THESIS ON NATURAL AND EXACT SCIENCES B208

Cyclopentane-1,2-dione and Cyclopent-2-en-1-one in Asymmetric Organocatalytic Reactions

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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 any academic degree.

/Gert Preegel/

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Tsüklopentaan-1,2-diooni ja tsüklopent-2-een-1-ooni asümmeetrilised organokatalüütilised reaktsioonid

GERT PREEGEL

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LIST OF PUBLICATIONS

I Preegel, G.; Noole, A.; Ilmarinen, K.; Järving, I.; Kanger, T.; Pehk, T.; Lopp, M. "Enantioselective Organocatalytic Michael Addition of Cyclopentane-1,2-diones to Nitroolefins" *Synthesis*, 2014, **46**, 2595–2600.

II Preegel, G.; Ilmarinen, K.; Järving, I.; Kanger, T.; Pehk, T.; Lopp, M. "Enantioselective Organocatalytic Michael Addition-Cyclization Cascade of Cyclopentane-1,2-dione with Substituted (E)-2-oxobut-3-enoates" *Synthesis*, 2015, **47**, 3805–3812.

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Author's Contribution to the Publications

The contributions by the author to the papers included in the thesis are as follows:

I – The idea for this project originated with Artur Noole. I carried out the screening, scope, analysis and writing of the manuscript draft. I also participated in the final manuscript preparation.

II – I participated in the planning of experiments, carried out the screening and the scope and characterized the products. I wrote the manuscript draft and participated in the final manuscript preparation.

III – The idea for the project originated with Rasmus Mose. The screening was performed by Rasmus. The scope of the chalcones and the crystal X-ray analysis were performed by Magnus. The scope and further transformations of nitroolefins were carried out by me. The manuscript draft was written by Rasmus Mose.

ABBREVIATIONS

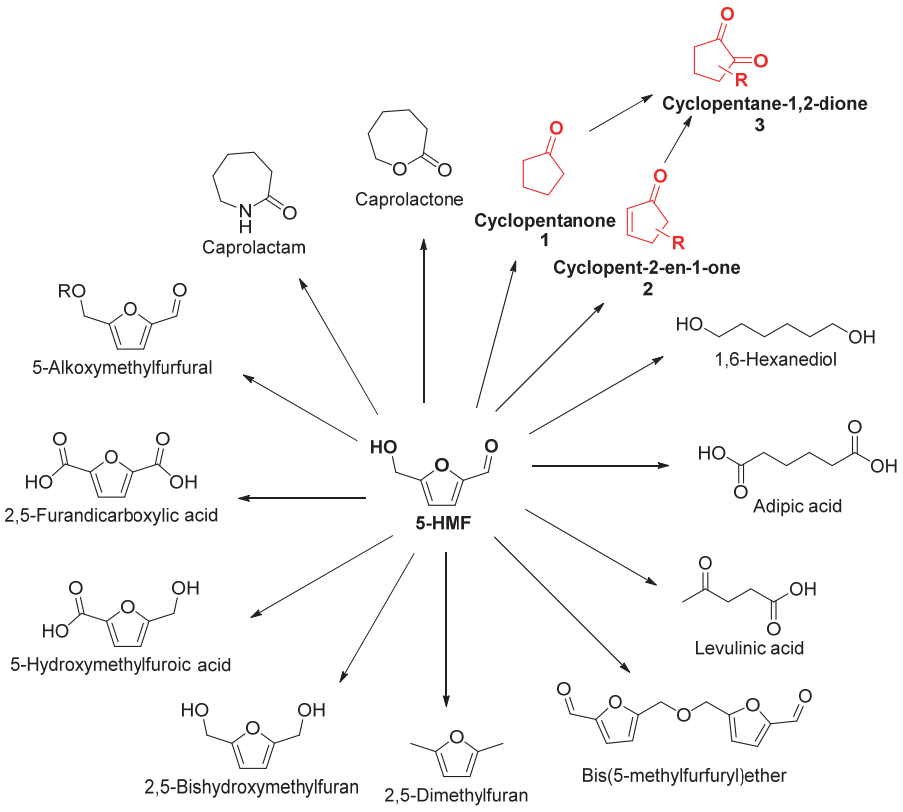
Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
˚C	degrees Celsius
m-CBPA	*meta*-chloroperoxybenzoic acid
DMSO	Dimethyl sulfoxide
dr	diastereomeric ratio
E	electophile
ee	enantiomeric excess
Et	ethyl
EWG	electron-withdrawing group
FCC	flash column chromatography
5-HMF	5-hydroxymethyl-2-furfural
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
In situ	in original location
LUMO	lowest unoccupied molecular orbital
Me	methyl
p-NBA	*para*-nitrobenzoic acid
NBS	*N*-Bromosuccinimide

NMR	nuclear magnetic resonance
Nu	nucleophile
Org cat	organocatalytic
OTf	trifluoromethanesulfonate
Ph	phenyl
PPG	poly(propylene glycol)
*i*Pr	isopropyl
rt	room temperature
SA	salicylic acid
SOMO	singly occupied molecular orbital
TBAF	t*etra*-N-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tos	*para*-toluenesulfonyl
UPC^2	ultraperformance convergence chromatography

INTRODUCTION

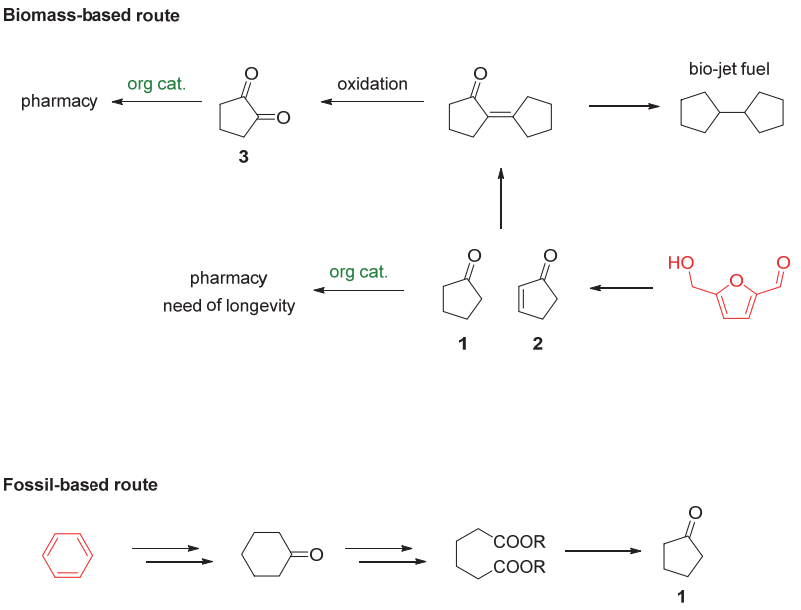
Due to the rising importance of renewable energy, the paradigm of oil as having a monopoly on carbon and energy resources has been changing for almost two decades. In particular, the oldest source of exploited renewable energy – biomass – which can be used as an energy resource and also as a raw material for making different precursors for the medical industry, has received great attention. Although biomass as an energy resource is not yet economically competitive compared to other renewable energy resources, the concept of using biomass as a raw material for the chemical industry has recently become a possibility for diversifying the selection of chemical precursors. Taking into account that global bio-fuel production in 2013 was around 110 billion litres, and that it is produced on 0.01% of the whole agricultural land, the potential of biomass is obvious.

Biomass has been the focus of research for decades in the search for the grand project, and what to do with biomass as a carbon source for the chemical industry. One of the most prominent plans in the field of biomass usage is the conversion of biomass into chemically viable 5-hydroxymethyl-2-furfural (5-HMF), which can be used in further derivatizations (Scheme 1).



Scheme 1. Possible 5-HMF derivatives

One of the conversions that has been somehow overlooked is selectively converting biomass via 5-HMF into cyclopentanone **1** and cyclopent-2-en-1-one **2**.[1] These compounds both can be converted to cyclopentane-1,2-diones.[2] Nowadays these compounds are used as precursors for making additives to increase the volumetric heating value of conventional bio-jet fuels.[3] How productive is it to burn this valuable material at an altitude of 10000 meters? We support the concept of using these molecules as starting materials/platform molecules for making new high value-added fine chemicals in an efficient and green– organocatalytic way.



Scheme 2. Possibilities for further derivatization of **1** and **2**

Our group has shown that 3-alkylcyclopentane-1,2-diones are adequate starting materials for a natural product, such as homocitric acid[4] or lycoperdic acid,[5] or for nucleoside derivatives having antiviral activity.[6] In food chemistry, 3-methyl-cyclopentane-1,2-dione, also known as cyclotene, is used as a flavouring agent that has the aroma of coffee. It is known that many cyclic vicinal diketones possess the quality of having coffee-, tobacco- or caramel-like aromas.[7] The easiest way to get hold of cyclopentane-1,2-dione is through aldol-condensation cyclopentanone **1**, giving a bicyclic intermediate that can be ozonolysed to cyclopentane-1,2-dione **3** and the starting material cyclopentanone **1**.[2a]

This thesis examines how cyclopent-2-en-1-one **2** and cyclopentane-1,2-dione **3** can be used in different asymmetric organocatalytic reactions to produce more complex chiral molecules and intermediates for the fine chemical industry.

1. LITERATURE OVERVIEW

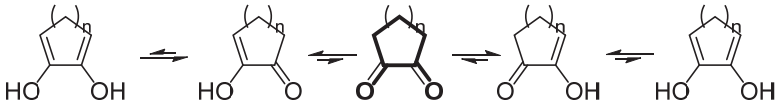
In this section, an overview of the derivatization of cyclic 1,2-dicarbonyl compounds, organocatalytic reactions with common catalysts used in transformations, and the Diels-Alder cycloaddition is given.

1.1. CYCLIC CARBONYL COMPOUNDS

The carbonyl group has been one of the most popular moieties to functionalize in chemistry and is one of the most abundant functional groups found in nature. Although there have been numerous examples of the functionalization of ketones, somehow only a few research groups have focused on vicinal dicarbonyl compounds. We focus here only on examples of the α-alkylation/functionalization of dicarbonyl compounds.

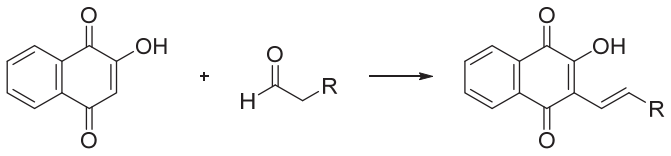
1.1.1. FUNCTIONALIZATION OF 1,2-DIKETONES

In the present chapter, we concentrate on the substitution reaction of cyclic 1,2-diketone in the α-position. Cyclic 1,2-diketones have distinctive keto-enol tautomerization between two different tautomers, shown in Scheme 3. As a result of this equilibrium, the nucleophilicity of 1,2-diketones is lowered.



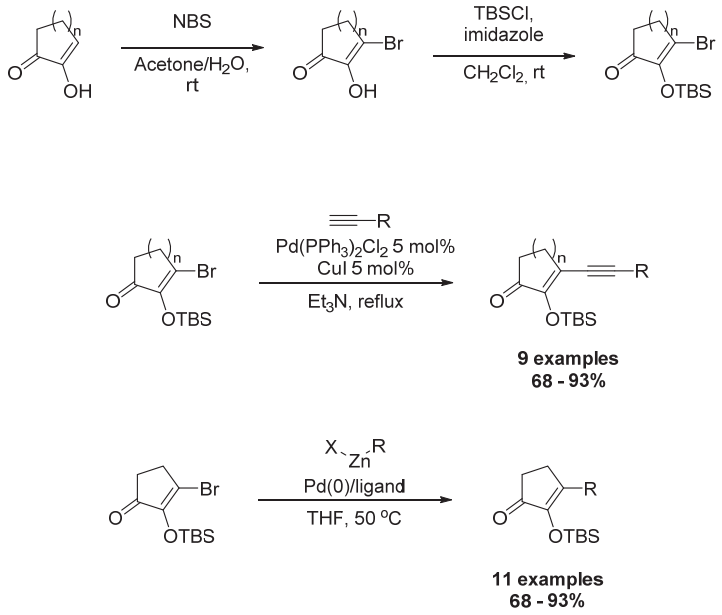
Scheme 3. Keto-enol tautomerization of cyclic 1,2-diketones

Most of the reported reactions require substantial activation of the 1,2-diketone via derivatization to overcome the activation barrier. Hooker condensation between 2-hydroxy-1,4-naphthoquinone and aliphatic aldehyde was the first 1,2-diketone α-alkylation reaction (Scheme 4).[8] Other possibilities of assembling α-substituted 1,2-diketones are presented below. A Heck coupling reaction has been used to produce 3-alkylated product between 2-hydroxy-3-iodo-1,4-naphthoquinone and electron-deficient alkenes. [9] Additionally, a Sonogashira coupling of 2-hydroxy-1,4-naphthoquinone-3-halides has been used.[10]A gold-catalyzed Nazarov reaction was used to build the above-mentioned products in moderate yield.[11] Isotetronic acid halide derivates can give α-addition reactions in Suzuki couplings.[12] 3-triflate replacement in 2-arylchromones by a Stille coupling has been reported.[13]



Scheme 4. First α-alkylation reaction published by Hooker

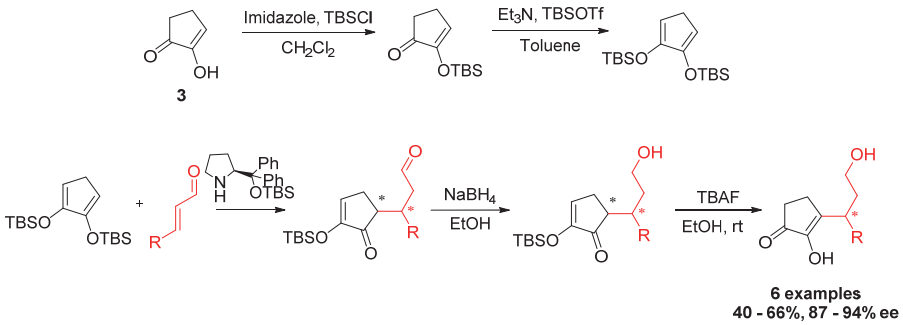
Our group has shown that Negishi[5] and Sonogashira[14] cross-coupling reactions can be performed with different substitutions to the five-membered vicinal diketone, giving 3-alkylated product (Scheme 5).



Scheme 5. Cross-coupling reactions of cyclopentane-1,2-dione derivates

It has also been shown that a Mukaiyama-Michael addition reaction can be performed in an organocatalytic way with cyclopentenol-silyl-ethers to α,β-unsaturated aldehydes.[15] Although this involves an organocatalytic reaction, the work required to make cyclopentenol-silyl-ether is laborious and the overall yield of the substituted

chiral product is moderate. However, the enantioselectivity of the reaction is good (Scheme 6).



Scheme 6. Mukaiyama-Michael addition reaction by Reile et al.

To our knowledge, no direct α-alkylation of cyclopentane-1,2-diones in an organocatalytic manner has been reported in the literature before.

1.2. ORGANOCATALYTIC REACTIONS AND CATALYSTS

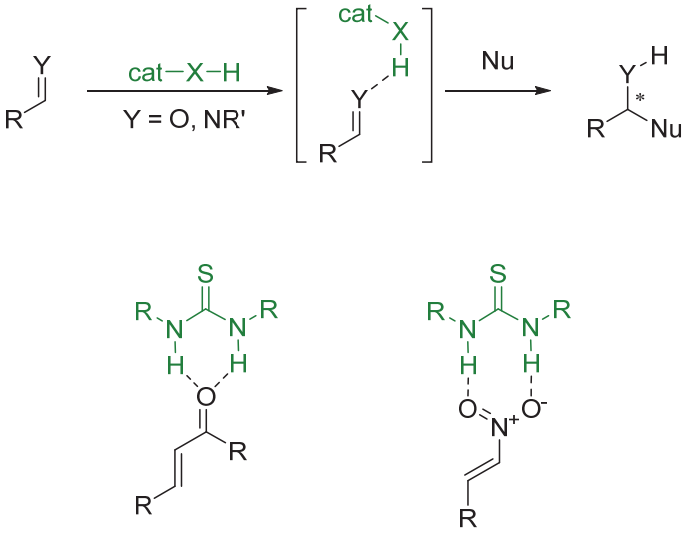
For the preparation of enantioenriched compounds, there are two different approaches: achiral synthesis together with the chiral resolution of racemate, or asymmetric synthesis from achiral starting compounds. The chiral compounds can be elaborated in three different ways: by using starting materials from natural chiral pools, by using a chiral auxiliary, and by using a chiral catalyst. The last of these mentioned ways is the most cost-effective and environmentally friendly. For that reason, the use of chiral catalysts has been the focus of asymmetric synthetic chemistry for decades.[16] William S. Knowles, Ryoji Noyori and K. Barry Sharpless were awarded the Nobel Prize in 2001 for their work on catalytic asymmetric reactions.[17]

Together with asymmetric metal-catalysis and bio-catalysis, organocatalysis is being considered as a third pillar of asymmetric catalysis, having several benefits: easy to handle, cost effective, non-toxic, simple to use, and the catalysts are stable in air and water. The possibility of obtaining both enantiomers by organocatalysis is especially attractive for the pharmaceutical industry in the preparation of non-metal-contaminated chiral intermediates and products.[18]

At the present time, a large number of different organocatalysts have been employed in the development of new asymmetric transformations, including Brønsted acids[19] and bases[20], Lewis acids[21] and bases[22], phase-transfer catalysts[23], hydrogen-bonding catalysts,[24] asymmetric counter anion-directing catalysts,[25] and covalent catalysts.[26]

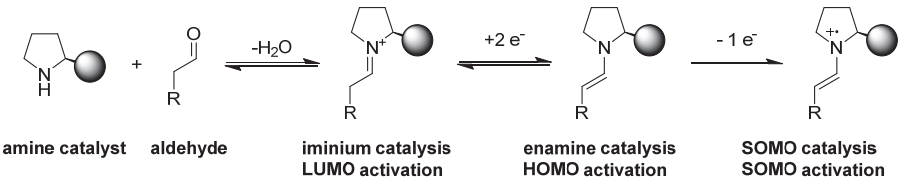
As noted above, many organocatalytic pathways with different catalysts have been found. However, we focused on two organocatalytic activation modes: aminocatalysis and hydrogen-bonding catalysis.

In hydrogen bonding catalysis, a chiral H-donor catalyst will decrease the LUMO level of electrophile through a hydrogen bond, making the electrophile more prone to accept the enantiofacial attack of a carbon nucleophile. After a nucleophilic addition reaction, the catalyst will be deliberated and ready to enter into a new catalytic cycle (Scheme 7).[27]



Scheme 7. General concept of hydrogen-bond catalysis and the activation of nitro and carbonyl moieties

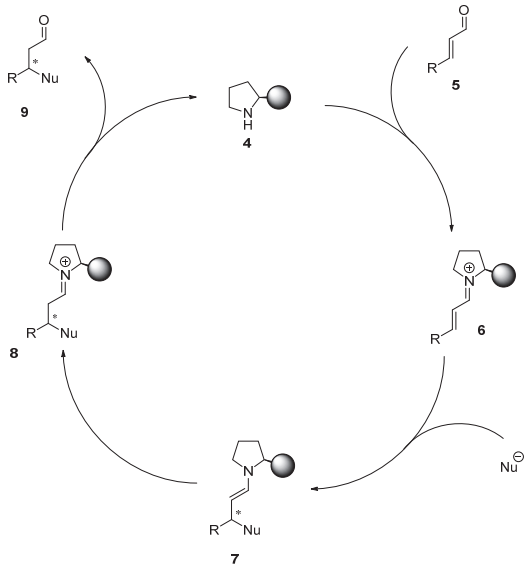
Primary and secondary amine catalysts have a key position in aminocatalysis. There are a few known possibilities of activating the starting material in aminocatalysis: enamine activation by raising the energy of HOMO, iminium ion activation by lowering the energy of LUMO, and SOMO activation (Scheme 8). There have been numerous studies discussing the activation mechanism, and the HOMO and LUMO activations. The main concept is presented in Schemes 9 and 10.



Scheme 8. Three activation possibilities in aminocatalysis

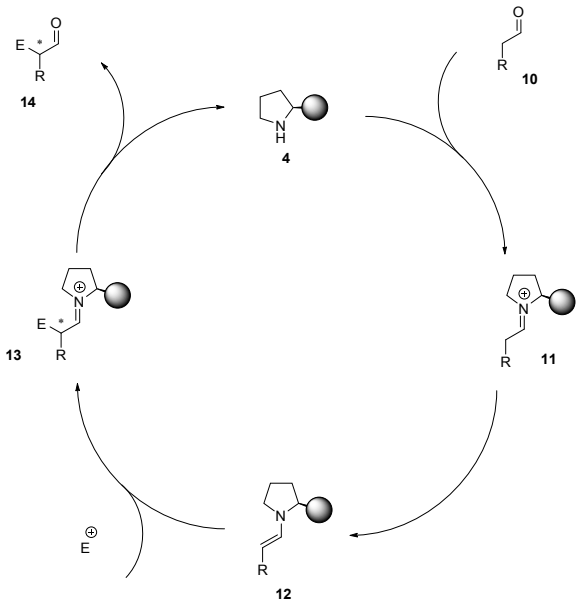
The first LUMO-lowering strategy developed for organocatalysis was the iminium-ion catalysis. This type of catalysis is based on the ability to activate a carbonyl-based Michael-acceptor with an amine catalyst, forming the more reactive iminium-ion species. The iminium-ion reaction with a nucleophile under mild conditions follows.

As shown in Scheme 9, the general mechanism for iminium activation begins with the condensation of the catalyst **4** and carbonyl compound **5**. Water is discharged and iminium-ion **6** is generated. These activated species can be attacked by a nucleophile forming an enamine intermediate **7**. Protonation at α-position generates iminium-ion **8**, which upon hydrolysis by *in situ* generated water forms a β-functionalized product **9** and deliberates the catalyst **4**, which is ready to enter into the next catalytic cycle.



Scheme 9. General mechanistic cycle of iminium ion activation

The catalytic cycle of the enamine-mediated α-functionalization starts with the condensation of the catalyst **4** and carbonyl compound **10**. Water is discharged and an iminium-ion **11** is generated. Deprotonation of **11** affords an enamine intermediate **12**, which performs as a nucleophile by attacking an electrophile and forming an iminium-ion intermediate **13**. The hydrolysis of the iminium-ion **13** releases the functionalized aldehyde **14**. Furthermore, the catalyst **4** is deliberated and can participate in the next catalytic cycle (Scheme 10).



Scheme 10. General mechanistic cycle of enamine activation

1.2.1. *CINCHONA* ALKALOIDS

Cinchona alkaloids can be extracted from the bark of *Cinchona* and *Remijia* genus plants, which are found in South America.[28] One of the species of *cinchona* can also be found on the Coat of Arms of Peru (Figure 1). Among many bioactivities,[28] *Cinchona* alkaloids show antimalarial activity and have been used since the 17th century.[29] It was the first effective chemical compound used for the treatment of an infectious disease.[29]

Figure 1. Coat of Arms of Peru with depicted *Cinchona* tree

The biggest concentration of *Cinchona* alkaloids in tree bark is in the species *Cinchona ledgeriana*, and over 700 metric tons is annually extracted from the tree bark.[30]

Although *Cinchona* bark has been used since the 17th century, the first isolation and determination of quinine from the bark was performed in 1820 by two French chemists, Pierre-Joseph Pelletier and Joseph-Bienaime Caventou.[31] Louis Pasteur in 1853 was the first to use quinine in the resolution of racemates.[32]

One hundred and twenty-four years after the first isolation of quinine, Woodward et al. performed the first total synthesis of quinine in 1944,[33] and in 2001 the first stereocontrolled total synthesis of natural alkaloid was published by Stork and his co-workers.[34]

Nowadays, the *Cinchona* alkaloids are widely used as organic chirality inducers in many catalytic reactions. By using this compound or its derivatives in homogeneous or heterogeneous catalysis, one can generate C-C, C-O and C-X bonds in an asymmetric way in a synthesis of numerous chiral compounds.

The chemical properties of *Cinchona* alkaloid can be further elaborated and fine-tuned. Quinuclidine nitrogen can be used as a chiral base or in a protonated form as a cation which, together with an anion, can be used as a phase-transfer catalyst. Also, its terminal vinyl moiety can be used for the immobilization of the catalyst to achieve enhanced rigidity of the molecule. The secondary alcohol moiety of the compound is mostly used as an H-bond donor and can be easily derivatized to afford a series of primary amine and thiourea organocatalysts. Different properties of *Cinchona* alkaloids are illustrated in Figure 2.

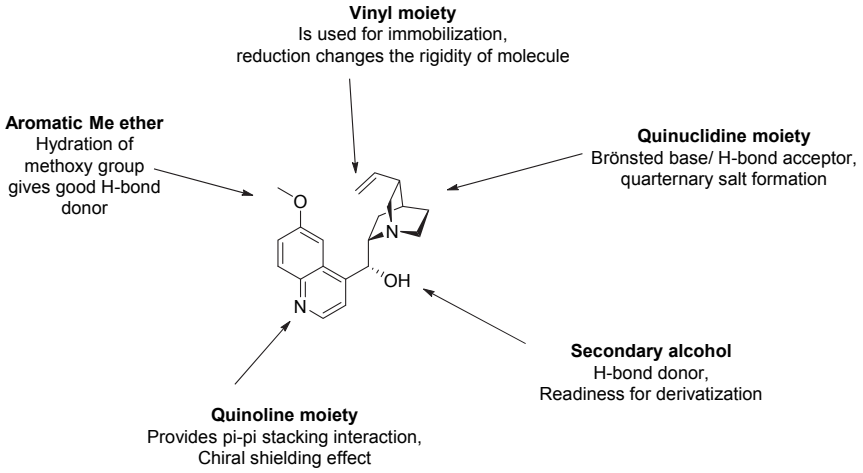
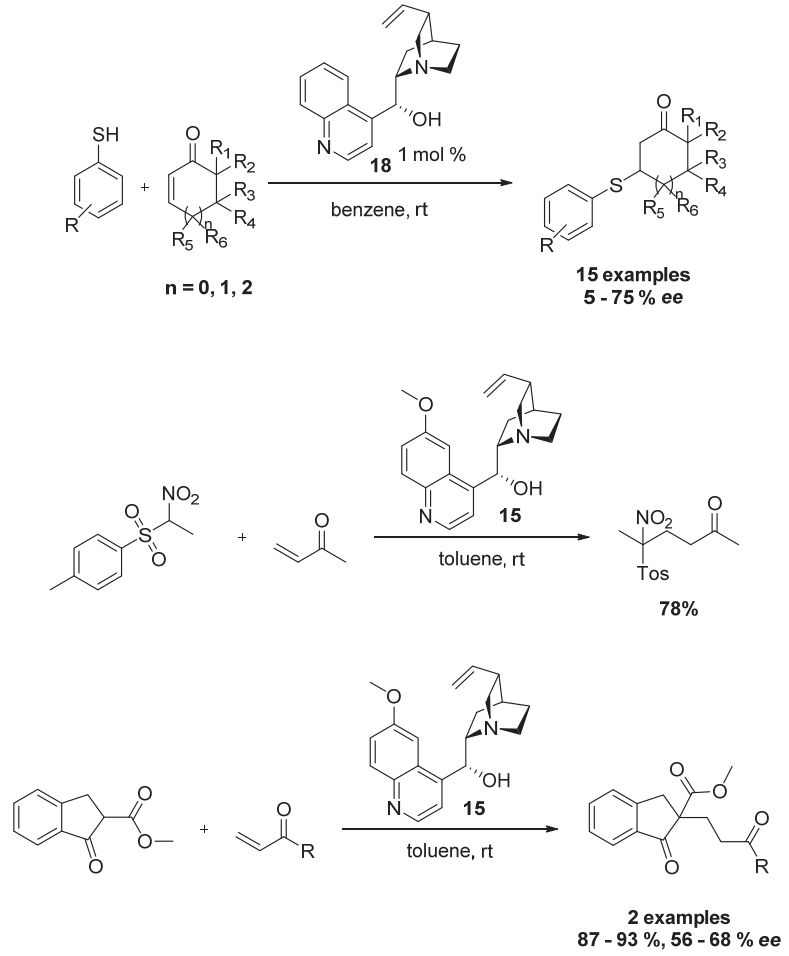


Figure 2. Properties of quinine structural units

The first reactions where *Cinchona* alkaloids were used as bifunctional catalysts were performed in the 70s by the Wynberg group, showing the enantioselective addition of aromatic thiols to conjugated cycloalkenones[35] and a Michael addition to methyl vinyl ketones and aldehydes[36] (Scheme 11). Wynberg's Michael addition reaction was, to our knowledge, the first asymmetric Michael addition reaction with determined enantiomeric excess[35b], although the first chiral Michael addition reaction was published in 1973 by Swedish researchers, who used optically active 2-(hydroxymethyl)-quinuclidine as a catalyst.[37] Wynberg's proposed mechanism was found to be quite close to the optimum reaction mechanism found by Houk.[38]



Scheme 11. Wynberg's work on a Michael reaction[35,36]

Commonly used *Cinchona* alkaloids are shown in Figure 3.

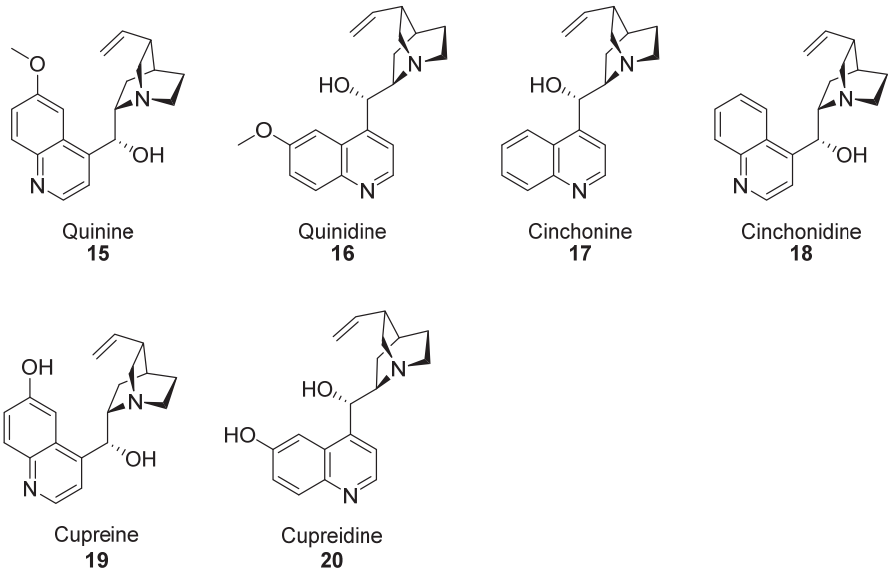


Figure 3. Common alkaloids found in *Cinchona* tree bark

1.2.2. *CINCHONA*-BASED PRIMARY AMINE CATALYSTS

The primary amine catalyst is one of the oldest catalytic motifs in nature.[39] A lot of effort has been put into finding different primary amine catalysts acting as natural mimics for asymmetric chemical synthesis. In this section, we focus on the development of *Cinchona*-based primary amine catalysts.

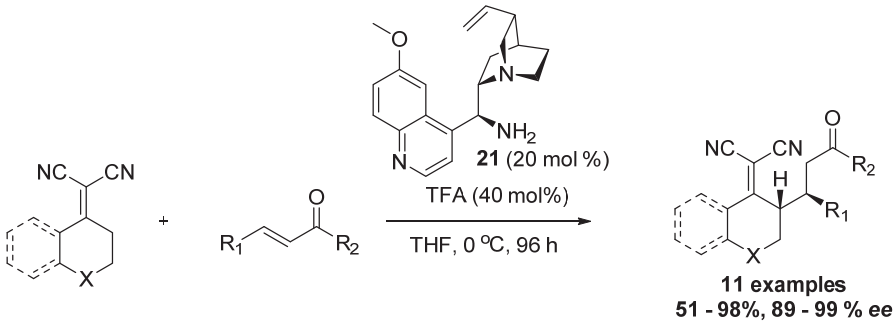
In a search for general *Cinchona*-based amino-catalysts the amino group is inserted into the *Cinchona* structure. The first milestone enantiopure 9-amino(9-deoxy)cinchona alkaloid was prepared in 1995 by Brunner et al. using *Cinchona* alkaloids as a precursor for the Mitsunobu-Staudinger reaction sequence, giving primary amine catalysts in 60 % yield.[40]

The prime purpose of a catalyst is to functionalize carbonyl compounds (aldehydes and ketones) in different reactions, and to afford excellent yields and stereoselectivity.

Primary amines are capable of overcoming the difficulties of secondary amine catalysts in generating congested covalent intermediates with bulkier carbonyl compounds, particularly with α,β-unsaturated ketones and α-substituted α,β-unsaturated aldehydes.[41]

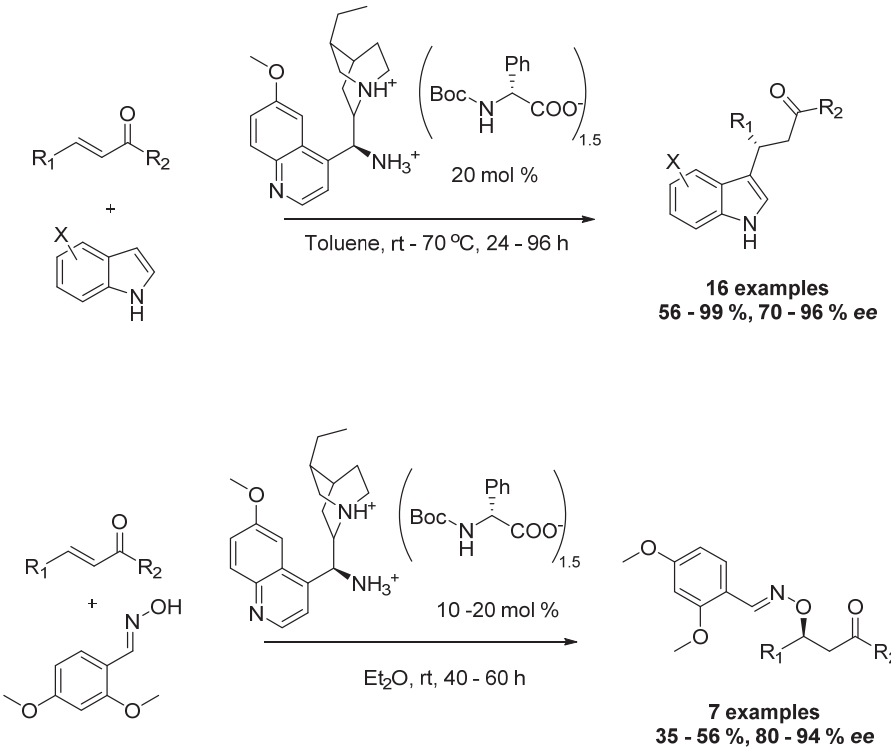
Also, a high degree of flexibility in the primary amine catalyst is a major benefit for finding a suitable conformer for a specific reaction by changing the solvent[42] or protonating the quinuclidine moiety.[43]

In 2007, Ying-Chun Chen published the first paper where a 9-amino-9-deoxyepiquinine **21** catalyst was used in a highly asymmetric Michael addition reaction between α,α-dicyanoalkene and α,β-unsaturated ketones (Scheme 12). It was mentioned in their article that secondary amine catalysts did not give any result related to the bulkiness of the secondary amine.[44] So, they used iminium ion activation of α,β-unsaturated ketones with a primary amine catalyst. Generally, acid is used as an additive in order to enhance the catalytic turnover by accelerating the condensation of catalyst to the carbonyl group. It has been noted that a twofold excess of acid is commonly used to achieve iminium ion activation. It is worth taking into consideration that an equimolar amount of acid is usually needed to create enamine activation.



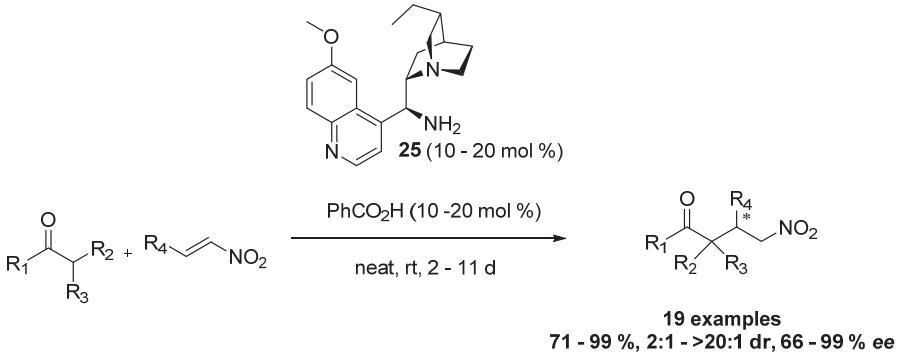
Scheme 12. Asymmetric Michael reaction of α,α-dicyanoalkene and α,β-unsaturated ketones[44]

In 2007 Melchiorre et al. published two papers on the use of α,β-unsaturated ketones in the Friedel – Crafts alkylation of indole reaction[45] and on a β-hydroxylation reaction[46] that yielded highly enantioselective products in the iminium ion activation of α,β-unsaturated ketones (Scheme 13). In both reactions, a salt which consisted of 9-amino(9-deoxy)epi-hydroquinine cation and a chiral (*R*)-N-Boc phenylglycine counter-ion was used.



Scheme 13. Iminium ion activation of α,β-unsaturated ketones in asymmetric synthesis[45,46]

In the same year, Connon and McCooey[47] published the first Michael addition reaction using *Cinchona* alkaloid as a primary amine catalyst to activate ketones and α-substituted aldehydes through enamine activation to obtain products in high stereoselectivity (Scheme 14).



Scheme 14. Michael reaction using enamine activation[47]

Over time, different C-[41] N-[48] O-[49] and S-[50] centred nucleophiles have been used in addition reactions to enones.

Commonly used *Cinchona*-based primary amines are shown in Figure 4. As mentioned above, other frequently used derivatizations of the *Cinchona* alkaloid moieties are cleavage of the ether functionality on the quinoline structure to the hydroxyl group and hydrogenation of the vinylic double bond.

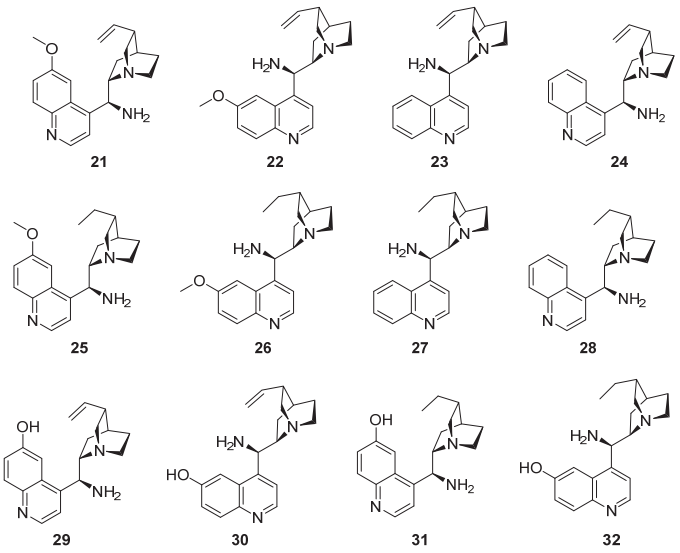


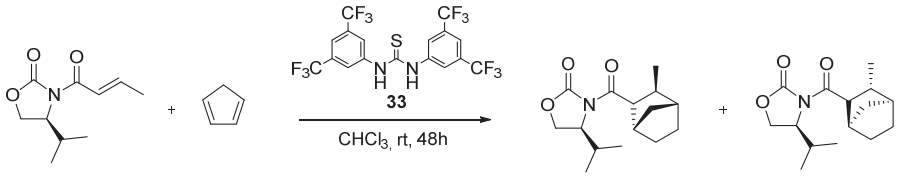
Figure 4. Common primary amines derived from *Cinchona* alkaloids

1.2.3. H-BONDING DONOR CATALYSTS

The other broad group of catalysts are H-bonding donor catalysts. The evident benefits of these catalysts are high catalytic output, stability in air and water, and reusability. Similarly to aminocatalysis, the role of H-bonding catalysts is to activate carbonyl groups in chemical reactions.

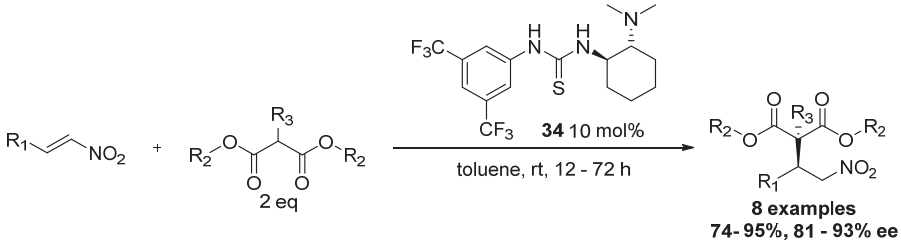
The thiourea group, having hydrogen coordinative properties, is one of the most used H-bonding donor moieties in organocatalysis. There are numerous reviews and books on the scope of using the concept of weak hydrogen-bond activation and coordination to activate various substrates in organocatalytic reactions. Here we present only a few examples from the H-bonding catalyst development.[51]

In 2002 Schreiner's group was the first to apply the hydrogen-bonding donor catalyst using a thiourea moiety to activate N-acyloxazolidinone in a Diels-Alder reaction with cyclopentadiene (Scheme 15).[52]



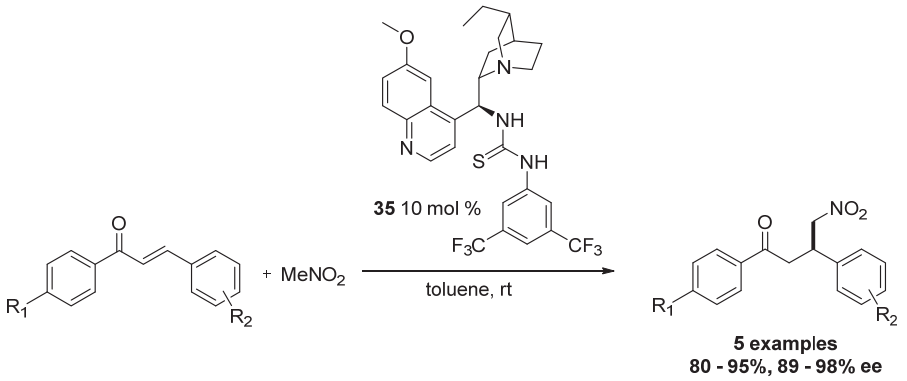
Scheme 15. Thiourea moiety in H-bond donor catalysis[52]

In 2003 Takemoto and co-workers introduced the first enantioselective Michael addition of malonates to nitroolefins using an asymmetric bifunctional H-bonding organocatalysts, giving high to excellent yields and enantioselectivities (Scheme 16).[53] A thiourea moiety is expected to coordinate to nitro olefins and a tertiary amine to a nucleophile.



Scheme 16. Takemoto bifunctional catalyst in Michael reaction[53]

The Hungarian professor Soos and his co-workers reported in 2005 the use of a new type of *Cinchona* alkaloid-derived chiral bifunctional thiourea organocatalyst **35**, which combined H-bonding catalyst capability to coordinate the electrophile with a sterically complex *Cinchona* alkaloid moiety to the coordinate nucleophile, to afford a highly efficient reaction with excellent enantioselectivity (Scheme 17).[54]



Scheme 17. Soos-type catalyst in a Michael addition[54]

Although in organocatalysis thiourea was widely dominant, a new type of catalyst **36** was reported in 2008 by Rawal et al.[55] The idea was based on the difference of H-bond distances in thiourea catalysts (according to calculations, around 2.13 Å) and squaramide (an H-bond distance of 0.6 Å longer), which broadens the scope of H-bonding catalysis and therefore opens up opportunities to use new types of starting materials for activation (Figure 5 and Scheme 18).[55]

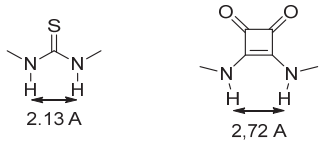
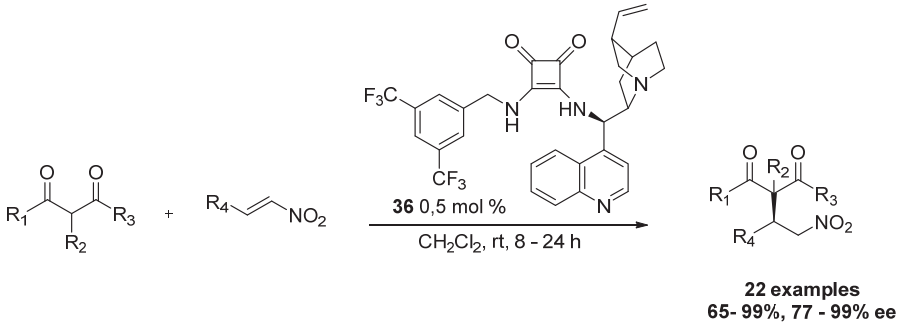


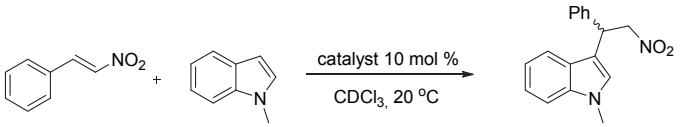
Figure 5. H-bond distance difference

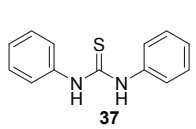


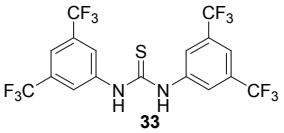
Scheme 18. Squaramide catalyst in a Michael reaction[55]

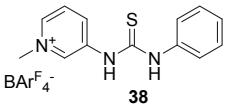
Recently, Steven R. Kass reported a new class of thiourea catalysts based on Schreiner's thiourea but changing bis(3,5-bis(triflouromethyl)phenyl groups to di-N-methylpyridinium ions, which makes it possible to enhance the thiourea catalyst activity up to 400 times, as shown in Table 1.[56]

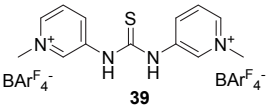
Table 1: Activity of Schreiner's type thiourea catalysts[56]









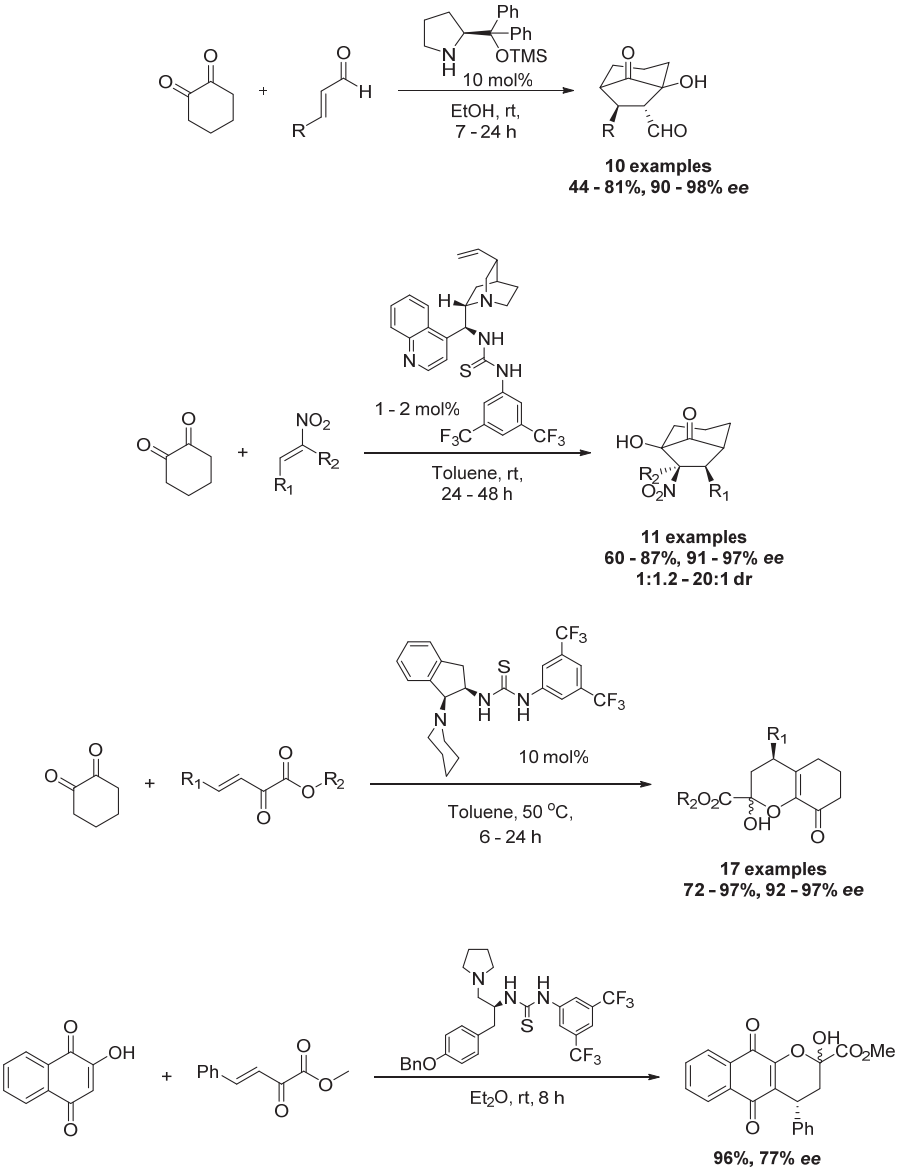


Entry	cat.	k (M^{-1} h^{-1})	$t_{1/2}$ (h)	k_{rel}
1		2.8×10^{-3}	1100	
2	**37**	3.9×10^{-3}	820	0.035
3	**33**	1.1×10^{-1}	29	1.0
4	**38**	7.1×10^{-1}	4.5	6.5
5	**39**	45	0.071 (4.3 m)	410

1.3. MICHAEL REACTIONS OF 1,2-DIKETONES

Arthur Michael published the first 1,4-addition reaction as early as in 1887.[57] Since then, enormous work has been done investigating the possibilities of the reaction. In this overview, Michael addition reactions of 1,3-dicarbonyl compounds are not discussed. Surprisingly, 1,2-dicarbonyl compounds have been almost neglected by the scientific community. Due to keto-enol tautomerization, these compounds can be characterized as Michael donors and acceptors. To the best of our knowledge, there are no examples of the reactions of five-membered cyclic 1,2-dicarbonyl compounds in organocatalytic Michael additions to different electrophiles. There are only a few examples of 6-membered cyclic 1,2-dicarbonyl compounds used in organocatalytic

Michael reactions to different Michael acceptors: to α,β-unsaturated aldehydes[58], nitroalkenes[59] and ketoesters [60] (Scheme 19).



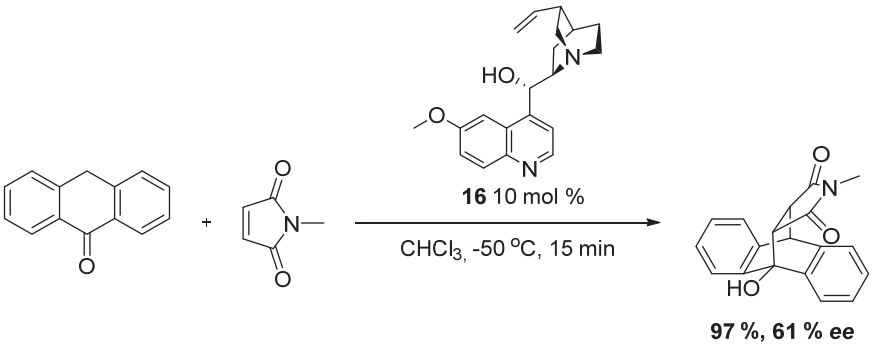
Scheme 19. Some examples of 1,2-dicarbonyl Michael additions[58-60]

1.4. ORGANOCATALYZED CYCLOADDITIONS

The first [4+2] cycloaddition reaction between cyclopentadiene and 1,4-benzoquinone was published in 1928 by Otto Paul Hermann Diels and Kurt Alder.[61] For that achievement, they were awarded the Nobel Prize in 1950. Since then, numerous cycloaddition examples have been published. The reaction has remained one of the most influential organic transformations in the field. Although, cycloaddition has been well-known and well-studied for a long time, organocatalytic cycloadditions have been reported only recently, along with the increasing expansion of organocatalysis in organic synthesis. The present overview will focus on organocatalytic Diels-Alder cycloadditions.

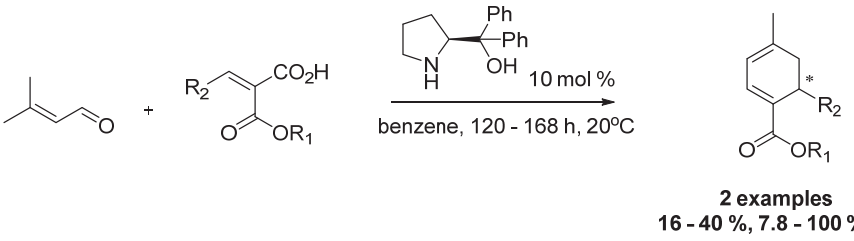
1.4.1. DIELS-ALDER CYCLOADDITION

In 1989 the first asymmetric organocatalytic Diels-Alder reaction between anthrone and N-methyl maleimide, using *Cinchona* alkaloid **16** as a catalyst, was published (Scheme 20). It appeared as a single reaction product article.[62]



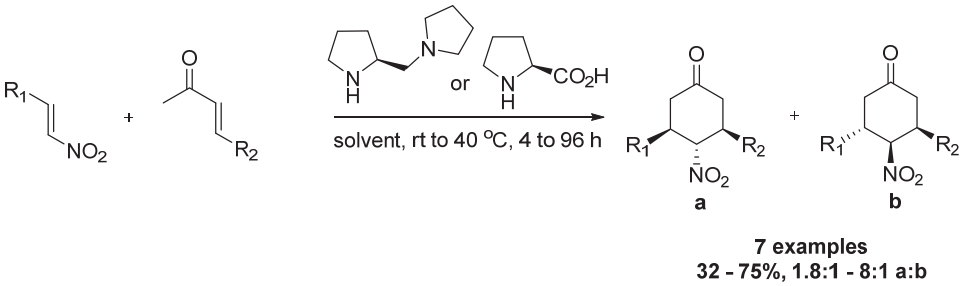
Scheme 20. First asymmetric organocatalytic Diels-Alder reaction[62]

In 1998 Serebryakov[63] published the first aminocatalytic asymmetric Diels-Alder reaction by activating α,β-unsaturated aldehyde (3-methyl-butenal) *in situ* with secondary amines by generating a more reactive dienal functionality, which reacts with dienophiles, giving a chiral [4+2] product (Scheme 21). The article also emphasizes the importance of hydrogen bond formation in the mechanism of stereoinduction.



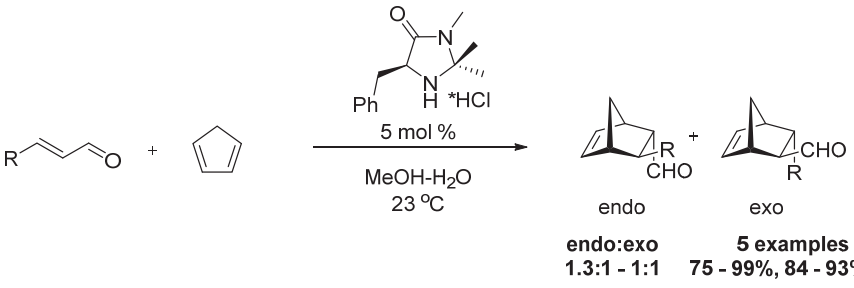
Scheme 21. First asymmetric aminocatalytic Diels-Alder reaction[63]

In 2002 Barbas et al. published the first organocatalytic asymmetric Diels-Alder reaction of α,β-unsaturated ketones with nitro olefins by activating ketones through a cross-dienamine activation strategy (Scheme 22).[64]



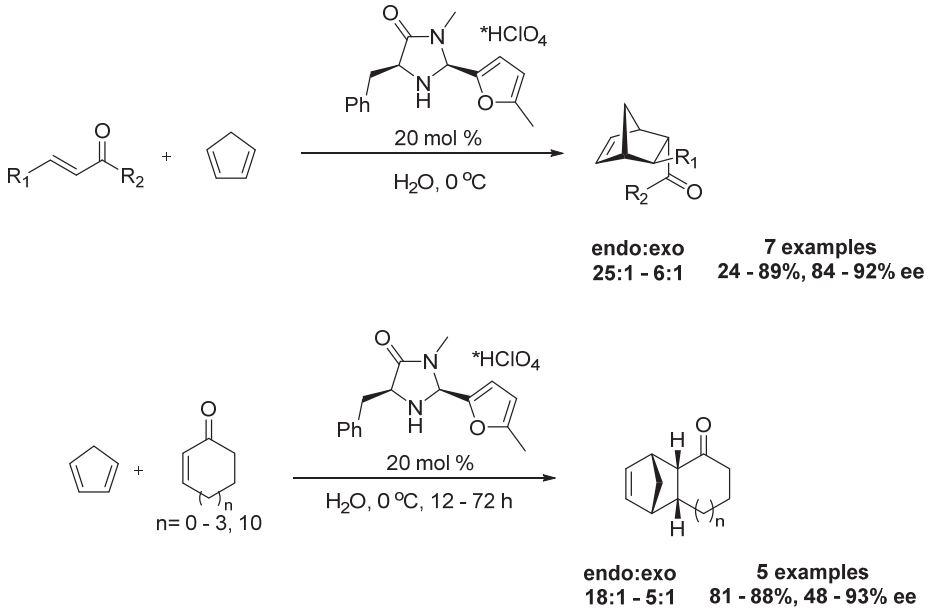
Scheme 22. Diels-Alder reaction α,β-unsaturated ketones with nitro olefins[64]

In 2000, Prof. MacMillan published the results of the first [4+2] cycloaddition performed in a highly enantioselective organocatalytic manner. α,β-unsaturated aldehydes were activated by an imidazolidinone organocatalysts, providing LUMO lowering activation; these reacted with various dienes, giving a Diels-Alder cycloaddition in excellent yield and enantioselectivity, although without *exo-endo* selectivity (Scheme 23).[65]



Scheme 23. Iminium ion activation of aldehydes in a Diels-Alder reaction[65]

MacMillan continued with the investigation of Diels-Alder cycloadditions and a few years later reported the first enantioselective organocatalytic [4+2] cycloaddition of α,β-unsaturated ketones with dienes using a modified imidazolidinone salt catalyst to lower the LUMO of ketones by forming an iminium ion.[66] In the study, they also showed the possibility of conducting a [4+2] cycloaddition with various cyclic α,β-unsaturated ketones, as shown in Scheme 24.



Scheme 24. Iminium ion activation of keto-enones in a Diels-Alder reaction[66]

Cyclopent-2-en-1-one **2** has been used in Diels-Alder reactions with different dienophiles acting as the 4π diene. Cross-dienamine activation has been used to enhance the HOMO activation of cyclopent-2-en-1-one **2**.

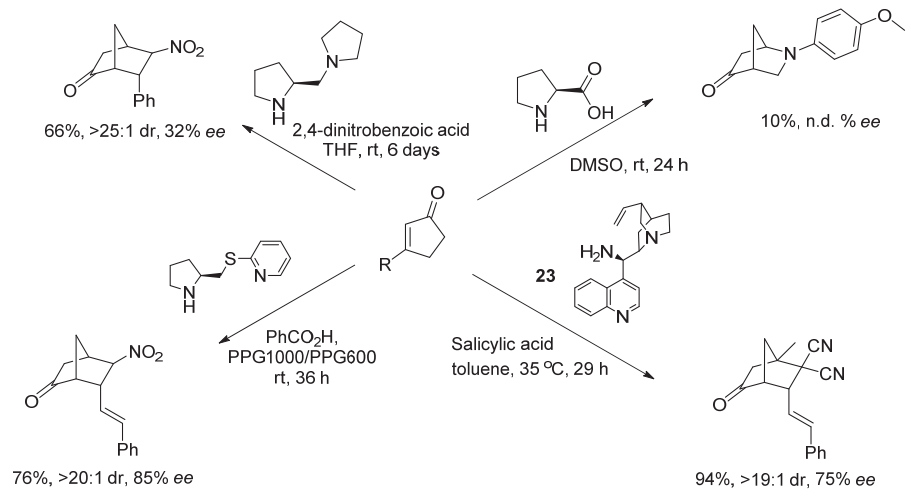
In 2005 Córdova et al. demonstrated the first direct organocatalytic one-pot three-component asymmetric aza-Diels-Alder reaction with high stereoselectivity, using (*S*)-proline as a catalyst.[67] It is important to mention that cyclohex-2-en-1-one as a precursor for 4π diene gave excellent results, while cyclopent-2-en-1-one gave very poor results (Scheme 25, top right). Some years later, Wang et al.[68] and Carter et al.[69] reported the same results.

In 2007 Córdova et al. reported, to the best of our knowledge, the first cross-dienamine activated asymmetric Diels-Alder reaction, providing a bicyclic product. A major part of the investigation was conducted with 4,4-dimethylcyclohex-2-en-1-one, but in the

article there is also one entry with cyclopent-2-en-1-one, reporting moderate enantioselectivity (Scheme 25, top left).[70]

In 2012 Xu et al. showed that poly-conjugated nitroolefin systems can also react with cyclopent-2-en-1-one, giving a [4+2] cycloaddition reaction. Unfortunately, only a single entry reported good stereoselectivity (Scheme 25, bottom left).[71]

In 2012, Chen et al. published an article in which they reported a [4+2] cycloaddition between β-substituted cyclopent-2-en-1-one and poly-conjugated malononitrile (Scheme 25, bottom right).[72]



Scheme 25. Work done with cyclopent-2-en-1-one[67, 70-72]

1.5. SUMMARY OF LITERATURE OVERVIEW

Within the last two decades, besides enzyme- and metal-catalysis, organocatalysis has become a strong chemistry workhorse, with reaction methods developed that afford valuable products for natural product synthesis and the pharmaceutical industry. According to the literature data, 5-membered rings have not been studied sufficiently. Cyclopentane-1,2-diones have been almost neglected, and the other 5-membered ring compounds have usually afforded unsatisfactory results, with only a few good examples.

2. AIMS OF THE PRESENT WORK

The present work aims to increase the possibilities of using cyclopentane-1,2-dione **3** and cyclopent-2-en-1-one **2** as relevant starting materials for organocatalytic reactions to obtain valuable chiral products that have a broad utility value.

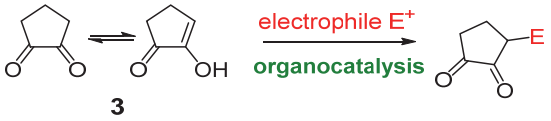
The main aims of the work:

- To investigate the use of cyclopentane-1,2-diones **3** in asymmetric organocatalytic Michael additions to different Michael acceptors.
- To elaborate the use of cyclopent-2-en-1-one **2** in asymmetric organocatalytic Diels-Alder reactions with common classes of electron-deficient alkenes.

3. RESULTS AND DISCUSSION

3.1. ASYMMETRIC ORGANOCATALYTIC MICHAEL ADDITION OF CYCLOPENTANE-1,2-DIONE

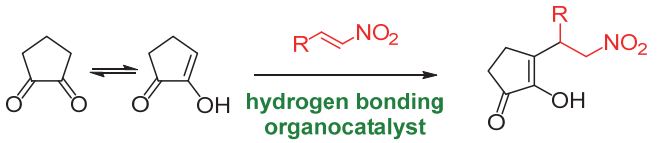
Our group has previously demonstrated that a derivative of cyclopentane-1,2-dione 2,3-bis((*tert*-butyldimethylsilyl)oxy)cyclopenta-1,3-diene reacts readily in a Mukaiyama-Michael reaction with α,β-unsaturated aldehydes under aminocatalytic conditions (Scheme 6). Chiral 3-substituted cyclopentane-1,2-diones were obtained in moderate to good yields (up to 66%) and in excellent enantioselectivities (up to 94% *ee*). Although the stereoselectivity of the addition reaction was excellent, the starting material - disilyl enol ether - is complicated to synthesize and handle. In addition, the yield of the Mukaiyama-Michael reaction is moderate. In the present work, we investigated the possibilities of using unprotected cyclopentane-1,2-dione **3** in reactions with different electrophiles (Scheme 26).



Scheme 26. General view of the concept

3.1.1 NITROOLEFINS AS MICHAEL ACCEPTORS

First, the reaction of cyclopentane-1,2-dione **3** with nitroolefins **40**, the most common electrophile used in organocatalysis, was studied. The general practice in activating nitroolefins is to use hydrogen-bonding donor organocatalysts.



Scheme 27. Cyclic 1,2-diones in Michael reactions with nitroolefins

3.1.1.1. PRELIMINARY EXPERIMENTS

During the preliminary experiments, cyclopentane-1,2-dione and *trans*-β-nitrostyrene were allowed to react at room temperature, using *Cinchona* alkaloid-derived thiourea as a catalyst. Complete consumption of the substrate was observed within 1 hour. As the reaction product, 3-substituted diketone **41a** in excellent 93% yield and moderate 62% *ee* was obtained (Table 2, entry 1). Unlike cyclohexane-1,2-dione, the formation of a functionalized bicyclo[2.2.1]heptanone scaffold was not observed.

3.1.1.2. SCREENING OF OPTIMAL CONDITIONS

In the search for the optimal conditions of the Michael addition reaction, different catalysts, solvents and temperatures were tested. To find the most efficient catalyst, we screened two types of bifunctional H-bonding catalysts (Figure 6): quinine-derived thiourea catalysts **35** and **45**, and squaramide catalysts **42**, **43** and **44**. The results are presented in Table 2 (entries 2, and 9-12). The most optimal catalyst was thiourea catalyst **35**, giving the optimal balance between enantioselectivity (76% *ee*) and yield (85%).

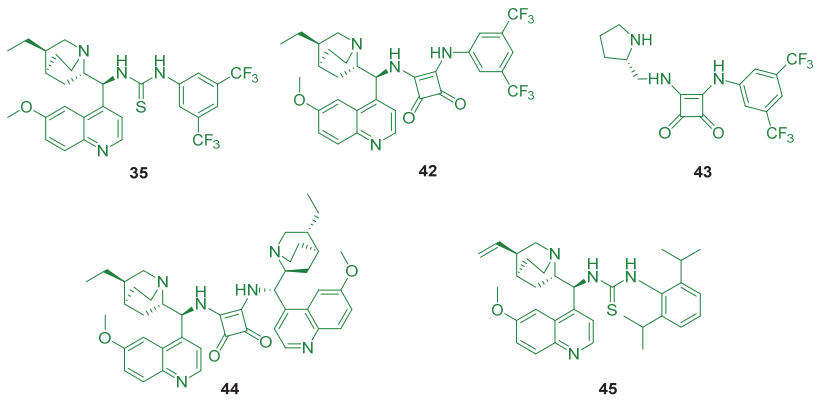


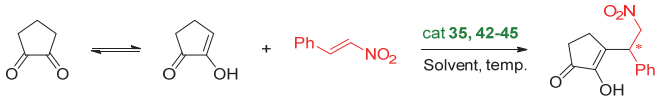
Figure 6. Catalysts investigated in a Michael reaction to nitroolefins

In a search for the optimal solvent for the reaction, aprotic solvents, such as dichloromethane, chloroform and toluene, were screened at room temperature. Under the applied conditions, the solvent had little or no influence on the reaction outcome.

To improve the reaction, the influence of temperature on the selectivity of the Michael addition was investigated. We observed that in toluene at lower temperatures the reaction selectivity dropped considerably (Table 2, entry 1 vs. entries 4 and 5). Similar

temperature dependence had been found earlier and was explained by Jang et al. as being a result of the self-aggregation of the catalyst.[73] By raising the reaction temperature to 50 °C, the selectivity was improved. An additional temperature increase to 80 °C caused a slight selectivity drop (Table 2, entries 1 and 5 vs. 6 and 7). In halogenated solvents, temperature dependence was not observed (Table 2, entries 1 and 6 vs. 3 and 8).

Table 2. Screening of optimal conditions for a Michael addition of cyclopentane-1,2-dione to (*E*)-β-nitrostyrene



3 **40a** **41a**

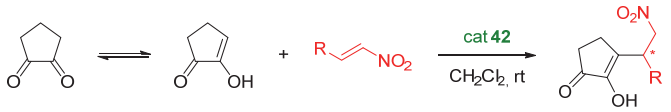
Entry[a]	Solvent	Catalyst 4 [5 mol %]	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	Toluene	35	rt	1	93	62
2	CH_2Cl_2	35	rt	4	88	78
3	$CHCl_3$	35	rt	4	85	76
4	Toluene	35	0	3	77	50
5	Toluene	35	-20	3	61	36
6	Toluene	35	50	0.5	79	76
7	Toluene	35	80	0.1	77	70
8	$CHCl_3$	35	50	1	77	73
9	$CHCl_3$	42	rt	2	83	78
10	$CHCl_3$	43	rt	24	2	46
11	$CHCl_3$	44	rt	2	43	72
12	$CHCl_3$	45	rt	3	97	68

[a]Unless otherwise noted, the reactions were performed with **3** (0.24 mmol), **40a** (0.2 mmol) and **35** (5 mol%) in the corresponding solvent (0.7 mL). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

3.1.1.3. REACTION SCOPE

To evaluate the generality of the reaction under optimal conditions (rt, CH_2Cl_2, catalyst **35** 5 mol %), we examined different nitrostyrenes in reaction with cyclopentane-1,2-dione. The results are shown in Table 3. As can be seen in Table 3, halogen substitution (chlorine and bromide) in the *para* and *meta* positions of the aromatic ring of nitrostyrene was tolerated, giving good yield and stereoselectivity (Table 3, entries 2 and 3). In addition, electron-donating groups were tolerated in the reaction (Table 3, entries 4 and 8). Nitroolefins with heteroaromatic (Table 3, entries 9 and 10) or aliphatic (Table 3, entry 11) substituents could also be used in the reaction, affording good enantioselectivities (68 – 70 % *ee*) and good to excellent yields (67 – 96%). Since the aliphatic nitroolefin was less reactive than its aromatic counterparts, a longer reaction time was needed with (*E*)-(2-nitrovinyl)cyclohexane **40k**.

Table 3. Scope of Michael addition of cyclopentane-1,2-dione to nitroolefins



3 40 41

Entry[a]	R	Product	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph	41a	4	85	76
2	*p*-Cl(C_6H_4)	41b	2	82	62
3	*m*-Br(C_6H_4)	41c	3	70	56
4	*p*-MeO(C_6H_4)	41d	5	90	64
5	*p*-CF_3O(C_6H_4)	41e	2	77	60
6	*p*-CF_3(C_6H_4)	41f	3	60	70
7	*m*-Me(C_6H_4)	41g	3	48	70
8	*o*-Me(C_6H_4)	41h	3	71	60
9	2-furyl	41i	2	96	70
10	2-thiophenyl	41j	2	79	68
11	cyclohexyl	41k	24	67	70

[a] Unless otherwise noted, the reactions were performed with **3** (0.24 mmol), **40** (0.2 mmol) and **35** (5 mol%) in the CH_2Cl_2 (0.7 mL). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

The absolute configuration of compound **41b** was determined by single-crystal X-ray diffraction, shown in Figure 7. The absolute configurations of all other compounds in the series were assigned based on analogy from that.

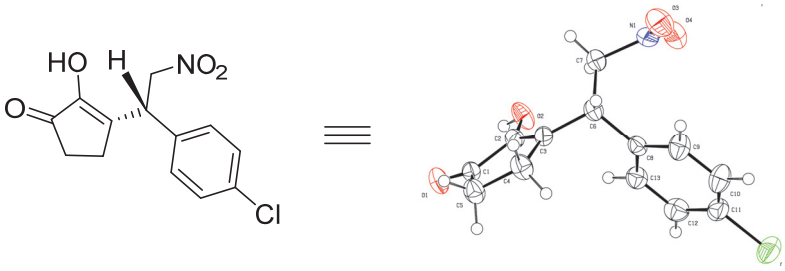
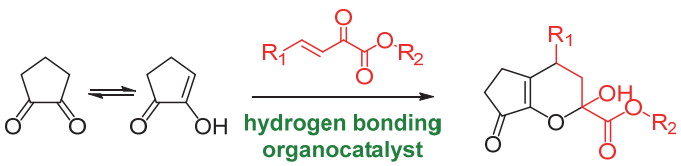


Figure 7. X-ray crystal structure of **41b**

3.1.2. (E)-2-OXOBUT-3-ENOATES AS MICHAEL ACCEPTORS

As demonstrated above, the use of a strong electrophile with cyclopentane-1,2-dione readily afforded in the Michael addition 3-substituted products. The question arose: what happens if the electrophile bears a competing vicinal carbonyl group moiety? In the reaction of α,β-unsaturated keto esters with cyclopentane-1,2-dione, four competing carbonyl groups are present, in which two pairs are in vicinal position. Therefore, bifunctional hydrogen bonding catalysts, activating both the electrophile and the nucleophile, seemed a reasonable choice for the organocatalytic reaction. Vicinal amines have been shown to activate reactions by activating and coordinating starting materials through H-bonding activation.



Scheme 28. Cyclopentane-1,2-dione in Michael reactions with α-ketoesters.

3.1.2.1. PRELIMINARY RESULTS

The preliminary results of the reaction of cyclopentane-1,2-dione **3** with phenylsubstituted β,γ-unsaturated α-ketoester **46a-Me** by using Soos's type organocatalyst **35** in toluene were promising, affording hemiacetal **47a** in low yield (35%) and excellent stereoselectivity (dr >20:1, 96% *ee*, Table 4, entry 1) in a short reaction time (15 minutes). To our delight, the formation of mainly one diastereomer was observed.

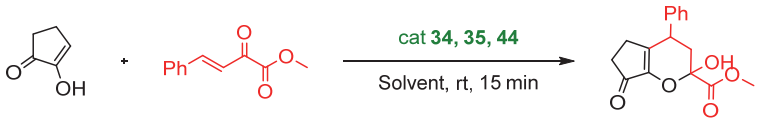
3.1.2.2. SCREENING OF OPTIMAL CONDITIONS

To find the optimal reaction conditions, a model reaction of cyclopentane-1,2-dione **3** with methyl (*E*)-2-oxo-4-phenylbut-3-enoate **46a-Me** was screened, using a variety of catalysts and solvents. The results are presented in Table 4.

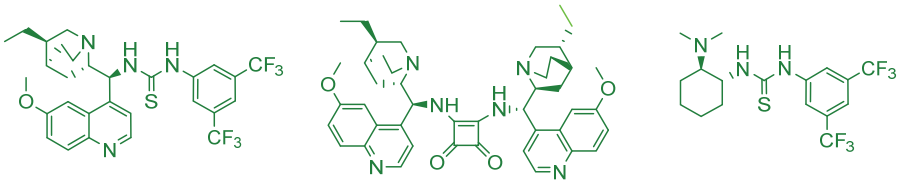
In the search for the optimal solvent, we found that with catalyst **35** the stereoselectivity of reaction did not largely depend on the used aprotic solvents. Toluene (Table 4, entry 1), halogen containing solvents (Table 4, entries 2 and 3) and ethers (Table 4, entry 4) were almost equal in the reaction. The best yield (75 %) was obtained with CH_2Cl_2.

In the search for the optimal catalyst, the reactions were performed in CH_2Cl_2 with Soos **35**, Takemoto-type **34** and squaramide **44** catalysts. All of the used H-bonding catalysts resulted in excellent stereoselectivity in the reaction. The best yield of product **47a** (89%) was obtained with the Takemoto-type catalyst **34** (loading of 5 mol%) in a very short reaction time (15 minutes; Table 4, entry 6).

Table 4. Screening of the catalyst and the solvent



3 46a-Me 47a-Me



35 44 34

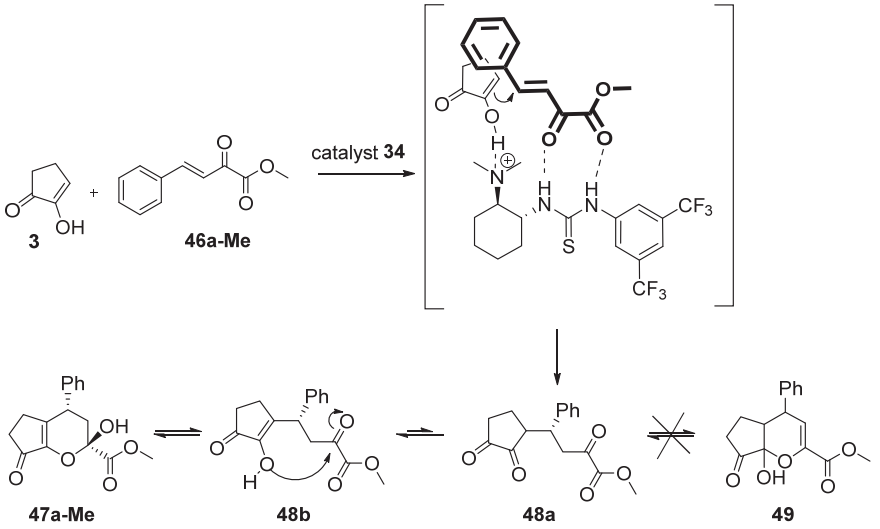
Entry[a]	Solvent	Cat. [mol %]	Yield, [%]	d.r.[b]	*ee*, [%]
1	Toluene	35, [10]	35	>20:1	96
2	CH_2Cl_2	35, [10]	75	>20:1	95
3	$CHCl_3$	35, [10]	70	>20:1	95
4	THF	35, [10]	63	>20:1	98
5	CH_2Cl_2	44, [5]	66	>20:1	95
6	CH_2Cl_2	34, [5]	89	>20:1	96[c]

[a] Conditions: **3**, (0.24 mmol); **46a-Me** (0.2 mmol); catalyst (5 and 10 mol%); room temperature, 15 minutes; isolated yield after column chromatography; *ee* determined by HPLC analysis on a Chiralpak AS-H column. Always a single diastereoisomer was obtained. [b] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c] Formation of the opposite enantiomer was observed.

We propose that the reaction proceeds according to a pathway presented in Scheme 29, where cyclopentane-1,2-dione **3** acts as a nucleophile and methyl(*E*)-2-oxo-4-phenylbut-3-enoate **46a-Me** as an electrophile, both activated by the bifunctional organocatalyst.

The Michael acceptor **46a-Me** is activated via the hydrogen bond donor activation of thiourea moiety in a Takemoto catalyst. At the same time, the tertiary amino group of the bifunctional catalyst **34** acts as a hydrogen bond acceptor and coordinates

substrate **3** into a suitable position for the reaction. A Michael addition of the ketoenol form of cyclopentane-1,2-dione **3** to β,γ-unsaturated ketoester **46a-Me** takes place, forming an adduct **48a** (in equilibrium with its enol tautomer **48b**). In the preferred transition state, the *si*-face of the acceptor is favoured, affording product in *R*-configuration. Because of the stability of the single keto-enol tautomer in cyclopentane-1,2-dione moiety, only one stereogenic centre is formed in the first step of the cascade. The following stereoselective cyclization of **48a** (*R*-configuration) via hemiacetalization of enol **48b** (*S*-configuration) resulted in hemiacetal **47a** (*S*-configuration), which was isolated as a single diastereomer with OH and Ph groups in *trans*-position (according to NMR spectra and single-crystal X-ray analysis). Dehydration product **49** was not detected.



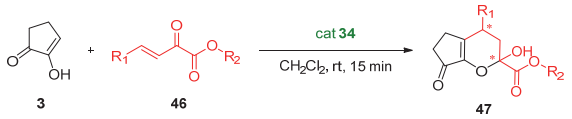
Scheme 29. The proposed reaction pathway of the Michael addition

3.1.2.3. REACTION SCOPE

Under the optimal conditions, the scope of the cascade reaction of cyclopentane-1,2-dione **3** with substituted (*E*)-2-oxo-3-butenoates **46** was studied. The obtained results are presented in Table 5.

Both electron-donating **46e** and electron-withdrawing **46b-d, f** groups on the aromatic ring of the Michael acceptor reacted smoothly and afforded excellent stereoselectivies (Table 5, entries 4-8). In addition, heteroaromatic thiophene substituted ketoester **46g** afforded the hemiacetal **47g** in slightly lower yield but in very high stereoselectivity (Table 5, entry 9). The change of methyl ester **46a-Me** to the bulkier ethyl (**46a-Et**) and isopropyl ester (**46a-*i*Pr**) slightly decreased the yield and enantioselectivity of the reaction (Table 5, entries 1-3). It is noteworthy that alicyclic β,γ-unsaturated-α-ketoester **46h** also afforded the addition-cyclization product **47h** in very high enantioselectivity, although in slightly lower yield (Table 5, entry 10). 3-Substituted cyclopentane-1,2-diones gave unsuccessful results in the reaction with (*E*)-2-oxo-3-butenoates.

Table 5. Scope of the Michael reaction of cyclopentane-1,2-dione with ketoesters



3 46 47

Entry[a]	R_1	R_2	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	Me	47a-Me	89	>20:1	96
2[e]	Ph	Et	47a-Et	66	>20:1	94
3[e]	Ph	*i*Pr	47a-*i*Pr	70	>20:1	87
4	*p*-Cl(C_6H_4)	Me	47b	73	>20:1	89
5	*o*-Br(C_6H_4)	Me	47c	93	>20:1	95
6	*o*-Cl(C_6H_4)	Me	47d	48	>20:1	94
7	*p*-MeO(C_6H_4)	Me	47e	69	>20:1	91
8	*p*-NO_2(C_6H_4)	Me	47f	86	>20:1	94
9	2-thiophenyl	Me	47g	59	>20:1	88
10	cyclohexyl	Me	47h	42	>20:1	90

[a] Reactions were performed with **3** (0.24 mmol), **46** (0.2 mmol) and catalyst **34** (5 mol%) in CH_2Cl_2 and room temperature. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy on crude reaction mixture. [d] Determined by HPLC on a Chiralpak AS-H coloumn. [e] Reaction time 1h.

The absolute configuration of compound **47b** was determined by single-crystal X-ray diffraction analysis, giving (2*R*, 4*S*) configuration. The absolute configurations of the other obtained compounds were proposed by analogy with that crystal structure (Figure 9).

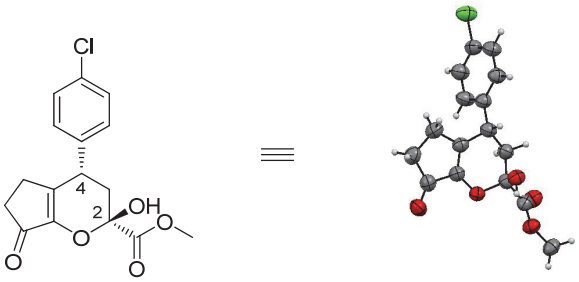
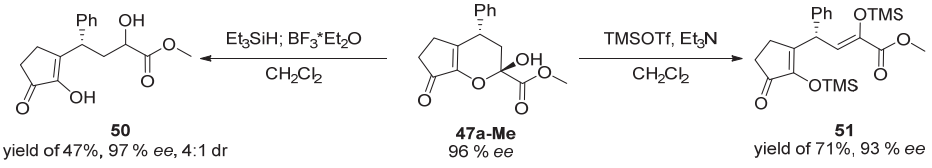


Figure 9. X-ray structure of compound **47b**.

Two selected transformations were carried out. Bicyclic product **47a-Me** was reduced, obtaining monocyclic ester **50**. Two diastereoisomers were obtained in a 4 to 1 ratio, with the thermodynamically more stable *trans*-isomer prevailing (Scheme 30, left).

Furthermore, bicyclic product **47a-Me** was treated with an excess of silylating agent, giving disilylated product **51** (Scheme 30, right). As discussed above 3-substituted diketones are valuable precursors for further derivatizations, e.g. for asymmetric oxidation, resulting in lactone carboxylic acids.[74]



50
yield of 47%, 97 % *ee*, 4:1 dr

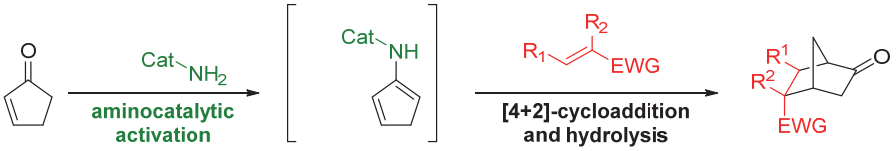
47a-Me
96 % *ee*

51
yield of 71%, 93 % *ee*

Scheme 30. Transformation of hemiacetal **47a-Me**

3.2. ASYMMETRIC ORGANOCATALYTIC DIELS-ALDER REACTIONS WITH CYCLOPENTENONE TO DIFFERENT ELECTRON-DEFICIENT OLEFINS

In this chapter, the asymmetric aminocatalytic reaction of cyclopent-2-en-1-one **2** with different dienophiles is presented, and its versatility in the diversification of privileged structures is proved (Scheme 31). Cyclopent-2-en-1-one **2** can be activated through cross-dienamine activation, giving electron-rich diene, which can readily react with dienophiles, giving multifunctionalized norcamphor scaffolds.



Scheme 31. Aminocatalytic Diels-Alder reaction of cyclopent-2-en-1-one **2**

3.2.1. PRELIMINARY RESULTS

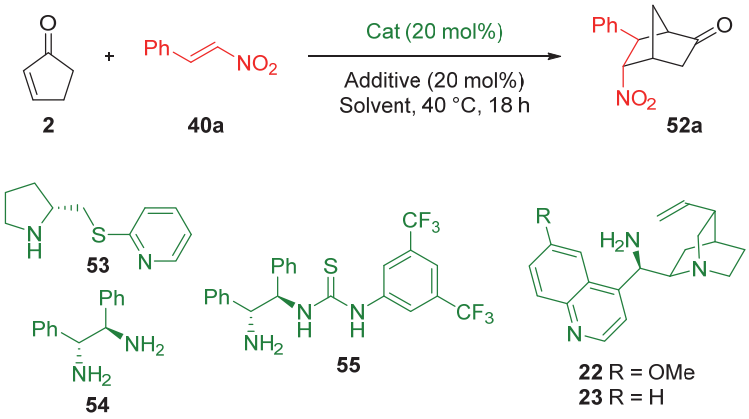
First we concentrated on the development of the Diels-Alder reaction between cyclopent-2-en-1-one **2** and nitrostyrene **40a**. In the presence of the secondary aminocatalyst **53**, the reaction was found to proceed, giving desired product **52a** only in very low yield (9%) and in almost racemic form (5% *ee*) (Table 6, entry 1). Due to the polymerization of nitro-olefin **40a**, the observed conversion of the substrate was higher than the reaction yield.

3.2.2. SCREENING OF OPTIMAL CONDITIONS

To find the optimal conditions, a variety of catalysts, solvents and additives were screened. In the search for the optimal catalyst, different secondary and primary aminocatalysts were screened. The best result was obtained with the quinine-based primary catalyst **22**, giving 49% yield with high enantioselectivity (83 % *ee*).

Solvent screening showed that enantioselectivity (90 % *ee*) and yield (52 %) could be increased by using toluene as a solvent (Table 6, entry 5). Several additives were checked and it was noted that additives had only a small influence on the enantioselectivity. Stronger acids decreased the yield of product **52a**. By prolonging the reaction time to 30 h, the reaction outcome was improved. The formation of one diastereomer was always observed.

Table 6. Screening of the optimal conditions for the Diels-Alder reaction of cyclopent-2-en-1-one **2** with (*E*)-β-nitrostyrene **40a**



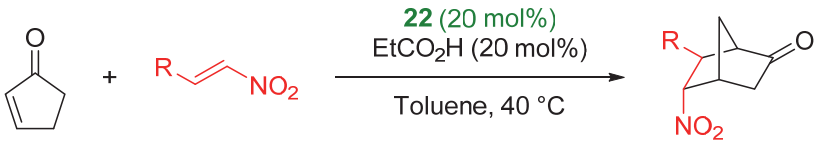
Entry[a]	Cat.	Solvent	Additive	Conv./Yield [%][c]	dr [c]	*ee* [%][d]
1	53	$CDCl_3$	$EtCO_2H$	50/9	>20:1	-5[f]
2	54	$CDCl_3$	$EtCO_2H$	67/26	>20:1	-28[f]
3	55	$CDCl_3$	$EtCO_2H$	42/5	>20:1	1
4	22	$CDCl_3$	$EtCO_2H$	79/49	>20:1	83
5	22	Toluene	$EtCO_2H$	91/52	>20:1	90
6	22	THF	$EtCO_2H$	35/17	>20:1	91
7	22	Heptane	$EtCO_2H$	100/18	>20:1	82
8	22	Toluene	$PhCO_2Na$	68/20	>20:1	91
9	22	Toluene	$PhCO_2H$	100/51	>20:1	90
10	22	Toluene	SA	90/44	>20:1	91
11	22	Toluene	*p*-NBA	90/34	>20:1	87
12	22	Toluene	TFA	62/14	>20:1	90
13	23	Toluene	$EtCO_2H$	73/39	>20:1	84
14[b]	22	Toluene	$EtCO_2H$	89/65[e]	>20:1	90

[a] Reactions were performed with **2** (0.2 mmol), **40a** (0.1 mmol), cat (0.02 mmol), additive (0.02 mmol) in solvent (0.1 mL). [b] **2** (0.15 mmol) and 30 h reaction time. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture with 1,3,5-tris(trifluoromethyl)benzene as internal standard. [d] Determined by chiral UPC^2. [e] **52a** was isolated in 62% after FCC on silica gel. [f] Formation of opposite enantiomer was observed.

3.2.3. REACTION SCOPE

Reaction scope was investigated with a series of nitrostyrenes and cyclopent-2-en-1-one **2**, shown in Table 7. Electron-donating and electron-withdrawing substituents in the aromatic ring were well-tolerated (Table 7, entries 2-8). To our delight, polyaromatic and heteroaromatic nitroolefins also gave the corresponding products **52r** and **52i** in good yields and high enantioselectivities (Table 7, entries 9 and 10). Also, polyconjugated nitrodiene **40s** reacted with cyclopent-2-en-1-one **2** in lower yield but maintained a high enantioselectivity comparable with other nitroolefins (Table 7, entry 11).

Table 7. Scope of the Diels-Alder reaction of cyclopent-2-en-1-one **2** with nitrostyrenes **3**



2 **40** **52**

Entry[a]	R	Product	Yield [%][b]	dr [c]	*ee* [%][d]
1	Ph	52a	62	>20:1	90
2	*p*-Me(C_6H_4)	52l	50	>20:1	90
3	*p*-F(C_6H_4)	52m	56	>20:1	89
4	*p*-Br(C_6H_4)	52n	56	>20:1	92
5	*o*-Cl(C_6H_4)	52o	81	>20:1	95
6	*o*-MeO(C_6H_4)	52p	79	>20:1	95
7	*m*-MeO(C_6H_4)	52q	48	>20:1	90
8	*p*-MeO(C_6H_4)	52d	48	>20:1	86
9	2-naphthyl	52r	49	>20:1	89
10	2-furyl	52i	59	>20:1	84
11	PhCH=CH	52s	41	9:1	87

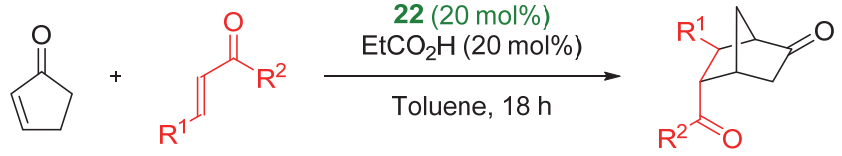
[a] Reactions were performed with **2** (0.15 mmol), **40** (0.1 mmol), **22** (0.02 mmol), propionic acid (0.02 mmol) in Toluene (0.1 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture [d] Determined by chiral UPC[2].

In the study of other possible electron-deficient olefins, it was found that chalcones also underwent Diels-Alder reactions with cyclopent-2-en-1-one **2**. It was found that chalcones **56** were less prone to react with cyclopent-2-en-1-one **2** than nitrostyrenes **40**, but also showed resistance to polymerization. Therefore, reactions were performed at higher temperatures.

In a preliminary experiment, cyclopent-2-en-1-one **2** was allowed to react with chalcone **56a**, obtaining the desired cycloadduct **57a** in 79% yield and in 93% *ee* (Table

8, entry 1). Electron-withdrawing and electron-donating groups performed well in the aromatic ring of chalcones (Table 8, entries 2-12). It should be mentioned that the reaction could also be conducted under elevated temperature (100 ˚C) without loss of enantioselectivity (87% *ee,* Table 8, entry 7). Poly- and heteroaromatic moieties were tolerated, giving products **57h-j** in 47-62% yields and 87-91% *ee* (Table 8, entries 8-10). Also, it was shown that chalcones could be substituted in the aromatic ring (R^2) giving 85-91% yields and excellent enantioselectivities of 96-99% *ee* (Table 8, entries 11 and 12). Furthermore, aliphatic groups in chalcones (compounds **56m** and **56n**) could also be used in the reaction, providing excellent stereoselectivities (>20:1 dr, 91-92% *ee*), although with low yield (19-32%; Table 8).

Table 8. Scope of the Diels-Alder reaction of cyclopent-2-en-1-one **2** with chalcones **56**



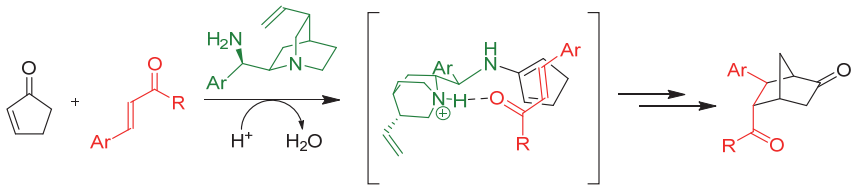
2 **56** **57**

Entry[a]	R^1/R^2	Product	T [˚C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph/Ph	57a	60	79	>20:1	93
2	*p*-Br(C_6H_4)/Ph	57b	60	66	>20:1	96
3	*m*-NO_2(C_6H_4)/Ph	57c	40	63	>20:1	96
4	*p*-NO_2(C_6H_4)/Ph	57d	40	52	>20:1	99
5	*o*-MeO(C_6H_4)/Ph	57e	60	75	>20:1	99
6	*m*-MeO(C_6H_4)/Ph	57f	80	52	>20:1	96
7	*p*-MeO(C_6H_4)/Ph	57g	100	38	>20:1	87
8	2-furyl/Ph	57h	80	62	>20:1	87
9	2-thiophenyl/Ph	57i	80	58	>20:1	91
10	2-naphthyl/Ph	57j	80	47	>20:1	91
11	Ph/ *p*-NO_2(C_6H_4)	57k	60	85	>20:1	96
12	*p*-Br(C_6H_4)/*p*-NO_2(C_6H_4)	57l	40	91	>20:1	99
13[e]	Me/Ph	57m	40	32	>20:1	91
14[f]	Ph/Me	57n	60	19	>20:1	92

[a] Reactions were performed with **2** (0.2 mmol), **56** (0.1 mmol), **22** (0.02 mmol), propionic acid (0.02 mmol) in Toluene (0.1 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture [d] Determined by chiral UPC^2. [e] Reaction time 50 h. [f] Reaction time 72 h.

We propose a Diels-Alder reaction mechanism that is similar to a recent mechanistic study published by Houk.[75] The Diels-Alder reaction transition state has been described graphically in Scheme 32, where the Cinchona alkaloid-derived primary amine

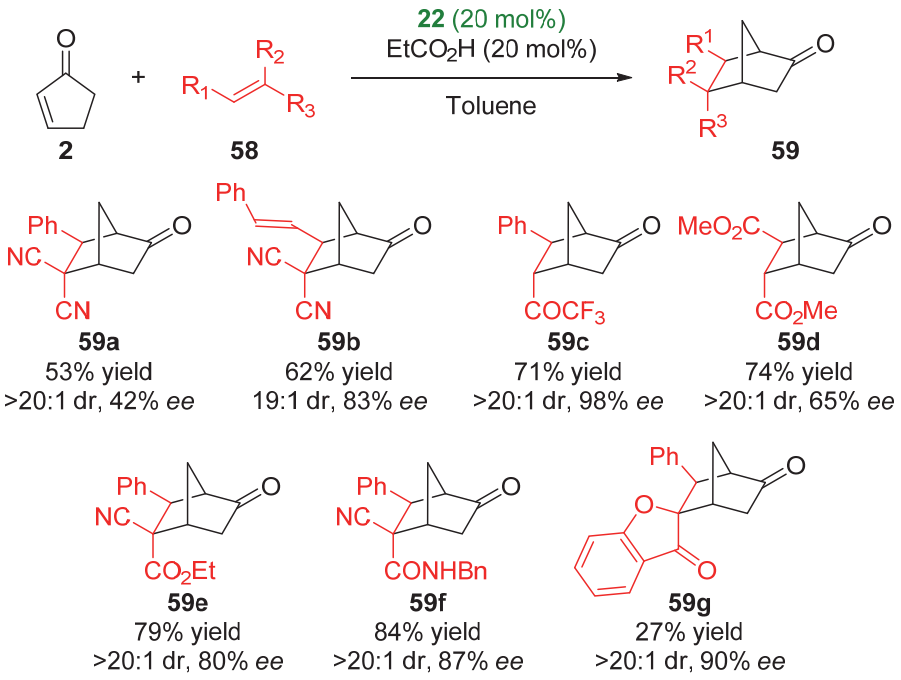
condenses with cyclopent-2-en-1-one, creating a more reactive cross-dienamine. The dienophile is coordinated and activated by a protonated quinuclidine moiety by hydrogen bonding. After the Diels-Alder reaction, the catalyst is liberated into a new catalytic cycle. The bicyclic product retains its *trans*-configuration.



Scheme 32. Proposed Diels-Alder reaction pathway

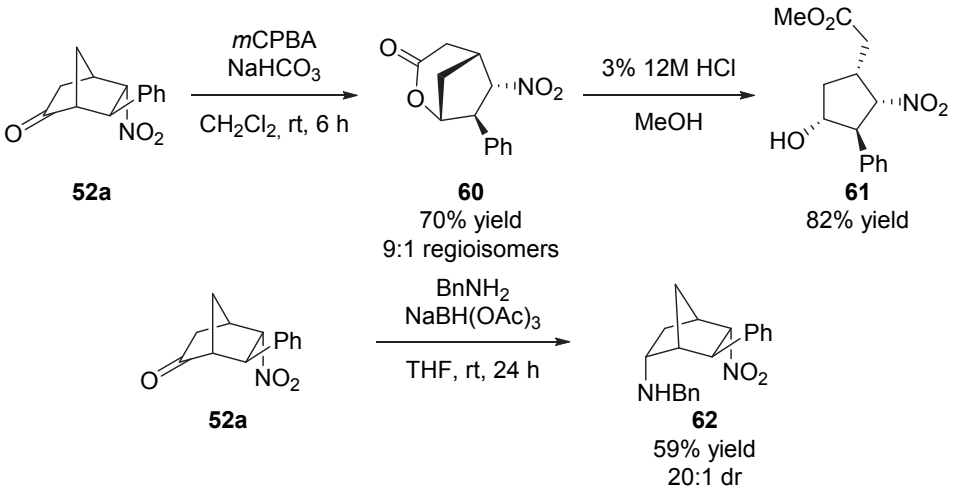
Usually, bifunctionalized aminocatalytic reactions can cope with only narrow variations of the H-bond acceptor groups in electrophiles. Optimization of the conditions for different electrophiles demands a huge amount of experimental work. However, in our case we saw excellent performance of the used primary amine catalyst under the same reaction conditions. So, we were eager to determine other electron-deficient alkenes for the reaction. To our delight, cyclopent-2-en-1-one reacted with the most common classes of electron-deficient alkenes. The results are presented in Table 9. It should be noted that all reactions performed were done without further optimization.

Table 9. Scope of Diels-Alder reaction of cyclopentenone **2** with dienophiles **58**[a]



[a] Reactions were performed with **2** (0.2 mmol), 58 (0.1 mmol), **22** (0.02 mmol), propionic acid (0.02 mmol) in toluene (0.1 mL). Isolated yield is given in each case. The dr values were determined by ^{1}H NMR spectroscopy on the crude reaction mixture, and *ee* values were determined by chiral UPC^2.

As shown in Table 9, the Diels-Alder reaction of cyclopent-2-en-1-one **2** can be performed very well with a variety of electron-deficient alkenes, for example with malononitrile derivative **58a**, polyconjugated malononitrile derivative **58b**, CF_3-enone **58c**, dimethyl fumarate **58d**, *trans*-α-cinnamate **58e**, *trans*-α-cinnamate derivative **58f** and benzylidenebenzofuranone **58g**. With the above-mentioned olefins, it is possible to generate quarternary stereocenters and spirocyclic norcamphor scaffolds with high yields and stereoselectivities. This illustrates the generality of the developed organocatalytic system, affording the use of different dienophiles in the Diels-Alder reaction, under the same reaction conditions.



Scheme 33. Synthetic transformations of cycloadduct **52a**

To increase the relevance of the Diels-Alder reaction, two transformations were conducted with norcamphor scaffold **52a**. Baeyer-Villiger oxidation followed by acidic ring opening provided highly substituted cyclopentane scaffold **61**, having 4 contiguous stereocenters (Scheme 33, top). Diastereoselective reductive amination gave product **62**, which can be used in the synthesis of bioactive compounds (Scheme 33, bottom).

The absolute configurations of the compounds **57l** and **62** were determined by a single-crystal X-ray diffraction and the configurations of all remaining products were assigned by analogy (Figures 10 and 11).

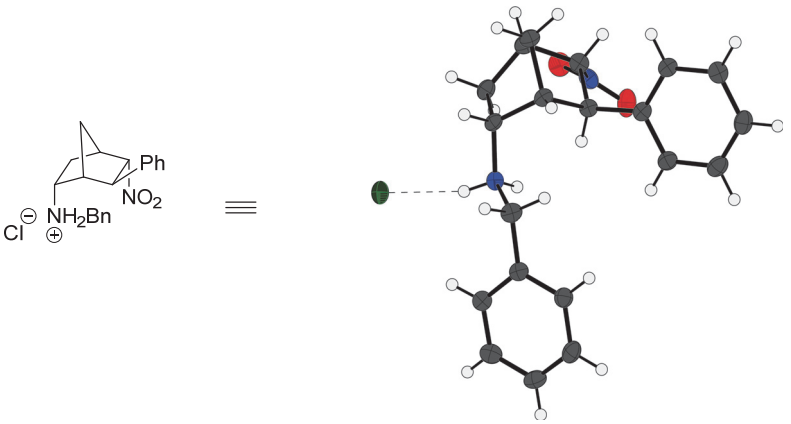


Figure 10. X-ray crystal structure of compound **62**

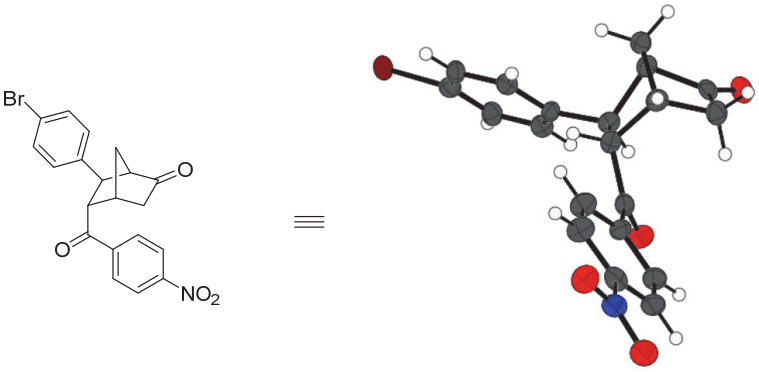


Figure 11. X-ray structure of compound **57l**

CONCLUSIONS

An effective asymmetric organocatalytic Michael addition reaction of cyclopentane-1,2-dione to nitroolefins resulting in 3-substituted 2-hydroxycyclopent-2-en-1-ones with excellent yields and good enantioselectivities has been described.

The absolute configurations of nitro-ketone products were determined based on analogy with the X-ray diffraction analysis of 3-[1-(4-chlorophenyl)-2-nitroethyl]-2-hydroxycyclopent-2-enone, having the (*R*)-configuration.

A stereoselective organocatalytic Michael addition-cyclization cascade reaction of cyclopentane-1,2-dione with substituted (E)-2-oxobut-3-enoates was elaborated, giving substituted bicyclic dihydropyran derivatives with excellent yield and high stereoselectivity.

The absolute configuration of the obtained substituted bicycles were determined based on analogy with the X-ray diffraction analysis of methyl 4-(4-chlorophenyl)-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[b]pyran-2-carboxylate, having a (2*R*, 4*S*)-configuration.

Electron-withdrawing and -donating substituents in Michael acceptors did not change the outcome of the enantioselectivity. Also, heteroaromatic and aliphatic substituent were well tolerated, giving comparable results.

A stereoselective organocatalytic Diels-Alder reaction of cyclopent-2-en-1-one to the most common classes of electron-deficient olefins, giving 5,6-substituted norcamphor scaffolds with good to excellent yield and stereoselectivity, has been described. The proposed protocol is general for a wide range of substrates and reagents.

The absolute configurations of norcamphor scaffolds were determined based on analogy with the X-ray diffraction analysis of 6-(4-bromophenyl)-5-(4-nitrobenzoyl)bicyclo[2.2.1]heptan-2-one with 1*R*,4*R*,5*S*,6*S* and N-benzyl-5-nitro-6-phenylbicyclo[2.2.1]heptan-2-amine salt with a 1*R*,4*R*,6*S* configuration.

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PUBLICATION I

Preegel, G.; Noole, A; Ilmarinen, K.; Järving, I.; Kanger, T.; Pehk, T.; Lopp, M. Enantioselective Organocatalytic Michael Addition of Cyclopentane-1,2-diones to Nitroolefins *Synthesis* **2014**, 46, 2595 – 2600.

Enantioselective Organocatalytic Michael Addition of Cyclopentane-1,2-diones to Nitroolefins

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Abstract: Organocatalytic Michael additions of cyclopentane-1,2-dione to different nitroolefins have been investigated. Cyclopentane-1,2-dione undergoes an organocatalytic reaction with substituted nitroolefins giving 3-substituted products in good to high yields (48–97%) and good stereoselectivity (up to 76% ee).

Key words: Michael addition, asymmetric synthesis, asymmetric catalysis, enantioselectivity, electrophilic addition, ketones

The synthesis of substituted alicyclic rings and heterocycles in a stereocontrolled manner is an important and challenging task in building skeletons of organic compounds. The availability of convenient synthetic methods for the construction of cyclic systems depends, along with other factors, on the number of carbon atoms in the ring. There are many excellent examples describing the synthesis of substituted cyclohexanes,[1] but the synthesis of analogously substituted cyclopentanes remains a challenge and requires further development,[2] especially because the five-membered carbocyclic core is an important and common structural fragment in many natural and bioactive compounds.[3]

We have been engaged in the development of stereocontrolled methods for the synthesis of substituted cyclopentanes and lactone-acids by generating chirality via the asymmetric oxidation of cyclopentane-1,2-diones.[4] Therefore, we are developing new methods that deliver substituted cyclopentane-1,2-diones as crucial starting compounds in order to broaden the scope of this general methodology. Additionally, cyclopentane-1,2-diones have also been used as precursors for the synthesis of various bioactive compounds.[5]

Asymmetric organocatalytic methods often offer the most efficient and environmentally benign approach for enantioselective synthesis.[6] Our contribution to the field covers several new reactions for building C–C, C–O, and C–N bonds in different structures.[7]

The organocatalytic Michael addition of ketone enolates with nitroolefins to afford substituted nitroaldehydes with high enantio- and diastereoselectivities and yields has been well investigated.[8,9] The enols and enolates of 1,2-diketones are less nucleophilic than those of ketones. However, it has been demonstrated that cyclohexane-1,2-dione reacts in the presence of bifunctional thiourea and ephedrine derivatives with nitroolefins affording substituted bicyclo[3.2.1]octanes.[10] The cascade transformation using transition-metal catalysis has also been reported.[11] Unsaturated aldehydes, although less active Michael acceptors than nitroolefins, undergo a Michael–aldol cascade with cyclohexane-1,2-dione affording a bicyclo[3.2.1]octane skeleton (Scheme 1, paths A and B).[12] The organocatalytic reactions outlined in Scheme 1 have not been described for cyclopentane-1,2-diones. This is not surprising, because different reactivities of cyclohexane-1,2-diones and cyclopentane-1,2-diones have also been observed previously in oxidation reactions.[13]

Recently, we demonstrated that a bis(*tert*-butyldimethylsilyl) enol ether of cyclopentane-1,2-dione reacts smoothly in a Mukaiyama–Michael reaction with unsaturated aldehydes under aminocatalytic conditions (Scheme 1, path C);[14] chiral cyclopentane-1,2-diones were obtained in good yields (up to 66%) and stereoselectivities (up to 94% ee). Cyclopentane-1,2-dione failed to react with unsaturated aldehydes under these conditions. In the present work, we investigated the possibilities of using unprotected cyclopentane-1,2-dione (**1**) in reactions with nitroolefins **2** (Scheme 1, path D). Hydrogen-bonding organocatalysts were used as asymmetry inducers and for the activation of the electrophile.

During preliminary experiments conducted at room temperature, we observed complete consumption of the starting materials within one hour, delivering nitro diketone **3a** in 93% yield with 62% ee (Table 1, entry 1). The formation of a functionalized bicyclo[2.2.1]heptanone skeleton was not observed.

In order to find the most efficient catalyst, we screened two types of bifunctional H-bonding catalysts (Figure 1), quinine-derived thiourea catalysts **4a** and **4e**, and squaramides **4b**, **4c**, and **4d**. The obtained results are presented in Table 1 (entries 2, and 9–12). Experiments revealed the thiourea catalyst **4a** to be the most selective and active catalyst for the reaction, affording the optimal balance between enantioselectivity (up to 78% in CH_2Cl_2) and yield (up to 88% in CH_2Cl_2).

To improve the selectivity of the reaction, we next investigated the influence of temperature on the selectivity of the Michael addition. We observed that in toluene at a lower temperature the reaction selectivity dropped con-

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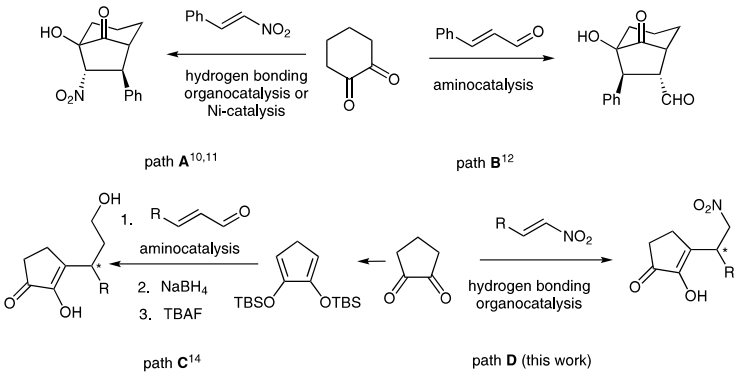
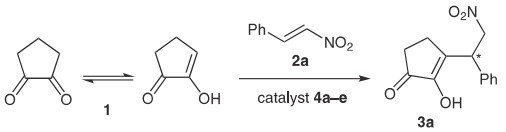


Scheme 1 Cyclic 1,2-diones in Michael reactions

siderably (entry 1 vs. 4 and 5). Similar temperature dependence was found earlier and rationalized by Jang et al. as being a result of the self-aggregation of the catalyst.[15] By increasing the reaction temperature up to 50 °C, the selectivity was improved. Additional temperature elevation caused a slight drop in selectivity (entries 1 and 5 vs. 6 and 7). In chlorinated solvents, no temperature dependence was observed (entries 1 and 6 vs. 3 and 8).

Table 1 Selection of the Conditions for a Michael Addition of 2-Hydroxycyclopent-2-enone **1** to Nitroolefin **2a**[a]



Entry	Solvent	Catalyst (5 mol%)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	toluene	**4a**	r.t.	1	93	62
2	CH_2Cl_2	**4a**	r.t.	4	88	78
3	$CHCl_3$	**4a**	r.t.	4	85	76
4	toluene	**4a**	0	3	77	50
5	toluene	**4a**	–20	3	61	36
6	toluene	**4a**	50	0.5	79	76
7	toluene	**4a**	80	0.1	77	70
8	$CHCl_3$	**4a**	50	1	77	73
9	$CHCl_3$	**4b**	r.t.	2	83	78
10	$CHCl_3$	**4c**	r.t.	24	2	46
11	$CHCl_3$	**4d**	r.t.	2	43	72
12	$CHCl_3$	**4e**	r.t.	3	97	68

[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), **4** (5 mol%), solvent (0.7 mL).
[b] Isolated yield of **3a**.
[c] Determined by HPLC analysis on a chiral stationary phase.

In the search for the optimal solvent for the reaction, dichloromethane, chloroform, and toluene were screened at room temperature. Under the used conditions, the solvent had little or no influence on the reaction outcome. Because of experimental convenience, dichloromethane and chloroform were chosen for further optimization.

Under optimal conditions [catalyst **4a** (5 mol%), CH_2Cl_2 or $CHCl_3$, r.t.], we next examined the substrate scope of the reaction. The results are presented in Scheme 2.

On the basis of these results, we may conclude that the reaction tolerates a variety of aromatic nitroolefins, with little dependence on the electronic nature of the substituent. The substituents in the aromatic ring also had little or no influence on the enantioselectivity. Nitroolefins with heteroaromatic substituents or an aliphatic cyclohexane group can also be used in the reaction to give products **3i–k**. Aliphatic substitution reduces the reactivity of the nitroolefin, and therefore a prolonged reaction time is necessary, for example the formation of **3k**.

The absolute configuration of compound **3b** was determined by X-ray crystal structure analysis (Figure 2). The absolute configurations of other compounds in the series were assigned in analogy.

In summary, we have developed a chiral thiourea **4a** catalyzed Michael addition reaction of cyclopentane-1,2-dione with nitroolefins under mild conditions. The reaction has a wide substrate scope, as even an aliphatic nitroolefin yielded the expected product in good yield and selectivity. The developed methodology offers straightforward access to useful building blocks containing versatile functional groups, broadening the possibilities of using these synthons in chemical transformations.

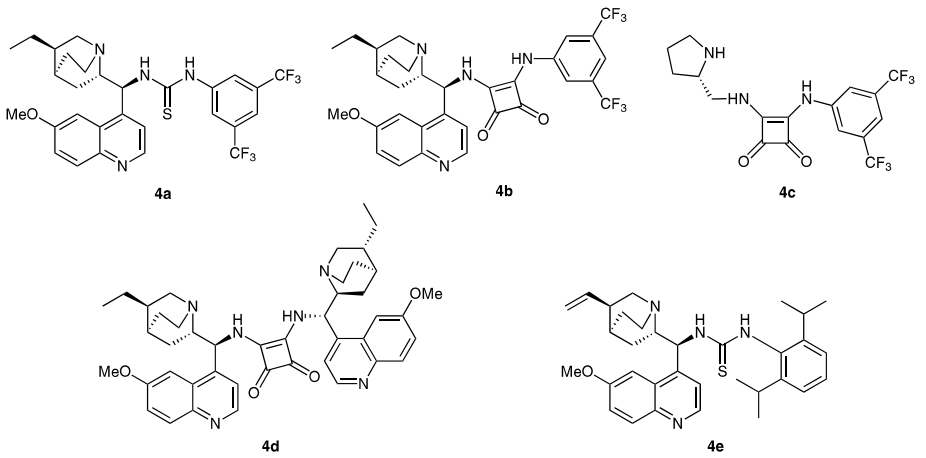
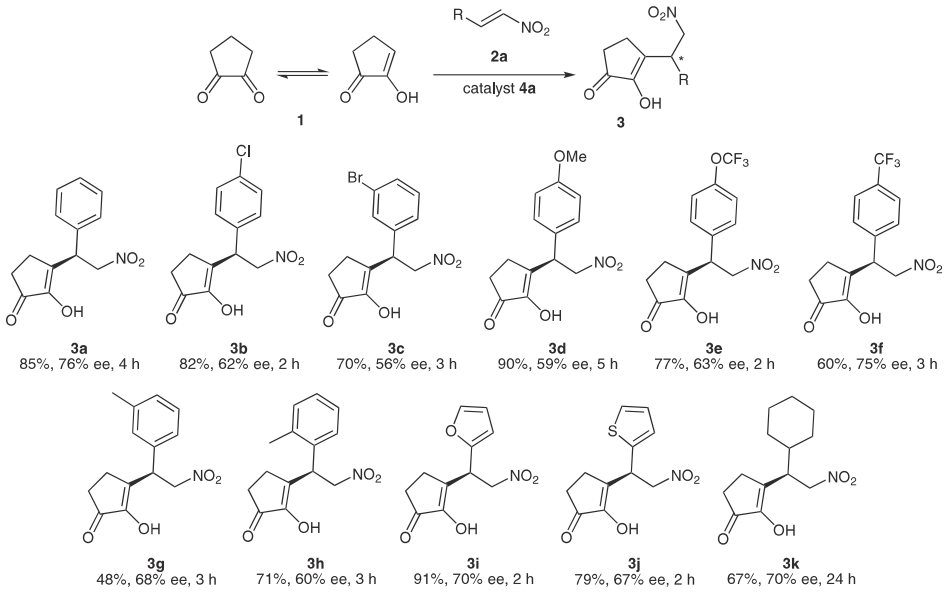


Figure 1 Catalysts investigated



Scheme 2 Screening of the substrate scope of the Michael addition. *Reagents and conditions*: **1** (0.24 mmol), **2** (0.2 mmol), **4a** (5 mol%), CH_2Cl_2 (0.7 mL). Isolated yields are given; ee values were determined by HPLC analysis on a chiral stationary phase.

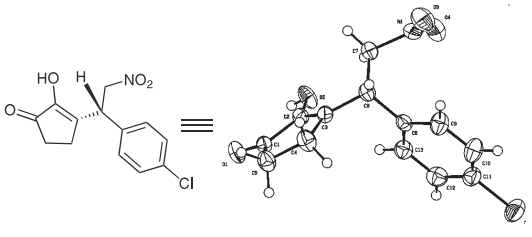


Figure 2 X-ray crystal structure of **3b**

Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a 400 MHz instrument. Solvent peaks ($CHCl_3/CDCl_3$ $\delta = 7.3/77.2$) were used as chemical shift references. Chiral HPLC was performed using Chiralcel OD-H and Chiralpak AD-H columns. Mass spectra were recorded by using Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Optical rotations were obtained by using an Anton Paar GWB Polarimeter MCP500. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. Absolute structure of the single crystal was obtained with Bruker SMART X2S benchtop diffractometer. Precoated silica gel 60 F_{254} plates

were used for TLC, whereas for column chromatography Merck silica gel was used. Commercial reagents were generally used as received. CH_2Cl_2 and EtOAc were distilled from P_2O_5.

Synthesis of Catalysts

Thioureas **4a**[16] and **4e**[7b,17] and squaramides **4b**,[18] **4c**,[19] and **4d**[20] were prepared according to literature procedures.

Synthesis of Starting Materials

Cyclopentane-1,2-dione was prepared according to the literature procedure[21] from commercially available cyclopentanone. Nitroolefins **2a–k** were synthesized according to a literature procedure[22] from commercially available aldehydes and nitromethane.

(*R*)-2-Hydroxy-3-(2-nitro-1-phenylethyl)cyclopent-2-enone (3a); Typical Procedure

2-Hydroxycyclopent-2-enone (**1**, 23.5 mg, 0.2 mmol), nitrostyrene **2a** (29.5 mg, 0.24 mmol), and organocatalyst **4a** (6 mg, 0.01 mmol) were dissolved in CH_2Cl_2 (0.7 mL). The mixture was stirred at r.t. for 4 h. The mixture was purified by column chromatography (silica gel, CH_2Cl_2–EtOAc, 25:1) to give **3a** as a white solid; yield: 42 mg (85%); mp 154 °C; 76% ee [HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 254 nm): t_R = 24.97 (major), 17.45 min (minor)].

$[\alpha]_D^{25}$ –42.3 (*c* 0.05, MeOH).

IR (KBr): 3302, 2922, 1690, 1641, 1551, 1382, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 6.20 (s, 1 H), 5.31 (dd, *J* = 13.8, 8.6 Hz, 1 H), 4.91 (dd, *J* = 13.8, 7.3 Hz, 1 H), 4.52–4.45 (m, 1 H), 2.50–2.34 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.1, 148.8, 141.4, 136.8, 129.3, 128.4, 128.0, 76.6, 45.4, 31.7, 24.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}NO_4$: 248.0917; found: 248.0925.

(*R*)-3-[1-(4-Chlorophenyl)-2-nitroethyl]-2-hydroxycyclopent-2-enone (3b)

White solid; yield: 46 mg (82%); mp 144–146 °C; 62% ee [HPLC (Chiralcel AD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 31.28 (major), 33.47 min (minor)].

$[\alpha]_D^{25}$ –49.1 (*c* 0.05, MeOH).

IR (KBr): 3258, 2914, 1700, 1655, 1556, 1405, 1120, 840 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 2 H), 7.28–7.22 (m, 2 H), 6.03 (s, 1 H), 5.25 (dd, *J* = 13.8, 8.2 Hz, 1 H), 4.91 (dd, *J* = 13.8, 7.7 Hz, 1 H), 4.45 (t, *J* = 8.0 Hz, 1 H), 2.52–2.31 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.7, 148.8, 140.2, 135.2, 134.4, 129.6, 129.3, 76.4, 44.8, 31.7, 24.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}ClNO_4$: 282.0528; found: 282.0531.

(*R*)-3-[1-(3-Bromophenyl)-2-nitroethyl]-2-hydroxycyclopent-2-enone (3c)

White solid; yield: 45 mg (70%); mp 163 °C; 56% ee [HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 20.6 (major), 31.1 min (minor)].

$[\alpha]_D^{25}$ –35.8 (*c* 0.04, MeOH).

IR (KBr): 3335, 2923, 1696, 1655, 1551, 1407, 1125, 780, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 2 H), 7.26–7.20 (m, 2 H), 5.91 (s, 1 H), 5.27 (dd, *J* = 13.9, 8.4 Hz, 1 H), 4.90 (dd, *J* = 13.9, 7.5 Hz, 1 H), 4.44 (t, *J* = 7.9 Hz, 1 H), 2.52–2.34 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.6, 148.9, 139.7, 139.0, 131.6, 131.0, 130.9, 126.6, 123.3, 76.23, 45.0, 31.6, 24.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}BrNO_4$: 326.0022; found: 326.0029.

(*R*)-2-Hydroxy-3-[1-(4-methoxyphenyl)-2-nitroethyl]cyclopent-2-enone (3d)

White solid; yield: 50 mg (90%); mp 98–100 °C; 59% ee [HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 20.8 (major), 26.7 min (minor)].

$[\alpha]_D^{25}$ +41.9 (*c* 0.04, MeOH).

IR (KBr): 3278, 2918, 1701, 1655, 1554, 1407, 1250, 843 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 2 H), 6.91–6.85 (m, 2 H), 6.18 (s, 1 H), 5.26 (dd, *J* = 13.7, 8.5 Hz, 1 H), 4.88 (dd, *J* = 13.7, 7.5 Hz, 1 H), 4.42 (t, *J* = 8.0 Hz, 1 H), 3.79 (s, 3 H), 2.50–2.33 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.1, 159.5, 148.6, 141.9, 129.1, 128.6, 114.7, 76.8, 55.3, 44.7, 31.7, 24.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}NO_5$: 278.1023; found: 278.1004.

(*R*)-2-Hydroxy-3-{2-nitro-1-[4-(trifluoromethoxy)phenyl]ethyl}cyclopent-2-enone (3e)

Yellow liquid; yield: 51 mg (77%); 63% ee [HPLC (Chiralcel AD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 19.9 (major), 18.9 min (minor)].

$[\alpha]_D^{25}$ –3.2 (*c* 0.02, MeOH).

IR (KBr): 3323, 2925, 1706, 1661, 1557, 1510, 1264, 1117, 857 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2 H), 7.24–7.16 (m, 2 H), 6.62 (s, 1 H), 5.26 (dd, *J* = 14.1, 7.1 Hz, 1 H), 4.93 (dd, *J* = 13.9, 7.7 Hz, 1 H), 4.50 (t, *J* = 8.0 Hz, 1 H), 2.54–2.35 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 149.1, 141.0, 135.5, 129.5, 121.8, 120.4 (q, *J* = 257.7 Hz), 76.4, 44.8, 31.8, 24.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{13}F_3NO_5$: 332.074; found: 332.0743.

(*R*)-2-Hydroxy-3-{2-nitro-1-[4-(trifluoromethyl)phenyl]ethyl}cyclopent-2-enone (3f)

Yellow liquid; yield: 82 mg (60%); 75% ee [HPLC (Chiralcel AD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 22.1 (major), 25.2 min (minor)].

$[\alpha]_D^{25}$ –66.4 (*c* 0.04, MeOH).

IR (KBr): 3323, 2924, 1715, 1673, 1558, 1326, 1134, 850 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.1 Hz, 2 H), 7.46 (d, *J* = 8.1 Hz, 2 H), 6.66 (s, 1 H), 5.31 (ddd, *J* = 13.9, 8.1, 1.7 Hz, 1 H), 4.97 (dd, *J* = 13.9, 7.8 Hz, 1 H), 4.57 (t, *J* = 7.9 Hz, 1 H), 2.54–2.33 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 149.3, 140.8, 140.6, 130.7 (dd, *J* = 65.5, 32.7 Hz), 128.5, 126.3 (dd, *J* = 7.4, 3.7 Hz), 123.8 (dd, *J* = 544.5, 272.3 Hz), 76.1, 45.1, 31.8, 24.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{13}F_3NO_4$: 316.0791; found: 316.0800.

(*R*)-2-Hydroxy-3-[2-nitro-1-(*m*-tolyl)ethyl]cyclopent-2-enone (3g)

White solid; yield: 52 mg (48%); mp 107–108 °C; 68% ee [HPLC (Chiralcel AD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 28.0 (major), 18.0 min (minor)].

$[\alpha]_D^{25}$ –58.3 (*c* 0.04, MeOH).

IR (KBr): 3314, 2928, 1693, 1658, 1561, 1404, 833, 794 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 1 H), 7.15–7.06 (m, 3 H), 6.34 (s, 1 H), 5.29 (dd, *J* = 13.8, 8.6 Hz, 1 H), 4.90 (dd, *J* = 13.8, 7.3 Hz, 1 H), 4.48–4.41 (m, 1 H), 2.51–2.36 (m, 4 H), 2.34 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 148.8, 141.9, 139.2, 136.7, 129.2, 129.1, 128.7, 125.0, 76.6, 45.4, 31.8, 24.7, 21.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_4$: 262.1074; found: 262.1081.

(*R*)-2-Hydroxy-3-[2-nitro-1-(*o*-tolyl)ethyl]cyclopent-2-enone (3h)
Yellow liquid; yield: 37 mg (71%); 60% ee [HPLC (Chiralcel AD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 18.0 (major), 28.4 min (minor)].

$[\alpha]_D^{25}$ +43.4 (*c* 0.04, MeOH).

IR (KBr): 3369, 2922, 1712, 1655, 1555, 1378, 1117, 794, 706 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.17 (m, 4 H), 6.66 (s, 1 H), 5.28 (dd, *J* = 16.0, 10.8 Hz, 1 H), 4.91–4.82 (m, 2 H), 2.49–2.32 (m, 7 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.5, 149.3, 142.1, 136.4, 135.1, 131.3, 128.1, 127.2, 127.0, 76.0, 40.8, 31.8, 24.5, 19.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_4$: 262.1074; found: 262.1091.

(*R*)-3-[1-(Furan-2-yl)-2-nitroethyl]-2-hydroxycyclopent-2-enone (3i)
Yellow liquid; yield: 43 mg (91%); 70% ee [HPLC (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 254 nm): t_R = 13.1 (major), 16.2 min (minor)].

$[\alpha]_D^{25}$ +28.3 (*c* 0.04, MeOH).

IR (KBr): 3492, 2925, 1716, 1673, 1558, 1407, 1106, 910 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 1.8, 0.7 Hz, 1 H), 6.35 (dd, *J* = 3.2, 1.9 Hz, 1 H), 6.25 (d, *J* = 3.3 Hz, 1 H), 5.87 (s, 1 H), 5.10 (dd, *J* = 13.4, 8.3 Hz, 1 H), 4.93 (dd, *J* = 13.4, 7.3 Hz, 1 H), 4.81 (t, *J* = 7.8 Hz, 1 H), 2.52–2.42 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.5, 149.3, 148.9, 142.9, 138.1, 110.7, 108.1, 74.4, 37.9, 31.7, 24.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_5$: 238.071; found: 238.071.

(*R*)-2-Hydroxy-3-[2-nitro-1-(thiophen-2-yl)ethyl]cyclopent-2-enone (3j)
White solid; yield: 40 mg (79%); mp 120–121 °C; 67% ee [HPLC (Chiralcel AD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 254 nm): t_R = 36.8 (major), 43.2 min (minor)].

$[\alpha]_D^{25}$ –49.9 (*c* 0.04, MeOH).

IR (KBr): 3315, 2918, 1699, 1658, 1552, 1407, 1124, 662 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, *J* = 5.1, 1.3 Hz, 1 H), 7.00 (ddd, *J* = 8.6, 4.3, 2.3 Hz, 2 H), 6.57 (s, 1 H), 5.28–5.18 (m, 1 H), 4.91 (dq, *J* = 14.4, 7.1 Hz, 2 H), 2.54–2.42 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 148.9, 140.8, 138.3, 127.4, 126.3, 125.6, 76.7, 39.6, 31.9, 24.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_5S$: 254.0482; found: 254.0486.

(*R*)-3-(1-Cyclohexyl-2-nitroethyl)-2-hydroxycyclopent-2-enone (3k)
White solid; yield: 34 mg (67%); mp 117–118 °C; 70% ee [HPLC (Chiralcel AD-H, hexane–*i*-PrOH, 90:10, 1 mL/min, 230 nm): t_R = 17.9 (major), 20.4 min (minor)].

$[\alpha]_D^{25}$ –3.7 (*c* 0.04, MeOH).

IR (KBr): 3344, 2926, 2856, 1694, 1655, 1558, 1408, 1107 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (s, 1 H), 4.84 (dd, *J* = 12.8, 10.7 Hz, 1 H), 4.67 (dd, *J* = 12.9, 4.7 Hz, 1 H), 3.19 (ddd, *J* = 10.9, 7.9, 4.7 Hz, 1 H), 2.52–2.39 (m, 4 H), 1.84–1.59 (m, 6 H), 1.33–0.99 (m, 5 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.6, 150.0, 142.7, 75.3, 44.4, 39.0, 31.8, 31.1, 30.9, 26.1, 26.1, 26.0, 25.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{20}NO_4$: 254.1387; found: 254.1389.

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PUBLICATION II

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Enantioselective Organocatalytic Michael Addition–Cyclization Cascade of Cyclopentane-1,2-dione with Substituted (*E*)-2-oxobut-3-enoates

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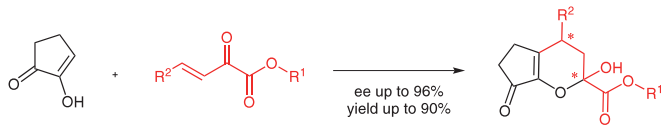

R^1 = Me, Et, *i*-Pr
R^2 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, cyclohexyl

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Abstract An organocatalytic cascade Michael addition-cyclization reaction of cyclopentane-1,2-dione with substituted (*E*)-2-oxobut-3-enoates, creating two stereocenters and giving bicyclic hemiacetals **3** in excellent yield (up to 93%) and enantioselectivity (up to 96% ee) was developed. From 2-chlorophenyl-substituted (*E*)-2-oxobut-3-enoate, the adduct revealed pseudo-atropisomerism from the hindered rotation of the phenyl ring. The hemiacetal **3** was reduced with Et_3SiH and Lewis acid affording substituted 1,2-cyclopentanedione **8**, and disilylated with an excess of TMSOTf and Et_3N to the dienol disilyl ether **9**.

Key words organocatalysis, cascade reactions, atropisomerism, stereoselectivity

Asymmetric organocatalytic cascade reactions, because of their efficiency and experimental simplicity, have been the focus of researchers for many years. Different nucleophiles and eletrophiles have been used to build various reaction cascades. Among the structural fragments, the 1,3-dicarbonyl compounds have been found suitable for different cascade reactions and, therefore, have been investigated thoroughly.[1–6] Thus, different cyclic 1,3-dicarbonyl compounds have been successfully used as nucleophiles with unsaturated[1] and saturated aldehydes,[2] with acetates of nitroalkenes,[3] with α-hydroxymethyl nitroalkenes,[4] with β-formyl esters,[5] and with α,β-unsaturated N-acylated succinimides.[6]

In contrast, 1,2-dicarbonyl compounds have received little attention. There are only a few examples of the use of cyclohexane-1,2-dione: nucleophilic additions to aldehydes,[7] nitroalkenes,[8] and keto esters.[9] Similar 2-hydroxy-1,4-naphthoquinones have also been used as Michael donors with keto esters.[10] For cyclopentane-1,2-dione there is only one example of the reaction with nitrostyrenes.[11] Additionally, the reaction with α,β-unsaturated aldehydes with cyclopentane-1,2-dione dienolate was described by our group recently.[12]

Many research groups have reported the usefulness of 2-oxobut-3-enoates substituted 1,2-dicarbonyl compounds in various reactions.[13] These compounds when acting as Michael acceptors afford different cyclic structures of interest: 3-substituted indoles,[14] 4-hydroxycoumarins,[15] hemiacetal esters,[16] and amino acid derivatives from isocyanides.[17] In addition, these compounds undergo organocatalytic cascade aldol reaction with 1,3-dicarbonyl compounds giving a bicyclic pyran derivative,[18] a hetero-Diels–Alder reaction with aldehydes[19] and dihydropyrans.[20] Similar pyran substructural units have been previously synthesized via Nazarov cyclization[20] and by a tandem Nazarov cyclization–Michael addition sequence.[21] Substituted pyrans and similar structural units are present in several antiviral ingredients, being valuable intermediates in the synthesis of bioactive compounds.[22]

In this article, we present our results on a cascade reaction of cyclopentane-1,2-dione (**1**) with substituted α-keto esters **2** giving novel bicyclic pyran derivatives **3** in excellent yields and stereoselectivities.

In organocatalysis, hydrogen bonding catalysis has been widely studied in recent years,[23] because of its evident benefits: high catalytic output, stability in air and water, and reusability. Similar to aminocatalysts, the H-bonding catalysts activate carbonyl groups in chemical reactions. In our case, four carbonyl groups are present in the reaction of α,β-unsaturated keto esters with cyclopentane-1,2-dione in which two pairs of them are in vicinal position. Therefore, bifunctional hydrogen bonding catalysts, activating both electrophile and nucleophile, seemed a reasonable choice from the group of the organocatalysts.

The preliminary results of the cascade reaction with cyclopentane-1,2-dione (**1**) with phenyl-substituted keto ester **2a** by using Soos's type organocatalyst **4a** in toluene were promising, affording hemiacetal **3a** in 35% yield with excellent stereoselectivity (96% ee, Table 1, entry 1) in a very short reaction time (15 min). The formation of predominantly only one diastereomer was observed.

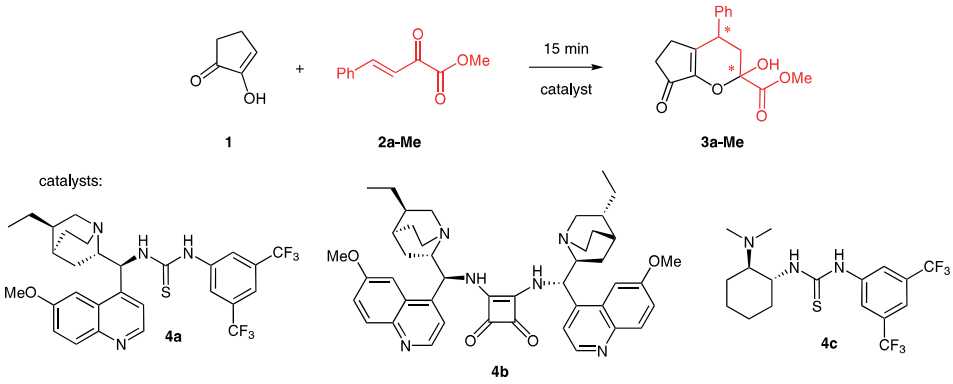
To find the optimal reaction conditions, a model reaction with cyclopentane-1,2-dione (**1**) and phenyl-substituted keto ester **2a-Me** was screened using different catalysts and solvents. The results are presented in Table 1.

We found that with catalyst **4a** the stereoselectivity of the reaction did not notabaly depend on the solvent; the stereoselectivity in toluene, dichloromethane, $CHCl_3$, and THF was almost equal. However, the best yields of product **3** were obtained in dichloromethane (Table 1, entries 1–4). Therefore, the screening of the catalysts was made using dichloromethane as the solvent. All of the used H-bonding catalysts resulted in very high stereoselectivity in the reaction. The best yield of product **3a** (89%) was obtained with the Takemoto-type catalyst **4c** (loading of 5 mol%), also affording excellent stereoselectivity (96% ee) in a very short reaction time (15 min, entry 6).

We propose that the reaction proceeds according to a pathway presented in Scheme 1, where one of the 1,2-dicarbonyl compounds, 1,2-cyclopentanedione (**1**), acts as a nucleophile and the other, 2-oxobut-3-enoate **2a-Me**, as an electrophile, both activated by the catalyst.

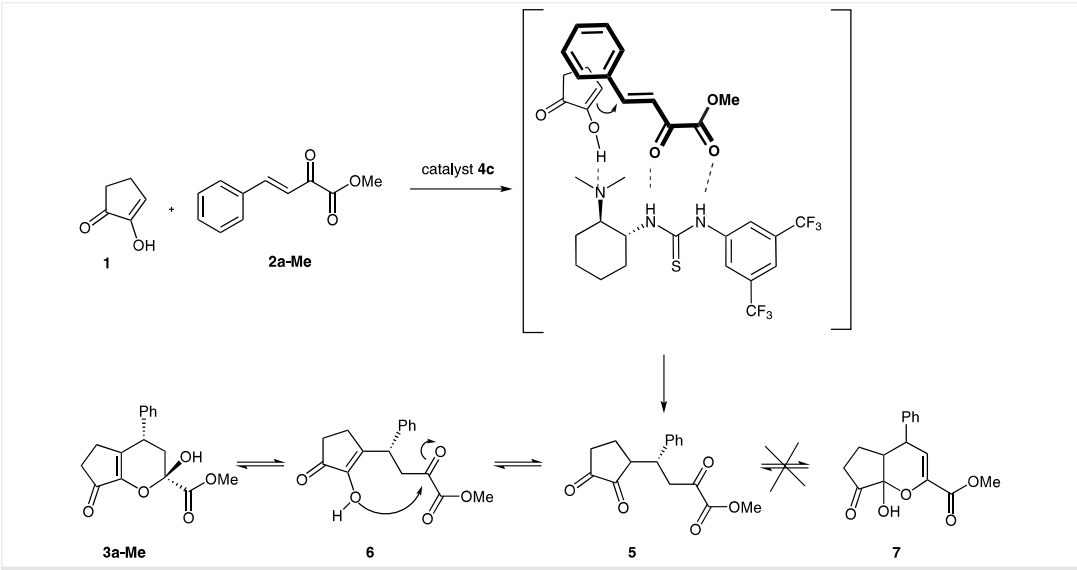
First, a Michael addition of the cyclopentane-1,2-dione (**1**) (in keto–enol form) to α,β-unsaturated keto ester **2a-Me** takes place, forming an adduct **5** (in equilibrium with its enol tautomer **6**). The Michael acceptor is activated via hydrogen bonds of the thiourea catalyst. At the same time, the tertiary amino group of the bifunctional catalyst **4c** acts as a hydrogen bond, acceptor shifting the equilibrium of cyclic diketone **1** towards the nucleophilic enol form. Because of keto–enol tautomerism, only one stereogenic center is formed in the first step of the cascade. In the preferred transition state, the *si*-face of the acceptor is favored, affording product in *R*-configuration. The following stereoselective cyclization of **5** (*R*-configuration) via hemiacetalization of enol **6** (*S*-configuration) resulted in hemiacetal **3a-Me** (*S*-configuration), which was isolated as a single diastereomer with OH and Ph groups in the *trans*-position (according to

Table 1 Screening of the Catalyst and the Solvent[a]



Entry	Solvent	Catalyst **4** (mol%)	Product **3a-Me**	
			Yield (%)	ee (%)
1	toluene	**4a** (10)	35	96
2	CH_2Cl_2	**4a** (10)	75	95
3	$CHCl_3$	**4a** (10)	70	95
4	THF	**4a** (10)	63	98
5	CH_2Cl_2	**4b** (5)	66	95
6	CH_2Cl_2	**4c** (5)	89	96[b]

[a] Conditions: **1** (0.24 mmol), **2a-Me** (0.2 mmol), catalyst **4** (5 and 10 mol%); r.t., 15 min; isolated yield after column chromatography; ee determined by HPLC analysis on a Chiralpak AS-H column. Always a single diastereoisomer was obtained.
[b] Formation of the opposite enantiomer was observed.



Scheme 1 The proposed reaction pathway

NMR spectra and X-ray crystal structure analysis, the absolute configuration according to X-ray crystal structure analysis). Dehydration product **7** was not detected.

Under the used conditions (catalyst **4c**, 5 mol%; α,β-unsaturated methyl keto ester **2a-Me**, CH_2Cl_2, r.t., 15 min,), the scope of the cascade reaction of cyclopentane-1,2-dione (**1**) with substituted (*E*)-2-oxobut-3-enoates **2** was investigated. The obtained results are presented in Scheme 2. Always the formation of single diastereoisomers was observed.

The electronic properties of the aromatic ring of α,β-unsaturated keto esters **2** did not influence the reaction: both **2e** (with an electron-donating group) and **2f** (with an electron-withdrawing group) reacted smoothly and afforded similar stereoselectivities. In addition, heteroaromatic thiophene substituted **2g** afforded the hemiacetal **3g** in slightly lower yield, but with good stereoselectivity. The change of methyl ester **2a-Me** to the more bulkier ethyl **2a-Et** and isopropyl ester **2a-*i*Pr** slightly decreased the yield and enantioselectivity of the reaction. It is noteworthy that alicyclic β-unsaturated-α-keto ester **2h** also afforded the addition-cyclization product **3h** with good enantioselectivity, although in slightly lower yield. 3-Substituted cyclopentane-1,2-diones gave unsuccessful results in the reaction with (*E*)-2-oxobut-3-enoates.

A special case was the 2-Cl-substituted hemiacetal **3d** (Scheme 2). In the NMR spectra, a hindered rotation of the singly 2-chloro-substituted phenyl ring around the substituted pyran ring was observed and a dynamic equilibrium between the two conformers exists. This phenomenon is best illustrated by the temperature dependence of the NMR spectra of the compound **3d**. In Figure 1, the fragments from ^1H and ^{13}C spectra of **3d** at room temperature and at –20 °C are presented.

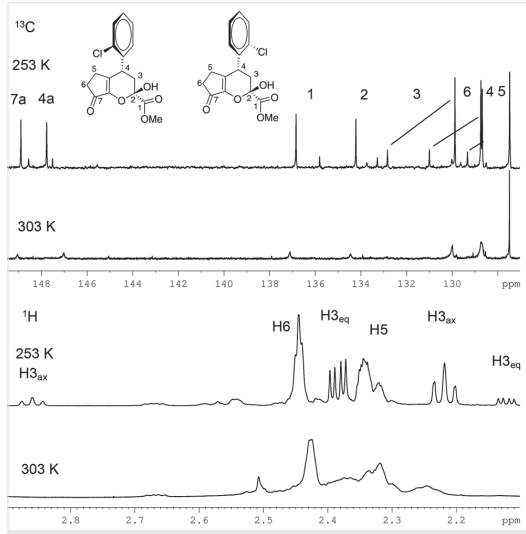
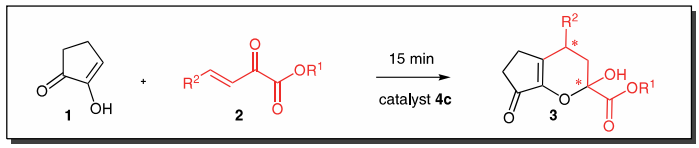


Figure 1 Fragments from ^{13}C and ^1H NMR spectra of compound **3d** at 303 and 253 K, showing the rotational isomers of the 2-Cl-substituted phenyl ring



3a-Me
89%, 96% ee

3a-Et[a]
66%, 94% ee

3a-*i*Pr[a]
70%, 87% ee

3b
73%, 89% ee

3c
93%, 95% ee

3d
48%, 94% ee

3e
69%, 91% ee

3f
86%, 94% ee

3g
59%, 88% ee

3h
42%, 90% ee

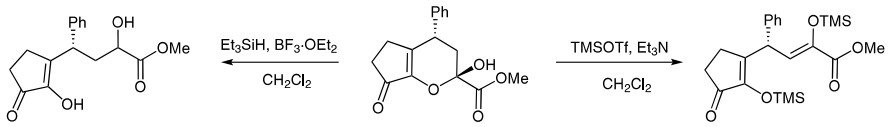
Scheme 2 Scope of the reaction. All yields are isolated yields after column chromatography; all ee values were determined by HPLC on a Chiralpak AS-H column. [a] Reaction time 1 h.

The spectra of **3d** single diastereomer and the temperature dependence of the isomeric ratio point to atropisomerism with a comparatively low energy interconversion barrier between unequally populated rotational isomers. Atropisomers are usually defined with a half-life of at least 1000 seconds at 300 K.[24,25] In the present case, the room temperature half-life of **3d** is in millisecond range, with an atropisomer ratio of 5 to 1, the main isomer being *P* (a*R*, axially Rectus, plus) with the chlorine atom pointing towards the OH group (Figure 1). The assignment of the *P* configuration of the main isomer is based on the large downfield shift of H-3$_{ax}$ from the inductive effect of chlorine in the minor isomer, the strongest NOE effect being from H-6 of the main isomer to H-3$_{ax}$ and on the AM1 calculations of the optimized geometry of the *P* and *M* (a*S*, axially Sinister, minus) conformers of **3d** with an Arguslab 4.0.1[26] program. In both the *P* and *M* conformers, the calculated dihedral angle between C2*C1*C4H4 for optimized geometry was close to zero degree, which is also close to that obtained from X-ray data for compound **3b** (Figure 2, 3.5°). The *P*-isomer was calculated to be more stable by 1.1 kcal/mol, which should be compared with the experimental value from the 5 to 1 ratio of the isomers, giving a 0.95 kcal/mol energy difference for the conformers.

Figure 2 X-ray crystal structure of compound **3b**

The absolute configuration of the product **3b** was determined by an X-ray single crystal structure analysis to be 2*R*,4*S*. The absolute configurations of the other obtained compounds were proposed by analogy with the crystal structure (Figure 2).

By reducing bicyclic product **3a-Me** with Et_3SiH in the presence of Lewis acid, the monocyclic product **8** was obtained (Scheme 3). The keto group in the keto ester moiety



8
47%, 97% ee, 4:1 dr

3a-Me
96% ee

9
71%, 93% ee

Scheme 3 Transformation of hemiacetal **3a-Me** to substituted cyclopentane-1,2-dione derivatives

was reduced to an alcohol group. Two diastereoisomers were obtained in a 4 to 1 ratio with the prevailing thermodynamically more stable *trans*-isomer.

Furthermore, bicyclic product **3a-Me** when treated with an excess of silylating agent TMSOTf and Et_3N gave a disilylated dienol **9** (Scheme 3). The compounds **8** and **9** are valuable starting materials for further derivatizations, for example, for asymmetric oxidation, resulting in lactone carboxylic acids.[27]

Full assignments of the ^1H and ^{13}C chemical shifts are based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 and 800 MHz instruments. The residual solvent peaks ($CHCl_3/CDCl_3$, δ = 7.26/77.2) or TMS (TMS, δ = 0.00) were used as the chemical shift references. The chiral HPLC was performed using a Chiralpak AS-H column. The mass spectra were recorded on Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. The optical rotations were measured using an Anton Paar GWB Polarimeter MCP 500. The IR spectra were recorded on a Bruker Tensor 27 Fourier transform IR spectrophotometer. The absolute structure of a single crystal was obtained with a Rigaku Saturn944+ diffractometer. The Merck precoated silica gel 60 F_{254} plates were used for TLC, whereas for column chromatography the Merck 60 (0.040–0.063 mm) mesh silica gel was used. The commercial reagents and solvents were generally used as received.

Cyclopentane-1,2-dione (**1**) was prepared according to literature procedure[28] from commercially available cyclopentanone. γ-Aryl-β,γ-unsaturated-α-keto esters **2a–g** were prepared according to literature procedure[29] from the corresponding commercially available carbaldehydes and pyruvic acid. γ-Alkyl-β,γ-unsaturated-α-keto ester **2h** was prepared also according to the literature procedure[30] from the corresponding carbaldehyde and methyl pyruvate.

Thiourea catalysts **4a**,[31] **4c**,[32] and squaramide catalyst **4b**[33] were prepared according to the literature procedures.

4-Substituted Methyl 2-Hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylates; Methyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3a-Me); Typical Procedure

2-Hydroxycyclopent-2-enone (**1**; 23.5 mg, 0.24 mmol), keto ester **2a** (38.0 mg, 0.2 mmol), and the organocatalyst **4c** (4.1 mg, 0.01 mmol) were dissolved in CH_2Cl_2 (0.7 mL). The mixture was stirred at r.t. until completion of the reaction (TLC monitoring, eluent: CH_2Cl_2–EtOAc, 25:1). The mixture was purified by column chromatography (CH_2Cl_2–EtOAc, 25:1) to afford **3a-Me** as a white solid; yield: 51 mg (89%); mp 124–126 °C; $[\alpha]_D^{25}$ +152.4 (*c* 0.05, MeOH); 96% ee [deteremined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (9:1), 1 mL/min, 254 nm; t_R (major) = 37.7 min, t_R (minor) = 62.7 min].

IR (KBr): 3244, 2981, 1753, 1696, 1646, 1455, 1288, 1140, 1113, 1016, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 5 H), 4.83 (s, 1 H), 3.98 (ddm, *J* = 11.9, 6.8 Hz, 1 H), 3.86 (s, 3 H), 2.42–2.24 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.7, 169.3, 148.4, 148.2, 139.5, 129.1, 128.2, 127.6, 95.6, 53.6, 38.4, 36.1, 32.8, 23.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{16}O_5]^+$: 289.1071; found: 289.1071.

Ethyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3a-Et)

Yield: 40 mg (66%); colorless oil; $[\alpha]_D^{25}$ +139.3 (*c* 0.04, MeOH); 94% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 9.8 min, t_R (minor) = 18.7 min].

IR (film): 3392, 2983, 1748, 1712, 1648, 1495, 1454, 1228, 1137, 1110, 1024, 844, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.21 (m, 5 H), 4.72 (d, *J* = 1.7 Hz, 1 H), 4.38–4.24 (m, 2 H), 3.97 (ddm, *J* = 11.9, 6.6 Hz, 1 H), 2.43–2.24 (m, 6 H), 1.33 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.4, 168.9, 148.5, 148.0, 139.6, 129.1, 128.3, 127.6, 95.5, 63.3, 38.5, 36.2, 32.8, 23.3, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{17}H_{18}O_5]$: 303.1227; found: 303.1231.

Isopropyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3a-*i*-Pr)

Yield: 44 mg (70%); white solid; mp 55–56 °C; $[\alpha]_D^{25}$ +130.5 (*c* 0.04, MeOH); 87% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 7.5 min, t_R (minor) = 11.8 min].

IR (KBr): 3229, 2983, 1741, 1699, 1643, 1495, 1405, 1246, 1179, 1099, 846, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 5 H), 5.12 (hept, *J* = 6.3 Hz, 1 H), 4.70 (d, *J* = 1.9 Hz, 1 H), 3.99–3.91 (m, 1 H), 2.43–2.23 (m, 6 H), 1.29 and 1.33 (2 d, *J* = 6.3 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.8, 166.6, 146.8, 146.2, 137.9, 127.3, 126.5, 125.7, 93.6, 69.8, 36.8, 34.4, 31.0, 21.4, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{18}H_{20}O_5]^+$: 317.1384; found: 317.1384.

Methyl (2*R*,4*S*)-4-(4-Chlorophenyl)-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3b)

Yield: 47 mg (73%); white solid; mp 141–142 °C; $[\alpha]_D^{25}$ +186.0 (*c* 0.04, MeOH); 89% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 20.1 min, t_R (minor) = 29.5 min].

IR (KBr): 3400, 2955, 1753, 1708, 1648, 1492, 1381, 1244, 1180, 1111, 1015, 845, 818 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2 H), 7.20–7.15 (m, 2 H), 4.77 (s, 1 H), 3.96 (ddm, *J* = 11.9, 6.9 Hz, 1 H), 3.87 (s, 3 H), 2.44–2.21 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.4, 169.1, 148.5, 147.1, 138.0, 133.4, 129.6, 129.3, 95.5, 53.7, 37.9, 36.0, 32.7, 23.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{16}H_{15}ClO_5]^+$: 323.0681; found: 323.0681.

Methyl (2*R*,4*S*)-4-(4-Bromophenyl)-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3c)

Yield: 68 mg (93%); white solid; mp 140–142 °C; $[\alpha]_D^{25}$ +119.5 (*c* 0.05, MeOH); 95% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 19.5 min, t_R (minor) = 30.8 min].

IR (KBr): 3400, 2954, 1753, 1708, 1648, 1489, 1283, 1244, 1179, 1112, 1073, 1010, 904, 818 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.49 (m, 2 H), 7.14–7.09 (m, 2 H), 4.68 (s, 1 H), 3.94 (ddm, *J* = 11.9, 6.9 Hz, 1 H), 3.87 (s, 3 H), 2.43–2.21 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.4, 169.1, 148.5, 146.9, 138.5, 132.3, 130.0, 121.5, 95.5, 53.7, 38.0, 36.0, 32.7, 23.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{16}H_{15}BrO_5]^+$: 367.0176; found: 367.0174.

Methyl (2*R*,4*R*)-4-(2-Chlorophenyl)-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3d)

Yield: 31 mg (48%); white solid; mp 65–66 °C; $[\alpha]_D^{25}$ +82.3 (*c* 0.04, MeOH); 94% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 16.8 min, t_R (minor) = 40.0 min].

IR (KBr): 3400, 2955, 1754, 1710, 1648, 1440, 1284, 1229, 1180, 1112, 1077, 1036, 904, 758 cm^{-1}.

2*R*,4*R*-Isomer (major, *P*-configuration)

^1H NMR (800 MHz, $CDCl_3$, 253 K): δ = 7.42 (dd, *J* = 8.0, 1.0 Hz, 1 H, H-3*), 7.29 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1 H, H-5*), 7.24 (td, *J* = 8.0, 1.5 Hz, 1 H, H-4*), 7.13 (dd, *J* = 7.5, 1.5 Hz, 1 H, H-6*), 5.11 (d, *J* = 1.3 Hz, 1 H, OH), 4.63 (dd, *J* = 12.2, 6.1 Hz, 1 H, H-4), 3.84 (s, 3 H, OCH_3), 2.44 (m, 2 H, H-6), 2.37 (dd, *J* = 13.6, 6.1 Hz, 1 H, H-3*eq*), 2.32 (m, 2 H, H-5), 2.21 (ddd, *J* = 13.6, 12.2, 1.3 Hz, 1 H, H-3*ax*); * refers to the numbering of the aromatic ring.

^{13}C NMR (201 MHz, $CDCl_3$, 253 K): δ = 201.3 (C-7), 169.2 (CO_2), 149.1 (C-7a), 147.9 (C-4a), 137.0 (C-1*), 134.4 (C-2*), 130.0 (C-3*), 128.9 (C-6*), 128.8 (C-4*), 127.6 (C-5*), 95.6 (C-2), 54.0 (OCH_3), 35.1 (C-3), 34.5 (C-4), 32.7 (C-6), 23.2 C-5); * refers to the numbering of the aromatic ring.

2*R*,4*R*-Isomer (minor, *M*-configuration)

^1H NMR (800 MHz, $CDCl_3$, 253 K): δ = 7.36 (br m, 1 H, H-6*), 7.34 (br m, 1 H, H-3*), 7.29 (br m, 2 H, H-4*, H-5*), 5.09 (d, *J* = 1.3 Hz, 1 H, OH), 4.35 (br m, 1 H, H-4), 3.85 (s, 3 H, OCH_3), 2.85 (br t, *J* = 2 × 12.5 Hz, 1 H, H-3*ax*), 2.44 (m, 2 H, H-6), 2.32 (m, 2 H, H-5), 2.11 (dd, *J* = 13.5, 5.8 Hz, 1 H, H-3*eq*); * refers to the numbering of the aromatic ring.

^{13}C NMR (201 MHz, $CDCl_3$, 253 K): δ = 201.2 (C-7), 169.4 (CO_2), 148.7 (C-7a), 147.7 (C-4a), 136.0 (C-1*), 133.4 (C-2*), 133.0 (C-3*), 131.2 (C-6*), 129.5 (C-4*), 127.6 (C-5*), 95.5 (C-2), 54.0 (OCH_3), 39.7 (C-4), 32.8 (C-6), 32.0 (C-3), 23.8 C-5); * refers to the numbering of the aromatic ring.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{16}H_{15}ClO_5]^+$: 323.0681; found: 323.0678.

Methyl (2*R*,4*R*)-2-Hydroxy-4-(4-methoxyphenyl)-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3e)

Yield: 44 mg (69%); white solid; mp 64–66 °C; $[\alpha]_D^{25}$ +162.2 (*c* 0.04, MeOH); 91% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 25.3 min, t_R (minor) = 53.9 min].

IR (KBr): 3398, 2955, 1753, 1708, 1646, 1513, 1442, 1253, 1179, 1110, 1077, 1030, 838, 819 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.12 (m, 2 H), 6.93–6.88 (m, 2 H), 4.64 (d, *J* = 1.7 Hz, 1 H), 3.92 (dd, *J* = 11.7, 6.6 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 2.41–2.24 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.6, 169.3, 159.0, 148.6, 148.2, 131.4, 129.2, 114.4, 95.6, 55.3, 53.7, 37.6, 36.2, 32.8, 23.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{17}H_{18}O_6]^+$: 319.1176; found: 319.1176.

Methyl (2*R*,4*S*)-2-Hydroxy-4-(4-nitrophenyl)-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3f)

Yield: 57 mg (86%); white solid; mp 145–146 °C; $[\alpha]_D^{25}$ +137.2 (*c* 0.04, MeOH); 94% ee [determined by HPLC on Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 52.3 min, t_R (minor) = 84.2 min].

IR (KBr): 3307, 2958, 1758, 1707, 1644, 1521, 1439, 1346, 1142, 1116, 980, 865, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.23 (m, 2 H), 7.46–7.41 (m, 2 H), 4.74 (s, 1 H), 4.12 (t, *J* = 9.2 Hz, 1 H), 3.88 (s, 3 H), 2.46–2.20 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.1, 168.8, 148.8, 147.5, 147.1, 145.1, 129.2, 124.4, 95.3, 53.8, 38.4, 35.8, 32.7, 23.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{16}H_{15}NO_7]^+$: 334.0921; found: 334.0919.

Methyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-(thiophen-2-yl)-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3g)

Yield: 35 mg (59%); white solid; mp 132–133 °C; $[\alpha]_D^{25}$ +122.8 (*c* 0.04, MeOH); 88% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 26.4 min, t_R (minor) = 45.1 min].

IR (KBr): 3243, 2951, 1751, 1696, 1647, 1436, 1296, 1108, 1013, 706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 1 H), 7.03–6.96 (m, 2 H), 4.75 (d, *J* = 1.3 Hz, 1 H), 4.34 (dd, *J* = 10.5, 7.9 Hz, 1 H), 3.88 (s, 3 H), 2.46–2.31 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.5, 169.1, 147.5, 147.2, 141.9, 127.1, 125.9, 124.7, 95.6, 53.8, 36.3, 33.6, 32.7, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{14}H_{14}O_5S]^+$: 295.0635; found: 295.0634.

Methyl (2*R*,4*S*)-4-Cyclohexyl-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3h)

Yield: 25 mg (42%); white solid; mp 114 °C; $[\alpha]_D^{25}$ +49.5 (*c* 0.05, MeOH); 90% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 15.2 min, t_R (minor) = 21.3 min].

IR (KBr): 3231, 2925, 2851, 1738, 1689, 1643, 1439, 1290, 1113, 1003, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.54 (s, 1 H), 3.86 (s, 3 H), 2.80–2.72 (m, 1 H), 2.58–2.41 (m, 4 H), 2.04 (dt, *J* = 13.7, 6.3 Hz, 1 H), 1.95 (dd, *J* = 13.4, 6.2 Hz, 1 H), 1.87–1.62 (m, 5 H), 1.38–1.04 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.5, 169.7, 149.7, 148.6, 95.8, 53.6, 38.6, 36.5, 32.8, 31.0, 28.2, 28.0, 26.8, 26.6, 26.4, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{22}O_5]^+$: 295.1540; found: 295.1539.

Methyl 2-Hydroxy-4-(2-hydroxy-3-oxocyclopent-1-en-1-yl)-4-phenylbutanoate (8)

According to a modified literature procedure,[34] hexahydrocyclopenta[*b*]pyran-2-carboxylate **3a-Me** (80 mg, 0.28 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). Et_3SiH (49 mg, 0.42 mmol) and $BF_3{\cdot}OEt_2$ (45 mg, 0.32 mmol) were added under dry argon flow at –76 °C. The mixture was warmed to 0 °C over 4 h and stirred overnight at 0 °C. The reaction was quenched with H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by column chromatography (CH_2Cl_2–EtOAc, 5:1) to afford the product as a transparent oil; yield: 38 mg (47%); colorless oil; $[\alpha]_D^{25}$ –6.8 (*c* 0.04, MeOH); 97% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 22.7 min, t_R (minor) = 30.8 min].

IR (film): 3356, 2954, 1695, 1651, 1601, 1495, 1441, 1391, 1225, 1102, 913, 732, 703 cm^{-1}.

Ratio of 2*S*/2*R* = 4:1. In the most stable conformation, the chain from C-1 to phenyl ring is *trans* oriented. In this conformation, H-2 and H-4 from *S*,*S*-isomer are low-field shifted from the OH group of the five-membered ring and from the 2-OH, correspondingly. The 2*S*,4*S*-isomer is, according to AM1 calculations, more stable by 0.56 kcal/mol.

2*S*,4*S*-Isomer (major)

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 4 H, C_6H_5 H-*o*,*m*), 7.21–7.19 (m, 1 H, C_6H_5 H-*p*), 6.14 (br s, 1 H, enol OH), 4.19 (dd, *J* = 10.4, 5.5 Hz, 1 H, H-4), 4.15 (dd, *J* = 9.3, 3.7 Hz, 1 H, H-2), 3.65 (s, 3 H, OCH_3), 3.06 (br s, 1 H, 2-OH), 2.68 (ddd, *J* = 13.9, 10.4, 3.7 Hz, 1 H, H-3), 2.39 (m, 1 H, H-5*), 2.32 (m, 2 H, H-4*), 2.27 (m, 1 H, H-5*), 2.15 (ddd, *J* = 13.9, 9.3, 5.5 Hz, 1 H, H-3); * refers to the numbering of cyclopentenyl ring.

^{13}C NMR (201 MHz, $CDCl_3$): δ = 203.7 (C-3*), 175.4 (CO_2), 148.8 (C-2*), 146.9 (C-1*), 141.4 (C-*i*), 128.9 (C-*m*), 128.2 (C-*o*), 127.3 (C-*p*), 68.9 (C-2), 52.8 (OCH_3), 41.6 (C-4), 37.0 (C-3), 31.9 (C-4*), 23.8 C-5*); * refers to the numbering of cyclopentenyl ring.

2*R*,4*S*-Isomer (minor)

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 4 H, C_6H_5 H-*o*,*m*), 7.21–7.19 (m, 1 H, C_6H_5 H-*p*), 6.07 (br s, 1 H, enol OH), 4.19 (dd, *J* = 9.9, 5.8 Hz, 1 H, H-4), 4.15 (dd, *J* = 9.6, 3.5 Hz, 1 H, H-2), 3.70 (s, 3 H, OCH_3), 2.91 (br s, 1 H, 2-OH), 2.57 (ddd, *J* = 14.0, 9.9, 3.5 Hz, 1 H, H-3), 2.39 (m, 1 H, H-5*), 2.32 (m, 2 H, H-4*), 2.27 (m, 1 H, H-5*), 2.26 (ddd, *J* = 14.0, 9.6, 5.9 Hz, 1 H, H-3); * refers to the numbering of cyclopentenyl ring.

^{13}C NMR (201 MHz, $CDCl_3$): δ = 203.9 (C-3*), 175.7 (CO_2), 148.3 (C-2*), 147.7 (C-1*), 140.5 (C-*i*), 129.0 (C-*m*), 128.4 (C-*o*), 127.4 (C-*p*), 68.5 (C-2), 52.8 (OCH_3), 42.2 (C-4), 37.0 (C-3), 31.8 (C-4*), 24.1 C-5*); * refers to the numbering of cyclopentenyl ring.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{18}O_5]^+$: 291.1188; found: 291.1228.

Methyl (*Z*)-4-{3-Oxo-2-[(trimethylsilyl)oxy]cyclopent-1-en-1-yl}-4-phenyl-2-[(trimethylsilyl)oxy]but-2-enoate (9)

According to a modified literature procedure,[35] hexahydrocyclopenta[*b*]pyran-2-carboxylate **3a-Me** (50 mg, 0.17 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). Et_3N (45 mg, 0.53 mmol) and TMSOTf (118 mg, 0.53 mmol) were added, respectively, to the mixture at 0 °C. The reaction mixture was stirred at r.t. until the end of reaction (TLC monitoring, eluent: CH_2Cl_2–EtOAc, 10:1). The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined and dried (Na_2SO_4). CH_2Cl_2 was evaporated and the crude product was purified by column chromatography (CH_2Cl_2–EtOAc 40:1) to give **9** as a transparent oil; yield: 53 mg (71%); colorless oil; $[\alpha]_D^{25}$ –12.3 (*c* 0.04, MeOH); 93% ee [determined by HPLC: Chiralpak OD-H; hexane–*i*-PrOH (99:1), 1 mL/min, 254 nm; t_R (major) = 5.3 min, t_R (minor) = 5.7 min].

IR (film): 2956, 1728, 1712, 1643, 1494, 1439, 1498, 1252, 1139, 1112, 872, 849, 758, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 5 H), 6.50 (d, *J* = 9.9 Hz, 1 H), 5.12 (d, *J* = 9.9 Hz, 1 H), 3.78 (s, 3 H), 2.53–2.44 (m, 1 H), 2.39–2.29 (m, 3 H), 0.25–0.23 (m, 9 H), 0.18–0.15 (m, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.4, 165.2, 153.0, 149.2, 141.3, 140.9, 128.9, 127.7, 127.0, 120.2, 52.2, 41.2, 32.2, 23.0, 1.2, 0.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{22}H_{32}O_5Si_2]^+$: 433.1822; found: 433.1855.

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Supporting Information

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PUBLICATION III

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Direct Access to Multifunctionalized Norcamphor Scaffolds by Asymmetric Organocatalytic Diels–Alder Reactions

*Rasmus Mose, Magnus E. Jensen, Gert Preegel, and Karl Anker Jørgensen**

Abstract: *A general organocatalytic cross-dienamine activation strategy to produce chiral multifunctionalized norcamphor compounds having a large diversity in substitution pattern is presented. The strategy is based on a Diels–Alder reaction of an amino-activated cyclopentenone reacting with most common classes of electron-deficient olefins, such as nitro-, ester-, amide-, and cyano-substituted olefins, chalcones, conjugated malononitriles, CF_3-substituted enones, and fumarates. The corresponding norcamphor derivatives are formed in good yield, excellent enantioselectivities, and with complete diastereoselectivity. Furthermore, it is demonstrated that quaternary stereocenters and spiro norcamphor compounds can be formed with high stereoselectivity. The present development provides a simple, direct, and efficient approach for the preparation of important norcamphor scaffolds.*

The Diels–Alder reaction is one of the most important synthetic transformations known and it provides easy access to six-membered carbo- and heterocycles in a chemo-, regio-, and stereoselective manner.[1] Considerable effort has been devoted to the development of catalytic asymmetric versions of this reaction, with most examples focusing on a LUMO-lowering strategy through activation of electron-deficient dienophiles with chiral Lewis acids.[2] The HOMO-activation strategy is mainly dominated by organocatalytic approaches focused on enamine-,[3] dienamine-,[4] and trienamine[5] activation of alkyl- and vinyl aldehydes and ketones with chiral aminocatalysts.

The bicyclo[2.2.1]heptane scaffold is an important molecular entity and a Reaxys substructure search on this scaffold returned more than 100000 hits, of which more than 15000 compounds have shown bioactivity.[6] A vast number of bioactive compounds have been applied within all areas of the life sciences and a few examples are shown in Figure 1. Sordarins, a new class of selective antifungal agents, and camphor are natural products containing the bicyclo-[2.2.1]heptane scaffold.[7] Numerous synthetic drugs and drug candidates have been created based on the bicyclo-[2.2.1]heptane scaffold. Both Setrobuvir and LMV-601 are antiviral agents displaying activity against hepatitis C and HPV respectively.[8] The library of uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists are potential new drugs as this receptor has been targeted for the treatment of

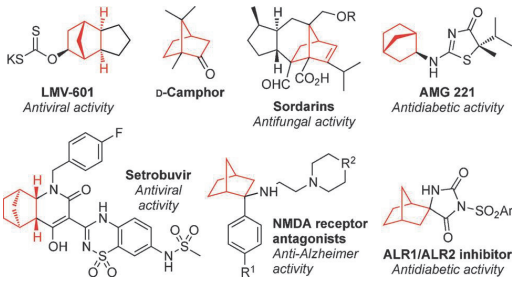

Figure 1. A few selected bioactive compounds containing the bicyclo-[2.2.1]heptane scaffold.

Alzheimer's disease, but is also implicated in a range of other neurological and neuropsychiatric diseases.[9] AMG 221, an inhibitor of 11β-HSD1, has entered clinical trials for the treatment of type II diabetes, while the ALR1/ALR2 inhibitors also show promising in vivo antidiabetic activity.[10]

We envisioned that organocatalysis could be used to develop a simple, direct, and efficient approach for the preparation of this very important molecular scaffold, providing a method that was diversity oriented, both in terms of substrates and substituents. Diels–Alder reactions of linear dienamines yield allylic amines, which cannot undergo hydrolysis. Thus, to achieve catalytic turnover, the amino-catalyst needs to be excluded in another manner (for example by E1cB elimination).[4a] A more direct strategy for the Diels–Alder reaction can be achieved by applying cross-dienamines which directly results in hydrolyzable enamines and thus catalytic turnover.[11]

Surprisingly, organocatalytic cross-dienamine-activated Diels–Alder reactions of cyclopentenones have been almost completely ignored, whereas numerous examples have been reported on the reactions of open-chain vinyl ketones,[12] cyclohexenones,[12d,13] and cycloheptenones.[13b–g] In fact, only three papers have been published, each containing a single entry, on the Diels–Alder reaction of cyclopentenone with for example, electron-deficient polyenes (with modest results),[13f–h] whereas several papers report unsuccessful attempts.[13a–c] This stands in stark contrast to the importance of the bicyclo[2.2.1]heptane scaffold.

Herein, we will present the asymmetric aminocatalytic reaction of cyclopentenone with a variety of different dienophiles and investigate its versatility towards the diversification of privileged structures (Scheme 1).

Initially, we focused our attention on the development of the Diels–Alder reaction between cyclopentenone **2** and nitrostyrene **3a**. The reaction was found to proceed in the

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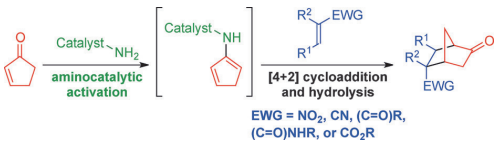
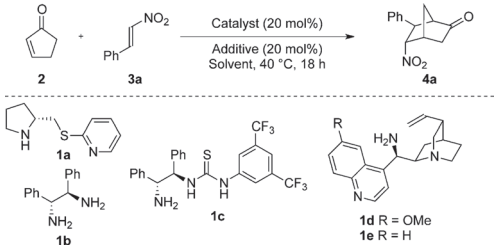


Scheme 1. Aminocatalytic Diels–Alder reactions providing multifunctionalized norcamphor scaffolds.

presence of catalyst **1a**, but the desired product **4a** was only formed in 9% yield as a nearly racemic mixture (5% *ee*; Table 1, entry 1). It was observed that the conversion was much higher than the corresponding yield, which was ascribed to a polymerization of **3a**. Improved yield (26%) and enantioselectivity (28% *ee*) were obtained when primary aminocatalyst **1b** was employed (Table 1, entry 2). In an attempt to improve yield and enantiocontrol, the bifunctionalized catalyst **1c**, derived from **1b**, was employed. However, only the racemate of **4a** was obtained in a very low yield (entry 3). The quinine-based catalyst **1d**[14] was found to be superior to all other catalysts applied, producing **4a** in good

Table 1: Screening of the reaction conditions for the Diels–Alder reaction of cyclopentenone **2** and nitrostyrene **3a**.



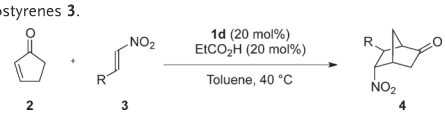
Entry[a]	Cat.	Solvent	Additive	Conv./Yield [%][c]	d.r.[c]	*ee*[%][d]
1	**1a**	$CDCl_3$	$EtCO_2H$	50/9	>20:1	−5[f]
2	**1b**	$CDCl_3$	$EtCO_2H$	67/26	>20:1	−28[f]
3	**1c**	$CDCl_3$	$EtCO_2H$	42/5	>20:1	1
4	**1d**	$CDCl_3$	$EtCO_2H$	79/49	>20:1	83
5	**1d**	Toluene	$EtCO_2H$	91/52	>20:1	90
6	**1d**	THF	$EtCO_2H$	35/17	>20:1	91
7	**1d**	Heptane	$EtCO_2H$	100/18	>20:1	82
8	**1d**	Toluene	$PhCO_2Na$	68/20	>20:1	91
9	**1d**	Toluene	$PhCO_2H$	100/51	>20:1	90
10	**1d**	Toluene	SA	90/44	>20:1	91
11	**1d**	Toluene	*p*-NBA	90/34	>20:1	87
12	**1d**	Toluene	TFA	62/14	>20:1	90
13	**1e**	Toluene	$EtCO_2H$	73/39	>20:1	84
14[b]	**1d**	Toluene	$EtCO_2H$	89/65[e]	>20:1	90

[a] Reactions were performed with **2** (0.2 mmol), **3a** (0.1 mmol), **1** (0.02 mmol), and additive (0.02 mmol) in solvent (0.1 mL). [b] **2** (0.15 mmol) and 30 h reaction time. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture with 1,3,5-tris(trifluoromethyl)benzene as the internal standard. [d] Determined by ultra-performance convergence chromatography (UPC^2) on a chiral stationary phase. [e] **4a** was isolated in 62% yield after flash column chromatography on silica gel. [f] Negative *ee* values indicate that the opposite enantiomer of **4a** was formed preferentially. *p*-NBA = *p*-nitrobenzoic acid, SA = salicylic acid, TFA = trifluoroacetic acid.

yield (49%) and high enantioselectivity (83% *ee*; entry 4). A solvent screening revealed that enantiocontrol could be enhanced in toluene (90% *ee*) while maintaining the same yield as in $CDCl_3$ (entries 4–7). Several additives were evaluated and found only to have minor influences on the enantioselectivity of the reaction (87–91% *ee*; Table 1, entries 8–12). The reaction performed best in weakly acidic mediums, whereas bases or stronger acids reduced the yield of **4a** (entries 8, 11, 12). Finally, the yield could be improved by increasing the reaction time to 30 h (entry 14).

To evaluate the generality of the reaction, a series of nitrostyrenes **3** were subjected to the reaction with cyclopentenone **2** (Table 2). Both electron-donating and electron-

Table 2: Scope of the Diels–Alder reaction of cyclopentenone **2** with nitrostyrenes **3**.



Entry[a]	R	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	**4a**	62	>20:1	90
2	*p*-Me(C_6H_4)	**4b**	50	>20:1	90
3	*p*-F(C_6H_4)	**4c**	56	>20:1	89
4	*p*-Br(C_6H_4)	**4d**	56	>20:1	92
5	*o*-Cl(C_6H_4)	**4e**	81	>20:1	95
6	*o*-MeO(C_6H_4)	**4f**	79	>20:1	95
7	*m*-MeO(C_6H_4)	**4g**	48	>20:1	90
8	*p*-MeO(C_6H_4)	**4h**	48	>20:1	86
9	2-naphthyl	**4i**	49	>20:1	89
10	2-furyl	**4j**	59	>20:1	84
11	PhCH=CH	**4k**	41	9:1	87

[a] Reactions were performed with **2** (0.15 mmol), **3** (0.1 mmol), **1d** (0.02 mmol), and propionic acid (0.02 mmol) in toluene (0.1 mL). [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] Determined by UPC^2 on a chiral stationary phase.

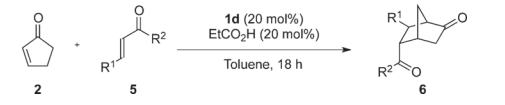
withdrawing substituents on the aromatic system were well-tolerated (entries 2–8), whereas aliphatic nitroolefins or very electron-poor nitro-substituted nitrostyrenes primarily lead to polymerization of the nitroolefin.[15] Nitrostyrenes **3f–h**, with a methoxy group placed in each position on the aromatic ring, were evaluated (entries 6–8). Both yields and enantioselectivities followed the order *ortho* > *meta* > *para* and **4f–h** could be obtained in 48–79% yield and 86–95% *ee*. This trend was also apparent for the halide-substituted nitrostyrenes **3c–e** (entries 3–5). Polyaromatic, as well as heteroaromatic moieties, could be implemented in the products **4i** and **4j** in good yields and with high enantioselectivities (entries 9, 10). In a final reaction, the less reactive nitrodiene **3k** was reacted with **2** and product **4k** was obtained with 87% *ee*, but in a lower yield relative to the other entries (entry 11).

During the study of the scope of nitrostyrenes **3**, we realized that chalcones **5** also readily underwent a Diels–Alder reaction with cyclopentenone **2** under identical reaction conditions. This type of cross-enone reaction has previously been deemed difficult as a result of self-condensation of the starting materials.[12a,16] Generally, chalcones **5**

were found to be slightly less reactive than **3**, but also more stable towards polymerization. As a result, most reactions were performed at higher temperatures. Thus, it turned out that the present catalytic method could be expanded to also include chalcones providing access to new classes of differently substituted norcamphor compounds.

In the first experiment, chalcone **5a** was reacted with cyclopentenone **2**. The desired cycloadduct **6a** was obtained in 79% yield and 93% *ee* (Table 3, entry 1). Both weakly and strongly electron-withdrawing groups were well-tolerated on

Table 3: Scope of the Diels–Alder reaction of cyclopentenone **2** with chalcones **5**.



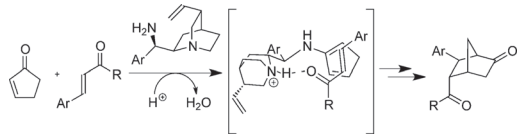
2 **5** **6**

Entry[a]	R^1/R^2	Product	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph/Ph	**6a**	60	79	>20:1	93
2	*p*-Br(C_6H_4)/Ph	**6b**	60	66	>20:1	96
3	*m*-NO_2(C_6H_4)/Ph	**6c**	40	63	>20:1	96
4	*p*-NO_2(C_6H_4)/Ph	**6d**	40	52	>20:1	99
5	*o*-MeO(C_6H_4)/Ph	**6e**	60	75	>20:1	99
6	*m*-MeO(C_6H_4)/Ph	**6f**	80	52	>20:1	96
7	*p*-MeO(C_6H_4)/Ph	**6g**	100	38	>20:1	87
8	2-furyl/Ph	**6h**	80	62	>20:1	87
9	2-thiophenyl/Ph	**6i**	80	58	>20:1	91
10	2-naphthyl/Ph	**6j**	80	47	>20:1	91
11	Ph/*p*-NO_2(C_6H_4)	**6k**	60	85	>20:1	96
12	*p*-Br(C_6H_4)/*p*-NO_2-(C_6H_4)	**6l**	40	91	>20:1	99
13[e]	Me/Ph	**6m**	40	32	>20:1	91
14[f]	Ph/Me	**6n**	60	19	>20:1	92

[a] Reactions were performed with **2** (0.2 mmol), **5** (0.1 mmol), **1d** (0.02 mmol), and propionic acid (0.02 mmol) in toluene (0.1 mL). [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] Determined by UPC^2 on a chiral stationary phase. [e] Reaction time 50 h. [f] Reaction time 72 h.

the aromatic rings (entries 2–4, 11, 12). The nitro-substituted chalcones **5c**,**d** having the nitro group in the *meta* and *para* positions readily underwent reactions with **2** to form products **6c** and **6d** in good yields and with almost perfect enantioselectivities (entries 3, 4).[17] Electron-donating groups in *ortho*, *meta*, and *para* positions were also evaluated and, as for the nitrostyrenes **3f–h**, both yields and enantioselectivities followed the order *ortho* > *meta* > *para* for **5e–g** (entries 5–7). It should be noted that a temperature of 100 °C was necessary for the reaction with **5g**. Although the product could only be obtained in a low yield (38%), it still performed well in terms of enantioselectivity (87% *ee*) considering the high reaction temperature. Polyaromatic and heteroaromatic moieties could also be incorporated in the products **6h–j** in 47–62% yields and 87–91% *ee* (entries 8–10). Additionally, it was demonstrated that substituents on the other aromatic ring (R^2) could also be present when using chalcone compounds **5k** and **5l**, giving the desired products **6k** and **6l** in 85–91% yields and 96–99% *ee* (entry 11, 12). With aliphatic groups in either the R^1 or R^2 position, vinyl ketones **5m** and **5n** underwent the reaction with excellent stereoselectivities (>20:1 d.r., 91–92% *ee*), albeit in low yield (19–32%).It should be noted that the reaction of enone **5n** may pose a potential challenge, as two cross-dienamines are possible. However, only one product **6n** was formed in the reaction.

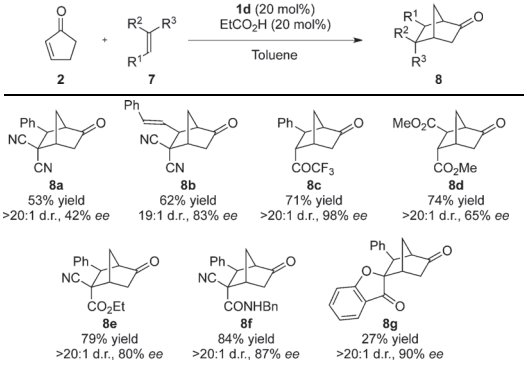
A recent paper by Houk and Lam described the mechanistic aspects of an organocatalytic intramolecular aldol reaction catalyzed by cinchona alkaloid primary amines.[18] Based on the reaction mechanism proposed by the authors, we suggest a related transition state for this intermolecular aminocatalyzed Diels–Alder reaction (Scheme 2). Initially,



Scheme 2. Proposed reaction pathway for the aminocatalyzed cycloaddition reaction.

the cinchona alkaloid aminocatalyst condenses with cyclopentenone to form a cross-dienamine intermediate. By protonation of the quinuclidine part of the catalyst, the dienophile is activated and directed into the appropriate position by hydrogen bonding. After the cycloaddition step, the formed enamine is hydrolyzed to the corresponding ketone while liberating the aminocatalyst. Based on the diastereoselectivity obtained, we propose that the reaction might proceed via an asynchronous concerted cycloaddition, as more than 20:1 d.r. is obtained for all products except two (Table 2, entry 11 and Table 4, compound **8b** (see below)). However, we cannot exclude that a stepwise mechanism

Table 4: Scope of the Diels–Alder reaction of cyclopentenone **2** with dienophiles **7**.[a]



[a] Reactions were performed with **2** (0.2 mmol), **3** (0.1 mmol), **1d** (0.02 mmol), and propionic acid (0.02 mmol) in toluene (0.1 mL). In each case, the yield given is that of the isolated product. The d.r. values were determined by ^{1}H NMR spectroscopy on the crude reaction mixture, and ee values were determined by UPC^2 on a chiral stationary phase.

might also be operating for some dienophiles, such as those in which the reacting olefin is in conjugation with another olefin.

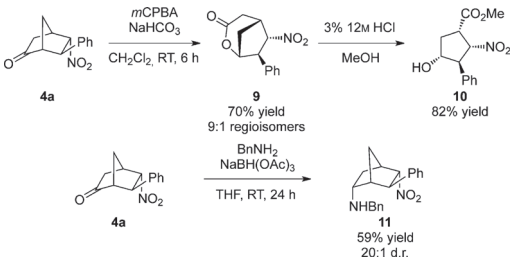
Normally, bifunctionalized catalysts are sensitive towards small variations of the hydrogen-bond acceptor groups of the electrophiles and extensive screenings need to be performed for each electrophile applied. Since the present reaction performed well for both nitrostyrenes and chalcones under identical reaction conditions, we were curious to see how well the reaction would perform towards different types of dienophiles. It turned out that the organocatalytically activated cyclopentenone shows unique general reactivity, as it reacts with most common classes of electron-deficient olefins. Furthermore, it allows for the formation of quaternary stereocenters and spirocyclic compounds. Table 4 shows an example of each of these reactions, without outlining all of the different substituent patterns as shown for the nitroolefins (Table 2) and chalcones (Table 3), and shows that varying the substituents does not change the diastereoselectivity of the reaction significantly. The following reactions were performed without further optimization of the reaction conditions used for the nitroolefins and chalcones.

Although the reaction with malononitrile **7a** only produced the cycloadduct **8a** in moderate enantioselectivity (42% *ee*), the reaction with the polyconjugated malononitrile **7b** afforded **8b** in good yield and high enantioselectivity (62% yield, 83% *ee*). Pleasingly, the CF_3-substituted enone **7c** readily underwent the cycloaddition to produce **8c** in 71% yield and almost perfect enantioselectivity (98% *ee*). The cycloadduct **8d** (from reaction of *trans*-dimethyl fumarate) could easily be generated in high yield but with modest enantiomeric excess. It was also demonstrated that quaternary stereocenters could be incorporated into the bicyclo-[2.2.1]heptane scaffold by reaction of cyclopentenone **2** with cyanoacrylate **7e** or cyanoacrylamide **7f** to produce the desired cycloadducts **8e** and **8f** in high yield and enantioselectivities (79–84% yield, 80–87% *ee*). Finally, the spiro norcamphor **8g** could also be obtained with high enantiomeric excess, albeit in low yield under these nonoptimized reaction conditions. The examples in Table 4 highlight the generality of the catalytic system, since different types of dienophiles **7** can be applied under identical conditions as for nitrostyrenes **3** and chalcones **5**.

A few selected transformations were performed on **4a** to demonstrate the synthetic potential of the substituted norcamphor products. First, a Baeyer–Villiger oxidation led to the lactone **9** which could be ring-opened under acidic conditions to provide the highly substituted cyclopentane **10** containing four contiguous stereocenters (Scheme 3, top). Many bioactive products contain an amine moiety attached to the bicyclo[2.2.1]heptane scaffold (Figure 1). Therefore, we demonstrated a diastereoselective reductive amination of **4a** to form compound **11**, containing an additional stereocenter, in good yield (59%; Scheme 3, bottom).

The absolute configurations of compounds **6l** and **11** were unambiguously determined by single-crystal X-ray diffraction and the configurations of all remaining products were assigned by analogy.[19]

In conclusion, we have demonstrated a straightforward procedure for the generation of a variety of 5,6-substituted



Scheme 3. Synthetic transformations of cycloadduct **4a**. mCPBA = *meta*-chloroperbenzoic acid.

norcamphor derivatives by means of an asymmetric organocatalytic reaction. Remarkably, the reaction conditions turned out to be very general allowing most common electron-deficient olefins to be applied in the cycloaddition without further optimizations. The norcamphor scaffolds are obtained in generally good to high yields and high to excellent stereoselectivities, providing a simple and efficient process for the preparation of an important class of privileged structures. Additionally, a few selected transformations were demonstrated to show that an additional stereocenter could be introduced by a diastereoselective reductive amination and that the norcamphor products could undergo an oxidative ring-opening reaction to generate highly substituted cyclopentanes.

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Keywords: asymmetric catalysis · cross-dienamines · Diels–Alder reactions · norcamphor · organocatalysis

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ABSTRACT

In the present work, an investigation of asymmetric organocatalytic reactions of cyclopent-2-en-1-one (Diels-Alder reaction) and cyclopentane-1,2-dione (Michael reaction) with electron-deficient olefins has been carried out.

It was found that the activation of cyclopentane-1,2-dione and nitro-olefins by bifunctional thiourea organocatalysts can result in a Michael reaction product of 3-substituted diketones in a high yield (up to 90%) and good enantioselectivity (up to 76% *ee*). In further derivatization, bioactive compounds can be obtained.

By changing nitro-olefins to unsaturated ketoesters, in the presence of organocatalysts a reaction still occurs with additional cyclization, resulting in heterobicyclic hemiacetals in excellent yield (up to 93%) and stereoselectivity (dr > 20:1; up to 96% *ee*). With further derivatization, bioactive compounds are obtained.

It has also been shown that multifunctionalized bioactive norcamphor scaffolds are synthesized through an asymmetric organocatalytic Diels-Alder reaction between cyclopent-2-en-1-one and the most common classes of electron-deficient olefins. For this, a Cinchona alkaloid primary amine derivate was used as a catalyst.

KOKKUVÕTE

Käesolevas töös uuriti tsüklopent-2-een-1-ooni ja tsüklopentaan-1,2-diooni asümmeetrilisi organokatalüütilisi reaktsioone (esimesel juhul Diels-Alderi reaktsiooni ja teisel juhul Michael reaktsiooni) elektronvaeste olefiinidega.

Uurimuse tulemusel leidsime, et aktiveerides tsüklopentaan-1,2-diooni ning nitroalkeene bifunktsionaalsete tiouurea-organokatalüsaatoriga saame Michaeli reaktsiooni produktideks kõrge saagise (kuni 90%) ning hea enantioselektiivsusega (kuni 76% *ee*) 3-asendatud 2-hüdroksütsüklopent-2-en-1-ooni derivaate, mida on võimalik edasi muundada bioaktiivseteks molekulideks.

Vahetades nitroalkeenid küllastamata ketoestrite vastu, saame tulemuseks kaskaadreaktsiooni Michaeli reaktsioon – tsükliseerumine, mille tulemusena saame suurepärase saagise (kuni 93%) ja stereoselektiivsusega (dr > 20:1; kuni 96% *ee*) heterobitsüklilised poolatsetaalid, milledest on samuti võimalik edasiste muundamiste käigus luua bioaktiivseid ühendeid.

Töötati välja norkampri asendatud derivaatide sünteesi tee tsüklopent-2-een-1-ooni ja elektronvaesete alkeenide Diels-Alderi reaktsiooni kaudu. Töös sünteesiti rida bitsüklilisi struktuure, mis võivad olla lähteühenditeks bioaktiivse ühendite saamiseks. Organokatalüsaatorina kasutati Cinchona alkaloidi primaarse amiini derivaate.

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7. Teadustöö

Uute asümmetriliste meetodite välja töötamine kasutades organokatalüsaatoreid, kõrgemat järku asümmeetrilised tsükkel-liitumised, reaktsiooni mehhanismide uurimine, 1,2-diketoonide süntees ning reaktsioonide uurimine

8. Tunnustused

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02.2015 – 10.2015	Aarhus University, Denmark; visiting PhD (DoRa T6) (supervisor Karl Anker Jørgensen)
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5. R&D-related managerial and administrative work

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6. Supervised thesis

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Development of new asymmetric synthetic methods using organocatalysis, higher order asymmetric cycloadditions, the study of mechanisms, synthesis and derivatization of 1,2-diketones.

8. Awards

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ORIGINAL PUBLICATIONS

1) Preegel, G.; Noole, A.; Ilmarinen, K.; Järving, I.; Kanger, T.; Pehk, T.; Lopp, M. "Enantioselective Organocatalytic Michael Addition of Cyclopentane-1,2-diones to Nitroolefins" *Synthesis*, 2014, **46**, 2595–2600.

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