TALLINN UNIVERSITY OF TECHNOLOGY
DOCTORAL THESIS
10/2019

Organocatalytic Asymmetric Michael Addition to Cyclopropyl Derivatives

KÄRT REITEL

TTÜ PRESS

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This dissertation was accepted for the defence of the degree 13/02/2019

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Defence of the thesis: 15/03/2019, Tallinn

Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for doctoral or equivalent academic degree.

Kärt Reitel

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ISSN 2585-6898 (publication)
ISBN 978-9949-83-399-3 (publication)
ISSN 2585-6901 (PDF)
ISBN 978-9949-83-400-6 (PDF)

TALLINNA TEHNIKAÜLIKOOL
DOKTORITÖÖ
10/2019

Tsüklopropaani derivaatide asümmeetriline organokatalüütiline Michaeli liitumisreaktsioon

KÄRT REITEL

Contents

List of Publications

The list of author's publications, on the basis of which the thesis has been prepared:

I Reitel, K.; Lippur, K.; Järving, I.; Kudrjašova, M.; Lopp, M.; Kanger, T. Asymmetric Aminocatalytic Michael Addition of Cyclopropane-Containing Aldehydes to Nitroalkenes. *Synthesis*, **2013**, *45*, 2679-2683.

II Kaasik, M.; Noole, A.; Reitel, K.; Järving, I.; Kanger, T. Organocatalytic Conjugate Addition of Cyclopropylacetaldehyde Derivatives to Nitro Olefins: en Route to β- and γ-Amino Acids. *European Journal of Organic Chemistry*, **2015**, *8*, 1745-1753.

III Reitel, K.; Kriis, K.; Järving, I.; Kanger, T. Study of asymmetric organocatalyzed [3+2] annulation of cyclopropenone and β-ketoester *Chemistry of Heterocyclic Compounds*, **2018**, *54*, 929-933.

Author's Contribution to the Publications

Contribution to the papers in this thesis are:

I Planning and carrying out of all of the experiments, characterization of the obtained products, and a major role in the manuscript preparation.

II Planning and carrying out of some of the experiments, characterization of some obtained products, and a minor role in the manuscript preparation.

III Planning and carrying out of all of the experiments, characterization of the obtained products, and a major role in the manuscript preparation.

Introduction

Organocatalysis has received a lot of attention in organic synthesis and in addition to other catalytic systems due to the advantages of these processes in terms of synthetic efficiency and sustainability[1]. Small enantiopure molecules are utilized as catalysts to achieve the target synthesis in a short and stereoselective manner in a wide range of solvents and for a broad scope of substrates.

An organocatalytic Michael reaction is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound, catalyzed by primary or secondary amines via enamine intermediates. During the reaction a new carbon-carbon bond is formed.[2] In year 1963 Stork et al[3] demonstrated the use of enamines in stoichiometric reactions for α-functionalization of carbonyl compounds. The first catalytic approach to enamines was published in the early 1970's simultaneously by two groups: Hajos and Parrish,[4] and Eder, Sauer and Wiechert.[5]

There are several methods for generating a new carbon-carbon bond, but the development of an asymmetric organocatalytic conjugate addition remains an important challenge in organic synthesis.

This doctoral thesis is focused on an enantioselective organocatalyzed Michael addition applied for the synthesis of a cyclopropyl group containing compounds. A cyclopropane ring fragment can be found in many natural and synthetic compounds, and exhibit a wide range of biological activities. In the course of the work a general and straightforward method for the synthesis of β- and γ-amino acid precursors was developed. The reaction allowed the one-step introduction of a cyclopropane ring and two different nitrogen-containing functional groups into the target compound (Publications I and II). Additionally, the selective [3+2] annulation of cyclopropenones was investigated in order to afford chiral butenolides (Publication III).

Abbreviations

Ar	aryl
Asn	Asparagine
Asp	L-aspartic acid
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bu	butyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
d.r.	diastereomeric ratio
ee	enantiomeric excess
e.r.	enantiomeric ratio
EWG	electron-withdrawing group
GABA	γ-aminobutyric acid
Gln	Glutamine
HFIP	hexafluoroisopropanol
Et	ethyl
LG	leaving group
Me	methyl
MIRC	Michael-initsiated ring closure

*n*Bu	normal butyl
NMM	*N*-methylmorpholine
*i*Pr	isopropyl
*n*Pr	normal propyl
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
pK_a	acid dissociation constant at logarithmic scale
Pro	L-proline
PPTS	pyridinium *para*-toluene sulfonate
PTC	phase transfer catalyst
p-TsOH	*para*-toluenesulfonic acid
R	unspecified substituent
rt	room temperature
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAI	tetrabutylammonium iodide
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethysilyl
TClCA	trichloroisocyanuric acid
TEA	triethylamine
TFA	trifluoroacetic acid
TEMPO	2,2,6,6-tetramethylpiperidinoxy
THF	tetrahydrofuran
TMS	trimethylsilyl
TS	transition state

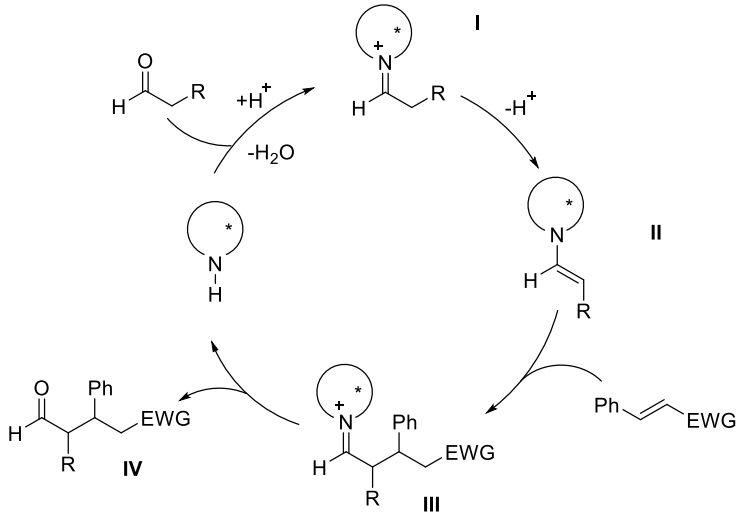
1 Literature overview

The Michael addition of aldehydes to nitroalkenes is of particular interest because of the valuable synthetic intermediates γ-nitro carbonyl compounds[6] that are generated. The nitro group allows various asymmetric transformations into other functional groups leading to a variety of useful building blocks, such as chiral γ-amino alcohols[7], γ-amino acids[8], γ-butyrolactones[9] and substituted pyrrolidines[10,11].

The literature overview covers the Michael reaction catalyzed by proline-based organocatalysts following the enamine pathway.

1.1 Aminocatalytic Michael reaction

The Michael reaction is a powerful tool in organic chemistry; during the Michael addition a new carbon-carbon bond is formed. The reaction itself is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound or to a double bond connected to a strongly electron-withdrawing substituent. In the asymmetric aminocatalytic Michael reaction, a chiral catalyst is used and the catalytic system involves enamine or iminium activation with chiral secondary or primary amines (Scheme 1).[12] In the catalytic cycle an iminium ion **I** is generated by the reversible reaction between a chiral amine catalyst and a carbonyl compound. The formation of nucleophilic enamine intermediate **II** occurs because of the deprotonation at the α-position of the iminium ion, due to the increase of C-H acidity. Then a nucleophilic addition of the obtained enolate equivalent **II** to an electron poor double bond connected with a strongly electron-withdrawing substituent affords an α-substituted iminium ion **III**. After hydrolysis the Michael adduct **IV** is formed and the regenerated catalyst is ready to start a new catalytic cycle.



Scheme 1. *Catalytic cycle of the Michael reaction.*

The stereochemistry of the product is determined by facial selectivity of the nucleophilic attack of the enamine and can be explained by the limiting "electronic" or "steric" transition states (Figure 1). The geometry of the enamine (*E* or *Z*) is determined by the catalyst structure. The *E*-enamine is thermodynamically favored due to steric shielding and is predominant unless other interactions favor the *Z*-enamine (Figure 1).

The relative size of the two sides of the *E*-enamine depends on the carbonyl substituent X. The hydrogen from aldehyde starting material leads to the formation of the relatively more stable *anti*-rotamer; in the case of ketones, the less-hindered moiety is the double bond, which gives *syn*-rotamer, as long as other interactions are not involved. However, the stabilizing H-bonding in the transition state can force the formation of *syn*-rotamer in the case of aldehyde and *anti*-rotamer in the case of ketones.[12]

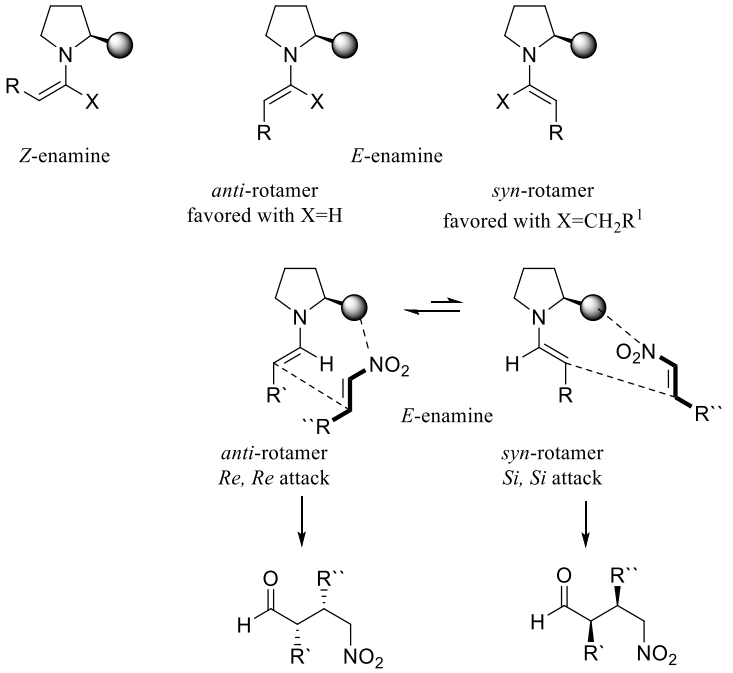
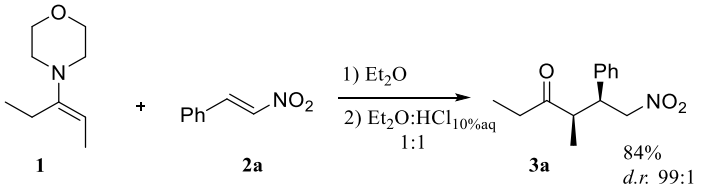


Figure 1. *The geometry of the enamine and transition states.*[12]

It may be concluded that in the catalytic enantioselective conjugate addition the preferred diastereoselectivity and enantioselectivity depend on electronic or steric interactions and the absolute configuration of the chiral catalyst.

In 1981 the Michael addition of achiral enamines with aliphatic, alicyclic and arylsubstituted nitro olefins affording γ-nitroketones in good yields and excellent diastereoselectivities was published by Seebach and co-workers[13]. Morpholine was used to generate the (*E*)-enamine **1** (Scheme 2). To explain the excellent diastereoselectivity, they proposed a rule known as Seebach`s topological rule.[13] (This general rule is applicable to many donor-acceptor π-systems.)



Scheme 2. *Michael addition of (E)-enamine to (E)-nitro olefin.*

As shown in Figure 2, in aprotic media, under kinetic control, the preferred approach of two prochiral centers can be predicted (Figures 2a, 2b and 2c). All the existing bonds are staggered. The donor (enamine) (C=D)-bond is in a *gauche* (synclinal) arrangement between the (C=A) and the (C-H)-bonds of the acceptor (α,β-unsaturated system), with the H-atom, the smaller substituent on the donor component, in an anti (antiperiplanar) position with respect to the (C=A)-bond (Figure 2a). If the components can exist in (*E/Z*) (*anti*/*syn*)-isomeric forms (Figures 2b and 2c), the actual donor and acceptor atoms are situated close to each other (to minimize the charge separation or to allow for chelation of metal ions).

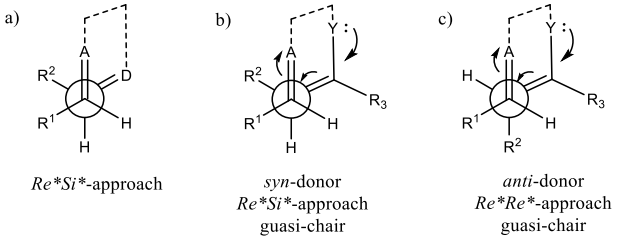


Figure 2. *Seebach`s topological rule.*[13]

In a Michael addition of enamine derived from the amine and carbonyl group to nitro olefin, the enamine double bond is in a *gauche* arrangement between the C=C and C-H bond (Figure 3). As the donor (enamine) and acceptor (α,β-unsaturated system) atoms are situated close to each other, the bigger substituent on enamine is an antiperiplanar position with respect to the C=A bond (Figure 1c), leading to the *Re, Re* approach and affording *syn* product.

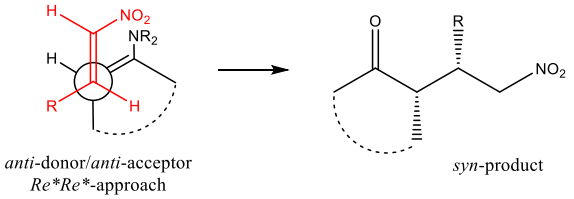
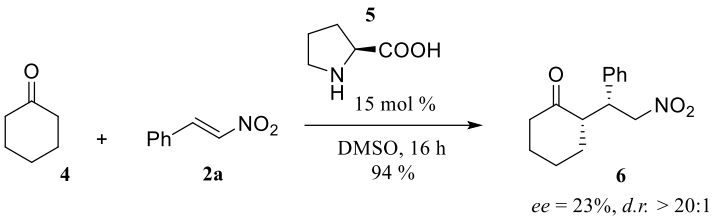


Figure 3. *Seebach`s topological rule for a Michael addition of enamine to the acceptor.*[13]

The rule may not hold when very bulky groups R^1, R^2 and substituents on Y are present or the protic solvent is used an anti- rather than *gauche*-relationship, allowing better solvation of the donor and acceptor heteroatoms, is kinetically preferred.

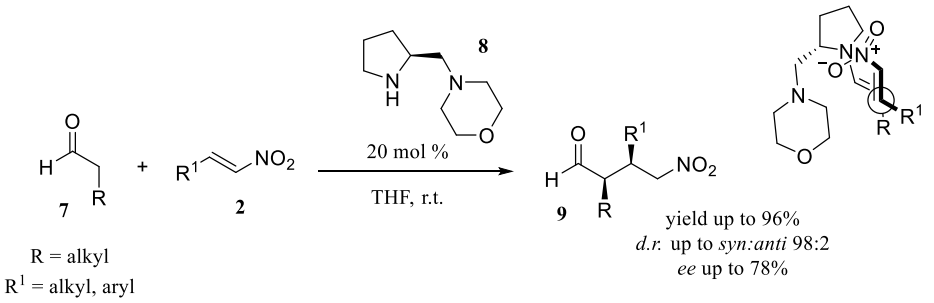
1.1.1 Asymmetric aminocatalytic Michael reaction

Over the years, a significant number of different catalytic systems for a Michael reaction have been used[14]; in 2001 the organocatalytic version of a Michael reaction was developed independently by List et al[15] and Betancourt and Barbas III[16]. The List group reported the proline-catalyzed Michael addition of unmodified ketones to nitro olefins with modest enantioselectivities (Scheme 3).[14]



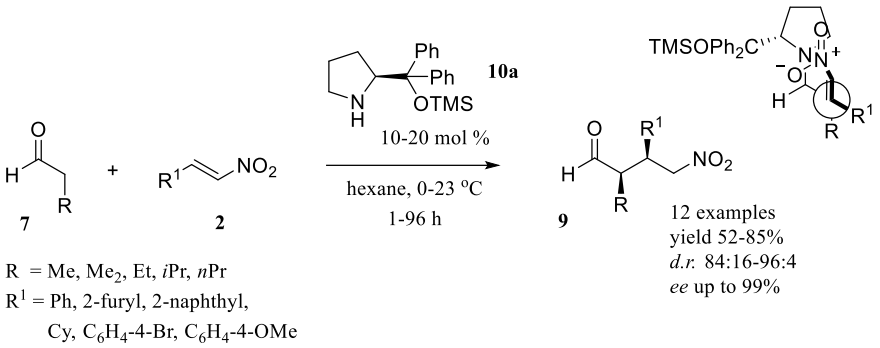
Scheme 3. *An L-proline **5** catalyzed Michael addition of ketones **4** to nitrostyrene **2a**.*

Only a few months later, Betancourt and Barbas III published an (*S*)-2-(morpholinomethyl)-pyrrolidine **8** catalyzed Michael addition of aldehydes **7** to nitro olefins **2** (Scheme 4).[16] The reaction proceeded in good yield (up to 96%) and in a high *syn*-selective manner (*d.r.* up to 98:2). They explained the high obtained *syn*-selectivity through an acyclic synclinal model, in which there are favorable electrostatic interactions between the partially positive nitrogen of the enamine and the partially negative nitro group in the transition state. The approach of the nitro olefin from the less hindered *Si*-face of the enamine would produce the observed stereochemistry.[16] The proposed transition state is depicted in Scheme 4.



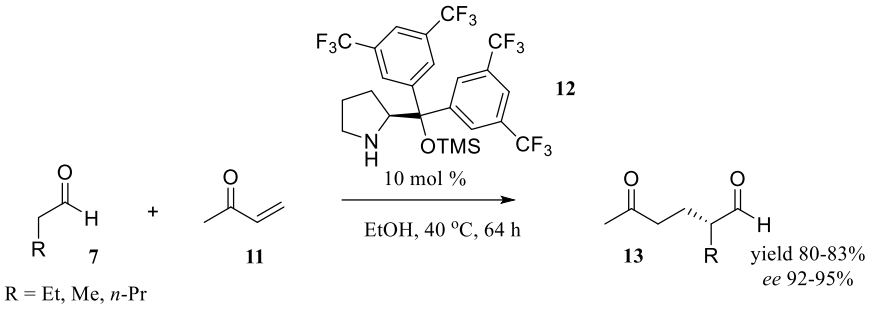
Scheme 4. *(S)-2-(morpholinomethyl)-pyrrolidine **8** catalyzed Michael addition of aldehydes to nitro olefins.*

In 2005 Hayashi et al[17] reported a diphenylprolinol silyl ether **10a** catalyzed asymmetric Michael addition of aldehydes **7** and nitro alkenes **2** (Scheme 5); the adducts **9** were obtained in nearly optically pure forms in almost all cases. The introduction of a siloxy group into the proline structure led to an increase in the catalytic activity, allowing a decrease in catalyst loading and shorter reaction times. The increase in catalytic activity can be explained by the effective formation of the corresponding enamine without the generation of the aminal, which would be formed in the case of diphenylprolinol. And the bulky diphenylsiloxymethyl group on the pyrrolidine ring promoted the selective formation of the *anti*-enamine and selective shielding of the *Re*-face of the enamine double bond.



Scheme 5. *Catalytic asymmetric Michael reaction of aldehydes **7** and nitro alkenes **2**.*

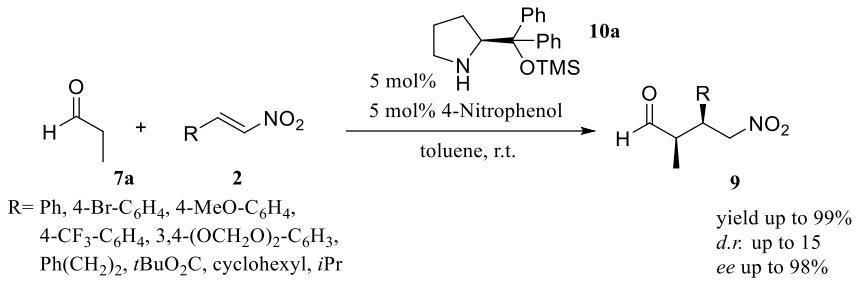
At the same time Jørgensen et al discovered that diphenylprolinol silyl ether is an effective organocatalyst for the Michael addition of aldehydes **7** to methylvinyl ketone **11**.[18] They found that *S*-diarylprolinol silyl ether **12** catalyzed a Michael addition of aldehydes **7** to methylvinyl ketone **11** is highly stereoselective and all products were obtained in high yields and excellent enantiomeric excesses (Scheme 6).



Scheme 6. *Organocatalyzed enantioselective Michael addition of aldehydes **7** to methylvinyl ketone **11**.*

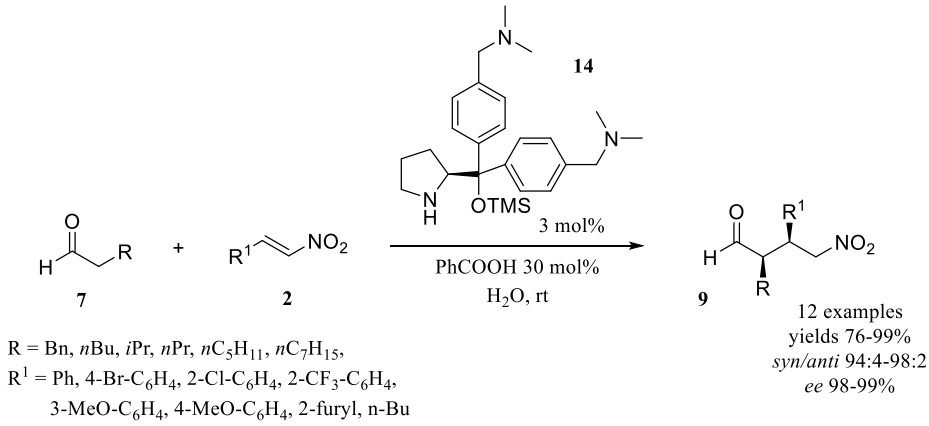
They also investigated the effect of catalyst structure on the enantioselectivity of the reaction. They concluded that the asymmetric induction observed with catalyst *S*-diarylprolinol silyl ether completely relies on selective enamine conformation and steric shielding. The bulky aryl and silyl substituents of the catalyst can efficiently shield the *Re*-face of the favored *E*-configuration of the enamine leading to a *Si* attack.

Seebach and Hayashi[19] investigated various acidic additives in the Michael addition of propanal **7a** to β-nitrostyrene catalyzed by prolinol ether **10a**. Their results showed that 4-nitrophenol acts as the best additive in the addition of propanal to a series of different nitro alkenes, causing rate accelerations (reaction time decrease from 6 h to 15 min when nitrostyrene **2a** was used), with retention of excellent stereoselectivity (Scheme 7).



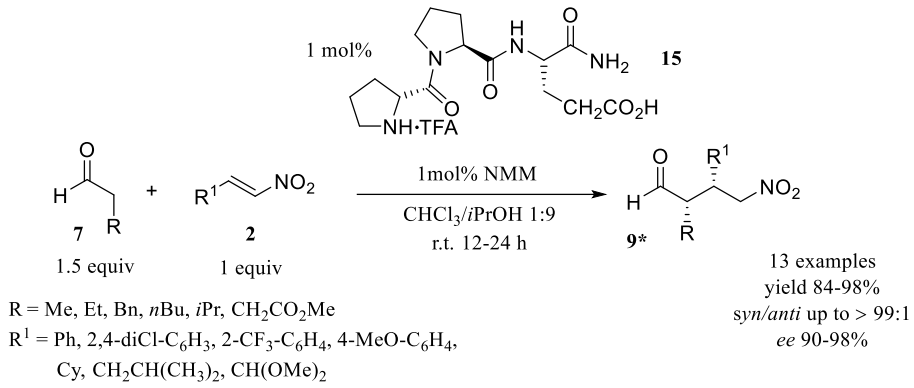
Scheme 7. The Michael addition in the presence of 4-nitrophenol.

Ni et al[20] designed a new water-soluble recyclable and highly active organocatalyst **14** (Scheme 8). The reaction was carried out under mild conditions using 3 mol% of catalyst. The catalytic system was easily recovered and reused at least six times without significant loss of catalytic activity or stereoselectivities.



Scheme 8. *Diarylprolinol silyl ether salt catalyzed Michael addition on water.*[21]

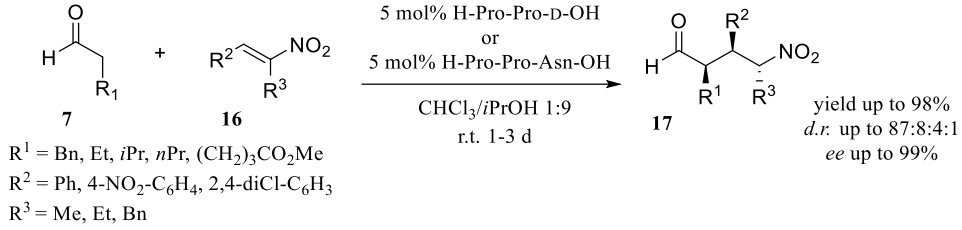
Wennemers et al[22] used the TFA salt of their tripeptide catalyst H-D-Pro-Pro-Xaa-NH_2 **15** (Xaa=acidic amino acid) in the Michael addition of aliphatic aldehydes to nitro alkenes (Scheme 9). They showed that carboxylic acid plays a crucial role in coordinating and thereby orienting the nitro olefin into a position that allows for the excellent stereochemical induction that was observed for peptidic catalyst. Also the D-Pro-Pro motif was the major contributor to the high asymmetric induction of peptidic catalysts of the type H-D-Pro-Pro-Xaa-NH_2 in which Xaa is an amino acid with a carboxylic acid in the side chain.



Scheme 9. *Michael addition reactions of aldehydes to nitro olefins catalyzed by tripeptide TFA salt* ***15****.*

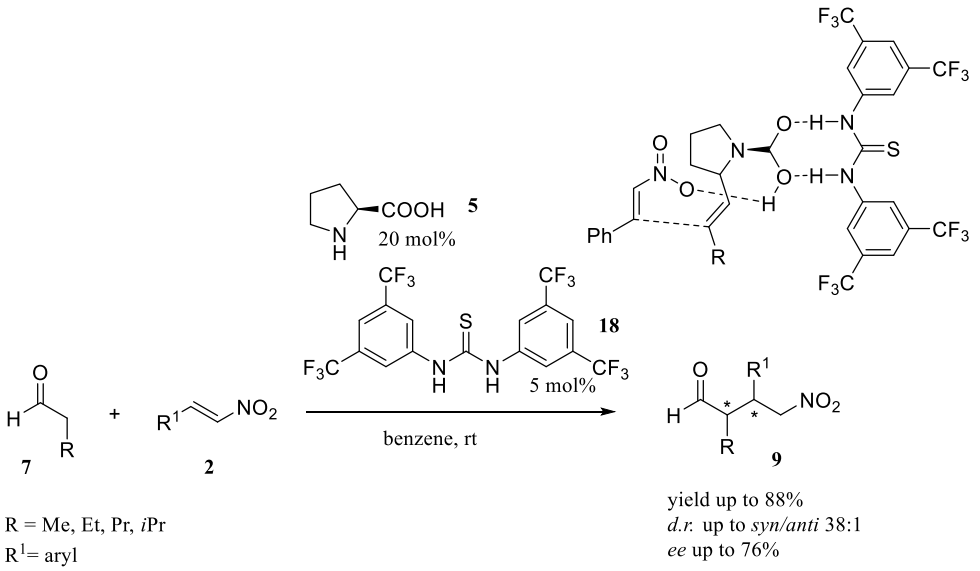
They investigated the additive effects on the catalytic efficiency of peptides. The obtained results showed that no additives were necessary for the high catalytic efficiency of this tripeptide catalytic system.

Wennemers and Duschmalé[23] used tripeptides of the type Pro-Pro-Xaa as catalysts for a Michael addition of aldehydes **7** to α,β-disubstituted nitro olefins **16**. In the presence of 5 mol% of either H-Pro-Pro-D-Gln-OH or H-Pro-Pro-Asn-OH, γ-nitroaldehydes **17** bearing three consecutive stereogenic centers were obtained in good to excellent yields, diastereoselectivities, and enantiomeric excesses (Scheme 10).



Scheme 10. *Tripeptide catalyzed Michael addition of aldehydes to α,β-disubstituted nitro olefins.*

Eymur and Demir[24] used a proline-thiourea self-assembled organocatalyst for the enantioselective Michael addition of aldehydes **7** to nitro alkenes **2** (Scheme 11). In the presence of 20 mol% of L-proline **5** and 5 mol% of thiourea **18**, moderate to good enantioselectivity and high *syn*-selectivity were obtained in both branched and unbranched aliphatic aldehydes. When the reaction was carried out without the thiourea additive, the reaction was very slow (36 h, conversion ≤ 6%), with low stereoselectivity.



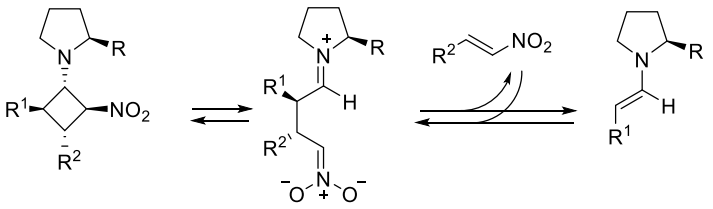
Scheme 11. *Achiral thiourea **18** and L-proline **5** catalyzed Michael reaction.*

To explain higher syn-diastereoselectivities and enantioselectivities with respect to proline, they proposed a TS (Scheme 11). Due to hydrogen bonding between thiourea and carboxylic group of proline the selective formation of the anti-enamine is favored and its *Re*-face is shielded, leading to a *Si* attack.

Various other chiral proline-based organocatalysts[2,25] have been developed and screened for the Michael addition of aldehydes to nitro alkenes. As a powerful tool creating a new carbon-carbon bond, the aminocatalyzed Michael addition will remain developing field of research.

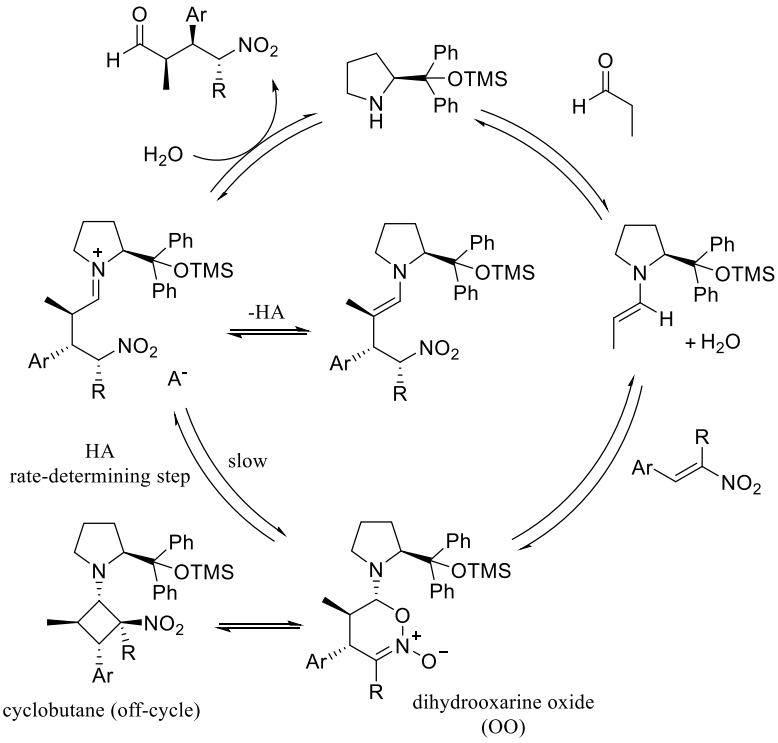
1.1.2 Revised mechanism for the Michael addition of aldehydes to nitroalkenes catalyzed by diaryl prolinol silyl ether

Mechanistic studies and the origin of stereoselectivity in the α-functionalization of aldehydes have been investigated by several research groups.[19,26] Seebach and Hayashi[19] investigated an organocatalyzed Michael addition of aldehydes to nitroalkenes, *in situ* NMR studies led to the identification of a stable cyclobutane species, existing as a single diastereomer. They proposed that cyclobutane is an off-cycle resting state of the catalyst, by which the zwitterion intermediate is removed from the catalytic cycle resulting from a reversible attack of the enamine on the nitro olefin (Scheme 12).



Scheme 12. *The cyclobutane is an off-cycle resting state of the catalyst and reversibility of the formal [2 + 2] cycloaddition.[19]*

Pihko et al[27] published the revised mechanism for the Michael addition of aldehydes to nitroalkenes catalyzed by diaryl prolinol silyl ethers. They proposed that the dihydrooxarine oxide (OO) is the key intermediate in an organocatalytic Michael addition of aldehydes to nitroalkenes (Scheme 13). They demonstrated that the sluggish reaction rates observed in reactions with α-alkyl-substituted nitroalkenes are in fact due to slow protonation of the OO intermediate and not a result of the intrinsically lower reactivities of the nitroalkenes (Scheme 13).



Scheme 13*. Revised mechanism for the Michael addition of aldehydes to nitroalkenes catalyzed by diphenylprolinol silyl ether.*[27]

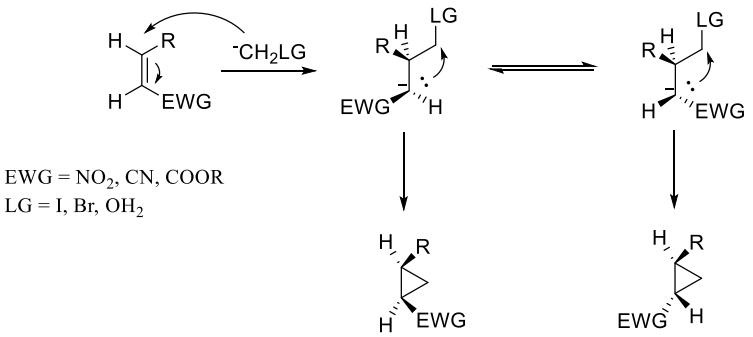
In conclusion, dihydrooxarine oxides (OO) are key on-cycle intermediates in the Michael additions of aldehydes to nitroalkenes catalyzed by diaryl prolinol ethers.

1.2 Synthesis of cyclopropane ring-containing amino acid precursors

The highly strained cyclopropane moiety is an important motif in many biologically active compounds.[28] Several methods have been developed to obtain chiral cyclopropane ring-containing compounds, such as the Simmons–Smith reaction[29], using a transition metal-catalyzed reaction starting from carbene intermediates[30] or organocatalysis.[31] This chapter will give a short overview of the use of organocatalytic Michael-initiated ring closure and the Kulinkovich reaction as a method of choice.

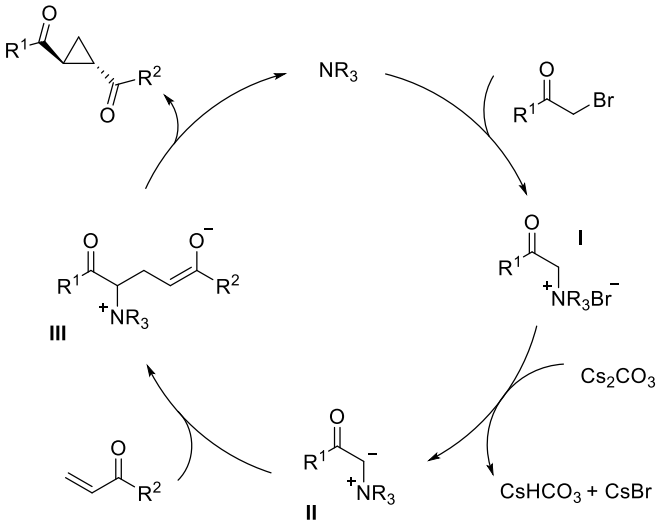
1.2.1 Michael-initiated ring closure (MIRC)

The Michael-initiated ring-closing reaction is an efficient tool for the synthesis of cyclopropanes.[32] Using chiral auxiliaries linked to the Michael acceptor has been the choice for asymmetric induction;[33] recently the growing popularity of organocatalysis has merged: enantiomeric H-bond, amino- and PTC-catalysts have been used to achieve high enantioselectivity of the cyclization. Cyclopropanation reactions involving a conjugate addition to an electrophilic alkene to produce an enolate, which then subsequently undergoes an intramolecular ring closure, are defined as Michael-initiated ring-closure (MIRC) reactions (Scheme 14).[33]



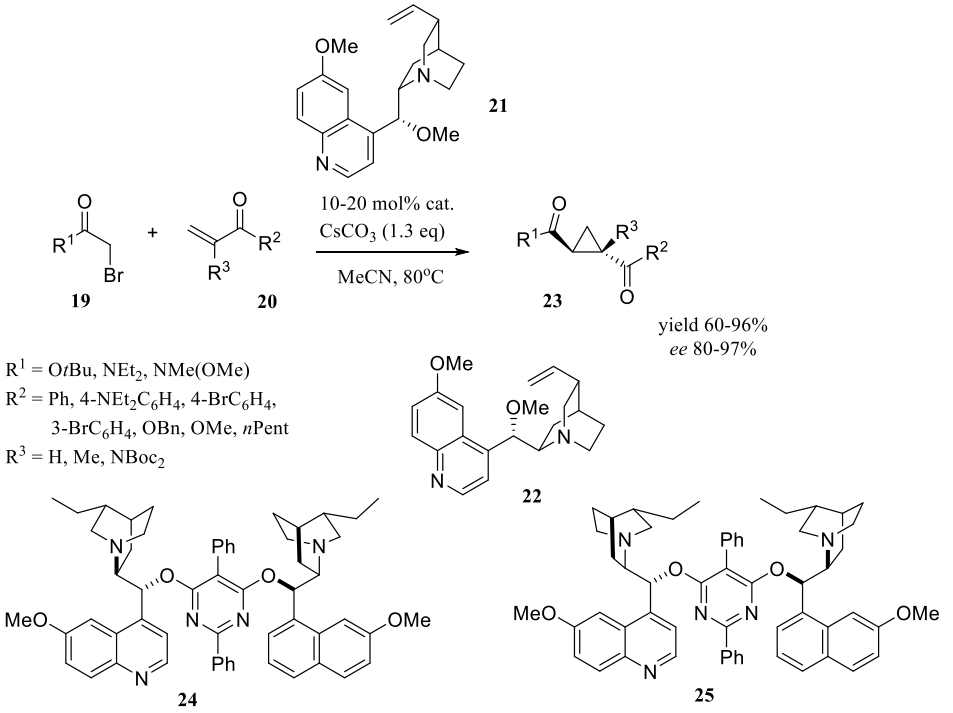
Scheme 14 . *Michael-initiated ring-closure cyclopropanation reaction.*

Gaunt et al[34] reported an enantioselective organocatalytic cyclopropanation reaction. During the reaction an α-bromo carbonyl compound undergoes S_N2 displacement with tertiary amine catalyst to form a quaternary ammonium salt **I**: deprotonation with base will afford the ylide **II**, which undergoes conjugated addition to alkene to form enolate **III**, and intramolecular cyclization generates the cyclopropane (Scheme 15).



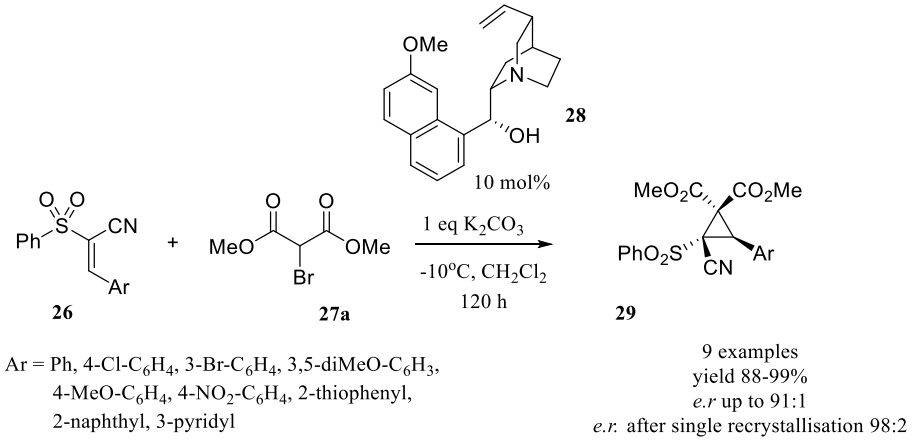
Scheme 15. *Proposed catalytic cycle.*

The reaction was carried out in acetonitrile in the presence of 10-20 mol% of the quinine or quinidine series of cinchona alkaloid as catalysts. Cyclopropane derivatives **23** were obtained in high yield and enantioselectivity (Scheme 16). The opposite enantiomer was also synthesized by using the quinidine-derived catalyst. Using acetamide as a Michael donor afforded cyclopropane in excellent yield and 93% *ee*.



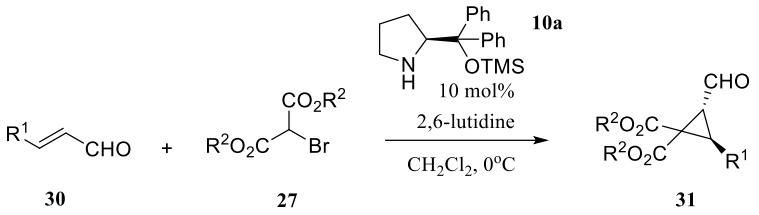
Scheme 16. *Enantioselective organocatalytic cyclopropanation.*

Aitken et al[35] showed that cyanosulfone **26** can be used as a Michael acceptor in the MICR cyclopropanation with methyl bromomalonate **27a**. Using 10 mol% of bifunctional cinchona alkaloid **28**, they obtained highly functionalized cyclopropane derivatives **29** in high yields and enantioselectivities (Scheme 17).



Scheme 17. *Asymmetric cyclopropanation of conjugated cyanosulfones.*

Wang et al reported the synthesis of chiral diester substituted cyclopropanes **31** from α,β-unsaturated aldehydes **30** with bromomalonate **27**.[36] The reaction was catalyzed by chiral diphenylprolinol TMS ether **10a** in the presence of 2,6-lutidine. Cyclopropanecarbaldehydes **31** were obtained in high enantio- and diastereo-selectivities (Scheme 18).

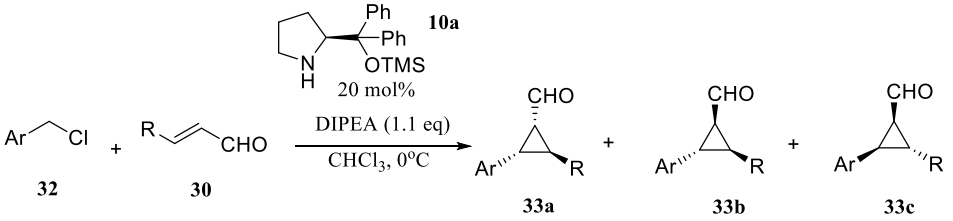


R^1 = Ph, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-ClC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 2-$MeOC_6H_4$, 2-furanyl, Et, *n*-C_5H_{11}
R^2 = Me, Et, *i*Pr, Bn

16 examples
yield 42-95%
ee 90-98%
d.r. >30/1

Scheme 18. *Diphenylprolinol TMS ether catalyzed cyclopropanation.*

Two groups simultaneously published a method for the enantioselective cyclopropanation of enals using benzyl chlorides as nucleophilic and electrophilic reagents.[37,38] In general, benzyl halides are considered to be an electrophilic species, but adding strong EWGs, such as –NO_2, on the *ortho* and/or *para*-positions of the aromatic ring changes the reactivity as a result of strong inductive and resonance effects, and in the presence of a weak base they could act as nucleophiles. Meazza et al[38] reported the enantioselective cyclopropanation of enals using benzyl chlorides **32** as bifunctional reagents; cyclopropane derivatives **33a-c** were obtained in good yields and enantioselectivities and with moderate to excellent diastereoselectivities (Scheme 19).



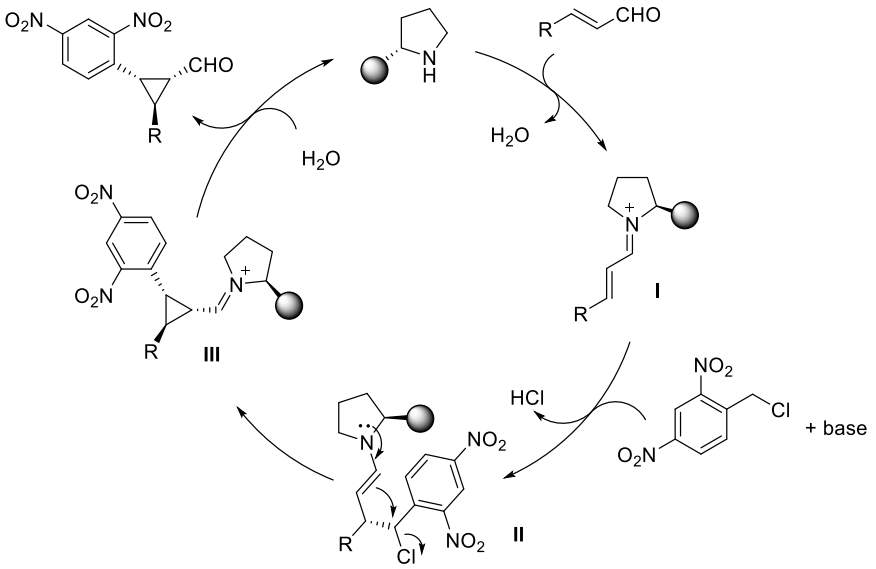
Ar = 2,4-$(NO_2)_2C_6H_3$, 2-NO_2-4-CF_3-C_6H_3
R = Me, Et, *n*Pr, nC_7H_{15}, CO_2Et, Ph, 4-CN-C_6H_4, 4-NO_2-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4,

16 examples
yield for major product 47-99%
ee up to 99/95/98
d.r. up to 8:3:1

Scheme 19. *Asymmetric cyclopropanation catalyzed by diphenylprolinol silyl ether* ***10a.***

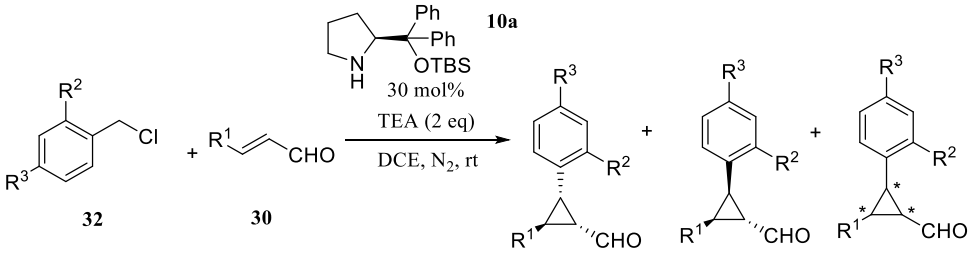
Screening of the substrate bearing other aromatic substituents showed that the cyclopropanation reaction requires two strong EWGs on the aromatic ring of the benzylic chloride in order to enhance the acidity and nucleophilicity of the benzylic position. They also proposed a plausible catalytic cycle for asymmetric cyclopropanation (Scheme 20). The iminium ion **I** was generated by the reversible reaction between α,β-unsaturated aldehyde and chiral amine. The bulky group of catalyst shielded the *Si*-face of an

α,β-unsaturated iminium ion **I**. Intermediate **III** was formed by a nucleophilic attack of benzyl chloride predominantly on the *Re*-face of iminium ion **I** via a Michael addition, followed by an intramolecular ring-closing reaction between the enamine and the secondary alkyl chloride. After the hydrolysis of iminium ion **III** the desired product was formed and the catalyst was regenerated.



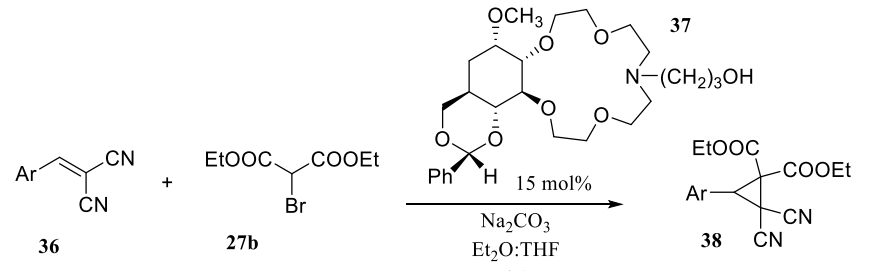
Scheme 20. *Plausible catalytic cycle for the enantioselective intermolecular cyclopropanation.*

Wang et al used diphenylprolinol TBS ether **10b** for the synthesis of chiral trisubstituted diarylcyclopropanecarbaldehydes **35a-c** from substituted benzyl chloride **32** and α,β-unsaturated aldehydes **30**.[37] The reaction was carried out under mild conditions using 30 mol% of diphenylprolinol TBS ether **10b** as a catalyst (Scheme 21). Trisubstituted diarylcyclopropane-carbaldehydes **35a-c** were obtained in good to high yields and excellent enantioselectivities.



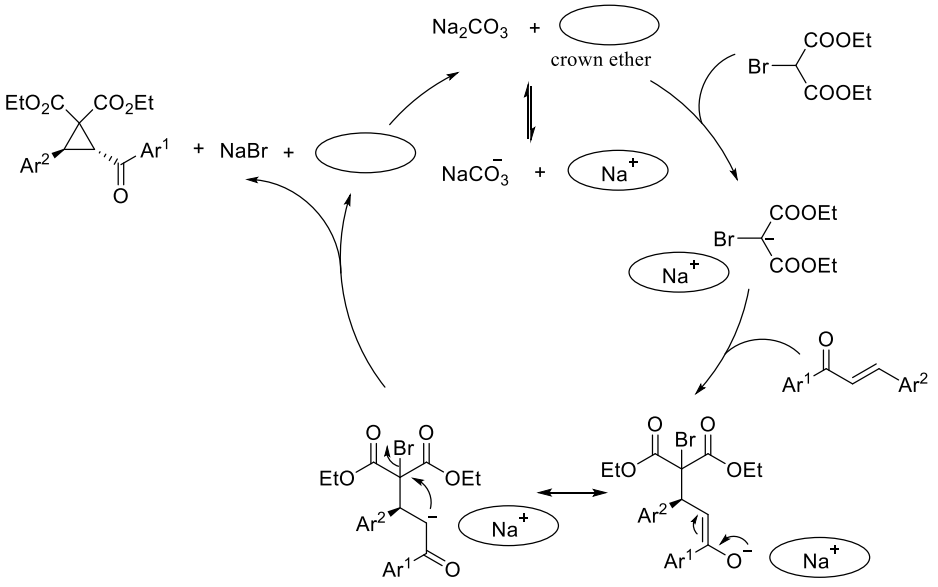
Scheme 21. *Diphenylprolinol TBS ether-catalyzed cyclopropanation.*

Rapi et al[39] reported the synthesis of cyclopropane derivatives **38** in high enantioselectivities using monosaccaharide-base chiral crown ether **37** as a phase transfer catalyst; four types of Michael acceptors were used: chalcones, 2-acrylidenemolonitriles, 2-acrylidene-1,3-indandiones and 2-benzylidene-1,3-diphenyl-1,3-propanediones. The reaction of benzylidenemalononitriles **36** with diethyl bromomalonate **27b** in the presence of 15 mol% of sugar-based crown ether **37** resulted in chiral cyclopropane derivatives **38** with modest to good yields and with variable enantioselectivities (Scheme 22). The proposed mechanism for the formation of *trans* product under a phase transfer catalyzed condition is depicted in Scheme 23.



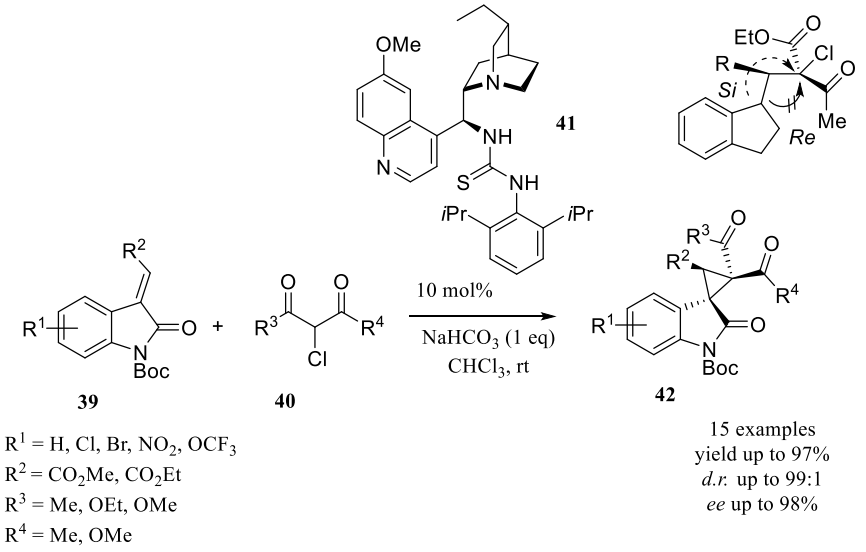
Ar = Ph, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 2-MeO-C_6H_4, 3-MeO-C_6H_4, 4-Me-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 2-NO_2-C_6H_4,3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2-$(CH_3)_2$N-C_6H_4, 1-Naphthyl, 2-Naphthyl, Piperonyl, 2-Furyl, 2-Thienyl

Scheme 22. *Crown ether catalyzed MIRC reaction of diethyl bromomalonate with benzylidenemalononitriles.*



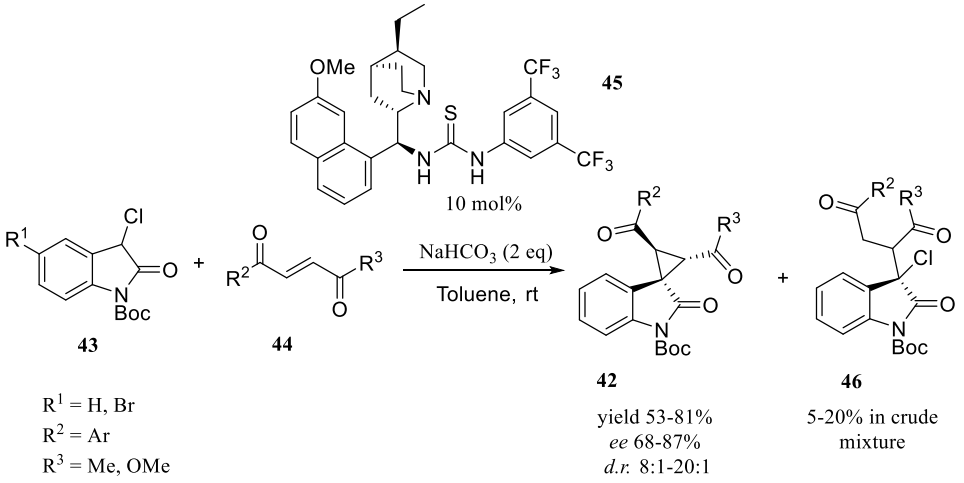
Scheme 23. *Proposed mechanism for the formation of trans-product.*

Our research group has previously investigated an enantioselective spiro-cyclopropanation reaction in collaboration with Prof. Malkov, the results of a Michael-initiated ring closure between oxindole derivative **39** (alkylidene oxindoles and 3-chlorooxindoles) and unsaturated α-halo-β-dicarbonyl compounds **40** (Scheme 24)[40] or α,β-unsaturated aldehydes[41] were reported.



Scheme 24. *Quinine-derived thiourea catalyzed spirocyclopropanation.*

Quinine-derived thiourea was the best for this reaction, providing high stereoselectivity in both cascade steps. *Si*-facial selectivity for the major diastereoisomer was observed. To broaden the scope of spirooxindoles **42**, a Michael-initiated ring closure cascade reaction between 3-chlorooxindole **43** and unsaturated 1,4-dicarbonyl **44** compounds was developed (Scheme 25).[42]

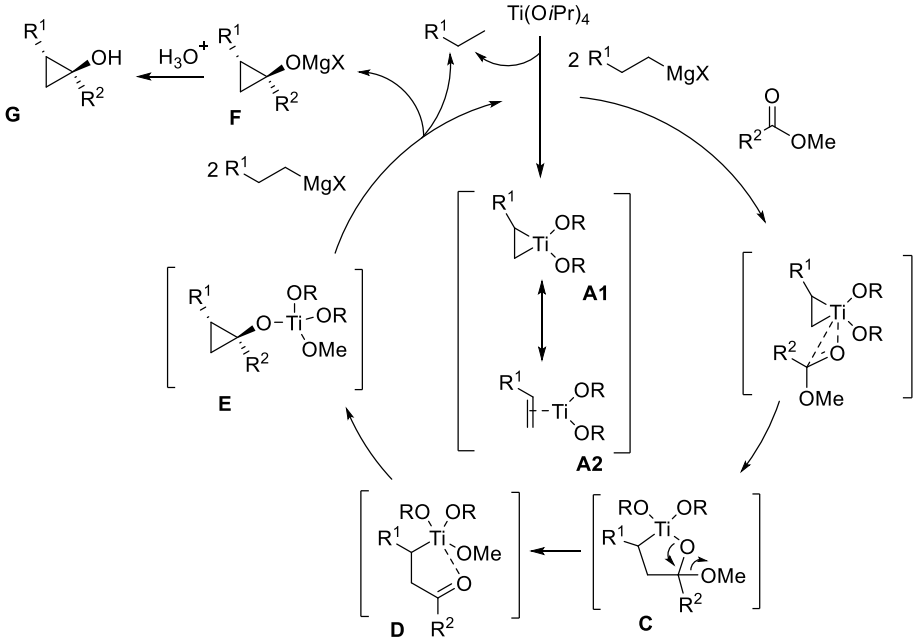


Scheme 25. *Michael-initiated ring closure.*

The chlorooxindole nitrogen atom was protected with Boc to increase the acidity of the C–H bond at C3 and provide the opportunity for the formation of additional H-bonds between the catalyst and the substrate. The spiro-products **42** were obtained in moderate yields and with very high diastereo- and enantioselectivities; in all cases, uncyclized Michael adduct was observed.

1.2.2 Kulinkovich reaction

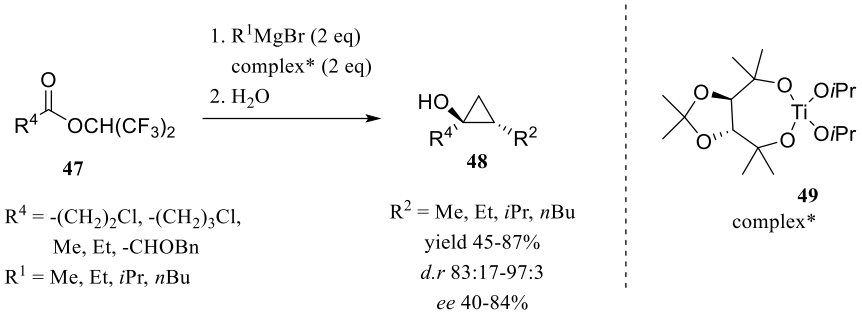
In the Kulinkovich reaction[43,44,45] a Grignard reagent reacts with titanium(IV)isopropoxide affording a thermally unstable diethyltitanium compound, which undergoes β-hydride elimination, leading to the formation of titanacyclopropane **A1** which then reacts with the ester, affording the intermediate **C**. The 1,2-insertion of the carbonyl group of the ester occurs at the less hindered carbon-titanium bond, because of unfavorable repulsion between the ester and R^1 group in the transition state. After elimination of an alkoxy group a β-metallated ketone **D** is formed. An intramolecular nucleophilic addition to the keto function leads to the formation of complex **E** titanium(IV)tetraalkoxide, which then reacts with 2 equivalents of Grignard reagent to regenerate a dialkoxytitanacyclopropane. The product **F** exists in the form of a magnesium alkoxide; after hydrolysis the expected product **G** is formed (Scheme 26).



Scheme 26. *Catalytic cycle of titanium-mediated cyclopropanation reaction.[45]*

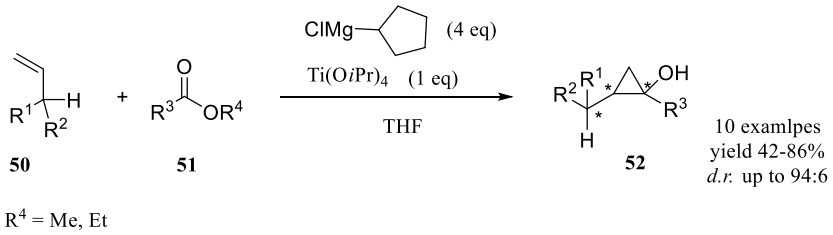
The first report on enantioselective Kulinkovich hydroxycyclopropanation was published by Corey et al;[46] enantiomeric excesses of up to 78% were achieved with the TADDOL-derived chiral catalyst; since then there has been progress in the development of asymmetric Kulinkovich hydroxycyclopropanation. Kulinkovich et al[47] investigated the dependence of the stereoselectivity of the cyclopropanation reaction of γ,γ-diphenyl-γ-butyrolactone and carboxylic esters **47** with alkylmagnesium bromides in

the presence of titanium(IV)TADDOLates **49**. An improved enantioselectivity of *cis*-1,2-disubstituted cyclopropanols **48** was obtained (Scheme 27).



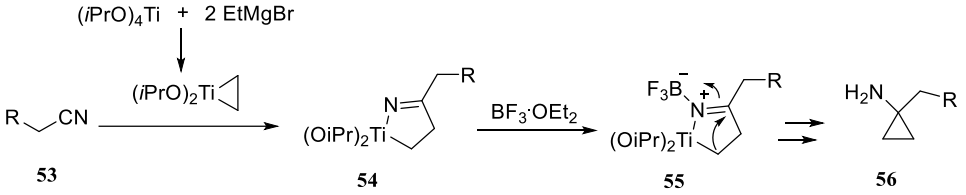
Scheme 27. *Cyclopropanation of trifluoroisopropyl alkanoates **47**.*

Recently Hurski et al[48] reported the diastereoselective hydroxycyclopropanation of alkenes **50** bearing a stereocenter in the allylic position. Cyclopropanols **52** were obtained with up to 94:6 diastereoselectivity and in good yields (up to 86%).



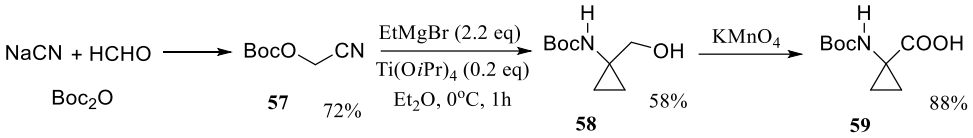
Scheme 28. *The diastereoselective synthesis of cyclopropanols **52** from alkenes **50**.*

There are two modifications from the Kulinkovich reaction for the direct synthesis of cyclopropylamines **56**. In the Kulinkovich-Szymoniak reaction[49] alkylnitriles **53** are used for the synthesis of primary cyclopropylamines **56** (Scheme 29).



Scheme 29. *Synthesis of cyclopropylamines from alkanenitriles.*

Szymoniak et al[50] demonstrated the application of the reaction by synthesizing Boc-protected aminocyclopropanecarboxylic acid (Scheme 30). Aminocyclo-propanecarboxylic acid (ACC), its ethyl-substituted derivative and (guanidinylmethyl)-substituted derivative are natural products and have important biological activities (Figure 4).[51]



Scheme 30. *Synthesis of Boc-protected aminocyclopropanecarboxylic acid* ***59****.*

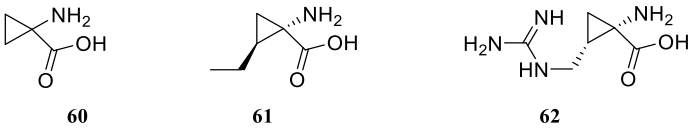
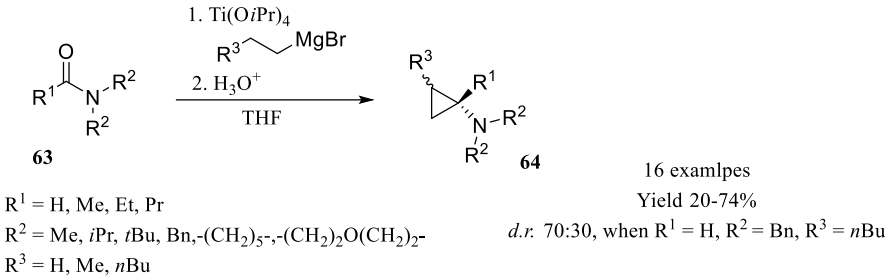


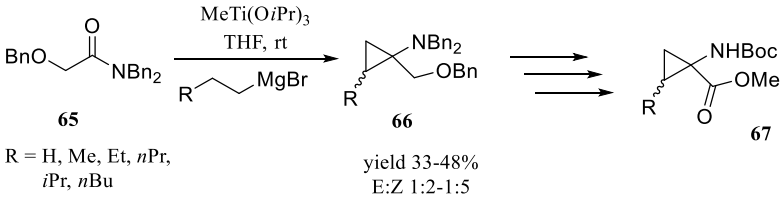
Figure 4. *1-aminocyclopropanecarboxylic acid and its naturally occurring derivatives.*

In the second reaction known as a Kulinkovich-de Meijere reaction,[52,53,54] *N,N*-dialkylamides and dialkylformamides **63** are used for the preparation of cyclopropylamines **64** (Scheme 31). The reaction required 1 equivalent of Ti(O*i*Pr)$_4$, as using standard Kulinkovich reaction conditions 0.2 equivalents afforded poor yield compared to the reaction, when a stoichiometric amount of titanium(IV)iso-propoxide was used.



Scheme 31. *Synthesis of cyclopropylamines from N,N-dialkylamides.*

Kordes et al[55] reported the synthesis of methanoamino acid starting from *N,N*-dibenzylcarboxamides **65**. The amide was cyclopropanated by the addition of various alkylmagnesium bromides, affording a mixture of two expected diastereomers **66** with moderate yield. Over several steps, the obtained cyclopropylamines were transformed to *N*-Boc-protected aminocyclo-propanecarboxylic acid methyl esters **67** (Scheme 32).



Scheme 32. *Cyclopropanation of N,N-dibenzylcarboxamides.*

They also developed a method for the synthesis of γ-aminobutyric acid (GABA) analog **74**. One example is depicted in Scheme 33.[55] The inclusion of two of the γ-aminobutyric acid backbone carbon atoms into a cyclopropane ring provides conformationally restricted GABA analogs (Figure 5); its structural analogues are of great interest for the treatment of diverse neurodegenerative disorders, including Parkinson's and Alzheimer's diseases.[56]

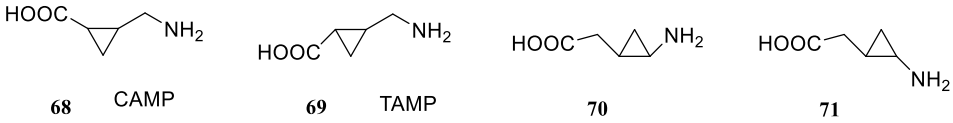
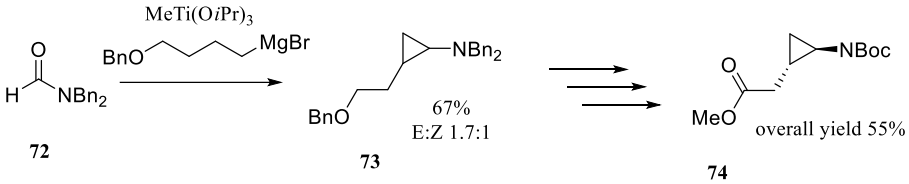
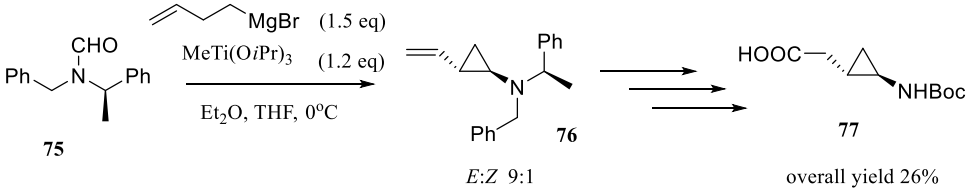


Figure 5. *Cis and trans isomers α,β-methano-GABA.*[57]



Scheme 33. *Synthesis of GABA analog.*

Aitken et al[57] reported a Kulinkovich–de Meijere reaction where they used a chiral amide **75**; the reaction showed high *trans* stereoselectivity, providing access to non-racemic *trans* cyclopropylamines **76**. Enantiomerically pure *N*-protected *trans*-β,γ-methano-GABA derivative **77** was synthesized over four steps (Scheme 34).



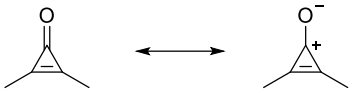
Scheme 34. *Synthesis of enantiomerically pure trans-β,γ-methano-GABA derivative* ***77****.*

1.2.3 Summary of the synthesis of cyclopropane ring-containing amino acid precursors

Amino acids containing cyclopropane moiety[58] in their backbone are versatile building blocks for the synthesis of bioactive compounds. However, the synthesis often requires several steps and enantiopure starting material, and thus the methods for the preparation of cyclopropane ring-containing compounds in enantiomerically pure form are still evolving.

1.3 [3+2] annulation of cyclopropenones

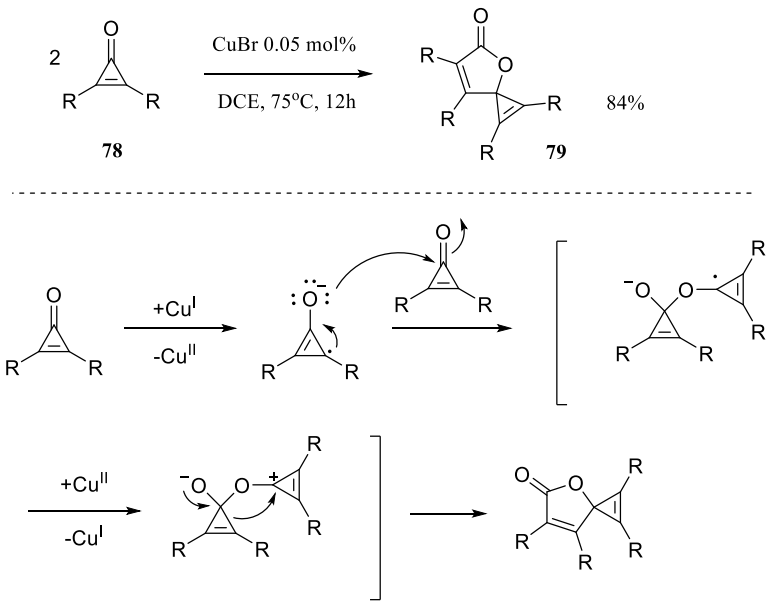
Cyclopropenone[59] is an amphiphilic molecule, which can react with both nucleophilic and electrophilic reagents. In the resonance structure a negative charge on an oxygen atom leads to enhanced nucleophilicity of the oxygen atom compared to ordinary carbonyl compound. Cyclopropenones can undergo various types of ring-opening annulation.



Scheme 35. *The resonance structure of cyclopropenone.*

During the ring-opening [3+2] annulation, in which C=N, C=C, C=O, C=S, N=N, N=O, and C≡C bonds couple with cyclopropenones, five-membered rings are formed. The insertion of a carbonyl group into a cyclopropenone C–C bond will afford 2-furanones (butenolides). The butenolide core is an important motif of various natural compounds.[60] This chapter will give a short overview of the [3+2] annulation of cyclopropenones with a carbonyl group.

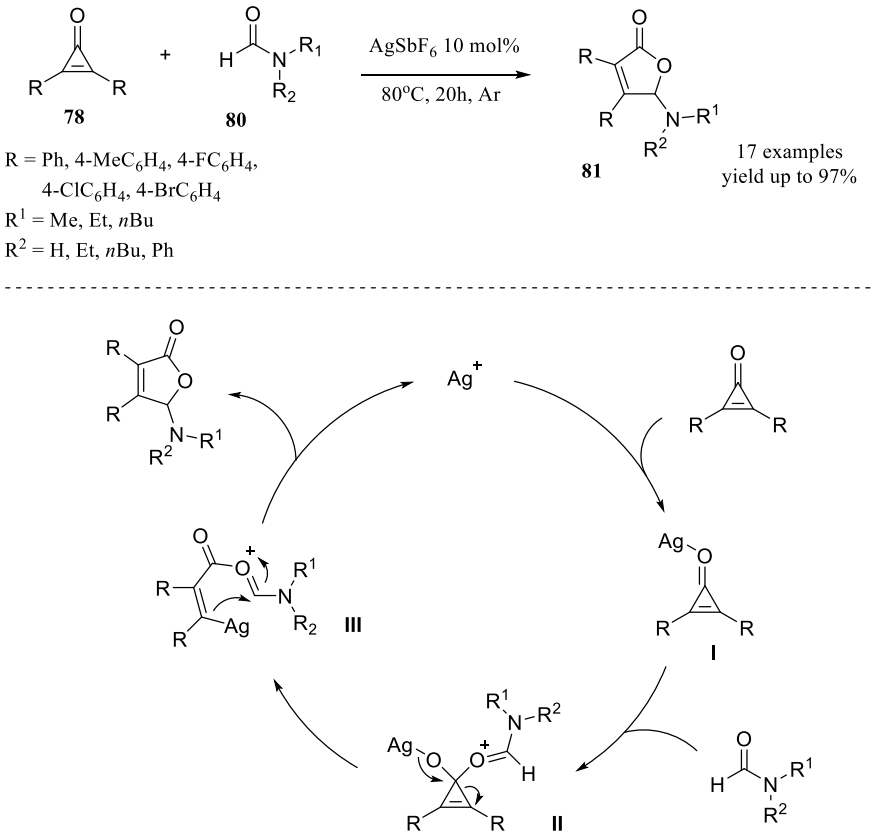
Kröner et al found that cyclopropenone **78** and its alkyl- and aryl-substituted derivatives dimerize upon heating (100 °C) to a spirolactone **79** with yields between 40% and 50%. In the model system they investigated catalytic amount of Pd(II), Pt(0) and Ru(0); in most cases the yield of spiroproduct **79** was low.[61] But by changing the catalytic system to Cu(I) bromide, the spirolactone **79** was obtained in 84% yield. They also proposed a possible mechanism for the generation of spirolactones from two equivalents of cyclopropenone **78** in the presence of Cu(I) bromide (Scheme 36).



Scheme 36. *Cu(I)-catalyzed [3+2] annulation of cyclopropenone **78** and proposed mechanism.*

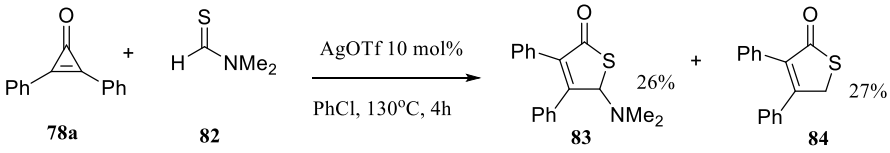
Recently, two groups have published the Ag(I)-catalyzed [3+2] annulation of cyclopropenones **78** with amides. Ren et al[62] reported the $AgSbF_6$-catalyzed annulation of cyclopropenones **78** with formamides **80**; the reaction occurs via β-carbon elimination followed by an intramolecular nucleophilic attack affording γ-aminobutenolides **81** with high yields. The reaction is limited by the substituents on the nitrogen atom; bulkier groups afforded low yield and with free formamide there was no reaction. The plausible

reaction mechanism is shown in Scheme 37. The species **I** was produced by the reaction of cyclopropenone with Ag catalyst, and then the 1,2-addition of carbonyl of formamide to cyclopropenone followed by a ring-opening process generated amphiphilic intermediate **III**, which underwent intramolecular nucleophilic addition to release the [3+2] annulation product.[62]



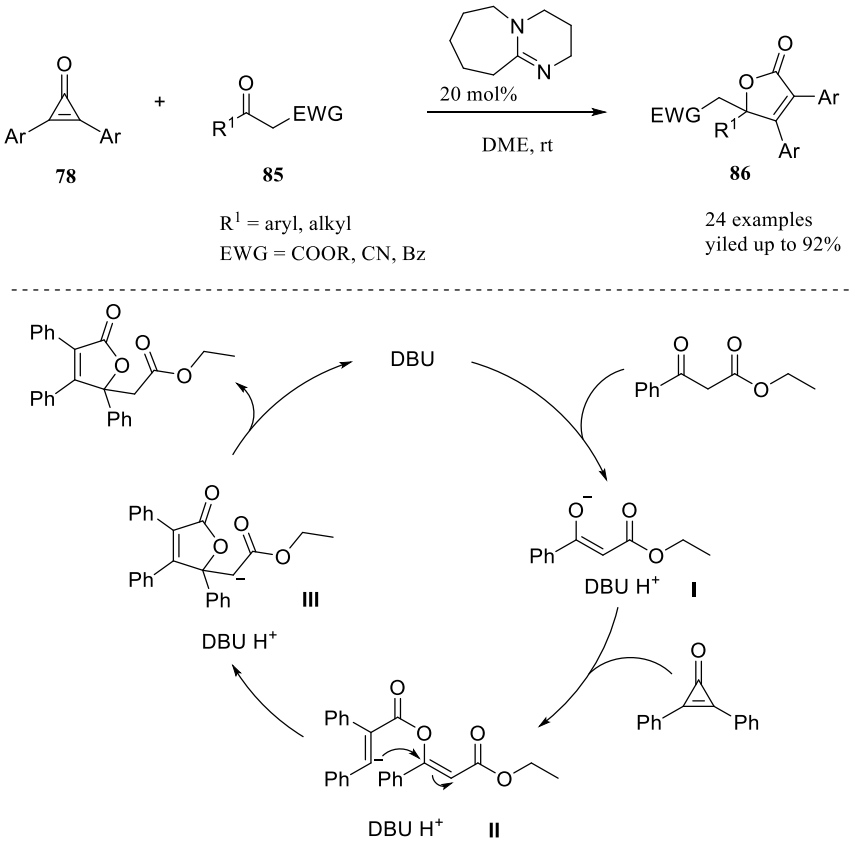
Scheme 37. *Ag(I)-catalyzed [3+2] annulation of cyclopropenones **78** and formamides **80**.*

Suzuki et al[63] used the AgOTf for the ring-opening [3+2] annulation of cyclopropenones **78a** with amides, obtaining 5-amino-2-furanones with moderate to high yield up to 98%. They also showed that *N,N*-dimethylthioformamide **82** can react under similar conditions (Scheme 38). The presence of a 10 mol% of AgOTf resulted in the formation of the expected [3+2] annulation product **83** and product **84** with eliminated dimethylamino group.



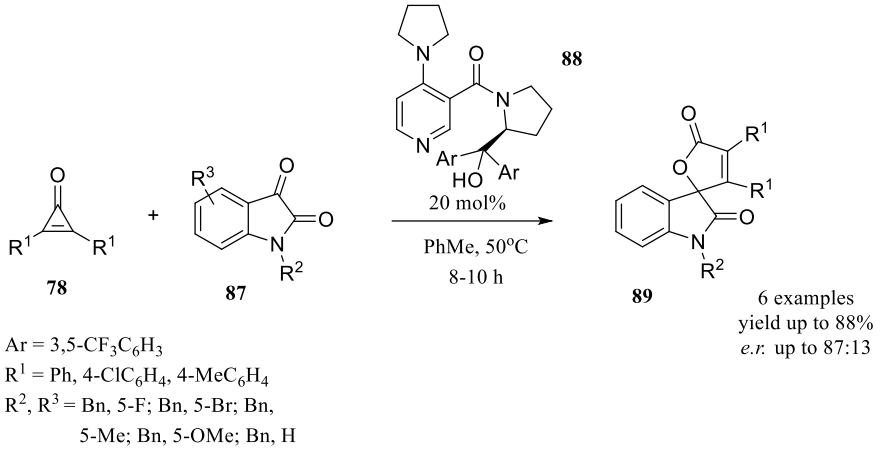
Scheme 38. *AgOTf catalyzed annulation of cyclopropenones **78a** with thioformamide **82**.*

Lin et al[64] published an organocatalyzed [3+2] annulation of cyclopropenones **78** and β-ketoesters **85** (Scheme 39). The reaction mechanism is explained by the formation of enol intermediate **I** through the deprotonation of β-ketoester by base; then in situ-formed nucleophilic oxygen anion attacks the carbonyl group of cyclopropenone, realizing the ring-opening process and affording a Michael addition acceptor **II,** and then an intramolecular Michael addition takes place affording intermediate **III**, after protonation racemic product is formed.



Scheme 39. *Organocatalyzed [3+2] annulation of cyclopropenones **78** and β-ketoesters **85**.*

Du et al[65] used a chiral Lewis base to catalyze a [3+2] cycloaddition of cyclopropenones with isatins. A chiral prolinol-derived pyridine catalyst afforded spirooxindole furan-2-ones in high yields and good *e.r.* values (Scheme 40).



Scheme 40. *[3+2] cycloaddition of diaryl cyclopropenones **78** with isatins **87** catalyzed by chiral Lewis base **88**.*

There are different ways to synthesize butenolides, the above-mentioned cyclopropane-carbonyl coupling, which was conducted under basic conditions using organic base[64,65] or a metal catalyst, but the straightforward method for the synthesis of enantiomerically enriched butenolides through a [3+2] annulation of cyclopropenones has remained mostly unexplored.

2 Aims of the present work

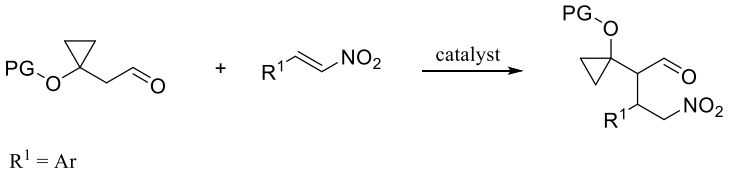
The general aim of the present work was to broaden the scope of Michael donors for asymmetric organocatalytic Michael reaction to obtain amino acid precursors and to investigate various organocatalytic activation modes for the synthesis of chiral butenolides. Specific aims of this thesis were:

- Investigate the asymmetric organocatalytic synthesis of a cyclopropane-containing Michael adduct starting from 1-(2-oxoethyl)cyclopropyl acetate **93**;
- Use amine-functionalized cyclopropylacetaldehyde derivative in a Michael reaction to obtain β- and γ-amino acid precursors;
- Investigate different catalytic systems for the [3+2] annulation of 1,2-diphenylcyclopropen-3-one **78** and 3-oxo-3-phenylpropanoate **85**.

3 Results and discussion

3.1 Synthesis of alkylidenecyclopropanes (Article I)

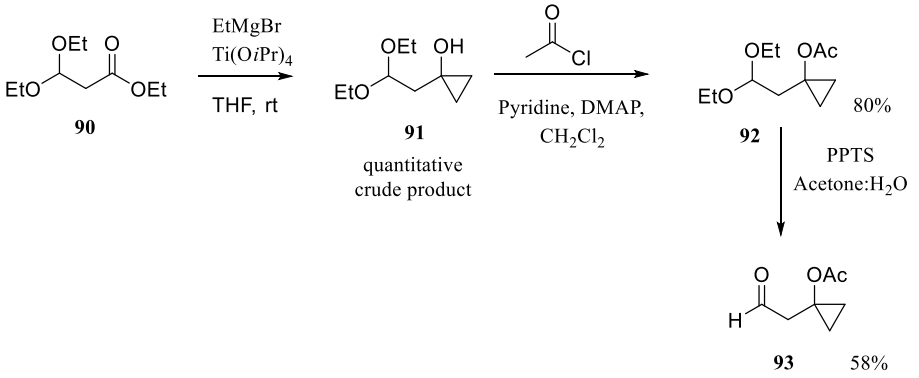
The scope of the carbonyl Michael donors used in an asymmetric aminocatalytic reaction is wide, but to the best of our knowledge, aldehydes containing cyclopropane moiety had not previously been used at the time we started this project. The general idea of the synthesis of cyclopropane-containing aldehydes through a catalytic Michael addition is depicted in Scheme 41.



R^1 = Ar

Scheme 41. *Proposed reaction for the formation of cyclopropane-containing Michael adduct.*

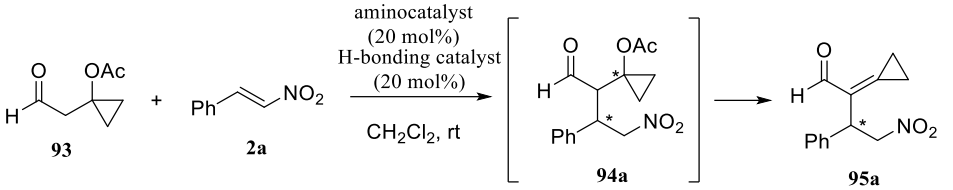
We started the synthesis of 1-(2-oxoethyl)cyclopropyl acetate **93** from commercially available starting material 3,3-diethyloxypropionate **90**. A Kulinkovich reaction of 3,3-diethyloxypropionate furnished the cyclopropanol **91** in quantitative yield. Acylation of the hydroxyl group afforded cyclopropyl acetate **92**, which was treated with PPTS to cleave the acetal and aldehyde **93** was formed with a 46% overall yield (Scheme 42).



Scheme 42. *The synthesis of 1-(2-oxoethyl)cyclopropyl acetate.*

The preliminary experiments for the Michael addition were carried out between aldehyde **93** and nitrostyrene **2a** in DCM at room temperature in the presence of 20 mol% catalyst and 20 mol% of co-catalyst. In the first attempt to obtain a Michael adduct, 20 mol% of pyrrolidine and 20 mol% of diethylthiourea were used. The racemic product was obtained in 58% yield (Table 1, entry 1). The NMR spectroscopic data showed the β-elimination of the acetate group and the formation of double bond (Scheme 43), affording α,β-unsaturated carbonyl compound **95a** derived from Michael adduct **94a** via elimination. To avoid the elimination, we tried to protect the hydroxyl group in compound **91** as benzyl ether, using 2 equivalent benzyl bromide, 1.5 equivalent

sodium hydride and a catalytic amount of TBAI; unfortunately a mixture of products was obtained. We decided to move on to an acyl-protected aldehyde.



Scheme 43. *Michael addition of 1-(2-oxoethyl)cyclopropyl acetate to nitrostyrene.*

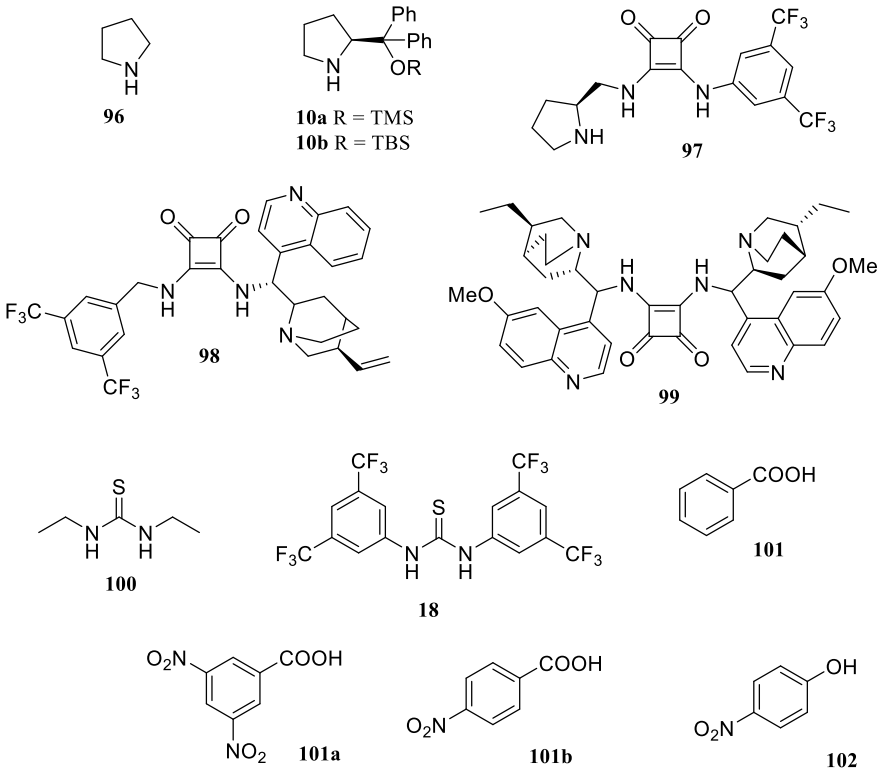
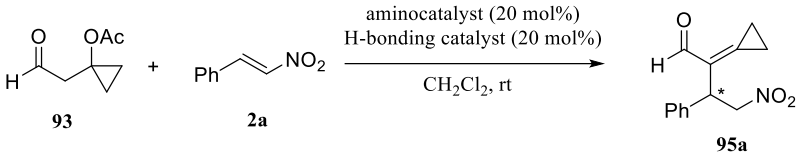


Figure 6. *Catalysts and co-catalysts screened for the synthesis of alkylidene cyclopropane derivatives.*

Then various organocatalysts were investigated in a model reaction between aldehyde **93** and nitrostyrene **2a** (Scheme 43). To our surprise, using the most widely used diphenylprolinol silyl ether **10a**, there was no reaction (Table 1, entry 4). The additional activation of the Michael acceptor (nitrostyrene) with achiral thiourea **100** was necessary (Table 1, entry 2). The combination of an achiral secondary amine **96** with chiral squaramide derivatives **98** and **99** resulted in racemic product with slow reaction (Table 1, entries 5 and 6). The chiral squaramide derivative **97**, which contained both aminocatalytic and H-bonding catalytic moieties, was also found to be inactive (Table 1, entry 7). A stronger H-bond donor thiourea **18** as a co-catalyst afforded similar yield and

enantioselectivity to diethylthiourea **100** (Table 1, compare entries 2 and 8). Using dichloroethane as a solvent decreased the yield to 24% (Table 1, entry 9). The optimal ratio of aldehyde **93** and nitrostyrene **2a** was 3:1 (compare entries 10 and 11) respectively.

Tabel 1. *Screening of the reaction conditions.*[a]



Entry	Amino-catalyst	H-bonding catalyst	Time, d	Solvent	Yield, %	*ee*,[b] %
1	**96**	**100**	4	CH_2Cl_2	58	rac
2	**10a**	**100**	4	CH_2Cl_2	34	90
3	**10a**	**100**	8	toluene	15	89
4	**10a**	**-**	4	CH_2Cl_2	-[c]	nd
5	**96**	**99**	1	CH_2Cl_2	52	rac
6	**96**	**98**	6	CH_2Cl_2	38	rac
7	**97**	**-**	9	CH_2Cl_2	-[c]	nd
8	**10a**	**18**	3	CH_2Cl_2	32	92
9	**10a**	**18**	1	$C_2H_4Cl_2$	24	87
10[d]	**10a**	**18**	1	CH_2Cl_2	58	93
11[e]	**10a**	**18**	1	CH_2Cl_2	41	89

[a]Reaction conditions: compound **93** (1.0 equiv.), compound **2a** (1.0 equiv.), aminocatalyst (20 mol%) and H-bonding catalyst (20 mol%) in CH_2Cl_2 were stirred at ambient temperature. [b]Enantiomeric excess was determined by chiral HPLC analysis from isolated product. [c]No reaction. [d]The ratio between aldehyde **93** and nitrostyrene **2a** was 3:1. [e]The ratio between aldehyde and nitrostyrene was 1:3.

Next, we screened the effects of various co-catalysts on the model reaction (Table 2). It is known from the literature that an acidic co-catalyst accelerates the reaction considerably, affording Michael adducts in high yields and selectivities.[18,26] We investigated the effect of additional basic and acidic additives. Adding 20 mol% of K_2CO_3 afforded lower enanioselectivity (*ee* 81%, Table 2, entry 3) while an additional amount of *p*-TsOH (Table 2, entry 4) resulted in a mixture of products. An aminocatalyst **10b** containing a sterically more demanding *tert*-butyldiphenylsilyl group did not influence the stereoselectivity and a minor decrease in the yield was observed (Table 2, entry 5). Benzoic acid **101** or its derivatives afforded similar enantioselectivities (*ee* from 91-92%) and yields (Table 2, entries 6-8), except 3,5-dinitrobenzoic acid **101a**, which gave a very slow reaction and the yield was not determined. The best results were obtained in the presence of 4-nitrophenol **102** (Table 2, entries 9 and 11), a minor decrease in the yield was observed when *tert*-butyldiphenylsilylprolinol **10b** was used as a catalyst (Table 2, entry 11).

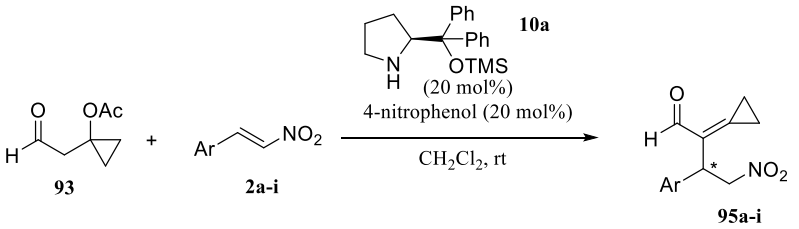
Tabel 2. *Screening of the co-catalyst.*[a]

Entry	Amino-catalyst	Co-catalyst	Time, d	Solvent	Yield, %	*ee*,[b] %
1	**10a**	**18**	3	CH_2Cl_2	32	92
2[c]	**10a**	**18**	1	CH_2Cl_2	41	89
3[d]	**10a**	**18**	1	CH_2Cl_2	43	81
4[e]	**10a**	**18**	1	CH_2Cl_2	mixture	nd
5[c]	**10b**	**18**	1	CH_2Cl_2	36	89
6[c]	**10a**	**101**	1	CH_2Cl_2	43	91
7	**10a**	**101a**	1	CH_2Cl_2	-[f]	91
8	**10a**	**101b**	1	CH_2Cl_2	40	92
9	**10a**	**102**	1	CH_2Cl_2	60	93
10[c]	**10a**	**102**	1	CH_2Cl_2	58	93
11[c]	**10b**	**102**	1	CH_2Cl_2	56	92

[a]Reaction conditions: compound **93** (1.0 equiv.), compound **2a** (1.0 equiv.), aminocatalyst (20 mol%) and co-catalyst (20 mol%) in CH_2Cl_2 were stirred at ambient temperature for 24 h. [b]Enantiomeric excess was determined by chiral HPLC analysis from isolated product. [c]The ratio between aldehyde and nitrostyrene was 1:3. [d]An additional amount of K_2CO_3 (20 mol%) was added to the reaction mixture. [e]An additional amount of *p*-TsOH (20 mol%) was added to the reaction mixture. [f]The yield was not determined.

With optimal conditions in hand, aldehyde **93** (1 equiv.), nitrostyrene **2a** (1 equiv.), diphenylprolinol silyl ether **10a** (0.2 equiv.) and 4-nitrophenol **102** (0.2 equiv.) in DCM at room temperature, the influence of different substituents in the aromatic core of nitro olefins **2** was investigated (Table 3). We were also interested in the catalytic activity of thiourea **18** and did parallel scope screening with it (Table 3, entries 3, 5, 8, 11, 13 and 15).

Table 3. *Scope of the reaction.*[a]



Entry	Ar	Time, d	Product	Yield, %	*ee*,[b] %
1	Ph	1	**95a**	60	93
2	4-ClC_6H_4	1	**95b**	38	95
3[c]	4-ClC_6H_4	1	**95b**	50	93
4	2-ClC_6H_4	1	**95c**	38	95
5[c]	2-ClC_6H_4	1	**95c**	50	91
6	2-BrC_6H_4	1	**95d**	42	99
7	4-$MeOC_6H_4$	1	**95e**	27	87
8[c]	4-$MeOC_6H_4$	6	**95e**	23	84
9	4-$(F_3CO)C_6H_4$	1	**95f**	50	96
10	4-$NO_2C_6H_4$	1	**95g**	35	97
11[c]	4-$NO_2C_6H_4$	4	**95g**	36	86
12	2-naphthyl	1	**95h**	34	92
13[c]	2-naphthyl	4	**95h**	42	87
14	2-thienyl	1	**95i**	27	85
15[c]	2-thienyl	4	**95i**	39	81

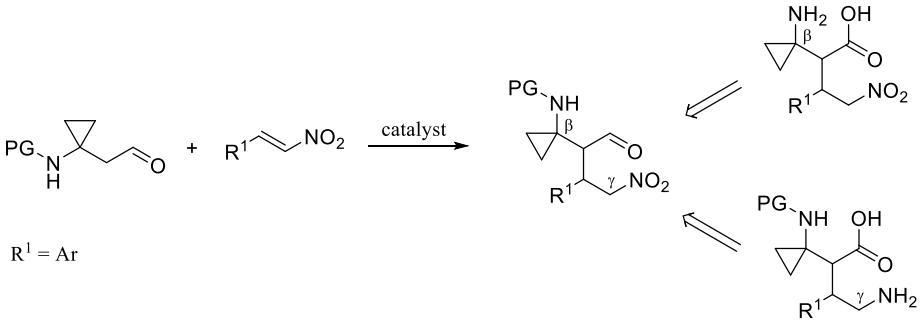
[a]Reaction conditions: compound **93** (1.0 equiv.), compounds **2a-i** (1.0 equiv.), aminocatalyst **10a** (20 mol%) and co-catalyst **102** (20 mol%) in CH_2Cl_2 were stirred at ambient temperature for 24 h. [b]Enantiomeric excess was determined by chiral HPLC analysis from isolated product. [c]Thiourea **18** was used instead of 4-nitrophenol and the ratio between the aldehyde and nitro olefin was 1:3.

Electron-donating and -withdrawing groups of the nitro olefins did not have a noticeable effect on the reaction and the obtained products were isolated in similar yields (from 23-60%) and enantioselectivities (*ee* from 81-99%). Slightly decreased selectivities were observed in the reaction with methoxy- and 2-thienyl substituted nitro olefins (Table 3, entries 7,8,14 and 15). Using thiourea **18** as a co-catalyst and a higher ratio of nitro olefins afforded better yields (Table 3, entries 3,5,13 and 15).

In conclusion, the synthesis of alkylidenecyclopropane aldehydes **95** via an aminocatalytic Michael addition to nitro olefins **2** with moderate yields and in high enantiomeric purity up to 99% was described. The stereoselectivity of the reaction is determined by the nonracemic aminocatalyst and additional activation of the Michael acceptor is needed.

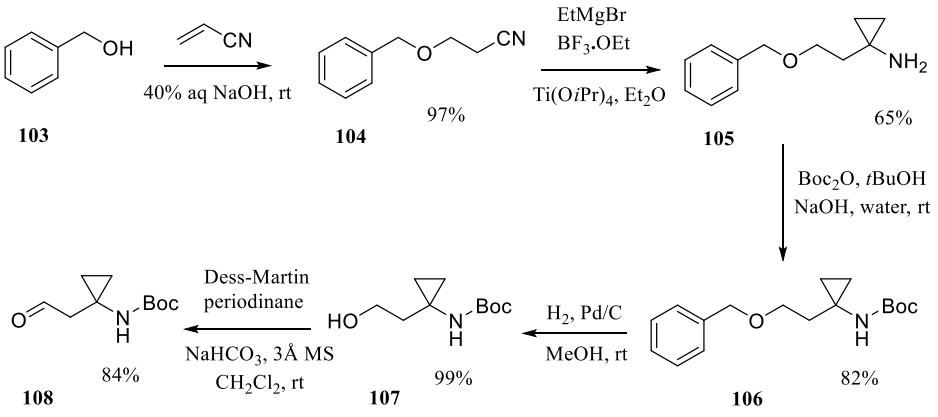
3.2 Synthesis of β- and γ-amino acid precursors (Article II)

Having obtained good results with the 1-(2-oxoethyl)cyclopropyl acetate **93**, we investigated a similar organocatalytic approach; we intended to synthesize amine-functionalized cyclopropylacetaldehyde derivative to avoid β-elimination of the acetate group and achieve a direct synthesis of β- and γ-amino acid precursors (Scheme 44).



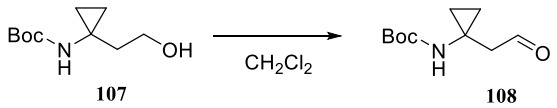
Scheme 44. *Proposed reaction for the synthesis of amino acid precursors.*

Amine-functionalized cyclopropylacetaldehyde derivative **108** was prepared from benzyl alcohol **103**.[66] The Michael addition of benzyl alcohol to acrylonitrile was followed by a Kulinkovich-Szymoniak reaction.[67] Then the amino group was protected with a Boc-protection group. The benzyl group was removed from the oxygen atom. The oxidation of the hydroxyl group with Dess-Martin periodinane afforded the desired amine-containing cyclopropanecarbaldehyde **108** in an 18% overall yield (Scheme 45).

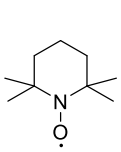


Scheme 45. *Synthesis of amine-containing cyclopropanecarbaldehyde **108**.*

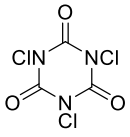
Table 4. *Screening of oxidation reagents.*



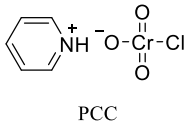
107 108



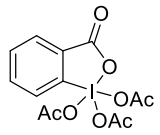
TEMPO



TClCA



PCC

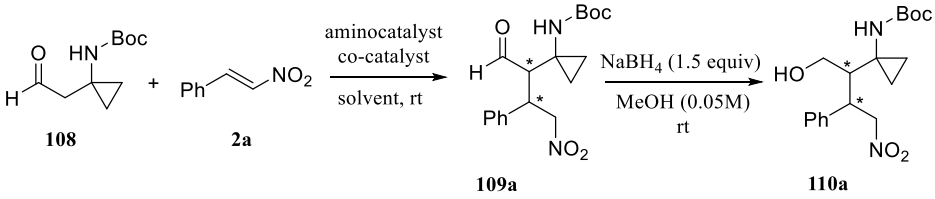


Dess-Martin periodinane

Entry	Oxidation reagent	Additive	T, °C	Time, min	Yield, %
1	TEMPO	TClCA	-20 → 0	35	59
2	PCC	Celite®	rt	260	66
3	Dess-Martin periodinane	$NaHCO_3$, 3Å MS	rt	30	84

There are examples where TEMPO is used as an oxidation reagent to obtain aldehyde from primary alcohols.[68] Using TEMPO for oxidation led to the formation of an expected aldehyde **108** with a moderate 59% yield. We turned our attention to other oxidation reagents. PCC afforded a higher yield of 66%, but the crude mixture contained inseparable side products with polarities similar to those of aldehyde **108** (Table 4, entry 2). Finally, when Dess-Martin periodinane was used an 84% yield of aldehyde **108** was obtained.

Next, we focused our attention on screening for reaction conditions, we knew from our previous work (Publication I) that a reaction between the cyclopropane containing aldehyde and nitro olefins would not proceed without a co-catalyst. Different aminocatalysts and co-catalysts were screened for the model reaction between the aldehyde **108** and nitrostyrene **2a** (Scheme 46). As is shown in the reaction scheme, the obtained aldehyde **109a** was reduced *in situ* for the corresponding alcohol **110a**, because isolating the aldehyde **109a** in small scale afforded insufficient yield. Later, the isolation of aldehyde **109a** was demonstrated in a larger 1.0 mmol scale.



108 2a 109a 110a

Scheme 46. *Synhesis of β- and γ-amino acid precursors.*

Jørgensen-Hayashi type catalysts **10a** and **10b** with various H-bonding co-catalysts were tested, such as 4-nitrophenol, achiral thioureas and Takemoto's thioureas (Figure 7). The best diastereoselectivity and enantioselectivity were achieved with the combination of *tert*-butyldiphenylsilylprolinole **10b** and thiourea **18**. The study revealed

that a prolinol derivative **10b** with a sterically more demanding TBS-group is clearly beneficial in terms of diastereoselectivity and enantioselectivity and decreasing the catalyst loading to an equal amount of co-catalyst did not affect the selectivity; only a minor decrease in the yield was observed. A detailed optimization procedure is described in Article II.

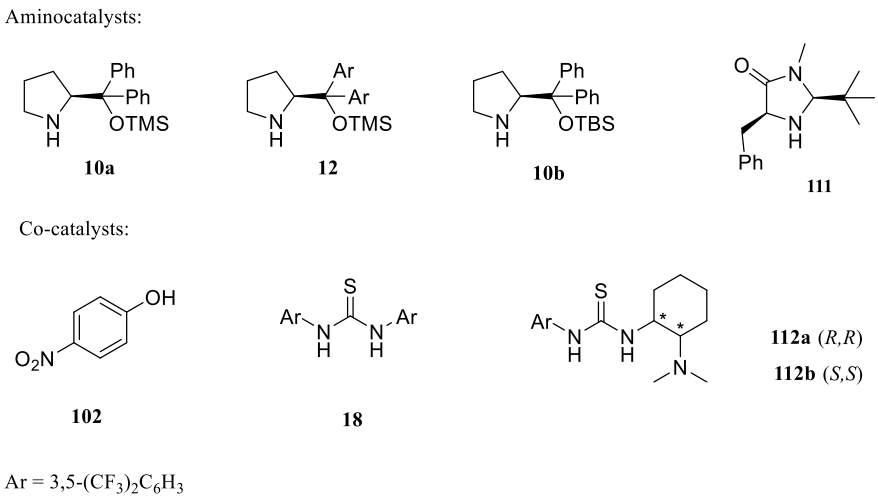
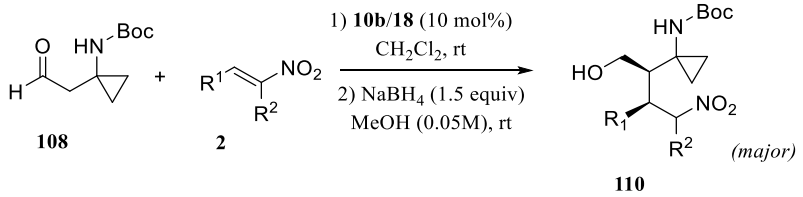


Figure 7. *Aminocatalysts and co-catalysts screened for the synthesis of β- and γ-amino acid precursors.*

Next, the scope of the reaction was investigated. The yields and *ee* values of the conjugated addition of cyclopropylacetaldehyde derivative **108** and nitro alkenes are presented in Table 5. Electron-donating and -withdrawing groups of the nitro olefins did not have any noticeable effect on the reaction selectivity; the obtained products were isolated in similar yields (from 56-78%), in high diastereoselectivities (*dr* 89:11-95:5) and in high enantioselectivities (*ee* 98-99%). In the case of *meta*- and *ortho*-bromo phenyl substituted nitro olefins, the reaction times were longer and the yields were lower due to steric hindrance (Table 5, entries 3 and 5). The cause of the long reaction time in the reaction between aldehyde **108** and *para*-nitro-phenyl substituted nitro olefin (Table 5, entry 6), was low solubility of the nitro olefin in DCM.

Heteroaromatic nitro olefins afforded lower diastereoselectivities (*dr* 80:20-88:12, Table 5, entries 7-9) which is distinctive to electron-rich aromatic substituents. The lowest enantioselectivities were obtained with pyridyl- and naphthyl-substituted nitro alkenes (Table 5, entries 9, 10); in the case of nitro alkene **2m**, higher catalyst loadings were needed to obtain the full conversion and the product was isolated as an aldehyde **109m** due to its high polarity. With ester-substituted nitro alkene **2o** (Table 5, entry 12), an excellent enantioselectivity was retained for both isomers (*ee* 99% and *ee* 92%); the low diastereoselectivity might have been due to epimerization of the α-position of the carboxyl group. To avoid possible lactonization, the product was isolated as an aldehyde **109o**. The reaction proceeded more slowly with aliphatic substrate **2p** (table 5, entry 13) and the product was isolated as an aldehyde **109p**. An α-substituted nitro olefin did not react, which corresponds to previously published work by Pihko et al.[27]

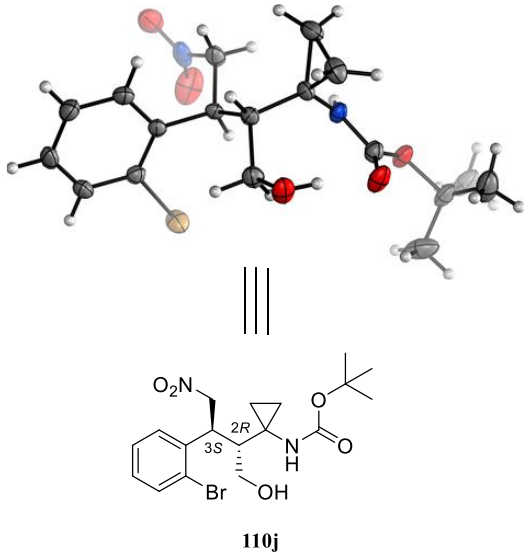
Table 5. *Scope of the reaction between aldehyde* ***108*** *and nitro alkenes* ***2****.*[a]



Entry	R^1	R^2	Time	Product	Yield, %	*dr*[b]	*ee*,[c]%
1	C_6H_5	H	25 h	**110a**	74	95:5	99
2	4-MeO-C_6H_4	H	28 h	**110e**	70	89:11	98
3	2-Br-C_6H_4	H	49 h	**110j**	65	95:5	99
4	4-Cl-C_6H_4	H	2 d	**110b**	78	95:5	98
5	3-Br-C_6H_4	H	46 h	**110k**	56	94:6	99
6	4-NO_2-C_6H_4	H	79 h	**110g**	69	95:5	98
7	furan-2-yl	H	1 d	**110l**	79	80:20	97
8	2-thienyl	H	29[d]h	**110i**	75	86:14	94
9	pyridine-3-yl	H	6 d	**110m**	56[e]	88:12	93
10	naphthalene-1-yl	H	5 d	**110h**	74	85:18	93
11	C_6H_5-C≡C	H	1 d	**110n**	86	69:31	97/65
12	$CH_3CH_2O(O)C$	H	47 h	**110o**	57[e]	72:28	99/92
13	C_6H_{11}	H	7 d	**110p**	47[e]	83:17	99
14	C_6H_5	CH_3	7 d	**110q**	–[g]	–	–
15	$-(CH_2)_4-$		7 d	**110r**	–[g]	–	–

[a]Reaction conditions: compound **108** (1.2 equiv.), compounds **2a-r** (1.0 equiv.), aminocatalyst **10b** (10 mol%) and co-catalyst **18** (10 mol%) in CH_2Cl_2 (0.38 M) were stirred at ambient temperature for 24 h. For the reduction $NaBH_4$ (1.5 equiv) was used in MeOH at room temperature. [b]Diastereomeric ratio was determined from the crude mixture by ^1H NMR spectroscopy for aldehyde **109**. [c]Enantiomeric excess was determined by chiral HPLC analysis from isolated product **110**. [d]15 mol% of **10b/18** was used. [e]Product was isolated as aldehyde **109 m/o/p**. [g]No reaction.

The relative and absolute stereochemistry of the alcohol **110j** was established by single-crystal X-ray diffraction and the other compounds in the series were assigned by analogy (Figure 8).



110j

Figure 8. *X-ray structure of alcohol* ***110j****.*

Based on the geometry of the *anti*-product (2*R*,3*S* configuration), a possible mechanism of a Michael addition between the cyclopropylacetaldehyde derivative **108** and nitro olefin **2** was proposed (Figure 9). The *anti*-configured Michael products are not very common. In 2004 Alexakis et al published a Michael addition of hydroxyacetone and nitro olefins, where they obtained *anti*-selectivity.[69] The formation of *anti*-configuration Michael products can be explained by the Z configuration[70] of the reactive enamine, which can be stabilized by intramolecular hydrogen bonding.[71] Z-configuration of enamine is caused by hydrogen bonding between the nitrogen atom of the pyrrolidine ring and the NH of the HNBoc group (Figure 9, **I**). According to Seebach`s topological rule, the absolute stereochemistry is determined by a sterically less hindered nucleophilic attack from the *Re*-face of the enamine on the *Si*-face of the nitro olefin to give the product with a 2*R*,3*S* configuration (Figure 9, TS). From previous mechanistic studies[26] it is known that the key intermediate in the Michael reaction is a six-membered dihydrooxazine oxide OO; in our case its supports the C2 *R*-configuration. The OO intermediate hydrogen bonding between the carbamoyl group from the cyclopropane species and the nitrogen atom from the enamine will force the cyclopropyl- and aryl- (R^1) substituents in *cis* to each other **II**.

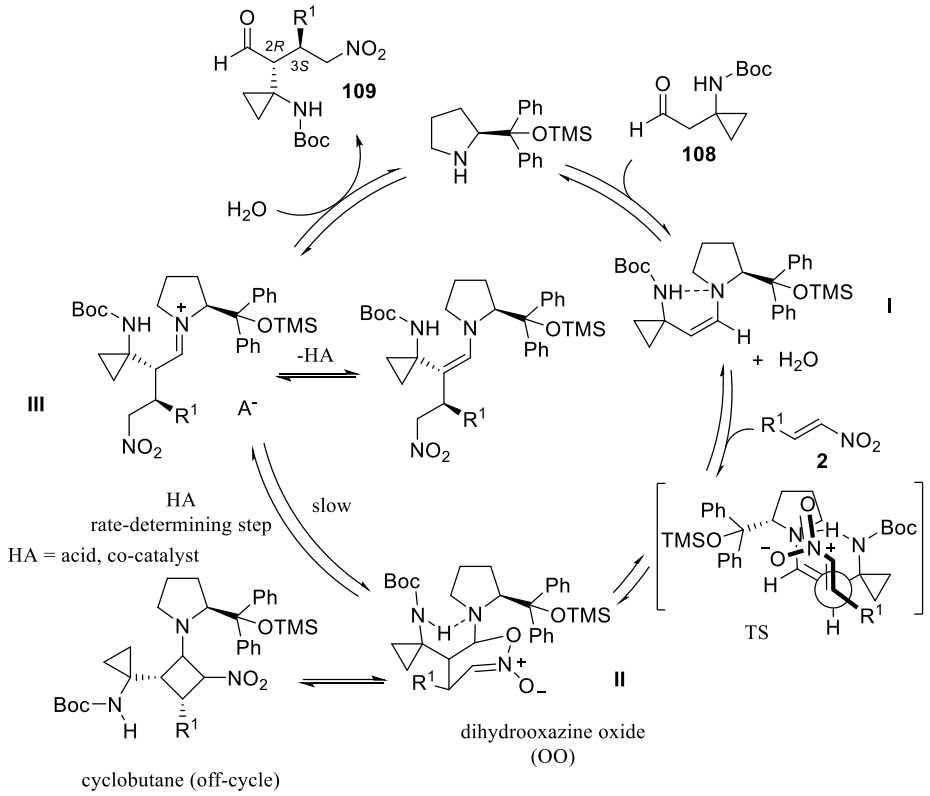
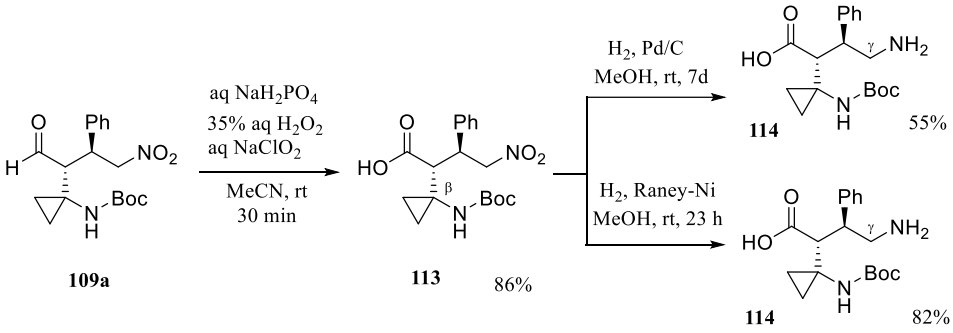


Figure 9. *Proposed mechanism for the Michael addition.*

The synthesis of β- and γ-amino acid was continued by MSc Mikk Kaasik and published in his master theses (Scheme 47). The aldehyde **109a** was converted to the corresponding Boc-protected β-amino acid **113**; further reduction of the nitro group afforded γ-amino acid **114**, and two different methods were used for the reduction.

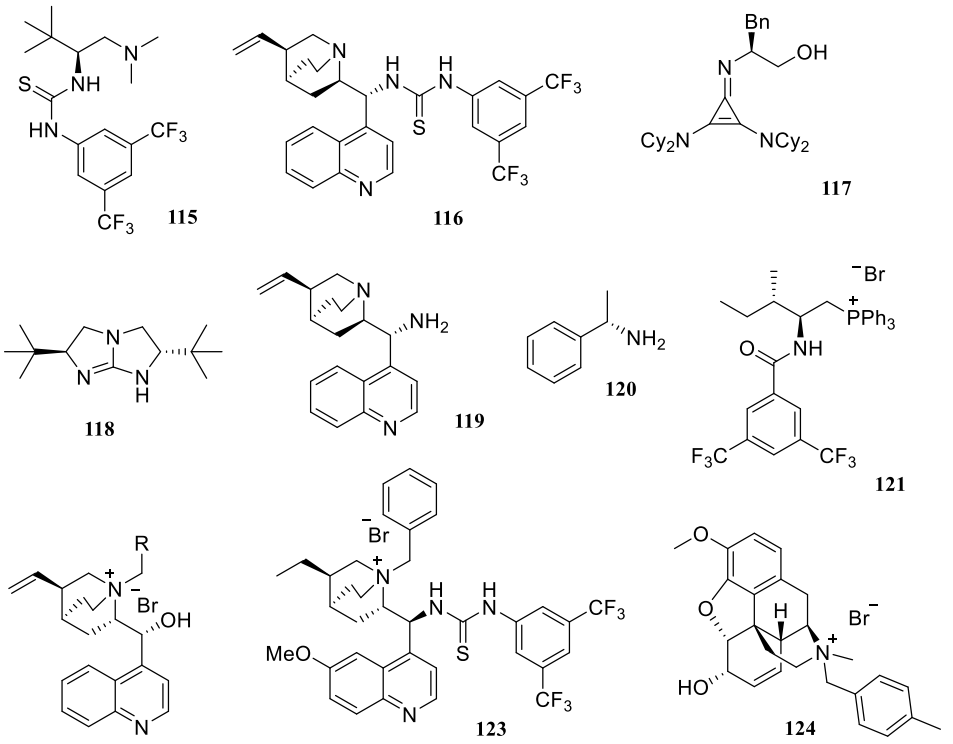


Scheme 47. *Synthesis of β- and γ-amino acid.*[72]

In conclusion, we have developed a method for the synthesis of β- and γ-amino precursors **109/110** via an aminocatalytic Michael addition to nitro olefins **2** with moderate to good yields (47-86%) and in good to high diastereo- and enantioselectivities (*dr* 69:31-95:5; *ee* 93-99%).

3.3 Study of the asymmetric organocatalalyzed [3+2] annulation of cyclopropenone and β-ketoester (Article III)

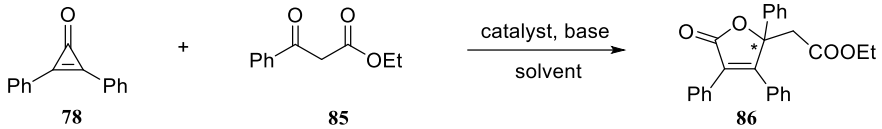
Inspired by the study of the non-asymmetric organocatalyzed [3+2] annulation of cyclopropenone and β-ketoester reported by Lin et al[64], we were interested in the asymmetric version of the reaction. To explore the activation methods of the synthesis of chiral butenolide **86**, four different catalytic approaches were investigated: bifunctional thiourea catalysis, chiral base catalysis, aminocatalysis and phase-transfer catalysis.



Scheme 48. *Catalysts screened for the synthesis of butenolide* ***86****.*

In the first approach, we assumed the enolization of the β-ketoester **85** in the presence of a bifunctional catalyst. Unfortunately, product **86** was not formed by the amino acid-derived thiourea **115** and alkaloid-based thiourea **116** (Table 6, entries 1 and 2). We concluded that the nitrogen atoms in catalysts structures were not basic enough to enolize the β-ketoester. The addition of a base did not improve the situation (Table 6, entry 3). This might have been due to the similar pK_a values of catalyst **116** and β-ketoester **85** (respectively 12.39[73] and 14.2[74] in DMSO), as the deprotonation by DBU is competitive between the catalyst and β-ketoester **85**.

Table 6. *Catalyst screening for the asymmetric synthesis of butenolide **86**.*[a]



Entry	Catalyst	Base	Yield, %	*ee*,[b] %
1	**115**	-	-	-
2	**116**	-	-	-
3	**116**	DBU	-	-
4	**117**	-	62[c]	*rac*[d]
5[e]	**118**	-	31	6
6[f]	**119**	DABCO	nd	*rac*
7[f]	**120**	K_2CO_3	31	6
8[f]	**120**	DIPEA	traces	*rac*
9[g]	**120**	DBU	52	*rac*
10	**121**	50% aq KOH	28	10
11[h]	**122a**	50% aq KOH	13[c]	6
12	**122b**	50% aq KOH	17[c]	*rac*
13	**122c**	50% aq KOH	22[c]	14
14	**122d**	50% aq KOH	8	24
15[i]	**122d**	50% aq KOH	49	*rac*
16[j]	**122d**	50% aq KOH	40	*rac*
17[k]	**122d**	50% aq KOH	18	*rac*
18	**123**	50% aq KOH	12	10
19	**124**	50% aq KOH	29[c]	*rac*

[a]Reaction conditions: compound **78** (1.5 equiv.), compound **85** (1.0 equiv.), catalyst (20 mol%) and the base (20 mol%) in CH_2Cl_2 (0.1 M) were stirred at rt for 24 h. [b]Enantiomeric excess was determined by chiral HPLC from the isolated product **86**. [c]Conversion was determined from the ratio of compound **86** to **85** by ^{1}H NMR spectroscopy in the crude mixture. [d]Enantiomeric excess was determined by chiral HPLC for the sample isolated by preparative TLC from the crude mixture. [e]Reaction at 60 °C. [f]Reaction time 10 days. [g]Reaction time 5 h. [h]Reaction time 1 h. [i]Reaction in THF. [j]Reaction in DME. [k]Reaction in toluene at 0 °C.

Then we investigated the catalytic activity of chiral bases. The catalyst **117** was chosen due to its high Brønsted basicity and its ability to act as a hydrogen bond donor (primary hydroxyl group in the core structure). The strong bases **117** and **118** afforded racemic product with moderate (Table 6, entry 4) or low (Table 6, entry 5) yields.

Amino-catalysts **119** and **120** turned out to also be unsuitable for this reaction, affording product in very low selectivity (Table 6, entries 6-9). The obtained results proved the proposed reaction mechanism.[64]

Next, we turned our attention to phase-transfer catalysis. Four different phase-transfer catalysts were tested. An amino acid-derived phosphonium salt **121** catalyzed reaction with additional base afforded product **86** with low yield and enantioselectivity (Table 6, entry 10). The highest enantiomeric purity of **86** was achieved with Cinchona alkaloid derived ammonium salt **122d** with additional base (Table 6,

entry 14). However, bifunctional Cinchona alkaloid-based thiourea **123** and codeine derivative **124** failed to perform (Table 6, entries 15-16).

Having determined the potential catalytic system (**122d** in CH_2Cl_2/aq KOH), we started exploring the influence of various substituents at the nitrogen atom of the alkaloid catalyst **122**. Four different R-groups were tested and all four catalysts **122a-d** performed quite similarly (Table 6, entries 11-14), the conversion varied between 13-22%. The bulkiest, anthracen-9-yl group at the nitrogen atom made the catalyst more selective, affording the highest *ee* value (24%). The reaction was also conducted in different solvents (Table 6, entries 15-17). This had some effect on the reaction rate (conversions were between 18% and 49%), while the obtained product **86** was racemic.

Finally, in order to improve the conversion, the influence of the loading of the base was investigated. Increasing the amount of base to a 0.6 equivalent afforded almost full conversion; the isolated yield was 54% without loss in selectivity. Further increasing it made the reaction faster, but selectivity dropped to 15%. We concluded, that a 0.6 equivalent of aqueous KOH was optimal in our catalytic system. There are two competitive pathways for the reaction: a base-catalyzed background reaction leading to the racemic product, and a PTC-catalyzed asymmetric reaction. The stronger the base we used, the higher conversion of the product **86** we got, while the enantioselectivity of the reaction declined.

The study revealed that in principal the use of phase-transfer catalysis could be the method of choice as the highest enantiomeric purity of compound **86** was achieved with cinchona alkaloid-derived ammonium salt **122d** in a CH_2Cl_2/aq KOH biphasic system, but further investigation is needed.

Conclusions

The organocatalytic Michael reaction of a cyclopropane-ring containing compounds was investigated and conditions for the selective formation of different addition products were established. Various asymmetric organocatalytic methods for [3+2] annulations of diphenylcyclopropenone and β-ketoester were investigated. The following features of organocatalytic Michael addition and [3+2] annulation were explored and improved:

A method for the asymmetric synthesis of alkylidenecyclopropane derivatives **95a-i** through the organocatalytic Michael addition was developed. Alkylidenecyclopropane derivatives **95a-i** were obtained in high enantiomeric purities (85–99% *ee*). All reactions were highly enantioselective and the substitution pattern did not influence the selectivity.

A general straightforward method for the synthesis of β- and γ-amino acid precursors **110** was developed. The reaction allowed the one-step introduction of a cyclopropane ring and two different nitrogen-containing functional groups into the target compound.

The organocatalytic conjugate addition of cyclopropylacetaldehyde derivative **108** to nitro olefin **2** was used to synthesize Boc-protected β-amino acid **113** and γ-amino acid **114**.

Various asymmetric organocatalyzed [3+2] annulations of diphenylcyclopropenone **78** and β-ketoester **85** were investigated, resulting in the formation of chiral ethyl 2-(5-oxo-2,3,4-triphenyl-2,5-dihydrofuran-2-yl) acetate **86** with moderate to high yield.

In spite of various asymmetric organocatalytic methods and optimization procedures applied to achieve enantioselectivity, the enantiomeric purity of the product **86** remained low. The best results were obtained using sterically demanding PTC catalyst **122d** in a biphasic system of DCM and aqueous KOH. A dependence between the base loading, reaction time and selectivity was observed: a higher base loading afforded faster reaction and lower enantioselectivity.

4 Experimental

Full assignment of ^{1}H and ^{13}C chemical shifts was based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used [CDCl3 δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR)] as internal standards. The ^{1}H NMR peaks are reported as follows: s = singlet, br = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet. High resolution mass spectra were recorded on an Agilent Technologies 6540 UHD Accurate Mass Q-TOF LC/MS spectrometer using AJ-ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT infrared spectrophotometer. Optical rotations were obtained using an Anton Paar GWB Polarometer MCP 500. Chiral HPLC was performed using ether Chiralpak AS-H (250 x 4.6 mm), Lux Amylose-2, Chiralcel OD-H (250 x 4.6 mm) or Chiralpak AD-H (250 x 4.6 mm) columns. Precoated silica gel 60 F_{245} plates from Merck were used for TLC, whereas for column chromatography silica gel Kieselgel 40-63 µm was used. Purchased chemicals and solvents were used as received. DCM and EtOAc were distilled over phosphorous pentoxide. Reactions sensitive to oxygen or moisture were conducted under an argon atmosphere in flame-dried glassware.

General method for the aminocatalytic Michael addition of cyclopropane-containing aldehyde to nitroalkenes (Publication I)

To aldehyde **93** (0.35 mmol) was added 4-nitrophenol **102** (0.07 mmol), nitro alkene **2** (0.35 mmol), and a solution of catalyst **10a** (0.07 mmol) in CH_2Cl_2 (0.2 mL). The mixture was stirred at r.t. until completion of the reaction (TLC monitoring). The mixture was diluted with CH_2Cl_2 (6 mL) and washed with aq 1M NaOH (6 mL) and brine (6 mL). After concentration under reduced pressure, the crude product was purified by column chromatography (EtOAc-hexane, 1:10) to afford alkylidenecyclopropane **95**.

2-Cyclopropylidene-4-nitro-3-phenylbutanal 95a

Yellow oil; yield 60% (46 mg); R_f = 0.42 (EtOAc-hexane, 2:5); *ee* 93%, determined by HPLC [Chiralcel OD-H; hexane:iPrOH 8:2; 1 mL/min, 230 nm, t_r = 27.19 min (major), t_r = 24.69 min (minor)]. $[\alpha]_D^{25}$ = -84.0 (*c* 0.075, MeOH); IR (neat): ν = 2831, 1680, 1553, 1431, 1216, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 7.34-7.21 (m, 5 H), 5.11 (dd, *J* = 12.7, 8.9 Hz, 1 H), 4.97-4.90 (m, 1 H), 4.83 (dd, *J* = 12.7, 7.1 Hz, 1 H), 1.58-1.44 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ =192.0, 149.4, 137.8, 130.3, 129.1, 128.0, 127.9, 77.2, 42.5, 3.5, 1.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{14}NO_3^+$ $[M + H]^+$ 232.0968; found 232.0971.

General methods for the organocatalytic Michael addition of cyclopropylacetaldehyde derivative to nitroalkenes (Publication II)

General Procedure A: In a 1.5 mL reactor, aldehyde **108** (1.2 equiv., 37 mg, 0.19 mmol), nitro olefin **2** (1 equiv., 0.15 mmol), cocatalyst **18** (10 mol%, 7.7 mg, 0.015 mmol), and catalyst **10b** (10 mol%, 5.7 mg, 0.015 mmol) were dissolved in CH_2Cl_2 (0.4 mL). The reaction mixture was stirred for 1–7 d at room temp. and then it was diluted with MeOH (3 mL), and cooled to 0 °C. $NaBH_4$ (8.8 mg, 0.23 mmol) was added, and the reaction mixture was stirred at room temp., for 25 min. The reaction was quenched with satd. aq. NH_4Cl solution (3 mL), and then the mixture was diluted with water (3 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography using a mixture of CH_2Cl_2/EtOAc or hexane/EtOAc.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-1-Hydroxy-4-nitro-3-phenylbutan-2-yl]cyclopropyl}-carbamate 110:** Synthesized according to general procedure A. The product was isolated (41 mg, 74 %) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 95:5) with an *ee* of 99 % for the major diastereoisomer [HPLC: Lux Amylose-2; hexane/*i*PrOH, 85:15; 1 mL/min; 25 °C; 230 nm; t_R = 7.4 (minor), t_R = 8.9 (major) min]. $[\alpha]_D^{25}$= –9.5 (*c* = 1.00, acetone), m.p. 173–176 °C. IR: ν = 3349, 3270, 1681, 1556, 1368, 1285, 1257, 1166, 1066, 1032, 763 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.35–7.26 (m, 4 H), 7.26–7.20 (m, 1 H), 6.84 (s, 1 H), 5.68–5.57 (m, 1 H), 4.96 (t, *J* = 12.5 Hz, 1 H), 4.35 (dd, *J* = 7.5, 4.5 Hz, 1 H), 3.58 (td, *J* = 11.7, 4.2 Hz, 1 H), 3.36–3.24 (m, *J* = 10.1 Hz, 1 H), 3.23–3.09 (m, 1 H), 1.49–1.45 (m, *J* = 4.2 Hz, 1 H), 1.44 (s, 9 H), 1.05–0.94 (m, 3 H), 0.94–0.87 (m, 1 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]acetone): δ = 158.6, 140.3, 129.4, 129.1, 128.1, 80.2, 80.0, 63.7, 51.7, 45.4, 32.0, 28.5, 14.85, 14.77 ppm. HRMS (ESI): calcd. for $C_{18}H_{27}N_2O_5^+$ [M + H]$^+$ 351.1914; found 351.1895.

General Procedure B: In a 1.5 mL reactor, aldehyde **108** (1.2 equiv., 37 mg, 0.19 mmol), nitro olefin **2** (1 equiv., 0.15 mmol), cocatalyst **18** (10 mol-%, 5.7 mg, 0.015 mmol), and catalyst **10b** (10 mol%, 5.7 mg, 0.015 mmol) were dissolved in CH_2Cl_2 (0.4 mL). The reaction mixture was stirred for 1–7 d at room temp., and then the mixture was directly purified by silica gel column chromatography using a mixture of heptane/EtOAc.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-4-nitro-1-oxo-3-phenylbutan-2-yl]-cyclopropyl}-carbamate 109:** Synthesized according to general procedure B. The product was isolated (299 mg, 86 %) as a white solid. The enantiomeric purity was retained as 98 % *ee* [HPLC: Chiralpak AD-H; hexane/EtOH, 9:1; 1 mL/min; 25 °C; 210 nm; t_R = 6.44 (minor), t_R = 7.28 (major) min]. IR: ν = 3384, 2979, 1715, 1555, 1434, 1367, 1270, 1161, 1031, 701 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.44 (d, *J* = 2.1 Hz, 1 H), 7.35–7.27 (m, 3 H), 7.25–7.21 (m, 2 H), 5.65 (dd, *J* = 13.0, 4.4 Hz, 1 H), 5.02 (s, 1 H), 4.83 (dd, *J* = 12.9, 9.9 Hz, 1 H), 3.96 (td, *J* = 10.5, 4.2 Hz, 1 H), 2.25 (d, *J* = 11.5 Hz, 1 H), 1.45 (s, 9 H), 1.35–1.29 (m, 1 H), 0.97–0.80 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.2, 155.9, 136.9, 129.4, 128.4, 128.3, 80.4, 79.0, 61.4, 42.8, 31.0, 28.4, 15.2, 14.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{25}N_2O_5^+$ [M + H]$^+$ 349.1758; found 349.1794.

(2*R*,3*S*)-2-(1-((tert-butoxycarbonyl)amino)cyclopropyl)-4-nitro-3-phenyl-butanoic acid 113[72]

tert-Butyl *N*-{1-[(2*R*,3*S*)-4-Nitro-1-oxo-3-phenylbutan-2-yl]-cyclopropyl}-carbamate **109** (41 mg, 0.12 mmol) was dissolved in MeCN (350 µL, 0.33 M), and aq NaH_2PO_4 (90 µL, 0.83 M) was added. The reaction mixture was cooled to 0°C. 35% aq H_2O_2 (10 µL) and aq $NaClO_2$ (216 µL, 0.94 M) were added. The mixture was stirred for 30 min at room. temp., and then $Na_2S_2O_3$ was added, and the reaction mixture was stirred at room temp. for 1 h. Then it was diluted with aq $NaHCO_3$ (3 mL, 1 M) and aq NaH_2PO_4 (3 mL, 0.83 M), and extracted with CH_2Cl_2 (5 x 4.5 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated to give the product (38 mg, 86%) as a white solid. $[\alpha]_D^{25}$= –31.0 (*c* = 0.05, $CHCl_3$), m.p. 95–97 °C. IR: ν = 3445, 2979, 1712, 1553, 1498, 1456, 1368, 1165, 1078, 759, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.09 (m, 5H), 5.68–5.60 (m, 1 H), 4.74–4.62 (m, 1 H), 3.90 (td, *J* = 10.8, 4.3, Hz, 1 H), 2.18 (d, *J* = 11.5, Hz, 1 H), 1.62 (s, 1 H), 1.46 (s, 9 H), 0.94 (dt *J* = 11.2, 6.4 Hz, 1 H), 0.85 (dt, *J* = 10.0, 6.5 Hz, 1 H), 0.76 (dt, *J* = 11.0, 5.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.2, 156.1,

138.0, 128.8, 128.3, 128.0, 80.4, 79.1, 56.8, 43.9, 32.0, 28.5, 16.9, 13.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}N_2O_6Na^+$ $[M + Na]^+$ 387.1527; found 387.1529.

(2*R*,3*S*)-4-amino-2-(1-((tert-butoxycarbonyl)amino)cyclopropyl)-3-phenyl-butanoic acid 114 (method 1)[72]

(2*R*,3*S*)-2-(1-((tert-butoxycarbonyl)amino)cyclopropyl)-4-nitro-3-phenylbutanoic acid **113** (48 mg, 0.13 mmol) was dissolved in MeOH (4.8 mL, 0.55 M), and a suspension of Raney-Ni (300 mg) was added. The mixture was stirred for 23h at ambient temperature, under an H_2 atmosphere. The reaction mixture was filtered through Celite®, and the filtrate was washed with aq MeCN (75 mL, MeCN/H_2O 2:1). The filtrate was concentrated and the crude product was purified by reversed phase column chromatography [gradient H_2O/AcOH (2000/1)/MeCN] to give the product (36 mg, 82%) as a white solid. $[\alpha]_D^{25}$ = –2.2 (*c* = 0.26, H_2O), m.p. 150–155 °C. IR: ν = 3419, 2978, 2931, 2879, 1713, 1581, 1496, 1455, 1391, 1367, 1170, 1076, 762, 701 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 7.43–7.28 (m, 5H), 4.28–4.14 (m, 1 H), 3.33–3.15 (m, 2 H), 2.19 (d, *J* = 10.8, Hz, 1 H), 1.45 (s, 9 H), 1.27–1.17 (m, 1 H), 1.01 (dt, *J* = 11.9, 6.4 Hz, 1 H), 0.90 (dt, *J* = 10.3, 6.3 Hz, 1 H), 0.82–0.72 (m, 1 H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 178.1, 157.5, 138.3, 129.1, 128.4, 128.0, 80.8, 59.2, 43.9, 43.2, 31.6, 27.7, 15.7, 12.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{27}N_2O_4^+$ $[M + H]^+$ 334.1965; found 335.1973.

(2*R*,3*S*)-4-amino-2-(1-((tert-butoxycarbonyl)amino)cyclopropyl)-3-phenyl-butanoic acid 114 (method 2)[72]

(2*R*,3*S*)-2-(1-((tert-butoxycarbonyl)amino)cyclopropyl)-4-nitro-3-phenylbutanoic acid **113** (24 mg, 0.07 mmol) was dissolved in MeOH (5 mL) under an argon atmosphere, and Pd/C (5%, 27 mg) was added. The reaction mixture was stirred for 7 d under H_2 atmosphere. The reaction mixture was filtered through Celite®, and the filtrate was washed with CH_2Cl_2/(MeOH/NH_3) (4:1). The filtrate was concentrated to give the product (12 mg, 55%) as a white solid.

General method for the synthesis of ethyl 2-(5-oxo-2,3,4-triphenyl-2,5-dihydrofuran-2-yl)-acetate 86 (Publication III)

To a 4 ml test tube was sequentially added cyclopropenone **78** (30.9 mg, 0.15 mmol), β-ketoester **85** (19.2 mg, 0.1 mmol), catalyst (0.02 mmol, 20 mol%), base (0.2–5.0 equiv), and solvent (1 ml). The reaction mixture was stirred at room temperature for the indicated time. Completion of the reaction was monitored by TLC and ^1H NMR spectroscopy. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography on silica gel to afford the pure product **86**, eluent petroleum ether – EtOAc, 20:1. Colorless oil. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ = 7.34–7.42 (m, 5H), 7.29–7.34 (m, 1H), 7.20–7.27 (m, 7H), 6.82–6.85 (m, 2H), 4.16 (qd, *J* = 7.1, *J* = 4.7 Hz, 2H), 3.40 (d, *J* = 15.4 Hz, 1H), 3.28 (d, *J* = 15.4 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ = 171.9, 168.3, 162.9, 137.2, 131.7, 129.7, 129.4, 129.3, 129.0, 128.8, 128.7, 128.3, 127.5, 125.7, 87.0, 61.3, 40.1, 14.3 ppm. HRMS (ESI): calcd. for $C_{26}H_{23}O_4$ $[M + H]^+$ 399.1591; found 399.1599.

***Table 7**. Supporting information concerning compounds discussed in the thesis but not presented in the Experimental section can be found in the corresponding publications.*

Entry	Compound number in thesis	Compound number in publication		
		I	II	III
1	**2a**	**5a**	**2a**	
2	**10a**	**6a**	**3**	
3	**10b**	**6b**	**7**	
4	**12**		**12**	
5	**18**	**10b**	**10**	
6	**78**			**1**
7	**85**			**2**
8	**86**			**3**
9	**90**	**1**		
10	**91**	**2**		
11	**92**	**3**		
12	**93**	**4**	**1a**	
13	**95a**	**11a**		
14	**95b**	**11b**		
15	**95c**	**11c**		
16	**95d**	**11d**		
17	**95e**	**11e**		
18	**95f**	**11f**		
19	**95g**	**11g**		
20	**95h**	**11h**		

21	**95i**	**11i**		
22	**97**	**9**		
23	**98**	**8**		
24	**99**	**7**		
25	**100**	**10a**		
26	**102**		**9**	
27	**108**		**1b**	
28	**109**		**5a**	
29	**110a**		**6a**	
30	**110b**		**6d**	
31	**110e**		**6b**	
32	**110g**		**6f**	
33	**110h**		**6j**	
34	**110i**		**6h**	
35	**110j**		**6c**	
36	**110k**		**6e**	
37	**110l**		**6g**	
38	**110m**		**6i**	
39	**110n**		**6k**	
40	**110o**		**6l**	
41	**110p**		**6m**	
42	**110q**		**6n**	
43	**110r**		**6o**	
44	**111**		**8**	

45	**112a**		**13a**	
46	**112b**		**13b**	
47	**115**			**I**
48	**116**			**II**
49	**117**			**III**
50	**118**			**IV**
51	**119**			**V**
52	**120**			**VI**
53	**121**			**VII**
54	**122a**			**VIIIa**
55	**122b**			**VIIIb**
56	**122c**			**VIIIc**
57	**122d**			**VIIId**
58	**123**			**IX**

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Acknowledgements

This work was conducted in the Department of Chemistry and Biotechnology of Tallinn University of Technology, and was financially supported by the Estonian Ministry of Education and Research (grant nos. IUT 19-32, PUT 1468) and "TUT Institutional Development Program for 2016-2022" Graduate School in Biomedicine and Biotechnology receiving funding from the European Regional Development Fund under program ASTRA 2014-2020.4.01.16-0032 in Estonia.

First, and above all, I would like to thank my supervisor, Professor Tõnis Kanger, for his thorough supervision, support and motivation throughout these years. I would like to thank Professor Margus Lopp for giving me the opportunity to work in the Department of Chemistry and Biotechnology.

I thank all the members of the Group of Organic Chemistry for lending a helping hand whenever needed and creating an enjoyable atmosphere in the lab.

Special thanks go to all the previous and current PhD students in our group, who shared ups and downs with me in this long journey: Kristin, Marju, Kerti, Kadri, Riina, Maksim, Artur and Mikk!

My endless gratitude goes to my family for their unconditional support.

Abstract

Organocatalytic Asymmetric Michael Addition to Cyclopropyl Derivatives

There is a continuous demand for new efficient methods that can be applied for the synthesis of enantiopure compounds. Asymmetric organocatalytic synthesis is widely used method for the synthesis of chiral compounds. This thesis is focused on an enantioselective organocatalyzed Michael addition applied for the synthesis of a cyclopropyl group containing compounds. During the study conditions for the selective formation of different addition products were established. The highly strained cyclopropane moiety is an important motif in many biologically active compounds. Several methods have been developed to obtain chiral cyclopropane ring-containing compounds. Quite often the synthesis requires several steps and enantiopure starting material, thus the preparation methods of cyclopropane ring-containing compounds in enantiomerically pure form still pose a challenge.

The results of this thesis are divided into three chapters. The first study describes the synthesis of alkylidenecyclopropane derivatives via an asymmetric aminocatalytic Michael addition of aldehyde to nitroalkene derivatives. The novelty of the approach lies in the use of 1-(2-oxoethyl)cyclopropyl acetate **93**, as an aldehydes containing cyclopropane moiety had not been previously used as Michael donor in the Michael reaction. The developed method offers a new possibility to obtain several multifunctional compounds that have a broad synthetic utility.

The second chapter presents the use of amine-functionalized cyclopropylacetaldehyde as Michael donor for the synthesis of amino acid precursors. This allows the one-step introduction of the cyclopropane ring, as well as two different nitrogen-containing functional groups into the target compound. We have developed a general straightforward route to β- and γ-amino acid precursors.

The third chapter describes the study of the asymmetric organocatalyzed [3+2] annulation of cyclopropenone and β-keto ester. The aim of the study was to investigate various organocatalytic activation modes for the synthesis of chiral butenolides. Four different catalytic approaches were investigated: bifunctional thiourea catalysis, chiral base catalysis, aminocatalysis and phase-transfer catalysis. The study revealed that in principal the use of phase-transfer catalysis could be the method of choice, but further investigation is needed.

Lühikokkuvõte
Tsüklopropaani derivaatide asümmeetriline organokatalüütiline Michaeli liitumisreaktsioon

Aina kasvav nõudlus enantiomeerselt puhaste ainete järele sunnib teadlasi otsima nii uusi meetodeid kui ka leidma sobivaid lähteühendeid nende sünteesimiseks. Asümmeetrilised organokatalüütilised reaktsioonid on laialt levinud meetodid kiraalsete ühendite saamisel. Organokatalüüsi kõrval on käesolevas doktoritöös teiseks läbivaks teemaks tsüklopropaani ringi sisaldavad ühendid. Tsüklopropaani fragment on levinud struktuurielement bioloogiliselt aktiivsetes ühendites. Sageli hõlmab tsüklopropaani fragmenti sisaldava kiraalse ühendi süntees mitut etappi ja enantiomeerselt puhta lähteaine kasutamist. Seega on aktuaalne töötada välja sünteesimeetodeid uute seda tüüpi ühendite saamiseks.

Antud töös uuriti asümmetrilist organokatalüütilist Michaeli liitumisreaktsiooni tsüklopropaani fragmenti sisaldava aldehüüdi **93** ja nitroolefiinide vahel. Töötati välja enantioselektiivne organokatalüütiline meetod kasutades kiraalset aminokatalüsaatorit, mille efektiivsust tõstis sobiva vesinikdonoorse akiraalse ko-katalüsaatori lisamine. Michaeli liitumisreaktsiooni tulemusena saadi alkülideen tsüklopropaani derivaate kõrge enantiomeerse puhtustega (*ee* 85-99%), reaktsiooni käigus elimineerius atsüülrühm.

Vältimaks võimalikku elminieerumisreaktsiooni sünteesiti aminorühma sisaldav tsükloropaankarbaldehüüd **108**, ning viidi läbi organokatalüütiline Michaeli liitumis-reaktsioon sünteesitud aldehüüdi ja niroolefiinide vahel. Reaktsiooni tulemusena saadi β- ja γ-aminohapete eelühendid kõrge diastereo- ja enantiomeerse puhtusega (*d.r.* kuni 95:5 ja *ee* 93-99%).

Asümmeetrilised organokatalüütilised kaskaadreaktsioonid on levinud meetodid kiraalsete heteroaromaatsete ühendite saamiseks. Seetõttu keskenduti töö teises osas asümmeetrilise organokatalüütilise sünteesimeetodi leidmisele tsüklopropenooni ja β-ketoestri vahelise liitumisreaktsiooni jaoks. Uuriti nelja erinevat asümmeetrilise aktiveerimise meetodit kiraalse produkti saamiseks: bifunktsionaalne tiouurea katalüüs, aluskatalüüs, aminokatalüüs ja faaside-vaheline katalüüs.

Uuritud meetoditest osutus sobivaks asümmeetriline faaside-vaheline katalüüs. Valitud meetod vajab täiendavat uurimist, kuna katalüüsi käigus saadud produkti enantiomeerne puhtus jäi madalaks.

Appendix

Publication I

Reitel, K.; Lippur, K.; Järving, I.; Kudrjašova, M.; Lopp, M.; Kanger, T. Asymmetric Aminocatalytic Michael Addition of Cyclopropane-Containing Aldehydes to Nitroalkenes. *Synthesis* **2013**, *45*, 2679-2683.

Asymmetric Aminocatalytic Michael Addition of Cyclopropane-Containing Aldehydes to Nitroalkenes

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Received: 15.02.2013; Accepted: 14.04.2013

Abstract: An asymmetric aminocatalytic approach to alkylidenecyclopropane derivatives via Michael addition of aldehydes to nitroalkene derivatives was developed.

Key words: asymmetric catalysis, Michael addition, amines, organocatalysis, alkylidenecyclopropane

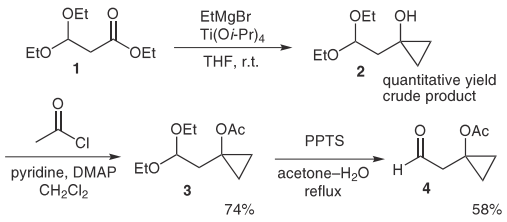
The asymmetric organocatalytic Michael addition of nucleophiles derived from carbonyl compounds to nitroolefins is a well-studied reaction.[1] The scope of the carbonyl Michael donors used in the reaction is wide, also includes derivatives of aldehydes and ketones. To the best of our knowledge, cyclopropane-containing aldehydes have not previously been used as Michael donors.

The asymmetric synthesis of cyclopropane-containing compounds is still a challenge so, considering the high synthetic utility of the derived compounds, new strategies to synthesize nonracemic functionalized cyclopropane derivatives are needed.[2] The Michael addition of cyclopropane-containing aldehydes to nitroolefins is an attractive option to synthesize such derivatives, especially considering the variety of efficient catalytic systems known for the asymmetric Michael reaction.[3] We report here the results of α-functionalization of aldehydes with nitrostryrene derivatives, which is a part of our ongoing research on organocatalysis.[4]

The synthetic route to the starting aldehyde **4** is depicted in Scheme 1. Kulinkovich reaction[5] of ethyl 3,3-diethoxypropanoate (**1**) led to cyclopropanol **2** in quantitative crude yield. Acetylation of the hydroxy group of crude **2** afforded cyclopropyl acetate **3** that underwent deacetalization with pyridinium 4-toluenesulfonate (PPTS) to afford aldehyde **4**.

The reaction between aldehyde **4** and nitrostyrene **5a** in the presence of various organocatalysts (Figure 1) was investigated as a model process (Table 1).

Surprisingly, no reaction occurred with the most widely used diphenylprolinol silyl ether **6a**[6] (Table 1, entry 1). The reaction proceeded only when the H-bonding catalyst *N*,*N*′-diethylthiourea (**10a**) was added, affording the product in low yield but with high stereoselectivity (entry 2).



Scheme 1 Synthesis of 1-(2-oxoethyl)cyclopropyl acetate **4**

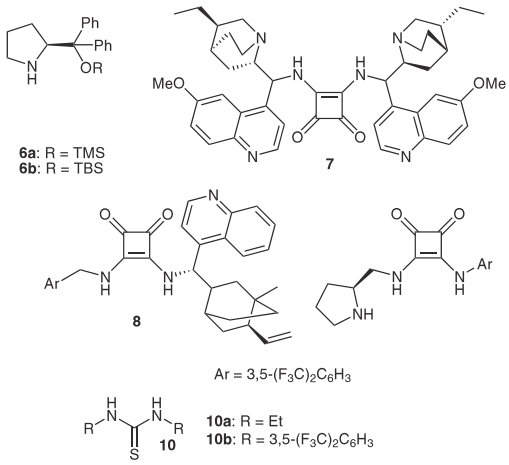


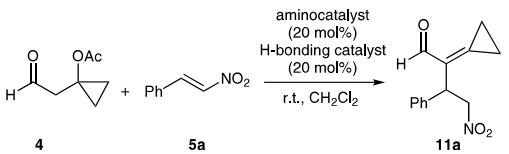
Figure 1 Catalysts and co-catalysts screened

In all cases elimination of the acetoxy group occurred, affording alkylidenecyclopropane derivative **11a**.

The presence of an aminocatalyst is essential for the formation of the Michael donor from the aldehyde. Nitrostyrene can be activated via an H-bonding catalyst. In principal, if either of the catalysts is nonracemic, an enantioselective reaction may occur. In our experiments, the combination of an achiral secondary amine (pyrrolidine) with chiral squaramide derivatives **7**[7] and **8**[8] resulted in a racemic product after a very slow reaction (entries 4 and 5). Catalyst **9**,[9] possessing both aminocatalytic and H-bonding catalytic properties in the same molecule, was also found to be inactive (entry 3). We concluded that the

SYNTHESIS 2013, 45, 2679–2683
Advanced online publication: 30.04.2013
DOI: 10.1055/s-0033-1338704; Art ID: SS-2013-C0131-ST

Table 1 Screening of Catalysts for Michael Addition



Entry	Aminocatalyst	H-Bonding catalyst	Time (d)	Yield (%)	ee (%)
1	**6a**	–	4	–[a]	–
2	**6a**	**10a**	4	34	90
3	**9**	–	9	–[a]	–
4	pyrrolidine	**8**	6	38	*rac*
5	pyrrolidine	**7**	1.5	42	*rac*

[a] No reaction.

stereoselectivity of the reaction is determined by the non-racemic aminocatalyst and hence the influence of the co-catalyst was investigated.

The mechanistic aspects of the Michael addition to nitrostyrene have been thoroughly studied.[10] It was proposed that the rate-determining step of the reaction is the protonation of the cyclobutane derivative of the iminium nitronate intermediate. Recently Pihko and co-workers[11] suggested that the key intermediates of the reaction are six-membered dihydrooxazine species. They also found that the acidic co-catalyst 4-nitrophenol accelerates the reaction considerably, affording Michael adducts in high yields and selectivity, even with α-alkyl nitroalkenes.

Based on these observations, we screened the effects of various co-catalysts on the yield and the stereoselectivity of the model reaction (Table 2).

Table 2 Screening of Co-catalysts[a]

Entry	Aminocatalyst	Co-catalyst	Yield (%) of **11a**	ee (%)
1	**6a**	**10a**	43	90
2	**6a**	**10b**	41	89
3	**6b**	**10b**	36	89
4	**6a**	benzoic acid	43	91
5	**6a**	3,5-dinitrobenzoic acid	–[b]	91
6	**6a**	4-nitrobenzoic acid	40	92
7	**6a**	4-nitrophenol	60	93
8	**6b**	4-nitrophenol	56	92

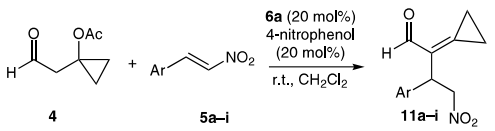
[a] Conditions: aldehyde **4** (0.35 mmol), nitrostyrene **5a** (0.35 mmol), aminocatalyst (20 mol%), co-catalyst (20 mol%), CH_2Cl_2, r.t., 24 h.
[b] Not determined.

Achiral thioureas **10a** and **10b** as co-catalysts revealed a similar effect affording products in comparable yields and stereoselectivities (Table 2, entries 1 and 2). Changing the trimethylsilyl protective group of the aminocatalyst **6a** to the sterically more demanding *tert*-butyldiphenylsilyl group in **6b** did not influence the stereoselectivity, but slightly lowered the yield (entry 3). Quite similar results were obtained by adding benzoic acid or its derivatives (entries 4–6). 4-Nitrophenol was found to be the most selective and high-yielding co-catalyst (entries 7 and 8).

The reaction selectivity and yield depend on the acidity of the co-catalysts and 4-nitrophenol has an optimal pK_a value (pK_a in DMSO: **10b**, 8.5;[12] benzoic acid, 11.6;[13] 3,5-dinitrobenzoic acid, 6.8;[14] 4-nitrobenzoic acid, 8.9;[14] 4-nitrophenol, 10.8[15]).

With optimal reaction conditions in hand, the substrate scope for aldehyde **4** with different nitroolefins **5a–i** was explored (Table 3).

Table 3 Scope of the Reaction



Entry	Ar	Time (d)	Product	Yield (%)	ee (%)
1	Ph	1	**11a**	60	93
2	4-ClC_6H_4	1	**11b**	38	95
3	2-ClC_6H_4	1	**11c**	38	95
4	2-BrC_6H_4	1	**11d**	42	99
5	4-$MeOC_6H_4$	4	**11e**	27	87
6	4-$(F_3CO)C_6H_4$	1	**11f**	50	96
7	4-$O_2NC_6H_4$	4	**11g**	35	97
8	2-naphthyl	4	**11h**	34	92
9	2-thienyl	1	**11i**	27	85

We observed that all reactions were highly enantioselective and the substitution pattern did not influence the selectivity. Alkylidenecyclopropane derivatives **11** were obtained in high enantiomeric purity (85–99% ee). However, the yields of the reactions remained moderate; increasing the reaction time did not increase the yield of the product.

We conclude that the above-described enantioselective route to alkylidenecyclopropane aldehydes via aminocatalytic Michael addition to nitroalkenes offers a new possibility of obtaining several multifunctional compounds that have a broad synthetic utility.

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signal was used [δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR)] as an internal standard. Mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT infrared spectrophotometer. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. Chiral HPLC was performed using Chiralcel OJ-H and Chiralpak AD-H columns. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel KSK 40–100 μm was used. Chemicals were purchased from the Aldrich Chemical Co and were used as received. Reactions sensitive to oxygen or moisture were conducted under an argon atmosphere in flame-dried glassware.

1-(2,2-Diethoxyethyl)cyclopropan-1-ol (2)

To a soln of ethyl 3,3-diethoxypropanoate (**1**, 10.315 g, 54 mmol) in THF (54 mL) was added Ti(O*i*-Pr)$_4$ (3.29 mL, 11 mmol) at 0 °C and 1.5 M EtMgBr in THF (105 mL, 157 mmol) over 6 h under an argon atmosphere; the deep black soln was stirred at r.t. for 12 h. The mixture was concentrated under reduced pressure. The precipitate was diluted with CH_2Cl_2 (100 mL) and quenched with sat. NH_4Cl (15 mL) and filtered through a Celite pad. The filtrate containing aqueous and organic layers was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were extracted with sat. $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude product **2** (9.408 g, quant) as a slightly yellow liquid; R_f = 0.31 (EtOAc–heptane, 3:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (t, *J* = 5.8 Hz, 1 H), 3.76–3.68 (m, 2 H), 3.60 (d, *J* = 2.5 Hz, 1 H), 3.59–3.51 (m, 2 H), 1.88 (d, *J* = 5.8 Hz, 2 H), 1.22 (t, *J* = 7.1 Hz, 6 H), 0.75 (q, *J* = 5.2 Hz, 2 H), 0.44 (q, *J* = 5.2 Hz, 2 H).

NMR spectroscopic data were in agreement with literature data.[16]

1-(2,2-Diethoxyethyl)cyclopropyl Acetate (3)

To a soln of 1-(2,2-diethoxyethyl)cyclopropan-1-ol (**2**, 9.408 g, 54 mmol) in CH_2Cl_2 (50 mL) was added pyridine (8.730 g, 108 mmol) and DMAP (0.112 g, 0.918 mmol) at 0 °C. A soln of AcCl (4.910 g, 81 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C and the mixture was stirred for 8 h at r.t. The reaction was quenched by the addition of H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were washed with sat. $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was distilled in vacuo (bp 72–74 °C/1.9 mbar), affording **3** (8.71 g, 74%) as a pale yellow liquid; R_f = 0.49 (EtOAc–heptane, 3:10).

IR (neat): 2976, 1750, 1371, 1229, 1200, 1127, 1063 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.70 (t, *J* = 5.35 Hz, 1 H), 3.64 (q, *J* = 7.03 Hz, 1 H), 3.62 (q, *J* = 7.16 Hz, 1 H), 3.52 (q, *J* = 7.16 Hz, 1 H), 3.50 (q, *J* = 7.03 Hz, 1 H), 2.07 (d, *J* = 5.4 Hz, 2 H), 1.98 (s, 3 H), 1.20 (t, *J* = 7.09 Hz, 6 H), 0.87–0.79 (m, 2 H), 0.79–0.72 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 101.3, 61.5, 57.1, 38.9, 21.5, 15.5, 11.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}O_4Na$: 239.1254; found: 239.1255.

1-(2-Oxoethyl)cyclopropyl Acetate (4)

To a soln of 1-(2,2-diethoxyethyl)cyclopropyl acetate (**3**, 1.00 g, 4.6 mmol) in a mixture of acetone (9 mL) and H_2O (0.25 mL) was added at r.t. PPTS (0.196 g, 0.782 mmol); the mixture was refluxed for 8 h. The mixture was concentrated under reduced pressure and the precipitate was diluted with CH_2Cl_2 (13 mL) and washed with sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexanes, 1.5:10) to afford **4** (0.364 g, 58%) as a colorless liquid; R_f = 0.27 (EtOAc–heptane, 3:10).

IR (neat): 2841, 1747, 1729, 1371, 1223, 1172, 858 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (t, *J* = 2.5 Hz, 1 H), 2.76 (d, *J* = 2.5 Hz, 2 H), 1.98 (s, 3 H), 1.04–0.98 (m, 2 H), 0.88–0.81 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.3, 171.2, 55.1, 48.9, 21.3, 11.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_7H_{11}O_3$: 143.0703; found: 143.0705.

Alkylidenecyclopropanes; General Procedure

To aldehyde **4** (50 mg, 0.35 mmol) was added 4-nitrophenol (10 mg, 0.07 mmol), nitroalkene **5** (0.35 mmol), and a soln of catalyst **6a** (23 mg, 0.07 mmol) in CH_2Cl_2 (0.2 mL).The mixture was stirred at r.t. until completion of the reaction (TLC monitoring). The mixture was diluted with CH_2Cl_2 (6 mL) and washed with aq 1 M NaOH (6 mL) and brine (6 mL). After concentration under reduced pressure, the crude product was purified by column chromatography (EtOAc–hexanes, 1:10) to afford alkylidenecyclopropane **11**.

2-Cyclopropylidene-4-nitro-3-phenylbutanal (11a)

Yellow oil; yield: 46 mg (60%); R_f = 0.42 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –84.0 (*c* 0.075, MeOH).

The ee of the product was determined by HPLC (Chiralcel OD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 8:2, 1 mL/min, UV 230 nm): t_R = 27.19 (major), 24.69 min (minor).

IR (neat): 2831, 1680, 1553, 1431, 1216, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 7.34–7.21 (m, 5 H), 5.11 (dd, *J* = 12.7, 8.9 Hz, 1 H), 4.97–4.90 (m, 1 H), 4.83 (dd, *J* = 12.7, 7.1 Hz, 1 H), 1.58–1.44 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.0, 149.4, 137.8, 130.3, 129.1, 128.0, 127.9, 77.2, 42.5, 3.5, 1.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_3$: 232.0968; found: 232.0971.

3-(4-Chlorophenyl)-2-cyclopropylidene-4-nitrobutanal (11b)

Yellow oil; yield: 39 mg (38%); R_f = 0.41 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –90.0 (*c* 0.081, MeOH).

The ee of the product was determined by HPLC (Chiralpak AD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 9:1, 1 mL/min, UV 230 nm): t_R = 10.03 (major), 11.54 min (minor).

IR (neat): 2833, 2725, 1680, 1553, 1376, 1217, 1092, 1014, 830 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 7.30–7.25 (m, 2 H), 7.20–7.16 (m, 2 H), 5.06 (dd, *J* = 12.28, 8.0 Hz, 1 H), 4.88 (dd, *J* = 7.8, 7.6 Hz, 1 H), 4.82 (dd, *J* = 12.37, 7.51 Hz, 1 H), 1.59–1.42 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.91, 149.75, 136.29, 133.83, 129.99, 129.33, 129.21, 76.91, 41.95, 3.52, 1.91.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}ClNO_3$: 266.0578; found: 266.0559.

3-(2-Chlorophenyl)-2-cyclopropylidene-4-nitrobutanal (11c)

Yellow oil; yield: 39 mg (38%); R_f = 0.35 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –52.5 (*c* 0.072, MeOH).

The ee of the product was determined by HPLC (Chiralpak AD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 95:5, 1 mL/min, UV 230 nm): t_R = 11.02 (major), 10.33 min (minor).

IR (neat): 2834, 1681, 1555, 1279, 1177, 1135, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1 H), 7.40–7.36 (m, 1 H), 7.25–7.18 (m, 3 H), 5.39–5.34 (m, 1 H), 5.07 (dd, *J* = 13.43, 8.95

Hz, 1 H), 4.82 (dd, *J* = 13.49, 6.92 Hz, 1 H), 1.57–1.49 (m, 2 H), 1.47–1.38 (m, 1 H), 1.38–1.32 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.1, 151.7, 134.8, 134.2, 130.4, 129.1, 128.8, 128.7, 127.2, 75.4, 39.8, 3.8, 2.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}ClNO_3$: 266.0578; found: 266.0582.

3-(2-Bromophenyl)-2-cyclopropylidene-4-nitrobutanal (11d)
Yellow oil; yield: 45 mg (42%); R_f = 0.39 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –37.6 (*c* 0.104, MeOH).

The ee of the product was determined by HPLC (Chiralcel OJ-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 9:1, 1 mL/min, UV 230 nm): t_R = 35.62 (major), 34.29 min (minor).

IR (neat): 2848, 1681, 1553, 1437, 1375, 1225, 1024, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 7.59 (dd, *J* = 7.90, 1.2 Hz, 1 H), 7.28–7.19 (m, 2 H), 7.16–7.11 (m, 1 H), 5.40–5.33 (m, 1 H), 5.06 (dd, *J* = 13.6, 9.0 Hz, 1 H), 4.80 (dd, *J* = 13.6, 6.8 Hz, 1 H), 1.58–1.47 (m, 2 H), 1.47–1.39 (m, 1 H), 1.36–1.28 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.1, 151.7, 136.5, 133.8, 129.4, 128.8, 128.8, 127.8, 124.9, 75.4, 42.3, 3.9, 2.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}BrNO_3$: 310.0073; found: 310.0088.

2-Cyclopropylidene-3-(4-methoxyphenyl)-4-nitrobutanal (11e)
Yellow oil; yield: 25 mg (27%); R_f = 0.30 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –43.0 (*c* 0.043, MeOH).

The ee of the product was determined by HPLC (Chiralpak AD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 9:1, 1 mL/min, UV 230 nm): t_R = 12.18 (major), 13.44 min (minor).

IR (neat): 2960, 1747, 1681, 1555, 1373, 1278, 1135, 897, 845, 702, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 7.19–7.13 (m, 2 H), 6.85–6.79 (m, 2 H), 5.07 (dd, *J* = 12.4, 8.5 Hz, 1 H), 4.90–4.83 (m, 1 H), 4.79 (dd, *J* = 12.4, 7.3 Hz, 1 H), 3.77 (s, 3 H), 1.57–1.44 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.1, 159.2, 149.0, 130.6, 129.7, 129.0, 114.4, 77.4, 55.4, 41.8, 3.5, 1.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_4$: 262.1074; found: 262.1084.

2-Cyclopropylidene-4-nitro-3-[4-(trifluoromethoxy)phenyl]butanal (11f)
Yellow oil; yield: 56 mg (50%); R_f = 0.41 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –95.7 (*c* 0.061, MeOH).

The ee of the product was determined by HPLC (Chiralpak AD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 95:5, 1 mL/min, UV 230 nm): t_R = 9.94 (major), 11.64 min (minor).

IR (neat): 2835, 1681, 1555, 1263, 1220, 1166, 852, 677 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 7.32–7.26 (m, 2 H), 7.17–7.13 (m, 2 H), 5.08 (dd, *J* = 12.6, 8.3 Hz, 1 H), 4.97–4.90 (m, 1 H), 4.84 (dd, *J* = 12.6, 7.4 Hz, 1 H), 1.60–1.43 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.9, 149.9, 148.8, 136.5, 130.0, 129.4, 121.5, 120.6 (q, $^1J_{CF}$ = 257 Hz), 76.9, 41.9, 3.5, 1.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}F_3NO_4$: 316.0791; found: 316.0786.

2-Cyclopropylidene-4-nitro-3-(4-nitrophenyl)butanal (11g)
Yellow oil; yield: 34 mg (35%); R_f = 0.26 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –52.9 (*c* 0.055, MeOH).

The ee of the product was determined by HPLC (Chiralpak AD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 8:2, 1 mL/min, UV 230 nm): t_R = 14.25 (major), 19.13 min (minor).

IR (neat): 2838, 1681, 1556, 1521, 1375, 1349, 1177, 856, 717 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 8.19–8.14 (m, 2 H), 7.64–7.42 (m, 2 H), 5.09 (dd, *J* = 12.3, 7.8 Hz, 1 H), 5.04–5.00 (m, 1 H), 4.91 (dd, *J* = 12.2, 7.3 Hz, 1 H), 1.64–1.48 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.6, 150.7, 147.6, 145.1, 129.4, 129.0, 124.3, 76.4, 42.4, 3.6, 2.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}N_2O_5$: 277.0819; found: 277.0822.

2-Cyclopropylidene-3-(naphthalen-2-yl)-4-nitrobutanal (11h)
Yellow oil; yield: 34 mg (34%); R_f = 0.40 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –171.9 (*c* 0.066, MeOH).

The ee of the product was determined by HPLC (Chiralpak AD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 95:5, 1 mL/min, UV 230 nm): t_R = 17.54 (major), 19.69 min (minor).

IR (neat): 2832, 1681, 1555, 1376, 1223, 856, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 7.82–7.76 (m, 3 H), 7.70 (d, *J* = 1.4 Hz, 1 H), 7.51–7.43 (m, 2 H), 7.33 (dd, *J* = 8.6, 1.9 Hz, 1 H), 5.19 (dd, *J* = 12.5, 8.8 Hz, 1 H), 5.13–5.07 (m, 1 H), 4.94 (dd, *J* = 12.5, 6.8 Hz, 1 H), 1.59–1.46 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.1, 149.7, 135.2, 133.4, 132.8, 130.3, 128.9, 128.0, 127.8, 126.9, 126.6, 126.4, 125.7, 77.1, 42.5, 3.6, 1.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_3$: 282.1125; found: 282.1132.

2-Cyclopropylidene-4-nitro-3-(thiophen-2-yl)butanal (11i)
Yellow oil; yield: 23 mg (27%); R_f = 0.47 (EtOAc–hexanes, 2:5); $[\alpha]_D^{25}$ –76.7 (*c* 0.042, MeOH).

The ee of the product was determined by HPLC (Chiralpak AD-H, 250 × 4.6 mm, column, hexane–*i*-PrOH, 95:5, 1 mL/min, UV 230 nm): t_R = 12.00 (major), 13.29 min (minor).

IR (neat): 2836, 2727, 1681, 1556, 1374, 1279, 1137, 1068, 703, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 7.18 (dd, *J* = 5.0, 1.4 Hz, 1 H), 6.94 (ddd, *J* = 3.6, 1.4, 0.7 Hz, 1 H), 6.92 (dd, *J* = 5.0, 3.6 Hz, 1 H), 5.27–5.20 (m, 1 H), 5.08 (dd, *J* = 13.0, 9.0 Hz, 1 H), 4.86 (dd, *J* = 13.0, 7.1 Hz, 1 H), 1.58–1.49 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.6, 150.1, 140.5, 130.1, 127.3, 126.1, 125.1, 77.6, 37.7, 3.5, 2.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_3S$: 238.0532; found: 238.0540.

Acknowledgment

The authors thank the Estonian Science Foundation (Grant No. 8289), the Ministry of Education and Research (Grant No. 0140060s12), and the EU European Regional Development Fund (3.2.0101.08-0017) for financial support, and Prof. Oleg Kulinkovich for discussions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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Publication II

Kaasik, M.; Noole, A.; Reitel, K.; Järving, I.; Kanger, T. Organocatalytic Conjugate Addition of Cyclopropylacetaldehyde Derivatives to Nitro Olefins: en Route to β- and γ-Amino Acids. *European Journal of Organic Chemistry* **2015**, *8*, 1745-1753.

EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201403387

Organocatalytic Conjugate Addition of Cyclopropylacetaldehyde Derivatives to Nitro Olefins: en Route to β- and γ-Amino Acids

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Keywords: Organocatalysis / Michael addition / Small ring systems / Amino acids

Cyclopropane-containing amino acids are important pharmaceuticals and biologically active compounds. A new organocatalytic asymmetric Michael reaction has been developed. This allows the one-step introduction of the cyclopropane ring, as well as two different nitrogen-containing functional groups (*tert*-butoxycarbonylamino and nitro) into the target compounds. All the products were isolated in good yields with moderate to excellent enantio- and diastereoselectivities.

Introduction

Cyclopropane stands out among other ring systems (four-, five-, and six-membered rings) owing to its unique reactivity profile. Various methods have been developed for the asymmetric synthesis of cyclopropanes: the Simmons–Smith reaction,[1] MIRC (Michael-induced ring closure),[2] transition-metal-catalysed decomposition of diazo compounds,[3] the Kulinkovich reaction,[4] double alkylation of glycine,[5] rearrangement of lactones,[6] and miscellaneous other methods, which have been reviewed by Pellissier.[7] However, many of these methods are limited in their substrate scope, and involve the use of expensive transition metals or hazardous starting materials. Therefore, new and efficient methods for the introduction of a cyclopropane fragment under mild conditions continue to be very important.

Amino acids play a central role as the "building blocks of life". They are the key starting materials for peptide synthesis, and also for the synthesis of various lead compounds for the pharmacological industry that contain amino acid functionalities. Unnatural (and natural) β-amino acids have been synthesised by aza-Michael additions,[8] aziridine or epoxide openings, carbene-catalysed umpolung reactions, oxidation etc.[9] Although numerous methods have been reported for the formation of the C–N bond in β-amino acids, the introduction of a cyclopropane ring at the position α to the nitrogen remains a challenge.

Many natural and synthetic chiral amino acids containing a cyclopropane core have been identified (Figure 1).[10] Inspired by the unique properties introduced by the cyclopropane ring to a wide variety of different compounds, we recently reported a simple Michael-addition reaction of cyclopropylacetaldehyde derivative **1a** to nitro alkenes **2** (Scheme 1).[11] This simple reaction, promoted by chiral secondary amine **3** and *p*-nitrophenol, delivered a series of alkylidene cyclopropanes **4** in moderate to good yields (27–60%) with high enantioselectivities (85–97% *ee*). The β-elimination of the acetate group excluded the possibility of the formation of diastereoisomers, and the products could be used as building blocks for further transformations, providing an excellent starting point for further studies.

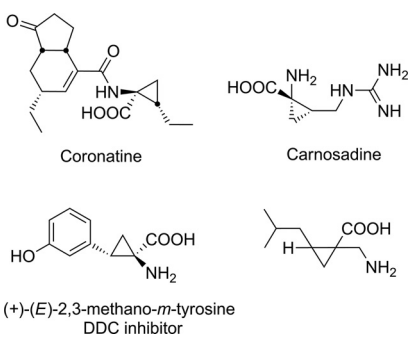
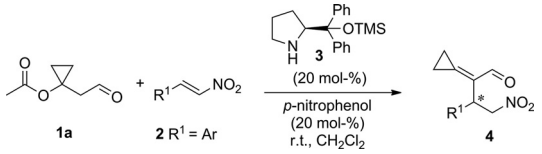


Figure 1. Cyclopropane-containing amino acids; DDC = Dopa decarboxylase.



Scheme 1. Previous work; TMS = trimethylsilyl.

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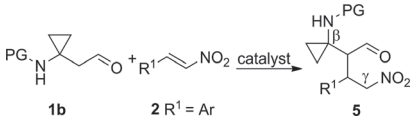
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403387.

We realised that by replacing the acetate group with an amino functionality we could not only eradicate the elimination pathway, but also achieve a direct synthesis of β- and γ-amino acid precursors.[12]

Results and Discussion

In this paper, we report a simple, one step organocatalytic asymmetric Michael reaction between amine-functionalised cyclopropylacetaldehyde derivative **1b** and nitro alkenes **2**. Inspired by the considerations mentioned above, as well as by our previous work (Scheme 1), we envisioned that replacing the acetate moiety by a protected amino group could provide an easy route to precursors of β-amino acids (Scheme 2). Not only that, but γ-amino acids could also be prepared from the Michael adducts by reduction of the nitro group.



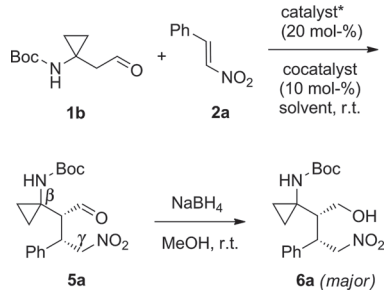
1b **2** R^1 = Ar **5**

Scheme 2. Proposed reaction for the formation of amino acid precursors; PG = protecting group.

Aldehyde **1b** was synthesised starting from cheap, commercially available starting materials (Scheme 3).[13] Michael addition of benzyl alcohol to acrylonitrile followed by Kulinkovich cyclopropanation, Boc (*tert*-butoxycarbonyl) protection, debenzylation, and Dess–Martin oxidation gave amine-functionalised aldehyde **1b** in five steps. The Boc protecting group allows the two nitrogen-containing functionalities to be discriminated in the further derivatisation of amino acid precursors **11**.

Based on our previous findings with acetate-containing aldehyde **1a**, preliminary experiments for the Michael addition were carried out in CH_2Cl_2 at room temperature in the presence of a chiral catalyst and an acidic cocatalyst (Table 1; Figure 2).[10]

Table 1. Screening for the reaction between amino aldehyde **1b** and nitrostyrene **2a**.

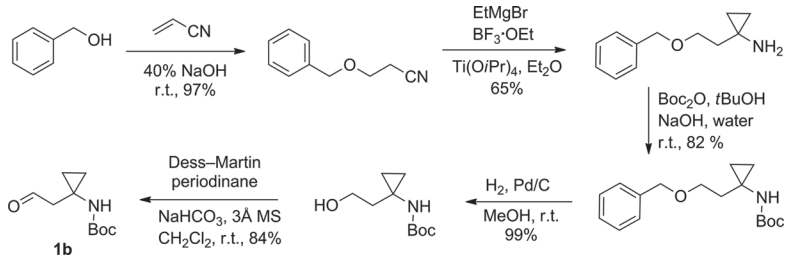


1b **2a** **5a** **6a** *(major)*

Entry	Catalyst/ cocatalyst	Solvent	Time [h]	Yield [%][d]	*dr*[e]	*ee* [%][f]
1	**3/9**	CH_2Cl_2	20	53	86:14	70
2	**3/10**	CH_2Cl_2	17	49	88:12	96
3	**3/9**[a]	CH_2Cl_2	23	74	75:25	98
4	**3/10**[a]	CH_2Cl_2	24	69	83:17	92
5	**12/10**[a]	CH_2Cl_2	4 d	traces	n.d.	n.d.
6	**8/10**[a]	CH_2Cl_2	7 d	–	–	–
7	**7/10**[a]	CH_2Cl_2	20	85	94:6	97
8	**7/10**[a]	toluene	30	72	90:10	95
9	**7/10**[a]	$CHCl_3$	24	63	90:10	95
10	**7/10**[b]	CH_2Cl_2	26	74	95:5	98
11	**7/10**[b,c]	CH_2Cl_2	29	60	95:5	98
12	**7/13a**[b]	CH_2Cl_2	7 d	30	58:42	55
13	**7/13b**[b]	CH_2Cl_2	7 d	traces	n.d.	n.d.

[a] 20 mol-% of cocatalyst was used. [b] 10 mol-% of catalyst was used. [c] 5 mol-% of cocatalyst was used. [d] Isolated yield of **6a**. [e] Determined from the crude mixture by ^{1}H NMR spectroscopy for aldehyde **5**. [f] Determined by chiral HPLC for alcohol **6a**.

Treatment with Jørgensen–Hayashi type catalyst **3** in the presence of *p*-nitrophenol followed by in situ reduction gave the corresponding alcohol (i.e., **6**) in 53% yield with moderate selectivity (Table 1, entry 1). The aldehydes (i.e., **5**) can be isolated, as was later demonstrated for a large scale synthesis of **5a**. However, on a small scale, the yields of aldehyde **5** were inconsistent. A great improvement in enantioselectivity was observed by switching to thiourea-based cocatalyst **10** (Table 1, entry 2). Increasing the cocatalyst loading to 20 mol-% increased the yield significantly for reactions cocatalysed by both *p*-nitrophenol **9** and thiourea **10**



1b

Scheme 3. Synthesis of amine-containing cyclopropanecarbaldehyde **1b**.

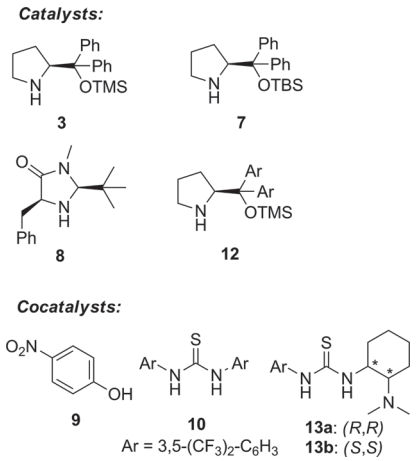


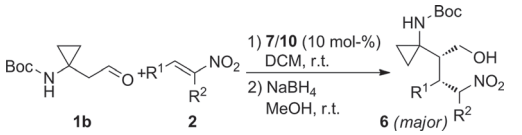
Figure 2. Catalysts and cocatalysts used during the reaction optimisation; TBS = *tert*-butyldimethylsilyl.

(Table 1, entries 3 and 4). Chiral amines **12** and **8** failed to give the expected product, and almost no reaction was seen after 4–7 d (Table 1, entries 5 and 6). Significant enhancements of both diastereoselectivity and enantioselectivity were observed with combinations of catalyst **7** and cocatalyst **10** (Table 1, entry 7). Switching the solvent to toluene or chloroform had a detrimental effect on the yield and diastereoselectivity (Table 1, entries 8 and 9). However, the catalyst loading for both chiral amine **7** and thiourea **10** was successfully lowered to 10 mol-% (Table 1, entry 10). A further decrease in catalyst loading resulted in a drop in the reaction rate and yield (Table 1, entry 11). Replacing the achiral cocatalyst with Takemoto's thiourea (both enantiomers were tested) resulted in the isolation of the product with a diastereoisomeric ratio of almost 1:1 and moderate enantioselectivity, or no reaction at all (Table 1, entries 12 and 13).

Having established the optimal conditions (10 mol-% of both amine **7** and thiourea **10** in CH_2Cl_2 at r.t.) we went on to explore the full scope of the reaction. Nitro alkenes with both electron-donating and electron-withdrawing groups gave the expected Michael adducts in good yields and high diastereo- and enantioselectivities (Table 2, entries 1–6). With a *para*-nitrophenyl-substituted nitro alkene, the reaction time increased due to the low solubility of **2f** (Table 2, entry 6).

Heteroaromatic nitro olefins **2** were also compatible with the reaction conditions, although in some cases prolonged reaction times (Table 2, entries 9 and 10) or higher catalyst loadings (Table 2, entry 9) proved necessary to achieve full conversion. Propargyl-substituted nitro alkene **2k** gave the corresponding product with a lower diastereoselectivity, but in a high yield, and with an excellent enantioselectivity for the major diastereomer (Table 2, entry 11). With ester-substituted nitro olefin **2l**, complete regioselectivity was observed (Table 2, entry 12). Although the diastereoselectivity

Table 2. Screening for the reaction between aldehyde **1b** and nitro alkenes **2**.



1b 2

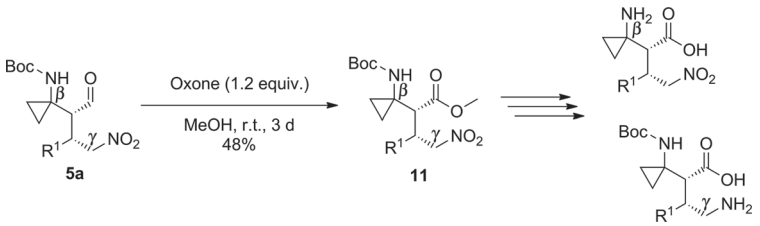
Entry	2	R^1	R^2	Time [h]	Yield [%][c]	*dr*[d]	*ee* [%][e]
1	**2a**	C_6H_5	H	25	74	95:5	99
2	**2b**	4-MeO-C_6H_4	H	28	70	89:11	98
3	**2c**	2-Br-C_6H_4	H	49	65	95:5	99
4	**2d**	4-Cl-C_6H_4	H	48	78	95:5	98
5	**2e**	3-Br-C_6H_4	H	46	56	94:6	99
6	**2f**	4-NO_2-C_6H_4	H	79	69	95:5	98
7	**2g**	furan-2-yl	H	24	79	80:20	97
8	**2h**	thiofuran-2-yl	H	29[a]	75	86:14	94
9	**2i**	pyridine-3-yl	H	6 d	56[b]	88:12	93[f]
10	**2j**	naphthalene-1-yl	H	5 d	74	85:15	93
11	**2k**	C_6H_5-C≡C	H	24	86	69:31	97/65
12	**2l**	$CH_3CH_2O(O)C$	H	47	57[b]	72:28	99/92[f]
13	**2m**	C_6H_{11}	H	7 d	47[b]	83:17	99[f]
14	**2n**	C_6H_5	CH_3	7 d	–	–	–
15	**2o**	–$(CH_2)_4$–		7 d	–	–	–

[a] 15 mol-% of **7/10** was used. [b] Product was isolated as aldehyde **5**. [c] Isolated yield of **6a**. [d] Determined from the crude mixture by ^{1}H NMR spectroscopy for aldehyde **5a**. [e] Determined by chiral HPLC for alcohol **6**. [f] Determined by chiral HPLC for aldehyde **5**.

was moderate, an excellent level of enantiocontrol was retained for both isomers.

Aliphatic substrate **2m** proved considerably less reactive than the aromatic nitro alkenes, but nevertheless, the product was isolated in moderate yield, with good diastereoselectivity and high enantioselectivity (Table 2, entry 13). An α-substituted nitro olefin (α-methyl nitrostyrene **2n**) and a α,β-disubstituted aliphatic nitro olefin (1-nitrocyclohexene **2o**) did not react, even after 7 d in the presence of 30 mol-% of catalyst and cocatalyst (Table 2, entries 14 and 15).

The formation of the *anti*-configured Michael products can be rationalised by the *Z* configuration of the reactive enamine (Figure 3). It has been shown that enamine formation can be substrate controlled, and that the *Z*-enamine can be stabilised by intramolecular hydrogen bonding.[14] We suppose that a hydrogen bond between the nitrogen atom of the pyrrolidine ring and the NH of the NHBoc group is responsible for the *Z* configuration of the enamine. As predicted by Seebach's synclinal transition state model, the *anti*-configured Michael product is obtained.[15] The absolute stereochemistry is determined by a sterically less hindered nucleophilic attack from the *Re*-face of the enamine onto the *Si*-face of the nitrostyrene to give the product with a 2*R*,3*S* configuration. Based on previous studies of the mechanism of the Michael addition of aldehydes to nitro olefins[16] (most recently by Pihko et al.),[17] the key intermediate in the reaction is a six-membered dihydrooxazine oxide (OO). Although according to Pihko et al. the OO



Scheme 4. Formation of ester **11** from aldehyde **5a**.

species are in equilibrium with cyclobutanes, only the OO intermediates can be protonated in the rate-determining step, thus leading to the expected Michael adducts. The great importance of an acidic additive was also supported by our work, as no reaction occurred without an acidic co-catalyst. However, with acetate-substituted aldehyde **1a**, *p*-nitrophenol **9** proved to be the most active and selective cocatalyst, but for aldehyde **1b**, thiourea **10** gave the products with higher diastereoselectivities.

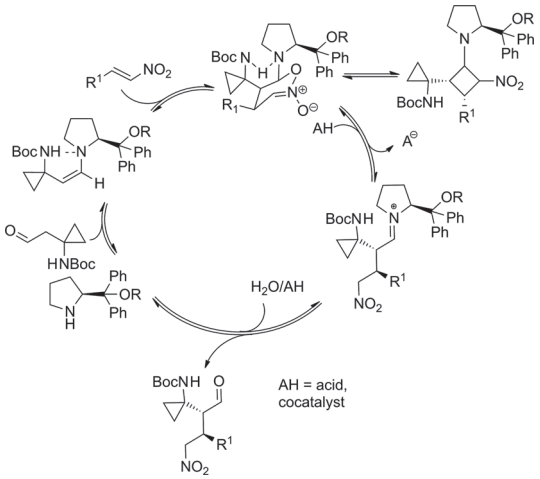


Figure 3. Proposed mechanism for the Michael addition.

To further investigate the feasibility of forming β-amino acids from Michael adducts **5**, aldehyde **5a** was converted into the corresponding methyl ester (i.e., **11**) under oxidative conditions (unoptimised; Scheme 4). Saponification of the ester group in **11** and deprotection of the amine would lead to the corresponding cyclopropane β-amino acids.[18] A formal synthesis of γ-amino acids can be achieved by reduction of the nitro group[19] in ester **11** (Scheme 4). Also, cyclopropyl-substituted pyrrolidine derivatives could be obtained from aldehyde **5** through intramolecular reductive amination,[20] or the corresponding γ-lactams from ester **11**.[21]

The absolute and relative stereochemistry of the products was established by single-crystal X-ray diffraction of one of the products (i.e., **6c**). The stereochemistry of the other compounds in the series was assigned by analogy (Figure 4).

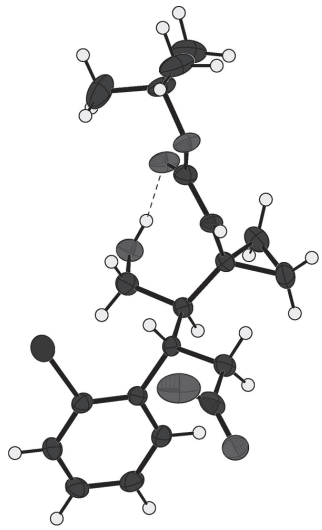


Figure 4. X-ray structure of alcohol **6c**.[22] The absolute configuration was determined based on the anomalous dispersion effect.

Conclusions

In summary, we have developed a general, straightforward route to β- and γ-amino acid precursors **5/6**, as well as to unsaturated cyclopropane-containing aldehydes **4**. Both series of products can serve as building blocks for further chemical transformations. We have shown that aldehyde **5a** can be converted into the corresponding ester (i.e., **11**), which can serve as the starting material for the formation of amino acids.

Experimental Section

General Information: Commercially available reagents were used without further purification. CH_2Cl_2 and chloroform were dried by distillation from P_2O_5, diethyl ether from $LiAlH_4$, and MeOH and toluene from sodium metal. All air- or moisture-sensitive reactions

were carried out under an argon atmosphere using oven-dried glassware. The reactions were monitored by thin-layer chromatography (TLC) with silica-gel-coated aluminum plates (Merck 60 F254), which were visualised with $KMnO_4$, anisaldehyde, or ninhydrin stains, yields refer to chromatographically purified or crystallised products. ^1H NMR spectra were recorded at 400 MHz, and are reported in parts per million (δ) relative to tetramethylsilane. Spectra were calibrated using residual solvent signals. Data for ^1H NMR spectra are given as follows: chemical shift δ (ppm), multiplicity (s = singlet, br. = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constant J [Hz], and relative integration. ^{13}C NMR spectra were recorded at 100 MHz, and are reported in parts per million (δ) relative to tetramethylsilane. Spectra were calibrated using solvent signals. HRMS spectra were recorded with an Agilent Technologies 6540 UHD accurate-mass Q-TOF LC–MS spectrometer using AJ-ESI ionisation. Optical rotations were measured with an Anton Paar GWB MCP500 polarimeter. Chiral HPLC was carried out using either a Lux Amylose-2, a Chiralcel OD-H, a Chiralcel OJ-H, a Chiralpak AD-H, or a Chiralpak AS-H column.

3-(Benzyloxy)propanenitrile: Synthesised according to a literature procedure. Analytical data matched those reported in the literature.[23] Yield 13.4 g, 97%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 5 H), 4.59 (s, 2 H), 3.69 (t, J = 6.4 Hz, 2 H), 2.62 (t, J = 6.4 Hz, 2 H) ppm.

1-[2-(Benzyloxy)ethyl]cyclopropan-1-amine: Synthesised according to a literature procedure. Analytical data matched those reported in the literature.[24] Yield 8.5 g, 65%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.53 (s, 2 H), 3.68 (t, J = 6.3 Hz, 2 H), 1.87 (s, 2 H), 1.73 (t, J = 6.3 Hz, 2 H), 0.60–0.55 (m, 2 H), 0.45–0.41 (m, 2 H) ppm.

***tert*-Butyl *N*-{1-[2-(Benzyloxy)ethyl]cyclopropyl}carbamate:** 1-(2-Benzyloxyethyl)cyclopropylamine (4.533 g, 23.7 mmol) was dissolved in water (40.5 mL) and *tert*-butanol (28.3 mL), and the mixture was cooled to 0 °C. NaOH (1.043 g, 26.1 mmol) was added, followed by di-*tert*-butyl dicarbonate (5.69 g, 26.1 mmol) over 10 min. The reaction mixture was stirred for 17 h at ambient temperature. The resulting crystals were collected by filtration, washed with cold water and dried under vacuum to give the product. To obtain further product, the aqueous washings were extracted with Et_2O (2 × 50 mL), and the combined organic extracts were concentrated. The resulting residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 30:1) to give further product. The total yield was 5.6 g (82%), m.p. 78–79 °C. IR: $\tilde{\nu}$ = 3367, 1694, 1509, 1254, 1171, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 4 H), 7.31–7.26 (m, 1 H), 4.90 (s, 1 H), 4.51 (s, 2 H), 3.63 (t, J = 6.5 Hz, 2 H), 1.85 (t, J = 5.7 Hz, 2 H), 1.41 (s, 9 H), 0.81–0.69 (m, 2 H), 0.68–0.59 (m, J = 5.8 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6, 138.6, 128.4, 127.5, 79.1, 72.9, 68.3, 36.2, 31.3, 28.4, 13.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{26}NO_3^+$ $[M + H]^+$ 292.1907; found 292.1910.

***tert*-Butyl *N*-[1-(2-Hydroxyethyl)cyclopropyl]carbamate:** *tert*-Butyl *N*-{1-[2-(benzyloxy)ethyl]cyclopropyl}carbamate (326 mg, 1.12 mmol) was dissolved in methanol (21 mL) in a pressure reactor under an argon atmosphere, and Pd/C (5%; 28 mg) was added. The reaction mixture was stirred for 3 d under H_2 gas (up to 21 bar pressure). The reaction mixture was filtered through Celite®, and the filtrate was concentrated to give the product (224 mg, 99%) as a white solid. The analytical data matched those reported in the literature. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.97 (s, 1 H), 4.05 (t, J = 6.8 Hz, 1 H), 3.71 (q, J = 6.0 Hz, 2 H), 1.63 (t, J = 5.4 Hz, 2 H), 1.44 (s, 9 H), 0.87–0.70 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 80.0, 59.7, 41.1, 29.7, 28.3, 14.1 ppm. HRMS (ESI): calcd. for $C_{10}H_{20}NO_3^+$ $[M + H]^+$ 202.1438; found 202.1432.

***tert*-Butyl *N*-[1-(2-Oxoethyl)cyclopropyl]carbamate (1b):** *tert*-Butyl *N*-[1-(2-hydroxyethyl)cyclopropyl]carbamate (347 mg, 1.72 mmol) and molecular sieves (3 Å) were suspended in CH_2Cl_2 (33 mL) and $NaHCO_3$ (1.065 g, 12.68 mmol) and then Dess–Martin periodinane (1.567 g, 3.69 mmol) were added. The mixture was stirred for 30 min at room temp., then it was diluted with CH_2Cl_2 (30 mL), and poured into saturated $NaHCO_3$ solution (50 mL) containing sodium thiosulfate (9 g). The resulting mixture was stirred for 10 min, and then it was filtered through Celite®. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and passed through a phase separator. The residue was purified by silica gel column chromatography (heptane/EtOAc, 4:1) to give **1b** (290 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.85 (t, J = 1.5 Hz, 1 H), 5.11 (s, 1 H), 2.67 (s, 2 H), 1.42 (s, 9 H), 0.92–0.87 (m, 2 H), 0.72 (q, J = 5.4 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.5, 155.7, 79.8, 51.1, 28.51, 28.46, 13.6 ppm. HRMS (ESI): calcd. for $C_{10}H_{18}NO_3^+$ $[M + H]^+$ 200.1281; found 200.1278.

General Procedure A: In a 1.5 mL reactor, aldehyde **1b** (1.2 equiv., 37 mg, 0.19 mmol), nitro olefin **2** (1 equiv., 0.15 mmol), cocatalyst **10** (10 mol-%, 7.7 mg, 0.015 mmol), and catalyst **7** (10 mol-%, 5.7 mg, 0.015 mmol) were dissolved in CH_2Cl_2 (0.4 mL). The reaction mixture was stirred for 1–7 d at room temp., and then it was diluted with methanol (3 mL), and cooled to 0 °C. $NaBH_4$ (8.8 mg, 0.23 mmol) was added, and the reaction mixture was stirred at room temp. for 25 min. The reaction was quenched with satd. aq. NH_4Cl solution (3 mL), then the mixture was diluted with water (3 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography using a mixture of CH_2Cl_2/EtOAc or hexane/EtOAc.

General Procedure B: In a 1.5 mL reactor, aldehyde **1b** (1.2 equiv., 37 mg, 0.19 mmol), nitro olefin **2** (1 equiv., 0.15 mmol), cocatalyst **10** (10 mol-%, 5.7 mg, 0.015 mmol), and catalyst **7** (10 mol-%, 5.7 mg, 0.015 mmol) were dissolved in CH_2Cl_2 (0.4 mL). The reaction mixture was stirred for 1–7 d at room temp., and then the mixture was directly purified by silica gel column chromatography using a mixture of heptane/EtOAc.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-1-Hydroxy-4-nitro-3-phenylbutan-2-yl]cyclopropyl}carbamate (6a):** Synthesised according to general procedure A. The product was isolated (41 mg, 74%) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 95:5) with an *ee* of 99% for the major diastereoisomer [HPLC: Lux Amylose-2; hexane/*i*PrOH, 85:15; 1 mL/min; 25 °C; 230 nm; t_R = 7.4 (minor), 8.9 (major) min]. $[\alpha]_D^{25}$ = –9.5 (c = 1.00, acetone), m.p. 173–176 °C. IR: $\tilde{\nu}$ = 3349, 3270, 1681, 1556, 1368, 1285, 1257, 1166, 1066, 1032, 763 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 7.35–7.26 (m, 4 H), 7.26–7.20 (m, 1 H), 6.84 (s, 1 H), 5.68–5.57 (m, 1 H), 4.96 (t, J = 12.5 Hz, 1 H), 4.35 (dd, J = 7.5, 4.5 Hz, 1 H), 3.58 (td, J = 11.7, 4.2 Hz, 1 H), 3.36–3.24 (m, J = 10.1 Hz, 1 H), 3.23–3.09 (m, 1 H), 1.49–1.45 (m, J = 4.2 Hz, 1 H), 1.44 (s, 9 H), 1.05–0.94 (m, 3 H), 0.94–0.87 (m, 1 H) ppm. ^{13}C NMR (101 MHz, [D_6]acetone): δ = 158.6, 140.3, 129.4, 129.1, 128.1, 80.2, 80.0, 63.7, 51.7, 45.4, 32.0, 28.5, 14.85, 14.77 ppm. HRMS (ESI): calcd. for $C_{18}H_{27}N_2O_5^+$ $[M + H]^+$ 351.1914; found 351.1895.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-1-Hydroxy-3-(4-methoxyphenyl)-4-nitrobutan-2-yl]cyclopropyl}carbamate (6b):** Synthesised according to general procedure A. The product was isolated (42 mg, 70%) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 89:11)

with an *ee* of 98% for the major diastereoisomer [HPLC: Chiralcel AS-H; hexane/EtOH, 85:15; 1 mL/min; 25 °C; 230 nm; t_R = 7.5 (minor), 9.0 (major) min]. IR: $\tilde{\nu}$ = 3342, 3246, 1681, 1557, 1381, 1368, 1287, 1177, 1072, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 5.01 (dd, J = 12.7, 5.6 Hz, 1 H), 4.95 (s, 1 H), 4.54 (dd, J = 12.7, 9.7 Hz, 1 H), 4.29–4.19 (m, 1 H), 3.76 (s, 3 H), 3.53 (td, J = 10.0, 5.7 Hz, 1 H), 3.37–3.26 (m, 2 H), 1.41 (s, 9 H), 1.32–1.24 (m, 1 H), 1.11 (ddt, J = 15.8, 12.6, 6.2 Hz, 2 H), 0.85–0.77 (m, 1 H), 0.66–0.58 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 157.4, 129.8, 128.9, 114.6, 80.7, 80.0, 62.9, 55.4, 51.4, 44.1, 31.6, 28.4, 15.2, 14.7 ppm. HRMS (ESI): calcd. for $C_{19}H_{29}N_2O_6^+$ [M + H]$^+$ 381.2020; found 381.2023.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-3-(2-Bromophenyl)-1-hydroxy-4-nitrobutan-2-yl]cyclopropyl}carbamate (6c):** Synthesised according to general procedure A. The product was isolated (43 mg, 65%) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 95:5) with an *ee* of 99% for the major diastereoisomer [HPLC: Lux Amylose-2; hexane/*i*PrOH, 85:15; 1 mL/min; 25 °C; 230 nm; t_R = 7.7 (minor), 8.5 (major) min]. $[\alpha]_D^{25}$ = –10.8 (c = 1.00, $CHCl_3$), m.p. 191–193 °C. IR: $\tilde{\nu}$ = 3401, 3324, 1685, 1554, 1515, 1380, 1367, 1167, 1071, 1027, 762 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]acetone): δ = 7.58 (dd, J = 8.0, 1.2 Hz, 2 H), 7.37 (t, J = 8.1 Hz, 1 H), 7.20–7.13 (m, 1 H), 7.02 (s, 1 H), 5.60 (dd, J = 13.4, 4.5 Hz, 1 H), 5.06 (t, J = 12.5 Hz, 1 H), 4.36 (dd, J = 9.9, 4.6 Hz, 1 H), 4.30 (td, J = 11.7, 5.0 Hz, 1 H), 3.63–3.50 (m, 1 H), 3.02 (td, J = 11.6, 4.5 Hz, 1 H), 1.51 (td, J = 10.6, 4.6 Hz, 1 H), 1.45 (s, 9 H), 1.06–0.93 (m, 3 H), 0.91–0.84 (m, 1 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]acetone): δ = 158.7, 140.0, 133.9, 129.7, 129.1, 128.9, 126.8, 80.0, 79.3, 62.7, 53.1, 43.0, 31.3, 28.6, 14.9, 14.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{25}BrN_2O_5Na^+$ [M + Na]$^+$ 451.0839; found 451.0839.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-3-(4-Chlorophenyl)-1-hydroxy-4-nitrobutan-2-yl]cyclopropyl}carbamate (6d):** Synthesised according to general procedure A. The product was isolated (47 mg, 78%) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 95:5) with an *ee* of 98% for the major diastereoisomer [HPLC: Chiralcel OJ-H; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; 230 nm; t_R = 16.4 (minor), 18.4 (major) min]. $[\alpha]_D^{25}$ = –15.8 (c = 1.00, $CHCl_3$), m.p. 163–166 °C. IR: $\tilde{\nu}$ = 3400, 1689, 1555, 1494, 1368, 1165, 1087, 1015, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.3 Hz, 2 H), 7.10 (d, J = 8.3 Hz, 2 H), 5.09 (dd, J = 12.9, 5.3 Hz, 1 H), 5.04 (s, 1 H), 4.56 (dd, J = 12.8, 10.0 Hz, 1 H), 4.22 (s, 1 H), 3.60 (td, J = 10.2, 5.4 Hz, 1 H), 3.30 (s, 2 H), 1.43 (s, 9 H), 1.34–1.26 (m, 1 H), 1.20–1.11 (m, 1 H), 1.07 (dt, J = 10.2, 6.4 Hz, 1 H), 0.94–0.79 (m, 1 H), 0.71–0.56 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 136.6, 134.0, 129.4, 129.3, 80.9, 79.7, 62.9, 51.2, 44.2, 31.6, 28.4, 15.13, 15.08 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}ClN_2O_5^+$ [M + H]$^+$ 385.1525; found 385.1522.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-3-(3-Bromophenyl)-1-hydroxy-4-nitrobutan-2-yl]cyclopropyl}carbamate (6e):** Synthesised according to general procedure A. The product was isolated (37 mg, 56%) as a pale yellow crystalline solid, as a mixture of diastereoisomers (*dr* 94:6) with an *ee* of 99% for the major diastereoisomer [HPLC: Chiralpak AD-H; hexane/*i*PrOH, 95:5; 1 mL/min; 25 °C; 210 nm; t_R = 15.2 (minor), 17.0 (major) min]. $[\alpha]_D^{25}$ = –11.9 (c = 1.00, $CHCl_3$), m.p. 74–76 °C. IR: $\tilde{\nu}$ = 3254, 1689, 1555, 1367, 1286, 1256, 1165, 1074, 789, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 7.9 Hz, 1 H), 7.31 (s, 1 H), 7.19 (t, J = 7.8 Hz, 1 H), 7.10 (d, J = 7.7 Hz, 1 H), 5.19–5.03 (m, 2 H), 4.56 (dd, J = 13.0, 9.8 Hz, 1 H), 3.56 (td, J = 10.2, 5.5 Hz, 1 H), 3.38–3.22 (m, 2 H), 1.43 (s, 9 H), 1.29 (tdd, J = 15.2, 10.0, 5.0 Hz, 1 H), 1.11 (ddt, J = 28.4, 9.9, 6.2 Hz, 2 H), 0.92–0.80 (m, 1 H), 0.69–0.59 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.5, 140.5, 131.3, 130.9, 130.8, 126.7, 123.3, 80.9, 79.5, 62.9, 51.2, 44.3, 31.4, 28.4, 15.1, 15.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}BrN_2O_5^+$ [M + H]$^+$ 429.1020; found 429.1012.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-1-Hydroxy-4-nitro-3-(4-nitrophenyl)butan-2-yl]cyclopropyl}carbamate (6f):** Synthesised according to general procedure A. The product was isolated (42 mg, 69%) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 95:5) with an *ee* of 98% for the major diastereoisomer [HPLC: Chiralpak AD-H; hexane/*i*PrOH, 85:15; 1 mL/min; 25 °C; 210 nm; t_R = 13.5 (minor), 22.8 (major) min]. $[\alpha]_D^{25}$ = –12.3 (c = 1.00, $CHCl_3$), m.p. 170–176 °C. IR: $\tilde{\nu}$ = 3231, 1678, 1557, 1524, 1378, 1348, 1290, 1256, 1162, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.7 Hz, 1 H), 7.38 (d, J = 8.7 Hz, 2 H), 5.24 (dd, J = 13.1, 5.0 Hz, 2 H), 5.12 (s, 1 H), 4.63 (dd, J = 13.1, 10.4 Hz, 1 H), 4.09 (t, J = 6.9 Hz, 1 H), 3.79 (td, J = 10.6, 5.0 Hz, 1 H), 3.38–3.17 (m, 2 H), 1.44 (s, 9 H), 1.36–1.27 (m, 1 H), 1.15 (dt, J = 10.4, 6.3 Hz, 1 H), 1.06 (dt, J = 9.8, 6.2 Hz, 1 H), 1.01–0.94 (m, 1 H), 0.69 (ddd, J = 10.0, 6.6, 5.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 147.7, 145.8, 129.1, 124.4, 81.1, 79.2, 62.8, 51.1, 44.3, 31.8, 28.4, 15.7, 15.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}N_3O_7^+$ [M + H]$^+$ 396.1765; found 396.1760.

***tert*-Butyl *N*-{1-[(2*R*,3*R*)-3-(Furan-2-yl)-1-hydroxy-4-nitrobutan-2-yl]cyclopropyl}carbamate (6g):** Synthesised according to general procedure A. The product was isolated (41 mg, 79%) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 80:20) with an *ee* of 97% for the major diastereoisomer [HPLC: Lux Amylose-2; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; 230 nm; t_R = 12.0 (minor), 12.7 (major) min]. IR: $\tilde{\nu}$ = 3337, 3250, 1678, 1558, 1538, 1368, 1288, 1166, 1090, 751 cm^{-1}. For major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 1.3 Hz, 1 H), 6.31 (dd, J = 3.1, 1.9 Hz, 1 H), 6.18 (d, J = 3.1 Hz, 1 H), 4.90 (dd, J = 12.9, 5.7 Hz, 1 H), 4.85 (s, 1 H), 4.66 (dd, J = 12.8, 9.5 Hz, 1 H), 4.31 (dd, J = 9.4, 5.1 Hz, 1 H), 3.88–3.74 (m, 1 H), 3.47 (pd, J = 12.2, 4.8 Hz, 2 H), 1.40 (s, 9 H), 1.39–1.35 (m, 1 H), 1.10 (ddt, J = 25.2, 9.9, 6.1 Hz, 2 H), 0.84–0.76 (m, 1 H), 0.61 (ddd, J = 9.9, 6.8, 5.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 151.1, 142.6, 110.7, 108.6, 80.6, 77.4, 62.2, 50.2, 38.7, 32.0, 28.3, 15.9, 14.1 ppm. For minor diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, J = 1.3 Hz, 1 H), 6.33 (dd, J = 3.2, 1.9 Hz, 1 H), 6.20 (d, J = 3.2 Hz, 1 H), 4.85 (s, 1 H), 4.73 (d, J = 2.2 Hz, 1 H), 4.71 (s, 1 H), 4.58 (dd, J = 8.5, 6.6 Hz, 1 H), 3.88–3.74 (m, 2 H), 3.64 (ddd, J = 12.3, 8.5, 6.6 Hz, 1 H), 1.43 (s, 9 H), 1.34–1.28 (m, 1 H), 1.03–0.96 (m, 1 H), 0.90 (dt, J = 10.0, 6.5 Hz, 1 H), 0.29 (ddd, J = 10.3, 6.8, 5.6 Hz, 1 H), 0.22–0.15 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8, 151.9, 142.1, 110.9, 108.0, 80.9, 76.6, 62.5, 50.3, 38.0, 32.3, 28.4, 14.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{25}N_2O_6^+$ [M + H]$^+$ 341.1707; found 341.1708.

***tert*-Butyl *N*-{1-[(2*R*,3*R*)-1-Hydroxy-4-nitro-3-(thiophen-2-yl)butan-2-yl]cyclopropyl}carbamate (6h):** Synthesised according to general procedure A using 15 mol-% of both catalyst and cocatalyst. The product was isolated (41 mg, 75%) as a white crystalline solid, as a mixture of diastereoisomers (*dr* 86:14) with an *ee* of 94% for the major diastereoisomer [HPLC: Lux Amylose-2; hexane/*i*PrOH, 85:15; 1 mL/min; 25 °C; 230 nm; t_R = 8.3 (minor), 9.8 (major) min]. IR: $\tilde{\nu}$ = 3346, 3253, 1679, 1558, 1440, 1368, 1090, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 5.1 Hz, 1 H), 6.94 (dd, J = 5.1, 3.5 Hz, 1 H), 6.88 (dd, J = 3.4, 0.8 Hz, 1 H), 5.04 (dd, J = 12.9, 5.7 Hz, 1 H), 4.87 (s, 1 H), 4.58 (dd, J = 12.9, 9.3 Hz, 1 H), 4.23 (t, J = 7.3 Hz, 1 H), 4.00 (td, J = 9.5, 5.9 Hz, 1 H), 3.50 (t, J = 7.0 Hz, 2 H), 1.42 (s, 9 H), 1.31 (dt, J = 9.6, 6.8 Hz, 1 H), 1.20–1.05 (m, 2 H), 0.89–0.82 (m, 1 H), 0.66 (ddd, J = 10.0, 6.8,

5.4 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 140.8, 127.3, 126.6, 125.3, 80.8, 80.4, 62.6, 52.3, 40.3, 31.8, 28.4, 15.5, 14.6 ppm. HRMS (ESI): calcd. for $C_{16}H_{25}N_2O_5S^+$ [M + H]$^+$ 357.1479; found 357.1477.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-4-Nitro-1-oxo-3-(pyridin-3-yl)butan-2-yl]cyclopropyl}carbamate (5i):** Synthesised according to general procedure B. The product was isolated (30 mg, 56%) as a yellow viscous resin, as a mixture of diastereoisomers (*dr* 88:12). IR: $\tilde{\nu}$ = 3213, 1714, 1556, 1368, 1252, 1166, 1078, 756 cm^{-1}. For major diastereoisomer: 93% *ee* [HPLC: Chiralcel AS-H; hexane/EtOH, 93:7; 1 mL/min; 25 °C; 210 nm; t_R = 18.8 (minor), 23.8 (major) min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 1.7 Hz, 1 H), 8.53–8.47 (m, 2 H), 7.59 (d, *J* = 7.5 Hz, 1 H), 7.25–7.22 (m, 1 H), 5.61 (dd, *J* = 13.2, 3.7 Hz, 1 H), 5.17 (s, 1 H), 4.85 (dd, *J* = 12.9, 10.4 Hz, 1 H), 4.02 (td, *J* = 10.0, 3.7 Hz, 1 H), 2.30 (d, *J* = 10.7 Hz, 1 H), 1.42 (s, 9 H), 1.34–1.25 (m, 1 H), 1.02–0.92 (m, *J* = 17.7, 9.3 Hz, 2 H), 0.92–0.85 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.76, 156.0, 149.7, 149.5, 136.2, 133.4, 124.0, 80.6, 78.3, 61.1, 40.0, 30.8, 28.3, 15.2, 14.2 ppm. For minor diastereoisomer: 91% *ee* [HPLC: Chiralcel AS-H; hexane/EtOH, 93:7; 1 mL/min; 25 °C; 210 nm; t_R = 14.4 (minor), 16.2 (major) min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1 H), 8.58–8.45 (m, 2 H), 7.59 (d, *J* = 7.5 Hz, 1 H), 7.30 (dd, *J* = 7.8, 4.9 Hz, 1 H), 5.17 (s, 1 H), 5.02 (dd, *J* = 13.2, 2.7 Hz, 1 H), 4.80–4.72 (m, 1 H), 4.14–4.07 (m, 1 H), 2.17 (d, *J* = 9.8 Hz, 1 H), 1.41 (s, 9 H), 1.13–1.01 (m, 2 H), 0.42 (dt, *J* = 10.2, 6.4 Hz, 1 H), 0.26 (dt, *J* = 10.0, 6.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.83, 155.8, 150.0, 149.6, 135.6, 133.8, 123.9, 80.6, 77.8, 59.9, 39.8, 31.7, 28.3, 16.5, 13.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{24}N_3O_5^+$ [M + H]$^+$ 350.1710; found 350.1709.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-1-Hydroxy-3-(naphthalen-1-yl)-4-nitrobutan-2-yl]cyclopropyl}carbamate (6j):** Synthesised according to general procedure A. The product was isolated (46 mg, 74%) as a yellow-brown crystalline solid, as a mixture of diastereoisomers (*dr* 85:15) with an *ee* of 93% for the major diastereoisomer [HPLC: Lux Amylose-2; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; 230 nm; t_R = 13.7 (minor), 18.2 (major) min]. IR: $\tilde{\nu}$ = 3417, 1689, 1555, 1500, 1368, 1256, 1162, 781 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.5 Hz, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 7.33 (d, *J* = 7.3 Hz, 1 H), 5.21–5.11 (m, 1 H), 5.01 (s, 1 H), 4.76–4.65 (m, 2 H), 4.18 (dd, *J* = 9.1, 4.1 Hz, 1 H), 3.33 (dtd, *J* = 15.7, 12.4, 4.1 Hz, 2 H), 1.55–1.49 (m, 1 H), 1.42 (s, 9 H), 1.21–1.08 (m, 2 H), 0.87–0.72 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.5, 134.8, 134.3, 131.9, 129.4, 128.5, 127.0, 126.2, 125.5, 124.1, 122.4, 80.6, 79.8, 62.6, 52.8, 37.2, 31.6, 28.4, 15.6, 14.8 ppm. HRMS (ESI): calcd. for $C_{22}H_{29}N_2O_5^+$ [M + H]$^+$ 401.2071; found 401.2071.

***tert*-Butyl *N*-{1-[(2*R*,3*S*)-1-Hydroxy-3-(nitromethyl)-5-phenylpent-4-yn-2-yl]cyclopropyl}carbamate (6k):** Synthesised according to general procedure A. The product was isolated (50 mg, 86%) as a beige crystalline solid, as a mixture of diastereoisomers (*dr* 69:31). IR: $\tilde{\nu}$ = 3264, 1681, 1558, 1367, 1170, 757, 692 cm^{-1}. For major diastereoisomer: 97% *ee* [HPLC: Chiralcel OD-H; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; 210 nm; t_R = 9.6 (minor), 10.6 (major) min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.37 (m, 2 H), 7.34–7.27 (m, 3 H), 5.26 (s, 1 H), 4.71–4.55 (m, 2 H), 3.94 (dd, *J* = 11.9, 10.1 Hz, 1 H), 3.84 (dd, *J* = 12.1, 4.7 Hz, 1 H), 3.81–3.71 (m, 1 H), 1.38 (s, 9 H), 1.24–1.18 (m, 2 H), 1.16–1.09 (m, 1 H), 0.92–0.76 (m, 1 H), 0.60 (ddd, *J* = 9.9, 6.9, 5.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 131.80, 128.84, 128.46, 122.2, 86.6, 84.5, 80.7, 77.6, 61.3, 49.7, 33.2, 32.7, 28.3, 17.0, 13.1 ppm. For minor diastereoisomer: 65% *ee* [HPLC: Chiralcel OD-H; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; 210 nm; t_R = 12.8 (major), 14.7 (minor) min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.37 (m, 2 H), 7.34–7.27 (m, 3 H), 5.23 (s, 1 H), 4.71–4.55 (m, 2 H), 3.81–3.71 (m, 2 H), 3.62 (td, *J* = 8.1, 6.0 Hz, 1 H), 1.40 (s, 9 H), 1.30–1.25 (m, 1 H), 1.16–1.09 (m, 1 H), 1.03 (dt, *J* = 9.8, 6.4 Hz, 1 H), 0.92–0.76 (m, *J* = 15.7, 11.6, 11.1, 5.9 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.7, 131.78, 128.79, 128.51, 122.4, 86.3, 85.4, 80.9, 77.4, 62.7, 49.3, 32.6, 31.9, 28.3, 16.2, 14.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{27}N_2O_5^+$ [M + H]$^+$ 375.1914; found 375.1911.

Ethyl (2*R*,3*R*)-3-{1-[(*tert*-Butoxycarbonyl)amino]cyclopropyl}-2-(nitromethyl)-4-oxobutanoate (5l): Synthesised according to general procedure B. The product was isolated (30 mg, 57%) as a yellow viscous liquid, as a mixture of diastereoisomers (*dr* 72:28). IR: $\tilde{\nu}$ = 3377, 1714, 1557, 1371, 1251, 1166, 1078 cm^{-1}. For major diastereoisomer: 99% *ee* [HPLC: Chiralcel OD-H; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; 210 nm; t_R = 7.6 (major), 10.3 (minor) min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 5.26–5.17 (m, 1 H), 5.00 (dd, *J* = 14.7, 2.6 Hz, 1 H), 4.88 (s, 1 H), 4.29–4.11 (m, 2 H), 3.71–3.63 (m, 1 H), 2.35 (d, *J* = 9.0 Hz, 1 H), 1.40 (s, 9 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.16–1.11 (m, 1 H), 1.09–1.02 (m, 1 H), 1.01–0.94 (m, 1 H), 0.86–0.75 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.2, 171.2, 155.9, 80.7, 73.4, 62.17, 57.3, 41.8, 30.4, 28.3, 14.6, 14.1, 14.0 ppm. For minor diastereoisomer: 92% *ee* [HPLC: Chiralcel OD-H; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; 210 nm; t_R = 9.1 (major), 20.5 (minor) min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 4.88 (s, 1 H), 4.75–4.69 (m, 2 H), 4.29–4.11 (m, 2 H), 3.79 (td, *J* = 8.8, 5.8 Hz, 1 H), 1.97 (d, *J* = 9.8 Hz, 1 H), 1.40 (s, 9 H), 1.32 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 1 H), 1.22–1.17 (m, 1 H), 0.86–0.75 (m, 1 H), 0.69–0.64 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.0, 171.4, 155.6, 80.5, 73.5, 62.2, 58.3, 41.0, 29.8, 28.3, 15.1, 14.1, 14.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{25}N_2O_7^+$ [M + H]$^+$ 345.1656; found 345.1652.

***tert*-Butyl *N*-{1-[(2*R*,3*R*)-3-Cyclohexyl-4-nitro-1-oxobutan-2-yl]cyclopropyl}carbamate (5m):** Synthesised according to general procedure B using 15 mol-% of both catalyst and cocatalyst. The product was isolated (26 mg, 47%) as a yellow solid, as a mixture of diastereoisomers (*dr* 83:17) with an *ee* of 99% for the major diastereoisomer [HPLC: Chiralpak AD-H; hexane/*i*PrOH, 98:2; 1 mL/min; 25 °C; 210 nm; t_R = 25.7 (minor), 29.0 (major) min]. IR: $\tilde{\nu}$ = 3390, 2929, 1707, 1555, 1368, 1169 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (d, *J* = 3.4 Hz, 1 H), 4.99 (s, 1 H), 4.74 (dd, *J* = 13.7, 4.8 Hz, 1 H), 4.59 (dd, *J* = 14.0, 6.3 Hz, 1 H), 2.99 (d, *J* = 9.5 Hz, 1 H), 1.87 (dd, *J* = 10.6, 3.4 Hz, 1 H), 1.79–1.63 (m, 5 H), 1.58–1.44 (m, 1 H), 1.42 (s, 9 H), 1.28–0.73 (m, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.4, 155.7, 80.3, 75.1, 59.7, 40.6, 39.4, 31.4, 31.2, 28.4, 27.7, 26.7, 26.5, 26.3, 16.3, 14.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{31}N_2O_5^+$ [M + H]$^+$ 355.2227; found 355.2221.

Methyl (2*R*,3*S*)-2-{1-[(*tert*-Butoxycarbonyl)amino]cyclopropyl}-4-nitro-3-phenylbutanoate (11)

Step 1: *tert*-Butyl *N*-[1-(2-oxoethyl)-cyclopropyl]carbamate (**1b**) (1.05 equiv., 209 mg, 1.05 mmol), (*E*)-(2-nitrovinyl)benzene (**2a**) (1 equiv., 149 mg, 1.00 mmol), (*S*)-2-{[(*tert*-butyldimethylsilyl)oxy]-diphenylmethyl}pyrrolidine (**7**) (10 mol-%, 37 mg, 0.10 mmol), and 1,3-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**10**) (10 mol-%, 50 mg, 0.10 mmol) were dissolved in CH_2Cl_2 (2.5 mL). The mixture was stirred at room temp. until TLC indicated full conversion. After 24 h, the reaction was complete. The mixture was directly purified by silica gel column chromatography using a mixture of heptane and EtOAc as eluent to give compound **5a** (299 mg, 86%) as a white solid, *dr* 95:5 and 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ

= 9.44 (d, J = 2.1 Hz, 1 H), 7.35–7.27 (m, 3 H), 7.25–7.21 (m, 2 H), 5.65 (dd, J = 13.0, 4.4 Hz, 1 H), 5.02 (s, 1 H), 4.83 (dd, J = 12.9, 9.9 Hz, 1 H), 3.96 (td, J = 10.5, 4.2 Hz, 1 H), 2.25 (d, J = 11.5 Hz, 1 H), 1.45 (s, 9 H), 1.35–1.29 (m, 1 H), 0.97–0.80 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.2, 155.9, 136.9, 129.4, 128.4, 128.3, 80.4, 79.0, 61.4, 42.8, 31.0, 28.4, 15.2, 14.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{25}N_2O_5^+$ $[M + H]^+$ 349.1758; found 349.1794.

Step 2: *tert*-Butyl *N*-{1-[(2*R*,3*S*)-4-nitro-1-oxo-3-phenylbutan-2-yl]-cyclopropyl}carbamate **5a** (35 mg, 0.1 mmol) and oxone (74 mg, 0.120 mmol) were suspended in MeOH, and the mixture was stirred at room temp. until TLC indicated full conversion. The mixture was filtered, the filter residue was washed with CH_2Cl_2, and the combined filtrates were concentrated. The resulting residue was purified by silica gel column chromatography (heptane/EtOAc, 10:1 to 5:1) to give the product (18 mg, 48%) as a white solid. The enantiomeric purity was retained as 98% *ee* [HPLC: Chiralpak AD-H; hexane/*i*PrOH, 90:10; 1 mL/min; 25 °C; t_R (minor) = 6.44 min; t_R (major) = 7.28 min]. IR: $\tilde{\nu}$ = 3384, 2979, 1715, 1555, 1434, 1367, 1270, 1161, 1031, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.15 (m, 5 H), 5.78 (dd, J = 12.9, 4.1 Hz, 1 H), 5.33 (s, 1 H), 4.74 (dd, J = 12.9, 10.5 Hz, 1 H), 3.97–3.87 (m, 1 H), 3.35 (s, 3 H), 2.20 (d, J = 11.9 Hz, 1 H), 1.68–1.58 (m, 1 H), 1.48 (s, 9 H), 0.96 (ddd, J = 7.6, 6.2, 1.7 Hz, 1 H), 0.79–0.72 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 155.9, 137.4, 128.8, 128.2, 128.1, 80.3, 78.6, 56.8, 51.9, 44.0, 31.7, 28.5, 16.6, 13.5 ppm. HRMS (ESI): calcd. for $C_{19}H_{27}N_2O_6^+$ $[M + H]^+$ 379.1864; found 379.1839.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra, HPLC chromatograms.

Acknowledgments

The authors thank the Estonian Ministry of Education and Research (grant numbers IUT 19-32 and IUT 19-9) and the European Union (EU) (European Regional Development Fund, grant 3.2.0101.08-0017) for financial support. Dr. Aleksander-Mati Müürisepp and Ms. Tiina Aid from Tallinn University of Technology are thanked for assistance with MS and IR measurments, respectively.

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Received: October 23, 2014
Published Online: January 29, 2015

Publication III

Reitel, K.; Kriis, K.; Järving, I.; Kanger, T. Study of asymmetric organocatalyzed [3+2] annulation of cyclopropenone and β-ketoester *Chemistry of Heterocyclic Compounds* **2018**, *54*, 929-933.

DOI 10.1007/s10593-018-2372-1

Chemistry of Heterocyclic Compounds **2018**, *54*(10), 929–933

Study of the asymmetric organocatalyzed [3+2] annulation of cyclopropenone and β-keto ester

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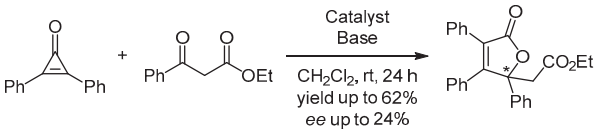
Published in Khimiya Geterotsiklicheskikh Soedinenii,
2018, *54*(10), 929–933

Submitted August 31, 2018
Accepted October 4, 2018



Various asymmetric organocatalytic approaches for the [3+2] annulation of 1,2-diphenylcyclopropen-3-one and ethyl 3-oxo-3-phenylpropanoate have been investigated, resulting in the formation of ethyl 2-(5-oxo-2,3,4-triphenyl-2,5-dihydrofuran-2-yl)acetate in moderate yield and low enantiomeric purity.

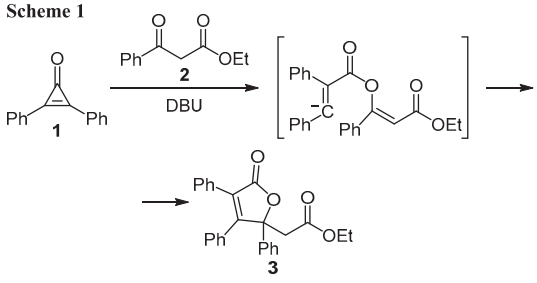
Keywords: chiral ammonium salt, cyclopropenone, asymmetric reaction, organocatalyzed [3+2] annulation, phase-transfer catalysis.

Cyclopropenones[1] are versatile three-carbon synthons in numerous chemical transformations due to their amphiphilic properties – they can react with both electrophiles and nucleophiles. So far, the organocatalytic [3+2] cycloaddition[2] with the cleavage of the C–C single bond has been used to synthesize pyrrolinone derivatives.[3] The organocatalyzed [3+2] annulation of cyclopropenones and β-keto esters provides a direct approach to highly substituted butenolides[4] with excellent chemoselectivity. The butenolide core has been identified as the structural motif in many pharmaceutical and natural products, such as butyrolactone I,[5] triptolide[6] and its water soluble prodrug analog.[7]

Lin et al. developed a nonasymmetric organocatalyzed [3+2] annulation of cyclopropenone **1** and β-keto ester **2** for the construction of highly substituted butenolide **3** in racemic form with excellent chemoselectivity (Scheme 1).[4] They proposed a plausible mechanism of the reaction. The key intermediate is obtained *via* a ring opening of the cyclopropenone by an O-nucleophile attack of the enolate. The quaternary stereogenic center is formed in the following intramolecular Michael addition, leading to butenolide **3**.

Organocatalysis offers a range of asymmetric methods for the activation of the reaction including the formation of covalently bound discrete intermediates or the creation of hydrogen-bonded networks to induce enantiodiscrimination of the transition state. Both starting compounds can be activated independently or fixed *via* a bifunctional catalyst into one catalytic complex. For carbonyl or 1,3-dicarbonyl compounds, thioureas or squaramides are often used;[8] for the formation of enolates, chiral bases are exploited.[9] Bifunctional catalysts,[10] such as cinchona alkaloid-based thioureas, make possible the simultaneous activation of electrophiles *via* the hydrogen bonds and nucleophiles *via* the protonation of a basic tertiary amine in a quinuclidine fragment. Considering the ionic nature of the key intermediate, phase-transfer catalysis with a chiral quaternary ammonium[11] or phosphonium salts[12] are also an option.

Scheme 1



Herein we describe our studies on the asymmetric organocatalytic synthesis of butenolide **3**. Catalysts explored for the synthesis are depicted in Figure 1.

We started our studies with an H-bonding catalysis. The model reaction between diphenylcyclopropenone **1** (0.15 mmol) and β-keto ester **2** (0.1 mmol) was carried out

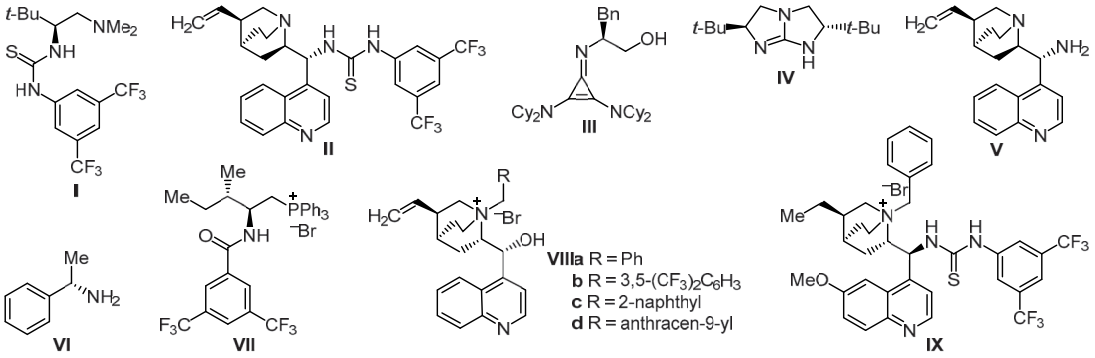
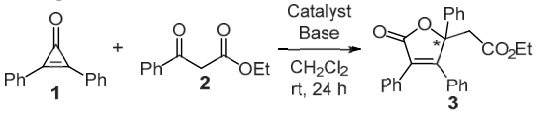


Figure 1. Catalysts explored for the synthesis of compound **3**.

in the presence of 20 mol % thiourea[13] **I** in CH_2Cl_2 (1 ml) at room temperature. The structure of an alkaloid containing thiourea allows for simultaneous combination of the chiral base (tertiary amine) for the enolate formation and H-bonding for the activation of the cyclopropenone (thiourea unit). Unfortunately, there was no reaction during 24 h at ambient temperature in the presence of catalyst **I** or **II** (20 mol %). Even the addition of 20 mol % of DBU afforded no product.

Therefore, we shifted our attention to chiral base catalysis. Bifunctional catalyst **III** is based on a cyclopropenimine scaffold and its basicity is comparable to guanidines.[14] In addition to its high Lewis basicity, it is also a hydrogen bond donor.[15] The reaction catalyzed by cyclopropenimine **III** gave racemic product **3** in moderate yield (Table 1, entry 1). Monofunctional chiral guanidine **IV** (Table 1, entry 2) afforded low yield and selectivity.

Table 1. Catalytic methods for the asymmetric synthesis of compound **3***



Entry	Catalyst	Base	Isolated yield, %	*ee*,** %
1	**III**	–	62***	*rac*[*4]
2[*5]	**IV**	–	31	6
3[*6]	**V**	DABCO	ND	*rac*
4[*6]	**VI**	K_2CO_3	31	6
5[*7]	**VI**	DBU	52	*rac*
6	**VII**	50% aq KOH	28	10
7	**VIIId**	50% aq KOH	8	24
8	**IX**	50% aq KOH	12	10

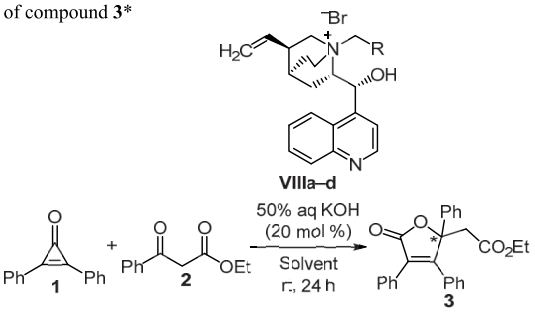
* Reaction conditions: compounds **1** (0.15 mmol), **2** (0.1 mmol), catalyst (20 mol %), base (20 mol %) in CH_2Cl_2 (1.0 ml).
** Enantiomeric excess was determined by chiral HPLC analysis.
*** Conversion was determined from the ratio of compound **3** to **2** by ^{1}H NMR spectroscopy in the crude mixture.
*[4] Enantiomeric excess was determined by chiral HPLC for the sample isolated by preparative TLC from the crude mixture.
*[5] Reaction was carried out at 60°C.
*[6] Reaction time 10 days.
*[7] Reaction time 5 h.

The aminocatalysts **V** and **VI** were also tested, but the racemic product **3** was obtained in low or moderate yields over a very long reaction time (Table 1, entries 3, 4). In the presence of DBU, a nonselective background reaction dominated leading to the fast formation of the racemic product (Table 1, entry 5).

The use of chiral ammonium salt-based phase-transfer catalysts (PTCs) has contributed significantly to the field of asymmetric catalysis.[11] PTCs are capable of stereoselective and noncovalent activation of enolates, and the vast majority of such catalysts contain an additional hydroxyl group as the second coordination site.[16] Chiral phosphonium salts possess similar properties and are also widely used in asymmetric catalysis.[12] In the presence of PTC, a biphasic system of 50% aqueous solution of KOH and CH_2Cl_2 was used. Reaction catalyzed by phosphonium salt **VII**[17] afforded product **3** with low yield and enantioselectivity (Table 1, entry 6). The highest enantiomeric purity of compound **3** was achieved with cinchona alkaloid-derived ammonium salt **VIIId** under basic conditions (Table 1, entry 7). The bifunctional thiourea – cinchona alkaloid-containing catalyst **IX** afforded low enantioselectivity with low yield (Table 1, entry 8).

The obtained results revealed that the use of PTCs could be the method of choice. Next, the influence of various substutents at the nitrogen atom of the alkaloid catalyst was investigated (Table 2). A benzyl-derived catalyst gave low conversion to compound **3** and low enantioselectivity (Table 2, entry 1). The catalyst with electron-withdrawing trifluoromethyl groups in the aromatic ring (Table 2, entry 2) provided racemic product **3** with low conversion. A minimal change in selectivity and conversion was obtained with 2-naphthyl-substituted catalyst (Table 2, entry 3). The bulkier R group at the nitrogen atom made the catalyst more selective (Table 2, entry 4) with similar results in terms of conversion to compound **3**. A catalyst containing anthracen-9-yl moiety **VIIId** was chosen for further screening; the yield increased when DME and THF were used, but the selectivity dropped, affording racemic product **3** in both cases (Table 2, entries 5, 6). Using PhMe as a solvent made the reaction slower and the enantioselectivity decreased (Table 2, entry 7). In most cases, the elongation of the reaction time did not improve the outcome.

Table 2. Catalyst screening for the asymmetric synthesis of compound **3***



Entry	Solvent	*T*, °C	R	Conversion,** %	*ee*,*** %
1	CH_2Cl_2	rt	Ph	13*[4]	6
2	CH_2Cl_2	rt	3,5-$(CF_3)_2C_6H_3$	17	*rac*
3	CH_2Cl_2	rt	2-Naphthyl	22	14
4	CH_2Cl_2	rt	Anthracen-9-yl	22	24
5	DME	rt	Anthracen-9-yl	40	*rac*
6	THF	rt	Anthracen-9-yl	49	*rac*
7	PhMe	0	Anthracen-9-yl	18	4

* Reaction conditions: compounds **1** (0.15 mmol), **2** (0.1 mmol), catalyst (20 mol %), solvent (1.0 ml).
** Conversion was determined from the ratio of compound **3** to **2** by ^{1}H NMR spectroscopy in the crude mixture.
*** Enantiomeric ratio was determined by chiral HPLC analysis of the sample isolated by preparative TLC from the crude mixture.
*[4] Reaction time, 1 h.

We then turned our attention to improving the efficiency of the reaction and investigated the influence of the base on the selectivity of the model reaction in the presence of 20 mol % of catalyst **VIIId**. The results of the screening experiments are presented in Table 3.

Table 3. Base screening for the asymmetric synthesis of compound **3***

Entry	Solvent	Base (equiv)	Conversion,** %	*ee*,*** %
1	CH_2Cl_2	50% aq KOH (0.2)	22	24
2	PhMe	50% aq KOH (0.2)	18*[4]	4
3	PhMe	KOH (2)	99	8
4	CH_2Cl_2	$CsCO_3$ (5)	99*[5]	*rac*
5	PhMe	$CsCO_3$ (5)	99*[5]	*rac*
6	PhMe	$CsCO_3$ (0.2)	42	*rac*
7	CH_2Cl_2	$CsCO_3$ (0.2)	14	4
8	CH_2Cl_2	$K_3PO_4 \cdot H_2O$ (0.2)	14	19
9	CH_2Cl_2	Potassium citrate tribasic monohydrate (0.2)	ND	*rac*
10	CH_2Cl_2	*t*-BuOLi (0.2)	89	*rac*
11	CH_2Cl_2	$LiOH \cdot H_2O$ (0.2)	90	*rac*

* Reaction conditions: compounds **1** (0.15 mmol), **2** (0.1 mmol), catalyst **VIIId** (20 mol %), and base in solvent (1.0 ml) were stirred at ambient temperature for 24 h.
** Conversion was determined from the ratio of compound **3** to **2** by ^{1}H NMR spectroscopy in the crude mixture.
*** Enantiomeric excess was determined by chiral HPLC analysis of the sample isolated by preparative TLC from the crude mixture.
*[4] Reaction was carried out at 0°C.
*[5] Reaction time 1 h.

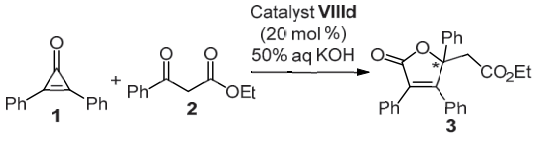
A 0.2 equiv of the 50% aqueous solution of KOH in CH_2Cl_2 afforded low conversion to compound **3** with 24% enantioselectivity (Table 3, entry 1). When the reaction was conducted in PhMe, the conversion was similar to the one in the aforementioned entry, but the selectivity decreased (*ee* of compound **3** is 4%, Table 3, entry 2). The use of solid KOH afforded high yield but decreased the enantioselectivity (Table 3, entry 3). Almost full conversion was obtained at room temperature in the presence of 5 equiv of Cs_2CO_3, but the product was racemic (Table 3, entries 4, 5). Lowering the amount of the base decreased the conversion to 42% affording racemic product **3** (Table 3, entry 6). The only reaction in the presence of Cs_2CO_3 that led to nonracemic product was carried out in CH_2Cl_2, but the enantiomeric purity of the product was still low (Table 3, entry 7). Then, different potassium salts were screened (Table 3, entries 8, 9), but the conversions and selectivities were lower compared to that obtained with KOH (Table 3, entry 1). Next, Li salts were evaluated (Table 3, entries 10, 11); the conversion determined by ^{1}H NMR spectroscopy increased and racemic products were obtained.

The highest enantiomeric purity of compound **3** was achieved with cinchona alkaloid-derived ammonium salt **VIIId** in the presence of a 0.2 equiv of 50% aq KOH (Table 4, entry 1). We decided to investigate the influence of the 50% aq KOH loading on the yield and selectivity. Results are shown in Table 4. Increasing the amount of the base to 0.5 equiv afforded product **3** with the same selectivity, but in higher yield (Table 4, entry 2).

When the base loading was increased to 0.6 equiv, product **3** was formed in 2 h with no change in enantioselectivity or yield (Table 4, entry 3). Further increasing of the base loading up to 1 equiv led to a faster reaction and after 1 h, full conversion was achieved sacrificing enantioselectivity, which decreased from 24 to 15% (Table 4, entry 4).

In conclusion, the organocatalyzed [3+2] annulation of 2,3-diphenylcycloprop-2-en-1-one and ethyl 3-oxo-3-phenylpropanoate was investigated, resulting in the formation of

Table 4. Influence of the KOH amount on the conversion, yield, and *ee* of compound **3***



Entry	50% aq KOH, equiv	Time, h	Conversion,** %	Isolated yield, %	*ee*,*** %
1	0.2	24	22	8	24
2	0.5	2	84	54	24
3	0.6	2	94	54	24
4	1	1	99	60	15

* Reaction conditions: compounds **1** (0.15 mmol), **2** (0.1 mmol), catalyst **VIIId** (20 mol %), 50% aq KOH in CH_2Cl_2 (1.0 ml) were stirred at room temperature.
** Conversion was determined from the ratio of compound **3** to **2** by ^{1}H NMR spectroscopy in the crude mixture.
*** Enantiomeric excess was determined by chiral HPLC analysis.

chiral ethyl 2-(5-oxo-2,3,4-triphenyl-2,5-dihydrofuran-2-yl)acetate with low to moderate yield. In spite of various asymmetric organocatalytic methods and optimization procedures applied to achieve enantioselectivity, the enantiomeric purity of the target compound remained low. The best results were obtained using sterically demanding phase-transfer catalyst 1-{(1*S*)-[(2*S*,4*S*,5*R*)-1-benzyl-5-ethyl-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methyl}-3-[3,5-bis(trifluoromethyl)phenyl]thiourea bromide in CH_2Cl_2/aq KOH biphasic system. The dependence between the base loading, reaction time, and selectivity was observed – a higher base loading afforded faster reaction and lower enantioselectivity.

Experimental

^1H and ^{13}C NMR spectra, as well as all 2D experiments, were recorded on a Bruker Avance III 400 instrument (400 and 100 MHz, respectively) in $CDCl_3$ or CD_3OD, using TMS or residual solvent signals as internal standards ($CDCl_3$: 7.26 ppm for ^1H nuclei, 77.16 ppm for ^{13}C nuclei; CD_3OD: 3.31 ppm for ^1H nuclei, 49.00 ppm for ^{13}C nuclei). All peak assignments were confirmed by ^1H–^1H COSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC experiments. High-resolution mass spectra (ESI) were recorded on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer. Optical rotations were measured on an Anton Paar GWB Polarimeter MCP500. Enantiomeric excess of compound **3** was determined by chiral HPLC (Chiralcel OD-H 250 × 4.6 mm column, eluent hexane–*i*-PrOH, 9:1, flow rate 1 ml/min, λ 254 nm). Retention time of the major enantiomer t_R 8.72 min, minor enantiomer t_R 12.65 min. TLC was performed on precoated silica gel 60 F_{254} plates, and Kieselgel 40–63 μm silica gel was used for column chromatography. The reactions were carried out under air atmosphere without additional moisture elimination unless stated otherwise.

Purchased chemicals and solvents were used as received. Chiral catalysts **I**,[17] **II**,[18] **III**,[12] **V**,[19,20] **VII**,[17] **VIII**[21] were prepared according to the corresponding literature procedures. Analytical data were in accordance to the reported. Atom numbering in the assignments of the synthesized compounds is depicted in the Supplementary information file.

Ethyl 2-(5-oxo-2,3,4-triphenyl-2,5-dihydrofuran-2-yl)-acetate (3) (General method). To a 4-ml test tube, cyclopropenone **1** (30.9 mg, 0.15 mmol), β-keto ester **2** (19.2 mg, 0.1 mmol), catalyst (0.02 mmol, 20 mol %), base (0.2–5.0 equiv), and solvent (1 ml) were sequentially added. The reaction mixture was stirred at room temperature for the indicated time. Completion of the reaction monitored by TLC and ^1H NMR spectroscopy. The solvent was removed under reduce pressure and the crude mixture purified by flash column chromatography on silica gel to afford the pure product, eluent petroleum ether – EtOAc, 20:1. Colorless oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.1, CH_3); 3.28 (1H, d, *J* = 15.4, CCH_2C=O); 3.40 (1H, d, *J* = 15.4, CCH_2C=O); 4.16 (2H, qd, *J* = 7.1, *J* = 4.7, OCH_2CH_3); 6.82–6.85 (2H, m, H Ph); 7.20–7.27 (7H, m, H Ph); 7.29–7.34 (1H, m, H Ph); 7.34–7.42 (5H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.3 (OCH_2CH_3); 40.1 (CH_2); 61.3 (OCH_2CH_3); 87.0 (C-3); 125.7 (2C Ph); 127.5 (Ph); 128.3 (2C Ph); 128.7 (3C Ph); 128.8 (4C Ph); 129.0 (C Ph); 129.3 (2C Ph); 129.4 (C Ph); 129.7 (C Ph); 131.7 (C Ph); 137.2 (C-4); 162.9 (C-5); 168.3 (C(1)=O); 171.9 (C(7)=O). Found, *m*/*z*: 399.1599 $[M+H]^+$. $C_{26}H_{23}O_4$. Calculated, *m*/*z*: 399.1591.

1-{(1*S*)-[(2*S*,4*S*,5*R*)-1-Benzyl-5-ethylazabicyclo[2.2.2]-octan-2-yl](6-methoxyquinolin-4-yl)methyl}-3-[3,5-bis-(trifluoromethyl)phenyl]thiourea bromide (IX) was synthesized by a reported method.[22,23] Yellow solid, mp 134°C, $[\alpha]_D^{25}$ –67.2 (*c* 0.09 $CHCl_3$). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.4, CH_2CH_3); 1.12–1.20 (1H, m, 7-CH_2); 1.41–1.53 (2H, m, CH_2CH_3); 1.85–1.89 (2H, m, 3,4-CH); 1.92–2.02 (1H, m, 5-CH_2); 2.06–2.20 (1+1H overlapping signals, m, 5,7-CH_2); 3.18–3.27 (1H, m, 6-CH_2); 3.40–3.51 (1H, m, 2-CH_2); 3.75–3.84 (1H, m, 6-CH_2); 4.08 (3H, s, OCH_3); 4.68 (1H, d, *J* = 12.8, CH_2Ph); 4.88–4.92 (2H, m, 2-CH_2, 8-CH); 5.21 (1H, d, *J* = 12.7, CH_2Ph); 7.30 (1H, d, *J* = 10.5, 9-CH); 7.52 (1H, dd, *J* = 9.3, *J* = 2.3, H-7'); 7.55–7.57 (3H, m, H-3,5 Ph, H-4"); 7.60–7.65 (3H, m, H-2,4,6 Ph); 7.75 (1H, d, *J* = 4.8, H-3'); 7.93 (2H, br. s, H-2",6"); 8.02 (1H, d, *J* = 9.2, H-8'); 8.15 (1H, br. d, H-5'); 8.81 (1H, d, *J* = 4.7, H-2'). ^{13}C NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 11.5 (CH_2CH_3); 25.6 (C-4); 26.0 (C-5); 26.1 (CH_2CH_3); 28.8 (C-7); 36.4 (C-3); 51.2 (C-2); 55.7 (C-9); 56.9 (OCH_3); 63.7 (C-6); 66.9 (CH_2Ph); 70.6 (C-8); 103.8 (C-5'); 119.1 (br. s, C-4"); 121.0 (C-3'); 124.5 (q, *J* = 272.0, $2CF_3$); 124.6 (C-7'); 124.7 (br. s, C-2",6"); 128.6 (C-4a'); 128.8 (C-1 Ph); 130.5 (C-3,5 Ph); 131.8 (C-8'); 131.9 (C-4 Ph); 132.9 (q, *J* = 34.0, C-3",5"); 134.7 (C-2,6 Ph); 142.3 (C-1"); 145.1 (C-4'); 145.9 (C-8a'); 148.7 (C-2'); 160.6 (C-6'). Signal of the C=S atom was not identified due to the weak peak signal (low solubility of the compound in CD_3OD). Found, *m*/*z*: 687.2587 $[M–Br]^+$. $C_{36}H_{37}F_6N_4OS$. Calculated, *m*/*z*: 687.2586.

Supplementary information file containing ^1H and ^{13}C spectra of both compounds and HPLC chromatogram of racemic compound **3** is available at the journal website at http://link.springer.com/journal/10593.

The authors thank the Estonian Ministry of Education and Research (Grant Nos. IUT 19-32, IUT 19-9, and PUT1468) and the Centre of Excellence in Molecular Cell Engineering 2014-2020.4.01.15-0013 for financial support.

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