DOCTORAL THESIS

Asymmetric Organocatalytic Reactions of Cyclopentane-1,2-dione

Estelle Silm

TALLINNA TEHNIKAÜLIKOOL
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TAL TECH PRESS

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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 other doctoral or equivalent academic degree.

Estelle Silm

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signature

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Tsüklopentaan-1,2-diooni asümmeetrilised organokatalüütilised reaktsioonid

ESTELLE SILM

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Contents

List of publications

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

I Preegel, G.; Silm, E.; Kaabel, S.; Järving, I.; Rissanen, K.; Lopp, M. Asymmetric Organocatalytic Michael Addition-Cyclization Cascade of Cyclopentane-1,2-dione with Substituted α,β-Unsaturated Aldehydes. *Synthesis* **2017**, *49*, 3118-3125.

II Silm, E.; Kaabel, S.; Järving, I.; Kanger, T. Asymmetric Organocatalytic Michael Addition-Cyclisation Cascade of Cyclopentane-1,2-dione with Alkylidene Malononitriles. *Synthesis* **2019**, *51*, 4198-4204.

III Silm, E.; Järving, I.; Kanger, T. Asymmetric Organocatalytic Michael Addition of Cyclopentane-1,2-dione to Alkylidene Oxindole. *Beilstein J. Org. Chem.* **2022**, *18*, 167-173.

Author's contribution to the publications

Contribution to the papers in this thesis are:

I The author played a significant role in the synthetic preparation and characterisation of the compounds. The author played a minor role in the preparation of the manuscript. The author played a significant role in the preparation of the supporting information.

II The author played a major role in the synthetic preparation and characterisation of the compounds used in the study, and the development of the synthetic procedure. The author wrote the manuscript and compiled the supporting information.

III The author played a major role in the development of the synthetic procedure, and prepared and characterised the compounds used in the study. The author wrote the manuscript and compiled the supporting information.

Introduction

The ability to construct chiral molecules is a valuable skill in synthetic and medicinal chemistry. Chirality plays a vital role in biological systems. For example, some drugs have an enantiomer that is more active than the other or one of the enantiomers has an unwanted effect. From the medicinal chemistry point of view, the synthesis of new enantiomerically enriched or pure compounds is very desirable. Asymmetric organocatalysis is one of the methods for the formation of carbon-carbon bonds in an enantioselective manner.

Asymmetric organocatalysis has received a lot of attention in the 21st century. By using small optically pure organic molecules as catalysts, compounds with high enantiomeric purities can be synthesised. The reaction setup is usually uncomplicated and the catalysts can be derived from natural compounds. The rapid development of organocatalysis began in 2000 and has grown ever since. The pioneering chemists Benjamin List and David MacMillan were awarded the Nobel Prize in Chemistry in 2021 for their development of a new method for building molecules: asymmetric organocatalysis.

Among the different starting materials for synthesising complex molecules are cyclic diketones. There are many examples with cyclic 1,3-diones and cyclohexane-1,2-dione. However, the studies utilising cyclopentane-1,2-dione are scarce.

This doctoral thesis is focused on the asymmetric organocatalytic Michael addition reactions of cyclopentane-1,2-dione (CPD). Considering the small number of examples in the literature, this work increases the possibilities of using CPD as a valuable starting material. The results demonstrate the synthetic utility of CPD (**Publications I–III**). First of all, the Michael addition/cyclisation cascade with α,β-unsaturated aldehydes was investigated (**Publication I**). Then, the addition/cyclisation cascade with alkylidene malononitriles was studied (**Publication II**). Lastly, the Michael addition of CPD to Boc-protected alkylidene oxindoles was reported (**Publication III**). In addition to the above-mentioned publications, the results of this work have been presented at international conferences in Estonia, Italy and Portugal.

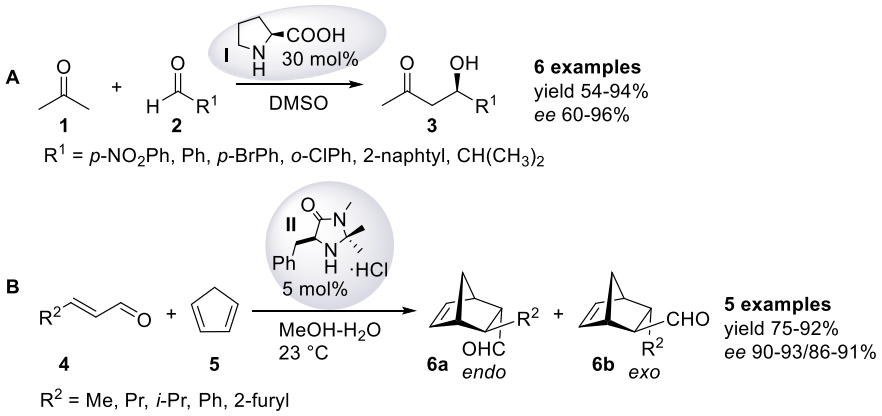
Abbreviations

Boc	*tert*-butyloxycarbonyl
cat.	catalyst
CPD	cyclopentane-1,2-dione
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DHP	dihydropyridine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
e.g.	*exempli gratia*, for example
ee	enantiomeric excess
El	electrophile
eq	equivalent
et al.	*et alia*, and others
etc.	*et cetera*, and other similar things
HOMO	highest occupied molecular orbital
i.e.	*id est*, that is
LDA	lithium diisopropylamide
LiHDMS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
MW	microwave
NOE	nuclear Overhauser effect
Nu	nucleophile
PG	protecting group
rac	racemic
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl
XB	halogen bond

1 Literature overview

1.1 Organocatalysis

Besides enzymatic catalysis[1,2] and transition-metal catalysis[3], organocatalysis[4] is considered the third principal method in asymmetric catalysis. Since its modern emergence, organocatalysis has grown immensely and in 2021 List and MacMillan received the Nobel Prize in Chemistry[5] for "the development of asymmetric organocatalysis". In 2000, they published their findings at the same time independently from each other. Benjamin List[6] showed in his publication that small organic molecules (*i.e.* proline) could catalyse reactions via enamine mechanism that previously mainly enzymes had been used for (Scheme 1, **A**). Meanwhile, MacMillan[7] introduced iminium catalysis and coined the term *organocatalysis* (Scheme 1, **B**).

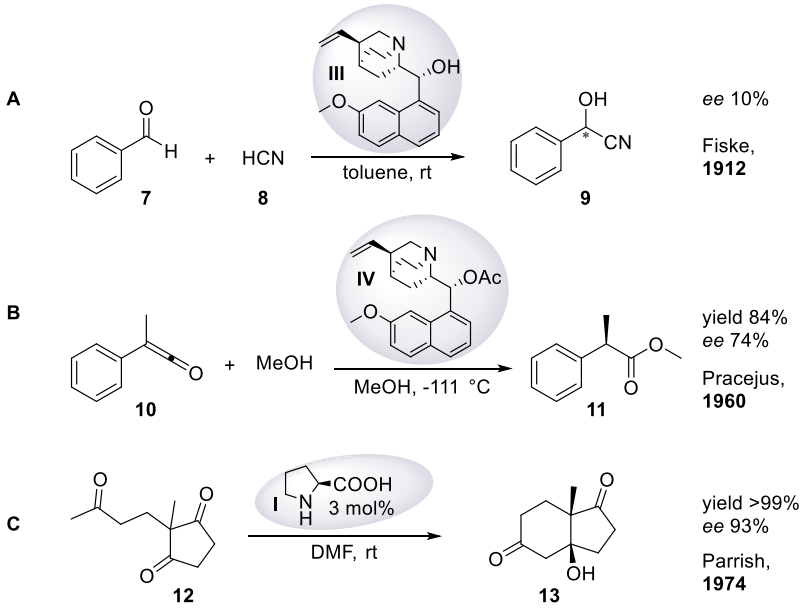


Scheme 1 *Enamine catalysed aldol reaction and iminium catalysed Diels-Alder cycloaddition*

From these results, it was clear what advantages organocatalysis could offer and therefore the field started to developed rapidly. The benefits of using small organic molecules as catalysts are the following: generally, they are more stable in air and water than metal catalysts, are easily synthesisable from natural compounds, they provide less complex reaction setups and usually both enantiomers are available.[8] Organocatalysts can be divided into two groups according to their activation mechanisms: covalent catalysts (*e.g.* amines and *N*-heterocyclic carbenes) and non-covalent catalysts (*e.g.* H-bonding and XB-bonding catalysts). In the first group, in the transition state, the catalyst is covalently bonded to the substrate, whereas in the latter group, the transition state between the catalyst and the substrate is formed by non-covalent weak interactions. In this work, amino- and H-bonding catalysts (*i.e.* thioureas and squaramides) are used, and therefore a brief overview of them is given.

It is important to note that small organic molecules were used as catalysts in the last century as well. In 1912 Bredig and Fiske[9] described a cinchona alkaloid catalysed cyanohydrin synthesis that can be considered the first organocatalytic asymmetric reaction (Scheme 2, **A**). After that, in 1960 Pracejus[10] used amines to achieve some enantioselectivity in the synthesis of 2-phenylpropionic acid methyl ester (Scheme 2, **B**). A major stepping-stone in early organocatalysis occurred in 1974, when Hajos and Parrish[11] reported an organocatalytic aldol reaction with excellent enantioselectivities

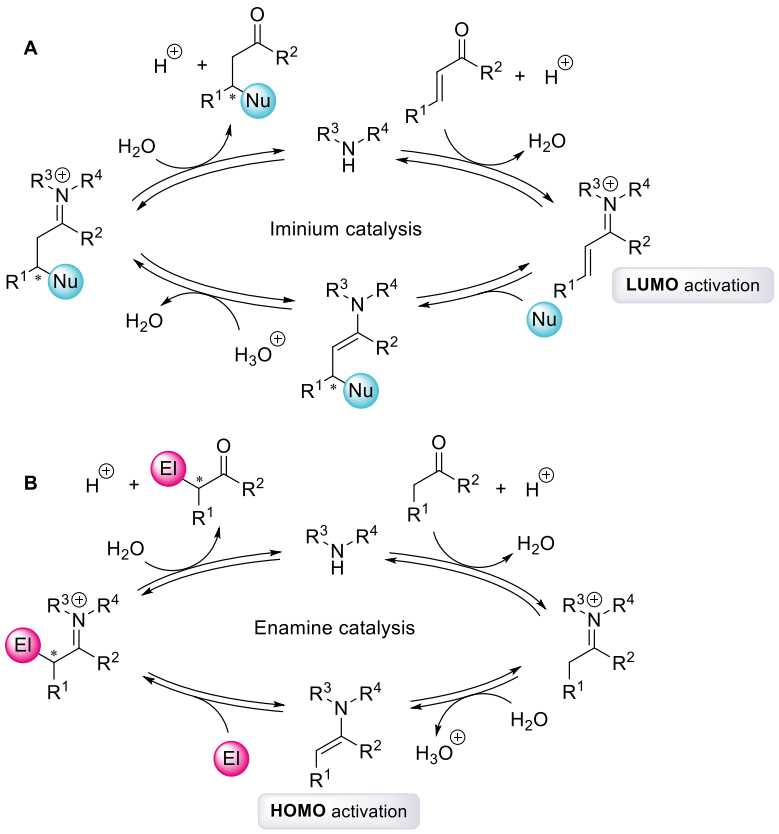
(Scheme 2, **C**) catalysed by (*S*)-proline. However, the publication did not present organocatalysis as a method applicable for other reactions. Therefore, the explosive growth of organocatalysis as a field only happened in the next century.



Scheme 2 *The historical background of asymmetric organocatalysis*

1.1.1 Aminocatalysis

Chiral aminocatalysts are used for the effective asymmetric functionalisation of carbonyl compounds. These catalysts can have two types of activation modes: through an iminium or through an enamine intermediate. Iminium catalysis is used to activate α,β-unsaturated carbonyl compounds. The reactive intermediate is formed through condensation between the chiral secondary amine catalyst and the α,β-unsaturated carbonyl substrate. After the addition of a nucleophile, a β-functionalised enamine is formed, and following hydrolysis, an asymmetric product and an aminocatalyst are released (Scheme 3, **A**). Enamine catalysis is used to activate carbonyl compounds with a proton in the α-position. A reactive nucleophilic intermediate is formed through condensation between a chiral aminocatalyst and a carbonyl compound, followed by the deprotonation of an iminium ion. This chiral enamine intermediate attacks an electrophile and forms an α-functionalised iminium ion and, after hydrolysis, an asymmetric product and a catalyst are released (Scheme 3, **B**).[12,13,14] In principle, the catalyst acts as a chiral auxiliary.[15] The chiral amine temporarily binds to the starting compound, thus inducing chirality. An important difference is that only a catalytic amount of chiral amine can be used. Stereoselectivity arises from either steric bias or through secondary interactions with reagents.



Scheme 3 *Activation modes of aminocatalysis*

The most common catalysts in this category are proline derivatives[16,17], imidazolidinones[7], amino acids[18] and chiral primary amines[19]; examples are shown in Figure 1.

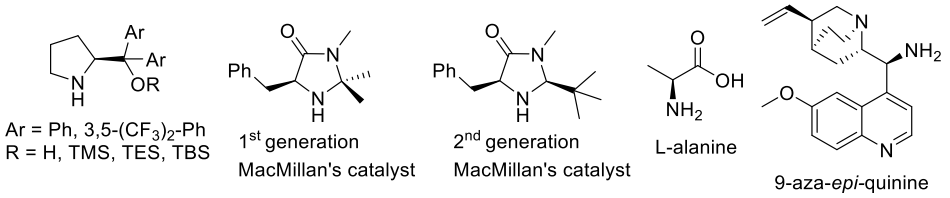


Figure 1 *Common aminocatalysts*

1.1.2 H-bonding catalysis

H-bonding catalysts can be applied in combination with substrates that have the ability to form hydrogen bonds (hydrogen bond acceptors).[20] These catalysts can be monofunctional (activation of the electrophile via H-bonding) or multifunctional (activation of the electrophile via H-bonding and the nucleophile via a general base, bringing the reaction partners together). Non-covalent interactions are weaker and less directional, but still can lead to high levels of enantioselectivity.[21] The most common catalysts in this category are thioureas and squaramides. These catalysts differ in terms of: 1) duality of squaramides, 2) H-bonding directionality and 3) rigidity (Figure 2).[22,23]

The duality refers to the fact that the squaramide moiety is both a hydrogen bond acceptor and a donor. The rigidity of squaramides is a consequence of the planar structure of the cyclobutenedione ring, which contains two coplanar carbonyls and two amino groups that are almost coplanar, which means the lone pairs of nitrogen atoms are delocalised through the cyclobutenedione system and this accounts for the limited conformational changes. Squaramides are in their *anti-anti* conformation; the *syn-anti* conformation is observed only in specifically engineered systems[24], although thioureas can be in their *anti-anti* or *syn-anti* conformations (Figure 2).

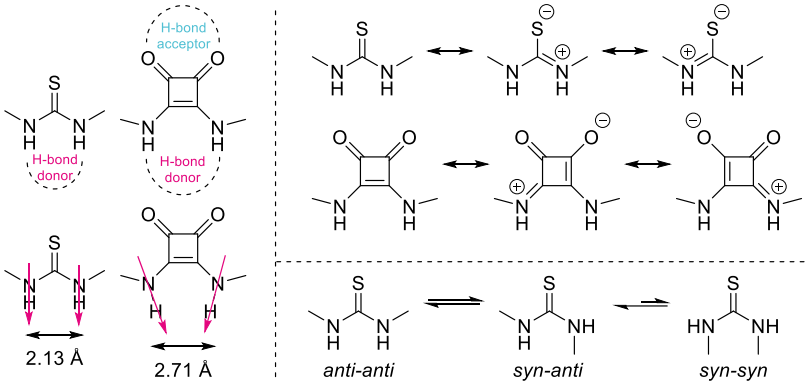
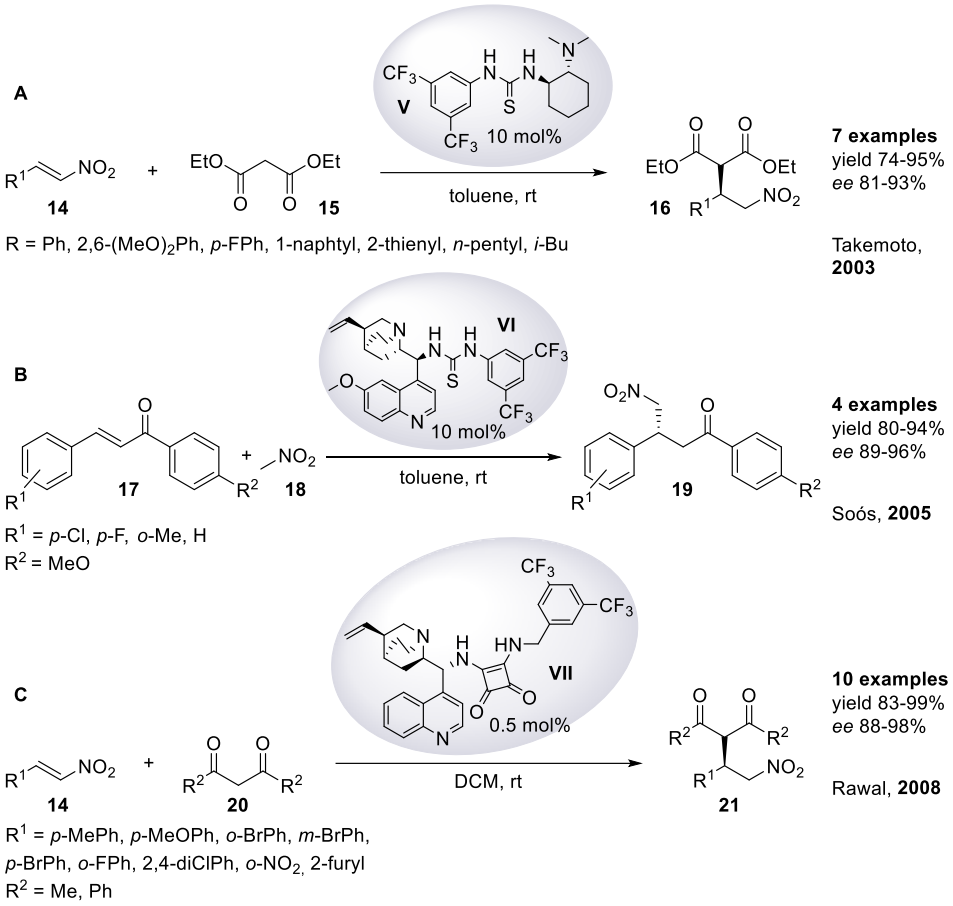


Figure 2 *Differences between thioureas and squaramides*

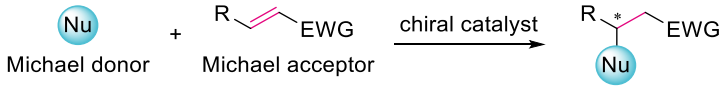
In 2003, Takemoto's group introduced a basic moiety in the thiourea catalyst that could activate the nucleophile, which therefore led to an efficient catalyst for the Michael reaction of malonates **15** to nitroolefins **14** (Scheme 4, **A**).[25] This was the first emergence of bifunctional H-bonding catalysis, which activated both the electrophile and the nucleophile. A few years later, Soós and his group combined complex cinchona alkaloids with thioureas, achieving excellent enantioselectivities and yields in the Michael reaction of nitromethane **18** with chalcones **17** (Scheme 4, **B**).[26] Other H-bond donor motifs have been less investigated. Rawal et al. demonstrated in 2008 a new family of H-bonding catalysts based on squaramides[27] which provided excellent yields and enantiomeric excesses (Scheme 4, **C**).



Scheme 4 *Selected examples in the development of H-bonding catalysis*

1.2 Asymmetric Michael addition

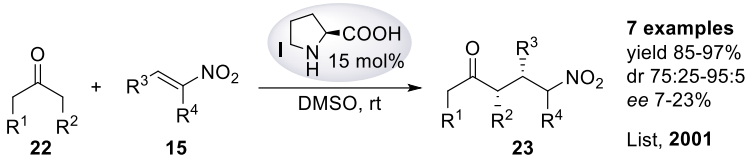
The Michael addition is one of the most versatile methods for the construction of carbon-carbon[28,29,30] (or carbon-heteroatom[31,32,33]) bonds. The Michael reaction is the addition of a nucleophile (Michael donor) to the β-position of an α,β-unsaturated carbonyl compound or a double bond with a strong electron withdrawing group (Michael acceptor) (Scheme 5). Arthur Michael reported the first example in 1887.[34] Nowadays, due to the rapid development of highly efficient asymmetric organocatalysis, there are numerous examples of asymmetric Michael additions with a diverse combination of Michael donors (β-ketoesters, malonates, aldehydes, ketones, amines etc.) and acceptors (α,β-unsaturated carbonyl compounds, unsaturated nitro compounds etc.).[35] This chapter focuses on the formation of C-C bonds, and therefore aza-, oxa- and thio-Michael addition reactions are not discussed.



Scheme 5 *Asymmetric Michael reaction*

1.2.1 Asymmetric aminocatalytic Michael addition

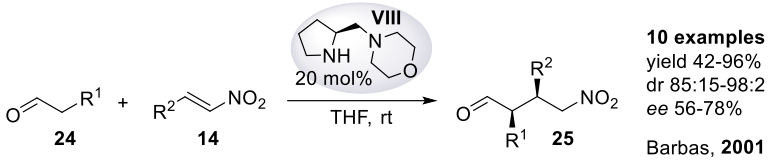
One of the most studied asymmetric Michael reactions is between carbonyl compounds and nitroalkenes, which leads to products that have synthetic versatility because of the nitro group. The earliest examples are from List[36] and Barbas.[37] List's group developed an L-proline **I** catalysed Michael addition of ketones **22** to nitroalkenes **15**. Overall, the yields were very high (85-97%) but the enantioselectivites were quite poor (≤23%), although excellent *syn*-diastereoselecitivites were obtained (75:25-95:5) (Scheme 6).



R^1 = H; R^2 = H, Me; R^1-R^2 = -$CH_2CH_2CH_2$-, -CH_2SCH_2-
R^3 = Ph, *i*-Pr, 3-Me-but-1-en-1-yl ; R^3-R^4 = -$CH_2CH_2CH_2CH_2$-; R^4 = H

Scheme 6 *L-proline catalysed conjugated addition of ketones to nitroalkenes*

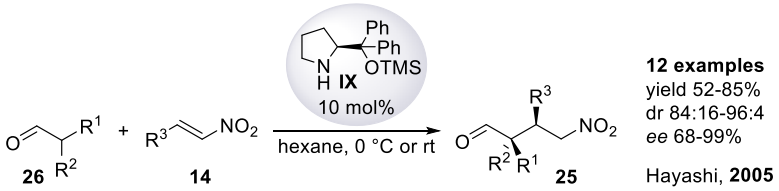
Barbas utilised aldehydes **24** as donors, along with an aminocatalyst, and also obtained *syn*-products (Scheme 7). They found that a diamine catalyst **VIII** gave better results than an L-proline **I** and its analogues, which provided only trace amounts of the adducts. Compared to the previous example, better diastereomeric ratios and higher enantioselectivities were achieved. With a bulkier substituent on the aldehyde, the enantiomeric excess slightly increased.



R^1 = Me, Et, Bu, *i*-Pr, *i*-Bu
R^2 = Ph, 1-naphtyl, 2-naphtyl, *o*-CF_3Ph, 2-thienyl, *n*-pentyl

Scheme 7 *(S)-2-(morpholinomethyl)-pyrrolidine catalysed Michael addition*

A few years later, Hayashi designed a diphenylprolinol silyl ether catalyst **IX** and obtained excellent results in the Michael reaction of aldehydes **26** to nitroalkenes **14** (Scheme 8).[16] They explained the higher activity of the silyl ether as the effective formation of the enamine without generation of an aminal (which would be formed in the case of diphenyl prolinol). All of the adducts **25** were prepared in nearly optically pure forms, except with isobutyraldehyde (*ee* 68%).



R^1 = Me, *i*-Pr, Et, *n*-Pr, R^2 = H; R^1, R^2 = Me
R^3 = Ph, *p*-Br, *p*-OMe, 2-furyl, *n*-Bu, Cy, 2-naphtyl

Scheme 8 *Diphenylprolinol silyl ether catalysed addition of aldehydes to nitroalkenes*

The stereoselectivity of the enamine catalysed Michael reaction is induced by the geometry of the enamine intermediate and the facial selectivity of the attack. The facial selectivity is influenced by the substituent of the chiral aminocatalyst (omitted in Figure 3). Due to steric effects, the enamine is preferably in *E*-configuration, which then undergoes a *syn*-Michael addition. With specific substituents, it has been shown that the enamine favours *Z*-configuration because of intramolecular hydrogen bonding,[38,39] and therefore undergoes an *anti*-Michael addition. According to Seebach's topological rule,[40] the enamine is in an acyclic synclinal transition state with the substrate and provides *syn*-products (Figure 3). Both Barbas[37] and Hayashi[16] explained their *syn*-selectivity as the formation of an *E*-enamine and acyclic synclinal transition state proposed by Seebach.

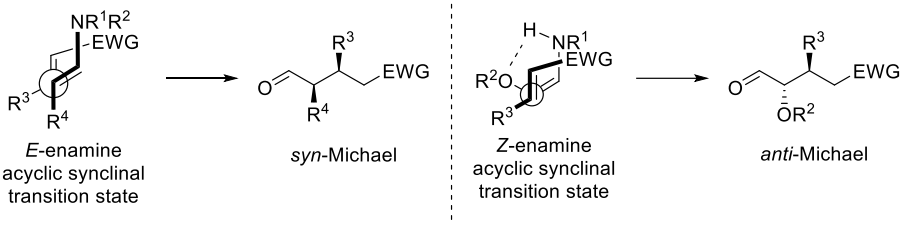
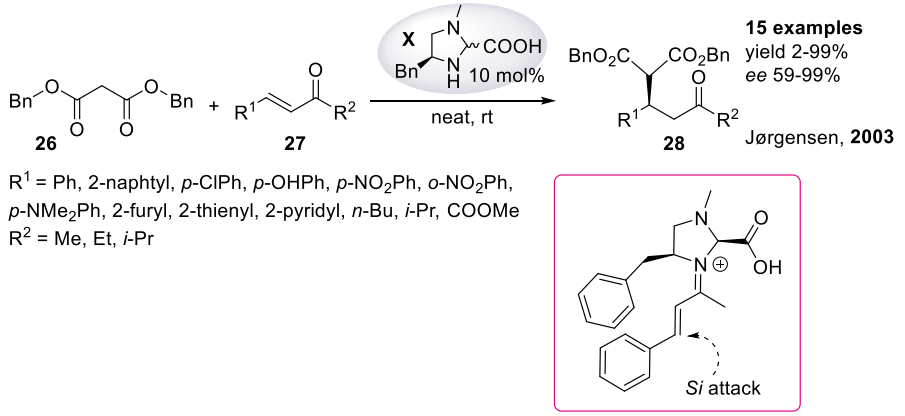


Figure 3 *E- and Z-enamine transition states leading to Michael adducts*

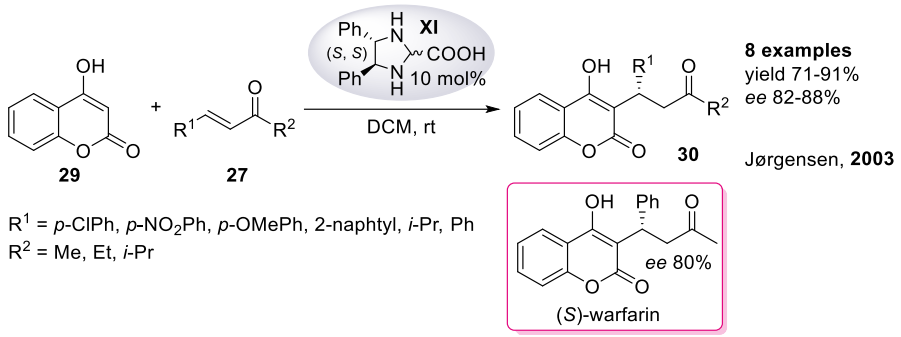
In the previous examples, the enamine catalysis was utilised to activate the carbonyl compound: a Michael donor (HOMO activation). In the next cases, the Michael acceptor – an α,β-unsaturated carbonyl compound – was activated instead (LUMO activation).

The first enantioselective Michael addition of malonates **26** to acyclic α,β-unsaturated carbonyl compounds **27** was reported by Jørgensen.[41] The reaction was catalysed by the highly efficient imidazolidine catalyst **X** via iminium catalysis. The selectivity of the reaction is explained by the formed (*E*, *E*)-iminium intermediate, where the *Re* face is shielded by the benzyl group and allows the attack to occur from the *Si* face (Scheme 9). The authors have previously shown that the transition states from the *trans*-diastereomer of the catalyst were calculated to be higher in energy[42] and therefore not favoured.



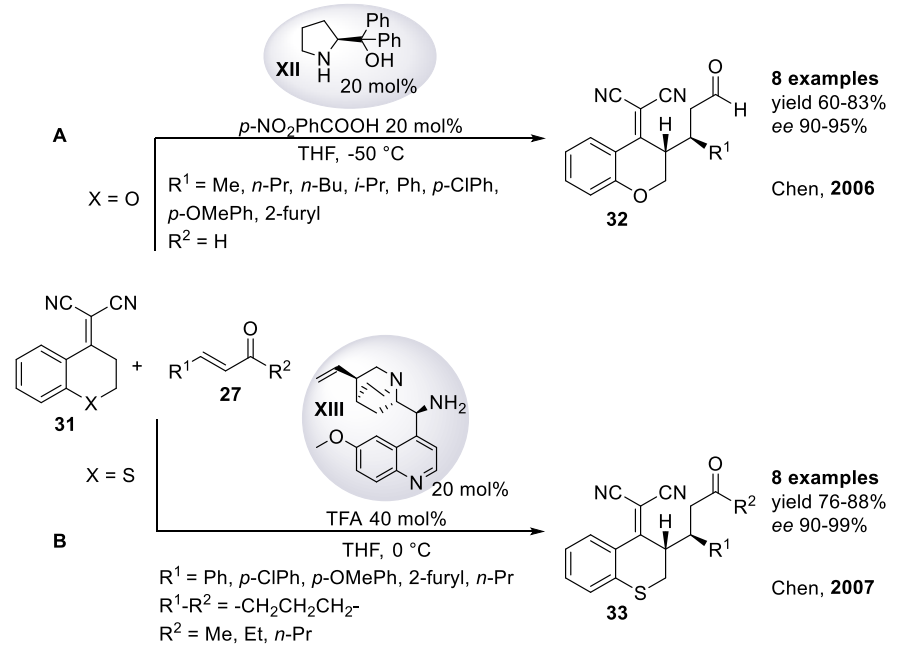
Scheme 9 *Imidazolidine catalysed Michael reaction of malonates to α,β-unsaturated ketones*

Warfarin is an anticoagulant (blood thinner) and it is prescribed as a racemate. The bioactivity of (*S*)-enantiomer is five to eight times higher than that of the (*R*)-enantiomer. The synthesis of the more active isomer was accomplished by using the (*S*, *S*)-imidazolidine catalyst **XI**.[43] (*R*)-Warfarin was obtained when the reaction was catalysed by (*R*, *R*)-imidazolidine. The reaction scope included different α,β-unsaturated ketones **27** (Scheme 10) and also various cyclic 1,3-dicarbonyl compounds.



Scheme 10 *Utilisation of an imidazolidine catalyst in warfarin synthesis*

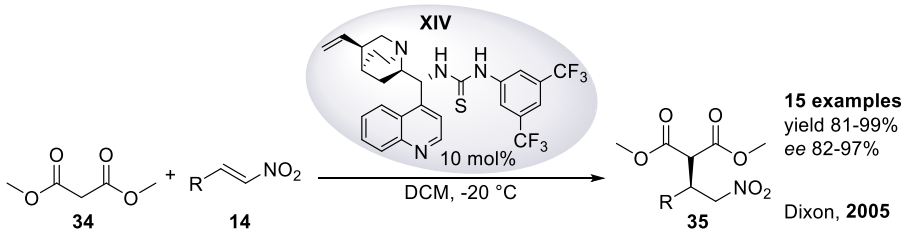
The last examples are of a vinylogous Michael addition of α,α-dicyanoalkenes **31** to α,β-unsaturated aldehydes **27**. In 2006, Chen et al.[44] expanded the scope of substrates of the Michael reaction by using α,α-dicyanoalkenes **31**. By activating the acceptor with diphenylprolinol **XII**, they obtained the desired products **32** in moderate to high yields and excellent *ee* values (Scheme 11, **A**). In this catalytic system, unfortunately ketones showed no reactivity. A year later, the same group overcame the problem by using a primary amine catalyst **XIII** derived from quinine.[45] In both cases, they observed excellent diastereoselectivities (dr >99:1) (Scheme 11, **B**).



Scheme 11 *Secondary and primary amine catalysed Michael additions*

1.2.2 H-bond catalysed asymmetric Michael addition

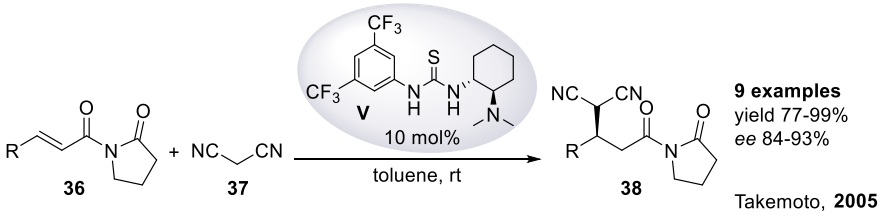
In April 2005[26], Soós demonstrated that bifunctional thiourea derivatives of cinchona alkaloids are capable of activating both the nucleophile and electrophile, thus achieving excellent results in a Michael reaction of nitromethane to chalcones (Scheme 4, **B**). A few months later, in August 2005, Dixon's group envisaged the same approach: combining a thiourea moiety with a cinchonine alkaloid skeleton would give rise to an efficient bifunctional catalyst. The addition of malonate esters **34** to nitroalkenes **14** provided the adducts **35** in high yields and in high enantioselectivities (Scheme 12).[46]



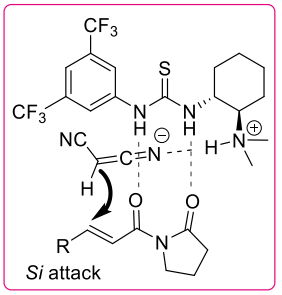
R = Ph, 2-naphtyl, *o*-ClPh, *o*-BrPh, *m*-BrPh, *p*-BrPh, *p*-MePh, *m*-MePh, *o*-OMePh, *m*-OMePh, *p*-OMePh, 2-furyl, 2-thienyl, *n*-pentyl, Cy

Scheme 12 *Cinchonine derived thiourea catalysed Michael addition*

To further extend the synthetic utility of bifunctional thioureas, Takemoto and his co-workers took on a different type of Michael acceptor, an α,β-unsaturated imide, which they thought had the ideal structure to form hydrogen bonds through the two carbonyl groups. The proposed transition state (Scheme 13) led to the formation of products derived from an attack from the *Si* face. Various α,β-unsaturated imides **36** were tolerated and throughout the scope high yields, reasonable reaction times and high enantioselectivities were achieved, except with the electron-rich substrate (R = *p*-OMePh), where the reaction was slower and the yield decreased slightly.

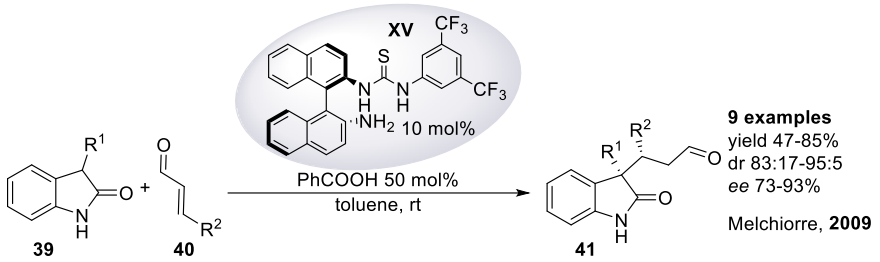


R = Ph, *p*-ClPh, *p*-CF_3Ph, *p*-OMePh, 1-naphtyl, 2-furyl, $PhCH_2CH_2$, Me, *t*-Bu



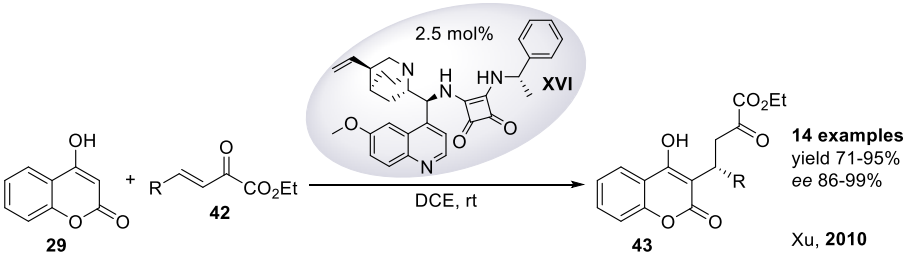
Scheme 13 *Bifunctional thiourea catalysed addition of malononitrile to imides*

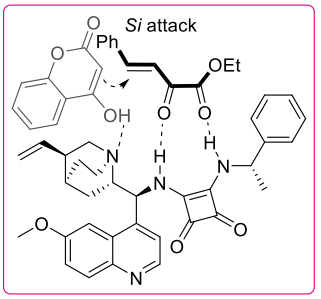
An oxindole moiety with quaternary carbon stereocentre is found in numerous bioactive compounds.[47] These structures can be synthesised by a Michael addition of oxindoles to alkenes. The first asymmetric pathway starting from unprotected oxindoles **39** was suggested by Melchiorre's group.[48] In the presence of a novel bifunctional chiral primary amine thiourea catalyst **XV**, the products **41** with two adjacent stereocentres were obtained in moderate to high yields, with good diastereomeric ratios and excellent enantioselectivities (Scheme 14).



Scheme 14 *Primary amine thiourea catalysed Michael reaction of unprotected oxindoles to α,β-unsaturated aldehydes*

Inspired by the utility of squaramides reported by Rawal (Scheme 4, **C**),[27] Xu and his group investigated the squaramide **XVI** promoted Michael addition of 4-hydroxycoumarins **29** to β,γ-unsaturated α-ketoesters **42** (Scheme 15).[49] Changing the amine moiety of the catalyst to the alkaloid framework increased the enantioselectivity but, when using thiourea with the same alkaloid moiety, the reaction performed poorly. The stereochemical outcome of the reaction is explained by the hydrogen bonding of the catalyst to the α-ketoester and the hydrogen bonding of the quinuclidine moiety to the 4-hydroxycoumarin **29**; therefore the attack may have come from the *Si* face (Scheme 15).

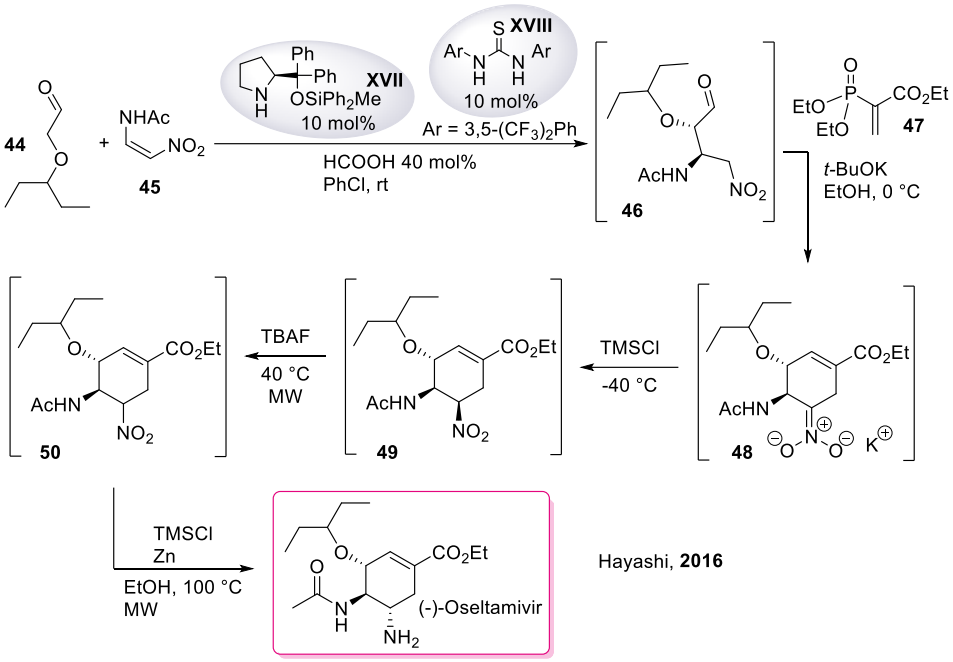




Scheme 15 *Squaramide promoted addition of 4-hydroxycoumarins to ketoesters*

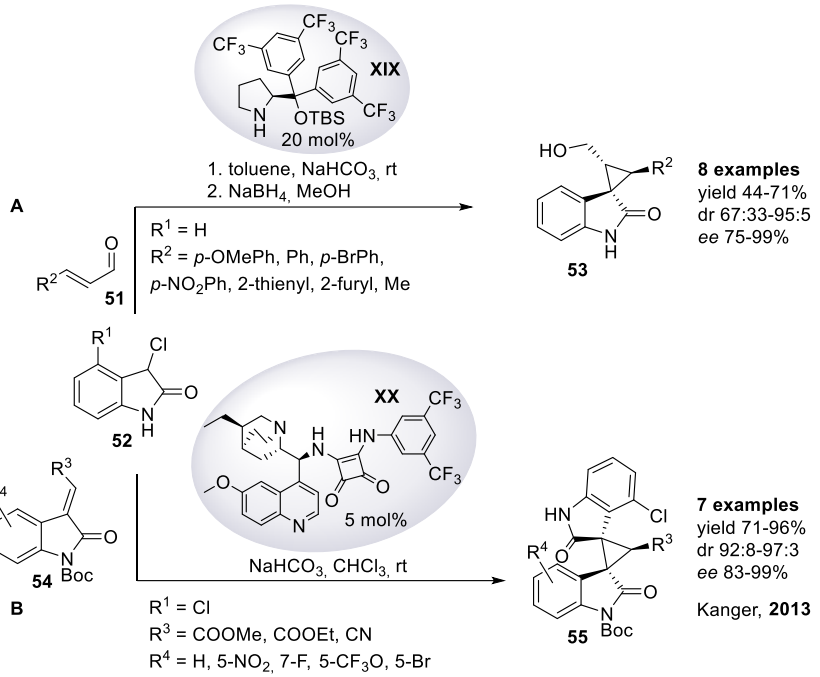
1.2.3 Asymmetric Michael addition in cascade reactions

The conjugate addition reaction has been applied in cascade reactions, which has led to very effective synthetic methodologies for the one-step synthesis of highly complex molecules.[50] (−)-Oseltamivir phosphate (Tamiflu) is an antiviral medication that is used in the treatment of type A and B human influenza. In 2016, Hayashi et al.[51] improved the synthesis of (−)-oseltamivir,[52] especially regarding time consumption. In only 60 minutes, they managed to synthesise the target compound in a one-pot manner in five steps with 15% yield and with one purification (Scheme 16). The first Michael reaction requires the presence of all three catalysts (prolinole derivative **XVII**, Schreiner's achiral thiourea **XVIII** and formic acid) to be optimised in terms of speed, yield and selectivity. Then, by adding ethyl acrylate derivative **47**, a Michael addition and Horner-Wardsworth-Emmons reaction occurred. Since time was the main concern, it was further reduced by applying microwave (MW) irradiation in the last two reactions.



Scheme 16 *Total synthesis of (-)-oseltamivir*

The spirocyclic oxindole motif can be found in many bioactive molecules.[53] The chiral quaternary centre at the third position in the oxindole is both very interesting and challenging to prepare.[54] The Michael reaction can be perfectly utilised in an organocatalytic cascade procedure for the formation of spirooxindoles. Kanger et al. developed two different strategies in one publication to synthesise spirocompounds **53** and **55** from 3-chlorooxindoles **52**: an aminocatalytic cascade with α,β-unsaturated aldehydes **51** (Scheme 17, **A**) and an H-bonding promoted cascade with methyleneindolinones **54** (Scheme 17, **B**). The diastereomeric ratio was improved when a substituent was introduced in the 4-position of the 3-chlorooxindole.[55] In 2014, Boc-protected 3-chlorooxindole was used in the synthesis of spirocyclopropane derivatives.[56]



Scheme 17 *Two different strategies for synthesising spirooxindoles*

1.3 Cyclic diketones

Diketones are a class of compounds that are very versatile precursors in organic synthesis. The structure of 1,3-diketones is especially prevalent in a plethora of compounds that show a variety of biological and pharmaceutical activities.[57] The highly active methylene between the two carbonyl groups gives rise to the diverse chemistry of 1,3-diketones.[58] Due to keto-enol tautomerism, diketones can be in keto or enol form. 1,2-diketones **56** are mostly in their enol form, because of the stabilising intermolecular hydrogen bonds formed, and in 1,3-diketones **57** the keto and enol forms are distributed almost equally (Figure 4).[59,60]

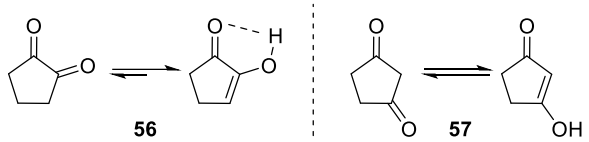


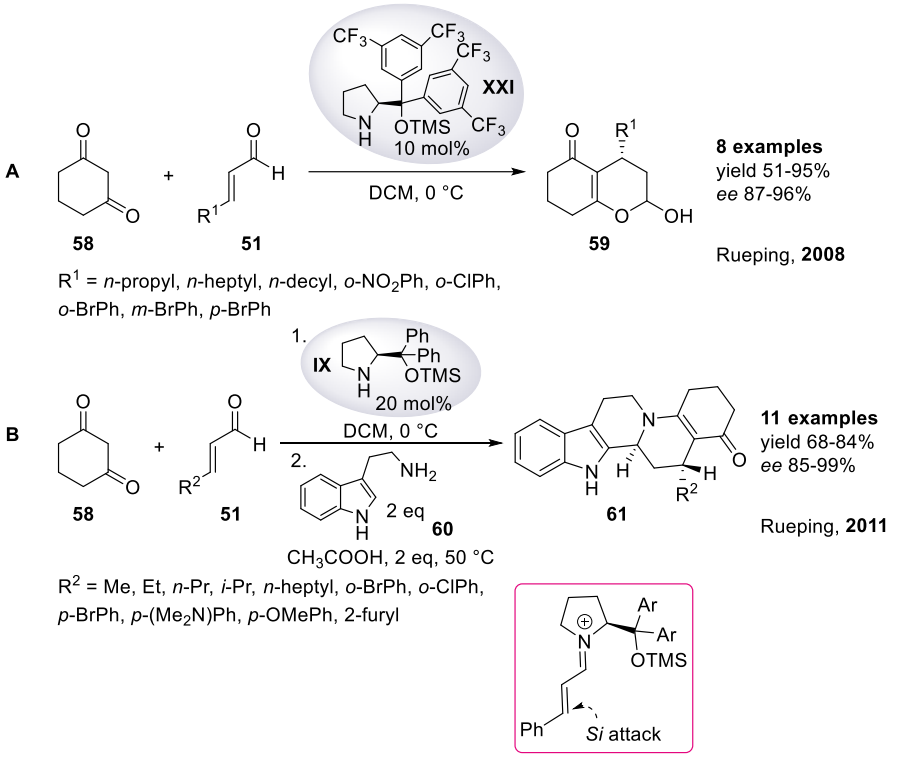
Figure 4 *Keto-enol tautomerisation diketones*

Cyclic 1,3-diketones have received a lot of attention due to the fact that they are very reactive and the products are highly useful. Cyclic 1,2-diketones, however, have been less investigated.

1.3.1 Reactions of cyclohexane-1,3-diones

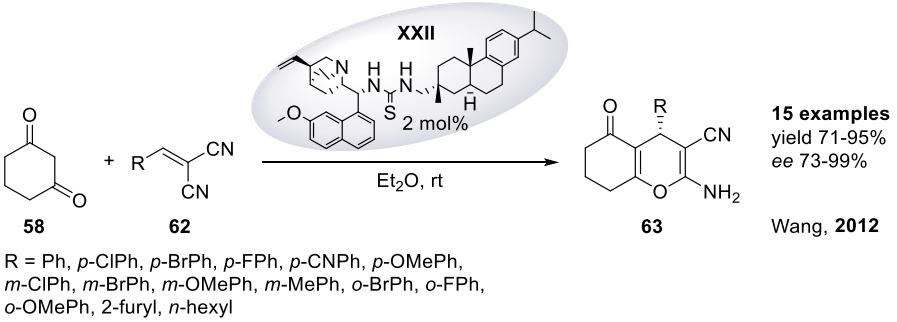
Because of the lack of enantioselective benzopyrane and chromenone synthesis methods, in 2008 Rueping et al. proposed an asymmetric organocatalysed pathway starting from cyclohexane-1,3-dione **58** and α,β-unsaturated aldehydes **51** (Scheme 18, **A**).[61] The addition/cyclisation cascade reaction was catalysed by diaryl prolinol ether **XXI**.

The obtained hemiacetals **59** could be later transformed into biologically active lactones, oxadecalinones and benzopyranes. A few years later, Rueping's group employed their previously developed strategy for hemiacetals **59** and synthesised indoloquinolizidines **61** in a one-pot manner (Scheme 18, **B**).[62]



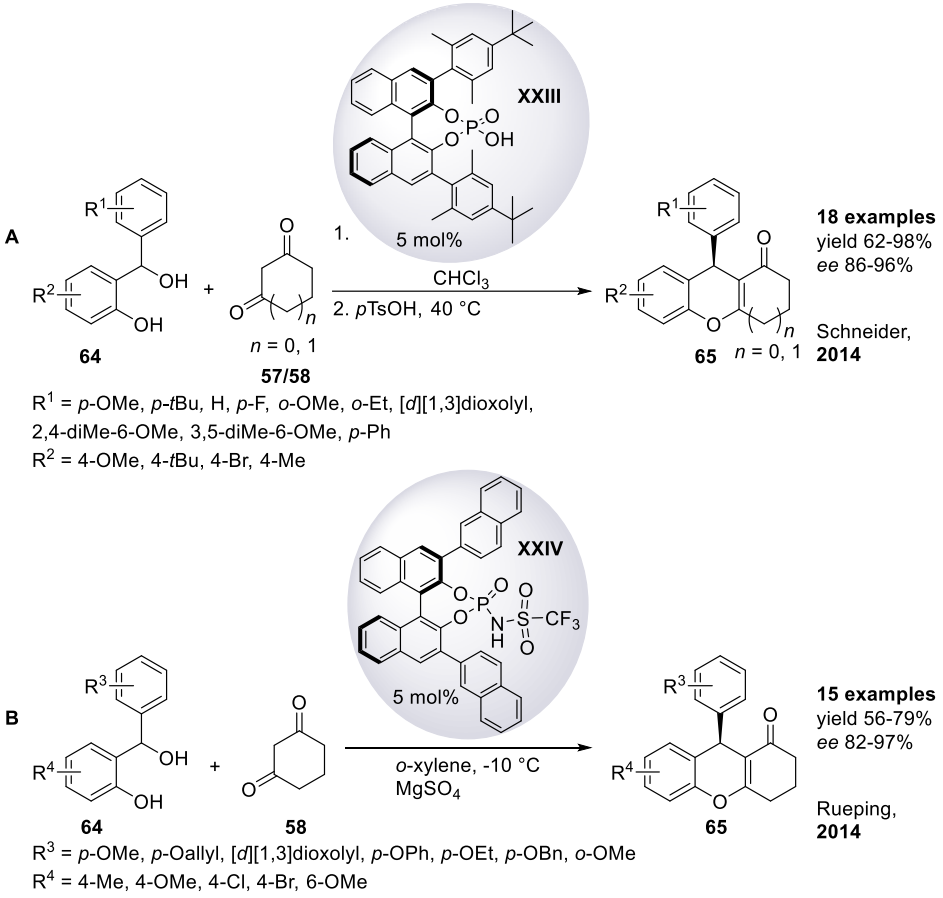
Scheme 18 *Synthesis of hemiacetals and indoloquinolizidines via aminocatalysis*

Wang et al. used their formerly developed novel bifunctional thiourea catalyst based on abietic acid[63] **XXIII** to catalyse the synthesis of 2-amino-4*H*-chromenes **63**. They obtained the products in high yields and in high enantioselectivities (Scheme 19). When they extended the conditions to a one-pot three-component reaction with aromatic aldehydes, malononitrile and cyclohexane-1,3-dione **58**, there was no loss in the enantioselectivity of the products.[64]



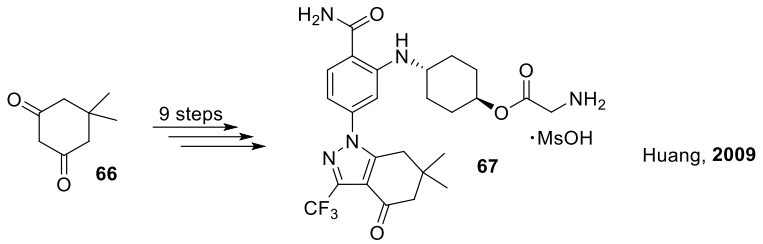
Scheme 19 *Synthesis of 2-amino-4H-chromenes catalysed by bifunctional thiourea*

In 2014, both Schneider[65] (Scheme 20, **A**) and Rueping[66] (Scheme 20, **B**), within the span of a few months, published the synthesis of tetrahydroxanthenones **65**. In both cases, BINOL-based chiral catalysts were employed. Schneider used the phosphoric acid derivative **XXIII**, and Rueping used *N*-triflyl phosphoramide[67] **XXIV**.



Scheme 20 *Chiral phosphoric acid catalysed* ***A*** *and phophoramide catalysed* ***B*** *syntheses of xanthene derivatives*

β-Diketones have also been valuable materials for the total synthesis of different bioactive compounds.[57,68] For example, Huang et al.[69] prepared indazol-4-ones from dimedone and then used them to produce compound **67**, which turned out to be a potential inhibitor for Hsp90 (heat shock protein 90), which stabilises proteins for tumour growth (Scheme 21).

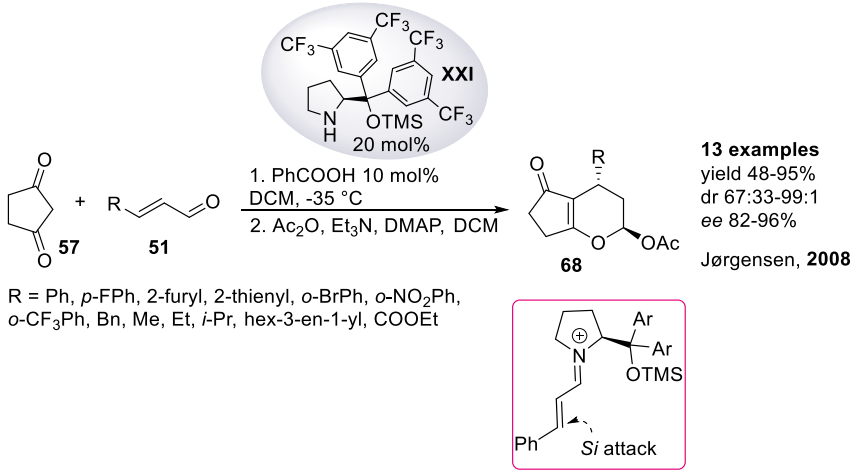


Scheme 21 *Total synthesis of Hsp90 inhibitor*

1.3.2 Reactions of cyclopentane-1,3-diones

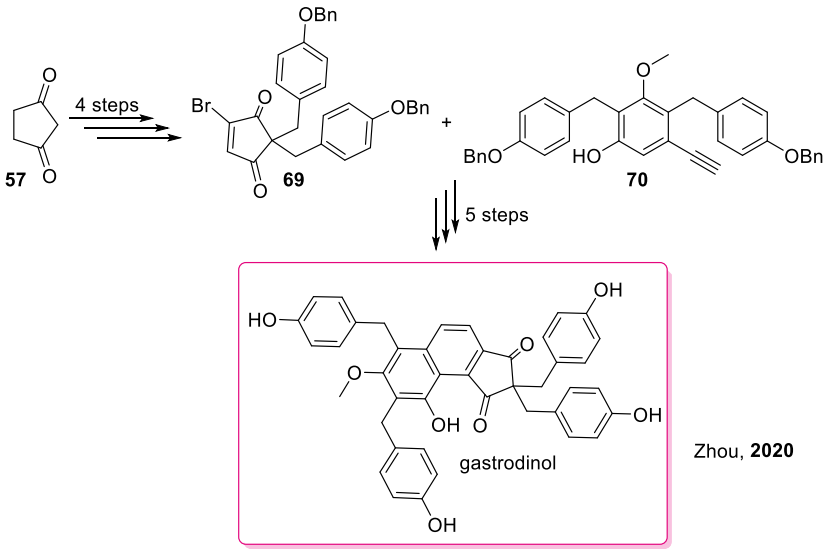
The five-membered cyclic β-dicarbonyl fragment is less common in bioactive compounds and this may be why they are less studied. There are only a couple of examples of organocatalytic enantioselective reactions of cyclopentane-1,3-dione **57** and a few instances where the five-membered cycle has been used as a single case in a larger substrate scope. From the latter, we get the overall idea that the conditions for six-membered 1,3-diketones are not always suitable for five-membered diketones.[65,70,71,72]

A pyran moiety is a quite common fragment in natural products.[73,74] Jørgensen and his group envisioned that via an organocatalytic cascade reaction between cyclopentane-1,3-dione **57** and α,β-unsaturated aldehydes **51** they would obtain enantiomerically enriched substituted 3,4-dihydropyrans **68**.[75] The reaction was catalysed by diarylprolinol silyl ether **XXI** and for separation purposes, they acetylated the obtained hemiacetal (Scheme 22).



Scheme 22 *Diaryl prolinol catalysed Michael addition of cyclopentane-1,3-dione to α,β-unsaturated aldehydes, followed by acetylation*

Gastrodinol has exhibited notable cytotoxic activity against the five human cancer cell lines *in vitro*. In 2020, the first total synthesis of gastrodinol[76] was published in which cyclopentane-1,3-dione **57** was the starting material for one of the key segments (Scheme 23).

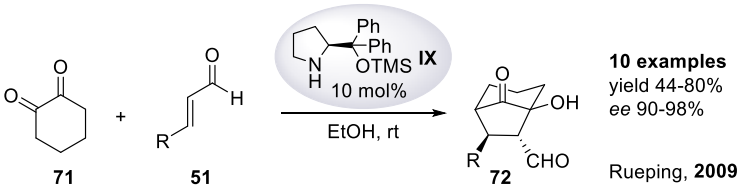


Scheme 23 *Total synthesis of gastrodinol*

1.3.3 Reactions of cyclohexane-1,2-diones

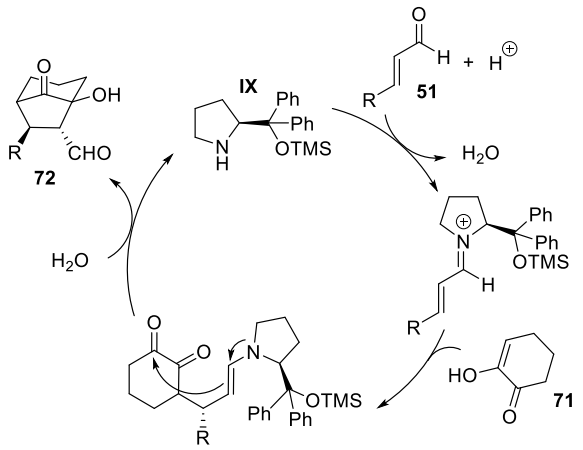
Overall, cyclic 1,3-diketones have been studied more than cyclic 1,2-diketones. The authors mentioned in this chapter have stated that the utilisation of 1,2-diones has not been as widespread as that of 1,3-diones, and their reactivity has been almost unexplored.

Following an efficient organocatalytic asymmetric addition/cyclisation cascade with cyclohexane-1,3-dione **58** (Scheme 18),[61] Rueping also examined the reactivity of cyclohexane-1,2-dione **71**. In contrast to their previous findings, cyclic 1,2-diketone followed the iminium/enamine activated (Scheme 25) Michael addition/aldol reaction cascade pathway, leading to chiral bicyclo[3.2.1]octane-6-carbaldehydes **72** (Scheme 24).[77]



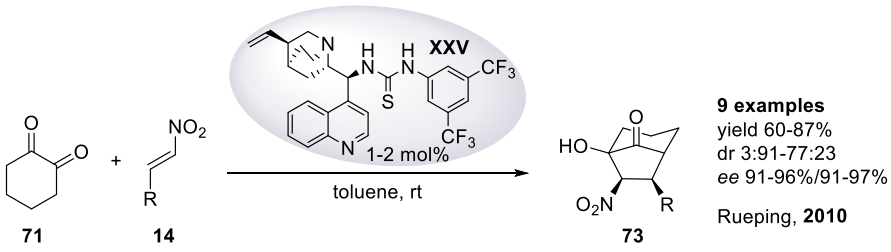
R = Ph, *p*-OMePh, *p*-BrPh, *m*-BrPh, *o*-NO_2Ph, *p*-$N(Me)_2$Ph, benzo[1,3]dioxol-5-yl, 2-furyl, 2-thienyl, *n*-Bu

Scheme 24 *Michael addition/aldol cascade catalysed by diaryl prolinol*



Scheme 25 *Iminium/enamine activation of Michael addition/cyclisation cascade*[77]

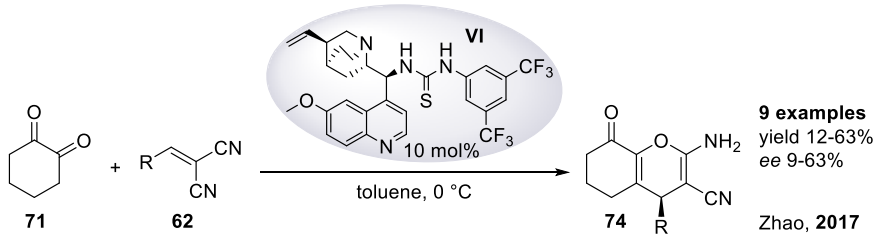
Rueping continued to expand the scope of cyclohexane-1,2-dione **71** reactions by applying another Michael acceptor: nitroalkene **14**. The cascade was catalysed by only 1-2 mol% of alkaloid derived thiourea **XXV** and the products **73** were isolated in high yields with excellent optical purities (Scheme 26).[78]



R = Ph, *p*-MePh, *o*-OMePh, *m*-OMePh, *p*-OMePh, *p*-FPh, *o*-FPh, 3,4-$(Cl)_2$Ph, *m*-BrPh

Scheme 26 *Michael addition/Henry reaction cascade catalysed by alkaloid derived thiourea*

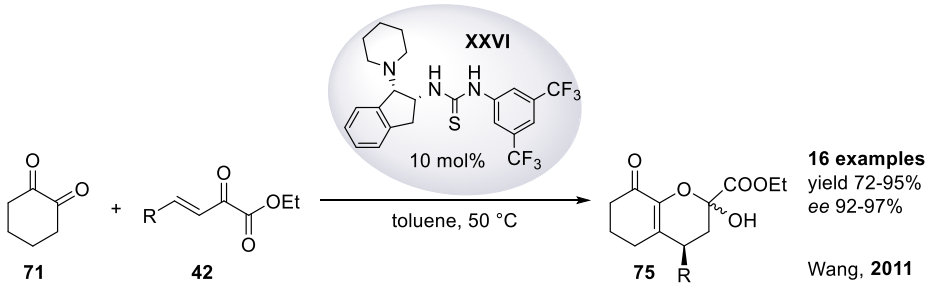
Zhao et al. have also investigated the cascade reaction between cyclohexane-1,2-dione **71** and benzylidene malononitriles **62**. The yield and enantioselectivity were much lower than that of the previous examples listed above; the highest achieved *ee*-value was only 63% (Scheme 27).[79]

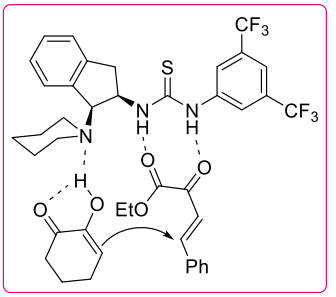


R = Ph, *p*-ClPh, *p*-BrPh, *p*-CNPh, *p*-NO_2Ph, *m*-BrPh, *p*-MePh, 2-thienyl, *n*-hexyl

Scheme 27 *Thiourea catalysed Michael addition/cyclisation reaction*

Later, to utilise 1,2-diones as interesting synthetic blocks, Wang's group developed a Michael addition/cyclisation cascade[80] to β,γ-unsaturated α-ketoesters **42** catalysed by indane based thiourea[81] **XXVI**. One of the diastereomers of the obtained hemiketals **75** was kinetically favoured (>10:1). The novel indane derived organocatalyst **XXVI** provided the perfect dihedral angle between the amino and thiourea fragments, resulting in the excellent stereoselectivity observed throughout the substrate scope (Scheme 28).



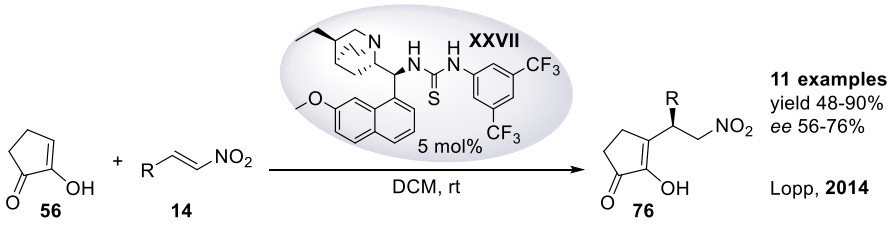


Scheme 28 *Michael addition/cyclisation reaction of cyclohexan-1,2-dione to β,γ-unsaturated α-ketoesters*

1.3.4 Reactions of cyclopentane-1,2-diones

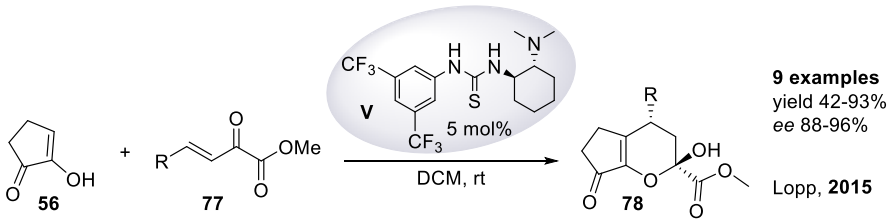
There were no examples related to cyclopentane-1,2-dione **56** until 2004, when Lopp et al. synthesised highly valuable chemicals starting from cyclopentane-1,2-dione.[82,83,84]

The first publication devoted only to the reactivity of cyclopentane-1,2-dione **56** was published by Lopp et al. in 2014.[85] They used a thiourea catalyst **XXVII** to activate both nitroalkene **14** and diketone **56**. The reaction tolerated different substituents in the aromatic ring and even an aliphatic nitroalkene was used (Scheme 29).

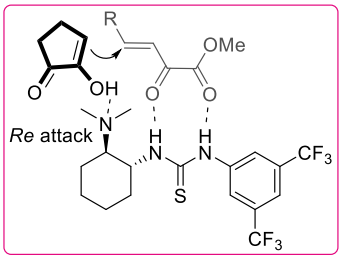


Scheme 29 *Thiourea catalysed Michael addition of cyclopentane-1,2-dione to nitroalkenes*

Shortly after, a Michael addition/cyclisation cascade reaction with (*E*)-2-oxobut-enoates **77** was developed by the same group.[86] Fortunately, the formation of only one diastereoisomer was observed. Takemoto's catalyst **V** activated both the Michael acceptor and the diketone via hydrogen bonding, the former through the amino groups and the latter through the tertiary amine moiety (Scheme 30).



R = Ph, *p*-ClPh, *p*-BrPh, *o*-ClPh, *p*-OMePh, *p*-NO_2Ph, 2-thienyl, Cy



Scheme 30 *Michael addition/cyclisation cascade catalysed by Takemoto's catalyst*

2 Aims of the present work

Asymmetric organocatalysis has become a powerful tool for obtaining enantiomerically enriched compounds. A Michael addition is one of the most versatile methods for forming a C–C bond. Combining these two provides an excellent opportunity to synthesise complex molecules. The main objective of this work is to broaden the possible organocatalytic Michael reactions of cyclopentane-1,2-dione **56**.

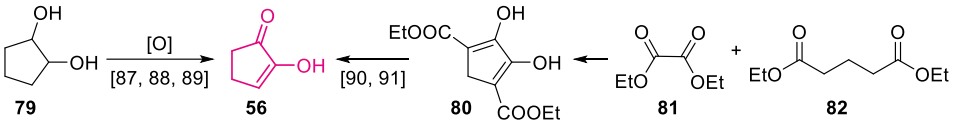
The specific aims of the thesis are:

- To synthesise cyclopentane-1,2-dione **56** in an efficient manner;
- to expand the scope of Michael acceptors in the reaction with cyclopentane-1,2-dione **56**;
- to develop new methods for synthesising enantioenriched substituted cyclopentenones starting from cyclopentane-1,2-dione **56**;
- to develop organocatalytic cascade reactions to obtain valuable enantiomerically enriched pyrans;
- to determine the relative and absolute configurations of the novel compounds.

3 Results and discussion

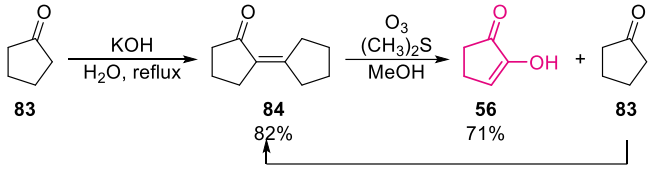
3.1 Synthesis of cyclopentane-1,2-dione 56

There are several methods for synthesising cyclopentane-1,2-dione **56**. Previously, our group obtained CPD by making use of different oxidation methods of diol **79** to dione **56**. These include aerobic oxidation with a Pt/C catalyst[87,88] and Swern oxidation;[89] other oxidants can also be used. Another option is to use Claisen and then Dieckmann condensations of diethyl oxalate **81** and diethyl glutarate **82,** which is not considered atom efficient, since only five carbons among the 15 of the starting materials are in the final product (Scheme 31).[90,91]



Scheme 31 *Cyclopentane-1,2-dione syntheses*

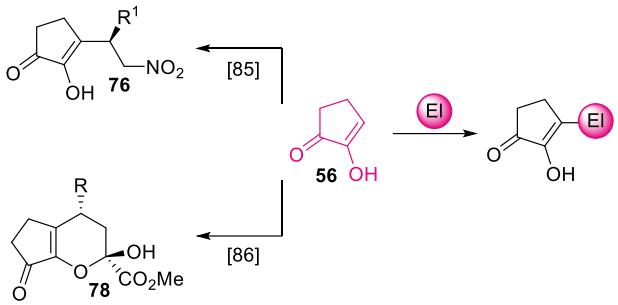
In this work, for synthesising CPD **56** we used a method published by Wrobel and Cook in 1980 which had been unconsidered for 40 years.[92] This procedure is simple and convenient, and the starting material, cyclopentanone **83**, is commercially available and cheap. First, an aldol condensation is necessary to form the 2-cyclopentylidenecyclopentanone **84**. Then, ozonolysis is carried out and, using dimethyl sulfide as the reducing agent, the desired diketone **56** and cyclopentanone **83** as a by-product are obtained (Scheme 32). After recrystallisation, the diketone **56** is obtained with an overall yield of 58%. The cyclopentanone **83** can then be recycled to synthesise the aldol condensation product **84**.



Scheme 32 *Cyclopentane-1,2-dione synthesis via aldol condensation and ozonolysis*

3.2 Reactions of CPD with substituted α,β-unsaturated aldehydes (Publication I)

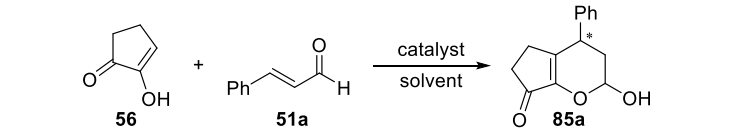
The investigation of Michael addition reactions of cyclopentane-1,2-dione was based on our previous work with CPD. Our group has developed asymmetric organocatalytic methods for synthesising differently substituted cyclopentane-1,2-diones from electrophiles, such as nitroalkenes **14** and β,γ-unsaturated α-ketoesters **77** (Scheme 29, Scheme 30).[85,86] These were the only examples investigating the reactivity of CPD at that time. Since a Michael addition reaction is a powerful C-C bond forming tool, we started to look into other electrophiles that could be used in the Michael reaction with CPD (Scheme 33). We assumed that with α,β-unsaturated aldehydes a cascade reaction would occur, consisting of a Michael addition followed by a cyclisation reaction.



Scheme 33 *Reactions of CPD with electrophiles*

The model Michael acceptor for screening the suitable catalyst and solvent was *trans*-cinnamaldehyde **51a**. α,β-Unsaturated aldehydes can be activated via an iminium catalysis, and therefore proline-type catalysts were screened. Starting with L-proline **I** in EtOH, the yield of the obtained hemiacetal **85a** was very low and the *ee* was only 16%. Next, with diarylprolinol **XII** the reaction was slightly slower; the yield increased to 61% but the enantiomeric excess remained low. By protecting the hydroxyl group with TMS (**IX**), the enantioselectivity increased dramatically, even more so with the bulkier TBS protecting group (**XXIX**). Different protic and aprotic solvents were screened and the best results in terms of both yield and enantioselectivity were obtained in DCM (Table 1, entry 11).

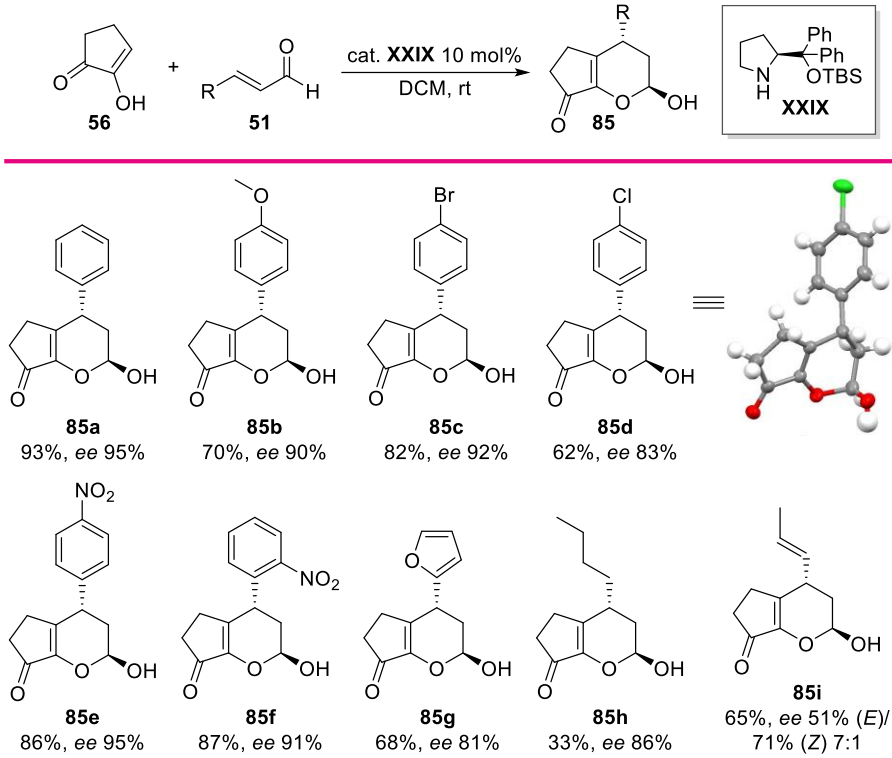
Table 1 *Optimisation of the model reaction*



Entry[a]	Catalyst, 10 mol%	Solvent	Time, h	Yield, %[b]	*ee*, %[c]
1	**I**	EtOH	18	6.5	16
2	**XII**	EtOH	24	61	21
3	**IX**	EtOH	1.5	59	79
4	**XXVIII**	EtOH	24	20	-70
5	**XXIX**	EtOH	18	83	85
6	**XXIX**	MeOH	24	74	88
7	**XXIX**	THF	24	72	96
8	**XXIX**	toluene	5	83	97
9	**XXIX**	$CHCl_3$	2	76	98
10	**XXIX**	DCE	6	72	96
11	**XXIX**	DCM	2	93	95

[a] Reaction conditions: **56** (0.24 mmol), **51a** (0.2 mmol), catalyst (10 mol%), solvent (0.7 mL), rt. [b]Isolated yield after column chromatography. [c] Determined by chiral HPLC.

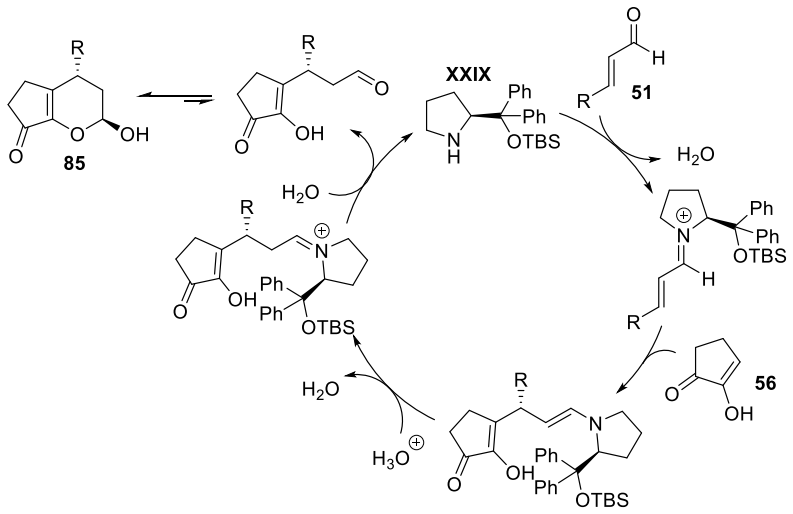
With these optimal conditions, the scope of the reaction was studied. The reaction tolerated different electron-withdrawing (**85c-f**) and electron-donating (**85b**) groups in the aromatic ring, as well as heteroaromatic (**85g**) and alkyl substrates (**85h**, **i**), although the yield and *ee* decreased with the latter. Using *p*-methoxy **51b** and *p*-Cl **51d** substituted starting materials, the yields were lower than average. Surprisingly, the sterically more hindered *o*-NO_2-cinnamaldehyde **51f** gave a high yield. The absolute configuration of **85d** was assigned by a single crystal X-ray diffraction and the configurations of compounds **85** were assigned by analogy (Scheme 34).



Reaction conditions: **56** (0.24 mmol), **51** (0.2 mmol), cat. **XXIX** (10 mol%), DCM (0.7 mL), rt; isolated yields after column chromatography; determined by chiral HPLC.

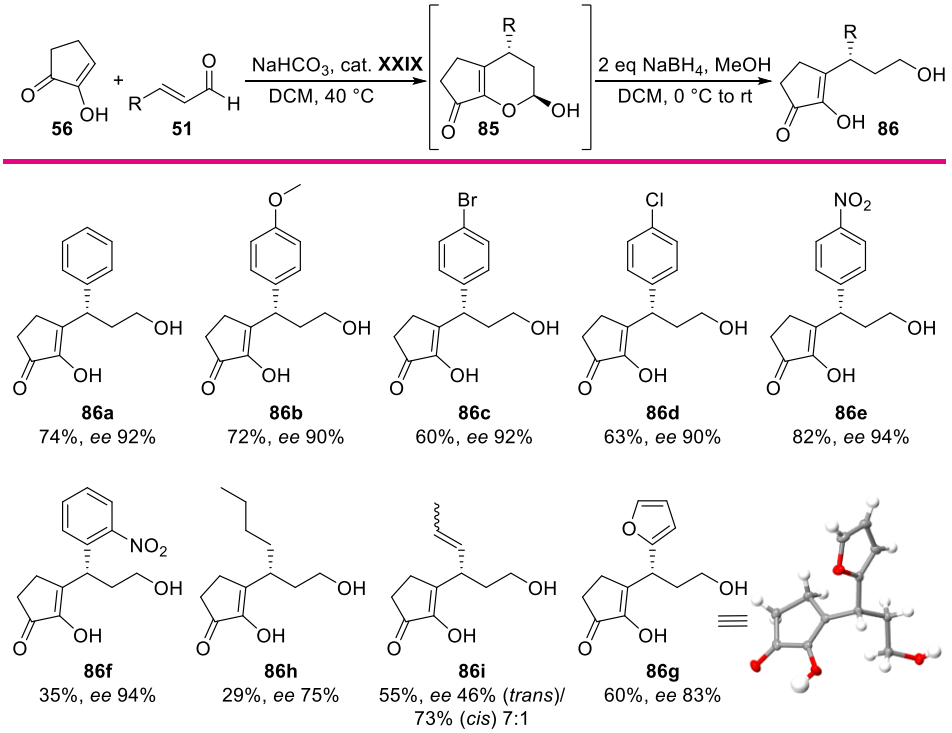
Scheme 34 *Scope of the Michael addition/cyclisation cascade*

The Michael addition was catalysed by diarylprolinol silyl ether **XXIX**. In the proposed catalytic cycle, the first step was iminium ion formation and the activation of the unsaturated carbonyl compound **51**. Then, the attack of cyclopentane-1,2-dione **56** occurred and, after the release of the catalyst, the formed aldehyde cyclised and formed the bicyclic hemiacetal **85** (Scheme 35).



Scheme 35 *Proposed catalytic cycle*

Generally, an acidic additive is utilised to accelerate the condensation step, but here a basic additive probably activated the nucleophile.[93] Therefore, additional screening of basic additives was done and the best results were obtained with $NaHCO_3$: 98% yield and *ee* >99% (see **Publication I**). With these conditions, we developed a one-pot procedure for the Michael addition/cyclisation cascade and the reduction of the formed products **85** (Scheme 36). The yields and *ee* values were not too much affected by electron-withdrawing or electron-donating substituents in the phenyl ring. High enantioselectivity was retained but the yields of the final products were very low in some cases, for example *p*-Br-substituted **86c** and *o*-NO_2-substituted **86f**. The cascade followed the same mechanism as before, and therefore the same absolute configurations were obtained, which was confirmed by the single crystal X-ray diffraction of **86g**.



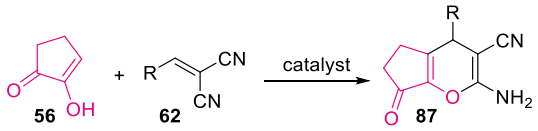
Reaction conditions: **56** (0.24 mmol), **51** (0.2 mmol), $NaHCO_3$ (0.02 mmol), catalyst **XXIX** (10 mol%), DCM (0.7 mL), MeOH (0.5 mL); isolated yields after column chromatography; *ee* determined by chiral HPLC.

Scheme 36 *Scope of the one-pot cascade and reduction*

In summary, an efficient method for the asymmetric organocatalytic synthesis of bicyclic hemiacetals **85** and 3-substituted cyclopentane-1,2-diones **86** was developed. Some of the products **86** were obtained with better yields than with the previous method which utilised cyclopentane-1,2-dione bis-silyl enol ether in a Mukaiyama-Michael reaction.[94] However, if we consider the overall low yield of the synthesis of bis-silyl enol ether of CPD, all of the obtained yields of **86** were improvements.

3.3 Reactions of CPD with alkylidene malononitriles (Publication II and unpublished results)

To further investigate the behaviour of CPD with other Michael acceptors, we studied the reaction between cyclopentane-1,2-dione **56** and alkylidene malononitriles **62** (Scheme 37). The products **87** of this Michael addition/cyclisation cascade are highly substituted 4*H*-pyrans, which have broad biological and pharmacological properties.[95,96]



Scheme 37 *Michael addition/cyclisation cascade of CPD with alkylidene malononitriles*

The chosen electrophile, benzylidene malononitrile **62a**, can be activated via a hydrogen bonding catalysis. Therefore, the selected samples were thioureas, a squaramide, two bulkier thioureas and a urea (Figure 5). In toluene (0.2 M) at room temperature, the Takemoto's catalyst **XXX** and the dihydroquinine derived squaramide **XXXII** displayed low enantioselectivity, 31% and 27% *ee* respectively. The enantiomeric excess was even lower when thiourea **XXXIV** with two alkaloid moieties was used, 13% *ee*. Although catalyst **XXXIII** provided the highest *ee*-value, 56%, the synthesis for it is quite time consuming, and therefore a quinine derived catalyst **XXVII** was considered most reasonable (in toluene at room temperature, 74% yield and *ee* 54%). Further solvent screening demonstrated the influence of the solvent on enantioselectivity: in THF the *ee* was 47% and in its greener alternative, 2-MeTHF, it was racemic. Additional optimisations of concentration and temperature led to the best results obtained with 10 mol% catalyst **XXVII** in toluene (0.02 M) at −20 °C (see **Publication II**).

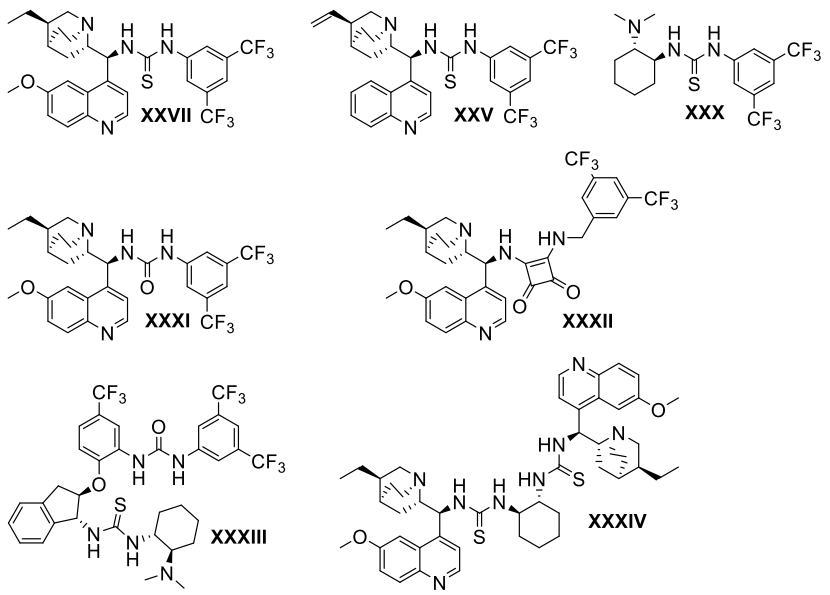
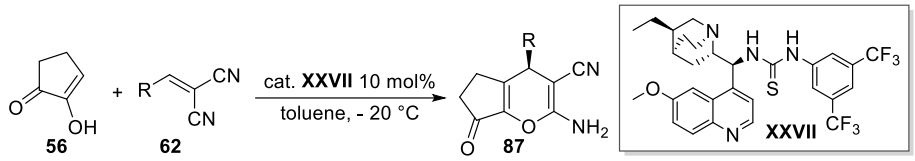
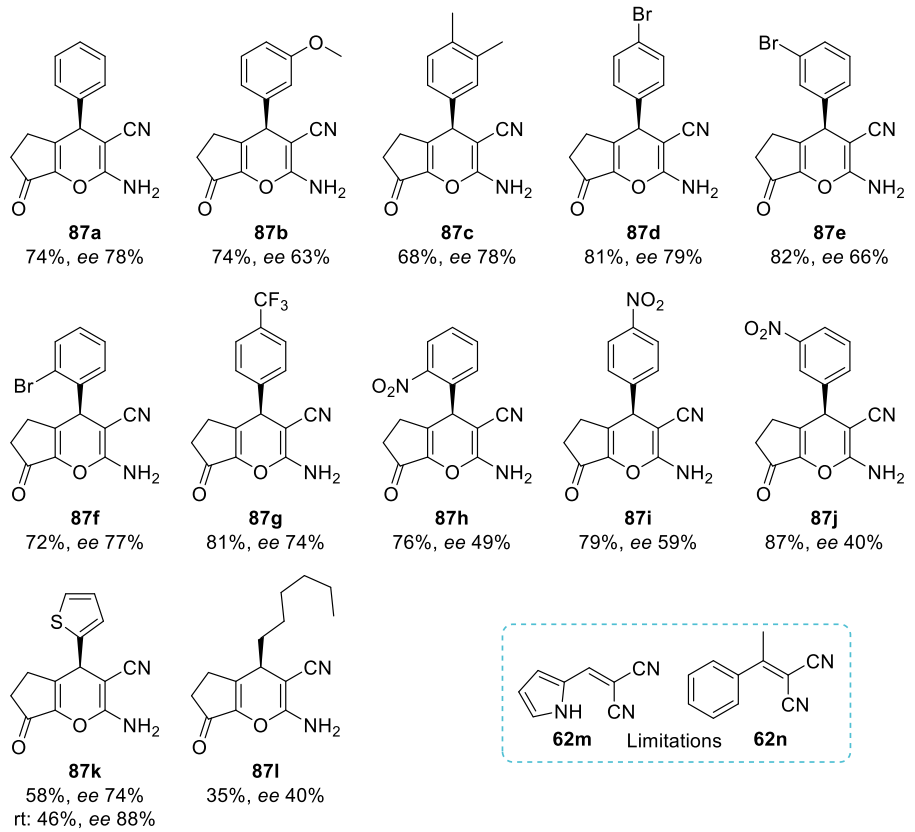


Figure 5 *Catalysts screened*

Having determined the optimal conditions, other malononitrile derivatives **62** were applied (Scheme 38). Overall, both electron-withdrawing (**87d-j**) and electron-donating groups (**87b**, **c**) were tolerated. However, the enantioselectivities with nitro-substituted benzylidene malononitriles **62h-j** were lower than average. Probably the nitro group competes in hydrogen bonding with the nitrile groups, therefore influencing the selectivity. Heteroaromatic **62k** and alkyl-substituted **62l** malononitriles also underwent cascade reactions smoothly. The reaction had some limitations in its scope: pyrrole-derived malononitrile **62m** was likely too electron-rich for the reaction to occur and the substituted double bond in **62n** was sterically too hindered. Comparing these results to those of cyclohexane-1,2-dione **71**[79] (Scheme 27), we can conclude that cyclopentane-1,2-dione **56** gives better yields and enantioselectivities in reaction with substituted malononitriles **62**. Additionally, the potential for racemisation of the product was explored and no racemisation took place (see **Publication II**).

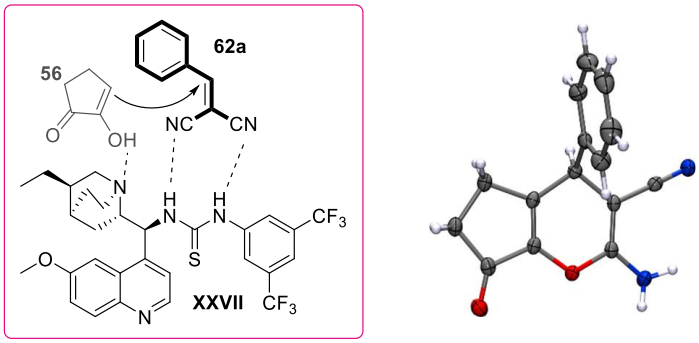




Reaction conditions: 0.02 M solution of **56** (1 eq), **62** (1.1 eq), catalyst **XXVII** (10 mol%), toluene, -20 °C; isolated yields after column chromatography, *ee* determined by chiral HPLC.

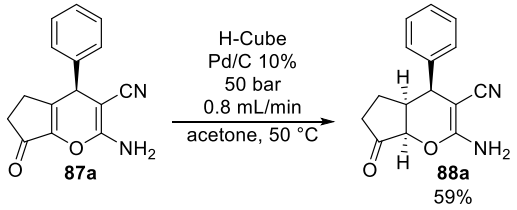
Scheme 38 *Scope of the Michael addition/cyclisation cascade*

It is believed that the thiourea catalyst activated both the nucleophile, CPD **56**, and the electrophile, benzylidene malononitrile **62a**. A reasonable transition state is shown in Scheme 39. The attack of CPD **56** came from the *Si*-face, and then after cyclisation and imine-enamine tautomerisation the product with *R*-configuration was formed. This is in accordance with the single-crystal X-ray diffraction data of compound **87a** and the products **87** were assigned by analogy.



Scheme 39 *The proposed transition state and the X-ray crystal structure of compound* ***87a***

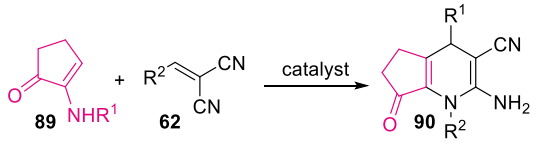
We demonstrated the synthetic utility of obtained pyrans **87** by reducing the compound **87a** in a continuous flow reactor in the presence of a Pd catalyst (Scheme 40). NOE experiments were used to confirm the *cis*-configuration of the main diastereomer **88a** (see **Publication II**, Supporting Information). Even in harsher conditions, the reduction of the enamine double bond did not occur, probably due to its low reactivity under those conditions.



Scheme 40 *The reduction of* ***87a***

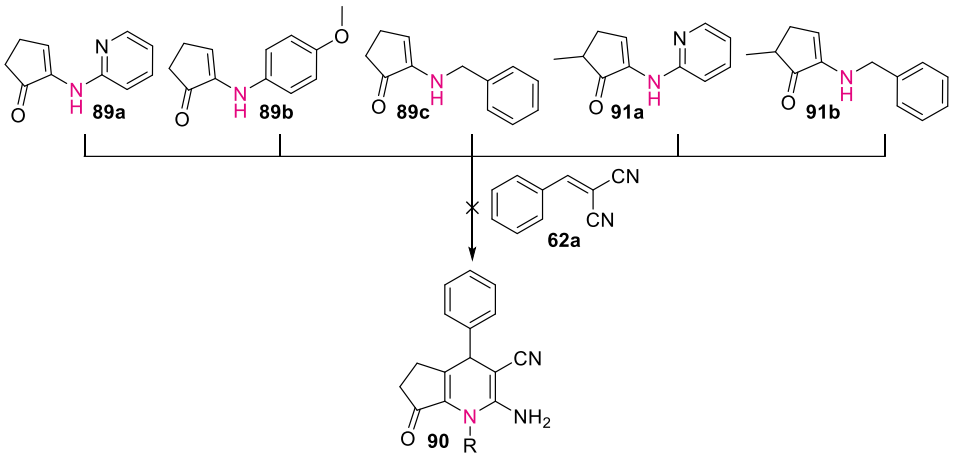
3.3.1 Synthesis of 1,4-dihydropyridines 90 from enamines (unpublished results)

Before starting this project, the initial idea was to synthesise 1,4-dihydropyridines **90** from enamines **89** of cyclopentane-1,2-dione and benzylidene malononitriles **62** (Scheme 41). 1,4-Dihydropyridines (1,4-DHP) have shown a broad range of pharmacological properties, although they were primarily developed for cardiovascular agents.[97] Their importance and application make them desirable target molecules.



Scheme 41 *Proposed synthesis of 1,4-DHPs*

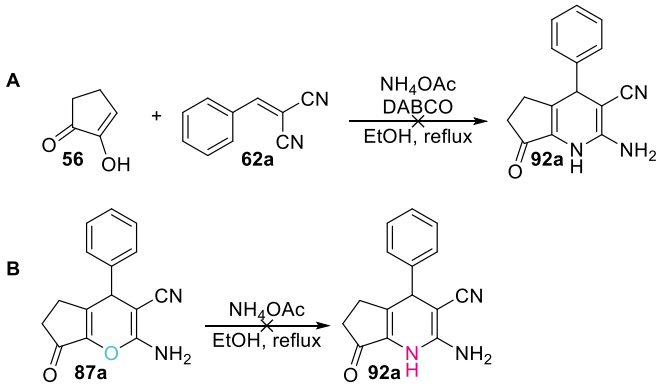
Different enamines **89** and **91** and benzylidene malononitrile **62a** were subjected to reactions with catalysts, such as DABCO, imidazole, quinine derived thiourea, achiral thiourea and cyclopropenimine (Scheme 42). Unfortunately none of these reactions were successful: mostly no reaction occurred. Other electrophiles were also tried, including nitrostyrene, cinnamaldehyde and methyl (*E*)-2-oxo-4-phenylbut-3-enoate, but none of these reacted with the enamine. The outcome is surprising considering the higher nucleophilicity of enamines compared to enols.



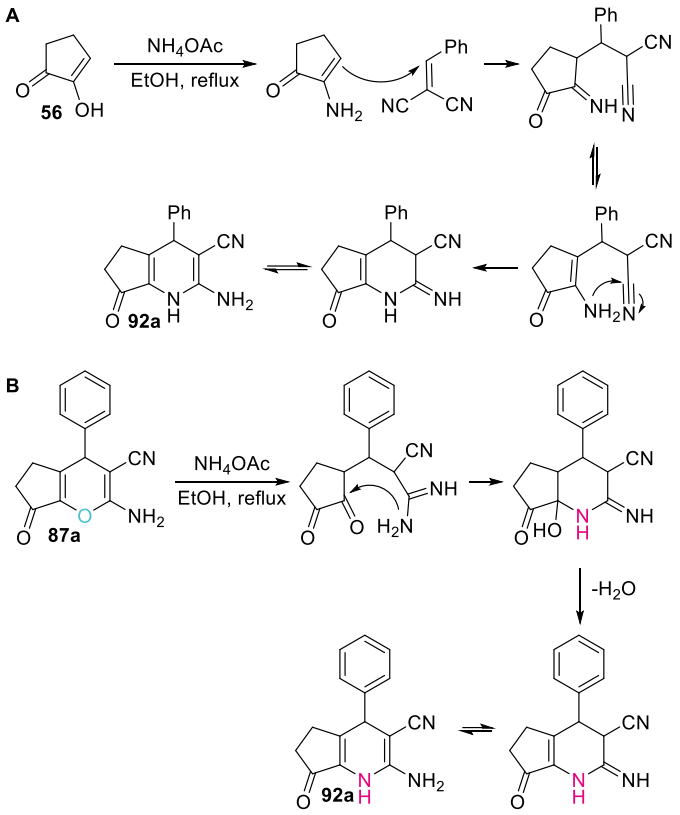
Scheme 42 *Unsuccessful attempts with enamines* ***89*** *and* ***91***

3.3.2 Synthesis of 1,4-dihydropyridines 92 (unpublished results)

Considering the previous unsuccessful reactions, a different strategy for the synthesis of dihydropyridines was applied. Carrying out the cascade reaction in the presence of an ammonium salt at an elevated temperature (Scheme 43, **A**) or refluxing the 4*H*-pyrans **87** in the presence of either ammonia or an ammonium salt (Scheme 43, **B**) should provide 1,4-dihydropyrdines **92**.[98,99,100] In reaction **A,** CPD **56** should first form the enamine, which then attacks the benzylidene malononitrile **62a**. Then, after intramolecular cyclisation and imine-enamine tautomerisation the 1,4-DHP is formed (Scheme 44, **A**). The reaction **B** is an ammonolysis reaction; the ammonium acetate decomposes upon heating to ammonia and acetic acid. Next, the ammonia attacks the pyran **87a**, and after water elimination and imine-enamine tautomerisation 1,4-DHP is formed. Unfortunately, these methods did not provide the 1,4-DHP; only the starting material pyran **87a** was retrieved.



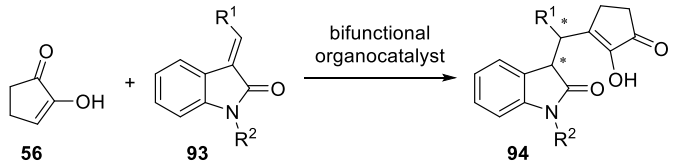
Scheme 43 *Unsuccessful synthesis of 1,4-DHPs*



Scheme 44 *Proposed reaction mechanisms for the synthesis of 1,4-DHPs*

3.4 Reactions of CPD with alkylidene oxindoles (Publication III)

The last electrophiles chosen to react with CPD **56** were alkylidene oxindoles **93**. The oxindole moiety is abundant in many bioactive molecules, as stated in Chapter 1.2, therefore making them very interesting compounds to investigate. Our group has previously developed several methods for the synthesis of spiro-[101,55,102,56] and 3,3-disubstituted oxindoles.[103,104] Herein, the behaviour of CPD **56** in the Michael addition to alkylidene oxindoles **93** was studied (Scheme 45).



Scheme 45 *Michael reaction of CPD with alkylidene oxindoles*

Preliminary experiments with unprotected benzylidene oxindole and cyclopentane-1,2-dione **56** in the presence of K_2CO_3 or dihydroquinine derived thiourea **XXVII** gave a complex reaction mixture. By protecting the oxindole nitrogen with a Boc-group, we managed to obtain the racemic product in 31% yield and to identify it properly. The asymmetric Michael addition of cyclopentane-1,2-dione **56** to *N*-protected oxindole

derivatives **93** was investigated in the presence of H-bonding catalysts. We believed that a bifunctional H-bonding catalyst could activate the CPD **56** through the tertiary amino group of the alkaloid moiety, and the oxindole **93** through the thiourea or squaramide moiety (Figure 6).

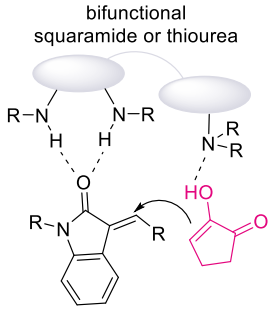


Figure 6 *Possible activation mode*

The addition reaction of CPD **56** to Boc-protected benzylidene oxindole **93a** with thiourea catalyst **XXVII** in chloroform was sluggish and the desired product was obtained as a mixture of chromatographically inseparable diastereomers in only 12% yield (see **Publication III**). What is more, the reaction did not occur at all with the achiral Schreiner's thiourea **XVIII**. Considering the necessity of the bifunctionality of the catalyst and the poor result of thiourea **XXVII**, squaramides were tested (Figure 7). The yield with quinidine-derived squaramide with phenyl-substituent **XXXV** was moderate and the enantioselectivity was low, 43%/27% (major/minor). Changing the aromatic substituent to a benzyl group (**VII**) increased the enantioselectivity to 80%/87%. Furthermore, cinchonine-derived squaramide **XXXVI** achieved the highest *ee*-values (85%/92%), and a subsequent solvent screening was performed using this catalyst. Chloroform turned out to be the most suitable solvent. In all cases, the yields were moderate (12-59%), and to improve them, the concentrations of the substrates were varied. With 2 equivalents of Boc-protected benzylidene oxindole **93a** and 1 equivalent of CPD **56** in chloroform in the presence of catalyst **XXXVI**, the highest yield (74%) and enantiomeric purity (90%/94%) were obtained. Decreasing the temperature to 0 °C increased the reaction time drastically, from 2h to 23h, and increased the enantioselectivity of the minor diastereomer only 3%; thus carrying out the reaction at room temperature was preferable.

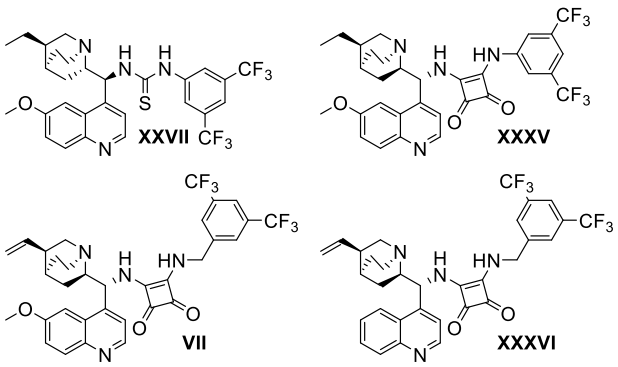
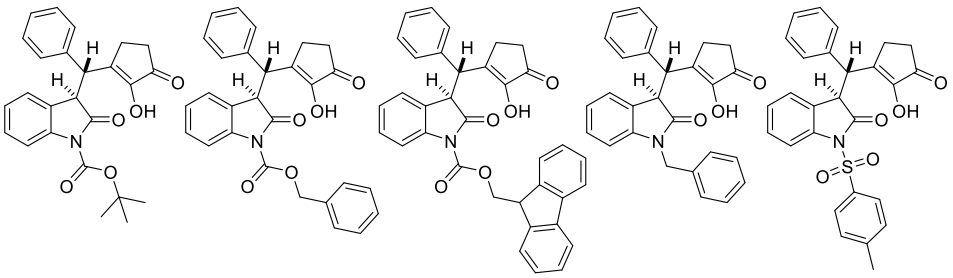


Figure 7 *Catalyst screened*

Next, the influence of the *N*-protecting group (PG) was investigated (Figure 8). Both Cbz **94b** and the sterically more demanding Fmoc **94c** PG slightly decreased the enantioselectivity. *N*-Benzyl-protected oxindole **93d** did not react with cyclopentane-1,2-dione **56** under these conditions at all, therefore product **94d** was not obtained. This must be because the carbonyl moiety in the *N*-protecting group and electron-withdrawing properties of the PG are necessary for the coordination of the catalyst. The reaction with tosyl-protected starting material **93e** was slow and the yield was low. All in all, the optimal conditions for this Michael addition are: 1 equivalent of **56**, 2 equivalents of Boc-protected **93**, in chloroform, at room temperature in the presence of 10 mol% of catalyst **XXXVI**.



94a
2 h, 75% yield
dr 2.6:1
ee 90%/94%

94b
2 h, 70% yield
dr 2.9:1
ee 82%/88%

94c
1 h, 52% yield
dr nd
ee 82%/82%

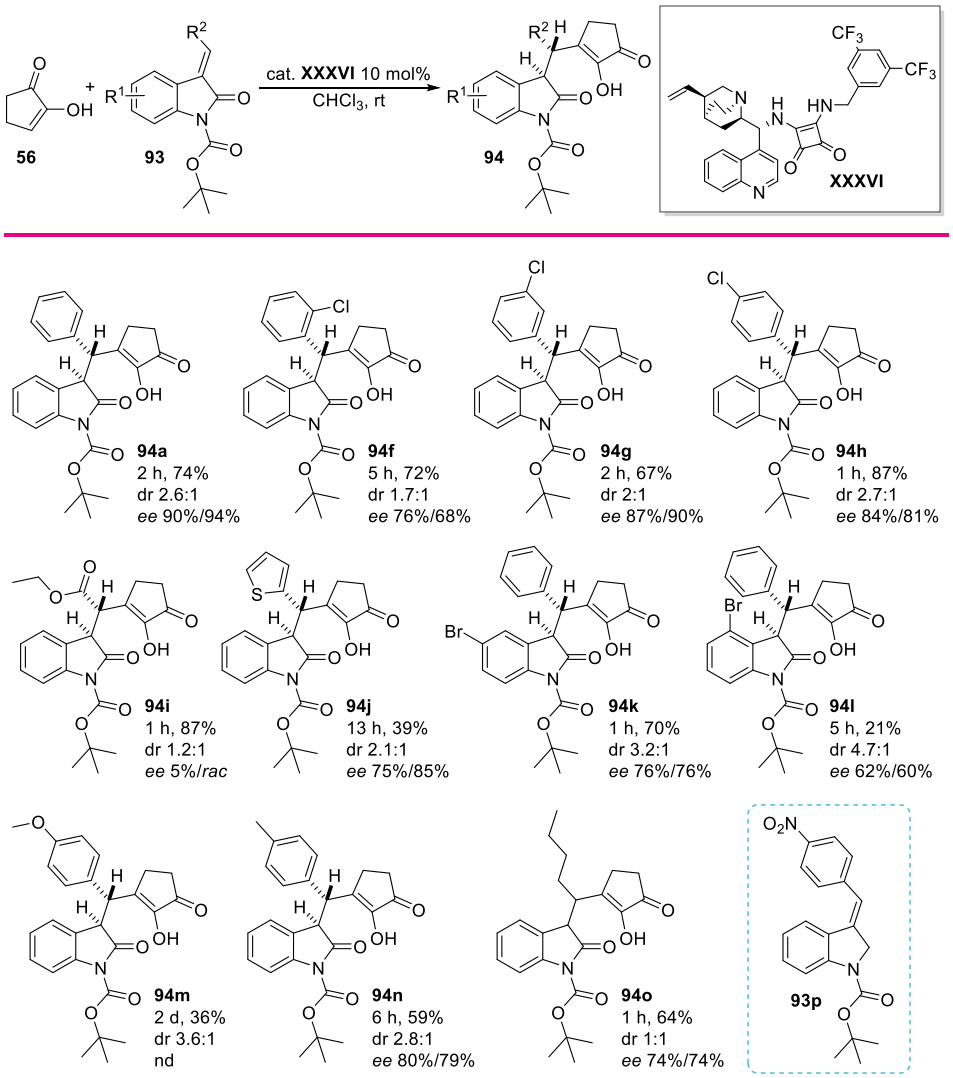
94d
no reaction

94e
1 d, 42% yield
dr 2.1:1
ee nd

Figure 8 *Influence of N-protecting groups*

After establishing the optimal conditions, the scope of the organocatalytic addition of CPD **56** to oxindole derivatives **93** was examined (Scheme 46). There was a minor influence of the position of the chloride in the aromatic ring. The reaction with *N*-Boc *o*-Cl-benzylidene oxindole **93f** was slower than with *m*- and *p*-Cl substrates, and the *ee* values for both the major and minor diastereomers were lower. The highest enantiomeric excess was achieved with the phenyl-substituted product **94a**. The adduct **94i** was obtained as a racemic mixture, which could have been due to the competing coordination moiety or the higher acidity of the C-H proton at the α-position of the ester moiety at the stereogenic centre that could have caused racemisation. The reaction with thiophenyl-substituted oxindole was very slow and provided the product **94j** in very low yield, 39%, and in moderate enantioselectivities of the diastereomers (75%/85%). The substitution in the oxindole core increased the diastereomeric ratio, especially when 4-Br oxindole **93l** was used, although the yield drastically decreased and because of the sterical hindrance the reaction proceeded more slowly. Unexpectedly, the addition to *N*-Boc *p*-OMe benzylidene malononitrile **93m** was very sluggish and the product **94m** was obtained in only 36% yield. Also, the reaction with *p*-Me-substituted starting material **93n** was slower than average, but the *ee* remained high. The reaction proceeded smoothly with alkylidene oxindole **93o**, even though the diastereomeric ratio was 1:1, which could mean that π-π interaction could also be important in the transition state. The reaction with *p*-NO_2 benzylidene oxindole **93p** did not occur, and the poor solubility of **93p** could have been responsible. Throughout the scope diastereoselectivities were moderate or were missing for the compounds with non-aromatic substituents (**94i**, **94o**). All of the products were obtained with *anti*-configurations of the vicinal diastereotopic hydrogens. This was determined by the comparison of the $^3J_{HH}$ coupling constants of the

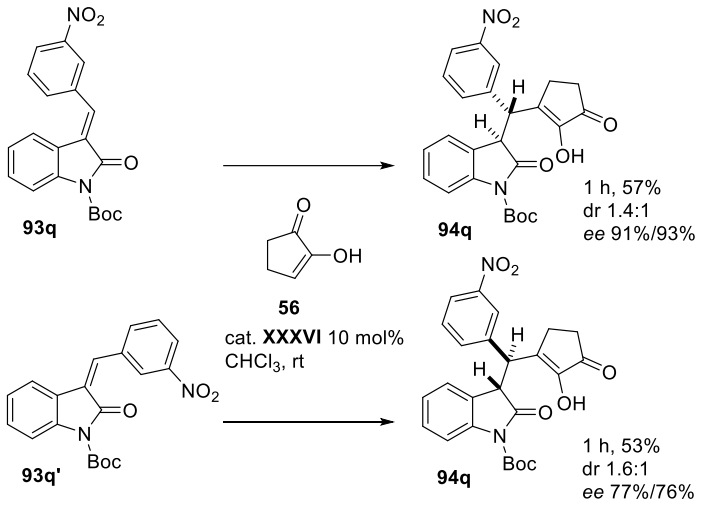
major (~9 Hz) and minor diastereomers (~5 Hz). Unfortunately, all of the attempts to crystallise the compounds **94** were unsuccessful and absolute configuration was not determined. Only relative configurations of major diastereomers are depicted in the Figures and Schemes.



Reaction conditions: 0.2 M solution of **56** (1 eq), **93** (2 eq), catalyst **XXXVI** (10 mol%), chloroform, rt; isolated yields after column chromatography, *ee* determined by chiral HPLC.

Scheme 46 *Scope of the Michael addition of CPD* ***56*** *to oxindoles* ***93***

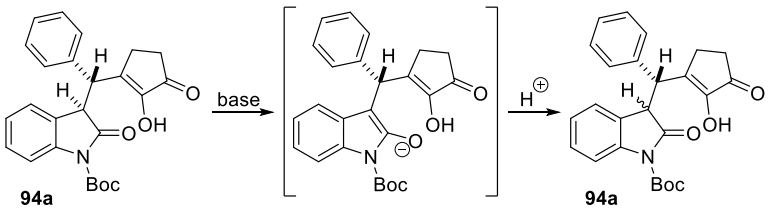
Only *E*-isomers were used in the investigation of the reaction scope. In the case of the 3-NO_2-substituted benzylidene oxindole **93q,** both *E*- and *Z*-isomers were tested. The change in the configuration of the double bond gave rise to an increase in the opposite enantiomer but provided the same *anti*-diastereomer (Scheme 47). The yields and diastereoselectivities were similar, although the enantioselectivity was lower when the *Z*-isomer was used.



Scheme 47 *Comparison of E- and Z-starting materials*

Overall, the diastereoselectivity of the reaction was low, and with the aim of increasing the ratio we considered enolisation followed by diastereoselective protonation.[105,106] The adjacent chiral centre could have potentially influenced the outcome of the protonation of the formed enolate. Since the racemate of **94a** had a higher diastereomeric ratio, both kinetic and thermodynamic conditions for its enolisation were applied. In both cases, the ratio decreased and, surprisingly, more of the *syn*-isomer was formed. The enantiomerically enriched **94a** behaved similarly and the dr ratio decreased.

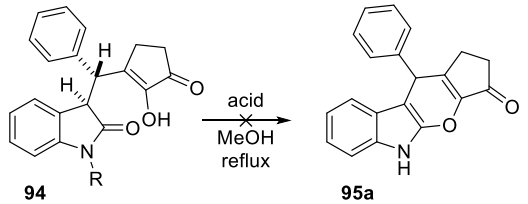
Table 2 *Epimerisation of* ***94a***



Entry	Starting compound	dr (*anti*:*syn*)	Conditions	Product dr (*anti*:*syn*)
1	**94a** (*rac*)	6.3:1	LDA, THF, -78 °C, 30 min, then sat. aq. NH_4Cl	2.7:1
2	**94a** (*rac*)	6.3:1	*t*-BuOK/*t*-BuOH, rt, overnight	2.6:1
3	**94a**	2.5:1	LiHDMS, THF, -78 °C, 30 min, then sat. aq. NH_4Cl	2.2:1

One of our objectives was to cyclise the products **94**, either as a cascade reaction or in a separate step. The used cascade reaction conditions did not produce a cyclic product, and therefore cyclisation as a separate step was investigated. It has been previously reported that substituted oxindoles can be transformed to indolopyrans in acidic

conditions.[107] Refluxing **94a** in methanol in the presence of acid only cleaved the Boc protecting group (which was expected), but no further cyclisation took place. No reaction occurred in the case of already deprotected starting compound (Scheme 48). The driving force in the reference 107 could have been the conjugation in the formed tricyclic product. In our case, there would be no conjugation in the formed product, which could explain why the reaction did not occur.



94 **95a**

R = Boc
acid: HCl, *p*TsOH

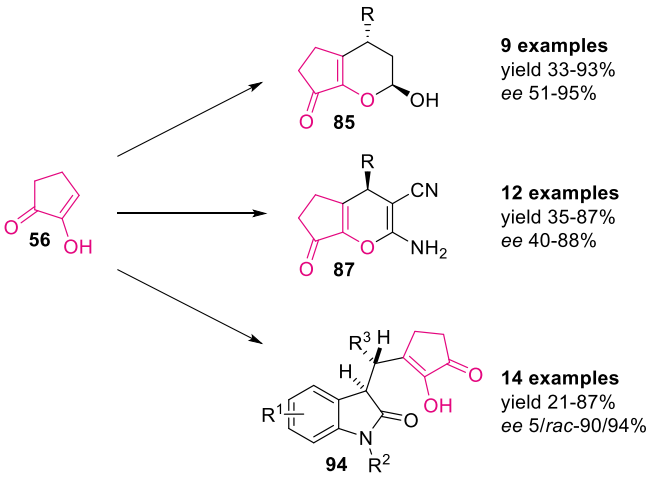
Scheme 48 *Cyclisation experiments of* ***94***

In conclusion, the asymmetric organocatalysed synthesis of various 3-substituted oxindoles **94** from cyclopentane-1,2-dione **56** has been described. The products **94** were obtained in high enantioselectivities and moderate diastereoselectivities. Unfortunately, the attempts to increase the diastereomeric ratio and cyclise the compounds **94** were unsuccessful.

4 Conclusions

In this study, three organocatalytic asymmetric reactions of cyclopentane-1,2-dione were described (Scheme 49).

- Cyclopentane-1,2-dione **56** was synthesised by the ozonolysis of an appropriate alkene **84** with an overall yield of 58%.
- The chemical potential of cyclopentane-1,2-dione **56** was investigated with different Michael acceptors. These contributed to the increase in the synthetic potential of cyclopentane-1,2-dione **56**.
    - Efficient methods for synthesising bicyclic hemiacetals **85** and 3-substituted cyclopentane-1,2-diones **86** were developed, using α,β-unsaturated aldehydes **51** and an aminocatalyst **XXIX**. The formed products were obtained in up to high yields (33-93%) and in good to excellent enantiopurities (51-95%).
    - An efficient cascade reaction for the synthesis of substituted 4*H*-pyrans **87** was developed, using alkylidene malononitriles **62** and a thiourea catalyst **XXVII** via H-bonding catalysis. The products were obtained in up to high yields (35-87%) and in moderate to good enantiopurities (40-88%).
    - An efficient method for the synthesis of 3-substituted cyclopentane-1,2-diones **94** with two adjacent stereocentres was developed, using alkylidene oxindoles **93** and a squaramide catalyst **XXXVI** via H-bonding catalysis. The products were obtained in low to high yields (21-87%), high enantioselectivities (21-87%) and moderate diastereoselectivities (1:1-4.7:1).
- The absolute configurations of compounds **85**, **86** and **87** and the relative configuration of compounds **94** were determined.



Scheme 49 *New asymmetric reactions of CPD*

5 Experimental

Full assignment of ^{1}H and ^{13}C chemical shifts were based on the 1D and 2D FT NMR spectra measured with a Bruker Avance III 400 MHz instrument. Residual solvent signals were used ($CDCl_3$ δ = 7.26 ^{1}H NMR, 77.2 ^{13}C NMR) as internal standards. The reactions were monitored by thin layer chromatography (TLC) with silica gel-coated aluminium plates (Merck 60 F254) and NMR. Purchased chemicals and solvents were used as received. EtOAc was distilled over phosphorous pentoxide. Petroleum ether has a boiling point of 40-60 °C.

2-(pyridin-2-ylamino)cyclopent-2-en-1-one 89a

In a round bottom flask, equipped with a condenser, cyclopentane-1,2-dione **56** (200 mg, 2 mmol), 2-aminopyridine (1 eq), activated neutral alumina (100 eq) and toluene (4 mL) is stirred and heated to reflux for 24 h. Upon reaction completion, alumina is removed by filtration and the residue is purified by column chromatography eluting with DCM:EtOAc (5% →10%) to afford the product **89a** 31 mg (9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.24 (1H, m), 7.75 (1H, t, *J* = 3.2 Hz), 7.56-7.48 (1H, m), 6.80-6.73 (2H, m), 6.70 (1H, d, *J* = 8.3 Hz), 2.72-2.68 (2H, m), 2.48-2.44 (2H, m). ^{13}C NMR (100 MHz,) δ 204.8, 154.4, 148.1, 138.3, 137.6, 133.3, 115.6, 110.8, 32.5, 24.7.

2-((4-methoxyphenyl)amino)cyclopent-2-en-1-one 89b

To a solution of cyclopentanone **56** (442 µL, 5 mmol) in toluene (25 mL) was added 2,2,6,6-tetramethylpiperidine (128 µL, 0.75 mmol), TFA (19 µL, 0.25 mmol) and *p*-anisidine (307 mg, 2.5 mmol) under argon atmosphere. Then the atmosphere was swapped for oxygen atmosphere and stirred for 4 h at 100 °C. The mixture is evaporated under reduced pressure to remove the solvent. The given residue was purified by column chromatography (PE:EtOAc 10% → 20%) affording the product **89b** 95 mg (19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-6.93 (m, 2H), 6.91-6.81 (m, 2H), 6.59 (t, *J* = 3.3. Hz, 1H), 6.01 (br. s, 1H), 3.79 (s, 3H), 2.68-2.54 (m, 2H), 2.54-2.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 154.5, 141.2, 135.4, 123.1, 118.9, 114.8, 55.8, 32.8, 23.9.

1-(benzylamino)cyclopent-2-en-1-one 89c

To a solution of cyclopentane-1,2-dione **56** (100 mg, 1 eq) and *p*-toluenesulfonic acid monohydrate (0.2 eq) in toluene (5 mL) equipped with Dean-Stark apparatus was added benzylamine (1.2 eq). After 20 minutes the diketone was consumed according to the TLC plate. The reaction mixture was concentrated and purified by column chromatography eluting with DMC:EtOAc (10%) to afford the product **89c** 95 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (5H, m), 5.9 (1H, t, *J* = 3.1 Hz), 4.2 (2H, s), 2.51-2.45 (2H, m), 2.44-2.39 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 146.1, 138.6, 128.6, 127.4, 127.3, 122.1, 48.6, 33.6, 23.6.

5-methyl-2-(pyridin-2-ylamino)cyclopent-2-en-1-one 91a

In a round bottom flask, equipped with a condenser, 2-methylcyclopentane-1,2-dione (1 g, 10.2 mmol), 2-aminopyridine (1 eq), activated neutral alumina (100 eq) and toluene (20 mL) is stirred and heated to reflux for 43 h. Upon reaction completion, alumina is removed by filtration and the residue is purified by column chromatography eluting with DCM:EtOAc (5% →10%) to afford the product **91a** 681 mg (37%). The NMR data is in agreement with the literature.[108]

2-(benzylamino)-5-methylcyclopent-2-en-1-one 91b

To a solution of 3-methylcyclopentane-1,2-dione (500 mg, 1 eq) and *p*-toluenesulfonic acid monohydrate (0.2 eq) in DCM was added 1.2 g of molecular sieves 3Å powder. This mixture stirred for 30 minutes and then benzylamine (1.2 eq) was added. The solvent was exchanged to toluene and Dean-Stark apparatus was installed. The reaction stirred in reflux for 3 h, after that at room temperature for 2 days. When starting material was consumed, the powdered sieves were removed by filtration and the residue was purified by column chromatography eluting with DCM:EtOAc (0% →10%) to afford the product **91b** 577 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (5H, m), 5.78 (1H, t, *J* = 3.2 Hz), 4.15 (2H, s), 2.69 (1H, ddd, *J* = 17.6, 6.3, 3.3 Hz), 2.43-2.30 (1H, m), 2.01 (1H, ddd, *J* = 17.6, 3.1, 2.1 Hz), 1.14 (3H, d, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 145.1, 138.7, 128.6, 127.4, 120.5, 48.6, 39.1, 33.0, 16.5.

Table 3 *Supporting information concerning compounds discussed in the thesis but not presented in the Experimental section can be found in the corresponding publications.*

Entry	Compound number in thesis	Compound number in publication		
		I	**II**	**III**
1	**I**	**4a**		
2	**VII**			**C**
3	**IX**	**4c**		
4	**XII**	**4b**		
5	**XXV**		**F**	
6	**XXVII**		**A**	**B**
7	**XXVIII**	**4d**		
8	**XXIX**	**4e**		
9	**XXX**		**B**	
10	**XXXI**		**G**	
11	**XXXII**		**C**	
12	**XXXIII**		**D**	
13	**XXXIV**		**E**	
14	**XXXV**			**A**
15	**XXXVI**			**D**
16	**51a**	**2a**		
17	**51b**	**2b**		
18	**51c**	**2c**		
19	**51d**	**2d**		
20	**51e**	**2e**		
21	**51f**	**2f**		
22	**51g**	**2g**		
23	**51h**	**2h**		
24	**51i**	**2i**		
25	**56**	**1**	**1**	**1**
26	**62a**		**2a**	
27	**62b**		**2b**	
28	**62c**		**2c**	
29	**62d**		**2d**	

30	**62e**		**2e**	
31	**62f**		**2f**	
32	**62g**		**2g**	
33	**62h**		**2h**	
34	**62i**		**2i**	
35	**62j**		**2j**	
36	**62k**		**2k**	
37	**62l**		**2l**	
38	**62m**		**2m**	
39	**62n**		**2n**	
40	**85a**	**3a**		
41	**85b**	**3b**		
42	**85c**	**3d**		
43	**85d**	**3c**		
44	**85e**	**3e**		
45	**85f**	**3f**		
46	**85g**	**3g**		
47	**85h**	**3h**		
48	**85i**	**3i**		
49	**86a**	**5a**		
50	**86b**	**5b**		
51	**86c**	**5d**		
52	**86d**	**5c**		
53	**86e**	**5e**		
54	**86f**	**5f**		
55	**86g**	**5g**		
56	**86h**	**5h**		
57	**86i**	**5i**		
58	**87a**		**3a**	
59	**87b**		**3b**	
60	**87c**		**3c**	
61	**87d**		**3d**	
62	**87e**		**3e**	
63	**87f**		**3f**	
64	**87g**		**3g**	
65	**87h**		**3h**	
66	**87i**		**3i**	
67	**87j**		**3j**	
68	**87k**		**3k**	
69	**87l**		**3l**	
70	**88a**		**4a**	
71	**93a**			**2a**
72	**93b**			**2b**
73	**93c**			**2c**
74	**93d**			**2d**
75	**93e**			**2e**

76	**93f**			**2f**
77	**93g**			**2g**
78	**93h**			**2h**
79	**93i**			**2i**
80	**93j**			**2j**
81	**93k**			**2k**
82	**93l**			**2l**
83	**93m**			**2m**
84	**93n**			**2n**
85	**93o**			**2o**
86	**93p**			**2p**
87	**93q**			**2q**
88	**93q'**			**2q'**
89	**94a**			**3a**
90	**94b**			**3b**
91	**94c**			**3c**
92	**94e**			**3e**
93	**94f**			**3f**
94	**94g**			**3g**
95	**94h**			**3h**
96	**94i**			**3i**
97	**94j**			**3j**
98	**94k**			**3k**
99	**94l**			**3l**
100	**94m**			**3m**
101	**94n**			**3n**
102	**94o**			**3o**
103	**94q**			**3q**

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I would like to thank Professor Lopp for the fascinating lectures that eventually led me to the fourth floor of the science building. I joined his lab in the first year of my bachelor studies, under the supervision of Dr. Gert Preegel. I still remember (although vaguely) that my first task was to synthesise cyclopentane-1,2-dione starting from Claisen and then Dieckmann condensations. I am very appreciative of the knowledge I gained throughout those years!

I am extremely grateful to my supervisor, Professor Tõnis Kanger, for taking me under his wing after a year and a half-long failed project at the start of my doctoral studies. He was very eager to keep me motivated and we both had the same objective in mind: to defend the thesis as soon as possible. I also would like to thank Dr. Dzmitry Kananovich for reviewing my thesis.

I had the great pleasure of working with all of the colleagues on the fourth floor and I wish all the best to the next "orderer of reagents". I certainly cherish all of the friends that I have made during my studies. Thank you Anna for the memories, Aleksandra for always being there for me, Kaarel for making us laugh, Mikk for the boardgame nights (which still continue even when he is in Denmark) and endless book recommendations, Dmitri for the positivity, Mariliis for the competitive (and contagious) spirit in Ligretto, Anni for the interesting talks and Kristin for her support in everything. Of course it goes without saying that I am thankful for all of the chemistry related advice from all of them. I also would like to thank Dr. Sandra Kaabel for the X-ray analysis of the crystal structures and Jevgenija for the attempts that were unfortunately unsuccessful.

I am thankful to my parents, sister and Silver, who encouraged me to study and not to worry about the future. I love the fact that Silver would discuss different problems with me and wanted to know more even though the subject was far from his speciality.

Abstract
Asymmetric Organocatalytic Reactions of Cyclopentane-1,2-dione

Starting with the pioneering works of List and MacMillan in 2000, asymmetric organocatalysis has grown tremendously. Synthesising new chiral molecules has become an interesting and important challenge to pursue, particularly in medicinal chemistry. One of the methods to construct a carbon-carbon bond enantioselectively is a Michael reaction, where asymmetric organocatalysis can be applied.

In general, diketones are versatile starting materials in organic synthesis. However, the number of examples using cyclopentane-1,2-dione (CPD) as a starting compound for synthesising more complex molecules are limited. Hence, the aim of this work is to expand the possibilities of CPD utilisation.

Three different electrophiles were chosen to investigate their reactions with CPD. Depending on the characteristics of the substrates either aminocatalysis or hydrogen bonding catalysis was applied. To start with, a diarylprolinol silyl ether catalysed Michael addition/cyclisation cascade reaction of CPD with α,β-unsaturated aldehydes was investigated. Different aldehyde substrates were tolerated and substituted 3,4-dihydropyrans were obtained in moderate to high yields (33-93%) and enantiomeric purities (*ee* 51-95%). Also, a one-pot procedure for the cascade cyclization and reduction of the formed enantioenriched aldehyde intermediate was developed. 3-Substituted cyclopentane-1,2-diones were obtained in better yields than those of the previous method in the literature.

Then, the Michael addition/cyclisation cascade of CPD to alkylidene malononitriles was studied. The cascade was catalysed by a dihydroquinine derived thiourea and provided 4*H*-pyrans in moderate yields (35-87%) and *ee*-values (*ee* 40-88%). The enantioselectivity decreased in the presence of nitro group acting as a competitive hydrogen bond acceptor (*ee* 40-59%). The pyran moiety is often found in important biological molecules, and therefore the new synthesized pyrans could also possess interesting biological properties.

Finally, we developed an asymmetric Michael addition of CPD to alkylidene oxindoles in the presence of a bifunctional squaramide catalyst. The adducts have two adjacent stereocentres, but unfortunately the diastereomeric ratio was generally low (1:1-4.7:1). However, the enantioselectivities were moderate to high (62%/60%-90%/94%), except for one instance where almost a racemic compound was obtained, likely due to additional catalyst coordinating moiety in the substrate or racemisation of the product.

In conclusion, this work broadens the scope of the asymmetric organocatalytic reactions of cyclopentane-1,2-dione and provides new methods for synthesising different substituted enantioenriched pyrans and 3-substituted cyclopentane-1,2-diones.

Lühikokkuvõte
Tsüklopentaan-1,2-diooni asümmeetrilised organokatalüütilised reaktsioonid

Organokatalüüs on viimase paarikümne aasta jooksul kiiresti arenenud. Seda suuresti tänu teedrajavatele keemikutele, Benjamin Listile ja David MacMillanile, kes 2000. aastal avaldasid kaks asümmeetrilise organokatalüüsi jaoks olulist publikatsiooni. Uute kiraalsete molekulide sünteesist on saanud huvipakkuv ja vajalik väljakutse, eriti meditsiinilises keemias. Michaeli liitumine on üks efektiivsetest meetoditest, mis võimaldab luua süsinik-süsinik sidet, samuti saab selles reaktsioonis rakendada asümmeetrilist organokatalüüsi ning selle abil sünteesida kiraalseid ühendeid.

Diketoone, nii lineaarseid kui ka tsüklilisi, saab orgaanilises sünteesis kasutada paljude erinevate ühendite sünteesiks. Sellegipoolest on tsüklopentaan-1,2-diooni (TPD) rakendamisest vähe näited. Sellest tulenevalt on selle töö eesmärgiks laiendada TPD kasutust.

Valiti välja kolm erinevat elektrofiili, et uurida nende reaktsiooni TPD-ga. Vastavalt substraatide omadustele kasutati kas aminokatalüüsi- või vesiniksideme katalüüsi. Kõigepealt uuriti diarüülprolinoolsilüüleetri katalüüsitud Michaeli liitumise/tsükliseerimise kaskaadi TPD ja α,β-küllastumata aldehüüdidega. Reaktsioonis kasutati erinevaid asendatud aldehüüde ning tulemusena saadi asendatud 3,4-dihüdropüraanid mõõdukate kuni kõrgete saagistega (33-93%) ja enantiomeersete puhtustega (51-95%). Lisaks sellele, viidi nii kaskaadreaktsioon kui taandamine läbi "ühe-kolvi" reaktsioonina. Sünteesitud 3-asendatud tsüklopentaan-1,2-dioonide saagised paranesid võrreldes eelnevalt kirjanduses leiduva meetodiga.

Seejärel uuriti dihüdrokiniinipõhise tiokarbamiidi katalüüsitud Michaeli liitumise/tsükliseerimise kaskaadi TPD ja alkülideenmalononitriilidega. 4*H*-püraanid sünteesiti keskmiste saagiste (35-87%) ja *ee*-väärtustega (*ee* 40-88%). Kui substraat sisaldas nitrorühma, siis see avaldas mõju enantioselektiivsusele (*ee* 40-59%), sest nimetatud funktsionaalrühm on konkureeriv vesiniksidemete aktseptor. Tänu püraani tsükli sisaldumisele mitmetes bioloogiliselt tähtsates molekulides, on ka uued sünteesitud püraanid huvipakkuvad vaheühendid nii meditsiinilises keemias kui ka orgaanilises sünteesis.

Järgnevalt töötati välja TPD asümmeetriline Michaeli liitumine alkülideenoksindoolidele, mida katalüüsiti bifunktsionaalse skvaaramiidiga. Produktidel on kaks kõrvutiasetsevat stereogeenset tsentrit, kuid kahjuks oli tekkinud diastereomeeride suhe üldiselt väike (1:1-4.7:1). Sellegipoolest saadi produktid suhteliselt kõrge enantiomeerse puhtusega (62%/60-90%/94%). Erandiks olid esterrühma ja happelist prootonit sisaldavad produkt, mis viisid reaktsiooni enantioselektiivsuse langemiseni (*ee* 5%/*rac*).

Antud doktoritöö laiendab tsüklopentaan-1,2-diooni asümmeetriliste organokatalüütiliste reaktsioonide valimit ja pakub uusi meetodeid erinevate enantiomeerselt rikastatud püraanide ja 3-asendatud tsüklopentaan-1,2-dioonide sünteesiks.

Appendix 1

Publication I

Preegel, G.; Silm, E.; Kaabel, S.; Järving, I.; Rissanen, K.; Lopp, M. Asymmetric Organocatalytic Michael Addition-Cyclization Cascade of Cyclopentane-1,2-dione with Substituted α,β-Unsaturated Aldehydes. *Synthesis* **2017**, *49*, 3118-3125.

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Synthesis G. Preegel et al. Paper

Asymmetric Organocatalytic Michael Addition–Cyclization Cascade of Cyclopentane-1,2-dione with Substituted α,β-Unsaturated Aldehydes

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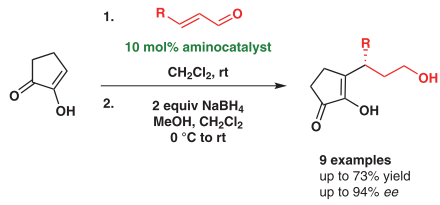

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Abstract An asymmetric organocatalytic Michael addition–cyclization cascade reaction has been developed using cyclopentane-1,2-dione as a Michael donor and α,β-unsaturated aldehydes as Michael acceptors. Bicyclic hemiacetals were obtained in excellent yields and enantioselectivities. On the basis of the results, a one-pot reaction has been developed to obtain chiral 3-substituted cyclopentane-1,2-diones and substituted dihydropyrans in good yields and excellent enantioselectivity.

Key words organocatalysis, asymmetry, diketones, dihydropyran, Michael addition

At the present time, chemical synthesis is directed at sustainability, looking for cleaner and more effective reactions to get compounds of interest. In the biomass conversion discipline, one of the conversions that has been somehow neglected is selective conversion of biomass via 5-HMF to cyclopentanone and cyclopent-2-en-1-one.[1] Both of these compounds can be easily converted into cyclopentane-1,2-diones (**1**).[2] These are compounds of many uses, including as precursors with the means to increase the heating value of conventional bio-jet fuels.[3] Also derivatives of cyclopentane-1,2-dione can be used as flavoring agents.[4] We have used these molecules as starting materials/platform molecules for making new high value-added fine chemicals, such as nucleoside analogues[5] and several bioactive natural compounds[6] and their analogues.[7] On the other hand, aminocatalysis has been an important research topic for 10 years, providing the most widely used organocatalysts in the field.[8]

We have previously shown that a Mukaiyama–Michael addition reaction of cyclopentane-1,2-dione dienol silyl ethers proceeds in an organocatalytic way with α,β-unsaturated aldehydes.[9] The preparation of the intermediate cyclopentane-1,2-dione dienol silyl ethers, however, is a laborious and complicated procedure, making the overall yield of the substituted chiral product low, although the addition reaction proceeds in excellent enantioselectivity (Scheme 1, path C).[9] We have also shown previously that α-alkylation of cyclopentane-1,2-diones in an organocatalytic manner can be carried out with β,γ-unsaturated-α-keto esters and with nitroolefins (Scheme 1, paths A and B).[10,11] Several other organocatalytic reactions of cyclic diketones with excellent stereoselectivity have also been investigated: Rueping carried out two cascade reactions with cyclohexane-1,2-dione and cyclohexane-1,3-dione, giving bicyclic product in up to excellent yields and enantioselectivity (Scheme 1, paths D and E);[12] Jørgensen's group has also shown that cyclopentane-1,3-diones undergo a cascade reaction with α,β-unsaturated aldehydes, giving bicyclic product in excellent yields and stereoselectivity (Scheme 1, path F).[13] Here we present the results of using α,β-unsaturated aldehydes as electrophiles in a direct reaction with cyclopentane-1,2-dione.

We started with cyclopentane-1,2-dione (**1**) and *trans*-cinnamaldehyde (**2a**) with L-proline (**4a**) as the aminocatalyst in ethanol and obtained hemiacetal **3a** in very low yield (6.5%) and with low enantioselectivity (16%; Table 1, entry 1). By using bulkier aminocatalysts, better yields and enantioselectivities were obtained (Table 1, entries 2–5). The best result was achieved with the bulkiest catalyst, **4e**, giving 83% yield and 85% ee (Table 1, entry 5). The opposite enantiomer was also obtained with a catalyst derived from D-proline (Table 1, entry 4).

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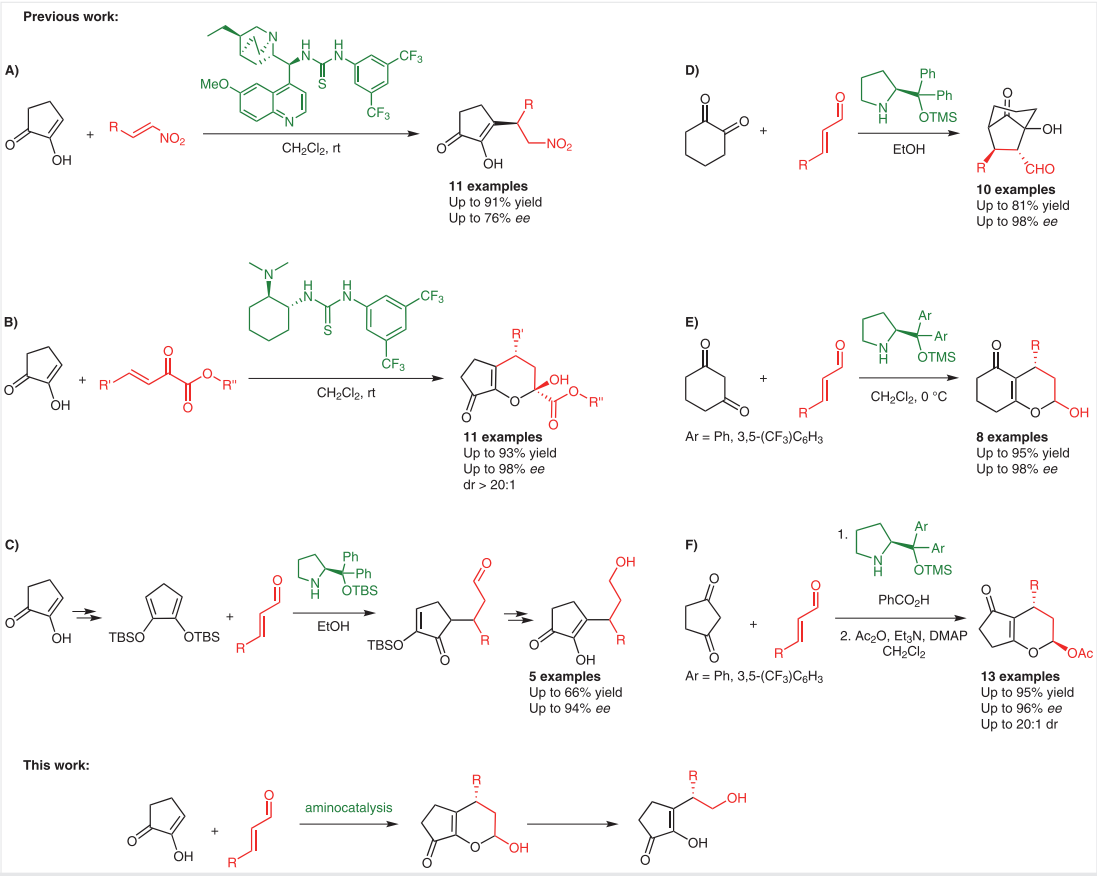
In a search for an optimal solvent for the reaction, different polar and non-polar solvents were screened. The results are presented in Table 2. We found that the halogen-containing solvents gave the best stereoselectivity. In chloroform, the reaction was complete in 2 hours, giving a good yield (76%) and with excellent enantioselectivity (98% ee; Table 2, entry 5). In 1,2-dichloroethane, similar results were obtained after 6 hours of reaction (72% yield and 96% ee; Table 2, entry 6). The best result was obtained with dichloromethane, affording an excellent yield (93%) and enantioselectivity (95% ee; Table 2, entry 7) in a fast reaction (after 2 h).

Using these optimal conditions the scope of the reaction with different aldehydes was investigated. As seen in Scheme 2, the reaction tolerates different α,β-unsaturated aldehydes with various electronic densities. Electron-donating and -withdrawing groups at the aromatic ring both gave good to excellent yields and enantioselectivities (**3b** and **3e**). Also, a heteroaromatic ring was tolerated, giving product **3g** in 68% yield and 81% ee. Furthermore, an alkyl α,β-unsaturated aldehyde can also be used in the reaction, affording **3h** with good enantioselectivity (86% ee), although with low yield (33% only). Finally, hexa-2,4-dienal (**2i**) resulted in a 1,4-addition reaction only, giving **3i** in an average yield 65% and enantioselectivity 51% ee. As the used starting material **2i** was a 1:7 mixture of *cis*- and *trans*-isomers, the product obtained was also a 1:7 mixture of *cis*/*trans* isomers.

The absolute configuration of compound **3c** was determined by a single-crystal X-ray diffraction to be (2*S*,4*S*) (Figure 1) and the absolute configurations of compounds **3** were assigned by analogy.

As excellent yields were obtained only in some cases with *trans*-cinnamaldehydes, additional screening of possible basic additives, with the usual co-catalyst enhancing



Scheme 1 Previous and proposed work on cyclic diketones

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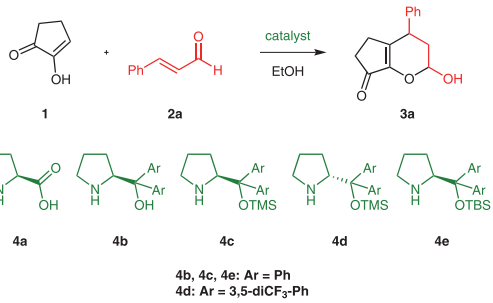
Table 1 Screening of Organocatalysts[a]

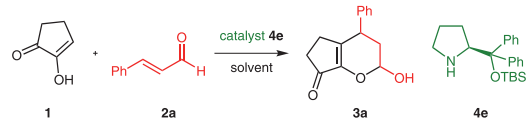


4b, 4c, 4e: Ar = Ph
4d: Ar = 3,5-diCF$_3$-Ph

Entry	Catalyst (10 mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**4a**	18	6.5	16
2	**4b**	24	61	21
3	**4c**	1.5	59	79
4	**4d**	24	20	70[d]
5	**4e**	18	83	85

[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), catalyst **4** (0.02 mmol), EtOH (0.7 mL), r.t.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC.
[d] Opposite enantiomer formed.

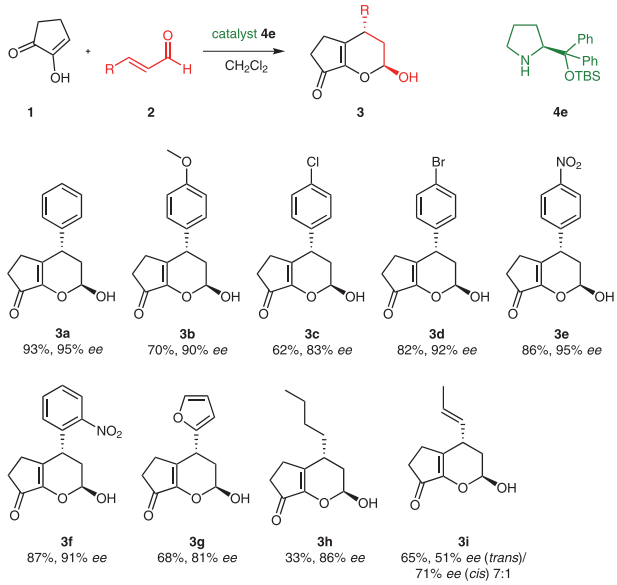
Table 2 Screening of Solvents[a]



Entry	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	EtOH	18	83	85
2	MeOH	24	74	88
3	THF	24	72	96
4	toluene	5	83	97
5	$CHCl_3$	2	76	98
6	$C_2H_4Cl_2$	6	72	96
7	CH_2Cl_2	2	93	95

[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), catalyst **4e** (0.02 mmol), solvent (0.7 mL), r.t.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC.

the condensation of aminocatalyst to aldehyde, was performed. It was found (see Table 3) that the best additive was $NaHCO_3$, leading to perfect yield (98%) and outstanding enantioselectivity (>99% ee) of the reaction (Table 3, entry 6).



Scheme 2 Scope of the reaction. *Reagents and conditions*: **1** (0.24 mmol), **2** (0.2 mmol), catalyst **4e** (0.02 mmol), CH_2Cl_2 (0.7 mL), r.t.; isolated yields after column chromatography, the major diastereomer is presented; ee determined by chiral HPLC.

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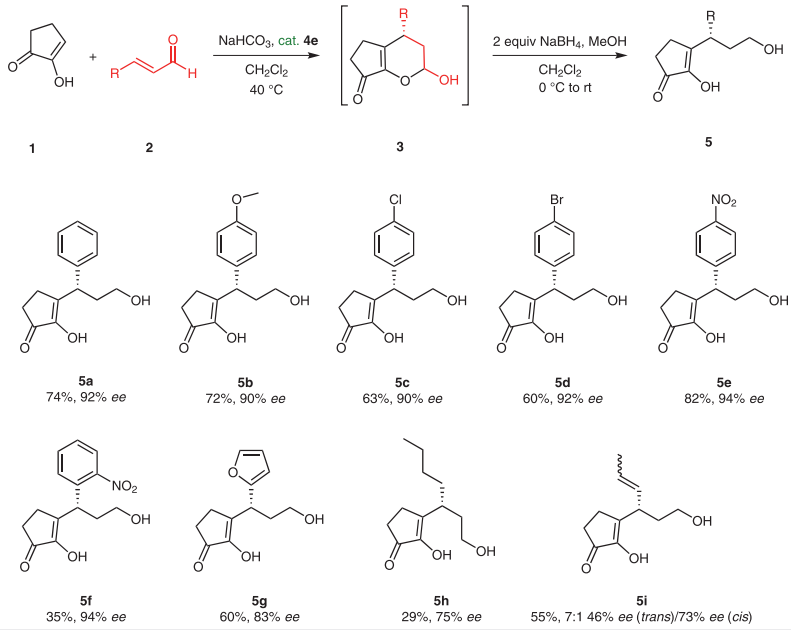


Scheme 3 One-pot reaction in the synthesis of chiral 3-substituted cyclopentane-1,2-diones **5**. *Reagents and conditions*: **1** (0.24 mmol); **2** (0.2 mmol), $NaHCO_3$ (0.02 mmol), catalyst **4e** (0.02 mmol), CH_2Cl_2 (0.7 mL), r.t.; isolated yields after column chromatography, ee determined by chiral HPLC.

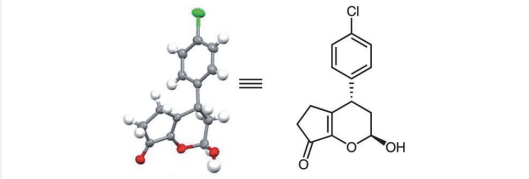
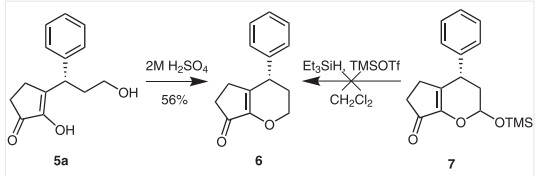


Figure 1 X-ray crystal structure (see Supporting Information for details) and the absolute configuration of **3c**



Scheme 4 Transformation to dihydropyran

With these optimum conditions (solvent CH_2Cl_2, catalyst **4e**, and additive $NaHCO_3$), we developed a one-pot procedure for the reaction sequence: Michael addition, cyclization reaction and reduction of the formed aldehyde with $NaBH_4$. This cascade of reactions resulted in a single product **5** (Scheme 3).

All of the used substrates gave excellent enantioselectivities, with good to satisfactory overall yields. We made an attempt to reduce acetal **7** directly to the dihydropyran according to Oshima et al.[14] but without success. Instead, the cyclization of enol **5** proceeded easily in the presence of a strong acid, yielding dihydropyran **6** in 56% yield (not optimized) (Scheme 4).

In conclusion, a novel efficient method of making bicyclic hemiacetals **3a–i** and 3-substituted cyclopentane-1,2-diones **5a–i** has been developed, giving good yields and excellent enantioselectivities. The method may be used for the synthesis of a wide variety of substituted dihydropyrans **6**.

Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent peaks ($CHCl_3/CDCl_3$, δ = 7.26/77.2) or TMS (δ = 0.00) were used as chemical shift references. Chiral HPLC was performed using Phenomenex Lux® 3µm amylose-2, Chiralcel OD-H, and Chiralpak AS-H and OJ-H columns. Mass spectra were recorded by using Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS

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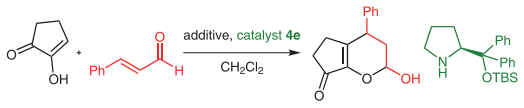
Table 3 Screening of Additives[a]



1 2a 3a 4e

Entry	Additive (10 mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	–	2	93	95
2	NaOAc	1.5	93	94
3	pyridine	3	95	94
4	DMAP	1	93	94
5	K_2CO_3	4	84	94
6	$NaHCO_3$	3.5	98	>99
7	Na_2CO_3	2.5	98	95
8	Et_3N	2.5	94	94
9	DIPEA	1.5	93	94
10	DABCO	2	99	95
11	DBU	2.5	82	95
12	imidazole	1	99	93

[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), additive (0.02 mmol), catalyst **4e** (0.02 mmol), CH_2Cl_2 (0.7 mL), r.t.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC.

spectrometer by using AJ-ESI ionization. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. IR spectra were recorded on a Bruker Tensor 27 Fourier transform infrared spectrophotometer. Absolute structure of the single crystal with Bruker-Nonius Kappa CCD diffractometer. TLC: Merck precoated silica gel 60 F_{254} plates; column chromatography: Merck 60 (0.040–0.063 mm) mesh silica gel. Commercial reagents and solvents were generally used as received. Racemic samples of all compounds were prepared following the general procedure using pyrrolidine as catalyst.

Cyclopentane-1,2-dione (**1**) was prepared according to a literature procedure[2a] from commercially available cyclopentanone. Aldehydes **2a–i** and catalysts **4a–e** are commercially available and were used without further purification.

4-Substituted 2-Hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one 3a–i; General Procedure A

2-Hydroxycyclopent-2-en-1-one (**1**, 23.5 mg, 0.24 mmol), aldehyde **2** (25.2 µL, 0.2 mmol), and aminocatalyst **4e** (7.3 mg, 0.02 mmol) were dissolved in CH_2Cl_2 (0.7 mL). The mixture was stirred at r.t. until completion of the reaction (TLC monitoring). The mixture was purified by column chromatography (CH_2Cl_2/EtOAc 25:1) to yield the product.

(2*S*,4*S*)-2-Hydroxy-4-phenyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3a)

Following GPA gave **3a** after purification as a white solid; yield: 43 mg (93%); mp 149 °C; 95% ee [HPLC (Chiralcel OD-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 8.2 (major), 6.8 min (minor)]; $[\alpha]_D^{25}$ +186.8 (*c* 0.04, $CHCl_3$).

IR (KBr): 3377, 2929, 1701, 1645, 1494, 1454, 1408, 1394, 1283, 1121, 1090, 910, 733, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2 H), 7.32–7.27 (m, 1 H), 7.24–7.19 (m, 2 H), 5.82 (d, *J* = 2.8 Hz, 1 H), 5.09 (s, 1 H), 4.00 (dd, *J* = 11.5, 6.1 Hz, 1 H), 2.40–2.31 (m, 3 H), 2.28–2.24 (m, 2 H), 1.99 (dd, *J* = 13.5, 11.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.8, 148.6, 148.5, 140.7, 129.1 (2 C), 128.3 (2 C), 127.4, 92.9, 37.6, 35.7, 32.7, 23.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}O_3$: 231.1016; found: 231.1016.

(2*S*,4*S*)-2-Hydroxy-4-(4-methoxyphenyl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3b)

Following GPA gave **3b** after purification as a yellow oil; yield: 36 mg (70%); 90% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 18.6 (major), 29.5 min (minor)]; $[\alpha]_D^{25}$ +133.9 (*c* 0.05, $CHCl_3$).

IR (KBr): 3379, 2932, 1703, 1644, 1611, 1583, 1513, 1442, 1394, 1347, 1250, 1087, 1034, 794 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.09 (m, 2 H), 6.93–6.86 (m, 2 H), 5.77 (br s, 1 H), 4.53 (br s, 1 H), 3.93 (dd, *J* = 11.4, 6.1 Hz, 1 H), 3.82 (s, 3 H), 2.40–2.36 (m, 2 H), 2.31 (ddd, *J* = 13.8, 6.2, 2.5 Hz, 1 H), 2.27–2.23 (m, 2 H), 2.01–1.91 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 158.9, 148.7, 148.4, 132.5, 129.3 (2 C), 114.5 (2 C), 92.9, 55.5, 36.7, 35.7, 32.8, 23.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}O_4$: 261.1121; found: 261.1103.

(2*S*,4*S*)-4-(4-Chlorophenyl)-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3c)

Following GPA gave **3c** after purification as a white solid; yield: 33 mg (62%); mp 168 °C; 83% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 13.9 (major), 18.8 min (minor)]; $[\alpha]_D^{25}$ +233.2 (*c* 0.04, $CHCl_3$).

IR (KBr) 3356, 2947, 1699, 1649, 1492, 1435, 1230, 1088, 844 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.3 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 5.79 (s, 1 H), 4.68 (s, 1 H), 3.97 (dd, *J* = 11.3, 6.0 Hz, 1 H), 2.41–2.36 (m, 2 H), 2.36–2.29 (m, 1 H), 2.27–2.20 (m, 2 H), 1.94 (t, *J* = 12.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 148.7, 147.4, 139.1, 133.3, 129.7 (2 C), 129.3 (2 C), 92.8, 37.0, 35.6, 32.7, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_3Cl$: 265.0626; found: 265.0626.

(2*S*,4*S*)-4-(4-Bromophenyl)-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3d)

Following GPA gave **3d** after purification as a white solid; yield: 50 mg (82%); mp 173 °C; 92% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 16.0 (major), 27.7 min (minor)]; $[\alpha]_D^{25}$ +190.1 (*c* 0.04, $CHCl_3$).

IR (KBr): 3354, 2947, 1699, 1649, 1489, 1127, 870, 843, 531 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 5.80 (d, *J* = 1.9 Hz, 1 H), 5.11 (s, 1 H), 3.97 (dd, *J* = 11.3, 5.9 Hz, 1 H), 2.41–2.36 (m, 2 H), 2.36–2.28 (m, 1 H), 2.28–2.21 (m, 2 H), 1.94 (t, *J* = 12.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 148.7, 147.2, 139.6, 132.3 (2 C), 130.1 (2 C), 121.3, 92.7, 37.1, 35.5, 32.7, 23.6.

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HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_3Br$: 309.0121; found: 309.0130.

(2*S*,4*S*)-2-Hydroxy-4-(4-nitrophenyl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3e)

Following GPA gave **3e** after purification as a white solid; yield: 47 mg (86%); mp 160 °C; 95% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 27.8 (major), 41.5 min (minor)]; $[\alpha]_D^{25}$ +184.7 (*c* 0.03, $CHCl_3$).

IR (KBr): 3305, 2931, 1693, 1646, 1607, 1516, 1345, 862, 754, 715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.6 Hz, 2 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 5.85 (d, *J* = 2.0 Hz, 1 H), 5.27 (s, 1 H), 4.16 (dd, *J* = 12.4, 6.5 Hz, 1 H), 2.45–2.40 (m, 2 H), 2.40–2.34 (m, 1 H), 2.33–2.21 (m, 2 H), 1.98 (t, *J* = 12.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.5, 149.0, 148.3, 147.4, 145.9, 129.3 (2 C), 124.4 (2 C), 92.5, 37.5, 35.5, 32.7, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_5N$: 276.0866; found: 276.0875.

(2*S*,4*R*)-2-Hydroxy-4-(2-nitrophenyl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3f)

Following GPA gave **3f** after purification as a white solid; yield: 48 mg (87%); mp 160 °C; 91% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 28.5 (major), 43.9 min (minor)]; $[\alpha]_D^{25}$ +234.3 (*c* 0.05, $CHCl_3$).

IR (KBr): 3356, 2925, 1700, 1648, 1607, 1524, 1351, 789, 750, 719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.62 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.49–7.43 (m, 1 H), 7.30 (dd, *J* = 7.8, 1.0 Hz, 1 H), 5.80 (d, *J* = 1.8 Hz, 1 H), 4.71 (br s, 1 H), 4.57 (dd, *J* = 10.7, 6.2 Hz, 1 H), 2.56 (ddd, *J* = 13.6, 6.1, 2.5 Hz, 1 H), 2.45–2.39 (m, 2 H), 2.35–2.28 (m, 1 H), 2.27–2.18 (m, 1 H), 1.99 (t, *J* = 11.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 150.4, 149.5, 146.2, 135.2, 133.3, 130.4, 128.3, 124.9, 92.7, 35.4, 33.2, 32.7, 23.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_5N$: 276.0866; found: 276.0872.

(2*S*,4*R*)-4-(Furan-2-yl)-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3g)

Following GPA gave **3g** after purification as a white solid; yield: 30 mg (68%); mp 160 °C; 81% ee [HPLC (Chiralcel OD-H, hexane/*i*-PrOH 95:5, 1 mL/min, 254 nm): t_R = 19.6 (major), 15.8 min (minor)]; $[\alpha]_D^{25}$ +162.1 (*c* 0.04, $CHCl_3$).

IR (KBr): 3375, 2926, 1702, 1647, 1505, 1120, 1088, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 1.8, 0.7 Hz, 1 H), 6.35 (dd, *J* = 3.1, 1.9 Hz, 1 H), 6.19 (d, *J* = 3.1 Hz, 1 H), 5.80 (d, *J* = 2.7 Hz, 1 H), 5.05 (s, 1 H), 4.13 (dd, *J* = 11.1, 5.9 Hz, 1 H), 2.44–2.36 (m, 3 H), 2.33–2.21 (m, 2 H), 2.15 (t, *J* = 12.4 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.6, 153.3, 148.1, 146.4, 142.3, 110.4, 106.9, 92.7, 32.8, 31.8, 31.1, 23.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}O_4$: 221.0808; found: 221.0815.

(2*S*,4*R*)-4-Butyl-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3h)

Following GPA gave **3h** after purification as a yellow oil; yield: 14 mg (33%); 86% ee [HPLC (Chiralcel OJ-H, hexane/*i*-PrOH 9:1, 1 mL/min, 254 nm): t_R = 10.7 (major), 8.6 min (minor)]; $[\alpha]_D^{25}$ +36.7 (*c* 0.04, $CHCl_3$).

IR (KBr): 3316, 2926, 1691, 1634, 1461, 1395, 1098, 948, 846, 715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (s, 1 H), 4.79 (s, 1 H), 2.81–2.70 (m, 1 H), 2.61–2.52 (m, 1 H), 2.49–2.36 (m, 3 H), 2.18–2.09 (m, 1 H), 1.81–1.70 (m, 1 H), 1.58–1.47 (m, 1 H), 1.42–1.28 (m, 5 H), 0.97–0.88 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 150.6, 147.8, 92.9, 32.8, 32.3, 31.5, 30.1, 29.0, 23.5, 22.9, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}O_3Na$: 233.1148; found: 233.1151.

(2*S*,4*S*)-2-Hydroxy-4-[(*E*)-prop-1-en-1-yl]-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3i)

Following GPA from **2i** (*trans*/*cis* 7:1) gave **3i** after purification as an orange oil; yield: 25 mg (65%); ratio *trans*/*cis* 7:1; *cis*-isomer 71% ee [HPLC (Chiralcel OJ-H, hexane/*i*-PrOH 9:1, 1 mL/min, 254 nm): t_R = 16.9 (major), 13.8 min (minor)]; *trans*-isomer 51% ee [HPLC (Chiralcel OJ-H, hexane/*i*-PrOH 9:1, 1 mL/min, 254 nm): t_R = 24.4 (major), 11.3 min (minor)]; $[\alpha]_D^{25}$ +99.7 (*c* 0.05, $CHCl_3$).

IR (KBr): 3382, 2925, 1698, 1643, 1440, 1395, 1102, 914, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75–5.59 (m, 2 H), 5.38–5.29 (m, 1 H), 4.82 (br s, 1 H), 3.36 (dd, *J* = 15.5, 8.6 Hz, 1 H), 2.57–2.33 (m, 4 H), 2.14–2.05 (m, 1 H), 1.77–1.67 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 149.2, 147.6, 129.5, 128.7, 92.7, 34.6, 33.3, 32.8, 23.9, 18.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}O_3Na$: 217.0835; found: 217.0837.

2-Hydroxy-3-(1-substituted 3-hydroxypropyl)cyclopent-2-en-1-ones 5a–i; General Procedure B

2-Hydroxycyclopent-2-en-1-one (**1**, 23.5 mg, 0.24 mmol), aldehyde **2** (25.2 µL, 0.2 mmol), aminocatalyst **4e** (7.3 mg, 0.02 mmol), and $NaHCO_3$ (0.02 mmol) were dissolved in CH_2Cl_2 (0.7 mL). The mixture was stirred at 40 °C until completion of the reaction (TLC and NMR monitoring). The mixture was cooled to 0 °C and dry MeOH (0.5 mL) and $NaBH_4$ (12.6 mg, 0.33 mmol) were added. The mixture was stirred at 0 °C for 30 min and was warmed to r.t. When the reaction was completed CH_2Cl_2 (0.5 mL) and sat. aq NH_4Cl solution (0.5 mL) were added to the mixture. The mixture was extracted with CH_2Cl_2 (3 × 1 mL) and organic phase was dried with phase separator and concentrated. Mixture was purified by column chromatography (CH_2Cl_2/MeOH, 50:1) to yield the product.

(*S*)-2-Hydroxy-3-(3-hydroxy-1-phenylpropyl)cyclopent-2-en-1-one (5a)

Following GPB gave **5a** after purification as a white solid; yield: 28 mg (74%); mp 117 °C; 92% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 9.1 (major), 13.8 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H), 6.52 (br s, 1 H), 4.20 (t, *J* = 7.9 Hz, 1 H), 3.71–3.61 (m, 2 H), 2.45–2.17 (m, 6 H), 2.09 (br s, 1 H).

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^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.6, 148.5, 148.3, 141.3, 128.8 (2 C), 128.0 (2 C), 127.0, 60.8, 41.4, 34.5, 31.8, 23.0.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-2-Hydroxy-3-(3-hydroxy-1-(4-methoxyphenyl)propyl)cyclopent-2-en-1-one (5b)

Following GPB gave **5b** after purification as a white solid; yield: 32 mg (72%); mp 106 °C; 90% ee [HPLC (Chiralpak AS-H, hexane/EtOH 9:1, 1 mL/min, 254 nm): t_R = 29.6 (major), 26.4 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.10 (s, 1 H), 4.13 (t, *J* = 8.0 Hz, 1 H), 3.79 (s, 3 H), 3.71–3.60 (m, 2 H), 2.44–2.18 (m, 6 H), 1.86 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 158.6, 148.3, 148.1, 133.3, 128.9 (2 C), 114.1 (2 C), 60.8, 55.3, 40.6, 34.9, 31.7, 23.0.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-3-[1-(4-Chlorophenyl)-3-hydroxypropyl]-2-hydroxycyclopent-2-en-1-one (5c)

Following GPB gave **5c** after purification as a white amorphous solid; yield: 28 mg (63%); 90% ee [HPLC (Chiralpak AS-H, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 8.9 (major), 11.2 min (minor)]; $[\alpha]_D^{25}$ –55.1 (*c* 0.11, $CHCl_3$).

IR (KBr): 3317, 2919, 1691, 1646, 1490, 1031, 822 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 2 H), 7.26–7.21 (m, 2 H), 6.24 (s, 1 H), 4.21–4.13 (m, 1 H), 3.71–3.60 (m, 2 H), 2.43–2.15 (m, 6 H), 1.92 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 148.5, 147.1, 139.8, 132.8, 129.3 (2 C), 128.9 (2 C), 60.6, 40.8, 34.7, 31.7, 23.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}ClO_3$: 267.0782; found: 267.0785.

(*S*)-3-[1-(4-Bromophenyl)-3-hydroxypropyl]-2-hydroxycyclopent-2-en-1-one (5d)

Following GPB gave **5d** after purification as a white solid; yield: 31 mg (60%); mp 105 °C; 92% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 8.9 (major), 10.6 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 6.16 (s, 1 H), 4.18–4.12 (m, 1 H), 3.69–3.61 (m, 2 H), 2.44–2.15 (m, 6 H), 1.71 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 148.4, 146.9, 140.3, 131.8 (2 C), 129.7 (2 C), 120.9, 60.5, 40.9, 34.6, 31.7, 23.1.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-2-Hydroxy-3-[3-hydroxy-1-(4-nitrophenyl)propyl]cyclopent-2-en-1-one (5e)

Following GPB gave **5e** after purification as a white solid; yield: 49 mg (82%); mp 109 °C; 94% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 16.8 (major), 19.5 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 9.0, 1.2 Hz, 2 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 6.09 (s, 1 H), 4.34–4.27 (m, 1 H), 3.68 (t, *J* = 6.1 Hz, 2 H), 2.46–2.21 (m, 6 H), 1.77 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.9, 149.0, 148.9, 147.0, 145.0, 128.8 (2 C), 124.0 (2 C), 60.3, 41.4, 34.5, 31.7, 23.3.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-2-Hydroxy-3-[3-hydroxy-1-(2-nitrophenyl)propyl]cyclopent-2-en-1-one (5f)

Following GPB gave **5f** after purification as a yellow oil; yield: 16 mg (35%); 94% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 20.6 (major), 36.4 min (minor)]; $[\alpha]_D^{25}$ +100.3 (*c* 0.11, $CHCl_3$).

IR (KBr): 3332, 2922, 1697, 1653, 1526, 1355, 1108, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.60 (dtd, *J* = 9.1, 8.0, 1.4 Hz, 2 H), 7.40 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1 H), 6.42 (s, 1 H), 4.56 (t, *J* = 7.7 Hz, 1 H), 3.71–3.61 (m, 2 H), 2.52–2.22 (m, 6 H), 2.16 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.0, 149.7, 148.6, 144.6, 135.3, 132.3, 129.3, 127.3, 123.7, 59.9, 36.4, 35.0, 31.2, 24.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_5$: 278.1023; found: 278.1027.

(*R*)-3-[1-(Furan-2-yl)-3-hydroxypropyl]-2-hydroxycyclopent-2-en-1-one (5g)

Following GPB gave **5g** after purification as a white solid; yield: 22 mg (60%); mp 120 °C (dec.); 83% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 9.9 (major), 14.4 min (minor)]; $[\alpha]_D^{25}$ –86.0 (*c* 0.11, $CHCl_3$).

IR (KBr): 3427, 3124, 2939, 1697, 1651, 1506, 1447, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 1.8, 0.7 Hz, 1 H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1 H), 6.17 (d, *J* = 3.2 Hz, 1 H), 5.73 (s, 1 H), 4.39 (dd, *J* = 8.8, 7.0 Hz, 1 H), 3.74–3.59 (m, 2 H), 2.49–2.38 (m, 3 H), 2.33–2.21 (m, 2 H), 2.09 (m, 1 H), 1.79 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.7, 154.2, 148.6, 144.9, 141.9, 110.2, 106.3, 60.3, 34.4, 33.5, 31.7, 22.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_4$: 223.0965; found: 223.0967.

(*R*)-2-Hydroxy-3-(1-hydroxyheptan-3-yl)cyclopent-2-en-1-one (5h)

Following GPB gave **5h** after purification as a white solid; yield: 11 mg (29%); mp 97 °C; 75% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 6.7 (major), 21.0 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (s, 1 H), 3.63 (ddd, *J* = 11.0, 6.2, 4.7 Hz, 1 H), 3.52 (ddd, *J* = 11.1, 8.9, 5.4 Hz, 1 H), 3.05–2.94 (m, 1 H), 2.46–2.35 (m, 4 H), 1.95–1.81 (m, 1 H), 1.70–1.60 (m, 1 H), 1.58–1.50 (m, 2 H), 1.39–1.15 (m, 4 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 150.4, 149.6, 60.8, 35.9, 34.6, 32.8, 31.9, 29.9, 22.7, 21.7, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}O_3$: 213.1485; found: 213.1487.

The spectral properties of the compound coincided with literature data.[9]

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(*S*,*E*)-2-Hydroxy-3-(1-hydroxyhex-4-en-3-yl)cyclopent-2-en-1-one (5i)

Following GPB from **2i** (*trans*/*cis* 7:1) gave **5i** after purification as a white amorphous solid; yield: 18 mg (55%); ratio *trans*/*cis* 7:1; *trans*-isomer 46% ee; *cis*-isomer 73% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 7.8 (major *trans*), 20.0 (minor *trans*), 7.3 (major *cis*), 10.8 min (minor *cis*)]; $[\alpha]_D^{25}$ –14.2 (*c* 0.09, $CHCl_3$).

IR (KBr): 3340, 2920, 1697, 1650, 1102 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.19 (s, 1 H), 5.66–5.64 (m, 1 H), 5.54–5.44 (m, 1 H), 3.70–3.59 (m, 2 H), 3.55 (dd, *J* = 15.0, 7.2 Hz, 1 H), 2.47–2.37 (m, 4 H), 2.06 (br s, 1 H), 1.95–1.78 (m, 2 H), 1.69 (dd, *J* = 7.9, 2.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 148.7, 148.1, 130.0, 127.3, 60.7, 38.9, 35.3, 31.8, 22.7, 17.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{17}O_3$: 197.1172; found: 197.1173.

4-Phenyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6)

Compound **6** was synthesized using the following modified procedure of Rueping et al.[12b] Precursor **5a** (27 mg, 0.1 mmol) was dissolved in 2 M H_2SO_4 solution (0.6 mL). The mixture was stirred at r.t. for 1 h. The solution was quenched with aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 1 mL). The combined organic phases were dried and the residue was purified by column chromatography (CH_2Cl_2/EtOAc 5:1) to give a colorless oil; yield: 14 mg (56%).

IR (KBr): 3491, 2916, 1701, 1650, 1408, 1234, 1126, 1015, 773, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 4.2 (dd, *J* = 8.6, 7.3 Hz, 1 H), 3.72–3.60 (m, 2 H), 2.46–2.16 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.5, 148.4, 148.2, 141.3, 128.7 (2 C), 128.0 (2 C), 127.0, 60.8, 41.4, 34.7, 31.8, 23.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_2$: 215.1067; found: 215.1076.

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Supporting Information

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Appendix 2

Publication II

Silm, E.; Kaabel, S.; Järving, I.; Kanger, T. Asymmetric Organocatalytic Michael Addition-Cyclisation Cascade of Cyclopentane-1,2-dione with Alkylidene Malononitriles. *Synthesis* **2019**, *51*, 4198-4204.

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Synthesis E. Silm et al. Paper

Asymmetric Organocatalytic Michael Addition–Cyclisation Cascade of Cyclopentane-1,2-dione with Alkylidene Malononitriles

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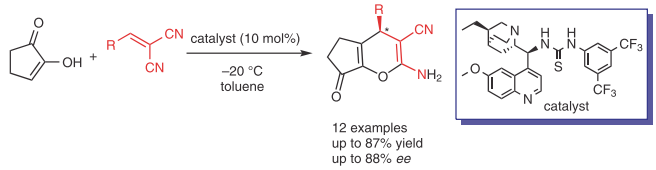

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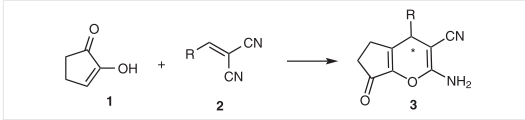
Abstract An asymmetric organocatalytic cascade reaction between cyclopentane-1,2-diones and alkylidene malononitriles affords highly substituted 4*H*-pyrans in moderate to high enantiomeric excess. The selective reduction of a bridged double bond leads to the formation of *cis*-substituted cyclopentanone with three contiguous stereogenic centres.

Key words organocatalysis, asymmetric catalysis, diketone, pyran, cascade reaction

Cascade reactions have been an interesting topic for many researchers over the years.[2] Such transformations are atom- and step-economical and proceed in a one-pot manner; thus, there is no need for additional protection/deprotection steps or purification of intermediates. These synthetic and operational advantages make this approach more sustainable and environmentally friendly than classical syntheses. Forming several bonds in one step is very appealing for the development of new strategies for the construction of complex molecules, even more so if high stereoselectivity is achieved in the presence of a chiral catalyst or auxiliary. In the last two decades organocatalysis[3] has proven to be competitive with metal[2c,4] and enzymatic catalysis,[5] so asymmetric organocatalytic cascade reactions are now a valuable approach for synthetic chemists.[3b,3c] Starting with the pioneering work by Barbas[6] of a consecutive Michael addition and aldol condensation (i.e., Robinson annulation), synthetic chemists have proceeded to quadruple asymmetric cascades, where several chemical bonds and stereogenic centres are formed in complex structures in controlled ways.[7]

Among the different starting materials suitable for cascade reactions, cyclic diketones are widely used. Various cyclic 1,3-diketones have been investigated in one-pot reactions with unsaturated aldehydes,[8–10] acetates of nitroalkenes,[11] cyanoacrylates and alkylidene malononitrile derivatives.[12] Cyclic 1,2-dicarbonyl compounds have been investigated less in cascade reactions. It has been previously shown that cyclohexane-1,2-diones undergo a cascade with nitroolefins,[13] benzylidenemalononitriles[14] and α,β-unsaturated aldehydes.[15] However, cyclopentane-1,2-diones are less reactive and do not afford the cascade reactions with Michael acceptors characteristic of cascades involving cyclohexane-1,2-diones. Only single-bond-forming organocatalytic enantioselective reactions with nitroolefins[16] and cascade reactions with α,β-unsaturated aldehydes[17] were described by our group recently. Highly reactive (*E*)-2-oxobut-3-enoates[18] were needed to run the cascade reaction.[19] Considering the previous research that our group has conducted on cyclopentane-1,2-dione and the reported cascade reactions using diketones, we assumed that the cyclopentane-1,2-dione **1** would undergo a Michael reaction with alkylidene malononitriles **2**, followed by the intramolecular cyclisation of the adduct to afford multifunctionalised bicycles **3** with one stereocentre (Scheme 1).



Scheme 1 General scheme for the cascade reaction

Derived compounds are highly substituted 4*H*-pyrans with a comprehensive list of biological and pharmacological properties, such as kinase inhibition,[20] IK_{CA} channel blocker behaviour[21] and antitumor properties.[22]

Chiral thioureas[23] and squaramides[24] are widely used as catalysts in asymmetric Michael additions. We assumed that H-bonds could activate alkylidene malononitrile suffi-

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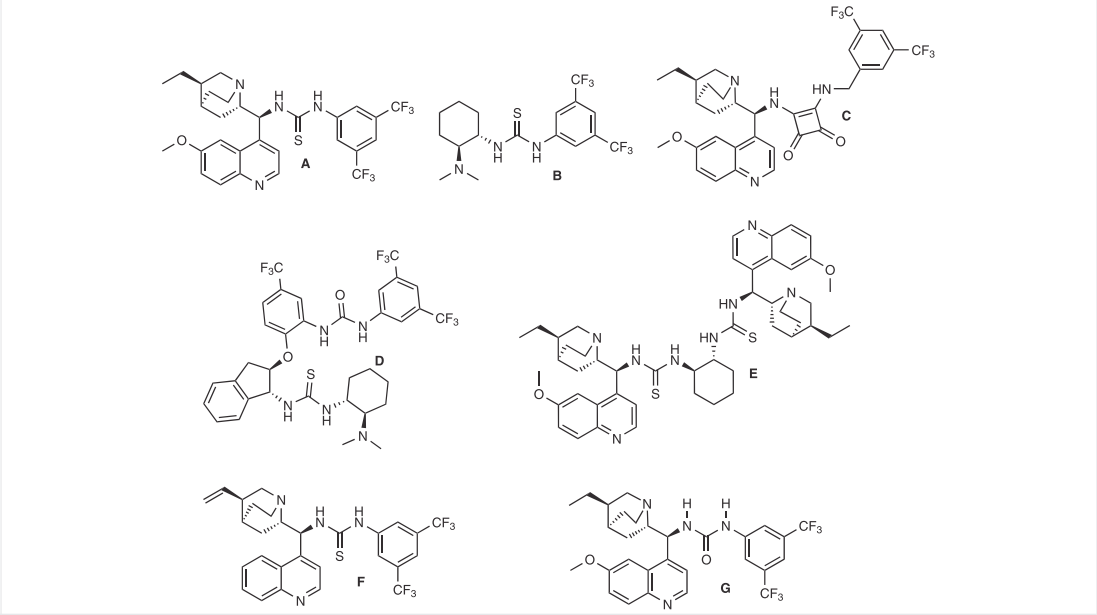

Figure 1 Catalysts screened in the model reaction

ciently to trigger the cascade. Therefore, various H-bond catalysts (Figure 1) were screened in the model reaction between cyclopentane-1,2-dione and benzylidene malonitrile (Table 1).

First, different catalysts were screened at room temperature. The model reaction in the presence of 10 mol% thiourea **A** afforded the product within two hours in 74% yield (Table 1, entry 1). Soos's bifunctional catalysts **F** (entry 6) gave the same stereoselectivity (54% *ee*), eliminating the influence of the double bond and the methoxy substituent. With Takemoto's catalyst **B** and squaramide **C** (entries 2 and 3) the product was obtained with low enantioselectivity. The enantioselectivity found with double-activated Pihko's catalyst[25] **D** (entry 4) was similar to that obtained with thiourea **A**. Double thiourea **E** afforded the product in low enantiomeric purity (13% *ee*). Since the synthetic pathway for catalyst **A** is less time- and resource-consuming than for catalyst **D**, the former was seen as the most reasonable catalyst. Next, we looked into solvent effects on the reaction. The stereoselectivity was very dependent on the solvent used (entries 1 and 7–9). Compared to toluene, the enantiomeric excess was slightly lower in THF. Its greener alternative, 2-MeTHF, gave a racemic product and in CH_2Cl_2 the product obtained was almost racemic. In addition, the reaction was run at various temperatures (entries 1 and 10). The results indicated that catalyst aggregation[26] might take place. Finally, to minimise that effect, the reaction mixture was diluted 10 times and an increase in enantioselectivity was achieved (entry 11), even more so at lower temperature (entry 14). The overall best result was attained using alkaloid-derived thiourea **A** and toluene at –20 °C (entry 14).

Using these optimal conditions, the scope of the reaction was investigated. Both electron-withdrawing (**3d–j**; Scheme 2) and electron-donating groups (**3b**, **3c**; Scheme 2) were tolerated. The electronic properties of the aromatic ring and also the position of the substituent did not seem to have a significant influence on the yield; however, the enantioselectivity was more influenced when nitro-substituted benzylidene malononitriles were used. It is supposed that the nitro group competes with the H-bonding acceptor to influence the enantioselectivity. In addition, heteroaromatic malononitrile derivative **2k** afforded the product in slightly lower yield but with good *ee*. Furthermore, alkylidene malononitrile could also be used in this cascade, although it affords the product in much lower yield and lower enantioselectivity. Pyrrole derived malononitrile **2m** is probably too electron-rich and therefore did not react with cyclopentane-1,2-dione **1**. It is assumed that the product **3n** did not form because the substrate **2n** was too sterically hindered for the first addition to take place.

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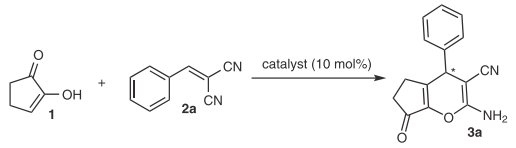
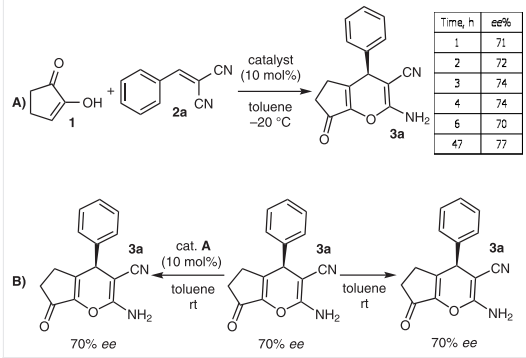
Table 1 Screening Conditions for the Reaction



Entry[a]	Catalyst	Solvent	Time (h)	Temp (°C)	*ee* (%)[b]	Yield (%)[c]
1	**A**	toluene	2	r.t.	54	74
2	**B**	toluene	1	r.t.	31	nd
3	**C**	toluene	1	r.t.	27	nd
4	**D**	toluene	3	r.t.	56	nd
5	**E**	toluene	1	r.t.	13	nd
6	**F**	toluene	3	r.t.	54	74
7	**A**	CH_2Cl_2	3	r.t.	5	nd
8	**A**	THF	2.5	r.t.	47	77
9	**A**	2-MeTHF	2.5	r.t.	*rac*	nd
10	**A**	toluene	4.5	–20	53	nd
11	**A**	toluene[d]	2	r.t.	70	82
12	**A**	mesitylene[d]	15	r.t.	70	79
13	**G**	toluene[d]	20	–20	65	78
14	**A**	toluene[d]	3	–20	75	78
15	**A**	toluene[d]	2	60	31	74
16	**A**	toluene[d]	13 days	–78	53	nd

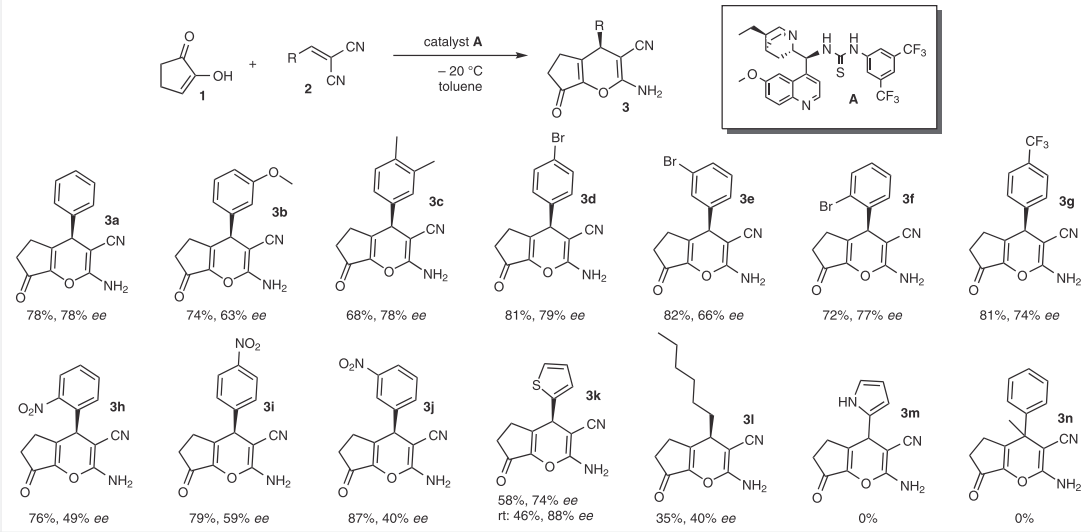
[a] Reaction conditions: 0.2 M solution of **1** (1 equiv), **2a** (1.1 equiv), catalyst (0.1 equiv).
[b] *ee* determined by chiral HPLC analysis either from isolated product or preparative TLC.
[c] Isolated yield after column chromatography; nd = not determined.
[d] 0.02 M solution of **1**.

To eliminate racemisation from consideration, the enantiomeric purity of the product was checked throughout the reaction for a period of 47 hours (Scheme 3). The *ee* was constant and varied only within the detection error. Two additional experiments with the product were also carried out. The product **3a** was stirred for 24 hours in toluene either with 10 mol% of catalyst **A** or without it (Scheme 3). The results showed that no racemisation was observed under either of these conditions.



Scheme 3 Racemisation studies: (A) throughout the reaction, (B) with the product **3a**

The *R*-absolute configuration of compound **3a** was determined by single-crystal X-ray diffraction (Figure 2) and the absolute configurations of the products **3** were assigned by analogy.



Scheme 2 Scope of the reaction. *Reagents and conditions*: 0.02 M solution **1** (1 equiv), **2** (1.1 equiv), catalyst **A** (0.1 equiv), toluene, –20 °C; isolated yields after column chromatography; *ee* determined by chiral HPLC.

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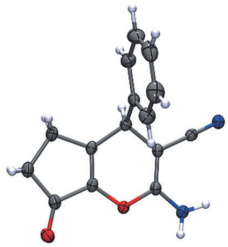
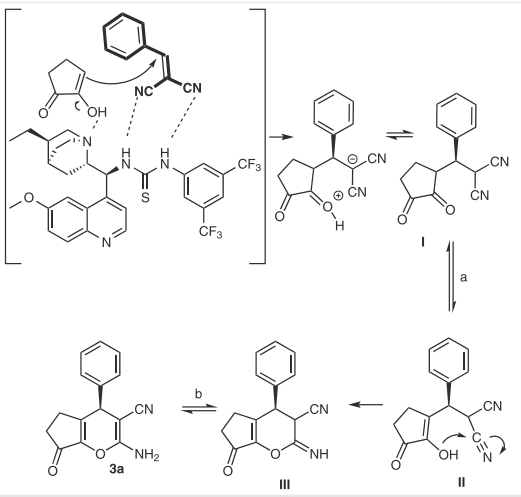


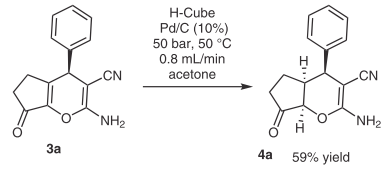
Figure 2 X-ray crystal structure of compound **3a**

A plausible reaction pathway is shown in Scheme 4. It is believed that both reactants are activated by the catalyst: alkylidene malononitrile via hydrogen bonds with thiourea moiety and diketone via hydrogen bond with a tertiary amino group of quinuclidine moiety. The stereodetermining step is the first Michael addition step. According to the geometry of **3a**, the attack of the cyclopentane-1,2-dione on alkylidene malononitrile occurs from the *Si*-face, affording intermediate **I** with *R*-configuration of the stereogenic centre. An O-nucleophile attack of the enol form **II** on the cyano group leads to the cyclisation. The target compound **3a** is isolated as an enamine tautomer of imine **III**.



Scheme 4 Proposed transition state and reaction pathway: a) keto–enol tautomerisation; b) imine–enamine tautomerisation

To show the synthetic utility of the obtained substituted pyrans, compound **3a** was reduced using an H-Cube Pro continuous-flow reactor in the presence of a Pd catalyst (Scheme 5). The reduction was *cis*-selective, affording only *cis*-substituted cyclopentanone. The configuration of the main diastereomer **4a** was confirmed by NOE experiments (see Supporting Information for details).



Scheme 5 The reduction of **3a**

In summary, we have developed a new, efficient organocatalytic cascade for the synthesis of substituted 4*H*-pyrans. The cascade is efficiently catalysed by chiral bifunctional thiourea **A** to provide bicyclic 4*H*-pyrans **3a–l** in moderate to high yields and enantioselectivities. The selective reduction of the bridged double bond leads to cyclopentanone derivatives with three contiguous stereogenic centres.

Full assignment of ^{1}H and ^{13}C chemical shifts were based on the 1D and 2D FT NMR spectra measured with a Bruker Avance III 400 MHz instrument. Residual solvent signals were used ($CDCl_3$: δ = 7.26 ^{1}H NMR, δ = 77.2 ^{13}C NMR; $(CD_3)_2CO$: δ = 2.05 ^{1}H NMR, δ = 29.84/206.26 ^{13}C NMR) as internal standards. High-resolution mass spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionisation. Optical rotations were obtained with an Anton Paar GWB Polarimeter MCP 500. Chiral HPLC was performed by using Chiralpak AD-H, Chiralcel OJ-H, Chiralcel OD-H columns. Precoated silica gel 60 F254 plates were used for TLC. Commercial reagents and solvents were generally used as received. Toluene was distilled over sodium and CH_2Cl_2 was distilled over phosphorus pentoxide.

Racemic compounds were prepared by following the general procedure using DABCO as catalyst. Cyclopentane-1,2-dione (**1**) was prepared according to a reported procedure[27] from commercially available cyclopentanone. Alkylidene malononitriles were prepared via Knoevenagel condensation from commercially available malononitrile and commercially available aldehydes. Catalysts **A**, **E**, **F**,[28] **C**,[29] **B**,[30] **D**[25] and **G**[31] were prepared according to reported procedures.

Synthesis of 3; General Procedure

To a solution of cyclopentane-1,2-dione (0.07 mmol) and catalyst (0.007 mmol) in toluene (3.5 mL) was added substituted malononitrile (0.08 mmol). The mixture was stirred until the reaction was complete (TLC and/or NMR monitoring). The mixture was purified by column chromatography (CH_2Cl_2/EtOAc, 19:1) to afford the product.

(*R*)-2-Amino-7-oxo-4-phenyl-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3a)

By following the general procedure (1.5 mmol scale), compound **3a** (78% yield, 301 mg) was obtained as an off-white solid; mp 215 °C (decomp); 78% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 21.2 (minor), 30.8 (major) min]; $[\alpha]_D^{20}$ –117.5 (*c* 0.14, acetone).

IR: 3339, 2191, 1713, 1679, 1621, 1593, 1491, 1404, 1111, 752, 698 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.43–7.35 (m, 2 H), 7.35–7.28 (m, 3 H), 6.28 (s, 2 H), 4.5 (s, 1 H), 2.55–2.28 (m, 3 H), 2.20–2.09 (m, 1 H).

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^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.4, 148.5, 146.1, 142.3, 129.7, 129.0, 128.5, 119.8, 58.3, 43.1, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{13}N_2O_2]^+$: 253.0972; found: 253.0960.

(*R*)-2-Amino-4-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3b)

By following the general procedure, compound **3b** (74% yield, 14.9 mg) was obtained as a yellow solid; mp 143 °C (decomp); 63% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 24.2 (minor), 40.0 (major) min]; $[\alpha]_D^{20}$ –78.8 (*c* 0.07, acetone).

IR: 3323, 2194, 1714, 1678, 1639, 1593, 1492, 1412, 1284, 1113, 1048, 750 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.35–7.27 (m, 1 H), 6.91–6.86 (m, 3 H), 6.28 (s, 2 H), 4.47 (s, 1 H), 3.8 (s, 3 H), 2.52–2.30 (m, 3 H), 2.23–2.14 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.4, 161.2, 148.4, 146.1, 143.9, 130.8, 121.1, 119.8, 114.8, 113.7, 58.2, 55.5, 45.1, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{15}N_2O_3]^+$: 283.1077; found: 283.1074.

(*R*)-2-Amino-4-(3,4-dimethylphenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3c)

By following the general procedure, compound **3c** (68% yield, 13.6 mg) was obtained as a yellow-brown solid; mp 144 °C (decomp); 78% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 12.0 (minor), 13.9 (major) min]; $[\alpha]_D^{20}$ –51.3 (*c* 0.03, acetone).

IR: 3345, 2923, 2198, 1718, 1680, 1644, 1608, 1503, 1412, 1383, 1357, 1109, 773 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.14 (d, *J* = 7.7 Hz, 1 H), 7.07 (s, 1 H), 7.02 (dd, *J* = 7.7, 1.6 Hz, 1 H), 6.23 (s, 1 H), 4.40 (s, 1 H), 2.50–2.41 (m, 1 H), 2.40–2.33 (m, 2 H), 2.24 (d, *J* = 5.3 Hz, 6 H), 2.18–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.2, 148.9, 139.8, 137.8, 136.7, 130.8, 130.0, 126.4, 119.9, 58.5, 42.7, 23.6, 19.8, 19.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{17}H_{17}N_2O_2]^+$: 281.1285; found: 281.1283.

(*R*)-2-Amino-4-(4-bromophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3d)

By following the general procedure, compound **3d** (81% yield, 19.1 mg) was obtained as a brownish solid; mp 184 °C (decomp); 79% *ee* [HPLC (Chiralcel OD-H; hexane/*i*-PrOH, 9:1; 25 °C; 1 mL/min; 254 nm): t_r = 26.5 (minor), 34.2 (major) min]; $[\alpha]_D^{20}$ –13.6 (*c* 0.05, acetone).

IR: 3325, 2191, 1716, 1681, 1633, 1590, 1486, 1402, 1111, 1010, 754 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.61–7.55 (m, 2 H), 7.34–7.27 (m, 2 H), 6.34 (s, 2 H), 4.54 (s, 1 H), 2.53–2.30 (m, 3 H), 2.24–2.12 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.4, 147.6, 146.3, 147.7, 122.0, 119.7, 57.8, 42.5, 33.4, 23.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_8BrN_2O_2]^-$: 326.9775; found: 326.9757.

(*R*)-2-Amino-4-(3-bromophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3e)

By following the general procedure, compound **3e** (82% yield, 19.1 mg) was obtained as a yellowish solid; mp 162 °C (decomp); 65% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 18.4 (minor), 21.3 (major) min]; $[\alpha]_D^{20}$ –67.4 (*c* 0.07, acetone).

IR: 3317, 2191, 1720, 1678, 1638, 1607, 1471, 1415, 1110, 1071, 749 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.56–7.47 (m, 2 H), 7.39–7.33 (m, 2 H), 6.37 (s, 2 H), 4.56 (s, 1 H), 2.56–2.28 (m, 3 H), 2.25–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.5, 147.4, 146.4, 145.0, 131.9, 131.8, 131.7, 128.1, 123.4, 119.6, 57.7, 42.7, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $[C_{15}H_{11}BrN_2O_2Na]^+$: 352.9896; found: 352.9887.

(*R*)-2-Amino-4-(2-bromophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3f)

By following the general procedure, compound **3f** (72% yield, 17 mg) was obtained as a dark-yellow solid; mp 144 °C (decomp); 77% *ee* [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 7:3; 35 °C; 0.9 mL/min; 254 nm): t_r = 20.9 (minor), 24.0 (major) min]; $[\alpha]_D^{20}$ –77.5 (*c* 0.08, acetone).

IR: 3381, 2197, 1718, 1677, 1645, 1594, 1463, 1417, 1109, 1051, 767, 749 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.65 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.49–7.37 (m, 2 H), 7.27 (ddd, *J* = 8.0, 7.2, 1.9 Hz, 1 H), 6.38 (br s, 2 H), 5.10 (s, 1 H), 2.63–2.51 (m, 1 H), 2.39 (qdd, *J* = 18.8, 6.5, 1.5 Hz, 2 H), 2.22–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 196.9, 161.8, 147.3, 134.0, 131.8, 130.5, 129.5, 124.2, 119.4, 100.9, 57.2, 33.4, 23.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_8BrN_2O_2]^-$: 326.9775; found: 326.9757.

(*R*)-2-Amino-7-oxo-4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3g)

By following the general procedure, compound **3g** (81% yield, 18.4 mg) was obtained as a yellow solid; mp 167 °C (decomp); 74% ee [HPLC (Chiralcel OJ-H; hexane/*i*-PrOH, 8:2; 1 mL/min; 254 nm): t_r = 24.9 (major), 30.0 (minor) min]; $[\alpha]_D^{20}$ –72.6 (*c* 0.09, acetone).

IR: 3328, 2190, 1720, 1682, 1638, 1589, 1420, 1331, 1123, 764 cm^{-1}.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.76 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 6.41 (s, 2 H), 4.67 (s, 1 H), 2.57–2.30 (m, 3 H), 2.23–2.11 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.5, 147.2, 146.8, 146.5, 129.9, 126.7, 126.6, 119.6, 57.4, 42.8, 33.4, 23.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{16}H_{10}F_3N_2O_2]^-$: 319.0700; found: 319.0691.

(*R*)-2-Amino-4-(2-nitrophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3h)

By following the general procedure, compound **3h** (76% yield, 16.1 mg) was obtained as an orange solid; mp 157 °C (decomp); 49% *ee* [HPLC (Chiralcel OD-H; hexane/*i*-PrOH, 8:2; 25 °C; 1 mL/min; 254 nm): t_r = 21.6 (major), 26.8 (minor) min]; $[\alpha]_D^{20}$ –21.5 (*c* 0.05, acetone).

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IR: 3321, 2197, 1721, 1679, 1643, 1590, 1526, 1420, 1402, 1113, 765 cm^{-1}.

^1H NMR (400 MHz, $(CD_3)_2CO$): δ = 7.99–7.95 (m, 1 H), 7.84–7.75 (m, 1 H), 7.67–7.56 (m, 2 H), 6.54 (s, 2 H), 5.19 (s, 1 H), 2.65–2.31 (m, 3 H), 2.24–2.14 (m, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.0, 161.8, 150.6, 146.8, 146.6, 136.3, 134.6, 132.5, 129.9, 125.1, 119.3, 57.3, 38.0, 33.4, 23.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_{10}N_3O_4]^-$: 296.0677; found: 296.0657.

(*R*)-2-Amino-4-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3i)

By following the general procedure, compound **3i** (79% yield, 16.7 mg) was obtained as an orange solid; mp 214 °C (decomp); 59% *ee* [HPLC (Chiralpak AD-H; hexane/*i*-PrOH, 8:2; 25 °C; 1 mL/min; 254 nm): t_r = 21.6 (major), 30.0 (minor) min]; $[\alpha]_D^{20}$ –65.8 (*c* 0.14, acetone).

IR: 3330, 2193, 1716, 1679, 1610, 1519, 1491, 1458, 1425, 1107, 746 cm^{-1}.

^1H NMR (400 MHz, $(CD_3)_2CO$): δ = 8.33–8.22 (m, 2 H), 7.71–7.62 (m, 2 H), 6.46 (br s, 2 H), 4.75 (s, 1 H), 2.53 (ddt, *J* = 17.2, 6.4, 1.8 Hz, 1 H), 2.45–2.30 (m, 2 H), 2.20 (ddt, *J* = 17.2, 6.2, 1.3 Hz, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.0, 161.2, 149.5, 148.5, 146.6, 130.3, 124.8, 119.5, 57.1, 42.7, 33.4, 23.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $[C_{15}H_{10}N_3O_4]^-$: 296.0677; found: 296.0520.

(*R*)-2-Amino-4-(3-nitrophenyl)-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3j)

By following the general procedure, compound **3j** (87% yield, 18.8 mg) was obtained as a pale-yellow solid; mp 208 °C (decomp); 40% *ee* [HPLC (Chiralpak AD-H; hexane/*i*-PrOH, 8:2; 25 °C; 1 mL/min; 254 nm): t_r = 20.0 (major), 27.5 (minor) min]; $[\alpha]_D^{20}$ –48.8 (*c* 0.11, acetone).

IR: 3318, 2192, 1722, 1683, 1648, 1590, 1526, 1413, 1112, 758 cm^{-1}.

^1H NMR (400 MHz, $(CD_3)_2CO$): δ = 8.24–8.19 (m, 2 H), 7.85 (dt, *J* = 7.6, 1.3 Hz, 1 H), 7.77–7.70 (m, 1 H), 6.47 (br s, 1 H), 4.80 (s, 1 H), 2.54 (ddt, *J* = 17.5, 6.4, 1.9 Hz, 1 H), 2.49–2.31 (m, 2 H), 2.20 (ddt, *J* = 17.5, 6.4, 1.8 Hz, 1 H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 197.1, 161.7, 149.7, 146.8, 146.6, 144.6, 135.5, 131.2, 123.7, 123.6, 119.5, 57.3, 42.7, 33.5, 23.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{12}N_3O_4]^+$: 298.0822; found: 298.0804.

(*R*)-2-Amino-7-oxo-4-(thiophen-2-yl)-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3k)

By following the general procedure, compound **3k** (58% yield, 10.7 mg) was obtained as a brown solid; mp 207 °C (decomp); 74% *ee* [HPLC (Chiralpak AD-H; hexane/EtOH/IPA, 90:5:5; 25 °C; 1 mL/min; 254 nm): t_r = 44.0 (major), 63.3 (minor) min]; $[\alpha]_D^{20}$ –94.4 (*c* 0.06, acetone).

IR: 3323, 3108, 2921, 2195, 1715, 1678, 1637, 1590, 1402, 1111, 779, 728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 1 H), 7.02–6.7 (m, 2 H), 4.80 (br s, 1 H), 4.74 (s, 1 H), 2.57–2.39 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.0, 159.5, 147.2, 145.0, 143.9, 127.3, 126.1, 126.13, 126.07, 118.8, 59.9, 37.1, 32.9, 23.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{13}H_{11}N_2O_2S]^+$: 259.0536; found: 259.0517.

(*R*)-2-Amino-4-hexyl-7-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (3l)

By following the general procedure, compound **3l** (62% yield, 24.5 mg) was obtained as an off-white solid; mp 106–111 °C; 40% *ee* [HPLC (Chiralpak AD-H; hexane/*i*-PrOH, 9:1; 25 °C; 1 mL/min; 254 nm): t_r = 10.9 (major), 18.9 (major) min]; $[\alpha]_D^{20}$ –60.4 (*c* 0.08, acetone).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.68 (br s), 3.44 (t, *J* = 4.6 Hz, 1 H), 2.63–2.38 (m, 4 H), 1.85–1.61 (m, 2 H), 1.43–1.23 (m, 7 H), 1.18–1.04 (m, 1 H), 0.91–0.83 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.0, 160.6, 149.8, 146.9, 119.5, 58.0, 35.5, 33.0, 32.8, 31.8, 29.4, 25.1, 23.3, 22.7, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{21}N_2O_2]^+$: 261.1598; found: 261.1575.

(4*S*,4a*S*,7a*R*)-2-Amino-7-oxo-4-phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*b*]pyran-3-carbonitrile (4a)

Compound **3a** (35 mg, 0.14 mmol) was dissolved in acetone (14 mL, 0.01 M). The reaction parameters were set on the H-Cube Pro: full H_2, 50 bar, 50 °C and 0.8 mL/min flow rate. The instrument was fitted with 10% Pd/C CatCart and the process was started. After evaporation the mixture was purified by column chromatography (CH_2Cl_2/EtOAc, 12:1→5:1) to afford the product **4a** (58% yield, 20.5 mg) as a light-orange solid; mp 148–150 °C.

IR: 3340, 2948, 2183, 1752, 1596, 1492, 1453, 1411, 1129, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) = 7.36–7.31 (m, 2 H), 7.31–7.27 (m, 1 H), 7.24–7.18 (m, 2 H), 4.61 (br s, 2 H), 4.35 (d, *J* = 5.1 Hz, 1 H), 4.05 (d, *J* = 6.7 Hz, 1 H), 2.65 (dtd, *J* = 9.4, 6.7, 5.3 Hz, 1 H), 2.00 (dd, *J* = 8.7, 4.7 Hz, 2 H), 1.86 (dq, *J* = 13.3, 9.1 Hz, 1 H), 1.55 (ddt, *J* = 13.0, 7.7, 4.4 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (major diastereomer) = 209.7, 162.9, 138.7, 128.8, 128.5, 127.8, 120.4, 79.5, 57.5, 39.0, 38.0, 34.5, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{15}N_2O_2]^+$: 255.1128; found: 255.1134.

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Supporting Information

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Appendix 3

Publication III

Silm, E.; Järving, I.; Kanger, T. Asymmetric Organocatalytic Michael Addition of Cyclopentane-1,2-dione to Alkylidene Oxindole. *Beilstein J. Org. Chem.* **2022**, *18*, 167-173.

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Asymmetric organocatalytic Michael addition of cyclopentane-1,2-dione to alkylidene oxindole

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Full Research Paper

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Abstract

An asymmetric Michael reaction between cyclopentane-1,2-dione and alkylidene oxindole was studied in the presence of a multifunctional squaramide catalyst. Michael adducts were obtained in high enantioselectivities and in moderate diastereoselectivities.

Introduction

Diketones are generally very versatile starting materials in organic synthesis [1,2]. Specifically, due to their keto–enol tautomerism and high reactivity, diketones are excellent precursors for different pharmaceuticals [3]. Cyclic 1,3-diketones have been widely exploited to access enantiomerically enriched scaffolds with increased molecular complexity. There are many examples of the organocatalytic synthesis of fused cycles starting from the cyclohexane-1,3-dione. For example, Rueping et al. demonstrated that the cyclohexane-1,3-dione undergoes a cascade reaction with α,β-unsaturated aldehydes [4] and they later employed the method to synthesise indoloquinolizidines [5]. Moreover, six-membered and five-membered cyclic 1,3-diketones have been investigated in reactions with acetates of nitroalkenes [6], cyanoacrylates and benzylidene malononitriles [7], *ortho*-hydroxy-benzhydryl alcohols [8], α,β-unsaturated pyrazolamides [9] and, 2-oxobut-3-enoates [10]. A 1,2-dicarbonyl moiety is also an important structural fragment present in various natural products and biologically active compounds [11]. 1,2-Diketones have been used for the synthesis of photosensitive polymers [12] and substituted imidazoles [13,14] and have been used in carbohydrate chemistry [15]. Cyclic six-membered 1,2-diketones have been shown to react with benzylidene malononitriles [7,16], β-nitrostyrenes [17] and substituted propionaldehydes [18]. For a while, there were no examples related to cyclopentane-1,2-dione (CPD). In 2004, the first instance of using CPD as a precursor for high value-added fine chemicals such as a homocitric acid lactone was published by our group [19]. Since then we have developed synthetic pathways for lycoperdic acid [20] and nucleoside analogues [21] starting from CPD. The organocatalytic methods for the synthe-

sis of substituted cyclopentane diones were uninvestigated until 2014 when we showed that CPD undergoes a Michael addition with nitrostyrenes [22]. Subsequently, different cascade reactions for CPD have been developed: with highly reactive (*E*)-2-oxobut-3-enoates [23], α,β-unsaturated aldehydes [24] and alkylidene malonates [25].

Herein, we report the results of an asymmetric organocatalytic Michael addition of CPD to alkylidene oxindoles.

Results and Discussion

Chiral multifunctional thioureas [26,27] and squaramides [28] are extensively used as catalysts in asymmetric Michael additions. We believed that a bifunctional hydrogen-bonding catalyst would activate both CPD via a tertiary amino group of a quinuclidine moiety acting as a base via anion-binding, and an oxindole through the squaramide or thiourea moieties of the catalyst as hydrogen bond donors (Figure 1) [29-32].

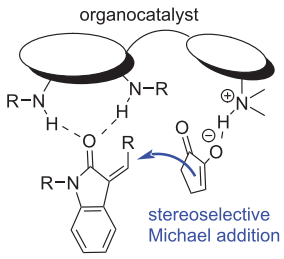


Figure 1: Model of the catalyst action.

Therefore, squaramide and thiourea catalysts were screened in a model reaction between CPD **1** and Boc-protected benzylidene oxindole **2a** at room temperature in the presence of 10 mol % of catalyst (Figure 2).

First, the quinidine-derived squaramide **A** was used and the desired product was obtained as a mixture of chromatographically inseparable diastereoisomers in 53% yield but in low enantiomeric excess for both diastereomers (Table 1, entry 1). With the quinine-derived thiourea **B**, the reaction was slow and the yield was very low, 12% (Table 1, entry 2). For that reason, we focused on the screening of squaramides. Squaramides were found to be more selective catalysts than thioureas. When squaramide **C** was used as a catalyst, the product was isolated in 80%/87% ee (major/minor diastereoisomer) (Table 1, entry 3). The enantioselectivity was even higher with the cinchonine-derived squaramide **D**, 85%/92% (major/minor) (Table 1, entry 4). To further optimise the reaction, we screened different solvents (apolar, polar aprotic, and chlorinated solvents) (Table 1, entries 5–7). According to the obtained results chloroform was clearly superior to other solvents. Previously the isolated yield of the product had been moderate and to increase the yield the substrate concentration was varied. A substantial excess of CPD (five equivalents) led to a very slow reaction and a decrease in enantioselectivity (Table 1, entry 8). It was assumed that the binding between CPD and the catalyst was stronger than the binding between the substituted oxindole and the squaramide decreasing the effective concentration of the catalyst. Taking this into consideration, 2 equiv of substituted oxindole was used and the reaction proceeded smoothly in 2 h in high enantioselectivity (90%/94% ee), in high yield (74%) but in moderate

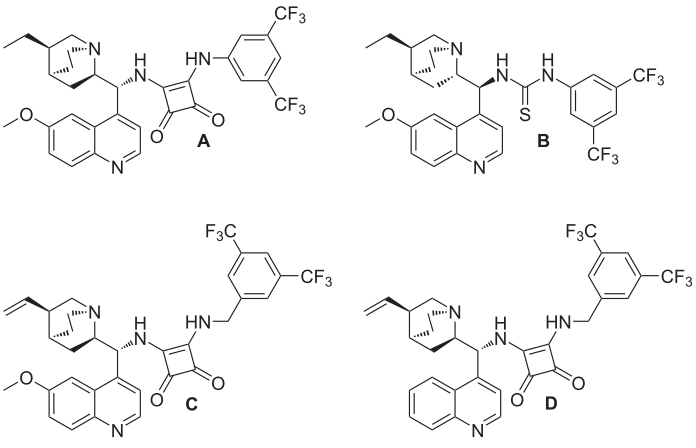
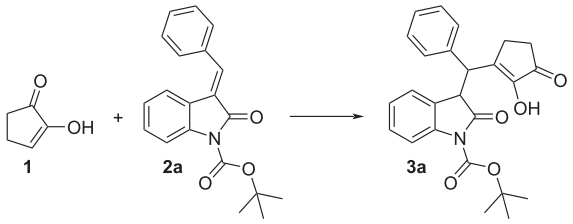


Figure 2: Catalysts screened.

Table 1: Screening conditions for the reaction[a].



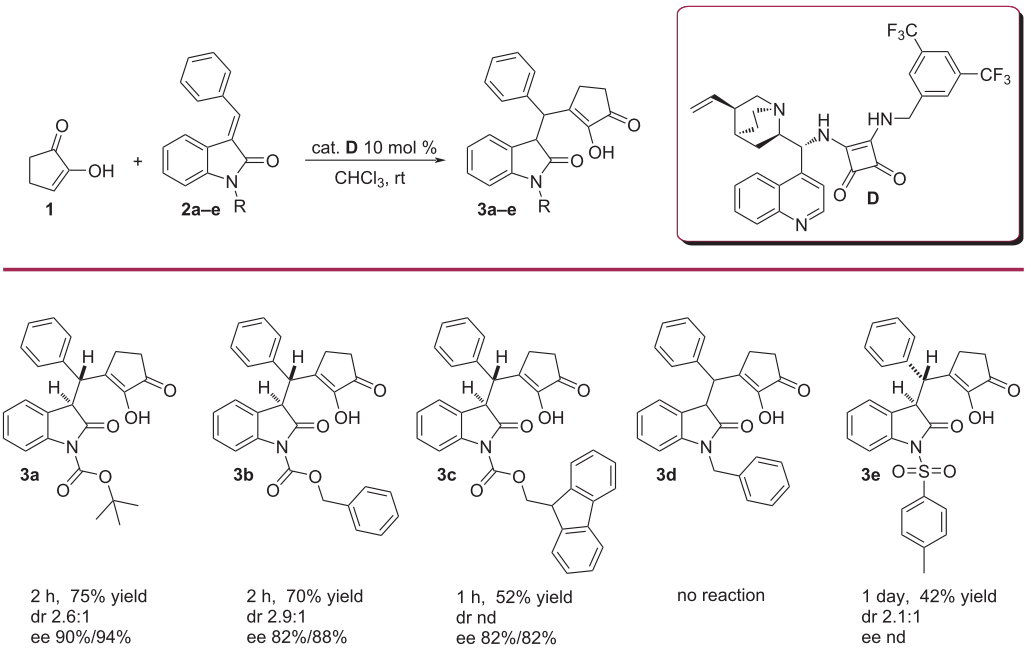
Entry	Catalyst	Solvent	Temp.	Time	Yield[b]	dr	ee%[c] (major/minor)
1	**A**	chloroform	rt	2 h	53%	3:1	43/27
2	**B**	chloroform	rt	6 days	12%	3.8:1	–57/–67
3	**C**	chloroform	rt	7 h	59%	2.4:1	80/87
4	**D**	chloroform	rt	2.5 h	58%	3:1	85/92
5[d]	**D**	toluene	rt	2 days	54%	2.5:1	77/81
6[d]	**D**	THF	rt	2 days	44%	2.6:1	68/74
7[d]	**D**	DCM	rt	1 day	51%	2.5:1	83/83
8[e]	**D**	chloroform	rt	12 days	59%	2.2:1	71/87
9[f]	**D**	chloroform	rt	2 h	74%	2.6:1	90/94
10[f]	**D**	chloroform	0 °C	23 h	75%	2.7:1	90/97

[a]Reaction conditions: 0.2 M solution of **1** (1 equiv), **2** (1 equiv), catalyst (0.1 equiv). [b]Isolated yield after column chromatography. [c]ee determined by chiral HPLC analysis. [d]1.5 equiv of **1**; [e]5 equiv of **1**; [f]2 equiv of **2a**.

diastereoselectivity (Table 1, entry 9). Next, we looked onto the effect of lower temperature on the reaction. At 0 °C the reaction was approximately 10 times slower and only the ee of the minor diastereoisomer increased by 3% (Table 1, entry 10), so there was no justification for carrying out the reaction at a lower temperature because of the longer time needed.

Next, we screened different protecting groups for the oxindole. Previously, Boc-protected oxindole **2a** gave us the product in 75% yield, in dr 2.6:1 and in ee 90%/94% (Scheme 1, **3a**). With a Cbz-protecting group the enantioselectivity decreased to 82%/88% (Scheme 1, **3b**). The use of a sterically more demanding Fmoc-protecting group decreased the ee values even more for the minor diastereoisomer (Scheme 1, **3c**). Surprisingly, with benzyl-protected oxindole, the reaction did not proceed (Scheme 1, **3d**), which implies that the carbonyl group of the carbamate moiety in the *N*-protecting group and electron-withdrawing properties of the protection groups are essential for coordination with the catalyst and for the reactivity of the Michael acceptor. Using a tosyl-protected oxindole the reaction was sluggish, the yield was low and the enantioselectivity could not be determined (Scheme 1, **3e**). These experiments revealed that the best results were achieved in chloroform at room temperature with catalyst **D**, using 1 equiv of diketone and 2 equiv of *N*-Boc-substituted oxindole **2a**.

Under optimised conditions, the substrate scope of the reaction was examined by using various substituted oxindoles with an *E*-configuration of the double bond. The results are presented in Scheme 2. Both electron-withdrawing (Scheme 2, **3f**–**h**) and electron-donating groups (Scheme 2, **3m**,**n**) at the phenyl ring of the benzylidene moiety were tolerated. The position of the halide at the aromatic ring did not have a major effect on the yield or the enantioselectivity. *Ortho*-, *meta*- and *para*-chlorophenyl-substituted starting materials afforded products in similar enantioselectivities (Scheme 2, **3f**–**h**). However, the reaction was slower with the sterically more hindered *ortho*-chloro substrate (Scheme 2, **3f**). When instead of a benzylidene-containing substrate an alkylidene with an extra ester moiety was used, the enantioselectivity was lost and the product **3i** was obtained as a racemic mixture. Either additional coordination with the catalyst or a lack of π–π-interaction may have been responsible for that. Also, a higher C–H acidity of the proton at the stereogenic centre and possible racemisation can't be excluded. A heteroaromatic oxindole derivative afforded the product **3j** in lower yield and high ee values. 4- and 5-bromo oxindole derivatives (**2l** and **2k**, respectively) were also used as starting compounds. If the substituent in the oxindole ring was further from the reaction centre, the outcome was not affected (Scheme 2, **3k**). However, when using a 4-bromo-substituted oxindole, the reaction was slower, the yield drastically decreased and the en-



Scheme 1: Screening of different *N*-protecting groups. Reaction conditions: 0.2 M solution of **1** (1 equiv), **2** (1 equiv), of catalyst **D** (0.1 equiv), chloroform, at room temperature; isolated yields after column chromatography; ee determined by chiral HPLC.

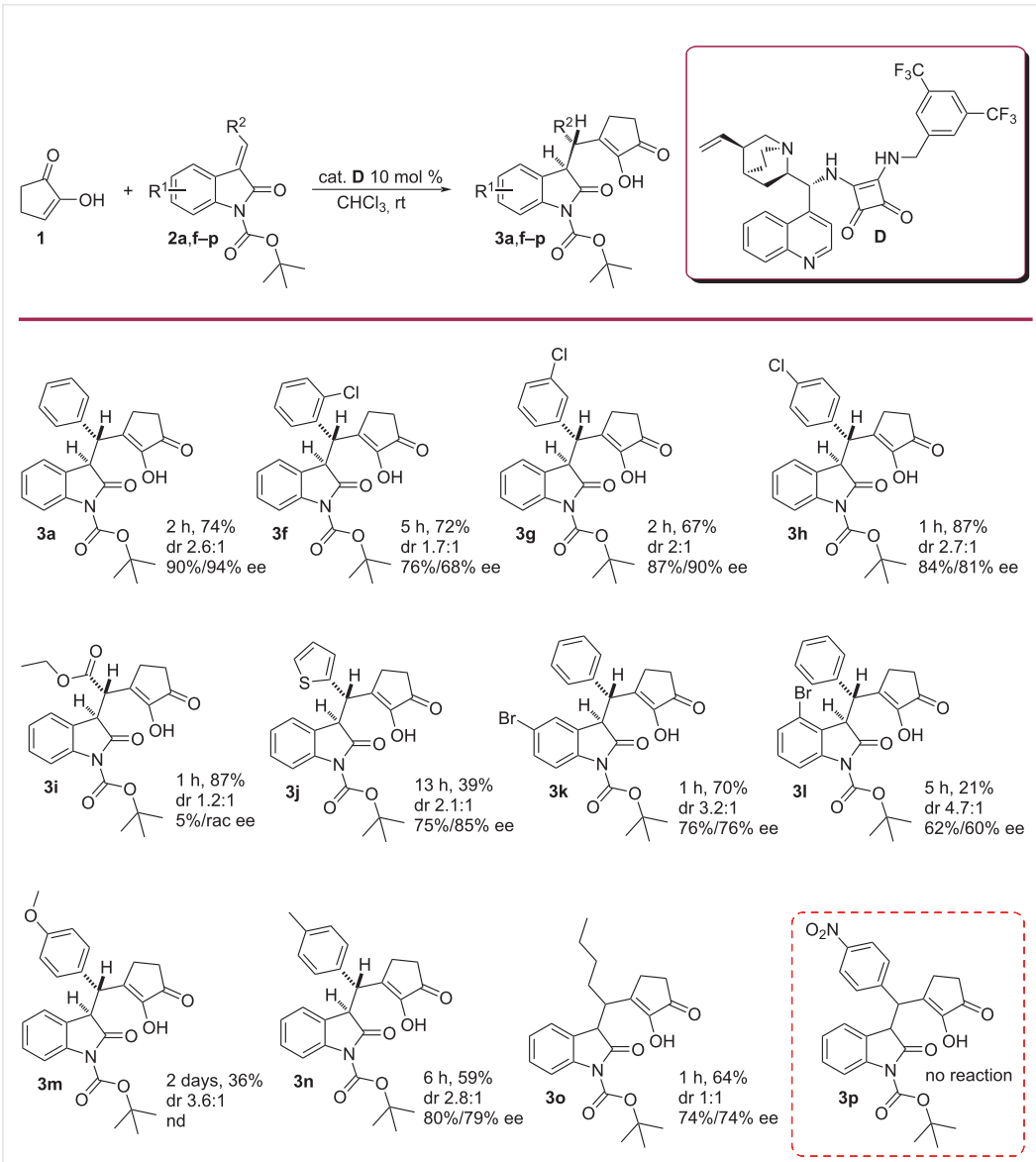
antioselectivity was moderate (Scheme 2, **3l**). The reaction with an electron-donating *p*-MeO-substituted benzylidene oxindole was very sluggish and did not reach full conversion (Scheme 2, **3m**). The product **3m** was obtained with only 36% yield and with undetermined enantiomeric purity, since the peaks were not separable in various HPLC methods. Similarly, the *p*-Me-substituted oxindole was also slow in reacting and the yield was moderate, but the enantioselectivity remained high (Scheme 2, **3n**). The reaction tolerated alkylidene oxindoles, although the product was obtained in a slightly lower yield and enantioselectivity (Scheme 2, **3o**). The reaction did not occur when starting compound **2p** was tried. This was probably because of the very poor solubility of the starting material. Generally, the diastereoselectivities of the reactions were moderate (dr 2.1:1–3.6:1) throughout the scope. The diastereoselectivity was missing or was very low for the compounds with non-aromatic substituents at the double bond (**3i** and **3o**).

The relative *anti*-configuration of the vicinal diastereotopic hydrogens was determined by comparing the $^3J_{HH}$ coupling constants of the major diastereomer with those of the minor diastereomer. The constants were larger for the major diastereomer, meaning vicinal hydrogens were in *anti*-configuration.

In all previous experiments only *E*-isomers were used. In the case of the 3-nitro-substituted starting material **2q** we managed to separate isomers and carried out the reaction with both the *E*- and *Z*-isomer. In these experiments, both isomers afforded the same major diastereoisomer but opposite enantiomers (Scheme 3, **3q**). The diastereoselectivities were similar for the isomers.

Since the diastereoselectivity of the reaction was low, we attempted to increase the ratio of diastereoisomers via enolisation followed by diastereoselective protonation (Table 2). As the racemate of **3a** was obtained in a higher diastereomeric ratio (6.3:1) we applied kinetic and thermodynamic conditions for the epimerisation of it (Table 2, entries 1 and 2, respectively). Unfortunately, in both cases the diastereomeric ratio decreased and the amount of more stable *syn* diastereoisomer increased. A similar trend was observed when starting from the enantiomerically enriched **3a** (Table 2, entry 3).

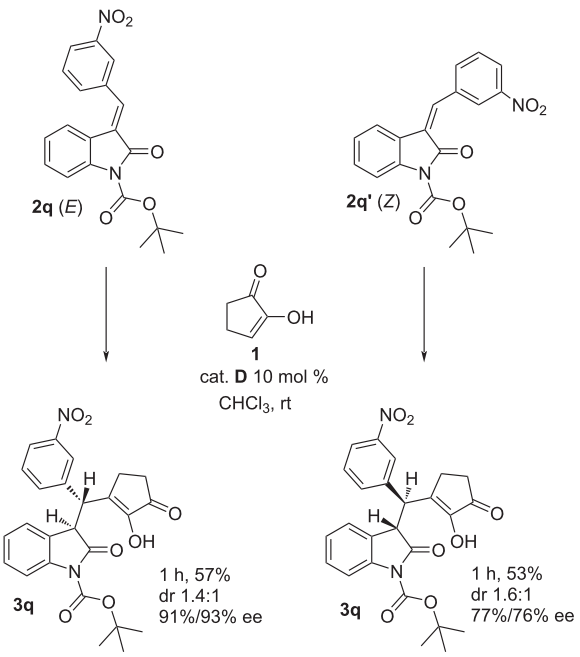
It has been shown that substituted oxindoles can be converted to indolopyrans via intramolecular cyclisation [33]. We also tried synthesizing 4*H*-pyrans in acidic conditions but no cyclised product was detected.



Scheme 2: Scope of the reaction (the relative configuration of the major diastereoisomer is depicted). Reaction conditions: 0.2 M solution of 1 equiv of **1**, 2 equiv of **2**, 0.1 equiv of catalyst **D**, chloroform, at room temperature; isolated yields after column chromatography; ee determined by chiral HPLC.

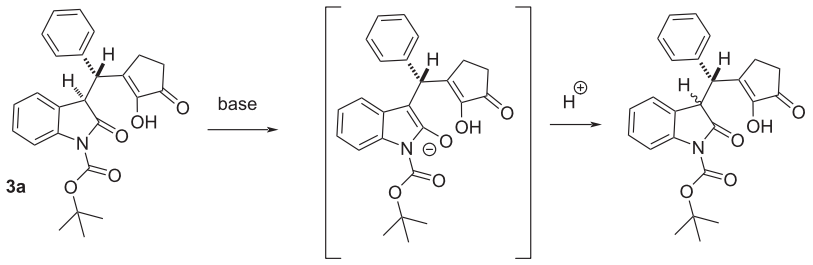
Conclusion

In summary, we have developed a new asymmetric organocatalytic Michael addition of cyclopentane-1,2-dione to alkylidene oxindoles catalysed by bifunctional squaramide which leads to products in high enantioselectivities and moderate diastereoselectivities. The scope of alkylidene oxindoles is reasonably wide including aromatic and aliphatic substituents at the double bond and also substituents in the oxindole core. The work widens the synthetic utility of cyclopentane-1,2-diones.



Scheme 3: Comparison reactions of *E*- and *Z*-isomers (the relative configurations of the major diastereoisomers are depicted). Reaction conditions: 0.2 M solution of 1 equiv of **1**, 2 equiv of **2**, 0.1 equiv of catalyst **D**, chloroform, at room temperature; isolated yields after column chromatography; ee determined by chiral HPLC.

Table 2: Epimerisation of **3a**.



Entry	Starting compound		Conditions	Product (dr)
		dr		
1	**3a** (rac)	6.3:1	LDA, THF; −78 °C, 30 min, then sat. aq. NH_4Cl	2.7:1
2	**3a** (rac)	6.3:1	*t*-BuOK/*t*-BuOH, rt, overnight	2.6:1
3	**3a**	2.5:1	LiHDMS, THF; −78 °C, 30 min, then sat. aq. NH_4Cl	2.2:1

Supporting Information

Supporting Information File 1

Experimental details, NMR spectra, HPLC chromatograms.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-18-S1.pdf]

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