Enantio- and Regioselective Iridium-Catalyzed Asymmetric Hydrogenation of Olefins

From Development to Total Synthesis

Cristiana Margarita
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Abstract
The work presented in this thesis concerns the iridium-catalyzed asymmetric hydrogenation of cyclic olefins and allylic alcohols for the preparation of useful chiral intermediates with various substitution patterns. The strategy provides stereoselective control for both non-functionalized and functionalized substrates and aims to be implemented in the stereoselective preparation of chiral building blocks having more than one stereocenter. The first part (Chapter 2) is focused on the asymmetric hydrogenation of 1,4-cyclohexadienes bearing a number of different functionalities. The development of a novel set of imidazole-based Ir-N,P catalyst enabled the efficient and enantioselective hydrogenation of prochiral substrates. In addition, the challenging regioselective mono-hydrogenation of only one of the two trisubstituted double bonds of the diene was accomplished.

The sequential preparation of chiral cyclic allylsilanes by means of iridium-catalyzed asymmetric hydrogenation and their employment in the Hosomi-Sakurai reaction was also studied (Chapter 3). Several patterns of alkyl substitution on the prochiral olefins were evaluated and the hydrogenation afforded the allylsilanes in high conversions and excellent enantiomeric excesses. These chiral silanes were then used in the TiCl₄-promoted allylation of aldehydes, which took place with high diastereoselectivity.

In Chapter 4, the kinetic resolution of allylic alcohols via asymmetric hydrogenation is described. High selectivity was observed for a broad range of substrates using a combination of an Ir-N,P catalyst and K₂CO₃ under mild reaction conditions. This highly efficient process is complementary to our previously reported asymmetric hydrogenation/DKR protocol. The final part (Chapter 5) covers the application of Ir-catalyzed hydrogenations as key steps in total synthesis. A sequential strategy involving enantio- and regioselective hydrogenations was successfully employed in the synthesis of the natural sesquiterpene (-)-Juvabione. In the following project, two allylic alcohols were hydrogenated to prepare chiral intermediates for a convergent formal synthesis of the renin inhibitor Aliskiren.

Keywords: Asymmetric hydrogenation, Iridium, Regioselectivity, Kinetic resolution, Total synthesis.

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"Master, moving stones around is one thing, but this is totally different!"

- Luke Skywalker
The work presented in this thesis concerns the iridium-catalyzed asymmetric hydrogenation of cyclic olefins and allylic alcohols for the preparation of useful chiral intermediates with various substitution patterns. The strategy provides stereocontrol for both non-functionalized as well as functionalized substrates and aims to be implemented in the stereoselective preparation of chiral building blocks having more than one stereocenter. The first part (Chapter 2) is focused on the asymmetric hydrogenation of 1,4-cyclohexadienes bearing a number of different functionalities. The development of a novel set of imidazole-based Ir-N,P catalyst enabled the efficient and enantioselective hydrogenation of prochiral substrates. In addition, the challenging regioselective mono-hydrogenation of only one of the two trisubstituted double bonds of the diene was accomplished. The sequential preparation of chiral cyclic allylsilanes by means of iridium-catalyzed asymmetric hydrogenation and their employment in the Hosomi-Sakurai reaction was also studied (Chapter 3). Several patterns of alkyl substitution on the prochiral olefins were evaluated and the hydrogenation afforded the allylsilanes in high conversions and excellent enantiomeric excesses. These chiral silanes were then used in the TiCl₄-promoted allylation of aldehydes, which took place with high diastereoselectivity. In Chapter 4, the kinetic resolution of allylic alcohols via asymmetric hydrogenation is described. High selectivity was observed for a broad range of substrates using a combination of an Ir-N,P catalyst and K₂CO₃ under mild reaction conditions. This highly efficient process is complementary to our previously reported asymmetric hydrogenation/DKR protocol. The final part (Chapter 5) covers the application of Ir-catalyzed hydrogenations as key steps in total synthesis. A sequential strategy involving enantio- and regioselective hydrogenations was successfully employed in the synthesis of the natural sesquiterpene (−)-Juvabione. In the following project, two allylic alcohols were hydrogenated to prepare chiral intermediates for a convergent formal synthesis of the renin inhibitor Aliskiren.
List of Publications

This thesis is based on the following papers, which are referred to by Roman numerals I-V. Reprints were made with the kind permission from the publishers and the contribution by the author to each publication is clarified in the “Contribution list”.

I. **Enantio- and Regioselective Ir-Catalyzed Hydrogenation of Di- and Trisubstituted Cycloalkenes**
   B. K. Peters,‡ J. Liu,‡ C. Margarita,‡ W. Rabten,‡ S. Kerdphon,‡ A. Orebom, T. Morsch and P. G. Andersson*

II. **Ir-Catalyzed Asymmetric and Regioselective Hydrogenation of Cyclic Allylsilanes and Generation of Quaternary Stereocenters via the Hosomi-Sakurai Allylation**
   W. Rabten, C. Margarita and P. G. Andersson*

III. **Highly Efficient Kinetic Resolution of Allylic Alcohols via Iridium-Catalyzed Asymmetric Hydrogenation**
    H. Wu,‡ C. Margarita,‡ J. Jongcharoenkamol, T. Singh, M. Nolan and P. G. Andersson*
    *Manuscript*

IV. **Asymmetric Total Synthesis of (−)-Juvabione via Sequential Ir-Catalyzed Hydrogenations**
    J. Zheng, C. Margarita, S. Krajangsri and P. G. Andersson*

V. **Formal Total Synthesis of Aliskiren**
    B. K. Peters, J. Liu, C. Margarita and P. G. Andersson*

‡Authors contributed equally to this work.
Publications not included in this thesis:

VI. Evolution and Prospects of the Asymmetric Hydrogenation of Unfunctionalized Olefins
C. Margarita and P. G. Andersson*

VII. Transition-Metal-Catalyzed Regioselective Asymmetric Mono-Hydrogenation of Dienes and Polyenes
C. Margarita, W. Rabten and P. G. Andersson*
Abbreviations

Abbreviations and acronyms are used in agreement with standards of the subject. Non-standard and additional ones that appear in the thesis are listed here.

* stereogenic center
Ar aryl
BArF₄ tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
cat. catalyst
cod 1,5-cyclooctadiene
conv. conversion
Cy cyclohexyl
DCE 1,2-dichloroethane
DCM dichloromethane
DFT Density Functional Theory
DIBAL-H diisobutylaluminium hydride
DIPAMP 1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DIPEA diisopropyl ethylamine
DIPT diisopropyl tartrate
DKR Dynamic Kinetic Resolution
DMAP 4-dimethylaminopyridine
DMF dimethylformamide
dr diastereomeric ratio
DTBB 4,4′-ditert-butylbiphenyl
ee enantiomeric excess
ent enantiomer
equiv. equivalent
EWG electron-withdrawing group
FDA Food and Drug Administration
GC Gas Chromatography
Het heterocycle
Hex hexyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>HPLC</td>
<td>High-Performance Liquid Chromatography</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>KR</td>
<td>Kinetic Resolution</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>L-3,4-dihydroxyphenylalanine</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>n.d.</td>
<td>no data</td>
</tr>
<tr>
<td>NHC</td>
<td>N-Heterocyclic Carbene</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorocromate</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>PHOX</td>
<td>phosphino-oxazoline</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-toluensulfonic acid</td>
</tr>
<tr>
<td>PVP</td>
<td>polyvinylpyridine</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>selectivity factor</td>
</tr>
<tr>
<td>SFC</td>
<td>Supercritical Fluid Chromatography</td>
</tr>
<tr>
<td>SI</td>
<td>supporting information</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
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Catalysts

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Catalysts
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1. Introduction

1.1 Asymmetric catalysis

The development of methods for the preparation of enantiopure molecules has a great impact on contemporary society, since their involvement in the pharmaceutical, agrochemical and fragrance industries is constantly expanding. Single enantiomeric drugs constitute in fact the largest portion of novel medicinal entities approved by the US FDA and worldwide, as only one enantiomer is usually responsible for the desired biological activity. Asymmetric synthesis provides a general approach to the preparation of enantiomerically enriched compounds and asymmetric catalysis is a particularly attractive aspect of asymmetric synthesis. A catalyst is defined as a material that in small amount increases the rate of a chemical reaction without being consumed. In asymmetric catalysis, a small amount of chiral catalyst can provide optically active materials in large quantities. This requires the efficient transfer of chirality from the catalyst to the substrate by means of interactions in the transition state. Compared to other methods, the isolation of the product is facilitated, with less undesired material to remove. This means that asymmetric catalysis can help to minimize the impact on the environment in addition to avoiding biological adverse side effects. However, the removal of residual transition metal impurities from final products is necessary for safety concerns. As a general strategy, chiral metal complexes are used as homogeneous catalysts and they usually undergo some modification to obtain the true catalytic species. The non-reactive coordination sites on the metal are occupied by auxiliary ligands, whose electronic and steric properties have a strong impact on the reaction. For this reason, the design of chiral ligands is of fundamental importance for efficient asymmetric catalysis. Optimized chiral metal complexes should be able to both accelerate the reaction rate and also discriminate between diastereomeric transition states. Most reactions are based on the conversion of a planar sp\(^2\) carbon structure into a tetrahedral sp\(^3\) carbon structure (Scheme 1), and this includes the hydrogenation of alkenes, imines and ketones as well as the addition of other reagents.
1.2 Transition metal-catalyzed asymmetric hydrogenation of olefins

The enantioselective hydrogenation of olefins is renowned as one of the most fundamental transformations in asymmetric catalysis, as it is a convenient strategy to create stereogenic centers in target molecules. Due to the excellent atom economy and high levels of enantioselectivity, the process is relevant both to academia and industry. Rh- and Ru-based catalytic systems are highly efficient and represent the optimal choice for functionalized olefins;\(^4\)-\(^8\) they are commonly employed for asymmetric hydrogenation in industrial processes. For example, the use of the Knowles’ Rh/DIPAMP catalyst for asymmetric hydrogenation was the first commercial application of a transition metal-catalyzed asymmetric reaction (Scheme 2). The reaction is used in the synthesis of the drug L-DOPA, a treatment for Parkinson’s disease.\(^9\)-\(^10\)

**Scheme 1.** Alkene hydrogenation: an example of asymmetric catalysis by sp\(^2\) to sp\(^3\) conversion.

**Scheme 2.** Synthesis of the L-DOPA drug for treatment of Parkinson’s disease.
These catalytic species are generally substrate specific and ligands may require some tuning before optimal results are obtained for new classes of olefins. Moreover, they generally require the presence of a chelating functionality in the substrate and typically display poor activity and enantiomeric excess (ee) for non-functionalized olefins. Chiral metalloocene-based catalysts were reported to be efficient and enantioselective in the hydrogenation unfunctionalized olefins, but harsh reaction conditions were required and the poor stability of the organometallic complexes prevented their further development and application. However, with the advent of iridium-based catalysts, not requiring coordinating groups, the asymmetric reduction of minimally functionalized alkenes could be achieved, leading to a great development of the field.

1.2.1. Ir-N,P-ligated catalysts

The central role of iridium in homogeneous catalytic hydrogenation can be traced back to the development of Crabtree’s catalyst, [Ir(cod)(PCy3)(py)]PF6 (Figure 1). It is a crystalline salt, showing good stability against oxidation, making it easier to handle than many other air-sensitive organometallic compounds. It constitutes a highly active hydrogenation catalyst for unfunctionalized tri- and tetrasubstituted olefins.

![Figure 1. Crabtree’s catalyst.](image1)

The groups of Helmchen, Williams and Pfaltz introduced the use of PHOX ligands in asymmetric catalysis. Then, the Pfaltz group employed PHOX-based chiral mimics of Crabtree’s complex (Figure 2) for the asymmetric hydrogenation of imines and aryl-substituted alkenes. Stability issues of the catalysts under hydrogenation conditions (deactivation due to forming hydride-bridged trimers) were solved by replacement of the counteranion PF6-. The use of the bulky counter-anion BArF− in weakly coordinating solvents (e.g. DCM) favored the hydrogenation, granting a dramatic increase of the reaction rate and allowed lowering the catalyst loadings to less than 1 mol%.

![Figure 2. Ir-PHOX catalyst.](image2)
By variation of the ligand structure, numerous Ir-N,P catalysts have been developed. The phenyl ring has been modified and the oxazoline replaced with other heterocycles. New complexes allowed the expansion of the substrate scope to a broad variety of olefins, and a class of pyridine-based ligands for the hydrogenation of purely alkyl-substituted alkenes was developed. An excellent example of the application of these systems to total synthesis provided γ-tocopherol as a single diastereoisomer in 98% ee, controlling two stereocenters in one reductive step (Scheme 3).

Scheme 3. Asymmetric hydrogenation of γ-tocotrienyl acetate.

The Burgess group developed another remarkably effective class of ligands containing N-heterocyclic-carbenes, where the NHC is replacing a phosphine, while the Andersson group reported various successful classes of chiral N,P-ligands, including different heterocyclic structures, for example phosphine-thiazole, -oxazole and -imidazole ligands (Figure 3).

This variation in the heterocycle gives rise to different properties and geometries of the bicyclic ligand, and also enables the tuning of the electron density on the N-atom, which in turn affects the electrophilicity of the iridium center. These catalysts are highly effective at low loadings for the hydrogenation of aryl-containing trisubstituted alkenes and many other classes of diversely substituted olefins.

Figure 3. Examples of catalysts developed in the Andersson group.
1.2.2. Mechanism and stereoselectivity

The mechanistic aspects of the Ir-catalyzed hydrogenation of olefins have been studied by various groups. The most widely accepted mechanism to date involves an Ir(III)/Ir(V) catalytic cycle and it was proposed by the Andersson and Burgess groups by means of DFT calculations, first on simplified truncated models and then on the full structure of a reported Ir-N,P catalyst. The catalytic cycle (Scheme 4) begins with the coordination of a H$_2$ molecule, which displaces a solvent molecule to give intermediate A. The rate-determining migratory insertion step occurs simultaneously to the oxidative addition of the coordinated dihydrogen molecule, which also facilitates it, to form the Ir(V) species B. Reductive elimination liberates the alkane product and coordination of new dihydrogen and alkene molecules regenerates species A. This reaction pathway has also been supported by recent experimental findings: low-temperature NMR studies by the Pfaltz group led to the identification of a fundamental intermediate, an Ir(III) dihydride alkene complex, akin to A. This species was described as a resting state of the catalyst, since the requirement of coordination of an additional hydrogen molecule to proceed to the migratory insertion step was demonstrated. The proposed catalytic cycle is thought to be operating for most of unfunctionalized olefins, with possible exceptions due to the specific electronic properties of the substrate.

Scheme 4. Proposed Ir(III)/Ir(V) catalytic cycle for the Ir-N,P-catalyzed hydrogenation of olefins.
In order to rationalize the stereochemical outcome of the Ir-catalyzed hydrogenation of prochiral olefins, a selectivity model has been developed in the Andersson group.\textsuperscript{54} The model has proven to be able to predict the correct absolute configuration of the major enantiomer of the reduced products for various olefins. It is based on the observation of the steric bulk in the iridium coordination sphere from the point of view of the incoming alkene, \textit{trans} to the phosphorus atom. The chiral N,P-ligand structure and absolute configuration define the most occupied areas around the metal center, and this is better visualized by dividing the space into four quadrants (Figure 4).

\textit{Figure 4. Quadrant model.}

The bulky group (R) near the nitrogen atom in the ligand, commonly an aryl substituent, occupies the most hindered quadrant (dark grey area). The arrangement dictates the favored coordination of trisubstituted olefins, as positioning their smallest substituent (H) in this occupied space minimizes steric interaction. The addition of hydrogen from the coordinated face of the alkene results in the predicted absolute configuration of the chiral product. The model was also found capable of justifying the observed preferential formation of \textit{trans} isomers in the hydrogenation of 1,5-substituted unconjugated cyclohexadienes.\textsuperscript{56} It suggests that after the first hydrogenation takes place, the mono-hydrogenated product is released and the remaining double bond is coordinated from the opposite face. Therefore, the second hydrogenation occurs and generates the resulting \textit{trans} isomer of the fully saturated product (Figure 5).

\textit{Figure 5. Trans selectivity in the hydrogenation of cyclohexadienes.}
1.3 Main objectives of the thesis

The following projects envision the Ir-catalyzed asymmetric hydrogenation as an efficient method to induce stereocontrol on systems that have normally been considered difficult to access. Of particular interest are cyclohexane units bearing multiple chiral centers, especially in the case of alkyl substitution. The lack of coordinating functional groups in the vicinity of the double bonds and the geometry of the cyclic prochiral precursors make them challenging substrates for asymmetric hydrogenation. Since the resulting saturated motifs are common elements in a number of natural and biologically active compounds, they constitute a class of synthetically relevant targets. Another objective was to explore regioselective mono-hydrogenations of dienes that allow for further functionalization of the chiral mono-hydrogenated products. The methodology is aimed at providing more complex structures from enantioenriched cyclic compounds in a sequential manner, as demonstrated by application of this strategy to the total synthesis of (−)-Juabione. Another class of substrates investigated in the Ir-catalyzed asymmetric hydrogenation are allylic alcohols. Their highly enantioselective reduction was employed as a key step in the formal total synthesis of Aliskiren, and in a more recent work, we are studying their efficient kinetic resolution via asymmetric hydrogenation.
2. Enantio- and Regioselective Ir-Catalyzed Hydrogenation of Di- and Trisubstituted Cycloalkenes (Paper I)

As already briefly mentioned, the interest in the enantioselective reduction of minimally functionalized olefins is related to the possibility of stereocontrol on alkyl moieties of natural products. The substituted cyclohexane ring represents one of the scaffolds that are significant to total synthesis and pharmaceutical chemistry (see examples in Figure 6).

Previous reports from the Andersson group described a direct strategy to access chiral cyclohexanes in high enantioselectivity by means of sequential Birch reduction of aromatic compounds followed by Ir-catalyzed asymmetric hydrogenation. The abundance and ready availability of the aromatic substrates make this methodology a rapid pathway to obtain widely diverse substitution patterns in the products. These initial studies provided excellent results, but only partially investigated the potential of the strategy. Therefore, this project focused on the expansion of the substrate scope to a broad variety of cyclic olefins, which can be divided in different classes according to substitution (Figure 7). In addition, one important target of the work was to optimize the iridium catalyst structure in order to reach an improved generality and functional group tolerance.

Figure 6. Substituted cyclohexane motif in natural and pharmaceutical compounds.
2.1 Substrate synthesis – Birch reduction

The general methodology developed in these studies involves the preparation of the appropriate aromatic compounds, which are then subjected to Birch reduction, and the subsequent asymmetric hydrogenation of the resulting non-conjugated cyclohexadienes (Scheme 5).

Scheme 5. General procedure for the asymmetric hydrogenation of cyclohexadienes.

The class of minimally functionalized substrates included alkyl-substituted benzene or naphthalene derivatives and various aryl ethers. The group of substrates bearing remote functionalities on a substituent chain contained examples of free and silyl-protected primary alcohols, a methyl ester and an additional aromatic ring. Cyclohexadienes or cyclohexenes having functional groups directly bound to the ring structure such as carboxylic acids, a ketone and a diester were also prepared. The last class of cyclic olefins that was evaluated is constituted by heterocycle-containing compounds, which were synthesized starting from indole and carbazole derivatives. For targets including functional groups that are not compatible with this Birch reaction route, the corresponding dienes could be obtained by means of Diels-Alder cycloaddition as a convenient alternative (Scheme 6).

Scheme 6. Preparation of cyclohexadienes via Diels-Alder reaction.
However, most cyclohexadienes were prepared from Birch reduction, and the procedure was generally conducted using an excess of lithium metal in liquid ammonia, in presence of an alcohol as proton source. When necessary, the aromatic substrate was dissolved in a co-solvent, typically THF, prior to ammonia condensation. The regioselectivity of the reduction, directed by the electron-donating alkyl and ether groups, enabled obtaining the desired non-conjugated dienes.

2.2 N,P-ligand design

In the search for optimal activity and enantioselectivity in the hydrogenation of prochiral olefins, ligand structure plays a critical role and its design constitutes the main focus in numerous contributions to this field. It is not uncommon to encounter cases of reported classes of ligands where their structural variety has proved to be crucial in order to achieve high ee’s for a wide number of substrates. Some catalytic systems provide indeed excellent results but still remain substrate specific, thus it is needed to further investigate the ligand properties to overcome this lack of generality. Ligand libraries are usually developed in such a manner to facilitate structure variation and tune the steric or electronic properties. The most successful ligands that were previously reported for the cyclohexadienes substrate class are thiazole i and imidazole ii (Figure 8). For this project it was decided to evaluate the effect of diverse aryl substitution on imidazole ligands.

2.2.1. Iridium catalysts preparation and evaluation

The synthesis of new imidazole N,P-ligands was carried out. The variation of the phenyl ring to different aryl groups including 4-methyl, 2-methyl, 2,5-dimethyl, 4-methoxy, 2,5-dimethoxy and 4-fluorine substituents granted both electronic and steric diversity (Figure 8).

![Figure 8. Previously developed (i and ii), and novel imidazole-based Ir-N,P catalysts (iii–viii).](image-url)
The synthetic route for the imidazole N,P-ligand class was followed as previously developed in the Andersson group (Scheme 7).  

![Scheme 7. Synthetic pathway for the imidazole catalysts.](image)

The ethyl ester of 2-aminonicotinic acid 1 was condensed with the appropriate 2-bromoacetophenone derivative to furnish the bicyclic imidazole core bearing the desired aryl substitution (2). Subsequent saturation of the six-membered heterocycle (3) and LAH reduction of the ester moiety gave primary alcohols (4). The racemic primary alcohols were separated by preparative HPLC on chiral stationary phase and the sequent synthetic steps were carried out on the optically pure intermediates. Conversion to tosylate (5) and substitution with a boron-protected phosphine group produced compounds 6. The final stages of the catalysts synthesis involved the generation of the free aryl phosphines (7) and complexation of the resulting ligands with [Ir(cod)Cl]$_2$ followed by anion exchange with NaBAr$_F$. The new iridium catalysts (iii–viii) were isolated as orange solids and they were subsequently evaluated in the asymmetric hydrogenation of cyclohexadienes. Results from a preliminary screening are presented in Table 1. The selected cyclic substrates were hydrogenated in full conversion in most cases using a 0.5 mol% catalyst loading, while the enantioselectivity varied with the imidazole substitution. For the 4-methyl derivative (iii) a slight enhancement of the enantioselectivity was found compared to the parent structure of catalyst ii, while the 4-methoxy substituted catalyst vi produced lower ee’s. Ligands bearing both 2- and 4-methyl or 2- and 4-methoxy substitution (v and vii) were found to give the best results, providing high ee in all three cases.
Table 1. Preliminary catalyst screening.\textsuperscript{a-c}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>i conv. ee (%)</th>
<th>ii conv. ee (%)</th>
<th>iii conv. ee (%)</th>
<th>iv conv. ee (%)</th>
<th>v conv. ee (%)</th>
<th>vi conv. ee (%)</th>
<th>vii conv. ee (%)</th>
<th>viii conv. ee (%)</th>
</tr>
</thead>
</table>

\*Reaction conditions: 0.125 mmol of substrate, 0.5 mol% catalyst, 1 mL of CH\textsubscript{2}Cl\textsubscript{2}, 50 bar of H\textsubscript{2}, 17 h, rt. \*Concentration determined by \textsuperscript{1}H NMR spectroscopy. \*Enantiomeric excess determined by HPLC or GC analysis using a chiral stationary phase. \*Only starting material was detected other than the product.

Table 2. Asymmetric hydrogenation of minimally functionalized cyclohexadienes.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Catalyst Yield (%)</th>
<th>ee (%)</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Catalyst Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me-Me</td>
<td>Me-Me</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
<td>99</td>
<td>14</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>Et-Et</td>
<td>Et-Et</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
<td>99</td>
<td>15</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr-Et</td>
<td>i-Pr-Et</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
<td>99</td>
<td>16</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr-i-Pr</td>
<td>i-Pr-i-Pr</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
<td>99</td>
<td>17</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
<tr>
<td>5</td>
<td>Me-Me</td>
<td>Me-Me</td>
<td>v</td>
<td>91</td>
<td>18</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
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<td>99</td>
</tr>
<tr>
<td>6</td>
<td>4-Me-C\textsubscript{6}H\textsubscript{4}</td>
<td>4-Me-C\textsubscript{6}H\textsubscript{4}</td>
<td>v</td>
<td>81</td>
<td>19</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
<td>99</td>
<td>20</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
<tr>
<td>8</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
<td>99</td>
<td>21</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
<tr>
<td>9</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}</td>
<td>MeO-C\textsubscript{6}H\textsubscript{4}</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
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<td>22</td>
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<td>v</td>
<td>99\textsuperscript{a}</td>
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<td>19a</td>
<td>v</td>
<td>71\textsuperscript{a}</td>
<td>98</td>
<td>23</td>
<td>Ph-Me</td>
<td>v</td>
<td>97\textsuperscript{a}</td>
</tr>
<tr>
<td>11</td>
<td>20a</td>
<td>20a</td>
<td>v</td>
<td>68\textsuperscript{a}</td>
<td>98</td>
<td>24</td>
<td>Me-8a</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
<tr>
<td>12</td>
<td>21a</td>
<td>21a</td>
<td>i</td>
<td>81\textsuperscript{a}</td>
<td>98</td>
<td>25</td>
<td>J-Bu-10a</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
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<td>13</td>
<td>22a</td>
<td>22a</td>
<td>v</td>
<td>95\textsuperscript{a}</td>
<td>99</td>
<td>26</td>
<td>J-Bu-10b</td>
<td>v</td>
<td>99\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\*Reaction conditions: 0.125 mmol of substrate, 0.5 mol% catalyst, 1 mL of CH\textsubscript{2}Cl\textsubscript{2}, 50 bar of H\textsubscript{2}, 17 h, rt. \*Predicted absolute stereochemistry for the major product (\textgreater{}90% trans observed, unless otherwise stated). \*Isolated yield unless otherwise specified. \*Determined by HPLC or GC analysis using a chiral stationary phase. \*Conversion determined by \textsuperscript{1}H NMR spectroscopy. \*Trans <80%.
2.3 Substrate scope

The first class of cyclohexadienes, bearing minimal functionality, was then evaluated in the hydrogenation (Table 2). High enantioselectivity (94 to 99% ee) was observed for alkyl derivatives (11a–14a, entries 1–4) using the novel 2,4-dimethyl imidazole catalyst v. Excellent results (99% ee) were also obtained with the same catalyst for dienes containing aryl groups (15a–17a, entries 5–7) and optimal selectivity was maintained in the case of different enol ethers (18a–24a, entries 8–14, 98–99% ee). This demonstrated that acid-sensitive functional groups are tolerated by the imidazole catalytic system under hydrogenation conditions. Only in a few cases (entries 12, 17, 21) the best enantioselectivity was achieved with a different catalyst: thiazole-based catalyst i. Alkyl-substituted tetrahydronaphthalenes (9a and 10a, entries 24 and 25) were hydrogenated in 94 and 92% ee using another ligand in the recently developed series: the 2,4-dimethoxy substituted imidazole, catalyst vii. Next, substrates containing remote functional groups were investigated; for example, a free primary alcohol was introduced three carbons away from the double bond (33a) and the hydrogenation with the novel catalyst v granted good yield and excellent enantioselectivity (99% ee, entry 1, Table 3). Silyl-protected alcohols, both located two and three carbons away from the ring (34a and 35a) afforded similarly good yields and optimal selectivity with the same choice of ligand (99% ee, entries 2 and 3).

**Table 3.** Asymmetric hydrogenation of remotely functionalized cyclohexadienes. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product b</th>
<th>Catalyst</th>
<th>Yield (%) c</th>
<th>ee (%) d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;OH 33a</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;OH 33b</td>
<td>v</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OTBDMS 34a</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OTBDMS 34b</td>
<td>v</td>
<td>86&lt;sup&gt;•&lt;/sup&gt;</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;OH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OTBDMS 35a</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;OH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OTBDMS 35b</td>
<td>v</td>
<td>87&lt;sup&gt;•&lt;/sup&gt;</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OMe 36a</td>
<td>Me&lt;sup&gt;·&lt;/sup&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OMe 36b</td>
<td>ix</td>
<td>97&lt;sup&gt;•&lt;/sup&gt;</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>MeO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OMe&lt;sub&gt;2&lt;/sub&gt; 37a</td>
<td>MeO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OMe&lt;sub&gt;2&lt;/sub&gt; 37b</td>
<td>v</td>
<td>79&lt;sup&gt;•&lt;/sup&gt;</td>
<td>97</td>
</tr>
</tbody>
</table>

aReaction conditions: 0.125 mmol of substrate, 0.5 mol% catalyst, 1 mL of CH<sub>2</sub>Cl<sub>2</sub>, 50 bar of H<sub>2</sub>, 17 h, rt. bPredicted absolute stereochemistry for the major product. cIsolated yield. dDetermined by HPLC or GC analysis using a chiral stationary phase. e<sup>Trans</sup> <80%.
It was also possible to find the appropriate conditions to hydrogenate the methyl ester 36a in high yield and selectivity (92%), however with the use of a different catalyst, oxazole-based ix (Figure 9). A good result in the case of aryl ether 37a (entry 5) was again obtained with catalyst v, reaching 97% ee.

Figure 9. Additional catalysts employed in the study.

The possibility to have functionality directly bonded to the cyclic unit was then explored. Carboxylic acids 38a and 39a were successfully hydrogenated in 99% ee and high yields (entries 1 and 2, Table 4), using respectively thiazole-based ligand i and imidazole x (Figure 9).

Table 4. Asymmetric hydrogenation of cyclic olefins with varied functionality.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product\textsuperscript{b}</th>
<th>Catalyst</th>
<th>Yield (%)\textsuperscript{c}</th>
<th>ee (%)\textsuperscript{d}</th>
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<tr>
<td>1</td>
<td>COOH</td>
<td>COOH</td>
<td>i</td>
<td>91\textsuperscript{e}</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>COOH</td>
<td>COOH</td>
<td>x</td>
<td>98\textsuperscript{e}</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>O</td>
<td>v</td>
<td>98\textsuperscript{f}</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>COOMe</td>
<td>COOMe</td>
<td>v</td>
<td>99\textsuperscript{g}</td>
<td>97</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 0.125 mmol of substrate, 0.5 mol% catalyst, 1 mL of CH\textsubscript{2}Cl\textsubscript{2}, 50 bar of H\textsubscript{2}, 17 h, rt. \textsuperscript{b}Predicted absolute stereochemistry for the major product. \textsuperscript{c}Isolated yield unless otherwise specified. \textsuperscript{d} Determined by HPLC or GC analysis using a chiral stationary phase. \textsuperscript{e}>95% trans-dimethyl product. \textsuperscript{f}For both cis-fused diastereoisomers (1:1). \textsuperscript{g} Conversion determined by \textsuperscript{1}H NMR spectroscopy.
Substrates containing a ketone functionality (40a) and a diester (41a) were also found to give excellent enantioselectivity, 99% and 97% ee respectively, using the most successful catalyst v (entries 3 and 4). The last class of prochiral cyclic substrates that were evaluated included heterocyclic compounds (Table 5). Catalyst v was once again found to be the best option for indole or carbazole derivatives containing methyl or methoxy substituents; 99% ee could be obtained in all four cases (entries 1, 4, 5 and 7). Longer alkyl chains on the dihydroindole structure (n-Bu and n-Hex, entries 2 and 3) were handled better with the thiazole catalyst i, reaching good yields and 90% and 92% ee respectively.

Table 5. Asymmetric hydrogenation of cyclic olefins with fused or conjugated heterocycles.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Productb</th>
<th>Catalyst</th>
<th>Yield (%)c</th>
<th>ee (%)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td><img src="image1" alt="Structure" /></td>
<td>v</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td><img src="image2" alt="Structure" /></td>
<td>i</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>n-Hex</td>
<td><img src="image3" alt="Structure" /></td>
<td>i</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td><img src="image4" alt="Structure" /></td>
<td>v</td>
<td>99a</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>MeO</td>
<td><img src="image5" alt="Structure" /></td>
<td>v</td>
<td>99a</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>n-Bu</td>
<td><img src="image6" alt="Structure" /></td>
<td>ii</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure" /></td>
<td><img src="image8" alt="Structure" /></td>
<td>v</td>
<td>99a</td>
<td>99</td>
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<td><img src="image9" alt="Structure" /></td>
<td><img src="image10" alt="Structure" /></td>
<td>i</td>
<td>99a</td>
<td>99</td>
</tr>
</tbody>
</table>

aReaction conditions: 0.125 mmol of substrate, 0.5 mol% catalyst, 1 mL of CH₂Cl₂, 50 bar of H₂, 17 h, rt. bPredicted absolute stereochemistry for the major product. cIsolated yield unless otherwise specified. dDetermined by HPLC or GC analysis using a chiral stationary phase. eConversion determined by ¹H NMR spectroscopy.
It was also possible to hydrogenate the alkyl-substituted dihydrocarbazole 47a in 90% ee and high yield using imidazole-based catalyst ii (entry 6). The last substrate in this series bears a thiophene ring directly bonded on the cyclohexadiene unit (49a) and the use of thiazole catalyst i granted excellent conversion and enantioselectivity (99% ee, entry 8). The majority of the hydrogenations typically proceeded with complete consumption of the starting material and high conversions to the saturated compounds were observed, with only occasional formation of small amounts of side-products. However, in some cases, the high volatility of the products can explain lower isolated yields. For the majority of substrates generating two chiral centers upon hydrogenation, >90% of the trans isomer was observed (for exceptions see footnotes in Tables 1–5).

2.4 Regioselective hydrogenation

When developing methods for the hydrogenation of compounds containing more than one double bond, it is obviously an attractive option to generate and control multiple stereogenic centers in one step. However, it can also be of considerable importance to optimize regioselective procedures, which would preserve certain olefins to enable further modifications of the chiral hydrogenated product. While most Ir-N,P-ligated catalytic systems allow to leave the less reactive tetrasubstituted olefins intact, there are only few examples of regioselective hydrogenations for substrates containing two trisubstituted double bonds.59-62 Previously in the Andersson group, it was found that an added base (PVP) helped to preserve enol ethers from reduction in the asymmetric hydrogenation of cyclohexadienes.56

Table 6. Regioselective hydrogenations.\textsuperscript{a}

\begin{tabular}{llll}
Entry & H\textsubscript{2} (bar) & time (h) & conv. \\
1 & Me_{4}-C\textsubscript{F}_{3}-C\textsubscript{6}H\textsubscript{4} & 50 & 17 & 99 (99% ee) \\
2 & 17a & 5 & 0.5 & 94 (99% ee) & 6 \\
3 & Me & 50 & 17 & 99 (99% ee) \\
4 & 49a & 50 & 5 & 83 (99% ee) & 17 \\
\end{tabular}

\textsuperscript{a}Reaction conditions: 0.125 mmol of substrate, 0.5 mol\% catalyst v, 1 mL of CH\textsubscript{2}Cl\textsubscript{2}. Conversion determined by \textsuperscript{1}H NMR spectroscopy. Enantiomeric excess determined by HPLC or GC analysis using a chiral stationary phase.
In this study, a similar regioselectivity was obtained for aryl-conjugated cyclic diene substrates (17a and 49a), by optimization of the reaction conditions (Table 6). Lowering the hydrogen pressure and reducing the reaction time afforded predominantly the mono-hydrogenated products and excellent enantioselectivity was maintained (99% ee, entries 2 and 4).

2.5 Conclusion

To summarize, this project allowed expanding the scope of asymmetric hydrogenation to various cyclic dienes, which are typically regarded as challenging substrates. The preparation of novel chiral imidazole-based N,P-ligands, by variation of the aryl group substitution, afforded an efficient iridium catalyst (v), which showed great activity, enantioselectivity and functional group tolerance. This generality represents one important advantage of the described methodology. It was possible to hydrogenate a large number of prochiral dienes in high ee’s (90–99%) and the different substrate classes included examples of alkyl substituents, primary alcohols, esters, carboxylic acids and heterocyclic rings. The saturated products bearing two chiral centers were mainly formed as the trans isomer, with the majority of cases reaching >90% selectivity. Finally, the catalysts generally operated at low loadings (0.5–1 mol%) using 50 bar of hydrogen pressure, thus not requiring special or harsher conditions compared to the majority of Ir-catalyzed hydrogenations. Moreover, cases of regioselective hydrogenation between two trisubstituted olefins were reported, enabling further studies and synthetic possibilities.
In the optimization of asymmetric catalytic transformations, an important objective is to provide useful methods that can be introduced into synthetic pathways to chiral bioactive molecules. One desirable aspect of said methods lies in the chance to induce stereocontrol on multiple chiral centers in few steps. Regioselective asymmetric hydrogenations of dienes offer many possibilities since the chiral product maintains the useful functionality of a double bond that can be employed in subsequent reactions. To increase the versatility of the procedure, it is possible to envision the preservation of an allylic system rather than a simple olefin. Exploiting the allylic reactivity, new functionalities can be easily included to access higher molecular complexity. The level of enantioselectivity imposed by the asymmetric hydrogenation would then provide such useful intermediates in optically enriched form, enabling high stereocontrol also in the subsequent steps.

In this project cyclohexadienes featuring an allylic silane functional group were subjected to the Ir-catalyzed asymmetric hydrogenation. The double bonds bearing the silane moiety are tetrasubstituted, both ensuring their lower reactivity towards reduction and allowing for the generation of quaternary stereocenters. The planned method involves then the use of the hydrogenated enantioenriched cyclic allylsilanes in the Hosomi-Sakurai reaction (Scheme 8).

**Scheme 8. Sequential asymmetric hydrogenation/Hosomi-Sakurai reaction.**

Previous reports on the reactivity of cyclic allylsilanes in the Hosomi-Sakurai reaction showed that the procedure could provide high diastereoselectivity. It is hence possible to imagine this route as a
convenient approach to induce stereocontrol on chiral alkyl regions of
natural products (as suggested for example for the intermediate of
Sonomolide A, Figure 10).}

\[ \text{Sonomolide A} \]

**Figure 10.** Cyclic allylsilanes in the preparation of intermediates for Sonomolide A.

3.1 Hosomi-Sakurai reaction

3.1.1. Mechanism

The addition of allylsilanes to carbon electrophiles promoted by Lewis acids is generally referred to as the Hosomi-Sakurai reaction.\(^6\) Scheme 9 shows an example of the allylation of aldehydes, the most common class of electrophiles, using titanium tetrachloride as promoter. The addition to the electrophile generates a carbocation intermediate, which is stabilized by the presence of the \(\beta\)-silicon due to its hyperconjugation effect. As shown, donation of electron density from the filled \(\sigma\)-orbital of the C-Si bond to the empty \(p\)-orbital gives rise to this particularly robust stabilization.

\[ \text{Scheme 9. Example of Lewis acid-promoted allylation of aldehydes.} \]

The mechanism involves activation of the electrophile by the Lewis acid, and then the addition occurs in a manner to minimize steric repulsion among the groups on the reagents, which generally proceeds via *syn* addition when substituted allylsilanes are used. However, the choice of the Lewis acid might also produce a chelating effect and reverse this trend. Halides deriving from the Lewis acid are able to cleave the C-Si bond, forming a stable Si-X bond. For this reason, the Lewis acid is usually needed in stoichiometric
amounts. Finally, the generation of the homoallylic alcohol product occurs with an overall allyl inversion (Scheme 10).

**Scheme 10.** Mechanism of the TiCl₄-promoted allylation of carbonyl electrophiles.

The presence of a stereogenic center on the silane directs the stereochemistry of the allylation.⁶⁶ For example, Shea and coworkers reported on the use of a chiral bicyclic silane affording homoallylic alcohols as single diastereoisomers in the reaction with various aldehydes (Scheme 11).⁶⁴

**Scheme 11.** Stereoselective Hosomi-Sakurai reaction of a chiral bicyclic silane.

With absolute stereocontrol by the organosilane, little or no loss of stereochemical information is generally observed. Hence this approach was found suitable and applied in total synthesis.⁶⁷ However, the employment of cyclic silyl reagents is not so common. In an important study by Organ and coworkers, cyclic allylsilanes were reacted with a variety of aldehydes and acid chlorides in high diastereoselectivity, with a preferential formation of the *trans* products (Scheme 12).⁶³

**Scheme 12.** Diastereoselective Hosomi-Sakurai reaction of cyclic allylsilanes with aldehydes.
3.2 Chiral cyclic allylsilanes preparation

In this project it was anticipated that the Ir-catalyzed asymmetric hydrogenation could provide a direct strategy for the preparation of chiral cyclic allylsilanes in high enantioselectivity. In order to preserve the desired functionality on the cyclic substrates, two olefins on the prochiral molecules were differentiated by their substitution pattern. The trisubstituted double bonds bearing alkyl substituents would be selectively hydrogenated, while the tetrasubstituted olefin could maintain intact the allylsilane. The preparation of such prochiral dienes was planned as shown in Scheme 13.

Starting from simple commercially available materials such as benzyl alcohols, the silyl moiety could be installed in two steps via a benzyl chloride intermediate. The resulting aromatic silanes were subjected to Birch reduction to generate the corresponding cyclohexadienes possessing a trisubstituted olefin. These compounds were then investigated as substrates for the regio- and enantioselective iridium catalyzed hydrogenation. The planned procedure was successfully extended to the preparation of a variety of alkyl-substituted silyl cyclohexadienes and the following objective of the study was to find a suitable catalytic system for their asymmetric hydrogenation.

3.2.1. Asymmetric hydrogenation optimization

Dimethyl-substituted silane 53a was chosen as model substrate for the hydrogenation catalyst screening. Ir-N,P catalysts containing thiazole and imidazole ligands were evaluated, as they were found to be the most efficient for the hydrogenation of cyclohexadienes. In our previous report, it was already mentioned that the ligand properties proved to be crucial to reach a clean reaction and high selectivity, especially in presence of acid-sensitive functional groups. In the case of this allylsilane, the ligand effects turned out to be more dramatic. It was found that only one of the tested catalysts was able to provide full conversion to the desired saturated product. Most ligand structures, which are likely to generate more acidic iridium species under hydrogenation conditions, afforded mixtures of the hydrogenated product and volatile compounds (entries 1–5), most likely formed through protodesilylation of the allylic substrate (Scheme 14). The effect of basic additives (PVP and KHCO₃) was also studied; they allowed improving the
conversion, but only moderate enantioselectivity was reached (70 and 71\% ee, entries 6 and 7). It was however possible to reach 95\% conversion and 98\% ee with catalyst vii (entry 8, Table 7). This dimethoxy-substituted imidazole catalyst was selected to further explore the reaction conditions. By replacing DCM with $\alpha,\alpha,\alpha$-trifluorotoluene a clean and more reproducible reaction was obtained, with full conversion and 99\% ee (entry 9). With the optimized conditions in hand, the hydrogenation was extended to analogous cyclic silanes.

**Table 7. Asymmetric hydrogenation screening for cyclic allylsilane 53a.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>cat.</th>
<th>solvent</th>
<th>additive</th>
<th>conv.%(b)</th>
<th>ee %(c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>ii</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>viii</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>75</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>xi</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>v</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>ii</td>
<td>CH$_2$Cl$_2$</td>
<td>PVP</td>
<td>99</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>ii</td>
<td>CH$_2$Cl$_2$</td>
<td>KHCO$_3$</td>
<td>99</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>vii</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>vii</td>
<td>PhCF$_3$</td>
<td>-</td>
<td>99</td>
<td>99</td>
</tr>
</tbody>
</table>

\*\*Reaction conditions: 0.05 mmol substrate, 0.5 mol% catalyst, 0.5 mL of solvent, 10 bar of H$_2$, 18 h, rt. \*\*Conversion determined by $^1$H NMR spectroscopy. \*\*Enantiomeric excess determined by GC analysis using a chiral stationary phase.

**Scheme 14. Possible protodesilylation pathway generating undesired byproducts.**
3.2.2. Substrate scope

The expansion of the substrate scope to different cyclic allylsilanes included variation of the alkyl chain length and their position on the ring. 4- and 5-substituted aromatic silanes were prepared, bearing methyl, ethyl, \textit{n}-butyl and isobutyl groups. The presence of bulkier substituents directly on the tetrasubstituted olefin was also explored. The results from the asymmetric hydrogenation of these substrates are summarized in Table 8. Catalyst \textbf{vii} performed excellent in the reduction, regardless of the substitution pattern. Hydrogenations occurred with high conversion, allowing the isolation of the saturated allylic silanes in good to excellent yields (70–96\%). Substrates having longer chains on the trisubstituted olefin tended to give slightly lower enantioselectivity, but overall remarkable \textit{ee}’s (92–99\%) were obtained.

\textit{Table 8. Substrate scope of the asymmetric hydrogenation of cyclic allylsilanes}.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product\textsuperscript{b}</th>
<th>Yield (%)\textsuperscript{c}</th>
<th>\textit{ee} (%)\textsuperscript{d}</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product\textsuperscript{b}</th>
<th>Yield (%)\textsuperscript{c}</th>
<th>\textit{ee} (%)\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>54a</td>
<td>84</td>
<td>92</td>
<td>5</td>
<td>Et</td>
<td>58a</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>\textit{n}-Bu</td>
<td>55a</td>
<td>84</td>
<td>93</td>
<td>6</td>
<td>\textit{n}-Bu</td>
<td>59a</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>\textit{i}-Bu</td>
<td>56a</td>
<td>96</td>
<td>99</td>
<td>7</td>
<td>\textit{i}-Bu</td>
<td>60a</td>
<td>70</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>\textit{t}-Bu</td>
<td>57a</td>
<td>70</td>
<td>99</td>
<td>8</td>
<td>\textit{t}-Bu</td>
<td>61a</td>
<td>95</td>
<td>98</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 0.05 mmol substrate, 0.5 mol% catalyst, 0.5 mL of solvent, 10 bar of H\textsubscript{2}, 18 h, rt. \textsuperscript{b}Predicted absolute configuration for the major product. \textsuperscript{c}Isolated yield. \textsuperscript{d}Enantiomeric excess determined by GC analysis using a chiral stationary phase.
3.3 Diastereoselective Hosomi-Sakurai allylation

3.3.1 Optimization

The prepared enantioenriched allylsilanes were then evaluated in the Hosomi-Sakurai reaction. The initial reactivity optimization studies employed the dimethyl allylsilane 53b as a model substrate and benzaldehyde as electrophile. Screening of different Lewis acids showed that TiCl₄ was the appropriate choice in order to have a cleaner and selective reaction (Table 9). SnCl₄ promoted the allylation as well, although producing more side-products and showing opposite diastereoselectivity (entry 2). SiCl₄ caused mainly the desilylation of the starting material. The use of BF₃•Et₂O did not afford the desired product and generated complex reaction mixtures. It is also known that TBAF can be used to initiate fluoride-promoted allylations (a complementary process based on nucleophile activation rather than Lewis acid coordination of the electrophile). However, we observed no such reactivity for the investigated cyclic silanes. TiCl₄ was then chosen to continue the selectivity optimization. The reaction mixture was kept at -78 °C with a dry ice/acetone cooling bath for 1 h using DCM as the solvent. Finally, the addition of 3Å molecular sieves led to an increased yield (68%, entry 6).

Table 9. Screening of Lewis acids for the Hosomi-Sakurai allylation.ᵃ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>additive</th>
<th>drᵇ</th>
<th>Yield (%)ᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiCl₄</td>
<td>-</td>
<td>5:1</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₄</td>
<td>-</td>
<td>1:6</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>SiCl₄</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>BF₃•Et₂O</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>TBAF</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>TiCl₄</td>
<td>3Å MS</td>
<td>5:1</td>
<td>68</td>
</tr>
</tbody>
</table>

ᵃReaction conditions: 0.15 mmol substrate, 1 equiv. Lewis acid, 1 equiv. PhCHO, 1.5 mL of CH₂Cl₂, 1 h, -78 °C.ᵇDiastereomeric ratio determined by ¹H NMR spectroscopy.ᶜIsolated yield.
Once the conditions were established, the diastereoselectivity of the reaction was investigated. The final allylation product contains three stereogenic centers, which can give rise to a maximum of eight possible stereoisomers. The stereochemical outcome is controlled by the preferred mode of allylsilane addition (antiperiplanar TS and minimizing steric hindrance) and the presence of the existing chiral center. In the reaction of cyclic allylsilane 53b with benzaldehyde the final allylation product contains three stereogenic centers, which can give rise to a maximum of eight possible stereoisomers. The stereochemical outcome is controlled by the preferred mode of allylsilane addition (antiperiplanar TS and minimizing steric hindrance) and the presence of the existing chiral center. In the reaction of cyclic allylsilane 53b with benzaldehyde only two diastereoisomers 62a and 62b were observed. Their ratio was optimized by further varying the reaction conditions. Interestingly, the dr was found to be highly concentration-dependent (Table 10), even though the reason for this particular trend is not yet clear.

**Table 10. Concentration dependence in the Hosomi-Sakurai allylation.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>concentration (M)</th>
<th>dr *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>0.22</td>
<td>12:1</td>
</tr>
<tr>
<td>4</td>
<td>0.60</td>
<td>30:1</td>
</tr>
</tbody>
</table>

*Diastereomeric ratio determined by $^1$H NMR spectroscopy.

With an initial concentration of 0.03 M allylsilane in DCM, the dr for the homoallylic alcohol 62 was 3:1. Increasing the substrate concentration to 0.1 M, 0.22 M and lastly 0.6 M afforded the final optimized dr of 30:1 (entry 4). This result is comparable to diastereoselectivities that had been previously reported in the literature for less hindered cyclic silanes.63 It is worth highlighting that in our case, with the use of tetrasubstituted allylsilanes, challenging quaternary stereocenters are generated. Finally, the enantioenriched silane (S)-53b (98% ee) deriving from asymmetric hydrogenation was employed in the reaction. As expected, the optical purity was preserved and the allylation product could be isolated in 97% ee.
3.3.2. Substrate and electrophile scope

The Hosomi-Sakurai reaction with benzaldehyde was then extended to other cyclic silanes. High stereoselectivity was obtained in most cases (Table 11). Changing the position of the methyl substituent (63) did not alter the $dr$ and a ratio of 31:1 was observed (entry 1). The ethyl-substituted product 64 (entry 2) could be isolated as a single diastereoisomer and the $n$-butyl-substituted counterpart 65 (entry 3) was obtained with a $dr$ of 34:1. Product 66 having an isobutyl substituent could also be obtained with a high $dr$ of 24:1 (entry 4).

Table 11. Silanes substrate scope for the allylation of benzaldehyde.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
<th>$dr$\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>42</td>
<td>31:1</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>69 (single diastereoisomer observed)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>37</td>
<td>34:1</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>30</td>
<td>24:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 0.35 mmol substrate, 1.1 equiv. TiCl\textsubscript{4}, 1.1 equiv. PhCHO, 0.6 mL of CH\textsubscript{2}Cl\textsubscript{2}, 1 h, -78 °C. \textsuperscript{b}Isolated yield. \textsuperscript{c}Diastereomeric ratio and relative stereochemistry determined by $^1$H NMR spectroscopy.

Then, in order to further evaluate the utility of the developed strategy, a selection of aldehydes were subjected to the reaction using dimethyl allylsilane 53b (Table 12). The use of cyclohexanecarboxaldehyde afforded homoallylic alcohol 67 as a single diastereoisomer (entry 1). The isobutyl-
and ethyl-substituted compounds 68 and 69 were obtained with high ratios of 24:1 and 46:1, respectively (entries 2 and 3). Using isobutyraldehyde resulted in a less selective allylation, with a \( dr \) of 9:1 (entry 4). In the last example, cyclopentanecarboxaldehyde was employed and the product 71 was again obtained with great diastereoselectivity (49:1, entry 5).

**Table 12. Aldehyde scope for the Hosomi-Sakurai reaction.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
<th>( dr ) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>65 single diastereoisomer observed</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>32</td>
<td>24:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>40</td>
<td>46:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>56</td>
<td>9:1</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>42</td>
<td>49:1</td>
</tr>
</tbody>
</table>

\(^{a}\)Reaction conditions: 0.35 mmol substrate, 1.1 equiv. TiCl\(_4\), 1.1 equiv. PhCHO, 0.6 mL of CH\(_2\)Cl\(_2\), 1 h, -78 °C. \(^{b}\)Isolated yield. \(^{c}\)Diastereomeric ratio and relative stereochemistry determined by \(^{1}\)H NMR spectroscopy.
3.4 Conclusion

In conclusion, the enantioselective preparation of chiral cyclic allylsilanes with alkyl substituents by means of iridium catalyzed asymmetric hydrogenation was developed. This useful class of reagents was obtained in excellent ee’s (92–99%) and isolated yields (70–96%). The procedure makes use of an imidazole-based ligand (vii) that demonstrated a unique behavior in the hydrogenation, without affecting the allylsilane moiety. The synthetic significance of the method was demonstrated by employing the prepared chiral reagents in the Hosomi-Sakurai allylation. The reaction of cyclic silanes and benzaldehyde promoted by TiCl₄ furnished the corresponding homoallylic alcohols in high dr and preserved optical purity (97% ee). Finally, different electrophiles were tested, allowing the variation of molecular complexity of the products. It is noteworthy how the reported strategy can tackle a challenging target as the generation of multiple stereocenters in high selectivity on cyclohexane structures comprising mainly alkyl substitution. Further expansion of the electrophile scope and the application to total synthesis are the ideal forthcoming objectives for this methodology.
4. Kinetic Resolution of Allylic Alcohols via Iridium-Catalyzed Asymmetric Hydrogenation (Paper III)

4.1 Kinetic resolution

Kinetic resolution (KR) processes rely on a simple concept: the different rate of reaction exhibited by the two enantiomers in a racemic mixture with a chiral reagent or catalyst. As shown in Scheme 15, the enantiomer reacting faster is readily converted to the product, while the other is retained and gradually sees an increase in its optical purity. Given the conditions for the process, kinetic resolutions have as primary goal the recovery of the enantioenriched starting material with a maximum ideal yield of 50%.

![Scheme 15. General concept of kinetic resolution.](image)

The factors that determine a successful kinetic resolution are related to the ability of the chiral reagent or catalyst to distinguish between the two enantiomers of the substrate. This can be measured by calculation of a specific parameter reflecting the difference in reaction rates, the *selectivity factor* \( s \). The \( s \) factor is obtained by taking into account the conversion obtained in the process (\( c \), ideally 50%) and the enantiomeric excess of the remaining starting material (Equation 1).

\[
s = \frac{k_R}{k_S} = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]}
\]

(1)
It is normally difficult to completely exclude the slow-reacting enantiomer from being converted, especially at the end of the reaction when most of the fast-reacting stereoisomer is consumed, and statistics interfere with the systems selectivity. Therefore, in order to achieve the highest enantiopurity of the resolved substrate, it is sometimes necessary to exceed the 50% conversion limit. Beyond enzymatic applications, well-known highly efficient kinetic resolutions of racemic secondary alcohols have been carried out via Sharpless epoxidations (Scheme 16a) or Fu’s catalytic acylations (Scheme 16b). General methods for the KR of allylic alcohols have been well investigated, and their development is continuously evolving. In particular, the use of a catalyst as resolving agent is an attractive method, because of the small amounts of chiral material required.

\[ R^1\chem{\cdots}R^2, OH \xrightarrow{\text{Ti(OH)Pr}_{14}} R^1\chem{\cdots}R^2, OH + R^1R^2, O\chem{\cdots} \]

b) Fu, acylation

\[ \text{Me}_2N \quad \text{Ph} \quad \text{Fe} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \]

\[ OH \quad R^1 \quad R \quad R \quad R \quad R \]

\[ \xrightarrow{\text{Ac}_2O, NEt_3} \quad t\text{-amyl alcohol, 0 °C} \]

c) Noyori, asymmetric hydrogenation

\[ \text{OH} \quad \xrightarrow{(R)\text{-Ru(BINAP)}} \quad \text{MeOH} \quad \xrightarrow{\text{H}_2} \quad \text{OH} \]

d) Previous work: Andersson, asymmetric hydrogenation - DKR

\[ \text{H}_2 \quad \xrightarrow{\text{Ir-N.P}} \quad \text{AcOH} \quad (10 \text{ mol%}) \]

e) This work: asymmetric hydrogenation - KR

\[ \text{H}_2 \quad \xrightarrow{\text{Ir-N.P}} \quad \text{K}_2\text{CO}_3 \quad (20 \text{ mol%}) \]

**Scheme 16. Catalytic KR of allylic alcohols.**
4.1.1 Project background

The KR of allylic alcohols via asymmetric hydrogenation using a Ru-BINAP catalyst was reported by Noyori in 1988. This system was found to be more efficient on cyclic structures, with s factors up to 76 (Scheme 16c). The use of catalytic hydrogenation in resolutions is rather appealing since catalysts can be both highly selective and effective at low loadings, and it is an inherently atom-economical process. One possible limitation of this method is that separation of the hydrogenated product and resolved allylic alcohol is not as straightforward as compared to methods (e.g. acylation or oxidation), where a large change in polarity occurs in the reaction. A broad substrate scope is desirable when developing kinetic resolution with synthetic catalysts, so that the use of a more specialized chiral system is justified by the wide applicability of the process. In some cases, KR can be of particular value in practical terms over direct enantioselective catalysis, for instance if the racemic alcohol is very inexpensive and readily available, or if other asymmetric methods do not yet reach high levels of enantioselectivity. We have recently developed the first example of dynamic kinetic resolution (DKR) of allylic alcohols in Ir-catalyzed asymmetric hydrogenation (Scheme 16d). In DKR processes, all the racemic starting material can be converted to the enantiomerically enriched product, due to in situ racemization of the substrate. The racemization can be achieved with addition of an appropriate co-catalyst. In our case, the iridium N,P catalyst was found to be able to promote both hydrogenation and racemization. The catalytic system demonstrated excellent ability to resolve racemic secondary allylic alcohols, especially with the aid of an acid additive (AcOH). The corresponding saturated alcohols bearing two stereocenters were obtained in high stereoselectivities and yields.

We observed that, by switching to a basic additive, a kinetic resolution of allylic alcohols could be performed. The study began using α,β-disubstituted cinnamyl alcohols. In principle, both the product and the resolved substrate are valuable and could be obtained in a highly enantioenriched form, as indicated by high s factor values. However, since the procedure is a complementary strategy to the DKR, we mainly focused on the remaining starting alcohol resolution. The operational similarity in the KR and the DKR/asymmetric hydrogenation protocols show how practical and easily tunable the reactivity of the system is.
4.2 Optimization

The optimization studies were carried out using racemic allylic alcohol (±)-72. The choice of the Ir-N,P catalyst was based on the DKR project results, thus thiazole-based catalyst xii (Table 13) was employed in the screening. In the first entry, the acidic conditions developed for the DKR protocol (10 mol% AcOH) were used as comparison.

Table 13. Optimization of reaction conditions. *

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>additive</th>
<th>conv. (%)b</th>
<th>ee of 72 (%)c</th>
<th>s*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Toluene</td>
<td>HOAc (10 mol %)</td>
<td>91 (78)</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>None</td>
<td>89 (81)</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>K3PO4</td>
<td>43</td>
<td>62.5</td>
<td>20.5</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>KOAc (10 mol %)</td>
<td>44</td>
<td>65.7</td>
<td>23.6</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>K2CO3</td>
<td>56</td>
<td>94.6</td>
<td>25.9</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>KHCO3</td>
<td>54 (98)</td>
<td>85.5</td>
<td>17.2</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>Na2CO3</td>
<td>54</td>
<td>89.7</td>
<td>21.4</td>
</tr>
<tr>
<td>8</td>
<td>Benzene</td>
<td>K2CO3</td>
<td>58</td>
<td>97.7</td>
<td>24.6</td>
</tr>
<tr>
<td>9</td>
<td>CH2Cl2</td>
<td>K2CO3</td>
<td>55 (75)</td>
<td>37.9</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>PhCF3</td>
<td>K2CO3</td>
<td>50</td>
<td>79.0</td>
<td>21.4</td>
</tr>
</tbody>
</table>

*aReaction conditions: (±)-72 (0.05 mol), 0.5 mol% catalyst and 20 mol% additive in the solvent (1.0 mL) under 1 bar H2 at room temperature for 10 min, unless otherwise specified. bConversion was determined by 1H NMR spectroscopy, the combined recovery ratio of 72 and 73 > 99%, unless the number was specified in parentheses. cEnantiomeric excesses were determined by SFC analysis (see SI for details). dThe selectivity factors s = ln[(1-c)(1-ee)]/ln[(1-c)(1-ee)]. 3 min reaction time.
In this case, 72 was mainly converted to the hydrogenated product (91%) and analysis of the remaining allylic alcohol confirmed that a racemization process was occurring. Excluding the acidic additive from the reaction mixture (entry 2) still indicated considerable racemization: 89% conversion was achieved and the remaining starting material was obtained in only 11% ee. However, the addition of a base to the reaction mixture demonstrated clearly that the racemization could be inhibited, enabling a KR/hydrogenation process. Several bases were screened. As shown in entry 3, using K$_3$PO$_4$ was found to limit the conversion (43%) and resolved 72 (63% ee) with good selectivity ($s = 21$). The use of KOAc (entry 4) gave similar results, improving the $s$ factor to 24, still with similar conversion. The best result was obtained by adding K$_2$CO$_3$ to the reaction (entry 5): the hydrogenation proceeded to 55% conversion and allylic alcohol 72 was resolved to excellent enantiopurity (95% ee). This corresponded to a selectivity factor of 26. Two other bases were tested (KHCO$_3$ and Na$_2$CO$_3$, entries 6 and 7) and both gave good levels of conversion, but lower enantioselectivity compared to K$_2$CO$_3$, which was therefore selected as basic additive. The effect of different solvents was then evaluated. Carrying out the reaction in benzene (entry 8) gave no significant improvement of the result obtained in toluene and the overall selectivity ($s = 25$) remained. When CH$_2$Cl$_2$ was evaluated (entry 9), a great suppression of the selectivity was found, and at 55% conversion the remaining alcohol 72 only showed 38% ee. This is probably due to the high hydrogenation rates normally observed in this solvent. The use of $\alpha,\alpha,\alpha$-trifluorotoluene (entry 10) also affected the selectivity, although in a less dramatic manner. The enantiomeric excess of 72 was 79% in this case. According to these results, we proceeded to employ 20 mol% K$_2$CO$_3$ in toluene.

### 4.3 Substrate scope

Once the appropriate base and solvent were established, we explored the allylic alcohol substrate scope. The beginning of the study concerned variation of the carbinol substitution, including several different alkyl substituents (Table 14). Substrate 74 containing an ethyl group was found to be an optimal candidate for KR, as it was resolved (99% ee) just over the ideal conversion (55%). The absolute configuration of 74 was assigned as (R) by comparison of its optical rotation with literature data. With an elongated alkyl chain, as the $n$-Bu group (alcohol 75), excellent results were maintained and only a slightly higher conversion (58%) was observed while still obtaining the starting material in 99% ee. High selectivity factors ($s > 30$) were obtained in both cases. The introduction of an isopropyl substituent (76) slowed down the reactivity, and the resolution had to be carried out
under 3 bar of H₂ with 1.0 mol% of catalyst xii. Under these conditions a very high selectivity was observed (s = 193), which gave the alcohol in 96% ee at 50% conversion. Increasing the bulk further to a t-butyl group (77) provided the same successful outcome (96% ee). Moving on to cyclic substituents, the system again performed with high efficiency: the cyclohexyl-bearing alcohol 78 could be obtained in 99% ee at 55% conversion (s = 49), and the cyclopentyl analogue 79 showed similarly excellent level of selectivity (99% ee, s = 41). A benzylic group worked equally well and afforded alcohol 80 in 99% ee at 54% conversion.

Table 14. Substrate scope – alkyl substitution.

<table>
<thead>
<tr>
<th>R</th>
<th>Reaction conditions: (±)-substrate (0.05 mol), 0.5 mol% catalyst and 20 mol% K₂CO₃ in toluene (1.0 mL) under 1 bar H₂ at room temperature for 1 h, unless otherwise specified in the SI. Conversion was determined by ¹H NMR spectroscopy. Enantiomeric excesses were determined by SFC analysis (see SI for details).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>Ir cat. xii H₂ (1 - 3 bar) K₂CO₃ toluene, rt</td>
</tr>
<tr>
<td>n-Bu</td>
<td></td>
</tr>
<tr>
<td>i-Pr</td>
<td></td>
</tr>
<tr>
<td>t-Bu</td>
<td></td>
</tr>
<tr>
<td>Cy</td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td></td>
</tr>
<tr>
<td>Bn</td>
<td></td>
</tr>
<tr>
<td>55% conv 99% ee s: 49</td>
<td>58% conv 99% ee s: 30</td>
</tr>
<tr>
<td>50% conv 96% ee s: 193</td>
<td>55% conv 99% ee s: 49</td>
</tr>
<tr>
<td>54% conv 99% ee s: 66</td>
<td>62% conv 99% ee s: 20</td>
</tr>
</tbody>
</table>

While the previously developed DKR reaction was restricted to compounds compatible with acidic conditions, the KR protocol allowed including some acid-sensitive substrates. Benzylic alcohol 81 is known to undergo acid-
catalyzed side-reactions under the standard Ir-N,P-catalyzed hydrogenation conditions, which, as previously mentioned, can be inherently acidic.\textsuperscript{68} For compound 81 the formation of carbocationic species is favored, and this resulted in a considerable amount of intramolecular cyclization product in previous hydrogenation attempts. Under the KR reaction conditions, the presence of K$_2$CO$_3$ efficiently avoided the generation of byproducts, and alcohol 81 could be resolved (99\% ee) even if at higher conversion (62\%, s = 20). The $\beta$-hydroxysilane 82 is a precursor for Peterson olefination, which is the main observed outcome under normal hydrogenation conditions. The Peterson reaction generates a conjugated diene, which is further reduced under the hydrogenation. With the use of base, silane 82 did not succumb to Peterson elimination, and the starting material underwent successful KR: 99\% ee at 57\% conversion (s = 35).

\textit{Table 15. Substrate scope – aryl substitution.}\textsuperscript{a}

\begin{center}
\begin{tabular}{cccc}
\hline
\textbf{Ar} & \textbf{Et} & \textbf{OH} & \textbf{Condition} \\
\hline
\textbf{83} & Et & OH & Ar + Ir cat. xii \ H$_2$ (1 bar) \ K$_2$CO$_3$ \ toluene, rt \\
54\% conv & 99\% ee & s: 61 \\
\textbf{84} & Et & OH & Ar \\
54\% conv & 99\% ee & s: 61 \\
\textbf{85} & Et & OH & Ar \\
53\% conv & 98\% ee & s: 65 \\
\textbf{86} & Et & OH & Ar \\
52\% conv & 96\% ee & s: 69 \\
\textbf{87} & Et & OH & Ar \\
56\% conv & 99\% ee & s: 44 \\
\textbf{88} & Et & OH & Ar \\
53\% conv & 99\% ee & s: 76 \\
\textbf{89} & Et & OH & Ar \\
54\% conv & 96\% ee & s: 39 \\
\textbf{90} & Et & OH & Ar \\
55\% conv & 99\% ee & s: 50 \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a}Reaction conditions: (±)-substrate (0.05 mol), 0.5 mol\% catalyst and 20 mol\% K$_2$CO$_3$ in toluene (1.0 mL) under 1 bar H$_2$ at room temperature for 10 min, unless otherwise specified in the SI. Conversion was determined by $^1$H NMR spectroscopy. Enantiomeric excesses were determined by SFC analysis (see SI for details).
Next, a series of ethyl-substituted alcohols were tested, varying the aryl moiety (Table 15). Having a p-Me group (substrate 83) still provided high selectivity. The starting material was resolved (99% ee) at 54% conversion (s = 61). With a p-OMe substituent (substrate 84) it was possible to obtain the same remarkable outcome. Halogen substituents in the para position (alcohols 85–87) produced similar results in the KR conditions: the substrates could be resolved in high ee (96 - 99%), with conversions just above 50% (52 - 56%). Optimal resolution was also observed for alcohol 88, where the methyl substituent was in the meta position, only 53% conversion was necessary to reach 99% ee (s = 76). Heteroaromatic substrates containing a thiophene ring (89 and 90) were then evaluated. Regardless of the substitution position, the KR afforded excellent ee’s (96 and 99%, respectively) for the allylic alcohols at 54 - 55% conversion. The tolerance towards this type of substrates shows that no direct coordination to sulfur is occurring to interfere with the catalyst activity.

Finally, allylic alcohols bearing various functional groups were investigated (Table 16). Firstly, $\beta$-carbonyl functionalities were investigated, due to their potential for further employment in synthesis. The ethyl ester 91 granted efficient kinetic resolution (99% ee) at 57% conversion, corresponding to a selectivity factor of 42. The KR of ketones 92 and 93 led to good selectivity (s > 30), however with different results in the enantiopurity of the remaining starting material (99 and 89% ee, respectively). A very efficient KR could be obtained even on the bulky ester 94, which was resolved (99% ee) at 52% conversion (s = 116). Challenging tertiary alcohols (95 and 96) were also examined. These compounds represent more difficult substrates since the increased bulk hinders their reactivity, and the tertiary alcohol is also acid-sensitive and prone to side-reactions. An increased hydrogen pressure was required in this case. However, even if requiring a higher conversion (72%), compound 95 could be obtained in high ee (99%, s = 10). Comparable results were obtained for the isopropyl-substituted alcohol 96, showing excellent ee (99%) at 70% conversion (s = 11). Despite the lower selectivity factors, these results are very promising, since the catalytic system is employed in the KR of a quaternary stereocenter. The presence of a chloride (allylic alcohol 97) was also well tolerated in the KR, and the starting material was obtained in high ee (99%), even if with a conversion close to 60% (s = 22). The reaction proved less efficient on fully aliphatic substrates 98 and 99. However the cyclic alcohol 98 reached optimal resolution (99% ee) at 64% conversion (s = 16), while compound 99 could be resolved to 96% ee, but only at high conversion of the starting material (79%). A possible reason for this outcome can be the reduced steric hindrance around the double bond, making it more difficult for the catalyst to discriminate between the enantiomeric alcohols. Modification of the substituent on the olefin also led to lower selectivities. Introduction of an ethyl group (substrate
reduced the selectivity, but still reaching good enantioenrichment (55% conversion, 85% ee). When testing a vinyl fluoride (101) or the cyclic alcohol 102, it was possible to reach high enantiopurity (91 and 99% ee, respectively). However, increased conversion was needed (71 and 75%), and this indicated inferior selectivity (s = 6 and 9). In these cases, the amount of recovered starting alcohol is lower, but still in highly enantioenriched form.

Table 16. Substrate scope – various substitution.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conversion</th>
<th>Enantiomeric Excess</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>57%</td>
<td>99% ee</td>
<td>s: 42</td>
</tr>
<tr>
<td>92</td>
<td>55%</td>
<td>99% ee</td>
<td>s: 49</td>
</tr>
<tr>
<td>93</td>
<td>51%</td>
<td>89% ee</td>
<td>s: 38</td>
</tr>
<tr>
<td>94</td>
<td>52%</td>
<td>99% ee</td>
<td>s: 116</td>
</tr>
<tr>
<td>95</td>
<td>72%</td>
<td>99% ee</td>
<td>s: 10</td>
</tr>
<tr>
<td>96</td>
<td>70%</td>
<td>99% ee</td>
<td>s: 11</td>
</tr>
<tr>
<td>97</td>
<td>62%</td>
<td>99% ee</td>
<td>s: 22</td>
</tr>
<tr>
<td>98</td>
<td>64%</td>
<td>99% ee</td>
<td>s: 16</td>
</tr>
<tr>
<td>99</td>
<td>79%</td>
<td>96% ee</td>
<td>s: 5</td>
</tr>
<tr>
<td>100</td>
<td>55%</td>
<td>85% ee</td>
<td>s: 15</td>
</tr>
<tr>
<td>101</td>
<td>71%</td>
<td>91% ee</td>
<td>s: 6</td>
</tr>
<tr>
<td>102</td>
<td>75%</td>
<td>99% ee</td>
<td>s: 9</td>
</tr>
</tbody>
</table>

*aReaction conditions: (±)-substrate (0.05 mol), 0.5 mol% catalyst and 20 mol% K₂CO₃ in toluene (1.0 mL) under 1 bar H₂ at room temperature for 1 h, unless otherwise specified in the SI. Conversion was determined by ¹H NMR spectroscopy. Enantiomeric excesses were determined by SFC analysis (see SI for details).*
4.4 Origin of selectivity

To understand the origin of enantiodiscrimination, a preliminary DFT study was carried out and correlated with the previously developed quadrant selectivity model\textsuperscript{34} (Figure 11a). When the TS for the reaction of the matched enantiomer (S)-72 with catalyst xii was modeled (o-Tol groups were approximated to Ph for calculation purposes), an attractive interaction between lone pair electrons on the OH and the axial Ir-H was found (2.52 Å distance). (Figure 11b). For (S)-72 this interaction leads to a conformation with the methyl group at the carbinol pointing away from the N,P ligand backbone, an arrangement that is favored for steric reasons. However, the hydrogen bond also seems to dictate the conformation of the mismatched allylic alcohol (R)-72 (Figure 11c). The OH group is still in close proximity of the hydride (2.59 Å distance), leading to a conformation where the methyl group is now directed towards the N-heterocyclic ring of the ligand. The interaction thus occurs at the cost of a steric clash, resulting in a TS 3.0 kcal/mol higher in energy. These results suggest a reasonable explanation for the large differences in reaction rates observed in the hydrogenation of the allylic alcohol enantiomers. However, more refined calculations will aid to have a clearer picture of the overall kinetic resolution process.

4.5 Conclusion

The efficient kinetic resolution of a variety of allylic alcohols by means of Ir-N,P-catalyzed asymmetric hydrogenation has been developed. This highly selective process is related to our previously reported Ir-catalyzed DKR protocol and it could be operated by simple variation of the employed additives, making it easy to switch between complementary strategies obtaining either the starting material or the product with very high optical purity. High selectivity factors were observed with this methodology, affording the resolved alcohols in high ee, at good levels of conversion and within short reaction times. Mild hydrogen pressure, low loadings of catalyst (0.2 to 1.5 mol%) and basic additive (K$_2$CO$_3$, 20 mol%) were employed. The catalytic system demonstrated good functional group tolerance, including encouraging results on the particularly challenging KR of quaternary stereocenters.
**Figure 11. Suggested origin of selectivity.**
5. Applications in Total Synthesis: 
(−)-Juvabione and Aliskiren (Papers IV and V)

Although asymmetric hydrogenation is a widely developed method, there are still few examples of Ir-catalyzed asymmetric hydrogenation as a key step to prepare natural products and pharmaceuticals containing more than one stereogenic center. The most relevant example in this specific context is the application of Ir-PHOX catalysts by the Pfaltz group for the synthesis of γ-tocopherol. In this chapter, the use of Ir-catalyzed hydrogenations to introduce chirality in total synthesis intermediates is described. In particular, the first project was aimed to implement and demonstrate the usefulness of the recently investigated asymmetric and regioselective mono-hydrogenation of 1,4-cyclohexadienes. In the second project, a convergent method combining two fragments derived by hydrogenation of prochiral allylic alcohols is presented.

5.1 Asymmetric Total Synthesis of (−)-Juvabione via Sequential Ir-Catalyzed Hydrogenations

5.1.1 Introduction

Juvabione is a natural sesquiterpene showing insect juvenile hormone activity. It is produced in the bark of balsam fir (Abies balsamea) and it had been historically named the “paper factor” before its identification as the methyl ester of todomatic acid. The structure of Juvabione (103, Figure 12) contains two adjacent stereocenters and in nature it co-exists with its diastereoisomer epijuvabione (104). Since their structure elucidation, the stereoselective synthesis of these compounds has attracted large interest and several approaches have been reported. Many of the early reports for the asymmetric synthesis of Juvabione relied on the use of chiral pool-derived starting materials such as (+)-perillaldehyde or (+)-limonene. These methods are based on the manipulation of the existing chiral cyclic motif, which can be limited by the availability, purity and absolute configuration of the natural sources. A different approach to prepare chiral intermediates involves the use of enzymes: baker’s yeast reductions or lipase-mediated KR
have both been employed in the preparation of Juvabione. More recent strategies to tackle this stereoselective synthesis made use of transition metal catalysis and organocatalysis to induce chirality in the key steps.

Figure 12. Structures of (-)-Juvabione and (-)-epijuvabione.

Considering the new developments in regioselective mono-hydrogenation of cyclic dienes, we contemplated the possibility to implement this type of Ir-catalyzed asymmetric hydrogenation in the total synthesis of Juvabione. The key step would be the chemoselective hydrogenation of the unfunctionalized olefin of a diene, while preserving an enol ether (Scheme 17). While in many previous examples using Ru and Rh catalysts, functionalized olefins were preferably hydrogenated, the use of Ir-N,P ligated complexes can instead direct the hydrogenation selectivity toward alkyl-substituted double bonds. This reversal of reactivity allows to retain the enol ether functionality, while installing a stereogenic center on the alkyl chain. This type of regioselective hydrogenation is instrumental in controlling the stereoselectivity in our synthesis of Juvabione.

Scheme 17. Juvabione synthesis based on regioselective mono-hydrogenation.

5.1.2. Synthesis and optimization

As shown in Scheme 17, both the stereocenter on the cyclic structure and the one on the side-chain were planned to be generated by asymmetric hydrogenation. The styrene-type starting material is indeed a common motif in Ir-catalyzed hydrogenation substrates, usually resulting in high enantioselectivity. The performed synthesis involving the two sequential hydrogenations is outlined in Scheme 18.
Scheme 18. Total synthesis of (–)-Juvabione.
The first stereocenter was installed on the conjugated ester 105, which in turn was readily prepared by a Horner-Wadsworth-Emmons reaction of the TIPS-protected 4-hydroxyacetophenone with triethyl phosphonoacetate. Two different catalysts containing thiazole-N,P ligands were found to be successful for this asymmetric hydrogenation: ent-i and bicyclic ent-xii (Scheme 19). Both gave full conversion and high enantioselectivity (98% and 99% ee, respectively) in CH₂Cl₂ under 20 bar of H₂ and the catalyst loading could be decreased to 0.2 mol% without affecting the outcome. The bicyclic catalyst ent-xii was selected to carry out the large scale preparation of chiral saturated ester 106, allowing its isolation in 95% yield and 99% ee.

\[
\begin{align*}
\text{Scheme 19. Asymmetric hydrogenation of conjugated ester 105.}
\end{align*}
\]

The subsequent steps of the synthesis concerned the manipulation of the side-chain. In order to construct the isobutyl ketone function, chiral ester 106 was smoothly converted into the corresponding Weinreb amide (107, Scheme 18) and then treated with i-BuLi, giving the desired product 108 in 76% yield. At this point, the second hydrogenation requires the generation of the 1,4-cyclohexadiene motif via Birch reduction of the aromatic ring. For this purpose, protection of ketone 108 was required before breaking the aromaticity, thus it was transformed into a ketal (109) prior to reduction. The use of lithium metal in ammonia allowed the preparation of the desired 1,4-diene 110 in good yield (77%).

This compound, containing an alkyl-substituted double bond and a silyl enol ether, is a suitable substrate for regioselective asymmetric monohydrogenation. However, at this point, we carried out a separate study on the two sequential hydrogenations process. A model substrate containing both a cyclic diene and an adjacent stereocenter on an alkyl chain was needed, and we chose to synthesize it from (E)-2-(but-2-en-2-yl)naphthalene (111, Scheme 20). The aromatic starting material was first hydrogenated to both enantiomers (S)- and (R)-112 in 99% ee by using thiazole catalysts ent-i and
ent-x, which show opposite enantioselectivity. The resulting enantiomeric products were then reduced under Birch conditions to give the corresponding trienes (S)- and (R)-113, which were independently evaluated in a second asymmetric hydrogenation step.

Scheme 20. Preparation of model substrates for the sequential hydrogenation study.

As shown in Table 17, depending on the absolute configuration of the Ir-N,P catalyst and that of the enantiomeric substrates, matched and mismatched pairs arise. This results from interactions in the coordination pocket created by the chiral ligand around the iridium center, and depends both on the double bond substitution and on the pre-existing stereocenter. When hydrogenation of a matched substrate occurred, higher levels of stereoselectivity were observed, reaching excellent dr (98:2, 97:3 with ligands xiii and x on substrates (S)- and (R)-113 respectively). In the opposite case, diastereomeric ratios were found to be slightly lower, but the hydrogenations could still be run until full conversion and the overall selectivity was still high (90:10 and 94:6 with ligands x and xiii on substrates (S)- and (R)-113 respectively). These promising results clearly showed how the sequential strategy can be successful in the divergent generation of all four diastereoisomers 114a–d of the fully saturated product by careful selection of the hydrogenation catalysts.

Having assessed the potential of the asymmetric hydrogenation sequence, we moved forward to its application in the synthesis of (−)-Juvabione. It was then necessary to run optimization experiments on diene intermediate 110, in order to improve both stereo- and regioselectivity towards the mono-hydrogenated product 115a.
Table 17. Sequential hydrogenation stereoselectivity study.a

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Conversion and dr determined by 1H NMR spectroscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-113, 99% ee</td>
<td></td>
</tr>
<tr>
<td>[Ir catalyst (0.5 mol%)] 0.1 M substrate in CH₂Cl₂</td>
<td></td>
</tr>
<tr>
<td>H₂ (50 bar), rt, 16 h full conv.</td>
<td></td>
</tr>
<tr>
<td>114a:114b (84:16)</td>
<td></td>
</tr>
<tr>
<td>114a:114b (79:21)</td>
<td></td>
</tr>
<tr>
<td>114a:114b (98:2)</td>
<td></td>
</tr>
</tbody>
</table>

**a**Reaction conditions: 0.05 mmol of substrate, 0.5 mol% catalyst in 0.5 mL DCM at room temperature under H₂. Conversion and dr determined by 1H NMR spectroscopy.
Catalyst ent-x was selected according to its reported efficiency for regioselective hydrogenation of these type of substrates. The optimization of the hydrogenation conditions is summarized in Table 18. In this case, the hydrogenation required a basic additive to prevent hydrolysis of the enol ether. In addition, it was previously reported that the use of a base is also beneficial in minimizing the extent of over-reduction. When comparing KHCO₃ and K₃PO₄ as additives for the hydrogenation under 10 bar of H₂ (entries 1 and 2), the latter was found to perform better, lowering the amount of over-hydrogenated product 115b to 21\% and allowing full consumption of the starting material. Increasing the base loading further (15\%) led to lower reactivity, and only 77\% conversion could be reached under these reaction conditions (entry 3). However, employing a slightly higher hydrogen pressure (15 bar, entries 4 and 5) was enough to restore the reactivity while maintaining the same level of over-reduction (11\%).

**Table 18. Optimization of the diene regioselective mono-hydrogenation.**

<table>
<thead>
<tr>
<th>entry</th>
<th>base (mol%)</th>
<th>H₂ (bar)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>115b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHCO₃ (25)</td>
<td>10</td>
<td>18</td>
<td>92</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>K₃PO₄ (10)</td>
<td>10</td>
<td>18</td>
<td>99</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>K₃PO₄ (15)</td>
<td>10</td>
<td>24</td>
<td>77</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>K₃PO₄ (15)</td>
<td>15</td>
<td>24</td>
<td>99</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>K₃PO₄ (15)</td>
<td>15</td>
<td>20</td>
<td>99</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>K₃PO₄ (20)</td>
<td>15</td>
<td>24</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>K₃PO₄ (25)</td>
<td>15</td>
<td>24</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>K₃PO₄ (20)</td>
<td>20</td>
<td>24</td>
<td>99</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 0.10 mmol of substrate, 0.5 mol\% catalyst, base, in 1.0 mL PhCF₃ at room temperature under H₂. \(^b\)Determined by \(^1\)H NMR spectroscopy.
Following similar adjustments of both the base loading (entries 6 and 7) and pressure (entry 8), we were finally pleased to find reaction conditions (20 mol% K$_3$PO$_4$, 20 bar H$_2$) that resulted in the almost exclusive formation of the mono-hydrogenation product 115a (3% 115b, full conversion of diene 110). Applying the optimized hydrogenation procedure afforded intermediate 115a in 90% isolated yield. The remaining steps in the synthesis (Scheme 18) converted the preserved enol ether into a vinyl triflate, which was carried out adapting a procedure reported by Corey. Importantly, the method does not affect the double bond position, which would disrupt the chirality in our case. Vinyl triflate 116 was isolated in good yield (67%) and its dr could be established by GC analysis (94:6). The two final steps to convert this intermediate to (−)-Juabione were reported by Ogasawara and were performed accordingly. First, a Pd-catalyzed methoxycarbonylation was employed to introduce the conjugated ester function (117). Then, acidic hydrolysis of the ketal liberated the ketone group on the side-chain affording the target (−)-Juabione (103, 90%).

5.1.3. Conclusion
The total synthesis of the natural sesquiterpene Juabione was accomplished by implementing a sequential Ir-catalyzed asymmetric hydrogenation strategy that employed thiazole-based N,P-ligands. The installation of the first stereocenter on the target compound was directed via hydrogenation of a styrene-type double bond (99% ee). The key step consisted of the second hydrogenation, which proceeded both in stereo- and regioselective manner (94:6 dr) in presence of K$_3$PO$_4$. This method allowed the preparation of a chiral intermediate in which an enol ether could be retained. This function was successively converted into the required conjugated ester present in the target structure. In conclusion, (−)-Juabione was synthesized in 9 steps and 17% overall yield, starting from simple achiral precursors.
5.2 Formal Total Synthesis of Aliskiren

5.2.1 Introduction
Aliskiren (Figure 13) is an efficient third-generation renin inhibitor for the treatment of hypertension and renal failure. It was approved by FDA in 2007 and it has the advantage of oral administration.\textsuperscript{94-96} Previous approaches to its synthesis made use of chiral auxiliaries\textsuperscript{97-99} or organocatalysis\textsuperscript{100-101} to control the introduced stereogenic centers, while the use of catalytic asymmetric hydrogenation to prepare Aliskiren was reported by De Vries in 2007.\textsuperscript{102} Our planned synthesis of a key intermediate involved a convergent strategy that employed Ir-catalysts in the asymmetric hydrogenation of alkyl-substituted allylic alcohols.\textsuperscript{103} The target compound 118 (Scheme 21) is a late-stage intermediate in the synthesis of Aliskiren and contains two of the four stereogenic centers (C2 and C7). The remaining (C4 and C5) can be introduced later on an E-double bond, following a patented methodology.\textsuperscript{104}

![Figure 13. Aliskiren structure and stereochemistry.](image)

5.2.2 Synthesis and optimization
In our approach, we envisioned the target compound 118 being generated via a Julia-Kocienski olefination. This disconnection of the double bond provides the two fragments 119 and 120, each to be enantioselectively prepared (Scheme 21). The chirality on these two main fragments was planned to be installed by asymmetric hydrogenation of the corresponding allylic alcohols 121 and 122.

![Scheme 21. Aliskiren retrosynthesis and target intermediate.](image)
The starting material for the preparation of fragment 122 is an abundant natural compound: isovanillin. The initial steps consisted of manipulation of the ring substitution, which furnished bromide 123 as previously reported\(^\text{105}\) (Scheme 22). This intermediate was then coupled with methyl acetylenecarboxylate to produce alkyne 124 as a suitable precursor of the pure E-configured conjugated ester 125. The latter was prepared via a highly stereoselective organocuprate addition at low temperature, which was optimized (-100 °C, THF, 1 h) to give a 99/1 E/Z ratio and found to be reproducible on a large scale (10 mmol). Finally, DIBAL-H reduction afforded the desired E-allylic alcohol fragment 122. The pure geometry of the double bond is crucial to ensure high enantioselectivity of the following hydrogenation, as the different isomers commonly give rise to opposite enantiomers.

Scheme 22. Synthesis of fragment 122.

For the synthesis of the second E-configured fragment 121 (Scheme 23) we chose to start from commercially available ethyl-3-butenoate. After alkylation (126) and epoxidation with m-CPBA, treatment of intermediate 127 under basic conditions furnished fragment 121 as pure E isomer.\(^\text{106}\) The isolation of the desired allylic alcohol is aided by the spontaneous cyclization of the Z isomer to a volatile lactone, which was removed during workup.

Scheme 23. Synthesis of fragment 121.
With the appropriate $E$-configured prochiral allylic alcohols in hand, we proceeded to evaluate them in the asymmetric hydrogenation step. Several Ir-N,P catalysts were screened for the reduction of fragment 122 under 50 bar of H$_2$ in CH$_2$Cl$_2$ (Table 19). The best result in terms of both activity and enantioselectivity (93%) was obtained when the bicycle thiazole catalyst ent-xii was employed. The asymmetric hydrogenation of fragment 121 required higher pressure (100 bar) and the use of a basic additive (PVP) to reach satisfactory results: imidazole catalyst ent-ii performed best in this case, affording full conversion and high enantioselectivity (97%). In a brief screening of solvents, it was found that high conversion and ee could be maintained, but not improved.

**Table 19. Asymmetric hydrogenation of allylic alcohols 121 and 122.$^a$**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ent-xii</td>
<td>CH$_2$Cl$_2$</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>ent-ii</td>
<td>CH$_2$Cl$_2$</td>
<td>99</td>
<td>83</td>
</tr>
<tr>
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<td>ent-i</td>
<td>CH$_2$Cl$_2$</td>
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<td>5</td>
<td>ent-xii</td>
<td>DCE</td>
<td>99</td>
<td>91</td>
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<td>6</td>
<td>ent-xii</td>
<td>Toluene</td>
<td>99</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>ent-xii</td>
<td>PhCF$_3$</td>
<td>99</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>ent-xii</td>
<td>CF$_3$CH$_2$OH</td>
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<td>92</td>
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</table>

<table>
<thead>
<tr>
<th>catalyst</th>
<th>conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ent-xii</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>ent-ii</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>ent-i</td>
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<td>64</td>
</tr>
<tr>
<td>x</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
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<td>ent-ii</td>
<td>25</td>
<td>82</td>
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$^a$Reaction conditions: 0.065 mmol substrate, 1.0 mol% catalyst, 0.5 mL CH$_2$Cl$_2$, 100 bar H$_2$ for 121, 50 bar H$_2$ for 122, rt, 17 h. In the hydrogenation of 121, 1.5 mg of polyvinylpyridine was added. Conversion determined by $^1$H NMR spectroscopy. No side products were detected. Enantiomeric excess determined by HPLC, SFC or GC on a chiral stationary phase.

The two resulting chiral alcohols 119 and 120 could thus be obtained in 97% and 91% isolated yield, respectively, by use of the selected catalysts ent-xii and ent-ii. These intermediates were then further transformed into the required fragments for the final olefination step (Scheme 24). While alcohol 119 was oxidized with PCC to the corresponding chiral aldehyde 128, the other fragment (120) was tosylated (129), then substituted with 1-Ph-1H-tetrazole-5-thiol and oxidized to sulfone 130. Finally, the two fragments were coupled in the Julia-Kocienski reaction to prepare the Aliskiren key intermediate 118 in good yield (63%). The 1-Ph-1H-tetrazole group was selected as it resulted in a very high $E$ selectivity in the olefination (> 95%).
5.2.3. Conclusion

The asymmetric hydrogenation of two allylic alcohol fragments using Ir-N,P catalysts was employed in a convergent strategy for the preparation of a key intermediate of Aliskiren, a renin inhibitor drug. Bicyclic thiazole and imidazole ligands proved highly efficient in the hydrogenation of the prochiral alcohols 121 and 122 (97% and 93% ee, respectively). The resulting chiral intermediates 128 and 130 were then connected via a Julia-Kociensky olefination, to obtain the target compound 118 in good yield and high E-selectivity (95%). Overall, the late-stage intermediate of Aliskiren was obtained in 11 steps and 18% yield.
6. Summary

In the first two projects presented in this thesis, the Ir-catalyzed asymmetric hydrogenation of substituted 1,4-cyclohexadienes was further developed and extended to a large number of substrates to obtain chiral cyclohexanes with varied substitution patterns. Cyclic olefins generally constitute challenging substrates for enantioselective hydrogenation; however, the design of a novel class of imidazole-based N,P-ligands enabled high efficiency, improved functional group tolerance and even accomplished remarkable regioselective hydrogenations. As additional objective, synthetically useful functional groups such as silanes were included on the prochiral dienes, in order to enable subsequent reactions of the chiral saturated products. A versatile protocol was developed, in which the Hosomi-Sakurai reaction was applied to the chiral cyclic allylsilane hydrogenation products. These silanes reacted with different aldehydes, generating multiple stereogenic centers on a cyclohexane unit with high stereoselectivity.

The third project regarded the kinetic resolution of allylic alcohols by asymmetric hydrogenation, using a basic additive and an iridium bicyclic-thiazole catalyst. The method was highly efficient for a wide range of substrates, showing significant $s$ factor values. Remarkably, the reactivity of the system towards KR or DKR via asymmetric hydrogenation can be modulated by simple variation of the reaction additives. Moreover, promising results in the KR of tertiary alcohols were also obtained.

In the final chapter, two applications of Ir-catalyzed asymmetric hydrogenation in total synthesis were described. The natural sesquiterpene (–)-Juvabione was prepared via a sequential hydrogenation strategy, enabled by regioselective mono-hydrogenation discriminating between different trisubstituted olefins. The other example focused on the synthesis of a late-stage intermediate of the renin inhibitor Aliskiren. In this case, the project relied on a convergent approach that combined two chiral fragments derived by highly enantioselective hydrogenation of allylic alcohols.
De två första projekten som presenteras i denna avhandling är baserade på den iridium-katalyserade asymmetriska hydrogeneringen av substituerade 1,4-cyklohexadiener och applicerades på ett stort antal substrat för att erhålla kiralna cyklohexaner med varierande substitutionsmönster. Cykliska olefiner utgör generellt utmanande substrat för enantioselektiv hydrogenering och utvecklingen av en ny klass av imidazolbaserade N, P-ligander resulterade i hög effektivitet, förbättrat tolerans och till och med anmärkningsvärda regioselektiva hydrogeneringar. Syntetiskt användbara funktionella grupper såsom silaner inkluderades på de prokiralna dienerna för att möjliggöra efterföljande reaktioner av de kiralna produktarna. Ett mångsidigt protokoll utvecklades, i vilket Hosomi-Sakurai-reaktionen applicerades på de kiralna cyklishka allylsilanhydrogeneringsprodukterna. De reagerade med olika aldehyder, vilket genererade flera stereogena centra på en cyklohexan med hög stereoselektivitet.


Contribution List

**Paper I**: Synthesized and characterized a number of substrates and one Ir-N,P catalyst. Wrote part of the manuscript and the supporting information.

**Paper II**: Prepared part of the substrates and evaluated them in the asymmetric hydrogenation. Took part in the screening for reaction conditions and electrophile scope investigation. Participated in the preparation of the manuscript and supporting information.

**Paper III**: Synthesized several substrates and evaluated them in the kinetic resolution. Participated in the optimization of reaction conditions. Wrote the manuscript and a minor part of supporting information.

**Paper IV**: Performed several steps of the synthesis. Took part in the optimization of reaction conditions for the asymmetric hydrogenation, preparation of ketone and vinyl triflate. Wrote the manuscript and part of the supporting information.

**Paper V**: Synthesized two Ir-N,P catalysts. Took part in the screening for the hydrogenation of allylic alcohols. Wrote part of the supporting information.
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