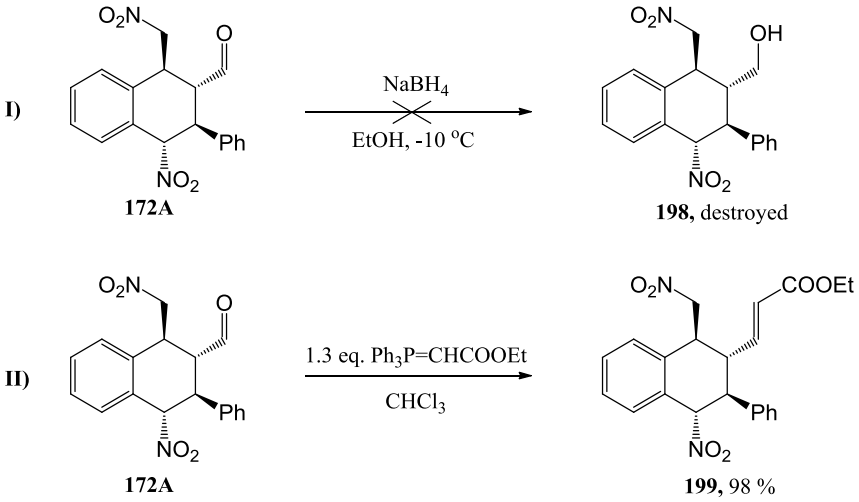
171 **18a** **172A** **172B**

Entry[a]	Solvent	Additive	Time [d]	Yield [%][b]	*dr*[c] (**172A:172B**)	*ee* [%][d]
1	$CHCl_3$	-	2	63	2:1	n.d.
2	Toluene	-	4	60	2:1	n.d.
3	THF	-	4	50	2:1	n.d.
4	Et_2O	-	4	58	1:1	n.d.
5	MeOH	-	2	decomposed[g]	-	n.d.
6	DCM	-	2	decomposed[g]	-	n.d.
7	DMF	-	2	decomposed[g]	-	n.d.
8	MeCN	-	2	decomposed[g]	-	n.d.
9	$CHCl_3$ (dry)[e]	-	2	65	2:1	n.d.
10	$CHCl_3$ (at 0 °C)[f]	-	3	35	2:1	n.d.
11	$CHCl_3$	PhCOOH	2	59	n.d.	n.d.
12	$CHCl_3$	AcOH	1	decomposed[g]	n.d.	n.d.
13	$CHCl_3$	Et_3N	2	55	n.d.	n.d.
14	$CHCl_3$	NaOAc	2	57	n.d.	n.d.

a) Unless otherwise indicated, all reactions were performed on 0.5 mmol scale with 1.0 equiv. **171**, 1.0 equiv. **18a** and 0.2 equiv. catalyst in 1 mL of solvent at room temperature. b) Yield of isolated product **172** after flash column chromatography. c) Determined by ^{1}H-NMR of the crude product. d) Determined by HPLC on a chiral stationary phase. e) Reaction performed in dry solvent and in argon atmosphere. f) Reaction was performed at 0 °C. g) Based on the NMR spectrum of the crude product. n.d. = not determined

The instability of product **172** turned out to be problematic for determining the enantioselective excess as well. In the conditions of chiral HPLC and GC, the tetralin product was immediately destroyed. To overcome this problem, an attempt for increasing the stability

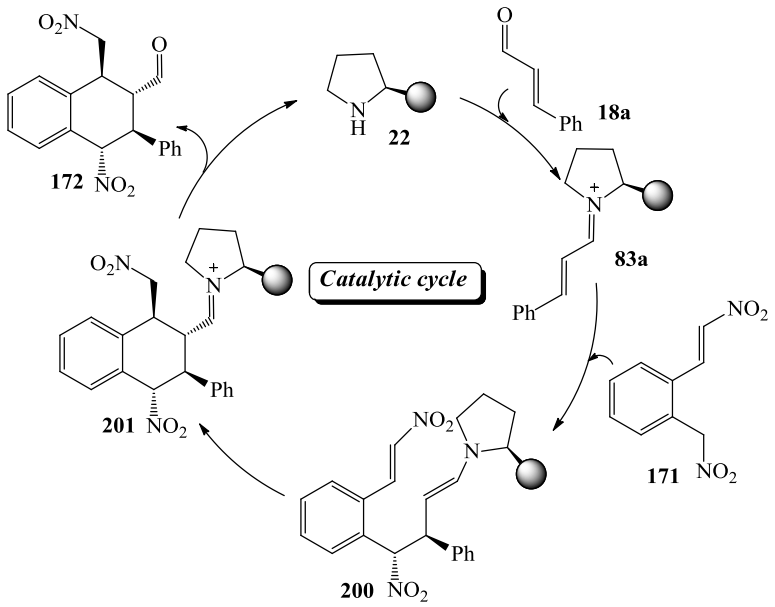
of the product by derivatization was made. However, trials to reduce the aldehyde group to alcohol **198** resulted in the decomposition of compound **172** after just 5 min (Scheme 36, Eqn I). Performing a Wittig reaction to the corresponding α,β-unsaturated ester **199** proceeded with quantitative yield (Scheme 36, Eqn II), however, compound **199** was still not stable enough and any attempts for measuring the enantioselective excess were unsuccessful.



Scheme 36. Derivatization of the tetralin product **172**.

3.1.3. Proposed mechanism of the domino reaction

In the first step cinnamaldehyde **18a** is activated by the catalyst **22** through formation of the corresponding iminium ion **83a** (Scheme 37). This is a suitable acceptor for the first Michael reaction and a conjugate addition of substrate **171** to **83a** takes place. As a result the enamine **200** is formed, which then undergoes intramolecular Michael addition to the nitroalkene part of the molecule. After hydrolysis of **201**, the tetralin product **172** is formed and the catalyst is regenerated.



Scheme 37. Proposed mechanism of the domino reaction.

The relative configuration of both diastereomers was determined by the values of the coupling constants between the protons in the NMR spectra (Figure 4). In diastereomer **172A** all substituents are in *trans*-position to each other, while for diastereomer **172B** the coupling constants indicate *trans*-position for H_a-H_b and H_b-H_c but *cis* for H_c-H_d. According to the obtained results in other (*S*)-diphenylprolinol TMS-ether [(*S*)-**22**] catalyzed Michael additions to enals under iminium activation [95], the absolute configuration of the C-3 stereogenic center was always assigned to be *R*. Based on these results, the absolute configuration of the 1,2,3,4-tetrahydronaphthalenes **172** was assigned to be 1*S*,2*S*,3*R*,4*S* for the major diastereomer **172A** and 1*S*,2*S*,3*R*,4*R* for the minor diastereomer **172B**.

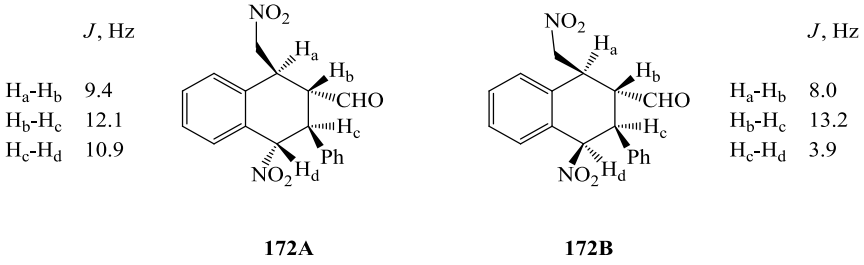


Figure 4. Relative and absolute configuration of the two diastereomers **172A** and **172B** of the tetralin product.

3.1.4. Modification of the 2-(nitromethyl)nitrostyrene substrate

The inability to measure the enantiomeric excess of the product due to its instability turned out to be a major setback for this project. Another significant drawback of the method was the low diastereoselectivity of the reaction. Furthermore, the two obtained diastereomers could not be separated by conventional techniques. However, the biggest problem remained the low efficiency of the synthetic pathway for achieving 2-(nitromethyl)nitrostyrene **171**. The synthesis of substrate **171** (described previously in Section 3.1.1, Scheme 35) includes four steps over 7-8 days with an overall yield of only 2.5 %. This time- and mostly effort-consuming synthesis deterred the attention from the main aim of the project, namely further optimization of the domino reaction for overcoming the other existent setbacks.

In an attempt to find a solution for the mentioned drawbacks, it was envisioned that a modification of substrate **171** to compounds **202-205** would afford products with the same tetralin scaffold in the conditions of the domino reaction (Figure 5). Moreover, substrates **202-205** could be synthesized through a shorter, more efficient pathway, thus allowing the focus to be set on the cascade reaction itself.

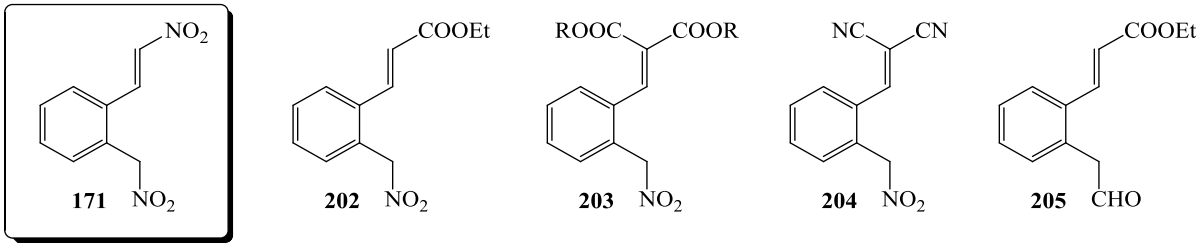
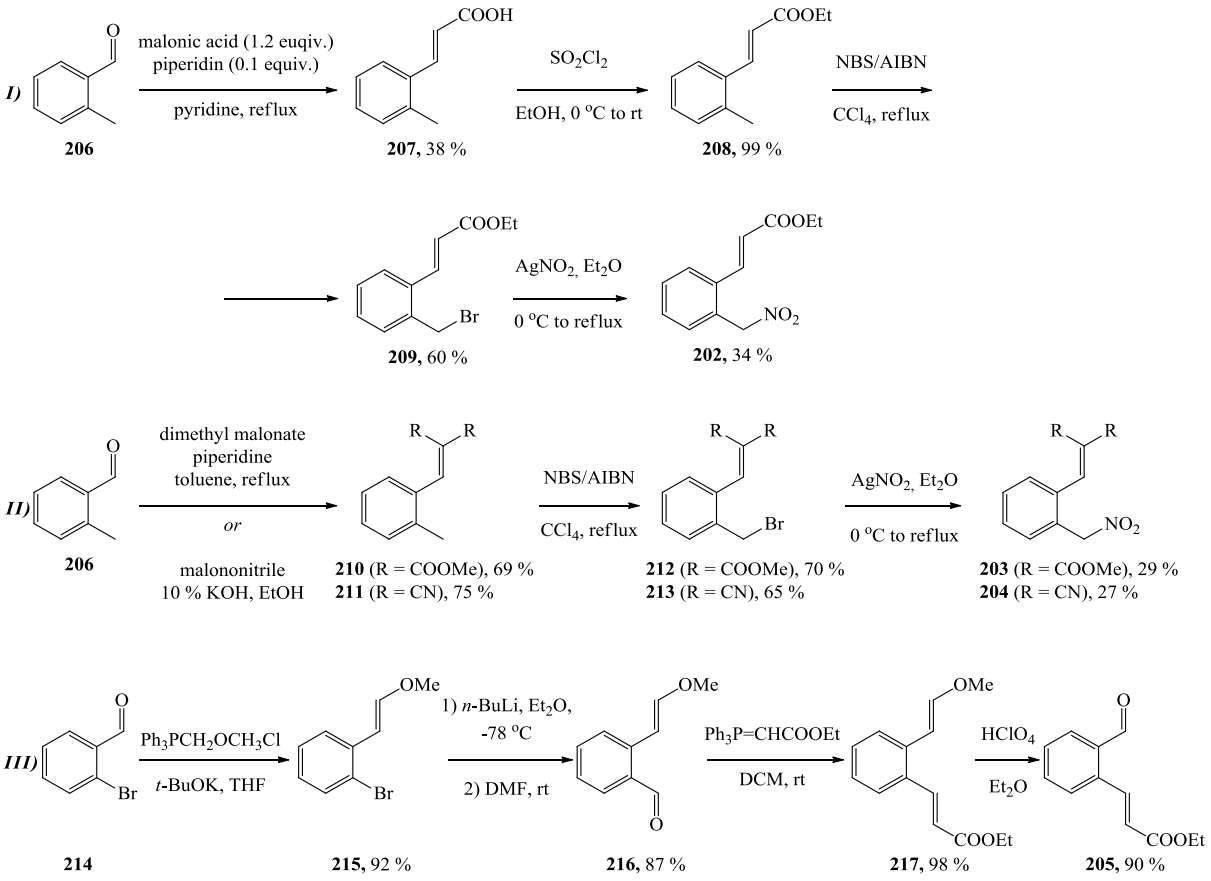


Figure 5. Analogues to 2-(nitromethyl)nitrostyrene **171**.

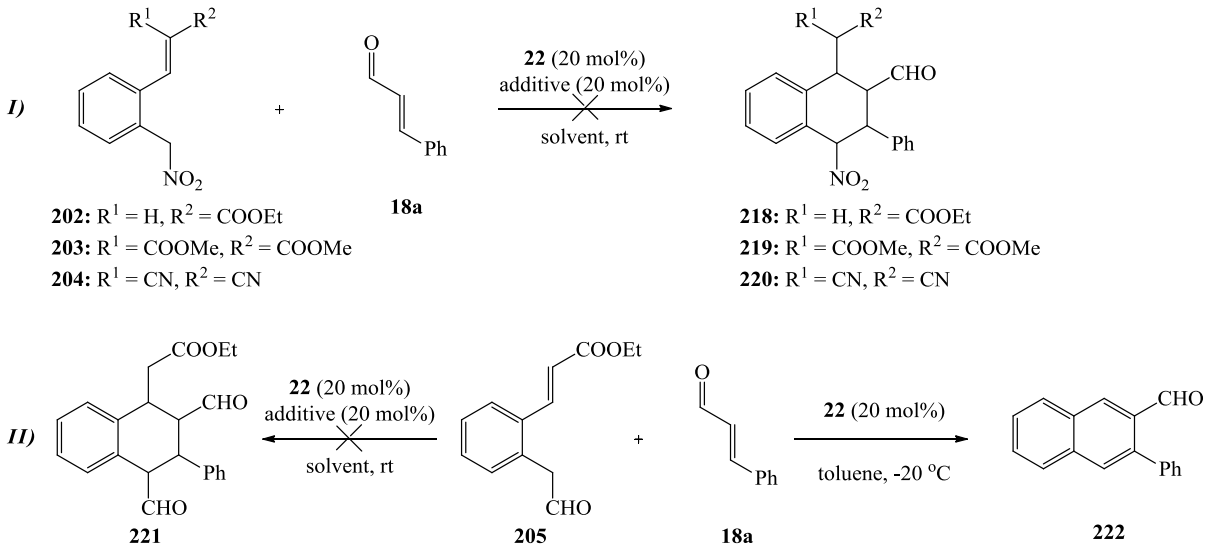
The synthesis of substrates **202-205** is presented in Scheme 38. For compounds **202-204** (Scheme 38, Eqn I and II), the first step is a Knoevenagel condensation for building the corresponding α,β-unsaturated moiety starting from 2-methylbenzaldehyde **206**. Next, bromination with NBS at benzylic position takes place. The last step involves substitution of the bromine atom to nitro group, affording the desired compounds **202-204**. The synthesis of compound **205** starts from 2-bromobenzaldehyde **214** (Scheme 38, Eqn III). After a Wittig reaction to intermediate **215**, a formylation reaction affords the aldehyde **216**, which can be subsequently transformed to the α,β-unsaturated ester **217**. At last, reaction with $HClO_4$ cleaves the methyl ether, furnishing the aimed compound **205** after tautomerisation.



Scheme 38. Synthesis of substrates **202-205**.

With substrates **202-205** in hand, domino Michel/Michael reactions with cinnamaldehyde **18a** in the presence of TMS-protected diphenylprolinol **22** as a catalyst were carried out (Scheme 39, Eqn I and II). For each case, the cascade sequence was performed in different solvents – chloroform, toluene, ether and methanol. Basic (Et_3N, NaOAc) and acidic (PhCOOH, AcOH) additives were tested as well. However, no reactions took place and none of the desired tetralin products **218-221** could be obtained. Furthermore, in the case of substrate **205** (Scheme 39, Eqn II), a reaction affording the fully aromatized product **222** was observed. Any attempts to avoid the aromatization turned out to be inefficient, even when the temperature was decreased to -20 °C.

Considering the previously mentioned drawbacks of the domino reaction between 2-(nitromethyl)nitrostyrene **171** and α,β-unsaturated aldehydes as well as the unsuccessful trials aiming the development of new domino reactions for the construction of 1,2,3,4-tetrahydronaphthalenes, the project was terminated.

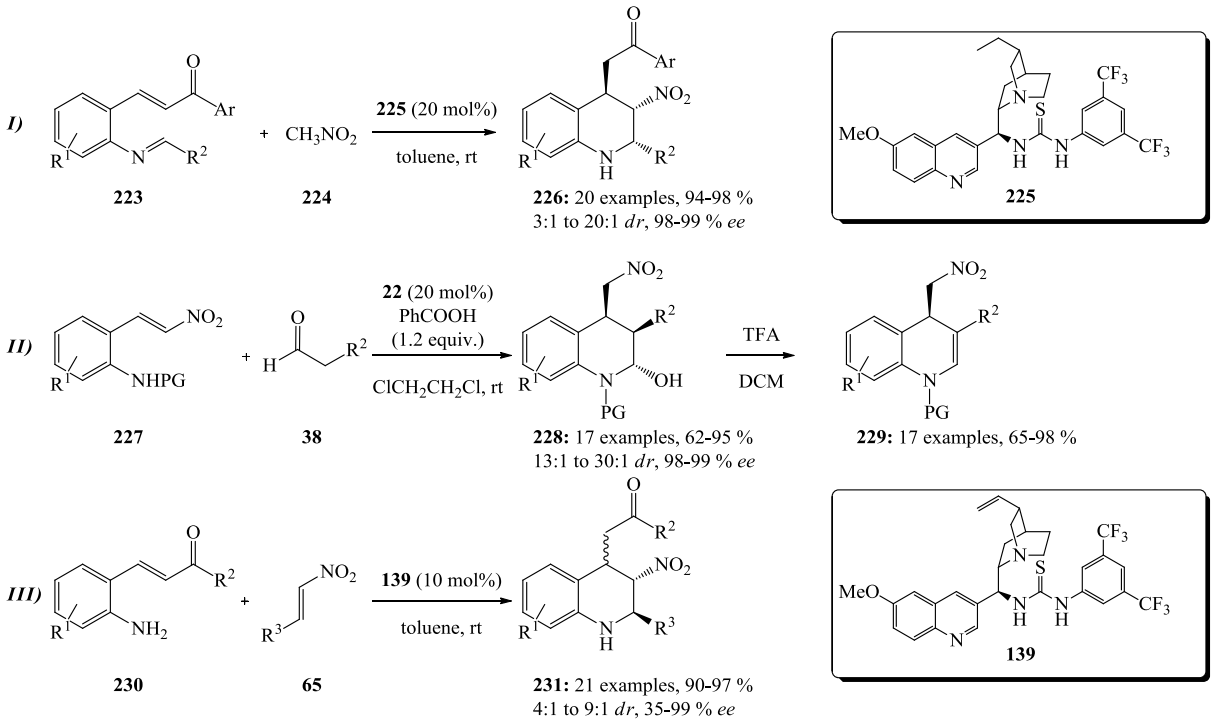


Scheme 39. Attempt towards the synthesis of tetralin products **218-221** *via* Michael/Michael domino sequence.

3.1.5. Expanding the domino process for the construction of tetrahydroquinolines

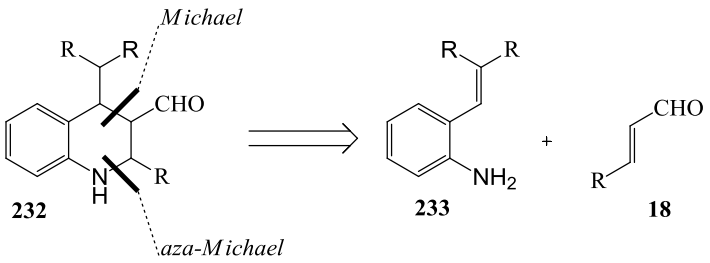
The tetrahydroquinoline skeleton is an important structural unit found in many biologically active natural compounds and synthetic pharmaceutical preparations. In fact, tetrahydroquinoline derivatives display a broad range of biological, medicinal and pharmacological properties and are constituents of bradykinin antagonists[100], antiallergic agents[101], antitumor agents[102], NMDA receptor antagonists[103] and antithrombotic agents.[104]

In 2011 Xu and co-workers reported a highly enantioselective chiral bifunctional thiourea catalyzed asymmetric tandem Michael/aza-Henry reaction for the synthesis of substituted tetrahydroquinolines **226** in excellent yields and selectivities (Scheme 40, Eqn I).[105] The reaction between chalcones **223** and nitromethane **224** affords the corresponding products **226**, which are the *cis*-isomers at the 2,3-position. Later, in order to further explore the synthesis of quinolines with diverse stereochemical features, the same group developed a domino aza-Michael/Michael sequence, achieving the *trans*-isomers **231** at the 2,3-position (Scheme 40, Eqn III).[106] A different approach towards quinolines was reported by Kim and co-workers (Scheme 40, Eqn II).[107] Starting from 2-(amino)nitrostyrenes **227** and linear aldehydes **38** in conditions of secondary amine organocatalysis, tetrahydroquinolines **228** are obtained in a highly stereoselective manner *via* Michael/aza-cyclization cascade reaction. Furthermore, this method provides an alternative access to chiral 1,4-dihydroquinolines **229**, which are challenging to synthesize by other methodologies.



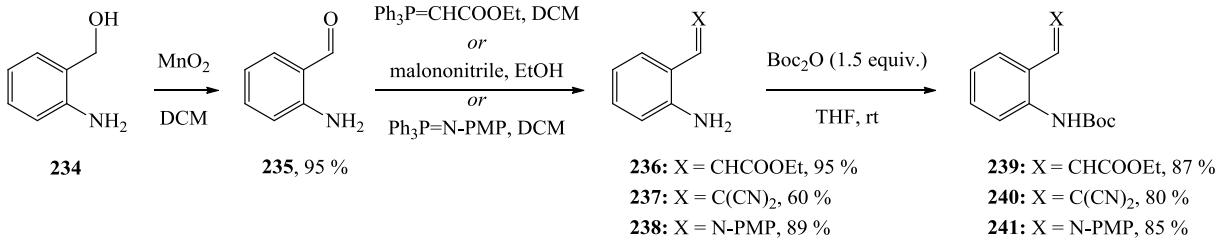
Scheme 40. Some prominent examples for the synthesis of tetrahydroquinolines *via* organocatalytic domino reactions.

It was envisioned that the tetrahydroquinoline scaffold **232** could be obtained through domino aza-Michael/Michael sequence starting from anilines **233** bearing unsaturated moiety and α,β-unsaturated aldehydes **18** in conditions of secondary amine catalysis (Scheme 41).



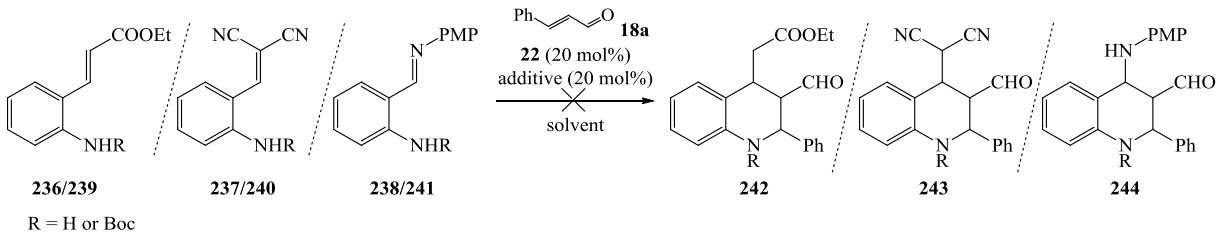
Scheme 41. Retrosynthetic analysis of tetrahydroquinolines **232**.

For the purpose of developing a domino aza-Michael/Michael reaction, first, different appropriate substrates bearing an amino group (donor for the first aza-Michael addition) and an unsaturated moiety (acceptor for the second Michael addition) were synthesized (Scheme 42). 2-Aminobenzaldehyde **235** was obtained from 2-aminobenzylalcohol **234** through an oxidation reaction with manganese (IV) oxide. Subsequent Wittig, Knoevenagel or aza-Wittig reaction afforded substrates **236-238**. Further protection of the amino group was carried out and as a result compounds **239-241** were obtained.



Scheme 42. Synthesis of substrates **236-241**.

With substrates **236-241** in hand, domino aza-Michel/Michael reactions with cinnamaldehyde **18a** in the presence of TMS-protected diphenylprolinol **22** as a catalyst were carried out (Scheme 43). For each case, the cascade sequence was performed in different solvents – chloroform, toluene, ether and methanol. Basic (Et_3N, NaOAc) and acidic (PhCOOH) additives were tested as well. However, no reactions took place and none of the desired tetraquinoline products **242-244** could be obtained.



Scheme 43. Attempts for the development of a domino aza-Michael/Michael sequence for the synthesis of tetrahydroquinolines.

Considering the unsuccessful trials aiming the development of new domino reactions for the construction of tetrahydroquinolines, the project was terminated.

3.2. Asymmetric synthesis of 4,5-disubstituted 3-hydroxy-1*H*-pyrrol-2(5H)-ones

The 1*H*-pyrrol-2(5H)-one core **245** is present in many pharmaceutical and natural compounds and exhibits a broad spectrum of biological activities – anti-inflammatory[108], antiviral[109], antiallergic[110], as well as antitumor.[111] Synthetic compounds bearing this scaffold display great potential for the treatment of neuronal disorders, especially Alzheimer's disease, Down syndrome and Parkinson disease.[112] Compound **246** and its derivatives were found to have potential analgesic activity[113], while compound **247** has antiamnesic activity (Figure 6).[114] The pyrrolinone **248** is a key intermediate for the synthesis of a highly functionalized pyrrolidine, which is a promising candidate for development as an antiinfluenza drug.[115] Thus the pyrrolone scaffold still remains a therapeutic target in the modern medicinal chemistry.

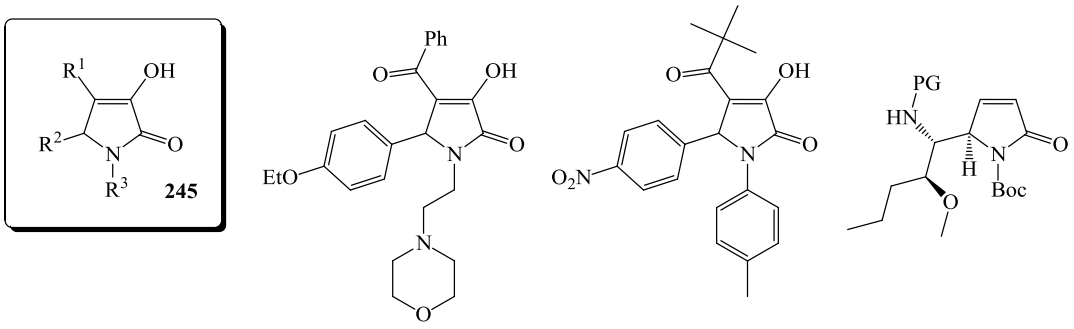
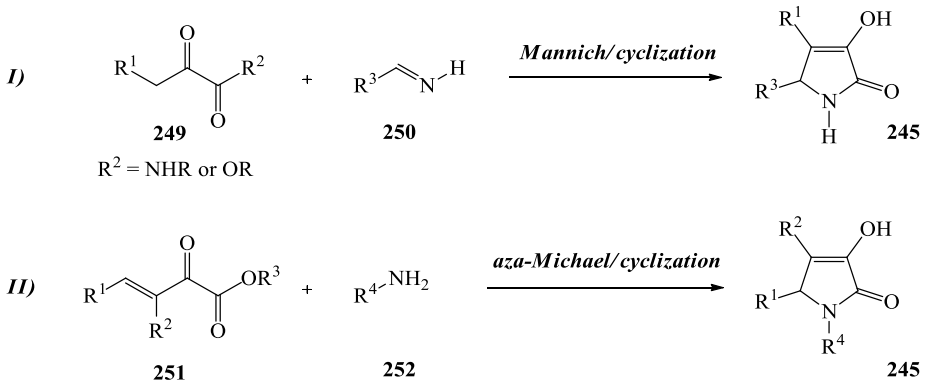


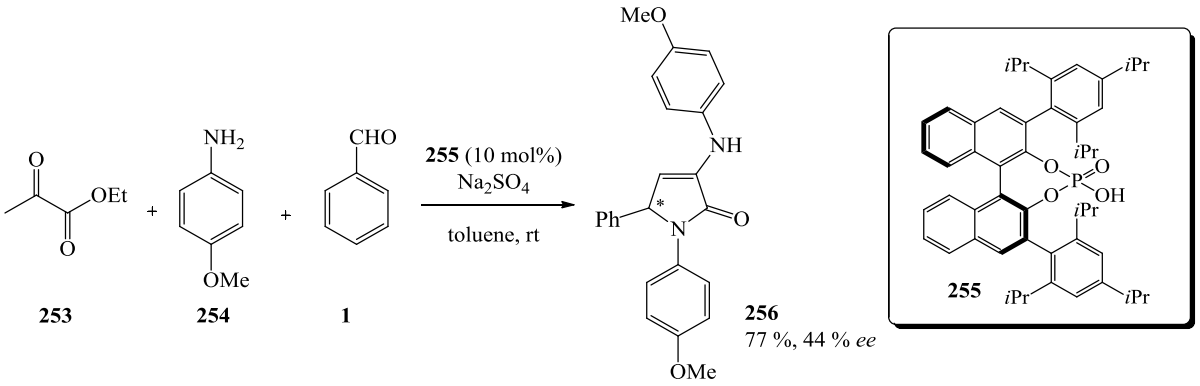
Figure 6. Some examples of biologically active pyrrolones.

Due to the wide range of biological activities and their synthetic importance as intermediates, pyrrol-2-ones **245** have been explored by a number of groups. The two general synthetic approaches for the construction of such structures are presented in Scheme 44. The first pathway involves the reaction between α-ketoesters/α-ketoamides **249** and aldimines **250** (Scheme 44, Eqn I).[116] Initially a Mannich reaction takes place, followed by an intramolecular cyclization to form the lactam ring. Alternatively, compound **245** can be synthesized *via* aza-Michael/cyclization sequence starting from β,γ-unsaturated-α-ketoesters **251** and amines **252** (Scheme 44, Eqn II).[117] In the majority of publications however, the pyrrol-2-ones **245** are obtained as racemates. For the need of enantiomerically pure products, methodologies for the kinetic resolution of the racemic mixtures have been developed.[118]



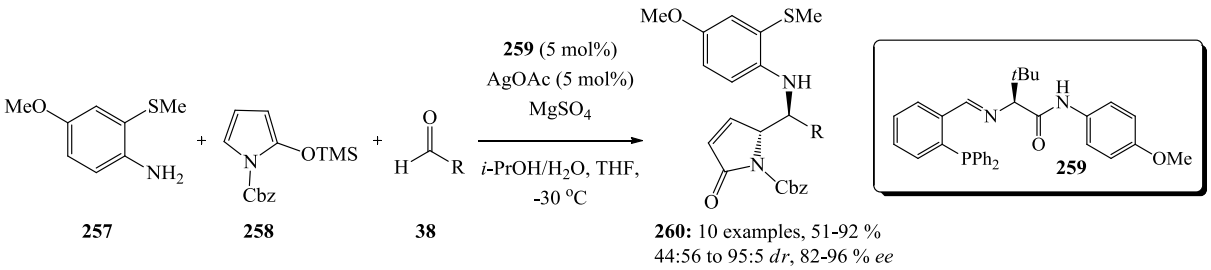
Scheme 44. General synthetic approaches towards pyrrol-2-ones **245**.

An asymmetric version for the construction of the 1*H*-pyrrol-2(5H)-one core through an organocatalytic three-component reaction of pyruvates, aldehydes and anilines was reported in 2008 (Scheme 45).[119] The authors explored achiral thioureas and phosphoric acids as catalysts for promoting the process, achieving the desired racemic products with high yields. With the developed protocol in hand, they briefly examined the asymmetric version of the reaction between ethyl pyruvate **253**, *p*-anisidine **254** and benzaldehyde **1**, utilizing readily available chiral thioureas and phosphoric acids. However, their efforts led to only moderate enantioselectivities – the best result of 44 % *ee* was obtained with the chiral phosphoric acid **255**, bearing the large steric bulk at the 3,3'-positions.



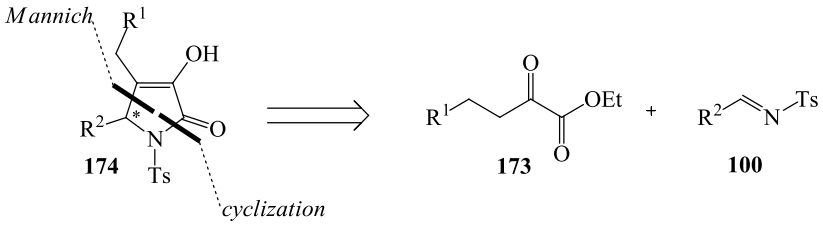
Scheme 45. First asymmetric organocatalytic reaction for the synthesis of pyrrol-2-ones **256**.

Although not organocatalytic, an interesting approach towards pyrrol-2-ones was developed by Zanardi and co-workers (Scheme 46).[120] An asymmetric vinylogous Mukaiyama-Mannich reaction between pyrrole-based silyl dienolates **258**, anilines **257** and aldehydes **38** affords the corresponding products **260** in a highly efficient manner. The process is successfully promoted by the combination of the Hoveyda-Snapper amino-acid based chiral ligand **259** and silver (I) catalyst.



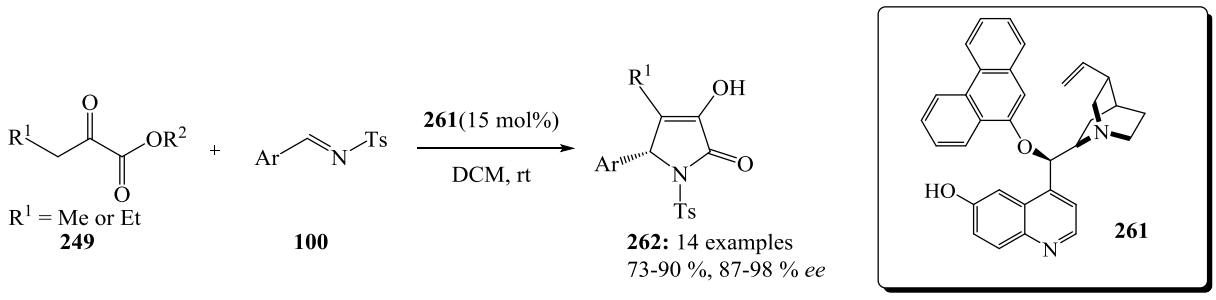
Scheme 46. Asymmetric vinylogous Mukaiyama-Mannich reaction for the synthesis of pyrrol-2-ones **260**.

Considering the significance of the pyrrol-2-one core as well as the lack of an efficient organocatalytic method for its asymmetric synthesis, it was envisioned that products **174** could be obtained through domino Mannich/cyclization sequence under conditions of bifunctional hydrogen-bonding or Brønsted base organocatalysis, starting from α-ketoesters **173** and aldimines **100** (Scheme 47).



Scheme 47. Retrosynthetic analysis of 1*H*-pyrrol-2(5H)-one **174**.

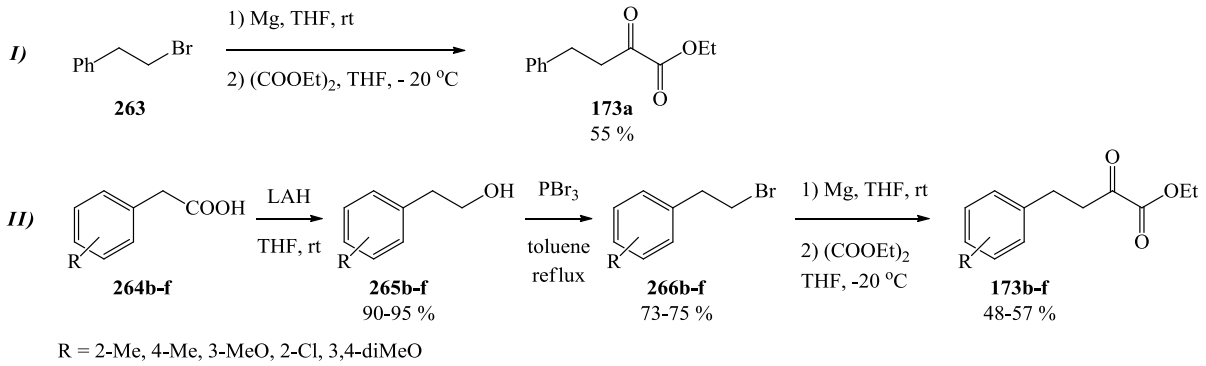
Unfortunately, while our work was still in progress, the same reaction between aliphatic α-ketoesters **249** and *N*-tosyl imines **100** in the presence of the Brønsted base catalyst **261** was published first by Li and co-workers in 2014 (Scheme 48). [121]



Scheme 48. Organocatalytic Mannich/cyclization cascade reaction for the synthesis of pyrrol-2-ones **262** catalyzed by the cinchona alkaloid catalyst **261**.

3.2.1. Synthesis of the starting materials

The α-ketoesters **173** could be achieved through the synthetic pathway presented in Scheme 49.



Scheme 49. Synthesis of α-ketoesters **173**.

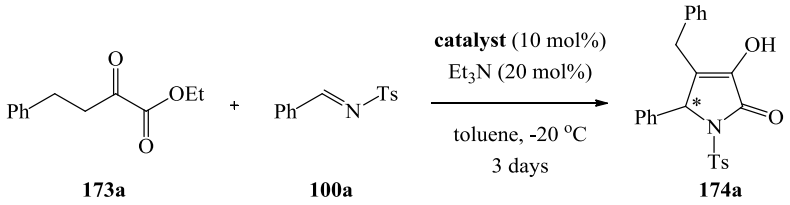
Ethyl 4-phenyl-2-oxobutanuate **173a** was obtained from the readily available 2-(bromoethyl)benzene **263** (Scheme 49, Eqn I). The alkylbromide **263** was converted to the corresponding Grignard reagent and then added to diethyl oxalate, affording the desired compound **173a** in 55 % yields.

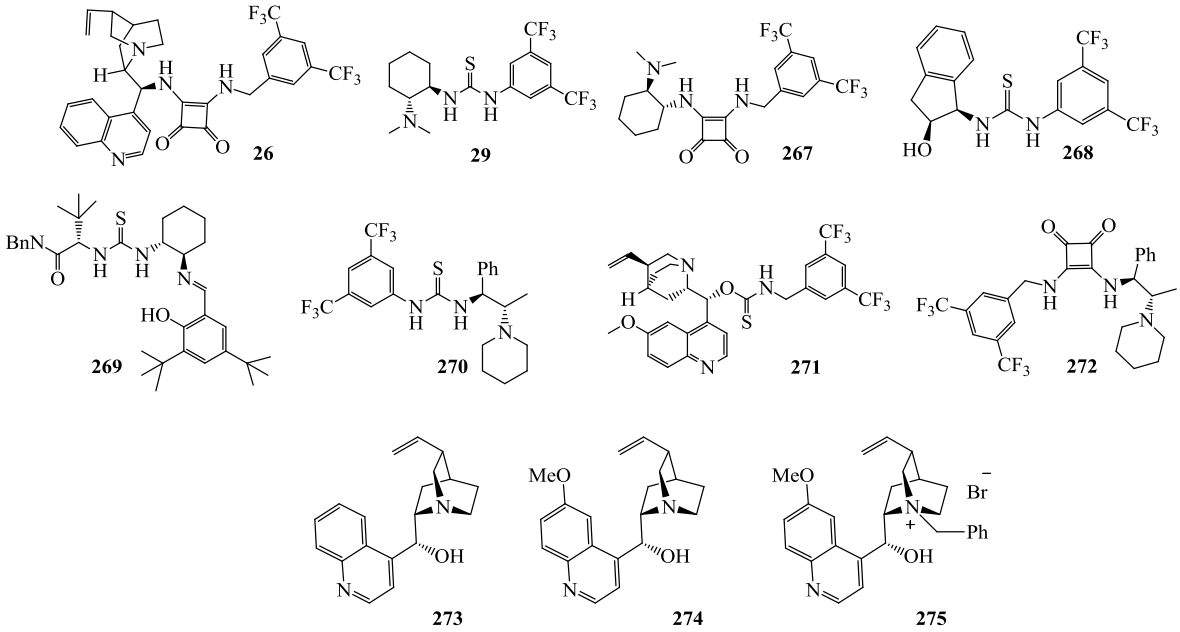
α-Ketoesters bearing a substituent on the aromatic ring were synthesized in three steps (Scheme 49, Eqn II). First, substituted phenylacetic acids **264** were reduced with LAH to the corresponding 2-phenylethanols **265**. Substitution of the hydroxyl group with bromine atom resulted in obtaining the alkylbromides **266**, which after subsequent Grignard reaction afforded the required substituted α-ketoesters **173**.

3.2.2. Optimization of the conditions for the domino Mannich/cyclization reaction

First, a series of catalysts was tested to determine the one that would efficiently catalyse the reaction. The investigation was performed with 1.0 equiv. of ethyl 4-phenyl-2-oxobutanoate **173a**, 1.5 equiv. of *N*-tosyl imine **100a**, 0.1 equiv. of the corresponding catalyst and 0.2 equiv. of Et_3N in toluene at -20 °C for 3 days (Table 3). Initially, it was envisioned that utilizing bifunctional hydrogen-bonding thiourea or squaramide catalysts would activate the imine **100a**, thus promoting the process. However, when common catalysts as **29** and **267-272** were applied, the desired product **174a** was obtained with moderate yields but in almost racemic fashion (Table 3, entries 2-8). The only hydrogen-bonding catalyst that furnished a better enantioselective outcome was catalyst **26** (Table 3, entry 1). Considering that asymmetric induction was achieved only when a catalyst bearing a cinchona alkaloid moiety was utilized, cinchonidine **273** and quinine **274** were tested in the conditions of the reaction as well (Table 3, entries 9-10). Surprisingly, with cinchonidine **273** the best result in terms of enantioselectivity was obtained – 49 % *ee*.

Table 3. Catalyst screening





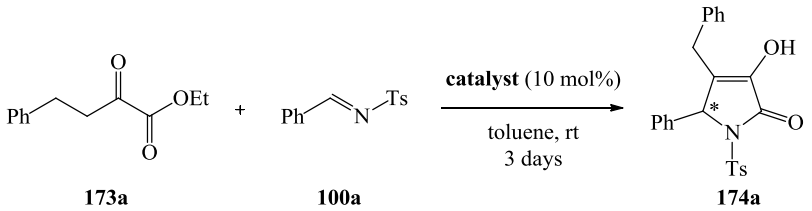
Entry[a]	1	2	3	4	5	6	7	8	9	10
Catalyst	**26**	**29**	**267**	**268**	**269**	**270**	**271**	**272**	**273**	**274**
Yield [%][b]	30	50	20	46	42	30	15	40	20	18
ee [%][c]	39	8	10	2	2	5	3	5	49	22

a) Unless otherwise indicated, all reactions were performed on 0.25 mmol scale with 1.0 equiv. **173a**, 1.5 equiv. **100a**, 0.2 equiv. Et_3N and 0.1 equiv. catalyst in 0.75 mL of toluene at -20 °C. b) Yield of isolated product **174a** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase.

The results of the catalyst screening raised the question if indeed the reaction was promoted by hydrogen-bonding activation. Generally, cinchona alkaloids are efficient Brønsted base catalysts due to the presence of a tertiary amine group in their molecules. In order to establish if the reaction was proceeding in conditions of hydrogen-bonding or Brønsted base catalysis, a small investigation of the reaction with different catalysts and with or without Et_3N as a basic additive was performed (Table 4). The test reactions were monitored by ^{1}H-NMR to determine if any conversion was observed, without any further isolation of the product. In the presence of Et_3N all reactions proceeded with furnishing product **174a**. Without a basic additive however, a reaction takes place only when cinchonidine **273** is applied as a catalyst (Table 4, entry 4). Furthermore, with catalyst **275** – quinine in which the amino group is converted to quaternary and thus there is no basic moiety present – no conversion was observed (Table 4, entry 5). Based on the results of this investigation, it could be concluded

that in fact the reaction between the α-ketoester **173a** and the imine **100a** was promoted by Brønsted base catalysis.

Table 4. Hydrogen-bonding activation *vs* Brønsted base catalysis



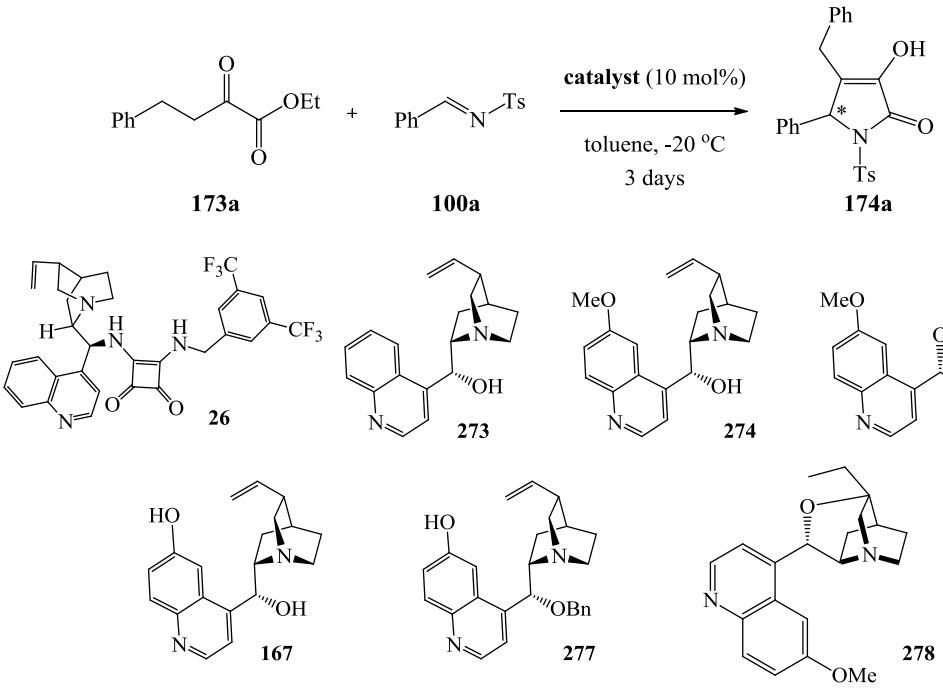
173a **100a** **174a**

Entry[a]	1	2	3	4	5
Catalyst	**29**	**270**	**26**	**273**	**275**
With Et_3N[b]	✓	✓	✓	✓	✓
Without Et_3N[b]	-	-	traces	✓	-

a) Unless otherwise indicated, all reactions were performed on 0.25 mmol scale with 1.0 equiv. **173a**, 1.5 equiv. **100a** and 0.1 equiv. catalyst in 0.75 mL of toluene at room temperature. b) All results are based on the ^{1}H-NMR spectra of the crude products.

Considering the new mode of activation required for the reaction, a new catalyst screening with only cinchona based catalysts was performed (Table 5). In the absence of triethylamine as a basic additive, the squaramide catalyst bearing a cinchona moiety **26** turned out to be ineffective in facilitating the reaction (Table 5, entry 1). With quinine **274** and quinidine **276** as catalysts, the product was obtained with low enantioselectivities (Table 5, entries 3-4). However, when cicnchonidine **273** and *O*-Bn-cupreine **277** were utilized, the stereochemical outcome of the reaction was improved to 53 % and 63 % *ee*, respectively (Table 5, entries 2 and 6). Surprisingly, in the presence of catalyst **278**, high enantioselectivity could be obtained 92 % (Table 5, entry 7). Comparable selectivity was also observed with cupreine **167** as a catalyst – 91 % (Table 5, entry 5). Furthermore, cupreine **167** showed the best result considering the yield of the reaction, albeit still quite low. Increasing the temperature from -20 ^{o}C to 0 ^{o}C however, resulted in slight improvement of the yield to 30 % without significant loss of selectivity (Table 5, entry 8). Therefore, further optimization of the conditions for the domino process was performed at 0 ^{o}C with cupreine **167** as a catalyst.

Table 5. Catalyst screening



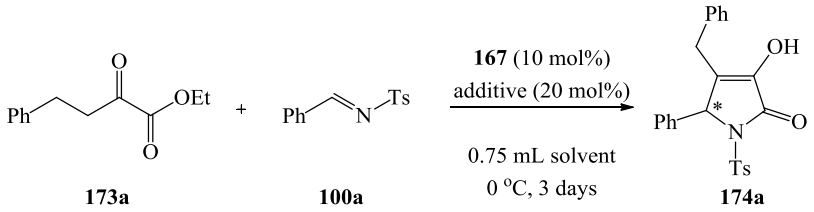
Entry[a]	1	2	3	4	5	6	7	8
Catalyst	**26**	**273**	**274**	**276**	**167**	**277**	**278**	**167** (0 °C)[d]
Yield [%][b]	traces	14	12	10	20	17	15	30
ee [%][c]	n.d.	53	27	-25	91	63	-92	90

a) Unless otherwise indicated, all reactions were performed on 0.25 mmol scale with 1.0 equiv. **173a**, 1.5 equiv. **100a** and 0.1 equiv. catalyst in 0.75 mL of toluene at -20 °C. b) Yield of isolated product **174a** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase. d) Reaction was performed at 0 °C.

With the appropriate catalyst determined, different solvents were tested as medium for the cascade sequence. In common solvents as DCM, ethyl acetate or benzene comparable results were observed (Table 6, entries 2, 6 and 10). Performing the reaction in THF, acetonitrile or DMF resulted in improvement of the yield of the reaction up to 72 %; however, the selectivity was significantly decreased in these cases (Table 6, entries 5 and 7-8). Diethyl ether turned out to be completely inefficient solvent for the process due to the extremely low solubility of the imine **100a** in it (Table 6, entry 4). The best result was obtained in chloroform – 46 % yield and 86 % *ee* (Table 6, entry 3).

Further tests to improve the outcome of the domino reaction by applying different weak organic and inorganic bases as additives were unsuccessful (Table 6, entries 11-21). Unfortunately, in the cases when the yield was increased, the stereocontrol of the reaction was lost.

Table 6. Optimization of the reaction conditions



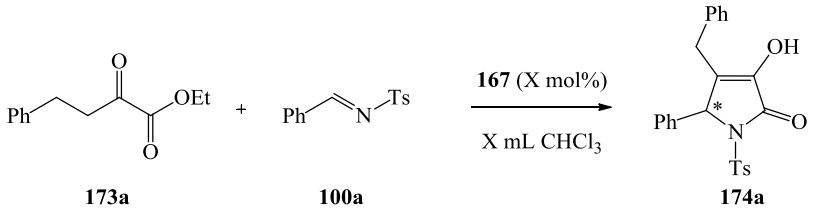
173a **100a** **174a**

Entry[a]	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	Toluene	-	30	90
2	DCM	-	35	61
3	$CHCl_3$	-	46	86
4	Et_2O	-	traces[d]	n.d.
5	THF	-	62	68
6	EtOAc	-	35	86
7	DMF	-	72	35
8	MeCN	-	67	rac
9	*i*-PrOH	-	50	32
10	benzene	-	25	88
11	$CHCl_3$	Na_2CO_3	74	55
12	$CHCl_3$	K_2CO_3	78	rac
13	$CHCl_3$	Cs_2CO_3	75	rac
14	$CHCl_3$	$NaHCO_3$	20	87
15	$CHCl_3$	KOAc	68	24
16	$CHCl_3$	KOH	17	43
17	$CHCl_3$	NaOH	10	83
18	$CHCl_3$	KH_2PO_4	22	80
19	$CHCl_3$	$(i\text{-Pr})_2NH$	65	57
20	$CHCl_3$	DBU	61	59
21	$CHCl_3$	piperidine	76	67

a) Unless otherwise indicated, all reactions were performed on 0.25 mmol scale with 1.0 equiv. **173a**, 1.5 equiv. **100a** and 0.1 equiv. catalyst **167** in 0.75 mL of solvent at 0 °C. b) Yield of isolated product **174a** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase. d) Determined by ^{1}H-NMR of the crude product.

Variation of some additional parameters of the reaction was performed in an attempt to further optimize the conditions for the domino sequence (Table 7). Increasing the catalyst loading to 20 mol% or the reaction temperature afforded the product with improved yield but lower enantiomeric excess (Table 7, entries 2-3). Altering the ratio of the starting materials or the concentration of the reaction on the other hand, resulted in decrease of both selectivity and yield (Table 7, entries 4-8).

Table 7. Optimization of the reaction conditions



173a **100a** **174a**

Entry[a]	X mol% **167**	Temperature [°C]	Equiv. **173a**	Equiv. **100a**	X mL $CHCl_3$	Yield [%][b]	*Ee [%]*[c]
1	10	0	1	1.5	0.75	46	86
2	20	0	1	1.5	0.75	56	68
3	10	rt	1	1.5	0.75	68	70
4	10	0	1	1	0.75	30	67
5	10	0	2	1	0.75	31	65
6	10	0	1	2	0.75	25	69
7	10	0	1	1.5	0.50	traces[d]	n.d.
8	10	0	1	1.5	1.50	38	60

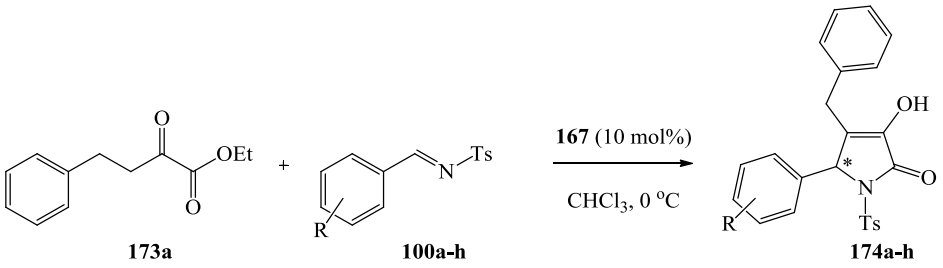
a) All reactions were performed on 0.25 mmol scale. b) Yield of isolated product **174a** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase. d) Determined by ^{1}H-NMR of the crude product. n.d. = not determined.

As a result of the investigation of the reaction, it was concluded that the optimal conditions for the domino Mannich/cyclization sequence are 1.0 equiv. of the α-ketoester **173**, 1.5 equiv. of the imine **100**, 0.1 equiv. cupreine **167** in 0.75 mL of chloroform at 0 °C.

3.2.3. Investigation of the scope of the reaction

With the optimal conditions for the domino process determined, differently substituted *N*-tosyl imines **100** were utilized in the reaction (Table 8). The presence of a methyl group as well as its position in the aromatic ring did not have any significant influence on the outcome of the reaction and the results obtained were comparable to those for the unsubstituted imine (Table 8, entries 2-3). However, when an electron-donating group was present, the reaction became sluggish, resulting in a decrease of the yield (Table 8, entry 4). Furthermore, in the case of the 3,4-(dimethoxyphenyl)imine **100e** the reaction rate was much slower and after 3 days only traces of the product **174e** were observed (Table 8, entry 5). With electron-withdrawing substituents on *p*-position in the benzene ring on the other hand, the corresponding products were obtained with higher yields but lower enantioselectivities (Table 8, entries 6-7). Surprisingly, when the 2-(bromophenyl)imine **100h** was applied in the reaction, very low sterocontrol was achieved (Table 8, entry 8).

Table 8. Reaction of ethyl 4-phenyl-2-oxobutanoate **173a** with *N*-tosyl imines **100a-g**



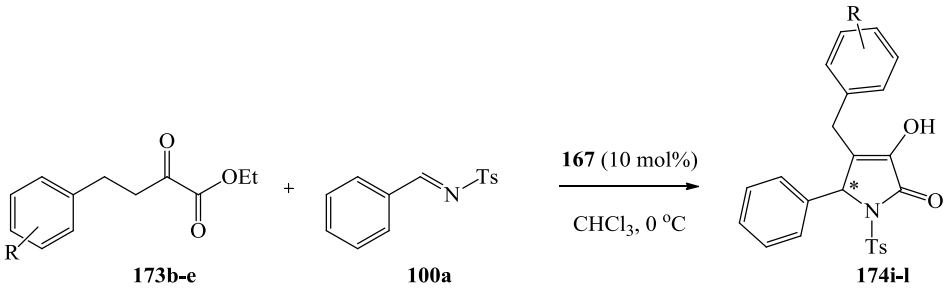
173a **100a-h** **174a-h**

Entry[a]	**100**	R	**174**	Yield [%][b]	*ee* [%][c]
1	**100a**	H	**174a**	46	86
2	**100b**	*o*-Me	**174b**	40	86
3	**100c**	*p*-Me	**174c**	43	87
4	**100d**	*p*-MeO	**174d**	35	54
5	**100e**	3,4-MeO	**174e**	traces[d]	n.d.
6	**100f**	*p*-Cl	**174f**	55	75
7	**100g**	*p*-NO_2	**174g**	63	80
8	**100h**	*o*-Br	**174h**	57	22

a) All reactions were performed on 0.25 mmol scale with 1.0 equiv. **173a**, 1.5 equiv. **100**, 0.1 equiv. cupreine **167** in 0.75 mL chloroform at 0 °C. b) Yield of isolated product **174** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase. d) Determined by ^{1}H-NMR of the crude product. n.d. = not determined

α-Ketoesters with different substituents on the aromatic ring were tested in the reaction as well (Table 9). While the presence of electron-donating and electron-withdrawing substituents did not influence significantly the yield of the reaction (Table 9, entries 3-4), the products **174i** and **174j** bearing *o*- or *p*-methyl group were obtained in higher yield – 62 and 65 %, respectively (Table 9, entries 1-2). Unexpectedly, the enantioselectivities observed for products **174i-l** were much lower.

Table 9. Reaction of *N*-tosyl imine **100a** with α-ketoesters **173b-e**

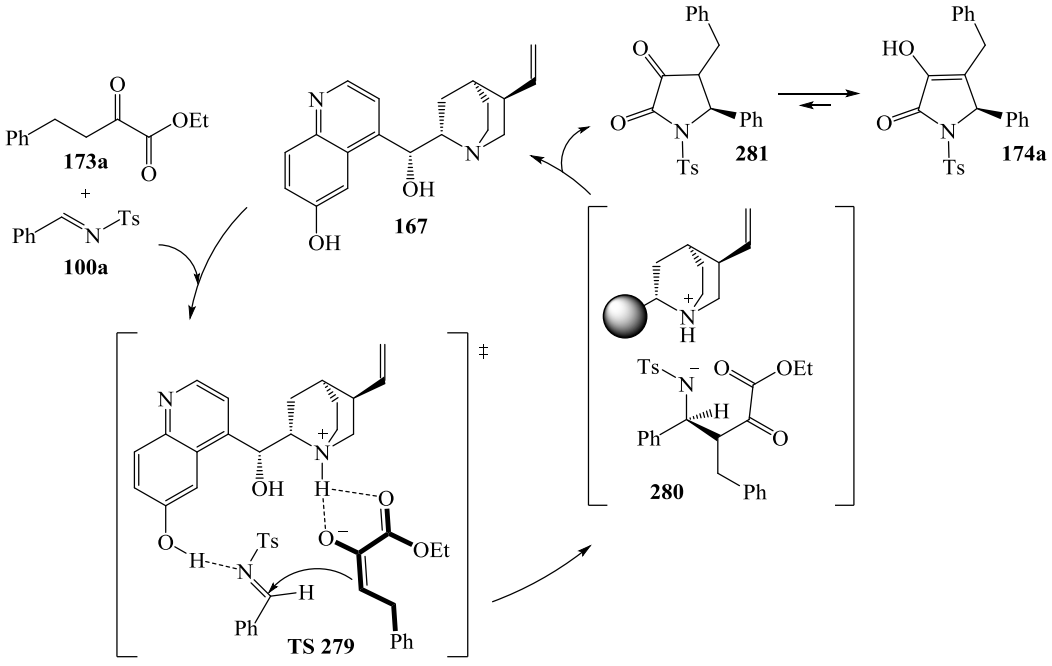


Entry[a]	**173**	R	**174**	Yield [%][b]	*ee* [%][c]
1	**173b**	*o*-Me	**174i**	62	46
2	**173c**	*p*-Me	**174j**	65	64
3	**173d**	*m*-MeO	**174k**	41	63
4	**173e**	*o*-Cl	**174l**	43	18

a) All reactions were performed on 0.25 mmol scale with 1.0 equiv. **173**, 1.5 equiv. **100a**, 0.1 equiv. cupreine **167** in 0.75 mL chloroform at 0 °C. b) Yield of isolated product **174** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase.

3.2.4. Proposed mechanism for the domino reaction

The proposed mechanism for the domino reaction is presented in Scheme 50.



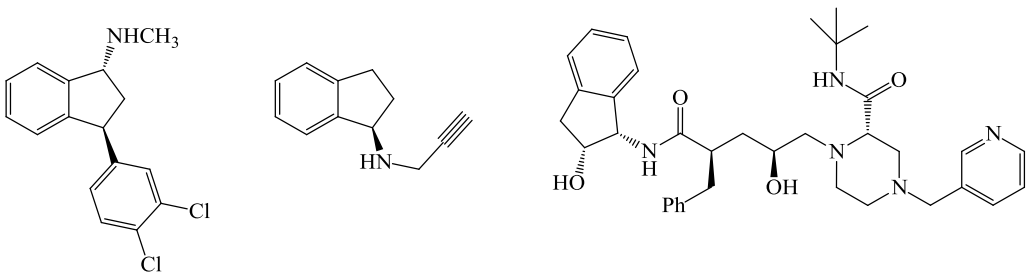
Scheme 50. Proposed mechanism for the domino Mannich/cyclization sequence.

Firstly, cupreine **167** activates both substrates. Through its tertiary amine group it deprotonates the α-ketoester **173a**, thus enhancing its nucleophilic nature. The hydroxyl group present in the catalyst on the other hand, activates the imine **100a**. Furthermore, the network of hydrogen bonds formed between the catalyst and both substrates ensure appropriate steric proximity and facilitates the attack of the enol form of the α-ketoester presumably to the *Si*-face of the imine. Subsequent cyclization for the formation of the amide bond affords the α-ketoamide **281**, which then tautomerizes to the more favoured enol form **174a**.

Considering that the reaction between aliphatic α-ketoesters and *N*-tosyl imines under conditions of Brønsted base catalysis was reported at the same time by Li (previously described in Chapter 3.2, Scheme 48), further work on this project was not continued.

3.3. Asymmetric synthesis of indanes *via* Michael/Michael domino reaction

The indane skeleton is widely spread in various natural products and serves as a valuable synthon for the synthesis of interesting complex organic compounds.[122] Furthermore, the chiral indane unit is a core structural element present in a large number of biologically and pharmaceutically active compounds.[123] For example, Indatraline **282** is a drug used in the treatment of depression and addiction (Figure 7)[124], whereas Rasagiline **283** is used as a monotherapy in Parkinson's desease.[125] Indinavir **284** on the other hand is a protease inhibitor utilized as a component for highly active antiretroviral therapy to treat HIV infection and AIDS.[126] Compounds bearing indane core were reported to display antipsychotic properties as well.[127]

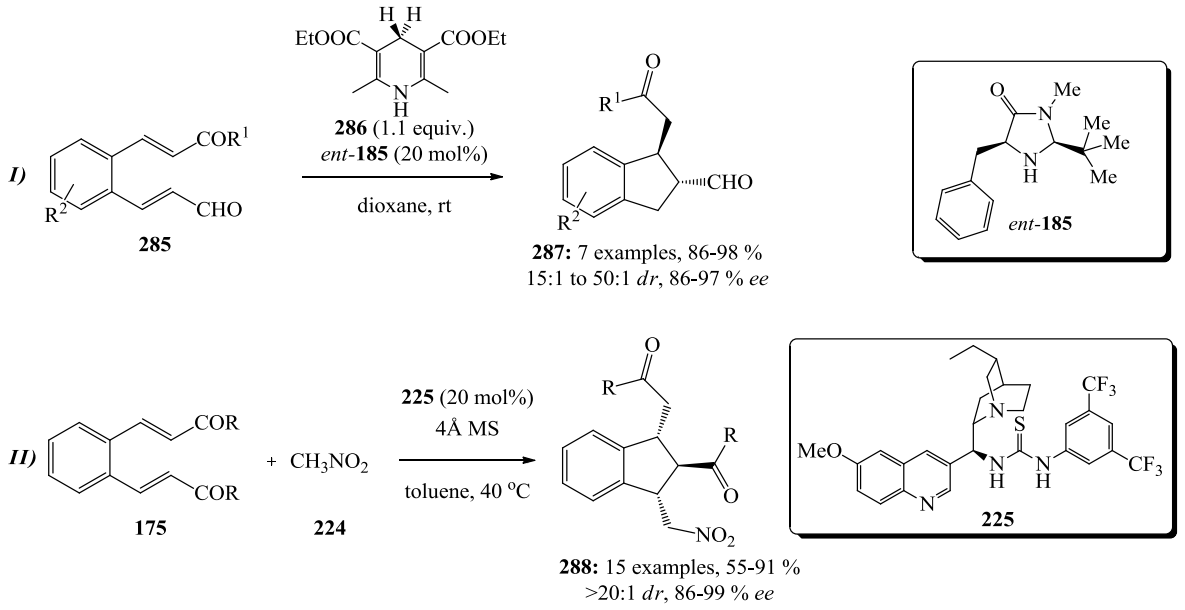


Indatraline **282** ***Rasagiline*** **283** ***Indinavir*** **284**

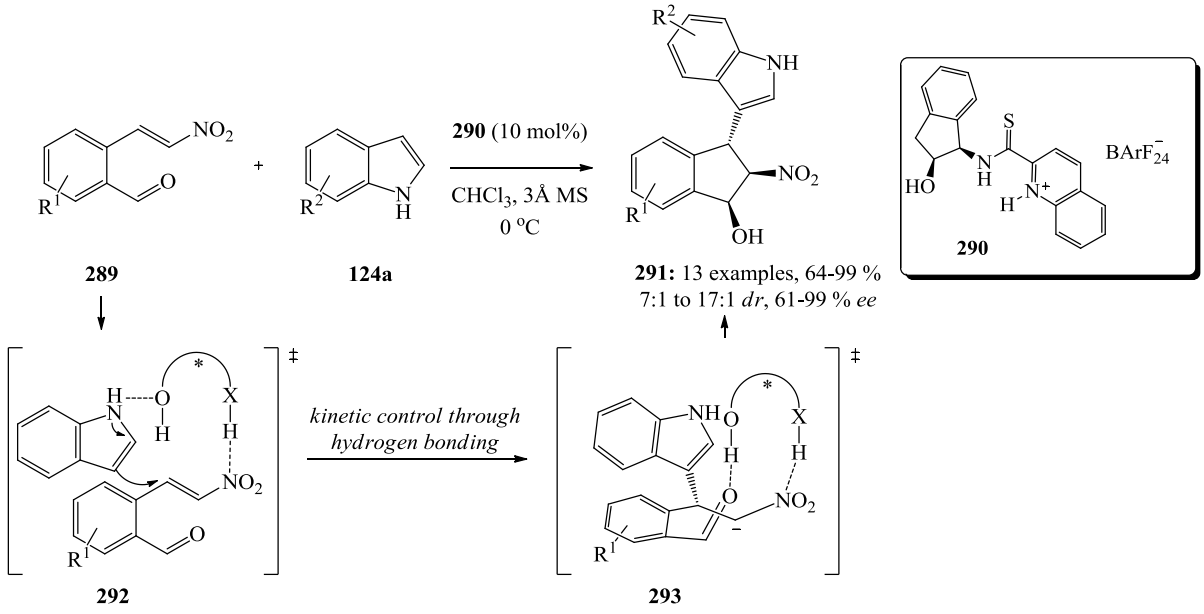
Figure 7. Some prominent examples of pharmaceutically active compounds bearing indane structural core.

In view of the importance of the indane derivatives for both organic and medicinal chemistry, the development of protocols for the preparation of polysubstituted indanes is of considerable interest. As a result different approaches towards such structures have been developed applying transition-metal complexes[128] or *N*-heterocyclic carbenes as catalysts.[129]

A successful organocatalytic domino conjugate reduction/Michael sequence was developed for the construction of indanes **287**, starting from formyl enones **285** and Hantzsch ester **286** as a hydrogen donor (Scheme 51, Eqn I).[130] The imidazolidinone-catalyzed reaction proceeds with excellent yields and selectivities, furnishing the corresponding *trans*-cyclic keto aldehydes. Furthermore, no products resulting from the conjugate reduction of the enone moiety were observed. Similar approach was utilized in 2014 by Wang and co-workers for obtaining multifunctionalized chiral indane derivatives **288** with three alternating *trans* stereocenters (Scheme 51, Eqn II).[131] It was envisioned that the *o*-divinylbenzenes **175** would react with nitromethane **224** as the active methylene-containing Michael donor to form the corresponding mono-Michael adducts through activation with bifunctional thiourea catalyst bearing a cinchona moiety. The resulting mono-Michael adduct would be then *in situ* deprotonated under Brønsted base catalysis, promoting the subsequent cyclization step. Indeed, products **288** were produced in moderate to good yields and excellent enantioselectivities.



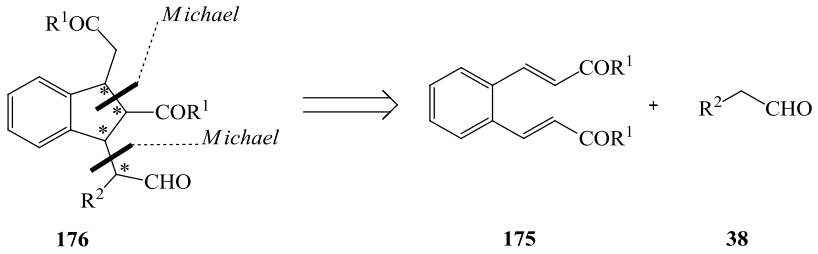
Scheme 51. Organocatalyzed asymmetric domino sequences for the synthesis of indanes.



Scheme 52. Organocatalytic domino Michael/Henry sequence for the construction of *cis*-vicinal indanes **291**.

Our group reported an asymmetric organocatalytic Michael/Henry domino reaction for generating the *cis*-vicinal trisubstituted indanes **291** in a highly enantioselective manner (Scheme 52).[132] The stereoselective outcome in this case was highly dependent on the effective *syn* binding mode of catalyst **290**. According to the proposed mechanism, first, a chemoselective hydrogen-bonding catalyzed Friedel-Crafts-type Michael addition proceeding through transition state **292** takes place. After the first stereocenter is built, the catalyst **290** forms hydrogen bonds to both the aldehyde and the nitro moiety through a *cis* matched transition state **293**. As a result, the final Henry reaction yields the desired *cis* kinetic product **291**.

Considering the importance of the polysubstituted indane core, it was envisioned that such structures could be obtained through a domino Michael/Michael sequence, starting from *o*-divinylbenzenes **175** and linear aldehydes **38** under conditions of secondary amine catalysis (Scheme 53).



176 **175** **38**

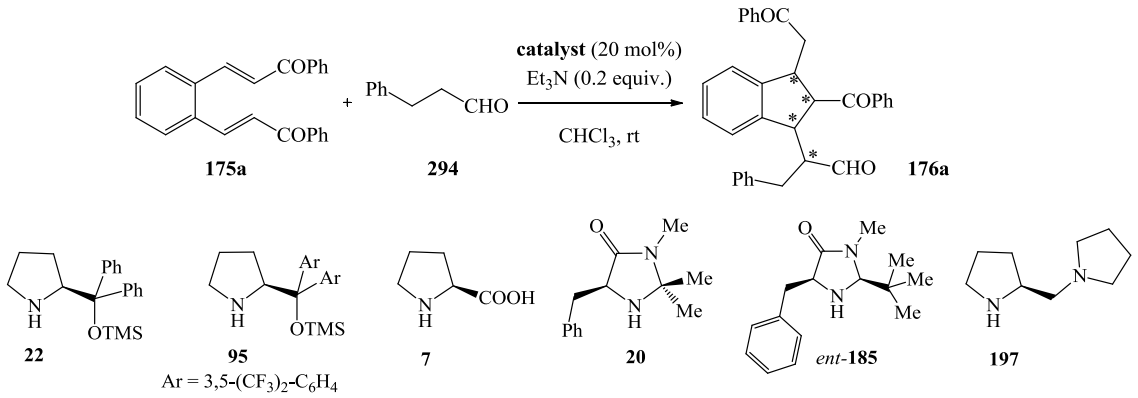
Scheme 53. Retrosynthetic analysis of 1,2,3-trisubstituted indanes **176**.

3.3.1. Optimization of the conditions of the domino reaction

As a first step of the optimization of the process, different secondary amine catalysts were tested (Table 10). The investigation was performed with the *o*-divinylketone **175a** and 3-phenylpropanal **294** in chloroform in the presence of the corresponding catalyst and triethylamine as a base.

Common catalysts as (*S*)-Proline **7**, Jørgensen catalyst **95**, as well as the secondary amine **197** turned out to be inefficient in promoting the reaction and only traces of the product **176a** were observed (Table 10, entries 2-3 and 6). The two imidazolidinone catalysts **20** and *ent*-**185** furnished the desired product with good enantioselectivity, albeit very low yields (Table 10, entries 4-5). The best result for this reaction was obtained with TMS-protected diphenylprolinol **22**, providing the product with 23 % yield and 90 % *ee* (Table 10, entry 1).

Table 10. Catalyst screening



Entry[a]	**Catalyst**	Yield [%][b]	*ee* [%][c]
1	**22**	23	90
2	**95**	traces[d]	n.d.
3	**7**	traces[d]	n.d.
4	**20**	10	92
5	***Ent*-185**	12	91
6	**197**	traces[d]	n.d.

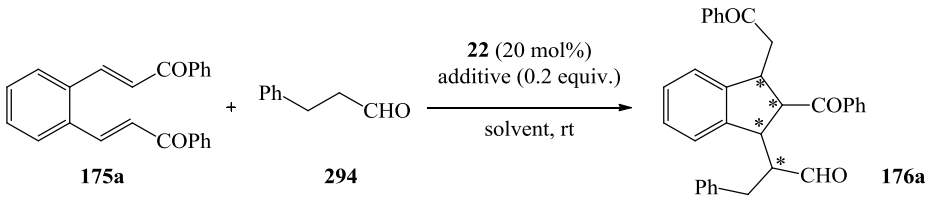
a) All reactions were performed on 0.25 mmol scale with 1.0 equiv. **175a**, 1.5 equiv. **294**, 0.2 equiv. catalyst, 0.2 equiv. triethylamine in 0.75 mL chloroform at room temperature. b) Yield of isolated product **176a** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase. d) Determined by the ^{1}H-NMR spectum of the crude product. n.d. = not determined

We then proceeded to testing different solvents for the domino sequence. While with toluene comparable results were obtained (Table 11, entries 3), performing the reaction in DCM and ethyl acetate afforded the product in lower yields (Table 11, entries 1 and 5, respectively). Common solvents as ethanol and diethyl ether, however, turned out to be inefficient medium for the cascade process and only traces of the desired product were observed (Table 11, entries 4 and 6). As a result, chloroform remained the solvent of choice (Table 11, entry 2).

Carrying out the domino reaction without basic additive resulted in a drastic decrease of the efficiency of the reaction, confirming the necessity of a base (Table 11, entry 8). Therefore, different organic and inorganic bases were employed as additives (Table 11, entries 9-18). However, neither of them proved to be a more efficient alternative and no improvement of the outcome of the reaction could be obtained.

Further attempts to improve the outcome of the domino process – increasing the temperature to 40 ^{o}C, varying the ratio of the starting materials, as well as increasing the amount of the catalyst and the basic additive – turned out to be inefficient.

Table 11. Optimization of the domino reaction



175a **294** **176a**

Entry[a]	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	DCM	Et_3N	15	n.d.
2	$CHCl_3$	Et_3N	23	90
3	Toluene	Et_3N	21	85
4	EtOH	Et_3N	traces[d]	n.d.
5	EtOAc	Et_3N	17	n.d.
6	Et_2O	Et_3N	traces[d]	n.d.
7	MeCN	Et_3N	10	n.d.
8	$CHCl_3$	-	7	92
9	$CHCl_3$	KOAc	<10%	n.d.
10	$CHCl_3$	NH_4OAc	<10%	n.d.
11	$CHCl_3$	Na_2CO_3	<10%	n.d.
12	$CHCl_3$	K_2CO_3	<10%	n.d.
13	$CHCl_3$	Cs_2CO_3	<10%	n.d.
14	$CHCl_3$	KH_2PO_4	<10%	n.d.
15	$CHCl_3$	$NaHCO_3$	<10%	n.d.
16	$CHCl_3$	KOH	<10%	n.d.
17	$CHCl_3$	DBU	<10%	n.d.
18	$CHCl_3$	Piperidine	<10%	n.d.

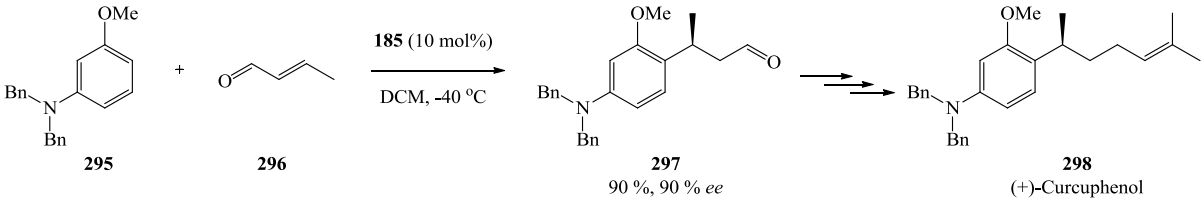
a) All reactions were performed on 0.25 mmol scale with 1.0 equiv. **175a**, 1.5 equiv. **294**, 0.2 equiv. **22**, 0.2 equiv. additive in 0.75 mL solvent at room temperature. b) Yield of isolated product **176a** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase. d) Determined by the ^{1}H-NMR spectum of the crude product. n.d. = not determined

Considering the unsuccessful trials aiming the development of a new domino reaction for the construction of 1,2,3-trisubstituted indanes **176**, the project was terminated.

3.4. Asymmetric organocatalytic Friedel-Crafts-type Michael addition of electron-rich arenes to nitroalkenes

Anilines and phenols are important synthetic targets due to their wide spread presence in pharmaceuticals, agrochemicals and fine chemicals.[133] The most common approach to their functionalization is Friedel-Crafts-type reactions, which in general are a powerful tool in synthetic organic chemistry.[134] However, most of the developed organocatalytic methodologies based on Friedel-Crafts-type reactions are focused on indoles and pyrroles and there are just few examples utilizing electron-rich arenes.[135]

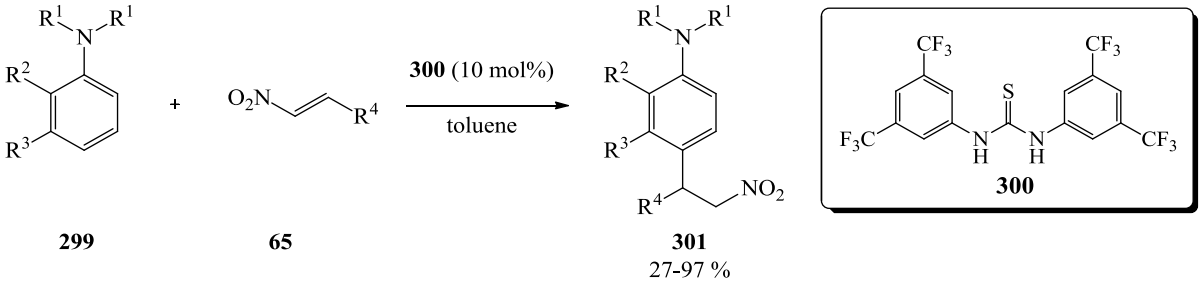
In 2002 MacMillan and co-workers first reported the enantioselective organocatalytic Friedel-Crafts-type addition of aniline derivatives to α,β-unsaturated aldehydes.[135a] Few years later the same reaction was utilized in the synthesis of (+)-Curcuphenol **298** – a bioactive sesquiterpene phenol, which exhibits antifungal, antitumor and antimalarial activity (Scheme 54).[135b]



Scheme 54. Synthesis of (+)-curcuphenol involving the enantioselective organocatalytic reaction between aniline derivative **295** and crotonaldehyde **296**.

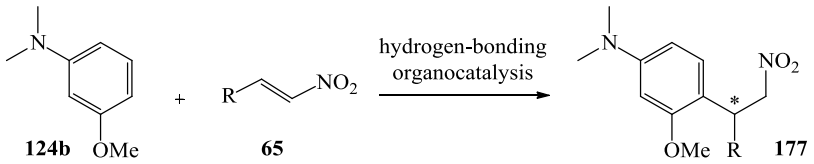
The addition of *N,N*-dimethyl-*m*-anisidine to α,β-unsaturated aldehydes was also exploited by our group to initiate a quadruple domino reaction for the synthesis of polyfunctionalized cyclohexenecarbaldehydes (the domino sequence was previously described in Chapter 1.4.3, Scheme 17).

Organocatalytic Friedel-Crafts-type addition of aniline derivatives **299** to nitroalkenes **65** has been reported as well, albeit in an achiral manner (Scheme 55).[136] The Schreiner catalyst **300** successfully facilitates the reaction and products **301** were obtained with up to 97 % yield.



Scheme 55. Friedel-Crafts-type addition of aniline derivatives **299** to nitroalkenes **65**.

Interestingly, an enantioselective organocatalytic version of the addition of aniline derivatives to nitroalkenes has not been reported so far. Considering the fact that this reaction is efficiently promoted by the achiral thiourea catalyst **300**, we decided to investigate the reaction in conditions of chiral hydrogen-bonding organocatalysis.



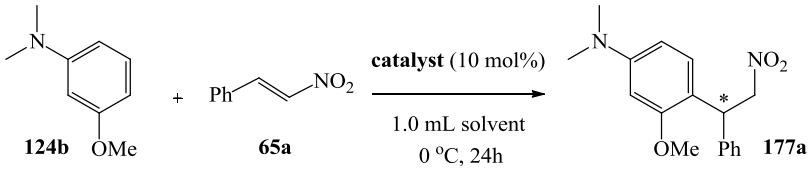
Scheme 56. Friedel-Crafts-type addition of aniline derivatives **124b** to nitroalkenes **65**.

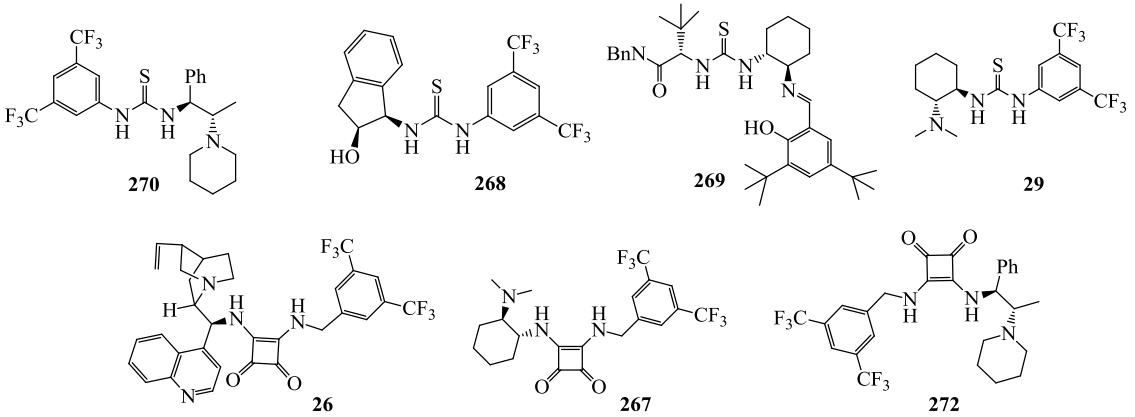
3.4.1. Optimization of the Friedel-Crafts-type Michael addition

First, a series of common thiourea and squaramide catalysts were tested to determine which one would efficiently facilitate the reaction. The investigation was performed with 1.5 equiv. *N,N*-dimethyl-m-anisidine **124b**, 1.0 equiv. phenylnitrostyrene **65a** and 0.1 equiv. of the corresponding catalyst in 1.0 mL toluene at 0 ^{o}C (Table 12, entries 1-7). All of the tested catalysts successfully promoted the reaction, furnishing the desired product **177a** with yields up to 93 %. However, none of them managed to exercise sufficient control over the stereochemical outcome of the reaction and enantiomeric excesses less than 3 % were observed. Decreasing the temperature to -20 ^{o}C or -40 ^{o}C did not result in any considerable improvement of the enantioselectivity (Table 12, entries 8-9). Furthermore, a short solvent screening was performed as well, with the assumption that the applied solvent might influence the stereocontrol of the reaction (Table 12, entries 10-15). However, in each case the product **177a** was obtained as a racemic mixture.

In view of the obtained results of the investigation of the reaction, work on this project was not continued.

Table 12. Optimization of the reaction conditions





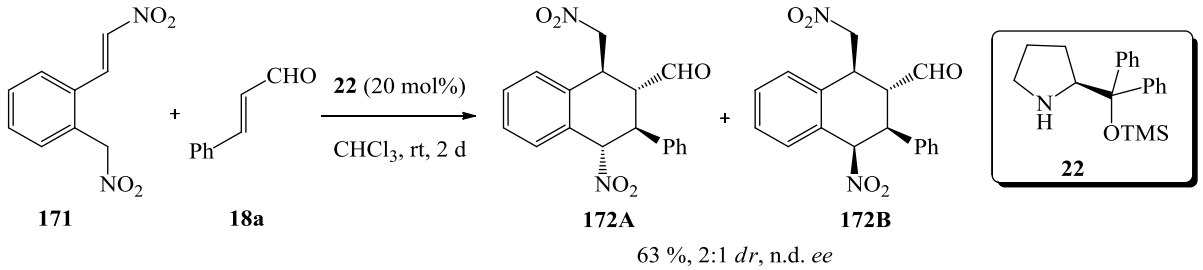
Entry[a]	**Catalyst**	Solvent	Yield [%][b]	*ee* [%][c]
1	**270**	toluene	93	3
2	**268**	toluene	90	<1
3	**269**	toluene	72	<1
4	**29**	toluene	39	2
5	**26**	toluene	54	<1
6	**267**	toluene	60	2
7	**272**	toluene	43	2
8	**270** (-20 °C)	toluene	36	3
9	**270** (-40 °C)	toluene	21	5
10	**270**	DCM	89	2
11	**270**	$CHCl_3$	91	2
12	**270**	EtOAc	65	<1
13	**270**	THF	74	<1
14	**270**	MeCN	80	<1
15	**270**	DMF	75	<1

a) Unless otherwise indicated, all reactions were performed on 0.50 mmol scale with 1.5 equiv. **124b**, 1.0 equiv. **65a** and 0.1 equiv. catalyst in 1.0 mL of toluene at 0 °C. b) Yield of isolated product **177a** after flash column chromatography. c) Determined by HPLC on a chiral stationary phase.

4. Research summary and future perspectives

4.2. Research summary

The first project of this work included the development of a Michael/Michael domino reaction for the construction of polysubstituted 1,2,3,4-tetrahydronaphthalenes **172** (Scheme 57).



Scheme 57. Asymmetric synthesis of polysubstituted 1,2,3,4-tetrahydronaphthalenes **172** *via* Michael/Michael domino reaction.

The reaction between 2-(nitromethyl)nitrostyrene **171** and cinnamaldehyde **18a** was successfully promoted by TMS-protected diphenylprolinol **22** through iminium-enamine activation pathway. The desired product was obtained in 63 % yield as two diastereomers in ratio 2:1. The instability of the product however, turned out to be problematic for measuring the enantiomeric excess. Furthermore, any attempts to overcome this setback by derivatization of the tetralin **172** proved unsuccessful. Another significant drawback was the low efficiency of the synthetic pathway for obtaining 2-(nitromethyl)nitrostyrene **171** – four step over 8 days with an overall yield of just 2.5 %. This time- and mainly effort-consuming synthesis deterred the attention from the main aim of the project, namely further optimization of the domino reaction for overcoming the other existent problems.

In an attempt to find a solution for the mentioned setbacks, it was envisioned that a modification of substrate **171** to compounds **202-205** would furnish products with the same tetralin scaffold in the conditions of the cascade reaction (Figure 8). Moreover, substrates **202-205** could be synthesized through a shorter, more efficient pathway, thus allowing the focus to be set on the domino reaction itself. When substrates **202-205** were applied in the conditions of the domino reaction however, no desired products could be obtained.

As an expansion of this project, different anilines bearing an unsaturated moiety at the *o*-position **236-241** were synthesized as well (Figure 8). Upon reaction with α,β-unsaturated aldehydes under conditions of secondary amine organocatalysis, they would afford polysubstituted tetrahydroquinolines – another important structural unit found in many biologically active compounds. Unfortunately, when substrates **236-241** were tested for a reaction with cinnamaldehyde in the presence of TMS-protected diphenylprolinol as a catalyst, no desired products were obtained.

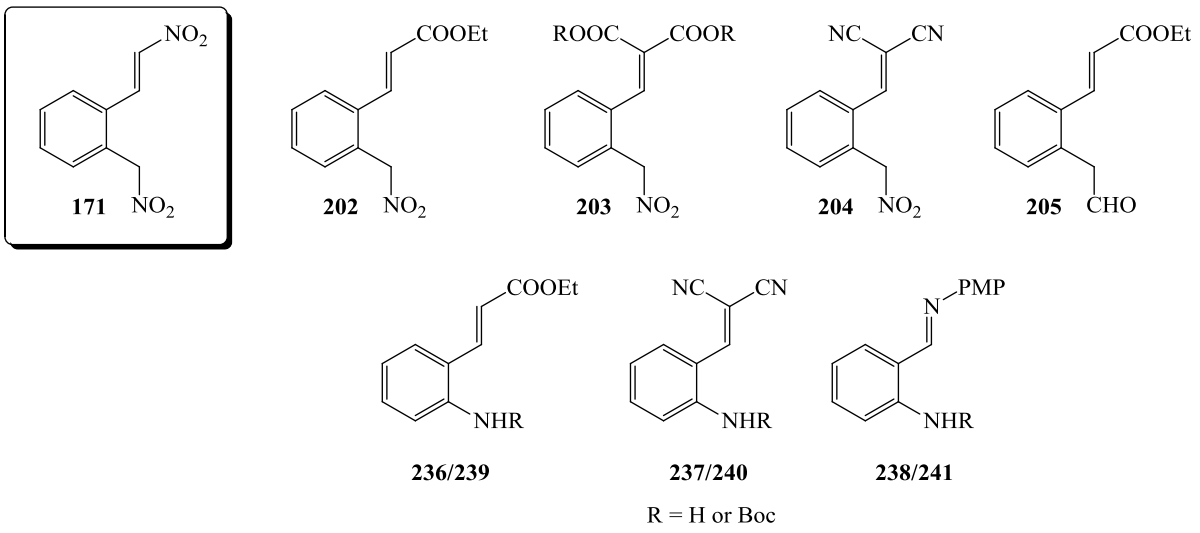
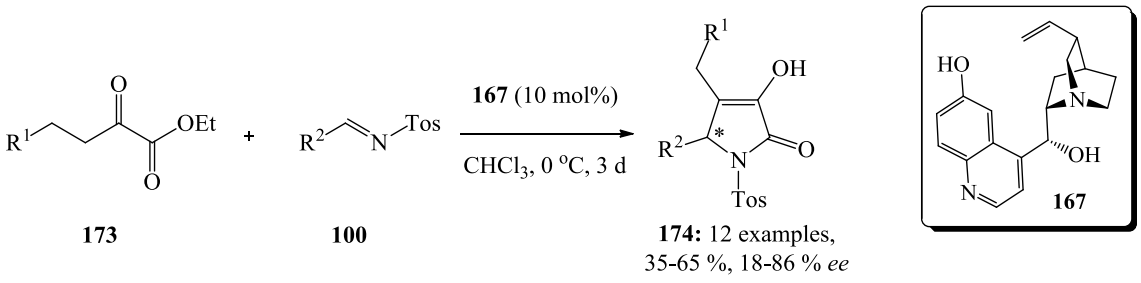


Figure 8. Modification of substrate **171**.

Considering the previously mentioned drawbacks of the domino reaction between 2-(nitromethyl)nitrostyrene **171** and α,β-unsaturated aldehydes **18** as well as the unsuccessful trials aiming the development of new domino reactions for the construction of tetrahydronaphthalenes and tetrahydroquinolines, the project was terminated.

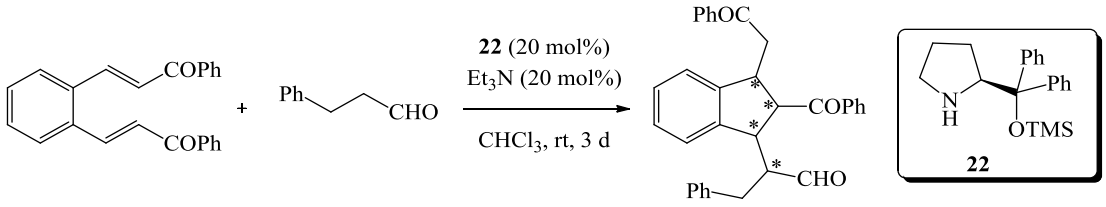
In the second project a new asymmetric organocatalyzed domino reaction for the construction of 4,5-disubstituted 3-hydroxy-1*H*-pyrrol-2(5H)-ones **174** was developed. Cupreine **167** successfully facilitated the Mannich/cyclization cascade sequence between α-ketoesters **173** and aldimines **100**. Different α-ketoesters and tosylimines bearing aromatic cycles were utilized in the conditions of the reaction, affording the corresponding products with medium to good yields and enantioselectivities.

Unfortunately, while our work was still in progress, the reaction between aliphatic α-ketoesters and tosylimines was independently reported first by Li and co-workers and any further work on this project was stopped.



Scheme 58. Asymmetric synthesis of 4,5-disubstituted 3-hydroxy-1*H*-pyrrol-2(5H)-ones **174** *via* Mannich/cyclization domino reaction.

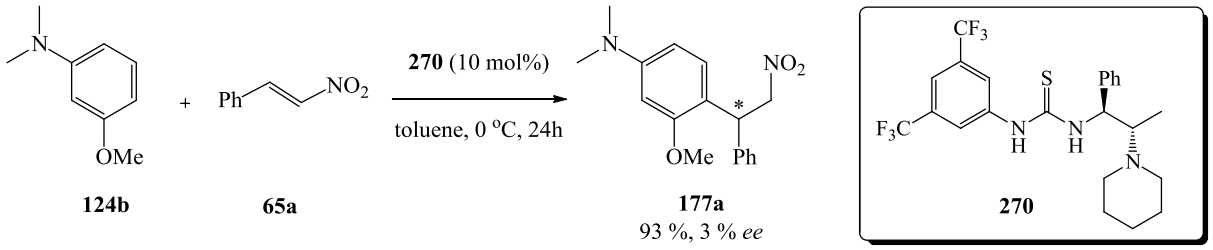
Next, the reaction between the *o*-divinylketone **175a** and 3-phenylpropanal **294** in conditions of secondary amine organocatalysis was investigated (Scheme 59). TMS-protected diphenylprolinol **22** proved to be efficient catalyst in terms of selectivity, providing the desired indane product **176a** as a single diastereomer with very high enantioselectivity (90 % *ee*). However, low yields were observed (<23 %). Moreover, any attempts to further optimize the conditions and improve the outcome of the reaction turned out to be completely unsuccessful. For that reason, the project was terminated at this point.



175a **294** **176a**
23 %, 90 % *ee*

Scheme 59. Asymmetric synthesis of 1,2,3-trisubstituted indanes **176** *via* Michael Michael domino reaction.

In the last project, an enantioselective organocatalytic Friedel-Crafts-type Michael addition of electron-rich arenes **124b** to nitroolefins **65** was studied (Scheme 60). A series of bifunctional hydrogen-bonding catalysts were tested for the reaction and all of them efficiently promoted the reaction, furnishing the desired product **177a** with yields up to 93 %. However, none of them managed to exercise sufficient control over the stereochemical outcome of the reaction and **177a** was always obtained as racemic mixtures. In view of the unsuccessful attempts to achieve enantioenriched products, work on this project was not continued.

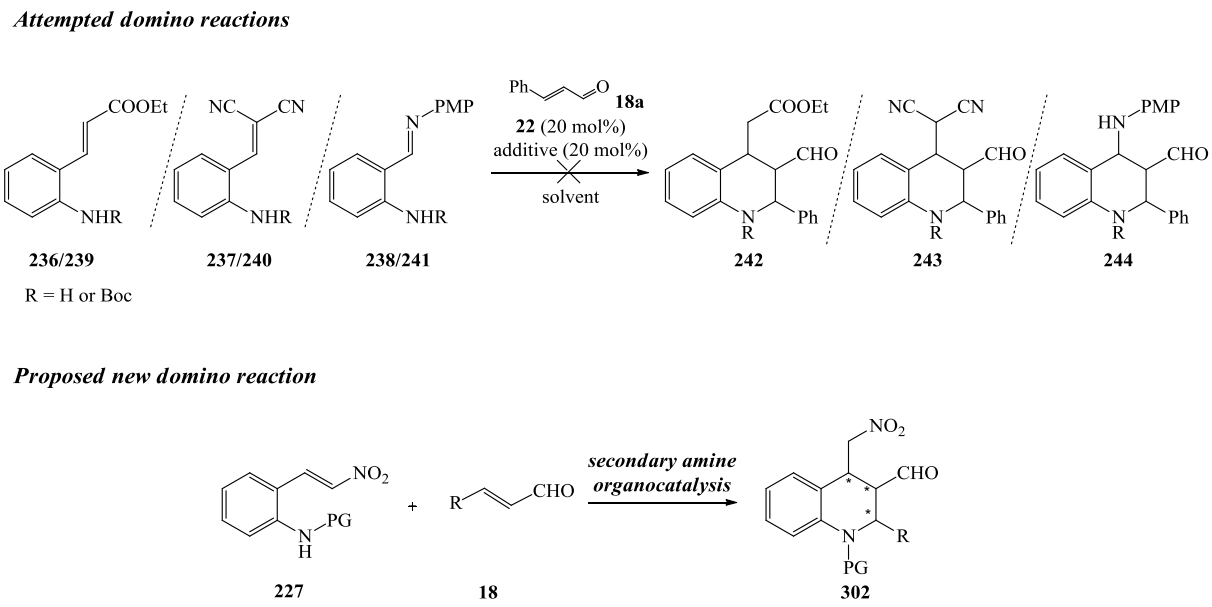


124b **65a** **177a**
93 %, 3 % *ee*
270

Scheme 60. Friedel-Crafts-type Michael reaction between anilines **124b** and nitroolefins **65** in conditions of hydrogen-bonding organocatalysis.

4.2. Perspectives

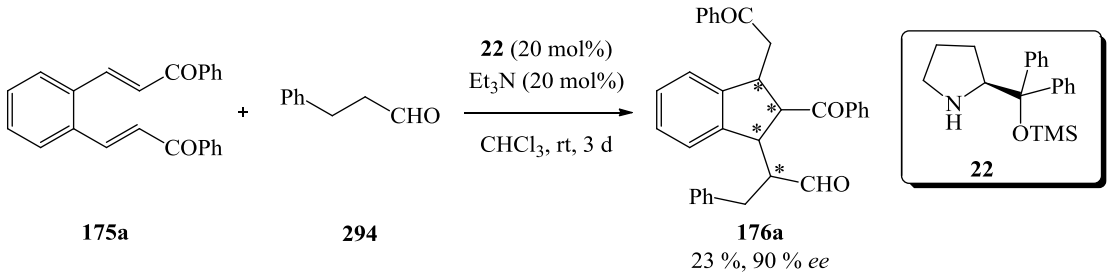
As a part of the first project of this work, it was described the attempts towards developing a new asymmetric domino aza-Michael/Michael reaction for the construction of tetrahydroquinolines **242-244** (Scheme 61). Unfortunately, none of the desired products **242-244** could be obtained. However, the observed results might be due to the general reversibility of the aza-Michael reaction. It might be possible, although not proven, that the first aza-Michael step proceeds, but the formed adducts could not be trapped fast enough in the subsequent Michael reaction. In view of this consideration, it can be imagined that such problem would be avoided with substrate **227** – aniline bearing a nitrovinyl moiety, which is known to possess the highest activity as a Michael acceptor. A reaction between substrates of type **227** and α,β-unsaturated aldehydes **18** in conditions of secondary amine organocatalysis would afford the corresponding tetraquinoline products **302.**



Scheme 61. Asymmetric synthesis of tetrahydroquinolines **302** *via* aza-Michael/Michael domino reaction.

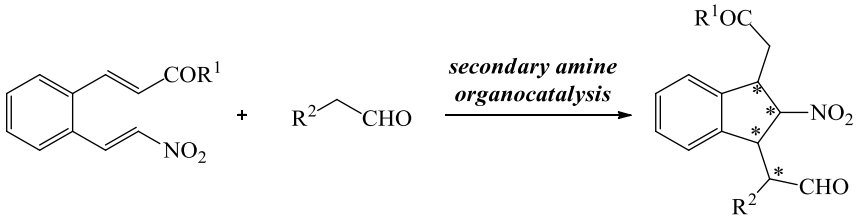
The third project of the present work involved the asymmetric domino Michael/Michael reaction between *o*-divinylketone **175a** and 3-phenylpropanal **294** for the construction of the 1,2,3-polysubstituted indane **176a** (Scheme 62). In the presence of TMS-protected diphenylprolinol **22**, very high enantioselectivities were obtained. However, any attempts to optimize the conditions for the cascade sequence resulted in low yields (<23 %). A possible explanation for the outcome of the domino process might be the lower activity of α,β-unsaturated ketones as a Michael acceptor, which would be of great importance especially for the first Michael addition step. Therefore, it can be imagined that substrate **303** bearing a nitrovinyl moiety would have enhanced activity towards Michael additions. Thus, indane structures of type **304** would be achieved in a more efficient manner upon reaction of **303** with aldehydes **38** promoted by secondary amine organocatalysts.

Attempted domino reaction



175a **294** **176a**
23 %, 90 % *ee*

Proposed new domino reaction



303 **38** **304**

Scheme 62. Asymmetric syntesis of 1,2,3-polysubstituted indanes **304** *via* Michael/ Michael domino reaction.

5. Experimental part

5.1. General information on the preparative work

General information

All reactions were performed in oven-dried glassware. Moisture sensitive reactions were carried out using standard Schlenk techniques under argon atmosphere.

All solvents were distilled, purified and dried according to standard procedures prior to use. Absolute THF and Et_2O were distilled over sodium-lead (Solvona) alloy/ benzophenone under argon atmosphere. Absolute DCM and DMF were purchased directly from Acros.

Chemicals

Chemicals were purchased from commercial suppliers (Acros, Sigma Aldrich, ABCR, Alfa Aesar, TCI Europe) and used without any further purification.

Used catalysts

The (S)-TMS α,α-diphenylprolinol catalyst was prepared in 4 steps from (S)-(-)-proline following the previously reported procedure.[137]

1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1S.2S)-1-phenyl-2-(piperidin-1-yl)propyl]thiourea catalyst was prepared in 3 steps following the previously reported procedure.[138]

Squaramide catalysts were prepared following the previously reported procedures.[139]

Cupreine and *O*-Bn-Cuprein catalysts were prepared following the previously reported procedure.[140]

(3S,8R,9S)-10,11-dihydroxy-3,9-epoxy-6'-hydroxycinchonane catalyst was prepared following the previously reported procedure.[141]

Reaction control

The evolution of performed reactions was monitored by analytical TLC using SIL G-25 UV_{254} from MACHERY NAGEL. Visualization was performed with UV-irradiation (254 nm) or by staining with potassium permanganate stain.

Preparative column chromatography

Purification of the products by flash column chromatography was performed using silica gel 60 (particle size range 0.040-0.063 mm) from Merck-Schuchardt as the stationary phase. Diameter and length of the glass columns as well as amount of silica gel varied depending on the amount of crude product and specific requirements of the separation problem.

5.2. General information on the analytical methods

Yields

The given yields refer to isolated and purified products.

Analytical HPLC

Analytical HPLC was performed with Hewlett-Packard 1050 Series or Agilent 1100 instruments, using the following columns: Chiralpak AS (10 µm, 250 mm x 4.6 mm), Chiralpak OD (10 µm, 250 mm x 4.6 mm), Chiralpak AD (10 µm, 250 mm x 4.6 mm), Chiralpak IA (5 µm, 250 mm x 4.6 mm), Chiralpak OJ (10 µm, 250 mm x 4.6 mm), Chiralpak IC (5 µm, 250 mm x 4.6 mm), Merck (*S,S*)-Whelk O1 (5 µm, 250 mm x 4 mm), LiChrosorb Si 60 (7 µm, 250 mm x 4.6 mm), Kromasil 100 Sil (5 µm, 150 mm x 4 mm).

Melting points

Melting points of obtained solids were measured on Tottoli-melting point apparatus Büchi 540.

Polarimetry

Optical rotations of products were measured on Perkin-Elmer P241. Concentrations are given in g/dL.

NMR Spectroscopy

NMR spectra were acquired at ambient temperature on Varian Mercury 600 or Innova 400 instruments. The chemical shifts are reported in parts per million (ppm) and the coupling constants are reported in Hertz (Hz). For describing the multiplicity the following abbreviations are used: s-singlet, bs-broad singlet, d-doublet, t-triplet, q-quartet, m-multiplet.

Mass Spectrometry

Mass spectra were acquired on Finnigen SSQ7000 (EI 70eV; CI 100 eV) and ThermoFisher Scientific LTQ-Orbitrap XL (ESI/HRMS ESI) instruments. Results are reported by presenting the mass of the fragments (*m/z*) and the peak intensity, compared to the intensity of the base peak (100 %). Peaks with intensity less than 3% are not reported.

IR Spectroscopy

IR spectra were acquired on Perkin-Elmer FT-IR Spectrum 100 using ATR-unit. Absorption bands are given in cm^{-1}, only signals with transmissions (T) $\leq$ 80% are reported. The peak intensity is described with the corresponding abbreviations: s = strong (0-40% T), m = medium (41-60% T), w = weak (61-80% T).

Elemental Analysis

Elemental analyses were measured on Vario EL Element Analyser instrument. A sample was determined to be authentic when the deviation ΔC, ΔH, ΔN between theoretically calculated and experimentally measured values is less than 0.5%.

5.3. General procedures

GP 1: *Synthesis of α-ketoesters*

GP 1.1*: Synthesis of 2-arylethanols*

To a suspension of LAH (1.5 equiv.) in dry THF under argon atmosphere at 0 ^{o}C, was added dropwise a solution of arylacetic acid (1 equiv.) in dry THF. The reaction mixture was allowed to stir at room temperature for 5 hours. It was then cooled down to 0 ^{o}C again and quenched with 10 % aqueous KOH. The product was extracted with EtOAc and the organic extracts were washed with brine, dried with sodium sulfate and then concentrated *in vacuo*. After column chromatography, the desired products ware obtained as clear liquids.

GP 1.2: *Synthesis of 2-aryl-1-bromoethanes*

To a solution of 2-arylethanol (1 equiv.) in toluene at 0 ^{o}C was added dropwise PBr_3 (0.3 equiv.) and the reaction mixture was refluxed for 2 hours. After cooling down to room temperature, saturated aqueous $Na_2S_2O_3$ was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with sodium sulfate and concentrated *in vacuo*. After column chromatography the desired products were obtained as clear liquids.

GP 1.3: *Synthesis of α-ketoesters*

Magnesium turnings (3 equiv.) were placed inside 3-necked flask. Dry THF and a piece of iodine were added and the resulting mixture was stirred until the yellow color of iodine had faded out. A solution of 2-aryl-1-bromoethane (1 equiv.) in THF was added dropwise over a period of 30 min at 0 ^{o}C. The reaction mixture was stirred further for 2 hours more.

The resulting Grignard reagent was added dropwise to a solution of diethyl oxalate (1.5 equiv.) in dry THF at 0 ^{o}C and the reaction mixture was stirred at room temperature for 15 h. It was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried with sodium sulfate and concentrated *in vacuo*. After column chromatography the desired products were obtained as clear oils.

GP 2: *Synthesis of tosylimines*

To a mixture of the corresponding substituted benzaldehyde (1 equiv.) and trimethyl ortoformate (1.5 equiv.) was added a catalytic amount of *para*-toluenesulfonic acid and the reaction was allowed to stir for 15 h at room temperature. 4-Toluenesulfonamide (1 equiv.)

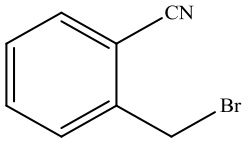
was then added and the resulting mixture was heated to 150 ^{o}C for 2 hours. After cooling down to room temperature, the crude product solidified and it was directly purified by recrystallization in EtOH.

GP 3: *Synthesis of substituted 3-hydroxy-1H-pyrrol-2(5H)-one through domino Mannich/ cyclization reaction*

A solution of cupreine **163** (0.025 mmol, 0.1 equiv.) in 0.75 mL solvent was left for 10 min at 0 ^{o}C and then were added the corresponding (E)-N-benzylidene-4-methylbenzenesulfonamide (0.375 mmol, 1.5 equiv.) and ethyl 4-phenyl-2-oxobutanoate (0.25 mmol, 1.0 equiv.). The reaction mixture was stirred at this temperature for 3 days and was then directly submitted to purification by flash column chromatography (eluent: *n*-pentane/ EtOAc 3:1) to afford the products as white solids or viscous oils.

5.4. Analytical data of synthesized compounds

2-(Bromomethyl)benzonitrile (194)



To a suspension of N-bromosuccinimide (6.9 g, 39.0 mmol, 1.3 equiv.) in 100 mL tetrachloromethane was added 2-methylbenzonitrile **193** (3.5 g, 30.0 mmol, 1.0 equiv.). To the reaction mixture was added catalytic amount of AIBN and it was refluxed for 8 hours. After the mixture was cooled down to room temperature, saturated aqueous $Na_2S_2O_3$ was added and the product was extracted three times with EtOAc, the extracts were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. 2-(Bromomethyl)benzonitrile (**194**) was obtained after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) as white solid.

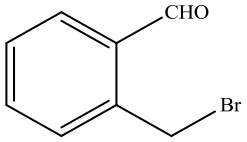
Yield m = 4.3 g (21.9 mmol, 73 %)

TLC R_f = 0.6 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 4.61 (s, 2H, CH_2Br), 7.39 (td, *J* = 7.5, 1.3 Hz, 1H, CH_{Ar}), 7.51-7.56 (m, 2H, CH_{Ar}), 7.63 (d, *J* = 7.5 Hz, 1H, CH_{Ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 29.4 (*C*H_2), 112.4 (*C*$_{Ar}$), 116.7 (*C*N), 129.0 (*C*H$_{Ar}$), 130.5 (*C*H$_{Ar}$), 133.2 (*C*H$_{Ar}$), 133.3 (*C*H$_{Ar}$), 141.1 (*C*$_{Ar}$).

2-(Bromomethyl)benzaldehyde (195)



To a solution of 2-(bromomethyl)benzonitrile **194** (3.9 g, 20.0 mmol, 1.0 rquiv.) in dry DCM (50 mL) under argon atmosphere at 0 °C was added dropwise diisobutyl aluminium hydride (DIBAL-H, 1.0 M, 20 mL, 20.0 mmol, 1.0 equiv.). After 30 min the ice-water bath was removed and the reaction mixture was stirred at room temperature for 5 h. It was then cooled down to 0 °C again and then poured into a beaker containing ice (100g) and HCl aqueous solution (5 N, 100 mL). The resulting mixture was then extracted with DCM and the extracts were washed with saturated $NaHCO_3$, dried with Na_2SO_4 and concentrated *in vacuo*. After

purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1), the product was obtained as clear bright yellow liquid.

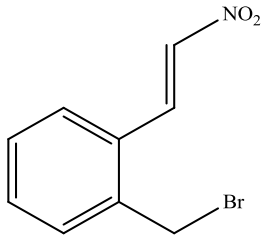
Yield m = 3.0 g (15.0 mmol, 75 %)

TLC R_f = 0.5 (*n*-pentane/EtOAc 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 4.93 (s, 2H, CH_2Br), 7.49 (dd, *J* = 7.2, 1.8 Hz, 1H, CH_{Ar}), 7.51 (td, *J* = 7.2, 1.8 Hz, 1H, CH_{Ar}), 7.58 (td, *J* = 7.2, 1.8 Hz, 1H, CH_{Ar}), 7.84 (td, *J* = 7.2 ,1.8 Hz, 1H, CH_{Ar}), 10.25 (C*H*O).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 29.5 (*C*H_2), 129.1 (*C*H_{Ar}), 131.7 (*C*H_{Ar}), 133.1 (*C*H_{Ar}), 133.8 (*C*H_{Ar}), 133.9 (*C*$_{Ar}$), 139.2 (*C*$_{Ar}$), 192.0 (*C*HO).

(E)-1-(Bromomethyl)-2-(2-nitrovinyl)benzene (196)



A solution of 2-(bromomethyl)benzaldehyde **195** (3.0 g, 15.0 mmol, 1.0 equiv.) and nitromethane (9.2 g, 8 mL, 150.0 mmol, 10.0 equiv.) at 0 °C was stirred for 5 min. Basic chromatographic alumina (3.0 g) was added and the reaction mixture was stirred further for 30 min at 0 °C and then 20 h at room temperature. DCM (15 mL) was then added and the reaction mixture was heated at 40 °C for 7 h. The mixture was filtered and concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 12:1) the product was obtained as yellow solid.

Yield m = 0.7 g (3.0 mmol, 20 %)

Melting point destroyed after 100 °C

TLC R_f = 0.4 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.59 (s, 2H, CH_2Br), 7.38-7.41 (m, 1H, CH_{Ar}), 7.43-7.47 (m, 2H, CH_{Ar}), 7.54-7.58 (m, 2H, CH_{Ar}, C*H*NO_2), 8.39 (d, *J* = 13.5 Hz, 1H, PhC*H*).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 29.8 (*C*H_2), 128.0 (*C*H_{Ar}), 129.3 (*C*$_{Ar}$), 129.6 (*C*H_{Ar}), 131.2 (*C*H_{Ar}), 132.1 (*C*H_{Ar}), 135.1 (Ph*C*H), 138.0 (*C*$_{Ar}$), 138.6 (Ph*C*H).

MS (EI, 70 eV): *m/z* (%) = 64 (21), 77 (5), 89 (11), 96 (6), 103 (5), 116 (100), 128 (17), 131 (7), 148 (4), 159 (16), 162 (40), 192 (10), 195 (11), 241 (8).

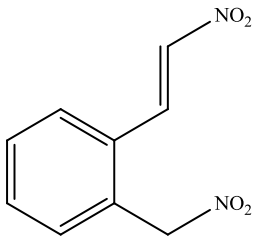
IR (ATR): 2970 (w), 2305 (w), 2099 (w), 1739 (s), 1630 (m), 1494 (s), 1333 (s), 1215 (s), 1070 (m), 954 (s), 837 (s), 765 (s), 720 (s) cm^{-1}.

Elemental analysis ($C_9H_8NO_2Br$)

Calculated: C = 44.66% H = 3.33% N = 5.79%

Found: C = 44.80% H = 3.25% N = 5.74%

(E)-1-(Ntiromethyl)-2-(2-nitrovinyl)benzene (171)



To a solution of (E)-1-(bromomethyl)-2-(2-nitrovinyl)benzene **196** (0.7 g, 3.0 mmol, 1.0 equiv.) in diethyl ether at 0 °C was added slowly silver nitrite (0.55 g, 3.6 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 3 h and then further refluxed for another 4 h. After cooling down to room temperature, the mixture was filtered and concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as yellow solid.

Yield m = 0.015 g (0.7 mmol, 24 %)

Melting point 125 °C

TLC R_f = 0.1 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.63 (s, 2H, CH_2NO_2), 7.52-7.59 (m, 4H, CHNO$_2$ and CH_{Ar}), 7.64-7.67 (m, 1H, CH_{Ar}), 8.33 (d, *J* = 13.4 Hz, 1H, PhCH).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 76.8 (CH_2), 128.1 (C_{Ar}), 129.7 (C_{Ar}), 130.7 (CH_{Ar}), 131.1 (CH_{Ar}), 132.2 (CH_{Ar}), 132.8 (CH_{Ar}), 134.5 (PhCH), 139.7 (CHNO$_2$).

MS (EI, 70 eV): *m/z* (%) = 46 (4), 51 (4), 63 (6), 77 (4), 89 (11), 103 (5), 116 (100), 131 (3), 162 (17), 208 (2).

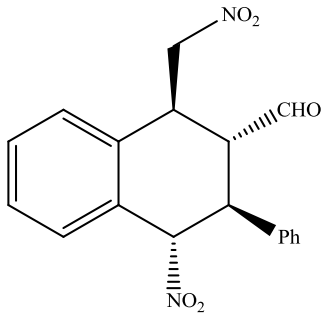
IR (ATR): 3119 (w), 2923 (w), 2856 (w), 1739 (s), 1630 (m), 1553 (s), 1499 (s), 1333 (s), 1218 (s), 958 (s), 845 (s), 765 (s), 668 (m) cm^{-1}.

Elemental analysis ($C_9H_8N_2O_4$)

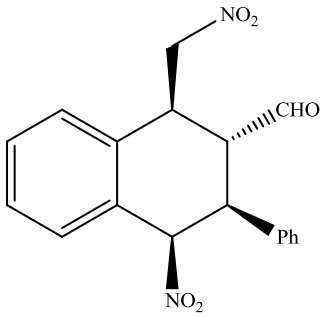
Calculated: C = 51.93% H = 3.87% N = 13.46%

Found: C = 51.80% H = 3.96% N = 13.36%

4-Nitro-1-(nitromethyl)-3-phenyl-1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (172)



major diastereomer



minor diastereomer

A solution of (E)-1-(nitromethyl)-2-(2-nitrovinyl)benzene **171** (104 mg, 0.5 mmol, 1.0 equiv.), cinnamaldehyde **18a** (79 mg, 0.075 mL, 0.6 mmol, 1.2 equiv.) and (*S*)-TMS diphenylprolinol catalyst **22** (32.5 mg, 0.1 mmol, 0.2 equiv.) in 1 mL solvent was stirred at room temperature for 2 days. The mixture concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 7:1) the product was obtained as yellow solid as a mixture of two diastereomers.

Yield m = 102 mg (0.3 mmol, 60 %)

TLC R_f = 0.3 (*n*-pentane/EtOAc 7:1)

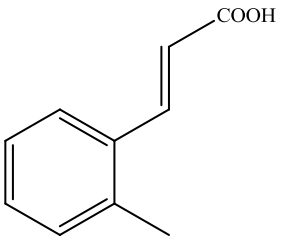
^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.47 (dd, *J* = 13.2, 3.9 Hz, 1H, C*H*Ph, minor diastereomer), 3.59- 3.66 (dt, *J* = 12.4, 9.4 Hz, 1H, C*H*CHO, major diastereomer), 3.79 (dd, *J* = 12.1, 10.9 Hz, 1H, C*H*Ph, major diastereomer), 4.12 (dt, *J* = 13.2, 8.0 Hz, 1H, C*H*CHO, minor diastereomer), 4.15-4.21 (m, 1H, C*H*CH_2NO_2, major diastereomer), 4.40 (dt, *J* = 8.0, 4.9 Hz, 1H, C*H*CH_2NO_2, minor diastereomer), 4.70 (dd, *J* = 14.3, 3.4 Hz, 1H, CH_2NO_2, major diastereomer), 4.83 (dd, *J* = 13.0, 4.9 Hz, 1H, CH_2NO_2, minor diastereomer), 4.93 (dd, *J* = 14.3, 5.2 Hz, 1H, CH_2NO_2, major diastereomer), 4.99 (dd, *J* = 13.0, 8.6 Hz, 1H, CH_2NO_2, minor diastereomer), 5.74 (d, *J* = 3.9 Hz, 1H, C*H*NO_2, minor diastereomer), 6.20 (d, *J* = 10.7 Hz, 1H, C*H*NO_2, major diastereomer), 7.16 (d, *J* = 7.8 Hz, 1H, CH_{Ar}), 7.26-7.30 (m, 2H, CH_{Ar}), 7.30-7.46 (m, 14H, CH_{Ar}), 7.49-7.54 (m, 1H, CH_{Ar}), 9.43 (s, 1H, C*H*O, major diastereomer), 9.59 (s, 1H, C*H*O, minor diastereomer).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 36.2 (*C*HCH_2NO_2, major diastereomer), 36.5 (*C*HCH_2NO_2, minor diastereomer), 45.0 (*C*HPh, minor diastereomer), 46.5 (*C*HPh, major

diastereomer), 48.2 (*C*HCHO, minor diastereomer), 51.8 (*C*HCHO, major diastereomer), 77.6 (*C*H_2NO_2, major diastereomer), 81.1 (*C*H_2NO_2, minor diastereomer), 90.5 (*C*HNO_2, minor diastereomer), 92.0 (*C*HNO_2, major diastereomer), 126.0 (*C*H_{Ar}, major diastereomer), 127.3 (*C*H_{Ar}, major diastereomer), 127.7 (*C*H_{Ar}, major diastereomer), 127.9 (2C, *C*H_{Ar}, major diastereomer), 128.1 (*C*H_{Ar}, minor diastereomer), 128.4 (2C, *C*H_{Ar}, minor diastereomer), 129.0 (2C, *C*H_{Ar}, minor diastereomer), 129.1 (*C*H_{Ar}, minor diastereomer), 129.3 (*C*H_{Ar}, minor diastereomer), 129.4 (*C*$_{Ar}$, minor diastereomer), 129.7 (*C*H_{Ar}, major diastereomer), 129.7 (2C, *C*H_{Ar}, major diastereomer), 129.8 (*C*H_{Ar}, minor diastereomer), 130.1 (*C*H_{Ar}, major diastereomer), 130.6 (*C*$_{Ar}$, major diastereomer), 131.7 (*C*H_{Ar}, minor diastereomer), 132.5 (*C*$_{Ar}$, major diastereomer), 134.4 (*C*$_{Ar}$, minor diastereomer), 135.2 (*C*$_{Ar}$, minor diastereomer), 135.4 (*C*$_{Ar}$, major diastereomer), 200.2 (*C*HO, major diastereomer), 200.5 (*C*HO, minor diastereomer).

IR (ATR): 2921 (w), 1726 (s), 1549 (s), 1441 (w), 1367 (s), 1227 (w), 1080 (w), 1034 (w), 742 (s), 703 (s) cm^{-1}.

2-Methylcinnamic acid (207)



To a solution of 2-methylbenzaldehyde **206** (6.0 g, 5.8 mL, 50.0 mmol, 1.0 equiv.) and malonic acid (6.3 g, 60.0 mmol, 1.2 equiv,) in 30 mL pyridine were added 2 mL piperidine and the reaction mixture was refluxed for 24 h. After cooling down to room temperature, it was poured in a flask containing 25 g ice and 25 mL conc. HCl. The product was filtered and after recrystallisation in EtOH, it was obtained as white crystals.

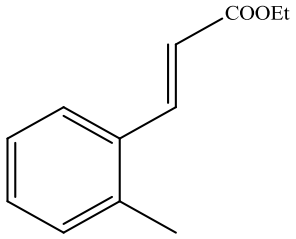
Yield m = 6.2 g (19.0 mmol, 38 %)

TLC R_f = 0.1 (*n*-pentane/EtOAc 5:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.46 (s, 3H, C*H*$_3$), 6.39 (d, *J* = 15.8 Hz, 1H, C*H*COOH), 7.20-7.25 (m, 2H, C*H*$_{Ar}$), 7.28-7.33 (m, *J* = 7.4 Hz, 1.0 Hz, 1H, C*H*$_{Ar}$), 7.59 (d, *J* = 7.4 Hz, 1H, C*H*$_{Ar}$), 8.10 (d, *J* = 15.8 Hz, 1H, PhC*H*).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 19.8 (*C*H$_3$), 118.2 (*C*HCOOH), 126.4 (CH$_{Ar}$), 126.6 (*C*H$_{Ar}$), 130.5 (*C*H$_{Ar}$), 130.9 (*C*H$_{Ar}$), 133.0 (*C*$_{Ar}$), 138.0 (*C*$_{Ar}$), 144.7 (Ph*C*H), 172.1 (*C*OOH).

Ethyl 2-methylcinnamate (208)



To a solution of 2-methylcinnamic acid **207** (6.2 g, 19.0 mmol, 1.0 equiv.) in 50 mL EtOH at 0 °C was added dropwise thionyl chloride (3.4 g, 2 mL, 28.5 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature for 15 h. It was then concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) the product was obtained as colourless clear liquid.

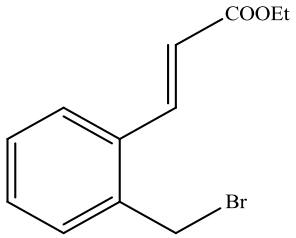
Yield m = 3.6 g (18.8 mmol, 99 %)

TLC R_f = 0.6 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.34 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.43 (s, 3H, CH_3), 4.27 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 6.36 (d, *J* = 15.9 Hz, 1H, CHCOOEt), 7.20 (t, *J* = 7.5 Hz, 2H, CH_{Ar}), 7.25-7.28 (m, 1H, CH_{Ar}), 7.54 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 7.97 (d, *J* = 15.9 Hz, 1H, PhCH).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 14.3 (OCH_2CH_3), 19.8 (CH_3), 60.5 (OCH_2CH_3), 119.3 (CHCOOEt), 126.3 (CH_{Ar}), 126.4 (CH_{Ar}), 129.9 (CH_{Ar}), 130.7 (CH_{Ar}), 133.4 (C_{Ar}), 137.6 (C_{Ar}), 142.3 (PhCH), 167.1 (COOEt).

Ethyl 2-(bromomethyl)cinnamate (209)



To a suspension of N-bromosuccinimide (4.3 g, 24.5 mmol, 1.3 equiv.) in 100 mL tetrachloromethane was added ethyl 2-methylcinnamate **208** (3.6 g, 18.8 mmol, 1.0 equiv.). To the reaction mixture was added catalytic amount of AIBN and it was refluxed for 8 hours. After the mixture was cooled down to room temperature, saturated aqueous $Na_2S_2O_3$ was added and it was extracted three times with EtOAc, the extracts were washed with brine, dried with

Na_2SO_4 and concentrated *in vacuo*. The product was obtained after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) as pale yellow liquid.

Yield m = 3.5 g (13.2 mmol, 60 %)

TLC R_f = 0.1 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.33 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 4.26 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.56 (s, 2H, CH_2Br), 6.42 (d, *J* = 15.7 Hz, 1H, CHCOOEt), 7.29-7.32 (m, 2H, CH_{Ar}), 7.33-7.35 (m, 1H, CH_{Ar}), 7.54-7.56 (m, 1H, CH_{Ar}), 8.03 (d, *J* = 15.7 Hz, 1H, PhCH).

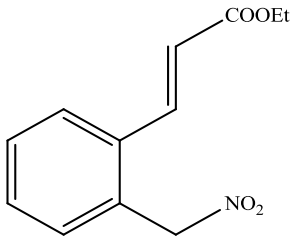
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 14.3 (CH_3), 30.6 (CH_2Br), 60.7 (CH_2), 121.0 (CHCOOEt), 127.2 (CH_{Ar}), 129.2 (CH_{Ar}), 130.3 (CH_{Ar}), 130.6 (CH_{Ar}), 133.7 (C_{Ar}), 136.6 (C_{Ar}), 140.5 (PhCH), 166.6 (COOEt).

MS (EI, 70 eV): *m/z* (%) = 58 (4), 63 (6), 77 (2), 89 (12), 91 (5), 105 (3), 115 (93), 133 (6), 145 (17), 161 (5), 175 (10), 189 (100), 223 (12), 268 (12).

IR (ATR): 2980 (m), 2325 (w), 2100 (w), 1710 (s), 1636 (s), 1464 (m), 1369 (m), 1299 (s), 1174 (s), 1033 (m), 974 (m), 865 (w), 761 (s), 702 (w) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{12}H_{13}O_2BrNa$: 290.9991; found: 290.9992.

Ethyl 2-(nitromethyl)cinnamate (202)



To a solution of ethyl 2-(bromomethyl)cinnamate **209** (0.8 g, 3.0 mmol, 1.0 equiv.) in diethylether at 0 °C was added slowly silver nitrite (0.55 g, 3.6 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 3 h and then further refluxed for another 4 h. After cooling down to room temperature, the mixture was filtered and concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow liquid.

Yield m = 0.235 g (1.0 mmol, 34 %)

TLC R_f = 0.3 (*n*-pentane/EtOAc 10:1)

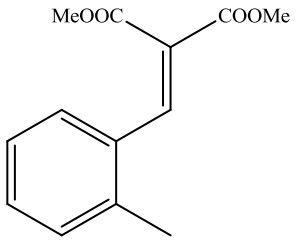
^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.33 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 4.27 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 5.60 (s, 2H, C*H*$_2$NO$_2$), 6.41 (d, *J* = 16.5 Hz, 1H, C*H*COOEt), 7.44 (d, *J* = 4.0 Hz, 2H, C*H*$_{Ar}$), 7.45-7.49 (m, 1H, C*H*$_{Ar}$), 7.66 (t, *J* = 7.4 Hz, 1H, C*H*$_{Ar}$), 7.95 (d, *J* = 16.5 Hz, 1H, PhC*H*).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 14.4 (*C*H$_3$), 60.9 (*C*H$_2$), 76.8 (*C*H$_2$NO$_2$), 122.6 (*C*HCOOEt), 127.4 (*C*H$_{Ar}$), 128.4 (*C*$_{Ar}$), 130.4 (CH$_{Ar}$), 130.6 (*C*H$_{Ar}$), 132.1 (*C*H$_{Ar}$), 135.3 (*C*$_{Ar}$), 139.7 (Ph*C*H), 165.2 (*C*OOEt).

MS (EI, 70 eV): *m/z* (%) = 58 (4), 63 (5), 77 (8), 89 (11), 91 (12), 103 (10), 117 (100), 131 (30), 145 (24), 159 (5), 175 (5), 189 (48), 205 (4), 235 (6).

IR (ATR): 2981 (m), 2326 (w), 2101 (w), 1711 (s), 1636 (s), 1553 (s), 1454 (w), 1369 (s), 1282 (s), 1176 (s), 1033 (m), 974 (m), 861 (m), 763 (s), 695 (m) cm^{-1}.

Dimethyl 2-(2-methylbenzylidene)malonate (210)



To a solution of 2-methylbenzaldehyde **206** (6 g, 5.8 mL, 50.0 mmol, 1.0 equiv.) in 100 mL benzene were added dimethyl malonate (6.6 g, 5.7 mL, 50.0 mmol, 1.0 equiv.) and 0.5 mL piperidine and the reaction mixture was refluxed for 24 h. After cooling down to room temperature, it was washed with water, 1N HCl and brine, dried with sodium sulfate and concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/ EtOAc 5:1) the product was obtained as colourless clear liquid.

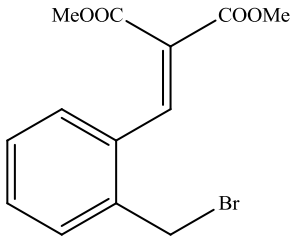
Yield m = 8.1 g (34.5 mmol, 69 %)

TLC R_f = 0.3 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.37 (s, 3H, C*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 7.15 (t, *J* = 7.6 Hz, 1H, C*H*$_{Ar}$), 7.20 (d, *J* = 7.6 Hz, 1H, C*H*$_{Ar}$), 7.25-7.29 (m, 2H, C*H*$_{Ar}$), 8.00 (s, 1H, PhC*H*).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 19.8 (*C*H$_3$), 52.5 (O*C*H$_3$), 52.6 (O*C*H$_3$), 126.1 (*C*H$_{Ar}$), 126.8 (*C*(COOMe)$_2$), 127.5 (*C*H$_{Ar}$), 130.2 (*C*H$_{Ar}$), 130.5 (*C*H$_{Ar}$), 132.4 (*C*$_{Ar}$), 137.7 (*C*$_{Ar}$), 142.4 (Ph*C*H), 166.8 (*C*OOMe), 166.9 (*C*OOMe).

Dimethyl 2-(2-(bromomethyl)benzylidene)malonate (212)



To a suspension of N-bromosuccinimide (8.0 g, 45.0 mmol, 1.3 equiv.) in 150 mL tetrachloromethane was added dimethyl 2-(2-methylbenzylidene)malonate **210** (8.0 g, 34.0 mmol, 1.0 equiv.). To the reaction mixture was added catalytic amount of AIBN and it was refluxed for 8 hours. After the mixture was cooled down to room temperature, saturated aqueous $Na_2S_2O_3$ was added and it was extracted three times with EtOAc, the extracts were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The product was obtained after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) as pale yellow liquid.

Yield m = 7.4 g (23.8 mmol, 70 %)

Melting point 63 °C

TLC R_f = 0.4 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.69 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 4.50 (s, 2H, C*H*$_2$Br), 7.28-7.30 (m, 1H, C*H*$_{Ar}$), 7.32-7.34 (m, 1H, C*H*$_{Ar}$), 7.35 (dd, *J* = 7.2 Hz, 1.4 Hz, 1H, C*H*$_{Ar}$), 7.39 (dd, *J* = 7.5 Hz, 0.8 Hz, 1H, C*H*$_{Ar}$), 8.13 (s, 1H, PhC*H*).

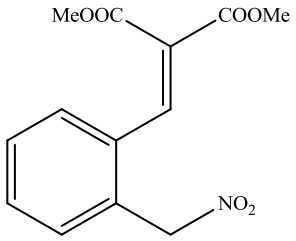
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 30.7 (*C*H$_2$Br), 52.8 (O*C*H$_3$), 52.9 (O*C*H$_3$), 128.4 (*C*H$_{Ar}$), 128.7 (*C*(COOMe)$_2$), 129.0 (*C*H$_{Ar}$), 130.4 (*C*H$_{Ar}$), 130.5 (*C*H$_{Ar}$), 133.0 (*C*$_{Ar}$), 136.5 (*C*$_{Ar}$), 140.6 (Ph*C*H), 164.0 (*C*OOMe), 166.3 (*C*OOMe).

MS (EI, 70 eV): *m/z* (%) = 59 (25), 63 (6), 89 (11), 115 (87), 129 (43), 143 (48), 171 (7), 173 (38), 189 (27), 201 (67), 219 (23), 233 (100), 252 (5), 283 (28), 313 (13).

IR (ATR): 2954 (w), 1725 (s), 1631 (m), 1439 (m), 1367 (m), 1217 (s), 1067 (s), 980 (w), 940 (w), 833 (w), 764 (m) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{13}H_{13}O_4BrNa$: 334.9889; found: 334.9889.

Dimethyl 2-(2-(nitromethyl)benzylidene)malonate (203)



To a solution of dimethyl 2-(2-(bromomethyl)benzylidene)malonate **212** (0.9 g, 3.0 mmol, 1.0 equiv.) in diethylether at 0 °C was added slowly silver nitrite (0.55 g, 3.6 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 3 h and then further refluxed for another 4 h. After cooling down to room temperature, the mixture was filtered and concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow liquid.

Yield m = 0.251 g (0.9 mmol, 29 %)

TLC R_f = 0.3 (*n*-pentane/EtOAc 5:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.65 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 5.52 (s, 2H, C*H*$_2$NO$_2$), 7.38 (dd, *J* = 5.2 Hz, 3.7 Hz, 1H, C*H*$_{Ar}$), 7.43-7.45 (m, 2H, C*H*$_{Ar}$), 7.46-7.47 (m, 1H, C*H*$_{Ar}$), 8.03 (s, 1H, PhC*H*).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 52.6 (O*C*H$_3$), 52.9 (O*C*H$_3$), 77.1 (*C*H$_2$NO$_2$), 128.3 (*C*(COOMe)$_2$), 128.5 (*C*H$_{Ar}$), 130.3 (*C*H$_{Ar}$), 130.4 (*C*H$_{Ar}$), 131.7 (*C*H$_{Ar}$), 133.7 (*C*$_{Ar}$), 134.6 (*C*$_{Ar}$), 140.4 (Ph*C*H), 163.6 (*C*OOMe), 165.7 (*C*OOMe).

MS (EI, 70 eV): *m/z* (%) = 45 (3), 59 (19), 63 (6), 77 (6), 89 (12), 102 (9), 115 (86), 129 (60), 143 (36), 157 (26), 171 (10), 173 (38), 189 (100), 201 (8), 205 (3), 219 (12), 233 (94), 248 (21), 249 (9), 279 (2).

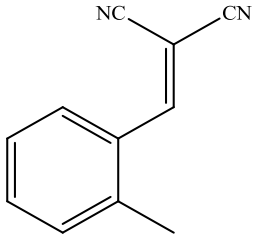
IR (ATR): 2959 (w), 1723 (s), 1629 (w), 1542 (s), 1441 (s), 1370 (m), 1219 (s), 1068 (m), 948 (w), 836 (w), 760 (s), 707 (m) cm^{-1}.

Elemental analysis ($C_{13}H_{13}NO_6$)

Calculated: C = 55.91% H = 4.69% N = 5.02%

Found: C = 55.89% H = 4.77% N = 4.67%

2-(2-Methylbenzylidene)malononitrile (211)



To a solution of 2-methylbenzaldehyde **206** (6.0 g, 5.8 mL, 50.0 mmol, 1.0 equiv.) and malononitrile (4.0 g, 60.0 mmol, 1.2 equiv.) in 50 mL ethanol was added 0.2 mL 10% KOH and the reaction mixture was stirred at room temperature for 4 h. The product was filtered and recrystallized in EtOH to afford 2-(2-methylbenzylidene)malononitrile **211** as white crystals.

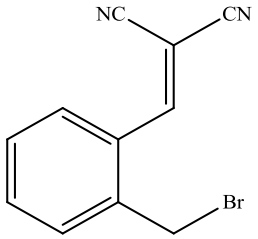
Yield m = 6.3 g (37.5 mmol, 75 %)

TLC R_f = 0.4 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.44 (s, 3H, C*H*$_3$), 7.33-7.35 (m, 2H, C*H*$_{Ar}$), 7.49 (t, *J* = 7.5 Hz, 1H, C*H*$_{Ar}$), 8.07 (d, *J* = 7.9 Hz, 1H, C*H*$_{Ar}$), 8.10 (s, 1H, PhC*H*).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 19.8 (*C*H$_3$), 83.9 (*C*(CN)$_2$), 112.5 (*C*N), 113.8 (*C*N), 127.1 (*C*H$_{Ar}$), 128.3 (*C*H$_{Ar}$), 129.9 (*C*$_{Ar}$), 131.4 (*C*H$_{Ar}$), 134.2 (*C*H$_{Ar}$), 139.8 (*C*$_{Ar}$), 158.2 (Ph*C*H).

2-(2-(Bromomethyl)benzylidene)malononitrile (213)



To a suspension of N-bromosuccinimide (8.0 g, 45.0 mmol, 1.25 equiv.) in 150 mL tetrachloromethane was added 2-(2-methylbenzylidene)malononitrile **211** (6.0 g, 36.0 mmol, 1.0 equiv.). To the reaction mixture was added catalytic amount of AIBN and it was refluxed for 8 hours. After the mixture was cooled down to room temperature, saturated aqueous $Na_2S_2O_3$ was added and it was extracted three times with EtOAc, the extracts were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The product was obtained after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) as pale yellow liquid.

Yield m = 5.7 g (23.4 mmol, 65 %)

Melting point 95 °C

TLC R_f = 0.4 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.50 (s, 2H, C*H*$_2$Br), 7.48-7.50 (m, 2H, C*H*$_{Ar}$), 7.56 (td, *J* = 7.8 Hz, 0.8 Hz, 1H, C*H*$_{Ar}$), 8.07 (d, *J* = 7.8 Hz, 1H, C*H*$_{Ar}$), 8.27 (s, 1H, PhC*H*).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 29.8 (*C*H$_2$Br), 85.9 (*C*(CN)$_2$), 112.1 (*C*N), 113.4 (*C*N), 129.2 (*C*H$_{Ar}$), 129.8 (*C*$_{Ar}$), 129.9 (*C*H$_{Ar}$), 131.1 (*C*H$_{Ar}$), 134.1 (*C*H$_{Ar}$), 138.1 (*C*$_{Ar}$), 156.9 (Ph*C*H).

MS (EI, 70 eV): *m/z* (%) = 51 (5), 63 (8), 77 (3), 89 (5), 102 (2), 113 (14), 140 (100), 167 (95), 168 (20), 219 (6), 246 (37).

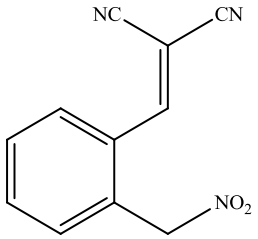
IR (ATR): 3037 (w), 2929 (w), 2230 (m), 1726 (s), 1582 (s), 1452 (m), 1365 (s), 1217 (s), 1068 (m), 925 (s), 852 (m), 757 (s) cm^{-1}.

Elemental analysis ($C_{11}H_7N_2Br$)

Calculated: C = 53.47% H = 2.86% N = 11.34%

Found: C = 53.21% H = 3.02% N = 10.87%

2-(2-(Nitromethyl)benzylidene)malononitrile (204)



To a solution of 2-(2-(bromomethyl)benzylidene)malononitrile **213** (0.74 g, 3.0 mmol, 1.0 equiv.) in diethylether at 0 °C was added slowly silver nitrite (0.55 g, 3.6 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 3 h and then further refluxed for another 4 h. After cooling down to room temperature, the mixture was filtered and concentrated *in vacuo*. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow liquid.

Yield m = 0.170 g (0.8 mmol, 27 %)

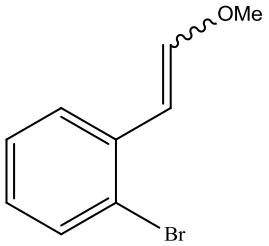
TLC R_f = 0.4 (*n*-pentane/EtOAc 5:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 5.61 (s, 2H, CH_2NO_2), 7.62-7.69 (m, 4H, CH_{Ar}), 8.11 (s, 1H, PhC*H*).

^{13}C-NMR (150 MHz, $CDCl_3$): δ [ppm] = 78.5 (*C*H_2NO_2), 87.4 (*C*$(CN)_2$), 111.6 (*C*N), 112.9 (*C*N), 129.1 (*C*H_{Ar}), 130.5 (*C*$_{Ar}$), 131.0 (*C*H_{Ar}), 132.0 (*C*H_{Ar}), 133.3 (*C*$_{Ar}$), 133.9 (*C*H_{Ar}), 156.6 (Ph*C*H).

IR (ATR): 1726 (w), 1587 (w), 1462 (w), 1367 (w), 1224 (m), 1039 (s), 754 (s) cm^{-1}.

1-Bromo-2-(2-methoxyvinyl)benzene (215)



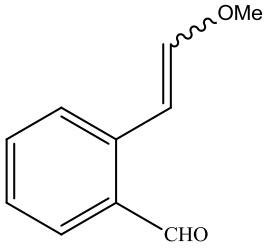
To a solution of (methoxymethyl)triphenylphosphonium chloride (7.54 g, 20.0 mmol, 1.1 equiv.) in dry THF under argon atmosphere at 0 °C, *t*-BuOK (2.7 g, 24.0 mmol, 1.2 equiv.) was added in small portions. After the addition was finished, the reaction mixture was stirred at that temperature for 30 min more. Then 2-bromobenzaldehyde **214** (3.7 g, 20.0 mmol, 1.0 equiv.) was added dropwise and the stirring was continued for 2 hours at room temperature. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The combined extracts were washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$. After the solvent was removed *in vacuo*, the product was purified by flash column chromatography (eluent: pentane/EtOAC 15:1). The product was obtained as a mixture of the *E* and *Z* isomers.

Yield m = 3.9 g (18.4 mmol, 92 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.60 (d, *J* = 7.2 Hz, 1H, C*H*), 6.09 (d, *J* = 12.8 Hz, 1H, C*H*), 6.25 (d, *J* = 7.2 Hz, 1H, C*H*), 6.96-7.02 (m, 4H, CH_{Ar}), 7.18-7.26 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H, CH_{Ar}), 7.52-7.55 (m, 1H, CH_{Ar}), 8.03 (d, *J* = 8.0 Hz, 1H, CH_{Ar}).

^{13}C-NMR (150 MHz, $CDCl_3$): δ [ppm] = 56.8 (O*C*H_3), 61.1 (O*C*H_3), 104.0 (*C*H), 104.6 (*C*H), 122.9 (*C*H_{Ar}), 123.2 (*C*H_{Ar}), 125.9 (*C*H_{Ar}), 127.3 (*C*H_{Ar}), 127.3 (*C*$_{Ar}$), 127.3 (*C*$_{Ar}$), 127.7 (*C*H_{Ar}), 130.5 (*C*H_{Ar}), 132.7 (*C*H_{Ar}), 133.1 (*C*H_{Ar}), 135.3 (*C*$_{Ar}$), 136.5 (*C*$_{Ar}$), 149.4 (*C*H), 150.7 (*C*H).

2-(2-Methoxyvinyl)benzaldehyde (216)



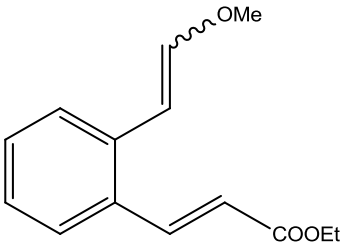
2.0 M *n*-BuLi in cyclohexane (8 mL, 19.2 mmol, 1.2 equiv.) was added dropwise to a stirring solution of compound **215** (3.4 g, 16.0 mmol, 1.0 equiv.) in dry THF at -78 °C under argon atmosphere. After stirring for 2 hours, DMF (1.84 mL, 24 mmol, 1.5 equiv.) was added and the reaction was allowed to stir at this temperature for 2 hours more. The reaction was then quenched at with water, extracted with EtOAc and the combined organic extracts were concentrated under reduced pressure. After purification by flash column chromatography (eluent: Pentane/EtOAc 20:1), the product was obtained as a mixture of *E* and *Z* isomers.

Yield m = 2.3 g (13.9 mmol, 87 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 3.76 (s, 3H, OC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 6.11 (d, *J* = 7.2 Hz, 1H, C*H*), 6.32 (d, *J* = 7.2 Hz, 1H, C*H*), 6.75 (d, *J* = 12.8 Hz, 1H, C*H*), 7.02 (d, *J* = 12.8 Hz, 1H, C*H*), 7.29-7.34 (m, 2H, C*H*$_{Ar}$), 7.42 (d, *J* = 7.6 Hz, 1H, C*H*$_{Ar}$), 7.47-7.53 (m, 2H, C*H*$_{Ar}$), 7.78-7.80 (m, 2H, C*H*$_{Ar}$), 7.86-7.89 (m, 1H, C*H*$_{Ar}$), 10.20 (s, 1H, C*H*O), 10.21 (s, 1H, C*H*O).

^{13}C-NMR (150 MHz, $CDCl_3$): δ [ppm] = 56.7 (O*C*H$_3$), 60.7 (O*C*H$_3$), 100.6 (*C*H), 101.2 (*C*H), 126.0 (*C*H$_{Ar}$), 126.1 (*C*H$_{Ar}$), 126.3 (*C*H$_{Ar}$), 130.2 (*C*H$_{Ar}$), 131.2 (*C*$_{Ar}$), 131.9 (*C*$_{Ar}$), 132.1 (*C*H$_{Ar}$), 132.5 (*C*H$_{Ar}$), 133.3 (*C*H$_{Ar}$), 133.7 (*C*H$_{Ar}$), 137.6 (*C*$_{Ar}$), 138.9 (*C*$_{Ar}$), 150.2 (*C*H), 152.3 (*C*H), 192.8 (*C*HO), 192.8 (*C*HO).

((2E)-Ethyl 3-(2-(methoxyvinyl)phenyl)acrylate (217)



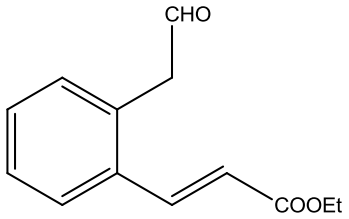
To a solution of compound **216** (1.6 g, 10.0 mmol, 1.0 equiv.) in DCM at room temperature, Ph_3P=CHCOOEt (4.5 g, 13.0 mmol, 1.3 equiv.) was added portionwise and the reaction was stirred overnight. It was then concentrated *in vacuo* and directly subjected to flash column chromatography (eluent: pentane/EtOAc 9:1).

Yield m = 2.3 g (9.8 mmol, 98 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.32 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.33 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 3.70 (s, 3H, OC*H*$_3$), 3.71 (s, 3H, OC*H*$_3$), 4.25 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 4.26 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 5.46 (d, *J* = 7.1 Hz, 1H, C*H*), 6.04 (d, *J* = 12.7 Hz, 1H, C*H*), 6.22 (d, *J* = 7.1 Hz, 1H, C*H*), 6.33 (dd, *J* = 15.9, 8.3 Hz, 2H, C*H*$_{Ar}$), 6.82 (d, *J* = 10.6 Hz, 1H, C*H*$_{Ar}$), 7.13-7.23 (m, 2H, C*H*$_{Ar}$), 7.26-7.32 (m, 3H, C*H*$_{Ar}$), 7.49-7.51 (m, 2H, C*H*$_{Ar}$), 7.81-7.84 (m, 1H, C*H*$_{Ar}$), 8.01 (d, *J* = 12.7, 2H, C*H*).

^{13}C-NMR (150 MHz, $CDCl_3$): δ [ppm] = 14.4 (*C*H$_3$), 14.5 (*C*H$_3$), 56.8 (O*C*H$_3$), 60.5 (O*C*H$_3$), 60.5 (O*C*H$_2$), 60.7 (O*C*H$_2$), 101.9 (*C*H), 102.2 (*C*H), 119.4 (*C*H), 119.5 (*C*H), 126.4 (*C*H$_{Ar}$), 126.7 (*C*H$_{Ar}$), 126.8 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 129.7 (*C*H$_{Ar}$), 130.0 (*C*H$_{Ar}$), 130.1 (*C*H$_{Ar}$), 132.0 (*C*H$_{Ar}$), 135.2 (*C*$_{Ar}$), 136.5 (*C*$_{Ar}$), 142.8 (*C*$_{Ar}$), 143.1 (*C*$_{Ar}$), 149.0 (*C*H), 151.2 (*C*H), 167.1 (*C*H), 167.2 (*C*H).

(E)-Ethyl 3-(2-(formylmethyl)phenyl)acrylate (205)



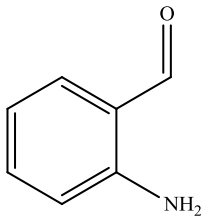
70 % perchloric acid in water (10.5 mL) was added dropwise to a stirring solution of compound **217** (1.74 g, 7.5 mmol) in diethyl ether at 0 °C. After 10 min, the cooling bath was removed and the stirring was continued for 2 hours more. The mixture was then diluted with water and extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over sodium sulphate and concentrated *in vacuo*. After purification by flash column chromatography (eluent: pentane/EtOAc 5:1), the product was obtained as a pale yellow liquid.

Yield m = 1.47 g (6.75 mmol, 90 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.34 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 3.89 (s, 2H, C*H*$_2$), 4.27 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 6.39 (d, *J* = 15.7 Hz, 1H, C*H*), 7.22 (d, *J* = 7.3 Hz, 1H, C*H*$_{Ar}$), 7.33-7.41 (m, 2H, C*H*$_{Ar}$), 7.64 (d, *J* = 7.3 Hz, 1H, C*H*$_{Ar}$), 7.83 (d, *J* = 15.7, 2H, C*H*), 9.75 (s, 1H, C*H*O).

^{13}C-NMR (150 MHz, $CDCl_3$): δ [ppm] = 14.3 (*C*H$_3$), 48.1 (*C*H$_2$), 60.7 (O*C*H$_2$), 121.0 (*C*H), 127.1 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 130.4 (*C*H$_{Ar}$), 131.4 (*C*H$_{Ar}$), 131.7 (*C*$_{Ar}$), 134.3 (*C*$_{Ar}$), 141.1 (*C*H), 166.6 (*C*O), 198.3 (*C*HO).

2-Aminobenzaldehyde (235)



To a solution of 2-aminobenzyl alcohol **234** (2.46 g, 20.0 mmol, 1.0 equiv.) in 50 mL DCM was added manganese (IV) oxide (3.64 g, 42.0 mmol, 2.1 equiv.) and the reaction mixture was stirred at room temperature for 48 h. Manganese oxide was then filtered off and the filtrate was concentrated *in vacuo*. Flash column chromatography (eluent: DCM) afforded the product as a yellow solid.

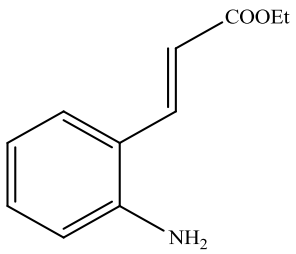
Yield m = 2.2 g (17.8 mmol, 89 %)

TLC R_f = 0.6 (DCM)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 6.11 (s, 2H, N*H*$_2$), 6.64 (d, *J* = 8.3 Hz, 1H, C*H*$_{Ar}$), 6.72-6.80 (m, 1H, C*H*$_{Ar}$), 7.28-7.35 (m, 1H, C*H*$_{Ar}$), 7.48 (dd, *J* = 7.8, 1.5 Hz, 1H, C*H*$_{Ar}$), 9.87 (s, 1H, C*H*O).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 116.0 (*C*H$_{Ar}$), 116.4 (CH$_{Ar}$), 118.8 (*C*$_{Ar}$), 135.2 (*C*H$_{Ar}$), 135.7 (*C*H$_{Ar}$), 149.9 (*C*$_{Ar}$), 194.2 (*C*HO).

(E)-Ethyl 3-(2-aminophenyl)acrylate (236)



To a solution of 2-aminobenzaldehyde **235** (0.85 g, 7.0 mmol, 1.0 equiv.) in 10 mL DCM was added the Wittig reagent Ph_3P=CHCOOEt (2.4 g, 7.0 mmol, 1.0 equiv.) and the reaction mixture was stirred at room temperature for 15 h. It was then concentrated *in vacuo* and after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as yellow solid.

Yield m = 1.3 g (6.7 mmol, 95 %)

Melting point 75 °C

TLC R_f = 0.1 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.31 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 3.98 (s, 2H, NH_2), 4.24 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 6.33 (d, *J* = 15.8 Hz, 1H, CHCOOEt), 6.67 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 6.74 (t, *J* = 7.5 Hz, 1H, CH_{Ar}), 7.11-7.17 (m, 1H, CHAr), 7.33-7.38 (m, 1H, CHAr), 7.80 (d, *J* = 15.8 Hz, 1H, PhCH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 14.3 (OCH_2CH_3), 60.4 (OCH_2CH_3), 116.7 (CHCOOEt), 118.1 (CH_{Ar}), 118.9 (CH_{Ar}), 119.8 (C_{Ar}), 128.1 (CH_{Ar}), 131.2 (CH_{Ar}), 140.0 (PhCH), 145.6 (C_{Ar}), 167.3 (COOEt).

MS (EI, 70 eV): *m/z* (%) = 89 (6), 118 (28), 128 (4), 146 (93), 174 (11), 191 (100).

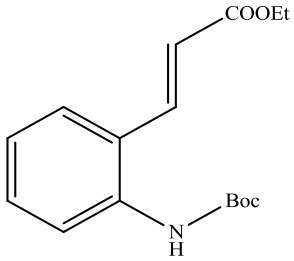
IR (ATR): 3462 (w), 3367 (m), 2976 (m), 1687 (s), 1611 (s), 1467 (s), 1311 (s), 1160 (s), 1025 (s), 861 (m), 801 (s), 750 (s) cm^{-1}.

Elemental analysis ($C_{11}H_{13}NO_2$)

Calculated: C = 69.09% H = 6.85% N = 7.31%

Found: C = 69.52% H = 6.37% N = 7.01%

(E)-Ethyl 3-(2-((tert-butoxycarbonyl)amino)phenyl)acrylate (239)



To a solution of (E)-ethyl 3-(2-aminophenyl)acrylate **236** (0.76 g, 4.0 mmol, 1.0 equiv.) in 10 mL THF was added di-*tert*-butyl dicarbonate (1.3 g, 6.0 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature for 24 h. It was then concentrated *in vacuo* and after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) the product was obtained as pale yellow solid.

Yield m = 1.01 g (3.5 mmol, 87 %)

Melting point 84 °C

TLC R_f = 0.4 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.51 (s, 9H, $C(CH_3)_3$), 4.26 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 6.38 (d, *J* = 15.8 Hz, 1H, CHCOOEt), 6.54 (s, 1H, NH), 7.10 (q, *J* = 7.6 Hz, 1H, CH_{Ar}), 7.32-7.38 (m, 1H, CHAr), 7.50 (dd, *J* = 7.8 Hz, 1.0 Hz, 1H, CH_{Ar}), 7.74-7.76 (m, 1H, CHAr), 7.83 (d, *J* = 15.8 Hz, 1H, PhCH).

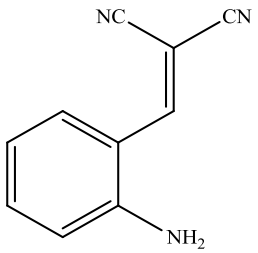
^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 14.3 (OCH_2CH_3), 28.3 ($C(CH_3)_3$), 60.7 (OCH_2CH_3), 81.0 ($C(CH_3)_3$), 120.5 (CHCOOEt), 123.0 (CH_{Ar}), 124.5 (CH_{Ar}), 127.1 (CH_{Ar}), 130.7 (CH_{Ar}), 136.5 (C_{Ar}), 139.3 (PhCH), 153.0 (C_{Ar}), 166.8 (COOEt).

MS (ESI): *m/z* (%) = 212 (38), 258 (45), 314 [(100, $M+Na^+$).

IR (ATR): 3341 (m), 2978 (w), 1700 (s), 1630 (m), 1511 (m), 1458 (m), 1373 (w), 1259 (s), 1150 (s), 1036 (s), 983 (w), 901 (w), 861 (w), 755 (m) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{16}H_{21}O_4NNa$: 314.1363; found: 314.1363.

2-(2-Aminobenzylidene)malononitrile (237)



To a solution of 2-aminobenzaldehyde **235** (0.605 g, 5.0 mmol, 1.0 equiv.) in 25 mL EtOH was added malononitrile (0.5 mmol, 7.5 mmol, 1.5 equiv.) and 0.2 mL 10% KOH and the reaction mixture was stirred at room temperature for 5 h. It was then concentrated *in vacuo* and after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) the product was obtained as pale yellow solid.

Yield	m = 0.507 g (3.0 mmol, 60 %)
Melting point	decomposition after 200 °C
TLC	R_f = 0.3 (*n*-pentane/EtOAc 10:1)

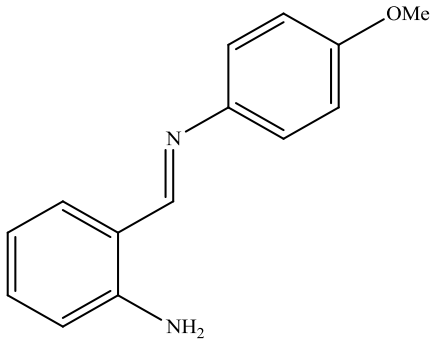
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.36 (s, 2H, NH_2), 7.30-7.37 (m, 1H, CHAr), 7.61-7.74 (m, 3H, CHAr), 8.30 (s, 1H, PhCH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 95.2 ($C(CN)_2$), 116.2 (CN), 121.8 (CN), 124.1 (CH_{Ar}), 126.4 (CH_{Ar}), 128.2 (CH_{Ar}), 133.3 (CH_{Ar}), 144.3 (PhCH), 149.1 (C_{Ar}), 154.8 (C_{Ar}).

MS (EI, 70 eV): *m/z* (%) = 115 (7), 142 (18), 169 (100).

IR (ATR): 3395 (s), 3322 (m), 3144 (s), 2222 (s), 2101 (w), 1739 (w), 1646 (s), 1489 (s), 1433 (s), 1374 (s), 1206 (s), 1111 (s), 921 (m), 853 (m), 740 (s), 691 (s) cm^{-1}.

(E)-tert-Butyl (2-(((4-methoxyphenyl)imino)methyl)phenyl)carbamate (238)



To a solution of 2-aminobenzaldehyde **235** (0.6 g, 5.0 mmol, 1.0 equiv.) in 10 mL DCM was added Ph_3P=N-PMP (2.9 g, 7.5 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature overnight. It was then concentrated *in vacuo* and after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as pale yellow solid.

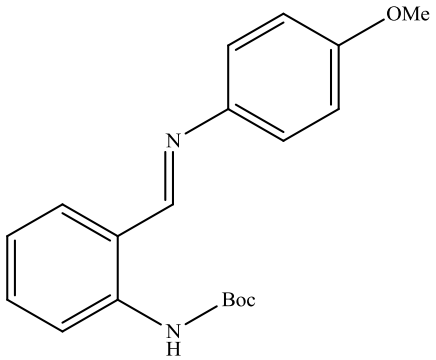
Yield m = 1.1 g (4.75 mmol, 95 %)

TLC R_f = 0.4 (*n*-pentane/EtOAc 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 3.83 (s, 3H, OCH_3), 6.92-6.96 (m, 2H, CH_{Ar}), 7.04 (td, *J* = 7.5 Hz, 1.1 Hz, 1H, CH_{Ar}), 7.23-7.28 (m, 2H, CH_{Ar}), 7.38 (dd, *J* = 12.2 Hz, 4.5 Hz, 2H, CH_{Ar}), 8.44 (d, *J* = 8.3 Hz, 1H, CH_{Ar}), 8.55 (s, 1H, PhC*H*), 12.15 (s, 2H, NH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 55.5 (OCH_3), 114.5 (2C, CH_{Ar}), 118.1 (CH_{Ar}), 120.4 (C_{Ar}), 121.2 (CH_{Ar}), 122.2 (2C, CH_{Ar}), 131.8 (CH_{Ar}), 133.8 (CH_{Ar}), 140.9 (C_{Ar}), 142.8 (C_{Ar}), 158.7 (C_{Ar}), 160.1 (Ph*C*H).

(E)-tert-Butyl (2-(((4-methoxyphenyl)imino)methyl)phenyl)carbamate (241)



To a solution of (E)-N-(2-aminobenzylidene)-4-methoxyaniline **238** (0.91 g, 4.0 mmol, 1.0 equiv.) in 10 mL THF was added di-*tert*-butyl dicarbonate (1.3 g, 6.0 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature for 24 h. It was then concentrated *in vacuo* and after purification by flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) the product was obtained as pale yellow solid.

Yield m = 1.1 g (3.4 mmol, 85 %)

TLC R_f = 0.4 (*n*-pentane/EtOAc 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.54 (s, 9H, C(C*H*$_3$)$_3$), 3.83 (s, 3H, OC*H*$_3$), 6.92-6.96 (m, 2H, C*H*$_{Ar}$), 7.04 (td, *J* = 7.5 Hz, 1.1 Hz, 1H, C*H*$_{Ar}$), 7.23-7.28 (m, 2H, C*H*$_{Ar}$), 7.38 (dd, *J* = 12.2 Hz, 4.5 Hz, 2H, C*H*$_{Ar}$), 8.44 (d, *J* = 8.3 Hz, 1H, C*H*$_{Ar}$), 8.55 (s, 1H, PhC*H*), 12.15 (s, 1H, N*H*).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 28.4 (3C, C(*C*H$_3$)$_3$), 55.5 (O*C*H$_3$), 79.9 (*C*(CH$_3$)$_3$), 114.5 (2C, *C*H$_{Ar}$), 118.1 (*C*H$_{Ar}$), 120.4 (*C*$_{Ar}$), 121.2 (*C*H$_{Ar}$), 122.2 (2C, *C*H$_{Ar}$), 131.8 (*C*H$_{Ar}$), 133.8 (*C*H$_{Ar}$), 140.9 (*C*$_{Ar}$), 142.8 (*C*$_{Ar}$), 153.5 (NH*C*O), 158.7 (*C*$_{Ar}$), 160.1 (Ph*C*H).

MS (EI, 70 eV): *m/z* (%) = 57 (19), 77 (4), 92 (4), 123 (3), 182 (5), 211 (13), 226 (80), 253 (9), 271 (10), 326 (100).

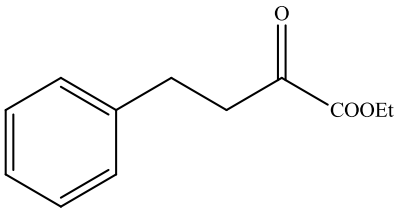
IR (ATR): 3415 (m), 2977 (w), 1723 (w), 1617 (w), 1462 (w), 1372 (m), 1276 (s), 1126 (s), 899 (m), 842 (w), 701 (w) cm^{-1}.

Elemental analysis ($C_{19}H_{22}N_2O_3$)

Calculated: C = 69.92% H = 6.79% N = 8.58%

Found: C = 69.92% H = 6.61% N = 8.43%

Ethyl 2-oxo-4-phenylbutanoate (173a)



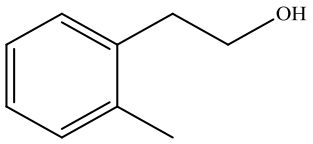
Synthesized according to *GP 1.3,* using (2-bromoethyl)benzene **263** (18.5 g, 13.7 mL, 100.0 mmol, 1.0 equiv.) and diethyl oxalate (21.9 g, 20 mL, 150.0 mmol, 1.5 equiv.). After flash column chromatography (eluent: *n*-pentane/EtOAc 7:1) the product was obtained as pale yellow oil.

Yield m = 11.3 g (55.0 mmol, 55 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.39 (t, *J* = 14.3 Hz, 3H, CH_3), 2.99 (t, *J* = 7.6 Hz, 2H, PhCH_2), 3.21 (t, *J* = 7.6 Hz, 2H, CH_2CO), 4.34 (q, *J* = 14.3 Hz, 2H, OCH_2), 7.22-7.25 (m, 3H, CH_{Ar}), 7.30-7.33 (m, 2H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 13.9 (*C*H_3), 29.0 (Ph*C*H_2), 41.0 (*C*H_2CO), 62.5 (O*C*H_2), 126.4 (*C*H_{Ar}), 128.4 (2C, *C*H_{Ar}), 128.6 (2C, *C*H_{Ar}), 140.1 (C_{Ar}), 160.8 (*C*OOEt), 193.6 (*C*O).

2-(2-Methylphenyl)ethanol (265b)



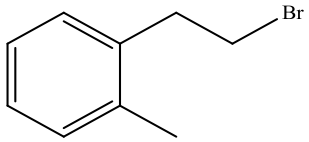
Synthesized according to *GP 1.1*, starting from 2-methylphenylacetic acid **264b** (4.5 g, 30.0 mmol, 1.0 equiv.) and LAH (1.71 g, 45.0 mmol, 1.5 equiv.) in 100 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 2:1) the product was obtained as pale yellow liquid.

Yield m = 3.7 g (27.0 mmol, 90 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.57 (s, 1H, O*H*), 2.33 (s, 3H, CH_3), 2.89 (t, *J* = 6.9 Hz, 2H, PhCH_2), 3.82 (t, *J* = 6.9 Hz, 2H, CH_2OH), 7.10-7.20 (m, 4H, CH_{Ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 19.4 (*C*H_3), 36.4 (Ph*C*H_2), 62.6 (*C*H_2OH), 126.0 (*C*H_{Ar}), 126.6 (*C*H_{Ar}), 129.6 (*C*H_{Ar}), 130.4 (*C*H_{Ar}), 136.4 (C_{Ar}), 136.5 (C_{Ar}).

1-(2-Bromoethyl)-2-methylbenzene (266b)



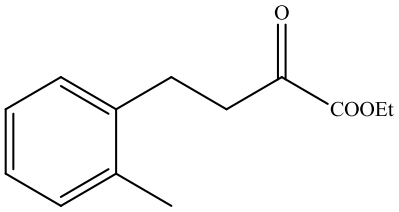
Synthesized according to *GP 1.2*, using 2-(2-methylphenyl)ethanol **265b** (3.7 g, 27.0 mmol, 1.0 equiv.) and PBr_3 (2.4 g, 0.85 mL, 9.0 mmol, 0.33 equiv.) in 10 mL toluene. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 4:1) the product was obtained as pale yellow liquid.

Yield m = 4.0 g (20.0 mmol, 74 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.35 (s, 3H, CH_3), 3.18 (t, *J* = 7.9 Hz, 2H, PhCH_2), 3.53 (t, *J* = 7.9 Hz, 2H, CH_2Br), 7.16-7.27 (m, 4H, CH_{Ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 19.3 (*C*H_3), 31.6 (Ph*C*H_2), 36.9 (*C*H_2Br), 126.2 (*C*H_{Ar}), 127.1 (*C*H_{Ar}), 129.3 (*C*H_{Ar}), 130.5 (CH_{Ar}), 136.1 (C_{Ar}), 137.1 (C_{Ar}).

Ethyl 4-(2-methylphenyl)-2-oxobutanoate (173b)



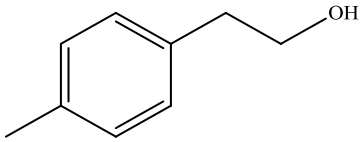
Synthesized according to *GP 1.3*, using 1-(2-bromoethyl)-2-methylbenzene **266b** (4.0 g, 20.0 mmol, 1.0 equiv.) and diethyl oxalate (4.4 g, 4 mL, 30.0 mmol, 1.5 equiv.) in 20 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow oil.

Yield m = 2.2 g (10.0 mmol, 50 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.39 (t, *J* = 7.1 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.94 (t, *J* = 6.8 Hz, 2H, PhCH_2), 3.12 (t, *J* = 6.8 Hz, 2H, CH_2CO), 4.30 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.12-7.15 (m, 4H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 13.9 (*C*H_3), 19.5 (*C*H_3), 26.6 (Ph*C*H_2), 39.6 (*C*H_2CO), 62.9 (O*C*H_2), 126.2 (*C*H_{Ar}), 126.5 (*C*H_{Ar}), 128.7 (*C*H_{Ar}), 130.4 (*C*H_{Ar}), 136.0 (C_{Ar}), 138.2 (C_{Ar}), 160.4 (*C*OOEt), 193.7 (*C*O).

2-(4-Methylphenyl)ethanol (265c)



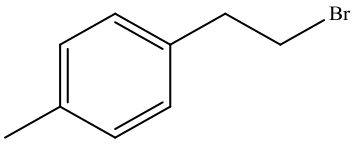
Synthesized according to *GP 1.1*, starting from 4-methylphenylacetic acid **264c** (4.5 g, 30.0 mmol, 1.0 equiv.) and LAH (1.71 g, 45.0 mmol, 1.5 equiv.) in 100 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 2:1) the product was obtained as pale yellow liquid.

Yield m = 3.8 g (28.0 mmol, 93 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.67 (s, 1H, O*H*), 2.33 (s, 3H, CH_3), 2.82 (t, *J* = 6.6 Hz, 2H, PhCH_2), 3.82 (t, *J* = 6.6 Hz, 2H, CH_2OH), 7.06-7.17 (m, 4H, CH_{Ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 21.0 (*C*H_3), 38.7 (Ph*C*H_2), 63.7 (*C*H_2OH), 128.9 (2C, *C*H_{Ar}), 129.3 (2C, *C*H_{Ar}), 135.3 (C_{Ar}), 136.0 (C_{Ar}).

1-(2-Bromoethyl)-4-methylbenzene (266c)



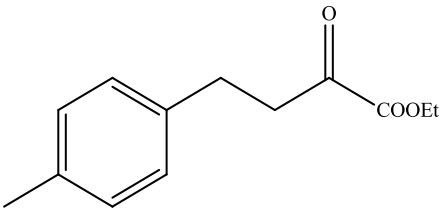
Synthesized according to *GP 1.2*, using 2-(4-methylphenyl)ethanol **265c** (3.8 g, 28.0 mmol, 1.0 equiv.) and PBr_3 (2.7 g, 0.95 mL, 10.0 mmol, 0.36 equiv.) in 10 mL toluene. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 4:1) the product was obtained as pale yellow liquid.

Yield m = 4.1 g (20.5 mmol, 73 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.35 (s, 3H, CH_3), 3.13 (t, *J* = 7.7 Hz, 2H, PhCH_2), 3.55 (t, *J* = 7.7 Hz, 2H, CH_2Br), 6.96-7.36 (m, 4H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.1 (*C*H_3), 33.2 (Ph*C*H_2), 39.0 (*C*H_2Br), 128.5 (2C, *C*H_{Ar}), 129.3 (2C, *C*H_{Ar}), 135.8 (C_{Ar}), 136.5 (C_{Ar}).

Ethyl 4-(4-methylphenyl)-2-oxobutanoate (173c)



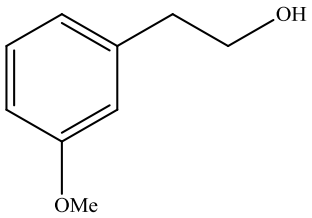
Synthesized according to *GP 1.3*, using 1-(2-bromoethyl)-4-methylbenzene **266c** (4.1 g, 20.5 mmol, 1.0 equiv.) and diethyl oxalate (4.5 g, 4.2 mL, 30.1 mmol, 1.5 equiv.) in 20 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow oil.

Yield m = 2.1 g (9.5 mmol, 46 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.35 (t, *J* = 7.1 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.92 (t, *J* = 7.6 Hz, 2H, PhCH_2), 3.15 (t, *J* = 7.6 Hz, 2H, CH_2CO), 4.30 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.07-7.12 (m, 4H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 14.0 (*C*H_3), 21.0 (*C*H_3), 28.5 (Ph*C*H_2), 41.1 (*C*H_2CO), 62.5 (O*C*H_2), 128.3 (2C, *C*H_{Ar}), 129.2 (2C, *C*H_{Ar}), 135.8 (*C*$_{Ar}$), 136.8 (*C*$_{Ar}$), 161.0 (*C*OOEt), 193.7 (*C*O).

2-(3-Methoxyphenyl)ethanol (265d)



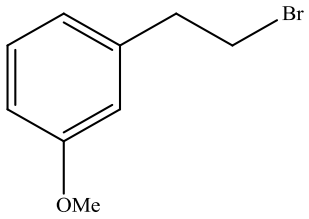
Synthesized according to *GP 1.1*, starting from 3-methoxyphenylacetic acid **264d** (5.0 g, 30.0 mmol, 1.0 equiv.) and LAH (1.71 g, 45.0 mmol, 1.5 equiv.) in 100 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 2:1) the product was obtained as pale yellow liquid.

Yield m = 4.2 g (27.6 mmol, 92 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.81 (s, 1H, O*H*), 2.83 (t, *J* = 6.6 Hz, 2H, PhCH_2), 3.79 (s, 3H, OCH_3), 3.83 (t, *J* = 6.6 Hz, 2H, CH_2OH), 6.76-6.79 (m, 2H, CH_{Ar}), 6.81 (d, *J* = 7.5 Hz, 1H, CH_{Ar}), 7.20-7.25 (m, 1H, CH_{Ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 39.2 (Ph*C*H_2), 55.2 (O*C*H_3), 63.5 (*C*H_2OH), 111.7 (*C*H_{Ar}), 114.8 (*C*H_{Ar}), 121.4 (*C*H_{Ar}), 129.5 (*C*H_{Ar}), 140.2 (C_{Ar}), 159.8 (C_{Ar}).

1-(2-Bromoethyl)-3-methoxybenzene (266d)



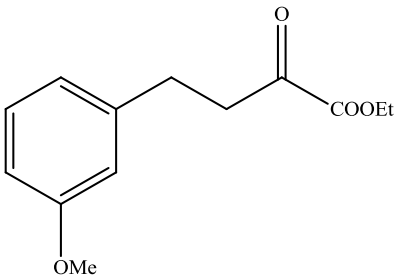
Synthesized according to *GP 1.2*, using 2-(3-methoxyphenyl)ethanol **265d** (4.4 g, 27.6 mmol, 1.0 equiv.) and PBr_3 (2.4 g, 0.85 mL, 9.0 mmol, 0.33 equiv.) in 10 mL toluene. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 4:1) the product was obtained as pale yellow liquid.

Yield m = 4.3 g (20.1 mmol, 73 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.14 (t, *J* = 9.4 Hz, 2H, PhCH_2), 3.57 (t, *J* = 9.4 Hz, 2H, CH_2Br), 3.81 (s, 3H, OCH_3), 6.77 (s, 1H, CH_{Ar}), 6.81 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 7.25 (d, *J* = 7.9 Hz, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 32.6 (Ph*C*H_2), 39.4 (*C*H_2Br), 55.2 (O*C*H_3), 112.2 (*C*H_{Ar}), 114.5 (*C*H_{Ar}), 121.0 (*C*H_{Ar}), 129.6 (*C*H_{Ar}), 140.4 (C_{Ar}), 159.8 (C_{Ar}).

Ethyl 4-(3-methoxyphenyl)-2-oxobutanoate (173d)



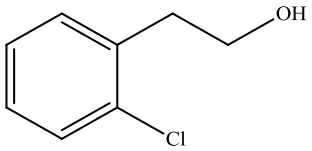
Synthesized according to *GP 1.3*, using 1-(2-bromoethyl)-3-methoxybenzene **266d** (4.3 g, 20.6 mmol, 1.0 equiv.) and diethyl oxalate (4.5 g, 4.2 mL, 30.9 mmol, 1.5 equiv.) in 20 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow oil.

Yield m = 2.7 g (11.0 mmol, 55 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.35 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 2.93 (t, *J* = 7.6 Hz, 2H, PhC*H*$_2$), 3.17 (t, *J* = 7.6 Hz, 2H, C*H*$_2$CO), 3.78 (s, 3H, OC*H*$_3$), 4.29 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 6.73-6.76 (m, 2H, C*H*$_{Ar}$), 6.78 (d, *J* = 7.6 Hz, 1H, C*H*$_{Ar}$), 7.17-7.23 (m, 1H, C*H*$_{Ar}$).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 14.0 (*C*H$_3$), 29.0 (Ph*C*H$_2$), 40.8 (*C*H$_2$CO), 55.1 (O*C*H$_3$), 62.5 (O*C*H$_2$), 111.7 (*C*H$_{Ar}$), 114.2 (*C*H$_{Ar}$), 120.7 (*C*H$_{Ar}$), 129.5 (*C*H$_{Ar}$), 141.7 (*C*$_{Ar}$), 159.7 (*C*$_{Ar}$), 160.9 (*C*OOEt), 193.6 (*C*O).

2-(2-Chlorophenyl)ethanol (265e)



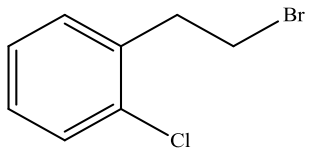
Synthesized according to *GP 1.1*, starting from 2-chlorophenylacetic acid **264e** (5.1 g, 30.0 mmol, 1.0 equiv.) and LAH (1.71 g, 45.0 mmol, 1.5 equiv.) in 100 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 2:1) the product was obtained as pale yellow liquid.

Yield m = 4.3 g (27.3 mmol, 91 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.83 (s, 1H, O*H*), 3.00 (t, *J* = 6.7 Hz, 2H, PhC*H*$_2$), 3.86 (t, *J* = 6.7 Hz, 2H, C*H*$_2$OH), 7.14-7.22 (m, 2H, C*H*$_{Ar}$), 7.25-7.28 (m, 1H, C*H*$_{Ar}$), 7.35 (dd, *J* = 7.7 Hz, 1.2 Hz, 1H, C*H*$_{Ar}$).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 36.8 (Ph*C*H$_2$), 61.9 (*C*H$_2$OH), 126.8 (*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 129.6 (*C*H$_{Ar}$), 131.3 (*C*H$_{Ar}$), 134.2 (*C*$_{Ar}$), 136.1 (*C*$_{Ar}$).

1-(2-Bromoethyl)-2-chlorobenzene (266e)



Synthesized according to *GP 1.2*, using 2-(2-chlorophenyl)ethanol **265e** (4.3 g, 27.3 mmol, 1.0 equiv.) and PBr_3 (2.4 g, 0.85 mL, 9.0 mmol, 0.33 equiv.) in 10 mL toluene. After

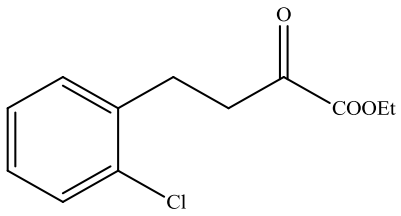
purification by flash column chromatography (eluent: *n*-pentane/EtOAc 4:1) the product was obtained as pale yellow liquid.

Yield m = 4.4 g (20.2 mmol, 74 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.30 (t, *J* = 7.5 Hz, 2H, PhCH_2), 3.60 (t, *J* = 7.5 Hz, 2H, CH_2Br), 7.20-7.25 (m, 2H, CH_{Ar}), 7.27 (d, *J* = 6.5 Hz, 1H, CH_{Ar}), 7.36-7.38 (m, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 31.0 (Ph*C*H_2), 37.2 (*C*H_2Br), 126.9 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 129.7 (*C*H_{Ar}), 131.2 (*C*H_{Ar}), 134.0 (C_{Ar}), 136.4 (C_{Ar}).

Ethyl 4-(2-chlorophenyl)-2-oxobutanoate (173e)



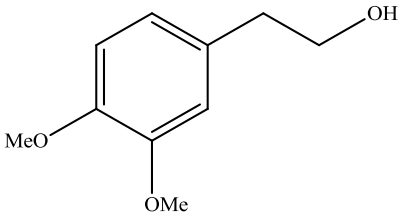
Synthesized according to *GP 1.3*, using 1-(2-bromoethyl)-2-chlorobenzene **266e** (4.4 g, 20.2 mmol, 1.0 equiv.) and diethyl oxalate (4.4 g, 4.1 mL, 30.3 mmol, 1.5 equiv.) in 20 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow oil.

Yield m = 2.4 g (9.9 mmol, 49 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.34 (t, *J* = 7.1 Hz, 3H, CH_3), 3.04 (t, *J* = 7.4 Hz, 2H, PhCH_2), 3.17 (t, *J* = 7.4 Hz, 2H, CH_2CO), 4.29 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.13-7.18 (m, 2H, CH_{Ar}), 7.24 (dd, *J* = 7.0 Hz, 2.3 Hz, 1H, CH_{Ar}), 7.32 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 13.9 (*C*H_3), 27.1 (Ph*C*H_2), 39.5 (*C*H_2CO), 62.7 (O*C*H_2), 127.0 (*C*H_{Ar}), 127.9 (*C*H_{Ar}), 129.6 (*C*H_{Ar}), 130.7 (*C*H_{Ar}), 133.9 (C_{Ar}), 137.7 (C_{Ar}), 160.9 (*C*OOEt), 193.3 (*C*O).

2-(3,4-Dimethoxyphenyl)ethanol (265f)



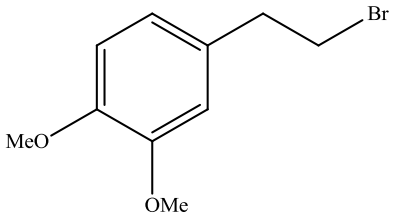
Synthesized according to *GP 1.1*, starting from 3,4-dimethoxyphenylacetic acid **264f** (5.9 g, 30.0 mmol, 1.0 equiv.) and LAH (1.71 g, 45.0 mmol, 1.5 equiv.) in 100 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 2:1) the product was obtained as pale yellow liquid.

Yield m = 4.9 g (27.0 mmol, 90 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.81 (s, 1H, O*H*), 2.78 (t, *J* = 6.4 Hz, 2H, PhCH_2), 3.80 (t, *J* = 6.4 Hz, 2H, CH_2OH), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.72-6.76 (m, 2H, CH_{Ar}), 6.80 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 38.7 (Ph*C*H_2), 55.8 (O*C*H_3), 55.9 (O*C*H_3), 63.7 (*C*H_2OH), 111.4 (*C*H_{Ar}), 112.3 (*C*H_{Ar}), 120.9 (*C*H_{Ar}), 131.0 (C_{Ar}), 147.7 (C_{Ar}), 149.0 (C_{Ar}).

1-(2-Bromoethyl)-3,4-dimethoxybenzene (266f)



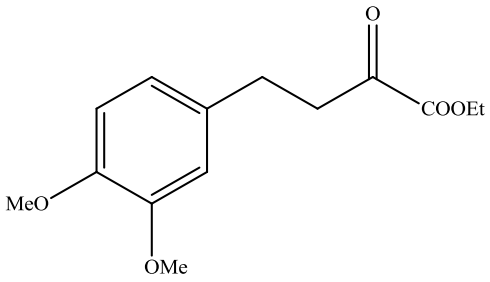
Synthesized according to *GP 1.2*, using 2-(3,4-dimethoxyphenyl)ethanol **265f** (4.9 g, 27.0 mmol, 1.0 equiv.) and PBr_3 (2.4 g, 0.85 mL, 9.0 mmol, 0.33 equiv.) in 10 mL toluene. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 4:1) the product was obtained as pale yellow liquid.

Yield m = 5.0 g (20.5 mmol, 76 %)

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.09 (t, *J* = 7.7 Hz, 2H, PhCH_2), 3.53 (t, *J* = 7.7 Hz, 2H, CH_2Br), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.72 (s, 1H, CH_{Ar}), 6.75 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 6.81 (d, *J* = 8.1 Hz, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 33.3 (Ph*C*H_2), 39.1 (*C*H_2Br), 55.9 (O*C*H_3), 56.0 (O*C*H_3), 111.3 (*C*H_{Ar}), 111.9 (*C*H_{Ar}), 120.7 (*C*H_{Ar}), 131.5 (C_{Ar}), 148.0 (*C*$_{Ar}$), 149.0 (*C*$_{Ar}$).

Ethyl 4-(3,4-dimethoxyphenyl)-2-oxobutanoate (173f)



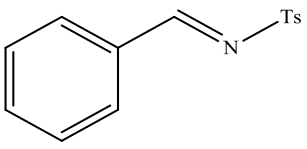
Synthesized according to *GP 1.3*, using 1-(2-bromoethyl)-3,4-dimethoxybenzene **266f** (5.0 g, 20.5 mmol, 1.0 equiv.) and diethyl oxalate (4.5 g, 4.2 mL, 30.8 mmol, 1.5 equiv.) in 20 mL THF. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 5:1) the product was obtained as pale yellow oil.

Yield m = 2.6 g (9.9 mmol, 48 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.32 (t, *J* = 7.1 Hz, 3H, C*H*$_3$), 2.88 (t, *J* = 7.5 Hz, 2H, PhC*H*$_2$), 3.13 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CO), 3.82 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 4.28 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 6.71 (dd, *J* = 5.5 Hz, 2.0 Hz, 2H, C*H*$_{Ar}$), 6.74-6.76 (m, 1H, C*H*$_{Ar}$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (*C*H_3), 28.6 (Ph*C*H_2), 41.1 (*C*H_2CO), 55.8 (O*C*H_3), 55.9 (O*C*H_3), 62.5 (O*C*H_2), 111.3 (*C*H_{Ar}), 111.7 (*C*H_{Ar}), 120.2 (*C*H_{Ar}), 132.7 (*C*$_{Ar}$), 147.5 (*C*$_{Ar}$), 148.9 (*C*$_{Ar}$), 160.9 (*C*OOEt), 193.7 (*C*O).

(E)-N-Benzylidene-4-methylbenzenesulfonamide (100a)



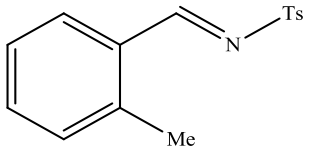
Synthesized according to *GP 2*, using benzaldehyde (2.1 g, 2.1 mL, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 3.7 g (14.5 mmol, 72 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.44 (s, 3H, CH_3), 7.35 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 7.49 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 7.89 (d, *J* = 7.9 Hz, 3H, CH_{Ar}), 7.93 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 9.03 (s, 1H, C*H*Ph).

^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 21.5 (*C*H_3), 127.9 (2C, *C*H_{Ar}), 129.0 (2C, *C*H_{Ar}), 129.7 (2C, *C*H_{Ar}), 131.1 (2C, *C*H_{Ar}), 132.1 (*C*$_{Ar}$), 134.8 (*C*$_{Ar}$), 134.9 (*C*H_{Ar}), 144.5 (*C*$_{Ar}$), 170.0 (*C*HPh).

(E)-N-[(2-Methylphenyl)methylene]-4-methylbenzenesulfonamide (100b)



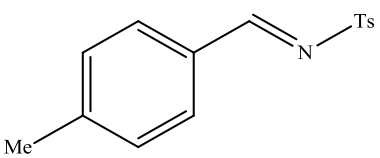
Synthesized according to *GP 2*, using 2-methylbenzaldehyde (2.4 g, 2.3 mL, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30,0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 4.2 g (15.4 mmol, 77 %)

^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 2.38 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.32-7.36 (m, 2H, CH_{Ar}), 7.44 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 7.55 (t, *J* = 7.2 Hz, 1H, CH_{Ar}), 7.84 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 7.93 (d, *J* = 7.8 Hz, 1H, CH_{Ar}), 9.24 (s, 1H, C*H*Ph).

^{13}C-NMR (151 MHz, DMSO-d_6): δ [ppm] = 19.4 (*C*H_3), 21.5 (*C*H_3), 127.1 (*C*H_{Ar}), 128.1 (2C, *C*H_{Ar}), 130.4 (2C, *C*H_{Ar}), 130.5 (*C*$_{Ar}$), 130.6 (*C*H_{Ar}), 132.1 (*C*H_{Ar}), 135.2 (*C*H_{Ar}), 135.4 (*C*$_{Ar}$), 142.8 (*C*$_{Ar}$), 144.9 (*C*$_{Ar}$), 170.4 (*C*HPh).

(E)-N-[(4-Methylphenyl)methylene]-4-methylbenzenesulfonamide (100c)



Synthesized according to *GP 2*, using 4-methylbenzaldehyde (2.4 g, 2.3 mL, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-

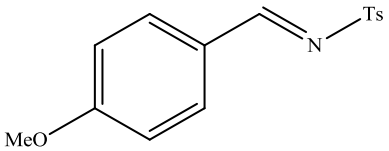
toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 4.3 g (15.8 mmol, 79 %)

^{1}H-NMR (600 MHz, DMSO-d$_6$): δ [ppm] = 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.34 (d, J = 7.9 Hz, 2H, CH_{Ar}), 7.42 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.81 (d, J = 7.9 Hz, 2H, CH_{Ar}), 7.88 (d, J = 8.0 Hz, 2H, CH_{Ar}), 9.07 (s, 1H, C*H*Ph).

^{13}C-NMR (151 MHz, DMSO-d$_6$): δ [ppm] = 21.5 (*C*H$_3$), 21.9 (*C*H$_3$), 128.0 (2C, *C*H$_{Ar}$), 130.0 (*C*$_{Ar}$), 130.4 (2C, *C*H$_{Ar}$), 130.6 (2C, *C*H$_{Ar}$), 131.8 (2C, *C*H$_{Ar}$), 135.5 (*C*$_{Ar}$), 144.9 (*C*$_{Ar}$), 146.7 (*C*$_{Ar}$), 171.6 (*C*HPh).

(E)-N-[(4-Methoxyphenyl)methylene]-4-methylbenzenesulfonamide (100d)



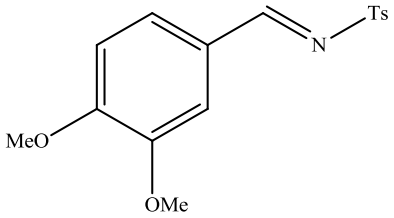
Synthesized according to *GP 2*, using 4-methoxybenzaldehyde (2.7 g, 2.4 mL, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 4.4 g (15.2 mmol, 76 %)

^{1}H-NMR (600 MHz, DMSO-d$_6$): δ [ppm] = 2.34 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.06 (dd, J = 8.8, 1.6 Hz, 2H, CH_{Ar}), 7.36-7.43 (m, 2H, CH_{Ar}), 7.78 (d, J = 8.8 Hz, 2H, CH_{Ar}), 7.96 (d, J = 8.8 Hz, 2H, CH_{Ar}), 9.01 (s, 1H, C*H*Ph).

^{13}C-NMR (151 MHz, DMSO-d$_6$): δ [ppm] = 21.5 (*C*H$_3$), 56.3 (O*C*H$_3$), 115.4 (2C, *C*H$_{Ar}$), 125.3 (*C*$_{Ar}$), 127.9 (2C, *C*H$_{Ar}$), 130.4 (2C, *C*H$_{Ar}$), 134.3 (2C, *C*H$_{Ar}$), 136.0 (*C*$_{Ar}$), 144.7 (*C*$_{Ar}$), 165.5 (*C*$_{Ar}$), 170.8 (*C*HPh).

(E)-N-[(3,4-Dimethoxyphenyl)methylene]-4-methylbenzenesulfonamide (100e)



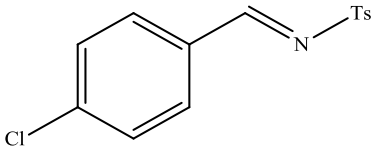
Synthesized according to *GP 2*, using 3,4-dimethoxybenzaldehyde (3.3 g, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 4.7 g (14.8 mmol, 74 %)

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm] = 2.36 (s, 3H, C*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 7.12 (dd, *J* = 8.4, 1.8 Hz, 1H, C*H*$_{Ar}$), 7.41 (d, *J* = 8.4 Hz, 2H, C*H*$_{Ar}$), 7.45 (d, *J* = 1.8 Hz, 1H, C*H*$_{Ar}$), 7.65 (dd, *J* = 8.4, 1.8 Hz, 1H, C*H*$_{Ar}$), 7.78 (d, *J* = 8.4 Hz, 2H, C*H*$_{Ar}$), 8.97 (s, 1H, C*H*Ph).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ [ppm] = 21.5 (*C*H$_3$), 56.0 (O*C*H$_3$), 56.4 (O*C*H$_3$), 111.2 (*C*H$_{Ar}$), 112.0 (*C*H$_{Ar}$), 125.2 (*C*$_{Ar}$), 127.9 (2C, *C*H$_{Ar}$), 129.1 (*C*H$_{Ar}$), 130.4 (2C, *C*H$_{Ar}$), 135.9 (*C*$_{Ar}$), 144.7 (*C*$_{Ar}$), 149.6 (*C*$_{Ar}$), 155.6 (*C*$_{Ar}$), 171.1 (*C*HPh).

(E)-N-[(4-Chlorophenyl)methylene]-4-methylbenzenesulfonamide (100f)



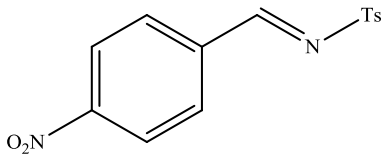
Synthesized according to *GP 2*, using 4-chlorobenzaldehyde (2.8 g, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 5.01 g (17.1 mmol, 86 %)

^{1}H-NMR (600 MHz, DMSO-d$_6$): δ [ppm] = 2.37 (s, 3H, C*H*$_3$), 7.43 (d, *J* = 8.5 Hz, 2H, C*H*$_{Ar}$), 7.61 (d, *J* = 8.5 Hz, 2H, C*H*$_{Ar}$), 7.81 (d, *J* = 8.3 Hz, 2H, C*H*$_{Ar}$), 7.98-8.02 (m, 2H, C*H*$_{Ar}$), 9.12 (s, 1H, C*H*Ph).

^{13}C-NMR (151 MHz, DMSO-d$_6$): δ [ppm] = 21.3 (*C*H$_3$), 128.1 (2C, *C*H$_{Ar}$), 129.9 (2C, *C*H$_{Ar}$), 130.5 (2C, *C*H$_{Ar}$), 131.5 (*C*$_{Ar}$), 133.3 (2C, *C*H$_{Ar}$), 135.1 (*C*$_{Ar}$), 140.4 (*C*$_{Ar}$), 145.2 (*C*$_{Ar}$), 170.9 (*C*HPh).

(E)-N-[(4-Nitrophenyl)methylene]-4-methylbenzenesulfonamide (100g)



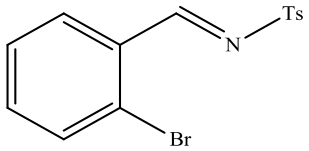
Synthesized according to *GP 2*, using 4-nitrobenzaldehyde (3.0 g, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 4.8 g (15.7 mmol, 79 %)

^{1}H-NMR (600 MHz, DMSO-d$_6$): δ [ppm] = 2.46 (s, 3H, C*H*$_3$), 7.39 (d, *J* = 7.9 Hz, 2H, C*H*$_{Ar}$), 7.91 (d, *J* = 8.2 Hz, 2H, C*H*$_{Ar}$), 8.12 (d, *J* = 8.2 Hz, 2H, C*H*$_{Ar}$), 8.33 (d, *J* = 7.9 Hz, 2H, C*H*$_{Ar}$), 9.12 (s, 1H, C*H*Ph).

^{13}C-NMR (151 MHz, DMSO-d$_6$): δ [ppm] = 21.9 (*C*H$_3$), 124.4 (2C, *C*H$_{Ar}$), 128.5 (2C, *C*H$_{Ar}$), 130.3 (2C, *C*H$_{Ar}$), 132.1 (2C, *C*H$_{Ar}$), 134.0 (*C*$_{Ar}$), 137.3 (*C*$_{Ar}$), 141.2 (*C*$_{Ar}$), 151.6 (*C*$_{Ar}$), 167.7 (*C*HPh).

(E)-N-[(2-Bromophenyl)methylene]-4-methylbenzenesulfonamide (100h)



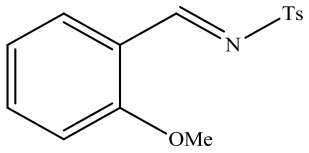
Synthesized according to *GP 2*, using 2-bromobenzaldehyde (3.7 g, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 5.4 g (16.0 mmol, 80 %)

^{1}H-NMR (600 MHz, DMSO-d$_6$): δ [ppm] = 2.42 (s, 3H, CH_3), 7.33-7.36 (m, 3H, CH_{Ar}), 7.39-7.43 (m, 1H, CH_{Ar}), 7.63 (dd, J = 8.0, 1.0 Hz, 1H, CH_{Ar}), 7.88 (d, J = 8.0 Hz, 2H, CH_{Ar}), 8.11 (dd, J = 7.8, 1.8 Hz, 1H, CH_{Ar}), 9.40 (s, 1H, C*H*Ph).

^{13}C-NMR (151 MHz, DMSO-d$_6$): δ [ppm] = 21.5 (*C*H$_3$), 127.9 (*C*H$_{Ar}$), 128.3 (2C, *C*H$_{Ar}$), 128.8 (C_{Ar}), 129.9 (2C, *C*H$_{Ar}$), 130.6 (*C*H$_{Ar}$), 131.1 (C_{Ar}), 133.8 (*C*H$_{Ar}$), 134.6 (C_{Ar}), 135.7 (*C*H$_{Ar}$), 144.9 (C_{Ar}), 169.2 (*C*HPh).

(E)-N-[(2-Methoxyphenyl)methylene]-4-methylbenzenesulfonamide (100i)



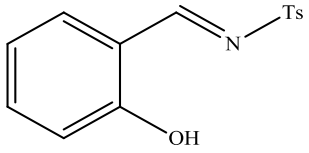
Synthesized according to *GP 2*, using 2-methoxybenzaldehyde (2.7 g, 2.4 mL, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 4.3 g (14.8 mmol, 74 %)

^{1}H-NMR (600 MHz, DMSO-d$_6$): δ [ppm] = 2.37 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 7.03 (t, J = 6.7 Hz, 1H, CH_{Ar}), 7.20 (dd, J = 8.1, 4.1 Hz, 1H, CH_{Ar}), 7.42 (d, J = 7.4 Hz, 2H, CH_{Ar}), 7.63-7.71 (m, 1H, CH_{Ar}), 7.80 (d, J = 7.4 Hz, 2H, CH_{Ar}), 7.86 (d, J = 7.8 Hz, 1H, CH_{Ar}), 9.33 (s, 1H, C*H*Ph).

^{13}C-NMR (151 MHz, DMSO-d$_6$): δ [ppm] = 21.5 (*C*H$_3$), 56.6 (O*C*H$_3$), 113.1 (*C*H$_{Ar}$), 120.2 (C_{Ar}), 121.4 (*C*H$_{Ar}$), 128.0 (2C, *C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 130.5 (2C, *C*H$_{Ar}$), 135.4 (C_{Ar}), 138.1 (*C*H$_{Ar}$), 144.9 (C_{Ar}), 162.0 (C_{Ar}), 166.2 (*C*HPh).

(E)-N-[(2-Hydroxyphenyl)methylene]-4-methylbenzenesulfonamide (100j)



Synthesized according to *GP 2*, using 2-hydroxybenzaldehyde (2.4 g, 2.1 mL, 20.0 mmol, 1.0 equiv.), trimethyl ortoformate (3.2 g, 2.3 mL, 30.0 mmol, 1.5 equiv.) and 4-

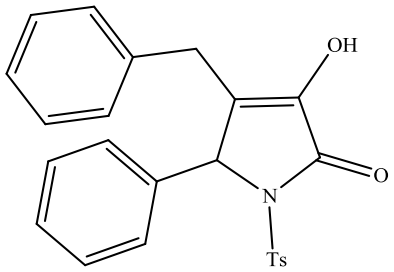
toluenesulfonamide (3.4 g, 20.0 mmol, 1.0 equiv.). After purification by recrystallization in EtOH, the product was obtained as white solid.

Yield m = 4.07 g (14.8 mmol, 74 %)

^{1}H-NMR (600 MHz, DMSO-d$_6$): δ [ppm] = 2.36 (s, 3H, CH_3), 6.88 (t, J = 7.5 Hz, 1H, CH_{Ar}), 6.99 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.42 (dd, J = 6.2, 3.7 Hz, 2H, CH_{Ar}), 7.48-7.53 (m, 1H, CH_{Ar}), 7.79 (t, J = 7.9 Hz, 3H, CH_{Ar}), 9.32 (s, 1H, CHPh), 11.01 (s, 1H, OH).

^{13}C-NMR (151 MHz, DMSO-d$_6$): δ [ppm] = 21.5 (CH$_3$), 117.6 (CH$_{Ar}$), 118.7 (C_{Ar}), 120.3 (CH$_{Ar}$), 128.0 (2C, CH$_{Ar}$), 129.2 (CH$_{Ar}$), 130.5 (2C, CH$_{Ar}$), 135.6 (C_{Ar}), 138.0 (CH$_{Ar}$), 144.8 (C_{Ar}), 161.7 (C_{Ar}), 167.1 (CHPh).

4-Benzyl-3-hydroxy-5-phenyl-1-tosyl-1H-pyrrol-2(5H)-one (170a)



Synthesized according to *GP 3*, starting from ethyl 2-oxo-4-phenylbutanoate **169a** (51.5 mg, 0.25 mmol, 1.0 equiv.), (E)-N-benzylidene-4-methylbenzenesulfonamide **100a** (97.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **163** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield m = 48.2 mg (0.12 mmol, 46 %)

Melting point 192 °C

ee 86 % (HPLC)

TLC R_f = 0.2 (*n*-pentane/EtOAc 3:1)

HPLC t_R = 6.4 min (major enantiomer)

t_R = 8.2 min (minor enantiomer)

Diacel Chiralpak IC, *n*-heptan/EtOH 9:1, 1.0 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.35 (s, 3H, CH_3), 2.86 (d, *J* = 15.1 Hz, 1H, CH_2), 3.84 (d, *J* = 15.1 Hz, 1H, CH_2), 5.34 (s, 1H, C*H*), 6.12 (s, 1H, O*H*), 6.99 (dd, *J* = 14.5, 7.2 Hz, 3H, CH_{Ar}), 7.06 (d, *J* = 8.0 Hz, 2H, CH_{Ar}), 7.22-7.27 (m, 4H, CH_{Ar}), 7.28-7.33 (m, 4H, CH_{Ar}), 7.81 (d, *J* = 8.3 Hz, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.5 (*C*H_3), 30.4 (*C*H_2), 63.4 (*C*H), 126.8 (*C*H_{Ar}), 127.7 (2C, *C*H_{Ar}), 128.1 (2C, *C*H_{Ar}), 128.9 (4C, *C*H_{Ar}), 129.0 (*C*H_{Ar}), 129.0 (2C, *C*H_{Ar}), 129.9 (2C, *C*H_{Ar}), 131.0 (*C*=C-OH), 135.7 (*C*$_{Ar}$), 135.8 (*C*$_{Ar}$), 137.9 (*C*$_{Ar}$), 141.4 (*C*$_{Ar}$), 145.3 (C=*C*-OH), 165.4 (*C*O).

MS (CI, 100 eV): *m/z* (%) = 266 (9), 294 (3), 377 (3), 419 (6), 420 (100) $[M+H]^+$.

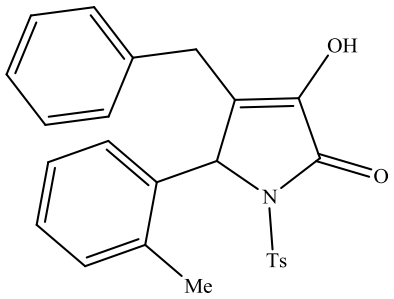
IR (ATR): 3340 (s), 3265 (s), 3028 (w), 1683 (s), 1596 (w), 1374 (s), 1302 (s), 1230 (s), 1156 (s), 1089 (s), 1026 (w), 901 (m), 818 (s), 747 (m), 689 (s) cm^{-1}.

Elemental analysis ($C_{24}H_{21}NO_4S$)

Calculated: C = 68.72% H = 5.05% N = 3.34%

Found: C = 69.74% H = 5.06% N = 3.45%

4-Benzyl-3-hydroxy-5-(2-methylphenyl)-1-tosyl-1H-pyrrol-2(5H)-one (170b)



Synthesized according to *GP 3*, starting from ethyl 2-oxo-4-phenylbutanoate **169a** (51.5 mg, 0.25 mmol, 1.0 equiv.), (E)-N-[(2-methylphenyl)methylene]-4-methylbenzenesulfonamide **100b** (102.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **163** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield m = 43.3 mg (0.1 mmol, 40 %)

Melting point 127 °C

ee 86 % (HPLC)

TLC R_f = 0.2 (*n*-pentane/EtOAc 3:1)

HPLC t_R = 9.9 min (major enantiomer)

t_R = 13.1 min (minor enantiomer)

Diacel Chiralpak IA, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.19 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.82 (d, *J* = 15.5 Hz, 1H, CH_2), 3.93 (d, *J* = 15.5 Hz, 1H, CH_2), 5.71 (s, 1H, C*H*), 6.46 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 6.70 (s, 1H, O*H*), 6.84-6.88 (m, 1H, CH_{Ar}), 7.01 (d, *J* = 8.1 Hz, 2H, CH_{Ar}), 7.06 (d, *J* = 8.1 Hz, 2H, CH_{Ar}), 7.17-7.21 (m, 2H, CH_{Ar}), 7.22-7.25 (m, 1H, CH_{Ar}), 7.25-7.29 (m, 4H, CH_{Ar}).

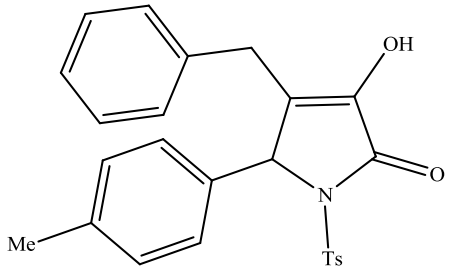
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 17.9 (*C*H_3), 21.6 (*C*H_3), 30.5 (*C*H_2), 59.2 (*C*H), 125.8 (*C*H_{Ar}), 126.2 (*C*H_{Ar}), 126.9 (*C*H_{Ar}), 127.8 (2C, *C*H_{Ar}), 128.5 (*C*H_{Ar}), 128.8 (2C, *C*H_{Ar}), 128.9 (2C, *C*H_{Ar}). 129.1 (2C, *C*H_{Ar}), 131.0 (*C*H_{Ar}), 131.2 (*C*=C-OH), 131.8 (C_{Ar}), 135.5 (C_{Ar}), 137.0 (C_{Ar}), 138.4 (C_{Ar}), 140.5 (C_{Ar}), 144.7 (C=*C*-OH), 166.0 (*C*O).

MS (EI, 70 eV): *m/z* (%) = 65 (11), 77 (4), 91 (100),103 (5), 105 (5), 115 (14), 129 (7), 131 (9), 143 (12), 145 (12), 155 (16), 192 (3), 205 (4), 221 (4), 233 (8), 278 (7), 433 (4).

IR (ATR): 3306 (w), 3015 (w), 1735 (s), 1369 (s), 1217 (s), 1147 (s), 1029 (w), 851 (w) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{25}H_{23}O_4NNaS$: 456.1240; found: 456.1239.

4-Benzyl-3-hydroxy-5-(4-methylphenyl)-1-tosyl-1H-pyrrol-2(5H)-one (174c)



Synthesized according to *GP 3*, starting from ethyl 2-oxo-4-phenylbutanoate **173a** (51.5 mg, 0.25 mmol, 1.0 equiv.), (E)-N-[(4-methylphenyl)methylene]-4-methylbenzenesulfonamide **100c** (102 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield m = 46.5 mg (0.11 mmol, 43 %)

Melting point 125 °C

ee 87 % (HPLC)

TLC R_f = 0.2 (*n*-pentane/EtOAc 3:1)

HPLC t_R = 14.1 min (major enantiomer)

t_R = 12.0 min (minor enantiomer)

Diacel Chiralpak IA, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.84 (d, *J* = 15.0 Hz, 1H, CH_2), 3.88 (d, *J* = 15.0 Hz, 1H, CH_2), 5.30 (s, 1H, C*H*), 6.87 (d, *J* = 6.8 Hz, 2H, CH_{Ar}), 7.00-7.07 (m, 5H, CH_{Ar}), 7.19-7.29 (m, 4H, CH_{Ar}), 7.32 (d, *J* = 7.8 Hz, 2H, CH_{Ar}).

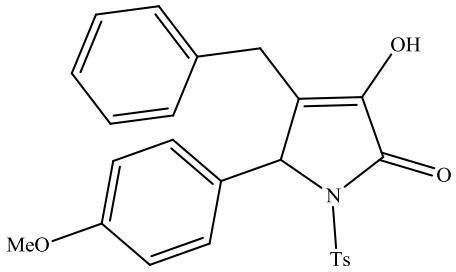
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.2 (*C*H_3), 21.6 (*C*H_3), 30.4 (*C*H_2), 63.8 (*C*H), 126.7 (*C*H_{Ar}), 127.8 (2C, *C*H_{Ar}), 128.3 (*C*H_{Ar}), 128.4 (*C*H_{Ar}), 128.7 (2C, *C*H_{Ar}), 128.9 (2C, *C*H_{Ar}), 129.1 (2C, *C*H_{Ar}), 129.3 (2C, *C*H_{Ar}), 130.2 (*C*=C-OH), 131.0 (*C*$_{Ar}$), 135.7 (*C*$_{Ar}$), 137.3 (*C*$_{Ar}$), 138.7 (*C*$_{Ar}$), 140.3 (*C*$_{Ar}$), 144.6 (C=*C*-OH), 166.2 (*C*O).

MS (EI, 70 eV): *m/z* (%) = 65 (13), 77(5), 91 (100), 105 (9), 115 (7), 118 (5), 129 (4), 145 (6), 155 (9), 221 (4), 235 (4), 274 (6), 178 (6), 433 (2).

IR (ATR): 3297 (s), 3026 (w), 2933 (w), 1700 (s), 1494 (w), 1367 (s), 1315 (s), 1162 (s), 1032 (s), 850 (m), 812 (m), 743 (w), 664 (w) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{25}H_{23}O_4NNaS$: 456.1240; found: 456.1239.

4-Benzyl-3-hydroxy-5-(4-methoxyphenyl)-1-tosyl-1H-pyrrol-2(5H)-one (174d)



Synthesized according to *GP 3*, starting from ethyl 2-oxo-4-phenylbutanoate **173a** (51.5 mg, 0.25 mmol, 1.0 equiv.), (E)-N-[(4-methoxyphenyl)methylene]-4-methylbenzene-sulfonamide **100d** (108.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield m = 39.3 g (0.09 mmol, 35 %)

Melting point 206 °C

ee 54 % (HPLC)

TLC R_f = 0.1 (*n*-pentane/EtOAc 3:1)

HPLC t_R = 12.6 min (major enantiomer)

t_R = 21.2 min (minor enantiomer)

Diacel Chiralpak IA, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.35 (s, 3H, C*H*$_3$), 2.88 (d, *J* = 15.0 Hz, 1H, C*H*$_2$), 3.84 (s, 3H, OC*H*$_3$), 3.87 (d, *J* = 15.0 Hz, 1H, C*H*$_2$), 5.31 (s, 1H, C*H*), 6.77 (d, *J* = 8.3 Hz, 2H, C*H*$_{Ar}$), 6.90 (d, *J* = 8.0 Hz, 2H, C*H*$_{Ar}$), 7.01 (d, *J* = 7.0 Hz, 2H, C*H*$_{Ar}$), 7.09 (d, *J* = 8.0 Hz, 2H, C*H*$_{Ar}$), 7.22-7.25 (m, 1H, C*H*$_{Ar}$), 7.25-7.29 (m, 2H, C*H*$_{Ar}$), 7.32 (d, *J* = 8.3 Hz, 2H, C*H*$_{Ar}$).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.6 (*C*H$_3$), 30.5 (*C*H$_2$), 55.4 (O*C*H$_3$), 63.5 (*C*H), 114.0 (2C, *C*H$_{Ar}$), 125.7 (*C*$_{Ar}$), 126.8 (*C*H$_{Ar}$), 127.9 (2C, *C*H$_{Ar}$), 128.7 (2C, *C*H$_{Ar}$), 128.9 (2C, *C*H$_{Ar}$), 129.2 (2C, *C*H$_{Ar}$), 129.7 (2C, *C*H$_{Ar}$), 130.0 (*C*=C-OH), 135.8 (*C*$_{Ar}$), 137.0 (*C*$_{Ar}$), 139.8 (*C*$_{Ar}$), 144.6 (C=*C*-OH), 160.0 (*C*$_{Ar}$), 165.5 (*C*O).

MS (EI, 70 eV): *m/z* (%) = 65 (13), 77 (7), 91 (100), 103 (4), 115 (11), 121 (6), 131 (4), 134 (4), 139 (4), 145 (4), 155 (8), 161 (11), 221 (4), 251 (9), 294 (6), 449 (2).

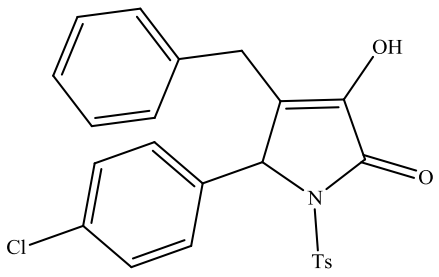
IR (ATR): 3299 (s), 3018 (w), 2949 (w), 1680 (s), 1602 (m), 1508 (m), 1451 (m), 1361 (s), 1313 (s), 1230 (s), 1171 (s), 1091 (s), 1026 (s), 824 (s), 747 (m) cm^{-1}.

Elemental analysis ($C_{25}H_{23}NO_5S$)

Calculated: C = 66.80% H = 5.16% N = 3.12%

Found: C = 66.67% H = 5.27% N = 3.02%

4-Benzyl-3-hydroxy-5-(4-chlorophenyl)-1-tosyl-1H-pyrrol-2(5H)-one (174f)



Synthesized according to *GP 3*, starting from ethyl 2-oxo-4-phenylbutanoate **173a** (51.5 mg, 0.25 mmol, 1.0 equiv.), (E)-N-[(4-chlorophenyl)methylene]-4-methylbenzene-sulfonamide **100f** (110.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield m = 62.3 mg (0.14 mmol, 55 %)

Melting point 201 °C

ee 75 % (HPLC)

TLC R_f = 0.3 (*n*-pentane/EtOAc 3:1)

HPLC t_R = 11.7 min (major enantiomer)

t_R = 23.3 min (minor enantiomer)

Diacel Chiralpak IA, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.37 (s, 3H, C*H*$_3$), 2.89 (d, *J* = 15.2 Hz, 1H, C*H*$_2$), 3.86 (d, *J* = 15.2 Hz, 1H, C*H*$_2$), 5.31 (s, 1H, C*H*), 6.35 (s, 1H, O*H*), 6.91 (d, *J* = 8.0 Hz, 2H, C*H*$_{Ar}$), 6.97-7.00 (m, 2H, C*H*$_{Ar}$), 7.11-7.14 (m, 2H, C*H*$_{Ar}$), 7.21 (d, *J* = 8.4 Hz, 2H, C*H*$_{Ar}$), 7.23-7.29 (m, 3H, C*H*$_{Ar}$), 7.35 (d, *J* = 8.4 Hz, 2H, C*H*$_{Ar}$).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.6 (*C*H$_3$), 30.4 (*C*H$_2$), 63.1 (*C*H), 127.0 (*C*H$_{Ar}$), 127.6 (2C, *C*H$_{Ar}$), 128.8 (2C, *C*H$_{Ar}$), 128.8 (2C, *C*H$_{Ar}$), 128.9 (2C, *C*H$_{Ar}$), 129.3 (2C, *C*H$_{Ar}$), 129.7 (2C, *C*H$_{Ar}$), 129.7 (*C*=C-OH), 132.7 (*C*$_{Ar}$), 134.8 (*C*$_{Ar}$), 135.5 (*C*$_{Ar}$), 136.7 (*C*$_{Ar}$), 140.1 (*C*$_{Ar}$), 145.1 (C=*C*-OH), 165.4 (*C*O).

MS (EI, 70 eV): *m/z* (%) = 65 (16), 77 (5), 83 (3), 89 (4), 91 (100), 103 (4), 115 (6), 131 (5), 143 (3), 155 (10), 192 (4), 198 (4), 298 (3), 453 (1).

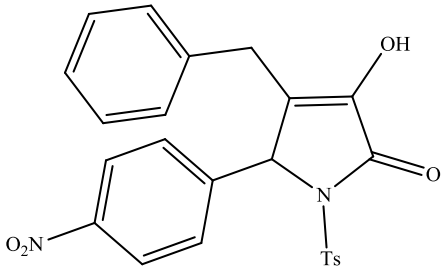
IR (ATR): 3294 (m), 3018 (w), 1731 (s), 1489 (w), 1446 (w), 1368 (s), 1218 (s), 1143 (s), 1090 (s), 1027 (m), 848 (m), 739 (w), 664 (w) cm^{-1}.

Elemental analysis ($C_{24}H_{20}NO_4SCl$)

Calculated: C = 63.50% H = 4.44% N = 3.09%

Found: C = 63.78% H = 4.55% N = 2.86%

4-Benzyl-3-hydroxy-5-(4-nitrophenyl)-1-tosyl-1H-pyrrol-2(5H)-one (174g)



Synthesized according to *GP 3*, starting from ethyl 2-oxo-4-phenylbutanoate **173a** (51.5 mg, 0.25 mmol, 1.0 equiv.), (E)-N-[(4-nitrophenyl)methylene]-4-methylbenzene-sulfonamide **100f** (114.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield	m = 73.1 mg (0.16 mmol, 63 %)
Melting point	241 °C
ee	80 % (HPLC)
TLC	R_f = 0.1 (*n*-pentane/EtOAc 3:1)
HPLC	t_R = 16.4 min (major enantiomer)
	t_R = 29.3 min (minor enantiomer)
	Diacel Chiralpak IA, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.38 (s, 3H, C*H*$_3$), 2.92 (d, *J* = 15.4 Hz, 1H, C*H*$_2$), 3.82 (d, *J* = 15.4 Hz, 1H, C*H*$_2$), 5.42 (s, 1H, C*H*), 5.71 (s, 1H, O*H*), 6.91-6.96 (m, 2H, C*H*$_{Ar}$), 7.11-7.16 (m, 4H, C*H*$_{Ar}$), 7.22-7.25 (m, 3H, C*H*$_{Ar}$), 7.42 (d, *J* = 8.3 Hz, 2H, C*H*$_{Ar}$), 8.07 (d, *J* = 8.3 Hz, 2H, C*H*$_{Ar}$).

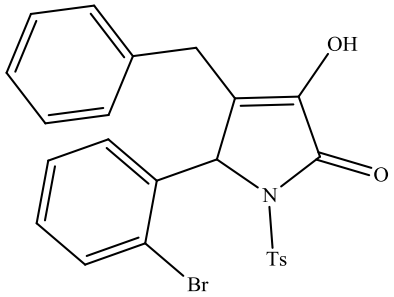
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.6 (*C*H$_3$), 30.5 (*C*H$_2$), 62.8 (*C*H), 123.8 (2C, *C*H$_{Ar}$), 127.2 (*C*H$_{Ar}$), 127.6 (2C, *C*H$_{Ar}$), 128.7 (2C, *C*H$_{Ar}$), 128.7 (*C*$_{Ar}$), 128.9 (2C, *C*H$_{Ar}$), 129.0 (2C, *C*H$_{Ar}$), 129.5 (2C, *C*H$_{Ar}$), 135.3 (*C*=C-OH), 136.3 (*C*$_{Ar}$), 140.3 (*C*$_{Ar}$), 141.8 (*C*$_{Ar}$), 145.6 (*C*$_{Ar}$), 148.1 (C=*C*-OH), 164.9 (*C*O).

MS (EI, 70 eV): *m/z* (%) = 65 (14), 77 (4), 91 (100), 131 (5), 155 (11), 192 (5), 250 (4), 309 (6), 464 (3).

IR (ATR): 3299 (w), 2970 (w), 1734 (s), 1515 (w), 1455 (w), 1358 (s), 1222 (s), 1148 (s), 1032 (m), 852 (w), 699 (m) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{24}H_{20}O_6N_2NaS$: 487.0934; found: 487.0934.

4-Benzyl-3-hydroxy-5-(2-bromophenyl)-1-tosyl-1H-pyrrol-2(5H)-one (174h)



Synthesized according to *GP 3*, starting from ethyl 2-oxo-4-phenylbutanoate **173a** (51.5 mg, 0.25 mmol, 1.0 equiv.), (E)-N-[(2-bromophenyl)methylene]-4-methylbenzenesulfonamide **100f** (126.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a yellow viscous oil.

Yield	m = 70.8 mg (0.14 mmol, 57 %)
ee	22 % (HPLC)
TLC	R_f = 0.2 (*n*-pentane/EtOAc 3:1)
HPLC	t_R = 10.1 min (major enantiomer)
	t_R = 13.8 min (minor enantiomer)
	Diacel Chiralpak IC, *n*-heptan/EtOH 9:1, 0.7 mL/min.

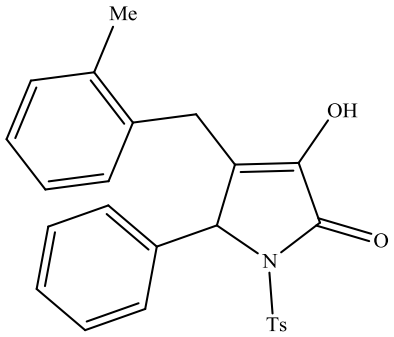
^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.38 (s, 3H, CH_3), 3.11 (d, *J* = 15.0 Hz, 1H, CH_2), 3.66 (d, *J* = 15.0 Hz, 1H, CH_2), 6.14 (s, 1H, C*H*), 6.59 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 6.96 (t, *J* = 7.3 Hz, 1H, CH_{Ar}), 7.04 (d, *J* = 7.3 Hz, 2H, CH_{Ar}), 7.12-7.19 (m, 5H, CH_{Ar}), 7.21-7.25 (m, 1H, CH_{Ar}), 7.51 (d, *J* = 8.1 Hz, 2H, CH_{Ar}), 8.61 (d, *J* = 8.1 Hz, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.7 (*C*H_3), 30.6 (*C*H_2), 62.5 (*C*H), 125.4 (C_{Ar}), 126.6 (*C*H_{Ar}), 127.6 (*C*H_{Ar}), 127.7 (*C*H_{Ar}), 128.0 (2C, *C*H_{Ar}), 128.5 (2C, *C*H_{Ar}), 128.8 (2C, *C*H_{Ar}), 129.4 (2C, *C*H_{Ar}), 130.0 (*C*H_{Ar}), 130.6 (C_{Ar}), 133.2 (*C*H_{Ar}), 133.7 (*C*=C-OH), 135.3 (C_{Ar}), 136.9 (C_{Ar}), 145.1 (C=*C*-OH), 166.0 (C_{Ar}), 171.3 (*C*O).

MS (CI, 100 eV): *m/z* (%) = 302 (8), 315 (9), 330 (26), 338 (24), 344 (30), 360 (17), 458 (44), 486 (34), 498 (100).

IR (ATR): 3302 (m), 3036 (w), 2928 (m), 1724 (s), 1598 (m), 1442 (m), 1368 (s), 1152 (s), 1034 (s), 835 (w), 752 (m), 667 (m) cm^{-1}.

4-(2-Methylbenzyl)-3-hydroxy-5-phenyl-1-tosyl-1H-pyrrol-2(5H)-one (174i)



Synthesized according to *GP 3*, starting from ethyl 4-(2-methylphenyl)-2-oxobutanoate **173b** (55.0 mg, 0.25 mmol, 1.0 equiv.), (E)-N-benzylidene-4-methylbenzenesulfonamide **100a** (97.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8. mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield	m = 67.2 g (0.16 mmol, 62 %)
Melting point	157 °C
ee	46 % (HPLC)
TLC	R_f = 0.2 (*n*-pentane/EtOAc 3:1)
HPLC	t_R = 8.6 min (major enantiomer)
	t_R = 10.5 min (minor enantiomer)
	Diacel Chiralpak IC, *n*-heptan/EtOH 9:1, 0.7 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.13 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.89 (d, J = 15.1 Hz, 1H, CH_2), 3.87 (d, J = 15.1 Hz, 1H, CH_2), 5.27 (s, 1H, CH), 6.82 (d, J = 7.4 Hz, 1H, CH_{Ar}), 6.97 (d, J = 7.4 Hz, 2H, CH_{Ar}), 7.03-7.07 (m, 2H, CH_{Ar}), 7.08-7.18 (m, 3H, CH_{Ar}), 7.21-7.31 (m, 4H, CH_{Ar}), 7.32-7.37 (m, 1H, CH_{Ar}).

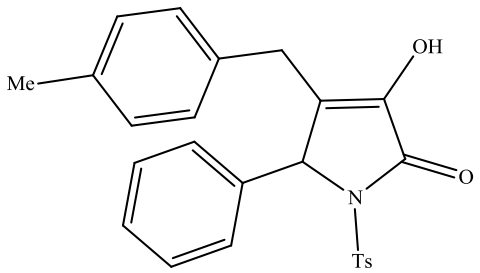
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 19.3 (*C*H_3), 21.5 (*C*H_3), 29.7 (*C*H_2), 64.8 (*C*H), 126.1 (*C*H_{Ar}), 126.5 (*C*H_{Ar}), 127.2 (*C*H_{Ar}), 127.6 (2C, *C*H_{Ar}), 128.6 (*C*H_{Ar}), 128.7 (2C, *C*H_{Ar}), 128.9 (*C*H_{Ar}), 129.2 (2C, *C*H_{Ar}), 129.7 (*C*$_{Ar}$), 129.8 (*C*H_{Ar}), 130.5 (*C*H_{Ar}), 134.0 (*C*=C-OH), 134.8 (*C*$_{Ar}$), 135.6 (*C*$_{Ar}$), 136.7 (*C*$_{Ar}$), 139.9 (*C*$_{Ar}$), 144.7 (C=*C*-OH), 165.5 (*C*O).

MS (EI, 70 eV): *m/z* (%) = 55 (3), 65 (17), 89 (6), 91 (100), 104 (15), 105 (69), 106 (46), 115 (20), 117 (7), 119 (6), 129 (8), 131 (9), 143 (4), 145 (13), 155 (18), 157 (5), 186 (9), 206 (11), 233 (8), 235 (5), 260 (6), 278 (16), 300 (6), 433 (6).

IR (ATR): 3297 (s), 3031 (w), 2930 (w), 1721 (s), 1371 (s), 1314 (s), 1226 (s), 1151 (s), 1033 (s), 850 (m), 747 (w), 667 (w) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{25}H_{23}O_4NNaS$: 456.1240; found: 456.1240.

4-(4-Methylbenzyl)-3-hydroxy-5-phenyl-1-tosyl-1H-pyrrol-2(5H)-one (174j)



Synthesized according to *GP 3*, starting from ethyl 4-(4-methylphenyl)-2-oxobutanoate **173c** (55.0 mg, 0.25 mmol, 1.0 equiv.), (E)-N-benzylidene-4-methylbenzenesulfonamide **100a** (97.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a white solid.

Yield	m = 70.4 mg (0.16 mmol, 65 %)
Melting point	164 °C
ee	64 % (HPLC)
TLC	R_f = 0.3 (*n*-pentane/EtOAc 3:1)
HPLC	t_R = 11.9 min (major enantiomer)
	t_R = 17.7 min (minor enantiomer)
	Diacel Chiralpak IA, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.33 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.81 (d, *J* = 15.1 Hz, 1H, CH_2), 3.86 (d, *J* = 15.1 Hz, 1H, CH_2), 5.35 (s, 1H, C*H*), 6.92 (d, *J* = 7.7 Hz, 2H, CH_{Ar}), 6.99 (d, *J* = 7.7 Hz, 2H, CH_{Ar}), 7.06-7.09 (m, 4H, CH_{Ar}), 7.25 (t, *J* = 7.6 Hz, 2H, CH_{Ar}), 7.29 (d, *J* = 8.2 Hz, 2H, CH_{Ar}), 7.33 (t, *J* = 7.6 Hz, 1H, CH_{Ar}).

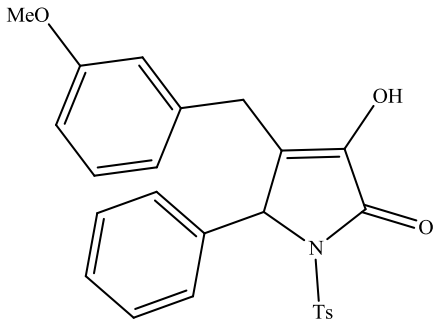
^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.1 (*C*H_3), 21.6 (*C*H_3), 30.0 (*C*H_2), 63.9 (*C*H), 127.7 (2C, *C*H_{Ar}), 128.4 (2C, *C*H_{Ar}), 128.7 (2C, *C*H_{Ar}), 128.8 (2C, *C*H_{Ar}), 128.9 (*C*H_{Ar}), 129.2 (2C, *C*H_{Ar}), 129.4 (2C, *C*H_{Ar}), 130.9 (*C*$_{Ar}$), 134.0 (*C*=C-OH), 134.1 (*C*$_{Ar}$), 135.6 (*C*$_{Ar}$), 136.4 (*C*$_{Ar}$), 140.1 (*C*$_{Ar}$), 144.7 (C=*C*-OH), 166.0 (*C*O).

MS (ESI): *m/z* (%) = 240 (18), 434 (27) $[M+H]^+$, 456 (100) $[M+Na]^+$.

IR (ATR): 3299 (s), 3031 (w), 2929 (w), 1719 (s), 1603 (w), 1494 (w), 1371 (s), 1313 (s), 1227 (s), 1154 (s), 1032 (s), 849 (m), 811 (m), 756 (w), 663 (w) cm^{-1}.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{25}H_{23}O_4NNaS$: 456.1240; found: 456.1240.

4-(3-Methoxybenzyl)-3-hydroxy-5-phenyl-1-tosyl-1H-pyrrol-2(5H)-one (174k)



Synthesized according to *GP 3*, starting from ethyl 4-(3-methoxyphenyl)-2-oxobutanoate **173d** (59.0 mg, 0.25 mmol, 1.0 equiv.), (E)-N-benzylidene-4-methylbenzenesulfonamide **100a** (97.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a colourless viscous oil.

Yield	m = 46.0 mg (0.1 mmol, 41 %)
ee	63 % (HPLC)
TLC	R_f = 0.2 (*n*-pentane/EtOAc 3:1)
HPLC	t_R = 13.5 min (major enantiomer)
	t_R = 21.9 min (minor enantiomer)
	Diacel Chiralpak IA, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.38 (s, 3H, CH_3), 2.83 (d, *J* = 15.0 Hz, 1H, CH_2), 3.76 (s, 3H, OCH_3), 3.79 (d, *J* = 15.0 Hz, 1H, CH_2), 5.35 (s, 1H, C*H*), 5.80 (s, 1H, O*H*), 6.52 (s, 1H, CH_{Ar}), 6.58 (d, *J* = 7.5 Hz, 1H, CH_{Ar}), 6.77 (dd, *J* = 8.2, 2.2 Hz, 1H, CH_{Ar}), 6.98 (d, *J* = 7.2 Hz, 2H, CH_{Ar}), 7.07 (d, *J* = 8.2 Hz, 2H, CH_{Ar}), 7.16-7.18 (m, 1H, CH_{Ar}), 7.24 (d, *J* = 7.5 Hz, 2H, CH_{Ar}), 7.28 (d, *J* = 8.2 Hz, 2H, CH_{Ar}), 7.33 (m, 1H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.6 (*C*H_3), 30.5 (*C*H_2), 55.2 (O*C*H_3), 63.8 (*C*H), 112.2 (*C*H_{Ar}), 114.6 (*C*H_{Ar}), 121.1 (*C*H_{Ar}), 127.7 (2C, *C*H_{Ar}), 128.4 (2C, *C*H_{Ar}), 128.7 (2C, *C*H_{Ar}), 128.9 (*C*H_{Ar}), 129.2 (2C, *C*H_{Ar}), 129.5 (*C*$_{Ar}$), 129.8 (*C*H_{Ar}), 134.0 (*C*=C-OH), 135.6 (*C*$_{Ar}$), 138.4 (*C*$_{Ar}$), 139.7 (*C*$_{Ar}$), 144.7 (C=*C*-OH), 159.8 (*C*$_{Ar}$), 165.3 (*C*O).

MS (EI, 70 eV): *m/z* (%) = 51 (3), 63 (3), 65 (17), 77 (14), 91 (100), 105 (13), 115 (12), 121 (42), 131 (6), 134 (4), 155 (19), 161(6), 173 (4), 186 (10), 198 (3), 221 (4), 249 (6), 251 (5), 260 (12), 294 (12), 300 (6), 449 (4).

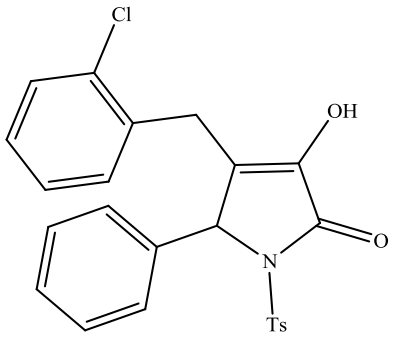
IR (ATR): 3304 (m), 2927 (m), 1722 (s), 1598 (m), 1453 (m), 1372 (s), 1231 (s), 1143 (s), 1043 (s), 780 (s), 673 (m) cm^{-1}.

Elemental analysis ($C_{25}H_{23}NO_5S$)

Calculated: C = 66.80% H = 5.16% N = 3.12%

Found: C = 66.68% H = 5.15% N = 2.90%

4-(2-Chlorobenzyl)-3-hydroxy-5-phenyl-1-tosyl-1H-pyrrol-2(5H)-one (174l)



Synthesized according to *GP 3*, starting from ethyl 4-(2-chlorophenyl)-2-oxobutanoate **173e** (60.0 mg, 0.25 mmol, 1.0 equiv.), (E)-N-benzylidene-4-methylbenzenesulfonamide **100a** (97.0 mg, 0.375 mmol, 1.5 equiv.) and cupreine **167** (8.0 mg, 0.025 mmol, 0.1 equiv.) as a catalyst for the domino reaction in 0.75 mL chloroform at 0 °C. After purification by flash column chromatography (eluent: *n*-pentane/EtOAc 3:1) the product was obtained as a colourless viscous oil.

Yield m = 48.7 mg (0.11 mmol, 43 %)

ee 18 % (HPLC)

TLC R_f = 0.2 (*n*-pentane/EtOAc 3:1)

HPLC t_R = 11.3 min (major enantiomer)

t_R = 13.7 min (minor enantiomer)

Diacel Chiralpak AD, *n*-heptan/EtOH 7:3, 0.5 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.34 (s, 3H, CH_3), 3.14 (d, *J* = 15.6 Hz, 1H, CH_2), 3.87 (d, *J* = 15.6 Hz, 1H, CH_2), 5.35 (s, 1H, C*H*), 6.08 (s, 1H, O*H*), 6.99 (dd, *J* = 10.1, 4.4 Hz, 3H, CH_{Ar}), 7.05 (d, *J* = 8.1 Hz, 2H, CH_{Ar}), 7.13-7.21 (m, 3H, CH_{Ar}), 7.22-7.25 (m, 3H, CH_{Ar}), 7.30-7.34 (m, 2H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.6 (*C*H_3), 28.5 (*C*H_2), 64.0 (*C*H), 126.9 (*C*H_{Ar}), 127.6 (2C, *C*H_{Ar}), 127.9 (*C*$_{Ar}$), 128.4 (2C, *C*H_{Ar}), 128.6 (2C, *C*H_{Ar}), 128.9 (*C*H_{Ar}), 129.2 (2C, *C*H_{Ar}), 129.6 (*C*H_{Ar}), 130.6 (*C*H_{Ar}), 131.2 (*C*H_{Ar}), 133.8 (*C*=C-OH), 134.0 (*C*$_{Ar}$), 134.4 (*C*$_{Ar}$), 135.6 (*C*$_{Ar}$), 140.4 (*C*$_{Ar}$), 144.7 (C=*C*-OH), 165.2 (*C*O).

MS (CI, 100 eV): *m/z* (%) = 300 (8), 328 (5), 361 (5), 367 (25), 395 (3), 414 (6), 435 (25), 437 (18), 454 (100) $[M+H]^+$.

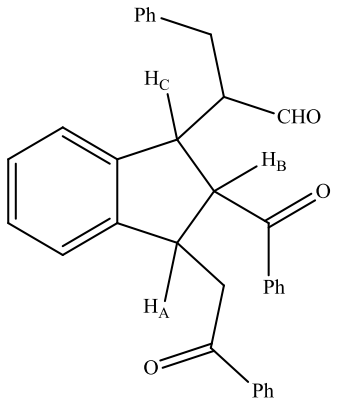
IR (ATR): 3297 (m), 2925 (m), 1725 (s), 1598 (m), 1452 (m), 1374 (s), 1308 (s), 1227 (s), 1141 (s), 1041 (s), 839 (m), 769 (m), 669 (m) cm^{-1}.

Elemental analysis ($C_{24}H_{20}NO_4SCl$)

Calculated: C = 63.50% H = 4.44% N = 3.09%

Found: C = 63.08% H = 4.38% N = 2.88%

2-(2-Benzoyl-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1H-inden-1-yl)-3-phenylpropanal (176a)



To a solution of (*S*)-TMS Prolinol **22** (16.2 mg, 0.05 mmol, 0.2 equiv.) in 0.75 mL $CHCl_3$ were added (2*E*,2'*E*)-3,3'-(1,2-phenylene)bis(1-phenylprop-2-en-1-one) **175a** (84.5 mg, 0.25 mmol, 1.0 equiv.), 3-phenylpropanal **294** (50.3 mg, 0.06 mL, 0.375 mmol, 1.5 equiv.) and Et_3N (7 μL, 0.05 mmol, 0.2 equiv.) and the reaction mixture was stirred at room temperature for 3 days. It was then subjected to flash column chromatography (eluent: *n*-pentane/EtOAc 10:1) and the product was obtained as white solid.

Yield m = 28.5 mg (0.06 mmol, 23 %)

ee 90 % (HPLC)

TLC R_f = 0.4 (*n*-pentane/EtOAc 10:1)

HPLC t_R = 11.1 min (minor enantiomer)

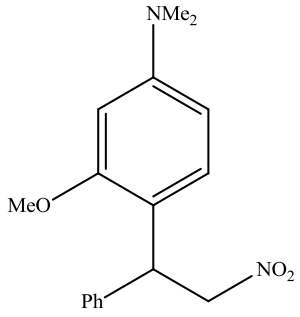
t_R = 13.5 min (major enantiomer)

Diacel Chiralpak OD, *n*-heptan/ *i*-PrOH 9:1, 1.0 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.32 (dd, *J* = 12.0, 13.8 Hz, 1H, CH_2Ph), 2.67 (dt, *J* = 3.0, 12.0 Hz, 1H, C*H*CHO), 2.80 (dd, *J* = 12.0, 13.8 Hz, 1H, CH_2Ph), 3.18 (dd, *J* = 6.1, 12.1 Hz, 1H, CH_2COPh), 3.49 (dd, *J* = 6.1, 12.1 Hz, 1H, CH_2COPh), 4.42 (dd, *J* = 3.0, 9.4 Hz, 1H, CH_C), 4.51 (d, *J* = 9.4 Hz, 1H, CH_B), 4.74 (dt, *J* = 6.1, 9.4 Hz, 1H, CH_A), 7.18 (dd, *J* = 4.6, 10.3 Hz, 2H, CH_{Ar}), 7.42-7.47 (m, 7H, CH_{Ar}), 7.48-7.54 (m, 7H, CH_{Ar}), 7.56-7.61 (m, 3H, CH_{Ar}), 9.49 (s, 1H, C*H*O).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 32.0 (*C*H_2Ph), 42.1 (*C*H_A), 43.6 (*C*H_2COPh), 45.8 (*C*H_C), 54.5 (*C*HCHO), 56.7 (*C*H_B), 126.0 (*C*H_{Ar}), 126.3 (*C*H_{Ar}), 127.4 (*C*H_{Ar}), 128.2 (*C*H_{Ar}), 128.2 (*C*H_{Ar}), 128.3 (*C*H_{Ar}), 128.4 (*C*H_{Ar}), 128.6 (2C, *C*H_{Ar}), 128.6 (*C*H_{Ar}), 128.7 (2C, *C*H_{Ar}), 129.1 (*C*H_{Ar}), 129.2 (*C*H_{Ar}), 130.2 (*C*H_{Ar}), 133.0 (*C*H_{Ar}), 133.2 (*C*H_{Ar}), 133.7 (*C*H_{Ar}), 135.4 (C_{Ar}), 136.9 (C_{Ar}), 137.0 (C_{Ar}), 137.9 (C_{Ar}), 138.7 (C_{Ar}), 141.7 (*C*H_{Ar}), 198.9 (*C*O), 199.2 (*C*O), 203.5 (*C*HO).

3-Methoxy-N,N-dimethyl-4-(2-nitro-1-phenylethyl)aniline (177a)



To a solution of nitrostyrene **65a** (75.0 mg, 0.5 mmol, 1.0 equiv.) in 1 mL toluene at 0 °C were added thiourea catalyst **270** (24.5 mg, 0.05 mmol, 0.1 equiv.) and 3-methoxy-N,N-dimethylaniline **124b** (113.0 mg, 0.75 mmol, 1.5 equiv.) and the reaction mixture was stirred for 24 h. It was then subjected directly to flash column chromatography (eluent: *n*-pentane/ EtOAc 5:1) and the product was obtained as bright yellow solid.

Yield	m = 139.5 mg (0.46 mmol, 93 %)
ee	3 % (HPLC)
TLC	R_f = 0.6 (*n*-pentane/EtOAc 5:1)
HPLC	t_R = 7.3 min (minor enantiomer)
	t_R = 9.2 min (major enantiomer)
	Diacel Chiralpak AD, *n*-heptan/EtOH 9:1, 1.0 mL/min.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.93 (s, 6H, N(CH_3)$_2$), 3.83 (s, 3H, OCH_3), 4.91-5.02 (m, 2H, CH_2), 5.12-5.18 (m, 1H, C*H*), 6.23 (d, *J* = 5.4 Hz, 2H, CH_{Ar}), 6.83-6.89 (m, 1H, CH_{Ar}), 7.18-7.24 (m, 1H, CH_{Ar}), 7.24-7.32 (m, 4H, CH_{Ar}).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 40.5 (*C*H), 42.9 (2C, N(*C*H_3)$_2$), 55.3 (O*C*H_3), 78.3 (*C*H_2), 96.1 (*C*H_{Ar}), 104.6 (*C*H_{Ar}), 115.4 (*C*$_{Ar}$), 127.0 (*C*H_{Ar}), 127.8 (2C, *C*H_{Ar}), 128.6 (2C, *C*H_{Ar}), 129.0 (*C*H_{Ar}), 139.7 (*C*$_{Ar}$), 151.3 (*C*$_{Ar}$), 157.7 (*C*$_{Ar}$).

6. Abbreviations

AIBN	Azobisisobutyronitrile
Ar	Aryl
BA	Benzoic acid
BINOL	1,1'-Bi-2-naphthol
Bn	Bebzyl
BOC	*Tert*-butoxycarbonyl
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzyl
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
EI	Electron ionization
ESI	Electrospray ionization
equiv.	Equivalent
HOMO	Highest Occupied Molecular Orbital
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy

IBX	*Ortho*-iodobenzoic acid
LAH	Lithium aluminium hydride
LUMO	Lowest Unoccupied Molecular Orbital
Mes	Mesityl
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
n.d.	Not determined
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
Nu	Nucleophile
o-FBA	*Ortho*-fluorobenzoic acid
Ox	Oxidant
PCC	Pyridinium Chlorochromate
PG	Protecting group
phen	Phenanthroline
Piv	Pivaloyl
PMP	*Para*-methoxyphenyl
p-TsOH	*Para*-toluensolfonic acid
rt	Room temperature
SOMO	Single Occupied Molecular Orbital
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl group
Ts	Tosyl
TS	Transition state

7. Literature

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