Chiral secondary amine catalyzed asymmetric cascade reactions

Dai, Lu

2012

Dai, L. (2012). Chiral secondary amine catalyzed asymmetric cascade reactions. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/50607>

<https://doi.org/10.32657/10356/50607>

Chiral Secondary Amine Catalyzed Asymmetric Cascade Reactions

DAI LU

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of

Doctor of Philosophy

2012

ACKNOWLEDGEMENTS

First of all, I want to express my heartfelt gratitude to my supervisors, including my previous supervisor Associate Professor Zhong Guofu, my current supervisor Associate Professor Park Cheol-Min, and co-supervisor Professor Loh Teck Peng, for offering me this cherish opportunity to be a PhD student in their groups. Professor Zhong introduced me to the amazing and intriguing fields of organocatalysis. I would like to thank him for his endless help and guidance in the research, as well as his valuable and critical advice. Professor Park fully supported me and my research since my transferring to his group and he gave careful reviewing for my paper and thesis. Professor Loh also helped me a lot during my last year's study in NTU.

Next, I would like to thank all my lab mates in both Prof. Zhong's group and Prof. Park's group, past and present, especially Mr. Zhu Di, Dr. Tan Bin, Dr. Zeng Xiaofei, Dr. Chua Pei Juan, Dr. Wang Fei, and Miss Leong Wen Yi Wendy, for providing me a wonderful and creative research environment and offering much discussions, assistance and research inspiration. Under such circumstance, I finished the projects included in this thesis. Besides, the lab mates in present lab showed me a lot of support, for which I will also thank. I am thankful to my undergraduate students: Lv Yunbo, Shao Yaling, and Michelle Pung Hui Lee.

In addition, I would like to extend my gratitude to all the laboratory staff in CBC, particularly Dr. Li Yongxin for his expertise in X-ray crystallography, Miss Goh Ee Ling for NMR tests, and Ms Zhu Wenwei for GC-MS, LC-MS and HRMS testing.

Last but not least, I would like to extend my thanks to my parents and all my friends for their love and continuous support.

Finally, Nanyang Technological University's generous sponsor of a research scholarship for my Ph.D study is much appreciated.

Table of Contents

Chapter 1 Introduction	1
1.1 Background	1
1.2 Activation Mode of Secondary Amines as Organocatalysts	2
1.3 Secondary Amine Catalyzed Asymmetric Reactions	3
1.3.1 <i>L</i> -proline Catalyzed Asymmetric Reactions	3
1.3.2 Diarylprolinol Silyl Ether Catalyzed Asymmetric Reactions	7
1.4 Organocatalytic Asymmetric Cascade Reactions	19
1.4.1 Hydrogen-Bond Catalyzed Cascade Reaction.....	20
1.4.2 Chiral Brønsted-Acid Catalyzed Cascade Reaction	22
1.4.3 NHC Catalyzed Cascade Reaction	24
1.4.4 Amine Catalyzed Cascade Reaction	25
1.4.4.1 Cascade Reactions Involving <i>L</i> -proline and Its Analogues	25
1.4.4.2 MacMillan's Chiral Imidazolidinone Catalyzed Cascade Reaction	28
1.4.4.3 Diarylprolinol Silyl Ether Catalyzed Cascade Reaction	29
1.5 Summary	32
1.6 References	33
Chapter 2.....	41
2.1 Abstract.....	41
2.2 Introduction	42
2.3 Results and Discussion	44
2.4 Conclusion.....	49

2.5 Experimental section	49
2.5.1 Procedure for the preparation of substrate	51
2.5.2 Procedure for synthesis of bicyclic isoxazolidines.	53
2.5.3 Characterization data.	53
2.6 Reference	69
Chapter 3	71
3.1 Abstract	71
3.2 Introduction	72
3.3 Results and discussion	72
3.4 Conclusion	79
3.5 Experimental section	80
3.5.1 Procedure for preparation of (E)-ethyl 4-(2-(4-methylphenylsulfonamido)phenyl)-2-oxobut-3-enoate 3:	80
3.5.2 Procedure for cascade aza-Michael-Michael-hemiacetalization reaction	81
3.5.3 Characterization data	81
3.6 Reference	98
Chapter 4	102
4.1 Abstract	102
4.2 Introduction	103
4.3 Results and discussion	105
4.4 Conclusion	110
4.5 Experimental section	111
4.5.1 Procedure for preparation of (E)-ethyl 4-(2-hydroxyphenyl)-2-oxobut-3-enoate 2: ...	111

4.5.2 General procedure for cascade oxo-Michael-Michael-Michael-aldol reaction	112
4.5.3 Characterization data	112
4.6 Reference.....	123

ABSTRACT

In recent years, enantioselective organocatalytic reactions have attracted more and more attention with variety of chiral organocatalysts. This thesis mainly focuses on the investigations of chiral secondary amine catalyzed asymmetric reactions.

The thesis is divided into four chapters. Firstly, a brief introduction to organocatalysis especially chiral secondary amine organocatalysts and cascade reactions are presented in chapter 1.

Chapter 2 describes an *L*-proline catalyzed one-pot synthesis of bicyclic isoxazolidines, which involves an α -Amination/condensation/nitrone [3+2] cycloaddition cascade process to afford products with good yields (state range) and good to excellent enantioselectivity (up to 99%).

Chapter 3 presents a novel, facile organocatalytic asymmetric cascade aza-Michael-Michael-hemiacetalization reaction for the synthesis of tetrahydroquinoline derivatives with good control of four stereogenic centers. This domino process yields highly diastereo- and enantioselective products with the use of the Jørgensen-Hayashi catalyst.

Chapter 4 is the derivative study for Chapter 3. Similar starting materials bear totally different cascade reaction process. This chapter introduces an asymmetric cascade oxo-Michael-Michael-Michael-aldol reaction. The reaction is also under the catalysis of Jørgensen-Hayashi catalyst and obtained product is highly diastereo- and enantioselective.

Chapter 1 Introduction

1.1 Background

Early in the 1970s, Hajos and Wiechert reported an intramolecular aldol condensation reaction catalyzed by the naturally occurring amino acid, *L*-proline (Scheme 1.1). The significance of this reaction was that the product obtained was enantioselectively synthesized by *L*-proline.^[1]

heme 1.1 The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

This seminal study opened a new page of this research field which is now termed as “organocatalysis”. In 2000, List and co-workers carried out an *L*-proline catalyzed intermolecular aldol reaction^[2], while Macmillan reported a novel imidazolidinone iminium for a highly enantioselective Diels-Alder reaction^[3], which contributed to the foundation of this intriguing new realm. Thereafter, many talented organic chemists focused their efforts on organocatalysis. Since then, many breakthroughs have been made in the field of organocatalysis, and it has become one of the fundamental parts of organic synthesis.

Organocatalysts are advantageous as they are relatively inexpensive, readily available, non-toxic and easy to handle. In many metal-catalyzed organic reactions, oxygen and moisture will be deleterious to these reactions, making it essential for the use of

anhydrous solvents and inert atmosphere. But in most organocatalytic reactions, there is no need for such stringent reaction conditions, rendering them industrially attractive.

Although organocatalysis has many disadvantages, such as larger catalyst loading and somehow limited substrate scope, it still attracts the attention of many research groups around the world. In the past few years, various organocatalysts such as amine catalysts, hydrogen-bonding catalysts, Brønsted acid catalysts, *N*-heterocarbene (NHC) catalysts and chiral phase-transfer catalysts (PTC) were developed. In this thesis, my research primarily focuses on secondary amine catalysts and their application to enantioselective asymmetric cascade reactions.

1.2 Activation Mode of Secondary Amines as Organocatalysts

There are three widely accepted activation modes for secondary amine catalysts: HOMO (highest occupied molecular orbital) activation, LUMO (lowest unoccupied molecular orbital) activation and SOMO (singly occupied molecular orbital) activation. These activation modes are characterized by the intermediates resulting from binding of the secondary amine catalyst to the carbonyl compound.

In HOMO activation, the energy of the HOMO of the enamine, formed by the condensation of a secondary amine and carbonyl compound and subsequent deprotonation, is raised to give activated nucleophiles. Conversely, in the case of LUMO activation, the energy of the LUMO of the iminium ion is lowered and will lead to a consequent enhancement of the acidity of the α -protons due to redistribution of the intermediate electrons (Figure 1.1).

Figure 1.1 HOMO and LUMO activation modes.

These two important concepts have made significant contributions to the development of organocatalysis. A great number of publications, which are based on these two activation modes, have been published.^[4]

During recent years, MacMillan and co-workers developed a new concept of secondary amine activation mode (SOMO), which results in the formation of an enamine intermediate bearing a single unpaired electron.^[5] The chiral imidazolidinone was proved to be a useful secondary amine catalyst in SOMO catalysis (Figure 1.2).

Figure 1.2 SOMO activation mode.

1.3 Secondary Amine Catalyzed Asymmetric Reactions

1.3.1 *L*-proline Catalyzed Asymmetric Reactions

In 2000, List, Barbas and Lerner first reported an *L*-proline catalyzed enantioselective intermolecular aldol condensation reaction of a ketone and aldehyde in DMF ^[2] (Scheme 1.2). This was one of the first examples of an enantioselective organocatalytic reaction which involves enamine activation. By using 30 mol% of *L*-proline as catalyst, the

desired product could be isolated in 97% yield and 96% ee.

Scheme 1.2 *L*-proline catalyzed intermolecular aldol reaction between acetone and aldehyde.

In 2000, *L*-proline catalyzed asymmetric Mannich reactions were reported by List and co-workers. The authors reported an *L*-proline catalyzed one-pot three-component Mannich reaction, which afforded the corresponding (*S*)-products in good yields (up to 90%) and excellent enantioselectivities (up to 96%) ^[6] (Scheme 1.3). With preformed *N*-PMP-protected α -imino ethyl glyoxylate as the imine component, excellent enantioselectivities were obtained.^[7]

Scheme 1.3 One-pot three-component Mannich reaction between acetone, aldehyde and *p*-anisidine.

When applied to reactions involving enolizable aliphatic aldehyde donors, *L*-proline proved to be an efficient catalyst. Barbas and co-workers reported the first example of an unmodified enolizable aliphatic aldehyde in asymmetric Mannich reactions.^[8] The *syn*-product was obtained as the sole product with good enantioselectivity.

As an important protocol for forming new carbon-carbon bonds, asymmetric Michael

reactions were developed by the use of enamine-generated catalysis, which may involve an iminium activation mode (Figure 1.3).

Figure 1.3 Activation modes for amine-catalyzed Michael reactions.

L-proline catalyzed asymmetric Michael reactions were first reported by Barbas and co-workers.^[9] This Robinson annulation reaction between methyl vinyl ketone and 2-methylcyclohexanone-1,3-dione gave rise to the desired annulation product in 49% yield and 76% ee (Scheme 1.4).

Scheme 1.4 *L*-proline catalyzed Robinson annulation reaction.

Later on, List and co-workers developed a Michael addition of cyclohexanone to nitroolefins mediated by *L*-proline. Although excellent yields and diastereoselectivities were obtained, the enantioselectivity was poor (23%). Hence, there is potential in improving this reaction by the development of a more efficient and powerful catalyst.^[10]

MacMillan and co-workers developed a chiral imidazolidinone secondary amine catalyst for Diels-Alder reactions, based on the activated α,β -unsaturated carbonyl compounds by the LUMO activation mode.^[11] Following that, Barbas reported the *in situ*

enamine activation of α,β -unsaturated ketones in which nitroolefins acted as dienophiles^[12] (Scheme 1.5).

Scheme 1.5 *L*-proline catalyzed Diels-Alder reactions via enamine activation.

Another notable report is the aminooxylation reaction of aldehydes with nitrobenzene that was independently discovered by Zhong, MacMillan and Hayashi (Scheme 1.6). Various aldehydes and ketones were successfully applied to this methodology, which led to the synthesis of many useful building blocks bearing α -functional carbonyl groups. Subsequently, 1,3-dicarbonyl compounds, enecarbamates, enamides and oxindoles were also found to be suitable substrates by the use of different organocatalysts.^[13]

Scheme 1.6 *L*-proline catalyzed α -aminoxylation of aldehydes.

In 2002, List and Jørgensen independently reported *L*-proline catalyzed α -amination of aldehydes and ketones^[14] (Scheme 1.7).

Scheme 1.7 *L*-proline catalyzed α -amination reaction.

In all these *L*-proline catalyzed reactions, the key intermediate is the enamine formed between the catalyst and carbonyl functional group. Houk and co-workers carried out computational studies to confirm that this proposed transition state was the most energetically favorable, and consistent with the observed enantioselectivity.^[15] Furthermore, Metzger and co-workers used ESI- mass spectrometry,^[16] while Gschwind *et al* used *in situ* NMR spectroscopy, to elucidate the enamine mechanism.^[17] More recently, List obtained the X-ray crystal structure of the proline-derived enamines, which also provides evidence for this mechanism.^[18]

1.3.2 Diarylprolinol Silyl Ether Catalyzed Asymmetric Reactions

The development of organocatalysts started off from modification of the proline skeleton. Some new catalysts were designed by changing the hydrogen bonding motifs and typically made to improve the ability to dually activate the substrate. However, these modifications alone were not adequate, and the introduction of bulky substituent groups was necessary to improve their catalytic ability. To date, the most widely used chiral secondary amine catalysts were developed by MacMillan, Jørgensen and Hayashi, namely, chiral imidazolidinone and diarylprolinol silyl ether (Figure 1.4).

Figure 1.4 MacMillan's catalyst and Jørgensen and Hayashi's catalyst.

MacMillan applied the imidazolidinone (**II**) derived secondary amine in many asymmetric transformations, including α -functionalization of aldehydes^[5a, 5b, 19] and ketones^[20], 1,3-dipolar cycloaddition^[21], Friedel – Crafts alkylation^[22], hydrogenation^[23] and intramolecular Diels-Alder reaction^[3, 24] (Scheme 1.8).

Scheme 1.8 Chiral imidazolidinone catalyzed α -functionalization of aldehydes.

In 2005, Jørgensen and Hayashi independently reported novel diarylprolinol silyl ethers (**III** and **IV**) as excellent catalysts for organocatalytic asymmetric reactions.^[25] This type of catalyst was soon explored in many organic transformations, and was proved to be synthetically useful, efficient, selective and robust. The catalyst was found to be involved in both the HOMO and LUMO activation mode. Meanwhile, the bulky groups of the catalyst produced excellent shielding on the *Si* face of the enamine and iminium intermediates, which led to preferential attack of the nucleophile from the *Re* face to

generate the product.

In a recently published review, Jørgensen explained the rationale behind the design plan of this catalyst, which drew inspiration from diarylmethylpyrrolidine and diarylprolinol due to their amino-catalytic activity.^[26] When diarylmethylpyrrolidine is used as the catalyst, good reactivity is commonly observed, albeit with low selectivity due to insufficient steric hindrance to induce high selectivity in most reactions. On the other hand, the prolinol system showed good stereoselectivity but poor reactivity for the formation of a “parasitic” oxazolidine. Thus the combination of these two catalysts with orthogonal characteristics was carried out, and led to the introduction of a protecting group on prolinol (Scheme 1.9), to give the famous “Jørgensen and Hayashi’s catalyst”.

Scheme 1.9 Catalyst design plan.

Generally, diarylprolinol silyl ether catalyzed enantioselective reactions are distinguished by four different pathways: enamine-, dienamine-, trienamine- and iminium-ion activation.

Catalyst **IV** was first used for the asymmetric α -sulfenylation of aldehydes^[25b]. During the catalyst screening, *L*-proline **I**, *L*-prolinamide **V**, diphenylmethylpyrrolidine

VI, and diphenylprolinol **VII** could not achieve satisfactory reaction activity or enantioselectivity (up to 56% yield and 52% ee). However, when diphenylprolinol silyl ether **III** was used, an improvement in yield (90%) and enantioselectivity (77%) was observed. The introduction of a more sterically-hindered 3,5-ditrifluoromethylphenyl group afforded a remarkable increase in the enantioselectivity (98%), while maintaining the excellent yield (90%) (Scheme 1.10).

Scheme 1.10 α -sulfonylation of aldehydes catalyzed by diarylprolinol silyl ether **IV**.

The catalyst was then investigated in the asymmetric α -fluorination of aldehydes.^[27] Among the commonly used secondary amine catalysts, catalyst **IV** showed the most superior results of 40% conversion and 87% ee, using a catalyst loading of 20 mol%. Further screening of the reaction conditions showed that the catalyst loading could be reduced to 1 mol%, and the presence of excess aldehyde could afford the mono-fluorinated products in good yields and high enantioselectivities.

Hayashi and co-workers employed catalyst **III** for the Michael addition of aldehydes to nitroolefins.^[25a] This was the first example of an α -C-C-bond formation by implementing a diarylprolinol silyl ether. This reaction was tolerated by various aliphatic

aldehydes and a series of nitroolefins to furnish products with excellent enantio- and diastereo- selectivity (99% ee and 19:1 dr) (Scheme 1.11).

Scheme 1.11 Michael addition to nitroolefins catalyzed by catalyst **III**.

Following studies proved the generality of diarylprolinol silyl ethers for asymmetric C - C, C - N, C - F, C - Br and C - S bond formations (Scheme 1.12).^[28] The results showed a remarkable selectivity and efficiency in all cases delivering the products with good yields (71-88%) and excellent enantioselectivities (90-98%). One point to note is that the absolute configuration of products derived from the α -aminations and Mannich reactions were opposite to those obtained by *L*-proline due to the change in the mode of catalyst stereinduction.^[29]

Scheme 1.12 Asymmetric α -functionalization of aldehydes catalyzed by catalyst **IV**.

In recent years, Jørgensen and co-workers reported the α -arylation reaction of aldehydes.^[30] The first successful trial resulted from quinones applied as the aromatic

partner with electron-rich aromatic moieties. Surprisingly, the bulky catalyst **IV** showed no reactivity in this transformation, while catalyst **III** proved efficient in a series of quinones and aldehydes. Later on, aminophenols were successfully used in the α -arylation reaction of aldehydes under electrochemical oxidative conditions, which provided another method to access *meta*-alkylated anilines (Scheme 1.13).

Scheme 1.13 α -arylation reaction of aldehyde catalyzed by **III**.

In 2006, chemists proposed dienamine catalysis in γ -amination of α,β -unsaturated aldehydes, which was followed by several similar examples.^{[31] [32]} This mode of activation proceeded via the intermediacy of a dienamine species and thus provided activation of the γ -position of the aldehyde. The prolinol silyl ether catalyst had two roles to play: the first is to generate the activated dienamine species and the second is to provide differentiation between the two faces (Scheme 1.14). The catalyst-enal condensation product rapidly isomerized to the *s-trans* dienamine, which was observed as an *E/Z* mixture of the distant double bond. Consecutive hydrolysis/isomerization furnished the γ -aminated enals in moderate yields (40-58%) and good enantioselectivities (88-93%).

Scheme 1.14 Dienamine activation mode.

Earlier this year, this methodology was extended to polyconjugated enals, such as 2,4-dienals, which underwent condensation with the diarylprolinol silyl ether to form a trienamine species.^[33] DFT calculations showed that the rotational barrier energy of the C4 - C5 single bond was slightly lower than that of the C2 - C3 bond, making it easier for bond rotation to occur, due to its distance from the bulky catalyst group. Hence, reaction of the *s-cis* diene and a reactive dienophile, such as olefinic azlactones and oxindoles, generated four stereogenic centers with high enantioselectivity (Scheme 1.15).

Scheme 1.15 Asymmetric reaction activated by trienamine activation mode.

LUMO activation of α,β -unsaturated aldehydes leads to the formation of an iminium ion intermediate between the aminocatalyst and enal substrate. Even when hard nucleophiles were employed, utilization of the diarylprolinol silyl ether catalyst gave rise to the 1,4-adduct as the sole product, thereby demonstrating its efficacy in suppressing the undesired 1,2-addition to the carbonyl group.

Dialkyl malonates were first used in iminium-ion-activated aromatic enals using diarylprolinol silyl ether catalysts as carbon nucleophiles (Scheme 1.16).^[34] The Michael adduct obtained serves as an important building block for chiral lactones and lactams.

Scheme 1.16 Enantioselective Michael addition of dialkyl malonate.

After this initial report, many examples were reported and among them, 1,3-diketones were employed as Michael donors. These highly enantioselective Michael adducts were easily cyclized to produce stable hemiacetals^[35] (Scheme 1.17).

Scheme 1.17 Enantioselective Michael addition of 1,3-diketones.

When α -substituted oxazolones were used as carbon nucleophiles, α,α -disubstituted α -amino acids could be easily accessed via an iminium-ion activation pathway in a protected form ^[36] (Scheme 1.18). In this study, introduction of a more bulky benzhydryl substituent at the C-2 position of the oxazolone led to higher diastereoselectivity. DFT calculations indicated that the facial selectivity of the nucleophile was driven by steric repulsion between the C-2 substituent of the oxazolone and the bulky group of the enal.

Scheme 1.18 Enantioselective synthesis of protected α,α -disubstituted α -amino acids.

Subsequently, many other carbon nucleophiles were developed for iminium-ion activated reactions catalyzed by diarylprolinol silyl ethers. Most of them involved a domino reaction which was initiated by a Michael addition followed by an annulation reaction to obtain a multi-substituted cyclo-product with several contiguous stereocenters.

Diarylprolinol silyl ether catalysts are now used in hetero-Michael additions to form

new C – O, C – N, C – S and C – P bonds.

Oxa-Michael reactions are known to be challenging reactions for α,β -unsaturated carbonyls because the formation of an acetal or ketal often competes with the conjugate addition. The first successful trial of oxa-Michael was achieved in 2007, in which oximes were identified as good protected oxygen-centered nucleophiles ^[37] (Scheme 1.19). This reaction was catalyzed by **IV** and proceeded smoothly in a highly enantioselective manner. The chiral carbonyl β -oxime ethers could be reduced to the corresponding 1,3-diols in high yields. Furthermore, the organocatalytic enantioselective β -hydroxylation of α,β -unsaturated aldehydes could be performed on a gram scale without loss of enantioselectivity.

Scheme 1.19 Enantioselective oxa-Michael reactions catalyzed by **IV**.

A similar reaction involving thiols was also developed, in which highly enantioselective γ -thio alcohols were achieved through nucleophilic attack of the thiol to α,β -unsaturated aldehydes, followed by reduction. ^[38] This methodology could be applied to multi-component domino addition-amination reactions to achieve amino thiols in moderate to good yields and high enantioselectivities (Scheme 1.20).

Scheme 1.20 Enantioselective sulfa-Michael reactions catalyzed by **IV**.

When nitrogen centered nucleophiles are used, the addition reaction is much easier. This can be seen from Aza-Michael reactions, in which triazoles, tetrazoles^[39] as well as succinimides^[40] were used as the nitrogen source. The diarylprolinol silyl ether catalyst induced good stereocontrol in the new C - N bond formation. For reactions between α,β -unsaturated aldehydes and 1,2,3-benzotriazoles or 1,2,3-triazoles, two regioisomeric products were obtained in up to a 2:1 ratio (Scheme 1.21).

Scheme 1.21 Enantioselective Aza-Michael reactions catalyzed by **IV**.

Around the same time, enantioselective C – P bond formations were developed via an iminium-ion activation pathway. Two kinds of different P(III): phosphites and phosphines were investigated.^[41] (Scheme 1.22) In the case of phosphite additions, it was important to choose compatible nucleophilic additives to enable oxidation of P(III) to P(V) via an Arbuzov-type dealkylation reaction proceeding at one of the phosphite alkoxy moieties.^[41a] Further investigations showed that the use of triisopropyl phosphite proceeded with the highest efficiency, with stoichiometric amounts of NaI as a nucleophilic additive. Later on, hydrophosphination of α,β -unsaturated aldehydes with phosphines were reported independently by two research groups.^[41b, 41c]

Scheme 1.22 Enantioselective phospho-Michael reactions catalyzed by **III** or **IV**.

1.4 Organocatalytic Asymmetric Cascade Reactions

The ability of diarylprolinol silyl ether catalysts to activate reactants via an enamine and iminium-ion intermediate makes them promising catalysts in cascade reactions.

Cascade reactions have attracted much attention in recent years.^[42] Their benefits include atom economy^[43], shorter reaction time, and low waste generation, which has consequently rendered them as a branch of “Green Chemistry”^[44]. Unlike multi-step

reactions, there is only one reaction environment and hence work-up and purification only need to be carried out once. A variety of terms, including “cascade”, “domino”, “tandem”, and “sequential” are used for this kind of reaction.^[45]

There are a few types of cascade reactions: nucleophilic cascade, electrophilic cascade, radical cascade, pericyclic cascade and transition-metal-catalyzed cascade.^[45]

Organocatalysts are suitable for catalytic cascade reactions because they can work via different activation modes. Besides, organocatalysts are relatively mild compared to their organometallic counterparts and can tolerate many functional groups.^[46]

In organocatalytic cascade reactions, enamine activation and iminium-ion activation are the most popular. They can realize good stereocontrol during bond formation. The combination of these two activations in a single operation makes it a milestone in amine-catalysis.

Besides amine catalysis, hydrogen-bonding and Brønsted-acid catalysis have also developed rapidly. For hydrogen-bonding catalysis, a LUMO-lowering pathway is involved and among the catalysts developed so far, thioureas are a prominent class for cascade reactions. Chiral phosphoric acids, which are an important class of Brønsted-acid catalysts, can activate the substrates by protonation of a suitable C=O, C=NR, or C=CR₂ bond and hence generate a chiral counter-ion.^[47] In recent years, *N*-heterocyclic carbenes (NHC) catalysis is also applied in cascade reactions through an “umpolung”^[48] to activate carbonyl groups.^[49]

1.4.1 Hydrogen-Bond Catalyzed Cascade Reaction

The first example of a thiourea-catalyzed cascade reaction was reported in 2005.

Takemoto and co-workers disclosed a Michael addition of γ,δ -unsaturated- β -ketoesters to nitroolefins catalyzed by bifunctional thiourea (**X**), followed by an intramolecular Michael addition to obtain highly functionalized cyclohexanones in high yields and enantioselectivities^[50] (Scheme 1.23). This methodology was applied successfully in the total synthesis of the frog alkaloid, (-)-epibatidine.

HEME 1.23 Thiourea catalyzed asymmetric tandem Michael/Michael reaction.

Takemoto and Pápai^[51] proposed two different transition states for this reaction (Figure 1.5). Both of them make use of a dual activation mechanism. Takemoto suggested that the thiourea moiety activated the nitroolefin electrophile, while the tertiary amine activated the enolized ketoester. This is opposite to what Papai proposed. These two proposed transition states have not been confirmed by experimental investigation.

Figure 1.5 Two transition states in thiourea catalyzed reactions

by Takemoto and Pápai

In 2008, Chen^[52] and Takemoto^[53] independently reported the first thiourea-catalyzed asymmetric three-component 1,3-dipolar cycloaddition of aldehydes, α -aminomalonates and nitroolefins (Scheme 1.24). The cascade reaction was initiated from imine formation and then followed by Michael addition and subsequent aza-Henry reaction to give an enantioselective multi-substituted pyrrolidine.

Scheme 1.24 Formal [3+2] cycloaddition reported by Takemoto and Chen.

Wang and co-workers developed a cascade reaction catalyzed by a cinchona alkaloid thiourea (**XII**).^[54] This process afforded direct access to thiochromanes in high efficiency. The reaction featured a new activation mode of organocatalytic dynamic kinetic resolution involving a Michael–retro-Michael–Michael–Michael cascade (Scheme 1.25).

Scheme 1.25 Wang's synthesis of 3-nitro-thiochromenes.

1.4.2 Chiral Brønsted-Acid Catalyzed Cascade Reaction

After the pioneering work of chiral phosphoric acid as organocatalysts by Prof. Terada and Prof. Akiyama in 2004, Rueping and co-workers first reported a chiral phosphoric acid (**XIII**) catalyzed enantioselective cascade transfer hydrogenation in 2006.^[55] They investigated the asymmetric transfer hydrogenation of 2-substituted quinoline derivatives to tetrahydroquinolines with a Hantzsch ester (Scheme 1.26). The reaction proceeded by a 1,4-hydride addition to the protonated quinoline, followed by isomerization of the enamine intermediate to the iminium ion and 1,2-addition to the amine.

Scheme 1.26 Asymmetric cascade transfer hydrogenation catalyzed by **XIII**.

Later in 2008, the same group performed a highly enantioselective reaction between an enamine, a vinyl ketone and a Hantzsch ester, during which the six steps included were all catalyzed by the same chiral phosphoric acid to afford functionalized tetrahydropyridines and azadecalinones.^[56]

In 2007, List and co-workers developed a highly enantioselective organocatalytic cascade sequence towards chiral substituted cyclohexylamines.^[57] This reaction involved

a concerted enamine, iminium and Brønsted catalysis. They found that an achiral amine in combination with a catalytic amount of a chiral Brønsted acid can accomplish an aldol addition-dehydration-conjugate reduction-reductive amination to provide potential intermediates of pharmaceutically active compounds in good yields and excellent enantioselectivities (Scheme 1.27).

Scheme 1.27 Cascade sequence towards chiral cyclohexylamines reported by List.

1.4.3 NHC Catalyzed Cascade Reaction

In 2004, Bode and Glorius independently reported *N*-heterocyclic carbenes (NHC) prepared from diarylimidazolium salts. This catalyst proved to be highly efficient for the formation of active homoenolates from α,β -unsaturated aldehydes, and soon became a novel access for C – C bond formation in organocatalysis.

Two years later, Bode and co-workers applied this catalyst in aza-Diels-Alder reactions^[58] with *N*-sulfonyl- α,β -unsaturated imines to yield highly enantioselective products with 97-99% ee.

Nair described an efficient synthesis of 1,3,4-trisubstituted cyclopentenones via homoenolate from enals and chalcones.^[59] In 2007, Bode and co-workers reported the synthesis of *cis*-1,3,4-trisubstituted cyclopentenones.^[60] The chiral NHC catalyst promoted the cascade intermolecular crossed-benzoin reaction and oxy-Cope rearrangement,

followed by tautomerization, intramolecular aldol reaction, acyl addition and decarboxylation, which led to excellent levels of enantioinduction (Scheme 1.28).

Scheme 1.28 NHC-catalyzed cis-cyclopentannulation of enals and chalcones.

In 2009, Bode and co-workers reported the stereodivergency of triazolium and imidazolium-derived NHC catalyzed cyclopentane synthesis.^[61] Structurally identical imidazolium and triazolium precatalysts afforded different major products.

1.4.4 Amine Catalyzed Cascade Reaction

Amine catalysts play an important role in organocatalytic cascade reactions for their ability to handle both the enamine and iminium ion activation mode, especially chiral secondary amine catalysts. Herein, we will briefly introduce some representative examples according to three kinds of main secondary amine organocatalysts: *L*-proline and its analogues, imidazolidinone and diarylprolinol silyl ethers.

1.4.4.1 Cascade Reactions Involving *L*-proline and Its Analogues

The first example of an *L*-proline catalyzed cascade reaction came out in 2000 by Barbas and Bui.^[62] The asymmetric Robinson annulation for the synthesis of Wieland –

Miescher ketone from methyl vinyl ketone and diketone obtained a moderate yield (49%) and ee (76%). This reaction underwent a Michael/aldol condensation, and the stereoselectivity was controlled by an iminium-ion activated intermediate. Although this example is not considered very successful from today's point of view, it opened the door towards iminium-enamine activated cascade reactions.

In 2006, Hong *et al.* reported the synthesis of *L*-proline catalyzed cyclohexenecarbaldehydes starting from crotonaldehyde.^[63] This reaction constituted a formal [3+3] cycloaddition via a Michael/Morita-Baylis-Hillman sequence through an iminium-enamine activation pathway. Although the diastereoselectivity was low (almost 1:1 dr), the two epimers were highly optically pure (80% and 95%) (Scheme 1.29).

Scheme 1.29 Hong reported formal [3+3] cycloaddition and mechanism.

Barbas and co-workers reported a *L*-proline-catalyzed trimerization of simple aldehydes to carbohydrates and polyketides constituted by two consecutive aldol reactions that goes through an enamine-enamine activation pathway.^[64] Later on, they reported a three-component cascade sequence for the synthesis of functionalized hydrazino alcohols.^[65] This reaction involved an α -amination and an aldol reaction to

afford the *anti* isomer with a single enantiomer (>99% ee) and *syn* isomer with moderate to good ee (13-91% ee) (Scheme 1.30).

Scheme 1.30 Proline-catalyzed three-component cascade reactions.

In 2008, Zhong reported a novel, practical and highly enantio- and diastereo-selective *L*-proline catalyzed domino reaction for the synthesis of functionalized tetrahydro-1,2-oxazines, which became the foundation for our interest in cascade reactions.^[66] In this study, *O*-alkylation took place at the α -position of the aldehyde, followed by a subsequent intramolecular aza-Michael reaction to close the ring and furnish the product with excellent yields and enantioselectivities (Scheme 1.31).

Scheme 1.31 Synthesis of tetrahydro-1,2-oxazines catalyzed by I.

Yamamoto and co-workers described a cascade nitroso aldol/Michael reaction to give the desired nitroso Diels - Alder adduct with high enantioselectivity.^[67] The regioselectivity of the product was opposite to that a typical nitroso aldol reaction.

The first example of an asymmetric formal [3+3] annulation of cyclic ketones with enones was reported by Tang.^[68] The bicyclic [3.3.1] skeleton was formed via a Michael/aldol reaction, with the formation of two new C - C bonds, four stereogenic

centers in a highly enantioselective fashion, under mild conditions (Scheme 1.32).

Scheme 1.32 Formal [3+3] annulation of cyclic ketones with enones.

In 2008, Xu and co-workers reported a pyrrolidine derivative catalyzed cascade oxa-Michael-Henry reaction starting from salicyl aldehydes and nitroolefins.^[69] The 3-nitro-2*H*-chromene obtained underwent nucleophilic attack on the β -position of the nitroolefin, cyclization, and dehydration, with high yield and enantioselectivity.

1.4.4.2 MacMillan's Chiral Imidazolidinone Catalyzed Cascade Reaction

Similar with *L*-proline and diarylprolinol silyl ether, chiral imidazolidinone was also utilized for organocatalytic cascade reactions.

In 2004, MacMillan employed this catalyst in the synthesis of (-)-Flustramine B.^[70] The key sequence in this synthesis was a conjugate addition, followed by heterocyclization. This strategy made it simple to synthesize a highly enantiopure natural product.

For iminium-enamine cascade reactions, the first example came from List and MacMillan, respectively.^[71] List's intramolecular reaction formed cyclic keto aldehydes from enal enones via a reductive Michael cyclization. After the enal was activated by **II**, hydride transfer occurred to afford an enamine intermediate, which undergoes a Michael addition to give the cyclized product (Scheme 1.33).

Scheme 1.33 Cascade reaction catalyzed by **II**.

The same authors also reported a cascade reaction involving conjugated addition of nucleophiles with enals, followed by addition of the enamine intermediate to electrophiles.^[72] In this reaction, the electrophile was chlorine and a wide range of nucleophiles such as furans, thiophenes, indoles, butenolides and tertiary aminoactone equivalents were tolerated. In almost all cases, high *syn* selectivity and excellent enantioselectivity (>99% ee) were obtained.

1.4.4.3 Diarylprolinol Silyl Ether Catalyzed Cascade Reaction

The diarylprolinol silyl ether catalyst is capable of activating aldehydes and α,β -unsaturated aldehydes by the enamine and iminium-ion pathway, making it ideal for cascade reactions. Normally, this kind of cascade reaction is based on conjugate addition of nucleophiles to α,β -unsaturated aldehydes, and then α -functionalization, which will generate at least two chiral centers.

In 2005, an epoxidation reaction of cinnamaldehydes was reported to take place using Jørgensen and Hayashi's catalyst under mild conditions.^[73] The mechanism included a conjugate addition of hydrogen peroxide to iminium-ion and then a nucleophilic displacement. This reaction was highly efficient in stereoselectivity and water was the

only byproduct. Two years later, a similar aziridination of α,β -unsaturated aldehydes was reported by Córdova^[74] (Scheme 1.34).

Scheme 1.34 Epoxidation and aziridination of α,β -unsaturated aldehydes.

Shortly after that, a study on a conjugate thiol addition to α,β -unsaturated aldehydes revealed that during iminium-ion/enamine activation, the enamine step could be intermolecular.^[38]

In 2006, a report which combined a thiol addition with an intramolecular aldol reaction occurred.^[75] This reaction documented a highly stereoselective synthesis of tetrahydrothiophene with three chiral centers (Scheme 1.35). The ring-closing reaction occurred via a highly organized intermediate bearing the aldehyde substituent in a pseudo-equatorial position, and the phenyl substituent was placed opposite the steric bulk of the catalyst. Addition of benzoic acid could speed up the reaction, which was thought to be an effect of faster iminium-ion formation and increased electrophilicity of the ketone in the aldol reaction by protonation.

Scheme 1.35 Formation of tetrahydrothiophenes catalyzed by **IV**.

In the same year, Enders et al. developed a triple cascade reaction involving an enamine/iminium-ion/enamine sequence to furnish a tetrasubstituted cyclohexene carbaldehydes with four stereocenters ^[76] (Scheme 1.36).

Scheme 1.36 Triple enamine/iminium-ion/enamine cascade reaction.

A different triple cascade reaction involving in iminium-ion/iminium-ion/enamine sequence was then reported to afford substituted cyclohexene carbaldehydes.^[77] This reaction underwent two consecutive conjugate additions of the carbon nucleophile followed by aldol condensation. An additional quaternary stereocenter could be obtained when malononitrile was substituted for cyano- or nitroacetate derivatives (Scheme 1.37).

Scheme 1.37 Triple iminium-ion/iminium-ion/enamine cascade reaction.

In 2010, a novel iminium-ion/enamine/Lewis acid cascade was presented by Jørgensen.^[78] Mechanistic studies revealed the cooperation of the organocatalyst and Lewis acid in the carbocyclization step. Even though two diastereoisomers of the intermediate were observed by ^1H NMR, only one isomer was obtained after the ring-closing. This was attributed to catalyst-controlled cyclization of only one of the diastereoisomers, while the interconversion of the intermediates occurred via a retro-Michael reaction.

1.5 Summary

The background of chiral secondary amine catalyzed organocatalytic asymmetric cascade reactions has been introduced. As the relatively new and emerging research field in organic synthesis, asymmetric cascade reactions show a promising future. During the course of my PhD studies, I have focused on the exploration of such reactions, which will be elaborated on in the following chapters.

1.6 References

- [1] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, 39, 1615; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, 10, 496.
- [2] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, 122, 2395.
- [3] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, 122, 4243.
- [4] a) A. Berkessel, H. Groger, *Asymmetric organocatalysis : from biomimetic concepts to applications in asymmetric synthesis*, Wiley-VCH, Weinheim ; [Great Britain], **2005**; b) P. I. Dalko, *Enantioselective organocatalysis : reactions and experimental procedures*, Wiley-VCH ; John Wiley [distributor], Weinheim Chichester, **2007**; c) B. List, *Chem. Rev.* **2007**, 107, 5413; d) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2007, 2575; e) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, 47, 4638; f) D. W. C. MacMillan, *Nature* **2008**, 455, 304; g) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, 38, 2178.
- [5] a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, 316, 582; b) H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, 129, 7004; c) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, 129, 4124.
- [6] B. List, *J. Am. Chem. Soc.* **2000**, 122, 9336.
- [7] A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, 124, 1842.
- [8] a) A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, 124, 1866; b) W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M.

- Turner, R. Thayumanavan, C. F. Barbas, III, *J. Org. Chem.* **2003**, 68, 9624.
- [9] T. Bui, C. F. Barbas, *Tetrahedron Lett.* **2000**, 41, 6951.
- [10] B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, 3, 2423.
- [11] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, 122, 4243.
- [12] R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C. F. Barbas, III, *Tetrahedron Lett.* **2002**, 43, 3817.
- [13] a) G. Zhong, *Angew. Chem., Int. Ed.* **2003**, 42, 4247; b) P. Merino, T. Tejero, *Angew. Chem. Int. Ed.* **2004**, 43, 2995; c) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, 125, 10808.
- [14] a) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bogevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, 124, 6254; b) B. List, *J. Am. Chem. Soc.* **2002**, 124, 5656.
- [15] a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, 123, 12911; b) S. Bahmanyar, K. N. Houk, *Org. Lett.* **2003**, 5, 1249; c) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, 125, 2475.
- [16] C. Marquez, J. O. Metzger, *Chem. Commun.* **2006**, 1539.
- [17] M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem. Int. Ed.* 49, 4997.
- [18] D. A. Bock, C. W. Lehmann, B. List, *Proc. Natl. Acad. Sci.* **2010**, 107, 20636.
- [19] a) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, 126, 4108; b) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, 127, 8826; c) H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, 130, 398; d) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, 322, 77; e) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, 131, 10875; f) A. E. Allen, D.

- W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260.
- [20] a) A. Mastracchio, A. A. Warkentin, A. M. Walji, D. W. C. MacMillan, *Proc. Natl. Acad. Sci.* **2010**, *107*, 20648; b) P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738.
- [21] W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874.
- [22] N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370.
- [23] S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *127*, 32.
- [24] R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616.
- [25] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
- [26] K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.*, published online 17 Aug, 2011.
DOI: 10.1021/ar200149w
- [27] M. Marigo, D. Fielenbach, A. Branton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703.
- [28] J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.
- [29] M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, 632.
- [30] a) J. Alemán, S. Cabrera, E. Maerten, J. Overgaard, K. A. Jørgensen, *Angew. Chem.*

- Int. Ed.* **2007**, *46*, 5520; b) K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2010**, *49*, 129.
- [31] S. Bertelsen, M. Marigo, S. Brandes, P. Din r, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.
- [32] a) R. M. de Figueiredo, R. Frhlich, M. Christmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 1450; b) K. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem. Int. Ed.* **2008**, *47*, 5827.
- [33] a) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053; b) H. Jiang, B. Gschwend, L. Albrecht, S. G. Hansen, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 9032.
- [34] S. Brandau, A. Landa, J. Franz n, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 4305.
- [35] a) P. T. Franke, B. Richter, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 6317; b) M. Rueping, E. Sugiono, E. Merino, *Chem. Eur. J.* **2008**, *14*, 6329.
- [36] a) S. Cabrera, E. Reyes, J. Aleman, A. Milelli, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 12031; b) Y. Hayashi, K. Obi, Y. Ohta, D. Okamura, H. Ishikawa, *Chem. Asian. J.* **2009**, *4*, 246.
- [37] S. Bertelsen, P. Din r, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 1536.
- [38] M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710.
- [39] P. Din r, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, *46*,

1983.

- [40] H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.* **2007**, *13*, 9068.
- [41] a) E. Maerten, S. Cabrera, K. A. Jørgensen, *J. Org.Chem.* **2007**, *72*, 8893; b) A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem. Int. Ed.* **2007**, *46*, 4504; c) I. Ibrahim, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo, A. Córdova, *Angew. Chem. Int. Ed.* **2007**, *46*, 4507.
- [42] a) L.-F. Tietze, G. Brasche, K. M. Gericke, *Domino reactions in organic synthesis*, Wiley-VCH, Weinheim, **2006**; b) T.-L. Ho, *Tandem organic reactions*, : Wiley, New York, **1992**.
- [43] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259.
- [44] P. T. Anastas, J. C. Warner, *Green chemistry : theory and practice*, Oxford University Press, Oxford [England] ; New York, **2000**.
- [45] K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.
- [46] C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.*, *2*, 167.
- [47] a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.
- [48] D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239.
- [49] a) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628; b) F.-G. Sun, X.-L. Huang, S. Ye, *J. Org.Chem.* **2009**, *75*, 273; c) E. Sanchez-Larios, M. Gravel, *J. Org.Chem.* **2009**, *74*, 7536.

- [50] Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron* **2006**, 62, 365.
- [51] A. Hamza, G. Schubert, T. Soos, I. Pápai, *J. Am. Chem. Soc.* **2006**, 128, 13151.
- [52] Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, 14, 9873.
- [53] J. Xie, K. Yoshida, K. Takasu, Y. Takemoto, *Tetrahedron Lett.* **2008**, 49, 6910.
- [54] J. Wang, H. Xie, H. Li, L. Zu, W. Wang, *Angew. Chem. Int. Ed.* **2008**, 47, 4177.
- [55] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, 43, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, 126, 5356; c) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, 45, 3683.
- [56] M. Rueping, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2008**, 47, 5836.
- [57] J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, 129, 7498.
- [58] M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, 128, 8418.
- [59] V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, 128, 8736.
- [60] P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, 129, 3520.
- [61] J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2009**, 11, 677.
- [62] T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, 41, 6951.
- [63] B.-C. Hong, M.-F. Wu, H.-C. Tseng, J.-H. Liao, *Org. Lett.* **2006**, 8, 2217.
- [64] N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, 43, 9591.
- [65] N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2003**, 5, 1685.
- [66] M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem. Int. Ed.* **2008**, 47, 10187.
- [67] Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, 126, 5962.

- [68] C.-L. Cao, X.-L. Sun, Y.-B. Kang, Y. Tang, *Org. Lett.* **2007**, 9, 4151.
- [69] D.-Q. Xu, Y.-F. Wang, S.-P. Luo, S. Zhang, A.-G. Zhong, H. Chen, Z.-Y. Xu, *Adv. Synth. Catal.* **2008**, 350, 2610.
- [70] J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci.* **2004**, 101, 5482.
- [71] a) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, 127, 15036; b) Y. Huang, W. Abbas, C. Larsen, D. MacMillan, *J. Am. Chem. Soc.* **2005**, 127, 15051.
- [72] Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, 127, 15051.
- [73] M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, 127, 6964.
- [74] J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem. Int. Ed.* **2007**, 46, 778.
- [75] S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, 128, 14986.
- [76] D. Enders, M. R. M. Huttl, C. Grondal, G. Raabe, *Nature* **2006**, 441, 861.
- [77] A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, 46, 1101.
- [78] a) K. L. Jensen, P. T. Franke, C. Arróniz, S. Koppelgaard, K. A. Jørgensen, *Chem. Eur. J.*, 16, 1750; b) G.-L. Zhao, F. Ullah, L. Deiana, S. Lin, Q. Zhang, J. Sun, I. Ibrahem, P. Dziedzic, A. Córdova, *Chem. Eur. J.* 16, 1585.

Chapter 2

One-pot Asymmetric Synthesis of Bicyclic Isoxazolidines Involves α -Amination/Condensation/Nitrone [3+2] Cycloaddition

2.1 Abstract

A novel and facile organocatalyzed one-pot asymmetric synthesis of bicyclic isoxazolidines was reported. This methodology used aldehyde and azodicarbonate as substrates and *L*-proline as catalyst via a cascade process involving an α -Amination/condensation/nitrone [3+2] cycloaddition to afford products with good yields and good to excellent enantioselectivity (up to 99%).

2.2 Introduction

The intramolecular cycloaddition between a nitron and alkene is an important methodology for the formation of many important structures present in natural products.^[1] This approach has an advantage of transforming simple primary cycloadducts to different heterocycles.^[2] For example, isoxazolidines can be easily converted to 1,3- amino alcohols under mild reaction conditions.^[3]

If the intramolecular cycloaddition of a nitron bearing an olefin moiety occurs, the regio- and diastereoselectivity will be significantly improved. According to Romeo's report^[4], the introduction of a stereogenic center at the α -position of a nitron can bring about asymmetric induction, which will lead to the generation of stereogenic centers.

In previous years, several organocatalytic asymmetric nitron [3+2] cycloadditions were reported.^[5] However, enantioselective intramolecular versions remained rare. Herein, we will disclose an organocatalytic asymmetric one-pot cascade reaction involving an amination/condensation/intramolecular nitron [3+2] cycloaddition sequence.

In 2003, our group described the α -aminooxylation of aldehydes with very good enantioselectivity.^[6] This was followed by a highly stereoselective synthesis of tetrahydro-1,2-oxazines by a tandem α -aminooxylation and aza-Michael addition.^[7] When substrates were screened, it was noticed that a change of the electron-withdrawing group on the aldehyde from a nitro or a malonate group, to an ester group, led to an unexpected bicyclic isoxazolidine byproduct (11%) with high regioselectivity, *endo/exo* selectivity and diastereoselectivity. This side product was thought to have been formed through an intramolecular nitron [3+2] cycloaddition (Scheme 2.1).

Scheme 2.1 Unexpected bicyclic isoxazolidine product from an intramolecular nitron
[3+2] cycloaddition.

In 2002, List and co-workers reported a *L*-proline catalyzed α -amination of aldehydes to obtain highly enantioselective α -amino aldehydes.^[8] This, combined with the earlier observation, prompted us to investigate whether introduction of a stereocenter at the α -position of the aldehyde, *in situ* condensation and intramolecular cycloaddition, could furnish enantiopure bicyclic isoxazolidines (Scheme 2.2).

Scheme 2.2 Retrosynthetic analysis for enantioselective synthesis of bicyclic
isoxazolidine derivatives.

2.3 Results and Discussion

We started to investigate the reaction with (*E*)-ethyl 7-oxohept-2-enoate and diethyl azodicarboxylate as the substrates. Monitoring of the reaction by TLC indicated that the first step was completed within 12 hours at room temperature. After addition of *N*-hydroxybenzenamine, a fast, clean and complete reaction occurred to furnish the desired product **3a** with 94% yield and 90% *ee*. To our delight, only one diastereoisomer was observed, which encouraged us to investigate this reaction further.

Lowering the temperature to 4 °C and -20 °C improved the enantioselectivity from 90% to 94% (Table 2.1, entries 1-3). When the reaction temperature was further lowered to -40 °C, the reaction did not proceed (Table 2.1, entry 4). Solvent screening revealed that DCM was the best (Table 2.1, entries 5-9). The catalyst loading was chosen to be 20 mol% because neither a decrease nor increase of the catalyst demonstrated a positive effect on the reaction result (Table 2.1, entries 10-11). The use of diphenylprolinol silyl ether as the catalyst gave unsatisfactory results (Table 2.1, entry 12).

Table 2.1 Optimization of reaction condition of asymmetric synthesis of bicyclic isoxazolidines catalyzed by *L*-proline.^a

Entry	T/ °C	Solvent	Yield/% ^b	<i>ee</i> / % ^c
1	23	DCM	94	90
2	4	DCM	90	92
3	-20	DCM	93	94
4	-40	DCM	<5	/

5	-20	CHCl ₃	52	90
6	-20	MeCN	38	88
7	-20	THF	43	55
8	-20	Et ₂ O	33	53
9	-20	toluene	43	89
10 ^d	-20	DCM	62	93
11 ^e	-20	DCM	67	88
12 ^f	-20	DCM	92	-18

^aReactions were performed with **1a** (0.15 mmol), **2a** (0.1 mmol), and catalyst *L*-proline (20 mol%) in solvents (0.3 mL). After **2a** was consumed, *N*-hydroxybenzenamine (0.15 mmol) was added. ^bYield of isolated product by flash chromatography. ^cDetermined by HPLC methods using a Chiralcel OD-H column. ^dUsed 10 mol% of catalyst. ^eUsed 40 mol% of catalyst. ^fUsed 10 mol% of diphenylprolinol silyl ether and 20 mol% of HOAc.

With the optimized reaction conditions in hand, the scope of the organocatalytic asymmetric cascade reaction was explored. A wide range of aldehydes with different ester groups and azodicarboxylates were tested, and the results are summarized in Table 2.2.

Table 2.2 Substrate scope of the Asymmetric Cascade Reaction.^a

Entry	(O)R ¹	R ²	Product	Yield/% ^b	ee/% ^c

1	OEt	Et	3a	93	94
2	OEt	<i>i</i> -Pr	3b	83	97
3	OEt	Bn	3c	88	63
4	OEt	<i>t</i> -Bu	3d	65	95
5	OMe	Et	3e	95	89
6	OMe	<i>i</i> -Pr	3f	73	94
7	O <i>i</i> -Pr	Et	3g	91	94
8	O <i>i</i> -Pr	<i>i</i> -Pr	3h	94	95
9	O <i>i</i> -Pr	Bn	3i	85	90
10	O <i>t</i> -Bu	Et	3j	95	90
11	O <i>t</i> -Bu	<i>i</i> -Pr	3k	87	97
12	OBn	Et	3l	93	96
13	OBn	<i>i</i> -Pr	3m	80	94
14	OBn	Bn	3n	79	90
15	Me	Et	3o	64	83
16	Me	<i>i</i> -Pr	3p	71	94

^aReactions were performed with **1** (0.15 mmol), **2** (0.1 mmol), and catalyst *L*-proline (20 mol%) in DCM (0.3 mL) at -20 °C. After **2** was completely consumed monitored by TLC, *N*-hydroxybenzenamine (0.15 mmol) was added. ^bYield of isolated product by flash chromatography. ^cDetermined by HPLC methods using Chiralcel OD-H, Chirapak AD-H, Chirapak AS-H columns.

It was found that a series of bicyclic isoxazolidines **3a-p** were obtained in good to

excellent yields (64-95%) with good to excellent enantioselectivities (up to 97%). The utilization of different dibenzyl azodicarboxylates gave rise to a lower enantioselectivity than DEAD and DIAD, which was consistent with List's results (Table 2.2, entries 1-3, 7-9, and 12-14). The more hindered azodicarboxylates generally gave better enantioselectivity, with the exception of (*E*)-benzyl 7-oxohept-2-enoate (Table 2.2, entries 12-13). When the electron-withdrawing group was changed from an ester to a ketone, a slight decrease in yield was observed after a prolonged reaction time (Table 2.2, entries 15-16). This may be attributed to a less reactive nitron substrate that results from a weaker electron-withdrawing group.

To study the effect of the ring size on the enantioselectivity, 6-alkenylaldehydes were applied in this organocatalytic asymmetric cascade reaction to afford bicyclic [4,3,0]-isoxazolidines **3q** and **3r** respectively, with DIAD and dibenzyl azodicarboxylate. The results were similar to the previous [3,3,0]-isoxazolidines **3a-p** (Scheme 2.3). Notably, only the *exo* product was observed, possibly due to the presence of the ester group next to the olefin moiety.

Scheme 2.3 Study of ring size and its effect on asymmetric synthesis of bicyclic isoxazolidines.

Furthermore, different substituted group on the phenyl ring of

N-hydroxybenzylamine can still achieve good results, which showed wide tolerance of this reaction (Figure 2.1).

Figure 2.1 Study of different *N*-hydroxyphenylamines for the asymmetric cascade reaction of bicyclic isoxazolidines.

However, we can deduce the configuration from the structure of the α -amination product. Consequently, the stereogenic centers created by spontaneous formation of C-C and C-O bonds in the intramolecular nitron [3+2] cycloaddition were assigned to be *R*, *R*, and *S* (Figure 2.1).

Hence we proposed the reaction mechanism as following: first, starting aldehyde bears an enamine activation mode to generate an enantioselective α -amino aldehyde; hence *N*-hydroxybenzylamine reacted with this enantiopure aldehyde to obtain nitrones, followed by intramolecular [3+2] cycloaddition. The highly diastereoselectivity resulted from rigid structure of bicyclic isoxazolidine and the highly enantioselectivity resulted from the stereocenter at α -position of aldehyde (Scheme 2.4).

Scheme 2.4 Proposed mechanism for the cascade reaction

2.4 Conclusion

A novel and facile organocatalyzed one-pot asymmetric synthesis of bicyclic isoxazolidines was reported. This methodology generated four chiral centers via a cascade process involving an α -Amination/condensation/nitron [3+2] cycloaddition to afford products with good yields (state range) and good to excellent enantioselectivity (up to 99%).

2.5 Experimental section

General experimental conditions

Thin layer chromatography (TLC)

Merck 60 F254 precoated silica gel plate (0.2 mm thickness).

The spots were visualized in UV-light ($\lambda = 254$ nm)

Stained with iodine, basic solution of potassium permanganate or potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Analytical high performance liquid chromatography (HPLC)

Shimadzu LC-20AD

Materials: *Daicel* Chiralpak AD-H (0.46 cm × 25 cm), Chiralpak AS-H (0.46 cm × 25 cm), Chiralcel OD-H (0.46 cm × 25 cm) columns.

Nuclear magnetic resonance spectroscopy (NMR)

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on Bruker AMX 400, 500 NMR spectrometers. Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (doublets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet)

High resolution mass spectrometry (HRMS)

Finnigan MAT 95XP spectrometer (GC) and

Waters Micromass Q-Tof Premier Mass spectrometer (LC).

X-ray structure analysis (X-RAY)

Bruker X8 APEX X-ray diffractometer.

Specific rotation ($[\alpha]$)

Schmidt + Haensdch polarimeter (Polartronic MH8)

1 cm cell (c given in g/100mL).

2.5.1 Procedure for the preparation of substrate.

A 250 mL of flask was fitted with a glass tube to admit ozone. Cyclopentene (3.4 g, 50 mmol) was charged with mixture of 180 mL DCM and 36 mL methonal. The flask was cooled to $-78^\circ C$ with dry ice-acetone bath. Ozone was bubbled until the color turns blue. After that, nitrogen was passed by until the color faded. Then the solution of phosphane (15 mmol) in 15 mL of DCM was added by syringe pump within 1 hour. Then the mixture was stirred at r.t. overnight.

The solvent was removed *in vacuo* and 70 mL of DCM and 50 mL of water were added in. The aqueous layer was extracted with two 75-mL portion of DCM. Combined organic layers were washed with 50 mL of brine and dried by anhydrous Na_2SO_4 . Removal of solvents and following flash chromatography gave the desired aldehyde as yellow oil.

The compound was prepared from *i*-propyl ester ylide to afford as yellow oil (0.385 g), yield 28%.

¹H-NMR (CDCl₃, 500 MHz): δ 1.28-1.29 (d, *J* = 6 Hz, 6H), 1.81-1.84 (t, *J* = 7.5 Hz, 2H), 2.25-2.27 (d, *J* = 6.5 Hz, 2H), 2.49-2.51 (d, *J* = 6.5 Hz, 2H), 5.05-5.08 (m, 1H), 5.82-5.85 (d, *J* = 16 Hz, 1H), 6.90-6.93 (m, 1H), 9.79 (s, 1H).

¹³C-NMR (CDCl₃, 125 MHz): δ 20.4, 21.9, 31.2, 43.0, 67.6, 122.8, 147.2, 166.0, 201.7.

The compound was prepared from benzyl ester ylide to afford as yellow oil (0.532 g), yield 31%.

¹H-NMR (CDCl₃, 500 MHz): δ 1.77-1.80 (t, *J* = 7.5 Hz, 2H), 2.23-2.25 (d, *J* = 7 Hz, 2H), 2.45-2.48 (m, 2H), 3.30 (s, 1H), 5.16 (s, 2H), 5.87-5.90 (dd, *J* = 15.5 Hz, 1H), 6.93-6.99 (m, 1H), 7.31-7.36 (m, 5H), 9.75 (s, 1H).

¹³C-NMR (CDCl₃, 125 MHz): δ 20.3, 31.3, 43.0, 52.9, 66.1, 121.9, 128.2, 128.6, 136.0, 148.3, 166.2, 201.6.

The compound was prepared from methyl ylide to afford as yellow oil (0.408 g), yield 58%.

¹H-NMR (CDCl₃, 300 MHz): δ 1.77-1.86 (m, 2H), 2.03 (s, 3H), 2.16-2.30 (m, 2H), 2.47-2.55 (m, 2H), 6.06-6.11 (d, *J* = 15.9 Hz, 1H), 6.70-6.80 (m, 1H), 9.77 (s, 1H).

2.5.2 Procedure for synthesis of bicyclic isoxazolidines.

L-proline (2.3 mg, 0.02 mmol) was added to a solution of (*E*)-ethyl 7-oxohept-2-enoate (**1a**, 25.5 mg, 0.15 mmol) and diethyl azodicarboxylate (**2a**, 17.4 mg, 0.1 mmol) in 0.3 mL of DCM at -20 °C, and the reaction was monitored by TLC. After the limited reactant was fully consumed, *N*-hydroxybenzenamine (17 mg, 0.15 mmol) was added. The reaction mixture was stirred for another 2 hours and then charged to silica gel column directly and purified by flash column chromatography.

2.5.3 Characterization data.

Prepared according to the general procedure from (*E*)-ethyl 7-oxohept-2-enoate (0.15 mmol) and diethyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (42 mg, 93% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.14-1.27 (m, 9H), 1.74-1.75 (d, *J* = 6.5 Hz, 1H), 1.91

(br, 1H), 2.12-2.19 (m, 2H), 3.48-3.49 (d, $J = 5.5$ Hz, 1H), 4.02-4.07 (m, 2H), 4.08-4.13 (m, 2H), 4.17-4.20 (t, $J = 7$ Hz, 2H), 4.31-4.31 (d, $J = 3$ Hz, 1H), 4.40 (s, 1H), 4.57 (s, 1H), 6.59 (br, 1H), 6.91-6.93 (m, 1H), 7.11 (s, 2H), 7.21-7.24 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3): δ 13.9, 14.2, 14.4, 21.0, 29.6, 50.6, 60.4, 61.4, 62.4, 62.8, 72.4, 82.5, 115.3, 121.8, 128.6, 149.5, 170.4, 171.2, 173.7.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, $\lambda = 254$ nm),

t_R (major) = 10.5 min, t_R (minor) = 18.6 min; 94% ee.

$[\alpha]_D^{23}$: 68.8 ($c = 1.2$, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{21}\text{H}_{30}\text{O}_7\text{N}_3$, m/z 436.2084, found 426.2081.

Prepared according to the general procedure from (*E*)-ethyl 7-oxohept-2-enoate (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (37 mg, 83% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (500 MHz, CDCl_3): δ 1.13-1.28 (m, 15H), 1.65 (s, 1H), 1.76 (s, 1H), 1.93 (s, 1H), 2.17 (br, 2H), 3.48-3.49 (m, 1H), 4.03-4.08 (m, 2H), 4.33-4.33 (d, $J = 3.5$ Hz, 1H), 4.35 (br, 1H), 4.60 (s, 1H), 4.91 (s, 1H), 4.95-5.00 (m, 1H), 6.29 (br, 1H), 6.91-6.94 (m, 1H), 7.12 (s, 2H), 7.22-7.25 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3): δ 13.9, 22.0, 22.0, 29.6, 50.7, 61.4, 64.2, 70.2, 70.6, 72.6, 82.5, 115.2, 121.8, 128.6, 144.7, 149.6, 155.1, 156.9, 170.4.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (major) = 6.8 min, t_R (minor) = 9.0 min; 97% ee.

$[\alpha]_D^{23}$: 73.7 (c = 1.1, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{23}\text{H}_{34}\text{O}_7\text{N}_3$, m/z 464.2397, found 464.2394.

Prepared according to the general procedure from (*E*)-ethyl 7-oxohept-2-enoate (0.15 mmol) and dibenzyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (49 mg, 88% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (500 MHz, CDCl_3): δ 1.16-1.19 (t, J = 6.5 Hz, 3H), 1.75 (s, 2H), 1.95 (br, 1H), 2.16 (s, 2H), 3.49 (s, 1H), 4.05-4.09 (m, 2H), 4.33 (br, 1H), 4.46 (br, 1H), 4.45-5.18 (br, 5H), 6.75 (br, 1H), 6.91-6.94 (m, 1H), 7.12-7.50 (m, 12H).

^{13}C NMR (125 MHz, CDCl_3): δ 13.9, 21.1, 29.5, 29.7, 50.4, 60.4, 61.4, 68.4, 72.3, 82.6, 115.3, 121.9, 128.0, 128.3, 128.5, 128.6, 135.4, 135.7, 149.4, 170.4, 171.2.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (major) = 28.3 min, t_R (minor) = 39.1 min; 63% ee.

$[\alpha]_D^{23}$: 40.9 (c = 0.9, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{31}\text{H}_{34}\text{O}_7\text{N}_3$, m/z 560.2397, found 560.2399.

Prepared according to the general procedure from (*E*)-ethyl 7-oxohept-2-enoate (0.15 mmol) and di-*tert*-butyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (32 mg, 65% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.14-1.16 (t, *J* = 6.5 Hz, 3H), 1.42 (s, 9H), 1.47 (s, 9H), 1.72 (s, 1H), 1.91 (s, 1H), 2.16(br, 2H), 3.47 (s, 1H), 4.03-4.08 (m, 2H), 4.32-4.32 (d, *J* = 2.5 Hz, 2H), 4.57 (s, 1H), 6.21 (br, 1H), 6.90-6.93 (m, 1H), 7.11 (s, 2H), 7.21-7.26 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 13.9, 14.1, 14.3, 24.0, 24.5, 25.1, 28.0, 28.2, 28.7, 29.7, 50.7, 60.3, 61.3, 72.7, 81.5, 82.5, 83.2, 115.2, 121.7, 122.3, 128.5, 147.2, 149.7, 154.2, 156.0, 166.5, 170.5, 199.7.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm),

*t*R (major) = 8.1 min, *t*R (minor) = 15.5 min; 95% ee.

[α]_D²³: 82.1 (c = 1.3, CHCl₃).

HRMS (ESI⁺) calcd for C₂₅H₃₈O₇N₃, *m/z* 492.2847, found 492.2841.

Prepared according to the general procedure from (*E*)-methyl 7-oxohept-2-enoate (0.15 mmol) and diethyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (40 mg, 95% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.18 (s, 3H), 1.26-1.27 (t, *J* = 5 Hz, 3H), 1.73-1.77 (m, 2H), 1.91 (s, 1H), 2.10-2.20 (m, 2H), 3.47-3.50 (m, 1H), 3.62 (s, 3H), 4.09-4.13 (m, 2H), 4.17-4.20 (t, *J* = 6.5 Hz, 2H), 4.28-4.32 (m, 1H), 4.42 (s, 1H), 4.55 (s, 1H), 6.56 (br, 1H), 6.91-6.94 (m, 1H), 7.11 (s, 2H), 7.22-7.25 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 14.4, 29.5, 50.5, 52.3, 62.4, 62.8, 72.2, 82.2, 115.5, 122.0, 128.6, 149.1, 155.5, 157.3, 170.9.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

*t*_R (major) = 12.4 min, *t*_R (minor) = 25.2 min; 89% ee.

[α]_D²³: 69.4 (c = 1.0, CHCl₃).

HRMS (ESI⁺) calcd for C₂₀H₂₈O₇N₃, *m/z* 422.1927, found 422.1906.

Prepared according to the general procedure from (*E*)-methyl 7-oxohept-2-enoate (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (33 mg, 73% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.22-1.26 (m, 12H), 1.73 (s, 1H), 1.92 (s, 1H), 2.08-2.18 (m, 2H), 3.48-3.49 (m, 1H), 3.61 (s, 3H), 4.32-4.33 (d, *J* = 3.5 Hz, 1H), 4.39 (s, 1H),

4.56-4.58 (m, 1H), 4.87 (s, 1H), 4.93-4.98 (m, 1H), 6.44 (br, 1H), 6.90-6.93 (m, 1H), 7.11 (s, 1H), 7.21-7.24 (m, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 14.2, 21.9, 29.7, 50.7, 51.5, 52.3, 60.4, 70.1, 72.5, 82.2, 115.4, 122.0, 128.6, 149.3, 155.1, 156.9, 170.9.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ= 254 nm),

*t*R (major) = 7.5 min, *t*R (minor) = 11.7 min; 94% ee.

[α]_D²³: 77.1 (c = 1.3, CHCl₃).

HRMS (ESI⁺) calcd for C₂₂H₃₂O₇N₃, *m/z* 450.2240, found 450.2249.

Prepared according to the general procedure from (*E*)-isopropyl 7-oxohept-2-enoate (0.15 mmol) and diethyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (41 mg, 91% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.10-1.14 (m, 6H), 1.20-1.28 (m, 6H), 1.75 (s, 1H), 1.92 (s, 1H), 2.09-2.21 (m, 2H), 3.45 (s, 1H) 4.09-4.13 (m, 4H), 4.20-4.21 (m, 1H), 4.38 (s, 1H), 4.60 (s, 1H), 4.87-4.91 (m, 1H), 6.47 (br, 1H), 6.90-6.93 (m, 1H), 7.10 (s, 2H), 7.21-7.27 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 14.4, 21.5, 21.5, 29.6, 50.9, 60.4, 62.4, 62.8, 69.1, 72.5, 82.7, 115.1, 121.7, 128.6, 149.8, 155.7, 157.3, 169.9.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ= 254 nm),

t_R (major) = 25.6 min, t_R (minor) = 34.4 min; 94% ee.

$[\alpha]_D^{23}$: 36.9 ($c = 1.2$, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{22}\text{H}_{32}\text{O}_7\text{N}_3$, m/z 450.2240, found 450.2256.

Prepared according to the general procedure from (*E*)-isopropyl 7-oxohept-2-enoate (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (46 mg, 94% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (500 MHz, CDCl_3): δ 1.09-1.13 (m, 6H), 1.22-1.27 (m, 12H), 1.73 (s, 1H), 1.76 (s, 1H), 1.92 (s, 1H), 2.10-2.27 (m, 2H), 3.44 (s, 1H), 4.30 (m, 2H), 4.63 (s, 1H), 4.90-4.97 (m, 2H), 6.36 (br, 1H), 6.91 (s, 1H), 7.11 (s, 1H), 7.22-7.27 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3): δ 21.5, 21.5, 22.0, 22.0, 29.7, 51.1, 64.2, 69.1, 70.1, 70.5, 72.8, 82.7, 115.0, 121.6, 128.6, 149.9, 155.1, 156.9, 169.9.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, $\lambda = 254$ nm),

t_R (major) = 11.8 min, t_R (minor) = 14.7 min; 95% ee.

$[\alpha]_D^{23}$: 55.6 ($c = 1.0$, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{24}\text{H}_{36}\text{O}_7\text{N}_3$, m/z 478.2553, found 478.2556.

Prepared according to the general procedure from (*E*)-isopropyl 7-oxohept-2-enoate (0.15 mmol) and dibenzyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (49 mg, 85% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.14-1.16 (m, 3H), 1.27-1.31 (m, 3H), 1.71-1.76 (m, 1H), 1.96 (s, 1H), 2.10-2.19 (m, 2H), 3.45 (s, 1H), 4.31 (s, 1H), 4.43 (s, 1H), 4.67 (s, 1H), 4.89-4.94 (m, 1H), 5.13-5.19 (m, 4H), 6.70 (br, 1H), 6.91-6.93 (m, 1H), 7.11 (s, 2H), 7.20 (s, 2H), 7.29-7.36 (m, 10H).

¹³C NMR (125 MHz, CDCl₃): δ 14.2, 21.1, 21.5, 21.5, 21.8, 21.9, 29.5, 29.7, 50.7, 60.4, 64.5, 68.1, 68.4, 69.1, 72.4, 82.8, 114.3, 115.1, 121.7, 128.0, 128.3, 128.5, 128.6, 129.1, 135.4, 135.6, 149.6, 157.0, 169.9, 171.2.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

*t*_R (major) = 20.6 min, *t*_R (minor) = 30.0 min; 90% ee.

[α]_D²³: 43.8 (c = 1.1, CHCl₃).

HRMS (ESI⁺) calcd for C₃₂H₃₆O₇N₃, *m/z* 574.2553, found 574.2548.

Prepared according to the general procedure from (*E*)-*tert*-butyl 7-oxohept-2-enoate (0.15 mmol) and diethyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (42 mg, 95% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.21-1.34 (m, 15H), 1.74-1.79 (m, 1H), 1.94 (s, 1H), 2.17-2.21 (m, 2H), 3.41-3.44 (m, 1H), 4.12-4.17 (m, 2H), 4.22-4.26 (m, 2H), 4.26 (s, 1H), 4.38 (s, 1H), 4.65 (s, 1H), 6.54 (br, 1H), 6.92-6.95 (m, 1H), 7.14 (s, 2H), 7.24-7.29 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 14.2, 14.4, 21.1, 27.7, 28.1, 29.7, 51.2, 60.4, 62.4, 62.8, 64.6, 72.6, 82.1, 83.1, 95.5, 115.1, 115.6, 116.3, 117.9, 121.5, 128.6, 149.9, 155.6, 157.5, 167.5, 169.6.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm),

*t*R (minor) = 53.4 min, *t*R (major) = 57.5 min; 90% ee.

[α]_D²³: 49.2 (c = 1.0, CHCl₃).

HRMS (ESI⁺) calcd for C₂₃H₃₄O₇N₃, *m/z* 464.2397, found 464.2393.

Prepared according to the general procedure from (*E*)-*tert*-butyl 7-oxohept-2-enoate (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (39 mg, 87% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.24-1.33 (m, 21H), 1.79 (s, 1H), 1.92 (s, 1H), 2.18 (m,

2H), 3.42 (s, 1H), 4.26 (s, 1H), 4.35 (s, 1H), 4.67 (s, 1H), 4.96-4.99 (m, 2H), 6.44 (br, 1H), 6.93 (m, 1H), 7.14 (s, 2H), 7.23-7.28 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 22.0, 22.0, 27.7, 28.1, 29.7, 30.9, 34.7, 51.5, 64.5, 70.1, 70.5, 72.9, 82.0, 83.2, 115.0, 121.5, 122.3, 128.6, 150.1, 157.1, 169.6.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm),

*t*R (major) = 10.1 min, *t*R (minor) = 14.3 min; 97% ee.

[α]_D²³: 59.4 (c = 1.0, CHCl₃).

HRMS (ESI⁺) calcd for C₂₅H₃₈O₇N₃, *m/z* 492.2710, found 492.2704.

Prepared according to the general procedure from (*E*)-benzyl 7-oxohept-2-enoate (0.15 mmol) and diethyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (46 mg, 93% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.18-1.28 (m, 6H), 1.71 (s, 1H), 1.91 (s, 1H), 2.11-2.19 (m, 2H), 3.52 (s, 1H), 4.10-4.14 (m, 2H), 4.19-4.20 (m, 2H), 4.37 (s, 1H), 4.43 (s, 1H), 4.57 (s, 1H), 5.01-5.07 (m, 2H), 6.48 (br, 1H), 6.91-6.94 (m, 1H), 7.12 (s, 2H), 7.21-7.25 (m, 5H), 7.31-7.32 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 14.4, 21.1, 29.5, 29.7, 60.4, 62.4, 62.8, 67.0, 72.2, 82.4, 115.3, 121.9, 128.2, 128.4, 128.6, 128.6, 135.3, 137.2, 143.0, 149.2, 155.5, 156.6, 157.3, 170.3.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm),

t_R (major) = 47.7 min, t_R (minor) = 63.5 min; 96% ee.

$[\alpha]_D^{23}$: 36.4 (c = 1.1, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{26}\text{H}_{32}\text{O}_7\text{N}_3$, m/z 498.2240, found 498.2246.

Prepared according to the general procedure from (*E*)-benzyl 7-oxohept-2-enoate (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (42 mg, 80% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl_3): δ 1.18-1.28 (m, 12H), 1.69-1.74 (m, 2H), 1.92 (s, 1H), 2.10-2.18 (m, 2H), 3.49-3.51 (m, 1H), 4.38-4.39 (d, J = 3.5 Hz, 1H), 4.59 (s, 1H), 4.89 (s, 1H), 4.94-4.99 (m, 1H), 5.01-5.07 (m, 2H), 6.31 (br, 1H), 6.91-6.94 (m, 1H), 7.12 (s, 2H), 7.21-7.25 (m, 5H), 7.31-7.34 (m, 2H).

¹³C NMR (125 MHz, CDCl_3): δ 22.0, 22.0, 29.7, 37.0, 50.7, 67.0, 70.2, 70.6, 72.5, 82.4, 115.3, 121.9, 128.2, 128.4, 128.6, 128.7, 135.3, 149.4, 155.1, 156.9, 170.3.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm),

t_R (major) = 24.0 min, t_R (minor) = 32.9 min; 94% ee.

$[\alpha]_D^{23}$: 35.6 (c = 1.0, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{28}\text{H}_{36}\text{O}_7\text{N}_3$, m/z 526.2553, found 526.2561.

Prepared according to the general procedure from (*E*)-benzyl 7-oxohept-2-enoate (0.15 mmol) and dibenzyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (49 mg, 79% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.69-1.78 (m, 1H), 1.92 (s, 1H), 2.12-2.15 (m, 2H), 3.38 (s, 1H), 4.21 (s, 1H), 4.37 (s, 1H), 4.65 (s, 1H), 5.11-5.17 (m, 4H), 6.46 (br, 1H), 6.87-6.90 (m, 1H), 6.98-7.00 (m, 1H), 7.09 (s, 2H), 7.18 (s, 2H), 7.28-7.34 (m, 16H). **¹³C NMR (125 MHz, CDCl₃):** δ 14.2, 27.8, 29.4, 29.7, 50.3, 67.0, 68.1, 68.3, 69.9, 72.0, 82.5, 115.3, 122.0, 128.0, 128.3, 128.4, 128.5, 128.6, 128.6, 128.7, 135.3, 135.4, 135.7, 149.1, 157.3, 170.3.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ= 254 nm),

*t*R (major) = 45.1 min, *t*R (minor) = 63.1 min; 90% ee.

[α]_D²³: 23.7 (c = 0.9, CHCl₃).

HRMS (ESI⁺) calcd for C₃₆H₃₆O₇N₃, *m/z* 622.2553, found 622.2593.

Prepared according to the general procedure from (*E*)-7-oxooct-5-enal (0.15 mmol) and

diethyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (26 mg, 64% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.23-1.37 (m, 6H), 1.88 (s, 1H), 2.05 (s, 1H), 2.17-2.19 (m, 1H), 2.64-2.31 (m, 5H), 3.52 (s, 1H), 3.89 (br, 1H), 4.02 (s, 1H), 4.09 (s, 1H), 4.21-4.22 (m, 3H), 4.46 (s, 2H), 6.10-6.13 (br, 1H), 6.99 (m, 1H), 7.15 (s, 2H), 7.29-7.32 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 14.2, 14.3, 14.4, 24.6, 26.0, 26.4, 27.0, 29.4, 29.7, 30.2, 31.8, 60.4, 62.4, 70.1, 87.9, 116.2, 122.2, 128.8, 131.8, 147.0, 147.5, 198.5, 210.8.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm),

*t*R (major) = 19.0 min, *t*R (minor) = 46.2 min; 83% ee.

[α]_D²³: 45.2 (c = 0.8, CHCl₃).

HRMS (ESI⁺) calcd for C₂₀H₂₈O₆N₃, *m/z* 406.1978, found 406.1996.

Prepared according to the general procedure from (*E*)-7-oxooct-5-enal (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (31 mg, 71% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.23-1.29 (m, 12H), 1.71 (s, 1H), 1.88 (s, 1H), 2.07 (s, 1H), 2.16-2.20 (m, 1H), 2.27 (s, 3H), 3.50-3.52 (m, 1H), 4.09 (m, 1H), 4.48 (m, 2H), 4.80 (s, 1H), 4.96-4.98 (m, 1H), 6.12 (br, 1H), 6.98-7.00 (m, 1H), 7.15 (s, 2H), 7.29-7.32 (m,

2H).

^{13}C NMR (125 MHz, CDCl_3): δ 14.2, 21.1, 22.0, 22.0, 26.0, 29.7, 60.4, 70.4, 88.0, 116.2, 117.9, 122.3, 128.8, 147.6, 154.1, 171.2, 209.7.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 98/2, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 18.7 min, t_R (major) = 28.9 min; 94% ee.

$[\alpha]_D^{23}$: 49.3 (c = 0.9, CHCl_3).

HRMS (ESI^+) calcd for $\text{C}_{22}\text{H}_{32}\text{O}_6\text{N}_3$, m/z 434.5061, found 434.5053.

Prepared according to the general procedure from (*E*)-methyl 8-oxooct-2-enoate (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (36 mg, 78% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (500 MHz, CDCl_3): δ 1.24-1.28 (m, 13H), 1.57-1.63 (m, 2H), 1.75 (s, 2H), 1.93-1.96 (m, 1H), 2.11-2.29 (m, 1H), 2.87 (s, 1H), 3.76 (s, 3H), 4.02 (br, 1H), 4.44-4.47 (d, J = 10.5 Hz, 1H), 4.94-4.97 (m, 2H), 6.47 (br, 1H), 6.92-6.95 (m, 1H), 7.15 (s, 2H), 7.22-7.26 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3): δ 14.2, 20.1, 22.0, 23.2, 28.4, 29.7, 44.4, 52.3, 70.0, 78.3, 115.4, 122.3, 128.7, 151.0, 171.5.

HPLC: Chiralcel OD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm),

t_R (major) = 8.7 min, t_R (minor) = 13.4 min; 99% ee.

$[\alpha]_D^{23}$: 38.3 ($c = 1.0$, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{23}\text{H}_{34}\text{O}_7\text{N}_3$, m/z 464.2397, found 464.2381.

Prepared according to the general procedure from (*E*)-methyl 8-oxooct-2-enoate (0.15 mmol) and dibenzyl azodicarboxylate (0.1 mmol) to provide the title compound as colorless oil (28 mg, 50% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.57-1.60 (m, 2H), 1.74 (s, 1H), 1.93-1.96 (m, 1H), 2.19-2.29 (m, 1H), 2.88 (s, 1H), 3.76 (s, 3H), 4.02 (br, 1H), 4.44-4.46 (d, $J = 9.5$ Hz, 1H), 5.16-5.18 (m, 4H), 6.67 (br, 1H), 6.93 (m, 1H), 7.08 (s, 2H), 7.19 (s, 2H), 7.25-7.33 (m, 15H).

¹³C NMR (125 MHz, CDCl₃): δ 14.2, 20.1, 21.0, 23.1, 28.4, 29.7, 37.1, 44.2, 52.4, 67.9, 78.3, 115.4, 122.4, 127.9, 128.1, 128.3, 128.5, 128.6, 128.7, 135.5, 136.0, 150.7, 171.5.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, $\lambda = 254$ nm),

t_R (major) = 23.7 min, t_R (minor) = 34.9 min; 91% ee.

$[\alpha]_D^{23}$: 47.9 ($c = 1.1$, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{31}\text{H}_{34}\text{O}_7\text{N}_3$, m/z 560.2397, found 560.2324.

Prepared according to the general procedure from (*E*)-ethyl 7-oxohept-2-enoate (0.15 mmol) and diisopropyl azodicarboxylate (0.1 mmol) and *para*-chlorophenyl hydroxylamine to provide the title compound as colorless oil (45 mg, 90% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.14-1.27 (m, 15H), 1.71-1.74 (m, 1H), 1.90 (s, 1H), 2.11-2.21 (m, 2H), 3.47 (m, 1H), 4.03-4.08 (m, 2H), 4.33-4.33 (d, *J* = 3.5 Hz, 2H), 4.60 (s, 1H), 4.90-4.98 (m, 2H), 6.36 (br, 1H), 7.08 (s, 2H), 7.17-7.26 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 13.9, 22.0, 22.0, 29.7, 61.5, 70.3, 70.7, 72.7, 82.5, 116.4, 126.6, 128.5, 148.4, 155.0, 170.3.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm),

*t*R (minor) = 12.5 min, *t*R (major) = 25.2 min; 98% ee.

[α]_D²³: 30.1 (c = 1.1, CHCl₃).

HRMS (ESI⁺) calcd for C₂₃H₃₃O₇N₃Cl, *m/z* 498.2410, found 498.2407.

Prepared according to the general procedure from (*E*)-ethyl 7-oxohept-2-enoate (0.15

mmol) and diisopropyl azodicarboxylate (0.1 mmol) and *para*-methylphenyl hydroxylamine to provide the title compound as colorless oil (34 mg, 72% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (500 MHz, CDCl₃): δ 1.17-1.28 (m, 15H), 1.75 (s, 1H), 1.92 (s, 1H), 2.13-2.20 (m, 2H), 3.26 (s, 3H), 3.44-3.49 (m, 1H), 4.06-4.10 (m, 2H), 4.30-4.31 (d, *J* = 4 Hz, 2H), 4.57 (s, 1H), 4.89 (s, 1H), 4.94-4.98 (m, 1H), 6.24 (br, 1H), 7.04 (m, 4H).

¹³C NMR (125 MHz, CDCl₃): δ 13.7, 14.1, 20.6, 21.9, 22.0, 22.7, 26.9, 29.7, 31.6, 34.6, 50.9, 61.4, 70.1, 70.5, 72.9, 82.4, 115.8, 129.2, 131.5, 147.1, 155.1, 156.9, 170.5.

HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm),

*t*R (minor) = 27.9 min, *t*R (major) = 34.6 min; 96% ee.

[α]_D²³: 32.6 (c = 1.0, CHCl₃).

HRMS (ESI⁺) calcd for C₂₄H₃₆O₇N₃, *m/z* 478.2553, found 478.2558.

2.6 Reference

- [1] a) T. Kano, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 11926; b) K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863; c) A. Padwa, W. H. Pearson, *Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products*, Wiley, Hoboken, NJ, **2003**; d) O. Tamura, N. Mita, T. Okabe, T. Yamaguchi, C. Fukushima, M. Yamashita, Y. Morita, N. Morita, H. Ishibashi, M. Sakamoto, *J. Org. Chem.* **2001**, *66*, 2602.
- [2] a) J. Bergman, H. C. v. d. Plas, M. Simonyi, *Heterocycles in bio-organic chemistry*, Royal Society of Chemistry, Cambridge, **1991**; b) U. Chiacchio, A. Rescifina, G. Romeo, Italian Society of Chemistry, Rome, **1997**, p. v.

- [3] a) S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. De Sarlo, *Tetrahedron Lett.* **1990**, 31, 3351; b) N. A. LeBel, N. Balasubramanian, *J. Am. Chem. Soc.* **1989**, 111, 3363.
- [4] a) U. Chiacchio, F. Casuscelli, A. Corsaro, V. Librando, A. Rescifina, R. Romeo, G. Romeo, *Tetrahedron* **1995**, 51, 5689; b) R. Romeo, D. Iannazzo, A. Piperno, M. A. Chiacchio, A. Corsaro, A. Rescifina, *Eur. J. Org. Chem.* **2005**, 2368.
- [5] a) P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, 47, 2411; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, 122, 9874; c) W. Du, Y.-K. Liu, L. Yue, Y.-C. Chen, *Synlett* **2008**, 2997; d) S. S. Chow, M. Nevalainen, C. A. Evans, C. W. Johannes, *Tetrahedron Lett.* **2007**, 48, 277.
- [6] G. Zhong, *Angew. Chem. Int. Ed.* **2003**, 42, 4247.
- [7] a) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang, G. Zhong, *Org. Lett.* **2008**, 10, 4585; b) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem. Int. Ed.* **2008**, 47, 10187.
- [8] B. List, *J. Am. Chem. Soc.* **2002**, 124, 5656.

Chapter 3

Enantioselective Organocatalytic Cascade aza-Michael-Michael-acetalization Reactions: Asymmetric Synthesis of Tetrahydroquinoline Derivatives

3.1 Abstract

An organocatalytic asymmetric cascade aza-Michael-Michael-hemiacetalization reaction for the synthesis of tetrahydroquinoline derivatives with good control of four stereogenic centers was developed. This domino process forms highly diastereo- and enantioselective products with the use of the Jørgensen-Hayashi catalyst. An important intermediate **6** was isolated, which proved that this reaction occurs via an iminium ion activation mode.

3.2 Introduction

Organocatalytic cascade/domino reactions have attracted increasing attention as methods to construct many bonds and rings in one simple operation.^[1] This has led to the development of enantioselective asymmetric cascade Michael-Michael reactions.^[2]

The enantioselective aza-Michael addition is a powerful methodology for the formation of intriguing frameworks containing new C-N bonds.^[3] Despite the usefulness of these reactions, few reports exist because they make use of less nucleophilic nitrogen-containing substrates.^[4]

In many natural products such as alkaloids, tetrahydroquinolines act as a key structural element.^[5] Tetrahydroquinoline derivatives have important utilities in pharmaceutical and agrochemical synthesis.^[6]

Our group previously reported several cascade reactions involving new C-N bond formations with high stereoselectivity.^[7] Herein, we report a novel organocatalytic asymmetric aza-Michael-Michael-hemiacetalization cascade reaction.

3.3 Results and discussion

Initially, we used (*E*)-ethyl 4-(2-(4-methylphenylsulfonamido)phenyl)-2-oxobut-3-enoate (**3**) as the model substrate, 20 mol% Jørgensen-Hayashi's catalyst **III**^[8], 0.1 mmol of **3**, and 0.15 mmol of cinnamaldehyde **5a**. To our delight, even though most of the starting material was recovered, the desired product **4a** was isolated in 11% yield with a 60:40 diastereomeric ratio (d.r.) and good enantioselectivity (93 % *ee*; Table 3.1, entry 1).

The use of chiral secondary amine catalysts **VII** and **I** gave inferior results (Table 3.1,

entries 2-3). Furthermore, acid additives were screened to complete consumption of the starting material, and trifluoroacetic acid was the best additive (Table 3.1, entries 4-6). Attempts to improve the diastereoselectivity of the reaction were carried out by solvent screening (Table 3.1). It was revealed that halogenated solvents gave the worst results (entries 6-7), nonpolar and polar solvents led to no improvement (entries 8-10), while ethereal solvents enhanced both the yield and diastereoselectivity (entries 11-13). The best solvent proved to be 1,4-dioxane, which afforded the desired product in 74 % yield, high diastereo- and enantioselectivity of 91:9 d.r. and 99 % *ee*, respectively (Table 3.1, entry 13). When the reaction temperature was decreased from room temperature to 4 °C, the d.r. was slightly improved, albeit with a prolonged reaction time (Table 3.1, entry 14).

Table 3.1 Optimization of the reaction conditions.^a

Entry	Solvent	Additive ^b	T/°C	Yield/% ^c	<i>dr</i> ^d	<i>ee</i> / % ^e
1	CH ₂ Cl ₂	/	23	11	60:40	93
2 ^f	CH ₂ Cl ₂	/	23	<5	n.d.	n.d.
3 ^g	CH ₂ Cl ₂	/	23	<5	n.d.	n.d.
4	CH ₂ Cl ₂	HOAc	23	19	68:32	93
5	CH ₂ Cl ₂	HClO ₄	23	13	78:22	93

6	CH ₂ Cl ₂	TFA	23	44	52:48	98
7	CHCl ₃	TFA	23	38	56:44	98
8	benzene	TFA	23	46	77:23	95
9	toluene	TFA	23	42	72:28	95
10	H ₂ O	TFA	23	35	61:39	94
11	THF	TFA	23	41	85:15	99
12	Et ₂ O	TFA	23	63	89:11	96
13	1,4-dioxane	TFA	23	74	91:9	99
14 ^[h]	1,4-dioxane	TFA	4	40	92:8	99

^aReaction conditions: **3** (0.1 mmol), **4a** (0.15 mmol) and catalyst **III** (20 mol%) in solvent (0.5 mL). ^badded 20 mol% additive. ^cYield of isolated product. ^dDetermined by ¹H NMR analysis of the crude reaction mixture. ^eDetermined by HPLC methods using a Chiralcel AD-H column. ^fUsed 20 mol% of catalyst **VII**. ^gUsed 20 mol% of catalyst **I**. ^hAfter 3 days, the reaction was not completed. N.d. = not determined.

With the optimized conditions in hand, the scope of the organocatalytic cascade reaction was explored. A wide range of cinnamaldehydes **5a-s** were tested under the optimized reaction conditions (20 mol% Jørgensen-Hayashi's catalyst and 20 mol% TFA in 0.5 mL of 1,4-dioxane at 23 °C), and the results are summarized in Table 3.2. A series of tetrahydroquinoline derivatives **4a-s** were obtained in moderate to good yields with excellent diastereo- and enantioselectivities (up to >95:5 d.r. and up to 99% *ee*). For almost all the cinnamaldehydes tested, the *ee* values were higher than 97%, but the yields and diastereoselectivities varied with the substituent on the aromatic ring. Generally,

ortho-, *meta*-, and *para*- substituted cinnamaldehydes were tolerated in this reaction. Strong electron-donating groups (*N*, *N*-dimethylamino- and methoxy-) at the *para*-position diminished the diastereomeric ratio significantly to 70:30 and 68:32, respectively (Table 3.2, entries 3 and 5). Cinnamaldehydes bearing furanyl and naphthyl groups were also successfully used in this reaction with 90:10 d.r. and 99 % *ee*, and 91:9 d.r. and 99 % *ee*, respectively (Table 3.2, entries 15-16).

Table 3.2 Scope of the reaction.^a

Reaction scheme: **3** + **5a-s** $\xrightarrow[23\text{ }^{\circ}\text{C}]{20\text{ mol\% cat III, 20 mol\% TFA, 1,4-dioxane}}$ **4a-s**

Entry	R	Product	Yield/% ^b	<i>dr</i> ^c	<i>ee</i> / % ^d
1	Ph	4a	74	91:9	99
2	4-NMe ₂ C ₆ H ₄	4b	62	70:30	98
3	3-MeO-4-AcOC ₆ H ₃	4c	70	>95:5	99
4	2-MeOC ₆ H ₄	4d	88	93:7	99
5	4-MeOC ₆ H ₄	4e	41	68:32	99
6	4-NO ₂ C ₆ H ₄	4f	79	>95:5	99
7	2-NO ₂ C ₆ H ₄	4g	75	92:8	97
8	4-BrC ₆ H ₄	4h	84	>95:5	99
9	4-ClC ₆ H ₄	4i	82	94:6	99
10	4-MeC ₆ H ₄	4j	71	88:12	99
11	3-MeC ₆ H ₄	4k	71	89:11	99

12	2-MeC ₆ H ₄	4l	58	85:15	99
13	2-BrC ₆ H ₄	4m	83	90:10	98
14	4-CF ₃ C ₆ H ₄	4n	74	89:11	98
15	2-furanyl	4o	59	90:10	99
16	2-naphthyl	4p	76	91:9	99
17	3-BrC ₆ H ₄	4q	79	94:6	99
18	3-ClC ₆ H ₄	4r	56	92:8	99
19	4-FC ₆ H ₄	4s	64	88:12	99

^aReaction conditions: Catalyst **III** (0.02 mmol) and TFA (0.02 mmol) were added to a solution of cinnamaldehyde (0.15 mmol) and **3** (0.1 mmol) in 1,4-dioxane (0.5 mL) at room temperature (23 °C). ^bYield of isolated product. ^cDetermined by ¹H NMR analysis of the crude reaction mixture. ^dDetermined by HPLC methods employing a Chiralcel AD-H column.

To determine the configuration of the tetrahydroquinoline derivatives, the relative configuration of the structure was determined by X-ray crystallographic analysis of compound **4m**. The configuration of the stereogenic centers, created by the domino formation of a C-N, C-C and C-O bond were assigned to be C7*R*, C13*S*, C14*S*, and C15*S*.

Figure 3.1 X-ray crystal structure of **4m**.

During substrate scope screening, it was observed that formation of **4f** was relatively sluggish, possibly due to decreased reactivity resulting from the presence of the nitro group. Surprisingly, absence of TFA generated product **6** (20 %) very early on in the reaction. ^1H NMR and X-ray crystallographic analysis showed that this was the result of the Jørgensen-Hayashi catalyst failing to release from the substrate. If 100 mol% of catalyst **I** was employed without TFA, almost quantitative **6** was obtained. Addition of 20 mol% of TFA to the solution of **6** also led to the formation of product **4f**.

As mentioned earlier, secondary amine catalyzed organocatalytic asymmetric reactions make use of the following activation modes: iminium ion activation, enamine activation, dienamine activation and trienamine activation.^[8b] Recently, crystallographic analysis and *in situ* NMR studies have made it possible to demonstrate the enamine^[9], dienamine^[10], and trienamine^[11] activation modes. Previous research confirmed the

existence of the iminium ion intermediate through iminium salts^[12] to prove the iminium ion activation mode. In our reaction, the isolation of **6** proved that the reaction pathway occurs via an iminium ion activation mode (Scheme 3.1).

Scheme 3.1 Capture of catalytic intermediate.

The following cascade reaction mechanism is proposed: firstly, an aza-Michael reaction occurs between a tosyl-protected amine and an iminium ion that results from the secondary amine catalyst and cinnamaldehyde. After that, the enamine acts as the Michael donor to nucleophilically attack the β -position of the keto ester. Finally, hemiacetalization takes place, the catalyst is released and the product is formed (Scheme 3.2).

Scheme 3.2 Proposed mechanism of the cascade reaction.

From X-ray analysis result, we can see that the stereoselectivity was determined by the multi-ring system. Generally, each of the six-membered rings tried to maintain chair configuration. Hence adjacent hydrogen atoms showed *anti*- position to each other. The stereoselectivity of hydroxyl group resulted from hindrance of phenyl ring of cinnamaldehyde. The enantioselectivity of product was controlled by the bulky group of catalyst.

3.4 Conclusion

In summary, we have developed a novel, facile organocatalytic asymmetric cascade aza-Michael-Michael-hemiacetalization reaction for the synthesis of tetrahydroquinoline derivatives with good control of four stereogenic centers. This domino process forms highly diastereo- and enantioselective products with the use of the Jørgensen-Hayashi

catalyst. An important intermediate **6** was isolated, which proved that this reaction occurs via an iminium ion activation mode.

3.5 Experimental section

3.5.1 Procedure for preparation of (*E*)-ethyl

4-(2-(4-methylphenylsulfonamido)phenyl)-2-oxobut-3-enoate **3**:

To a solution of 2-(ethoxycarbonyl)-2-oxoethylidenetriphenylphosphorane (**2**, 2.26 g, 6 mmol) in 20 mL of acetonitrile, a solution of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide (**1**, 0.825 g, 3 mmol) in MeCN was added dropwise. The mixture was stirred at room temperature overnight. After that, the mixture was heated at 50 °C for 72 hours. The solvent was evaporated off and the residue was taken up with 20 mL of ethyl acetate. Hydrochloric acid (5% wt a.q.) was used to adjust the pH to 6. The organic layer was separated, dried over anhydrous Na₂SO₄, and evaporated *in vacuo*. And the crude product was purified by FC (EtOAc/Hexane) to give the pure product **3** as yellow solid (0.58 g, 52% yield) which is exclusively *E* isomer.

¹H-NMR (CDCl₃, 400 MHz): δ 1.39-1.43 (t, *J* = 7.2 Hz, 3H), 2.35 (s, 3H), 4.35-4.41 (m, 2H), 6.72 (s, 1H), 7.07-7.11 (d, *J* = 16 Hz, 1H), 7.19-7.21 (d, *J* = 8 Hz, 2H), 7.29-7.31 (d, *J* = 8 Hz, 1H), 7.36-7.41, (m, 2H), 7.54-7.56 (d, *J* = 8 Hz, 2H), 7.60-7.62 (d, *J* = 8 Hz, 1H), 7.72-7.76 (d, *J* = 16 Hz, 1H).

¹³C-NMR (CDCl₃, 100 MHz): δ 14.1, 21.5, 62.7, 122.4, 127.3, 127.4, 127.6, 128.0,

129.8, 130.4, 132.2, 135.6, 142.3, 144.2, 161.9, 182.3.

3.5.2 Procedure for cascade aza-Michael-Michael-hemiacetalization reaction

phenylprolinol silyl ether (6.5 mg, 0.02 mmol) and triflic acid (2.3 mg, 0.02 mmol) were added to a solution of (*E*)-ethyl 4-(2-(4-methylphenylsulfonamido)-phenyl)-2-oxobut-3-enoate (**3**, 37.3 mg, 0.1 mmol) and *trans*-cinnamaldehyde (**5a**, 19.8 mg, 0.15 mmol) in 0.5 mL of dioxane at r.t., and the reaction was monitored by TLC. After the limited reactant was fully consumed, the reaction mixture was charged to silica gel column directly and purified by flash column chromatography.

3.5.3 Characterization data

Prepared according to the general procedure from **3** (0.1 mmol) and cinnamaldehyde (0.15 mmol) to provide the title compound as white solid (37.4 mg, 74% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.34 (t, J = 7.2 Hz, 3H), 1.73-1.79 (t, J = 11.4 Hz,

1H), 2.35 (s, 3H), 2.44-2.47 (d, $J = 12$ Hz, 1H), 4.23-4.32 (m, 2H), 4.72 (br, 1H), 5.21 (s, 1H), 5.23-5.31 (d, $J = 10.8$ Hz, 1H), 6.45 (s, 1H), 7.11-7.13 (d, $J = 8$ Hz, 1H), 7.19-7.28 (m, 7H), 7.38-7.41 (m, 3H), 7.82-7.84 (d, $J = 8$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 21.6, 29.2, 50.2, 61.7, 62.1, 90.8, 109.1, 123.5, 126.6, 126.8, 127.1, 127.7, 127.8, 128.1, 128.7, 129.4, 135.9, 136.0, 136.5, 141.0, 142.1, 143.7, 163.0.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, $\lambda = 254$ nm),

t_R (minor) = 10.0 min, t_R (major) = 31.7 min; 99% ee.

$[\alpha]_D^{23}$: -99.4 ($c = 2.9$, CHCl_3).

HRMS (ESI $^+$) calcd for $\text{C}_{28}\text{H}_{27}\text{O}_6\text{NSNa}$, m/z 528.1457, found 528.1463.

Prepared according to the general procedure from **3** (0.1 mmol) and *p*-dimethylaminocinnamaldehyde (0.15 mmol) to provide the title compound as brown oil (34.2 mg, 62% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3): δ 1.31-1.34 (t, $J = 7.2$ Hz, 3H), 1.77-1.83 (t, $J = 11.4$ Hz, 1H), 2.35 (s, 3H), 2.42-2.45 (d, $J = 12$ Hz, 1H), 2.90 (s, 3H), 4.23-4.30 (m, 2H), 4.37 (m, 1H), 5.20 (s, 1H), 5.23-5.26 (d, $J = 10.8$ Hz, 1H), 6.43-6.44 (d, $J = 1.6$ Hz, 1H), 6.63-6.65 (d, $J = 8.8$ Hz, 2H), 7.08-7.12 (m, 4H), 7.17-7.19 (d, $J = 7.6$ Hz, 1H), 7.24-7.27 (m, 1H), 7.32-7.41 (m, 4H), 7.76-7.78 (d, $J = 8$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 21.6, 29.2, 40.7, 50.0, 61.6, 61.8, 91.0, 109.1, 112.9, 123.4, 126.4, 127.1, 127.5, 127.7, 128.2, 129.3, 129.9, 136.1, 136.2, 136.7, 141.1, 143.4, 150.2, 162.9.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 11.7 min, t_R (major) = 33.0 min; 98% ee.

$[\alpha]_D^{23}$: -67.1 (c = 1.9, CHCl_3).

HRMS (ESI^+) calcd for $\text{C}_{30}\text{H}_{33}\text{O}_6\text{N}_2\text{S}$, m/z 549.2059, found 549.2076.

Prepared according to the general procedure from **3** (0.1 mmol) and 4-acetoxy-3-methoxy-cinnamaldehyde (0.15 mmol) to provide the title compound as light yellow liquid (57.0 mg, 70% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3): δ 1.28-1.31 (t, J = 7.2 Hz, 3H), 1.75-1.80 (t, J = 11.4 Hz, 1H), 2.27 (s, 3H), 2.33 (s, 3H), 2.44-2.47 (d, J = 12.8 Hz, 1H), 3.69 (s, 3H), 4.20-4.25 (m, 2H), 4.98 (s, 1H), 5.20 (s, 1H), 5.30-5.33 (d, J = 10.4 Hz, 1H), 6.41-6.41 (d, J = 2 Hz, 1H), 6.76-6.78 (d, J = 8 Hz, 2H), 6.84 (s, 1H), 6.90-6.92 (d, J = 8.4 Hz, 2H), 7.10-7.12 (d, J = 8 Hz, 2H), 7.17-7.19 (d, J = 7.6 Hz, 1H), 7.24-7.28 (m, 1H), 7.33-7.39 (m, 3H), 7.78-7.80 (d, J = 8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 20.6, 21.6, 29.1, 50.0, 55.8, 61.6, 61.8, 62.4, 66.1,

70.0, 90.7, 108.8, 111.1, 118.9, 122.8, 123.6, 126.7, 127.2, 127.6, 127.9, 129.4, 135.8, 135.9, 136.7, 139.2, 141.0, 141.1, 143.7, 151.1, 162.9, 169.0.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

*t*R (minor) = 12.0 min, *t*R (major) = 22.0 min; 99% ee.

$[\alpha]_D^{23}$: -53.5 (*c* = 3.2, CHCl₃).

HRMS (ESI⁺) calcd for C₃₁H₃₁O₉NNaS, *m/z* 616.1617, found 616.1624.

Prepared according to the general procedure from **3** (0.1 mmol) and 2-methoxycinnamaldehyde (0.15 mmol) to provide the title compound as yellow oil (47.3 mg, 88% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.33-1.36 (t, *J* = 7.2 Hz, 3H), 1.75-1.81 (t, *J* = 11.4 Hz, 1H), 2.36 (s, 3H), 2.46-2.49 (d, *J* = 12.4 Hz, 1H), 3.72 (s, 3H), 4.25-4.34 (m, 2H), 5.29 (s, 1H), 5.31 (s, 1H), 6.46-6.47 (d, *J* = 2.4 Hz, 1H), 6.76-6.84 (m, 3H), 7.13-7.31 (m, 6H), 7.37-7.43 (m, 3H), 7.85-7.87 (d, *J* = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.1, 50.1, 55.1, 61.2, 61.7, 62.0, 91.0, 109.1, 112.9, 123.4, 126.4, 127.1, 127.5, 127.7, 128.2, 129.3, 129.9, 136.1, 136.2, 136.7, 141.1, 143.4, 150.2, 162.9.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 11.4 min, t_R (major) = 28.2 min; 99% ee.

$[\alpha]_D^{23}$: -74.0 (c = 4.9, CHCl_3).

HRMS (ESI^+) calcd for $\text{C}_{29}\text{H}_{29}\text{O}_7\text{NNaS}$, m/z 558.1562, found 558.1559.

Prepared according to the general procedure from **3** (0.1 mmol) and *p*-methoxycinnamaldehyde (0.15 mmol) to provide the title compound as yellow oil (22.2 mg, 41% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3): δ 1.33-1.37 (t, J = 7.2 Hz, 3H), 1.77-1.83 (t, J = 11.4 Hz, 1H), 2.37 (s, 3H), 2.45-2.48 (d, J = 11.8 Hz, 1H), 3.78 (s, 3H), 4.25-4.34 (m, 2H), 5.23-5.24 (d, J = 1.6 Hz, 1H), 5.28-5.31 (d, J = 10.4 Hz, 1H), 6.47-6.47 (d, J = 2 Hz, 1H), 6.81-6.83 (d, J = 8.4 Hz, 2H), 7.13-7.22 (m, 5H), 7.28-7.43 (m, 3H), 7.79-7.81 (d, J = 8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 21.6, 29.1, 50.1, 55.3, 61.6, 61.7, 62.0, 90.9, 109.1, 114.1, 123.5, 126.5, 127.1, 127.6, 128.0, 128.2, 129.4, 134.2, 135.9, 136.0, 136.6, 141.0, 143.6, 159.1, 162.9.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 11.7 min, t_R (major) = 32.9 min; 99% ee.

$[\alpha]_D^{23}$: -39.5 (c = 3.7, CHCl_3).

HRMS (ESI^+) calcd for $\text{C}_{29}\text{H}_{29}\text{O}_7\text{NNaS}$, m/z 558.1562, found 558.1567.

Prepared according to the general procedure from **3** (0.1 mmol) and *p*-nitrocinnamaldehyde (0.15 mmol) to provide the title compound as yellow oil (43.4 mg, 79% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.35-1.39 (t, *J* = 7.2 Hz, 3H), 1.69-1.74 (t, *J* = 11.2 Hz, 1H), 2.38 (s, 3H), 2.44-2.47 (d, *J* = 11.8 Hz, 1H), 4.29-4.37 (m, 2H), 5.18 (s, 1H), 5.38-5.41 (d, *J* = 10.8 Hz, 1H), 6.48 (s, 1H), 7.15-7.17 (d, *J* = 8 Hz, 2H), 7.21-7.23 (d, *J* = 7.2 Hz, 1H), 7.28-7.34 (m, 1H), 7.40-7.44 (m, 5H), 7.88-7.90 (d, *J* = 8 Hz, 1H), 8.08-8.10 (d, *J* = 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.2, 49.8, 61.7, 62.0, 90.3, 108.8, 123.7, 124.0, 126.6, 126.9, 127.1, 127.8, 127.9, 128.0, 129.6, 135.0, 135.3, 136.1, 140.9, 144.2, 147.3, 149.4, 163.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

*t*R (minor) = 17.5 min, *t*R (major) = 48.5 min; 99% ee.

[α]_D²³: -52.9 (c = 5.4, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₈NaSN₂, *m/z* 573.1308, found 573.1293.

Prepared according to the general procedure from **3** (0.1 mmol) and 2-nitrocinnamaldehyde (0.15 mmol) to provide the title compound as yellow oil (41.2 mg, 75% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.29-1.33 (t, *J* = 7.2 Hz, 3H), 1.98-2.04 (t, *J* = 11.2 Hz, 1H), 2.35 (s, 3H), 2.42-2.45 (d, *J* = 12.8 Hz, 1H), 4.21-4.37 (m, 2H), 4.61-4.62 (d, *J* = 3.6 Hz, 1H), 5.46 (s, 1H), 5.99-6.01 (d, *J* = 10 Hz, 1H), 6.47 (s, 1H), 7.13-7.15 (m, 3H), 7.25-7.27 (m, 1H), 7.30-7.40 (m, 5H), 7.45-7.48 (m, 1H), 7.73-7.75 (d, *J* = 8 Hz, 1H), 7.80-7.82 (d, *J* = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 28.9, 50.8, 55.3, 61.6, 90.2, 108.7, 123.8, 124.3, 126.9, 127.1, 127.8, 128.2, 128.6, 129.5, 129.6, 133.3, 135.2, 135.5, 135.7, 137.4, 141.2, 144.0, 149.0, 162.6.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

*t*_R (minor) = 12.3 min, *t*_R (major) = 19.6 min; 97% ee.

[α]_D²³: 28.7 (c = 4.8, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₈NaSN₂, *m/z* 573.1308, found 573.1306.

Prepared according to the general procedure from **3** (0.1 mmol) and 4-bromocinnamaldehyde (0.15 mmol) to provide the title compound as colorless oil (49 mg, 84% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.36 (t, J = 7.2 Hz, 3H), 1.68-1.73 (t, J = 11.4 Hz, 1H), 2.35 (s, 3H), 2.42-2.45 (d, J = 12.8 Hz, 1H), 4.24-4.33 (m, 2H), 5.07 (br, 1H), 5.16 (s, 1H), 5.24-5.27 (d, J = 10.8 Hz, 1H), 6.44-6.44 (d, J = 1.6 Hz, 1H), 7.09-7.13 (m, 4H), 7.18-7.20 (d, J = 7.6 Hz, 1H), 7.28-7.30 (d, J = 7.6 Hz, 1H), 7.36-7.40 (m, 5H), 7.81-7.83 (d, J = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.2, 50.0, 61.7, 61.8, 90.6, 109.0, 121.7, 123.6, 126.7, 127.1, 127.7, 128.1, 128.6, 129.4, 131.9, 135.6, 135.7, 136.4, 140.9, 141.2, 143.8, 163.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 9.3 min, t_R (major) = 23.0 min; 99% ee.

$[\alpha]_D^{23}$: -115.5 (c = 2.1, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₆NaSNBr, m/z 606.0562, found 606.0564.

Prepared according to the general procedure from **3** (0.1 mmol) and 4-chlorocinnamaldehyde (0.15 mmol) to provide the title compound as colorless oil (44.3 mg, 82% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.36 (t, J = 7.2 Hz, 3H), 1.68-1.74 (t, J = 11.4 Hz, 1H), 2.35 (s, 3H), 2.42-2.45 (d, J = 12 Hz, 1H), 4.24-4.33 (m, 2H), 5.08 (br, 1H), 5.15 (s, 1H), 5.26-5.28 (d, J = 10.8 Hz, 1H), 6.44-6.45 (d, J = 2 Hz, 1H), 7.11-7.23 (m, 7H), 7.28-7.30 (m, 1H), 7.36-7.40 (m, 3H), 7.81-7.83 (d, J = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.2, 50.0, 61.6, 61.8, 90.6, 109.0, 123.6, 126.7, 127.1, 127.7, 128.1, 128.2, 128.9, 129.4, 133.5, 135.6, 135.7, 136.4, 140.7, 140.9, 143.8, 163.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 8.5 min, t_R (major) = 22.8 min; 99% ee.

$[\alpha]_D^{23}$: -110.3 (c = 3.3, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₆NaSNCl, m/z 562.1067, found 562.1069.

Prepared according to the general procedure from **3** (0.1 mmol) and 4-methylcinnamaldehyde (0.15 mmol) to provide the title compound as colorless oil (36.6 mg, 71% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.36 (t, J = 7.2 Hz, 3H), 1.73-1.79 (m, 1H), 2.28 (s, 3H), 2.35 (s, 3H), 2.43-2.46 (d, J = 12 Hz, 1H), 4.24-4.33 (m, 2H), 5.22-5.23 (d, J = 1.6 Hz, 1H), 5.27-5.30 (d, J = 10.8 Hz, 1H), 6.45-6.45 (d, J = 2 Hz, 1H), 7.04-7.06 (d, J = 8 Hz, 2H), 7.18-7.20 (d, J = 7.6 Hz, 1H), 7.27-7.29 (d, J = 7.6 Hz, 1H), 7.35-7.41 (m, 3H), 7.81-7.83 (d, J = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.1, 21.6, 29.2, 50.2, 61.7, 61.9, 90.9, 109.1, 123.5, 126.5, 126.7, 127.1, 127.6, 128.2, 129.4, 129.4, 136.0, 136.6, 137.4, 139.2, 141.0, 143.6, 163.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 8.4 min, t_R (major) = 21.8 min; 99% ee.

$[\alpha]_D^{23}$: -83.6 (c = 4.2, CHCl₃).

HRMS (ESI⁺) calcd for C₂₉H₂₉O₆NaSN, m/z 542.1613, found 542.1609.

Prepared according to the general procedure from **3** (0.1 mmol) and 3-methylcinnamaldehyde (0.15 mmol) to provide the title compound as colorless oil (36.7 mg, 71% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.34-1.37 (t, *J* = 7.2 Hz, 3H), 1.74-1.80 (m, 1H), 2.27 (s, 3H), 2.37 (s, 3H), 2.45-2.48 (d, *J* = 12.8 Hz, 1H), 4.25-4.35 (m, 2H), 4.66 (br, 1H), 5.25 (s, 1H), 5.27-5.30 (d, *J* = 10.4 Hz, 1H), 6.47-6.48 (d, *J* = 2 Hz, 1H), 7.02-7.04 (m, 3H), 7.13-7.17(m, 3H), 7.21-7.23 (d, *J* = 7.6 Hz, 1H), 7.28-7.32 (m, 1H), 7.39-7.43 (m, 3H), 7.85-7.87 (d, *J* = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.4, 21.6, 29.1, 50.1, 61.7, 62.1, 90.9, 109.8, 123.5, 123.8, 126.5, 127.2, 127.4, 127.6, 128.2, 128.5, 128.6, 129.4, 135.9, 136.1, 136.6, 138.3, 141.0, 142.0, 143.6, 163.0.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ= 254 nm),

*t*R (minor) = 8.5 min, *t*R (major) = 20.6 min; 99% ee.

[α]_D²³: -114.3 (c = 2.9, CHCl₃).

HRMS (ESI⁺) calcd for C₂₉H₂₉O₆NaSN, *m/z* 542.1613, found 542.1629.

Prepared according to the general procedure from **3** (0.1 mmol) and 2-methylcinnamaldehyde (0.15 mmol) to provide the title compound as colorless oil (30.3 mg, 58% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.33-1.36 (t, *J* = 7.2 Hz, 3H), 1.78-1.84 (t, *J* = 11.4 Hz, 1H), 2.38 (s, 3H), 2.47-2.50 (d, *J* = 12.8 Hz, 1H), 2.54 (s, 3H), 4.24-4.33 (m, 2H), 5.13 (s,

1H), 5.57-5.60 (d, $J = 11.2$ Hz, 1H), 6.48-6.48 (d, $J = 2$ Hz, 1H), 6.96-6.98 (d, $J = 7.6$ Hz, 1H), 7.06-7.37 (m, 14H), 7.72-7.74 (d, $J = 8$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 19.3, 21.6, 29.2, 51.1, 58.1, 59.9, 61.7, 90.5, 109.2, 123.5, 126.5, 126.6, 127.1, 127.3, 127.5, 127.7, 128.2, 129.4, 129.8, 130.5, 135.1, 135.9, 136.3, 136.4, 140.7, 140.8, 143.6, 163.0.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, $\lambda = 254$ nm),

t_R (minor) = 6.6 min, t_R (major) = 13.9 min; 99% ee.

$[\alpha]_D^{23}$: -82.1 ($c = 3.0$, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{29}\text{H}_{29}\text{O}_6\text{NaSN}$, m/z 542.1613, found 542.1627.

Prepared according to the general procedure from **3** (0.1 mmol) and 2-bromocinnamaldehyde (0.15 mmol) to provide the title compound as white solid (48.3 mg, 83% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3): δ 1.32-1.35 (t, $J = 7.2$ Hz, 3H), 1.77-1.83 (t, $J = 11.4$ Hz, 1H), 2.38 (s, 3H), 2.48-2.51 (d, $J = 12.8$ Hz, 1H), 4.23-4.32 (m, 2H), 4.54 (br, 1H), 5.35 (s, 1H), 5.77-5.80 (d, $J = 10.4$ Hz, 1H), 6.48 (s, 1H), 6.96-6.98 (d, $J = 7.6$ Hz, 1H), 7.06-7.50 (m, 12H), 7.86-7.88 (d, $J = 8$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 21.6, 28.9, 51.1, 60.0, 61.6, 90.2, 109.0, 122.2,

123.6, 126.6, 127.3, 127.7, 128.2, 128.4, 129.1, 129.3, 129.5, 132.9, 135.6, 135.8, 136.3, 141.0, 143.8, 162.8.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 8.4 min, t_R (major) = 14.6 min; 98% ee.

$[\alpha]_D^{23}$: -99.5 (c = 3.1, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₆NaSNBr, m/z 606.0562, found 606.0550.

Prepared according to the general procedure from **3** (0.1 mmol) and 4-trifluoromethylcinnamaldehyde (0.15 mmol) to provide the title compound as colorless oil (42.2 mg, 74% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.33-1.36 (t, J = 7.2 Hz, 3H), 1.69-1.75 (t, J = 11.4 Hz, 1H), 2.35 (s, 3H), 2.45-2.48 (d, J = 12.8 Hz, 1H), 4.25-4.34 (m, 2H), 5.10 (br, 1H), 5.16 (s, 1H), 5.34-5.37 (d, J = 10.8 Hz, 1H), 6.46-6.46 (d, J = 1.6 Hz, 1H), 7.12-7.14 (d, J = 8 Hz, 2H), 7.19-7.21 (d, J = 7.6 Hz, 1H), 7.28-7.32 (m, 1H), 7.34-7.36 (d, J = 8 Hz, 2H), 7.39-7.41 (m, 3H), 7.49-7.51 (d, J = 8 Hz, 2H), 7.84-7.86 (d, J = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.2, 50.0, 61.8, 61.9, 90.5, 108.9, 122.6, 123.6, 125.7, 125.8, 126.8, 127.1, 127.2, 127.8, 128.0, 129.5, 129.8, 130.1, 135.4, 135.6, 136.3, 140.9, 144.0, 146.1, 163.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 6.2 min, t_R (major) = 12.5 min; 98% ee.

$[\alpha]_D^{23}$: -53.6 (c = 5.4, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{29}\text{H}_{26}\text{O}_6\text{NaSNF}_3$, m/z 596.1331, found 596.1324.

Prepared according to the general procedure from **3** (0.1 mmol) and 3-(furan-2-yl)acrylaldehyde (0.15 mmol) to provide the title compound as light yellow solid (29.1 mg, 59% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.36 (t, J = 7.2 Hz, 3H), 2.03-2.09 (t, J = 11.2 Hz, 1H), 2.35 (s, 3H), 2.44-2.47 (d, J = 12.8 Hz, 1H), 4.24-4.33 (m, 2H), 4.64 (s, 1H), 5.55-5.58 (m, 2H), 6.29-6.29 (d, J = 1.6 Hz, 1H), 6.39-6.39 (d, J = 2.8 Hz, 1H), 6.44 (s, 1H), 7.11-7.13 (d, J = 8 Hz, 2H), 7.16-7.18 (d, J = 7.6 Hz, 1H), 7.23-7.34 (m, 3H), 7.40-7.42 (d, J = 8 Hz, 2H), 7.72-7.73 (d, J = 7.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 28.7, 47.0, 55.3, 61.7, 91.1, 107.6, 109.0, 110.4, 123.4, 126.9, 127.2, 127.5, 128.5, 129.4, 135.1, 135.9, 136.3, 140.9, 142.4, 143.7, 153.7, 162.9.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 11.0 min, t_R (major) = 17.6 min; 99% ee.

$[\alpha]_D^{23}$: -40.9 (c = 1.3, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{26}\text{H}_{25}\text{O}_7\text{NaSN}$, m/z 518.1249, found 518.1239.

Prepared according to the general procedure from **3** (0.1 mmol) and 3-(naphthalen-2-yl)acrylaldehyde (0.15 mmol) to provide the title compound as white solid (42.0 mg, 76% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.35 (t, J = 7.2 Hz, 3H), 1.81-1.87 (m, 1H), 2.33 (s, 3H), 2.50-2.53 (d, J = 12 Hz, 1H), 4.24-4.32 (m, 2H), 4.98 (br, 1H), 5.23 (s, 1H), 5.47-5.50 (d, J = 10.8 Hz, 1H), 6.46-6.47 (d, J = 2.4 Hz, 1H), 7.10-7.12 (d, J = 8 Hz, 2H), 7.20-7.23 (m, 2H), 7.29-7.32 (m, 1H), 7.39-7.44 (m, 5H), 7.65-7.70 (m, 4H), 7.86-7.88 (d, J = 7.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.2, 49.9, 61.7, 62.4, 90.8, 109.0, 123.6, 124.3, 126.0, 126.1, 126.2, 126.6, 127.2, 127.6, 127.4, 128.0, 128.2, 128.8, 129.4, 132.9, 133.2, 135.8, 136.0, 136.6, 139.2, 141.0, 143.7, 163.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 12.3 min, t_R (major) = 33.0 min; 99% ee.

$[\alpha]_D^{23}$: -40.9 (c = 1.3, CHCl₃).

HRMS (ESI⁺) calcd for C₃₂H₂₉O₆NaSN, m/z 578.1613, found 578.1608.

Prepared according to the general procedure from **3** (0.1 mmol) and 3-bromocinnamaldehyde (0.15 mmol) to provide the title compound as yellow oil (46.0 mg, 79% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.31-1.35 (t, *J* = 7.2 Hz, 3H), 1.66-1.72 (m, 1H), 2.35 (s, 3H), 2.40-2.43 (d, *J* = 12 Hz, 1H), 4.23-4.34 (m, 2H), 4.85 (br, 1H), 5.18 (s, 1H), 5.22-5.25 (d, *J* = 10.8 Hz, 1H), 6.63-6.64 (d, *J* = 2.4 Hz, 1H), 7.08-7.20 (m, 5H), 7.27-7.41 (m, 7H), 7.84-7.86 (d, *J* = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.1, 50.0, 61.6, 61.8, 90.5, 108.9, 122.7, 123.6, 125.4, 126.7, 127.1, 127.8, 128.1, 129.5, 129.9, 130.3, 130.9, 135.5, 135.6, 136.4, 141.0, 143.9, 144.4, 163.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

*t*_R (minor) = 8.8 min, *t*_R (major) = 22.2 min; 99% ee.

[α]_D²³: -128.5 (c = 2.6, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₆NaSNBr, *m/z* 606.0562, found 606.0567.

Prepared according to the general procedure from **3** (0.1 mmol) and 3-chlorocinnamaldehyde (0.15 mmol) to provide the title compound as yellow oil (30.1 mg, 56% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.35 (t, J = 7.2 Hz, 3H), 1.66-1.71 (t, J = 11.4 Hz, 1H), 2.35 (s, 3H), 2.40-2.43 (d, J = 12 Hz, 1H), 4.24-4.37 (m, 2H), 5.05 (br, 1H), 5.18 (s, 1H), 5.23-5.26 (d, J = 10.8 Hz, 1H), 6.43-6.44 (d, J = 2.4 Hz, 1H), 7.11-7.20 (m, 7H), 7.27-7.41 (m, 5H), 7.84-7.86 (d, J = 8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.1, 49.9, 61.6, 61.8, 90.6, 108.9, 123.6, 125.0, 126.7, 127.0, 127.1, 127.8, 128.0, 128.2, 129.4, 130.0, 134.5, 135.5, 135.7, 136.3, 141.0, 143.9, 144.1, 163.0.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 8.5 min, t_R (major) = 18.8 min; 99% ee.

$[\alpha]_D^{23}$: -65.6 (c = 2.9, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₆NaSNCl, m/z 562.1067, found 562.1061.

Prepared according to the general procedure from **3** (0.1 mmol) and 4-fluorocinnamaldehyde (0.15 mmol) to provide the title compound as colorless oil (33.6 mg, 64% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.31-1.35 (t, J = 7.2 Hz, 3H), 1.68-1.74 (m, 1H), 2.35 (s, 3H), 2.42-2.45 (d, J = 12.4 Hz, 1H), 4.24-4.32 (m, 2H), 5.14-5.14 (d, J = 1.6 Hz, 1H), 5.26-5.29 (d, J = 10.8 Hz, 1H), 6.44-6.44 (d, J = 2 Hz, 1H), 6.90-6.94 (t, J = 8.6 Hz, 2H), 7.11-7.13 (d, J = 8.4 Hz, 2H), 7.17-7.21 (m, 3H), 7.28-7.30 (d, J = 7.2 Hz, 1H), 7.35-7.40 (m, 3H), 7.80-7.82 (d, J = 7.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.2, 21.6, 29.2, 50.2, 61.5, 61.8, 90.7, 109.0, 115.5, 115.7, 123.6, 126.4, 127.1, 127.7, 128.1, 128.5, 128.5, 129.4, 135.7, 135.7, 136.5, 138.0, 138.0, 140.9, 143.8, 161.0, 163.0.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 9.5 min, t_R (major) = 29.5 min; 99% ee.

$[\alpha]_D^{23}$: -73.6 (c = 3.2, CHCl₃).

HRMS (ESI⁺) calcd for C₂₈H₂₆O₆NaSNF, m/z 546.1363, found 546.1368.

3.6 Reference

- [1] a) L. F. Tietze, B. Gordon, G. M. Kersten, *Domino Reactions in Organic Synthesis*, **2006**; b) D. Enders, C. Grondal, M. R. M. Hüttel, *Angew. Chem. Int. Ed.* **2007**, 46,

- 1570; c) H. Guo, J. Ma, *Angew. Chem., Int. Ed.* **2006**, *45*, 354; d) M. M. Hussian, J. W. Patrick, *Acc. Chem. Res.* **2008**, *41*, 883; e) Z. G. Li, B. Chad, C. He, *Chem. Rev.* **2008**, *108*, 3239; f) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134; g) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143; h) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967; i) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037.
- [2] a) Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron* **2006**, *62*, 365; b) H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 3732; c) H. Li, L. S. Zu, H. X. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*, 1833; d) V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12928; e) X. Sun, S. Sengupta, J. L. Petersen, H. Wang, J. P. Lewis, X. D. Shi, *Org. Lett.* **2007**, *9*, 4495; f) J. Wang, H. Xie, H. Li, L. Zu, W. Wang, *Angew. Chem., Int. Ed.* **2008**, *47*, 4177; g) X. F. Wang, Q. L. Hua, Y. Cheng, X. L. An, Q. Q. Yang, J. R. Chen, W. J. Xiao, *Angew. Chem., Int. Ed.* **2010**, *49*, 8379.
- [3] a) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328; b) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058; c) S. Fustero, D. Jimenez, J. Moscardo, S. Catalan, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283; d) Z.-Q. He, Q. Zhou, L. Wu, Y.-C. Chen, *Adv. Synth. Catal.*, *352*, 1904; e) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova, *Chem. Commun.* **2007**, 849; f) X. Lu, L. Deng, *Angew. Chem. Int. Ed.* **2008**, *47*, 7710; g) D. Perdicchia, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 3565; h) F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angewandte Chemie* **2008**, *120*, 8831; i) M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064;

- j) D. Uraguchi, D. Nakashima, T. Ooi, *J. Am. Chem. Soc.* **2009**, *131*, 7242; k) J. Vesely, I. Ibrahim, R. Rios, G.-L. Zhao, Y. Xu, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2193; l) J. Vesely, I. Ibrahim, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem. Int. Ed.* **2007**, *46*, 778.
- [4] a) H. Li, L. Zu, H. Xie, J. Wang, W. Wang, *Chem. Commun.* **2008**, 5636; b) X.-F. Wang, J. An, X.-X. Zhang, F. Tan, J.-R. Chen, W.-J. Xiao, *Org. Lett.*, *13*, 808.
- [5] D. H. Barton, K. Nakanishi, O. Meth-Cohn, *Comprehensive Natural Products Chemistry*, **1999**.
- [6] a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031; b) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem., Int. Ed.* **2006**, *45*, 3683; c) Y. G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357.
- [7] a) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem. Int. Ed.* **2008**, *47*, 10187; b) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang, G. Zhong, *Org. Lett.* **2008**, *10*, 4585; c) D. Zhu, M. Lu, L. Dai, G. Zhong, *Angew. Chem. Int. Ed.* **2009**, *48*, 6089.
- [8] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; b) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.*, published on 17 Aug, 2011. DOI: 10.1021/ar200149w; c) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703; d) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794; e) A. Mielgo, C. Palomo, *Chem. Asian. J.* **2008**, *3*, 922; f) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, *45*, 7876.
- [9] a) D. A. Bock, C. W. Lehmann, B. List, *Proc. Natl. Acad. Sci.*, *107*, 20636; b) C.

- Marquez, J. O. Metzger, *Chem. Commun.* **2006**, 1539; c) M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem. Int. Ed.*, **49**, 4997; d) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikozovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425.
- [10] M. B. Schmid, K. Zeitler, R. M. Gschwind, *J. Org. Chem.* **76**, 3005.
- [11] Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053.
- [12] a) U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru, *Helv. Chim. Acta* **2009**, *92*, 1225; b) D. Seebach, R. Gilmour, U. Grošelj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, L. B. McCusker, D. Šišak, T. Uchimaru, *Helv. Chim. Acta*, **93**, 603; c) D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999.

Chapter 4

Highly Efficient Asymmetric Cascade

Oxo-Michael-Michael-Michael-aldol Reaction:

Synthesis of Chromane Derivatives

4.1 Abstract

An organocatalytic asymmetric cascade oxo-Michael-Michael-Michael-aldol reaction for the synthesis of chromane derivatives with good control of five stereogenic centers between cinnamaldehyde and **2** was reported. This reaction bears a wide range of different cinnamaldehyde substrates for the possible synthesis of natural products and pharmaceuticals.

4.2 Introduction

Oxo-Michael reaction are considered to be one of the most important protocols to construct new carbon-oxygen bonds.^[1] In particular, intramolecular oxo-Michael reactions provide a facile route to synthesize oxoheterocycles, which are important frameworks in natural products and pharmaceuticals.^[2]

One example of oxoheterocycles are chromanes like rhodaurichromanolic acids A and B (Figure 4.1), which are isolated from the leaves and twigs of the *Rhododendron dauricum*.^[8]

Figure 4.1 Examples of chromanes as substructures in biologically interesting natural products of Rhodaurichromanolic acid A and B.

However, oxo-Michael reactions suffer from weak reactivity and reversibility, which leads to sluggish reaction rates and difficulties in developing asymmetric versions.^[1] Consequently, there are few reports on oxo-Michael reactions,^[3] especially its asymmetric versions.

Recently a few methods were reported to achieve highly enantioselective oxo-Michael reactions with organocatalysts like chiral secondary amines^[4], thioureas^[5], cinchona catalysts^[6] and Lewis acids^[7].

Organocatalytic asymmetric oxo-Michael cascade reactions were not explored much to date, most of which resulted in asymmetric 4*H*-chromenes^[9] or 2*H*-chromenes^[10]. In these examples, diarylprolinol silyl ether was utilized as the catalyst to initiate the formation of the “iminium-allenamine” and “enamine” intermediate. This is followed by nucleophilic attack and an aldol or Michael reaction to afford the product.

In the previous chapter, we designed a novel substrate, (*E*)-ethyl 4-(2-(4-methylphenylsulfonamido)phenyl)-2-oxobut-3-enoate, to react with α,β -unsaturated aldehydes and obtain a tetrahydroquinoline derivative with high enantioselectivity through an aza-Michael-Michael-hemiacetalization cascade. This prompted us to wonder what would happen if the nucleophile was changed from nitrogen to oxygen (Scheme 4.1).

Since

what about

heme 4.1 Initial synthesis protocol of enantioselective chromanes *via* oxo-Michael cascade reaction.

4.3 Results and discussion

Firstly, the *O*-substrate was synthesized using a similar procedure to the *N*-substrate.

Preliminary investigations using the previously established reaction conditions showed that reactant **2** was consumed, with the major spot being identified as the *Z*-isomer of **2**. When benzoic acid, a weaker acid, was used, a new product as well as complete consumption of cinnamaldehyde was observed by TLC. Addition of 2 equivalents of cinnamaldehyde led to full consumption of the enoate and formation of the oxo-Michael-Michael-Michael-aldol cascade product in good yields and enantioselectivity (77% yield, >99% *ee*).

Inspired by this result, we began to optimize the reaction conditions. When acetic acid was used, the yield decreased from 77% to 54%. Hence, benzoic acid was chosen as the most suitable acid because of its moderate acidity. Screening of solvents revealed no improvement in the results (Table 4.1, entries 3-10). Since the reaction time was relatively long (about 16 hours), the reaction temperature was raised from room temperature to 30 °C, with the hope of accelerating the reaction (Table 4.1, entry 11). However, a lower yield (54%) was obtained, possibly due to decomposition of the product at higher temperatures.

Table 4.1 Screening of Reaction Conditions.^a

Entry	Solvent	Yield/% ^b	d.r. ^c	<i>ee</i> / % ^d
1	DCM	73	88:12	>99
2 ^e	DCM	54	87:13	>99

3	CHCl ₃	49	90:10	98
4	Et ₂ O	58	90:10	99
5	Toluene	52	90:10	>99
6	dioxane	70	85:15	98
7	MeCN	48	78:22	95
8	THF	42	70:30	93
9	EA	55	82:18	97
10	Hexane	60	80:20	99
11 ^f	DCM	53	85:15	99

^aReaction conditions: **2** (0.105 mmol), **3a** (0.2 mmol) and catalyst (20 mol%) with benzoic acid (20 mol%) in solvent (0.5 mL). ^bYield of isolated product. ^cDetermined by ¹H NMR analysis of the crude reaction mixture. ^dDetermined by HPLC methods using a Chiralcel OD-H column. ^eUsed 20 mol% of acetic acid instead of benzoic acid. ^fThe reaction was operated at 30 °C.

With the optimized reaction conditions, we began to investigate the substrate scope (Table 4.2). A series of chromane derivatives **4a-4k** were obtained in moderate to good yields with excellent diastereoselectivity and enantioselectivity (up to 98:2 d.r. and up to >99% *ee*). For most of the aldehydes tested, the *ee* values were higher than 98%, while a variation in the yield and diastereoselectivity was observed. Generally, halogen-containing cinnamaldehydes could afford the desired products with good diastereoselectivities and yields (Table 4.2, entries 2, 3, and 5). For *para*- and *ortho*-nitrophenyl cinnamaldehyde (Table 4.2, entry 4 and 7), the isolated yields were relatively

low due to an incomplete reaction even after a prolonged reaction time. Cinnamaldehydes bearing a naphthyl group and a strong electron-donating methoxy group were also successfully used in this reaction (Table 4.2, entries 8-10). However, substrates containing a methyl group on the *para*-, *ortho*-, or *meta*- position gave sluggish yields (Table 4.2, entries 12-14). This may be due to the low reactivity of cinnamaldehyde.

Table 4.2 Substrate scope for oxo-Michael-Michael-Michael-aldol reaction.^a

Entry	Ar	Product	Yield/% ^b	<i>dr</i> ^c	<i>ee</i> / % ^d
1	Ph-	4a	73	88:12	>99
2	4-Br-Ph-	4b	91	95:5	99
3	4-Cl-Ph-	4c	80	98:2	99
4	4-NO ₂ -Ph-	4d	54	95:5	99
5	4-F-Ph-	4e	78	93:7	>99
6	2-Br-Ph-	4f	75	90:10	98
7	2-NO ₂ -Ph-	4g	45 ^e	93:7	98
8	2-Naph-	4h	88	94:6	99
9	4-MeO-Ph-	4i	58	98:2	98
10	2-MeO-Ph-	4j	52	82:18	99
11	4-AcO-3-MeO-Ph-	4k	69	95:5	>99
12 ^f	4-Me-Ph-	/	<10%	N.d.	N.d.

13 ^f	3-Me-Ph-	/	<10%	N.d.	N.d.
14 ^f	2-Me-Ph-	/	<10%	N.d.	N.d.

^aReaction conditions: Catalyst (0.02 mmol) and benzoic acid (0.02 mmol) were added to a solution of cinnamaldehyde (0.2 mmol) and **2** (0.105 mmol) in DCM (0.5 mL) at room temperature (23 °C). ^bYield of isolated product. ^cDetermined by ¹H NMR analysis of the crude reaction mixture. ^dDetermined by HPLC methods employing a Chiralcel AD-H or OD-H column. ^eRecovered 40% of starting material. ^fReaction time extended to 10 days.

To determine the configuration of the chromane derivatives, the relative configuration of the structure was determined by X-ray crystallographic analysis of compound **4d**. The configuration of the stereogenic centers were assigned to be C7*S*, C8*S*, C12*R*, C13*R*, and C14*R*. (Figure 4.2)

Figure 4.2 X-ray structure of **4d**.

The proposed reaction mechanism is as follows: firstly, an oxo-Michael reaction occurs between the phenol and iminium formed from cinnamaldehyde and the catalyst. Subsequently, the enamine is attacked by the olefin followed by the iminium species. After aldol reaction, the final product was obtained and the catalyst was released (Scheme 4.2).

Scheme 4.2 Proposed mechanism of this cascade reaction.

We conclude that the stereoselectivity was determined by the multi-ring system. Every substituted group on every six-membered ring showed *anti*- position for the reason of hindrance. The absolute configuration was determined by the excellent shielding of catalyst's bulky groups.

4.4 Conclusion

In summary, we have developed a novel and unexpected organocatalytic asymmetric cascade oxo-Michael-Michael-Michael-aldol reaction for the synthesis of chromane derivatives with good control of five stereogenic centers between cinnamaldehyde and 4-(2-hydroxyphenyl)-2-oxobut-3-enoate. This cascade process is highly diastereo- and enantioselective by using a prolinol silyl ether catalyst. This reaction bears a wide range of different cinnamaldehyde substrates for the possible synthesis of natural products and pharmaceuticals.

4.5 Experimental section

4.5.1 Procedure for preparation of

(*E*)-ethyl 4-(2-hydroxyphenyl)-2-oxobut-3-enoate **2**:

To a solution of 2-(ethoxycarbonyl)-2-oxoethylidenetriphenylphosphorane (**1**, 2.26 g, 6 mmol) in 20 mL of acetonitrile, salicylaldehyde (0.366 g, 3 mmol) was added dropwise. The mixture was stirred at room temperature overnight. After that, the mixture was heated at 45 °C for 72 hours. The solvent was evaporated off and the residue was taken up with 20 mL of ethyl acetate. Hydrochloric acid (5% wt a.q.) was used to adjust the pH to 6. The organic layer was separated, dried over anhydrous Na₂SO₄, and evaporated *in vacuo*. And the crude product was purified by FC (EtOAc/Hexane) to give the pure product **2** as yellow solid (0.26 g, 41% yield) which is *E* isomer.

¹H-NMR (CDCl₃, 400 MHz): δ 1.39-1.43 (t, *J* = 7 Hz, 3H), 4.37-4.43 (m, 2H), 6.65 (br, 1H), 6.88-6.90 (d, *J* = 8 Hz, 1H), 6.93-6.97 (t, *J* = 7.5 Hz, 1H), 7.28-7.32 (t, *J* = 7.5 Hz, 1H), 7.48-7.52 (d, *J* = 16.2 Hz, 1H), 7.56-7.58 (d, *J* = 7.6 Hz, 1H), 8.19-8.23 (d, *J* = 16.2 Hz, 1H).

¹³C-NMR (CDCl₃, 100 MHz): δ 14.0, 62.6, 116.7, 120.9, 121.0, 121.4, 130.0, 133.1, 144.9, 156.5, 162.8, 184.1.

HRMS (ESI⁺) calcd for C₁₂H₁₃O₄, *m/z* 221.0814, found 221.0821.

4.5.2 General procedure for cascade oxo-Michael-Michael-Michael-aldol reaction

Diphenylprolinol silyl ether (6.5 mg, 0.02 mmol) and benzoic acid (2.3 mg, 0.02 mmol) were added to a solution of (E)-ethyl 4-(2-hydroxyphenyl)-2-oxobut-3-enoate (**2**, 23.1 mg, 0.105 mmol) and *trans*-cinnamaldehyde (**3a**, 26.4 mg, 0.2 mmol) in 0.5 mL of dichloromethane at r.t., and the reaction was monitored by TLC. After the limited reactant was fully consumed, the reaction mixture was charged to silica gel column directly and purified by flash column chromatography.

4.5.3 Characterization data

Prepared according to the general procedure from **2** (0.105 mmol) and cinnamaldehyde (0.2 mmol) to provide the title compound as white solid (33.8 mg, 73% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.36 (t, J = 7.2 Hz, 3H), 3.40-3.44 (dd, J = 3.3 Hz, 1H), 3.56-3.61 (m, 1H), 4.21-4.32 (m, 2H), 4.37 (s, 1H), 4.49-4.50 (d, J = 3.4 Hz, 1H), 5.03-5.06 (d, J = 10.2 Hz, 1H), 6.56-6.57 (d, J = 1.6 Hz, 1H), 6.80-6.84 (t, J = 7.5 Hz,

1H), 6.87-6.89 (d, $J = 8.1$ Hz, 1H), 6.96-6.98 (d, $J = 7.7$ Hz, 1H), 7.10-7.14 (m, 1H), 7.27-7.30 (m, 3H), 7.35-7.39 (m, 2H), 7.49-7.53 (m, 5H), 9.34 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 34.3, 38.8, 40.8, 48.4, 63.0, 82.7, 117.0, 120.6, 121.8, 124.5, 127.5, 127.7, 128.4, 129.0, 129.1, 129.4, 138.1, 140.7, 141.3, 148.8, 154.8, 161.6, 192.2, 194.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, $\lambda = 254$ nm),

t_R (major) = 8.7 min, t_R (minor) = 13.6 min; >99% ee.

$[\alpha]_D^{23}$: -50.7 ($c = 0.6$, CHCl_3).

HRMS (ESI⁺) calcd for $\text{C}_{30}\text{H}_{26}\text{O}_5\text{Na}$, m/z 489.1678, found 489.1685.

Prepared according to the general procedure from **2** (0.105 mmol) and *p*-bromocinnamaldehyde (0.2 mmol) to provide the title compound as white solid (58.5 mg, 91% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3): δ 1.31-1.35 (t, $J = 7.2$ Hz, 3H), 3.32-3.35 (dd, $J = 3.2$ Hz, 1H), 3.51-3.57 (m, 1H), 4.24-4.30 (m, 2H), 4.44-4.45 (d, $J = 3.2$ Hz, 1H), 4.98-5.00 (d, $J = 10.4$ Hz, 1H), 6.55 (s, 1H), 6.81-6.88 (m, 2H), 6.94-6.96 (d, $J = 7.6$ Hz, 1H), 7.11-7.17 (m, 3H), 7.42-7.44 (d, $J = 8.4$ Hz, 2H), 7.48-7.50 (d, $J = 8.4$ Hz, 2H), 7.65-7.67 (d, $J = 8.4$ Hz, 2H), 9.34 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 34.2, 38.4, 40.6, 48.1, 63.1, 81.8, 117.0, 120.9, 121.3, 121.6, 123.4, 124.5, 128.6, 129.4, 132.1, 132.3, 137.1, 140.4, 140.6, 148.5, 154.6, 161.4, 191.9, 193.7.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 22.8 min, t_R (major) = 43.1 min; 99% ee.

$[\alpha]_D^{23}$: -10.1 (c = 1.0, CHCl_3).

HRMS (ESI^+) calcd for $\text{C}_{30}\text{H}_{25}\text{O}_5\text{Br}_2$, m/z 625.0014, found 625.0018.

Prepared according to the general procedure from **2** (0.105 mmol) and *p*-chlorocinnamaldehyde (0.2 mmol) to provide the title compound as white solid (42.7 mg, 80% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3): δ 1.31-1.35 (t, J = 7.2 Hz, 3H), 3.33-3.36 (dd, J = 3.2 Hz, 1H), 3.52-3.57 (m, 1H), 4.21-4.30 (m, 2H), 4.32 (s, 1H), 4.44-4.45 (d, J = 3.2 Hz, 1H), 4.99-5.02 (d, J = 10.4 Hz, 1H), 6.55 (s, 1H), 6.81-6.88 (m, 2H), 6.95-6.97 (d, J = 7.6 Hz, 1H), 7.11-7.15 (t, J = 7.6 Hz, 1H), 7.21-7.23 (d, J = 8.4 Hz, 2H), 7.33-7.35 (d, J = 8.4 Hz, 2H), 7.48-7.52 (m, 4H), 9.34 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 34.2, 38.3, 40.6, 48.2, 63.1, 81.8, 117.0, 120.9, 121.3, 124.5, 128.6, 129.0, 129.1, 129.2, 129.4, 129.5, 129.6, 133.5, 135.3, 136.5, 139.9,

140.7, 148.5, 154.6, 161.4, 192.0, 193.7.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm),

*t*R (minor) = 8.5 min, *t*R (major) = 22.8 min; 99% ee.

$[\alpha]_D^{23}$: -33.4 (*c* = 1.3, CHCl₃).

HRMS (ESI⁺) calcd for C₃₀H₂₄O₅NaCl₂, *m/z* 557.0898, found 557.0892.

Prepared according to the general procedure from **2** (0.105 mmol) and *p*-nitrocinnamaldehyde (0.2 mmol) to provide the title compound as yellow solid (30 mg, 54% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.35-1.39 (t, *J* = 7.1 Hz, 3H), 3.36-3.40 (dd, *J* = 3.2 Hz, 1H), 3.63-3.68 (m, 1H), 4.27-4.36 (m, 2H), 4.44 (s, 1H), 4.52-4.53 (d, *J* = 3.4 Hz, 1H), 5.18-5.21 (d, *J* = 10.3 Hz, 1H), 6.60 (s, 1H), 6.87-6.98 (m, 3H), 7.17-7.21 (t, *J* = 7.7 Hz, 1H), 7.50-7.52 (d, *J* = 8.4 Hz, 2H), 7.78-7.80 (d, *J* = 8.8 Hz, 2H), 8.26-8.28 (d, *J* = 8.3 Hz, 2H), 8.42-8.44 (d, *J* = 8.2 Hz, 2H), 9.39 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 34.2, 38.7, 40.6, 47.7, 63.4, 81.2, 117.2, 120.8, 121.4, 124.3, 124.4, 128.6, 128.7, 129.0, 130.2, 140.5, 144.9, 147.4, 148.1, 148.6, 148.6, 154.2, 161.1, 191.6, 193.0.

HPLC: Chiralpak OD-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL/min, λ = 254 nm),

*t*R (minor) = 30.9 min, *t*R (major) = 44.1 min; 99% ee.

[α]_D²³: -5.4 (c = 0.8, CHCl₃).

HRMS (ESI⁺) calcd for C₃₀H₂₄O₉NaN₂, *m/z* 579.1379, found 579.1385.

Prepared according to the general procedure from **2** (0.105 mmol) and 4-fluorocinnamaldehyde (0.2 mmol) to provide the title compound as light yellow solid (39.1 mg, 78% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.36 (t, *J* = 7.2 Hz, 3H), 3.32-3.36 (dd, *J* = 3.2 Hz, 1H), 3.50-3.55 (m, 1H), 4.20-4.28 (m, 2H), 4.35 (s, 1H), 4.42-4.43 (d, *J* = 3.2 Hz, 1H), 5.00-5.03 (d, *J* = 10.4 Hz, 1H), 6.59 (s, 1H), 6.83-6.89 (m, 2H), 6.97-6.99 (d, *J* = 7.6 Hz, 1H), 7.10-7.14 (t, *J* = 7.6 Hz, 1H), 7.20-7.22 (d, *J* = 8.4 Hz, 2H), 7.36-7.38 (d, *J* = 8.4 Hz, 2H), 7.49-7.53 (m, 4H), 9.33 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 34.3, 38.4, 40.7, 48.1, 63.0, 81.6, 117.1, 121.0, 121.4, 124.1, 128.7, 129.0, 129.1, 129.6, 129.8, 129.9, 130.3, 133.8, 135.9, 136.6, 139.9, 140.2, 148.7, 154.2, 161.6, 192.1, 193.6.

HPLC: Chiralpak OD-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 15.6 min, t_R (major) = 37.6 min; >99% ee.

$[\alpha]_D^{23}$: -42.3 (c = 1.2, CHCl_3).

HRMS (ESI^+) calcd for $\text{C}_{30}\text{H}_{24}\text{O}_5\text{NaF}_2$, m/z 525.2307, found 525.2310.

Prepared according to the general procedure from **2** (0.105 mmol) and 2-bromocinnamaldehyde (0.2 mmol) to provide the title compound as light yellow solid (47 mg, 75% yield) after silica gel chromatography (EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3): δ 1.25-1.29 (t, J = 7.2 Hz, 3H), 3.16 (br, 1H), 3.54-3.57 (m, 1H), 4.04-4.18 (m, 2H), 4.46-4.47 (d, J = 3.6 Hz, 1H), 4.69 (s, 1H), 5.64-5.66 (d, J = 9.6 Hz, 1H), 6.67 (s, 1H), 6.89-6.93 (m, 2H), 7.01-7.03 (m, 1H), 7.16-7.21 (m, 2H), 7.25-7.40 (m, 3H), 7.54-7.57 (t, J = 7.6 Hz, 1H), 7.71-7.76 (m, 3H), 9.43 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 13.8, 35.3, 38.9, 41.8, 46.1, 62.7, 79.9, 117.1, 120.8, 120.8, 123.4, 124.8, 125.8, 127.6, 128.7, 128.8, 129.0, 129.1, 130.6, 132.8, 133.9, 137.1, 139.8, 140.7, 148.6, 154.9, 162.6, 191.9, 196.0.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 25.2 min, t_R (major) = 43.9 min; 98% ee.

$[\alpha]_D^{23}$: 32.6 (c = 1.3, CHCl_3).

HRMS (ESI^+) calcd for $\text{C}_{30}\text{H}_{25}\text{O}_5\text{Br}_2$, m/z 625.0014, found 625.0011.

Prepared according to the general procedure from **2** (0.105 mmol) and 2-nitrocinnamaldehyde (0.2 mmol) to provide the title compound as yellow solid (25 mg, 45% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.27-1.30 (t, J = 7.2 Hz, 3H), 3.34-3.38 (m, 1H), 3.61-3.69 (dd, J = 3.2 Hz, 1H), 4.11-4.24 (m, 2H), 4.63-4.64 (d, J = 4 Hz, 1H), 4.82 (s, 1H), 5.78-5.80 (d, J = 10.2 Hz, 1H), 6.60 (s, 1H), 6.85-6.91 (m, 2H), 7.13-7.15 (t, J = 7.6 Hz, 1H), 7.38-7.40 (m, 2H), 7.48-7.50 (m, 1H), 7.60-7.70 (m, 2H), 7.88-7.90 (d, J = 7.6 Hz, 1H), 8.02-8.05 (d, J = 8 Hz, 1H), 8.13-8.18 (m, 2H), 9.28 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 35.2, 35.7, 42.1, 46.5, 62.9, 117.1, 120.7, 121.2, 124.7, 126.2, 126.3, 128.6, 128.9, 129.3, 129.9, 130.0, 133.8, 134.7, 136.2, 139.2, 148.5, 148.7, 149.3, 154.7, 162.0, 191.8, 195.9.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 18.6 min, t_R (major) = 29.1 min; 98% ee.

$[\alpha]_D^{23}$: 93.1 (c = 1.1, CHCl₃).

HRMS (ESI⁺) calcd for C₃₀H₂₄O₉NaN₂, m/z 579.1379, found 579.1378.

Prepared according to the general procedure from **2** (0.105 mmol) and 3-(naphthalen-2-yl)acrylaldehyde (0.2 mmol) to provide the title compound as white solid (49.8 mg, 88% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.36-1.40 (t, J = 7.2 Hz, 3H), 3.53-3.57 (dd, J = 3.7 Hz, 1H), 3.76-3.79 (m, 1H), 4.28-4.33 (m, 2H), 4.55 (s, 1H), 4.62-4.63 (d, J = 3.2 Hz, 1H), 5.26-5.28 (d, J = 10.4 Hz, 1H), 6.66 (s, 1H), 6.80-6.83 (t, J = 7.6 Hz, 1H), 6.89-6.91 (d, J = 8 Hz, 1H), 6.97-6.99 (d, J = 8 Hz, 1H), 7.09-7.13 (t, J = 7.6 Hz, 1H), 7.49-7.63 (m, 6H), 7.71-7.73 (d, J = 8.8 Hz, 1H), 7.84-7.87 (m, 2H), 7.92-7.94 (d, J = 8.4 Hz, 1H), 7.96-8.00 (m, 2H), 8.04-8.06 (d, J = 8.4 Hz, 2H), 9.35 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 34.3, 39.0, 40.6, 48.3, 63.1, 82.8, 117.0, 120.7, 121.7, 124.6, 126.2, 126.2, 126.5, 126.8, 126.8, 127.6, 127.7, 127.9, 128.0, 128.2, 128.5, 129.2, 129.3, 132.7, 133.3, 133.9, 135.5, 138.9, 140.8, 149.0, 154.9, 161.6, 192.2, 194.2.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 16.5 min, t_R (major) = 35.0 min; 99% ee.

$[\alpha]_D^{23}$: 31.3 (c = 1.7, CHCl₃).

HRMS (ESI⁺) calcd for C₃₈H₃₀O₅Na, m/z 589.1991, found 589.1989.

Prepared according to the general procedure from **2** (0.105 mmol) and 4-methoxycinnamaldehyde (0.2 mmol) to provide the title compound as colorless oil (30.5 mg, 58% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.31-1.35 (t, J = 7.2 Hz, 3H), 3.38-3.42 (dd, J = 3.7 Hz, 1H), 3.53-3.58 (m, 1H), 3.79 (s, 3H), 3.89 (s, 3H), 4.20-4.30 (m, 2H), 4.32 (s, 1H), 4.44-4.45 (d, J = 3.2 Hz, 1H), 4.98-5.00 (d, J = 10.4 Hz, 1H), 6.55-6.56 (d, J = 1.6 Hz, 1H), 6.79-6.83 (m, 1H), 6.85-6.87 (m, 1H), 6.88-6.90 (d, J = 7.2 Hz, 2H), 6.96-6.98 (d, J = 7.6 Hz, 1H), 7.04-7.06 (d, J = 8.4 Hz, 2H), 7.08-7.12 (m, 1H), 7.18-7.20 (d, J = 8.8 Hz, 2H), 7.46-7.48 (d, J = 8.8 Hz, 2H), 9.33 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 34.3, 38.1, 40.7, 48.7, 55.3, 55.4, 62.9, 76.7, 82.3, 114.4, 114.5, 117.0, 120.5, 121.8, 124.5, 128.4, 128.7, 129.0, 130.2, 133.4, 140.9, 148.9, 154.9, 158.9, 160.3, 161.6, 192.4, 194.2.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 14.2 min, t_R (major) = 42.9 min; 98% ee.

$[\alpha]_D^{23}$: -23.0 (c = 1.4, CHCl₃).

HRMS (ESI⁺) calcd for C₃₂H₃₀O₇Na, m/z 549.1889, found 549.1883.

Prepared according to the general procedure from **2** (0.105 mmol) and 2-methoxycinnamaldehyde (0.2 mmol) to provide the title compound as colorless oil (27.4 mg, 52% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.27-1.30 (t, J = 7.2 Hz, 3H), 3.38-3.40 (m, 2H), 3.92 (s, 3H), 3.97 (s, 3H), 4.12-4.26 (m, 2H), 4.42-4.43 (d, J = 3.2 Hz, 1H), 4.63 (s, 1H), 5.57-5.59 (d, J = 10.2 Hz, 1H), 6.61 (s, 1H), 6.82-6.89 (m, 4H), 6.96-6.98 (d, J = 12 Hz, 1H), 7.03-7.05 (d, J = 7.6 Hz, 1H), 7.11-7.19 (m, 3H), 7.26-7.27 (m, 1H), 7.42-7.44 (m, 1H), 7.62-7.65 (m, 1H), 9.35 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 32.9, 35.5, 41.0, 45.7, 55.4, 55.6, 62.4, 75.7, 116.9, 120.2, 120.3, 121.5, 122.1, 125.1, 126.5, 127.8, 127.9, 128.3, 128.6, 129.2, 129.9, 130.2, 140.2, 150.7, 155.2, 156.5, 156.8, 192.5, 196.1.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (minor) = 19.0 min, t_R (major) = 37.4 min; 99% ee.

$[\alpha]_D^{23}$: 15.5 (c = 1.2, CHCl₃).

HRMS (ESI⁺) calcd for C₃₂H₃₀O₇Na, m/z 549.1889, found 549.1892.

Prepared according to the general procedure from **2** (0.105 mmol) and 4-acetoxy-3-methoxycinnamaldehyde (0.2 mmol) to provide the title compound as colorless oil (44.5 mg, 69% yield) after silica gel chromatography (EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃): δ 1.32-1.36 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 3.41-3.43 (d J = 10.8 Hz, 1H), 3.56-3.62 (m, 1H), 3.91 (s, 6H), 4.23-4.31 (m, 2H), 4.33 (s, 1H), 4.52-4.52 (d, J = 2.8 Hz, 1H), 4.99-5.01 (d, J = 10 Hz, 1H), 6.63-6.65 (m, 2H), 6.82-6.88 (m, 2H), 6.96-6.98 (m, 2H), 7.05-7.18 (m, 5H), 9.37 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 20.7, 34.3, 38.7, 40.5, 48.1, 56.0, 56.1, 63.0, 82.4, 111.1, 112.5, 117.0, 119.1, 120.2, 120.8, 121.6, 122.7, 123.2, 124.6, 128.5, 136.9, 139.2, 140.1, 140.5, 140.6, 148.7, 151.6, 151.9, 154.6, 161.3, 168.9, 168.9, 192.2, 193.8.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 85/15, flow rate 1 mL/min, λ = 254 nm),

t_R (major) = 10.1 min, t_R (minor) = 23.7 min; >99% ee.

$[\alpha]_D^{23}$: 0.68 (c = 1.6, CHCl₃).

HRMS (ESI⁺) calcd for C₃₆H₂₄O₁₁Na, m/z 655.1216, found 655.1219.

4.6 Reference

[1] C. F. Nising, S. Brase, *Chem. Soc. Rev.* **2008**, 37, 1218.

- [2] a) Y. Tang, J. Oppenheimer, Z. Song, L. You, X. Zhang, R. P. Hsung, *Tetrahedron* **2006**, 62, 10785; b) Y.-L. Shi, M. Shi, *Org. Biomol. Chem.* **2007**, 5, 1499.
- [3] a) T. Shu, D.-W. Chen, M. Ochiai, *Tetrahedron Lett.* **1996**, 37, 5539; b) T. Tanaka, T. Kumamoto, T. Ishikawa, *Tetrahedron: Asymmetry* **2000**, 11, 4633.
- [4] a) L. S. Zu, S. L. Zhang, H. X. Xie, W. Wang, *Org. Lett.* **2009**, 11, 1627; b) H. Sunden, I. Ibrahim, G. L. Zhao, L. Eriksson, A. Cordova, *Chem.-Eur. J.* **2007**, 13, 574; c) E. Reyes, G. Talavera, J. L. Vicario, D. Bad á, L. Carrillo, *Angew. Chem., Int. Ed.* **2009**, 48, 5701; d) H. Li, J. Wang, T. E-Nunu, L. S. Zu, W. Jiang, S. H. Wei, W. Wang, *Chem. Commun.* **2007**, 507; e) P. Kotame, B. C. Hong, J. H. Liao, *Tetrahedron Lett.* **2009**, 50, 704; f) T. Kano, Y. Tanaka, K. Maruoka, *Tetrahedron* **2007**, 63, 8658; g) T. Govender, L. Hojabri, M. F. Matloubi, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, 17, 1763; h) S. Bertelsen, P. Diner, R. L. Johansen, K. A. Jorgensen, *J. Am. Chem. Soc.* **2007**, 129, 1536.
- [5] M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, 129, 3830.
- [6] a) C. Dittmer, G. Raabe, L. Hintermann, *Eur. J. Org. Chem.* **2007**, 5886; b) A. Merschaert, P. Delbeke, D. Daloze, G. Dive, *Tetrahedron Lett.* **2004**, 45, 4697; c) N. Saito, A. Ryoda, W. Nakanishi, T. Kumamoto, T. Ishikawa, *Eur. J. Org. Chem.* **2008**, 2759; d) E. Sekino, T. Kumamoto, T. Tanaka, T. Ikeda, T. Ishikawa, *J. Org. Chem.* **2004**, 69, 2760.
- [7] a) L. J. Wang, X. H. Liu, Z. H. Dong, X. Fu, X. M. Feng, *Angew. Chem., Int. Ed.* **2008**, 47, 8670; b) Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2010**, 132, 4056.
- [8] Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagishi, T. Fujioka, K. Mihashi, K.

- Mizuki, L. M. Cosentino, K. Fowke, S. L. Morris-Natschke, K.-H. Lee, *Tetrahedron* **2001**, 57, 1559.
- [9] a) C. Liu, X. Zhang, R. Wang, W. Wang, *Org. Lett.* **2010**, 12, 4948; b) X. Zhang, S. Zhang, W. Wang, *Angew. Chem. Int. Ed.* **2010**, 49, 1481.
- [10] R. Rios, H. Sunden, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2007**, 48, 2181.