DOCTORAL THESIS

Asymmetric Organocatalytic [2,3]-Wittig Rearrangement

Mariliis Kimm

TALLINNA TEHNIKAÜLIKOOL
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TAL TECH PRESS

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

Mariliis Kimm

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Asümmeetriline organokatalüütiline [2,3]-Wittigi ümberasetusreaktsioon

MARILIIS KIMM

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Contents

List of publications

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

I Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. Two Catalytic Methods of an Asymmetric Wittig [2,3]-Rearrangement. *J. Org. Chem.* **2017**, *82*, 2889–2897.

II Kimm, M.; Ošeka, M.; Kaabel, S.; Metsala, A.; Järving, I.; Kanger, T. [2,3]-Wittig Rearrangement as a Formal Asymmetric Alkylation of α-Branched Ketones. *Org. Lett.* **2019**, *21*, 4976–4980.

III Kimm, M.; Järving, I.; Ošeka, M.; Kanger, T. Asymmetric Organocatalytic [2,3]-Wittig Rearrangement of Cyclohexanone Derivatives. *Eur. J. Org. Chem.* **2021**, 3113–3120.

Author's contribution to the publications

Contribution to the papers in this thesis are:

I The author played a significant role in the synthetic preparation and characterization of the starting compounds and rearranged products (organocatalytic pathway). The author played a minor role in the preparation of the manuscript and the compilation of the supporting information.

II The author played a major role in the synthetic preparation and characterization of the compounds used in the study. The author played a significant role in the preparation of the manuscript and a major role in the compilation of the supporting information.

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Introduction

There is a continuous need for methods to construct new carbon-carbon bonds in an enantioselective manner. This task includes two crucial factors: finding a suitable chemical transformation, and applying an efficient enantioselective methodology for the selected reaction. It cannot be denied that efficiency and sustainability are important aspects of the modern organic synthesis and chemists implement them while creating new synthetic approaches.

One way to bring efficiency into the creation of new carbon-carbon bonds is to use 100% atom-efficient reactions, such as a [2,3]-Wittig rearrangement. In rearrangement reactions, all atoms of the starting material are incorporated into the structure of the product, making these reactions attractive from the efficiency point of view. Enantioenriched products can be obtained by using chiral catalysts, which are theoretically recoverable. For example, organocatalysis has proven to be a trustworthy tool for introducing chirality into molecules. The fact that organocatalysts are usually derived from chiral natural products makes them attractive in terms of sustainability.

The purpose of this thesis is to investigate asymmetric organocatalytic [2,3]-Wittig rearrangement, as the number of examples in the literature is rather limited. The main task is to provide solutions for the rearrangement of different starting compounds using various organocatalytic methods. This doctoral thesis gives an overview of the [2,3]-Wittig rearrangement history and focuses on asymmetric catalytic methods published so far. Also, the applications of asymmetric rearrangement are discussed.

The results demonstrate the [2,3]-Wittig rearrangement of several substrates using different organocatalytic methods (**Publications I - III**). First, the rearrangement of malonates was investigated (**Publication I**). Subsequently, the study was continued on various cyclic ketones (**Publications II - III**). Along with publication in peer-reviewed journals, the results of this research have been presented at international conferences in Estonia, Latvia, Germany, Italy and Portugal.

Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
B	base
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	benzyl
Cat.	catalyst
conv.	conversion
Cy	cyclohexyl
dr	diastereomeric ratio
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
E	electrophile
ee	enantiomeric excess
eq	equivalent
Et	ethyl
EWG	electron withdrawing group
Hal	halogen
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
IPA	isopropyl alcohol
*i*Pr	isopropyl
L	ligand
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
Me	methyl
MS	molecular sieves
*n*Bu	normal butyl
nd	not determined
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	nucleophile
OTf	trifluoromethanesulfonate / triflate
PG	protecting group
Ph	phenyl
p-NBA	*p*-nitrobenzoic acid
PTC	phase-transfer catalysis

rac	racemic
Ref.	reference
rt	room temperature
SAEP	(*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine
TBAF	tetrabutylammonium fluoride
*t*Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
t_R	retention time
Ts	tosyl

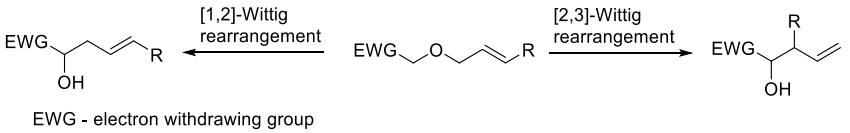
1 Literature overview

1.1 Wittig rearrangement

Sigmatropic rearrangement reactions are valuable and powerful tools for synthetic chemists in the creation of new carbon-carbon or carbon-heteroatom bonds.[1,2] These transformations represent a broad class of organic reactions, where the migration of an atom or a group from one atom (migration origin) to another (migration terminus) involves sigma bond reorganization within the same molecule (Figure 1).[2,3] The rearrangement reactions often provide access to products, which are complicated to obtain otherwise, and new stereogenic centers are frequently introduced into the molecule. The atom efficiency of the rearrangement reactions is 100%, thus making these transformations sustainable from the atom-economy point of view.[4]

Figure 1. *Sigmatropic rearrangement.*

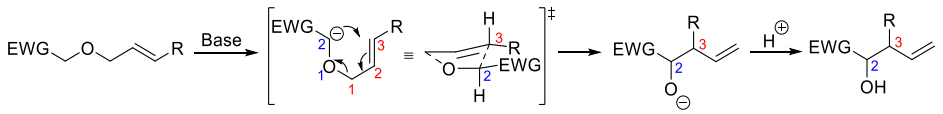
Wittig rearrangement is a class of sigmatropic rearrangements that can follow several pathways.[5–7] [1,2]-Wittig rearrangement and [2,3]-Wittig rearrangement are the most studied reactions performed on allyl ether derivatives and yielding homoallyl alcohols (Scheme 1). Despite the similarity, the mechanisms of [1,2]- and [2,3]-Wittig rearrangements are different. [1,2]-rearrangement proceeds via a radical sigma bond dissociation-recombination mechanism, while [2,3]-Wittig rearrangement proceeds through a polar pericyclic transition state. The other pathways, [1,4]- and [3,4]-Wittig rearrangement, are rare and can only be occasionally observed as minor side processes during [1,2]- and [2,3]-Wittig rearrangements.



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

1.1.1 [2,3]-Wittig rearrangement

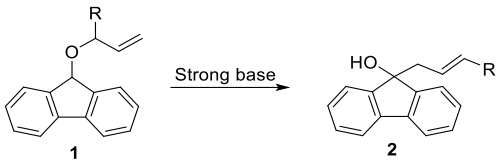
[2,3]-Wittig rearrangement is a pericyclic sigmatropic rearrangement reaction of allyl ethers to homoallyl alcohols induced by a base, resulting in the regiospecific formation of a new carbon-carbon bond (Scheme 2).[6,8] The numeric prefixes of the rearrangement describe the position of a newly constructed sigma bond relative to the starting material.[6] The numeration starts from the cleaved carbon-oxygen bond and proceeds down the chains.



Scheme 2. *The mechanism of [2,3]-Wittig rearrangement.*

The rearrangement starts from the deprotonation of an allyl ether and usually strong bases are employed (Scheme 2). The formed negative charge is commonly stabilized by an electron-withdrawing group.[6] The rearrangement proceeds via a concerted six-electron, five-membered pericyclic envelope-like transition state, which leads to the cleavage of a carbon-oxygen bond and to the formation of a new carbon-carbon bond.[3,9] The [2,3]-rearranged product is formed after protonation of the intermediate. Depending on the substituents of the substrate, products bearing up to two stereogenic centers can be formed. Considering these useful properties, [2,3]-Wittig rearrangement has been found to be useful in the synthesis of complex molecules.[10,11]

It appears that [2,3]-Wittig rearrangement was described for the first time in 1949 by Georg Wittig while performing a transformation on allyl fluorenyl ether **1a** (Scheme 3).[12] However, as the product **2a** can be potentially formed via both the [1,2]- and [2,3]-rearrangement pathways, the actual mechanism of the reaction was unclear until further investigations by Cast and Stevens in 1960.[13] In this study, the authors used substrate **1b** with an additional methyl group, which provided clear evidence that the reaction proceeds through the [2,3]-pathway.



Scheme 3. *[2,3]-Wittig rearrangement of the allyl fluorenyl ethers **1a** and **1b**.*

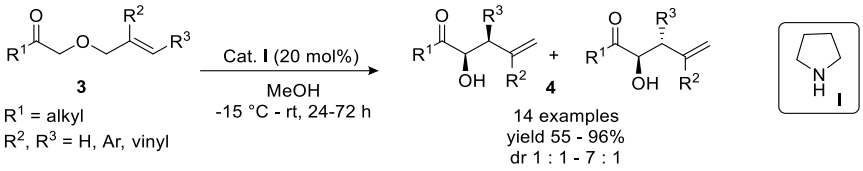
1.2 Asymmetric [2,3]-Wittig rearrangement

The development of asymmetric reactions has always played an important role in organic synthesis due to their wide applicability for the synthesis of natural products and pharmaceuticals. The present chapter focuses on the methods that generate enantioenriched products from achiral substrates, which are achieved by using chiral reagents, such as chiral auxiliary groups, bases, ligands or catalysts.[8,9] The development of the enantioselective versions of [2,3]-Wittig rearrangement started in the 1980s. For decades, [2,3]-Wittig rearrangement was carried out under strong basic conditions and the chirality was introduced by chiral reagents used in stoichiometric amounts. Nakai and co-workers reported the first examples of asymmetric [2,3]-Wittig rearrangement applying enantiomerically enriched oxazolines and amides as chiral auxiliaries.[14–16] The use of the chiral auxiliary has proven to be a reliable method since then, although, the scope is limited to carbonyl-containing substrates only in this case.[6] Also, the attachment and the removal of the auxiliary add additional steps to the reaction sequence. The Marshall research group provided the first example of a chiral base-induced enantioselective rearrangement and applied it for the synthesis of the natural product (+)-aristolactone.[17,18] This approach is useful for substrates lacking carbonyl functionality and asymmetric products are obtained by stereoselective metallation of an allyl ether.[6] The first example of the use of chiral ligands for rearrangement was published by Nakai.[19] It took a surprisingly long time for the loadings of chiral ligands to decrease from a stoichiometric to a catalytic amount.[20–22] The employment of chiral catalysts is a relatively new approach.[23] At the time our group started to investigate the asymmetric

organocatalytic version of [2,3]-Wittig rearrangement, only one organocatalytic example had been published in the literature.[24] The following sections will give an overview of organo- and metal catalytic asymmetric methods developed so far.

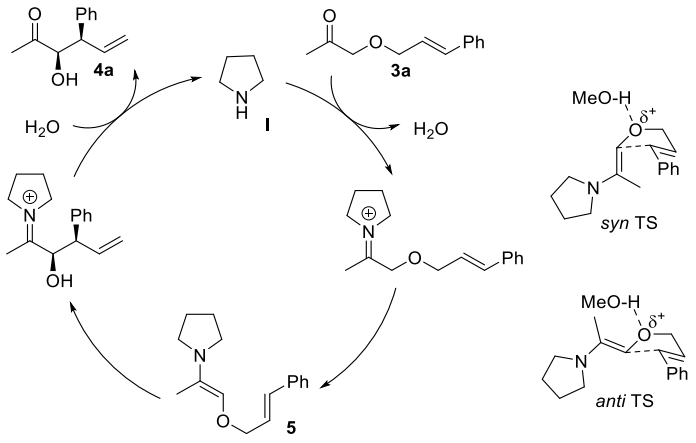
1.2.1 Asymmetric organocatalytic [2,3]-Wittig rearrangement

In 2006, the Gaunt research group reported the first organocatalytic [2,3]-Wittig rearrangement. The rearrangement is catalyzed by a secondary amine under mild reaction conditions without the use of a strong base. (Scheme 4).[24]



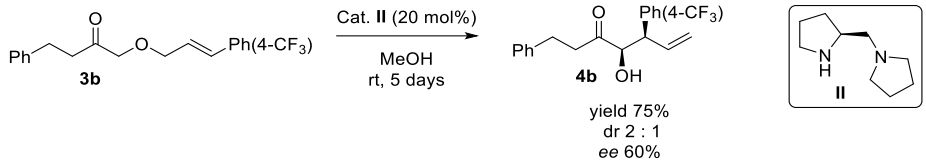
***Scheme 4**. Diastereoselective synthesis of α-hydroxyketones **4**.*

The [2,3]-Wittig rearrangement was conducted on aliphatic cinnamyloxyketones **3** using 20 mol% pyrrolidine **I** as a catalyst. Screening experiments provided useful information for understanding the reaction mechanism. When methanol was used as a solvent, full conversion was obtained significantly faster and the diastereoselectivity was reversed and improved compared to using other solvents. It was proposed that methanol is coordinated to the ether oxygen-atom through a hydrogen bond, which stabilizes the formed negative charge, accelerating the rearrangement up to 50 times faster and *syn*-isomer is favored over *anti*-isomer. Additional experiments provided evidence that the rearrangement proceeds via enamine **5** formation and is not base-mediated. The proposed catalytic cycle of the organocatalytic [2,3]-Wittig rearrangement is depicted below (Scheme 5). The condensation of the pyrrolidine **I** with the cinnamyloxyketone **3a** results in the formation of the iminium ion, which is converted to enamine **5**. The rearrangement of the enamine **5** presumably proceeds via the *syn* transition state (*syn* TS) and is followed by hydrolysis to release the α-hydroxyketone **4a** and the catalyst **I**.



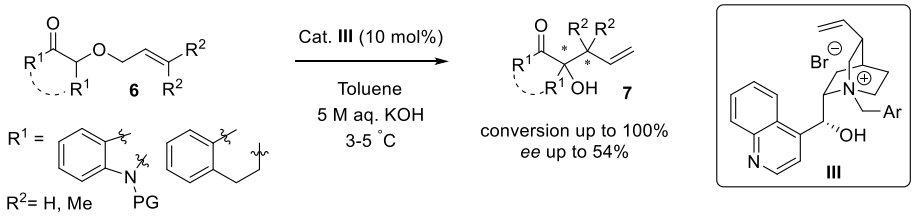
***Scheme 5.** Proposed catalytic cycle of organocatalytic [2,3]-Wittig rearrangement. Adapted from Ref. 24 with permission from John Wiley and Sons.*

After the development of the above-mentioned diastereoselective methodology, Gaunt et al. continued their investigation of an enantioselective rearrangement, catalyzed by a chiral amine **II** (Scheme 6). The process was challenging, and the authors could only provide one example where the rearranged product **4b** formed in 60% *ee*. This reaction represents the first example of asymmetric organocatalytic [2,3]-Wittig rearrangement. This conceptually new method laid the foundation for the development of asymmetric catalytic [2,3]-Wittig rearrangement.



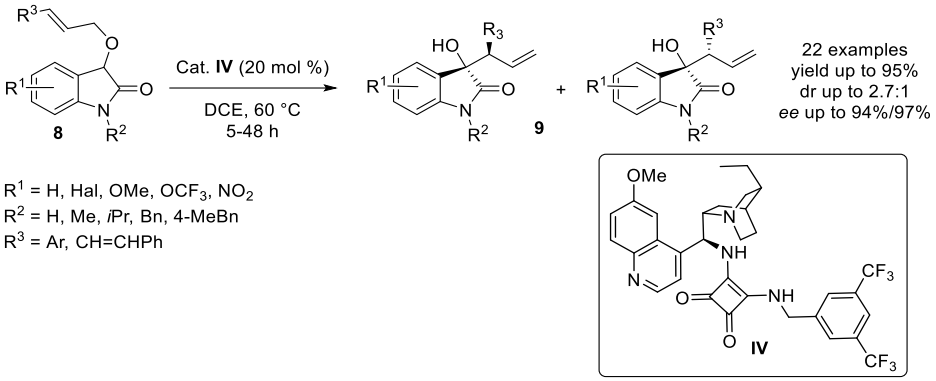
Scheme 6. *Enantioselective synthesis of α-hydroxyketone* ***4b****.*

Interestingly, it was almost a decade before the next article about asymmetric organocatalytic [2,3]-Wittig rearrangement was published. In 2015, the Denmark group reported the first enantioselective phase-transfer-catalyzed approach for the rearrangement of cyclic allyloxycarbonyl compounds **6** (Scheme 7).[25] The reaction proceeds via the formation of a chiral ammonium enolate intermediate under liquid-liquid phase-transfer conditions. Despite an enormous amount of work, the rearranged α-hydroxyketones **7** were obtained in only moderate enantioselectivities (*ee* up to 54%). The authors proposed that the low selectivity was caused by a racemic background reaction. Since the scope of asymmetric PTC-mediated intramolecular reactions remains small, the work of the Denmark group has great value in terms of expanding the methodology.



Scheme 7. *Enantioselective synthesis of α-hydroxyketones* ***7****.*

Simultaneously, our research group worked on the development of hydrogen-bond-mediated [2,3]-Wittig rearrangement of oxindole derivatives **8** (Scheme 8).[26] The 3-cinnamyloxyoxindoles **8** underwent rearrangement smoothly in the presence of a bifunctional squaramide **IV**. 3-hydroxyoxindoles **9** were obtained in excellent enantiomeric purities for both diastereomers. Despite the low diastereomeric ratio, the diastereomers were chromatographically separable on silica gel, providing an advantage for the further applications of this methodology.



***Scheme 8**. Enantioselective synthesis of 3-hydroxy 3-substituted oxindoles **9**.*

The proposed transition state for the [2,3]-Wittig rearrangement of 3-cinnamyloxyoxindole **8** is depicted below (Figure 2). It is assumed that the initial step is the deprotonation of the starting compound by a tertiary amine moiety of the catalyst **IV**. Two regions of the formed enolate can be activated through hydrogen bonds; the squaramide moiety coordinates the oxygen atom of the ether fragment and the negatively charged oxygen is coordinated by the quaternary ammonium ion. Depending on which face the attack occurs at, different diastereomers **9a** are formed. Insufficient stereodifferentiation between the two transition states is the main cause of a low diastereomeric ratio. Also, it was proposed that the π-π interactions could play an important role in the stabilization of the transition state. This work represents the first example of highly enantioselective hydrogen-bond-mediated [2,3]-Wittig rearrangement.

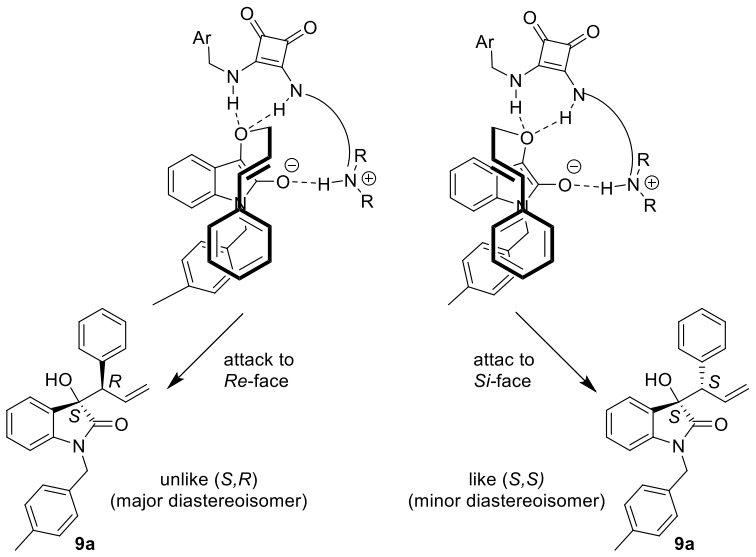
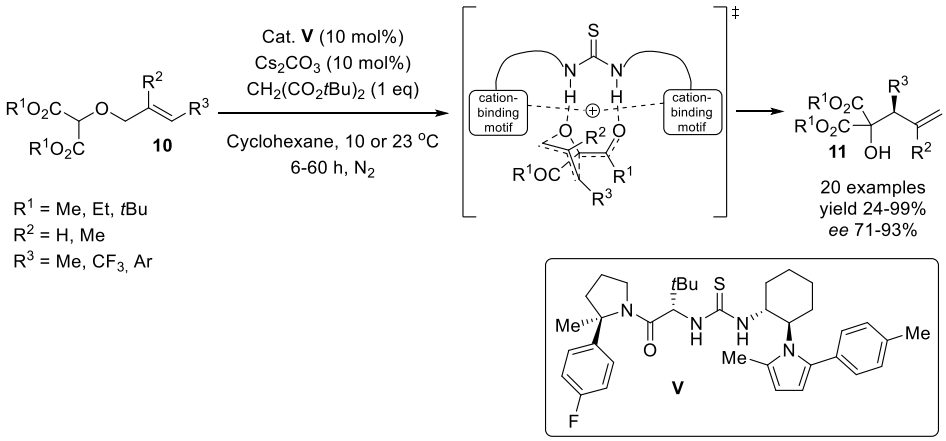


***Figure 2.** Proposed transition state for the [2,3]-Wittig rearrangement.*

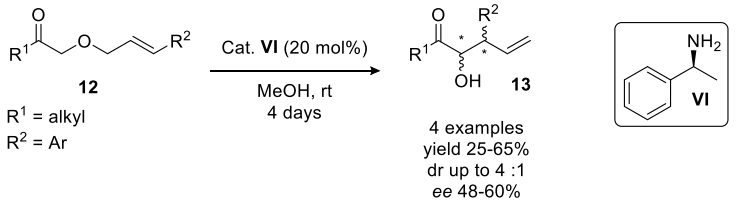
In 2016, the Jacobsen research group demonstrated an efficient synergistic ion-binding strategy for the [2,3]-Wittig rearrangement of α-allyloxycarbonyl compounds **10**.[27] The dual catalyst system consists of a chiral thiourea **V** and a Brønsted base co-catalyst

(Scheme 9). A Brønsted base Cs_2CO_3 together with a di-*tert*-butyl malonate initiate the reaction sequence by substrate **10** deprotonation and the formation of a cesium enolate ion pair. The structural motifs of the thiourea catalyst **V** play several roles in the organization of the transition state structure. The thiourea fragment is a hydrogen-bond donor and coordinates the enolized anionic starting material through noncovalent interactions. Additionally, the aryl groups of the catalyst **V** participate in the cation stabilization. Together, these interactions determine the transition state of the stereoselective rearrangement. The developed methodology provided α-hydroxymalonates **11** in excellent enantiomeric purities and yields.



Scheme 9. *Synthesis of α-hydroxymalonates **11** and the proposed transition state.*

Šebesta et al. investigated the [2,3]-Wittig rearrangement of aliphatic cinnamyloxyketones **12** catalyzed by a primary amine **VI** (Scheme 10).[28] The concept of this work is analogous to work previously published by Gaunt et al., i.e. the same reaction conditions and similar catalysts were applied for the rearrangement.[24] The authors provided several new substrates compared to Gaunt's work and the α-hydroxyketones **13** were obtained in moderate enantiomeric purities and yields.

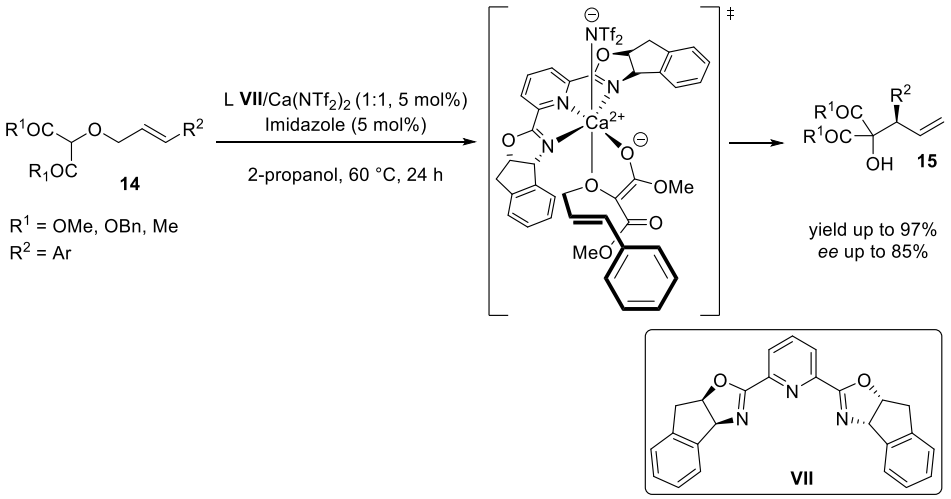


Scheme 10. *Synthesis of α-hydroxyketones **13**.*

1.2.2 Asymmetric metal-catalyzed [2,3]-Wittig rearrangement

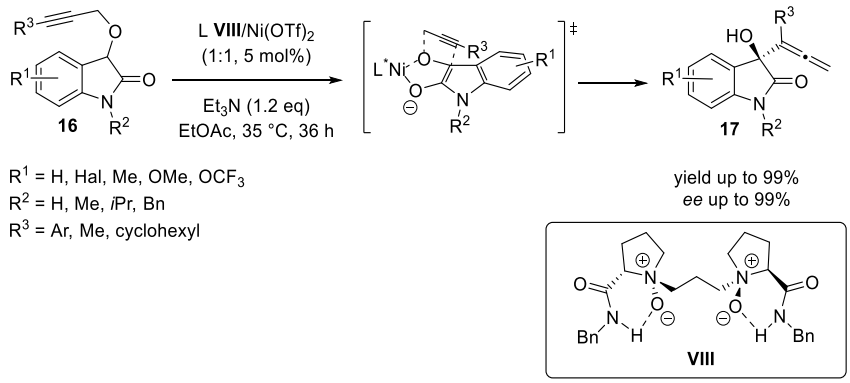
In 2017, our research group reported a calcium catalytic approach for the asymmetric [2,3]-Wittig rearrangement of cinnamyloxy-1,3-dicarbonyl compounds **14** (Scheme 11).[29] The catalytic system consists of calcium salt as a strong Lewis acid and a chiral Inda-Pybox ligand **VII** derived from pyridine and oxazoline groups. A sub-stoichiometric amount of imidazole was used as a Brønsted base to deprotonate the starting material **14**. It is assumed that the reaction starts with the formation of a 1:1 complex between the

Inda-Pybox ligand **VII** and $Ca(NTf_2)_2$, which was also confirmed by NMR and ESI-MS experiments. The chiral calcium complex coordinates to the enolized substrate **14** and the model depicted below is formed after the removal of the second trifluoromethanesulfonimide group from calcium. α-Hydroxymalonates **15** were synthesized in high enantioselectivities and yields. To the best of our knowledge, this is the first example of a Lewis acid-catalyzed asymmetric [2,3]-Wittig rearrangement.



Scheme 11. *Synthesis of α-hydroxymalonates **15** and a proposed model of complexation.*

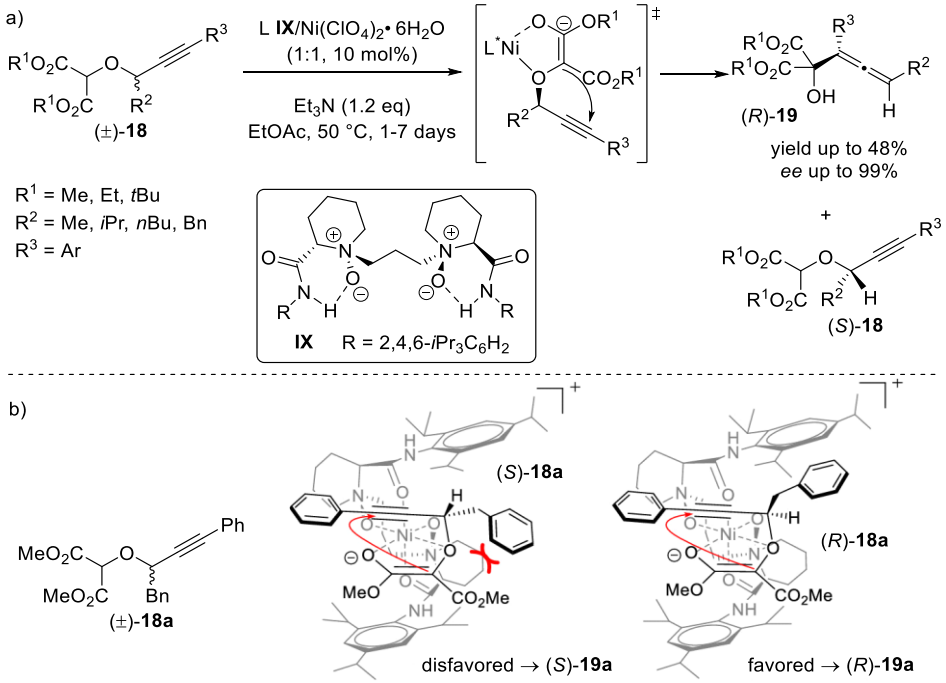
In 2018, the Feng research group developed the asymmetric [2,3]-Wittig rearrangement of propargyl oxindoles **16** catalyzed by a chiral nickel-complex (Scheme 12).[30] The complex of a chiral ligand **VIII** and $Ni(OTf)_2$ coordinates the substrate **16**, while triethylamine is used for deprotonation. Chiral 3-hydroxy 3-substituted oxindoles bearing allenyl groups **17** were obtained with excellent enantiomeric purities and in superior yields. Also, a successful example of chiral amplification was demonstrated. The chiral ligand **VIII** with an *ee* of 15% was sufficient to access products **17** with *ee* up to 92%. This work is a great expansion of organocatalytic methods reported previously and represents the first example of the asymmetric catalytic [2,3]-Wittig rearrangement of propargyl ethers.



Scheme 12. *Synthesis of 3-hydroxy 3-substituted oxindoles bearing allenyl groups **17**.*

Two years later, Feng et al. described a methodology where an efficient kinetic resolution of racemic propargyloxy malonates **18** was achieved via [2,3]-Wittig rearrangement (Scheme 13a).[31] The catalytic system consists of a chiral ligand **IX** and Ni(II)-salt forming a complex, which is responsible for the recognition of *R*-enantiomer of the enolized substrate **18a** over another and rearranging it to *R*-product **19a**. The *S*-enantiomer of the substrate **18a** stays intact due to the steric hindrance between the benzyl group of the substrate and the ligand (Scheme 13b).

The authors also demonstrated an example where the (*S*)-enantiomer of the substrate **18** was recovered and converted to a product (*S*)-**19** using the opposite enantiomer of the ligand **IX**. Thus, it is possible to synthesize both enantiomers of the product **19** with excellent enantiomeric purity. The reported method afforded α-hydroxymalonates **19** with excellent enantioselectivities and in high yields considering the highest possible yield of the methodology. An application of the methodology for the synthesis of the basic skeleton of cryptoresinol **32** was also demonstrated and will be discussed in the following chapter (Scheme 19).



Scheme 13. *a) Kinetic resolution of racemic propargyl ethers **18** and the synthesis of α-hydroxymalonates bearing allenyl groups **19**.*
*b) Proposed catalytic model for **18a**. Adapted from Ref. 31 with permission from the American Chemical Society.*

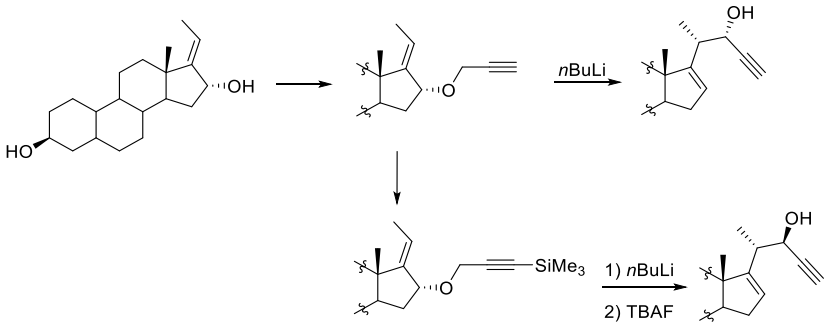
1.2.3 Summary of asymmetric [2,3]-Wittig rearrangement

For four decades, chemists have witnessed attempts at the development of new efficient asymmetric methods to conduct [2,3]-Wittig rearrangement. The reported asymmetric catalytic reactions have several advantages compared to previous approaches. Reactions can be carried out in an operationally simple setup, as they do not require completely

anhydrous conditions or low reaction temperatures. Moreover, stoichiometric amounts of strong bases, such as *n*BuLi and LDA or chiral auxiliaries and ligands are not required. However, the substrate scope of the reported examples is rather limited and there is still room for improvement.

1.3 The applications of asymmetric [2,3]-Wittig rearrangement in natural product synthesis

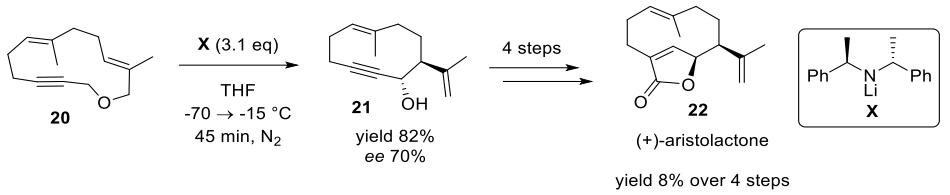
The [2,3]-Wittig rearrangement has found wide use in total synthesis for several reasons. This transformation is known for its ability to construct quaternary stereocenters, thus making it possible to introduce chirality into a molecule. Also, alcohol and alkene functionalities are good starting points for further transformations.[10] There are numerous examples of applications of the [2,3]-Wittig rearrangement in natural product synthesis. An asymmetric transmission is a commonly used process, where strong bases are employed without the use of any other chirality-inducing reagents. The chirality of a substrate is completely and specifically transferred to two newly formed chiral centers and a product is obtained with the same enantiomeric excess as the starting compound.[8] One of the first applications of this methodology was described for the stereocontrolled synthesis of steroid side chains, which are valuable precursors for several steroids (Scheme 14).[32] However, the number of asymmetric [2,3]-Wittig rearrangement methods starting from achiral substrates is limited. The following sections give a short overview of the synthesis of natural products and intermediates employing asymmetric [2,3]-Wittig rearrangement.



Scheme 14. *Synthesis of steroid side chains via [2,3]-Wittig rearrangement.*

1.3.1 The use of chiral bases

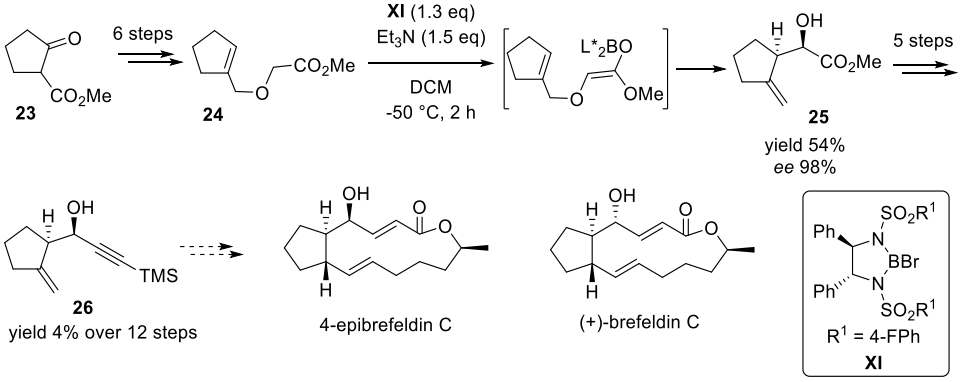
One of the first applications of asymmetric [2,3]-Wittig rearrangement for natural product synthesis was mentioned in the previous chapter (Scheme 15).[17,18,33] In 1987, the Marshall group developed a method for the asymmetric synthesis of (+)-aristolactone **22**, which is a member of the germacranolide class of sesquiterpenes.[17] The [2,3]-Wittig rearrangement of a 13-membered propargylic allyl ether **20** in the presence of a chiral lithium amide **X** provided the rearranged product **21** in good yield and moderate selectivity. The obtained homoallyl alcohol **21** was converted to (+)-aristolactone **22** over four steps in 8% yield.



Scheme 15. *Total synthesis of (+)-aristolactone* ***22****.*

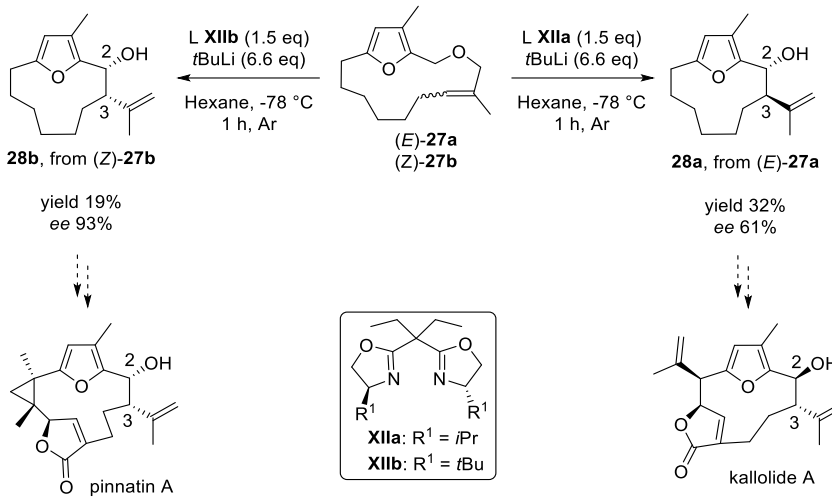
1.3.2 The use of chiral ligands

Nakai et al. investigated an enantioselective [2,3]-Wittig rearrangement which proceeds through the formation of a chiral boron ester enolate, and its possible applications.[34] Generated in situ from BBr_3 and a bis-sulfonamide controller ligand (L*), chiral boron reagent **XI** creates an enolate terminus with the substrate and facilitates rearrangement smoothly to provide α-hydroxyester **25** in very high enantioselectivity and good diastereoselectivity (Scheme 16). The authors claimed that this approach was the first example of an enantioselective [2,3]-Wittig rearrangement of the ester enolate. The applicability of the methodology was demonstrated for the synthesis of (epi)brefeldin C intermediate **26** starting with a commercially available ester **23**. Brefeldin C is a fungal metabolite and a biosynthetic precursor of brefeldin A, which is known for its antibacterial properties. The intermediate **26** was obtained over 12 steps with a total yield of 4%, showing excellent selectivities in the rearrangement step. Thus, the developed method showed its potential in natural product synthesis.



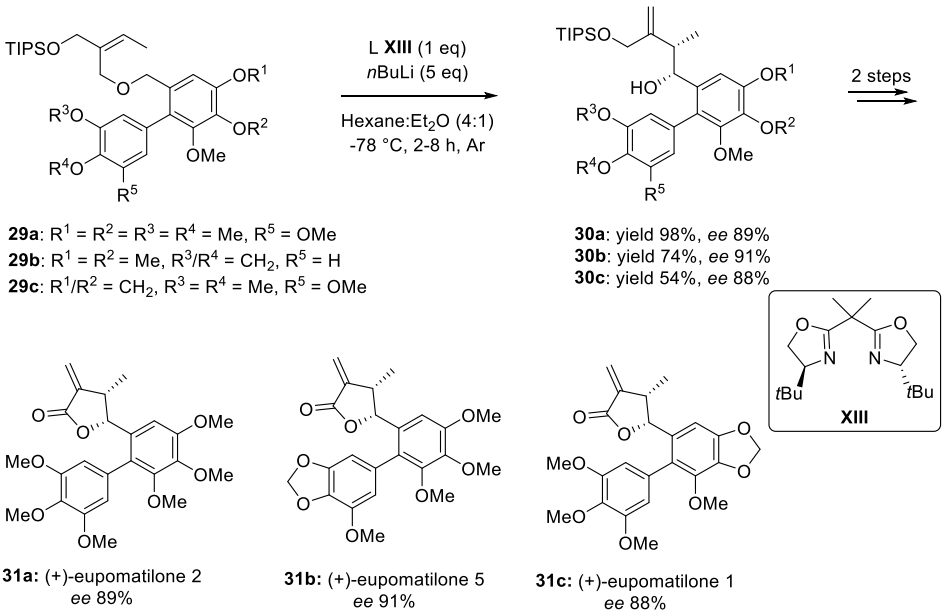
Scheme 16. *Formal synthesis of (epi)brefeldin C.*

In 2003, the Tsubuki research group reported an enantioselective [2,3]-Wittig rearrangement which makes it possible to construct new stereogenic centers at the second and third position of furanocyclic diterpenes kallolide A and pinnatin A (Scheme 17).[35] Kallolide A has anti-inflammatory properties and pinnatin A exhibits anti-tumor activity. [2,3]-Wittig rearrangement was investigated on (*E*)- and (*Z*)-cyclic furfuryl ethers **27**, which were treated with *t*BuLi in the presence of chiral bis(oxazoline) ligands **XII**. The homoallyl alcohols **28a** and **28b** formed in 61% *ee* and 93% *ee*, respectively. Although, the final synthesis of kallolide A and pinnatin A was not reported in the publication, the published work expands the synthetic methodology of asymmetric furanocyclic diterpenes.



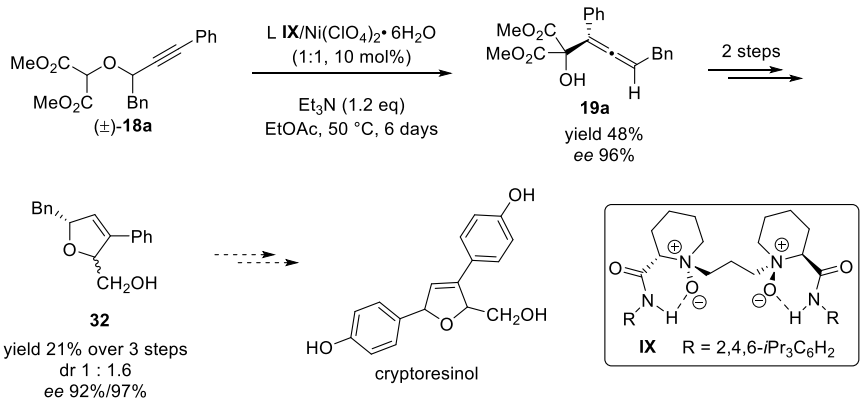
Scheme 17. *Synthesis of kallolide A and pinnatin A intermediates* ***28****.*

The Maezaki research group has published several successful examples of the [2,3]-Wittig rearrangement of allyl benzyl ethers in the presence of a chiral bis(oxazoline) ligand **XIII**.[22,36,37] Promising results encouraged the authors to test the capability of the methodology for the total synthesis of (+)-eupomatilone 1, 2 and 5 (Scheme 18).[38,39] Eupomatilones **31** belong to a lignan group and are found in the Australian shrub *Eupomatia bennettii*. [2,3]-Wittig rearrangement was applied to introduce chirality into the lactone fragment. Despite the use of highly substituted benzyl ethers **29**, the rearrangement proceeded smoothly and the homoallyl alcohols **30** were obtained in high yields and selectivities. The final products **31** were obtained over five or six steps with overall yield of 25-50%.



Scheme 18. *Total synthesis of eupomatilones 1, 2 and 5.*

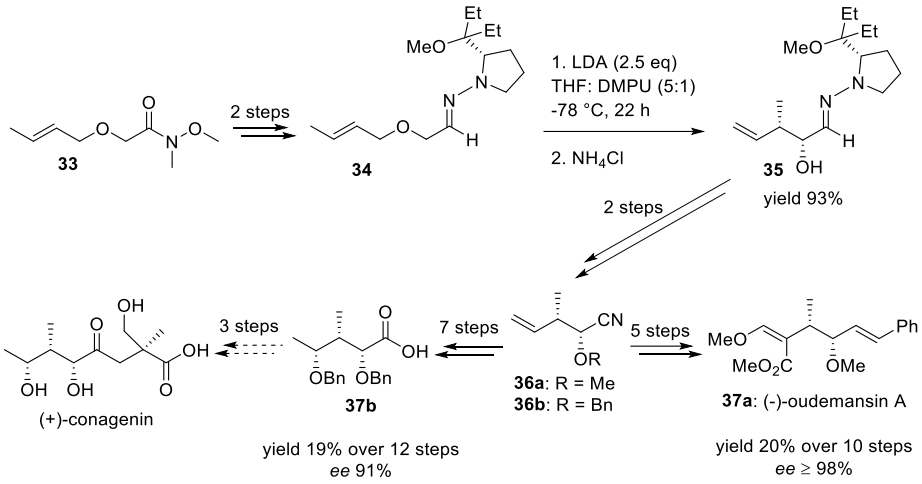
In 2020, Feng et al. demonstrated a rear example of an asymmetric catalytic [2,3]-Wittig rearrangement to access the 2,5-dihydrofuran structural motif that can be found in several natural products.[31] In this publication, the asymmetric synthesis of the basic skeleton of cryptoresinol **32** is presented (Scheme 19). Cryptoresinol is a type of norlignan, which has been used in traditional medicine.[40] The rearrangement product **19a** was obtained by a kinetic resolution of propargyloxy malonates **18a** and was discussed in the previous chapter (Scheme 13). The 2,5-dihydrofuran derivative **32** was synthesized over three steps from the propargyloxy malonates **18a** in total yield of 21% and excellent enantiomeric purity. Despite the moderate diastereoselectivity, the diastereomers were chromatographically separable.



***Scheme 19**. Asymmetric synthesis of the basic skeleton of cryptoresinol **32**.*

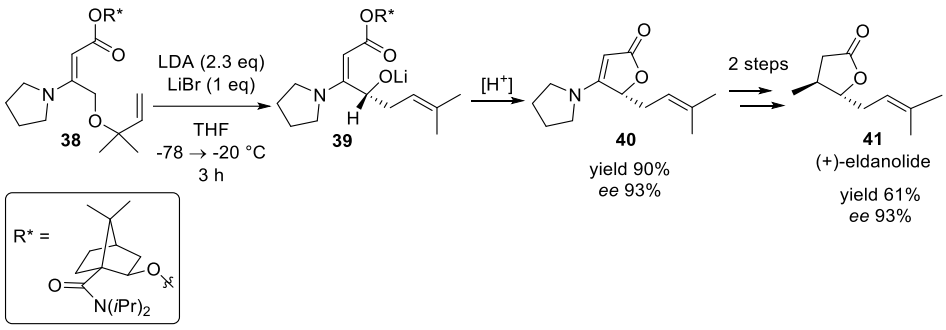
1.3.3 The use of chiral auxiliary groups

The Enders research group have reported several successful examples of the [2,3]-Wittig rearrangement of chiral SAEP hydrazones, synthesized from allyloxy ketones and chiral auxiliaries.[41–44] The authors continued their study of the total synthesis of (-)-oudemansin A, which exhibits strong antifungal activity.[45] In a subsequent publication, the formal synthesis of (+)-conagenin was investigated, which has shown its activity as an immunomodulator and as an anti-tumor agent.[46] The synthesis of both target molecules started with the preparation of a chiral SAEP hydrazone **34** from Weinreb amide **33**, followed by [2,3]-rearrangement for chirality insertion (Scheme 20). Despite the excellent yield of the rearrangement, the main drawbacks of the methodology are attachment and cleavage of a chiral auxiliary that add two extra steps to the reaction sequence. (-)-Oudemansin A **37a** was obtained over 10 steps and the precursor of (+)-conagenin **37b** over 12 steps, with overall yields of 19-20% and in excellent enantiomeric purities.



Scheme 20. *Total synthesis of (-)-oudemansin A* ***37a*** *and formal synthesis of (+)-conagenin.*

In 2009, Li et al. developed an approach for the synthesis of unsaturated lactones **40** from an ester **38** bearing a chiral auxiliary. The methodology was applied for the total synthesis of (+)-eldanolide **41** (Scheme 21).[47] (+)-Eldanolide is an attractant pheromone produced by a male African sugar stem borer. The reaction sequence starts with the [2,3]-Wittig rearrangement of the ester **38**, leading to the formation of a lithium alkoxide **39**. The chiral auxiliary is then cleaved upon hydrolysis and the formed intermediate cyclizes to an unsaturated lactone **40**. (+)-Eldanolide **41** was further obtained in two steps from the unsaturated lactone **40** in very high enantiomeric purity.



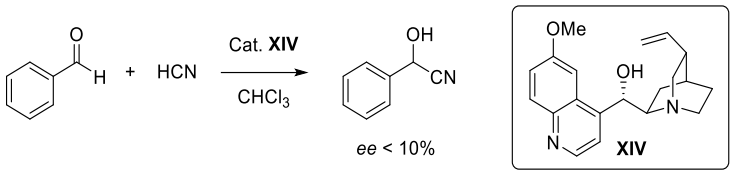
Scheme 21*. Total synthesis of (+)-eldanolide* ***41****.*

1.3.4 Summary of the applications of asymmetric [2,3]-Wittig rearrangement in natural product synthesis

Several asymmetric methods have been applied for the synthesis of natural products, e.g the use of chiral bases, ligands and auxiliary groups. Surprisingly, the number of examples is rather limited, especially considering how long asymmetric methods have been used. Despite that, asymmetric rearrangement has been successfully applied for several types of substrates: cyclic, aliphatic and highly substituted ones. Hence, [2,3]-Wittig rearrangement has proven to be a valuable method for chirality insertion to complex organic molecules. So far, organocatalytic methods have not been used in total synthesis and, thus, research on asymmetric organocatalytic methods is highly important.

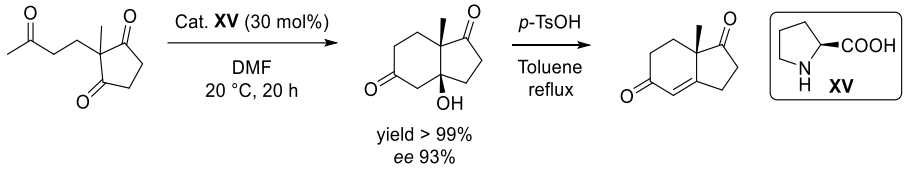
1.4 Asymmetric organocatalytic methods used in the thesis

Asymmetric organocatalysis, where small chiral organic molecules are used to obtain enantiomerically enriched products, has been extensively studied in recent decades.[48] However, the term "organocatalyst" dates back to 1900, when the Baltic German chemist Wilhelm Ostwald, a future Nobel Prize laureate, introduced it for the first time.[49] A decade later, the first asymmetric reaction, enantioselective hydrocyanation of benzaldehyde catalyzed by a Cinchona alkaloid **XIV**, was published by Bredig and Fiske (Scheme 22).[50]



Scheme 22*. First example of asymmetric organocatalysis.*

Presumably, the most important milestone in the development of modern organocatalysis is the Hajos–Parrish–Eder–Sauer–Wiechert reaction, which was reported in the early 1970s (Scheme 23).[51,52] This enamine-mediated aldol reaction in the presence of proline **XV** proceeded in excellent yield and enantioselectivity.



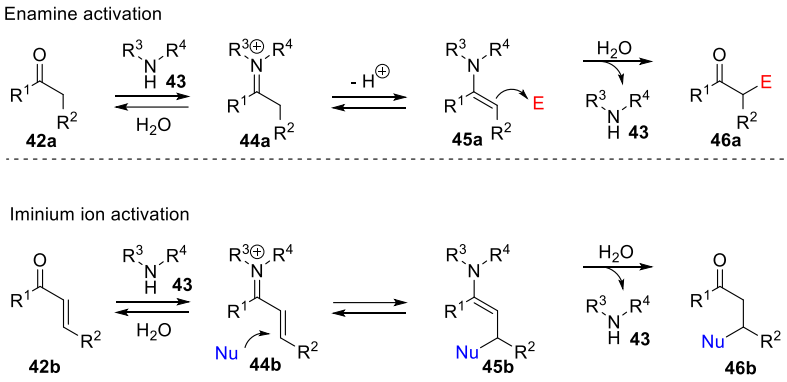
Scheme 23. *The Hajos–Parrish–Eder–Sauer–Wiechert reaction.*

However, it took 30 years until the unlimited potential of organocatalysis was finally harnessed. The "golden age" of organocatalysis started in the early 2000s, when the work of C. Barbas III, R. Lerner and B. List provided an enormous contribution to the development of enamine chemistry, and MacMillan et al. laid the foundation for iminium catalysis.[53,54]

Organocatalysis has several advantages over transition-metal catalysis: organocatalysts are often cheaper, less toxic and more stable than metal-based catalysts.[55] Usually, there is no need for an inert atmosphere or strictly anhydrous reaction conditions. Nowadays, organocatalysis is highly developed and provides methods for the activation of several substrate types. The activation modes are commonly classified in two ways: a) covalent and noncovalent, which involves a substrate-catalyst interaction, and b) Lewis base, Lewis acid, Brønsted base and Brønsted acid, which illustrates the chemical nature of the organocatalyst.[48]

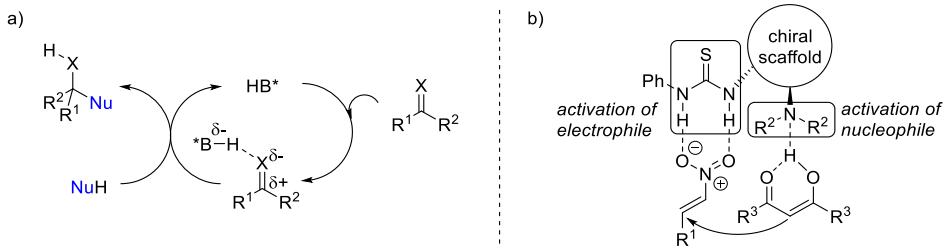
Aminocatalysis is a well-studied class of covalent activation, and is used for the enantioselective functionalization of carbonyl compounds.[56] Depending on the type of active intermediate, enamine **45a** or iminium **44b**, aminocatalysis can be sub-divided into enamine and iminium catalysis (Scheme 24). Enamine-mediated reactions start with the condensation of a chiral aminocatalyst **43** with the carbonyl compound **42a**, generating

an iminium ion **44a**, which is followed by enamine **45a** formation.[56,57] The latter process increases the energy of the highest occupied molecular orbital (HOMO) compared to a corresponding enol, thereby activating the carbonyl compound **42a** to react with an electrophile. In iminium ion-mediated reactions, the condensation of the catalyst **43** with an α,β-unsaturated compound **42b** generates the iminium ion intermediate **44b**.[56] The formation of the intermediate **44b** decreases the energy of the lowest unoccupied molecular orbital (LUMO) compared to the corresponding carbonyl compound, and thus increases the electrophilicity of the intermediate **44b**, making it more appealing for a nucleophile. In the case of both activation modes, the catalyst **43** and the final product **46** are liberated upon hydrolysis.



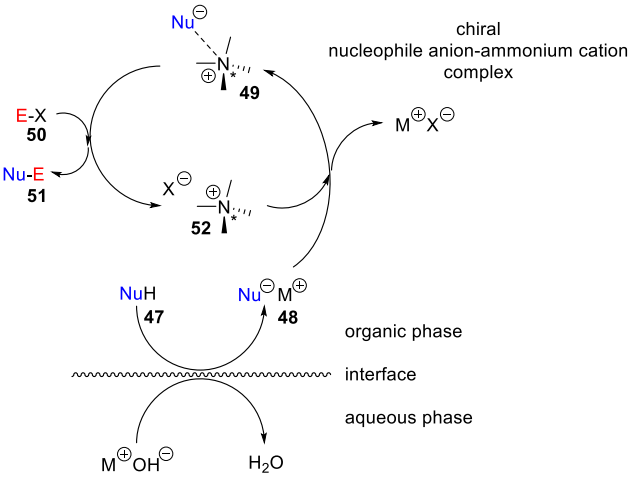
***Scheme 24**. Activation modes in aminocatalysis.*

In addition to covalent activation, noncovalent activation also has a great importance in asymmetric organocatalysis. Noncovalent interactions are weaker, less directional and more affected by entropy than covalent interactions.[58] Nevertheless, a suitable combination of multiple noncovalent interactions may operate in a way which leads to the creation of enantiomerically enriched products. Hydrogen-bond catalysis is a perfect example of this (Scheme 25a).[59] Hydrogen-bond catalysts activate substrates by forming hydrogen-bonding interactions with them, which decreases the LUMO and thereby accelerates the reaction.[48,60] Also, hydrogen bonds play a role in the charge stabilization of a transition state or intermediate. Bifunctional hydrogen-bond donor catalysts, which are extensively used, provide simultaneous activation and suitable orientation of both an electrophile and a nucleophile. Thus, these catalysts often provide higher stereoinduction and catalytic efficiency than monofunctional catalysts do.[60] In 2003, Takemoto et al. reported the first chiral bifunctional thiourea organocatalyst to perform a Michael reaction of malonates to nitroolefins (Scheme 25b).[61] This was a significant milestone for further extensive studies in the field of bifunctional organocatalysis.



***Scheme 25**. a) General mechanism for asymmetric hydrogen-bond catalysis. Adapted from Ref. 59 with permission from the Royal Society of Chemistry.*
b) Example of the activation of substrates in a Michael reaction. Adapted from Ref. 61 with permission from the American Chemical Society.

Phase-transfer catalysis (PTC) belongs to a transformation group where noncovalent ionic interactions are exploited. Phase-transfer reaction usually takes place in two- or three-phase systems and the reaction is mediated by a quaternary ammonium or phosphonium salt acting as a phase-transfer catalyst.[62] Commonly used substrates are carbonyl compounds and Schiff bases.[63] A reaction is initiated at the interface of two phases, where the substrate **47** is deprotonated by an inorganic base (Scheme 26).[48,63] The cation exchange **48** of the nucleophile results in the formation of a chiral complex **49** between a nucleophile anion and an ammonium cation **52**, which is now sufficiently lipophilic to move into organic phase to react with an electrophile **50**. Next, the product **51** is released, and the catalyst **52** returns to the interface for the next catalytic cycle. The stereoselective outcome is determined by the formation of a tight chiral ion pair intermediate **49**.[64] A pioneering study of efficient asymmetric PTC was published by Dolling et al. in 1984, in which they applied the cinchonine-derived quaternary ammonium salt for the alkylation of phenylindanone derivative.[65] Since then, the development of asymmetric PTC has steadily progressed.



***Scheme 26.** General mechanism for asymmetric phase-transfer catalysis by a chiral quaternary ammonium salt. Adapted from Ref. 48 with permission from John Wiley and Sons.*

2 Motivation and aims of the present work

Asymmetric [2,3]-Wittig rearrangement has proven to be a valuable method for the introduction of stereocomplexity and a new carbon-carbon bond to organic molecules. Considering these properties, [2,3]-Wittig rearrangement has shown its great potential in the synthesis of biologically active compounds and natural products. The scope of asymmetric organocatalytic examples of [2,3]-Wittig rearrangement is rather limited, so there is still room for further improvements in the methodology. Therefore, the main aims of the present work are:

- to develop straightforward methods for the synthesis of 2-cinnamyloxycarbonyl compounds as substrates for [2,3]-Wittig rearrangement;

- to elaborate an efficient asymmetric organocatalytic method of [2,3]-Wittig rearrangement for different types of substrates and expand the scope of the reaction;

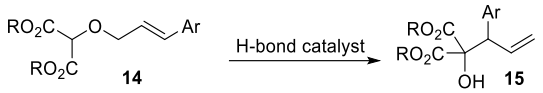
- to investigate the mechanism of asymmetric [2,3]-Wittig rearrangement and factors that influence the transformation;

- to determine the relative and absolute configuration of the new chiral [2,3]-rearranged products.

3 Results and discussion

3.1 Asymmetric organocatalytic [2,3]-Wittig rearrangement of malonates (Publication I)

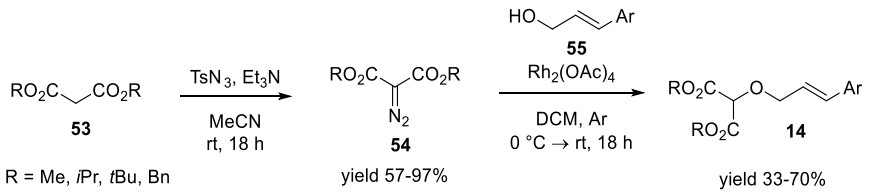
The investigation of the asymmetric organocatalytic [2,3]-Wittig rearrangement of 2-cinnamyloxymalonate derivatives **14** was inspired by our previous work carried out on oxindole derivatives **8** (Scheme 27).[29] We assumed that the organocatalytic rearrangement of malonates could proceed effectively for the following reasons. The α-carbon of a malonate is a good nucleophile due to the delocalization of a negative charge to carbonyl groups. As the deprotonation at the α-position of a 2-cinnamyloxymalonate **14** initiates the rearrangement, the nucleophilicity of the substrate is a crucial factor in terms of the initiation of the rearrangement. Secondly, malonates are capable of forming hydrogen bonds with organocatalysts, which has led to them being extensively used as substrates in organocatalytic reactions.



Scheme 27. *General scheme of the rearrangement of 2-cinnamyloxymalonates **15**.*

3.1.1 Synthesis of 2-cinnamyloxymalonates 14

2-cinnamyloxymalonates **14** were synthesized over two steps starting with symmetric and non-symmetric malonic esters **53** (Scheme 28). The reaction between malonates **53** and tosyl azide in the presence of triethylamine proceeded smoothly and diazomalonates **54** formed in good to excellent yields. The second step, a rhodium catalytic OH-insertion reaction, has proven effective previously for the synthesis of 3-cinnamyloxyoxindoles **8**. The reaction of diazomalonates **54** with cinnamyl alcohol derivatives **55** provided 2-cinnamyloxymalonates **14** in moderate yields, which was caused by the partial transesterification of malonyl esters by cinnamyl alcohol. The yields could be improved by transesterifying them back to **14** with *p*-TsOH in MeOH.

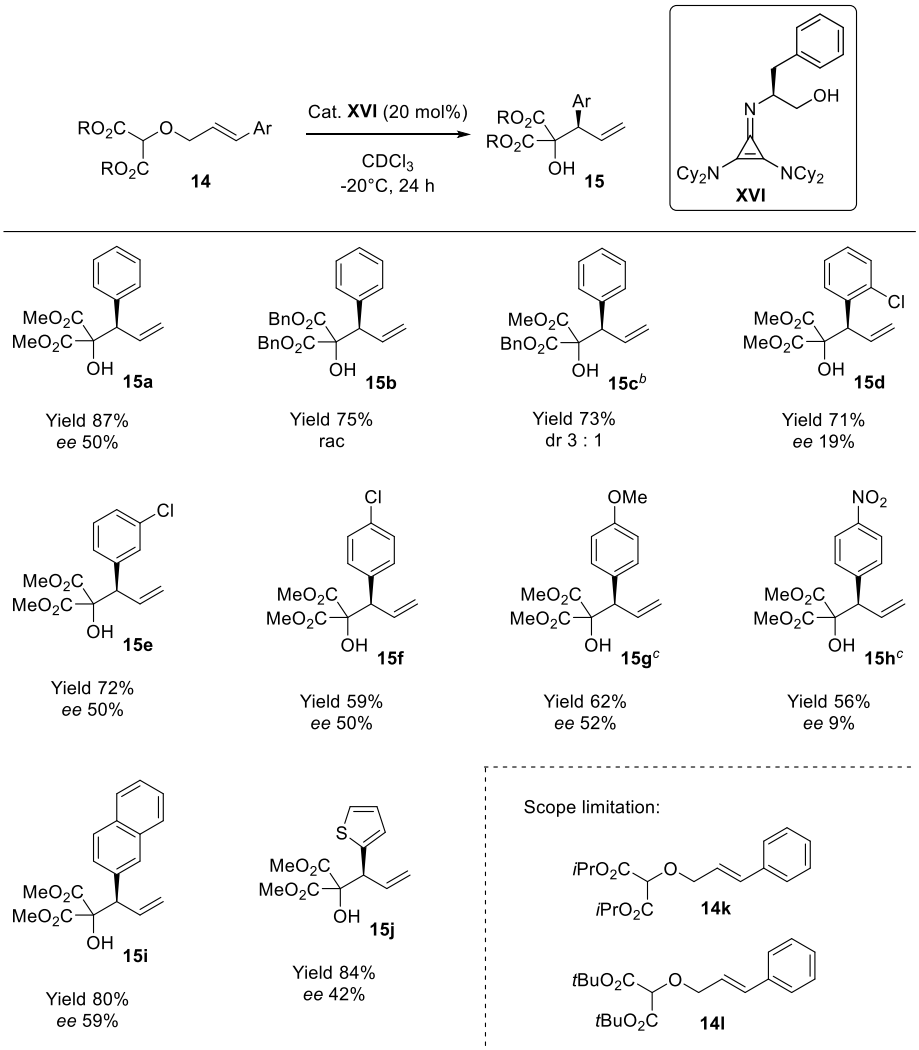


Scheme 28. *Synthesis of 2-cinnamyloxymalonates **14**.*

3.1.2 Asymmetric organocatalytic [2,3]-Wittig rearrangement of 2-cinnamyloxymalonates 14

Next, we focused on the development of an asymmetric organocatalytic rearrangement of 2-cinnamyloxymalonates **14**. In our previous study on oxindole derivatives **8**, we used a bifunctional squaramide **IV** as a catalyst. However, the C2 proton of 2-cinnamyloxymalonates is less acidic than the C3 proton of 3-cinnamyloxyoxindole; thus, a stronger base is required for the rearrangement. The screening experiments demonstrated the ability of highly basic catalysts, such as cyclopropenimines and

guanidines, to catalyze the [2,3]-Wittig rearrangement of malonates **14**. Full conversion and the highest observed selectivity (*ee* 50%) were obtained by using 20 mol% of a highly basic cyclopropenimine catalyst **XVI** in $CDCl_3$ while stirring the reaction mixture at -20 °C for 24 hours.



[a]Reaction conditions: 0.1 mmol scale, 20 mol% of cat. **XVI**, $CDCl_3$ (0.5 mL), -20 °C, 24 h. *ee* determined by chiral HPLC analysis of the isolated product. [b]dr determined by ^1H NMR analysis of the crude mixture. [c]Reaction was finished after 48 h.

***Figure 3**. Scope of the [2,3]-Wittig rearrangement of 2-cinnamyloxymalonates **14**.[a]*

Subsequently, the scope of the asymmetric organocatalytic [2,3]-Wittig rearrangement was investigated (Figure 3). We intended to improve the reaction selectivity by using malonic esters bulkier than the model compound **14a**. The reactions with symmetric malonic esters **14a-b**, **14k-l** and non-symmetric **14c** revealed that dimethylmalonate **14a** was still the optimal substrate, while the bulkier substrates **14k-l** remained unreactive. Unfortunately, the diastereomeric ratio of the non-symmetric

product **15c** was low and we could not determine the *ee* for this product, because the diastereomers were inseparable in chiral HPLC. Furthermore, we studied the effect of electron-withdrawing groups on the transformation (substrates **14d-f** and **14h**). The results with *para*- and *meta*-chloro-substituted substrates **14e**-**f** were comparable to the model compound **14a**, whereas the enantiopurities of *ortho*-chloro **15d** and *para*-nitro **15h** products were significantly lower. The nitro group is a strong hydrogen-bond acceptor, which may have had an influence on the transition state. The rearrangements of the substrates bearing electron-donating *para*-methoxyphenyl group **14g**, aromatic **14i** and heteroaromatic **14j** substituents proceeded smoothly. The absolute configuration of the rearranged product **14a** was determined by a comparison of the optical rotation with the data previously published by the Jacobsen group.[27] The configurations of other compounds in the series were assigned by analogy.

The rearrangement starts from the deprotonation of the substrate **14a** by a highly basic catalyst cyclopropenimine **XVI**, first designed by the Lambert group. The cyclopropenium ion coordinates the enolized starting material through hydrogen bonds, which determine the proposed transition state (Figure 4). Lambert et al. have previously observed that a weak noncovalent intramolecular CH···O interaction (0.5 kcal/mol) is responsible for the transition state organization.[66,67] In the control experiment with the catalyst, which has a methyl-protected hydroxy group and thus is incapable of forming additional hydrogen bonds, the selectivity decreased drastically, indicating the importance of weak interactions in the transition state.

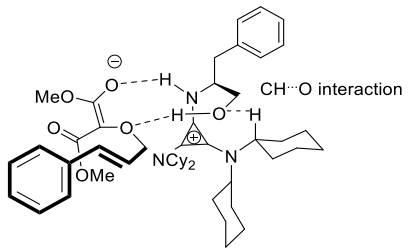


***Figure 4**. Proposed transition state of 2-cinnamyloxymalonate **14a** rearrangement.*

In summary, a method for the asymmetric organocatalytic [2,3]-Wittig rearrangement of 2-cinnamyloxymalonates **14** in the presence of highly basic cyclopropenimine **XVI** was developed. 2-allyl-2-hydroxymalonates **15** were isolated in good yields and moderate enantiomeric purities.

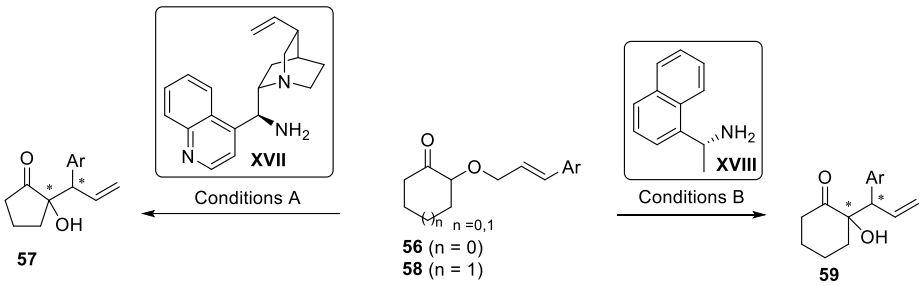
3.2 Asymmetric organocatalytic [2,3]-Wittig rearrangement of cyclic ketones (Publication II and III)

The asymmetric organocatalytic [2,3]-Wittig rearrangement of malonates produced moderate results, and thus we were curious to investigate the potential of cyclic ketones in rearrangement. Malonates and cyclic ketones have several differences which determine the reaction outcome and the choice of a suitable catalytic system: a) malonates are conformationally more flexible than cyclic ketones, and b) the α-proton of the malonate is more acidic compared to a cyclic ketone. Cyclic ketones may require a different catalytic approach than malonates and oxindoles, but, they are interesting substrates as they are often incorporated into natural products. Also, the asymmetric

[2,3]-Wittig rearrangement can be seen as a formal α-alkylation method of ketones, thus providing the solution for one of the most intriguing problems in asymmetric synthesis: the asymmetric alkylation of ketones.[68]

3.2.1 A comparison of five- and six-membered cyclic substrates

In this chapter, the asymmetric organocatalytic [2,3]-Wittig rearrangement of 2-cinnamyloxycyclopentanone **56** and 2-cinnamyloxycyclohexanone **58** derivatives is described (**Publications II** and **III**). The screening experiments revealed that both stereoselectivity and reactivity were affected if the optimal conditions of a five-membered cycle were applied to a six-membered cycle and vice versa (Scheme 29). This is presumably dictated by the different ring sizes and conformations of the substrates.



Scheme 29. *General scheme of the [2,3]-Wittig rearrangement of five- and six-membered cyclic substrates.*

Cyclopentanes are more strained, having a ring strain 6 kcal/mol higher than cyclohexanes.[69] Thus, the six-membered ring is conformationally more flexible and the number of possible stable conformations is higher than the five-membered one. Also, the substituents of the carbocycle may favor one specific orientation over another. The examined cyclic substrates bore a carbonyl group and an alkyl substituent at the α-position of the carbonyl group. For example, it has been proven that an alkyl substituent of a cyclohexanone ring is more stable in the equatorial than in the axial orientation (Figure 5).[69] These factors in combination with the pericyclic nature of [2,3]-Wittig rearrangement influence the transition state structure and thereby the reaction outcome.

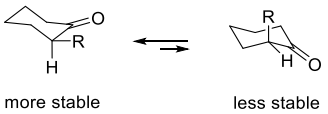


Figure 5. *Conformations of an alkyl-substituted cyclohexanone.*

3.2.2 [2,3]-Wittig rearrangement as a formal asymmetric alkylation method of α-branched ketones

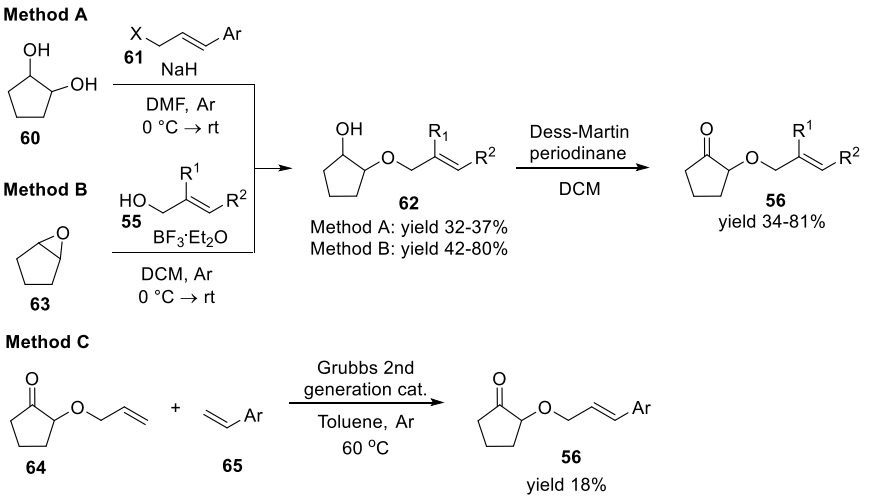
The creation of new carbon-carbon bonds catalytically, in an enantioselective manner, is one of the main targets of modern organic synthesis. The asymmetric α-alkylation of ketones has received a great deal of attention, although, the scope of direct asymmetric α-alkylations has remained underdeveloped.[68] The α-alkylation of α-branched ketones is even more problematic due to the steric hindrance and the inductive effect of the substituent.

[2,3]-Wittig rearrangement is a perfect tool for the enantioselective synthesis of homoallyl alcohols. On the other hand, [2,3]-Wittig rearrangement can also be seen as a formal alkylation method of α-branched ketones if suitable substrates are chosen. Compared to direct methods, formal alkylation methods permit access to a higher number of different starting materials and alkylating agents. Most commonly, transition metal catalysis is used for the α-alkylation of α-branched ketones.[70,71] Organocatalysis has offered methods which are mediated by phase-transfer catalysts,[72,73] bifunctional organocatalysts,[74–77] primary amines[78] and chiral phosphoric acids.[79,80] Photocatalytic methods have only applied to α-branched β-ketocarbonyl compounds.[81–84] The examples published so far are substrate specific, and so even indirect alkylation methods, such as asymmetric [2,3]-Wittig rearrangement, expand the existing alkylation methodology.

3.2.3 Synthesis of cyclic 2-cinnamyloxyketones

The synthesis of cyclic 2-cinnamyloxycycloketones **56** had not been described in the literature when we started this project. In previous studies, 2-cinnamyloxymalonates **14** and 3-cinnamyloxyoxindoles **8** were obtained by using the rhodium-catalyzed OH-insertion reaction. However, this approach was not suitable for the synthesis of cyclic 2-cinnamyloxyketones **56**, because the formation of a racemic [2,3]-rearranged product was observed exclusively.

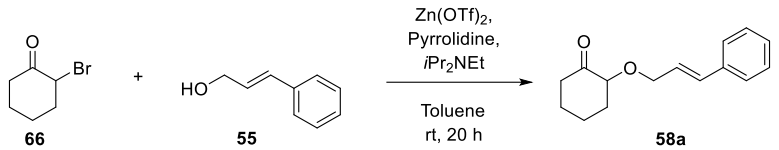
For **Publication II**, we synthesized 2-cinnamyloxycyclopentanones **56** using three different approaches. First, we tried the Williamson ether synthesis of a diol **60** and a cinnamyl halide derivative **61** (Scheme 30, Method A). Unfortunately, the product **62** formed in low yield, because of the overalkylation of the diol **60**. In addition, the cinnamyl halide derivatives **61** are not commercially available, and thus the conversion of cinnamyl alcohols **55** to halides **61** adds an additional step to the reaction sequence. The epoxide opening reaction with a cinnamyl alcohol **55** was mediated by a Lewis acid, which is required for the activation of the epoxide **63** (Scheme 30, Method B). However, the method was not suitable for the synthesis of substrates containing an additional ether or thioether fragment and double bond, most probably because of the presence of a Lewis acid. For both methods, alcohols **62** were oxidized to final ketones **56**. The cross-metathesis between a ketone **64** and a styrene derivative **65** was an alternative solution for synthesizing substrates, which were impossible to obtain otherwise (Scheme 30, Method C). Unfortunately, a low yield resulted from the self-metathesis of alkenes as a side reaction.



Scheme 30. *Three methods for the synthesis of 2-cinnamyloxycyclopentanones **56**.*

As the 2-cinnamyloxycyclopentanones **56** were synthesized over two or three steps and the process was highly time- and resource-consuming, our aim was to develop a one-step procedure for 2-cinnamyloxycyclohexanones **58**. The first attempt, a S_N2 reaction between a 2-bromoketone **66** and an alcohol **55**, was not successful. Inspired by the work of Limanto et al., we turned our attention to a zinc-amine-promoted reaction, which was successfully applied for the etherification of an 2-chloroketone with an aliphatic alcohol.[85] After optimization (see **Publication III**), we obtained 2-cinnamyloxycyclohexanones **58** in moderate yield (44%) when performing the reaction at room temperature in the presence of zinc triflate, Hünig's base and pyrrolidine in toluene for 20 hours (Table 1, entry 1). Zinc chloride, the optimal Lewis acid according to Limanto's work, showed lower yield than $Zn(OTf)_2$ (Table 1, entry 2). Toluene proved to be the best solvent for this transformation (Table 1, entry 3). Further experiments using different amounts of ketone **66** (1.2, 1.5 and 2 eq) showed that 1.5 eq of ketone **66** was the optimal choice for the reaction (Table 1, entries 1, 4-5). Finally, we tried to extend the reaction time to reach full conversion, but 2-cinnamyloxycyclohexanone **58a** was converted to a racemic [2,3]-Wittig rearrangement product **59a** (Table 1, entry 6). This observation illustrates the importance of finding a balance between the higher yield of the desired product and overreacting by pushing the transformation to a higher conversion. Different aromatic, heteroaromatic, crotyl- and propargyl-substituted substrates were obtained in moderate yields. The described method has several advantages over others used in **Publication II**. Not only is the yield of this one-step procedure comparable to the overall yield of the multi-step procedures, but it is also operationally simpler and faster. Moreover, expensive reagents, such as Dess-Martin periodinane and Grubbs catalyst, are not required. The developed method is also universal and the substrates in the series were synthesized this way.

Table 1. *Optimization of the reaction conditions for the synthesis of 2-cinnamyloxycyclohexanones* ***58****.*



66 **55** **58a**

Entry	Deviation from standard conditions	Isolated yield (%)
1[a]	none	44
2	Lewis acid: $ZnCl_2$ (0.4 eq)	26
3	solvent: THF (dry)	34
4	2-bromoketone (2 eq)	45
5	2-bromoketone (1.2 eq)	21
6	reaction time: 48 h	-

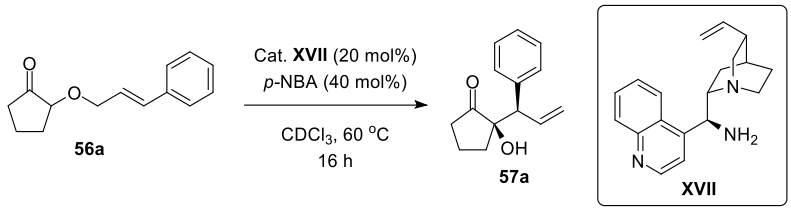
[a]Reaction conditions: 0.4 mmol scale, 1 eq of alcohol **55**, 1.5 eq of 2-bromoketone **66**, 0.4 eq of $Zn(OTf)_2$, 2 eq of *i*Pr_2NEt, 1 eq of pyrrolidine, rt, toluene (0.4 mL), 20 h.

3.2.4 Asymmetric organocatalytic [2,3]-Wittig rearrangement of 2-cinnamyloxycyclopentanones 56

We investigated the asymmetric organocatalytic [2,3]-Wittig rearrangement of 2-cinnamyloxycyclopentanone derivatives **56** after the successful starting material synthesis. This study was inspired by the publication of the Gaunt research group in which an enamine-catalyzed [2,3]-Wittig rearrangement was conducted on aliphatic ketones.[24] It had been proven beforehand that the bulkiness of a carbonyl compound dictates whether a primary or a secondary amine is able to catalyze the reaction.[57,86] Secondary amines are perfect catalysts for non-hindered carbonyl compounds. On the other hand, primary amines are commonly used for sterically more demanding α-branched ketones and aldehydes. Typically, an acidic co-catalyst is employed to accelerate the condensation of the aminocatalyst with the carbonyl compound. Therefore, during the optimization experiments, we focused on the use of primary amines in combination with acids.

After extensive optimization (see **Publication II** and the supporting information), full conversion and excellent enantiomeric excess (94% *ee*) for the major diastereomer were obtained after stirring the reaction at 60 °C in the presence of a Cinchona alkaloid-derived amine **XVII** and *p*-NBA (*p*-nitrobenzoic acid) in $CDCl_3$ (Table 2, entry 1). Lowering the temperature to 50 °C resulted in slightly higher enantioselectivities and decreased conversion (Table 2, entry 2). The use of TFA provided both diastereomers with the highest *ee*. However, the conversion decreased significantly (Table 2, entry 3). The necessity of an acidic co-catalyst was confirmed when the rearrangement was conducted without an acid (Table 2, entry 4). Finally, an experiment with molecular sieves demonstrated that the presence of water is crucial for the rearrangement (Table 2, entry 5). In the catalytic cycle, water is responsible for the release of the product **57** and the catalyst **XVII** upon hydrolysis.

Table 2. *Optimization of the asymmetric [2,3]-Wittig rearrangement of ketone* ***56a****.*



Entry	Deviation from standard conditions	Conv. (%)[b]	dr[b]	*ee* (%)[c]
1[a]	none	99	3.5 : 1	94/17
2	temperature: 50 °C	78	nd	96/35
3	acid: TFA	60	nd	95/56
4	no acid	15	nd	nd
5	additive: MS 4Å	traces	nd	nd

[a]Reaction conditions: 0.1 mmol scale, 20 mol% of cat **XVII**., 40 mol% of *p*-NBA, 60 °C, $CHCl_3$ (0.5 mL), 16 h. [b]Conversion and diastereomeric ratio determined by ^{1}H NMR analysis of the crude mixture. [c]*ee* determined by chiral HPLC analysis.

To better understand the reaction, we carried out a kinetic study of the [2,3]-Wittig rearrangement of the model compound **56a** (Figure 6). The consumption of the substrate **56a** was determined by taking crude samples for an NMR analysis over time. The rapid consumption of the starting compound **56a** pointed to the condensation of the catalyst **XVII** with the 2-cinnamyloxycyclopentanone **56a**. The α-hydroxyketone **57a** was detected after one hour. The substrate **56a** was consumed in 23 hours; however, the NMR yield of the product **57a** did not improve after the extended reaction time. We proposed that the lowered NMR yield was caused by the side reactions and the partial decomposition of the substrate **56a** at higher temperatures.

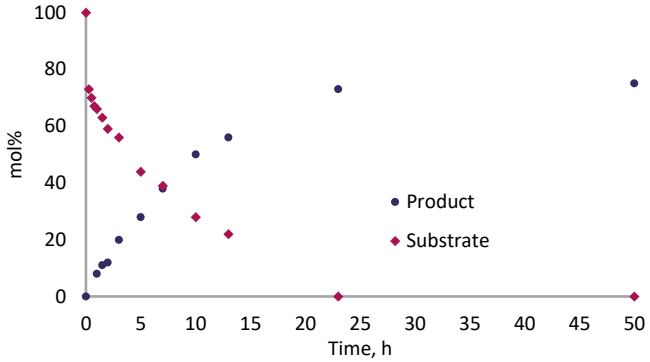


Figure 6*. Kinetic study of the [2,3]-Wittig rearrangement of model compound* ***56a****.*

In parallel with the kinetic studies, we also investigated the change in the enantiomeric excess and diastereomeric ratio of the [2,3]-rearranged products **57a** under the reaction conditions. A decrease in the enantiomeric excess for both diastereomers of rearranged products **57a** was observed (Figure 7). Although the *ee* of the major diastereomer (*syn*-isomer) remained very high throughout the entire reaction time, the *ee* of the minor diastereomer (*anti*-isomer) decreased rapidly and eventually became reversed. Based on the epimerization curve, it can be assumed that the minor diastereomer is formed in high enantioselectivity as a result of the rearrangement.

Considering the relatively high diastereomeric ratio, even low epimerization of the major enantiomer of the major diastereomer (*syn*-isomer) leads to the formation of the minor diastereomer (*anti*-isomer), causing its racemization. In additional control experiments, we found that the rearranged product **57a** is stable in the presence of an aminocatalyst or *para*-nitrobenzoic acid, but epimerizes under acidic aqueous conditions.

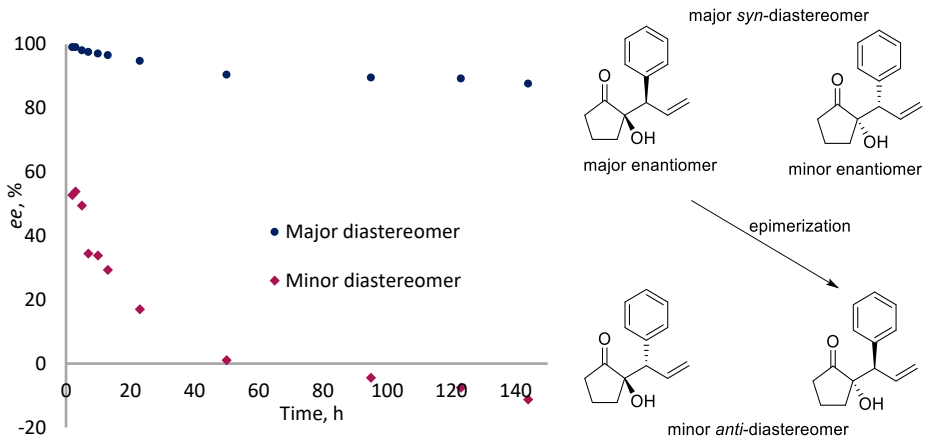
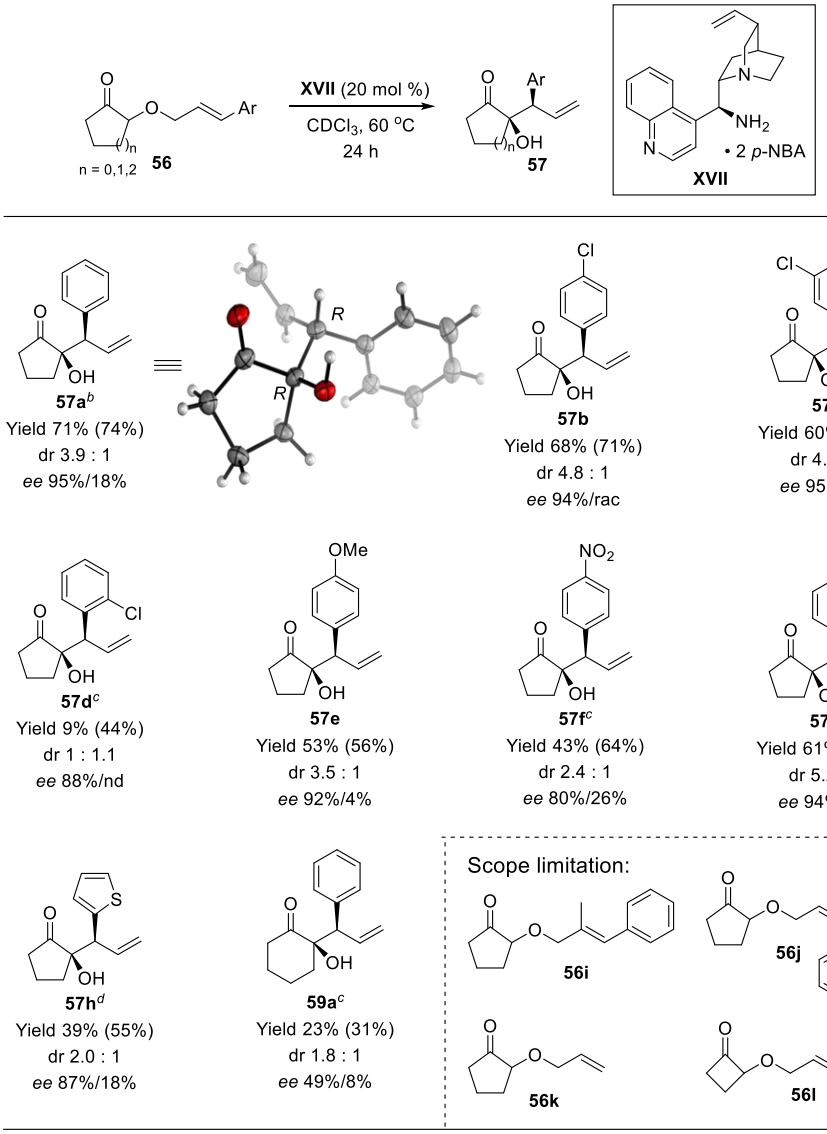


***Figure 7**. Epimerization of [2,3]-rearranged product **57a**.*

With optimal conditions in hand, we investigated the scope of the asymmetric aminocatalyzed [2,3]-Wittig rearrangement (Figure 8). The reaction with the model compound **56a** at 1 mmol scale proceeded smoothly and the product **57a** was isolated in good yield and with excellent enantiomeric purity for the major diastereomer. Next, the effects of substrates bearing electron-withdrawing **56b-d**, **56f** and electron-donating **56e** substituents were explored. Electron-donating compound **56e** and -withdrawing substrates **56b-c** were tolerated well, but, the rearrangement of *ortho*-chloro- and *para*-nitro-substituted compounds **56d** and **56f** proceeded sluggishly, even after running the reactions over an extended period of time. The low reactivity of the *ortho*-chloro compound **56d** was probably caused by a steric effect. 2-naphthyl-substituted α-hydroxyketone **57g** was obtained with the highest diastereomeric ratio in the reaction series. Rearrangement with the compound **56h** bearing a heteroaromatic substituent was rather slow and a decrease in *ee* was observed. The six-membered rearrangement product **59a** was obtained in low yield and enantiopurity, which motivated us to find a better solution in the next publication. Additionally, limitations on scope were revealed. Substrates **56i-k** remained unreactive under the optimal conditions and the decomposition of the 2-cinnamyloxycyclobutanone **56l** was observed by NMR spectroscopy. The relative and the absolute configurations of the major diastereomer of the product **57a** were assigned by a single crystal X-ray diffraction and the configurations of the other rearranged products **57** in the series were assigned by analogy (Figure 8).

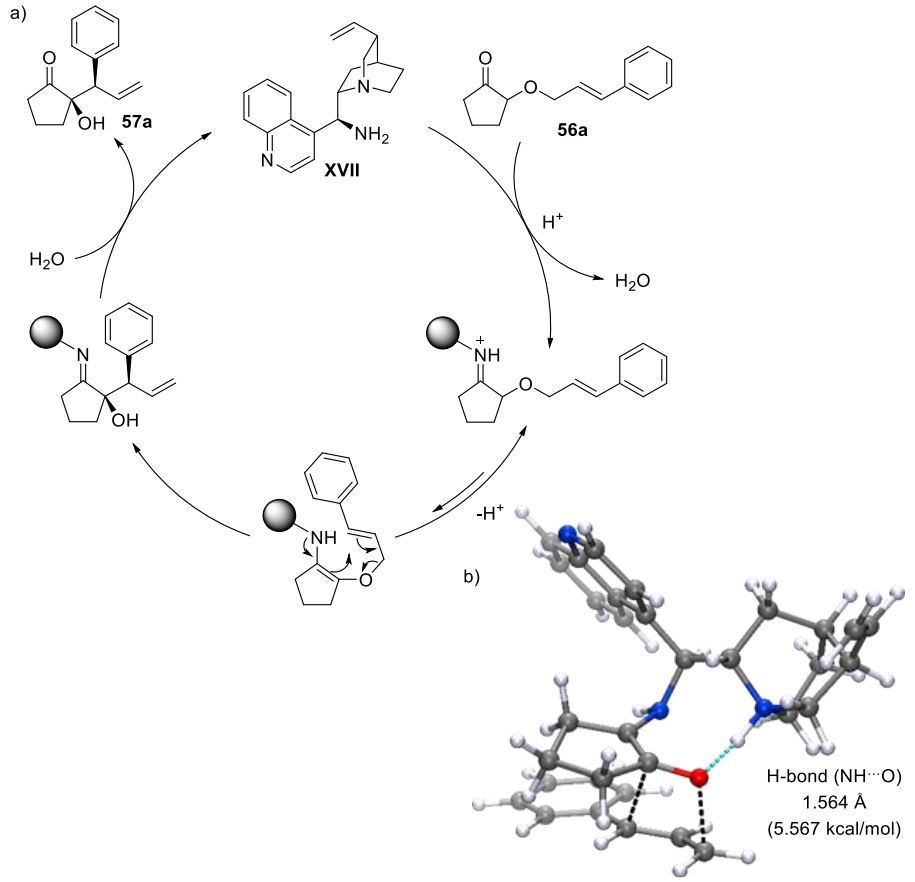


[a]Reaction conditions: 0.2 mmol scale, 20 mol% of cat. **XVII**, $CDCl_3$ (1 mL), 60 °C, 24 h. *ee* determined by chiral HPLC and dr by ^{1}H NMR analysis of the isolated product. NMR yield (in parentheses) determined by ^{1}H NMR analysis of the crude mixture. [b]1.0 mmol reaction scale, reaction time 30 h. [c]Reaction was stopped after 72 h. [d]Reaction was stopped after 48 h.

Figure 8. *Scope of the [2,3]-Wittig rearrangement of 2-cinnamyloxycyclopentanones* ***56****.*[a]

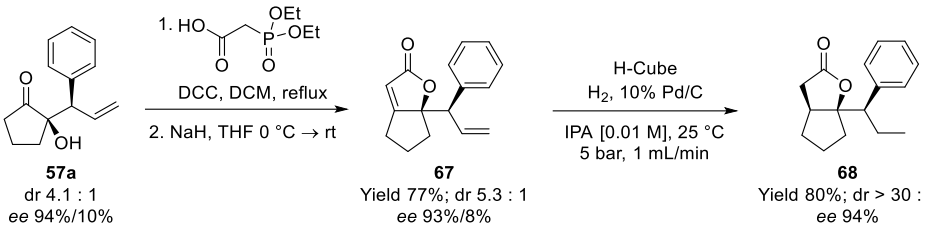
The proposed catalytic cycle of the [2,3]-Wittig rearrangement starts with the condensation of a primary amine **XVII** with the 2-cinnamyloxycyclopentanone **56a** under acidic conditions, which is followed by the formation of an iminium ion (Scheme 31a). There is an unfavorable equilibrium between the imine and the enamine, which is directed to the more stable imine. The formation of a reactive enamine is followed by a concerted [2,3]-rearrangement through a five-membered transition state and the α-hydroxyketone **57a** is liberated upon hydrolysis.

The absolute configuration of the major diastereomer of α-hydroxyketone **57a** was used to design the transition state leading to the formation of a major isomer (Scheme 31b). The DFT calculations of the five-membered transition state proved that the enamine was stabilized by a strong hydrogen bond (1.564 Å, 5.567 kcal/mol, depicted in light blue color) between the ether oxygen atom of the substrate **56a** and the protonated nitrogen atom of the quinuclidine moiety of the catalyst **XVII**.



Scheme 31. *a) Proposed catalytic cycle and b) DFT calculated transition state.*

Eventually, we demonstrated a straightforward approach for the construction of a bicyclic lactone **68**, starting with the rearranged product **57a**, inspired by the work of Ye and Jiang (Scheme 32).[87] The one-pot procedure started with the esterification of the tertiary hydroxyl group and was followed by an intramolecular Horner-Wadsworth-Emmons reaction. Next, the saturated lactone **67** was reduced and the product **68** containing three adjacent stereogenic centers was isolated as a single diastereomer. The enantiomeric ratio of the final product **68** remained throughout the synthesis. The relative configuration of **68** was determined by a 2D NOESY NMR experiment.



57a
dr 4.1 : 1
ee 94%/10%

67
Yield 77%; dr 5.3 : 1
ee 93%/8%

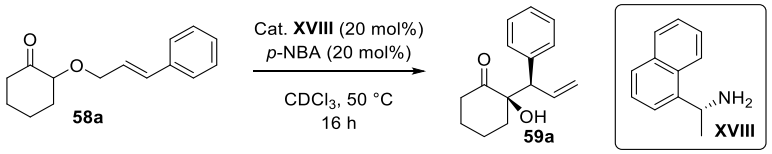
68
Yield 80%; dr > 30 : 1
ee 94%

***Scheme 32**. Derivatization of [2,3]-rearranged product **57a**.*

3.2.5 Asymmetric organocatalytic [2,3]-Wittig rearrangement of 2-cinnamyloxycyclohexanones 58

After the successful results achieved with the five-membered cyclic ketones **56**, we continued our study on 2-cinnamyloxycyclohexanone derivatives **58**. The optimization of reaction conditions (see **Publication III** and the supporting information) resulted in the formation of the rearrangement product **59a** in full conversion and with high enantiomeric purity and diastereomeric ratio (*ee* 80%, dr 6.8 : 1) (Table 3, entry 1). The reaction was conducted at 50 °C using a primary amine **XVIII** and *p*-NBA in $CDCl_3$ for 16 hours. Enantio- and diastereoselectivity improved at 40 °C but, unfortunately, the conversion was incomplete (Table 3, entry 2). *p*-NBA was the optimal co-catalyst for the rearrangement, while other acids were less effective (Table 3, entry 3). Despite low conversion, the rearrangement in anhydrous THF was highly enantioselective (Table 3, entry 4). The addition of water to THF improved the conversion without a significant loss of *ee*, but the conversion was still not sufficient to conduct the substrate scope exploration (Table 3, entry 5).

***Table 3**. Optimization of the asymmetric [2,3]-Wittig rearrangement of ketone **58a**.*



Entry	Deviation from standard conditions	Conv. (%)[b]	dr[b]	*ee* (%)[c]
1[a]	none	99	6.8 : 1	80/22
2	temperature: 40 °C	66	7.5 : 1	84/34
3	acid: 2,3,4,5-tetra-fluorobenzoic acid	93	5.4 : 1	75/29
4	solvent: THF (dry)	14	nd	93/81
5	solvent + additive: THF (dry) + H_2O (10 eq)	49	5.0 : 1	92/77

[a]Reaction conditions: 0.1 mmol scale, 20 mol% of cat. **XVIII**., 20 mol% of *p*-NBA, 50 °C, $CHCl_3$ (0.5 mL), 16 h. [b]Conversion and diastereomeric ratio determined by ^1H NMR analysis of the crude mixture. [c]*ee* determined by chiral HPLC analysis.

We realized that additional experiments were required before continuing with the scope of the [2,3]-Wittig rearrangement. It was observed that, similarly to cyclopentanones **57**, the enantiomeric excess and diastereomeric ratio of the α-hydroxyketones **59a** were not constant under reaction conditions. Hence, a longer reaction time might result in the loss of *ee*. Therefore, it is important to find the best combination of conversion and selectivity. For this reason, a kinetic study on the compound **58a** was carried out prior to the scope to investigate the reaction behavior over time (Figure 9). The procedure was

analogous to the one used in the previous study of 2-cinnamyloxycyclopentanone **56a** (Figure 6). The rapid consumption of the substrate **58a** was followed by the formation of product **59a**, which was already detectable after 0.5 hours. The six-membered substrate underwent rearrangement more readily than the five-membered one, as it required a 10 °C lower temperature to reach full conversion in 24 hours, and the isolated yield was higher, because 2-cinnamyloxycyclopentanone **56a** is more prone to decompose at higher temperature.

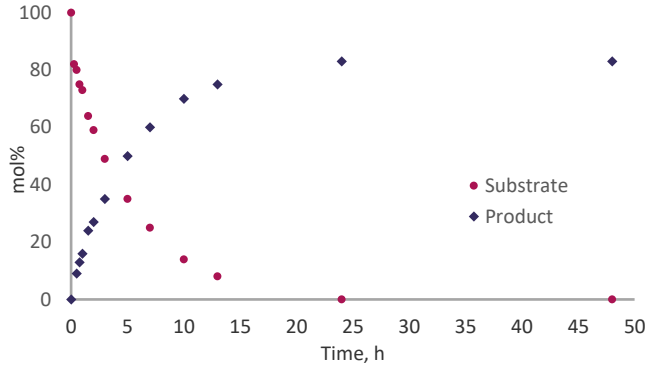


Figure 9. *Kinetic study of the [2,3]-Wittig rearrangement of model compound* ***58a****.*

Next, we investigated the change in the enantiomeric excess under the reaction conditions (Figure 10). After a significant drop, the *ee* reached plateaus after 10 hours and remained the same for a prolonged time. The kinetic observations demonstrated that the product **59a** could be obtained with the highest possible yield, and yet with satisfying enantioselectivity, after running the reaction for 24 hours. Thus, we concluded that 24 hours was the optimal reaction time.

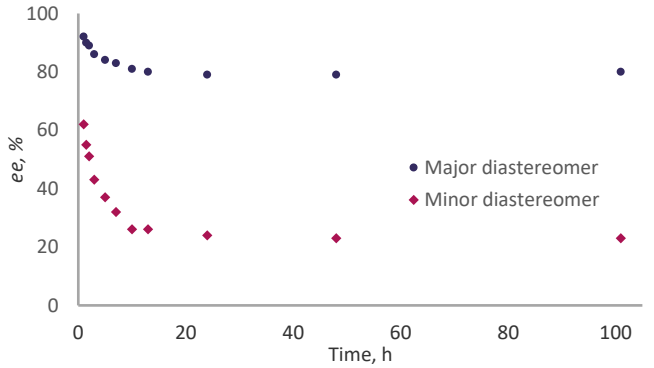
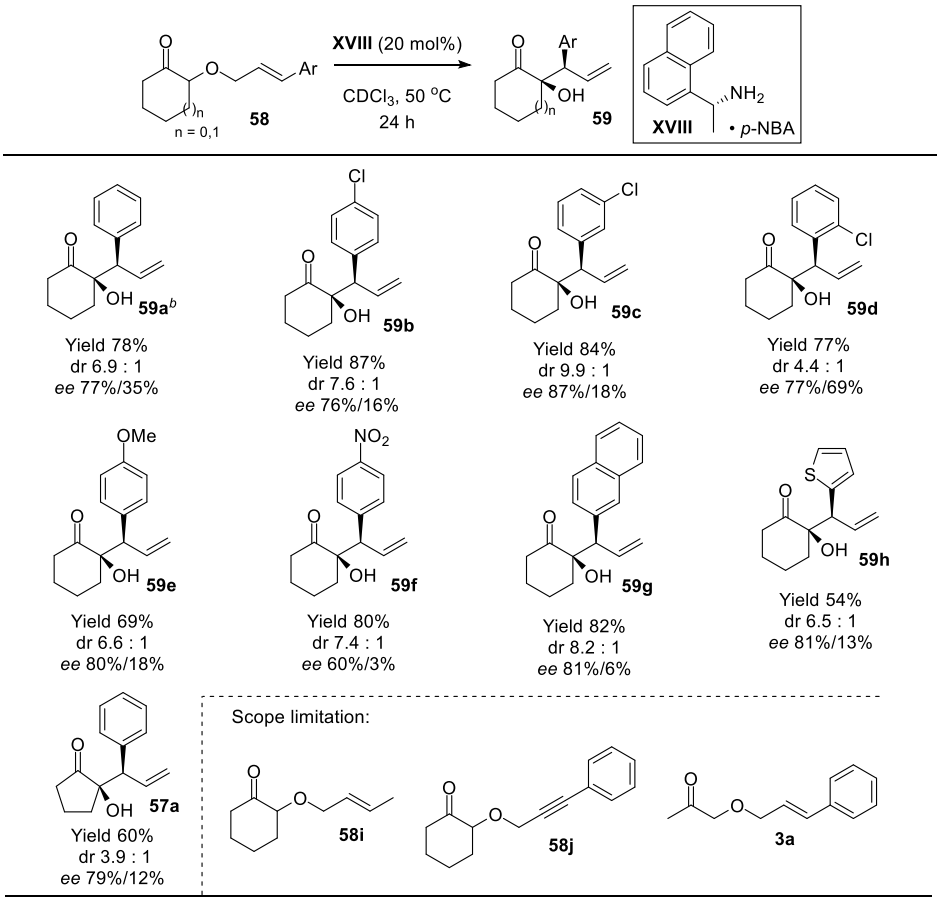


Figure 10*. [2,3]-rearranged product* ***59a*** *epimerization over time.*

After establishing the optimal conditions, the scope of the asymmetric [2,3]-Wittig rearrangement of 2-cinnamyloxycyclohexanone derivatives **58** was investigated. We conducted the rearrangement with the model compound **58a** at 1.0 mmol scale, which proceeded in good yield and enantioselectivity. Although there was some effect of the electron-withdrawing substituents (substrates **58b-d**, **58f**) and the electron-donating substituent (substrate **58e**) on the reaction, the corresponding rearrangement products

were isolated in high yields and stereoselectivities. The *meta*-chloro-substituted product **59c** stood out, with the highest enantiomeric excess in the reaction series, while the enantiomeric excess of *para*-nitro product **59f** was the lowest. It is worth noting that the rearrangement of all *para*-nitro-substituted substrates (**14h**, **56f** and **58f**) always proceeded with lower enantioselectivity than other substrates in the series. This was probably caused by the fact that the nitro group is a strong electron-withdrawing group, as well as a strong hydrogen-bond acceptor, which may influence the transition state. Aromatic and heteroaromatic products **59g-h** were obtained with similar enantiomeric purities. The rearrangement of 2-cinnamyloxycyclopentanone **56a** indicated clearly that the optimal conditions for five-membered substrates had already been determined in **Publication II** (yield 71%; dr 3.9 : 1; *ee* 95%/18%). Unfortunately, crotyl and propargyl ethers **58i-j** were unreactive. Rearrangement with the aliphatic ketone **3a** did not occur, confirming that the scope is limited to cyclic ketones only. The absolute configuration of the major diastereomer of the rearranged product **59a** was determined by a comparison of the chiral HPLC chromatogram with the data published previously in **Publication II**. The configurations of other products **59** in the series were assigned by analogy.



[a]Reaction conditions: 0.2 mmol scale, 20 mol% of cat. **XVIII**, $CDCl_3$ (1 mL), 50 °C, 24 h. *ee* determined by chiral HPLC and dr by ^1H NMR analysis of the isolated product. [b]1.0 mmol reaction scale.

Figure 11. *Scope of the [2,3]-Wittig rearrangement of 2-cinnamyloxycyclohexanones* ***58****.*[a]

3.2.6 Phase-transfer catalysis as an alternative method for the asymmetric [2,3]-Wittig rearrangement of 2-cinnamyloxycyclohexanones 58 (unpublished results)

As an alternative to enamine catalysis, we attempted to develop an asymmetric phase-transfer catalytic approach. Twenty-one different ammonium and phosphonium salts were tested, the majority of which were derived from Cinchona alkaloids, bearing different aromatic substituents and counter-anions (Figure 12). The preliminary results were somewhat promising indicating that the reaction proceeds under PTC conditions. Conversion, diastereo- and enantioselectivity were moderate (conv. = 17%, dr = 2 : 1 and *ee* = 35%/7%), although this was a good starting point for further experiments.

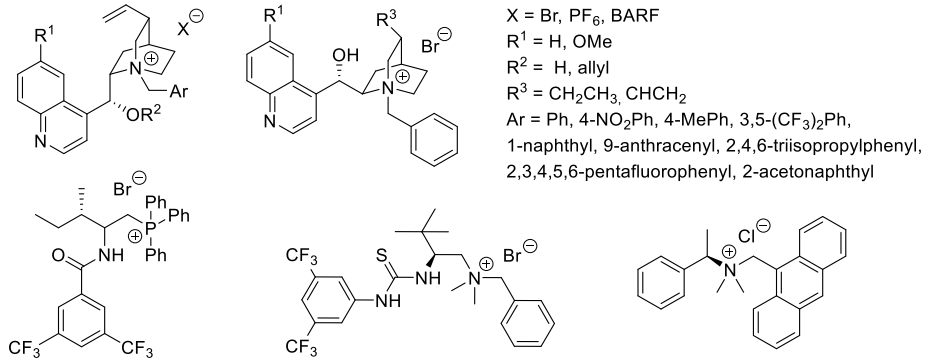
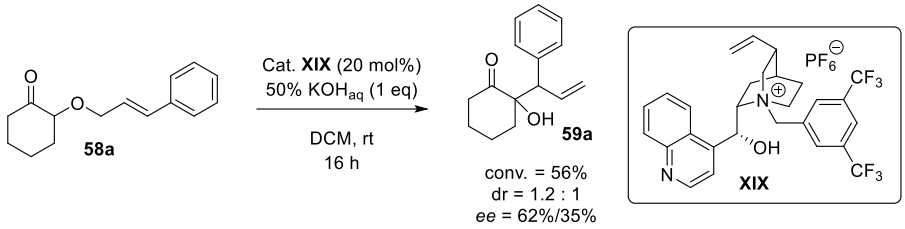


Figure 12. *The library of the screened catalysts.*

It was difficult to determine, which parameters had the strongest impact on conversion and enantioselectivity. However, some important factors were recognized. When the bromide anion of a catalyst was replaced with PF_6^-, the conversion doubled. Interestingly, the bulkier $BARF^-$ anion decreased the conversion and a racemic product was formed. The reactions with the catalysts bearing a 3,5-bis(trifluoromethyl)benzyl group showed enantioselectivities around 60%, but unfortunately a considerable decrease in conversion was observed. Next, we combined the best features into one catalyst (the most suitable alkaloid, counter-anion and a substituent of the quaternary nitrogen atom of the quinuclidine moiety), but the result was still far from ideal. One drawback was the occurrence of a racemic background reaction, which is a common problem for phase-transfer catalysis.

After carrying out almost 60 screening experiments with different combinations of catalysts, inorganic bases and solvents, we managed to obtain the rearranged product **59a** with moderate conversion and enantiomeric purity (Scheme 33). As the substrate **58a** and the product **59a** are chromatographically inseparable, the incomplete conversion is one of the main problems of this methodology. For this reason, we decided to focus on the investigation of the enamine-catalyzed [2,3]-Wittig rearrangement of 2-cinnamyloxycyclohexanones **58**.



Scheme 33. *The best results obtained using phase-transfer catalysis.*

3.2.7 Summary of the asymmetric organocatalytic [2,3]-Wittig rearrangement of cyclic ketones

The development of the enamine-catalyzed [2,3]-Wittig rearrangement of 2-cinnamyloxycyclopentanones **56** and 2-cinnamyloxycyclohexanones **58** has been described. The rearrangement provided five-membered α-hydroxyketones **57** in good yields (up to 71%) and diastereoselectivities (up to 5.2 : 1) and with excellent enantioselectivity for the major diastereomer (up to 95%). Despite the lower enantiomeric purities (up to 87%) of the six-membered products **59**, the yields and diastereomeric ratio improved (up to 87% and 9.9 : 1, respectively). Besides the enamine catalysis, the capability of the phase-transfer catalysis was investigated on 2-cinnamyloxycyclohexanones **58** giving somewhat promising results. A new straightforward method for the synthesis of 2-cinnamyloxycyclohexanones **58** was developed.

4 Conclusions

- A general method for the synthesis of 2-cinnamyloxymalonates **14** was developed. 2-cinnamyloxycyclopentanones **56** were obtained by using different multi-step procedures. An improved and straightforward one-step procedure was developed for the synthesis of 2-cinnamyloxycyclohexanones **58**.

- The hydrogen-bond-mediated [2,3]-Wittig rearrangement of 2-cinnamyloxymalonates **14** was catalyzed by the highly basic cyclopropenimine **XVI**. The rearranged products **15** were obtained in high yields and with moderate enantiopurities.

- The importance of hydrogen-bonding in the transition state organization between 2-cinnamyloxymalonate **14a** and the cyclopropenimine **XVI** was demonstrated.

- The enamine-mediated [2,3]-Wittig rearrangement of cyclic 2-cinnamyloxyketones **56** and **58** proceeded smoothly and the rearranged products **57** and **59** were isolated in good yields and with good to excellent enantiomeric purities.

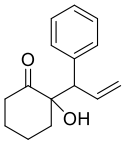
- The proposed transition state of the [2,3]-Wittig rearrangement of 2-cinnamyloxycyclopentanone **56a** was designed based on the X-ray crystal structure of the major diastereomer of the rearranged product **57a** and the DFT calculations. It was proposed that an intramolecular hydrogen bond between the substrate and the catalyst promotes the rearrangement.

5 Experimental section

Full assignment of ^{1}H and ^{13}C chemical shifts was based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used ($CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR)) as internal standards. Chiral HPLC was performed by using a Chiralpak AD-H (250 × 4.6 mm) column. Precoated silica gel 60 F254 plates from Merck were used for TLC. Purchased chemicals and solvents were used as received. EtOAc was distilled over phosphorus pentoxide. Petroleum ether has a boiling point of 40-60 °C. The reactions were performed under an air atmosphere.

5.1.1 Optimization of the phase-transfer-catalyzed [2,3]-Wittig rearrangement of 2-cinnamyloxycyclohexanone 58a

A phase-transfer catalyst (0.02 mmol, 20 mol%) was added to a mixture of 2-cinnamyloxycyclohexanone **58a** (0.1 mmol, 1 eq) and 50% KOH_{aq} (0.1 mmol, 1 eq) in DCM (0.5 mL). The reaction was stirred at rt for 16 h. The conversion and diastereomeric ratio were determined by ^{1}H NMR spectroscopic analysis of the crude mixture. The *ee* of the product **59a** was determined by a chiral HPLC analysis of the sample obtained by preparative TLC. The racemic standard was obtained from the rearrangement reaction of 2-cinnamyloxycyclohexanone **58a** in the presence of KOH (1 eq) in DCM.



59a

2-hydroxy-2-(1-phenylallyl)cyclohexan-1-one (59a). The compound was previously synthesized from 2-(cinnamyloxy)cyclohexan-1-one **58a** and characterized (see **Publications II** and **III**).
Major diastereomer: [Chiralpak AD-H column, hexane/iPrOH 99:1, flow rate 1 mL/min, 25°C, λ = 210 nm; t_R (major) = 29.4 min and t_R (minor) = 23.0 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.29 – 7.18 (m, 5H), 6.27 (ddd, *J*=17.1, 10.1, 9.5, 1H), 5.27 – 5.18 (m, 2H), 4.05 (s, 1H), 3.83 (d, *J*=9.5, 1H), 2.70 – 2.50 (m, 2H), 2.46 – 2.40 (m, 1H), 2.27 – 2.12 (m, 1H), 2.00 – 1.60 (m, 3H), 1.58 – 1.48 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 212.91, 139.09, 136.60, 128.65, 128.34, 127.38, 117.99, 81.08, 54.47, 39.34, 39.04, 28.38, 22.23. Minor diastereomer: [Chiralpak AD-H column, hexane/iPrOH 99:1, flow rate 1 mL/min, 25°C, λ = 210 nm; t_R (major) = 17.5 min and t_R (minor) = 12.9 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.44 – 7.40 (m, 2H), 7.37 – 7.30 (m, 2H), 7.29 – 7.17 (m, 1H), 6.07 (dt, *J*=17.4, 9.5, 1H), 5.06 – 5.00 (m, 2H), 4.24 (s, 1H), 3.82 (d, *J*=9.3, 1H), 2.75 – 2.54 (m, 2H), 2.26 – 2.12 (m, 1H), 2.01 – 1.59 (m, 4H), 1.38 (td, *J*=13.6, 4.1, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 213.64, 138.99, 136.27, 129.62, 128.55, 127.25, 116.88, 81.53, 54.21, 39.12, 38.48, 28.32, 22.32. **HRMS** (ESI) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{18}O_2Na$ 253.1199, found 253.1197.

***Table 4**. 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	**XVI**	**II**		
2	**XVII**		**B**	
3	**XVIII**			**X**
4	**3a**			**5**
5	**14a**	**1a**		
6	**14b**	**1d**		

7	**14c**	**1e**		
8	**14d**	**1h**		
9	**14e**	**1i**		
10	**14f**	**1j**		
11	**14g**	**1k**		
12	**14h**	**1l**		
13	**14i**	**1m**		
14	**14j**	**1n**		
15	**14k**	**1b**		
16	**14l**	**1c**		
17	**15a**	**2a**		
18	**15b**	**2d**		
19	**15c**	**2e**		
20	**15d**	**2h**		
21	**15e**	**2i**		
22	**15f**	**2j**		
23	**15g**	**2k**		
24	**15h**	**2l**		
25	**15i**	**2m**		
26	**15j**	**2n**		
27	**55**			**2**
28	**56a**		**1a**	**3k**
29	**56b**		**1b**	
30	**56c**		**1c**	
31	**56d**		**1d**	
32	**56e**		**1e**	
33	**56f**		**1f**	
34	**56g**		**1g**	
35	**56h**		**1h**	
36	**56i**		**1j**	
37	**56j**		**1k**	
38	**56k**		**1l**	
39	**56l**		**1m**	
40	**57a**		**2a**	**4k**
41	**57b**		**2b**	
42	**57c**		**2c**	
43	**57d**		**2d**	
44	**57e**		**2e**	
45	**57f**		**2f**	
46	**57g**		**2g**	
47	**57h**		**2h**	
48	**58a**		**1i**	**3a**

49	**58b**			**3b**
50	**58c**			**3c**
51	**58d**			**3d**
52	**58e**			**3e**
53	**58f**			**3f**
54	**58g**			**3g**
55	**58h**			**3h**
56	**58i**			**3i**
57	**58j**			**3j**
58	**59a**		**2i**	**4a**
59	**59b**			**4b**
60	**59c**			**4c**
61	**59d**			**4d**
62	**59e**			**4e**
63	**59f**			**4f**
64	**59g**			**4g**
65	**59h**			**4h**
66	**66**			**1**

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Abstract
Asymmetric organocatalytic [2,3]-Wittig rearrangement

There is a continuous need for new efficient methods to create new carbon-carbon bonds in an enantioselective manner. The [2,3]-Wittig rearrangement is a perfect tool for this objective. As a result of the rearrangement, homoallyl alcohols containing up to two new stereogenic centers and a new carbon-carbon bond can be formed with 100% atom-efficiency. The fascinating properties of this transformation have encouraged us to investigate this reaction more thoroughly. Organocatalysis has proven to be a powerful method for the synthesis of chiral products. Hydrogen-bond and enamine-mediated catalysis are commonly used organocatalytic strategies. However, the number of examples of the asymmetric organocatalytic [2,3]-Wittig rearrangement is limited. Therefore, the aim of the thesis is to develop new effective methods for the asymmetric organocatalytic [2,3]-Wittig rearrangement.

The results and discussion chapter of the thesis is divided into two subchapters on the basis of the substrate and its activation type. Both subchapters describe the synthesis of the starting compounds and their use in the asymmetric [2,3]-Wittig rearrangement. A rhodium catalytic OH-insertion reaction, inspired by our previous work on oxindole derivatives, provides 2-cinnamyloxymalonates in good yields. Three different multi-step procedures for the synthesis of 2-cinnamyloxycyclopentanones were developed. After several attempts, 2-cinnamyloxycyclohexanones were obtained by using a more efficient and straightforward one-step procedure.

The main focus of the thesis is the investigation of the asymmetric organocatalytic [2,3]-Wittig rearrangement. The first subchapter focuses on the hydrogen-bond-mediated [2,3]-Wittig rearrangement of 2-cinnamyloxymalonates, which provides rearranged products in moderate yields and enantioselectivities. In the second subchapter, the enamine-mediated [2,3]-Wittig rearrangement of cyclic 2-cinnamyloxyketones is investigated. The rearranged products were synthesized in good yields, and the enantioselectivity was improved significantly compared to the first study on malonate derivatives.

In conclusion, this work expands the scope of the asymmetric organocatalytic [2,3]-Wittig rearrangement and provides deeper insight into the reaction mechanism.

Lühikokkuvõte
Asümmeetriline organokatalüütiline [2,3]-Wittigi ümberasetusreaktsioon

Uute efektiivsete enantioselektiivsete süsinik-süsinik sidemete sünteesimeetodite järele on pidev nõudlus. [2,3]-Wittigi ümberasetusreaktsioon on selle jaoks ideaalne vahend, kuna ümberasetusreaktsiooni tulemusena moodustuvad 100% aatomefektiivsusega kuni kaht stereogeenset tsentrit sisaldavad homoallüülalkoholid ning tekib uus süsinik-süsinik side. Selle muundumise huvipakkuvad omadused innustasid meid reaktsiooni põhjalikumalt uurima. Organokatalüüs on ennast tõestanud võimsa meetodina kiraalsete produktide sünteesiks. Vesiniksideme ja enamiin-katalüüs on laialdaselt kasutatavad organokatalüüsi meetodid. Vaatamata sellele on kirjanduses vähe näiteid asümmeetrilisest organokatalüütilisest [2,3]-Wittigi ümberasetusreaktsioonist. Seega on doktoritöö põhieesmärgiks välja töötada uusi efektiivseid meetodeid asümmeetrilise organokatalüütilise [2,3]-Wittigi ümberasetusreaktsiooni läbiviimiseks.

Doktoritöö tulemuste ja arutelu osa on jagatud substraatide ja nende aktivatsioonitüüpide alusel kahte alapeatükki. Mõlemad alapeatükid kirjeldavad lähteühendite sünteesi ja nende rakendamist asümmeetrilises [2,3]-Wittigi ümberasetusreaktsioonis. Roodiumkatalüütiline OH-sisestusreaktsioon, mis on inspireeritud meie eelnevast uurimistööst oksindooli derivaatidel, võimaldab sünteesida kaneelalkoholi maloonestri derivaate kõrge saagisega. Töötati välja kolm erinevat mitmeetapilist sünteesimeetodit vastavate 2-asendatud tsüklopentanoonide saamiseks. Pärast mitmeid lähenemisi arendasime välja efektiivsema üheetapilise sünteesimeetodi.

Doktoritöö peamine eesmärk on asümmeetrilise organokatalüütilise [2,3]-Wittigi ümberasetusreaktsiooni uurimine. Esimene alapeatükk keskendub vesiniksidemete katalüütilisele kaneelalkoholi maloonestri atsükliliste derivaatide [2,3]-Wittigi ümberasetusreaktsioonile, mis võimaldab produkte saada mõõdukate saagiste ja enantioselektiivsustega. Teises alapeatükis uuritakse 2-asendatud tsükliliste ketoonide enamiin-katalüütilist [2,3]-Wittigi ümberasetusreaktsiooni. Ümberasetusproduktid sünteesiti kõrgete saagistega ning enantioselektiivsus paranes märgatavalt võrreldes atsükliliste malonaatide derivaatidega.

Kokkuvõttes, töö laiendab asümmeetrilise organokatalüütilise [2,3]-Wittigi ümberasetusreaktsiooni ulatust ja pakub sügavamat pilguheitu reaktsiooni mehhanismi.

Appendix 1

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

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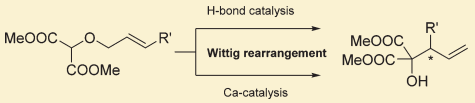
Supporting Information

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.

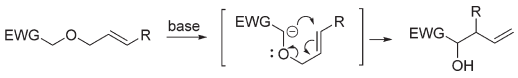


INTRODUCTION

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



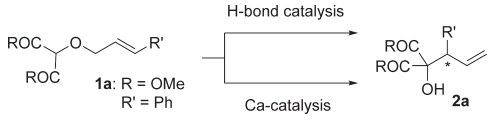
A great deal of effort has been invested in anion-promoted Wittig rearrangements. Usually strong Lewis bases, such as BuLi or *t*-BuLi are used to generate a carbanion.[2] For enantioselective reactions, chiral ligands have been used.[3]

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

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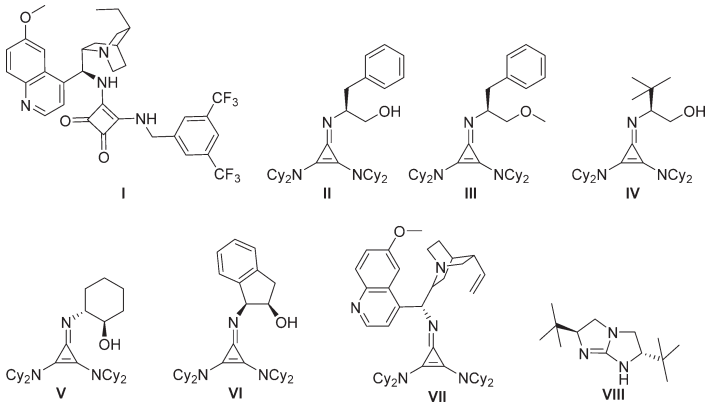
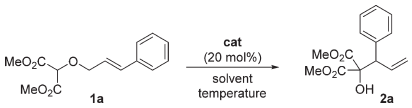


Figure 1. Catalysts screened for the organocatalytic Wittig [2,3]-rearrangement of cinnamyloxymalonates.

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

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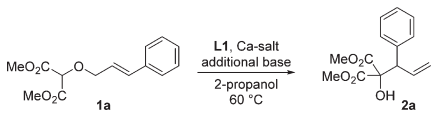
derivatives as most widely used in Ca^{2+}-catalysis,[14,15] although oxazolidines and bisoxazolidines have also been used in catalysis with other metals.[16] Also, the choice of solvent was 2-propanol, as we have previously shown its superiority over other solvents for Ca^{2+}-bisoxazoline-catalyzed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

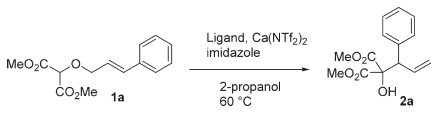
Table 2. Optimization of the Reaction Conditions of a Ca^{2+}-Catalyzed Rearrangement[a]



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

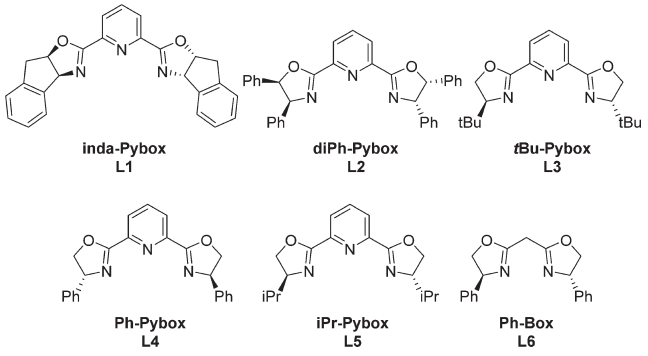


Figure 2. Bisoxazoline ligands used in the current study.

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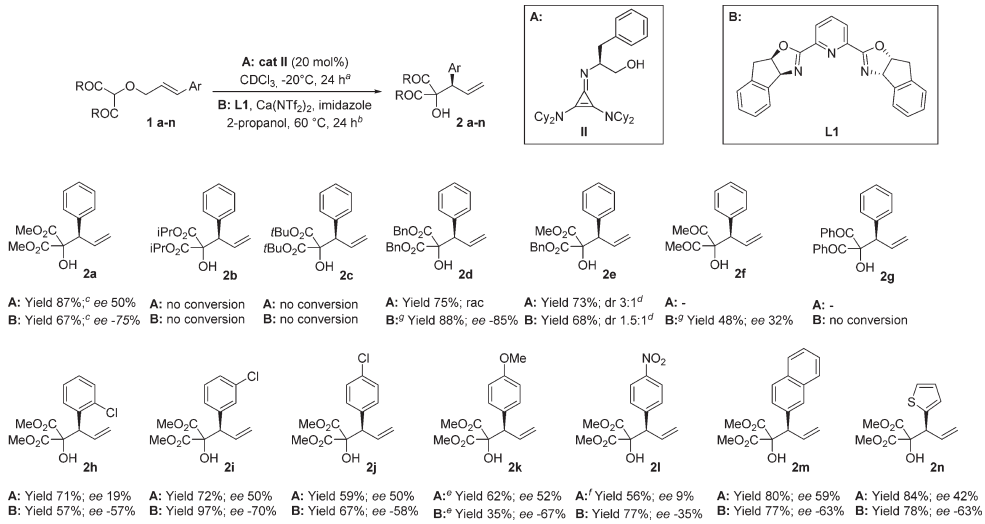
Scheme 3. Scope of the reaction (*R*-enantiomers obtained by organocatalytic method are depicted)



[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

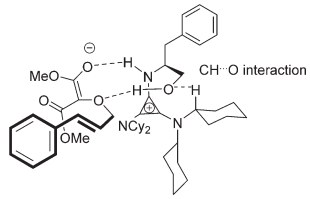


Figure 3. Model for the interaction of catalyst **II** with malonate derivative **1a** to account for the stereochemical outcome of the rearrangement.

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

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$Ca(NTf_2)_2$, 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).

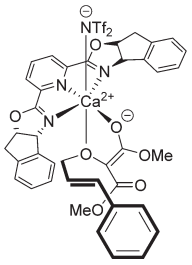

Figure 4. Model for the complexation of a Ca^{2+}/Inda-Pybox complex with compound **1a** to account for the stereochemical outcome of the rearrangement.

■ 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, CHtBu), 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, $CHCH_2$), 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

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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).

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^{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, $CHCl_3$).

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^{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)

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Notes

The authors declare no competing financial interest.

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Appendix 2

Publication II

Kimm, M.; Ošeka, M.; Kaabel, S.; Metsala, A.; Järving, I.; Kanger, T. [2,3]-Wittig Rearrangement as a Formal Asymmetric Alkylation of α-Branched Ketones. *Org*. *Lett*. **2019**, *21*, 4976–4980.

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Letter

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[2,3]-Wittig Rearrangement as a Formal Asymmetric Alkylation of α-Branched Ketones

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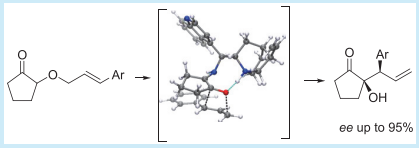
Supporting Information

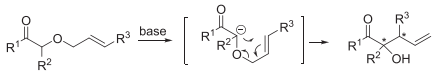
ABSTRACT: The enantioselective [2,3]-Wittig rearrangement of cinnamyloxycyclopentanone derivatives was performed in the presence of a *Cinchona*-based primary amine. The described method provides synthetically valuable α-hydroxy ketones with quaternary stereogenic centers in excellent enantiomeric purities. Relying on the X-ray crystal structure of the product and the DFT calculations, we propose that the rearrangement is promoted by an intramolecular hydrogen bond between the substrate and the catalyst.



The α-alkylation of ketones represents a fundamental method for the creation of a new C−C bond, giving access to the formation of a new stereogenic center.[1] Although the asymmetric α-alkylation of ketones has been the subject of intense discussion for decades, a general method for direct catalytic asymmetric α-alkylation has not yet been discovered.[2] Asymmetric alkylation of α-branched ketones that leads to the formation of a quaternary chiral center is an even more challenging task due to the steric hindrance and inductive effect of the alkyl substituent. The number of such transformations is limited. Transition metal catalysis is the most common tool for this purpose. However, the scope of these transformations is usually limited to α-allylations lacking examples of others alkyl electrophiles and substrates needing prefunctionalization in many cases.[3] Organocatalysis is another strategy for the asymmetric alkylation of α-branched ketones. The reported methods were mediated by phase-transfer catalysts,[4] bifunctional organocatalysts,[5] chiral phosphoric acids,[6] and primary amines.[7] Over the past decade, the area of photocatalysis has rapidly developed opening access to reaction pathways, which were previously impossible to reach under classic thermochemical conditions, but still photocatalytic methods were only applied to α-branched β-ketocarbonyl compounds.[8]

Since the direct asymmetric alkylation of α-branched ketones is an unmet target, every new method, even the indirect alkylation method, has great importance and expands the existing alkylation methodology. The [2,3]-Wittig rearrangement of α-branched ketones can be seen as a formal alkylation method (Scheme 1). The [2,3]-Wittig rearrangement is a transformation of allylic or propargylic ethers to homoallyl alcohols that makes it possible to generate a new C−C bond and to insert stereocomplexity into a structure.[9] The Wittig rearrangement has been applied as a key step for the synthesis of many natural products.[10] On the other hand, formed rearranged products are substituted α-hydroxy ketones, also known as acyloins. Acyloins are compounds of great synthetic importance, and can be found in natural products and biologically active compounds. The development of efficient catalytic methods to construct this functionality remains challenging.[11]

Scheme 1. Wittig Rearrangement of α-Branched Ketones



To date, only a limited number of asymmetric catalytic examples of [2,3]-Wittig rearrangement have been reported.[12,13] In 2006, Gaunt demonstrated the first example of asymmetric organocatalytic rearrangement on allyloxy ketones.[14] Nine years later, Denmark and co-workers obtained moderate enantioselectivities (up to 54% *ee*), when they applied phase-transfer catalysis to allyloxy oxindole and tetralone derivatives.[15] Simultaneously, our group reported a squaramide catalyzed rearrangement of oxindole derivatives with excellent enantiomeric control (dr up to 2.7:1; *ee* up to 94%/97%).[16] As a continuation of this research, in 2017 our group described [2,3]-Wittig rearrangement of allyloxy malonates catalyzed by a chiral calcium complex (*ee* up to 85%) and highly basic cyclopropenimine (*ee* up to 59%).[17] In the same year, Jacobsen and co-workers reported an effective synergistic ion-binding catalysis concept for the rearrangement of allyloxy-1,3-dicarbonyl compounds (*ee* up to 92%).[18] In 2018, Feng's research group described the first asymmetric nickel-catalytic rearrangement of propargyloxyoxindoles, affording products in high enantiomeric purities (up to 99% *ee*).[19] Very recently, Šebesta et al. reported an aminocatalytic rearrangement of allyoxyketones with moderate enantioselectivity (*ee* 60%).[20] Additionally, Alemán recently demonstrated a highly diastereoselective (dr up to 98:2) rearrangement of

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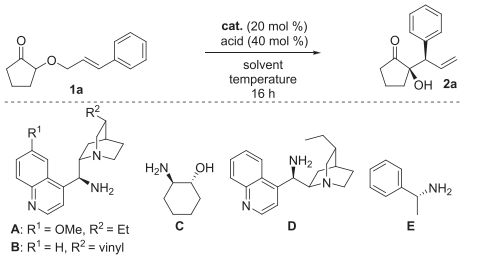
allylic and propargylic sulfoxides induced by a stoichiometric amount of strong bases.[21]

Inspired by Gaunt's pioneering work in the field, we examined the [2,3]-Wittig rearrangement of cyclic allyloxy ketones as a formal alkylation of α-branched ketones catalyzed by chiral primary amines. The superior ability of primary amines over secondary ones to effectively catalyze the functionalization of ketones and α-branched aldehydes was caused by steric factors that inhibited the condensation of the secondary amine to bulky carbonyl compounds and the enamine formation, which is the key intermediate of the amino catalyzed Wittig rearrangement.[22] Usually, an acidic cocatalyst is used to accelerate the condensation of the primary amine with the carbonyl moiety. With this knowledge in hand, we chose several primary amines for our model reaction of a [2,3]-Wittig rearrangement of cinnamyloxycyclopentanone **1a** under acidic conditions (Table 1).

The preliminary screening for the optimal reaction conditions revealed that a *Cinchona* alkaloid derived amine **A** catalyzes the [2,3]-Wittig rearrangement under acidic conditions providing products in high enantioselectivities (Table 1, entries 1−4). The most promising results in terms of conversion and selectivity were obtained when *para*-nitrobenzoic acid (*p*-NBA) was used as an acidic additive. Unfortunately, the diastereoisomeric ratio of the products could not be determined by the ^{1}H NMR analysis of the crude mixture due to the incomplete starting material conversion. A significant increase in the conversion was observed when the rearrangement reaction was catalyzed by *Cinchona* derived amine **B** and amino alcohol **C** with high enantioselectivity in the case of catalyst **B** (Table 1, entries 5 and 6). A brief solvent screening showed that the rearrangement is the most efficient in deuterochloroform (selected examples Table 1, entries 5, 7, and 8; see the Supporting Information for other examples). We managed to push the rearrangement to the full conversion by running the reaction at higher temperature with only a slight decrease in the selectivity (Table 1, entry 9). In the reaction catalyzed by amine **D**, the lower conversion and reversed enantioselectivity were observed (Table 1, entry 11). Although simple chiral α-methylbenzylamine is a very attractive catalyst to use, it provided the product with poor selectivity (Table 1, entry 12). We tried to further improve the reaction by varying acidic additives and their amount, but the best results both in terms of reactivity and selectivity were obtained with 40 mol % of *p*-NBA (Table 1, entries 5 and 13−18). Finally, in order to simplify the reaction setup, we prepared a salt of *p*-NBA and *Cinchona* derived amine **B** (ratio 2:1). The same conversion and selectivity was obtained when the preformed catalyst salt was used for the [2,3]-rearrangement. These conditions were chosen to investigate the scope of the reaction (Table 1, entry 19).

Table 1. Screening of the Catalysts and Optimization[a]



entry	cat.	acid	solvent	temp (°C)	conv (%)[b]	*ee* (%)[c]
1	**A**	TFA	$CDCl_3$	50	33	97/70
2	**A**	PhCOOH	$CDCl_3$	50	45	93/26
3	**A**	*p*-NBA	$CDCl_3$	50	45	98/52
4	**A**	EtCOOH	$CDCl_3$	50	35	86/13
5	**B**	*p*-NBA	$CDCl_3$	50	78	96/35
6	**C**	*p*-NBA[d]	$CDCl_3$	50	81	10/17
7	**B**	*p*-NBA	toluene	50	59	93/26
8	**B**	*p*-NBA	DCE	50	62	94/19
9[f]	**B**	*p*-NBA	$CDCl_3$	60	99	94/19
10[f]	**B**	*p*-NBA	$CHCl_3$	60	99	94/14
11	**D**	*p*-NBA	$CDCl_3$	60	76	−90/−7
12	**E**	*p*-NBA	$CDCl_3$	60	96	63/16
13	**B**	PhCOOH	$CDCl_3$	60	85	85/11
14	**B**	TFA	$CDCl_3$	60	60	95/56
15	**B**	*p*-NO_2-PhOH	$CDCl_3$	60	92	56/5
16	**B**	–	$CDCl_3$	60	14	nd
17	**B**	*p*-NBA[d]	$CDCl_3$	60	71	90/25
18	**B**	*p*-NBA[e]	$CDCl_3$	60	86	94/16
19[f,g]	**B** and 2·*p*-NBA salt		$CDCl_3$	60	99	94/17

[a]Reaction conditions: 0.1 mmol scale, 20 mol % of cat., 40 mol % of acid, solvent (0.5 mL). [b]Conversion determined by ^{1}H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis. [d]20 mol % of acid. [e]60 mol % of acid. [f]dr 3.5:1, determined by ^{1}H NMR analysis of the crude mixture. [g]Isolated yield 65%.

With optimal conditions in hand, the influence of substituents at the aromatic core of cinnamyloxycyclopentanone **1** was investigated (Scheme 2). A [2,3]-Wittig rearrangement of model substrate **1a** proceeded smoothly at 1.0 mmol scale and provided α-hydroxyketone **2a** in high yield and excellent enantioselectivity of the major diastereoisomer. The chlorine atom at the *para*- and *meta*-positions of cinnamyloxycyclopentanone **1** did not affect the reaction noticeably, and the rearranged products **2b** and **2c** were obtained in good yields and excellent enantiomeric purities. However, the rearrangement of *ortho*-chlorosubstituted cyclopentanone **1d** was very slow and full conversion was not achieved even under a longer reaction time. When substrate **1e** with an electron-donating methoxy group was used, the enantioselectivity of the major diastereoisomer remained excellent and the diastereoisomeric ratio slightly decreased compared to the unsubstituted substrate **1a**. The strong electron-withdrawing group lowered the reactivity of the substrate **1f** and the selectivity. Next, we studied the influence of different aromatic groups on the [2,3]-rearrangement of cyclopentanones. The substrate bearing a naphthyl group underwent a smooth rearrangement and provided α-hydroxyketone **2g** in good yield with the best diastereoselectivity in the series. A heteroaromatic 2-thienyl substituent in cyclopentanone **1h** caused a decrease in reactivity and selectivity. Transformations of substituted cyclohexanone and cyclobutanone derivates showed that, in the case of cinnamyloxycyclohexanone **1i**, the yield and enantioselectivity for the major diastereoisomer decreased drastically, while only the decomposition of cyclobutanone **1m** was observed by NMR spectroscopy. Finally, similarly to our previous results, no rearrangement of *cis*-cinnamyloxy- **1k** and allyloxy cyclopentanone **1l** was observed.[16] An additional methyl substituent

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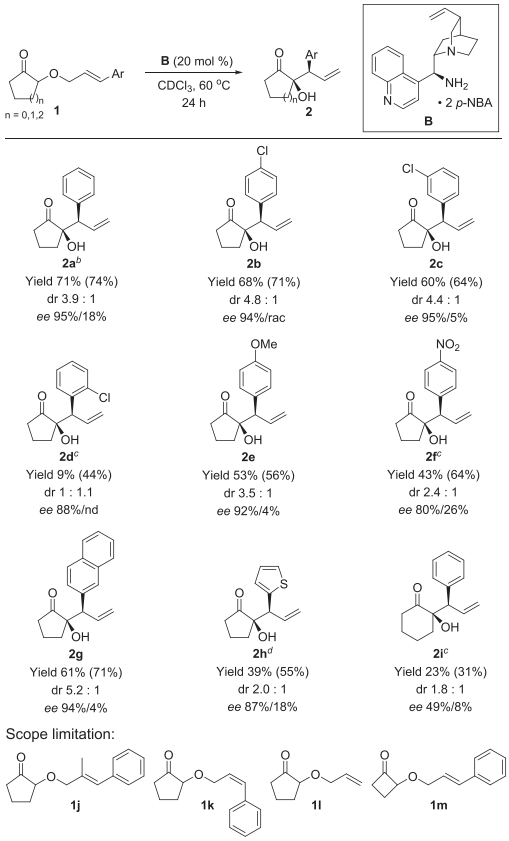
Scheme 2. Scope of the Reaction



[a]Reaction conditions: 0.2 mmol scale, 20 mol % of cat. **B**, $CDCl_3$ (1 mL), 60 °C, 24 h; *ee* determined by chiral HPLC and dr by ^{1}H NMR analysis of the isolated product. NMR yield (in parentheses) determined by ^{1}H NMR analysis of the crude mixture. [b]1.0 mmol reaction scale, reaction time 30 h. [c]Reaction was stopped after 72 h. [d]Reaction was stopped after 48 h.

at the double bond of substrate **1j** also suppressed the reaction completely.

The relative and absolute stereochemistry of the major diastereoisomer of the [2,3]-Wittig rearrangement product **2a** was unambiguously assigned by single crystal X-ray diffraction (Figure 1). The major enantiomer is a *syn*-isomer with an (*R*,*R*)-configuration of stereogenic centers. The configurations of other compounds in the series were assigned by analogy.

A proposed catalytic cycle of a [2,3]-Wittig rearrangement is depicted in Scheme 3a. The iminium ion is formed upon the condensation of aminocatalyst **B** with cinnamyloxycyclopentanone **1a** under acidic conditions followed by the formation of enamine.[22] The unfavorable equilibrium between imine and enamine is directed to the more stable imine, and thus the concentration of enamine is reduced. However, the enamine undergoes a concerted sigmatropic rearrangement through a five-membered transition state that leads to the cleavage of the allylic C−O bond and to the formation of a

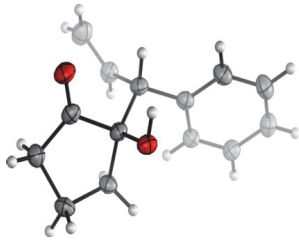
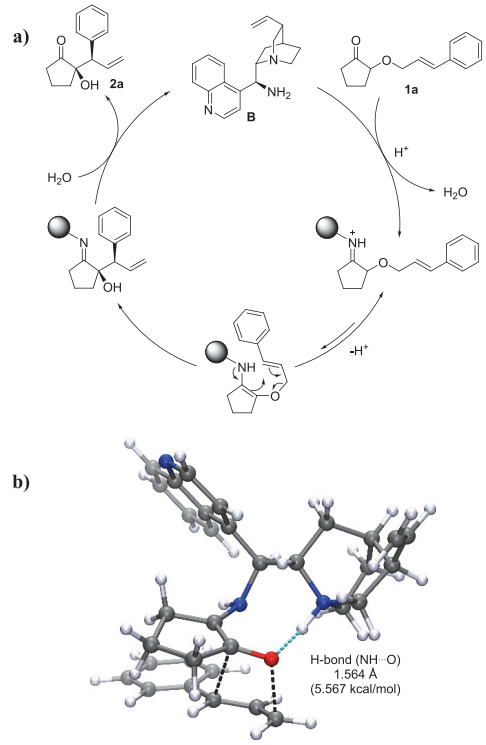


Figure 1. X-ray structure of [2,3]-rearranged product **2a** (major diastereoisomer).

Scheme 3. (a) Proposed Catalytic Cycle of the [2,3]-Wittig Rearrangement; (b) DFT Calculated Transition State of the [2,3]-Wittig Rearrangement



new C−C bond. Finally, α-hydroxyketone **2a** and catalyst **B** are released upon hydrolysis.

Based on the absolute configuration of α-hydroxyketone **2a**, we have designed and proven by DFT calculation the transition state of the rearrangement of cinnamyloxycyclopentanone **1a** leading to the formation of a major isomer (Scheme 3b). According to the calculations the five-membered transition state of enamine was stabilized by a strong hydrogen bond (1.564 Å, 5.567 kcal/mol, depicted in blue color) between the ether oxygen atom of the substrate and the protonated nitrogen atom of the quinuclidine moiety of the catalyst. This observation is in excellent agreement with our previous experimental results which demonstrated the

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importance of hydrogen-bond activation for promoting [2,3]-Wittig rearrangement.[17]

In order to further investigate the rate and the mechanism of the [2,3]-Wittig rearrangement of cinnamyloxycyclopentanone **1a**, we performed a kinetic study by taking crude samples for NMR analysis over time (Figure 2). A rapid consumption of

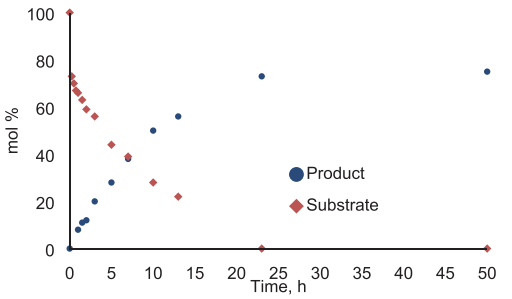
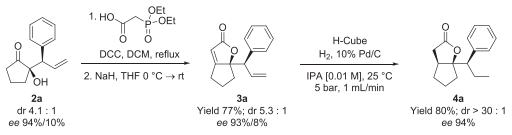


Figure 2. Kinetic study of a [2,3]-Wittig rearrangement of cinnamyloxycyclopentanone **1a**.

the starting material was observed during the first hour, which corresponded to imine formation by the condensation reaction; nevertheless, only traces of the products were detected. This observation was probably caused by the imine-enamine equilibrium and indicates that the unfavorable formation of the enamine intermediate was the rate-determining step. Although there was no starting material left after stirring the reaction for 23 h, the NMR yield of the products stayed at 75% even at the extended reaction time. The lowered reaction yield can be explained by side reactions, and the partial decomposition of the starting material, at higher temperature.

Finally, to demonstrate the utility of the α-hydroxyketones we decided to derivatize [2,3]-rearrangement product **2a** (Scheme 4).[23] The reaction sequence started with the

Scheme 4. Derivatization of [2,3]-Rearrangement Product 2a



esterification of the tertiary hydroxyl group followed by an intramolecular Horner−Wadsworth−Emmons reaction. Formed bicyclic product **3a** was isolated in high yield, and no decrease in enantiomeric excess was observed. Next, catalytic hydrogenation proceeded with high stereoselectively and provided saturated bicyclic lactone **4a** with three adjacent stereogenic centers as a single diastereoisomer. The relative configuration of **4a** was determined by 2D NOESY NMR experiment.

In conclusion, we have developed a formal asymmetric organocatalytic alkylation method of cyclic α-branched ketones based on [2,3]-Wittig rearrangement. The rearrangement was catalyzed by a *Cinchona*-derived amine, and cyclic α-hydroxyketones were obtained in excellent enantioselectivities and moderate yields and diastereoselectivities. We have proved by DFT calculations the importance of hydrogen bonding in the transition state stabilization. α-Hydroxyketones were further successfully derivatized to functionalized bicyclic products without a loss of stereoselectivity to demonstrate the utility of the [2,3]-rearranged products as building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01495.

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

Accession Codes

CCDC 1908273 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge 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.

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Notes

The authors declare no competing financial interest.

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Appendix 3

Publication III

Kimm, M.; Järving, I.; Ošeka, M.; Kanger, T. Asymmetric Organocatalytic [2,3]-Wittig Rearrangement of Cyclohexanone Derivatives. *Eur. J. Org. Chem.* **2021**, 3113–3120.

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Asymmetric Organocatalytic [2,3]-Wittig Rearrangement of Cyclohexanone Derivatives

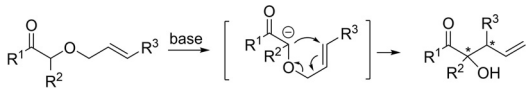
Mariliis Kimm,[a] Ivar Järving,[a] Maksim Ošeka,[a] and Tõnis Kanger*[a]

Asymmetric rearrangement reactions are one of the perfect tools for the construction of new carbon-carbon bonds in an enantioselective manner. The enantioselective [2,3]-Wittig rearrangement of cinnamyloxycyclohexanone derivatives, catalyzed by a commercially available primary amine, provided α-hydroxy ketones with high diastereo- and enantioselectivity. A new and straightforward procedure for the synthesis of cinnamyloxycyclohexanone derivatives was developed.

Introduction

There is a continuous need for methods to create new carbon-carbon bonds in an enantioselective manner. Asymmetric rearrangement reactions are perfect tools for that, especially due to their 100% atom efficiency. The [2,3]-Wittig rearrangement of allyl or propargyl ethers is a well-known sigmatropic reaction, which results in the formation of homoallyl or -allenyl alcohols.[1,2] The reaction is induced by a base and the transition state leads to the cleavage of the C–O bond and to the formation of a new C–C bond (Scheme 1). The [2,3]-Wittig rearrangement has been widely exploited as a key reaction for the synthesis of different biologically active compounds.[3–9] Despite its widespread use, the number of asymmetric catalytic methods is still limited.[10] Our group previously reported an asymmetric [2,3]-Wittig rearrangement of oxindole, malonate and cyclopentanone derivatives, in addition to an example of a diastereoselective [2,3]-sigmatropic rearrangement of N-allyl ammonium ylides.[11–14]

In 2006, Gaunt et al. described the first asymmetric organocatalytic rearrangement on aliphatic cinnamyloxyketones.[15] Almost a decade later, Denmark obtained moderate results using phase-transfer catalysis on allyloxy oxindole derivatives (*ee* up to 54%).[16] This publication was followed by our work where squaramide was applied for the rearrangement of cinnamyloxyoxindoles in excellent results (dr up to 2.7:1; *ee* up to 94%/97%).[11] Subsequently, Jacobsen's and our group carried out the rearrangement on cinnamyloxymalonates. Jacobsen's synergistic ion-binding catalysis concept provided the products in excellent results (*ee* up to 92%).[17] In our approach, good results were obtained when the rearrangement was catalyzed by a chiral calcium complex or by a cyclopropenimine catalyst (*ee* up to 85% and 59%, respectively).[12] In 2019, Šebesta et al. described the rearrangement of aliphatic cinnamyloxyketones using aminocatalysis and moderate enantioselectivity was obtained (*ee* up to 60%).[18]



Scheme 1. [2,3]-Wittig rearrangement of α-branched ketones.

We recently described a Wittig rearrangement of cyclic ketones as a method for the formal asymmetric alkylation of α-branched ketones.[13] The rearrangement of cinnamyloxycyclopentanones was performed in the presence of a *Cinchona* amine derived catalyst and the rearranged products were obtained in very good results (dr up to 5.2:1; *ee* up to 95%/18%). However, the method developed for the substituted cyclopentanones was incompatible with the corresponding cyclohexanone derivatives affording products in low dr and *ee* (dr 1.8:1; *ee* 49%/8%).

Here we discuss our study of an asymmetric organocatalytic [2,3]-Wittig rearrangement of cyclohexanone derivatives. Also, instead of a time- and resource-consuming two-step process for the synthesis of starting materials we describe a new more straightforward approach.

Results and Discussion

The most common way to synthesize the starting materials for a [2,3]-Wittig rearrangement is the oxyallylation of diazo compounds. However, the direct formation of racemic [2,3]-rearranged product was observed exclusively, when this approach was applied for the synthesis of cinnamyloxycyclohexanones by a rhodium-catalyzed O–H insertion reaction. Previously, we used two alternative methods to obtain starting compounds: a ring opening reaction of epoxide with cinnamyl alcohol derivatives and the alkylation of 1,2-cyclopentanediol with cinnamylbromide derivatives. The former method had limitations: alcohols containing additional ether or a thioether fragment did not give the desired product, probably because of the presence of Lewis acid needed for the activation of epoxide. The yields of the latter method remained low, up to 50%,

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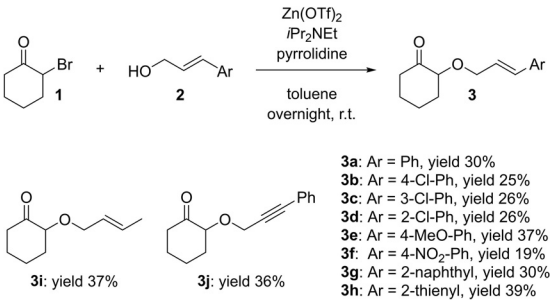
because of the overalkylation of the diol. As the cinnamyl bromide derivatives are not commercially available, the prior bromination of alcohols adds an additional step to the reaction sequence. In both cases the oxidation of cyclohexanol to corresponding ketone is needed.

For this publication our aim was to synthesize the starting materials in one step starting from 2-bromocyclohexanone **1**. As the S_N2 reaction between a bromoketone **1** and cinnamyl alcohol **2** did not occur, our next attempt was based on the work of Limanto et al., who described an example of a zinc-amine-promoted etherification of α-chlorocyclohexanone with an aliphatic alcohol.[19] The optimization of the synthesis of cinnamyloxycyclohexanone **3** was carried out (Table 1). The reaction under optimal conditions from Limanto's work resulted in the formation of the desired product in a very low yield (Table 1, entry 1). The change in the ratio of bases and Lewis acid increased the yield only slightly (Table 1, entries 2 and 3). Replacing $ZnCl_2$ with $Zn(OTf)_2$ afforded the product in higher yield (Table 1, entry 4). Unfortunately, the change of solvent and proceeding the reaction in THF did not improve the results (Table 1, entry 5). Lowering the equivalent of $Zn(OTf)_2$ to 0.3 had a negative effect on yield (Table 1, entry 6). Using 1.8 or 1.5 equivalent of ketone gave similar results, but the subsequent reduction to 1.2 equivalent caused a significant decrease of the yield (Table 1, entries 4, 7 and 8). Finally, only traces of cinnamyloxycyclohexanone were detected, when the reaction was stirred for an extended time in order to reach full conversion (Table 1, entry 9). The formation of the [2,3]-Wittig rearrangement product was observed instead indicating that the formed allyl ether underwent rearrangement under basic conditions. It is complicated to find a balance between the formation of the cinnamyloxycyclohexanone and the rearrangement products because higher temperatures and longer reaction times direct the reaction to the formation of the [2,3]-rearrangement product. Despite the moderate yields, this methodology has several advantages compared to previously published ones. It is a one-step procedure and it has a total yield comparable to the previously described two-step procedure. Furthermore, the oxidation and use of an expensive Dess-Martin periodinane is not needed.



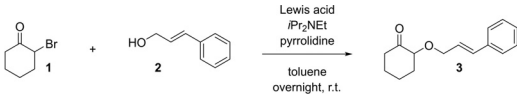
Scheme 2. Synthesis of cinnamyloxycyclohexanone derivatives.

Under optimal conditions (Table 1, entry 7) different cinnamyloxycyclohexanone derivatives **3a–j** were synthesized (Scheme 2). Despite the modest yields, the methodology provided us different aromatic and heteroaromatic as well as crotyl- and propargyl-substituted starting compounds for the rearrangement reaction.

After finding an optimal approach for the starting material synthesis, we continued by screening experiments of the rearrangement reaction. We focused on using chiral primary amines which are known as suitable catalysts for the amino-catalysis of ketones and α-branched aldehydes.[20] The use of secondary amines is problematic due to the bulkiness of both the amine and substrate. The steric hindrance inhibits the condensation of these species, and consequently enamine formation, which leads to a [2,3]-Wittig rearrangement. Acidic co-catalysts are also commonly employed to speed up the condensation of the primary amine with the carbonyl moiety.

The first screening experiment was carried out using standard conditions from our previous publication i.e. *p*-nitrobenzoic acid (*p*-NBA) and the *Cinchona*-derived amine **I** in $CDCl_3$ at 60 °C, showing low conversion of the starting material and moderate *ee* of the product (Table 2, entry 1). A significant increase in conversion was detected when α-methylbenzylamine **II** was used as a catalyst (Table 2, entry 2). A

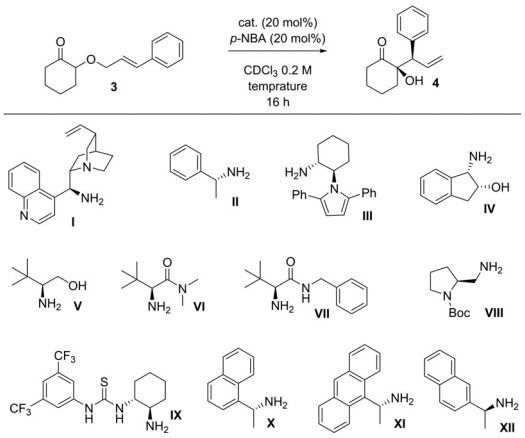
Table 1. Optimization of the reaction conditions for the synthesis of starting compounds.[a]



Entry	Ketone (eq)	Lewis acid (eq)	iPr_2NEt (eq)	Pyrrolidine (eq)	Isolated yield [%]
1	1.4	$ZnCl_2$, 1.2	1.5	0.3	18
2	2	$ZnCl_2$, 1.2	1.5	0.3	25
3	2	$ZnCl_2$, 0.4	2	1	26
4	2	$Zn(OTf)_2$, 0.4	2	1	45
5[b]	2	$Zn(OTf)_2$, 0.4	2	1	34
6	2	$Zn(OTf)_2$, 0.3	2	1	40
7	1.5	$Zn(OTf)_2$, 0.4	2	1	44
8	1.2	$Zn(OTf)_2$, 0.4	2	1	21
9[c]	1.5	$Zn(OTf)_2$, 0.4	2	1	–

[a] Reaction conditions: 0.4 mmol scale, 1 eq of cinnamyl alcohol, solvent (0.4 mL), 20 h, room temperature. [b] Reaction was carried out in THF. [c] Reaction time 48 h.

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



Entry	Cat	Temp [°C]	Conv [%][b]	dr[b]	ee_{major}/ee_{minor} [%][c]
1[d]	**I**	60	30	nd	61/8
2	**II**	60	99	5.0:1	63/5
3	**III**	60	nr	–	–
4	**IV**	60	7	–	–
5	**V**	60	11	–	–
6[d]	**VI**	60	62	3.2:1	76/59
7	**VII**	60	28	2.0:1	−22/−25
8	**VIII**	60	99	6.0:1	−10/rac
9	**IX**	60	19	2.4:1	−15/−17
10	**X**	60	99	5.9:1	79/21
11	**X**	50	99	6.8:1	80/22
12	**X**	40	66	7.5:1	84/34
13	**XI**	50	99	4.1:1	53/−43
14	**XII**	50	40	5.5:1	−70/−10

[a] Reaction conditions: 0.1 mmol scale, 20 mol% of cat., 20 mol% of *p*-NBA, $CDCl_3$ (0.5 mL). [b] Conversion and diastereoisomeric ratio determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by chiral HPLC analysis. [d] 40 mol% of *p*-NBA.

bulkier amine **III** and amino alcohols **IV**–**V** provided no or poor reactivity (Table 2, entries 3–5). The highest selectivity so far was obtained using an amide **VI** derived from tert-leucine; however, the conversion remained moderate (Table 2, entry 6). Unfortunately, the selectivity did not improve when the rearrangement was catalyzed by an amide **VII** or an ester **VIII**, containing a primary amine moiety (Table 2, entries 7 and 8). A bifunctional thiourea **IX** had no positive effect on selectivity (Table 2, entry 9). Both the diastereomeric ratio and *ee* improved when catalyst **X** bearing a α-substituted naphthyl group was used (Table 2, entry 10). It was found that a decrease in temperature increased the diastereomeric ratio, but full conversion was not obtained (Table 2, entries 11 and 12). Surprisingly, catalyst **XI** bearing a bulkier anthracenyl substituent or a β-naphthyl group (catalyst **XII**) had a deleterious effect on enantiomeric excess (Table 2, entries 13 and 14).

A kinetic study was performed to determine the reaction rate of the [2,3]-Wittig rearrangement of cinnamyloxycyclohexanone **3a** (Figure 1). Crude samples for NMR analysis were taken over time. A rapid consumption of the substrate was detected within the first hour, which corresponds to the

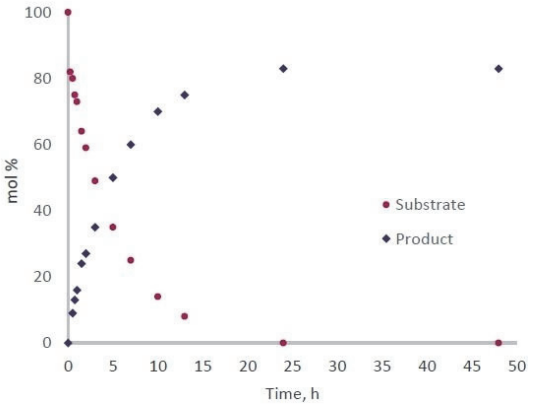


Figure 1. Kinetic study of a Wittig [2,3]-rearrangement of cinnamyloxycyclohexanone **3a**.

condensation of the catalyst with the carbonyl moiety of the cinnamyloxycyclohexanone. The first traces of the product were detected after 0.5 hour. Although the substrate was completely consumed in 24 h, the NMR yield reached just above 80% and remained the same after 48 hours. It is assumed that the lowered yield was potentially caused by side reactions and the partial decomposition of the substrate at higher temperature.

While screening for the optimal reaction conditions we noticed that the enantiomeric excess and diastereoisomeric ratio of the [2,3]-rearranged products **4** were not consistent under the reaction conditions. We investigated this phenomenon simultaneously with the kinetic study by preparing samples for chiral HPLC analysis by preparative TLC from the reaction mixture (Figure 2). During the first hours, a significant drop in the *ee* was observed. However, the enantiomeric excesses of chromatographically inseparable diastereoisomers reached plateaus after 10 hours and remained the same for prolonged time. Thus, these kinetic observations demonstrated that the

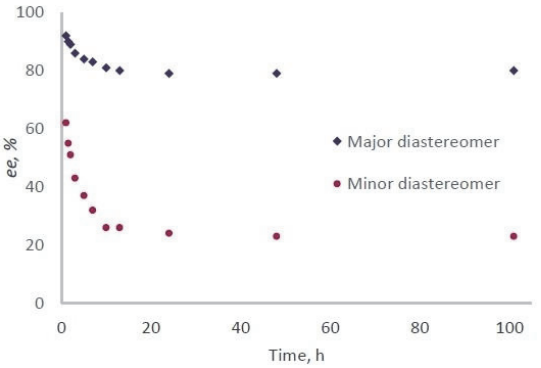
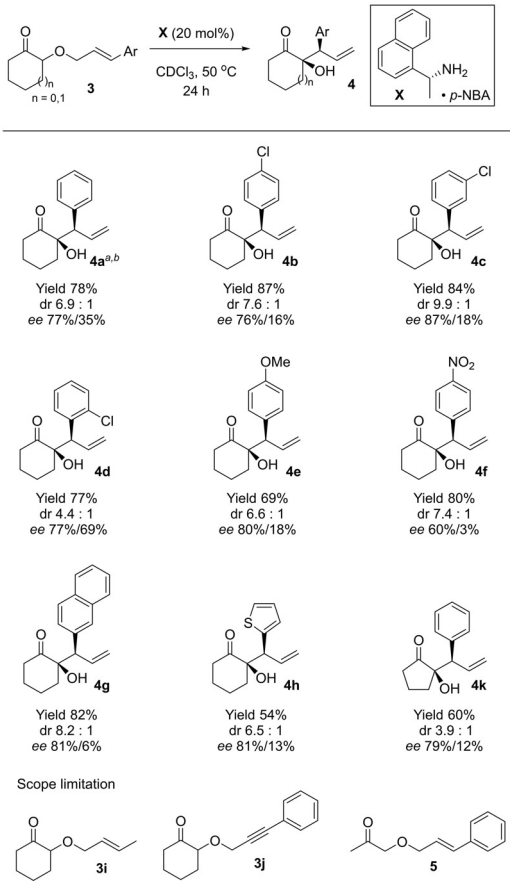


Figure 2. [2,3]-Rearranged product **4a** epimerization over time.

product can be obtained in the highest possible yield and yet with satisfying enantioselectivity after running the reaction for 24 hours. Thus, 24 hours was determined to be the optimal reaction time of the scope experiments. Finally, having established an optimal reaction time and conditions (for the solvent screening, see Supporting Information), we investigated the scope of the primary amine **X** catalyzed [2,3]-Wittig rearrangement of cinnamyloxycyclohexanone derivatives **3** to demonstrate the robustness of the developed method (Scheme 3). The reaction of the model substrate at 1.0 mmol scale afforded the α-hydroxyketone **4a** in good yield and enantiopurity. Substrates with electron-withdrawing substituents **3b–d**, **3f** and electron-donating substituents **3e** were tolerated. Rearrangement with *meta*-Cl substituted starting material **3c** showed the highest enantiomeric excess in the reaction series, while *para*-NO_2 substrate **3f** gave modest results. In addition, 2-naphthyl **4g** and a heteroaromatic 2-thienyl **4h** substituted products were obtained in comparable



Scheme 3. Scope of the reaction. [a] Reaction conditions: 0.2 mmol scale, 20 mol% of cat. **X**, $CDCl_3$ (1 mL), 50 °C, 24 h. *ee* determined by chiral HPLC and dr by ^{1}H NMR analysis of the isolated product. [b] 1.0 mmol reaction scale.

ee. An experiment with cinnamyloxycyclopentanone **3k** proved that the optimized conditions are not optimal for other ring sizes and the results were not improved over those our previous publication (yield 71%; dr 3.9:1; *ee* 95%/18%).[13] The six-membered substrate possesses less ring-strain compared to the five-membered and, thus, is more conformationally flexible. Finally, limitations of scope were revealed. Unfortunately, the rearrangement did not occur on crotyl ether **3i**. Propargyl ethers are widely used starting materials for the [2,3]-Wittig rearrangement, but no reaction with substrate **3j** occurred. As the aliphatic ketone **5** showed no reaction, it can be concluded that the scope is limited to cyclic ketones only.

The absolute configuration of the major diastereoisomer of the [2,3]-Wittig rearrangement product **4a** was determined by a comparison of the chiral HPLC chromatogram with the data published previously by us.[13] It is assumed that the main enantiomer is a *syn*-isomer with an (*R*,*R*)-configuration of stereogenic centers. The configurations of other compounds in the series were assigned by analogy.

Conclusion

In conclusion, we have described the asymmetric organocatalytic [2,3]-Wittig rearrangement of cinnamyloxycyclohexanone derivatives, catalyzed by a primary amine. This methodology provides cyclic α-hydroxyketones in good yields and with high diastereo- and enantioselectivities. A new step-efficient procedure for the synthesis of cinnamyloxycyclohexanone derivatives was also developed.

Experimental Section

General remarks. 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, unless note. Residual solvent signals were used ($CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR)) as internal standards. High resolution mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT – IR spectrophotometer. Chiral HPLC was performed by using Chiralpak AD-H (250×4.6 mm), Chiralcel OJ-H (250×4.6 mm) or Chiralpak AS-H (250×4.6 mm) columns. Precoated silica gel 60 F254 plates from Merck were used for TLC. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40–63 μm. Purchased chemicals and solvents were used as received. EtOAc was distilled over phosphorus pentoxide. Petroleum ether (PE) has a boiling point of 40–60 °C. The reactions were performed under air atmosphere without additional moisture elimination unless stated otherwise. Chiral catalysts **II**, **IV**, **VIII**, and **X**were commercially available from Aldrich, Acros Organics or Fluorochem. Catalysts **I**, **III**, **V**, **VI**, **VII**, **IX**, **XI** and **XII** were prepared according to literature procedures, and the analytical data matched with that of the literature.[21–28]

General Procedure for the Synthesis of 2-Cinnamyloxycyclohexanones 3a–j. To a solution of cinnamyl alcohol derivative (1.00 eq), zinc triflate (0.40 eq), diisopropylethylamine (2.00 eq) and pyrrolidine (1.00 eq) a mixture of 2-bromocyclohexanone (1.50 eq) in toluene (1 M) was added and the reaction was stirred overnight at room temperature. The reaction was quenched by addition of 1.0 M

HCl aqueous solution (5 mL) and extracted with DCM (6×10 mL). Combined organic layers were dried with phase separator, concentrated, and purified by column chromatography on silica gel twice (7–15% EtOAc in petroleum ether) and (2–8% EtOAc in PE/DCM 1/1 mixture). Partial decomposition of 2-cinnamyloxycyclohexanones **3** was observed at higher temperature. In order to avoid decomposition, solvent evaporation was performed at room temperature and obtained products **3** were stored at −20 °C.

2-(cinnamyloxy)cyclohexan-1-one (3 a). The title compound was obtained as a colorless oil in 30% yield (104 mg, 0.45 mmol) from 2-bromocyclohexanone (398 mg, 2.25 mmol) and cinnamyl alcohol (201 mg, 1.50 mmol) according to general procedure. R_f = 0.50 (PE /EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 2H, Ar-H), 7.35–7.27 (m, 2H, Ar-H), 7.26–7.20 (m, 1H, Ar-H), 6.60 (dt, J = 15.8, 1.5, 1H, C*H*Ar), 6.30 (ddd, J = 15.9, 6.5, 5.8, 1H, CH_2CH), 4.37 (ddd, J = 12.6, 5.8, 1.5, 1H, OCH_2), 4.13 (ddd, J = 12.6, 6.5, 1.4, 1H, OCH_2), 3.93 (ddd, J = 10.3, 5.5, 1.3, 1H, $CHOCH_2$), 2.63–2.45 (m, 1H, CH_2), 2.37–2.17 (m, 2H, CH_2), 2.08–1.90 (m, 2H, CH_2), 1.88–1.60 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.3, 136.7, 133.0, 128.7, 127.9, 126.7, 125.8, 81.8, 70.6, 40.8, 34.7, 27.8, 23.4.

(*E*)-2-((3-(4-chlorophenyl)allyl)oxy)cyclohexan-1-one (3 b). The title compound was obtained as a colorless oil in 25% yield (101 mg, 0.38 mmol) from 2-bromocyclohexanone (398 mg, 2.25 mmol) and 4-chlorocinnamyl alcohol (253 mg, 1.50 mmol) according to general procedure. R_f = 0.52 (PE/EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.7, 2H, Ar-H), 7.27 (d, J = 9.0, 2H, Ar-H), 6.56 (dt, J = 15.9, 1.5, 1H, C*H*Ar), 6.28 (ddd, J = 15.9, 6.3, 5.7, 1H, CH_2CH), 4.35 (ddd, J = 12.7, 5.8, 1.6, 1H, OCH_2), 4.11 (ddd, J = 12.7, 6.3, 1.4, 1H, OCH_2), 3.91 (ddd, J = 10.3, 5.6, 1.3, 1H, $CHOCH_2$), 2.58–2.49 (m, 1H, CH_2), 2.35–2.18 (m, 2H, CH_2), 2.10–1.89 (m, 2H, CH_2), 1.87–1.60 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.2, 135.3, 133.5, 131.5, 128.9, 127.9, 126.6, 82.1, 70.5, 40.8, 34.7, 27.8, 23.4. IR (neat): ν = 2942, 2866, 1721, 1593, 1491, 1450, 1090, 1013, 970, 837 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_2ClNa$ $[M+Na]^+$: 287.0809; found: 287.0796.

(*E*)-2-((3-(3-chlorophenyl)allyl)oxy)cyclohexan-1-one (3 c). The title compound was obtained as a white amorphous solid in 26% yield (140 mg, 0.53 mmol) from 2-bromocyclohexanone (531 mg, 3.00 mmol) and 3-chlorocinnamyl alcohol (337 mg, 2.00 mmol) according to general procedure. R_f = 0.48 (PE/EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 1H, Ar-H), 7.26–7.18 (m, 3H, Ar-H), 6.55 (dt, J = 15.9, 1.5, 1H, C*H*Ar), 6.31 (dt, J = 15.9, 5.9, 1H, CH_2CH), 4.37 (ddd, J = 12.9, 5.6, 1.6, 1H, OCH_2), 4.12 (ddd, J = 12.8, 6.2, 1.4, 1H, OCH_2), 3.91 (ddd, J = 10.3, 5.5, 1.3, 1H, $CHOCH_2$), 2.58–2.47 (m, 1H, CH_2), 2.39–2.15 (m, 2H, CH_2), 2.03–1.90 (m, 2H, CH_2), 1.87–1.60 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.1, 138.6, 134.6, 131.2, 129.9, 127.8, 127.5, 126.6, 124.8, 82.1, 70.3, 40.8, 34.7, 27.8, 23.4. IR (neat): ν = 2942, 2865, 1721, 1593, 1563, 1111, 966, 774 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_2ClNa$ $[M+Na]^+$: 287.0809; found: 287.0798.

(*E*)-2-((3-(2-chlorophenyl)allyl)oxy)cyclohexan-1-one (3 d). The title compound was obtained as a yellowish oil in 26% yield (140 mg, 0.53 mmol) from 2-bromocyclohexanone (531 mg, 3.00 mmol) and 2-chlorocinnamyl alcohol (337 mg, 2.00 mmol) according to general procedure. R_f = 0.50 (PE/EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (dd, J = 7.6, 1.9, 1H, Ar-H), 7.34 (dd, J = 7.5, 1.8, 1H, Ar-H), 7.24–7.15 (m, 2H, Ar-H), 6.99 (dt, J = 15.9, 1.6, 1H, C*H*Ar), 6.28 (ddd, J = 15.9, 6.3, 5.7, 1H, CH_2CH), 4.40 (ddd, J = 12.9, 5.7, 1.6, 1H, OCH_2), 4.18 (ddd, J = 12.9, 6.4, 1.5, 1H, OCH_2), 3.94 (ddd, J = 10.3, 5.5, 1.3, 1H, $CHOCH_2$), 2.59–2.47 (m, 1H, CH_2), 2.37–2.21 (m, 2H, CH_2), 2.05–1.89 (m, 2H, CH_2), 1.87–1.62 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.2, 134.9, 133.2, 129.8, 128.9, 128.84, 128.79, 127.1, 127.0, 82.0, 70.6, 40.9, 34.7, 27.8, 23.4. IR (neat): ν = 2941, 2865, 1721, 1470, 1441, 1111, 968, 752 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_2ClNa$ $[M+Na]^+$: 287.0809; found: 287.0798.

(*E*)-2-((3-(4-methoxyphenyl)allyl)oxy)cyclohexan-1-one (3 e). The title compound was obtained as a white amorphous solid in 37% yield (145 mg, 0.56 mmol) from 2-bromocyclohexanone (398 mg, 2.25 mmol) and 4-methoxycinnamyl alcohol (246 mg, 1.50 mmol) according to general procedure. R_f = 0.45 (PE/EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.7, 2H, Ar-H), 6.85 (d, J = 8.7, 2H, Ar-H), 6.54 (dt, J = 16.0, 1.4, 1H, C*H*Ar), 6.16 (ddd, J = 15.9, 6.7, 6.0, 1H, CH_2CH), 4.33 (ddd, J = 12.3, 6.0, 1.4, 1H, OCH_2), 4.10 (ddd, J = 12.3, 6.7, 1.3, 1H, OCH_2), 3.92 (ddd, J = 10.2, 5.6, 1.3, 1H, $CHOCH_2$), 3.80 (s, 3H, CH_2), 2.61–2.48 (m, 1H, CH_2), 2.37–2.19 (m, 2H, CH_2), 2.04–1.89 (m, 2H, CH_2), 1.87–1.61 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.4, 159.5, 132.7, 129.5, 127.9, 123.5, 114.1, 81.7, 70.8, 55.4, 40.8, 34.7, 27.8, 23.4. IR (neat): ν = 2949, 2868, 1715, 1605, 1509, 1251, 1174, 1129, 1110, 1033, 983, 845, 810 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_3Na$ $[M+Na]^+$: 283.1305; found: 283.1291.

(*E*)-2-((3-(4-nitrophenyl)allyl)oxy)cyclohexan-1-one (3 f). The title compound was obtained as a yellowish amorphous solid in 19% yield (80 mg, 0.29 mmol) from 2-bromocyclohexanone (398 mg, 2.25 mmol) and 4-nitrocinnamyl alcohol (268 mg, 1.50 mmol) according to general procedure. R_f = 0.72 (PE/EtOAc 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.9, 2H, Ar-H), 7.51 (d, J = 8.8, 2H, Ar-H), 6.70 (dt, J = 16.0, 1.7, 1H, C*H*Ar), 6.49 (dt, J = 16.0, 5.5, 1H, CH_2CH), 4.42 (ddd, J = 13.4, 5.3, 1.7, 1H, OCH_2), 4.16 (ddd, J = 13.4, 5.7, 1.6, 1H, OCH_2), 3.92 (ddd, J = 10.5, 5.6, 1.3, 1H, $CHOCH_2$), 2.63–2.47 (m, 1H, CH_2), 2.40–2.19 (m, 2H, CH_2), 2.09–1.89 (m, 2H, CH_2), 1.89–1.61 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.9, 147.1, 143.3, 131.1, 129.9, 127.2, 124.1, 82.6, 70.1, 40.9, 34.7, 27.7, 23.5. IR (neat): ν = 2957, 2862, 1715, 1595, 1517, 1452, 1337, 1186, 1152, 1126, 986, 862, 737 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NO_4Na$ $[M+Na]^+$: 298.1050; found: 298.1037.

(*E*)-2-((3-(naphthalen-2-yl)allyl)oxy)cyclohexan-1-one (3 g). The title compound was obtained as a yellowish amorphous solid in 30% yield (124 mg, 0.44 mmol) from 2-bromocyclohexanone (398 mg, 2.25 mmol) and (*E*)-3-(naphthalen-2-yl)prop-2-en-1-ol (276 mg, 1.50 mmol) according to general procedure. R_f = 0.50 (PE/EtOAc 3 : 1).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.76 (m, 3H, Ar-H), 7.74 (s, 1H, Ar-H), 7.61 (dd, J = 8.6, 1.8, 1H, Ar-H), 7.52–7.39 (m, 2H, Ar-H), 6.77 (dt, J = 15.9, 1.5, 1H, C*H*Ar), 6.43 (dt, J = 15.9, 6.1, 1H, CH_2CH), 4.42 (ddd, J = 12.6, 5.8, 1.5, 1H, OCH_2), 4.19 (ddd, J = 12.6, 6.5, 1.4, 1H, OCH_2), 3.96 (ddd, J = 10.3, 5.6, 1.3, 1H, $CHOCH_2$), 2.63–2.47 (m, 1H, CH_2), 2.42–2.20 (m, 2H, CH_2), 2.08–1.90 (m, 2H, CH_2), 1.88–1.62 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.3, 134.2, 133.7, 133.2, 133.0, 128.3, 128.1, 127.8, 126.7, 126.4, 126.2, 126.1, 123.7, 82.0, 70.7, 40.8, 34.7, 27.8, 23.4. IR (neat): ν = 2939, 2861, 1715, 1126, 1110, 1011, 863, 811, 749 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{19}H_{20}O_2Na$ $[M+Na]^+$: 303.1356; found: 303.1343.

(*E*)-2-((3-(thiophen-2-yl)allyl)oxy)cyclohexan-1-one (3 h). The title compound was obtained as a yellow oil in 39% yield (140 mg, 0.59 mmol) from 2-bromocyclohexanone (398 mg, 2.25 mmol) and (*E*)-3-(thiophen-2-yl)prop-2-en-1-ol (210 mg, 1.50 mmol) according to general procedure. R_f = 0.55 (PE/EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.13 (m, 1H, Ar-H), 6.98–6.93 (m, 2H, Ar-H), 6.73 (dq, J = 15.8, 1.1, 1H, C*H*Ar), 6.12 (dt, J = 15.7, 6.1, 1H, CH_2CH), 4.32 (ddd, J = 12.8, 5.8, 1.6, 1H, OCH_2), 4.08 (ddd, J = 12.8, 6.5, 1.4, 1H, OCH_2), 3.91 (ddd, J = 10.2, 5.5, 1.3, 1H, $CHOCH_2$), 2.61–2.47 (m, 1H, CH_2), 2.38–2.11 (m, 2H, CH_2), 2.04–1.88 (m, 2H, CH_2), 1.87–1.59 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.2, 141.8, 127.5, 126.1, 126.0, 125.4, 124.6, 81.9, 70.2, 40.8, 34.7, 27.8, 23.4. IR (neat): ν = 3429, 2940, 2864, 1720, 1449, 1112, 959, 854, 795, 702 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2SNa$ $[M+Na]^+$: 259.0763; found: 259.0751.

(*E*)-2-(but-2-en-1-yloxy)cyclohexan-1-one (3 i). The title compound was obtained as a colorless oil in 37% yield (93 mg, 0.55 mmol) from 2-bromocyclohexanone (398 mg, 2.25 mmol) and crotyl alcohol (108 mg, 1.50 mmol) according to general procedure. R_f = 0.68

(DCM/EtOAc 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (dqt, J = 14.8, 6.2, 1.1, 1H, CHCH$_3$), 5.65–5.52 (m, 1H, CH$_2$$CH$), 4.10 (ddt, J = 11.6, 5.9, 1.2, 1H, OCH_2), 3.93–3.80 (m, 2H, OCH_2, CHOCH$_2$), 2.61–2.42 (m, 1H, CH_2), 2.34–2.21 (m, 1H, CH_2), 2.23–2.12 (m, 1H, CH_2), 2.01–1.87 (m, 2H, CH_2), 1.82–1.62 (m, 3H, CH_2), 1.71 (dq, J = 6.4, 1.2, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.5, 130.2, 127.4, 81.7, 70.7, 40.8, 34.7, 27.8, 23.3, 17.9. IR (neat): ν = 2941, 2866, 1722, 1450, 1110, 967 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{16}O_2Na$ [M + Na]$^+$: 191.1043; found: 191.1037.

2-((3-phenylprop-2-yn-1-yl)oxy)cyclohexan-1-one (3 j). The title compound was obtained as a colorless oil in 36% yield (66 mg, 0.29 mmol) from 2-bromocyclohexanone (212 mg, 1.2 mmol) and 3-phenylprop-2-yn-1-ol (106 mg, 0.8 mmol) according to general procedure. R_f = 0.52 (PE/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.40 (m, 2H, Ar-H), 7.35–7.28 (m, 3H, Ar-H), 4.60 (d, J = 16.0, 1H, OCH_2), 4.48 (d, J = 16.0, 1H, OCH_2), 4.23–4.10 (m, 1H, CHOCH$_2$), 2.63–2.51 (m, 1H, CH_2), 2.42–2.24 (m, 2H, CH_2), 2.10–1.90 (m, 2H, CH_2), 1.87–1.59 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.8, 132.0, 128.7, 128.4, 122.7, 86.7, 84.9, 81.1, 58.0, 41.0, 34.7, 27.8, 23.5. IR (neat): ν = 2943, 2866, 1720, 1490, 1445, 1110, 1073, 795, 758, 692 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{16}O_2Na$ [M + Na]$^+$: 251.1043; found: 251.1030.

Synthesis of 2-(cinnamyloxy)cyclopentan-1-one (3 k). Prepared according to reported procedure.[13] Dess-Martin periodinane (636 mg, 1.50 mmol, 2 eq) was added to a solution of (*E*)-2-(cinnamyloxy)cyclopentan-1-ol (232 mg, 1 mmol, 1 eq) in DCM (10 mL) at room temperature. The reaction mixture was stirred for 4 h at room temperature and quenched by saturated $Na_2S_2O_3$ aqueous solution (10 mL), then diluted with saturated $NaHCO_3$ (10 mL) and extracted with DCM (5×15 mL). Organic layers were dried with phase separator, concentrated and purified by column chromatography on silica gel (5–7% EtOAc in petroleum ether/DCM 1/1 mixture), affording the **3 k** (161 mg, 0.70 mmol, 70% yield) as a colorless oil. R_f = 0.48 (PE/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 2H, Ar-H), 7.35–7.28 (m, 2H, Ar-H), 7.25 (d, J = 6.8, 1H, Ar-H), 6.63 (dt, J = 15.9, 1.5, 1H, CHAr), 6.30 (dt, J = 15.9, 6.2, 1H, CH$_2$$CH$), 4.44 (ddd, J = 12.6, 6.1, 1.5, 1H, OCH_2), 4.33 (ddd, J = 12.6, 6.3, 1.4, 1H, OCH_2), 3.94–3.83 (m, 1H, CHOCH$_2$), 2.40–2.17 (m, 3H, CH_2), 2.14–1.99 (m, 1H, CH_2), 1.94–1.68 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 216.4, 136.7, 133.4, 128.7, 128.0, 126.7, 125.6, 80.3, 71.0, 35.6, 29.7, 17.5.

Synthesis of 1-(cinnamyloxy)propan-2-one (5). Prepared according to reported procedure.[15] MeMgBr (0.55 mL of a 3.0 M solution in tetrahydrofuran, 1.65 mmol) was added dropwise to a solution of the 2-(cinnamyloxy)-1-morpholinoethan-1-one (288 mg, 3.83 mmol) in THF (15 mL) at −78 °C. The reaction mixture was allowed to warm to −20 °C over 1 h and stirred for 3 h at this temperature. HCl aq solution (3 M, 20 mL) was added to the reaction mixture and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with an $NaHCO_3$ aq saturated solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography on silica gel (10–25% EtOAc in petroleum ether), affording the **5** (129 mg, 0.68 mmol, 62% yield) as a colorless oil. R_f = 0.48 (PE/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.36 (m, 2H, Ar-H), 7.33 (ddd, J = 7.5, 6.7, 1.3, 2H, Ar-H), 7.29–7.22 (m, 1H, Ar-H), 6.63 (dt, J = 15.9, 1.5, 1H, CHAr), 6.29 (dt, J = 15.9, 6.2, 1H, CH$_2$$CH$), 4.23 (dd, J = 6.2, 1.4, 2H, OCH_2), 4.10 (s, 2H, CH_2OCH$_2$), 2.18 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.8, 136.5, 133.6, 128.8, 128.1, 126.7, 125.1, 75.4, 72.1, 26.5.

General Procedure for Asymmetric Organocatalytic [2,3]-Wittig Rearrangement of 2-Cinnamyloxycyclohexanone 3. Catalyst **X** (*p*-NBA salt, 25.1 mg, 0.04 mmol, 20 mol%) was added to a solution of 2-cinnamyloxycyclohexanone **3** (0.2 mmol, 1 eq) in $CDCl_3$ (1 mL). The reaction mixture was stirred at 50 °C for 24 hours. The reaction was quenched by addition of saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with DCM (6×10 mL). Organic layers were dried with phase separator, concentrated and the crude product was purified by column chromatography on silica gel (2–8% EtOAc in petroleum ether/DCM 1:1 mixture), affording the desired rearranged product **4** as a mixture of diastereoisomers. The enantiomeric purity was determined by chiral HPLC analysis of the isolated product. Racemic standards were obtained from the rearrangement reaction 2-allyloxy ketone **3** catalyzed by (±)-α-methylbenzylamine (1:1 *p*-NBA salt, 20 mol%) in $CHCl_3$.

(*R*)-2-hydroxy-2-((*R*)-1-phenylallyl)cyclohexan-1-one (4 a). The title compound was synthesized according to the general procedure from 2-(cinnamyloxy)cyclohexan-1-one **3 a** (230.3 mg, 1.0 mmol). The product was isolated as a white amorphous solid in 78% yield (179.0 mg, 0.78 mmol, dr 6.9:1). R_f = 0.65 (10% EtOAc in PE/DCM 1:1 mixture). Major diastereoisomer: *ee* 77% [Chiralcel OJ–H column, hexane/iPrOH 7:3, flow rate 1 mL/min, 35 °C, λ = 210 nm; t_R (major) = 12.0 min and t_R (minor) = 7.8 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.16 (m, 5H, Ar-H), 6.29 (ddd, J = 17.1, 10.1, 9.5, 1H, CHCH$_2$), 5.29–5.19 (m, 2H, CHCH_2), 4.06 (s, 1H, OH), 3.85 (d, J = 9.5, 1H, CHAr), 2.65 (td, J = 13.8, 6.4, 1H, CH_2), 2.56 (dq, J = 13.7, 3.1, 1H, CH_2), 2.45 (ddt, J = 13.7, 4.3, 2.1, 1H, CH_2), 2.25–2.15 (m, 1H, CH_2), 1.93–1.79 (m, 2H, CH_2), 1.70 (tt, J = 14.2, 4.5, 1H, CH_2), 1.55 (td, J = 13.4, 4.9, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.9, 139.1, 136.6, 128.7, 128.4, 127.4, 118.0, 81.1, 54.5, 39.3, 39.0, 28.4, 22.2. Minor diastereoisomer: *ee* 35% [Chiralcel OJ–H column, hexane/iPrOH 7:3, flow rate 1 mL/min, 35 °C, λ = 210 nm; t_R (major) = 9.9 min and t_R (minor) = 36.1 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 2H, Ar-H), 7.40–7.32 (m, 2H, Ar-H), 6.09 (dt, J = 17.5, 9.5, 1H, CHCH$_2$), 5.08–5.01 (m, 2H, CHCH_2), 4.26 (s, 1H, OH), 3.84 (d, J = 9.2, 1H, CHAr), 2.02–1.93 (m, 1H, CH_2), 1.40 (td, J = 13.6, 4.0, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 213.7, 139.0, 136.3, 129.6, 128.6, 127.3, 116.9, 81.5, 54.2, 39.1, 38.5, 28.3, 22.3. HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{18}O_2Na$ 253.1199, found 253.1197.

(*R*)-2-((*R*)-1-(4-chlorophenyl)allyl)-2-hydroxycyclohexan-1-one (4 b). The title compound was synthesized according to the general procedure from (*E*)-2-((3-(4-chlorophenyl)allyl)oxy)cyclohexan-1-one **3 b** (53.0 mg, 1.0 mmol). The product was isolated as a yellowish amorphous solid in 87% yield (46.0 mg, 0.17 mmol, dr 7.6:1). R_f = 0.71 (10% EtOAc in PE/DCM 1:1 mixture). IR (neat): ν = 3466, 2942, 2866, 1710, 1491, 1246, 1092 cm^{-1}. Major diastereoisomer: *ee* 76% [Chiralpak AD–H column, hexane/iPrOH 97:3, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 15.8 min and t_R (minor) = 18.5 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.8, 2H, Ar-H), 7.18 (d, J = 8.9, 2H, Ar-H), 6.20 (ddd, J = 17.1, 10.1, 9.4, 1H, CHCH$_2$), 5.25 (dd, J = 10.1, 1.6, 1H, CHCH_2), 5.20 (ddd, J = 17.1, 1.6, 0.8, 1H, CHCH_2), 4.04 (s, 1H, OH), 3.81 (d, J = 9.4, 1H, CHAr), 2.63–2.49 (m, 2H, CH_2), 2.47–2.39 (m, 1H, CH_2), 2.24–2.13 (m, 1H), 1.84–1.77 (m, 2H, CH_2), 1.75–1.47 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.8, 137.6, 136.2, 133.2, 129.7, 128.8, 118.4, 81.0, 53.8, 39.4, 39.0, 28.4, 22.2. Minor diastereoisomer: *ee* 16% [Chiralpak AD–H column, hexane/iPrOH 97:3, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 22.3 min and t_R (minor) = 44.2 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.6, 2H, Ar-H), 7.30 (d, J = 8.5, 2H, Ar-H), 6.00 (ddd, J = 17.0, 10.3, 9.2, 1H, CHCH$_2$), 5.06–4.99 (m, 2H, CHCH_2), 1.38 (td, J = 13.6, 4.1, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.0, 128.7, 117.3, 81.0, 53.5, 38.4, 28.3. HRMS (ESI) m/z calcd for $C_{15}H_{17}O_2ClNa$ [M + Na]$^+$: 287.0809; found: 287.0791.

(*R*)-2-((*R*)-1-(3-chlorophenyl)allyl)-2-hydroxycyclohexan-1-one (4 c). The title compound was synthesized according to the general procedure from (*E*)-2-((3-(3-chlorophenyl)allyl)oxy)cyclohexan-1-one **3 c** (53.0 mg, 1.0 mmol). The product was isolated as a yellowish oil in 84% yield (44.6 mg, 0.17 mmol, dr 9.9:1). R_f = 0.68 (10% EtOAc in PE/DCM 1:1 mixture). IR (neat): ν = 3465, 2942, 2866, 1710, 1594,

1571, 1246, 1082, 794 cm^{-1}. Major diastereoisomer: *ee* 87% [Chiralpak AD–H column, hexane/iPrOH 95:5, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 16.5 min and t_R (minor) = 10.9 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 1.8, 1.1, 1H, Ar-H), 7.20–7.11 (m, 3H, Ar-H), 6.20 (ddd, *J* = 17.0, 10.1, 9.4, 1H, *CH*CH_2), 5.26 (dd, *J* = 10.1, 1.6, 1H, CH*CH*$_2$), 5.21 (ddd, *J* = 17.1, 1.6, 0.7, 1H, CH*CH*$_2$), 4.07 (s, 1H, O*H*), 3.79 (d, *J* = 9.4, 1H, *CH*Ar), 2.64–2.49 (m, 2H, *CH*$_2$), 2.49–2.42 (m, 1H, *CH*$_2$), 2.24–2.13 (m, 1H, *CH*$_2$), 1.87–1.47 (m, 4H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.7, 141.1, 136.0, 134.4, 129.9, 128.6, 127.6, 126.5, 118.6, 80.9, 54.1, 39.4, 39.0, 28.4, 22.2. Minor diastereoisomer: *ee* 18% [Chiralpak AD–H column, hexane/iPrOH 95:5, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 8.6 min and t_R (minor) = 4.6 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 1H, Ar-H), 7.35–7.30 (m, 1H, Ar-H), 6.00 (ddd, *J* = 16.9, 10.3, 9.3, 1H, *CH*CH_2), 5.09–4.98 (m, 2H, CH*CH*$_2$), 4.25 (s, 1H, O*H*), 1.95 (dq, *J* = 13.8, 3.0, 1H, *CH*$_2$), 1.40 (td, *J* = 13.6, 4.2, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.3, 129.8, 127.8, 127.5, 117.4, 81.3, 53.9, 39.1, 38.4, 28.3, 22.3. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_2ClNa$ $[M+Na]^+$: 287.0809; found: 287.0795.

(*R*)-2-((*R*)-1-(2-chlorophenyl)allyl)-2-hydroxycyclohexan-1-one (4d). The title compound was synthesized according to the general procedure from (*E*)-2-((3-(2-chlorophenyl)allyl)oxy)cyclohexan-1-one **3d** (53.0 mg, 1.0 mmol). The product was isolated as a yellowish oil in 77% yield (40.8 mg, 0.15 mmol, dr 4.4:1). R_f = 0.70 (10% EtOAc in PE/DCM 1:1 mixture). IR (neat): ν = 3461, 2941, 2866, 1710, 1472, 1442, 1248, 1048, 921, 754 cm^{-1}. Major diastereoisomer: *ee* 77% [Chiralpak AD–H column, hexane/iPrOH 99:1, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 18.6 min and t_R (minor) = 14.8 min]. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71 (dd, *J* = 7.9, 1.8, 1H, Ar-H), 7.30 (dd, *J* = 7.9, 1.5, 1H, Ar-H), 7.19 (td, *J* = 7.6, 1.5, 1H, Ar-H), 7.12 (ddd, *J* = 7.9, 7.3, 1.8, 1H, Ar-H), 6.09 (ddd, *J* = 17.1, 10.0, 9.0, 1H, *CH*CH_2), 5.25 (ddd, *J* = 17.1, 1.6, 0.8, 1H, CH*CH*$_2$), 5.23 (dd, *J* = 10.0, 1.6, 1H, CH*CH*$_2$), 4.63 (d, *J* = 9.0, 1H, *CH*$_2$), 4.23 (s, 1H, O*H*), 2.76 (td, *J* = 13.8, 6.3, 1H, *CH*$_2$), 2.60 (dq, *J* = 13.7, 3.0, 1H, *CH*$_2$), 2.32 (ddt, *J* = 13.6, 4.3, 2.1, 1H, *CH*$_2$), 2.24–2.12 (m, 1H, *CH*$_2$), 1.93 (tt, *J* = 13.6, 3.7, 1H, *CH*$_2$), 1.88–1.74 (m, 1H, *CH*$_2$), 1.64 (qt, *J* = 14.2, 4.7, 1H, *CH*$_2$), 1.50 (td, *J* = 13.8, 4.4, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 213.6, 136.7, 136.0, 132.8, 130.5, 129.7, 128.4, 127.3, 118.5, 81.1, 48.0, 40.3, 38.3, 28.6, 22.4. Minor diastereoisomer: *ee* 69% [Chiralpak AD–H column, hexane/iPrOH 99:1, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 11.3 min and t_R (minor) = 13.0 min]. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.91 (dd, *J* = 7.9, 1.8, 1H, Ar-H), 7.39 (dd, *J* = 7.9, 1.5, 1H, Ar-H), 7.30–7.22 (m, 1H, Ar-H), 5.88 (ddd, *J* = 17.0, 10.1, 8.9, 1H, *CH*CH_2), 5.14–4.93 (m, 2H, CH*CH*$_2$), 4.59 (d, *J* = 8.9, 1H, *CH*$_2$), 4.37 (s, 1H, O*H*), 2.06–1.98 (m, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.8, 135.7, 134.4, 131.5, 129.6, 129.3, 122.6, 117.4, 82.0, 48.7, 39.7, 38.6, 28.5, 22.2. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_2ClNa$ $[M+Na]^+$: 287.0809; found: 287.0800.

(*R*)-2-hydroxy-2-((*R*)-1-(4-methoxyphenyl)allyl)cyclohexan-1-one (4e). The title compound was synthesized according to the general procedure from (*E*)-2-((3-(4-methoxyphenyl)allyl)oxy)cyclohexan-1-one **3e** (52.1 mg, 1.0 mmol). The product was isolated as a yellowish amorphous solid in 69% yield (35.8 mg, 0.14 mmol, dr 6.6:1). R_f = 0.67 (10% EtOAc in PE/DCM 1:1 mixture). IR (neat): ν = 3467, 2940, 2866, 1709, 1609, 1511, 1248, 1179, 1034 cm^{-1}. Major diastereoisomer: *ee* 80% [Chiralcel OJ–H column, hexane/iPrOH 8:2, flow rate 1 mL/min, 35 °C, λ = 210 nm; t_R (major) = 29.1 min and t_R (minor) = 10.2 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.7, 2H, Ar-H), 6.78 (d, *J* = 8.7, 2H, Ar-H), 6.23 (ddd, *J* = 17.0, 10.1, 9.4, 1H, *CH*CH_2), 5.26–5.11 (m, 2H, CH*CH*$_2$), 4.03 (s, 1H, O*H*), 3.79 (d, *J* = 9.4, 1H, *CH*Ar), 3.75 (s, 3H, O*CH*$_3$), 2.61 (td, *J* = 13.8, 6.4, 1H, *CH*$_2$), 2.52 (dq, *J* = 13.7, 3.1, 1H, *CH*$_2$), 2.42 (ddt, *J* = 13.6, 4.2, 2.1, 1H, *CH*$_2$), 2.23–2.11 (m, 1H, *CH*$_2$), 1.90–1.75 (m, 2H, *CH*$_2$), 1.68 (tt, *J* = 13.4, 4.4, 1H, *CH*$_2$), 1.51 (td, *J* = 13.4, 4.9, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 213.1, 158.8, 136.8, 131.2, 129.3, 117.6, 114.1, 81.2, 55.3, 53.6, 39.3, 39.0, 28.4, 22.2. Minor diastereoisomer: *ee* 18% [Chiralcel OJ–H column, hexane/iPrOH 8:2, flow rate 1 mL/min, 35 °C, λ = 210 nm; t_R (major) = 12.8 min and t_R (minor) = 51.9 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.7, 2H, Ar-H), 6.88 (d, *J* = 8.7, 2H, Ar-H), 6.03 (dt, *J* = 17.5, 9.4, 1H, *CH*CH_2), 5.05–4.96 (m, 2H, CH*CH*$_2$), 4.20 (s, 1H, O*H*), 3.80 (s, 3H, O*CH*$_3$), 3.78 (d, *J* = 9.4, 1H, *CH*Ar), 2.00–1.88 (m, 1H, *CH*$_2$), 1.37 (td, *J* = 13.7, 4.1, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 130.5, 116.6, 114.0, 81.6, 55.4, 53.4, 39.1, 38.5, 28.3, 22.3. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_3Na$ $[M+Na]^+$: 283.1305; found: 283.1294.

(*R*)-2-hydroxy-2-((*R*)-1-(4-nitrophenyl)allyl)cyclohexan-1-one (4f). The title compound was synthesized according to the general procedure from (*E*)-2-((3-(4-nitrophenyl)allyl)oxy)cyclohexan-1-one **3f** (55.1 mg, 1.0 mmol). The product was isolated as a red amorphous solid in 80% yield (44.2 mg, 0.16 mmol, dr 7.4:1). R_f = 0.78 (20% EtOAc in PE/DCM 1:1 mixture). IR (neat): ν = 3457, 2940, 2866, 1709, 1603, 1519, 1345 cm^{-1}. Major diastereoisomer: *ee* 60% [Chiralpak AD–H column, hexane/iPrOH 85:15, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 15.8 min and t_R (minor) = 17.8 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.8, 2H, Ar-H), 7.43 (d, *J* = 8.8, 2H, Ar-H), 6.23 (ddd, *J* = 17.1, 10.1, 9.4, 1H, *CH*CH_2), 5.31 (dd, *J* = 10.1, 1.4, 1H, CH*CH*$_2$), 5.25 (ddd, *J* = 17.1, 1.4, 0.7, 1H, CH*CH*$_2$), 4.05 (s, 1H, O*H*), 3.94 (d, *J* = 9.4, 1H, *CH*Ar), 2.65–2.52 (m, 2H, *CH*$_2$), 2.52–2.42 (m, 1H, *CH*$_2$), 2.29–2.12 (m, 1H, *CH*$_2$), 1.91–1.80 (m, 2H, *CH*$_2$), 1.78–1.62 (m, 1H, *CH*$_2$), 1.56 (ddd, *J* = 13.8, 10.3, 7.8, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.4, 147.2, 146.7, 135.2, 129.3, 123.8, 119.5, 80.9, 54.3, 39.5, 39.0, 28.4, 22.2. Minor diastereoisomer: *ee* 3% [Chiralpak AD–H column, hexane/iPrOH 85:15, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 32.5 min and t_R (minor) = 25.8 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.8, 2H, Ar-H), 7.61 (d, *J* = 8.8, 2H, Ar-H), 6.01 (ddd, *J* = 17.0, 10.2, 9.2, 1H, *CH*CH_2), 5.14–5.02 (m, 2H, CH*CH*$_2$), 4.33 (s, 1H, O*H*), 3.95 (d, *J* = 9.2, 1H, *CH*Ar), 1.42 (td, *J* = 14.5, 5.0, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.5, 146.8, 134.8, 130.5, 123.7, 118.3, 81.1, 53.8, 39.1, 38.4, 28.2, 22.3. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NO_4Na$ $[M+Na]^+$: 298.1050; found: 298.1032.

(*R*)-2-hydroxy-2-((*R*)-1-(naphthalen-2-yl)allyl)cyclohexan-1-one (4g). The title compound was synthesized according to the general procedure from (*E*)-2-((3-(naphthalen-2-yl)allyl)oxy)cyclohexan-1-one **3g** (56.1 mg, 1.0 mmol). The product was isolated as a yellowish amorphous solid in 82% yield (45.8 mg, 0.16 mmol, dr 8.2:1). R_f = 0.71 (10% EtOAc in PE/DCM 1:1 mixture). IR (neat): ν = 3464, 2940, 2865, 1708, 1598, 1247, 802, 744 cm^{-1}. Major diastereoisomer: *ee* 81% [Chiralpak AS–H column, hexane/iPrOH 99:1, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 23.4 min and t_R (minor) = 12.5 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.72 (m, 3H, Ar-H), 7.66 (s, 1H, Ar-H), 7.50–7.38 (m, 3H, Ar-H), 6.37 (ddd, *J* = 17.1, 10.2, 9.3, 1H, *CH*CH_2), 5.31–5.15 (m, 2H, CH*CH*$_2$), 4.15 (s, 1H, O*H*), 4.01 (d, *J* = 9.3, 1H, *CH*Ar), 2.71 (td, *J* = 13.8, 6.4, 1H, *CH*Ar), 2.60 (dq, *J* = 13.7, 3.1, 1H, *CH*$_2$), 2.42 (ddt, *J* = 13.5, 4.2, 2.1, 1H, *CH*$_2$), 2.26–2.16 (m, 1H, *CH*$_2$), 1.96–1.80 (m, 2H, *CH*$_2$), 1.68 (qt, *J* = 13.4, 4.4, 1H, *CH*$_2$), 1.56 (td, *J* = 13.6, 4.5, 1H, *CH*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.9, 136.8, 136.6, 133.5, 132.8, 128.3, 127.9, 127.7, 127.1, 126.6, 126.1, 125.8, 118.2, 81.3, 54.5, 39.6, 39.1, 28.5, 22.3. Minor diastereoisomer: *ee* 6% [Chiralpak AS–H column, hexane/iPrOH 99:1, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 19.4 min and t_R (minor) = 14.0 min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.80 (m, 3H, Ar-H), 6.15 (dt, *J* = 17.4, 9.3, 1H, *CH*CH_2), 5.10–5.04 (m, 2H, CH*CH*$_2$), 4.32 (s, 1H, O*H*), 1.40 (td, *J* = 13.7, 4.0, 1H, *CH*$_2$). HRMS (ESI) *m/z* calcd for $C_{19}H_{20}O_2Na$ $[M+Na]^+$: 303.1356; found: 303.1343.

(*R*)-2-hydroxy-2-((*S*)-1-(thiophen-2-yl)allyl)cyclohexan-1-one (4h). The title compound was synthesized according to the general procedure from (*E*)-2-((3-(thiophen-2-yl)allyl)oxy)cyclohexan-1-one **3h** (47.3 mg, 1.0 mmol). The product was isolated as a yellow oil in 54% yield (45.8 mg, 0.11 mmol, dr 6.5:1). R_f = 0.67 (10% EtOAc in PE/DCM 1:1 mixture). IR (neat): ν = 3464, 2942, 2865, 1711, 1636,

1443, 1247, 926, 699 cm^{-1}. Major diastereoisomer: *ee* 81% [Chiralpak AS–H column, hexane/iPrOH 97:3, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 13.6 min and t_R (minor) = 8.5 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (ddd, *J* = 5.2, 1.3, 0.6, 1H, Ar-H), 6.89 (dd, *J* = 5.1, 3.5, 1H, Ar-H), 6.84 (dd, *J* = 3.5, 1.2, 1H, Ar-H), 6.13 (ddd, *J* = 16.7, 10.3, 9.3, 1H, C*H*CH_2), 5.28–5.17 (m, 2H, CHCH_2), 4.24 (d, *J* = 9.2, 1H, C*H*Ar), 4.21 (s, 1H, O*H*), 2.65 (td, *J* = 13.7, 6.4, 1H, CH_2), 2.55–2.40 (m, 2H, CH_2), 2.24–2.14 (m, 1H, CH_2), 1.87–1.49 (m, 4H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.6, 140.7, 136.4, 126.5, 124.9, 124.9, 118.0, 80.8, 50.3, 39.0, 38.6, 28.4, 22.2. Minor diastereoisomer: *ee* 13% [Chiralpak AS–H column, hexane/iPrOH 97:3, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 12.3 min and t_R (minor) = 9.1 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.23 (m, 1H, Ar-H), 7.03 (dd, *J* = 3.5, 1.3, 1H, Ar-H), 6.99 (dd, *J* = 5.1, 3.5, 1H, Ar-H), 5.94 (ddd, *J* = 17.1, 10.1, 9.0, 1H, C*H*CH_2), 5.11–4.98 (m, 2H, CHCH_2), 4.21 (d, *J* = 9.0, 1H, C*H*Ar), 2.10 (dq, *J* = 13.9, 3.0, 1H, CH_2), 1.42 (td, *J* = 13.5, 4.3, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 213.0, 136.0, 126.5, 126.4, 125.3, 117.0, 81.1, 50.1, 38.8, 38.6, 28.2, 22.3. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2SNa$ $[M+Na]^+$: 259.0763; found: 259.0753.

(*R*)-2-hydroxy-2-((*R*)-1-phenylallyl)cyclopentan-1-one (4k). The title compound was synthesized according to the general procedure from 2-(cinnamyloxy)cyclopentan-1-one **3k** (43.3 mg, 1.0 mmol). The product was isolated as a white amorphous solid in 60% yield (26.0 mg, 0.12 mmol, dr 3.9:1). R_f = 0.65 (10% EtOAc in PE/DCM 1:1 mixture). Major diastereoisomer: *ee* 79% [Chiralcel OJ–H column, hexane/iPrOH 9:1, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 30.9 min and t_R (minor) = 24.5 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 2H, Ar-H), 7.27–7.22 (m, 1H, Ar-H), 7.22–7.15 (m, 2H, Ar-H), 6.31 (ddd, *J* = 16.9, 10.2, 9.6, 1H, C*H*CH_2), 5.26 (dd, *J* = 10.1, 1.7, 1H, CHCH_2), 5.22 (ddd, *J* = 16.9, 1.7, 0.8, 1H, CHCH_2), 3.52 (d, *J* = 9.5, 1H, C*H*Ar), 2.54 (s, 1H, O*H*), 2.40–2.13 (m, 3H, CH_2), 1.98–1.81 (m, 2H, CH_2), 1.68–1.49 (m, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.9, 138.8, 135.9, 128.8, 128.7, 127.4, 119.2, 80.4, 56.2, 36.1, 33.8, 17.1. Minor diastereoisomer: *ee* 12% [Chiralcel OJ–H column, hexane/iPrOH 9:1, flow rate 1 mL/min, 25 °C, λ = 210 nm; t_R (major) = 17.9 min and t_R (minor) = 12.5 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.20 (ddd, *J* = 17.0, 10.3, 8.4, 1H, C*H*CH_2), 5.22–5.20 (m, 1H, CHCH_2), 5.06 (dt, *J* = 17.0, 1.4, 1H, CHCH_2), 3.50–3.48 (m, 1H, C*H*Ar), 2.66 (s, 1H, O*H*), 2.09–2.00 (m, 1H, CH_2), 1.82–1.67 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.6, 135.5, 129.4, 128.7, 127.3, 119.0, 81.3, 53.6, 34.7, 33.3, 16.7. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{14}H_{16}O_2Na$ 239.1043, found 239.1041.

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Conflict of Interest

The authors declare no conflict of interest.

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Author's publications and conference presentations

Other publications

1. Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement of Oxindoles. *Org. Lett.* **2016**, *8*, 1358–1361.

Conference presentations

1. Kimm, M.; Ošeka, M.; Kanger, T. [2,3]-Wittig Rearrangement as a Formal Asymmetric α-Alkylation of α-Branched Ketones. International Symposium on Synthesis and Catalysis 2019 (IsySyCat2019), **2019**, Evora, Portugal. (Poster)
2. Kimm, M.; Ošeka, M.; Kanger, T. Wittig [2,3]-Rearrangement as a Formal Asymmetric α-Alkylation of α-Branched Ketones. XXII International Conference on Organic Synthesis (22-ICOS), **2018**, Florence, Italy. (Poster)
3. Kimm, M.; Ošeka, M.; Kanger, T. Wittig [2,3]-Rearrangement as a Formal Asymmetric α-Alkylation of α-Branched Ketones. Balticum Organicum Syntheticum 2018 (BOS 2018), **2018**, Tallinn, Estonia. (Poster)
4. Ošeka, M.; Kimm, M.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement. European Symposium of Organic Chemistry 2017 (ECOS 2017), **2017**, Cologne, Germany. (Poster)
5. Ošeka, M.; Kimm, M.; Kanger, T. Asymmetric Organocatalytic Wittig [2,3]-Rearrangement. Balticum Organicum Syntheticum 2016 (BOS 2016), **2016**, Riga, Latvia. (Poster)

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2017 Estonian National Contest for University Students, First Prize for MA thesis (Estonian Ministry of Education and Research)
2015 Cambrex Tallinn Bachelor Study Scholarship (The TalTech Development Fund, Estonia)

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