THESIS ON NATURAL AND EXACT SCIENCES B244

Enantioselective H-Bond Catalyzed Spirocyclopropanation and Wittig [2,3]-Rearrangement

MAKSIM OŠEKA

TTÜ PRESS

TALLINN UNIVERSITY OF TECHNOLOGY
School of Science
Department of Chemistry and Biotechnology

This dissertation was accepted for the defense of the degree of Doctor of Philosophy in Chemistry on November 20, 2017.

Supervisor:	Prof. Tõnis Kanger, Department of Chemistry and Biotechnology, School of Science, Tallinn University of Technology, Estonia
Reviewed by:	Dr. Kadri Kriis, Department of Chemistry and Biotechnology, School of Science, Tallinn University of Technology, Estonia
Opponents:	Prof. Petri M. Pihko, University of Jyväskylä, Department of Chemistry, Finland Assoc. Prof. Uno Mäeorg, University of Tartu, Institute of Chemistry, Chair of Organic Chemistry, Estonia

Defense of the thesis: 15th of December 2017, Tallinn

Declaration:

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

---
signature

ISSN 1406-4723
ISBN 978-9949-83-191-3 (publication)
ISBN 978-9949-83-192-0 (PDF)

LOODUS- JA TÄPPISTEADUSED B244

Enantioselektiivne H-sideme katalüüsitud spirotsüklopropaneerimine ja Wittigi [2,3]-ümberasetusreaktsioon

MAKSIM OŠEKA

TTÜ KIRJASTUS

Contents

List of publications 6
Author's contribution to the publications 6
Introduction 7
Abbreviations 8
1 Literature overview 10
1.1 Enantioselective H-bond mediated catalysis 10
1.2 Asymmetric spirocyclopropanation 12
1.2.1 Organocatalyzed spirocyclopropanation 13
1.2.2 Transition metal-catalyzed spirocyclopropanation 17
1.2.3 Summary of asymmetric spirocyclopropanation 19
1.3 Asymmetric Wittig [2,3]-rearrangement 19
1.3.1 Stoichiometric approach 20
1.3.2 Catalytic approach 23
1.3.3 Summary of an asymmetric Wittig [2,3]-rearrangement 25
2 Aims of the present work 26
3 Results and discussion 27
3.1 Asymmetric diastereoselective synthesis of spirocyclopropane derivatives of oxindole (Publication I) 27
3.2 Asymmetric organocatalytic Wittig [2,3]-rearrangement of oxindoles (Publication II) 33
3.3 Asymmetric organocatalytic Wittig [2,3]-rearrangement of malonates (Publication III) 43
4 Conclusions 47
5 Experimental 48
References 53
Publication I 57
Publication II 67
Publication III 73
Acknowledgments 85
Abstract 86
Lühikokkuvõte 87
Elulookirjeldus 88
Curriculum vitae 89

List of publications

I Ošeka, M.; Noole, A.; Žari, S.; Öeren, M.; Järving, I.; Lopp, M.; Kanger, T. Asymmetric Diastereoselective Synthesis of Spirocyclopropane Derivatives of Oxindole. *European Journal of Organic Chemistry* **2014**, 3599-3606.

II Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement of Oxindoles. *Organic Letters* **2016**, *18*, 1358-1361.

III Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. Two Catalytic Methods of an Asymmetric Wittig [2,3]-Rearrangement. *The Journal of Organic Chemistry* **2017**, *82*, 2889-2897.

Author's contribution to the publications

I, II and III (organocatalytic pathway):

Planning and carrying out the experiments, characterization of the obtained products, and major role in manuscripts preparation.

Introduction

Chirality plays an essential role in biological processes. The majority of naturally occurring molecules, such as amino acids, sugars, nucleic acids, alkaloids etc are present as single enantiomers. The development of new stereoselective methodologies for the synthesis of chiral products has significant importance for the synthetic chemistry. Opposite enantiomers of one compound can have different biological activities varying from lower activity of one enantiomer to quenching activity of each other towards one biological target.

With known chemistry techniques, almost every compound with high levels of stereocomplexity can be synthesized. Resolving racemic mixtures, using chiral auxiliaries or starting from natural chiral building blocks can be applied. However, the real challenge is to obtain the final chiral product atom efficiently with minimum reaction steps, thereby lowering the cost, time spent and amount of waste. Enzymatic transformations and asymmetric organometallic catalysis were generally used to achieve this goal until the end of the last century, when organocatalysis, using small enantiomerically pure organic molecules as catalysts, became a new popular research field of enantioselective synthesis. The organocatalytic approach does not require an inert atmosphere or completely dry conditions which makes it possible to use simple reaction setups.

This doctoral thesis is focused on the development of a new enantioselective H-bond catalyzed spirocyclopropanation and the Wittig [2,3]-rearrangement. A spirocyclopropane core structure can be found in many natural and synthetic compounds, exhibiting a wide range of biological activities, which has made them valuable synthetic targets (Publication I). The Wittig [2,3]-sigmatropic rearrangement of allylic or propargylic ethers is an efficient tool for the insertion of stereocomplexity into organic compounds and has found application as a key step for the total synthesis of various natural products (Publications II and III).

Abbreviations

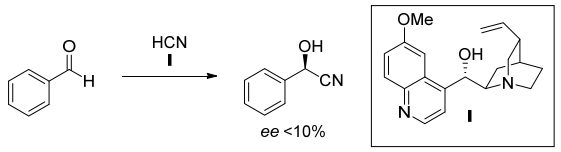
Ac	acetyl
aq.	aqueous
Ar	aryl
B	base
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butyloxycarbonyl
Bu	butyl
CC_{50}	concentration that reduced cell viability by 50%
Cy	cyclohexyl
d.r.	diastereomeric ratio
DCE	1,2-dichloroethane
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylmethanamide
DMSO	dimethyl sulfoxide
EC_{50}	half maximal effective concentration
ee	enantiomeric excess
Et	ethyl
EWG	electron-withdrawing group
EPR	electron paramagnetic resonance
equiv.	equivalent
HIV-1	human immunodeficiency virus, type 1
HMDS	bis(trimethylsilyl)amine, hexamethyldisilazane
HPLC	high pressure liquid chromatography
Huh7	well differentiated hepatocyte-derived carcinoma cell line
*i*Pr	isopropyl
*K*i	inhibitor affinity
L	ligand
LDA	lithium diisopropylamide
LG	leaving group
LUMO	lowest occupied molecular orbital
Me	methyl
MIRC	Michael-initiated ring-closure
MS	molecular sieves
MT4	human tumor cell line
MTBE	methyl *tert*-butyl ether
*n*Bu	normal butyl
NMR	nuclear magnetic resonance
Nu	nucleophile
PG	protecting group

Ph	phenyl
pK_a	acid dissociation constant at logarithmic scale
PTC	phase transfer catalysis
RP	reversed-phase
rt	room temperature
SAEP	(*S*)-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine
TACE	tumor necrosis factor α converting enzyme
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
Tf	triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl

1 Literature overview

1.1 Enantioselective H-bond mediated catalysis

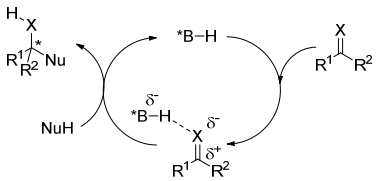
The cyanation of aldehyde in the presence of *Cinchona* alkaloid quinidine **I**, developed by Bredig in 1912, is considered to be the first example of an asymmetric organocatalytic reaction (Scheme 1).[1] Despite the early discovery, the field of organocatalysis remained rather unexploited for more than eighty years.



Scheme 1. First example of asymmetric organocatalysis.

Two main types of modern organocatalysis are recognized: covalent, in which a catalyst forms a covalent bond with a starting compound (amines and carbenes are used as catalysts) and non-covalent, in which a catalyst forms an active complex with starting materials through weak interactions. In this chapter a brief overview of H-bond mediated organocatalysis is given.

H-bond interactions play a fundamental role in the special folding of proteins and nucleic acids. Moreover, enzymatic reactions and biological molecular recognition would be impossible without hydrogen bonds.[2] In H-bond mediated reactions, the organocatalyst, as a donor, activates the electrophilic substrate by lowering its electron density (it decreases the LUMO). The chirality of the substrate-catalyst complex derived from the catalyst leads to an enantioselective attack of the nucleophile and the formation of an asymmetric product (Scheme 2).[3]



Scheme 2. General mechanism for the asymmetric H-bond mediated nucleophilic addition.

H-bond catalysis can be divided into two groups according to activation mode: simple hydrogen bonding and bifunctional catalysis (Figure 1).[4,5,6] These catalysts feature different activation mechanisms and reactivities.[7] In pioneering research, Jacobsen *et al.* used chiral thioureas as organocatalysts for the Strecker reaction, which demonstrated the great potential of asymmetric hydrogen bond catalysis.[5] Five years later, the Takemoto research group developed the first chiral bifunctional catalyst.[6] The chiral tertiary amino group of the catalyst serves as a base, while the thiourea fragment links to the electrophile and controls the nucleophilic attack. Also, an unmodified *Cinchona* alkaloid, such as quinidine **I**, containing the basic quinuclidine group and the hydroxy group as the H-bond donor can be used as a bifunctional catalyst.[8]

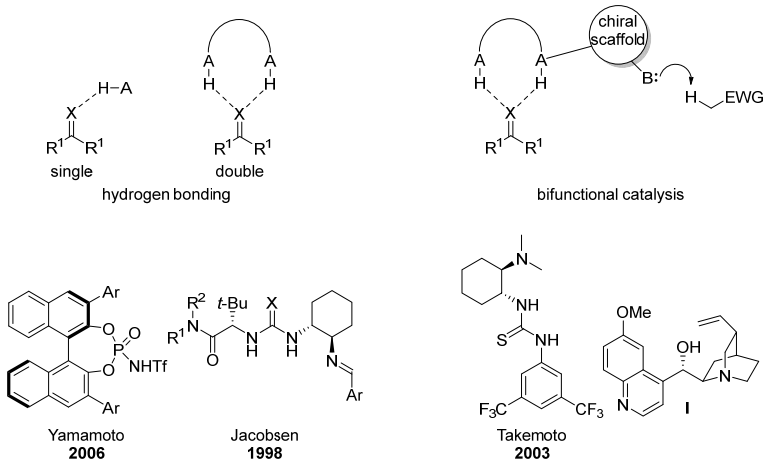


Figure 1. Modes of hydrogen bond catalysis.

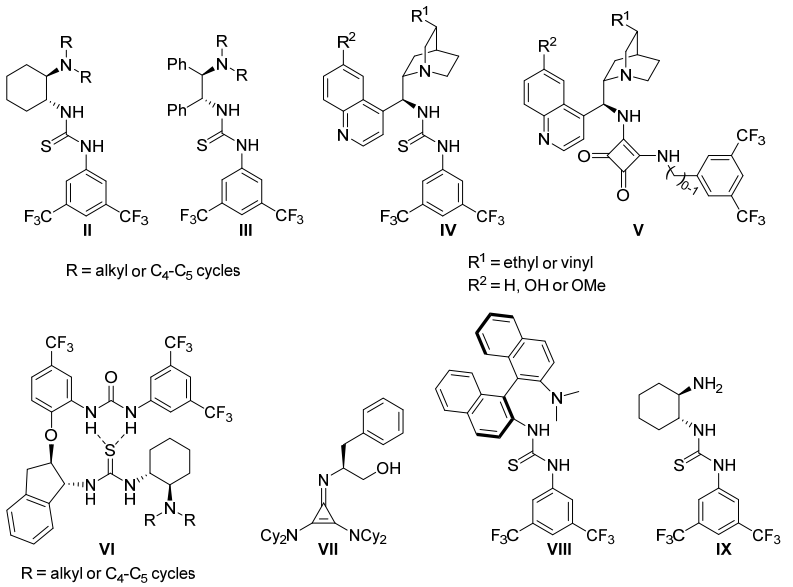


Figure 2. Examples of chiral bifunctional catalysts.

Over the years, a significant number of different bifunctional catalysts have been synthesized and applied in various reactions (Figure 2). While thioureas **II** and **III** are based on enantiomerically pure diamines, it is very common to use such natural products as *Cinchona* alkaloids as chiral cores in bifunctional catalysts (Soós-type thiourea **IV** and squaramide **V**).[9,10,11] In 2012 Pihko *et al.* reported a Mannich reaction catalyzed by a cooperatively assisted urea−thiourea catalyst **VI**.[12] In this novel catalyst, the urea group activates the thiourea group through intramolecular hydrogen bonds, strengthening the H-donor properties of the latter. Another example of the tuned bifunctional catalyst **VII** was reported by the Lambert group.[13] The new family of catalysts is based on a highly basic cyclopropenimine scaffold, whose basicity is comparable to that of guanidines. The bifunctionality of H-bond catalysts is not limited to Lewis/Brønsted basicity. In the work published by the Wang research group, the

tertiary amino group of BINOL-derived thiourea **VIII** promoted a Morita-Baylis-Hillman reaction by a nucleophilic addition to the substrate, which is activated by dual H-bonding.[14] Moreover, bifunctional catalysts bearing primary (thiourea **IX**) or secondary amino groups have been successfully applied in iminium/enamine activation catalysis.[15]

Although squaramide-based bifunctional catalysts are not as widely used as thiourea analogs, they have structural and electronic properties which can be beneficial in certain reactions (Figure 3).[16] The most important differences are a) H-bond formation duality in squaramides, b) H-bond spacing distances, c) disposition of the hydrogen bonds, d) rigidity and e) pK_a values (squaramides are more acidic).

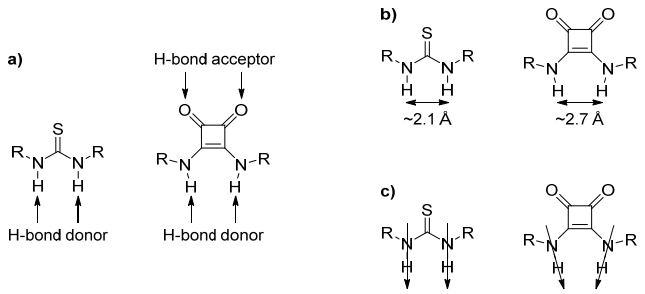


Figure 3. Differences in thioureas and squaramides.

To sum up, combining different chiral scaffolds with different hydrogen bonding fragments and activation modes provides great opportunity for the catalyst design. Asymmetric H-bond mediated catalysis has become a versatile tool in the modern organic synthesis and remains to be a gradually developing field of research.

1.2 Asymmetric spirocyclopropanation

Natural products containing the spirocyclopropane motif exhibit a wide range of biological activities and have inspired scientists to develop new methods for the synthesis of their analogs (Figure 4). For example, the fungal metabolite illudins M and S are highly cytotoxic against tumor cell lines (Huh7 and MT4).[17] Spirocyclopropyl oxindole **1**, which was isolated from the cells of cultured cyanobacteria, acts as an arginine vasopressin inhibitor.[18] Novel spirocyclopropyl hydroxamate **2** inhibits TACE and potentially can be applied in the treatment of various autoimmune disorders such as rheumatoid arthritis, Crohn's disease and psoriasis.[19] Synthetic spirocyclopropyl oxindole **3** has showed nanomolar level activities as an HIV-1 non-nucleoside reverse transcriptase inhibitor, whereas oxindoles **4** exhibit antitumor activity and are effective in the treatment of obesity and diabetes.[20,21]

From the synthetic point of view, constructing a substituted spirocyclopropane unit in the asymmetric fashion is an especially challenging task due to the presence of three continuous carbon stereocenters in the highly strained three-membered ring.[22] Several successful methods have been developed to achieve this goal and can be divided into two main groups: organocatalyzed and transition metal-catalyzed approaches. Spirocyclopropyl compounds containing different functional groups or substituents can be obtained depending on the type of the catalysis applied.[23]

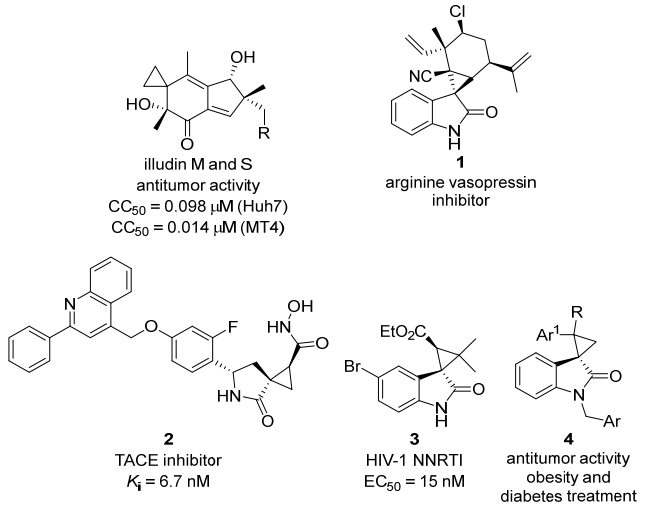
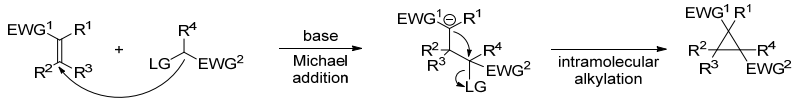


Figure 4. Bioactive compounds containing spirocyclopropane unit.

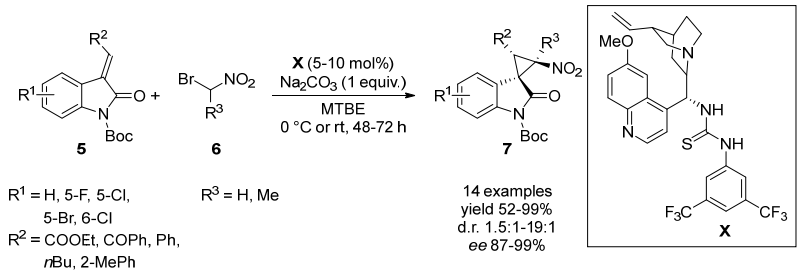
1.2.1 Organocatalyzed spirocyclopropanation

The selected organocatalytic methods described in this section are based on a Michael-initiated ring-closure mechanism, an efficient tool for the synthesis of cyclopropanes with high stereocontrol (Scheme 3).[24] The sequence starts with the conjugated addition to α,β-unsaturated electrophiles, which typically leads to the formation of an enolate or its synthetic equivalent and intramolecular ring closure. In theory, with an appropriate combination of reaction conditions and a catalyst in hand, a cyclopropane with three adjacent quaternary carbon centers can be obtained. Enantiomeric H-bond, amino and PTC-catalysts have been used to achieve high enantioselectivity of the cyclization.



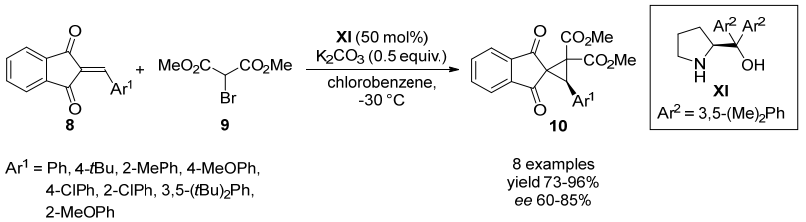
Scheme 3. Michael-initiated ring-closure mechanism.

A highly enantioselective cyclopropanation of alkylidene oxindole **5** with bromonitromethane **6** was reported by the Bencivenni group (Scheme 4).[25] The reaction is catalyzed by thiourea **X** and provides spirocyclopropyloxindole **7** in good to excellent yields and selectivities. Only an insignificant decrease in selectivity was observed when different R^1 and R^2 groups were tested. Products with two adjacent quaternary carbon centers were obtained when α-bromonitromethane **6** was used as a Michael donor. However, in this case the diastereoselectivity of the reaction was considerably lower. According to the authors, bromonitromethane **6** is activated by the basic quinuclidine moiety, while both carbonyl groups of the alkylidene oxindole **5** are simultaneously hydrogen-bonded to the thiourea fragment, which plays a crucial role in the stereochemical outcome of the reaction.



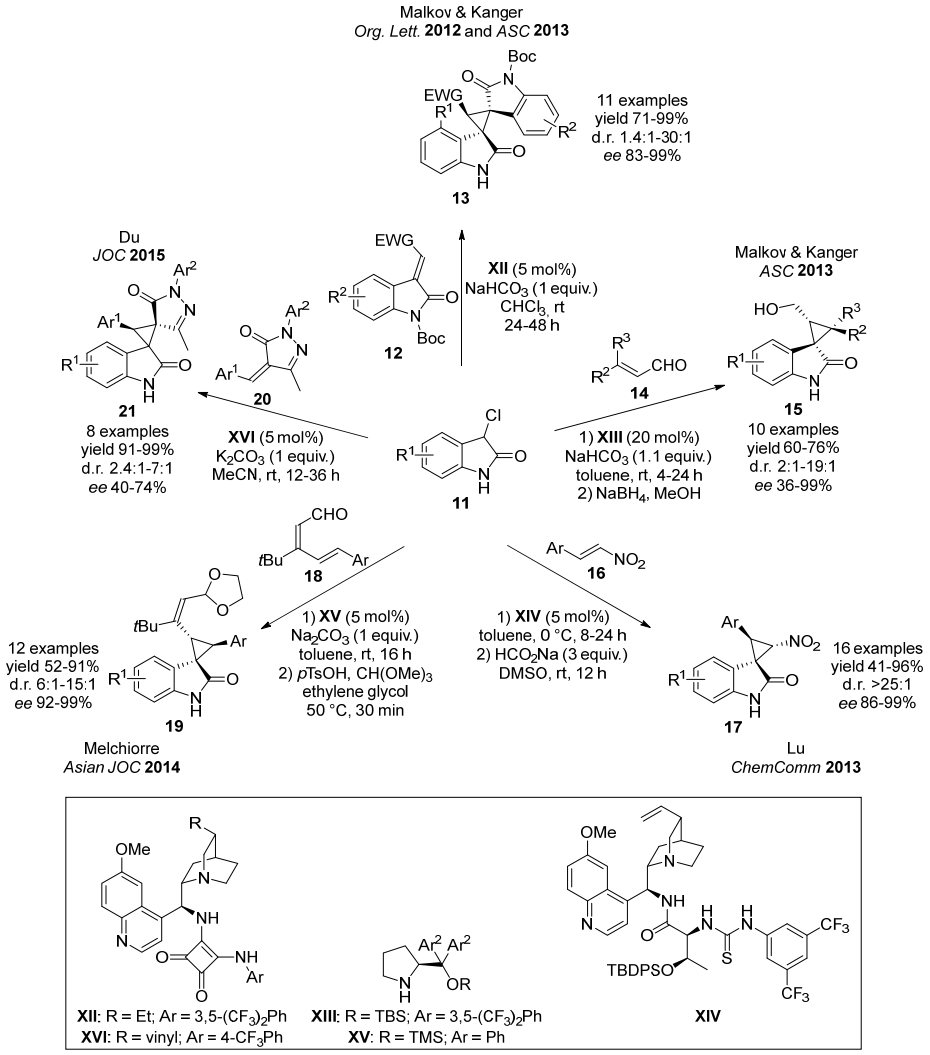
Scheme 4. Cyclopropanation of alkylidene oxindole **5**.

Only a few months later, Lattanzi *et al.* published another example of organocatalytic enantioselective spirocyclopropanation (Scheme 5).[26] The bifunctional catalyst **XI**, as a secondary amine, is usually used for iminium/enamine activation through condensation to carbonyl compounds. However, in this reaction it acts as a base by deprotonating bromomalonate **9** and coordinates Michael acceptor **8** through hydrogen bonding. Despite the similar activation mode compared to the previous example, cyclopropanation did not proceed under identical conditions when Soós-type thiourea catalysts were used. Although high catalyst loading was needed to obtain spirocyclopropanes **10** in excellent yields and good enantioselectivity, the given methodology confirmed the potential of the noncovalent catalysis for spirocyclopropanation.



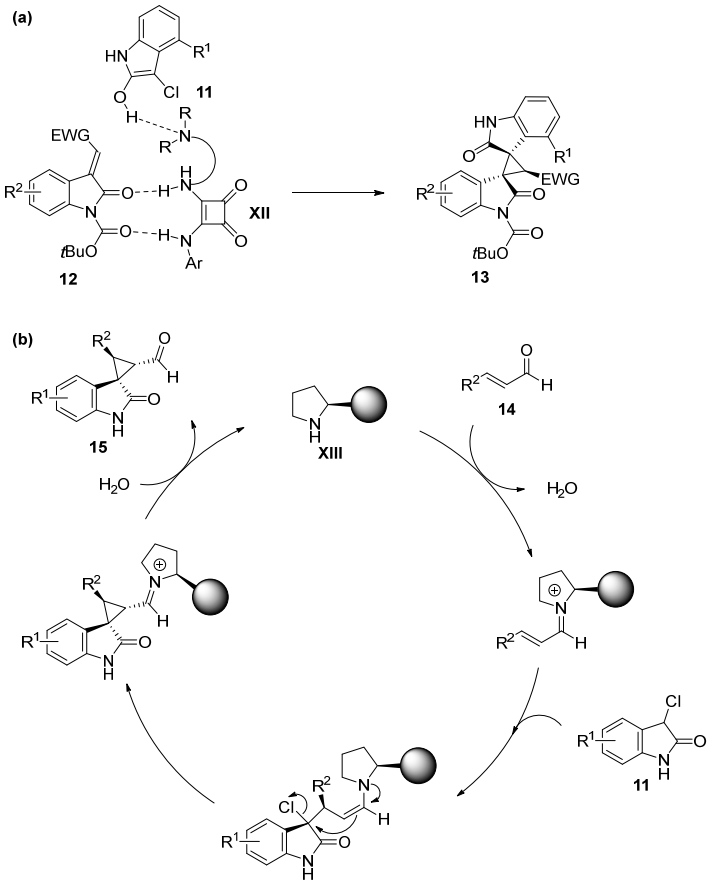
Scheme 5. Enantioselective synthesis of spirocyclopropane **10**.

In 2012, our research group in collaboration with Prof. Malkov reported the preliminary results of enantioselective spirocyclopropanation in which 3-chlorooxindole **11** was used as a Michael donor (Scheme 6).[27] On the one hand, the chlorine atom at the third position of the oxindole increases the acidity of the C3 proton. On the other hand, chlorine is a good leaving group, making 3-chlorooxindole **11** a perfect candidate for the formation of the quaternary stereocenter in cascade reactions. A year later, a new reaction of chlorooxindole **11** with α,β-unsaturated aldehydes **14**, leading to the formation of spirooxindoles **15**, was described, and a broadened scope of bis-spirooxindoles **13** was disclosed.[28] Our group has demonstrated that 3-chlorooxindoles **11** can participate in the reactions catalyzed by two different types of organocatalysts, which triggered other researchers to use it as a precursor in the synthesis of spirocyclopropyl oxindoles (Scheme 7).



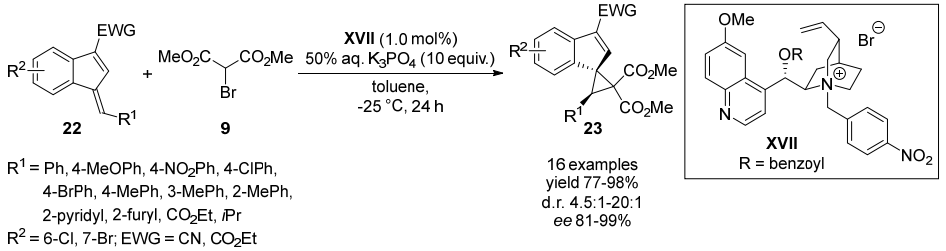
Scheme 6. Spirocyclopropanation of 3-chlorooxindole **11**.

Lu *et al.* reported a two-step procedure for the synthesis of spirocyclopropyl oxindoles **17**.[29] The first step is an enantioselective Michael addition of 3-chlorooxindoles **11** to nitrostyrene **16** catalyzed by thiourea **XIV** followed by the intramolecular trapping of the intermediate under basic conditions. The final products **17** were isolated with outstanding diastereo- and enantioselectivities. In the work of the Melchiorre group, the highly stereoselective synthesis of spirocyclopropyl oxindoles **19** was achieved by a cascade reaction that integrates a vinylogous iminium/dienamine tandem sequence.[30] The authors demonstrated the complete control of the δ-site selectivity of the 1,6-conjugated addition of 3-chlorooxindoles **11** to linear 2,4-dienals **18**, introducing a bulky group within the β-dienal structure. Du *et al.* described another example of the spirocyclopropanation of 3-chlorooxindole **11**, in which arylidenepyrazolone **20** was used as a Michael acceptor.[31] The highly functionalized spiro-pyrazolone-cyclopropane-oxindole **21** contains three motifs that can be found in many biologically active molecules, making it a particularly valuable compound for pharmaceutical studies.



Scheme 7. (a) H-bond activation; (b) iminium/enamine activation.

In one of the latest examples, Jørgensen *et al.* explored benzofulvenes **22** as Michael acceptors in asymmetric phase transfer catalysis, employing a *Cinchona* alkaloid based quaternary ammonium salt catalyst **XVII** (Scheme 8).[32] A wide range of cyclopropane spiroindenes **23** carrying different functional groups (aromatic, heteroaromatic, carbonyl and aliphatic) were synthesized in excellent yields and selectivities at a very low catalyst loading for organocatalysis.



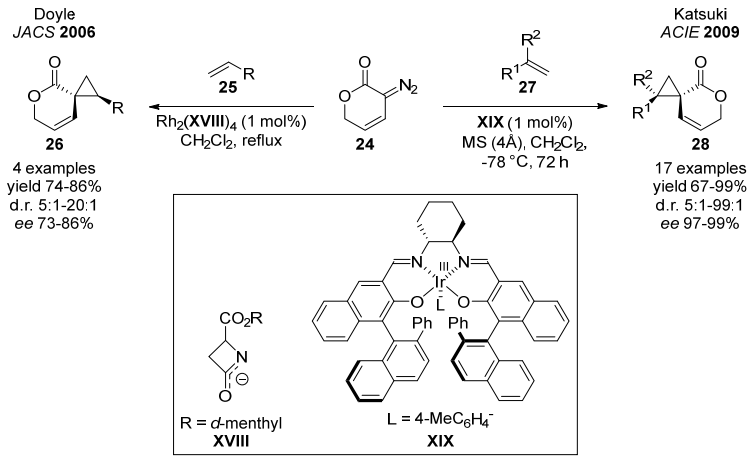
Scheme 8. Spirocyclopropanation of benzofulvenes **22**.

1.2.2 Transition metal-catalyzed spirocyclopropanation

Asymmetric organocatalytic Michael-initiated ring-closure reactions are generally limited to electron-deficient olefins and fail to incorporate electron-neutral olefins or the selectivity of such transformations is rather low. On the other hand, catalytic reactions involving metallocarbenes are well-known for cyclopropanation in which there is a formal addition to a carbon-carbon double bond of electron-neutral or rich olefins (Scheme 9).[33] Usually, active metallocarbene intermediates are formed upon the reaction of diazocarbonyl compounds with a transition metal catalyst. Nevertheless, this type of transformation is very sensitive to the steric hindrance and geometry of olefins, making it rather challenging to achieve high efficiency and stereocontrol in the catalytic cyclopropanation.[34]

Scheme 9. Metallocarbene intermediate in cyclopropanation.

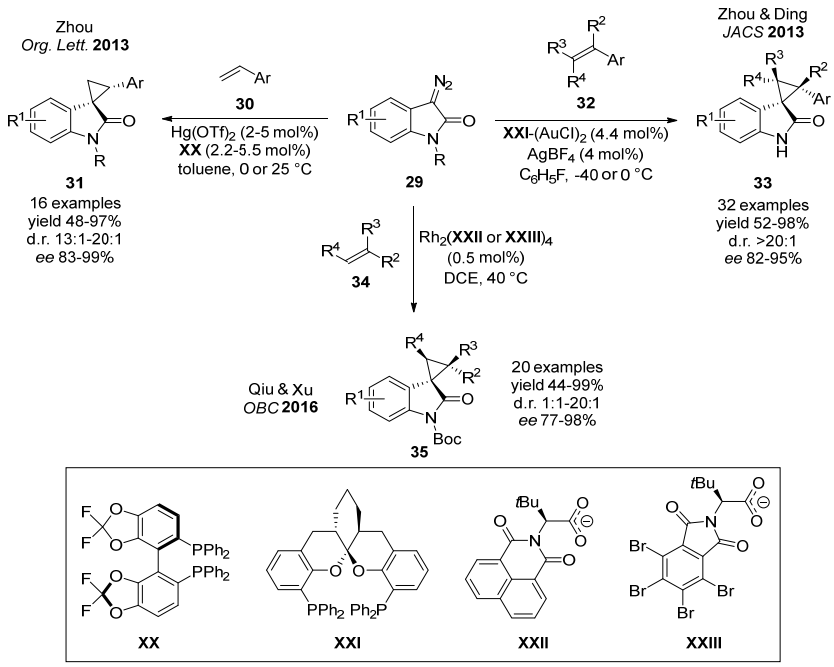
Doyle and co-workers reported the asymmetric rhodium-catalyzed spirocyclopropanation of diazolactone **24** (Scheme 10).[35] Although the reaction scope is limited to four substrates and the enantioselectivity is moderate, the synthesized α-spirocyclopropyl lactones **26** are very useful compounds that can be converted into various building blocks. Later, Katsuki's research group broadened the scope of the reaction considerably, by using an Ir(III)-catalyst.[36] Performing cyclopropanation at -78 °C, the authors achieved outstanding diastereo- and enantioselectivities (d.r. > 16:1 and *ee* > 97% in most cases).



Scheme 10. Spirocyclopropanation of diazolactone **24**.

Zhou *et al.* reported the first highly diastereo- and enantioselective mercury-catalyzed olefin cyclopropanation using diazooxindoles **29** (Scheme 11).[37] Generally, different substituents of the diazooxindoles **29** had little influence on the selectivity and spirocyclopropyl oxindoles **31** were isolated in high diastereomeric and enantiomeric purities and also in high yields. Although substituted styrenes **30** also worked reasonably well, disubstituted alkenes, such as *trans*-anethole, α-methylstyrene and indene, provided products in only moderate yields and enantiopurities. In view of this

challenge, the group turned their attention to the exploration of Au(I)-catalysis in asymmetric olefin cyclopropanation.[38] In the gold-catalyzed reaction, a broad range of highly substituted alkenes **32** were used, including 1,1-disubstituted, 1,1,2-trisubstituted, simple 1,2-disubstituted *cis* and *trans*, and terminal ones. The products **33** were isolated with generally excellent yields (up to 98%) and stereoselectivities (d.r. > 20:1 in all cases and 82-95% *ee*). However, only unprotected diazooxindoles **29** could be used in the gold-catalyzed version, whereas both protected and unprotected substrates were suitable for the mercury-catalyzed olefin cyclopropanation. Moreover, these methods are limited only to aryl substituted substrates, because very low reactivity and selectivity were observed in the reaction with alkyl-substituted olefins under gold-catalysis conditions (4 days, 18% yield and 70% *ee*), leaving room for further development.

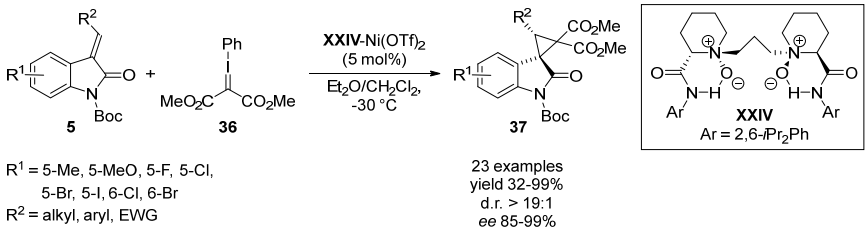


Scheme 11. Spirocyclopropanation of diazooxindoles **29**.

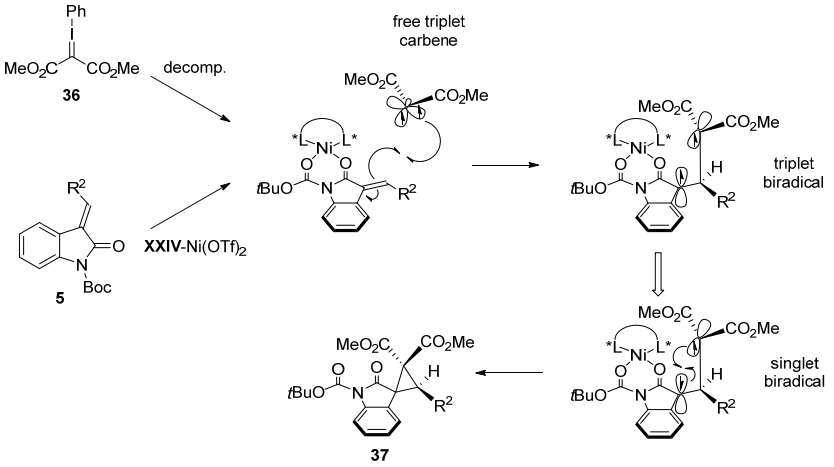
A similar approach was used by Qiu and Xu for the synthesis of spirocyclopropyl oxindoles **35** starting from Boc-protected diazooxindole **29**.[39] The dirhodium-catalysts used in this study are much more reactive towards alkyl-substituted alkene substrates, compared to gold- and mercury-catalysts. Both aryl- and alkyl-substituted spirocyclopropyl oxindoles **35** were synthesized with low catalyst loading in good to high yields and high to excellent enantioselectivities. The authors also claim that the steric effect of the Boc-protecting group plays a critical role in the stereoinduction process.

Alternatively to the methods described above, Feng's research group used phenyliodonium ylide malonate **36** for the cyclopropanation of alkylidene oxindole **5** (Scheme 12).[40] Phenyliodonium ylide decomposes under mild reaction conditions to form free triplet carbene, which undergoes an asymmetric electronic addition to the

double bond of alkylidene oxindole **5** activated by a chiral Lewis acid (nickel complex). The authors proved by EPR spectroscopy that the cyclopropanation occurs through a stepwise mechanism involving a biradical intermediate (Scheme 13). The transformation tolerated a wide range of substituents (both electron-donating and -withdrawing) in close proximity to the reaction center in alkylidene oxindole **5**. Spirocyclopropyl oxindoles **37** were obtained as single diastereoisomers in outstanding yields and enantioselectivities in most cases. Decreased reactivity was observed only for highly bulky substrate (R^2 = Cy).



Scheme 12. Spirocyclopropanation *via* free triplet carbene.



Scheme 13. Proposed stereochemical model.

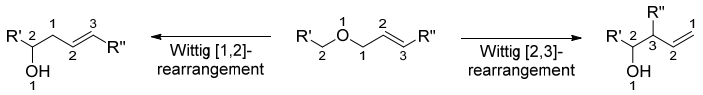
1.2.3 Summary of asymmetric spirocyclopropanation

Spirocyclopropanes are versatile building blocks for the synthesis of bioactive compounds. The asymmetric cyclopropanation of electron-deficient olefins is generally realized with an organocatalytic MIRC reaction sequence, while electron-neutral or rich olefins undergo cyclopropanation via transition metal-catalyzed carbene transfer. Organocatalytic methods are operationally simple and more flexible, whereas metal-catalyzed reactions are very sensitive to bulkiness and the geometry of substrates and usually require dry and oxygen-free conditions. On the other hand, excellent stereocontrol can be achieved in metal-catalyzed reactions even with very low catalyst loadings.

1.3 Asymmetric Wittig [2,3]-rearrangement

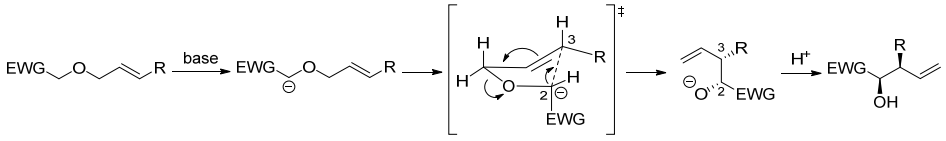
The Wittig rearrangement is a pericyclic sigmatropic reaction that leads to the formation of homoallyl alcohols from allyl ether derivatives.[41] The rearrangement of

allyl ether was first reported in 1949 by the G. Wittig research group.[42] Nevertheless, the mechanism of this reaction was unclear until 1960, when Cast and Stevens unambiguously proved that the transformation proceeds through a [2,3]-allylic shift.[43] While the Wittig [1,2]- and [2,3]-rearrangements are well described for the preparation of substituted alcohols (Scheme 14), [1,4]- and [3,4]-rearrangements remain rather unexamined. A comprehensive description of only the Wittig [2,3]-rearrangement is provided in this chapter.



Scheme 14. Wittig [1,2]- and [2,3]-rearrangement.

A Wittig [2,3]-rearrangement is induced by a base, which deprotonates allyl ether, and the formed carbanion is stabilized by an electron-withdrawing group (Scheme 15). The intermediate undergoes a concerted sigmatropic rearrangement through a five-membered envelope-like transition state that leads to the cleavage of the ether C–O bond and to the formation of a new C–C bond. Finally, the homoallyl alcohol is released after protonation. Because of the well-defined five-membered transition state, the reaction usually proceeds with a high level of stereocontrol caused by steric effects and electronic interactions. Depending on the substituents, up to two stereogenic centers can be formed.



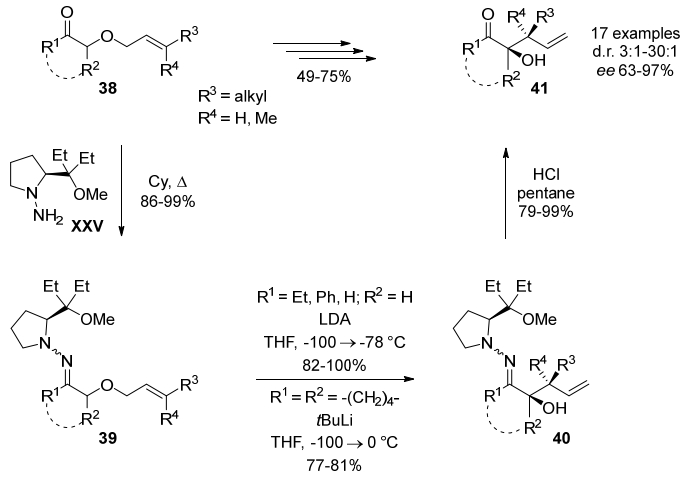
Scheme 15. Mechanism of a Wittig [2,3]-rearrangement.

The presented literature examples of asymmetric Wittig [2,3]-rearrangements can be divided into two main groups: the stoichiometric and catalytic approaches. In the first case, compounds applied for asymmetric induction are used in equivalent amounts, while the second approach requires only catalytic quantities of chiral compound. Although the first examples of the asymmetric Wittig [2,3]-rearrangement were reported by Nakai in 1984[44] and Marshall in 1987[45], there was only one example of an asymmetric organocatalytic Wittig rearrangement by the time our research group started this project in 2013.[46]

1.3.1 Stoichiometric approach

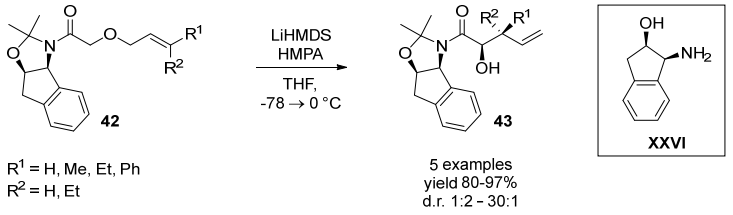
Enders and coworkers reported a highly stereoselective Wittig [2,3]-rearrangement of hydrazones **39** using chiral auxiliary SAEP **XXV** for asymmetric induction (Scheme 16).[47] α-Hydroxycarbonyl compounds **41** were synthesized over three steps in good total yields and stereoselectivities. The sequence started with the addition of hydrazine **XXV** to alkyloxycarbonyl compounds **38** and the formed hydrazone **39** underwent diastereoselective [2,3]-rearrangement under basic conditions. It is worth pointing out that hydrazones derived from aldehydes and acyclic ketones reacted smoothly with LDA at very low temperatures, while cyclic hydrazones were more sterically hindered and required a stronger base as well as higher temperatures. In the final step,

intermediates **40** were hydrolyzed under acidic conditions to yield α-hydroxycarbonyl compounds **41** with two stereogenic centers in high yields.



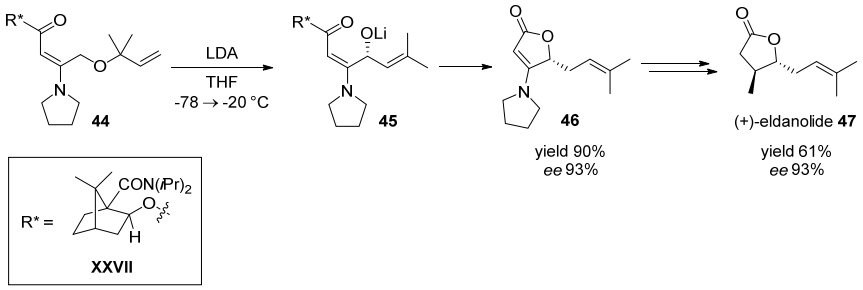
Scheme 16. Asymmetric Wittig [2,3]-rearrangement of SAEP hydrazones **39**.

A similar approach was applied by Kress *et al.*, but instead of carbonyl group derivatization the authors synthesized chiral amides **42** over a two-step procedure starting with the corresponding carboxylic acids and enantiomerically pure aminoindanol **XXVI** (Scheme 17).[48] Lithium enolates derived from amide **42** bearing *E*-alkenes underwent a [2,3]-rearrangement with a good level of stereocontrol. However, low and reversed diastereoselectivity was observed when a *Z*-substrate was submitted to the reaction. The authors also demonstrated that the obtained α-hydroxy amides **43** can be converted to functionalized cyclic and acyclic amino acid derivatives.



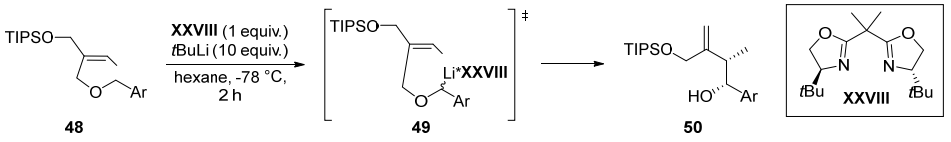
Scheme 17. Asymmetric Wittig [2,3]-rearrangement of aminoindanol-derived amides **43**.

Li's research group used the auxiliary **XXVII** derived from chiral secondary alcohol for the total synthesis of (+)-eldanolide **47** (Scheme 18).[49] Eldanolide **47** is the pheromone of the male African sugar stem borer. The Wittig [2,3]-rearrangement of chiral unsaturated ester **44** resulted in the formation of lithium alkoxide **45**, which underwent spontaneous lactonization, leading to the cleavage of the chiral auxiliary, and thus no additional step was needed to remove the auxiliary. Isolated in excellent yield and enantioselectivity, the unsaturated lactone **46** was transformed to (+)-eldanolide **47**, with a conserved enantiomeric excess over two steps.



Scheme 18. Total synthesis of (+)-eldanolide **47**.

The asymmetric [2,3]-Wittig rearrangement of various benzylic ethers **48** was reported by Maezaki and co-workers (Scheme 19).[50] A mixture of organolithium reagent and chiral ligand **XXVIII** was used in this approach in order to achieve the stereoselective lithiation of benzylic ether **48**. The described transformation is very sensitive to substituents in the aromatic core of the substrate. Although enantioselectivity up to 98% and yield up to 82% were achieved, a dramatic drop in yield and selectivity was observed when an electron-donating methoxy group was placed in *ortho*- or *para*-position.

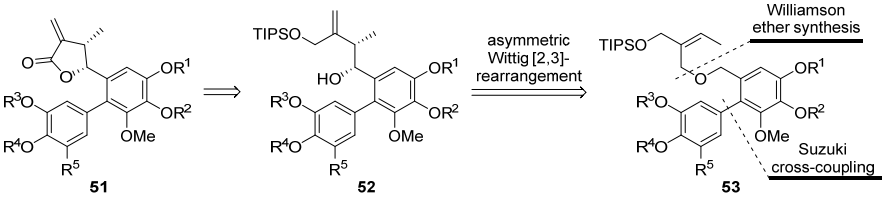


Ar = Ph, 4-MeOPh, 3-MeOPh, 2-MeOPh, 3,4-$(MeO)_2$Ph, 3,5-$(MeO)_2$Ph, 2,3-$(MeO)_2$Ph, 2,5-$(MeO)_2$Ph, 3,4,5-$(MeO)_3$Ph, 2-EtPh, 2-PhPh

11 examples
yield 32-82%
ee 8-98%

Scheme 19. Synthesis of homoallyl alcohols **50**.

Later, the same group demonstrated the application of the developed method in the total synthesis of eupomatilones **51**, which were isolated from the Australian shrub *Eupomatia bennettii* (Scheme 20).[51] The asymmetric [2,3]-Wittig rearrangement was used as a key step in this synthesis for the chirality insertion. The [2,3]-rearrangement proceeded well, even though the substrates were highly substituted and homoallyl alcohols **52** were isolated in high yields and selectivities. The final products were obtained over 5-6 steps in 23-50% total yield.



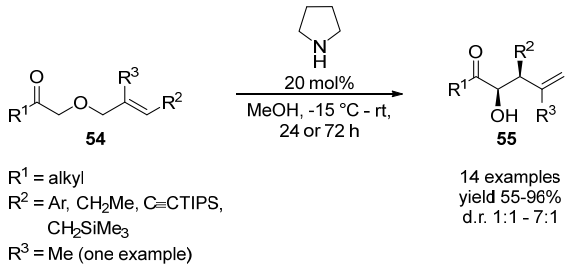
(+)-eupomatilone 2
(**a**: $R^1 = R^2 = R^3 = R^4$ = Me, R^5 = OMe);
(+)-eupomatilone 5
(**b**: $R^1 = R^2$ = Me, $R^3/R^4 = CH_2$, R^5 = H);
(+)-eupomatilone 1
(**c**: $R^1/R^2 = CH_2$, $R^3 = R^4$ = Me, R^5 = OMe)

a: yield 98%, *ee* 89%;
b: yield 74%, *ee* 91%;
c: yield 54%, *ee* 88%

Scheme 20. Total synthesis of eupomatilones **51**.

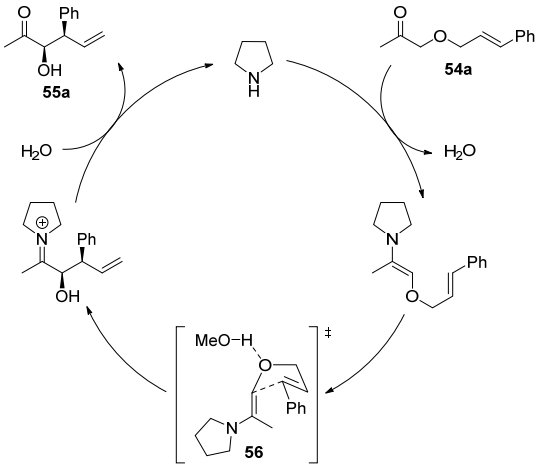
1.3.2 Catalytic approach

In 2006, the Gaunt research group described the organocatalytic Wittig [2,3]-rearrangement of allyloxyketones **54** using a secondary amine pyrrolidine as a catalyst (Scheme 21).[46] The substrate scope is broad, and the transformation proceeds with good diastereoselectivities under mild reaction conditions. The reaction setup is operationally simple and does not require dry or oxygen-free conditions.



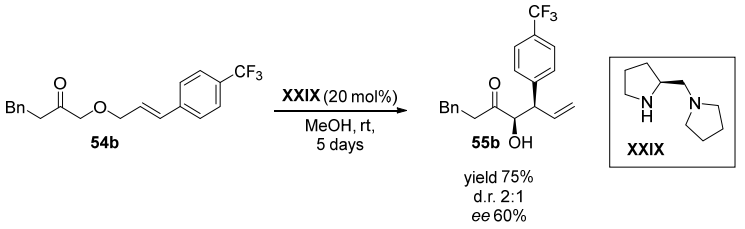
Scheme 21. Pyrrolidine-catalyzed Wittig [2,3]-rearrangement of allyloxyketones **54**.

The catalytic cycle starts with enamine formation upon the reaction between pyrrolidine and allyloxyketone **54a** (Scheme 22). Enamine with thermodynamically favored *E*-geometry undergoes a [2,3]-rearrangement *via* the *syn* transition state **56** to form α-hydroxyketone **55a** after the hydrolytic release of the catalyst. It is believed, that the hydrogen bond between methanol and the ether oxygen atom stabilizes the developing negative charge and accelerates the rearrangement.



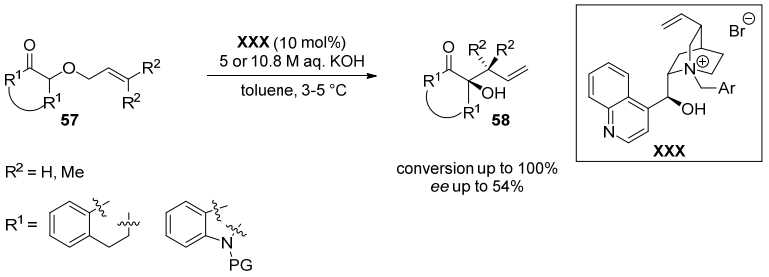
Scheme 22. Proposed mechanism of the pyrrolidine-catalyzed Wittig [2,3]-rearrangement.

The authors also reported the first enantioselective version of an organocatalytic Wittig [2,3]-rearrangement (Scheme 23). For this purpose the chiral L-proline-derived catalyst **XXIX** was used. Although the reaction rate was slow and α-hydroxyketone **55b** was isolated with modest stereoselectivities, this process demonstrated that the Wittig [2,3]-rearrangement is not limited to strong basic conditions and can proceed in an asymmetric catalytic fashion.

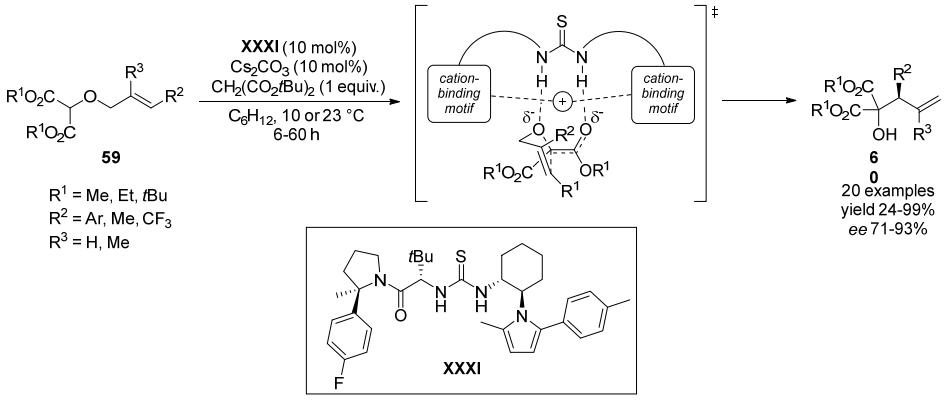


Scheme 23. Synthesis of α-hydroxyketone **55b**.

Nine years later, another example of the asymmetric organocatalyzed Wittig [2,3]-rearrangement was published by Denmark and Cullen (Scheme 24).[52] In this approach, chiral phase-transfer catalysts were used in order to facilitate the compound transfer between different phases and for asymmetric induction. Corresponding α-hydroxycarbonyl compounds **58** formed with very high conversion, but only modest enantioselectivities were observed despite the extensive catalyst screening. A racemic background reaction between substrate **57** and potassium hydroxide might be the reason for the low selectivity. Nevertheless, the presented results provide the proof of the concept for a new strategy for asymmetric sigmatropic rearrangement catalyzed by the phase-transfer catalyst.



Scheme 24. Asymmetric phase-transfer catalyzed Wittig [2,3]-rearrangement.

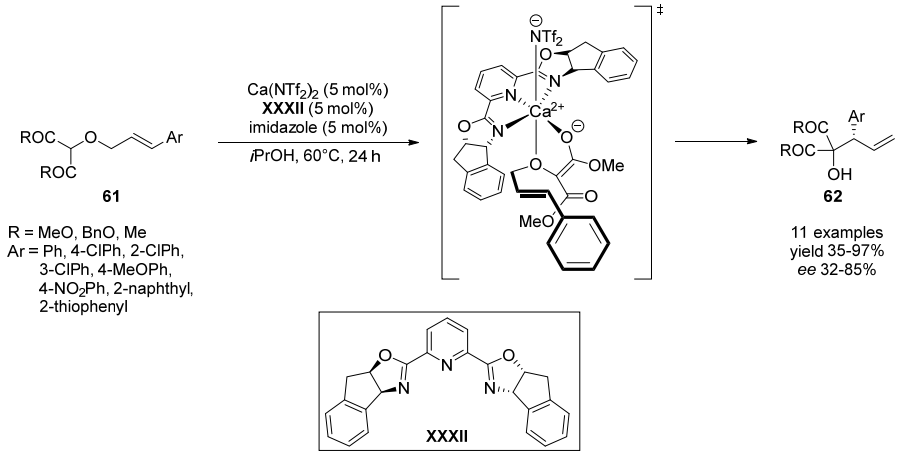


Scheme 25. Asymmetric ion-binding catalyzed Wittig [2,3]-rearrangement.

A year later, Jacobsen *et al.* demonstrated the novel synergistic ion-binding catalysis *via* the enantioselective catalytic Wittig [2,3]-rearrangement of allyloxymalonate **59** (Scheme 25).[53] The rearrangement proceeds through a diastereomeric transition state which is ion-binding stabilized by the polyfunctional catalyst **XXXI**. The thiourea moiety

of the catalyst **XXXI** forms hydrogen bonds with the deprotonated substrate, while arenes and amide encapsulate the cesium cation through cooperative cation–π and Lewis base interactions. Rearranged products **60** were isolated in good yields (in most cases over 80%) and in high enantioselectivities, showing the great utility of this method.

Simultaneously, our research group reported a calcium-catalyzed asymmetric Wittig [2,3]-rearrangement of a similar substrate, cinnamyloxymalonate **61** (Scheme 26).[54] Although α-hydroxymalonates **62** were isolated in good yield (generally over 70%), the selectivity of the reaction was modest. In order to improve the selectivity, bulkier substituents were introduced to the ester moiety (*i*Pr and *t*Bu). However, the reaction was inhibited completely in this case. The transition state of the rearrangement is formed upon the complexation of calcium salt, chiral ligand inda-Pybox **XXXII** and enolized substrate **61**. To the best of our knowledge, this is the first example of an asymmetric Lewis base catalyzed Wittig [2,3]-rearrangement.



Scheme 26. Asymmetric calcium-catalyzed Wittig [2,3]-rearrangement.

1.3.3 Summary of an asymmetric Wittig [2,3]-rearrangement

The catalytic approach to an asymmetric Wittig [2,3]-rearrangement has several advantages over the more traditional stoichiometric. First of all, the reactions were carried out under completely anhydrous conditions and low temperatures in the described stoichiometric methods, since very strong bases, such as LDA or highly flammable *t*BuLi, were used in equivalent amounts or in excess (1-10 equiv.). Additionally, chiral auxiliaries or ligands are also used in equivalent amounts, considerably lowering the atom efficiency of these methods. Moreover, additional steps for chiral auxiliary insertion and elimination are required. Reported catalytic methods are operationally simple and conducted under mild reaction conditions. Although catalytic asymmetric Wittig [2,3]-rearrangement reactions are very attractive, the scope of such transformations is limited, and thus the development of new methods is of great importance.

2 Aims of the present work

Compounds containing the spirocyclopropyl oxindole core structure are of great importance because of their useful biological properties. The organocatalytic MIRC reaction sequence is a convenient tool to obtain such chiral scaffolds. The asymmetric organocatalytic Wittig [2,3]-rearrangement is a still quite under-examined transformation. Rearranged products can be very useful building blocks in the total synthesis of natural products and their analogs. Based on that, we have defined the main aims of this thesis:

- Investigate the asymmetric organocatalytic synthesis of spirocyclopropyl oxindoles through the MIRC reaction sequence;

- Develop a method for the synthesis of allyl ethers with sufficiently acidic α-proton as starting materials for the hydrogen-bond mediated Wittig [2,3]-rearrangement;

- Explore the novel asymmetric organocatalyzed Wittig [2,3]-rearrangement and expand the scope of the transformation;

- Determine the relative and absolute stereochemistry of all new chiral products obtained in asymmetric H-bond catalyzed reactions.

3 Results and discussion

3.1 Asymmetric diastereoselective synthesis of spirocyclopropane derivatives of oxindole (Publication I)

Our group previously demonstrated the asymmetric synthesis of spirocyclopropyl oxindoles *via* an organocatalytic MIRC reaction sequence.[27,28,55] The transformation described in this section is a further development of this chemistry. From a stereochemical point of view, the synthesis of α,β-identically substituted spirocyclopropyl oxindole derivatives is challenging, because of the formation of two possible diastereoisomers. The desired enantiomeric *trans*-substituted product contains a non-stereogenic C-3 center, while an achiral *cis*-isomer has a pseudo-asymmetric center at C-3 in its structure (Figure 5a). For this purpose, symmetric unsaturated 1,4-dicarbonyl compounds were used. However, the asymmetric desymmetrization of unsaturated 1,4-dicarbonyl compounds is a challenging task for several reasons (Figure 5b). *Re*- and *Si*-attacks on the different carbons of the double bond lead to the formation of the same enantiomer. Moreover, the conjugated addition with respect to one carbonyl group (b) is a formal umpolung reaction to the α-carbon of the other carbonyl group (a). Although there are examples in the literature of unsaturated 1,4-dicarbonyl compounds having been applied in MIRC for the preparation of cyclopropanes[56], the asymmetric examples are rather limited.[57] To the best of our knowledge, there were no reports concerning asymmetric organocatalytic cyclopropanation of symmetric unsaturated 1,4-diketones at the time we published our results.

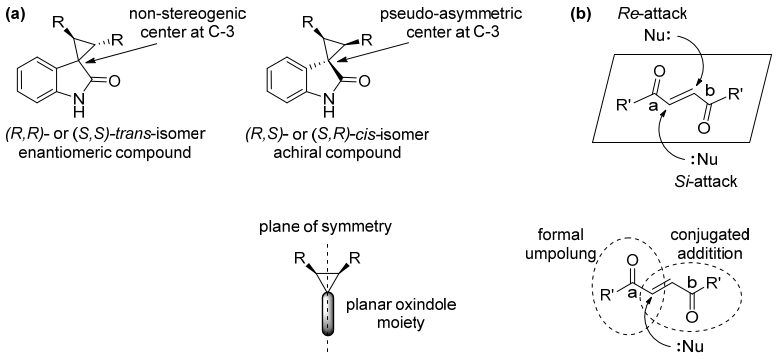
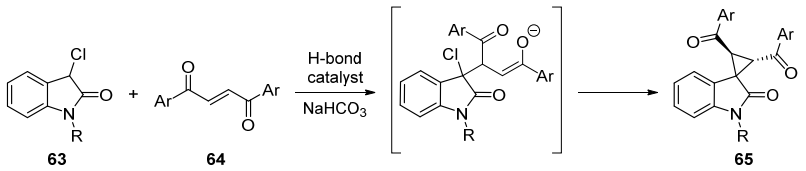


Figure 5. Stereochemical challenges.

In order to investigate the synthesis of α,β-identically substituted spirocyclopropyl oxindoles **65** through an organocatalytic MIRC reaction sequence, the cascade between 3-chlorooxindole **63** and unsaturated 1,4-diketones **64** was studied (Scheme 27). The cascade consists of the enantioselective Michael addition, followed by an intramolecular nucleophilic substitution leading to the formation of the cyclopropane moiety. At least one equivalent of base is required to neutralize the forming HCl, which can protonate the tertiary amino group of the organocatalyst and inhibit the reaction. Based on our previous experience in asymmetric desymmetrization of unsaturated 1,4-

dicarbonyl compounds, various chiral bifunctional hydrogen-bond catalysts were tested in this study (Figure 6).[58]



Scheme 27. General scheme for the synthesis of spirocyclopropyl oxindoles **65**.

In our initial experiments, NH unprotected 3-chlorooxindole was used as a synthetically preferable starting compound.[59] However, no reaction took place at room temperature in the presence of thiourea **XXXIV**. On the contrary, *N*-Boc-protected 3-chlorooxindole **63a** reacted smoothly with unsaturated aromatic 1,4-diketone **64a**, and spirocyclopropyl oxindole **65a** was isolated as a single diastereoisomer in good yield and enantioselectivity (Table 1, entry 1). The acidity of the C-H bond at C3 increased, when the oxindole nitrogen atom was protected with an electron-withdrawing group, which made the substrate more reactive.[60] On the other hand, additional H-bonds between the catalyst and the substrate can be formed when a Boc-group is introduced to the substrate.

In the model reaction, the ratio between spirocyclopropane oxindole **65a**, uncyclized Michael adduct **66a**, and achiral compound **67a** was determined by a ^{1}H NMR spectroscopic analysis of the crude mixture, while the enantiomeric purity was measured from the isolated product **65a**. To facilitate the purification of the desired product, after the completion of the reaction the crude mixture was treated with trifluoroacetic acid and the product was isolated as a free N-H oxindole as a single diastereoisomer.

First, various H-bond catalysts were screened. Whereas thiourea-based catalysts gave quite similar *ee* values for the desired product (Table 1, entries 1, 2 and 5), squaramide catalyst **XII** turned out to be clearly inappropriate for the cyclopropanation. The highest enantio- and diastereoselectivities were achieved with *Cinchona* alkaloid **XXXV**, but the poor yield obtained (21% for **65a**) made it practically unattractive (Table 1, entry 4). The highest yield (70%) was obtained by slightly sacrificing enantioselectivity when thiourea **XXXIV** was used (Table 1, entry 2). Thiourea **XXXIV** was chosen to further improve the efficiency of the cascade reaction.

Next, we tried to enhance the yield of the reaction by increasing the temperature and the catalyst loading. However, not only was the obtained yield lower, but also the selectivity decreased dramatically (Table 1, entry 6). Solvent screening revealed that the product **65a-NH** could be obtained in moderate yield in 48 h in different chlorinated solvents, but the best enantio- and diastereoselectivities were obtained in toluene (Table 1, entry 7). Decreasing the reaction temperature from room temperature to 4 °C had little influence on stereoselectivity, but an extended reaction time was required to achieve a reasonable yield (Table 1, entry 10).

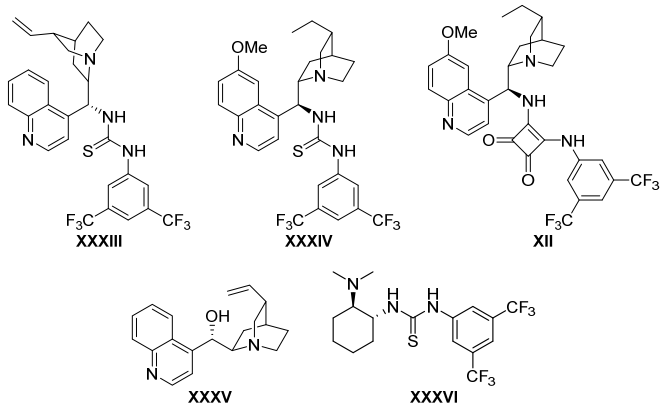
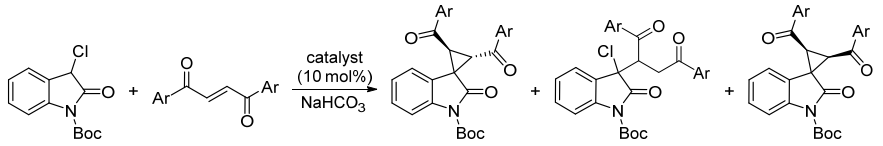


Figure 6. Catalysts screened for the synthesis of spirocyclopropyl oxindoles **65**.

Table 1. Screening of the catalysts and optimization.[a]



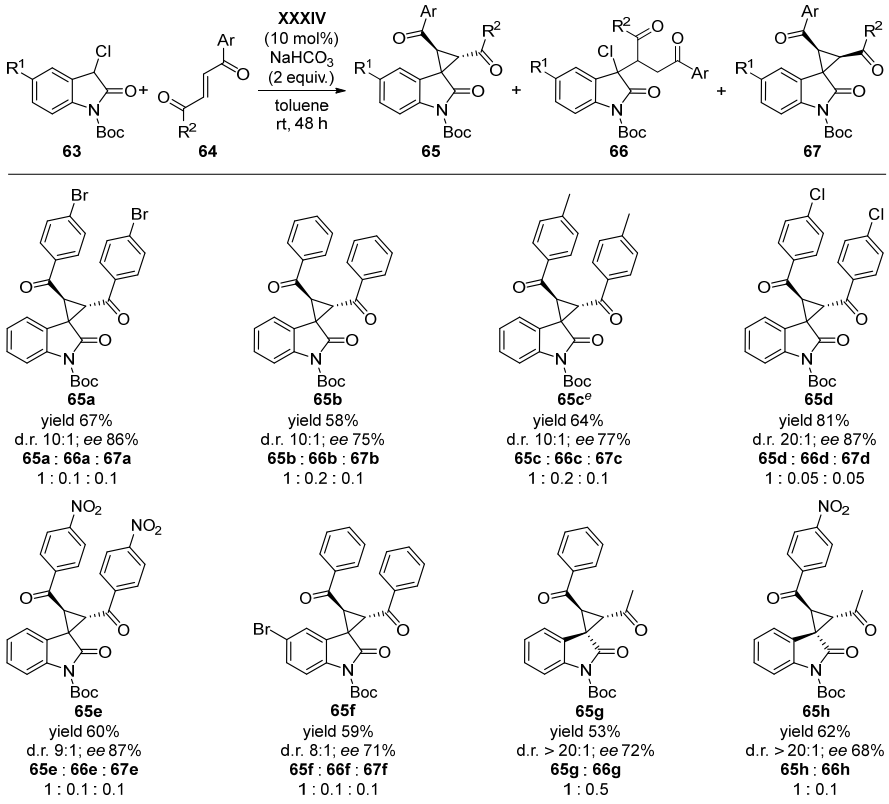
63a **64a** **a**: Ar = 4-BrPh **65a** **66a** **67a**

entry	catalyst	solvent	t (°C)	time (h)	ratio of **65a**:**66a**:**67a**[b]	yield (%)[c] N-Boc	yield (%)[c] N-H	*ee* (%)[d]
1	**XXXIII**	$CHCl_3$	rt	18	nd	61		-67[e]
2	**XXXIV**	$CHCl_3$	rt	48	1 : 0.1 : 0.2	70		67[e]
3	**XII**	$CHCl_3$	rt	48	1 : 0.9 : 0.5	nd		nd
4	**XXXV**	$CHCl_3$	rt	48	1 : 0.6 : 0.05	21		80[e]
5	**XXXVI**	$CHCl_3$	rt	48	1 : 0.6 : 0.2		42	-75
6	**XXXIV**[f]	$CHCl_3$	60	18	1 : 0.4 : 0.3		51	48
7	**XXXIV**	toluene	rt	48	1 : 0.1 : 0.1		57	86
8	**XXXIV**	DCM	rt	48	1 : 0.2 : 0.2		44	63
9	**XXXIV**	DCE	rt	48	1 : 0.2 : 0.2		44	65
10	**XXXIV**	toluene	4	96	1 : 0.2 : 0.1		59	90

[a]Unless otherwise stated, the reactions were carried out on a 0.1 mmol scale as a 0.2 M solution with 1 equiv. of **63a**, 1.2 equiv. of **64a**, 10 mol% of cat. and 2 equiv. of $NaHCO_3$. [b]The ratio of the products was determined by ^1H NMR from the crude mixture. [c]The main product **65a** or **65a-NH** was isolated as a single diastereoisomer. [d]Determined by chiral HPLC analysis from isolated N-H product. [e]Determined by chiral HPLC analysis from isolated N-Boc product. [f]20 mol% of the catalyst was used.

With optimal conditions in hand [**63** (1.2 equiv.), **64** (1 equiv.), $NaHCO_3$ (2 equiv.) and **XXXIV** (10 mol%) in toluene (0.2 M) at room temp.], the influence of different substituents in the aromatic core of symmetric unsaturated 1,4-diketones **64** was investigated (Figure 7). Electron-donating and -withdrawing groups of the diketones **64** did not have any noticeable effect on the reaction and the corresponding products with two tertiary stereocenters were isolated in similar yields (from 58 to 81%) and enantioselectivities (*ee* from 75 to 87%) (compounds **65a–e**). Diastereoselectivities varied from excellent (d.r. = 20:1 for compound **65d**) to high (d.r. = 9:1 for compound

65e). Slightly decreased selectivities were observed in the reaction with bromo-substituted 3-chlorooxindole (compound **65f**). However, the reaction between 3-chlorooxindole **63a** and aliphatic diketone [(*E*)-hex-3-ene-2,5-dione] did not proceed, which can be explained by the lower electrophilicity of aliphatic unsaturated ketones compared to aromatic ones. A similar observation was made by Yuan *et al.* in the case of the addition of 3-alkyl-substituted oxindoles to unsaturated 1,4-diketones.[61]

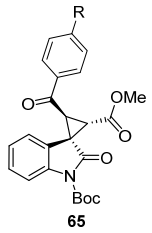


[a]The main product **65** was isolated as a single diastereoisomer. The diastereomeric ratio was determined by ^{1}H NMR from the crude mixture. *ee* was determined by chiral HPLC analysis from the isolated product. The ratio of the products was determined by ^{1}H NMR from the crude mixture. [e]The reaction was stirred for 96 h.

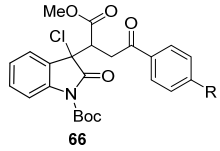
Figure 7. Scope of the synthesis of spirocyclopropyl oxindoles **65**.[a]

The reaction scope was then further broadened by introducing nonsymmetric unsaturated 1,4-dicarbonyl compounds, which led to the formation of spirocyclopropyl oxindoles **65** containing two tertiary and one quaternary stereogenic center. Although nonsymmetric unsaturated 1,4-diketones have two potential centers for Michael addition, the nucleophilic attack was regioselective. Two regioisomers of the acyclic intermediate **66** should give different diastereoisomers after intramolecular cyclization, but only one out of four possible stereoisomers was observed (Figure 7, compounds **65g** and **65h**). Unsaturated keto esters reacted smoothly with 3-chlorooxindole **63**, but the main product was non-cyclized compound **66**, which could not be separated from **65** (Figure 8). Similarly to nonsymmetric 1,4-diketones, only one diastereoisomer was

detected by a ^{1}H NMR spectroscopic analysis of the crude mixture, indicating that Michael addition to unsaturated keto esters was also regioselective.



65



66

	R	d.r.	**65** : **66**
i	Me	> 20:1	1 : 2
j	Cl	> 20:1	1 : 2

Figure 8. Spirocyclopropyl oxindoles **65** from unsaturated keto esters.

The relative stereochemistry of symmetric spirocyclopropyl oxindoles **65a**-**f** was determined by ^{1}H NMR spectroscopic analysis, whereas ^{1}H NOESY NMR experiments were used to establish the relative stereochemistry of *cis*-diastereoisomers **67a**-**f** and spirocyclopropyl oxindoles **65g**-**j**. The absolute stereochemistry of spirocyclopropyl oxindoles **65** was determined by vibrational circular dichroism (VCD) spectroscopy. For this purpose, the opposite enantiomers of compound **65c-NH** were synthesized using thiourea-based catalysts **XXXIV** and **XXXVI**. The VCD spectra of the enantiomers were measured and compared to the spectrum calculated by Dr Öeren (Figure 9). The assigned absolute stereochemistry was interpolated to other compounds in the series.

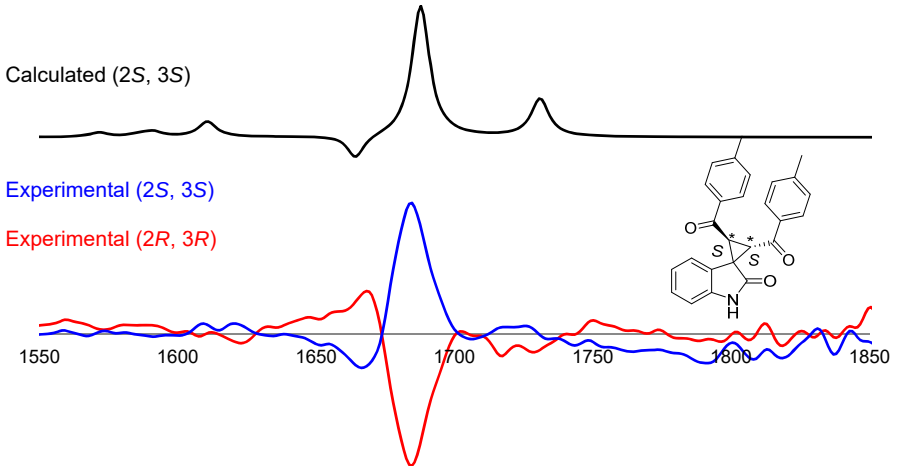
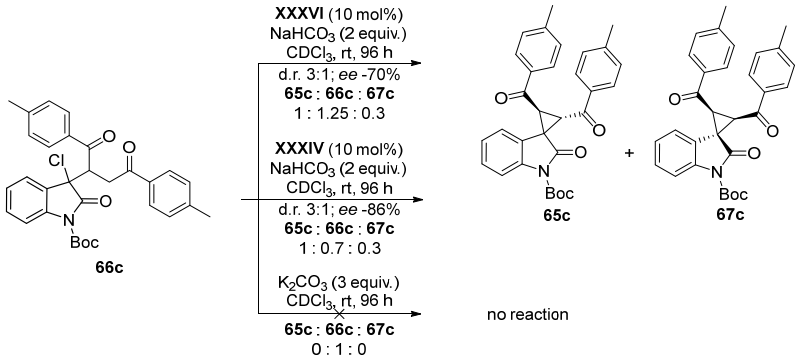


Figure 9. Absolute stereochemistry determination by VCD analysis of **65c-NH**.

A considerable amount of the non-cyclic Michael adduct **66** was almost always detected in the ^{1}H NMR spectroscopic analysis of the crude mixtures. This fact means that the cascade partially stops after the first step, lowering the yield of the desired product. Additional experiments with Michael adduct **66c** were conducted in order to better understand the mechanism and the stereocontrol of the MIRC spirocyclopropanation (Scheme 28). The Michael adduct **66c** (6:1 mixture of diastereoisomers) obtained from the reaction catalyzed by the thiourea catalyst **XXXVI** was cyclized under the same reaction conditions in the presence of catalysts **XXXIV** and **XXXVI**. These catalysts gave opposite enantiomers in the model reaction. Several interesting observations were made. First, the reaction rate was much lower compared

with the reaction between 3-chlorooxindole **63a** and unsaturated aromatic 1,4-diketone **64c**, which indicates the importance of the catalyst/substrate complex throughout the cascade reaction. Moreover, although the racemic product **65c** was obtained from the starting materials in the presence of an inorganic base, no reaction with non-cyclic intermediate **66c** was observed under the same conditions using the same base. Secondly, diastereoisomers of **66c** cyclize in the presence of catalyst **XXXIV** with different rates as the diastereomeric ratio of recovered **66c** was changed to 20:1, while in the presence of catalyst **XXXVI** the ratio remained unchanged (6:1). It is known that 3-chlorooxindoles afforded *syn*-products in Michael addition to nitrostyrenes,[27] but the relative stereochemistry of non-cyclized intermediate **66c** was not determined as during the cyclization the stereogenic center at C3 was lost. Finally, this study also hints that the stereochemistry of the final product **65c** is determined in the first step of the cascade (Michael addition) because two different chiral organocatalysts, **XXXIV** and **XXXVI**, afforded the same enantiomer in the reaction with non-cyclic intermediate **66c**, whereas in the separate reaction with starting materials **63a** and **64c**, enantiomers of **65c** were obtained.

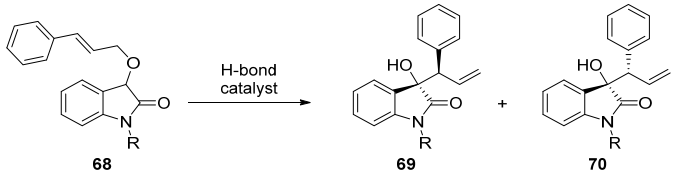


Scheme 28. Cyclization of Michael adduct **66c**.

In conclusion, the synthesis of α,β-identically substituted spirocyclopropyl oxindole through an asymmetric organocatalytic MIRC reaction sequence of symmetric unsaturated 1,4-diketones and 3-chlorooxindoles was described. This methodology provides products **65a**-**f** with two identically substituted tertiary stereocenters in moderate yields and with very high diastereo- and enantioselectivities. In the case of unsaturated 1,4-keto esters and non-symmetric diketones, the first conjugated addition is highly regioselective and provides spirocyclopropyl oxindoles **65g-j** containing two tertiary and one quaternary center with excellent diastereoselectivities. Additional experiments showed the importance of the catalyst/substrate complex throughout the cascade and that the Michael adduct **66** cyclizes very slowly under the reaction conditions. Finally, the stereochemical outcome of the spirocyclopropanation is defined in the first step of the cascade (Michael addition).

3.2 Asymmetric organocatalytic Wittig [2,3]-rearrangement of oxindoles (Publication II)

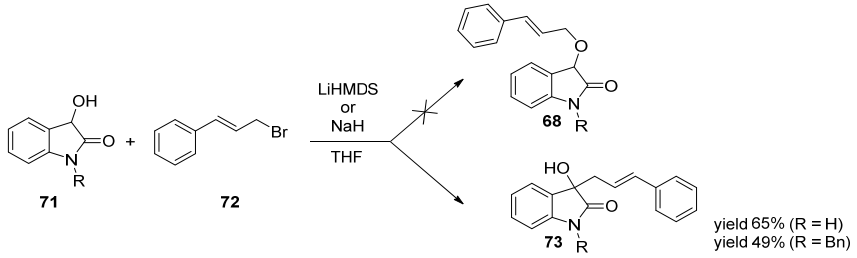
Inspired by the pioneering study of the organocatalytic Wittig [2,3]-rearrangement reported by the Gaunt research group, we decided to investigate this transformation by means of hydrogen-bond mediated catalysis.[46] We previously demonstrated that 3-halogen substituted oxindoles can be efficiently activated as nucleophiles *via* hydrogen-bonds for asymmetric organocatalytic transformations.[27,28,62] We assumed that 3-cinnamyloxyoxindole **68** could be activated in a similar fashion for the Wittig rearrangement (Scheme 29). The rearranged chiral 3-substituted 3-hydroxyoxindoles **69** and **70** are of great importance because they can be used as building blocks for the synthesis of biologically active compounds and natural products.[63]



68 **69** **70**

Scheme 29. General scheme for the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindoles **68**.

There were no examples in the literature describing the synthesis of 3-cinnamyloxyoxindoles **68** or its analogs at the time we started this project. First, we tried to obtain it through the conventional Williamson ether synthesis, starting from 3-hydroxyoxindole **71** and cinnamyl bromide **72** (Scheme 30).[64] For this purpose, a stoichiometric amount of a strong base was used. However, no formation of the desired product was observed. Instead, 3-alkyl-3-hydroxyoxindole **73** was obtained exclusively in moderate yields. The hydrogen atom at the C-3 position of the oxindole is highly acidic due to the negative charge stabilization by resonance and induction, making it very easy to deprotonate by a base. After several unsuccessful approaches, we finally developed a three-step procedure for the synthesis of 3-cinnamyloxyoxindole **68** that exploits the reactivity of metallocarbene species (Scheme 31).[65]

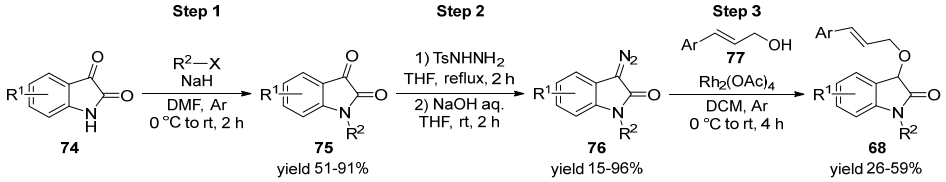


71 **72** **68** **73**

Scheme 30. Unsuccessful synthesis of 3-cinnamyloxyoxindole **68** through the Williamson reaction.

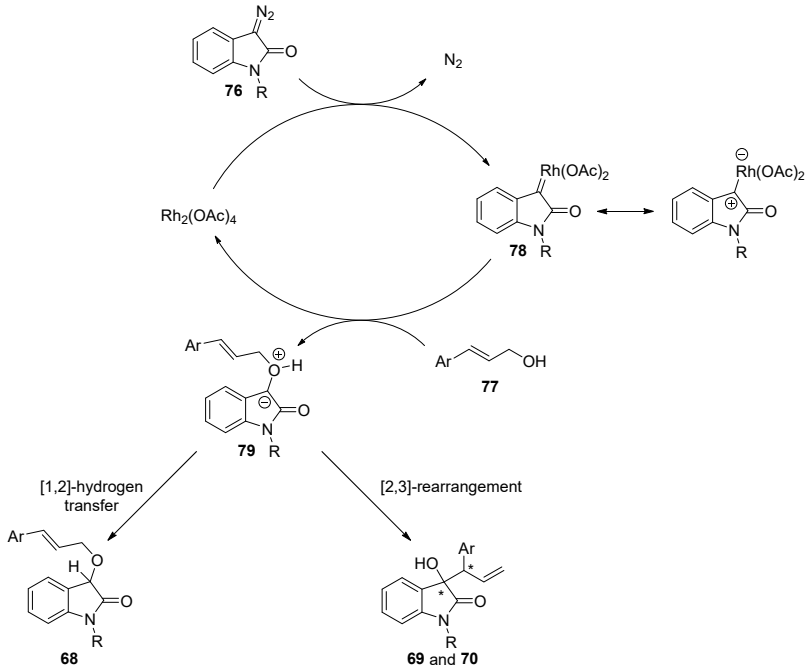
In the first step, the nitrogen atom of commercially available isatins **74** was protected with alkyl halides. Protected isatins **75** were converted to 3-diazooxindoles **76**, generally in high yields, following the modified procedure reported by Carreira *et al.* (Step 2).[66] In the last step, 3-cinnamyloxyoxindoles **68** were obtained in low to

moderate yields through the rhodium-catalyzed reaction between 3-diazooxindoles **76** and cinnamyl alcohols **77**,[67] which are either commercially available or can be easily prepared from substituted benzaldehydes by Horner-Wadsworth-Emmons and reduction reaction sequence.



Scheme 31. Synthesis of 3-cinnamyloxyoxindoles **68**.

In the Rh-catalyzed cinnamyl alcohol insertion reaction, rhodium acetate as a Lewis acid accepts electron density from the diazo carbon, which is followed by back electron donation from the metal, loss of N_2 and the formation of metallocarbene **78** (Scheme 32).[68] Next, the nucleophile insertion proceeds by the attack of the oxygen atom of cinnamyl alcohol **77** on the electrophilic carbene.[33a] The formed ylide **79** undergoes proton transfer, leading to 3-cinnamyloxyoxindole **68**. However, a [2,3]-sigmatropic rearrangement of ylide **79** also occurs as a side reaction, lowering the yield of the desired product. Although the total yield of the three-step procedure is low, starting compounds are inexpensive, rhodium acetate is used in a catalytic amount (0.5 mol%) and the synthesis is operationally simple. Moreover, to the best of our knowledge, this is presently the only possible approach to synthesize 3-cinnamyloxyoxindoles **68**.



Scheme 32. Rh-catalyzed cinnamyl alcohol insertion.

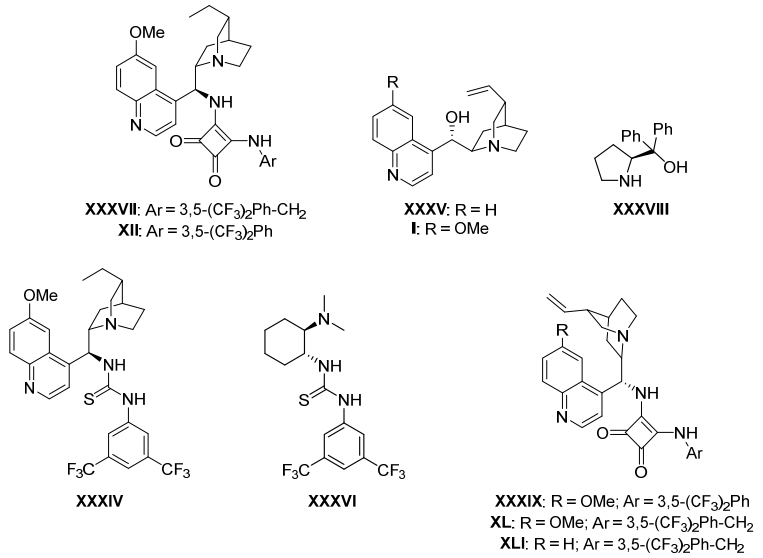
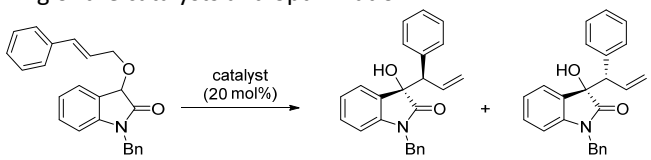


Figure 10. Catalysts screened for the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindoles **68a**.

Various chiral H-bonding catalysts were tested, such as *Cinchona* alkaloids, *Cinchona* alkaloid derived thioureas and squaramides, as well as Takemoto catalyst and prolinole derivative (Figure 10). Although the best diastereoselectivities were achieved with thiourea catalysts (Table 2, entries 1 and 6), the study revealed that squaramides are clearly beneficial in terms of enantioselectivity (Table 2, entries 3 and 5). In order to improve the rate of the [2,3]-rearrangement, we decided to run the reaction at a higher temperature. To our great delight, high conversion was obtained after 18 hours in the reaction catalyzed by squaramide **XXXVII** at 60 °C, with only a minor decrease in the enantioselectivity (Table 2, entry 13). Both conversion and enantioselectivity were further slightly improved when 1,2-dichloroethane was used as a solvent instead of chloroform (Table 2, entry 15). Decreasing the catalyst loading from 20 to 10 mol% resulted in a dramatic loss of reactivity and selectivity (Table 2, entries 16-18). Finally, in the control experiment without a catalyst, no rearrangement reaction was observed, which excludes the spontaneous racemic pathway.

Table 2. Screening of the catalysts and optimization.[a]



68a **69a** **70a**

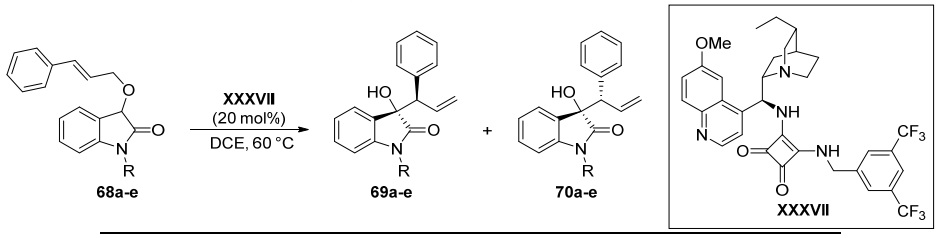
entry	catalyst	solvent	t (°C)	time (days)	conv. (%)[b]	yield (%)[c]	d.r. **69a**:**70a**[d]	*ee* (%)[e]
1	**XXXIV**	$CDCl_3$	rt	6	63	42	4.6:1	16 / 47
2	**XXXV**	$CDCl_3$	rt	6	38	37	3:1	-36 / -53
3	**XII**	$CDCl_3$	rt	6	59	56	1.6:1	36 / 83
4	**XXXVIII**	$CDCl_3$	60	6	26	19	2.7:1	29 / 18
5	**XXXVII**	$CDCl_3$	rt	6	62	61	2.5:1	92 / 93
6	**XXXVI**	$CDCl_3$	rt	6	37	29	6:1	-12 / -53
7	**I**	$CDCl_3$	rt	6	46	36	3.5:1	-58 / -37
8	**XXXIX**	toluene	rt	6	64	53	2:1	-50 / -82
9	**XXXIX**	THF	rt	6	69	61	1.2:1	-57 / -90
10	**XXXIX**	MTBE	rt	6	88	86	2.4:1	-36 / -78
11	**XXXVII**	DME	rt	6	47	nd	2.5:1	nd
12	**XXXVII**	MTBE	rt	6	71	65	2.5:1	81 / 89
13	**XXXVII**	$CDCl_3$	60	1	84[f]	90	2.3:1	88 / 90
14	**XXXVII**	MTBE	60	1	84[f]	88	2.3:1	82 / 86
15	**XXXVII**	DCE	60	1	100	87	2.5:1	90 / 93
16	**XL**[g]	DCE	60	4	85	70	2.1:1	-75 / -87
17	**XLI**[g]	DCE	60	7	83	60	2.3:1	-61 / -77
18	**XXXVII**[g]	DCE	60	4	87	49	2.5:1	73 / 75
19	no	DCE	60	2	0	-	-	-

[a]Reaction conditions: 0.1 mmol scale, 20 mol% of cat., solvent (0.5 mL). [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Overall isolated yield of the separated diastereoisomers. [d]Determined by RP HPLC analysis of the crude mixture. [e]Determined by chiral HPLC analysis of the isolated products. [f]Conversion measured after 18 hours. [g]10 mol% of the catalyst was used.

With optimal conditions in hand, we investigated how different *N*-protecting groups of oxindole can influence the organocatalytic Wittig [2,3]-rearrangement (Table 3). From the screening for the optimal conditions, we already knew that *N*-benzyl-protected 3-cinnamyloxyoxindole **68a** reacted smoothly, and rearranged products were isolated in high yields and enantiomeric purities for both diastereoisomers (Table 3, entry 1). However, from the synthetic point of view, the use of unprotected NH-oxindole is preferred.[59] Unfortunately, the rearrangement of 3-cinnamyloxyoxindole **68b** was slow and enantioselectivity decreased considerably for the major isomer (Table 3, entry 2). Based on our previous experience in MIRC chemistry of *N*-Boc-protected oxindoles,[55,62] we assumed that the Boc-protecting group on 3-cinnamyloxyoxindole **68** would positively affect the rearrangement by increasing the acidity of the hydrogen atom at C3 and introducing additional coordination sites for the catalyst. Unfortunately, all of

our attempts to synthesize *N*-Boc-protected 3-cinnamyloxyoxindole **68** were unsuccessful. In the rhodium-catalyzed reaction between *N*-Boc-3-diazooxindole and cinnamyl alcohols **77**, rearranged products **69** and **70** formed exclusively. We also tried to protect 3-cinnamyloxyoxindole **68b** by Boc_2O under several reaction conditions, but either a base-catalyzed [2,3]-rearrangement occurred or an inseparable mixture of the desired *N*-Boc-protected 3-cinnamyloxyoxindole **68** and 1,3-di-Boc-substituted cinnamyloxyoxindole was obtained. Clearly, *N*-Boc-protected 3-cinnamyloxyoxindole **68** was too reactive/unstable a substrate. Next, we turned our attention to simpler alkyl protecting groups, such as methyl and isopropyl. Though there were no problems in the syntheses of those substrates, the reaction rate and selectivity of the organocatalyzed rearrangement did not improve (Table 3, entries 3 and 4). As benzyl-protected 3-cinnamyloxyoxindole **68a** remained the best substrate in terms of reactivity and selectivity, we decided to slightly modify it with an additional methyl group in the *para*-position of the phenyl ring for more convenient determination of the conversion and diastereoisomeric ratio by a ^{1}H NMR analysis of the crude mixture (Table 3, entry 5). Although the diastereoselectivity of the reaction was rather moderate, the formed diastereoisomers were separable by column chromatography on silica gel. This may be an advantage in terms of biological studies, as enantiomerically enriched diastereoisomers may have different bioactivities.

Table 3. Screening of protective groups.[a]



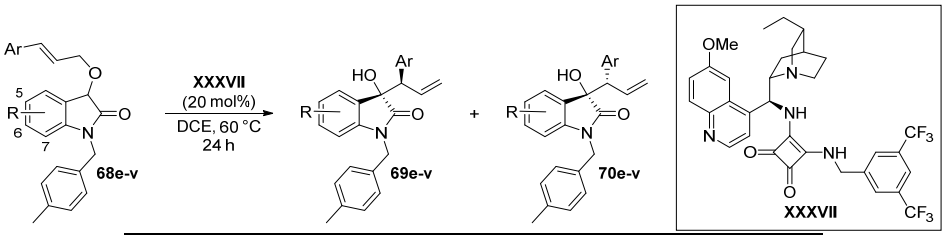
entry	R	time (h)	yield (%)[b]	d.r. **69**:**70**[c]	*ee* (%)[d]
1	**a**: Bn	24	87	2.5:1[e]	90 / 93
2	**b**: H	48	79	1.8:1	71 / 90
3	**c**: Me	48	79	2.5:1	80 / 86
4	**d**: *i*Pr	72	36	1.8:1	82 / 85
5	**e**: 4-MeBn	24	89	2.4:1	90 / 93

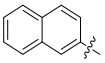
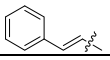
[a]Reaction conditions: 0.1 mmol scale, 20 mol% of cat. **XXXVII**, DCE (0.5 mL), 60 °C. [b]Overall isolated yield of the separated diastereoisomers. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC analysis of the isolated products. [e]Determined by RP HPLC analysis of the crude mixture.

The effect of various substituents in the aromatic ring of oxindole was studied (Table 4, entries 2-10). Halogen- and methoxy-substituted 3-cinnamyloxyoxindoles **68f-g** underwent a Wittig [2,3]-rearrangement with slightly decreased diastereoselectivities while the overall yield and enantioselectivities remained very high compared to the unsubstituted 3-cinnamyloxyoxindole **68e** (Table 4, entries 2-7). In the reaction with the oxindole containing a strongly electronegative trifluoromethoxy group, reversed but still low diastereoselectivity was observed (Table 4, entry 8). Although the electron-withdrawing nitro group at position 7 of oxindole did not noticeably affect the yield and

selectivity, 5-nitro-substituted products were isolated in the lower total yield and enantiomeric purity of the major diastereoisomer (Table 4, entries 9-10). The nitro group is known to be a strong hydrogen bond acceptor and the transition state of the reaction might be affected. Apart from the two examples, it can be concluded that electronic properties of the substituents in oxindole do not have a significant impact on the rearrangement.

Table 4. Scope of the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindoles **68**.



entry	R	Ar	yield (%)[b]	d.r. **69**:**70**[c]	*ee* (%)[d]
1	H	Ph	(**e**) 89	2.4:1	90 / 93
2	5-F	Ph	(**f**) 83[e]	1.6:1	91 / 92
3	5-Cl	Ph	(**g**) 82	1.4:1	90 / 94
4	5-Br	Ph	(**h**) 86	1.3:1	90 / 95
5	7-F	Ph	(**i**) 92	1.4:1	92 / 93
6	7-Cl	Ph	(**j**) 89[e]	1.3:1	91 / 95
7	5-MeO	Ph	(**k**) 92	2.0:1	93 / 95
8	5-CF_3O	Ph	(**l**) 82[e]	1:1.4	91 / 95
9	5-NO_2	Ph	(**m**) 71	1.3:1	80 / 90
10	7-NO_2	Ph	(**n**) 85[e]	1.1:1	89 / 93
11	H	4-ClPh	(**o**) 90	2.0:1	94 / 95
12	H	3-ClPh	(**p**) >95	1.9:1	93 / 95
13	H	2-ClPh	(**q**) 87 [f]	1:1.1	88 / 93
14	H	4-MeOPh	(**r**) 95	1.8:1	91 / 97
15	H	4-NO_2Ph	(**s**) 77 [g]	1.6:1	80 / 30
16	H		(**t**) 88	2.7:1	93 / 95
17	H		(**u**) 93	2.0:1	92 / 95
18	H		(**v**) 63	1.7:1	86 / 91

[a]Reaction conditions: 0.1 mmol scale, 20 mol% of cat. **XXXVII**, DCE (0.5 mL), 60 °C. [b]Overall isolated yield of the separated diastereoisomers. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC analysis of the isolated products. [e]Reaction was finished after 5 hours. [f]Reaction was finished after 48 hours. [g]Reaction was finished after stirring at rt for 48 hours.

Next, the influence of substituents at the cinnamyl phenyl ring was investigated. *para*- and *meta*-substituted derivatives reacted smoothly and rearranged products were obtained in excellent yields and enantioselectivities (Table 4, entries 11, 12 and 14).

Probably due to the steric effect, a longer reaction time was required to obtain full conversion when *ortho*-chloro substituted cinnamyloxyoxindole **68q** was used as a substrate (Table 4, entry 13). The rearrangement of *para*-nitro cinnamyloxyoxindole **68s** was conducted at room temperature, because the formation of the side product was detected when the reaction was stirred at a higher temperature (Table 4, entry 13). Moreover, the enantioselectivity of the minor diastereoisomer decreased dramatically, while the enantioselectivity of the major diastereoisomer remained relatively high. The reaction scope was then further broadened by different aromatic analogs of 3-cinnamyloxyoxindoles, which underwent the Wittig [2,3]-rearrangement efficiently under the same conditions (Table 4, entries 16-18).

Finally, the Wittig [2,3]-rearrangement was not observed under standard conditions when *cis*-3-cinnamyloxyoxindole **68w**, 3-allyloxy-**68x** or crotyloxyoxindoles **68y** and **68z**[i] were used as starting materials (Figure 11). A higher temperature (85 °C) and longer reaction time (48 hours) had no effect. Moreover, an additional substituent at the double bond almost completely suppressed the reaction of compound **68za** due to sterical hindrance.

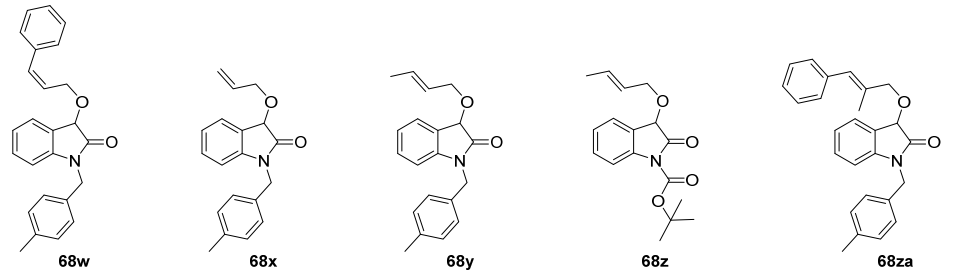


Figure 11. Scope limitation.

The relative and absolute stereochemistries of Wittig [2,3]-rearrangement products **69o** and **70i** were unambiguously assigned by single crystal X-ray diffraction and were interpolated to other compounds in the series (Figure 12). Based on the geometry of the products, two possible transition states were proposed (Figure 13). 3-cinnamyloxyoxindole **68** was deprotonated by the quinuclidine moiety of the catalyst and the formed enolate was coordinated by multiple hydrogen bonds to squaramide and the protonated amine of the catalyst. A *Re*-attack of enolate on the double bond of the cinnamyl group led to the formation of the major diastereoisomer **69**, while the attack on the *Si*-face gave the minor diastereoisomer **70**. As can be seen from the proposed model, transition states leading to different diastereoisomers are very similar, which may explain the low diastereoselectivity of the Wittig [2,3]-rearrangement.

[i] Rh-catalyzed alcohol insertion to *N*-Boc-3-diazooxindole was possible in the case of crotyl alcohol.

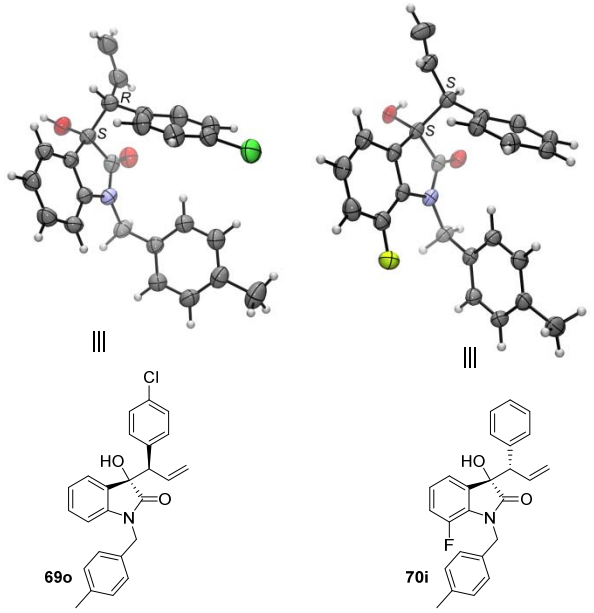


Figure 12. X-ray structures of [2,3]-rearranged products **69o** (major diastereoisomer) and **70i** (minor diastereoisomer).

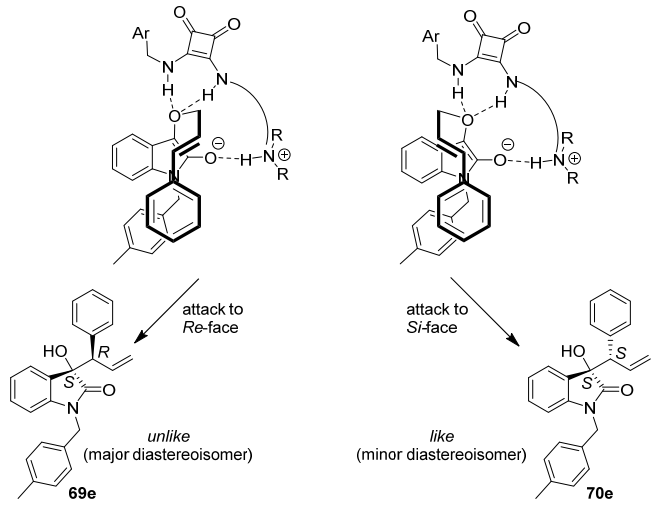


Figure 13. Proposed transition state for Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **68**.

We assumed that the low diastereoselectivity might have been caused by isomerization of the products. In order to prove this and further investigate the mechanism of the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindoles **68**, a kinetic study was performed. For this purpose, the reaction with 3-cinnamyloxyoxindole **68k** was carried out in deuterated chloroform and crude samples were taken over time (Figure 14). A ^{1}H NMR kinetic study revealed that the ratio between the diastereoisomers remained the same (2:1) throughout the entire reaction. This observation excluded isomerization of the products and proved that diastereoselectivity was defined by thermodynamic

control. From a kinetical point of view, a Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **68k** is the competitive first order reaction.[ii]

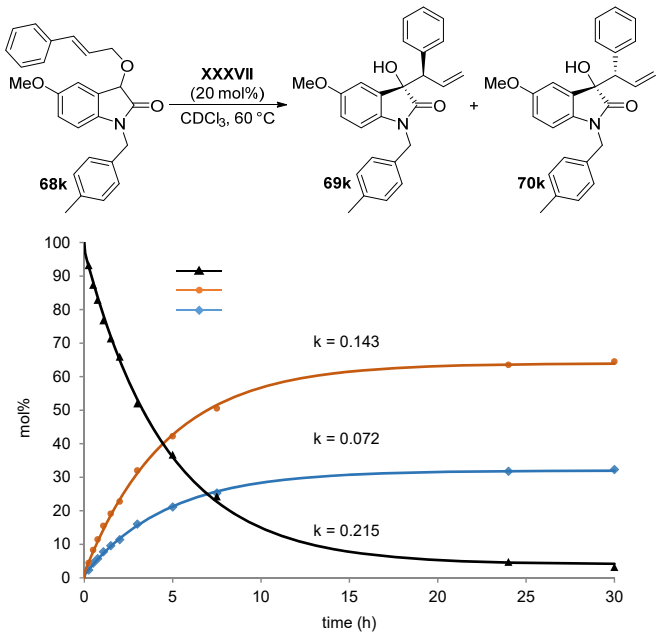
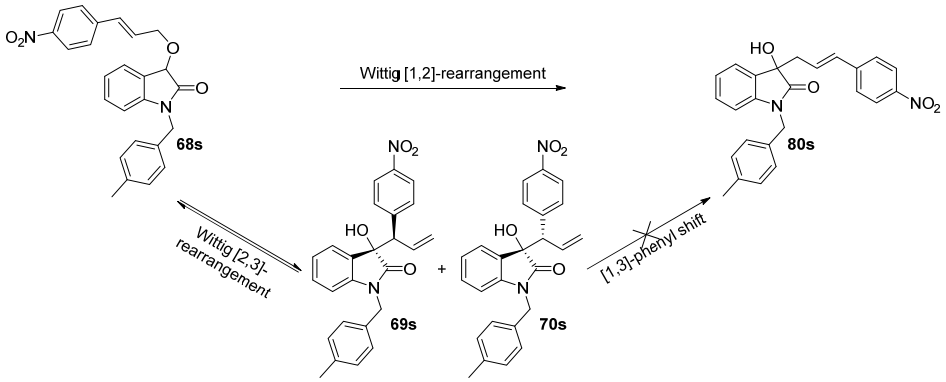


Figure 14. Kinetic study of the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **68k**.

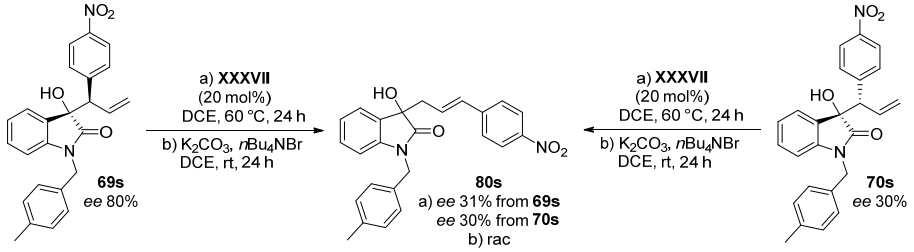
As mentioned previously, along with the [2,3]-rearranged compounds **69s** and **70s**, the formation of a side product was observed in the reaction with *para*-nitro cinnamyloxyoxindole **68s** after 5 hours at 60 °C. As the conversion was not complete, the reaction mixture was left to stir overnight. However, after 24 hours only the side product **80s** was detected by a crude ^{1}H NMR analysis (yield 67%, *ee* 23%). The formation of the [2,3]-rearranged products was preferred at room temperature and compounds **69s** and **70s** were isolated in 77% yield and enantioselectivities 80%/30% (Table 4, entry 13). There are two possible pathways leading to the side product **80s**: a phenyl shift of the [2,3]-rearranged products or a [1,2]-rearrangement of cinnamyloxyoxindole **68s** (Scheme 33). A similar observation was made by Denmark *et al.*, and they proposed the first pathway.[52] If the side product **80s** was formed by a [1,3]-phenyl shift of compounds **69s** and **70s**, the stereogenic center at the C-3 position of oxindole would be conserved and the enantiomeric excess would remain the same, because racemization is not possible at this position. To verify this concept, a set of control experiments was performed with the major and minor diastereoisomers separately, catalyzed by the chiral catalyst and inorganic base (Scheme 34).

[ii] See supporting information of Publication II for the calculation details.



Scheme 33. Possible pathways for the formation of the side product **80s**.

When squaramide **XXXVII** was used as a catalyst, the product **80s** was obtained in 31% *ee* starting from the main diastereoisomer **69s** (*ee* 80%) and in 30% from the minor diastereoisomer **70s** (*ee* 30%). In the reaction with potassium carbonate, racemic product was formed. The change in enantioselectivity excluded a [1,3]-phenyl shift and suggested that the Wittig [2,3]-rearrangement of cinnamyloxyoxindole **68s** is reversible under those reaction conditions, and product **80s** was formed by a [1,2]-rearrangement of cinnamyloxyoxindole **68s**. It can be concluded that [2,3]-rearranged products of cinnamyloxyoxindole **68s** are kinetic products, while the [1,2]-rearranged one is a thermodynamic product, as the formation of the latter is preferred at a higher temperature. In the literature, the Wittig [1,2]-rearrangement is described as a biradical process initiated by strongly basic reagents, such as BuLi, LDA and KH.[41] The fact that a [1,2]-rearrangement of 3-cinnamyloxyoxindole **68s** proceeded well in the absence of a strong base in the transformation described by us is very intriguing, because it might be the first example of the enantioselective organocatalytic Wittig [1,2]-rearrangement reaction. However, a more detailed investigation of the mechanism is required.

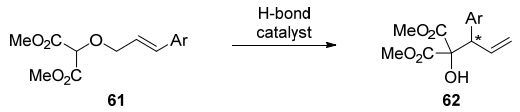


Scheme 34. Control experiments with the chiral catalyst and inorganic base.

To sum up, the first asymmetric organocatalytic hydrogen-bond mediated Wittig [2,3]-rearrangement was developed. The rearranged products **69** and **70** were isolated in very high yields (up to 95%) and enantioselectivities (up to 97%). The reaction tolerated well different substituents at the aromatic ring of oxindole and phenyl group, as well as the aromatic analogs of the cinnamyl side chain. The kinetic study demonstrated that the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **68** is the competitive first order reaction and no isomerization of the products occurred. Also, we have described the first enantioselective Wittig [1,2]-rearrangement catalyzed by a mild organocatalyst.

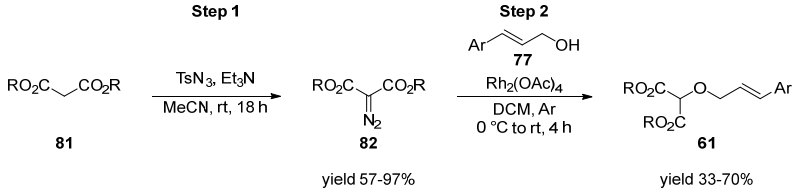
3.3 Asymmetric organocatalytic Wittig [2,3]-rearrangement of malonates (Publication III)

Our next goal was the further development of the chemistry described in the previous chapter. Based on the malonate core structure, compound **61** was chosen as a suitable substrate for an organocatalytic Wittig [2,3]-rearrangement, as there are many examples in the literature demonstrating the activation of malonate derivatives by hydrogen-bond catalysis (Scheme 35).[69]



Scheme 35. General scheme for the Wittig [2,3]-rearrangement of 2-cinnamyloxymalonate **61**.

From our previous experience with the synthesis of 3-cinnamyloxyoxindoles **68**, we decided to apply a similar strategy for the synthesis of 2-cinnamyloxymalonates **61**. Desired compounds were obtained by a two-step procedure starting with commercially available malonates **81** (Scheme 36). In the first step, malonates **81** were reacted with tosyl azide to produce diazo compounds **82** in good to excellent yields.[70] Diazomalonates **82** were subjected to rhodium-catalyzed cinnamyl alcohol **77** insertion, affording the 2-cinnamyloxymalonates **61**. The moderate yields of that transformation were caused by partial transesterification of malonyl ester by cinnamyl alcohol. In order to improve the yield, back transesterification with *p*TsOH in MeOH was conducted in some cases.



Scheme 36. Synthesis of 2-cinnamyloxymalonates **61**.

We started the catalyst screening from the squaramide **XXXVII**, which was the best catalyst in the case of the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **68** (Figure 15). However, it did not show any activity toward cinnamyloxymalonate **61a** even at a higher temperature and extended reaction time (Table 5, entry 1). When catalyst **VII** was used for the rearrangement, excellent reactivity and promising selectivity were achieved (Table 5, entry 2). This catalyst is based on the cyclopropenimine core and its basicity is comparable to guanidines.[71] In addition to high Brønsted basicity, cyclopropenimine derivative **VII** is also a hydrogen bond donor. Furthermore, a variety of catalyst **VII** analogues were synthesized in order to improve the enantioselectivity of the reaction. Although hydrochloric salts of the cyclopropenimine catalysts are stable at room temperature, as free bases the cyclopropenimine catalysts are rather unstable. A considerable rate of degradation of the catalysts **VII** and **XLIII** was observed in the reaction mixture when the reactions were stirred at room temperature overnight. The catalyst screening revealed that H-bonding played a significant role in the asymmetric induction, as enantioselectivity decreased dramatically when methyl-protected catalyst **XLII** was used (Table 5, entry

4). Lowering the temperature of the reaction increased the enantioselectivity to 50%, while full conversion was reached with a longer reaction time (Table 5, entry 3). Next, several solvents were tested for the transformation, but no improvement in the selectivity was achieved (Table 5, entries 10-14).

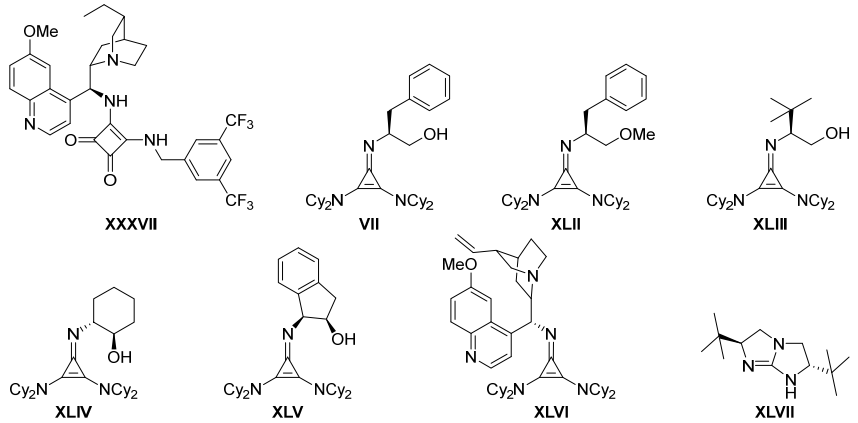
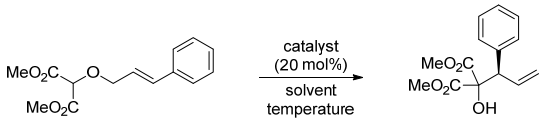


Figure 15. Catalysts screened for the organocatalytic Wittig [2,3]-rearrangement of cinnamyloxymalonates **61**.

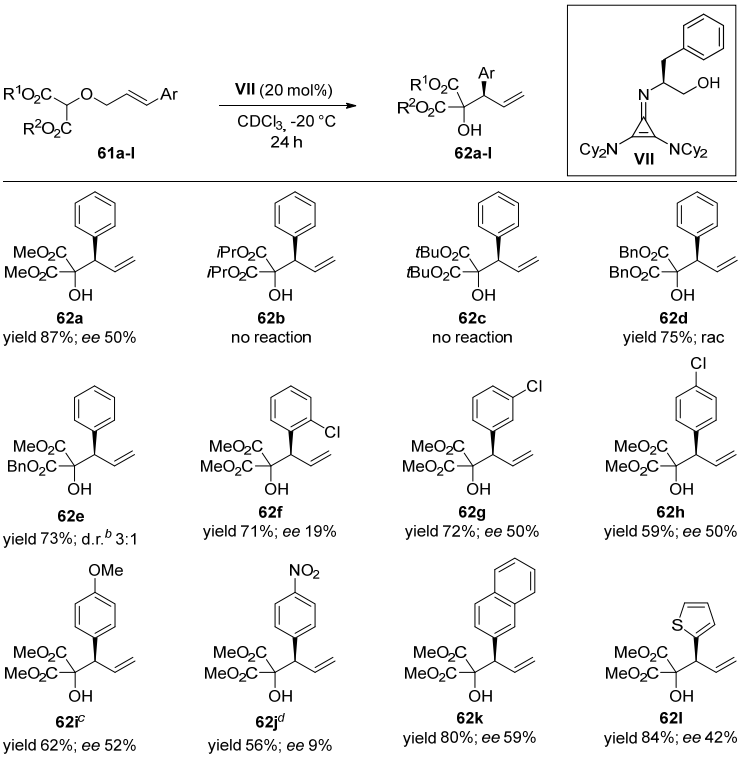
Table 5. Catalyst screening and optimization of the organocatalytic Wittig [2,3]-rearrangement of cinnamyloxymalonate **61a**[a]



entry	catalyst	solvent	temp. (°C)	time (h)	conv. (%)[b]	*ee* (%)[c]
1	**XXXVII**	$CDCl_3$	55	96	0	-
2	**VII**	$CDCl_3$	rt	2	100	33
3	**VII**	$CDCl_3$	-20	18	100	50
4	**XLII**	$CDCl_3$	rt	2	94	8
5	**XLIII**	$CDCl_3$	-20	23	97	52
6	**XLIV**	$CDCl_3$	-20	18	88	-37
7	**XLV**	$CDCl_3$	rt	18	45	*rac*
8	**XLVI**	$CDCl_3$	55	72	0	-
9	**XLVII**	$CDCl_3$	55	72	90	-20
10	**VII**	hexane/$CDCl_3$[d]	-20	5	100	45
11	**VII**	EtOAc	rt	23	80	17
12	**VII**	toluene	-20	20	83	28
13	**VII**	THF	-20	20	74	23
14	**VII**	Et_2O	-20	18	78	31
15	**VII**	MeOH	-20	18	100	*rac*
16	**VII**	$CDCl_3$	-20	48[e]	57	-

[a]Reaction conditions: 0.1 mmol scale, 20 mol% of cat., solvent (0.5 mL). [b]Conversion determined by ^1H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis of the sample obtained by preparative TLC. [d]Mixture 1:1. [e]Reaction conditions: 0.1 mmol scale, 10 mol% of cat., solvent (0.25 mL).

We tried to enhance the enantioselectivity of the organocatalytic Wittig [2,3]-rearrangement of cinnamyloxymalonate **61** by introducing bulkier groups to the carbonyl moiety (Figure 16). However, the method turned out to be very sensitive to steric hindrance, as no products were formed with isopropyl and *tert*-butyl derivatives **61b** and **61c**. Unexpectedly, a racemic product **62d** was obtained in the reaction with benzyl derivative, probably due to additional π-π interaction with the catalyst. Substrates with substituents in the cinnamyl aromatic ring and its analogs reacted smoothly and corresponding [2,3]-rearranged products were isolated in high yields and moderate enantioselectivities (apart from **62f** and **62j**). The absolute configuration of the [2,3]-rearranged products was determined by a comparison of the optical rotation of compound **62a** with the data published by Jacobsen.[53]



[a]Reaction conditions: 0.1 mmol scale, 20 mol% of **VII**, $CDCl_3$ (0.5 mL), -20 °C, 24 h. Enantiomeric excess is determined by chiral HPLC analysis of the isolated product. [b]Diastereoisomeric ratio is determined by ^1H NMR analysis of the crude mixture. [c]Reaction was stopped after 48 h. [d]Reaction was finished after 48 h.

Figure 16. Scope of the Wittig [2,3]-rearrangement of cinnamyloxymalonates **61**.[a]

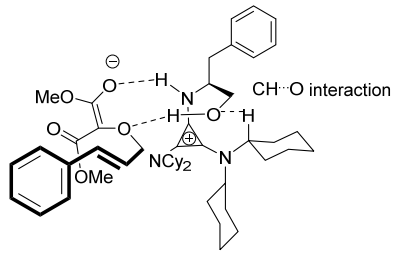


Figure 17. Proposed transition state for the Wittig [2,3]-rearrangement of cinnamyloxymalonate **61a**.

A Wittig [2,3]-rearrangement of cinnamyloxymalonate **61a** is initiated by the deprotonation of the malonate moiety of the substrate by the catalyst **VII**, affording an enolate anion and a cyclopropenium ion. The transition state, leading to enantiodiscrimination, is stabilized by hydrogen bonds between the formed ions and a weak intramolecular CH···O interaction (0.5 kcal/mol) (Figure 17).[72] A nucleophilic attack of the enolate on the *Re*-face of the cinnamyl double bond leads to the formation of *R*-enantiomer. The hydrogen bond between the OH group of the catalyst and the allylic oxygen promotes the [2,3]-rearrangement by stabilizing the developing negative charge on the latter. A similar activation model was previously proposed for the cycloaddition of azomethine ylides[73] and for a Mannich reaction.[74]

In conclusion, the further development of the H-bond mediated Wittig [2,3]-rearrangement has been described. The rearrangement of 2-cinnamyloxymalonates **61** was catalyzed by the highly basic cyclopropenimine **VII**, providing the corresponding products in high yields and moderate enantioselectivities.

4 Conclusions

- A method for the asymmetric synthesis of α,β-identically substituted spirocyclopropyl oxindoles through the organocatalytic MIRC reaction sequence was developed.

- A challenging asymmetric desymmetrization of unsaturated 1,4-dicarbonyl compounds was achieved *via* the reaction with 3-chlorooxindoles **63** in the presence of a hydrogen-bond catalyst. Spirocyclopropyl oxindoles **65a**-**f** with two identically substituted tertiary stereocenters were obtained in moderate yields and with very high diastereo- and enantioselectivities. The conjugated addition of 3-chlorooxindoles **63** to non-symmetric 1,4-dicarbonyl compounds is highly regioselective and provided spirocyclopropyl oxindoles **65g**-**j** containing two tertiary and one quaternary center with excellent diastereoselectivity.

- A general method for the synthesis of allyl ethers, containing highly acidic α-proton, was developed. 3-Cinnamyloxyoxindoles **68** and 2-cinnamyloxymalonates **61** were synthesized according to this method, starting with the cheap commercially available compounds.

- A highly enantioselective hydrogen-bond mediated Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindoles **68** was demonstrated. The transformation tolerated a wide range of substituents and provided 3-substituted 3-hydroxyoxindoles **69** and **70** in very high yields.

- The Wittig [2,3]-rearrangement of 2-cinnamyloxymalonates **61** was efficiently catalyzed by the highly basic cyclopropenimine **VII**. The importance of hydrogen-bonding between the catalyst and the substrate for the asymmetric induction was demonstrated.

- The choice of the catalyst is essential to achieve high efficiency and enantioselectivity of the reaction. Even for the same type of [2,3]-rearrangement reaction, the best catalyst for oxindole-based starting materials is totally inefficient in the case of malonate-based substrates.

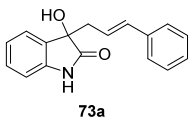
- The first enantioselective [1,2]-type rearrangement catalyzed by a mild organocatalyst was described.

5 Experimental

General information

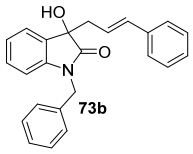
Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used (DMSO-d_6 δ = 2.50/39.52 and MeOD δ = 3.31/49.00) as internal standards. Chiral HPLC was performed using a Chiralpak AS-H (250 x 4.6 mm) column. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel Kieselgel 40-63 µm was used. Purchased chemicals and solvents were used as received. DCM and EtOAc were distilled over phosphorous pentoxide. Petroleum ether has a boiling point of 40-60 °C.

3-Cinnamyl-3-hydroxyindolin-2-one 73a. 3-Hydroxyoxindole was synthesized according to the literature procedure.[75] NaH (60% dispersion in mineral oil, 27 mg, 0.67 mmol, 1 equiv.) was added in one portion to the stirred solution of 3-hydroxyoxindole (100 mg, 0.67 mmol, 1 equiv.) in dry THF (6 mL) at 0 °C under an inert atmosphere. After stirring for 1 hour at room temperature, a solution of cinnamyl bromide (158 mg, 0.80 mmol, 1.2 equiv.) was added dropwise to the mixture. The reaction mixture was stirred for 4 hours at room temperature and then quenched by the addition of 15 mL sat. aq. NH_4Cl. The crude product was extracted with EtOAc (4 x 15 mL). Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel with DCM/MeOH (2-10% MeOH) as an eluent to provide **73a** (116 mg, 65%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 7.32 – 7.14 (m, 7H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.05 (s, 1H), 5.96 (ddd, *J* = 15.3, 8.2, 6.5 Hz, 1H), 2.75 (ddd, *J* = 13.3, 6.5, 1.6 Hz, 1H), 2.56 (dd, *J* = 13.4, 8.3 Hz, 1H). ^{13}C NMR (DMSO, 101 MHz) δ 178.8, 141.5, 136.9, 133.1, 131.6, 128.9, 128.6, 127.2, 125.8, 124.2, 123.4, 121.5, 109.5, 75.6, 41.3.

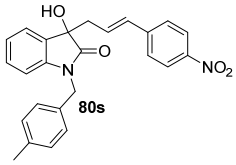


73a

1-Benzyl-3-cinnamyl-3-hydroxyindolin-2-one 73b. *N*-benzyl-3-hydroxyoxindole was synthesized according to the literature procedure.[75] A solution of *N*-benzyl-3-hydroxyoxindole (100 mg, 0.418 mmol, 1 equiv.) in THF (1 mL) was added over 10 min at -78 °C to a solution of LiHMDS [generated in situ from *n*BuLi (167 µL, 0.418 mmol, 2.5 M in hexanes) and hexamethyldisilazane (0.105 µL, 0.502 mmol) in THF (1 mL) at 0 °C]. The mixture was stirred at -78 °C for 40 min, and then cinnmayl bromide (99 mg, 0.502 mmol, 1.2 equiv.) in THF (0.8 mL) was added. The mixture was warmed slowly to room temperature and stirred overnight. Saturated aqueous NH_4Cl (6 mL) was added, and the mixture was extracted with EtOAc (4 x 6 mL). The combined organic fractions were dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with DCM/EtOAc (5-15% EtOAc) to give 73 mg (49%) of product **73b** as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.40 (d, *J* = 7.1 Hz, 1H), 7.32 – 7.12 (m, 9H), 7.08 – 7.00 (m, 3H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.29 (s, 1H), 5.81 (ddd, *J* = 15.4, 8.3, 6.5 Hz, 1H), 5.00 (d, *J* = 15.9 Hz, 1H), 4.68 (d, *J* = 15.9 Hz, 1H), 2.89 (ddd, *J* = 13.2, 6.6, 1.6 Hz, 1H), 2.76 (dd, *J* = 13.2, 8.4 Hz, 1H). ^{13}C NMR (DMSO, 101 MHz) δ 177.1, 142.1, 136.6, 136.1, 133.6, 130.9, 129.0, 128.6, 128.4, 127.3, 127.1, 127.0, 125.9, 124.0, 122.9, 122.4, 109.0, 75.5, 42.5, 41.4.



(*E*)-3-hydroxy-1-(4-methylbenzyl)-3-(3-(4-nitrophenyl)allyl)indolin-2-one 80s.



3-Cinnamyloxyoxindole **68s** (41 mg, 0.10 mmol, 1 equiv.) and squaramide **XXXVII** (13 mg, 20 mol%) were dissolved in 1,2-dichloroethane (0.5 mL) and stirred for 24 hours at 60 °C. Upon completion of the reaction, the mixture was directly purified by column chromatography on silica gel with DCM/EtOAc (20:1) as an eluent. The product was isolated as a yellowish amorphous solid in 67% yield (27 mg) and 23% *ee* [Chiralpak AS-H column; hexane:*i*PrOH 8:2, 0.8 mL/min, 30 °C, 210 nm; t_R (major) = 32.8 min and t_R (minor) = 39.3 min]. ^{1}H NMR (400 MHz, MeOD) δ 8.07 (d, *J* = 8.8 Hz, 2H), 7.45 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.29 – 7.20 (m, 3H), 7.15 – 7.05 (m, 3H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 2H), 6.46 (d, *J* = 15.9 Hz, 1H), 5.97 (ddd, *J* = 15.5, 8.5, 6.6 Hz, 1H), 5.02 (d, *J* = 15.5 Hz, 1H), 4.60 (d, *J* = 15.5 Hz, 1H), 3.06 – 2.85 (m, 2H), 2.15 (s, 3H). ^{13}C NMR (MeOD, 101 MHz) δ 179.4, 148.2, 144.9, 143.6, 138.3, 134.1, 133.9, 131.8, 130.7, 130.2, 128.9, 128.5, 128.0, 125.0, 124.8, 124.3, 110.8, 77.4, 44.2, 42.8, 21.0.

Table 6. 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**		**VII**	
2	**VII**			**II**
3	**XII**	**III**	**III**	
4	**XXXIII**	**I**		
5	**XXXIV**	**II**	**V**	
6	**XXXV**	**IV**	**II**	
7	**XXXVI**	**V**	**VI**	
8	**XXXVII**		**I**	**I**
9	**XXXVIII**		**IV**	
10	**XXXIX**		**VIII**	
11	**XL**		**IX**	
12	**XLI**		**X**	
13	**XLII**			**III**
14	**XLIII**			**IV**
15	**XLIV**			**V**
16	**XLV**			**VI**
17	**XLVI**			**VII**
18	**XLVII**			**VIII**
19	**61**			**1**
20	**61a**			**1a**
21	**61b**			**1b**
22	**61c**			**1c**
23	**61d**			**1d**
24	**61e**			**1e**
25	**61f**			**1h**
26	**61g**			**1i**

27	**61h**			**1j**
28	**61i**			**1k**
29	**61j**			**1l**
30	**61k**			**1m**
31	**61l**			**1n**
32	**62**			**2**
33	**62a**			**2a**
34	**62b**			**2b**
35	**62c**			**2c**
36	**62d**			**2d**
37	**62e**			**2e**
38	**62f**			**2h**
39	**62g**			**2i**
40	**62h**			**2j**
41	**62i**			**2k**
42	**62j**			**2l**
43	**62k**			**2m**
44	**62l**			**2n**
45	**63**	**1**		
46	**63a**	**1a**		
47	**64**	**2**		
48	**64a**	**2a**		
49	**65**	**3**		
50	**65a**	**3a**		
51	**65b**	**3b**		
52	**65c**	**3c**		
53	**65d**	**3d**		
54	**65e**	**3e**		
55	**65f**	**3f**		
56	**65g**	**3g**		
57	**65h**	**3h**		
58	**65i**	**3i**		
59	**65j**	**3j**		
60	**65c-NH**	**3c-NH**		
61	**66**	**4**		
62	**66c**	**4c**		
63	**67**	**5**		
64	**67c**	**5c**		
65	**68**		**1**	
66	**68a**		**1a**	
67	**68b**		**1b**	
68	**68c**		**1c**	
69	**68d**		**1d**	
70	**68e**		**1e**	
71	**68f**		**1f**	
72	**68g**		**1g**	

73	**68h**		**1h**	
74	**68i**		**1i**	
75	**68j**		**1j**	
76	**68k**		**1k**	
77	**68l**		**1l**	
78	**68m**		**1m**	
79	**68n**		**1n**	
80	**68o**		**1o**	
81	**68p**		**1p**	
82	**68q**		**1q**	
83	**68r**		**1r**	
84	**68s**		**1s**	
85	**68t**		**1t**	
86	**68u**		**1u**	
87	**68v**		**1v**	
88	**68w**		**1w**	
89	**68x**		**1x**	
90	**68y**		**1y**	
91	**68z**		**1z**	
92	**68za**		**1za**	
93	**69a**		**2a**	
94	**69b**		**2b**	
95	**69c**		**2c**	
96	**69d**		**2d**	
97	**69e**		**2e**	
98	**69f**		**2f**	
99	**69g**		**2g**	
100	**69h**		**2h**	
101	**69i**		**2i**	
102	**69j**		**2j**	
103	**69k**		**2k**	
104	**69l**		**2l**	
105	**69m**		**2m**	
106	**69n**		**2n**	
107	**69o**		**2o**	
108	**69p**		**2p**	
109	**69q**		**2q**	
110	**69r**		**2r**	
111	**69s**		**2s**	
112	**69t**		**2t**	
113	**69u**		**2u**	
114	**69v**		**2v**	
115	**70a**		**3a**	
116	**70b**		**3b**	
117	**70c**		**3c**	
118	**70d**		**3d**	

119	**70e**		**3e**	
120	**70f**		**3f**	
121	**70g**		**3g**	
122	**70h**		**3h**	
123	**70i**		**3i**	
124	**70j**		**3j**	
125	**70k**		**3k**	
126	**70l**		**3l**	
127	**70m**		**3m**	
128	**70n**		**3n**	
129	**70o**		**3o**	
130	**70p**		**3p**	
131	**70q**		**3q**	
132	**70r**		**3r**	
133	**70s**		**3s**	
134	**70t**		**3t**	
135	**70u**		**3u**	
136	**70v**		**3v**	
137	**75**		**S1**	
138	**76**		**S2**	
139	**76o**		**S2o**	

References

[1] (a) Bredig, G. *Chemiker-Zeitung* **1912**, *35*, 324. (b) Bredig, G.; Fiske, P. S. *Biochemische Zeitschrift* **1913**, *46*, 7.

[2] Pihko, P. M. (2009). Hydrogen Bonding in Organic Synthesis; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.

[3] Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406.

[4] Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

[5] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

[6] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[7] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

[8] (a) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (b) Wynberg, H. *Recueil, Journal of the Royal Netherlands Chemical Society* **1981**, *100*, 393.

[9] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

[10] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

[11] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

[12] Probst, N.; Madarász, Á.; Valkonen, A.; Pápai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8495.

[13] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552.

[14] Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.

[15] Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051.

[16] Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890.

[17] (a) Nord, C.; Menkis, A.; Broberg, A. *J. Nat. Prod.* **2015**, *78*, 2559. (b) Tanasova, M.; Sturla, S. J. *Chem. Rev.* **2012**, *112*, 3578.

[18] Masuyama, Y.; Kinugawa, N.; Kurusu, Y. *J. Org. Chem.* **1987**, *52*, 3704.

[19] Guo, Z.; Orth, P.; Wong, S.-C.; Lavey, B. J.; Shih, N.-Y.; Niu, X.; Lundell, D. J.; Madison, V.; Kozlowski, J. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 54.

[20] Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105.

[21] Sampson, P. B.; Liu, Y.; Li, S.-W.; Forrest, B. T.; Pauls, H. W.; Edwards, L. G.; Feher, M.; Patel, N. K. B.; Laufer, R.; Pan, G. *Kinase Inhibitors and Method of Treating Cancer with Same. U.S. Patent* WO 2010/115279A1, **2010**.

[22] Peterson, E. A.; Overman, L. E. *PNAS* **2004**, *101*, 11943.

[23] Cao, Z.-Y.; Zhou, J. *Org. Chem. Front.* **2015**, *2*, 849.

[24] For recent examples, see (a) Zhang, Y.; Lin, L.; Chen, Y.; Liu, Z.; Feng, Z. *Adv. Synth. Catal.* **2017**, *359*, 1831. (b) Fiandra, C. D.; Moccia, M.; Adamo, M. F. A. *Org. Biomol. Chem.* **2016**, *14*, 3105. (c) Bakó, P.; Rapi, Z.; Grün, A.; Nemcsok, T.; Hegedűs, L.; Keglevich, G. *Synlett* **2015**, *26*, 1847. (d) Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627.

[25] Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem. Eur. J.* **2011**, *17*, 2842.

[26] Russo, A.; Meninno, S.; Tedesco, C.; Lattanzi. A. *Eur. J. Org. Chem.* **2011**, 5096.

[27] Noole, A.; Järving, I.; Werner, F.; Lopp, M.; Malkov, A.; Kanger, T. *Org. Lett.* **2012**, *14*, 4922.

[28] Noole, A.; Ošeka, M.; Pehk, T.; Öeren, M.; Järving, I.; Elsegood, M. R. J.; Malkov, A.; Lopp, M.; Kanger, T. *Adv. Synth. Catal.* **2013**, *355*, 829.

[29] Dou, X.; Yao, W.; Zhou, B.; Lu, Y. *Chem. Commun.* **2013**, *49*, 9224.
[30] Silva, R. C.; Chatterjee, I.; Escudero-Adán, E.; Paixão, M. W.; Melchiorre, P. *Asian J. Org. Chem.* **2014**, *3*, 466.
[31] Li, J.-H.; Feng, T.-F.; Du, D.-M. *J. Org. Chem.* **2015**, *80*, 11369.
[32] Donslund, B. K.; Jessen, N. I.; Jakobsen, J. B.; Monleón, A.; Nielsen, R. P.; Jørgensen, K. A. *Chem. Commun.* **2016**, *52*, 12474.
[33] (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
[34] Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327.
[35] Bykowski, D.; Wu, K.-H.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 16038.
[36] Ichinose, M.; Suematsu, H.; Katsuki, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 3121.
[37] Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2013**, *15*, 42.
[38] Cao, Z.-Y.; Wang, X.-M.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K.-L. *J. Am. Chem. Soc.* **2013**, *135*, 8197.
[39] Chi, Y.; Qiu, L.; Xu, X. *Org. Biomol. Chem.* **2016**, *14*, 10357.
[40] Guo, J.; Liu, Y.; Li, X.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2016**, *7*, 2717.
[41] Wolfe, J. P. (2014). Comprehensive Organic Synthesis: The Wittig Rearrangement. 2nd ed. USA: Elsevier Ltd.
[42] Wittig, G.; Doser, H.; Lorenz, I. *Liebigs Ann. Chem.* **1949**, *562*, 192.
[43] Cast, J.; Stevens, T. S.; Holmes, J. *J. Chem. Soc.* **1960**, 3521.
[44] Mikami, K.; Fujimoto, K.; Kasuga, T.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 6011.
[45] Marshall, J. A.; Lebreton, J. *Tetrahedron Lett.* **1987**, *28*, 3323.
[46] McNally, A.; Evans, B.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2116.
[47] (a) Enders, D.; Plant, A.; Backhaus, D.; Reinhold, U. *Tetrahedron* **1995**, *51*, 10699. (b) Enders, D.; Backhaus, D.; Runsink, J. *Tetrahedron* **1996**, *52*, 1503. (c) Enders, D.; Bartsch, M.; Backhaus, D.; Runsink, J.; Raabe, G. *Synthesis* **1996**, 1438.
[48] Kress, M. H.; Yang, C.; Yasuda, N.; Grabowski, E. J. J. *Tetrahedron Lett.* **1997**, *38*, 2633.
[49] Li, Y.-J.; Ho, G.-M.; Chen, P.-Z. *Tetrahedron: Asymmetry* **2009**, *20*, 1854.
[50] (a) Hirokawa, Y.; Kitamura, M.; Maezaki, N. *Tetrahedron: Asymmetry* **2008**, *19*, 1167. (b) Kitamura, M.; Hirokawa, Y.; Maezaki, N. *Chem. Eur. J.* **2009**, *15*, 9911. (c) Kitamura, M.; Hirokawa, Y.; Yoshioka, Y.; Maezaki, N. *Tetrahedron* **2012**, *68*, 4280.
[51] (a) Hirokawa, Y.; Kitamura, M.; Kato, C.; Kurata, Y.; Maezaki, N. *Tetrahedron Lett.* **2011**, *52*, 581. (b) Hirokawa, Y.; Kitamura, M.; Mizubayashi, M.; Nakatsuka, R.; Kobori, Y.; Kato, C.; Kurata, Y.; Maezaki, N. *Eur. J. Org. Chem.* **2013**, 721.
[52] Denmark, S. E.; Cullen, L. R. *J. Org. Chem.* **2015**, *80*, 11818.
[53] Kennedy, C. R.; Guidera, J. A.; Jacobsen, E. N. *ACS Cent. Sci.* **2016**, *2*, 416.
[54] Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. *J. Org. Chem.* **2017**, *82*, 2889.
[55] (a) Noole, A.; Sucman, N.; Kabeshov, M.; Kanger, T.; Macaev, F.; Malkov, A. *Chem. Eur. J.* **2012**, *18*, 14929. (b) Noole, A.; Malkov, A. V.; Kanger, T. *Synthesis* **2013**, 2520.
[56] (a) Ferrary, T.; David, E.; Milanole, G, Besset, T.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 5598. (b) Kozhushkov, S. I.; Leonov, A.; de Meijere, A. *Synthesis* **2003**, 956. (c) Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* **2003**, 1704. (d) Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H., Fieldhouse, R.; Spey, S. E. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3267.

[57] (a) Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074. (b) Ibrahem, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem. Eur. J.* **2008**, *14*, 7867.
[58] Žari, S.; Kailas, T.; Kudrjashova, M.; Öeren, M.; Järving, I.; Tamm, T.; Lopp, M.; Kanger, T. *Beilstein J. Org. Chem.* **2012**, *8*, 1452.
[59] Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193.
[60] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.
[61] Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Chem. Eur. J.* **2012**, *18*, 6679.
[62] Ošeka, M.; Noole, A.; Žari, S.; Öeren, M.; Järving, I.; Lopp, M.; Kanger, T. *Eur. J. Org. Chem.* **2014**, 3599.
[63] (a) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (b) Coste, A.; Couty, F.; Evano, G. *C. R. Chim.* **2008**, *11*, 1544. (c) Kumar, A.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 9748. (d) Bergonzini, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 971. (e) Jayakumar, S.; Kumarswamyreddy, N.; Prakash, M.; Kesavan, V. *Org. Lett.* **2015**, *17*, 1066. (f) Tao, Z.-L.; Li, X.-H.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 4054.
[64] Williamson, A. W. *Philosophical Magazine* **1850**, *37*, 350.
[65] Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.
[66] Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505.
[67] Li, H.; Bonderoff, S. A.; Cheng, B.; Padwa, A. *J. Org. Chem.* **2014**, *79*, 392.
[68] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
[69] For recent examples, see (a) Neuvonen, A. J.; Földes, T.; Madarász, A.; Pápai, I.; Pihko, P. M. *ACS Catal.* **2017**, *7*, 3284. (b) Chowdhury, R.; Kumar, M.; Ghosh, S. K. *Org. Biomol. Chem.* **2016**, *14*, 11250. (c) Le Bailly, B. A. F.; Byrne, L.; Clayden, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 2132. (d) Huang, X.; Pham, K.; Yi, W.; Zhang, X.; Clamens, C.; Hyatt, J. H.; Jasinsk, J. P.; Tayvah, U.; Zhang, W. *Adv. Synth. Catal.* **2015**, *357*, 3820. (e) Ashokkumar, V.; Siva, A. *Org. Biomol. Chem.* **2015**, *13*, 10216.
[70] Wyatt, P.; Hudson, A.; Charmant, J.; Orpen, A. G.; Phetmung, H. *Org. Biomol. Chem.* **2006**, *4*, 2218.
[71] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552.
[72] (a) Bandar, J. S.; Sauer, G. S.; Wulff, W. D.; Lambert, T. H.; Vetticat, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 10700. (b) Bandar, J. S.; Barthelme, A.; Mazori, A. Y.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537.
[73] Lauridsen, V. H.; Ibsen, L.; Blom, J.; Jørgensen, K. A. *Chem. Eur. J.* **2016**, *22*, 3259.
[74] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799.
[75] Silvi, M.; Chatterjee, I.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 10780.

Publication I

Ošeka, M.; Noole, A.; Žari, S.; Öeren, M.; Järving, I.; Lopp, M.; Kanger, T. Asymmetric Diastereoselective Synthesis of Spirocyclopropane Derivatives of Oxindole. *European Journal of Organic Chemistry* **2014**, 3599-3606.

EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402061

Asymmetric Diastereoselective Synthesis of Spirocyclopropane Derivatives of Oxindole

Maksim Ošeka,[a] Artur Noole,[a] Sergei Žari,[a] Mario Öeren,[a] Ivar Järving,[a] Margus Lopp,[a] and Tõnis Kanger*[a]

Keywords: Organocatalysis / Asymmetric synthesis / Cyclization / Michael addition / Small ring systems

A new asymmetric organocatalytic synthesis of spirocyclopropane oxindoles has been developed. The method is based on the Michael addition of *N*-Boc-protected 3-chlorooxindole to unsaturated 1,4-dicarbonyl compounds, affording *trans*-substituted spirocyclopropane oxindole derivatives in high diastereo- and enantioselectivity.

Introduction

The synthesis of spirocyclic oxindole derivatives has recently gained considerable attention.[1] This core structure can be found in many natural and synthetic compounds exhibiting a diverse range of biological activities, including antimalarial,[2] anti-HIV,[3] and anticancer activities.[4] Their medical importance has made them valuable synthetic targets and has spurred research towards the creation of convenient and highly selective methods for their synthesis. The asymmetric construction of a spirocyclopropane motif is especially challenging due to the presence of three consecutive stereogenic centers in the highly strained three-membered ring. From a stereochemical point of view, the synthesis of α,β-identically substituted cyclopropane derivatives of oxindole is even more complex because of the formation of an enantiomeric *trans*-substituted derivative structure with a nonstereogenic C-3 center, together with an achiral diastereoisomeric *cis*-isomer with a pseudo-asymmetric center at C-3 (Figure 1).

Previously, we described the synthesis of spirocyclopropane oxindoles starting from alkylidene oxindoles or 3-chlorooxindoles.[5] The latter are very useful building blocks for the creation of all-carbon quaternary centers by cascade reactions using the dualistic properties of the carbon at the third position of oxindole. Chlorine increases the acidity of the C–H bond, making the carbon atom more nucleophilic, and chloride is also a good leaving group for the nucleophilic substitution. Thus, Michael-initiated ring closure (MIRC)[6] between α,β-unsaturated carbonyl compounds and 3-chlorooxindole is a straightforward method for spirocyclopropanation of oxindoles. Unsaturated 1,4-dicarbonyl compounds have also been used in MIRC for the preparation of substituted cyclopropanes,[7] although there are only few examples of asymmetric reactions.[8] To the best of our knowledge, there are no reports concerning asymmetric organocatalytic cyclopropanation on symmetric unsaturated 1,4-diketones.

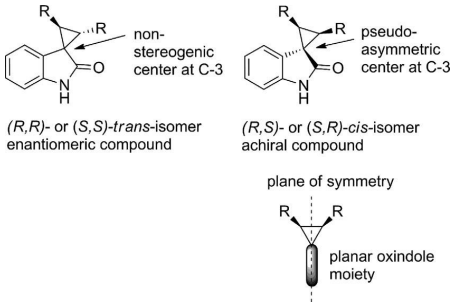
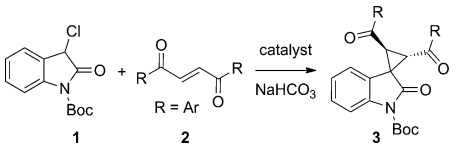


Figure 1. Stereochemistry of *trans*- and *cis*-substituted spirocyclopropane oxindoles.

Results and Discussion

To explore the feasibility of the synthesis of symmetric spirocyclopropane oxindoles, the cascade reaction between *N*-Boc-protected 3-chlorooxindoles **1** and aromatic unsaturated 1,4-diketones **2** was investigated (Scheme 1).



Scheme 1. General scheme for the synthesis of spirocyclopropane oxindoles.

[a] Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia
E-mail: kanger@chemnet.ee
http://www.chem.ttu.ee/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402061.

This reaction cascade is an example of enantioselective MIRC and consists of a Michael addition followed by an intramolecular nucleophilic substitution, leading to the formation of cyclopropane derivatives **3**. Based on our recent results in the asymmetric desymmetrization of unsaturated 1,4-diketones,[9] various enantiomeric thiourea, *Cinchona* alkaloid, or squaramide catalysts **I**–**V** were used to catalyze reactions (Figure 2).

In our first experiments, an unprotected NH oxindole as a synthetically preferable starting material was used.[10] However, due to the insufficient acidity of the hydrogen at C3, no reaction took place.[11]

N-Boc-protected 3-chlorooxindole **1a** reacted smoothly with unsaturated aromatic 1,4-diketone **2a** and provided spirocyclopropane oxindole **3a** in good yield and enantioselectivity (Table , entry 1). Protecting the oxindole nitrogen with an electron-withdrawing group increases the acidity of the C–H bond at C3. On the other hand, it provides the opportunity for the formation of additional H-bonds between the catalyst and the substrate. In this model reaction the ratio of spirocyclopropane oxindole **3a**, uncyclized Michael adduct **4a**, and achiral compound **5a**, together with the enantiomeric purity of **3a** were determined. To facilitate the purification of the product **3a**, the crude mixture was treated with trifluoroacetic acid (TFA) and the product was isolated as a free N-H oxindole **3a**-NH as a single diastereoisomer (side-products **4a** and **5a** were identified by ^{1}H NMR spectroscopic analysis of the crude mixture). All thiourea-derived catalysts gave quite similar *ee* values for the product (Table 1, entries 1, 2 and 5). Squaramide catalyst **III** was clearly inappropriate for the cyclopropanation. The highest enantio- and diastereoselectivity was achieved

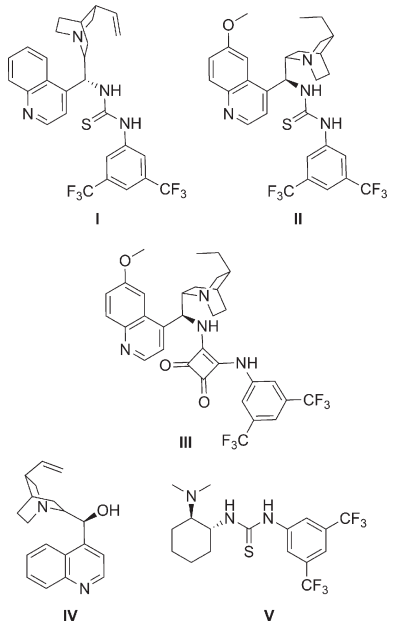
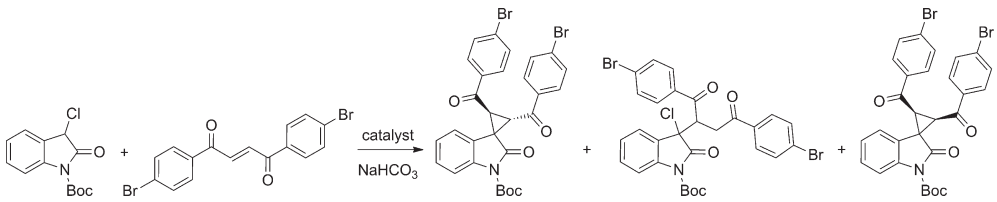


Figure 2. Catalysts used in the study.

with *Cinchona* alkaloid **IV**, but the poor yield obtained (21% for **3a**) made it unattractive for practical use (Table 1, entry 4). The highest yield (70%) was obtained by sacrificing enantioselectivity in running the reaction with catalyst **II** (Table 1, entry 2).

Table 1. Screening of the catalyst and optimization.[a]



Entry	Catalyst (mol-%)	Solvent	*t* [°C]	Time [h]	Ratio **3a**/**4a**/**5a**[b]	Yield [%][c]		*ee* [%][d]
						N-Boc	N-H	
1	**I** (10)	$CHCl_3$	r.t.	18	n.d.	61		–67
2	**II** (10)	$CHCl_3$	r.t.	48	1:0.1:0.2	70		67
3	**III** (10)	$CHCl_3$	r.t.	48	1:0.9:0.5	n.d.		n.d.
4	**IV** (10)	$CHCl_3$	r.t.	48	1:0.6:0.05	21		80
5	**V** (10)	$CHCl_3$	r.t.	48	1:0.6:0.2		42	–75
6	**II** (20)	$CHCl_3$	60	18	1:0.4:0.3		51	48
7	**II** (10)	toluene	r.t.	48	1:0.1:0.1		57	86
8	**II** (10)	CH_2Cl_2	r.t.	48	1:0.2:0.2		44	63
9	**II** (10)	DCE	r.t.	48	1:0.2:0.2		44	65
10	**II** (10)	toluene	4	96	1:0.2:0.1		59	90

[a] Reaction conditions (0.1 mmol scale, 0.2 M solution): **1** (1 equiv.), **2a** (1.2 equiv.), $NaHCO_3$ (2 equiv.). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c] The main product **3a** or **3a**-NH was isolated as a single diastereoisomer. [d] The *ee* of **3** was determined by chiral HPLC analysis of the isolated product.

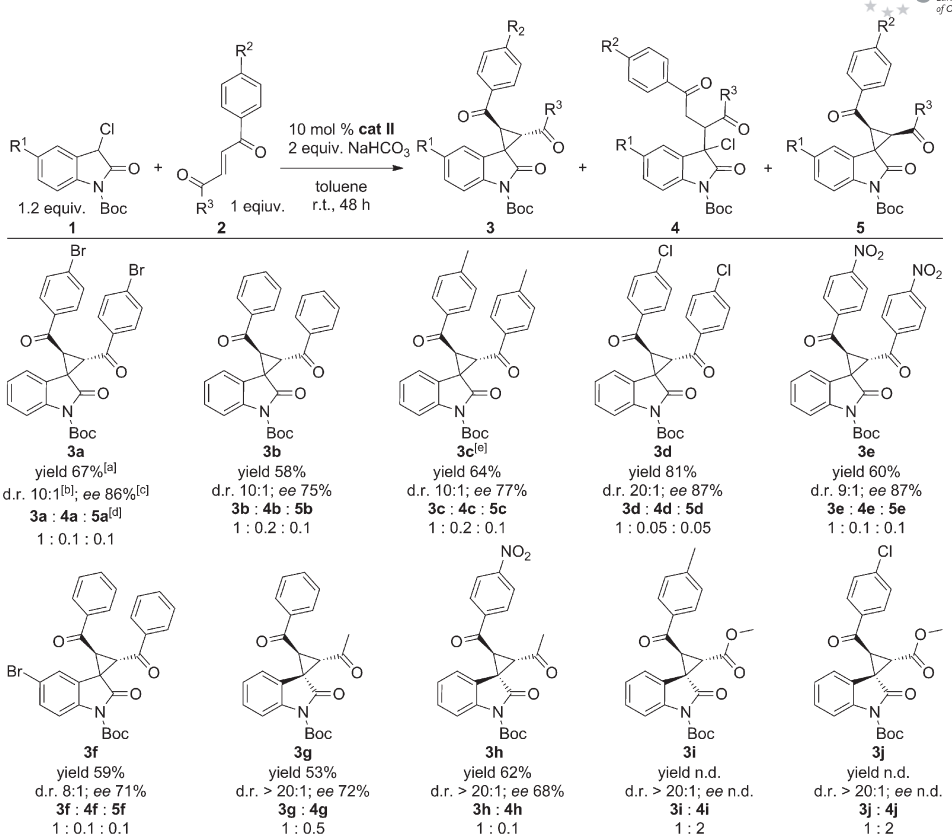


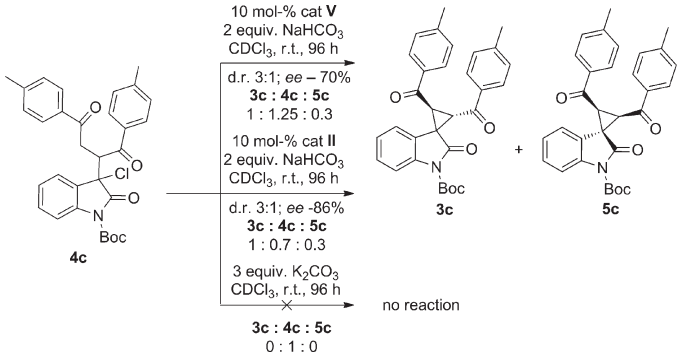
Figure 3. Scope of the reaction. [a] The main product **3** was isolated as a single diastereoisomer. [b] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c] The *ee* was determined by chiral HPLC analysis of the isolated product. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [e] The reaction was stirred for 96 h.

We then turned our attention to further improving the efficiency of the thiourea **II** catalyzed cascade reaction (Table 1, entries 6–9). Increasing temperature and catalyst loading did not improve the yield, instead, the selectivity decreased dramatically (Table 1, entry 6). Solvent screening revealed that the product **3a**-NH could be obtained in moderate yield in 48 h in all cases, but the best enantio- and diastereoselectivity were obtained in toluene (Table 1, entry 7). Decreasing the reaction temperature from room temperature to 4 °C had little influence on stereoselectivity, but an extended reaction time was required to achieve reasonable yield (Table 1, entry 10).

With optimal conditions in hand [**1** (1.2 equiv.), **2** (1 equiv.), $NaHCO_3$ (2 equiv.), and **II** (10 mol-%) in toluene at room temp.], the scope of the reaction was investigated first by using various symmetric diketones **2**. The obtained compounds and the product parameters are presented in Figure 3.

Electron-donating or electron-withdrawing substituents in the aromatic ring of the diketones **2** provided products with two tertiary stereocenters with similar results in terms of yield (from 58 to 81%) and enantioselectivity (*ee* from 75 to 87%) (Figure 3, compounds **3a**–**e**). Diastereoselectivity varied from excellent (Figure 3, compound **3d**) to high (Figure 3, compound **3e**). Bromo-substituted oxindole did not noticeably affect the results of the cascade (Figure 3, compound **3f**). However, the reaction between Boc-protected 3-chlorooxindole **1a** and aliphatic diketone [(*E*)-hex-3-ene-2,5-dione] did not proceed, probably due to the lower electrophilicity of the latter. A similar observation emerged from the work of Liao et al. in the case of the addition of 3-alkyl-substituted oxindoles to unsaturated 1,4-diketones.[12]

The scope of the reaction was then broadened to include nonsymmetric unsaturated 1,4-dicarbonyl compounds, which led to spiro-oxindoles containing two tertiary and one quaternary center (Figure 3, compounds **3g–j**). Although nonsymmetric unsaturated 1,4-diketones have two different electrophilic centers for Michael addition, the nucleophilic attack was regioselective. Two regioisomers of the intermediate should give different diastereoisomers after intramolecular cyclization, but only one out of four possible stereoisomers was formed (Figure 3, compound **3g** and **3h**).



Scheme 2. Cyclization of Michael adduct **4c**.

Unsaturated keto esters reacted smoothly with 3-chlorooxindole, but the main product was non-cyclized compound **4**, which could not be separated from **3** (Figure 3, compounds **3i** and **3j**). Even though only a small amount of **3** formed, the diastereoselectivity was very high, indicating that, similar to nonsymmetric 1,4-diketones, Michael addition to unsaturated keto esters was also regioselective.

The relative stereochemistry of symmetric spiro-oxindoles **3a–f** was determined by ^{1}H NMR spectroscopic analysis, whereas the absolute stereochemistry of one of the products, **3c**-NH, was determined by vibrational circular dichroism (VCD) (Figure 4).

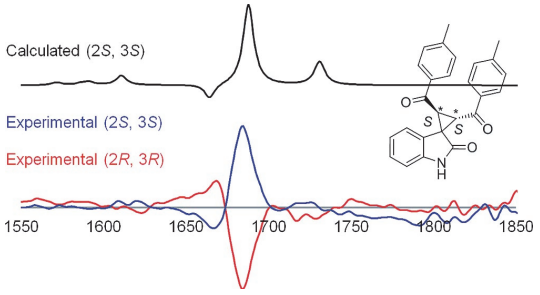


Figure 4. VCD analysis of **3c**-NH.

The assigned absolute stereochemistry was interpolated to other compounds in the series. The relative stereochemistry of spiro-oxindoles **3g–j** was determined by NOESY NMR experiments (for details, see the Supporting Information).

In an additional experiment, non-cyclic Michael adduct **4c** (6:1 mixture of diastereoisomers) was cyclized in the presence of organocatalysts **II** or **V** (Scheme 2). The reaction was very slow, indicating the importance of the catalyst/substrate complex throughout the cascade reaction. Diastereoisomers of **4c** cyclized in the presence of catalyst **II** with different rates, and the diastereomeric ratio of recovered **4c** changed to 20:1. In the presence of catalyst **V**, the ratio remained unchanged. It is known that 3-chlorooxindoles afford the *syn*-product in Michael addition to nitrostyrenes,[5a] but the relative stereochemistry of non-cyclized intermediate **4c** was not determined because during the cyclization the stereogenic center at C3 is lost. Although the racemic product **3c** was obtained from the starting materials in the presence of an inorganic base, no reaction with non-cyclic intermediate **4c** was observed under the same conditions using the same base. This study also suggests that the stereochemistry of the final product **3c** is determined in the first step of the cascade (Michael addition) because two different chiral organocatalysts **II** and **V** afforded the same enantiomer in reaction with non-cyclic intermediate **4c**, whereas enantiomers of **3c** were obtained in separate reactions with starting materials **1a** and **2c**.

Conclusions

Herein, we have described the synthesis of spiro-oxindoles through asymmetric organocatalytic reaction of symmetric unsaturated 1,4-diketones and 3-chlorooxindoles. This methodology provides products **3a–f** with two identically substituted tertiary stereocenters in moderate yields and with very high diastereo- and enantioselectivities. In the case of unsaturated 1,4-keto esters and non-symmetric diketones, the first conjugated addition is highly regioselective and provides spiro-oxindoles **3g–j** containing two tertiary and one quaternary center with excellent diastereoselectivity.

Experimental Section

General Methods and Materials: Full assignment of ^{1}H and ^{13}C chemical shifts was based on the 1D and 2D FT NMR spectra obtained with a Bruker Avance III 400 MHz instrument. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$: δ = 7.26/77.16 ppm; DMSO: δ = 2.50/39.52 ppm). HRMS spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Optical rotations were obtained with an Anton Paar GWB Polarimeter MCP500. Chiral HPLC was performed using a Chiralpak AD-H column. Precoated silica gel 60 F_{254} plates were used for TLC, and Merck silica gel was used for column chromatog-

raphy. Chiral catalysts **IV** and **V** were commercially available from Aldrich or Strem, and **I**, **II** and **III** were prepared according to reported procedures.[13,14] Commercial reagents were generally used as received. CH_2Cl_2 and EtOAc were distilled from P_2O_5.

General Procedure for the Synthesis of *N*-Boc-Oxindoles: *N*-Boc-oxindoles were prepared according to a reported procedure from commercially available oxindoles.[15] To a solution of the corresponding oxindoles (1 equiv.) in anhydrous THF (0.25 M), Na_2CO_3 (9 equiv.) and Boc_2O (2.5 equiv.) were added at room temperature and the resulting mixture was stirred at 70 °C for 12 h. The solid was filtered off and the solvent was evaporated. The crude product was purified by silica gel column chromatography (heptane/ethyl acetate, 10:1).

***tert*-Butyl 2-Oxoindoline-1-carboxylate:** The title compound was obtained as a pink solid in 70% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (ddd, J = 8.2, 1.0, 0.5 Hz, 1 H, ArH), 7.30 (dddt, J = 8.4, 7.5, 1.6, 0.9 Hz, 1 H, ArH), 7.24 (ddd, J = 7.4, 1.4, 0.6 Hz, 1 H, ArH), 7.13 (td, J = 7.5, 1.1 Hz, 1 H, ArH), 3.65 (s, 2 H, CH_2), 1.65 (s, 9 H, Boc) ppm.

***tert*-Butyl 5-Bromo-2-oxoindoline-1-carboxylate:** The title compound was obtained as a pink solid in 53% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.7 Hz, 1 H, ArH), 7.42 (ddt, J = 8.7, 1.8, 0.8 Hz, 1 H, ArH), 7.39–7.36 (m, 1 H, ArH), 3.64 (s, 2 H, CH_2), 1.63 (s, 9 H, Boc) ppm.

General Procedure for the Synthesis of *N*-Boc-3-chlorooxindoles 1a and 1b: A solution of corresponding *N*-Boc-oxindoles (1 equiv.) in THF (0.7 M) was added over 10 min at –78 °C to a solution of LiHMDS [generated in situ from *n*BuLi (1.6 M in hexanes, 2.2 equiv.) and hexamethyldisilazane (2.3 equiv.) in THF (0.5 M) at 0 °C]. The mixture was stirred at –78 °C for 40 min, then *N*-chlorosuccinimide (1.05 equiv.) was added in one portion. The mixture was warmed slowly to room temperature and stirred overnight. A mixture of saturated aqueous NH_4Cl and H_2O (1:1) was added, and the mixture was extracted with CH_2Cl_2. The combined organic fractions were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (heptane/ethyl acetate, 7:1).

***tert*-Butyl 3-Chloro-2-oxoindoline-1-carboxylate (1a):** The title compound was obtained as a red amorphous solid in 49% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.3 Hz, 1 H, ArH), 7.45 (d, J = 7.5 Hz, 1 H, ArH), 7.40 (dddd, J = 8.3, 7.7, 1.4, 0.8 Hz, 1 H, ArH), 7.22 (td, J = 7.6, 1.0 Hz, 1 H, ArH), 5.23 (s, 1 H, CH), 1.64 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.96, 148.84, 140.09, 130.88, 125.71, 125.25, 124.56, 115.58, 85.28, 52.10, 28.17 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{14}ClNO_3Na^+$ $[M + Na]^+$ 290.0554; found 290.0566.

***tert*-Butyl 5-Bromo-3-chloro-2-oxoindoline-1-carboxylate (1b):** The title compound was obtained as a red amorphous solid in 12% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.7 Hz, 1 H, ArH), 7.60–7.54 (m, 1 H, ArH), 7.52 (ddd, J = 8.7, 2.1, 0.7 Hz, 1 H, ArH), 5.20 (d, J = 1.0 Hz, 1 H, CH), 1.63 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.07, 148.66, 139.11, 133.86, 128.76, 126.48, 118.13, 117.29, 85.71, 51.36, 28.16 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{13}BrClNO_3Na^+$ $[M + Na]^+$ 367.9660; found 367.9674.

General Procedure for the Synthesis of Symmetric Unsaturated 1,4-Diketones 2a–d: Synthesized by Friedel–Crafts acylation reaction according to a reported procedure from the corresponding substituted benzenes and fumaryl chloride.[16]

(*E*)-1,4-Bis(4-bromophenyl)but-2-ene-1,4-dione (2a): Obtained as a tan brown solid in 46% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 2 H, 2× CH), 7.92 (d, J = 8.7 Hz, 4 H, 4× ArH), 7.68 (d, J = 8.7 Hz, 4 H, ArH, 4× ArH) ppm.

(*E*)-1,4-Diphenylbut-2-ene-1,4-dione (2b): Obtained as a bright-yellow solid in 70% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.03 (m, 4 H, 4× ArH), 8.01 (s, 2 H, 2× CH), 7.66–7.60 (m, 2 H, 2× ArH), 7.56–7.49 (m, 4 H, 4× ArH) ppm.

(*E*)-1,4-Di-*p*-tolylbut-2-ene-1,4-dione (2c): Obtained as a yellow solid in 45% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 2 H, 2× CH), 7.97 (d, J = 8.2 Hz, 4 H, 4× ArH), 7.32 (d, J = 8.0 Hz, 4 H, 4× ArH), 2.45 (s, 6 H, 2× $ArCH_3$) ppm.

(*E*)-1,4-Bis(4-chlorophenyl)but-2-ene-1,4-dione (2d): Obtained as a bright-yellow solid in 46% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.7 Hz, 4 H, 4× ArH), 7.98 (s, 2 H, 2× CH), 7.51 (d, J = 8.7 Hz, 4 H, 4× ArH) ppm.

(*E*)-1,4-Bis(4-nitrophenyl)but-2-ene-1,4-dione (2e): The title compound was prepared by a two-step procedure. In the first step, *p*-nitroacetophenone was transformed into *p*-nitro-α-oxo-benzeneacetaldehyde by using a reported procedure.[17] In the second step, *p*-nitro-α-oxo-benzeneacetaldehyde (375 mg; 2.09 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), and a solution of 1-*p*-nitrophenyl-2-triphenylphosphoranylidene-ethanone (1.2 g; 2.8 mmol/10 mL) in CH_2Cl_2 was added dropwise. After 10 min, a yellow solid started to precipitate. After completion of the reaction, the mixture was filtered, and the solid was washed with cold chloroform. The solid was recrystallized from the mixture of chloroform and ethyl acetate to give **3e** (450 mg, 66% yield). ^{1}H NMR (400 MHz, DMSO): δ = 8.39 (d, J = 8.9 Hz, 4 H, 4× ArH), 8.31 (d, J = 8.9 Hz, 4 H, 4× ArH), 7.94 (s, 2 H, 2× CH) ppm.

General Procedure for the Synthesis of Nonsymmetric Unsaturated 1,4-Diketones and Keto Esters 2g–j: Prepared by an in situ oxidation-Wittig reaction sequence according to a reported procedure from the corresponding Wittig reagents and either hydroxyacetone or methyl glycolate.[18]

(*E*)-1-Phenylpent-2-ene-1,4-dione (2g): Obtained as a light-yellow solid in 88% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.95 (m, 2 H, 2× ArH), 7.70 (d, J = 15.8 Hz, 1 H, CH), 7.66–7.60 (m, 1 H, ArH), 7.55–7.49 (m, 2 H, 2× ArH), 7.09 (d, J = 15.7 Hz, 1 H, CH), 2.44 (s, 3 H, CH_3) ppm.

(*E*)-1-(4-Nitrophenyl)pent-2-ene-1,4-dione (2h): Obtained as a light-yellow solid in 78% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 8.8 Hz, 2 H, 2× ArH), 8.14 (d, J = 8.9 Hz, 2 H, 2× ArH), 7.66 (d, J = 15.7 Hz, 1 H, CH), 7.14 (d, J = 15.7 Hz, 1 H, CH), 2.46 (s, 3 H, CH_3) ppm.

(*E*)-Methyl-4-oxo-4-(*p*-tolyl)but-2-enoate (2i): Obtained as an orange solid in 85% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 15.6 Hz, 1 H, CH), 7.91 (d, J = 8.2 Hz, 2 H, 2× ArH), 7.31 (d, J = 8.0 Hz, 2 H, 2× ArH), 6.88 (d, J = 15.5 Hz, 1 H, CH), 3.84 (s, 3 H, OCH_3), 2.43 (s, 3 H, $ArCH_3$) ppm.

(*E*)-Methyl-4-(4-chlorophenyl)-4-oxobut-2-enoate (2j): The title compound was obtained as a yellow solid in 87% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.7 Hz, 2 H, 2× ArH), 7.87 (d, J = 15.5 Hz, 1 H, CH),

7.48 (d, J = 8.7 Hz, 2 H, 2× ArH), 6.89 (d, J = 15.5 Hz, 1 H, CH), 3.85 (s, 3 H, OCH_3) ppm.

General Procedure for the Asymmetric Synthesis of Spirocyclopropane Oxindoles 3a–j: Unsaturated 1,4-dicarbonyl compound **2** (1 equiv., 0.1 mmol), *N*-Boc 3-chlorooxindole **1** (1.2 equiv., 0.12 mmol), $NaHCO_3$ (2 equiv., 16.8 mg, 0.2 mmol) and thiourea **II** (10 mol-%, 6.0 mg) were dissolved in toluene (0.5 mL) and stirred at room temp. for 48 h. The progress of the reaction was monitored by NMR spectroscopy. Upon completion of the reaction, the mixture was directly purified by silica gel column chromatography (heptane/ethyl acetate). The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude mixture and the enantiomeric purity was determined by chiral HPLC analysis.

(2*S*,3*S*)-*tert*-Butyl 2,3-Bis(4-bromobenzoyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3a): The title compound was synthesized according to the general procedure from *N*-Boc 3-chlorooxindole **1a** and (*E*)-1,4-bis(4-bromophenyl)but-2-ene-1,4-dione (**2a**). Product was isolated as a single diastereoisomer in 67% yield (42 mg) as a reddish solid with *dr* 10:1 (^{1}H NMR analysis of crude material) and *ee* 86% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 9:1; 1 mL/min; 25 °C; 230 nm; t_R = 18.5 (major), 24.0 (minor) min]. $[\alpha]_D^{25}$ = +180.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.2 Hz, 1 H, oxindole-H), 7.83 (d, J = 8.6 Hz, 2 H, 2× ArH), 7.67 (d, J = 8.5 Hz, 2 H, 2× ArH), 7.58 (d, J = 8.6 Hz, 2 H, 2× ArH), 7.53 (d, J = 8.5 Hz, 2 H, 2× ArH), 7.34 (td, J = 8.0, 1.3 Hz, 1 H, oxindole-H), 7.30 (dd, J = 7.8, 1.3 Hz, 1 H, oxindole-H), 7.15 (td, J = 7.6, 1.1 Hz, 1 H, oxindole-H), 4.35 (d, J = 8.0 Hz, 1 H, CH), 4.08 (d, J = 8.0 Hz, 1 H, CH), 1.57 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.7, 189.0, 169.7, 148.8, 140.4, 135.3, 134.9, 132.4, 132.3, 130.3, 130.1, 129.8, 129.3, 129.3, 124.9, 122.7, 122.0, 115.4, 85.3, 41.3, 40.5, 40.0, 28.2 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{29}H_{23}Br_2NO_5Na^+$ [M + Na]$^+$ 645.9835; found 645.9847.

[(2*S*,3*S*)-2′-Oxospiro(cyclopropane-1,3′-indoline)-2,3-diyl]bis[(4-bromophenyl)methanone] (3a-NH): To a stirred solution of **3a** (30 mg, 0.049 mmol) in chloroform (5 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. After stirring for 1 h at room temp. the mixture was concentrated to give the pure product (30 mg, quant) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ = 10.78 (s, 1 H, NH), 7.80 (d, J = 8.7 Hz, 2 H, 2× ArH), 7.73 (d, J = 8.7 Hz, 2 H, 2× ArH), 7.70 (d, J = 8.6 Hz, 2 H, 2× ArH), 7.62 (d, J = 8.6 Hz, 2 H, 2× ArH), 7.21 (td, J = 7.7, 1.2 Hz, 1 H, oxindole-H), 7.05 (d, J = 7.4 Hz, 1 H, oxindole-H), 6.94 (td, J = 7.6, 0.9 Hz, 1 H, oxindole-H), 6.89 (d, J = 7.7 Hz, 1 H, oxindole-H), 4.38 (d, J = 7.8 Hz, 1 H, CH), 4.06 (d, J = 7.8 Hz, 1 H, CH) ppm. ^{13}C NMR (101 MHz, DMSO): δ = 191.1, 190.4, 172.1, 142.6, 135.1, 134.9, 132.2, 132.0, 130.0, 129.8, 128.6, 128.4, 127.9, 123.6, 121.9, 121.7, 110.1, 38.3, 38.1 ppm. HRMS (ESI): *m*/*z* $C_{24}H_{15}Br_2NO_3Na^+$ calcd. for [M + Na]$^+$ 545.9311; found 545.9311.

(2*S*,3*S*)-*tert*-Butyl 2,3-Dibenzoyl-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3b): Synthesized according to the general procedure from *N*-Boc 3-chlorooxindole **1a** and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**2b**). The product was isolated as a single diastereoisomer in 58% yield (27 mg) as a pink solid with *dr* 10:1 (^{1}H NMR analysis of crude material) and *ee* 75% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 9:1; 1 mL/min; 25 °C; 230 nm; t_R = 12.27 (major), 18.8 (minor) min]. $[\alpha]_D^{25}$ = +387.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.96 (m, 2 H, 2× ArH), 7.89 (d, J = 8.1 Hz, 1 H, oxindole-H), 7.86–7.81 (m, 2 H, 2× ArH), 7.59–7.51 (m, 2 H, 2× ArH), 7.48–7.42 (m, 2 H, 2× ArH), 7.42–7.35 (m, 3 H, 2× ArH, oxindole-H), 7.32 (td, J = 8.0, 1.4 Hz, 1 H, oxindole-H), 7.15 (td, J = 7.7, 1.0 Hz, 1 H, oxindole-H), 4.45 (d, J = 8.1 Hz, 1 H, CH), 4.16 (d, J = 8.1 Hz, 1 H, CH), 1.57 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.7, 190.0, 169.8, 149.0, 140.4, 136.7, 136.2, 134.2, 133.8, 129.0, 128.9, 128.8, 128.7, 124.8, 123.2, 122.1, 115.2, 85.0, 41.4, 40.8, 40.3, 28.2 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{29}H_{25}NO_5Na^+$ [M + Na]$^+$ 490.1625; found 490.1639.

(2*S*,3*S*)-*tert*-Butyl 2,3-Bis(4-methylbenzoyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3c): (*E*)-1,4-di-*p*-tolylbut-2-ene-1,4-dione (**2c**; 1 equiv., 0.1 mmol), *N*-Boc 3-cholrooxindole **1a** (1.2 equiv., 0.12 mmol), $NaHCO_3$ (2 equiv., 16.8 mg, 0.2 mmol), and thiourea **II** (10 mol-%, 6.0 mg) were dissolved in toluene (0.5 mL) and stirred at room temp. for 96 h. Product was isolated as a single diastereoisomer in 64% yield (32 mg) as a pink solid with *dr* 10:1 (^{1}H NMR analysis of crude material) and *ee* 77% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 9:1; 1 mL/min; 20 °C; 230 nm; t_R = 17.9 (major), 22.1 (minor) min]. $[\alpha]_D^{25}$ = +209.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.2 Hz, 2 H, 2× ArH), 7.87 (ddd, J = 8.2, 1.0, 0.5 Hz, 1 H, oxindole-H), 7.73 (d, J = 8.2 Hz, 2 H, 2× ArH), 7.34 (ddd, J = 7.7, 1.3, 0.5 Hz, 1 H, oxindole-H), 7.30 (ddd, J = 8.2, 7.7, 1.4 Hz, 1 H, oxindole-H), 7.23 (d, J = 7.9 Hz, 2 H, 2× ArH), 7.18 (d, J = 7.9 Hz, 2 H, 2× ArH), 7.13 (td, J = 7.7, 1.1 Hz, 1 H, oxindole-H), 4.42 (d, J = 8.1 Hz, 1 H, CH), 4.13 (d, J = 8.1 Hz, 1 H, CH), 2.37 (s, 3 H, $ArCH_3$), 2.36 (s, 3 H, $ArCH_3$), 1.56 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.3, 189.7, 169.9, 149.0, 145.2, 144.7, 140.4, 134.3, 133.9, 129.6, 129.6, 129.0, 128.8, 128.7, 124.8, 123.4, 122.1, 115.2, 84.9, 41.2, 40.9, 40.4, 28.1, 21.9, 21.8 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{29}NO_5Na^+$ [M + Na]$^+$ 518.1938; found 518.1948.

***tert*-Butyl 3-Chloro-3-(1,4-dioxo-1,4-di-*p*-tolylbutan-2-yl)-2-oxoindoline-1-carboxylate (4c):** Obtained as a side product in the synthesis of **3c**. Compound **4c** (8.5 mg, 16%) was isolated as a red solid with *dr* 5:1 (^{1}H NMR analysis of crude material). For the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.2 Hz, 2 H, 2× ArH), 7.89–7.84 (m, 3 H, 2× ArH, oxindole-H), 7.45 (dd, J = 7.6, 0.8 Hz, 1 H, oxindole-H), 7.31–7.27 (m, 1 H, oxindole-H), 7.26–7.23 (m, 2 H, 2× ArH), 7.19 (d, J = 7.9 Hz, 2 H, 2× ArH), 7.05 (td, J = 7.6, 1.0 Hz, 1 H, oxindole-H), 5.48 (t, J = 5.3 Hz, 1 H, CH), 4.50 (dd, J = 18.7, 5.0 Hz, 1 H, CH_2), 3.34 (dd, J = 18.7, 5.6 Hz, 1 H, CH_2), 2.40 (s, 3 H, $ArCH_3$), 2.35 (s, 3 H, $ArCH_3$), 1.70 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.3, 196.8, 171.8, 149.2, 144.8, 144.6, 139.3, 133.7, 133.0, 130.7, 129.5, 129.5, 129.2, 128.8, 127.8, 125.0, 123.9, 115.7, 85.0, 64.1, 50.7, 37.3, 28.3, 21.8, 21.8 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_3OClNO_5Na^+$ [M + Na]$^+$ 554.1705; found 554.1709.

(1*s*,2*R*,3*S*)-*tert*-Butyl 2,3-Bis(4-methylbenzoyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (5c): Obtained as a side product in the synthesis of **3c**. Compound **5c** (4.3 mg, 9%) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.0 Hz, 1 H, oxindole-H), 7.84 (d, J = 8.2 Hz, 4 H, 4× ArH), 7.39 (td, J = 7.9, 1.3 Hz, 1 H, oxindole-H), 7.23 (td, J = 7.5, 1.0 Hz, 1 H, oxindole-H), 7.21 (d, J = 8.0 Hz, 4 H, 4× ArH), 7.03 (dd, J = 7.5, 0.8 Hz, 1 H, oxindole-H), 3.61 (s, 2 H, 2× CH), 2.38 (s, 6 H, 2× $ArCH_3$), 1.54 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.3, 167.6, 149.6, 144.2, 140.3, 134.4, 129.4, 128.9, 128.7, 127.2, 124.4, 118.1, 115.5, 84.4, 42.9, 36.7, 28.2, 21.9 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{29}NO_5Na^+$ [M + Na]$^+$ 518.1938; found 518.1940.

[(2*S*,3*S*)-2′-Oxospiro(cyclopropane-1,3′-indoline)-2,3-diyl]bis(*p*-tolylmethanone) (3c-NH): To a stirred solution of **3c** (30 mg, 0.06 mmol) in chloroform (5 mL) was added trifluoroacetic acid (0.5 mL) at

0 °C. After stirring for 1 h at room temp. the mixture was concentrated to give pure product (23 mg, quant) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (s, 1 H, NH), 7.85 (d, J = 8.2 Hz, 2 H, 2× ArH), 7.72 (d, J = 8.2 Hz, 2 H, 2× ArH), 7.31 (d, J = 7.6 Hz, 1 H, oxindole-H), 7.22 (td, J = 7.8, 1.0 Hz, 1 H, oxindole-H), 7.15 (d, J = 8.2 Hz, 2 H, 2× ArH), 7.14 (d, J = 8.1 Hz, 2 H, 2× ArH), 7.01 (td, J = 7.7, 0.9 Hz, 1 H, oxindole-H), 6.90 (d, J = 7.8 Hz, 1 H, oxindole-H), 4.38 (d, J = 7.9 Hz, 1 H, CH), 4.14 (d, J = 7.9 Hz, 1 H, CH), 2.34 (s, 3 H, $ArCH_3$), 2.33 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.5, 189.1, 172.2, 143.9, 143.5, 140.2, 133.2, 132.7, 128.5, 128.4, 127.7, 127.5, 127.4, 123.5, 121.7, 121.6, 109.2, 39.9, 38.6, 37.8, 20.7 (2× C) ppm. HRMS (ESI): m/z calcd. for $C_{26}H_{21}NO_3Na^+$ [M + Na]$^+$ 418.1414; found 418.1425.

(2*S*,3*S*)-*tert*-Butyl 2,3-Bis(4-chlorobenzoyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3d): Synthesized according to the general procedure from *N*-Boc-3-chlorooxindole **1a** and (*E*)-1,4-bis(4-chlorophenyl)but-2-ene-1,4-dione (**2d**). The product was isolated as a single diastereoisomer in 81% yield (43 mg) as a pink solid with *dr* 20:1 (^{1}H NMR analysis of crude material) and *ee* 87% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 9:1; 1 mL/min; 25 °C; 230 nm; t_R = 16.9 (major), 19.7 (minor) min]. $[\alpha]_D^{25}$ = +257.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.7 Hz, 2 H, 2× ArH), 7.89 (d, J = 7.9 Hz, 1 H, oxindole-H), 7.75 (d, J = 8.6 Hz, 2 H, 2× ArH), 7.40 (d, J = 8.7 Hz, 2 H, 2× ArH), 7.36 (d, J = 8.6 Hz, 2 H, 2× ArH), 7.34–7.29 (m, 2 H, 2× oxindole-H), 7.15 (td, J = 7.7, 0.9 Hz, 1 H, oxindole-H), 4.36 (d, J = 8.0 Hz, 1 H, CH), 4.09 (d, J = 8.0 Hz, 1 H, CH), 1.57 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.4, 188.8, 169.7, 148.8, 140.9, 140.4, 140.4, 134.8, 134.5, 130.2, 130.0, 129.3, 129.3, 129.2, 124.9, 122.7, 122.0, 115.4, 85.2, 41.3, 40.5, 40.0, 28.1 ppm. HRMS (ESI): m/z calcd. for $C_{29}H_{23}Cl_2NO_5Na^+$ [M + Na]$^+$ 558.0845; found 558.0859.

(2*S*,3*S*)-*tert*-Butyl 2,3-Bis(4-nitrobenzoyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3e): Synthesized according to the general procedure from *N*-Boc-3-chlorooxindole **1a** and (*E*)-1,4-bis-(4-nitrophenyl)but-2-ene-1,4-dione (**2e**). The product was isolated as a single diastereoisomer in 60% yield (33 mg) as a light-orange solid with *dr* 9:1 (^{1}H NMR analysis of crude material) and *ee* 87% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 8:2; 1 mL/min; 25 °C; 230 nm; t_R = 53.5 (major), 61.2 (minor) min]. $[\alpha]_D^{25}$ = +222.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 8.9 Hz, 2 H, 2× ArH), 8.25 (d, J = 8.9 Hz, 2 H, 2× ArH), 8.12 (d, J = 8.9 Hz, 2 H, 2× ArH), 7.97 (d, J = 8.9 Hz, 2 H, 2× ArH), 7.90 (d, J = 8.2 Hz, 1 H, oxindole-H), 7.38 (ddd, J = 8.3, 7.6, 1.4 Hz, 1 H, oxindole-H), 7.32 (dd, J = 7.8, 0.8 Hz, 1 H, oxindole-H), 7.18 (td, J = 7.7, 1.1 Hz, 1 H, oxindole-H), 4.41 (d, J = 7.8 Hz, 1 H, CH), 4.17 (d, J = 7.8 Hz, 1 H, CH), 1.56 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.3, 188.4, 169.4, 151.0, 150.8, 148.5, 140.6, 140.5, 140.1, 129.9, 129.8, 129.6, 125.1, 124.3, 124.2, 122.0, 121.8, 115.7, 85.6, 41.8, 40.3, 40.2, 28.1 ppm. HRMS (ESI): m/z calcd. for $C_{29}H_{23}N_3O_9Na^+$ [M + Na]$^+$ 580.1327; found 580.1342.

(2*S*,3*S*)-*tert*-Butyl 2,3-Dibenzoyl-5′-bromo-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3f): Synthesized according to the general procedure from *N*-Boc-3-chlorooxindole **1b** and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**2b**). The product was isolated as a single diastereoisomer in 59% yield (32 mg) as a light-orange solid with *dr* 8:1 (^{1}H NMR analysis of crude material) and *ee* 71% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 9:1; 1 mL/min; 25 °C; 230 nm; t_R = 9.7 (major), 13.1 (minor) min]. $[\alpha]_D^{25}$ = +215.5 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.98 (m, 2 H, 2× ArH), 7.86–7.82 (m, 2 H, 2× ArH), 7.80 (d, J = 8.7 Hz, 1 H, oxindole-H), 7.63–7.52 (m, 3 H, 2× ArH, oxindole-H), 7.50–7.38 (m, 5 H, 4× ArH, oxindole-H), 4.46 (d, J = 8.1 Hz, 1 H, CH), 4.13 (d, J = 8.1 Hz, 1 H, CH), 1.55 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.4, 189.6, 169.0, 148.8, 139.5, 136.6, 136.0, 134.3, 134.0, 132.0, 129.0, 129.0, 128.9, 128.7, 125.4, 125.3, 117.9, 116.8, 85.4, 41.2, 40.9, 40.4, 28.1 ppm. HRMS (ESI): m/z calcd. for $C_{29}H_{24}Br_1NO_5Na^+$ [M + Na]$^+$ 568.0730; found 568.0748.

(1*S*,2*S*,3*S*)-*tert*-Butyl 2-Acetyl-3-benzoyl-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3g): Synthesized according to the general procedure from *N*-Boc-3-chlorooxindole **1a** and (*E*)-1-phenylpent-2-ene-1,4-dione (**2g**). The product was isolated as a single diastereoisomer in 53% yield (21 mg) as a pink solid with *dr* > 20:1 (^{1}H NMR analysis of crude material) and *ee* 72% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 8:2; 1 mL/min; 25 °C; 230 nm; t_R = 10.1 (major), 7.7 (minor) min]. $[\alpha]_D^{25}$ = +181.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.2 Hz, 1 H, oxindole-H), 7.80–7.75 (m, 2 H, 2× ArH), 7.52 (tt, J = 7.0, 1.2 Hz, 1 H, ArH), 7.42–7.32 (m, 4 H, 2× ArH, 2× oxindole-H), 7.20 (td, J = 7.6, 0.9 Hz, 1 H, oxindole-H), 3.91 (d, J = 8.1 Hz, 1 H, CH), 3.77 (d, J = 8.1 Hz, 1 H, CH), 2.29 (s, 3 H, $COCH_3$), 1.55 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.2, 189.8, 169.7, 149.0, 140.5, 136.0, 133.9, 129.1, 128.9, 128.6, 124.8, 122.9, 122.3, 115.3, 85.0, 43.4, 41.1, 40.4, 32.1, 28.1 ppm. HRMS (ESI): m/z calcd. for $C_{24}H_{23}NO_5Na^+$ [M + Na]$^+$ 428.1468; found 428.1476.

(1*S*,2*S*,3*S*)-*tert*-Butyl 2-Acetyl-3-(4-nitrobenzoyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-1′-carboxylate (3h): Synthesized according to the general procedure from *N*-Boc-3-chlorooxindole **1a** and (*E*)-1-(4-nitrophenyl)pent-2-ene-1,4-dione (**2h**). The product was isolated as a single diastereoisomer in 62% yield (28 mg) as a red solid with *dr* > 20:1 (^{1}H NMR analysis of crude material) and *ee* 68% for the major isomer [Chiralpak AD-H; Hex/*i*PrOH, 8:2; 1 mL/min; 25 °C; 230 nm; t_R = 12.8 (major), 37.6 (minor) min]. $[\alpha]_D^{25}$ = +261.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.8 Hz, 2 H, 2× Ar), 7.96–7.90 (m, 3 H, 2× Ar, oxindole-H), 7.41 (ddd, J = 8.3, 7.6, 1.4 Hz, 1 H, oxindole-H), 7.32 (dd, J = 7.7, 0.9 Hz, 1 H, oxindole-H), 7.22 (td, J = 7.6, 1.0 Hz, 1 H, oxindole-H), 3.91 (d, J = 8.0 Hz, 1 H, CH), 3.75 (d, J = 8.0 Hz, 1 H, CH), 2.30 (s, 3 H, $COCH_3$), 1.55 (s, 9 H, Boc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.7, 188.8, 169.7, 150.7, 148.7, 140.4, 140.3, 129.5 (2× C), 125.0, 124.2, 122.3, 122.2, 115.5, 85.3, 43.3, 41.0, 39.8, 32.0, 28.1 ppm. HRMS (ESI): m/z calcd. for $C_{24}H_{22}N_2O_7Na^+$ [M + Na]$^+$ 473.1319; found 473.1319.

(1*R*,2*S*,3*S*)-1′-*tert*-Butyl 2-Methyl-3-(4-methylbenzoyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-1′,2-dicarboxylate (3i): Synthesized according to the general procedure from *N*-Boc-3-chlorooxindole **1a** and (*E*)-methyl-4-oxo-4-(*p*-tolyl)but-2-enoate (**2i**). The product was isolated as an inseparable mixture (13 mg) of **3i** (*dr* > 20:1) and one of the diastereoisomers of **4i** with ratio 1.2:1 (^{1}H NMR analysis of crude material). ^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of **3i** and **4i**, normalized to **3i**) = 7.97–7.90 (m, 3.48 H, ArH **4i**, oxindole-H **4i**, oxindole-H **3i**), 7.68 (d, J = 8.2 Hz, 2 H, 2× ArH **3i**), 7.52 (dd, J = 7.8, 0.9 Hz, 1 H, oxindole-H **3i**), 7.44 (dd, J = 7.7, 1.1 Hz, 0.8 H, oxindole-H **4i**), 7.43–7.37 (m, 1.9 H, 2× oxindole-H **4i**), 7.30 (d, J = 8.0 Hz, 1.7 H, 2× ArH **4i**), 7.22 (tdd, J = 7.6, 3.6, 1.0 Hz, 2 H, 2× oxindole-H **3i**), 7.17 (d, J = 8.0 Hz, 2 H, 2× ArH **3i**), 4.26 (dd, J = 10.5, 2.7 Hz, 0.8 H, CH **4i**), 3.94 (dd, J = 17.4, 10.5 Hz, 0.9 H, CH_2 **4i**), 3.82 (d, J = 8.1 Hz, 1 H, CH **3i**), 3.80 (dd, J = 17.4, 2.7 Hz, 0.8 H, CH_2 **4i**), 3.72 (s, 3 H, OCH_3 **3i**), 3.52 (d, J = 8.1 Hz, 1 H, CH **3i**), 3.45 (s, 2.5 H, OCH_3 **4i**), 2.43 (s, 2.4 H, $ArCH_3$ **4i**),

2.36 (s, 3 H, $ArCH_3$ **3i**), 1.67 (s, 8.4 H, Boc **4i**), 1.54 (s, 9 H, Boc **3i**) ppm. HRMS (ESI): *m/z* for **3i**: calcd. for $C_{25}H_{25}NO_6Na^+$ $[M + Na]^+$ 458.1574; found 458.1576. HRMS (ESI): *m/z* for **4i**: calcd. for $C_{25}H_{26}ClNO_6Na^+$ $[M + Na]^+$ 494.1341; found 494.1341.

(1*R*,2*S*,3*S*)-1′-*tert*-Butyl 2-Methyl-3-(4-chlorobenzoyl)-2′-oxospiro-[cyclopropane-1,3′-indoline]-1′,2-dicarboxylate (3j): Synthesized according to the general procedure from *N*-Boc-3-chlorooxindole **1a** and (*E*)-methyl-4-(4-chlorophenyl)-4-oxobut-2-enoate (**2j**). The product was isolated as an inseparable mixture (44 mg) of **3j** (*dr* > 20:1) and two diastereoisomers of **4j** with ratio 2:1.5:1 (^1H NMR analysis of crude material). ^1H NMR (400 MHz, $CDCl_3$): δ (mixture of **3j** and **4j**, normalized to **3j**) = 8.01–7.90 (m, 4.5 H), 7.88 (d, *J* = 8.2 Hz, 0.6 H, oxindole-H **4j**), 7.71 (d, *J* = 8.6 Hz, 2 H, 2× ArH **3j**), 7.55 (dd, *J* = 7.6, 1.3 Hz, 0.6 H, oxindole-H **4j**), 7.50 (dd, *J* = 7.9, 1.3 Hz, 1 H, oxindole-H **3j**), 7.49–7.37 (m, 5.9 H), 7.34 (d, *J* = 8.6 Hz, 2 H, 2× ArH **3j**), 7.25–7.17 (m, 2.2 H), 4.25 (dd, *J* = 10.5, 2.7 Hz, 0.8 H, CH **4j**), 4.20 (dd, *J* = 9.3, 3.5 Hz, 0.6 H, CH **4j**), 3.98–3.86 (m, 1.4 H, CH_2 **4j**), 3.83–3.74 (m, 1.37 H, CH_2 **4j**), 3.79 (d, *J* = 8.0 Hz, 1 H, CH **3j**), 3.72 (s, 3 H, OCH_3 **3j**), 3.49 (d, *J* = 8.0 Hz, 1 H, CH **3j**), 3.44 (s, 2.3 H, OCH_3 **4j**), 3.43 (s, 1.6 H, OCH_3 **4j**), 1.66 (s, 7.2 H, Boc **4j**), 1.66 (s, 5.3 H, Boc **4j**), 1.54 (s, 9 H, Boc **3j**) ppm. HRMS (ESI): *m/z* for **3j**: calcd. for $C_{24}H_{22}ClNO_6Na^+$ $[M + Na]^+$ 478.1028; found 478.1030. HRMS (ESI): *m/z* for **4j**: calcd. for $C_{24}H_{23}Cl_2NO_6Na^+$ $[M + Na]^+$ 514.0795; found 514.0800.

Supporting Information (see footnote on the first page of this article): Experimental data, computational details of the configuration assignment of **5c**, **3h**, and **3c**-NH. ^1H and ^{13}C NMR spectra, chiral HPLC chromatograms, and computational details.

Acknowledgments

The authors thank the Estonian Ministry of Education and Research (grant number IUT 19-32), and the EU European Regional Development Fund (3.2.0101.08-0017) for financial support.

[1] For recent reviews, see: a) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165–5181; b) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023–1052.

[2] a) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. Gonzalez-Paez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H. P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler, T. T. Diagana, *Science* **2010**, *329*, 1175–1180; b) B. K. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E. K. Schmitt, P. Krastel, E. Francotte, K. Kuhen, D. Plouffe, K. Henson, T. Wagner, E. A. Winzeler, F. Petersen, R. Brun, V. Dartois, T. T. Diagana, T. H. Keller, *J. Med. Chem.* **2010**, *53*, 5155–5164.

[3] T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y.-H. Wu, Y. He, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105–2108.

[4] P. B. Sampson, Y. Liu, S.-W. Li, B. T. Forrest, H. W. Pauls, L. G. Edwards, M. Feher, N. K. B. Patel, R. Laufer, G. Pan, *Kinase Inhibitors and Method of Treating Cancer with Same* U. S. Patent WO 2010/115279A1, **2010**.

[5] a) A. Noole, I. Järving, F. Werner, M. Lopp, A. Malkov, T. Kanger, *Org. Lett.* **2012**, *14*, 4922–4925; b) A. Noole, N. Sucman, M. Kabeshov, T. Kanger, F. Macaev, A. Malkov, *Chem. Eur. J.* **2012**, *18*, 14929–14933; c) A. Noole, M. Ošeka, T. Pehk, M. Öeren, I. Järving, M. R. Elsegood, A. Malkov, M. Lopp, T. Kanger, *Adv. Synth. Catal.* **2013**, *355*, 829–835; d) A. Noole, A. V. Malkov, T. Kanger, *Synthesis* **2013**, 2520–2524.

[6] For recent examples, see: a) M. Zhang, Y. Gong, W. Wang, *Eur. J. Org. Chem.* **2013**, 7372–7381; b) R. C. Dhakal, R. K. Die, *J. Org. Chem.* **2013**, *78*, 12426–12439; c) T. Ferrary, E. David, G. Milanole, T. Besset, P. Jubault, X. Pannecoucke, *Org. Lett.* **2013**, *15*, 5598–5601.

[7] a) S. I. Kozhushkov, A. Leonov, A. de Meijere, *Synthesis* **2003**, 956–958; b) R. Ballini, D. Fiorini, A. Palmieri, *Synlett* **2003**, 1704–1706; V. K. Aggarwal, H. W. Smith, G. Hynd, R. V. H. Jones, R. Fieldhouse, S. E. Spey, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3267–3276.

[8] a) Y. Chen, J. V. Ruppel, X. P. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 12074–12075; b) I. Ibrahem, G.-L. Zhao, R. Rios, J. Vesely, H. Sundén, P. Dziedzic, A. Córdova, *Chem. Eur. J.* **2008**, *14*, 7867–7879; c) For general review of asymmetric cyclopropanation, see: H. Pellissier, *Tetrahedron* **2008**, *64*, 7041–7095.

[9] S. Žari, T. Kailas, M. Kudrjashova, M. Öeren, I. Järving, T. Tamm, M. Lopp, T. Kanger, *Beilstein J. Org. Chem.* **2012**, *8*, 1452–1457.

[10] I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193–205.

[11] F. G. Bordwell, H. E. Fried, *J. Org. Chem.* **1991**, *56*, 4218–4223.

[12] Y.-H. Liao, X.-L. Liu, Z.-J. Wu, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *Chem. Eur. J.* **2012**, *18*, 6679–6687.

[13] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.

[14] H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang, C. E. Song, *Adv. Synth. Catal.* **2011**, *353*, 3196–3202.

[15] A. Arizpe, F. J. Sayago, A. I. Jimenez, M. Ordonez, C. Cativiela, *Eur. J. Org. Chem.* **2011**, 3074–3081.

[16] J. B. Conant, R. E. Lutz, *J. Am. Chem. Soc.* **1923**, *45*, 1301–1307.

[17] M. B. Floyd, M. T. Du, P. F. Fabio, L. A. Jacob, B. D. Johnson, *J. Org. Chem.* **1985**, *50*, 5022–5027.

[18] K. A. Runcie, R. J. K. Taylor, *Chem. Commun.* **2002**, 974–975.

Received: February 12, 2014
Published Online: April 22, 2014

Publication II

Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement of Oxindoles. *Organic Letters* **2016**, *18*, 1358-1361.

Organic LETTERS

Letter

pubs.acs.org/OrgLett

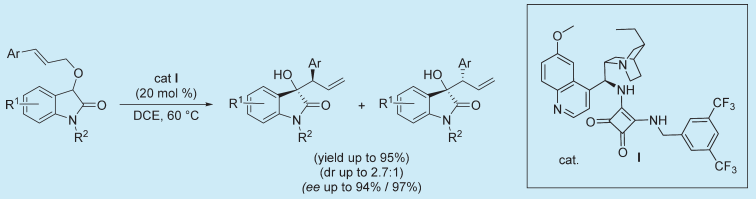
Asymmetric Organocatalytic Wittig [2,3]-Rearrangement of Oxindoles

Maksim Ošeka,[†] Mariliis Kimm,[†] Sandra Kaabel,[†,‡] Ivar Järving,[†] Kari Rissanen,[‡] and Tõnis Kanger*[,†]

[†]Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia

[‡]University of Jyvaskyla, Department of Chemistry, Nanoscience Center, P.O. Box 35, FI-40014 Jyvaskyla, Finland

Supporting Information

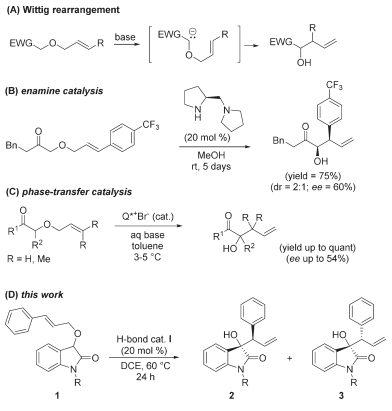


ABSTRACT: A highly enantioselective organocatalytic [2,3]-rearrangement of oxindole derivatives is presented. The reaction was catalyzed by squaramide, and this provides access to 3-hydroxy 3-substituted oxindoles in high enantiomeric purities.

An asymmetric [2,3]-sigmatropic rearrangement is an efficient tool for the creation of C−C or C−heteroatom bonds and the insertion of stereocomplexity into organic compounds. The rearrangement of allylic or propargylic ethers is called a Wittig rearrangement[1] (Scheme 1A), and it has been applied as a key step for the total synthesis of various natural products.[2] An anionic Wittig rearrangement involves the formation of an α-oxycarbanion, followed by a 2,3 allylic shift.[3] The anion formation is the promoter of the reaction. The use of strong Brønsted bases, such as BuLi or tBuLi, with chiral ligands is the most common strategy for acquiring asymmetric products in a [2,3]-rearrangement.[2,4] In addition, boron enolates have been used to achieve the goal.[5] Approaches based on chiral auxiliaries have also been used.[6] In all cases the oxyanion is obtained via enolization. However, the above-mentioned methods require a stoichiometric amount of a chiral ligand or chiral starting material and are very moisture sensitive, which has made scientists turn their attention to more efficient catalytic systems. This century has witnessed remarkable achievements in asymmetric organocatalysis, which has become a powerful methodology in organic synthesis.[7] In addition to the experimental simplicity (mild conditions; no need for an inert atmosphere or anhydrous conditions), organocatalytic reactions provide a wide range of activation types via covalent or noncovalent interactions. Bifunctional catalysts derived from *Cinchona* alkaloids simultaneously activate both the electro- and nucleophilic counterparts of the reaction, allowing for the implementation of various reactions.[8] To the best of our knowledge, only two examples of an asymmetric organocatalytic Wittig [2,3]-rearrangement have been published so far. In 2006, Gaunt et al. described an aminocatalytic Wittig rearrangement of α-allyloxy substituted ketones in the presence of a proline derivative (Scheme 1B).[9] The authors demonstrated the asymmetric reaction with moderate yield and selectivity for only one substrate, which makes the field relatively unexplored. Very recently, Denmark described a [2,3]-sigmatropic rearrangement under phase-transfer catalysis conditions (Scheme 1C).[10] However, the highest enantioselectivity obtained was moderate (*ee* 54%).

We previously demonstrated that 3-halogen substituted oxindoles can be easily and efficiently activated as nucleophiles via hydrogen bonds for various asymmetric organocatalytic

Scheme 1. Wittig [2,3]-Rearrangement



Received: January 28, 2016
Published: March 3, 2016

DOI: 10.1021/acs.orglett.6b00291
Org. Lett. 2016, 18, 1358−1361

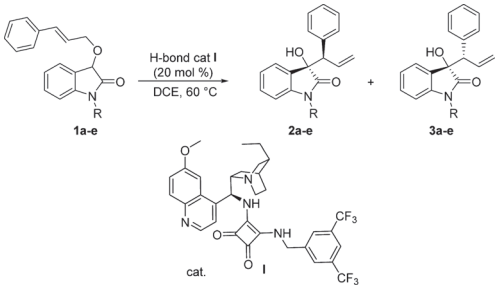
transformations.[11] We assumed that a similar activation of 3-substituted oxindoles could act as a trigger for the following Wittig rearrangement. Indeed, it was found that 3-cinnamyloxyoxindoles **1** afforded rearranged products in the presence of various H-bonding catalysts. Herein, we represent our results of the first hydrogen bond mediated asymmetric organocatalytic Wittig [2,3]-rearrangement (Scheme 1D). The obtained chiral 3-substituted 3-hydroxyoxindoles **2** and **3** are of great importance because they can be used as building blocks for the synthesis of biologically active compounds and natural products.[12]

Of the various chiral H-bonding catalysts screened (*Cinchona* alkaloids, *Cinchona* alkaloid derived thioureas and squaramides) the most efficient catalyst for the H-bond mediated Wittig [2,3]-rearrangement was squaramide **I**. According to our solvent and conditions optimization studies the reaction was performed in 1,2-dichloroethane at 60 °C (Scheme 1D) (see Supporting Information for the optimization details).

With optimal conditions in hand, the influence of various *N*-protecting groups of oxindoles was investigated (Table 1). In the model reaction with *N*-benzyl protected 3-cinnamyloxyoxindole **1a**, products were isolated in high yields and enantiomeric purities of both diastereoisomers (Table 1, entry 1). From the synthetic point of view, the use of unprotected NH-oxindole is preferred.[13] However, 3-cinnamyloxyoxindole **1b** reacted slowly and enantioselectivity decreased considerably for the major isomer (Table 1, entry 2). Protecting 3-cinnamyloxyoxindole with either a methyl or isopropyl group also did not increase the reaction rate and selectivity (Table 1, entries 3 and 4). As benzyl remained the best protective group in terms of reactivity and selectivity, we decided to slightly modify it with an additional methyl group in the *para*-position of the phenyl ring for more convenient determination of the conversion and diastereoisomeric ratio by ^{1}H NMR analysis of the crude mixture (Table 1, entry 5). Although the diastereoselectivity of the reaction was rather moderate, the formed diastereoisomers were separable by column chromatography on silica gel. This may be an advantage in terms of biological studies, as enantiomerically enriched diastereoisomers may have different activities.

The effect of various substituents in the aromatic ring of oxindole was studied. The obtained results are summarized in Table 2 (entries 2−10). The substitution with a halogen atom or electron-donating methoxy group at the fifth and seventh positions resulted in a slight decrease in diastereoselectivity while the overall yield and enantioselectivity remained very high compared to the unsubstituted 3-cinnamyloxyoxindole **1e** (Table 2, entries 2−7). When the aromatic ring of the oxindole was substituted with a strongly electronegative trifluoromethoxy group, reversed diastereoselectivity was observed (Table 2, entry 8). However, the diastereoselectivity remained low. Although substitution with the electron-withdrawing nitro group at position 7 did not remarkably affect the yield and selectivity, 5-nitro-substituted products were isolated in slightly lower yield and enantiomeric purity of the major diastereoisomer (Table 2,

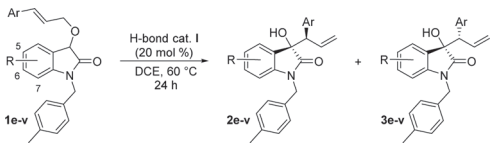
Table 1. Screening of Protective Groups[a]



entry	R	time (h)	yield (%)[b]	dr **2**:**3**[c]	*ee* (%)[d]
1	**a**: Bn	24	87	2.5:1[e]	90 / 93
2	**b**: H	48	79	1.8:1	71 / 90
3	**c**: Me	48	79	2.5:1	80 / 86
4	**d**: *i*-Pr	72	36	1.8:1	82 / 85
5	**e**: 4-MeBn	24	91[f]	2.2:1	94 / 97

[a]Reaction conditions: 0.1 mmol scale, 20 mol % of cat. **I**, DCE (0.5 mL), 60 °C. [b]Overall isolated yield of the separated diastereoisomers. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC analysis of the isolated products. [e]Determined by RP HPLC analysis of the crude mixture. [f]Reaction in 1.0 mmol scale.

Table 2. Scope of the Reaction[a]



entry	R	Ar	yield (%)[b]	dr **2**:**3**[c]	*ee* (%)[d]
1	H	Ph	(**e**) 91	2.2:1	94 / 97
2	5-F	Ph	(**f**) 83[e]	1.6:1	91 / 92
3	5-Cl	Ph	(**g**) 82	1.4:1	90 / 94
4	5-Br	Ph	(**h**) 86	1.3:1	90 / 95
5	7-F	Ph	(**i**) 92	1.4:1	92 / 93
6	7-Cl	Ph	(**j**) 89[e]	1.3:1	91 / 95
7	5-MeO	Ph	(**k**) 92	2.0:1	93 / 95
8	5-CF_3O	Ph	(**l**) 82[e]	1:1.4	91 / 95
9	5-NO_2	Ph	(**m**) 71	1.3:1	80 / 90
10	7-NO_2	Ph	(**n**) 85[e]	1.1:1	89 / 93
11	H	4-ClPh	(**o**) 90	2.0:1	94 / 95
12	H	3-ClPh	(**p**) >95	1.9:1	93 / 95
13	H	2-ClPh	(**q**) 87[f]	1:1.1	88 / 93
14	H	4-MeOPh	(**r**) 95	1.8:1	91 / 97
15	H	4-NO_2Ph	(**s**) 77[g]	1.6:1	80 / 30
16	H		(**t**) 88	2.7:1	93 / 95
17	H		(**u**) 93	2.0:1	92 / 95
18	H		(**v**) 63	1.7:1	86 / 91

[a]Reaction conditions: 0.1 mmol scale, 20 mol % of cat. **I**, DCE (0.5 mL), 60 °C. [b]Overall isolated yield of the separated diastereoisomers. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC analysis of the isolated products. [e]Reaction was finished after 5 h. [f]Reaction was finished after 48 h. [g]Reaction was finished after stirring at rt for 48 h.

DOI: 10.1021/acs.orglett.6b00291
Org. Lett. 2016, 18, 1358−1361

entries 9 and 10). It can be concluded that the electronic effects of the substituents in oxindole on the selectivity of the reaction are not substantial.

Next, the influence of substituents at the cinnamyl phenyl ring was investigated. *para*- and *meta*-chloro substituted 3-cinnamyloxyoxindole **1o** and **1p** underwent [2,3]-rearrangement smoothly affording corresponding products in excellent yields and enantioselectivities (Table 2, entries 11 and 12). In the reaction with *ortho*-chloro substituted substrate **1q**, full conversion was observed only after 48 h (Table 2, entry 13). Moreover, the diastereoselectivity of the reaction was the lowest in the scope and was reversed, while the enantioselectivity remained very high. The low reactivity and diastereoselectivity of 3-cinnamyloxyoxindole **1q** may be explained by steric hindrance between the chlorine atom and the catalyst. Substitution with an electron-donating methoxy group provided products in excellent yield, and the minor diastereoisomer was isolated in the highest enantiomeric purity (Table 2, entry 14). A strong electron-withdrawing group in the *para*-position caused a dramatic decrease in the enantioselectivity of the minor diastereoisomer, while the enantioselectivity of the major diastereoisomer remained relatively high. Due to the formation of side products the yield of the reaction was lower than that when using other compounds (Table 2, entry 15).

The reaction scope was then further broadened with different aromatic substituents (Table 2, entries 16–18). A [2,3]-rearrangement with 2-thienyl (**1t**) and 2-naphtyl (**1u**) analogs of cinnamyloxyoxindole proceeded very efficiently under the same conditions with slightly better diastereoselectivities and very high enantioselectivities (Table 2, entries 16 and 17). The formation of unidentified side product was observed in the case of the analog **1v** with an extended double bond sequence. The reaction resulted in a lower, but still reasonable, isolated yield of [2,3]-rearranged products **2v** and **3v** (Table 2, entry 18). Finally, our study revealed that the scope of the reaction was limited to *trans*-3-cinnamyloxyoxindoles and their aromatic analogs. No reaction was observed under standard conditions when *cis*-3-cinnamyl, 3-allyloxy-, or crotyloxyoxindole was used as starting material. Moreover, an additional substituent at the double bond almost completely suppressed the [2,3]-rearrangement due to the sterical hindrance (see Supporting Information for additional details).

The relative and absolute stereochemistry of Wittig [2,3]-rearrangement products **2o** and **3i** were unambiguously assigned by single crystal X-ray diffraction (Figure 1).[14]

The configurations of other compounds in the series were assigned by analogy. According to the observed geometries of the products, the following transition states for Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1e** are proposed (Figure 2).

It can be assumed that 3-cinnamyloxyoxindole **1** was deprotonated at the third position and enolized by the tertiary amine moiety of the catalyst. The formed intermediate was activated by the multiple hydrogen bond interactions by squaramide and the protonated amine of the catalyst. The attack of enolate to the *Re*-face of the cinnamyl led to the formation of the *unlike* diastereoisomer **2**, whereas the attack to the *Si*-face gave the *like* diastereoisomer **3**. Transition states leading to different diastereoisomers do not differentiate from each other substantially causing the low diastereoselectivity of the reaction. As only aromatic or heteroaromatic allyloxy substrates were efficient substrates for the rearrangement, it is expected that the

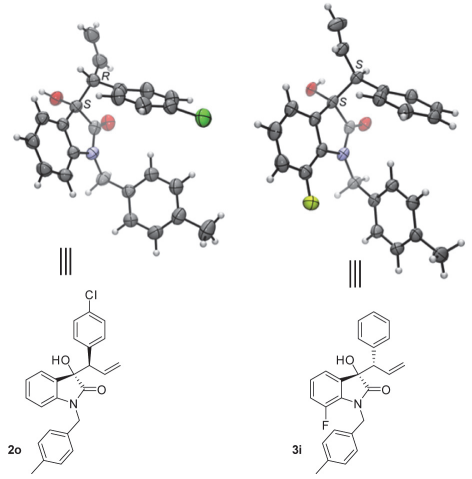


Figure 1. X-ray structures of [2,3]-rearranged products **2o** (major diastereoisomer) and **3i** (minor diastereoisomer).

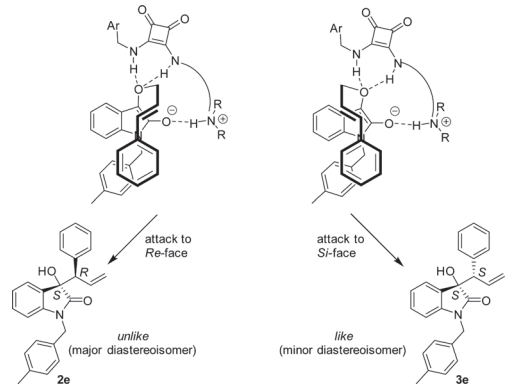


Figure 2. Proposed transition state for Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1e**.

π–π attractive interaction played an important role in the stabilization of the transition state.

In order to further investigate the mechanism of the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1k**, a kinetic study was performed (Figure 3). The reaction was carried out in deuterated chloroform, and crude samples were taken over time. ^{1}H NMR measurements revealed that the ratio between the two diastereomeric products, **2k** and **3k**, remained the same (2:1) throughout the entire reaction. It can be assumed that no isomerization of the products took place, and the diastereoselectivity was defined by the thermodynamic control.

In conclusion, we have developed the first highly selective asymmetric organocatalytic hydrogen bond mediated Wittig [2,3]-rearrangement. The rearrangement of 3-cinnamyloxyoxindole **1** was efficiently catalyzed by chiral squaramide **I** to provide 3-substituted 3-hydroxyoxindoles **2** and **3** in very high yields (up to 95%) and enantioselectivities (up to 97%). Although the diastereoselectivity of the reaction was low (dr

DOI: 10.1021/acs.orglett.6b00291
Org. Lett. 2016, 18, 1358–1361

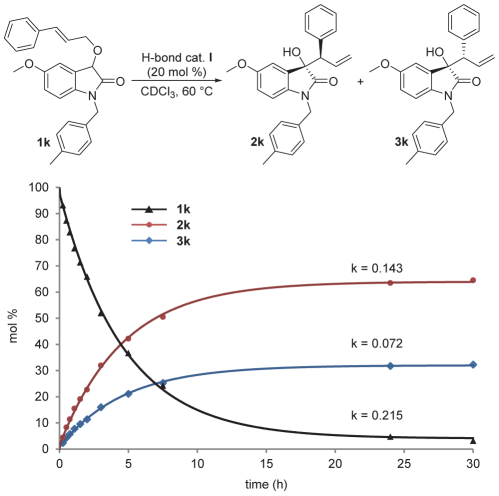


Figure 3. Kinetic study of Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1k**.

up to 2.7:1), the isomers were chromatographically separable. Both electron-donating and -withdrawing groups were well tolerated at the aromatic ring of the oxindole and phenyl group in the allyl chain as well as the aromatic analogs of the cinnamyl derivative.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00291.

Synthesis of starting compounds, optimization of the procedures, copies of ^{1}H and ^{13}C NMR spectra, HPLC chromatograms (PDF)

Crystallographic data of compound **2o** (CIF)

Crystallographic data of compound **3i** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tonis.kanger@ttu.ee.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Estonian Ministry of Education and Research (Grants Nos. IUT 19-32, IUT 19-9, and B25) and the Academy of Finland (KR Grant Nos. 263256 and 265328) for financial support.

■ REFERENCES

(1) For a recent review, see: (a) Wolfe, J. P. In *Comprehensive Organic Synthesis II, Carbon−Carbon σ-Bond Formation*; Marek, I., Ed.; Elsevier: Amsterdam, 2014; Vol. 3, pp 1038−1072. (b) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446−7479.

(2) (a) Isobe, M.; Chang, W.-C.; Tsou, P.-K.; Ploysuk, C.; Yu, C.-H. *J. Org. Chem.* **2015**, *80*, 6222−6237. (b) Blackburn, T. J.; Kilner, M. J.; Thomas, E. J. *Tetrahedron* **2015**, *71*, 7293−7309. (c) Hirokawa, Y.; Kitamura, M.; Mizubayashi, M.; Nakatsuka, R.; Kobori, Y.; Kato, C.; Kurata, Y.; Maezaki, N. *Eur. J. Org. Chem.* **2013**, *2013*, 721−727. (d) General review: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885−902.

(3) Nakai, T.; Tomooka, K. *Pure Appl. Chem.* **1997**, *69*, 595−600.

(4) For Brønsted bases/chiral ligand mediated examples of asymmetric [2,3]-rearrangement, see: (a) Kitamura, M.; Hirokawa, Y.; Maezaki, N. *Chem. - Eur. J.* **2009**, *15*, 9911−9917. (b) Wang, X.-J.; Marshall, J. A. *J. Org. Chem.* **1992**, *57*, 2747−2750. (c) Hirokawa, Y.; Kitamura, M.; Maezaki, N. *Tetrahedron: Asymmetry* **2008**, *19*, 1167−1170. (d) Kitamura, M.; Hirokawa, Y.; Yoshioka, Y.; Maezaki, N. *Tetrahedron* **2012**, *68*, 4280−4285. (e) Tomooka, K.; Komine, N.; Nakai, T. *Chirality* **2000**, *12*, 505−509. (f) Kawasaki, T.; Kimachi, T. *Tetrahedron* **1999**, *55*, 6847−6862.

(5) (a) Everett, R. K.; Wolfe, J. P. *Org. Lett.* **2013**, *15*, 2926−2929. (b) Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* **1994**, *35*, 5019−22. (c) Fujimoto, K.; Matsuhashi, C.; Nakai, T. *Heterocycles* **1996**, *42*, 423−435.

(6) For auxiliary controlled examples of asymmetric [2,3]-rearrangement, see: (a) Enders, D.; Backhaus, D.; Runsink, J. *Tetrahedron* **1996**, *52*, 1503−1528. (b) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066−1067.

(7) For recent reviews, see: (a) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 13860−13874. (b) Holland, M. C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 3862−3871. (c) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253−281. (d) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807−8864.

(8) (a) Yeboah, E. M. O.; Yeboah, S. O.; Singh, G. S. *Tetrahedron* **2011**, *67*, 1725−1762. (b) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330−2346.

(9) McNally, A.; Evans, B.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2116−2119.

(10) Denmark, S. E.; Cullen, L. R. *J. Org. Chem.* **2015**, *80*, 11818−11848.

(11) (a) Noole, A.; Järving, I.; Werner, F.; Lopp, M.; Malkov, A.; Kanger, T. *Org. Lett.* **2012**, *14*, 4922−4925. (b) Noole, A.; Ošeka, M.; Pehk, T.; Öeren, M.; Järving, I.; Elsegood, M. R.; Malkov, A.; Lopp, M.; Kanger, T. *Adv. Synth. Catal.* **2013**, *355*, 829−835. (c) Noole, A.; Malkov, A. V.; Kanger, T. *Synthesis* **2013**, *45*, 2520−2524. (d) Ošeka, M.; Noole, A.; Žari, S.; Öeren, M.; Järving, I.; Lopp, M.; Kanger, T. *Eur. J. Org. Chem.* **2014**, *2014*, 3599−3606.

(12) (a) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20−38. (b) Coste, A.; Couty, F.; Evano, G. *C. R. Chim.* **2008**, *11*, 1544−1573. (c) Kumar, A.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 9748−9762. (d) Bergonzini, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 971−974. (e) Jayakumar, S.; Kumarswamyreddy, N.; Prakash, M.; Kesavan, V. *Org. Lett.* **2015**, *17*, 1066−1069. (f) Tao, Z.-L.; Li, X.-H.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 4054−4057.

(13) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193−205.

(14) CCDC 1447017−1447018 contains the supplementary data for this structure. These data can be obtained via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

DOI: 10.1021/acs.orglett.6b00291
Org. Lett. 2016, 18, 1358−1361

Publication III

Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. Two Catalytic Methods of an Asymmetric Wittig [2,3]-Rearrangement. *The Journal of Organic Chemistry* **2017**, *82*, 2889-2897.

JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

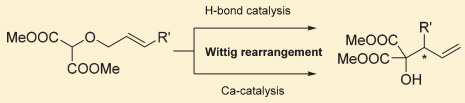
Two Catalytic Methods of an Asymmetric Wittig [2,3]-Rearrangement

Maksim Ošeka, Mariliis Kimm, Ivar Järving, Kristin Lippur, and Tõnis Kanger*

Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia

Supporting Information

ABSTRACT: Two different approaches for asymmetric catalytic Wittig [2,3]-rearrangement were developed. Allyloxymalonate derivatives were converted into homoallyl alcohols via organocatalytic or Ca^{2+}-catalyzed pathways in moderate to high enantioselectivities.

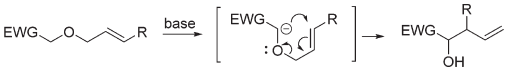


INTRODUCTION

Catalytic reactions are of fundamental importance in chemistry. Both metal-catalyzed and organocatalytic reactions are widely used in asymmetric synthesis. When a catalytic reaction is applied in a rearrangement reaction with a 100 % atom efficiency, it leads to a highly efficient process. In this context, the development of an asymmetric catalytic rearrangement reaction remains challenging.

The sigmatropic Wittig [2,3]-rearrangement of allyl ethers affording sterically hindered homoallyl alcohols with a potential stereogenic center is an efficient tool for the formation of a C−C bond (Scheme 1).[1]

Scheme 1. Base-Induced Wittig [2,3]-Rearrangement



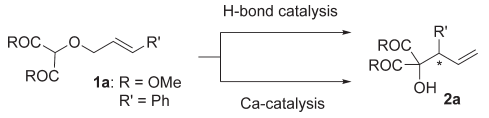
A great deal of effort has been invested in anion-promoted Wittig rearrangements. Usually strong Lewis bases, such as BuLi or *t*-BuLi are used to generate a carbanion.[2] For enantioselective reactions, chiral ligands have been used.[3]

Examples of catalytic asymmetric Wittig rearrangements remain scarce. The pioneering organocatalytic paper in this field was published by Gaunt in 2006.[4] Only one example of an aminocatalytic asymmetric reaction was described, and the obtained results remained moderate (ee 60%). Approximately 10 years later, new approaches were simultaneously published by Denmark[5] and by us.[6] Denmark used phase-transfer catalysis for the rearrangement of allyloxyoxindole derivatives in moderate enantioselectivities (ee up to 54%). We used squaramide-catalyzed reactions on the same substrate, affording products in high enantiomeric purity (ee up to 97%), but the diastereoselectivity of the reaction was low (up to 2.7:1). Recently, Jacobsen et al. published a conceptually new approach based on a synergistic ion-binding thiourea catalysis.[7] It was shown that in the transition state of [2,3]-sigmatropic rearrangements, a set of noncovalent interactions involving hydrogen bondings by thiourea and simultaneous ion-bindings was responsible for the enantioselectivity of the reaction. High yields and enantioselectivities were obtained by applying this concept to allyloxymalonate derivatives (ee up to 93%). The following is complementary in terms of described methods and provides new information on the asymmetric Wittig rearrangement.

RESULTS AND DISCUSSION

Herein we present two alternative methods for a Wittig [2,3]-sigmatropic rearrangement reaction of allyloxy-1,3-dicarbonyl compounds (Scheme 2).

Scheme 2. Two Approaches to a Wittig [2,3]-Rearrangement



The organocatalytic method is based on our previous experience with an asymmetric Wittig [2,3]-rearrangement of oxindole derivatives.[6] An alternative method is a metal-catalyzed reaction in the presence of chiral ligands. To the best of our knowledge, this is the first Lewis acid-catalyzed asymmetric Wittig [2,3]-rearrangement.[8] For the past 10 years, calcium catalytic reactions have shown very high potency toward 1,3-carbonyl compounds. Calcium salts combined with chiral ligands can promote high enantioselective outcomes in various reactions.[9−11]

It is proposed that the formation of an anion in the substrate serves as a trigger for the rearrangement reaction. Therefore, cinnamyloxymalonate **1a**, possessing an acidic proton, was chosen as a model compound.

Organocatalytic Wittig [2,3]-Rearrangement. The set of organocatalysts used is depicted in Figure 1. Our first choice was bifunctional squaramide **I**, which showed high enantiodiscrimination in the case of allyloxy-oxindole derivatives. The second group of catalysts (compounds **II**−**VII**) is based on a cyclopropenimine scaffold. These highly basic compounds are comparable to the basicity of guanidines.[12] In addition to their

Received: November 21, 2016
Published: February 22, 2017

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889−2897

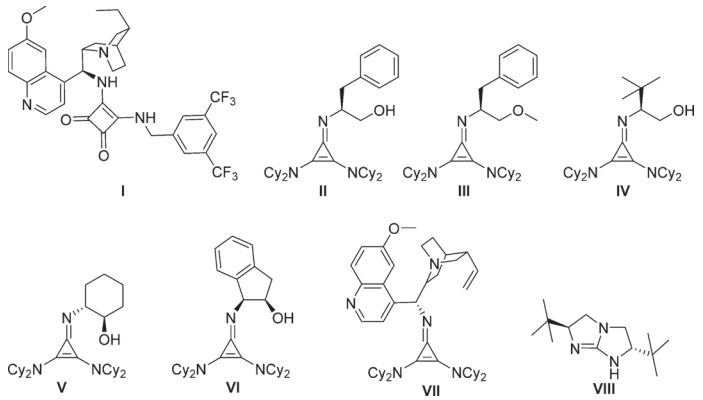
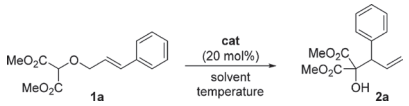


Figure 1. Catalysts screened for the organocatalytic Wittig [2,3]-rearrangement of cinnamyloxymalonates.

high Lewis basicity, they are also hydrogen-bond donors (except catalysts **III** and **VII**). Monofunctional chiral guanidine **VIII** was the last choice.[13]

The results of screening experiments are presented in Table 1. Chiral squaramide **I** did not show any activity toward cinnamyloxymalonate **1a** even at a higher temperature and extended reaction time (Table 1, entry 1). When highly basic cyclopropenimine **II** was used for the rearrangement, excellent reactivity and promising selectivity were achieved (Table 1, entry 2). Lowering the temperature of the reaction increased the enantioselectivity to 50%, while full conversion was reached with longer reaction time (Table 1, entry 3). Furthermore, a variety of catalyst **II** analogues is synthesized in order to improve the enantioselectivity of the reaction (Table 1, entries 4–8). Cyclopropenimine catalysts **II**–**VII** can be very easily prepared from amino-alcohols by a two-step procedure described by the Lambert group.[12] The instability of the cyclopropenimine catalysts as free bases should be noted. However, hydrochloric salts of the catalysts are stable at room temperature. Unfortunately, none of those analogues gave full conversion at a reasonable reaction time, and the selectivity in most cases was lower. Catalysts **III** and **VII** were exceptional with no hydrogen-bond donor sites. Although almost full conversion was obtained at room temperature in the presence of catalyst **III**, the enantioselectivity of the reaction was very low (ee of **2a** 8%, Table 1, entry 4). Sterically more hindered catalyst **VII** was inactive, affording no conversion (Table 1, entry 8). The reaction catalyzed by guanidine **VIII** gave poorer results (Table 1, entry 9). Since full conversion is particularly important in terms of purification as compounds **1** and **2** are chromatographically inseparable, catalyst **II** was chosen for further screening, despite the fact that catalyst **IV** was to some extent more selective. Also, catalyst **II** is more stable than catalyst **IV**. Next, several typical solvents for hydrogen-bond-mediated transformations were tested (Table 1, entries 10–13). It is known that apolar solvents are preferred for the hydrogen-bond-catalyzed reactions. Hexane was excluded because of low solubility of reactants in this solvent. The reaction was faster in the 1:1 mixture of hexane and chloroform than in $CDCl_3$, but the stereoselectivity was lower (Table 1, entries 3 and 10). Etheral solvents or toluene had no advantages over chloroform (Table 1, entries 12–14). As expected, racemic product was obtained in protonic solvent (Table 1, entry 15). The decrease of the amount of catalyst **II** led to only partial conversion after 2 days of the reaction (Table 1, entry 16).

Table 1. Catalyst Screening and Optimization of the Organocatalytic Wittig [2,3]-Rearrangement of Cinnamyloxymalonate 1a[a]



entry	catalyst	solvent	temp. (°C)	time (h)	conv. (%)[b]	ee (%)[c]
1	**I**	$CDCl_3$	55	96	0	–
2	**II**	$CDCl_3$	rt	2	100	33
3	**II**	$CDCl_3$	−20	18	100	50
4	**III**	$CDCl_3$	rt	2	94	8
5	**IV**	$CDCl_3$	−20	23	97	52
6	**V**	$CDCl_3$	−20	18	88	−37
7	**VI**	$CDCl_3$	rt	18	45	*rac*
8	**VII**	$CDCl_3$	55	72	0	–
9	**VIII**	$CDCl_3$	55	72	90	−20
10	**II**	hexane: $CDCl_3$[d]	−20	5	100	45
11	**II**	EtOAc	rt	23	80	17
12	**II**	toluene	−20	20	83	28
13	**II**	THF	−20	20	74	23
14	**II**	Et_2O	−20	18	78	31
15	**II**	MeOH	−20	18	100	*rac*
16	**II**	$CDCl_3$	−20	48[e]	57	–

[a]Reaction conditions: 0.1 mmol scale, 20 mol % of cat., solvent (0.5 mL). [b]Conversion determined by ^1H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis of the sample obtained by preparative TLC. [d]Mixture 1:1. [e]Reaction conditions: 0.1 mmol scale, 10 mol % of cat., solvent (0.25 mL).

Ca^{2+}-Catalyzed Wittig [2,3]-Rearrangement Reaction. Next, the results of a Ca^{2+}-catalyzed Wittig [2,3]-sigmatropic rearrangement reaction of allyloxy-1,3-dicarbonyl compounds will be discussed.

In a metal-catalyzed reaction, several factors besides the chiral ligand (such as the source of metal, the solvent, and the additional base) influence the stereoselectivity of the rearrangement. We limited the scope of ligands to bisoxazoline

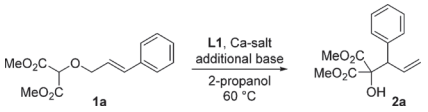
DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889–2897

derivatives as most widely used in Ca^{2+}-catalysis,[14,15] although oxazolidines and bisoxazolidines have also been used in catalysis with other metals.[16] Also, the choice of solvent was 2-propanol, as we have previously shown its superiority over other solvents for Ca^{2+}-bisoxazoline-catalyzed reactions.[17] (See Supporting Information for full optimization procedures.)

Initially different calcium salts were screened in the presence or absence of imidazole as an additional base (Table 2, entries 1–6). The addition of imidazole in a calcium chloride/**L1**-catalyzed reaction (Figure 2) was needed to yield higher conversion and enantioselectivity (Table 2, entries 1–2). The reaction with calcium iodide stopped after 6 h, and within 24 h, the reaction had not proceeded further. Calcium(II) bis(trifluoromethanesulfonimide) ($Ca(NTf_2)_2$) proved to be the superior of the Ca-salts (Table 2, entry 4), giving full conversion and enantiomeric excess of 75% in 24 h. Next, other organic bases were evaluated (Table 2, entries 7–10), but still the addition of imidazole gave slightly higher enantioselectivity than with the other bases. The presence of cesium carbonate gave a racemic product in 6 h, indicating that the inorganic base prevailed over the Ca^{2+}-complex (Table 2, entry 11).

After the optimized conditions for the coordinative neutral ligand **L1** were determined (Table 3, entry 1), we screened other bisoxazoline ligands (Table 3, entries 2–6). Unexpectedly, all of the ligands were less active and produced products with either low enantioselectivity or racemic outcome. We also assessed the complex formation by NMR and ESI-MS and found that the 1:1 complex between ligand **L1** and $Ca(NTf_2)_2$ formed immediately after mixing the two together (Figure S1 in SI) and was stable for at least up to 300 °C in ESI-MS (Figure S3 in SI).

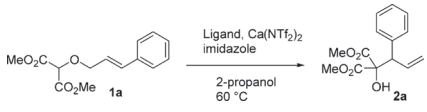
Table 2. Optimization of the Reaction Conditions of a Ca^{2+}-Catalyzed Rearrangement[a]



entry	Ca-salt	base	time	conv. (%)[b]	ee (%)[c]
1[d]	$CaCl_2$	–	3 d	58	39
2	$CaCl_2$	imidazole	3 d	92	49
3	CaI_2	imidazole	6 h[e]	36	64
4	$Ca(NTf_2)_2$	imidazole	24 h	99	75
5	$Ca(HFIP)_2$[f]	imidazole	1 h	99	*rac*
6	$Ca(HMDS)_2$[f]	imidazole	1 h	99	*rac*
7	$Ca(NTf_2)_2$	Et_3N	24 h	79	68
8	$Ca(NTf_2)_2$	DIPEA[f]	24 h	97	70
9	$Ca(NTf_2)_2$	morpholine	24 h	85	70
10	$Ca(NTf_2)_2$	pyridine	3 d	40	52
11[g]	$Ca(NTf_2)_2$	Cs_2CO_3	6 h	99	*rac*

[a]Reaction conditions: **1a** (0.1 mmol), **L1** (5 mol %), Ca salt (5 mol %), and base (5 mol %) in 2-propanol (1 mL) was stirred at 60 °C. [b]Conversion was determined by ^{1}H NMR of the crude product. [c]Enantiomeric excess was determined by chiral HPLC. [d]Reaction was carried out without additional base. [e]Reaction stopped after 6 h. [f]HFIP = hexafluoroisopropanyl, HMDS = hexamethyldisilazane, DIPEA = *N*,*N*-diisopropylethylamine. [g]Reaction was conducted at room temperature.

Table 3. Screening of Different Bisoxazoline Ligands[a]



entry	ligand	time	conv. (%)[b]	ee (%)[c]
1	**L1**	24 h	99	75
2	**L2**	3 d	12	–
3	**L3**	24 h	44	−12
4	**L4**	24 h	29	*rac*
5	**L5**	24 h	43	*rac*
6	**L6**	24 h	54	*rac*

[a]Reaction conditions: **1a** (0.1 mmol), ligand (5 mol %), $Ca(NTf_2)_2$ (5 mol %), and imidazole (5 mol %) in 2-propanol (1 mL) were stirred at 60 °C. [b]Conversion was determined by ^{1}H NMR of the crude product. [c]Enantiomeric excess was determined by chiral HPLC.

Scope of Two Alternative Methods for a Wittig [2,3]-Rearrangement Reaction. The scope of the reaction was evaluated by studying the effects of the substituents at the aromatic ring and at the carbonyl moiety. The two methods applied afforded comparable results in terms of yields and enantiomeric purities (Scheme 3). The main difference was in the enantioselection. In organocatalytic reactions, the main enantiomer was in *R*-configuration, and metal-catalyzed

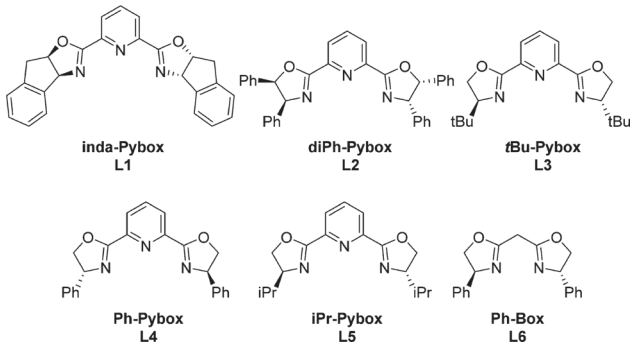
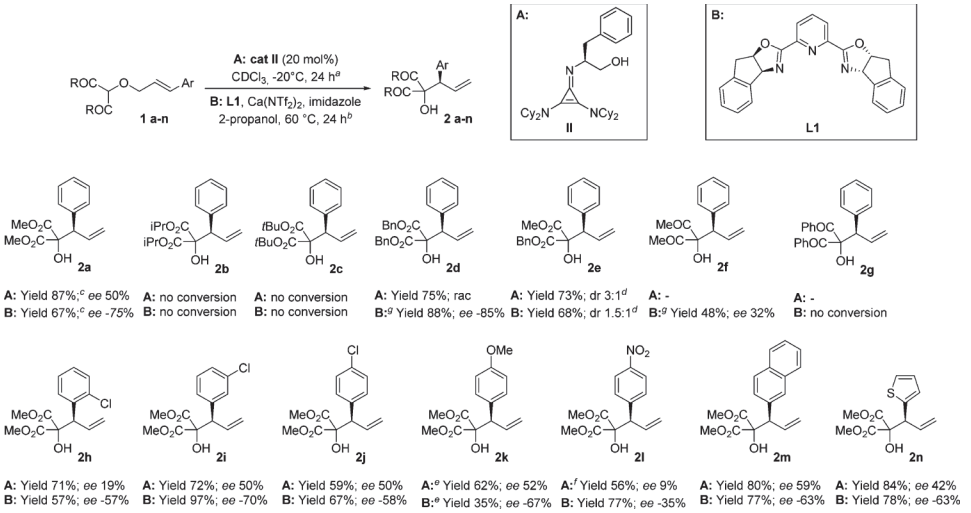


Figure 2. Bisoxazoline ligands used in the current study.

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889–2897

Scheme 3. Scope of the reaction (*R*-enantiomers obtained by organocatalytic method are depicted)



[a]Reaction conditions for the organocatalytic reaction **A:** 0.1 mmol scale, 20 mol % of cat. **II**, $CDCl_3$ (0.5 mL), −20 °C, 24 h. Enantiomeric excess is determined by chiral HPLC analysis of the isolated product. [b]Reaction conditions for the Ca^{2+}-catalyzed reaction **B: 1a−n** (0.1 mmol), **L1** (5 mol %), $Ca(NTf_2)_2$ (5 mol %), and imidazole (5 mol %) in 2-propanol (1 mL) were stirred at 60 °C for 24 h. [c]Isolated yield. [d]Diastereoisomeric ratio is determined by ^1H NMR analysis of the crude mixture. [e]Reaction was stopped after 48 h. [f]Reaction was finished after 48 h. [g]Reaction was finished after 6 h.

reactions afforded *S*-enantiomer as a major isomer. The absolute configuration was determined by a comparison of the optical rotation of compound **2a** with data published by Jacobsen.[7] Both methods are sensitive to steric hindrance, and no products were formed with isopropyl or *tert*-butyl derivatives **1b** and **1c**. Mixed ester **1e** was synthesized to explore the diastereoselectivity of the reaction. Unfortunately, the methods were characterized by low or moderate diastereoselectivity (for **2e** dr 1.5:1 and 3:1). Diketones **1f** and **1g** were poor starting materials for the rearrangement affording product with low yield or no conversion by Ca^{2+}-catalyzed reactions (organocatalytic reactions were not applied on these compounds). The organocatalytic method showed higher sensitivity toward the steric hindrance. Previously we have found that only *E*-isomers of phenyl-substituted allyloxy compounds were reactive in the case of organocatalytic rearrangement of oxindole derivatives.[6] The enantiomeric purity of the *o*-chlorophenyl derivative **2h** was lower in the case of the organocatalytic method compared with that obtained by metal-catalysis. *Meta*- and *para*-substitutions did not affect the results substantially (compounds **2i** and **2j**). Electron-donating, electron-withdrawing, and heteroaromatic substituents were tolerated under the reaction conditions (**2k−n**). Surprisingly low enantiomeric excess was obtained with nitrophenyl derivative **2l** by the organocatalytic method. This might be due to the fact that the nitro group is a very strong hydrogen-bond acceptor, and therefore the transition state could be completely different.

Based on the obtained results we propose transition-state models for both methods.

In the organocatalytic reaction, first the malonate derivative **1a** is deprotonated by a strongly basic catalyst affording an enolate anion and a cyclopropenium ion (Figure 3). It has been

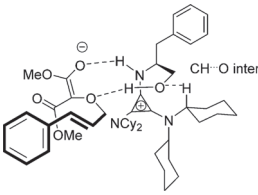


Figure 3. Model for the interaction of catalyst **II** with malonate derivative **1a** to account for the stereochemical outcome of the rearrangement.

shown that a weak intramolecular CH···O interaction (0.5 kcal/mol) is responsible for the transition-state organization in reactions catalyzed by chiral cyclopropenimines.[18] Our results indicate that the hydrogen-bond donor capability of the catalyst is essential for achieving high stereoselectivity. Catalysts **II** and **III** differ from each other by their hydrogen-bond-donating properties. Methoxy-protected catalyst **III** has no hydrogen-bond donors, by lowering the stereoselectivity of the reaction drastically (compare entries 2 and 4 in Table 1). The same observation had been made by Lambert.[18] It is assumed that in the enantiodetermining rearrangement step, the conformation of the substrate is fixed with hydrogen bonds. The hydrogen bond between the OH group of catalyst **II** and the allylic oxygen promotes the rearrangement. A similar activation model has previously been proposed for the cycloaddition of azomethine ylides[19] and for a Mannich reaction.[20]

Ca^{2+}/Pybox complexes have been previously investigated by NMR[21] and X-ray crystallography.[22] Based on these publications, it is assumed that in the Ca^{2+}-catalytic reaction, the *N*,*N*,*N*-tridentate Inda-Pybox ligand first forms a complex with

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889−2897

$Ca(NTf_2)_2$, which is a strong Lewis acid. Then, calcium enolate is formed with substrate **1a**, and the oxygen in the allyloxy group coordinates with calcium. Finally, the second trifluoromethanesulfonimide group is removed from calcium, giving the presented model (Figure 4).

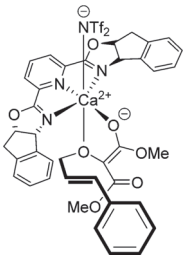


Figure 4. Model for the complexation of a Ca^{2+}/Inda-Pybox complex with compound **1a** to account for the stereochemical outcome of the rearrangement.

CONCLUSIONS

We have developed two independent asymmetric catalytic methods for a Wittig [2,3]-rearrangement. In the organocatalytic pathway, a highly basic substituted cyclopropenimine catalyst was used. In the metal-catalyzed reaction, a Ca^{2+}/bisoxazoline complex was employed. Our ongoing investigations are focused on mechanistic models in order to increase so far modest selectivities.

EXPERIMENTAL SECTION

General Remarks. Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a 400 MHz instrument. Residual solvent signals were used ($CDCl_3$ δ = 7.26 (^1H NMR), 77.16 (^{13}C NMR), and CD_3OD δ = 3.31 (^1H NMR), 49.00 (^{13}C NMR)) as internal standards. All peak assignments are confirmed by 2D experiments ($^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, $^1H-^{13}C$ HMBC). High-resolution mass spectra were recorded by using an Q-TOF LC/MS spectrometer by using ESI ionization. Optical rotations were obtained at 20 °C in $CHCl_3$ and calibrated with pure solvent as a blank. Chiral HPLC was performed by using Chiralpak AD-H (250 × 4.6 mm), Chiralcel OJ-H (250 × 4.6 mm), Chiralcel OD-H (250 × 4.6 mm), Chiralpak AS-H (250 × 4.6 mm), or Lux 3u Amylose-2 (250 × 4.6 mm) columns. Precoated silica gel 60 F254 plates were used for TLC. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40−63 μm. The measured melting points are uncorrected. Purchased chemicals and solvents were used as received. DCM was distilled over phosphorus pentoxide. Petroleum ether has a boiling point of 40−60 °C. The reactions were performed under air atmosphere without additional moisture elimination unless stated otherwise.

Catalysts **I**,[23] **VI**,[24] and **VIII**[25] were prepared according to literature procedures, and the analytical data matched with that of the literature. New catalysts **III**, **IV**, **V**, and **VII** were prepared according to the analogous literature procedure.[26] Catalyst **II** is commercially available as an HCl salt.

Ligands **L5** and **L6** were purchased and used as received. Ligands **L1**−**L4** were prepared according to the literature procedures.[27−30]

Synthesis of Catalysts III·HCl, IV·HCl, V·HCl, and VII. Dicyclohexylamine (6.0 equiv) was slowly added to a solution of tetrachlorocyclopropene (1.0 equiv) in DCM (0.1 M solution). A white precipitate formed as the reaction mixture was stirred for a further 4 h at room temperature. Next, primary amine (1.1 equiv) was added in one portion, and the reaction mixture was stirred overnight. The crude reaction mixture was filtered through a Celite plug, then washed with 1.0 M HCl (3×), dried with anhydrous sodium sulfate, and concentrated in vacuo to yield pure cyclopropenimine hydrochloride salt. The cyclopropenimine salt can be stored at room temperature without noticeable decomposition.

Free cyclopropenimine was obtained by dissolving the corresponding hydrochloride salt in DCM and washing the solution with 1.0 M aq NaOH, drying with anhydrous sodium sulfate and concentrating in vacuo.

(S)-N^1,N^1,N^2,N^2-Tetracyclohexyl-3-((1-methoxy-3-phenylpropan-2-yl)imino)cycloprop-1-ene-1,2-diamine Hydrochloride Salt ***III·HCl.*** The synthesis was conducted with (*S*)-phenylalaninol methyl ether, affording compound **III** as a brown amorphous solid in 90% yield (131 mg). Optical rotation for **III**: $[\alpha]_D^{20}$ −31.9 (*c* 0.11, $CHCl_3$).

Spectra data for **III·HCl**: ^1H NMR (400 MHz, CD_3OD) δ 7.33−7.20 (m, 5H, Ar), 3.96 (ddt, *J* = 9.5, 7.9, 4.6 Hz, 1H, NCH), 3.64 (dd, *J* = 9.5, 4.7 Hz, 1H, CH_2O), 3.54 (dd, *J* = 9.4, 8.2 Hz, 1H, CH_2O), 3.46−3.35 (m, 7H, CH_3 and NCyH), 3.04 (dd, *J* = 13.9, 4.4 Hz, 1H, CH_2Ph), 2.84 (dd, *J* = 13.9, 9.9 Hz, 1H, CH_2Ph), 1.95−1.18 (m, 40H, CyH). ^{13}C NMR (101 MHz, MeOD) δ 139.1, 130.4, 129.7, 127.9, 117.7, 115.9, 76.3, 61.4, 60.4, 59.6, 38.9, 33.3, 33.2, 26.71, 26.66, 25.7.

(S)-2-((2,3-Bis(dicyclohexylamino)cycloprop-2-en-1-ylidene)-amino)-3,3-dimethylbutan-1-ol Hydrochloride Salt ***IV·HCl.*** The synthesis was conducted with (*S*)-*tert*-leucinol, affording compound **IV·HCl** as an off-white solid in 85% yield (490 mg). Optical rotation for **IV·HCl**: $[\alpha]_D^{20}$ −46.9 (*c* 0.09, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H, OH), 6.83 (d, *J* = 9.8 Hz, 1H, NH), 4.10 (dd, *J* = 11.9, 9.7 Hz, 1H, CH_2OH), 3.78 (dd, *J* = 12.0, 4.0 Hz, 1H, CH_2OH), 3.42 (td, *J* = 9.7, 4.0 Hz, 1H, CH*t*Bu), 3.32 (tt, *J* = 11.9, 3.4 Hz, 4H, NCyH), 2.05−1.10 (m, 40H, CyH), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 119.0, 68.4, 59.7, 59.5, 34.9, 32.7, 26.9, 25.9, 25.8, 25.02, 24.99, 24.93. HRMS (ESI) calculated for $C_{33}H_{58}N_3O$, $[M + H]^+$: 512.4574, found 512.4569.

(1R,2R)-2-((2,3-Bis(dicyclohexylamino)cycloprop-2-en-1-ylidene)-amino)cyclohexan-1-ol Hydrochloride Salt ***V·HCl.*** The synthesis was conducted with (1*R*,2*R*)-2-aminocyclohexanol, affording compound **V·HCl**, obtained as an off-white solid in 87% yield (475 mg). Optical rotation for **V·HCl**: $[\alpha]_D^{20}$ −14.8 (*c* 0.11, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H, OH), 7.80 (d, *J* = 7.5 Hz, 1H, NH), 4.20−3.99 (m, 1H, CyH), 3.51−3.22 (m, 5H, CyH), 3.15−2.95 (m, 1H, CyH), 2.29−2.02 (m, 3H, CyH), 2.00−1.06 (m, 44H, CyH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 117.2, 115.0, 70.5, 63.6, 59.6, 34.00, 33.98, 32.32, 32.29, 29.0, 28.9, 25.85, 25.82, 25.79, 24.90, 24.84, 24.80, 24.7, 24.4. HRMS (ESI) calculated for $C_{33}H_{56}N_3O$, $[M + H]^+$: 510.4418, found 510.4412.

N^1,N^1,N^2,N^2-Tetracyclohexyl-3-(((R)-(6-methoxyquinolin-4-yl)-((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)imino)cycloprop-1-ene-1,2-diamine ***VII.*** The synthesis was conducted with (*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)-methanamine, affording compound **VII** after purification by column chromatography on silica gel (5% NH_3/MeOH in DCM), as an off-white solid in 26% yield (75 mg). Optical rotation for **VII**: $[\alpha]_D^{20}$ +157.1 (*c* 0.09, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.5 Hz, 1H, ArH), 8.00 (d, *J* = 9.2 Hz, 1H, ArH), 7.88 (s, 1H, ArH), 7.49 (d, *J* = 3.5 Hz, 1H, ArH), 7.38 (dd, *J* = 9.2, 2.6 Hz, 1H, ArH), 6.21 (ddd, *J* = 17.0, 10.2, 6.6 Hz, 1H, C*H*CH$_2$), 6.03 (d, *J* = 7.4 Hz, 1H, CHN), 5.23−5.10 (m, 2H, CHCH_2), 4.08 (s, 3H, OCH_3), 3.35−3.05 (m, 5H), 3.03−2.78 (m, 3H), 2.73−2.50 (m, 1H), 2.31 (q, *J* = 8.0 Hz, 1H), 2.00−0.52 (m, 45H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 147.9, 145.1, 140.1, 131.9, 128.3, 122.9, 115.7, 115.5, 113.8, 103.0, 58.7, 56.8, 49.2, 47.4, 39.6, 32.2, 31.9, 28.2, 25.2, 25.1, 24.6. HRMS (ESI) calculated for $C_{47}H_{68}N_5O$, $[M + H]^+$: 718.5418, found 718.5414.

Synthesis of Starting Materials 1a−n. The synthesis of compounds **1a** and **1c** was described by Jacobsen.[7] We used a slightly modified procedure. The synthesis of allyloxy-1,3-dicarbonyl compounds **1a−n** was achieved as follows: 1,3-Dicarbonyl compounds were reacted with tosyl azide to produce diaza compounds, which were subjected to a rhodium-catalyzed OH insertion reaction, affording the desired compounds **1**. A general procedure for the formation of **1a** is

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889−2897

presented. In the synthesis of **1a** and **1h−n**, transesterification of malonyl ester occurred, and to improve the yield, transesterification with *p*-TsOH in MeOH can be conducted. This procedure was performed only with compound **1a**.

Dimethyl 2-Diazomalonate. To a solution of tosyl azide (1.735 g, 8.8 mmol) in acetonitrile (12 mL), triethylamine (1.227 mL, 8.8 mmol) and dimethyl malonate (0.916 mL, 8 mmol) were added at 0 °C. The reaction mixture was stirred overnight at room temperature. Then, solvent was evaporated under reduced pressure, and the crude mixture purified by column chromatography on silica gel (10−20% EtOAc in petroleum ether/DCM 3/1 mixture), affording the title compound as a colorless oil (1.227 g, 97%).

Dimethyl 2-(Cinnamyloxy)malonate ***1a.*** To a 10 mL flask were added cinnamyl alcohol (322 mg, 2.4 mmol) and rhodium(II) acetate dimer (4.4 mg, 0.01 mmol). The flask was flushed with Ar, and DCM was added (5 mL). Dimethyl 2-diazomalonate (286 mg, 2 mmol) solution in DCM (5 mL) was added over 5 min at 0 °C. The reaction was stirred overnight at rt. After evaporating the solvent, the crude mixture was purified by column chromatography on silica gel (3−10% EtOAc in petroleum ether/DCM 3/1 mixture), affording compound **1a** as a colorless oil. The impure fractions were dried under vacuum and dissolved in MeOH (10 mL), *p*-toluenesulfonic acid (30 mg) was added, and the mixture was stirred at reflux overnight. After purification in the same conditions, the fractions were combined, affording compound **1a** as a colorless oil in 64% total yield (336 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2H, 2 × ArH), 7.35−7.29 (m, 2H, 2 × ArH), 7.29−7.23 (m, 1H, ArH), 6.64 (d, J = 15.9 Hz, 1H, CHAr), 6.28 (dt, J = 15.9, 6.5 Hz, 1H, CH_2CH), 4.64 (s, 1H, CH), 4.34 (dd, J = 6.5, 1.2 Hz, 2H, CH_2), 3.81 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 136.1, 134.9, 128.6, 128.1, 126.7, 123.7, 77.5, 71.8, 53.0. HRMS (ESI) calculated for $C_{14}H_{16}NaO_5$, $[M + Na]^+$: 287.0890, found 287.0879.

Diisopropyl 2-(Cinnamyloxy)malonate ***1b.*** Compound **1b** was obtained as a colorless oil in 70% yield (112 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H, 2 × ArH), 7.35−7.29 (m, 2H, 2 × ArH), 7.28−7.25 (m, 1H, ArH), 6.63 (d, J = 16.0 Hz, 1H, CHAr), 6.30 (dt, J = 15.9, 6.5 Hz, 1H, CH_2CH), 5.12 (hept, J = 6.3 Hz, 2H, $CH(CH_3)_2$), 4.52 (s, 1H, CH), 4.34 (dd, J = 6.5, 1.1 Hz, 2H, CH_2), 1.27 (d, J = 6.2 Hz, 6H, 2 × CH_3), 1.26 (d, J = 6.3 Hz, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 136.3, 134.7, 128.7, 128.2, 126.8, 124.3, 78.1, 71.7, 69.9, 21.8, 21.7. HRMS (ESI) calculated for $C_{18}H_{24}NaO_5$, $[M + Na]^+$: 343.1516, found 343.1510.

Di-tert-butyl 2-(Cinnamyloxy)malonate ***1c.*** Compound **1c** was obtained as a white solid in 62% yield (255 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 2H, 2 × ArH), 7.35−7.28 (m, 2H, 2 × ArH), 7.28−7.22 (m, 1H, ArH), 6.63 (d, J = 15.9 Hz, 1H, CHAr), 6.30 (dt, J = 15.9, 6.4 Hz, 1H, CH_2CH), 4.37 (s, 1H, CH), 4.32 (dd, J = 6.4, 1.2 Hz, 2H, CH_2), 1.49 (s, 18H, 2 × *t*Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 136.5, 134.3, 128.7, 128.1, 126.8, 124.6, 82.8, 79.0, 71.4, 28.1.

Dibenzyl 2-(Cinnamyloxy)malonate ***1d.*** Compound **1d** was obtained as a white solid in 56% yield (170 mg), mp 65−67 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.15 (m, 15H, 15xArH), 6.58 (d, J = 15.9 Hz, 1H, CHAr), 6.26 (dt, J = 15.9, 6.5 Hz, 1H, CH_2CH), 5.19 (s, 4H, CH_2Ph), 4.69 (s, 1H, CH), 4.34 (dd, J = 6.5, 1.1 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 136.2, 135.0, 128.7 (2C), 128.6, 128.5 (2C), 128.2, 126.8, 124.0, 77.7, 71.9, 67.7. HRMS (ESI) calculated for $C_{26}H_{24}NaO_5$, $[M + Na]^+$: 439.1516, found 439.1505.

1-Benzyl 3-Methyl 2-(cinnamyloxy)malonate ***1e.*** Compound **1e** was obtained as a colorless oil in 59% yield (146 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.23 (m, 10H, 10xArH), 6.60 (d, J = 15.9 Hz, 1H, CHAr), 6.27 (dt, J = 16.0, 6.5 Hz, 1H, CH_2CH), 5.26 (d, J = 12.3 Hz, 1H, CH_2Ph), 5.22 (d, J = 12.2 Hz, 1H, CH_2Ph), 4.66 (s, 1H, CH), 4.33 (dd, J = 6.5, 1.0 Hz, 2H, CH_2), 3.76 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 166.6, 136.2, 135.0, 128.73 (2C), 128.67, 128.4, 128.3, 126.8 (2C), 123.9, 77.7, 71.9, 67.7, 53.0. HRMS (ESI) calculated for $C_{20}H_{21}O_5$, $[M + H]^+$: 341.1384, found 341.1379.

3-(Cinnamyloxy)pentane-2,4-dione ***1f.*** Compound **1f** was obtained in 3 h at 5 °C, as a pale yellow oil, which solidifies in the freezer, in 62% yield (227 mg).

Spectra data for symmetric enol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.38 (s, 1H, OH), 7.44−7.39 (m, 2H, 2 × ArH), 7.37−7.31 (m, 2H, 2 × ArH), 7.30−7.26 (m, 1H, ArH), 6.68 (d, J = 15.9 Hz, 1H, CHAr), 6.36 (dt, J = 15.9, 6.1 Hz, 1H, CH_2CH), 4.31 (dd, J = 6.1, 1.3 Hz, 2H, CH_2), 2.20 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.5, 136.4, 135.7, 133.6, 128.8, 128.3, 126.7, 124.3, 75.3, 21.0. HRMS (ESI) calculated for $C_{14}H_{16}NaO_3$, $[M + Na]^+$: 255.0992, found 255.0986.

2-(Cinnamyloxy)-1,3-diphenylpropane-1,3-dione ***1g.*** Compound **1g** was obtained as a yellow amorphous solid in 27% yield (87 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.92 (m, 2H, 2 × ArH), 7.58−7.49 (m, 1H, ArH), 7.47−7.28 (m, 12H, 12 × ArH), 6.59 (d, J = 15.9 Hz, 1H, CHAr), 6.23 (dt, J = 15.9, 6.4 Hz, 1H, CH_2CH), 5.66 (s, 1H, CH), 4.83 (dt, J = 6.4, 1.4 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 168.8, 135.8, 134.6, 133.7, 133.0, 130.8, 129.7, 129.1, 129.0, 128.9, 128.7, 128.4, 128.2, 126.8, 122.7, 66.4, 60.7. HRMS (ESI) calculated for $C_{24}H_{20}NaO_3$, $[M + Na]^+$: 379.1305, found 379.1280.

Dimethyl (E)-2-((3-(2-Chlorophenyl)allyl)oxy)malonate ***1h.*** Compound **1h** was obtained as a white solid in 34% yield (91 mg), mp 53−55 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.3, 2.2 Hz, 1H, ArH), 7.35 (dd, J = 7.5, 1.8 Hz, 1H, ArH), 7.25−7.15 (m, 2H, 2 × ArH), 7.02 (d, J = 15.9 Hz, 1H, CHAr), 6.28 (dt, J = 15.9, 6.4 Hz, 1H, CH_2CH), 4.65 (s, 1H, CH), 4.38 (dd, J = 6.4, 1.1 Hz, 2H, CH_2), 3.82 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 134.4, 133.4, 130.9, 129.9, 129.3, 127.2, 127.0, 126.9, 77.7, 71.9, 53.1. HRMS (ESI) calculated for $C_{14}H_{15}ClNaO_5$, $[M + Na]^+$: 321.0500, found 321.0488.

Dimethyl (E)-2-((3-(3-Chlorophenyl)allyl)oxy)malonate ***1i.*** Compound **1i** was obtained as a colorless oil in 53% yield (149 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.35 (m, 1H, ArH), 7.29−7.20 (m, 3H, 3xArH), 6.59 (d, J = 15.9 Hz, 1H, CHAr), 6.30 (dt, J = 15.9, 6.3 Hz, 1H, CH_2CH), 4.62 (s, 1H, CH), 4.33 (dd, J = 6.3, 1.2 Hz, 2H, CH_2), 3.82 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 138.1, 134.7, 133.2, 130.0, 128.2, 126.8, 125.6, 124.9, 77.8, 71.6, 53.1. HRMS (ESI) calculated for $C_{14}H_{16}ClO_5$, $[M + H]^+$: 299.0681, found 299.0675.

Dimethyl (E)-2-((3-(4-Chlorophenyl)allyl)oxy)malonate ***1j.*** Compound **1j** was obtained as a white amorphous solid in 56% yield (159 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.28 (d, J = 8.8 Hz, 2H, 2 × ArH), 6.59 (d, J = 16.0 Hz, 1H, CHAr), 6.26 (dt, J = 15.9, 6.4 Hz, 1H, CH_2CH), 4.62 (s, 1H, CH), 4.32 (dd, J = 6.4, 1.1 Hz, 2H, CH_2), 3.81 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 134.7, 133.9, 133.5, 128.9, 128.0, 124.6, 77.8, 71.8, 53.1. HRMS (ESI) calculated for $C_{14}H_{15}ClNaO_5$, $[M + Na]^+$: 321.0500, found 321.0487.

Dimethyl (E)-2-((3-(4-Methoxyphenyl)allyl)oxy)malonate ***1k.*** Compound **1k** was obtained as a colorless oil in 63% yield (166 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H, 2 × ArH), 6.85 (d, J = 8.7 Hz, 2H, 2 × ArH), 6.57 (d, J = 15.9 Hz, 1H, CHAr), 6.14 (dt, J = 15.9, 6.7 Hz, 1H, CH_2CH), 4.63 (s, 1H, CH), 4.31 (dd, J = 6.7, 1.0 Hz, 2H, CH_3), 3.81 (s, 3H, OCH_3), 3.80 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 159.8, 134.9, 128.9, 128.1, 121.5, 114.1, 77.4, 72.2, 55.4, 53.1. HRMS (ESI) calculated for $C_{15}H_{18}NaO_6$, $[M + Na]^+$: 317.0996, found 317.0981.

Dimethyl (E)-2-((3-(4-Nitrophenyl)allyl)oxy)malonate ***1l.*** Compound **1l** was obtained as a yellow solid in 46% yield (147 mg), mp 58−60 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.7 Hz, 2H, 2 × ArH), 7.52 (d, J = 8.8 Hz, 2H, 2 × ArH), 6.74 (d, J = 16.0 Hz, 1H, CHAr), 6.47 (dt, J = 16.0, 5.9 Hz, 1H, CH_2CH), 4.63 (s, 1H, CH), 4.38 (dd, J = 5.9, 1.4 Hz, 2H, CH_2), 3.83 (s, 6H, 2 × CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.8, 147.4, 142.7, 131.6, 129.1, 127.3, 124.2, 78.2, 71.3, 53.2. HRMS (ESI) calculated for $C_{14}H_{15}NNaO_7$, $[M + Na]^+$: 332.0741, found 332.0732.

Dimethyl (E)-2-((3-(Naphthalen-2-yl)allyl)oxy)malonate ***1m.*** Compound **1m** was obtained as a pale yellow oil in 33% yield (97 mg).

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889−2897

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.77 (m, 3H, 3xArH), 7.75 (s, 1H, ArH), 7.60 (dd, J = 8.6, 1.7 Hz, 1H, ArH), 7.50−7.42 (m, 2H, 2 × ArH), 6.80 (d, J = 15.9 Hz, 1H, CH), 6.41 (dt, J = 15.9, 6.5 Hz, 1H, CH_2CH), 4.67 (s, 1H, CH), 4.39 (dd, J = 6.5, 1.2 Hz, 2H, CH_2), 3.82 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 135.1, 133.7, 133.6, 133.4, 128.4, 128.2, 127.8, 127.1, 126.5, 126.3, 124.3, 123.6, 77.7, 72.1, 53.1. HRMS (ESI) calculated for $C_{18}H_{18}NaO_5$, [M + Na]$^+$: 337.1046, found 337.1040.

Dimethyl (E)-2-((3-(Thiophen-2-yl)allyl)oxy)malonate ***1n.*** Compound **1n** was obtained as a yellow oil in 38% yield (102 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 4.9 Hz, 1H, ArH), 7.07−6.87 (m, 2H, 2 × ArH), 6.76 (d, J = 15.7 Hz, 1H, CHAr), 6.10 (dt, J = 15.7, 6.5 Hz, 1H, CH_2CH), 4.62 (s, 1H, CH), 4.29 (dd, J = 6.5, 1.2 Hz, 2H, CH_2), 3.81 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 141.2, 128.1, 127.5, 126.7, 125.2, 123.3, 77.6, 71.6, 53.1. HRMS (ESI) calcd for $C_{12}H_{14}NaO_5S$, [M + Na]$^+$: 293.0454, found 293.0447.

General Procedure for Organocatalytic Wittig [2,3]-Rearrangement of Allyloxy-1,3-dicarbonyl Compounds 1 (Method A). A solution of allyloxy-1,3-dicarbonyl compound **1** (0.1 mmol) in $CDCl_3$ (0.25 mL) was added to a cooled solution of catalyst **II** (20 mol %) in $CDCl_3$ (0.25 mL). The reaction mixture was stirred at −20 °C for 24 h. Upon completion of the reaction, the crude mixture was directly purified by flash chromatography on silica gel (0−10% EtOAc in petroleum ether/DCM 3/1 mixture), affording the desired product **2**. The enantioselectivity of the isolated product was determined by HPLC analysis, providing the product in (*R*)-configuration.

General Procedure for Ca^{2+}-Catalyzed Asymmetric Wittig [2,3]-Rearrangement of Allyloxy 1,3-Dicarbonyl Compounds 1 (Method B). To a solution of allyloxy 1,3-dicarbonyl compound **1** (0.1 mmol) in 2-propanol (1 mL), $Ca(NTf_2)_2$ (0.005 mmol), ligand **L1** (0.005 mmol) and imidazole (0.005 mmol) were added. The reaction mixture was stirred at 60 °C. Then, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (0−10% EtOAc in petroleum ether/DCM 3/1 mixture), affording the desired product **2**. The enantioselectivity of the isolated product was determined by HPLC analysis, providing the product in (*S*)-configuration.

Dimethyl (*R*)-2-Hydroxy-2-(1-phenylallyl)malonate 2a. Compound **2a** was obtained as a white solid, for Method A in 87% yield (23 mg) and for Method B in 67% yield (18 mg), mp 86−88 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (***R***)-**2a** 10.7 min and (***S***)-**2a** 9.6 min, and enantiomeric excess for compound **2a** for Method A was 50% and for Method B was 75%. Optical rotation for (***R***)-**2a** (ee 50%): $[\alpha]_D^{20}$ −28.8 (*c* 0.11, $CHCl_3$). Analytic data were in agreement with the literature data.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 2H, ArH), 7.31−7.20 (m, 3H, ArH), 6.18 (ddd, J = 17.1, 10.1, 9.1 Hz, 1H, $CHCH_2$), 5.23−5.13 (m, 2H, CH_2), 4.33 (d, J = 9.0 Hz, 1H, CHAr), 3.92 (s, 1H, OH), 3.84 (s, 3H, CH_3), 3.61 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.8, 138.1, 135.6, 129.3, 128.4, 127.5, 118.4, 82.7, 54.7, 53.8, 53.5. HRMS (ESI) for $C_{14}H_{16}NaO_5$, calculated for [M + Na]$^+$: 287.0890, found: 287.0889.

Dibenzyl (*R*)-2-Hydroxy-2-(1-phenylallyl)malonate 2d. Compound **2d** was obtained as a colorless oil, for Method A in 75% yield (29 mg) and for Method B in 88% yield (36 mg). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (***R***)-**2d** 31.1 min and (***S***)-**2d** 25.3 min, and enantiomeric excess for compound **2d** for Method A was 0% and for Method B was 85%. Optical rotation for (***S***)-**2d** (ee 85%): $[\alpha]_D^{20}$ −15.6 (*c* 0.15, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 10H, ArH), 7.24−7.19 (m, 3H, ArH), 7.17−7.09 (m, 2H, ArH), 6.16 (ddd, J = 17.0, 10.3, 8.9 Hz, 1H, $CHCH_2$), 5.22 (s, 2H, CH_2Ar), 5.12−5.03 (m, 2H, $CHCH_2$), 4.98 (d, J = 12.2 Hz, 1H, CH_2Ar), 4.93 (d, J = 12.2 Hz, 1H, CH_2Ar), 4.34 (d, J = 8.8 Hz, 1H, CHAr), 3.98 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 169.1, 138.1, 135.6, 134.9, 134.6, 129.4, 128.73 (2C), 128.68, 128.63, 128.61, 128.5, 128.4, 127.4, 118.4, 82.6, 68.6, 68.4, 54.4. HRMS (ESI) for $C_{26}H_{24}NaO_5$, calculated for [M + Na]$^+$: 439.1516, found: 439.1519.

1-Benzyl 3-Methyl-2-hydroxy-2-((*R*)-1-phenylallyl)malonate 2e. Compound **2e** was obtained as a colorless oil, for Method A in 73% yield (24 mg) and for Method B in 68% yield (23 mg).

NMR data for the main diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.19 (m, 10H, ArH), 6.22−6.09 (m, 1H, $CHCH_2$), 5.26 (s, 2H, CH_2Ar), 5.10−5.04 (m, 2H, $CHCH_2$), 4.33 (d, J = 8.9 Hz, 1H, CHAr), 3.93 (s, 1H, OH), 3.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.4, 138.2, 135.4, 135.0, 129.4, 128.8, 128.7, 128.6, 128.4, 127.5, 118.5, 82.6, 68.5, 54.5, 53.4. HRMS (ESI) for $C_{20}H_{20}NaO_5$, calculated for [M + Na]$^+$: 363.1203, found: 363.1193.

3-Hydroxy-3-(1-phenylallyl)pentane-2,4-dione 2f. Compound **2f** was obtained as a yellow oil, for Method B in 48% yield (11 mg). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 230 nm), major enantiomer 6.0 min, minor enantiomer 5.3 min, and enantiomeric excess for compound **2f** for Method B was 32%. Optical rotation for **2f** (ee 32%): $[\alpha]_D^{20}$ +2.7 (*c* 0.099, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 2H, ArH), 7.31−7.18 (m, 3H, ArH), 6.02 (ddd, J = 17.1, 10.2, 9.1 Hz, 1H, $CHCH_2$), 5.16−5.09 (m, 2H, CH_2), 4.95 (s, 1H, OH), 4.35 (d, J = 9.1 Hz, 1H, CHAr), 2.34 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 206.8, 138.1, 135.5, 129.1, 128.6, 127.5, 118.2, 94.0, 55.7, 26.4, 26.1. HRMS (ESI) for $C_{14}H_{16}NaO_3$, calculated for [M + Na]$^+$: 255.0992, found: 255.0987.

Dimethyl (*R*)-2-(1-(2-Chlorophenyl)allyl)-2-hydroxymalonate 2h. Compound **2h** was obtained as a white solid, for Method A in 71% yield (20 mg) and for Method B in 57% yield (17 mg); mp 35−37 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 99:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (***R***)-**2h** 35.3 min and (***S***)-**2h** 39.6 min, and enantiomeric excess for compound **2h** for Method A was 19% and for Method B was 57%. Optical rotation for (***R***)-**2h** (ee 19%): $[\alpha]_D^{20}$ −17.0 (*c* 0.11, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.8, 1.8 Hz, 1H, ArH), 7.35 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.21 (td, J = 7.6, 1.5 Hz, 1H, ArH), 7.15 (td, J = 7.6, 1.8 Hz, 1H, ArH), 6.00 (ddd, J = 16.9, 10.4, 8.4 Hz, 1H, $CHCH_2$), 5.20−5.16 (m, 1H, CH_2), 5.15 (d, J = 0.9 Hz, 1H, CH_2), 5.06 (d, J = 8.4 Hz, 1H, CHAr), 4.05 (d, J = 0.9 Hz, 1H, OH), 3.87 (s, 3H, CH_3), 3.58 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.7, 136.1, 134.8, 134.2, 130.3, 129.7, 128.5, 127.1, 118.9, 82.3, 54.0, 53.5, 49.0. HRMS (ESI) for $C_{14}H_{15}ClNaO_5$, calculated for [M + Na]$^+$: 321.0500, found: 321.0487.

Dimethyl (*R*)-2-(1-(3-Chlorophenyl)allyl)-2-hydroxymalonate 2i. Compound **2i** was obtained as a white solid, for Method A in 72% yield (21 mg) and for Method B in 97% yield (29 mg); mp 43−45 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (***R***)-**2i** 9.6 min and (***S***)-**2i** 8.5 min, and enantiomeric excess for compound **2i** for Method A was 50% and for Method B was 70%. Optical rotation for (***R***)-**2i** (ee 50%): $[\alpha]_D^{20}$ −28.0 (*c* 0.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.35 (m, 1H, ArH), 7.30−7.24 (m, 1H, ArH), 7.23−7.18 (m, 2H, ArH), 6.16−6.06 (m, 1H, $CHCH_2$), 5.22−5.18 (m, 1H, CH_2), 5.16 (s, 1H, CH_2), 4.30 (d, J = 8.9 Hz, 1H, CHAr), 3.94 (s, 1H, OH), 3.84 (s, 3H, CH_3), 3.64 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.5, 140.2, 135.0, 134.1, 129.63, 129.60, 127.7, 127.6, 119.0, 82.5, 54.2, 53.9, 53.6. HRMS (ESI) for $C_{14}H_{16}ClO_5$, calculated for [M + H]$^+$: 299.0681, found: 299.0670.

Dimethyl (*R*)-2-(1-(4-Chlorophenyl)allyl)-2-hydroxymalonate 2j. Compound **2j** was obtained as a white solid, for Method A in 59% yield (17 mg) and for Method B in 67% yield (20 mg); mp 47−49 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (***R***)-**2j** 16.9 min and (***S***)-**2j** 15.2 min, and enantiomeric excess for compound **2j** for Method A was 50% and for Method B was 58%. Optical rotation for (***R***)-**2j** (ee 50%): $[\alpha]_D^{20}$ −27.2 (*c* 0.09, $CHCl_3$).

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889−2897

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.5 Hz, 2H, ArH), 7.25 (d, J = 8.7 Hz, 2H, ArH), 6.11 (ddd, J = 17.5, 9.8, 8.9 Hz, 1H, C*H*CH_2), 5.20−5.16 (m, 1H, CH_2), 5.16−5.13 (m, 1H, CH_2), 4.31 (d, J = 8.8 Hz, 1H, CHAr), 3.94 (s, 1H, OH), 3.84 (s, 3H, CH_3), 3.63 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.5, 136.7, 135.2, 133.4, 130.8, 128.6, 118.7, 82.5, 53.91, 53.89, 53.6. HRMS (ESI) for $C_{14}H_{15}ClNaO_5$, calculated for $[M + Na]^+$: 321.0500, found: 321.0491.

Dimethyl (*R*)-2-Hydroxy-2-(1-(4-methoxyphenyl)allyl)-malonate 2k. Compound **2k** was obtained as a white solid, for Method A in 62% yield (17 mg) and for Method B in 35% yield (10 mg); mp 74−76 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:EtOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), (*R*)-**2k** 39.0 min and (*S*)-**2k** 21.8 min, and enantiomeric excess for compound **2k** for Method A was 52% and for Method B was 67%. Optical rotation for (*R*)-**2k** (ee 52%): $[\alpha]_D^{20}$ −24.9 (c 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 2H, ArH), 6.81 (d, J = 8.7 Hz, 2H, ArH), 6.15 (ddd, J = 17.1, 10.2, 8.8 Hz, 1H, C*H*CH_2), 5.22−5.11 (m, 2H, CH_2), 4.28 (d, J = 8.8 Hz, 1H, CHAr), 3.90 (s, 1H, OH), 3.83 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 3.62 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.8, 158.9, 135.8, 130.4, 130.1, 118.1, 113.8, 82.8, 55.3, 54.0, 53.7, 53.5. HRMS (ESI) for $C_{15}H_{18}NaO_6$, calculated for $[M + Na]^+$: 317.0996, found: 317.0998.

Dimethyl (*R*)-2-Hydroxy-2-(1-(4-nitrophenyl)allyl)malonate 2l. Compound **2l** was obtained as a yellow solid, for Method A in 56% yield (16 mg) and for Method B in 77% yield (24 mg); mp 99−101 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (*R*)-**2l** 23.8 min and (*S*)-**2l** 19.5 min, and enantiomeric excess for compound **2l** for Method A was 9% and for Method B was 35%. Optical rotation for (*R*)-**2l** (ee 9%): $[\alpha]_D^{20}$ −10.9 (c 0.13, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.6 Hz, 2H, ArH), 7.59 (d, J = 8.7 Hz, 2H, ArH), 6.11 (dt, J = 18.1, 9.2 Hz, 1H, C*H*CH_2), 5.22 (s, 1H, CH_2), 5.19 (d, J = 6.6 Hz, 1H, CH_2), 4.44 (d, J = 8.9 Hz, 1H, CHAr), 4.02 (s, 1H, OH), 3.86 (s, 3H, CH_3), 3.63 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.2, 147.3, 145.9, 134.4, 130.4, 123.5, 119.7, 82.2, 54.11, 54.07, 53.7. HRMS (ESI) for $C_{14}H_{16}NO_7$, calculated for $[M + H]^+$: 310.0921, found: 310.0910.

Dimethyl (*R*)-2-Hydroxy-2-(1-(naphthalen-2-yl)allyl)-malonate 2m. Compound **2m** was obtained as a white solid, for Method A in 80% yield (25 mg) and for Method B in 77% yield (24 mg); mp 89−91 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (*R*)-**2m** 24.9 min and (*S*)-**2m** 14.7 min, and enantiomeric excess for compound **2m** for Method A was 59% and for Method B was 63%. Optical rotation for (*R*)-**2m** (ee 59%): $[\alpha]_D^{20}$ −48.9 (c 0.06, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H, ArH), 7.83−7.74 (m, 3H, ArH), 7.53 (dd, J = 8.5, 1.6 Hz, 1H, ArH), 7.48−7.42 (m, 2H, ArH), 6.28 (ddd, J = 17.1, 10.2, 8.9 Hz, 1H, C*H*CH_2), 5.26−5.17 (m, 2H, CH_2), 4.52 (d, J = 8.8 Hz, 1H, CHAr), 4.00 (s, 1H, OH), 3.87 (s, 3H, CH_3), 3.58 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.0, 169.7, 135.7, 135.6, 133.5, 132.8, 128.3, 128.1, 128.0, 127.7, 127.5, 126.05, 125.97, 118.6, 82.9, 54.8, 53.8, 53.5. HRMS (ESI) for $C_{18}H_{18}NaO_5$, calculated for $[M + Na]^+$: 337.1046, found: 337.1039.

Dimethyl (*S*)-2-Hydroxy-2-(1-(thiophen-2-yl)allyl)malonate 2n. Compound **2n** was obtained as a white solid, for Method A in 84% yield (22 mg) and for Method B in 78% yield (21 mg); mp 54−56 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), (*R*)-**2n** 12.7 min and (*S*)-**2n** 11.7 min, and enantiomeric excess for compound **2n** for Method A was 42% and for Method B was 63%. Optical rotation for (*R*)-**2n** (ee 42%): $[\alpha]_D^{20}$ −35.5 (c 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (ddd, J = 5.1, 1.2, 0.5 Hz, 1H, ArH), 6.99 (ddd, J = 3.5, 1.2, 0.5 Hz, 1H, ArH), 6.93 (dd, J = 5.1, 3.5 Hz, 1H, ArH), 6.09 (ddd, J = 17.0, 10.1, 8.9 Hz, 1H, C*H*CH_2), 5.22 (ddd, J = 17.0, 1.4, 0.9 Hz, 1H, CH_2), 5.17 (ddd, J = 10.1, 1.5, 0.6 Hz, 1H, CH_2), 4.67 (d, J = 8.9 Hz, 1H, CHAr), 3.99 (d, J = 0.8 Hz, 1H, OH), 3.83 (s, 3H, CH_3), 3.70 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 169.5, 139.6, 135.3, 126.6, 126.5, 125.2, 118.7, 82.4, 53.79, 53.75, 50.5. HRMS (ESI) for $C_{12}H_{14}NaO_5S$, calculated for $[M + Na]^+$: 293.0454, found: 293.0446.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02786.

^{1}H and ^{13}C NMR spectra, HPLC data, additional optimization data of Ca-catalyzed reaction, NMR, and HRMS study of Ca complex (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tonis.kanger@ttu.ee

ORCID

Tõnis Kanger: 0000-0001-5339-9682

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Estonian Ministry of Education and Research (grant nos. IUT 19-32, IUT 19-9, and PUT 1468) and the Centre of Excellence in Molecular Cell Engineering (2014-2020.4.01.15-0013) for financial support.

■ REFERENCES

(1) For a recent review, see: (a) Wolfe, J. P. In *Comprehensive Organic Synthesis II, Carbon−Carbon σ-Bond Formation*; Marek, I., Ed.; Elsevier: Amsterdam, 2014; Vol. 3, pp 1038−1072. (b) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, I. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446−7479.

(2) (a) Isobe, M.; Chang, W.-C.; Tsou, P.-K.; Ploysuk, C.; Yu, C.-H. *J. Org. Chem.* **2015**, *80*, 6222−6237. (b) Blackburn, T. J.; Kilner, M. J.; Thomas, E. J. *Tetrahedron* **2015**, *71*, 7293−7309. (c) Hirokawa, Y.; Kitamura, M.; Mizubayashi, M.; Nakatsuka, R.; Kobori, Y.; Kato, C.; Kurata, Y.; Maezaki, N. *Eur. J. Org. Chem.* **2013**, *2013*, 721−727.

(3) (a) Kitamura, M.; Hirokawa, Y.; Maezaki, N. *Chem. - Eur. J.* **2009**, *15*, 9911−9917. (b) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1992**, *57*, 2747−2750. (c) Hirokawa, Y.; Kitamura, M.; Maezaki, M. N. *Tetrahedron: Asymmetry* **2008**, *19*, 1167−1170. (d) Kitamura, M.; Hirokawa, Y.; Yoshioka, Y.; Maezaki, N. *Tetrahedron* **2012**, *68*, 4280−4285. (e) Tomooka, K.; Komine, N.; Nakai, T. *Chirality* **2000**, *12*, 505−509. (f) Kawasaki, T.; Kimachi, T. *Tetrahedron* **1999**, *55*, 6847−6862.

(4) McNally, A.; Evans, B.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2116−2119.

(5) Denmark, S. E.; Cullen, L. R. *J. Org. Chem.* **2015**, *80*, 11818−11848.

(6) Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. *Org. Lett.* **2016**, *18*, 1358−1361.

(7) Kennedy, C. R.; Guidera, J. A.; Jacobsen, E. N. *ACS Cent. Sci.* **2016**, *2*, 416−423.

(8) For the Wittig rearrangement of ylide-type substrates, see: (a) Li, Z.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 396−401. (b) Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 7653−7654.

(9) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364−5365.

(10) Wilkins, L. C.; Melen, R. L. *Coord. Chem. Rev.* **2016**, *324*, 123−139.

(11) Harder, S. *Chem. Rev.* **2010**, *110*, 3852−3876.

(12) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552−5555.

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889−2897

(13) For chiral guanidine-catalyzed reactions, see: Leow, D.; Tan, C.-H. *Chem. - Asian J.* **2009**, *4*, 488−507.
(14) For reviews, see: (a) O'Reilly, S.; Guiry, P. *Synthesis* **2014**, *46*, 722−739. (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119−3154.
(15) Guillemot, G.; Neuburger, M.; Pfaltz, A. *Chem. - Eur. J.* **2007**, *13*, 8960−8970.
(16) (a) Wolf, C.; Moskowitz, M. *J. Org. Chem.* **2011**, *76*, 6372−6376. (b) Xu, H.; Wolf, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 12249−12252. (c) Wolf, C.; Xu, H. *Chem. Commun.* **2011**, *47*, 3339−3350.
(17) Lippur, K.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. *J. Org. Chem.* **2015**, *80*, 6336−6341.
(18) (a) Bandar, J. S.; Sauer, G. S.; Wulff, W. D.; Lambert, T. H.; Vetticat, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 10700−10707. (b) Bandar, J. S.; Barthelme, A.; Mazori, A. Y.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537−1547.
(19) Lauridsen, V. H.; Ibsen, L.; Blom, J.; Jørgensen, K. A. *Chem. - Eur. J.* **2016**, *22*, 3259−3263.
(20) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799−11802.
(21) Tsubogo, T.; Shimizu, S.; Kobayashi, S. *Chem. - Asian J.* **2013**, *8*, 872−876.
(22) Yamamura, M.; Miyake, J.; Imamura, Y.; Nabeshima, T. *Chem. Commun.* **2011**, *47*, 6801−6803.
(23) Lee, J. W.; Ryu, T. H.; Oh, S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224−7226.
(24) Bandar, J. S.; Barthelme, A.; Mazori, A. Y.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537−1547.
(25) Ye, W.; Leow, D.; Goh, S. L. M.; Tan, C.-T.; Chian, C.-H.; Tan, C.-H. *Tetrahedron Lett.* **2006**, *47*, 1007−1010.
(26) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552−5555.
(27) Jönsson, C.; Lundgren, S.; Haswell, S. J.; Moberg, C. *Tetrahedron* **2004**, *60*, 10515−10520.
(28) Meng, J.-c.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett.* **2005**, *46*, 4543−4546.
(29) Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron: Asymmetry* **2002**, *13*, 1651−1654.
(30) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500−508.

DOI: 10.1021/acs.joc.6b02786
J. Org. Chem. 2017, 82, 2889−2897

Acknowledgments

This work was conducted at the Department of Chemistry and Biotechnology of Tallinn University of Technology, and was financially supported by The Estonian Ministry of Education and Research (grant nos. IUT 19-32, IUT 19-9, B25, and PUT 1468), the Centre of Excellence in Molecular Cell Engineering (2014-2020.4.01.15-0013), The EU European Regional Development Fund (3.2.0101.08-0017), the Academy of Finland (KR grant nos. 263256 and 265328) and ASTRA "TUT Institutional Development Programme for 2016-2022" Graduate School of Functional Materials and Technologies (2014-2020.4.01.16-0032).

First of all, I would like to thank my supervisor, Professor Tõnis Kanger, for guiding me throughout the years of my PhD study, always allowing me to try out my ideas and trusting me to make decisions. I also thank Dr. Kadri Kriis for reviewing my thesis and Dr. Kristin Lippur and Mariliis Kimm for reading the manuscript and providing many useful remarks. I am grateful to Dr. Artur Noole, who introduced me to the world of organic synthesis and "infected" me with a passion for science. I thank my former and present co-workers, especially my lab-mates Artur, Sergei, Kristin and Kärt, for creating a pleasant work atmosphere and helping me out whenever I needed it. Also, I would like to thank the "lunch team" for sharing the best moments of the work day and for fruitful (sometimes science-related) discussions during it.

I would like to thank Professor Paolo Melchiorre for giving me the opportunity to join his group and for introducing me to photochemistry. Many thanks to the Melchiorre group, especially Danile, Bertrand, Luchino, Giacomo and Ana, for taking me into the "family"and making my stay in Tarragona very memorable: it has changed me both as a scientist and as a person.

My special thanks go to my bachelor's/master's student and present colleague Mariliis Kimm, who assisted me throughout the entire PhD period; without her help, I would have not achieved what I have.

Last but not least, I am deeply grateful to my mom, dad and sister for believing in me and supporting me no matter what.

Abstract

There is a continuous need for new efficient methods that can be applied for the asymmetric synthesis of bioactive compounds. H-bond mediated organocatalysis has demonstrated its great potential in the field of asymmetric synthesis. Spirocyclopropanation and Wittig [2,3]-rearrangement provide products with high levels of complexity which can be useful building blocks for further transformations.

The Michael-initiated spirocyclopropanation of chlorooxindoles with symmetric unsaturated 1,4-dicarbonyl compounds catalyzed by bifunctional thiourea was studied. The Boc-protection of chlorooxindoles was necessary in order to activate the substrate. α,β-identically substituted spirocyclopropyl oxindoles were obtained in high yields (up to 81%), and high diastereo- and enantioselectivities (d.r. up to 20:1 and *ee* up to 87%). In reactions with non-symmetric 1,4-dicarbonyl compounds, products with two tertiary and one quaternary centers formed as single diastereisomers.

After several attempts, we developed a method for the synthesis of substrates for the Wittig [2,3]-rearrangement, which is based on the rhodium-catalyzed cinnamyl alcohol insertion to diazo compounds. Although the yields of the reaction were moderate, the described approach is the only method available to obtain the desired substrates.

A bifunctional squaramide catalyzed Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindoles led to the formation of 3-substituted 3-hydroxyoxindoles in very high yields (up to 95% of total yield). Despite the fact that the diastereoselectivities were rather low, the diastereoisomers were chromatographically separable and enantioselectivities were excellent for both isomers (up to 94 and 97%).

A highly basic cyclopropenimine derivative was applied as the catalyst for the asymmetric Wittig [2,3]-rearrangement of 2-cinnamyloxymalonates, as the basicity of *Cinchona* alkaloid-derived catalysts was not sufficient for this transformation. [2,3]-rearranged products were isolated in high yields (up to 87%) and moderate enantiomeric purities (*ee* up to 59%). The catalyst design study revealed that the bifunctionality of the catalyst played a crucial role in the stabilization of the chiral transition state.

An unexpected compound was obtained in the reaction with *para*-nitro cinnamyloxyoxindole. We have proved that the obtained chiral compound was formed as a product of the enantioselective [1,2]-type rearrangement catalyzed by the bifunctional squaramide. This type of transformation has not previously been reported.

Lühikokkuvõte

Uute efektiivsete bioaktiivsete ühendite asümmeetrilise sünteesi meetodite järele on pidev nõudlus. H-sideme katalüüs omab asümmeetrilises katalüüsis suurt potentsiaali. Spirotsüklopropaneerimine ja Wittigi [2,3]-ümberasetusreaktsioon võimaldavad sünteesida keerulise struktuuriga ühendeid, mida saab kasutada lähteainetena edasisteks muundamisteks.

Uuriti bifunktsionaalse tiouurea poolt katalüüsitud Michaeli liitumise kaudu initsieeritud klorooksindoolide tsüklopropaneerimist sümmeetriliste küllastumata 1,4-dikarbonüülühenditega. Klorooksindoolide Boc-kaitserühm oli vajalik substraadi aktiveerimiseks. α,β-identselt asendatud spirotsüklopropüüloksindoolid saadi kõrge saagisega (kuni 81%), diastereo- ja enantioselektiivsusega (d.r. kuni 20:1 ja *ee* kuni 87%). Reaktsioonil mittesümmeetriliste 1,4-dikarbonüülühenditega moodustusid kahe tertsiaarse ja ühe kvaternaarse tsentriga produktid ühe diastereoisomeerina.

Pärast mitmeid lähenemisi arendasime välja meetodi Wittigi [2,3]-ümberasetusreaktsiooni substraatide sünteesiks, mis põhineb roodiumkatalüütilisel kaneelalkoholi sisestusreaktsioonil diasoühendile. Kuigi reaktsiooni saagised on keskpärased, on kirjeldatud lähenemine ainus võimalik meetod soovitud substraatide saamiseks.

Bifunktsionaalse skvaaramiidi poolt katalüüsitud 3-tsinnamüüloksüoksindoolide Wittigi [2,3]-ümberasetusreaktsiooni tulemusena moodustusid 3-asendatud 3-hüdroksüoksindoolid väga kõrge saagisega (summaarne saagis kuni 95%). Vaatamata madalatele diastereoselektiivsustele olid diastereoisomeerid kromatograafiliselt lahutatavad ja mõlema isomeeri enantiomeersed puhtused olid väga kõrged (*ee* kuni 94 ja 97%).

2-tsinnamüüloksümalonaatide asümmeetrilisel Wittigi [2,3]-ümberasetusreaktsioonil kasutati katalüsaatorina tugevalt aluselist tsüklopropeenimiini derivaati, kuna *Cinchona* alkaloididel põhinevad katalüsaatorid ei ole selle reaktsiooni katalüüsimiseks piisavalt aluselised. [2,3]-ümberasetusproduktid eraldati kõrge saagise (kuni 87%) ja keskpärase enantiomeerse puhtusega (*ee* kuni 59%). Katalüsaatori disainimine näitas, et katalüsaatori bifunktsionaalsus mängib olulist rolli kiraalse vaheoleku stabiliseerimisel.

Reaktsioonil *para*-nitrotsinnamüüloksüoksindooliga saadi ootamatu produkt. Tõestati, et saadud ühend moodustus enantioselektiivse [1,2]-tüüpi ümberasetusreaktsiooni, mida katalüüsis bifunktsionaalne skvaaramiid, tulemusena. Sellist tüüpi muundumist ei olnud varem kirjeldatud.

Elulookirjeldus

1. Isikuandmed

Ees- ja perekonnanimi:	Maksim Ošeka
Sünniaeg ja -koht:	10.07.1988, Tallinn
Kodakondsus:	Eesti

2. Kontaktandmed

Aadress:	Keemia ja biotehnoloogia instituut, TTÜ, Akadeemia tee 15, Tallinn 12618
Telefon:	+372 55592953
E-post:	maksim.osheka@gmail.com

3. Hariduskäik

Tallinna Tehnikaülikool	2013 – 2017 PhD
Tallinna Tehnikaülikool	2011 – 2013 *MSc*, *cum laude*
Tallinna Tehnikaülikool	2007 – 2011 *BSc*
Haabersti Vene Gümnaasium	1995 – 2007 keskharidus

4. Teenistuskäik

alates 2009	TTÜ, Keemia ja biotehnoloogia instituut (Prof. Tõnis Kangeri uurimisrühm)
10.2016 – 05.2017	The Institute of Chemical Research of Catalonia (ICIQ), Hispaania; külalisdoktorant (DoRa Pluss 1.2) (Prof. Paolo Melchiorre uurimisrühm)
01.2012 – 06.2012	Oslo University, Norra; külalismagistrant (Erasmus) (Prof. Lise-Lotte Gunderseni uurimisrühm)

5. Juhendatud lõputööd

2015 – 2017	Mariliis Kimmi magistritöö, kaitstud TTÜ-s
2013 – 2015	Mariliis Kimmi bakalaureusetöö, kaitstud TTÜ-s
2015 – 2017	Mari-Liis Ludvigi bakalaureusetöö, kaitstud TTÜ-s

6. Teadustöö

Uute asümmeetriliste organokatalüütiliste meetodite väljatöötamine ja rakendamine, reaktsioonimehhanismide uurimine.

7. Tunnustused

- TTÜ Arengufondi Cambrex Tallinn stipendium magistrantidele **2012**
- Erasmuse stipendium vahetusõpinguteks **2012**

Curriculum vitae

1. Personal data

Name:	Maksim Ošeka
Date and place of birth:	10.07.1988, Tallinn
Citizenship:	Estonian

2. Contact data

Address:	Department of Chemistry and Biotechnology, TUT, Akadeemia tee 15, Tallinn 12618
Phone:	+372 55592953
E-mail:	maksim.osheka@gmail.com

3. Education

Tallinn University of Technology	2013 – 2017 PhD
Tallinn University of Technology	2011 – 2013 *MSc*, *cum laude*
Tallinn University of Technology	2007 – 2011 *BSc*
Haabersti High School	1995 – 2007 Secondary education

4. Professional employment

From 2009	TUT, Department of Chemistry and Biotechnology (Prof. Tõnis Kanger research group)
10.2016 – 05.2017	The Institute of Chemical Research of Catalonia (ICIQ), Spain; visiting PhD (DoRa Pluss 1.2) (Prof. Paolo Melchiorre research group)
01.2012 – 06.2012	Oslo University, Norway; visiting master's student (Erasmus) (Prof. Lise-Lotte Gundersen research group)

5. Supervised theses

2015 – 2017	Mariliis Kimm *MSc* thesis, defended in TUT
2013 – 2015	Mariliis Kimm *BSc* thesis, defended in TUT
2015 – 2017	Mari-Liis Ludvig *BSc* thesis, defended in TUT

6. Scientific work

Development and application of new asymmetric organocatalytic methods, and research on reaction mechanisms.

7. Awards

- TUT Development Fund Scholarship of Cambrex Tallinn for master's students **2012**
- Erasmus scholarship for exchange studies **2012**

8. Original publications

1) Noole, A.; Ošeka, M.; Pehk, T.; Öeren, M.; Järving, I.; Elsegood, M. R. J.; Malkov, A.; Lopp, M.; Kanger, T. 3-Chlorooxindoles: Versatile Starting Materials for Asymmetric Organocatalytic Synthesis of Spirooxindoles. *Adv. Synth. Catal.* **2013**, *355*, 829-835.

2) Ošeka, M.; Noole, A.; Žari, S.; Öeren, M.; Järving, I.; Lopp, M.; Kanger, T. Asymmetric Diastereoselective Synthesis of Spirocyclopropane Derivatives of Oxindole. *European Journal of Organic Chemistry* **2014**, 3599-3606.

3) Gulbrandsen, H. S.; Hennum, M.; Osheka, M.; Read, M. L.; Gundersen, L.-L. Synthesis of Phenanthridine Derivatives Functionalized in the C-Ring by Means of IMDAF Reactions under Microwave or Conventional Heating Conditions. *European Journal of Organic Chemistry* **2014**, 8182-8190.

4) Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement of Oxindoles. *Organic Letters* **2016**, *18*, 1358-1361.

5) Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. Two Catalytic Methods of an Asymmetric Wittig [2,3]-Rearrangement. *The Journal of Organic Chemistry* **2017**, *82*, 2889-2897.

6) Schweitzer-Chaput, B.; Ošeka, M.; Melchiorre, P. Dithiocarbamate Anion Catalysis: Visible Light Mediated Catalytic Activation of Alkyl Electrophiles. *Manuscript in preparation*

7) Kimm, M.; Ošeka, M.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement as formal α-alkylation of ketones. *Manuscript in preparation*

DISSERTATIONS DEFENDED AT TALLINN UNIVERSITY OF TECHNOLOGY ON *NATURAL AND EXACT SCIENCES*

1. **Olav Kongas**. Nonlinear Dynamics in Modeling Cardiac Arrhytmias. 1998.
2. **Kalju Vanatalu**. Optimization of Processes of Microbial Biosynthesis of Isotopically Labeled Biomolecules and Their Complexes. 1999.
3. **Ahto Buldas**. An Algebraic Approach to the Structure of Graphs. 1999.
4. **Monika Drews**. A Metabolic Study of Insect Cells in Batch and Continuous Culture: Application of Chemostat and Turbidostat to the Production of Recombinant Proteins. 1999.
5. **Eola Valdre**. Endothelial-Specific Regulation of Vessel Formation: Role of Receptor Tyrosine Kinases. 2000.
6. **Kalju Lott**. Doping and Defect Thermodynamic Equilibrium in ZnS. 2000.
7. **Reet Koljak**. Novel Fatty Acid Dioxygenases from the Corals *Plexaura homomalla* and *Gersemia fruticosa.* 2001.
8. **Anne Paju**. Asymmetric oxidation of Prochiral and Racemic Ketones by Using Sharpless Catalyst. 2001.
9. **Marko Vendelin**. Cardiac Mechanoenergetics *in silico*. 2001.
10. **Pearu Peterson**. Multi-Soliton Interactions and the Inverse Problem of Wave Crest. 2001.
11. **Anne Menert**. Microcalorimetry of Anaerobic Digestion. 2001.
12. **Toomas Tiivel**. The Role of the Mitochondrial Outer Membrane in *in vivo* Regulation of Respiration in Normal Heart and Skeletal Muscle Cell. 2002.
13. **Olle Hints**. Ordovician Scolecodonts of Estonia and Neighbouring Areas: Taxonomy, Distribution, Palaeoecology, and Application. 2002.
14. **Jaak Nõlvak**. Chitinozoan Biostratigrapy in the Ordovician of Baltoscandia. 2002.
15. **Liivi Kluge**. On Algebraic Structure of Pre-Operad. 2002.
16. **Jaanus Lass**. Biosignal Interpretation: Study of Cardiac Arrhytmias and Electromagnetic Field Effects on Human Nervous System. 2002.
17. **Janek Peterson**. Synthesis, Structural Characterization and Modification of PAMAM Dendrimers. 2002.
18. **Merike Vaher**. Room Temperature Ionic Liquids as Background Electrolyte Additives in Capillary Electrophoresis. 2002.
19. **Valdek Mikli**. Electron Microscopy and Image Analysis Study of Powdered Hardmetal Materials and Optoelectronic Thin Films. 2003.
20. **Mart Viljus**. The Microstructure and Properties of Fine-Grained Cermets. 2003.
21. **Signe Kask**. Identification and Characterization of Dairy-Related *Lactobacillus.* 2003.
22. **Tiiu-Mai Laht**. Influence of Microstructure of the Curd on Enzymatic and Microbiological Processes in Swiss-Type Cheese. 2003.
23. **Anne Kuusksalu**. 2–5A Synthetase in the Marine Sponge *Geodia cydonium*. 2003.
24. **Sergei Bereznev**. Solar Cells Based on Polycristalline Copper-Indium Chalcogenides and Conductive Polymers. 2003.

25. **Kadri Kriis**. Asymmetric Synthesis of C_2-Symmetric Bimorpholines and Their Application as Chiral Ligands in the Transfer Hydrogenation of Aromatic Ketones. 2004.
26. **Jekaterina Reut**. Polypyrrole Coatings on Conducting and Insulating Substracts. 2004.
27. **Sven Nõmm**. Realization and Identification of Discrete-Time Nonlinear Systems. 2004.
28. **Olga Kijatkina**. Deposition of Copper Indium Disulphide Films by Chemical Spray Pyrolysis. 2004.
29. **Gert Tamberg**. On Sampling Operators Defined by Rogosinski, Hann and Blackman Windows. 2004.
30. **Monika Übner**. Interaction of Humic Substances with Metal Cations. 2004.
31. **Kaarel Adamberg**. Growth Characteristics of Non-Starter Lactic Acid Bacteria from Cheese. 2004.
32. **Imre Vallikivi**. Lipase-Catalysed Reactions of Prostaglandins. 2004.
33. **Merike Peld**. Substituted Apatites as Sorbents for Heavy Metals. 2005.
34. **Vitali Syritski**. Study of Synthesis and Redox Switching of Polypyrrole and Poly(3,4-ethylenedioxythiophene) by Using *in-situ* Techniques. 2004.
35. **Lee Põllumaa**. Evaluation of Ecotoxicological Effects Related to Oil Shale Industry. 2004.
36. **Riina Aav**. Synthesis of 9,11-Secosterols Intermediates. 2005.
37. **Andres Braunbrück**. Wave Interaction in Weakly Inhomogeneous Materials. 2005.
38. **Robert Kitt**. Generalised Scale-Invariance in Financial Time Series. 2005.
39. **Juss Pavelson**. Mesoscale Physical Processes and the Related Impact on the Summer Nutrient Fields and Phytoplankton Blooms in the Western Gulf of Finland. 2005.
40. **Olari Ilison**. Solitons and Solitary Waves in Media with Higher Order Dispersive and Nonlinear Effects. 2005.
41. **Maksim Säkki**. Intermittency and Long-Range Structurization of Heart Rate. 2005.
42. **Enli Kiipli**. Modelling Seawater Chemistry of the East Baltic Basin in the Late Ordovician–Early Silurian. 2005.
43. **Igor Golovtsov**. Modification of Conductive Properties and Processability of Polyparaphenylene, Polypyrrole and polyaniline. 2005.
44. **Katrin Laos**. Interaction Between Furcellaran and the Globular Proteins (Bovine Serum Albumin β-Lactoglobulin). 2005.
45. **Arvo Mere**. Structural and Electrical Properties of Spray Deposited Copper Indium Disulphide Films for Solar Cells. 2006.
46. **Sille Ehala**. Development and Application of Various On- and Off-Line Analytical Methods for the Analysis of Bioactive Compounds. 2006.
47. **Maria Kulp**. Capillary Electrophoretic Monitoring of Biochemical Reaction Kinetics. 2006.
48. **Anu Aaspõllu.** Proteinases from *Vipera lebetina* Snake Venom Affecting Hemostasis. 2006.
49. **Lyudmila Chekulayeva**. Photosensitized Inactivation of Tumor Cells by Porphyrins and Chlorins. 2006.

50. **Merle Uudsemaa**. Quantum-Chemical Modeling of Solvated First Row Transition Metal Ions. 2006.
51. **Tagli Pitsi**. Nutrition Situation of Pre-School Children in Estonia from 1995 to 2004. 2006.
52. **Angela Ivask**. Luminescent Recombinant Sensor Bacteria for the Analysis of Bioavailable Heavy Metals. 2006.
53. **Tiina Lõugas**. Study on Physico-Chemical Properties and Some Bioactive Compounds of Sea Buckthorn (*Hippophae rhamnoides* L.). 2006.
54. **Kaja Kasemets**. Effect of Changing Environmental Conditions on the Fermentative Growth of *Saccharomyces cerevisae* S288C: Auxo-accelerostat Study. 2006.
55. **Ildar Nisamedtinov**. Application of ^{13}C and Fluorescence Labeling in Metabolic Studies of *Saccharomyces* spp. 2006.
56. **Alar Leibak**. On Additive Generalisation of Voronoï's Theory of Perfect Forms over Algebraic Number Fields. 2006.
57. **Andri Jagomägi**. Photoluminescence of Chalcopyrite Tellurides. 2006.
58. **Tõnu Martma**. Application of Carbon Isotopes to the Study of the Ordovician and Silurian of the Baltic. 2006.
59. **Marit Kauk**. Chemical Composition of $CuInSe_2$ Monograin Powders for Solar Cell Application. 2006.
60. **Julia Kois**. Electrochemical Deposition of $CuInSe_2$ Thin Films for Photovoltaic Applications. 2006.
61. **Ilona Oja Açik**. Sol-Gel Deposition of Titanium Dioxide Films. 2007.
62. **Tiia Anmann**. Integrated and Organized Cellular Bioenergetic Systems in Heart and Brain. 2007.
63. **Katrin Trummal**. Purification, Characterization and Specificity Studies of Metalloproteinases from *Vipera lebetina* Snake Venom. 2007.
64. **Gennadi Lessin**. Biochemical Definition of Coastal Zone Using Numerical Modeling and Measurement Data. 2007.
65. **Enno Pais**. Inverse problems to determine non-homogeneous degenerate memory kernels in heat flow. 2007.
66. **Maria Borissova**. Capillary Electrophoresis on Alkylimidazolium Salts. 2007.
67. **Karin Valmsen**. Prostaglandin Synthesis in the Coral *Plexaura homomalla*: Control of Prostaglandin Stereochemistry at Carbon 15 by Cyclooxygenases. 2007.
68. **Kristjan Piirimäe**. Long-Term Changes of Nutrient Fluxes in the Drainage Basin of the Gulf of Finland – Application of the PolFlow Model. 2007.
69. **Tatjana Dedova**. Chemical Spray Pyrolysis Deposition of Zinc Sulfide Thin Films and Zinc Oxide Nanostructured Layers. 2007.
70. **Katrin Tomson**. Production of Labelled Recombinant Proteins in Fed-Batch Systems in *Escherichia coli*. 2007.
71. **Cecilia Sarmiento**. Suppressors of RNA Silencing in Plants. 2008.
72. **Vilja Mardla**. Inhibition of Platelet Aggregation with Combination of Antiplatelet Agents. 2008.
73. **Maie Bachmann**. Effect of Modulated Microwave Radiation on Human Resting Electroencephalographic Signal. 2008.

74. **Dan Hüvonen**. Terahertz Spectroscopy of Low-Dimensional Spin Systems. 2008.
75. **Ly Villo**. Stereoselective Chemoenzymatic Synthesis of Deoxy Sugar Esters Involving *Candida antarctica* Lipase B. 2008.
76. **Johan Anton**. Technology of Integrated Photoelasticity for Residual Stress Measurement in Glass Articles of Axisymmetric Shape. 2008.
77. **Olga Volobujeva**. SEM Study of Selenization of Different Thin Metallic Films. 2008.
78. **Artur Jõgi**. Synthesis of 4'-Substituted 2,3'-dideoxynucleoside Analogues. 2008.
79. **Mario Kadastik**. Doubly Charged Higgs Boson Decays and Implications on Neutrino Physics. 2008.
80. **Fernando Pérez-Caballero**. Carbon Aerogels from 5-Methylresorcinol-Formaldehyde Gels. 2008.
81. **Sirje Vaask**. The Comparability, Reproducibility and Validity of Estonian Food Consumption Surveys. 2008.
82. **Anna Menaker**. Electrosynthesized Conducting Polymers, Polypyrrole and Poly(3,4-ethylenedioxythiophene), for Molecular Imprinting. 2009.
83. **Lauri Ilison**. Solitons and Solitary Waves in Hierarchical Korteweg-de Vries Type Systems. 2009.
84. **Kaia Ernits**. Study of In_2S_3 and ZnS Thin Films Deposited by Ultrasonic Spray Pyrolysis and Chemical Deposition. 2009.
85. **Veljo Sinivee**. Portable Spectrometer for Ionizing Radiation "Gammamapper". 2009.
86. **Jüri Virkepu**. On Lagrange Formalism for Lie Theory and Operadic Harmonic Oscillator in Low Dimensions. 2009.
87. **Marko Piirsoo**. Deciphering Molecular Basis of Schwann Cell Development. 2009.
88. **Kati Helmja**. Determination of Phenolic Compounds and Their Antioxidative Capability in Plant Extracts. 2010.
89. **Merike Sõmera**. Sobemoviruses: Genomic Organization, Potential for Recombination and Necessity of P1 in Systemic Infection. 2010.
90. **Kristjan Laes**. Preparation and Impedance Spectroscopy of Hybrid Structures Based on $CuIn_3Se_5$ Photoabsorber. 2010.
91. **Kristin Lippur**. Asymmetric Synthesis of 2,2'-Bimorpholine and its 5,5'-Substituted Derivatives. 2010.
92. **Merike Luman**. Dialysis Dose and Nutrition Assessment by an Optical Method. 2010.
93. **Mihhail Berezovski**. Numerical Simulation of Wave Propagation in Heterogeneous and Microstructured Materials. 2010.
94. **Tamara Aid-Pavlidis**. Structure and Regulation of BDNF Gene. 2010.
95. **Olga Bragina**. The Role of Sonic Hedgehog Pathway in Neuro- and Tumorigenesis. 2010.
96. **Merle Randrüüt**. Wave Propagation in Microstructured Solids: Solitary and Periodic Waves. 2010.
97. **Marju Laars**. Asymmetric Organocatalytic Michael and Aldol Reactions Mediated by Cyclic Amines. 2010.

98. **Maarja Grossberg**. Optical Properties of Multinary Semiconductor Compounds for Photovoltaic Applications. 2010.
99. **Alla Maloverjan**. Vertebrate Homologues of Drosophila Fused Kinase and Their Role in Sonic Hedgehog Signalling Pathway. 2010.
100. **Priit Pruunsild**. Neuronal Activity-Dependent Transcription Factors and Regulation of Human *BDNF* Gene. 2010.
101. **Tatjana Knjazeva**. New Approaches in Capillary Electrophoresis for Separation and Study of Proteins. 2011.
102. **Atanas Katerski**. Chemical Composition of Sprayed Copper Indium Disulfide Films for Nanostructured Solar Cells. 2011.
103. **Kristi Timmo.** Formation of Properties of $CuInSe_2$ and $Cu_2ZnSn(S,Se)_4$ Monograin Powders Synthesized in Molten KI. 2011.
104. **Kert Tamm**. Wave Propagation and Interaction in Mindlin-Type Microstructured Solids: Numerical Simulation. 2011.
105. **Adrian Popp**. Ordovician Proetid Trilobites in Baltoscandia and Germany. 2011.
106. **Ove Pärn**. Sea Ice Deformation Events in the Gulf of Finland and This Impact on Shipping. 2011.
107. **Germo Väli**. Numerical Experiments on Matter Transport in the Baltic Sea. 2011.
108. **Andrus Seiman**. Point-of-Care Analyser Based on Capillary Electrophoresis. 2011.
109. **Olga Katargina**. Tick-Borne Pathogens Circulating in Estonia (Tick-Borne Encephalitis Virus, *Anaplasma phagocytophilum*, *Babesia* Species): Their Prevalence and Genetic Characterization. 2011.
110. **Ingrid Sumeri**. The Study of Probiotic Bacteria in Human Gastrointestinal Tract Simulator. 2011.
111. **Kairit Zovo**. Functional Characterization of Cellular Copper Proteome. 2011.
112. **Natalja Makarytsheva**. Analysis of Organic Species in Sediments and Soil by High Performance Separation Methods. 2011.
113. **Monika Mortimer**. Evaluation of the Biological Effects of Engineered Nanoparticles on Unicellular Pro- and Eukaryotic Organisms. 2011.
114. **Kersti Tepp**. Molecular System Bioenergetics of Cardiac Cells: Quantitative Analysis of Structure-Function Relationship. 2011.
115. **Anna-Liisa Peikolainen**. Organic Aerogels Based on 5-Methylresorcinol. 2011.
116. **Leeli Amon**. Palaeoecological Reconstruction of Late-Glacial Vegetation Dynamics in Eastern Baltic Area: A View Based on Plant Macrofossil Analysis. 2011.
117. **Tanel Peets**. Dispersion Analysis of Wave Motion in Microstructured Solids. 2011.
118. **Liina Kaupmees**. Selenization of Molybdenum as Contact Material in Solar Cells. 2011.
119. **Allan Olspert**. Properties of VPg and Coat Protein of Sobemoviruses. 2011.
120. **Kadri Koppel**. Food Category Appraisal Using Sensory Methods. 2011.

121. **Jelena Gorbatšova**. Development of Methods for CE Analysis of Plant Phenolics and Vitamins. 2011.
122. **Karin Viipsi**. Impact of EDTA and Humic Substances on the Removal of Cd and Zn from Aqueous Solutions by Apatite. 2012.
123. **David Schryer**. Metabolic Flux Analysis of Compartmentalized Systems Using Dynamic Isotopologue Modeling. 2012.
124. **Ardo Illaste**. Analysis of Molecular Movements in Cardiac Myocytes. 2012.
125. **Indrek Reile**. 3-Alkylcyclopentane-1,2-Diones in Asymmetric Oxidation and Alkylation Reactions. 2012.
126. **Tatjana Tamberg**. Some Classes of Finite 2-Groups and Their Endomorphism Semigroups. 2012.
127. **Taavi Liblik**. Variability of Thermohaline Structure in the Gulf of Finland in Summer. 2012.
128. **Priidik Lagemaa**. Operational Forecasting in Estonian Marine Waters. 2012.
129. **Andrei Errapart**. Photoelastic Tomography in Linear and Non-linear Approximation. 2012.
130. **Külliki Krabbi**. Biochemical Diagnosis of Classical Galactosemia and Mucopolysaccharidoses in Estonia. 2012.
131. **Kristel Kaseleht**. Identification of Aroma Compounds in Food using SPME-GC/MS and GC-Olfactometry. 2012.
132. **Kristel Kodar**. Immunoglobulin G Glycosylation Profiling in Patients with Gastric Cancer. 2012.
133. **Kai Rosin**. Solar Radiation and Wind as Agents of the Formation of the Radiation Regime in Water Bodies. 2012.
134. **Ann Tiiman**. Interactions of Alzheimer's Amyloid-Beta Peptides with Zn(II) and Cu(II) Ions. 2012.
135. **Olga Gavrilova**. Application and Elaboration of Accounting Approaches for Sustainable Development. 2012.
136. **Olesja Bondarenko**. Development of Bacterial Biosensors and Human Stem Cell-Based *In Vitro* Assays for the Toxicological Profiling of Synthetic Nanoparticles. 2012.
137. **Katri Muska**. Study of Composition and Thermal Treatments of Quaternary Compounds for Monograin Layer Solar Cells. 2012.
138. **Ranno Nahku**. Validation of Critical Factors for the Quantitative Characterization of Bacterial Physiology in Accelerostat Cultures. 2012.
139. **Petri-Jaan Lahtvee**. Quantitative Omics-level Analysis of Growth Rate Dependent Energy Metabolism in *Lactococcus lactis*. 2012.
140. **Kerti Orumets**. Molecular Mechanisms Controlling Intracellular Glutathione Levels in Baker's Yeast *Saccharomyces cerevisiae* and its Random Mutagenized Glutathione Over-Accumulating Isolate. 2012.
141. **Loreida Timberg**. Spice-Cured Sprats Ripening, Sensory Parameters Development, and Quality Indicators. 2012.
142. **Anna Mihhalevski**. Rye Sourdough Fermentation and Bread Stability. 2012.
143. **Liisa Arike**. Quantitative Proteomics of *Escherichia coli*: From Relative to Absolute Scale. 2012.

144. **Kairi Otto**. Deposition of In_2S_3 Thin Films by Chemical Spray Pyrolysis. 2012.
145. **Mari Sepp**. Functions of the Basic Helix-Loop-Helix Transcription Factor TCF4 in Health and Disease. 2012.
146. **Anna Suhhova**. Detection of the Effect of Weak Stressors on Human Resting Electroencephalographic Signal. 2012.
147. **Aram Kazarjan**. Development and Production of Extruded Food and Feed Products Containing Probiotic Microorganisms. 2012.
148. **Rivo Uiboupin**. Application of Remote Sensing Methods for the Investigation of Spatio-Temporal Variability of Sea Surface Temperature and Chlorophyll Fields in the Gulf of Finland. 2013.
149. **Tiina Kriščiunaite**. A Study of Milk Coagulability. 2013.
150. **Tuuli Levandi**. Comparative Study of Cereal Varieties by Analytical Separation Methods and Chemometrics. 2013.
151. **Natalja Kabanova**. Development of a Microcalorimetric Method for the Study of Fermentation Processes. 2013.
152. **Himani Khanduri**. Magnetic Properties of Functional Oxides. 2013.
153. **Julia Smirnova**. Investigation of Properties and Reaction Mechanisms of Redox-Active Proteins by ESI MS. 2013.
154. **Mervi Sepp**. Estimation of Diffusion Restrictions in Cardiomyocytes Using Kinetic Measurements. 2013.
155. **Kersti Jääger**. Differentiation and Heterogeneity of Mesenchymal Stem Cells. 2013.
156. **Victor Alari**. Multi-Scale Wind Wave Modeling in the Baltic Sea. 2013.
157. **Taavi Päll**. Studies of CD44 Hyaluronan Binding Domain as Novel Angiogenesis Inhibitor. 2013.
158. **Allan Niidu**. Synthesis of Cyclopentane and Tetrahydrofuran Derivatives. 2013.
159. **Julia Geller**. Detection and Genetic Characterization of *Borrelia* Species Circulating in Tick Population in Estonia. 2013.
160. **Irina Stulova**. The Effects of Milk Composition and Treatment on the Growth of Lactic Acid Bacteria. 2013.
161. **Jana Holmar**. Optical Method for Uric Acid Removal Assessment During Dialysis. 2013.
162. **Kerti Ausmees**. Synthesis of Heterobicyclo[3.2.0]heptane Derivatives *via* Multicomponent Cascade Reaction. 2013.
163. **Minna Varikmaa**. Structural and Functional Studies of Mitochondrial Respiration Regulation in Muscle Cells. 2013.
164. **Indrek Koppel**. Transcriptional Mechanisms of BDNF Gene Regulation. 2014.
165. **Kristjan Pilt**. Optical Pulse Wave Signal Analysis for Determination of Early Arterial Ageing in Diabetic Patients. 2014.
166. **Andres Anier**. Estimation of the Complexity of the Electroencephalogram for Brain Monitoring in Intensive Care. 2014.
167. **Toivo Kallaste**. Pyroclastic Sanidine in the Lower Palaeozoic Bentonites – A Tool for Regional Geological Correlations. 2014.

168. **Erki Kärber**. Properties of ZnO-nanorod/In_2S_3/$CuInS_2$ Solar Cell and the Constituent Layers Deposited by Chemical Spray Method. 2014.
169. **Julia Lehner**. Formation of Cu_2ZnSnS_4 and $Cu_2ZnSnSe_4$ by Chalcogenisation of Electrochemically Deposited Precursor Layers. 2014.
170. **Peep Pitk**. Protein- and Lipid-rich Solid Slaughterhouse Waste Anaerobic Co-digestion: Resource Analysis and Process Optimization. 2014.
171. **Kaspar Valgepea**. Absolute Quantitative Multi-omics Characterization of Specific Growth Rate-dependent Metabolism of *Escherichia coli*. 2014.
172. **Artur Noole**. Asymmetric Organocatalytic Synthesis of 3,3'-Disubstituted Oxindoles. 2014.
173. **Robert Tsanev**. Identification and Structure-Functional Characterisation of the Gene Transcriptional Repressor Domain of Human Gli Proteins. 2014.
174. **Dmitri Kartofelev**. Nonlinear Sound Generation Mechanisms in Musical Acoustic. 2014.
175. **Sigrid Hade**. GIS Applications in the Studies of the Palaeozoic Graptolite Argillite and Landscape Change. 2014.
176. **Agne Velthut-Meikas**. Ovarian Follicle as the Environment of Oocyte Maturation: The Role of Granulosa Cells and Follicular Fluid at Pre-Ovulatory Development. 2014.
177. **Kristel Hälvin**. Determination of B-group Vitamins in Food Using an LC-MS Stable Isotope Dilution Assay. 2014.
178. **Mailis Päri**. Characterization of the Oligoadenylate Synthetase Subgroup from Phylum Porifera. 2014.
179. **Jekaterina Kazantseva**. Alternative Splicing of *TAF4*: A Dynamic Switch between Distinct Cell Functions. 2014.
180. **Jaanus Suurväli**. Regulator of G Protein Signalling 16 (RGS16): Functions in Immunity and Genomic Location in an Ancient MHC-Related Evolutionarily Conserved Synteny Group. 2014.
181. **Ene Viiard**. Diversity and Stability of Lactic Acid Bacteria During Rye Sourdough Propagation. 2014.
182. **Kristella Hansen**. Prostaglandin Synthesis in Marine Arthropods and Red Algae. 2014.
183. **Helike Lõhelaid**. Allene Oxide Synthase-lipoxygenase Pathway in Coral Stress Response. 2015.
184. **Normunds Stivrinš**. Postglacial Environmental Conditions, Vegetation Succession and Human Impact in Latvia. 2015.
185. **Mary-Liis Kütt**. Identification and Characterization of Bioactive Peptides with Antimicrobial and Immunoregulating Properties Derived from Bovine Colostrum and Milk. 2015.
186. **Kazbulat Šogenov**. Petrophysical Models of the CO_2 Plume at Prospective Storage Sites in the Baltic Basin. 2015.
187. **Taavi Raadik**. Application of Modulation Spectroscopy Methods in Photovoltaic Materials Research. 2015.
188. **Reio Põder**. Study of Oxygen Vacancy Dynamics in Sc-doped Ceria with NMR Techniques. 2015.
189. **Sven Siir**. Internal Geochemical Stratification of Bentonites (Altered Volcanic Ash Beds) and its Interpretation. 2015.

190. **Kaur Jaanson**. Novel Transgenic Models Based on Bacterial Artificial Chromosomes for Studying BDNF Gene Regulation. 2015.
191. **Niina Karro**. Analysis of ADP Compartmentation in Cardiomyocytes and Its Role in Protection Against Mitochondrial Permeability Transition Pore Opening. 2015.
192. **Piret Laht**. B-plexins Regulate the Maturation of Neurons Through Microtubule Dynamics. 2015.
193. **Sergei Žari**. Organocatalytic Asymmetric Addition to Unsaturated 1,4-Dicarbonyl Compounds. 2015.
194. **Natalja Buhhalko**. Processes Influencing the Spatio-temporal Dynamics of Nutrients and Phytoplankton in Summer in the Gulf of Finland, Baltic Sea. 2015.
195. **Natalia Maticiuc**. Mechanism of Changes in the Properties of Chemically Deposited CdS Thin Films Induced by Thermal Annealing. 2015.
196. **Mario Öeren**. Computational Study of Cyclohexylhemicucurbiturils. 2015.
197. **Mari Kalda**. Mechanoenergetics of a Single Cardiomyocyte. 2015.
198. **Ieva Grudzinska**. Diatom Stratigraphy and Relative Sea Level Changes of the Eastern Baltic Sea over the Holocene. 2015.
199. **Anna Kazantseva**. Alternative Splicing in Health and Disease. 2015.
200. **Jana Kazarjan**. Investigation of Endogenous Antioxidants and Their Synthetic Analogues by Capillary Electrophoresis. 2016.
201. **Maria Safonova**. SnS Thin Films Deposition by Chemical Solution Method and Characterization. 2016.
202. **Jekaterina Mazina**. Detection of Psycho- and Bioactive Drugs in Different Sample Matrices by Fluorescence Spectroscopy and Capillary Electrophoresis. 2016.
203. **Karin Rosenstein**. Genes Regulated by Estrogen and Progesterone in Human Endometrium. 2016.
204. **Aleksei Tretjakov**. A Macromolecular Imprinting Approach to Design Synthetic Receptors for Label-Free Biosensing Applications. 2016.
205. **Mati Danilson**. Temperature Dependent Electrical Properties of Kesterite Monograin Layer Solar Cells. 2016.
206. **Kaspar Kevvai**. Applications of ^{15}N-labeled Yeast Hydrolysates in Metabolic Studies of *Lactococcus lactis* and *Saccharomyces Cerevisiae*. 2016.
207. **Kadri Aller**. Development and Applications of Chemically Defined Media for Lactic Acid Bacteria. 2016.
208. **Gert Preegel**. Cyclopentane-1,2-dione and Cyclopent-2-en-1-one in Asymmetric Organocatalytic Reactions. 2016.
209. **Jekaterina Služenikina**. Applications of Marine Scatterometer Winds and Quality Aspects of their Assimilation into Numerical Weather Prediction Model HIRLAM. 2016.
210. **Erkki Kask**. Study of Kesterite Solar Cell Absorbers by Capacitance Spectroscopy Methods. 2016.
211. **Jürgen Arund**. Major Chromophores and Fluorophores in the Spent Dialysate as Cornerstones for Optical Monitoring of Kidney Replacement Therapy. 2016.
212. **Andrei Šamarin**. Hybrid PET/MR Imaging of Bone Metabolism and Morphology. 2016.

213. **Kairi Kasemets**. Inverse Problems for Parabolic Integro-Differential Equations with Instant and Integral Conditions. 2016.
214. **Edith Soosaar**. An Evolution of Freshwater Bulge in Laboratory Scale Experiments and Natural Conditions. 2016.
215. **Peeter Laas**. Spatiotemporal Niche-Partitioning of Bacterioplankton Community across Environmental Gradients in the Baltic Sea. 2016.
216. **Margus Voolma**. Geochemistry of Organic-Rich Metalliferous Oil Shale/Black Shale of Jordan and Estonia. 2016.
217. **Karin Ojamäe**. The Ecology and Photobiology of Mixotrophic Alveolates in the Baltic Sea. 2016.
218. **Anne Pink**. The Role of CD44 in the Control of Endothelial Cell Proliferation and Angiogenesis. 2016.
219. **Kristiina Kreek**. Metal-Doped Aerogels Based on Resorcinol Derivatives. 2016.
220. **Kaia Kukk**. Expression of Human Prostaglandin H Synthases in the Yeast Pichia pastoris. 2016.
221. **Martin Laasmaa**. Revealing Aspects of Cardiac Function from Fluorescence and Electrophysiological Recordings. 2016.
222. **Eeva-Gerda Kobrin**. Development of Point of Care Applications for Capillary Electrophoresis. 2016.
223. **Villu Kikas**. Physical Processes Controlling the Surface Layer Dynamics in the Stratified Gulf of Finland: An Application of Ferrybox Technology. 2016.
224. **Maris Skudra**. Features of Thermohaline Structure and Circulation in the Gulf of Riga. 2017.
225. **Sirje Sildever**. Influence of Physical-Chemical Factors on Community and Populations of the Baltic Sea Spring Bloom Microalgae. 2017.
226. **Nicolae Spalatu**. Development of CdTe Absorber Layer for Thin-Film Solar Cells. 2017.
227. **Kristi Luberg**. Human Tropomyosin-Related Kinase A and B: from Transcript Diversity to Novel Inhibitors. 2017.
228. **Andrus Kaldma**. Metabolic Remodeling of Human Colorectal Cancer: Alterations in Energy Fluxes. 2017.
229. **Irina Osadchuk**. Structures and Catalytic Properties of Titanium and Iridium Based Complexes. 2017.
230. **Roman Borozнjak**. A Computational Approach for Rational Monomer Selection in Molecularly Imprinted Plolymer Synthesis. 2017.
231. **Sten Erm**. Use of Mother-Daughter Multi-Bioreactor Systems for Studies of Steady State Microbial Growth Space. 2017.
232. **Merike Kriisa**. Study of ZnO:In, Zn(O,S) and Sb_2S_3 Thin Films Deposited by Aerosol Methods. 2017.
233. **Marianna Surženko**. Selection of Functional Starter Bacteria for Type I Sourdough Process. 2017.
234. **Nkwusi God'swill Chimezie**. Formation and Growth of Cu_2ZnSnS_4 Monograin Powder in Molten CdI_2. 2017.
235. **Ruth Tomson**. Urea- and Creatinine-Based Parameters in the Optical Monitoring of Dialysis: The Case of Lean Body Mass and Urea Rebound Assessment. 2017.

236. **Natalja Jepihhina**. Heterogeneity of Diffusion Restrictions in Cardiomyocytes. 2017.
237. **Sophie Maria Teresa Marinucci de Reguardati**. High-Accuracy Reference Standards for Quantitative Two-Photon Absorption Spectroscopy. 2017.
238. **Martin Lints**. Optimised Signal Processing for Nonlinear Ultrasonic Nondestructive testing of Complex Materials and Biological Tissues. 2017.
239. **Maris Pilvet**. Study of $Cu_2(Zn,Cd)SnS_4$ Absorber Materials for Monograin Layer Solar Cells. 2017.
240. **Sirli Rosenvald**. Application of Gas Chromatography-Olfactometry (GC-O) and Correlation with Sensory Analysis. 2017.
241. **Jelena Maricheva**. Electrodeposition of Cadmium Chalcogenide Films for Hybrid Solar Cells. 2017.