DEVELOPMENT OF RHODIUM-CATALYZED REACTIONS FOR THE ENANTIOSELECTIVE DESYMMETRIZATION AND CARBONYLATION OF MESO ALKENES

by

Frederic Menard

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

GRADUATE DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TORONTO

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Development of Rhodium-Catalyzed Reactions for the Enantioselective Desymmetrization and Carbonylation of meso Alkenes

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Philosophiae doctor, Graduate Department of Chemistry
University of Toronto, 2010

Abstract

This thesis describes the discovery of catalytic reactions that create carbon-carbon bonds stereoselectively between substrates bearing an alkene and organoboronic acids reagents. Chiral rhodium(I) catalysts were found to react with various meso-symmetrical substrates, thereby resulting in enantioselective desymmetrization reactions. The methodologies presented herein allow the rapid synthesis of several chiral functionalized molecules; including branched homoallylic alcohols, cyclopentenyl hydrazines, and ketohydrazines.

The thesis is divided according to three main transformations: asymmetric allylic substitution of allylic carbonates, asymmetric ring-opening of [2.2.1]-diazabicycles, and carbonylation of alkenes or alkynes. Chapter 2 details the investigations of a ligand-controlled catalytic process to prepare either trans-2-arylcyclopent-3-enols (up to 94% ee), or trans-4-arylcyclopent-2-enols (up to 99% ee) as the major products starting from cyclic meso allylic dicarbonates. This rhodium-catalyzed methodology was extended to include linear allylic dicarbonates, thereby yielding chiral 2-arylbut-3-enols with up to 95% ee.

An enantioselective desymmetrization of strained alkenes by ring-opening of meso bicyclic hydrazines is described in Chapter 3. The reaction allows one to prepare trans-2-arylcyclopent-3-enyl hydrazides with up to 99% ee. In addition, an enantioselective hydroarylation process was identified to yield 5-aryl-2,3-diazabicyclo[2.2.1]heptanes. Mechanistic investigations showed that the reaction proceeds via an unusual C-H activation/1,4-migration of the rhodium catalyst.

Finally, Chapter 4 outlines the development of a mild catalytic acylation of pi systems. This mode of reactivity was optimized to promote the desymmetrization of [2.2.1]-diazabicycles via a formal allylic substitution with acyl anions as nucleophiles. The method yields densely functionalized trans-2-ketocyclopent-3-enyl hydrazides. In addition, preliminary studies demonstrate that the rhodium(I)-catalyzed acyl anion addition is also possible with other pi
electrophiles. For example, with alkyne, it provided a synthesis of cyclopentenones that complements the Pauson-Khand reaction. Overall, the catalytic transformations reported herein give access to seven classes of products stereoselectively; starting from simple reagents.
Acknowledgments

Reflecting back of the last four years of my PhD, I now fully appreciate the importance of my mentors and colleagues along the way. I wish I was not restricted to mere words to express my gratitude to those who helped make this journey a successful and memorable experience.

First and foremost I would like to thank my supervisor, Professor Mark Lautens for his positive support during the course of my thesis. The mentoring he provided me extends far beyond scientific knowledge. Above all, I am grateful for the scientific freedom he grants his students. From our perspective, this can sometimes be daunting, but it is an immensely rewarding experience. I also want to acknowledge his generosity in allowing me to present my modest research efforts at several conferences and meetings.

The members of my Supervisory Committee, Professors Rob Batey, Jik Chin, and Vy Dong, are kindly acknowledged for their sound advice and patience during many a scientific discussion. To Professor Kay M. Brummond, I also express my thanks for kindly accepting to serve as External Reviewer for this thesis.

For inspiration and advice, I am indebted to great past mentors: the late Dr. Pierre Dubreuil who showed me the beauty residing in chemistry, Dr. Francois Deschamps who believed I could make it as an organic chemist, Dr. Frank Fang who gave me a model which I should aspire to become, and Dr. Michel Couturier for elevating my experimental skills through extreme rigour and hardwork.

All the work reported here would have been virtually impossible without the help of the following departmental staff: Dr. Alan Lough for the stimulating discussions, Dr. Alex Young for allowing us to believe mass spectrometry analyses occur by magic, Dr. Tim Burrow for relentlessly working against the entropy of UofT’s NMR facility, Mr. Ken Greaves and Mr. Tony Adamo for the good laughs. I also wish to acknowledge Dr. Stan Skonieczny for the stimulating collaborations on the International Chemistry Olympiads. The first person I met when I visited UofT was Mrs. Anna-Liza Villavelez. Ever since, she has played a key role in ensuring we, silly graduate students, keep on track with the program—all the while keeping her joyful personality. I also sincerely thank Wilmer Walkas for his friendship and his relentless optimism.

Parts of this work result directly from close scientific collaborations with Bing Yu, Jane Panteleev, Gavin Tsui, and Dr. Jason Bexrud; I am deeply indebted to each of them for taking my modest ideas much further than initially anticipated. Dr. Karolin Geyer and Dr. Jacki Kitching are gratefully acknowledged for proof-reading my thesis and making suggestions to improve the manuscript.
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Mentoring students is probably one of the greatest pleasures of academic research. I was fortunate to supervise very talented students. I thank David Pérez (IUT Castres) for reminding me to keep an insatiable appetite for learning, Christian Weise (Leipzig Universität) for the amazing drive and determination, Daniela Sustac-Roman (UofT) for her contagious optimism, and Cécile Roux (U. Toulouse) for her eager enthusiasm.

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For their unwavering strenght and encouragement to pursue my dreams, I am grateful to my parents Roger and Lise. I understand my meandering academic path must have caused some qualms at times, but all is well in the end.

I sincerely thank Myriam for her love, support and understanding thoughout what were sometimes difficult times. You accepted to share my life and dreams, irrespective of where it may take us. Your important presence is often all that ties me back to reality.

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Lastly, I am deeply indebted to my students; who have taught me more than I have taught them.

Frederic Menard

Toronto, January 2010
I think that to keep trying new solutions is the way to do everything.

Richard P. Feynman
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### Abbreviations

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic/catalyst</td>
</tr>
<tr>
<td>conv.</td>
<td>conversion</td>
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<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>Δ</td>
<td>heat</td>
</tr>
<tr>
<td>d</td>
<td>day(s) (e.g., 2 d)</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>eq</td>
<td>equation</td>
</tr>
<tr>
<td>equiv.</td>
<td>molar equivalent(s)</td>
</tr>
<tr>
<td>EDG</td>
<td>electron donating group</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>h</td>
<td>hour(s) (e.g., 3 h)</td>
</tr>
<tr>
<td>hv</td>
<td>light irradiation</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative yield</td>
</tr>
<tr>
<td>Rf</td>
<td>retardation factor</td>
</tr>
<tr>
<td>rt (r.t.)</td>
<td>room temperature (22 °C)</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
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<tr>
<td>Vis</td>
<td>visible</td>
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**Chemical Abbreviations**

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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetoacetate</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
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<td>acetic anhydride</td>
</tr>
<tr>
<td>Alk</td>
<td>alkyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAP</td>
<td>1,1′-binaphthalene-2,2′-diphenylphosphine</td>
</tr>
<tr>
<td>BIPHEP</td>
<td>1,1′-biphenyl-2,2′-diphenylphosphine</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
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<td>t-Bu</td>
<td>tert-butyl</td>
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<td>Cbz</td>
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<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cy</td>
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</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N′-diisopropylethylamine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>diox.</td>
<td>1,4-dioxane</td>
</tr>
<tr>
<td>dms</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
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</tr>
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<td>ethyl acetate</td>
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<td>hexanes</td>
</tr>
<tr>
<td>IMes</td>
<td>N,N′-bismesitylimidazolium</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminium hydride</td>
</tr>
<tr>
<td>MCPBA</td>
<td>m-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
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<td>Mes</td>
<td>Mesityl</td>
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<tr>
<td>nbd</td>
<td>norbornadiene</td>
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<td>phenyl</td>
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<tr>
<td>PhH</td>
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<td>isopropyl</td>
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<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>R</td>
<td>undefined substituent</td>
</tr>
<tr>
<td>TBAF</td>
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</tr>
<tr>
<td>TBAI</td>
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</tr>
<tr>
<td>TBS</td>
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</tr>
<tr>
<td>TC</td>
<td>thiophene-2-carboxylate</td>
</tr>
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<td>trifluoroacetate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
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<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
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<td>tolyl</td>
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<tr>
<td>Troc</td>
<td>3,3,3-trichloroethoxycarbonyl</td>
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<tr>
<td>Tf</td>
<td>trifluoromethansulfonate</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
<tr>
<td>Xylyl (Xyl)</td>
<td>3,5-dimethylphenyl</td>
</tr>
</tbody>
</table>
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CHAPTER 1

GENERAL INTRODUCTION

Carbon atoms constitute the essence of organic chemistry. Despite tremendous advances in organic synthesis as a whole, one of the greatest challenges in organic chemistry still consists of inventing new reactions to construct – or modify – carbon molecular architecture.

Organic synthesis has evolved at an ever increasing pace over the last two centuries,\textsuperscript{1} to a state where it has now become commonly believed that any molecule can be made by chemists, given enough time and resources.\textsuperscript{2} This impression stems from the remarkable accomplishments from synthetic research groups in the 1990’s that completed the total synthesis of several natural products of great complexity. The synthetic sequences were typically very long (frequently 30 to 60 steps).

Parallel to total synthesis advances, the field of catalytic reactions with transition metals has undergone remarkable developments, particularly over the last 30 years. One of the most important aspects in using transition metals as catalysts is that they allow chemists to manipulate the oxidation states of reacting molecules while simultaneously creating new chemical bonds. This characteristic brings a desirable advantage to synthesis, for it allows one to effect several formal transformations in a single operation. Cutting down on the number of steps necessary to build molecules directly translates into shorter syntheses.

Catalysis with transition metals is now an indispensable tool for the modern chemical transformation of matter. Thanks to the pioneering work of organometallic chemists, the field of catalysis has expanded exponentially since the 1980s. For example, reactions such as hydrogenations with rhodium, palladium cross-coupling reactions, and ruthenium alkene cross-metatheses are broad-ranging and have found routine use in synthesis. However, asymmetric variants that provide only one enantiomer of a chiral product are far less general.\textsuperscript{3}

\textsuperscript{1} Whöler’s synthesis of urea in 1828 arguably constitutes the beginning of organic chemistry: Whöler, F. \textit{Annal. Phys. Chem.} \textbf{1828}, 88, 253.
\textsuperscript{3} A few exceptions include asymmetric hydrogenation, asymmetric epoxidation, and asymmetric dihydroxylation.
Transition metals are particularly well-suited to catalysis due to their low oxidation potentials, which translates into reversible reactivity in redox processes.\(^4\) Arguably the most important feature of transition metals is their aptitude to coordinate spectator ligands that can be adjusted to modify the physical environment as well as the electronic properties of the metal center. Yet, much remains to be done as we still need reliable ways to predict chemoselectivity, to control stereochemistry, and to rationally design new catalytic tools.

In the pharmaceutical industry, preparing compounds as single enantiomers can be of the utmost importance, since either enantiomer (mirror image) of a compound can have dramatically different effects. Only a chiral environment can distinguish between two enantiomers. Biological organisms are homochiral; they are made of molecules possessing the same sense of chirality at their individual stereocenters (i.e. L-amino acids, D-sugars). This means that biological systems will interact differently with either enantiomers of a molecule. The drug thalidomide is an infamous example illustrating the importance of this interaction: one enantiomer of thalidomide is a sedative, whereas the other creates deformities in the developing foetus (Figure 1-1).\(^5\)

![Figure 1-1 Enantiomers of the drug thalidomide.](image)

Therefore, there is an important need to have better methods to control the stereochemistry in chemical transformations. In this work, we will demonstrate that Rh catalysts are competent at creating new C–C bonds in high enantioselectivity.

1.1 Asymmetric Catalysis

The synthesis of enantiomerically pure chiral compounds via cost-effective methods has become an important goal in the chemical industry. Indeed, obtaining chiral molecules as single enantiomers circumvents the need to resolve a racemic mixture by costly processes (e.g., diastereomeric salts, chiral HPLC separation, biochemical resolution, or kinetic transformations). Another advantage is that, at the end of the reaction, only trace amounts of the

---

\(^4\) Examples of early transition metals include copper, iron, nickel, cobalt. Late transition metals include palladium, rhodium, ruthenium, platinum, iridium, osmium.

catalytic reagent have to be removed. This is an improvement in synthesis over the traditional alternative where a chiral auxiliary had to be attached to the starting material, and needed to be excised after the diastereoselective reaction.

In principle, in asymmetric catalysis, a chiral catalyst reacts with a prochiral functional group on the substrate to generate one stereoisomer of a product preferentially. A chiral catalyst will cause diastereomeric transition states of different energies depending on the nature of the interaction. This phenomenon influences the product outcome, and should favor the product arising from the lowest energy pathway. The most common prochiral compounds contain $sp^2$-hybridized carbons such as carbonyls and alkenes.

**C–C bond formation by nucleophilic addition to unactivated alkenes**

The body of knowledge amassed by pioneers in the field of asymmetric catalysis, such as Knowles, Noyori, and Sharpless in the late 1970’s, has led to a better understanding of asymmetric processes catalyzed by transition metals. Despite great advances in the field over the last 40 years, many difficulties have not yet been surmounted satisfactorily, especially when these methodologies are turned to intermolecular carbon-carbon (C–C) bond formation.

The enantioselective addition of carbon nucleophiles to unactivated alkenes is powerful, because it results in a rapid increase in the complexity of the products. However, whereas the stereoselective addition of carbon nucleophiles to activated alkenes has been a subject of intense study, fewer reports exist on the addition to unactivated alkenes.

Fundamentally, one of the factors that has impeded the development of catalytic addition of carbon nucleophiles to unactivated alkenes is their electronic nature. An alkene, being intrinsically electron-rich, will inherently prefer to react with electrophiles rather than nucleophiles. Consequently, the addition to unactivated alkenes has for long been limited to electrophilic additions in synthesis. Thus, except in marginal cases, the addition of hard carbon nucleophiles to unactivated alkenes remained unexploited until the advent of organometallic reagents. Since the seminal findings from Lippard in 1988 (showing 14% ee),

---


all asymmetric addition of C-nucleophiles to alkenes struggled with low to moderate levels of ee.\textsuperscript{10}

A breakthrough discovery was made in 1998 by Hayashi and Miyaura when rhodium catalysts were shown to promote addition “hard” $sp^2$ carbon nucleophiles to unsaturated alkenes with unprecedented enantioselectivity (Eqn 1-2).\textsuperscript{11} Concurrent developments in catalytic hydrogenation chemistry provided the ancillary chiral phophine ligands used as the source of chirality.

\begin{equation}
\text{Ar-B(OH)}_2 \quad \text{3\% Rh(C}_2\text{H}_4\text{)acac} \quad \text{(S)-BINAP} \quad \text{Dioxane/H}_2\text{O (10:1)} \quad 100 \, ^\circ\text{C}, 5 \, \text{h} \quad 70-99\% \\
\text{96-97\% ee}
\end{equation}

Two factors are likely to explain the success of the reaction: (1) the non-basic nature of the carbon nucleophile (as the Rh$^1$–C bond in the reactive complex displays very little polarity); and (2) Rh$^1$ seems to form much more stable complexes in solution with chiral ligands than other common transition metals such as Pd, Ni, Pt, or Cu.\textsuperscript{12}

**Rhodium in catalysis**

Organorhodium chemistry can be traced back to the Wilkinson complex, RhCl(PPh$_3$)$_3$, in the mid 1960’s.\textsuperscript{13} This rhodium complex proved to be the forerunner of modern organorhodium chemistry by opening up the field of homogeneous catalysis. Subsequently, rhodium has become the metal of choice in hydrogenation and hydroformylation reactions.

Despite the early interest it generated, the expansion of rhodium catalysis as a synthetic tool was much slower than that of organopalladium chemistry.\textsuperscript{14} Nevertheless, the interest in rhodium catalysis was rekindled by Hayashi’s seminal report in 1997, especially in the context of C–C bond forming reactions.\textsuperscript{15} From a synthetic perspective, these reactions can couple reagents in ways that have not been demonstrated with other metals. As ligand design


\textsuperscript{14} It has been suggested that rhodium catalysis was somewhat overshadowed in the 1980’s by high profile research groups forcefully asserting the supremacy of organopalladium chemistry (P.A. Evans, personal communication).

grew into a field of its own, more ligand sets became available to organic research groups. This was a key factor for organorhodium chemistry to come of age.

A striking feature of rhodium catalysis is the underlying difference in chemical reactivity and selectivity when comparing a specific transformation that is known with other metal complexes (e.g., Pd, Ni, or Ru catalysts). Indeed, rhodium catalysis provides unmatched levels of chemo-, regio-, and stereoselectivity, for reactions including cycloaditions, alkene additions, new carbenoid and nitrenoid reactions, and novel C–H insertion reactions that proceed via fundamentally different mechanisms.

Compared to other commonly used transition metals, rhodium presents new catalytic possibilities from a fundamental perspective. For example, nickel, palladium, and platinum typically operate within catalytic cycles shuttling between the (0) and (II) oxidation states. Since transmetallation can only occur with the metal(II) species, catalytic cycles must be designed to account for that behaviour. In contrast, rhodium typically shuttles between the (I) and (III) oxidation states in catalytic reactions and transmetalation can theoretically occur with both species. Thus, an organorhodium(I) complex can be generated directly – without oxidation of the metal, and is capable of reacting in ways not accessible to other metals. The direct transmetallation also results in lower energy pathways; translating into milder reaction conditions. Furthermore, oxidative additions to Rh(III) complexes are also possible and offer options for novel reactivity. Although not relevant to this work, there are now numerous examples of rhodium-catalyzed reactions in the literature that exploit Rh(II) catalysts in synthetic applications.\(^{16}\)

In this work, we have favored organoboronic acids as “hard” carbon nucleophiles. They are essentially synthetic equivalents of Grignard reagents, but their stability to moisture and oxygen allows them to be handled without special precautions – which is atypical of organometallic reagents.\(^ {17}\) This practical advantage has made them very popular reagents, to the point where an impressively wide selection of organoboronic acids are now commercially available. Another advantage is that organoboron reagents are not prone to significant background reactions.

We have decided to take advantage of rhodium’s tunability with appropriate ancillary ligands, to try to develop highly enantioselective reactions with symmetrical unactivated alkenes. Since the concept of enantioselective desymmetrization will play a rather predominant role in the following chapters, it seems advisable to have an early discussion of this topic.

---

1.2 Enantioselective Desymmetrization

The power of an enantioselective desymmetrization stems from the ability to control simultaneously the absolute stereochemistry of multiple stereocenters in a single transformation. Thus a molecule possessing an internal plane of symmetry is desymmetrized by reacting with a chiral reagent.\(^{18}\) Enantioselective desymmetrization strategies for the synthesis of small chiral molecules create value-added building blocks from simple, easily accessible starting materials.

Citations of desymmetrizations in the organic literature of the 1980’s and early 1990’s consisted of a number of examples of non-asymmetric desymmetrizations, a situation that has drastically reverted itself in the recent years. The term desymmetrization is nowadays nearly always accompanied by asymmetric or, more appropriately, enantioselective.\(^{19}\) The most effective strategy is to use meso molecules.\(^{20}\)

Desymmetrization of meso substrates

Meso compounds are molecules that possess at least two stereogenic centers and that have a mirror plane bisecting the molecule in a way that leaves the stereocenters with identical substitution, but opposite configuration.\(^{21,22}\) Consequently, meso molecules are achiral.

Synthesis relying on the desymmetrization of meso molecules generally involves two phases. First, a meso molecule needs to be synthesized with the focus being placed on the control of the relative stereochemical configuration. The key step normally takes place in the second step when the meso molecule is desymmetrized using a chiral reagent. This strategy is attractive because it can convert the totality of meso substrates into the desired chiral products, whereas kinetic resolution reactions of racemic substrates can lead only to a

---


\(^{21}\) According to Eliel’s definition: “meso is a stereodescriptor of a set of diastereomers that also includes at least one chiral member.” Eliel, E. L.; Wilen, S. H.; Mander, L. N. In Stereochemistry of Organic Compounds; John Wiley & Sons: New York, 1994.

\(^{22}\) A corollary precision is that the stereogenic centers must not all lie in the plane of symmetry.
maximum theoretical yield of 50%.\textsuperscript{23} Catalytic protocols have been devised to achieve efficient desymmetrizations, many of them using enzymatic processes.\textsuperscript{24}

Although \textit{meso} compounds have been known for more than 100 years,\textsuperscript{25} they remained underutilized by synthetic chemists until enantioselective synthesis emerged, and became truly useful with the advent of enantioselective catalysis. However, the success of the reaction is sometimes mitigated by the difficulty of accessing the starting materials. Thus more \textit{achiral} molecules have found their way in synthesis than \textit{meso} ones.

\textit{Meso} compounds offer an advantage over achiral ones in that they usually allow one to control the absolute stereochemistry of remote stereogenic centers. In contrast, most achiral substrates have no defined initial stereochemistry, therefore all stereocenters are created in the key desymmetrization step. \textit{Meso} molecules are usually prepared by \textit{syn} addition to $\pi$ systems, particularly \textit{via} cycloadditions reactions. The \textit{meso} compounds typically used in synthesis are small molecules. They are therefore used to generate chiral building blocks to elaborate more complex structures.

\subsection*{1.3 Enantioselective Desymmetrization Catalyzed by Transition Metals}

Advances in the subfield of catalytic enantioselective desymmetrization have kept in step with advances in catalysis as a whole. By far, the greatest number of enantioselective desymmetrization methods involve the formation of carbon–heteroatom bonds.\textsuperscript{26} In his review of the field in 1999, Willis concluded by mentioning that desymmetrization reactions involving catalytic enantioselective construction of C–C bonds were scarce.\textsuperscript{18a} Eight years later in Rovis’s 2007 review, still less than half of the examples listed involved C–C bond formation.\textsuperscript{18d} This is due in part to the fact that the substrate scope and that the efficiency of some of the processes is often too low for synthetic utility. The present work specifically aims at addressing the challenge of C–C bond forming reactions.

This section surveys the main classes of enantioselective desymmetrizations catalyzed by transition metals. Although reactions creating C–O and C–N bond in the key desymmetrization step are more abundant in the literature, emphasis will be put on C–C bond forming reactions.

\begin{itemize}
\item The properties of \textit{meso} compounds were the key elements in Emil Fischer’s assignment of the configuration of carbohydrates in 1904, see: Lichtenthaler, F. W. \textit{Angew. Chem., Int. Ed.} \textbf{1992}, \textit{31}, 1541.
\end{itemize}
1.3.1 C–O and C–N bond formation

The earliest examples of enantioselective desymmetrization were accomplished with C–O bond forming reactions. Among the main reaction classes for C–O bond formation using transition metal catalysts are found: asymmetric acylations,\textsuperscript{27,28} asymmetric oxidations of meso alkenes\textsuperscript{29} and of prochiral alcohols,\textsuperscript{30} asymmetric allylic substitutions of meso diols pioneered by Trost,\textsuperscript{31} and ring-openings of epoxides\textsuperscript{32} or meso cyclic anhydrides.\textsuperscript{33} For desymmetrization reactions creating C–N bonds, the more widespread include allylic substitutions\textsuperscript{30b} and ring-openings of electrophilic carbocycles.\textsuperscript{34}

1.3.2 C–C bond formation

Below are described the most salient classes of enantioselective desymmetrization reactions catalyzed by transition metals with C-nucleophiles. The list is intended to provide a contextual background rather than being exhaustive.

Asymmetric Allylic Alkylation (AAA). Trost and co-workers studied extensively the use of malonate-type nucleophiles with palladium(allyl) intermediates.\textsuperscript{35} For instance, desymmetrizing meso allylic dicarboxylates, the AAA with an enolized nitrosofule led to an enantiomerically pure key intermediate, where one of the oxygens of the nitro group displaced the second benzoate leaving group in an intramolecular reaction (Eqn 1-3).\textsuperscript{36} That


reaction was applied to the total synthesis of (+)-valienamine. Other catalytic systems using copper were examined by Pineschi and Gennari, and will be discussed in section 2.1.37

\[
\begin{align*}
\text{BzO} \cdots \text{...O} \text{Bz} & + \text{PhO}_2\text{S}\text{NO}_2 \\
\xrightarrow{[\text{Pd(allyl)}\text{Cl}_2, (0.25 \text{ mol}%)}, \text{Trost ligand}] & \text{PhO}_2\text{S} \cdots \text{NO} \cdots \text{O} \\
\xrightarrow{\text{Na}_2\text{CO}_3, \text{THF}/\text{H}_2\text{O}}, & 87\% \\
>99\% \text{ ee}
\end{align*}
\]

(1–3)

Ring opening of strained heterocycles. Following the pioneering work of Jacobsen in the enantioselective ring-opening of epoxides,38 Snapper and Hoveyda developed a titanium(IV)-catalyzed ring-opening of meso epoxides with cyanide nucleophiles (Eqn 1-4).39 The groups of Zhu,40 Mueller,41 and Waymouth42 also developed catalytic ring opening of epoxides or aziridines with carbanions; using alkynyllithiums, Grignard reagents, and trialkylaluminum, respectively. Copper catalysts with chiral phosphoramidites were also shown by Pineschi to ring-open cyclooctatetraene monoepoxies with dialkylzinc reagents.43

\[
\begin{align*}
\text{C} & + \text{TMS-CN} \\
\xrightarrow{\text{Ti(O-Pr)}_4, (20 \text{ mol}%)}, \text{chiral ligand (20 mol%)}, & \text{Toluene, } 4\degree \text{C} \\
\text{80\% conv.} & \text{87\% ee}
\end{align*}
\]

(1–4)

The ring strain of bridged structures was exploited by a number of research groups. The most common are [2.2.1]-heterobicycles prepared by cycloaddition with furans or pyrroles. As will be discussed in section 1.4, the group of Lautens developed a catalytic system to desymmetrize substituted oxabicycles with a wide range of organometallic nucleophiles. For example, both dialkylzincs and \(sp^2\) organoboronic acids were shown to ring-open heterobicycles in high enantioselectivity (Eqn 1-5).44,59–68 Feringa and Pineschi also showed

---

that diazabicycles could be ring-opened enantioselectively with dialkylzinc or trialkylaluminium reagents.\(^{45}\)

\[
\text{OTIPS} \quad + \quad \text{Et}_2\text{Zn} \quad \xrightarrow{\text{Pd(Tol-BINAP)Cl}_2} \quad \text{OTBS} \\
\text{DCM, r.t.} \quad 75\% \quad \text{(1-5)}
\]

**Anhydride opening.** The alkylative, or arylative, ring-opening of cyclic anhydrides generates synthetically useful keto-acids products. The first report on enantioselective desymmetrization of symmetrical anhydrides came from Rovis and coworkers in 2002 and used chiral Ni\(^{0}\) catalysts with dialkylzincs.\(^{46}\) Shortly thereafter, they reported the enantioselective addition of diarylzinc reagents under Pd\(^{II}\) catalysis.\(^{47}\) More recently, they showed that chiral Rh\(^{I}\) catalysts can add organoboron reagents to symmetrical anhydrides with high enantioselectivity (Eqn 1-6).\(^{48}\)

\[
\text{Me}^{\text{I}}\text{Me} \quad + \quad \text{Alk}_2\text{Zn} \quad \xrightarrow{[\text{Rh} (\text{nbd})\text{Cl}_2]} \quad \text{X} \\
\text{Taddeo-PNMe}_2 \quad \text{95\% ee} \quad \text{(1-6)}
\]

**Heck reaction.** The group of Shibasaki used a rare example of an asymmetric Heck reaction to differentiate enantiotopic alkenes and prepare an enantioenriched cis-decalin bearing a quaternary center (Eqn 1-7). The building block provided the chirality basis in the first total synthesis of (+)-vernolepin.\(^{49}\)

\[
\text{PivO} \quad \xrightarrow{9\% \text{Pd}_{\text{dba}}; \text{CHCl}_3; (R)-\text{BINAP} (11 \text{ mol\%})} \quad \cdot \quad \text{K}_2\text{CO}_3 (2 \text{ equiv}) \quad \text{t-BuOH (11 equiv)} \quad \text{DCE, 60 \degree C, 3 days} \\
\text{86\% ee} \quad \text{(1-7)}
\]

**Olefin metathesis.** A remarkable enantioselective synthesis of chiral heterocycles was reported by Hoveyda and Schrock. They designed a chiral molybdenum catalyst to realize

---


enantioselective ring-closing metathesis (RCM). The reaction delivers chiral dihydrofurans in high optical purity (Eqn 1-8).\textsuperscript{50} Grubbs and co-workers also developed a chiral version of their ruthenium RCM catalyst for enantioselective desymmetrizations of achiral trienes.\textsuperscript{51} An analogous chiral ruthenium catalyst was developed by Hoveyda and coworkers to effect enantioselective ring-opening metathesis (ROM).\textsuperscript{52}

\[
\text{\textbf{C–H insertions.}} \text{ The special case of C–H insertion reactions allows one to create new carbon-carbon bonds without pre-functionalization. The synthetic potential of catalytic asymmetric C–H insertion reactions of diazocarbonyl compounds for the synthesis of fused lactones was demonstrated by Doyle and co-workers.}\textsuperscript{53} \text{ They demonstrated that a carbene generated catalytically by a chiral rhodium(II) complex distinguished with excellent selectivity between two enantiotopic C–H bonds (Eqn 1-9). Since carbenoid intermediates are viewed as highly reactive species, such high selectivity is all the more impressive. Likewise, Davies and co-workers made important contributions to this area.}\textsuperscript{54}
\]

\[
\text{Me} \quad \text{\begin{align*}
\text{\text{O}} \\
\text{Me} \quad \text{\text{O}} \\
\text{N} \\
\text{Me} \\
\end{align*}} \quad \text{\begin{align*}
\text{\text{O}} \\
\text{Me} \\
\end{align*}} \\
\text{Rh(4S-MACIM)}_4 \quad \text{CH}_2Cl_2, \text{reflux} \\
\text{70\%} \\
\text{Me} \quad \text{\begin{align*}
\text{\text{O}} \\
\text{Me} \\
\end{align*}} \\
\text{Rh(4S-MACIM)}_4 \\
95\% \text{ee (99:1 d.r.)}
\]

Fu and Tanaka developed an intramolecular hydroacylation to prepare chiral cyclopentenones (Eqn 1-10).\textsuperscript{55} In contrast to the previous reaction where the C–H insertion was the


enantio-discriminating event, here the rhodium catalyst oxidatively adds to the aldehyde to generate an acylrhodium(III) complex, which then cyclizes by adding preferentially to one of the enantiotopic alkynes.

\[
\text{[Rh(Tol-BINAP)]BF}_4 \quad \text{DCM, 10 °C} \quad 94\% \quad 95\% \text{ ee}
\]

Cyclopropanation. Symmetrical molecules bearing prochiral divinyl groups were shown to undergo cyclopropanation with high enantio- and diastereoselectivity. The desymmetrization was demonstrated with Rh\(^{\text{I}}\),\(^{56}\) as well as with Cu\(^{\text{I}}\) catalysts,\(^{57}\) to generate highly functionalyzed cyclopropanes. Finally, although the process is not metal-catalyzed, enantioselective deprotonations must be mentioned. Chiral bases have attracted a lot of attention prior to the golden age of asymmetric catalysis. Their most common use is seen in the enantioselective deprotonation of meso or achiral ketones.\(^{58}\)

### 1.4 Desymmetrization of Strained Alkenes by Lautens & Co-workers

The Lautens group has had a long-standing interest in metal-catalyzed desymmetrization reactions of meso compounds.\(^{59}\) These reactions include the addition of nucleophiles such as hydrides, stabilized and nonstabilized carbanions, alcohols, amines, carboxylates, and thiols. Particular attention has been placed on the desymmetrization of oxobenzonorbornadienes, as the products are precursors to the medicinally important tetrahydronaphthalene moiety.

The genesis of enantioselective desymmetrization reactions in the Lautens group can be traced back to 1993 when a chiral amine was used to complex an alkylolithium to ring-open [3.2.1]-oxabicycles.\(^{60}\) Although some efforts were spent looking at the ring-opening of substrates bearing chiral auxiliaries, desymmetrization with chiral catalysts was rapidly shown to be a better strategy.\(^{61}\)

---

The first transition metal-catalyzed enantioselective desymmetrization of meso compounds from the group used nickel(0) to effect a reductive ring-opening with a hydride as nucleophile (Eqn 1-11).\(^6\) The method was exploited in a short synthesis of sertraline.\(^6\)

![Diagram 1-11](image)

**Scheme 1-1**

**Hard \(sp^3\) C-nucleophiles.** The strategy was extended to the addition of unstabilized \(sp^3\) carbanions with palladium as the metal catalyst. Using mainly dialkylzinc reagents, a wide range of heterobicyclic alkenes could be desymmetrized with high enantioselectivity (Scheme 1-1).\(^6\) In these cases, tolyl-BINAP and \(i\)-Pr-DIPOF ligands were key to obtaining high ee’s. This method afforded products with all cis substitution.

![Diagram](image)

**Soft nucleophiles.** When the addition of heteroatoms was investigated, rhodium(I) complexes turned out to be the best catalysts for the enantioselective ring-opening of oxabicycles. \([\text{Rh(cod)Cl}]_2\) precatalyst proved to be general and to allow the addition of alcohols, amines, carboxylates and thiols with high ee with Solvias’s chiral ligand \(t\)-BuJosiphos (Scheme 1-2).\(^6\) This work also exposed a ‘halide effect’ where it was shown that the


Chapter 1: General Introduction

1. General Introduction

A halide anion on the Rh(I) catalyst had a marked impact on the catalyst’s reactivity. Also, soft carbon nucleophiles, like malonates, added to the systems with the same diastereomeric outcome, i.e., to give trans products.

![Scheme 1-2]

**Scheme 1-2**

**Hard sp² C-nucleophiles.** The challenge of adding sp² carbon nucleophiles was solved by using organoboronic acid reagents as “hard” carbanion equivalent. In this case, rhodium(I) catalysts gave the best results. Again, the Rh¹/t-Bu-Josiphos combination allowed the highly enantioselective desymmetrization of meso bicyclic alkenes to obtain chiral carbocycles (Scheme 1-3). Palladium was the preferred catalyst for the ring-opening of certain azabicycles and was used in the total synthesis of (+)-homochelidonine. As in the case of hard sp³ nucleophiles, products all showed cis stereochemistry.

![Scheme 1-3]

**Scheme 1-3**

Still using organoboron reagents, the desymmetrization of other strained alkenes and alkynes was also demonstrated (Scheme 1-4). Although the reaction never led to high ee, it was nonetheless shown to yield highly substituted carbocyclic products with perfect

---


diastereocontrol. Simple starting materials allowed the preparation of complex molecules that would not be easily accessible by other means.

\[
\begin{align*}
\text{X} = \text{CH, N} \\
\text{R}_1 \rightarrow \text{Z}
\end{align*}
\]

\[
\begin{align*}
\text{R} + \text{B(pin)} & \xrightarrow{[\text{Rh(cod)Cl}]_2} \text{ligand} \\
\text{R} & \rightarrow \text{Z}
\end{align*}
\]

Scheme 1-4

Some general rules of reactivity emerged from the extensive body of work with the ring-opening of bicyclic alkenes. For instance, the relative stereochemistry of the product depends on the affinity of the nucleophiles for the metal catalyst, as illustrated in Scheme 1-5.

\[
\begin{align*}
\text{Soft Nu} & \rightarrow \text{trans} \\
\text{Hard Nu} & \rightarrow \text{cis}
\end{align*}
\]

Scheme 1-5

Soft nucleophiles (alcohols, amines, thiols, carboxylates, enolates) all presumably add via an anti attack of the alkene activated by complexation to the metal. In contrast, when a hard nucleophile is used (dialkylzincs, boronic acids) the organometallic complex reacts with alkenes via a carbo-metallation on the exo face. Coordination of the heteroatom bridgehead may also facilitate the delivery. In cases where there is no heteroatom at the bridgehead to coordinate the metal, such as with norbornene, then attack occurs on the more accessible exo face of the bicyclic alkene.

---

1.5 Thesis Overview

The development of new reactions to desymmetrize meso substrates was the initial focus of my research. This thesis describes the efforts to find rhodium(I) chiral catalysts to achieve the highly enantioselective formation of C–C bonds with alkenes. The general transformation is depicted in equation 1-12.

\[
\begin{align*}
\text{meso} & \quad \text{Nu} \quad \text{chiral catalyst} \quad \rightarrow \quad \text{products} \\
\end{align*}
\]

\(1-12\)

Chapter Two describes the investigations of a Rh-catalyzed addition of boronic acids to symmetric cycloalkenes bearing allylic leaving group (IV, Figure 1-2). A ligand-controlled mechanism was found and studied that allows one to access both 1,2-trans and 1,4-trans arylcyclopentenol products. Subsequent efforts to extend the methodology to linear alkenes V are also discussed.

Chapter Three details the studies that led to a highly enantioselective ring-opening reaction of bicyclic hydrazines of general structure II (Figure 1-2). The reaction allows one to synthesize the hydrazine analogs of the 1,2-trans arylcyclopentenes from the previous Chapter. A novel hydroarylation process was discovered. Mechanistic investigations of an unusual 1,4-migration of the rhodium catalyst, as well as the synthetic potential of this reaction, are also discussed.

Chapter Four outlines the development of a mild catalytic acylation reaction applied to the ring-opening of diazabicycles II. The reactivity of acyl anions with other electrophiles is also explored, in addition to initial studies to use N-heterocyclic carbenes to make the reaction enantioselective. The acylative reactions enabled by rhodium catalysis include a synthesis of cyclopentenones that complements the Pauson-Khand reaction.

\[
\begin{align*}
\text{I} & \quad \text{II} & \quad \text{III} & \quad \text{IV} & \quad \text{V} \\
X \quad \text{X} & \quad \text{X} & \quad \text{X} & \quad \text{X} & \quad \text{X} \\
\end{align*}
\]

\(X = O, NR, OR\)

Figure 1–2 Symmetrical substrates bearing decreasingly activated alkenes.
CHAPTER 2

ENANTIOSELECTIVE DESYMMETRIZATION OF ALLYLIC DIOL DERIVATIVES

This chapter describes a comprehensive study on the highly enantioselective allylic substitution of meso-cyclic dicarbonates using a chiral Rh(I)-biarylphosphine catalysts and arylboronic acids. Systematic investigations identified sets of ligands that can control the regioselectivity of the transformation. The method allows the rapid synthesis of chiral arylcyclopentenols from simple starting materials. It was also extended to the preparation of branched homoallylic alcohols.

2.1 Introduction

Enantioselective desymmetrization strategies create chiral molecules from simple starting materials.\(^1\) This approach is attractive with meso substrates because they can be fully converted into the desired chiral products. As discussed in Chapter 1, transition metal catalyzed reactions have allowed us and others to exploit this strategy successfully in the ring-opening of symmetrical bicyclic alkenes. Previous work from the Lautens group allows the preparation of a wide range of chiral 7- and 6-membered rings with Ni\(^0\), Pd\(^0\) and Rh\(^{1}\) catalysts, but smaller rings remained inaccessible. Extending the chemistry to the formation of 5-membered rings would be useful, since it is the most commonly found structural subunit in organic molecules.\(^2\) Retrosynthetic analysis of the desired 5-membered ring products III required us to abandon the ring-opening approach, since bicyclic substrates [2.1.1]-oxabicycles IV are not easily accessible (Figure 2-1). Instead, we selected meso-cyclic allylic diol derivatives V, which are known and readily accessible. The expected stereochemistry of


Chiral arylcyclopentenols III from V was based on our previous work. We were also interested in investigating the extension of the method to simple linear alkenes (VII). The use of VII would also test the generality of our methodology, because it is an unactivated allylic system.

Figure 2–1 Examples of chiral 7, 6, and 5-membered carbocycles accessible by a desymmetrization strategy.

Cyclic meso allylic diol derivatives V are challenging substrates for the proposed reaction due to the possibility of competing reaction pathways. Indeed, the metal-catalyzed allylic displacement reaction may take place via formal S$_{N}$2- or S$_{N}$2'-type processes, with overall inversion or retention of stereochemistry in both cases (Scheme 2-1). All four of these substitution motifs are present in biologically active compounds and natural products.\(^3\) Notably, at the outset of this project, no enantioselective synthesis of any of the four isomeric cyclopentenols with aromatic nucleophiles was reported.

Scheme 2-1 Substitution patterns accessible via AAS reactions.

Substituted cyclopentenols depicted in Scheme 2-1 are synthetically attractive, particularly because the alkene found in the products allows for further transformations (e.g., oxidative cleavage, ring-opening methathesis, dihydroxylation, cyclopropanation). In addition,\(^3\) For several examples, see: Corey, E.J.; Cheng, X.M. In *The Logic of Chemical Synthesis*; Wiley-VCH: New Jersey; 1995, 464 pages.
cyclopentenyl product X can be viewed as an syn-1,2-alkoxyaryl synthon equivalent after ring-cleavage of the alkene (XI). Figure 2-2 illustrates other potential core structures that are accessible by synthetic derivatization of X (see also Section 2.7).

![Figure 2-2 Examples of generic molecules bearing a anti-1,2-alkoxyaryl motif.](image)

Selecting allylic diol substrates meant entering a field extensively studied with Pd: the asymmetric allylic substitution (AAS).\(^4\) The use of this transformation has been demonstrated many times in the synthesis of a range of natural products.\(^5\) As discussed in section 1.4, several metal-catalyzed AAS reactions of allylic diol derivatives with “soft” nucleophiles are described in the literature (e.g., heteroatoms and enolates).\(^6\) However, there are surprisingly few examples of the same transformation with “hard” nucleophiles; even less so with cyclic allylic systems.

The field of metal-catalyzed AAS with non-stabilized sp\(^3\) carbon nucleophiles has grown considerably over the past six years, with copper being the most successful catalyst.\(^7\) The breadth of Cu-catalyzed asymmetric allyl alkylation reactions (AAA) has recently been the topic of an several reviews.\(^8\) Although several protocols can effect AAS with organomagnesium,\(^9\) organozinc,\(^10\) or organoaluminium reagents,\(^11\) the authors made a point to conclude by stating that the allylic arylation remained a largely unexploited field.

---


In addition, the selectivity challenges of asymmetric allylic reactions with metal catalysts (chemo-, regio- and enantioselectivity), are such that most efforts have concentrated on linear, mono-activated substrates (like cinnamyl derivatives, \( R = \text{Ar} \); Eqn 2-1).\(^\text{12}\) The poor regioselectivity often observed with cyclic allylic substrates has hampered the general use of this methodology with C-nucleophiles.

\[
\begin{align*}
\text{R} & \quad \text{X} \quad \text{or} \quad \text{X} \quad \text{R} \\
\text{Catalyst} & \quad \text{Nu} \\
\text{R} & \quad \text{Nu} \quad \text{X}
\end{align*}
\]

(2-1)

The specific aims of our work are to provide solutions for the following issues: (1) the addition of \( sp^2 \) C-nucleophiles, and (2) the regioselective addition to cyclic allylic substrates. In order to desymmetrize meso substrates, we looked at rhodium(I) complexes to catalyze the enantioselective formation of C–C bonds. Before discussing the results of our proposed methodology, we survey next the current literature on the addition of “hard” C-nucleophiles to allylic diol derivatives.

\subsection{2.2 Desymmetrization of meso Cyclic Allylic Diols}

\subsection{2.2.1 Enantioselective substitution of allylic diols with “hard” C–nucleophiles}

\textbf{\( sp^3 \) C–Nucleophiles.} Gennari and coworkers developed a Cu(II)-catalyzed reaction that is a rare example of cyclic allylic diols being competent substrates for an AAS reaction with \textit{any} hard nucleophiles. They found a chiral tridentate ligand which, in presence of copper(II), catalyzed the enantioselective alkylation of meso cyclic diol derivatives with dialkylzinc reagents (Scheme 2-2).\(^\text{13}\) The homoallylic alcohol derivatives were obtained in high ee with the substituents displaying a 1,2-trans relationship. The reaction was limited to small alkyl nucleophiles.

\begin{center}
\textbf{Scheme 2–2}
\end{center}

\begin{flushright}
\begin{align*}
\text{(EtO)}_2\text{PO(OEt)}_2 & \quad \text{EtZn (2 equiv)} \\
\text{Cu(OTf)}_2\text{PhH (10 mol%)} & \quad \text{imine ligand (10 mol%)} \\
\text{85%, 98% ee}
\end{align*}
\end{flushright}

\begin{footnotesize}
\quad \text{(b) Piarulli, U.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L.} \quad \textit{Org. Lett.} \textbf{2003}, \textit{5}, 4493.  \\
\end{footnotesize}
Only a few methods exist to achieve an AAS with linear allylic diol derivatives. These substrates however were not symmetrical. For example, in 1995, Bäckvall’s pioneering methodology used a linear butenyl substrate where the alkene was flanked with an acetate and a phenyl ether (Eqn 2-2).\textsuperscript{14} A copper(II) catalyst coordinated to a chiral N,S-ligand effected the $S_N2'$ addition of butylmagnesium regioselectively. The branched product was obtained with 34% ee.

$$\begin{align*}
\text{PhO}-\text{CH} \equiv \text{CH} \equiv \text{OAc} + n-\text{Bu-Mgl} \\
(1.25 \text{ equiv}) \\
\text{Et}_2\text{O}, 0^\circ\text{C} \\
100\% \text{ conv.}
\end{align*}$$

Similarly, Feringa reported 12 years later a related addition of dialkylzinc reagents to a butenediol derivative where only one of the alcohol groups was made into an acetate leaving group, the other one was protected with a silyl group.\textsuperscript{15} In this case, the branched alkylated product was obtained in 86% ee (Eqn 2-3).

$$\begin{align*}
\text{TBSO}-\text{CH} \equiv \text{CH} \equiv \text{OAc} + \text{Et}_2\text{Zn} \\
(2 \text{ equiv}) \\
\text{CuBr-Me}_2\text{S} (2 \text{ mol\%}) \\
\text{Ligand L1} (10 \text{ mol\%}) \\
\text{DCM}, -75^\circ\text{C}
\end{align*}$$

\textbf{$sp^2$ C–Nucleophiles.} The literature about reactions using hard $sp^2$ C-nucleophiles is scarce in AAS reactions. Organotin reagents remained for a long time the only $sp^2$ carbon source for catalytic displacements of allylic leaving groups, but the reported protocols are racemic, or diastereoselective at best.\textsuperscript{16} A unique example using aryl nucleophiles was reported by Gennari.\textsuperscript{17} Cyclic allylic diphosphonates were displaced enantioselectively by Ph$_2$Zn under copper catalysis with a chiral imine ligand (Eqn 2-4). Although the desymmetrized product was found to have only a moderate 68% ee, it constituted the state of the art when we began our investigations with these substrates.


\textsuperscript{15} van Zijl, A. W.; Lopez, F.; Minnaard, A. J.; Feringa, B. L. J. Org. Chem. 2007, 72, 2558.


\textsuperscript{17} Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. Angew. Chem., Int. Ed. 2003, 42, 234.
The addition of \( sp^2 \) organoboron reagents to allylic compounds was studied by several groups,\(^{18} \) but all reactions were racemic until a seminal report from Uemura in 2000.\(^{19} \) They reported a Ni-catalyzed asymmetric cross-coupling reaction of allylic monoacetates with arylboronic acids. Although the reaction gave only 50\% ee, it was the first time that enantio-enrichment was demonstrated with \( sp^2 \) nucleophiles in catalytic allylic substitution. Uemura’s report stood as the sole example of organoboron addition in AAS of allylic alcohols until our publication in 2006 about the work presented herein.

**AAS using rhodium catalysts**

Studies of asymmetric allylic substitution reactions by Evans have shown the stereospecific nature of the rhodium-catalyzed AAS with both heteroatoms\(^{20} \) and alkyl\(^{21} \) nucleophiles for linear allylic alcohol derivatives. Hayashi also reported a similar reaction with malonate nucleophiles using a chiral rhodium catalyst.\(^{22} \) However, despite its efficient use in conjugate addition reactions, there has been no report on the use of chiral rhodium catalysts with \( sp^2 \) carbon nucleophiles for the asymmetric allylic substitution reaction.\(^{23} \)

When we set out to explore this reaction with rhodium catalysts, it was unclear what kind of selectivity, if any, would be obtained.\(^{24} \) Whereas disastereoselective routes exist for the preparation of substituted products \( \text{VIII, IX and X} \), none are reported for the 1,2-\textit{cis} products \( \text{III} \) (Scheme 2-3).\(^{25} \) According to previous work from the Lautens group with oxabicyclic alkenes, we anticipated that 1,2-disubstituted products \( \text{III or X} \) might be favored. We also believed that a potential coordination of the leaving groups of \( \text{V} \) might help direct the attack of the Rh catalyst to favor \( \text{III} \).

---

Murakami and coworkers also recognized the unmet synthetic challenge presented by symmetrical diols. They reported independently an elegant approach, closely related to ours, which used unprotected alcohols directly (Eqn 2-5). Their reaction is noteworthy for its atom economy as the arylboroxine is presumed to serve a double role of nucleophile and activating agent for the alcohol leaving group. The authors reported only one example of moderate enantioselectivity at 78% ee. The communication was published during the course of our studies. In addition, it showed that there was ample room for improvement as the product ee varied widely (from 53 to 87% ee; Eqn 2-6). A related protocol will be discussed Section 2.8.

2.2.2 Other syntheses of chiral trans-1,2-substituted arylcyclopentenols

There are alternative synthetic strategies to prepare 1,2- and 1,4-arylcylopentenols. Surprisingly few, however, give these products in chiral form or enantiomerically enriched.

The synthesis of cyclopentenols via the ring-opening of vinyl epoxides 10 has been investigated. In early racemic reports of \( sp^2 \) C-nucleophiles under Pd-catalysis with cuprates and organotins, regioselectivity was an issue, with ratios of 1.7:1 in favor of 1,4-trans products. More recently, a variety of kinetic resolution methods were developed with copper catalysts to yield the same racemic epoxide 10. For example, Pineschi and coworkers found that dialkylzincs could be added in a regiodivergent manner in the presence of a chiral phosphoramidite ligand to give both 1,2- and 1,4-substituted trans cyclopentenols (Eqn 2-8).  

---

Using a very similar system, Alexakis and coworkers found that their chiral phosphoramidite, SimplePHOS, could increase the ratio of 1,4-trans product as well as the ee, but the yield was poor (Eqn 2-9).²⁹

In view of the difficulty of synthesizing cyclopentenols by enantioselective catalysis, the group of Kobayashi turned to diastereoselective synthesis, starting from a pre-desymmetrized, chiral monoacetate 11. Thus building on the pioneering work of Rajanbabu with Ni⁰ catalysts,³⁰ they established several methods for the addition of alkyl Grignard reagents. The reactions are all diastereoselective and use either nickel, copper, or palladium catalysts. It is noteworthy that both regiochemical and diastereochemical outcome can be controlled by the nature of the metal catalyst. For instance, copper and nickel catalysts favor the trans 1,4-regioisomer (Eqn 2-10),³¹ and palladium catalysts favor the cis 1,2-products (Eqn 2-11).³² The reactions require large excess of reagents or catalysts, and the isomeric ratios vary widely, depending on the Grignard reagent used, e.g., electron-deficient aryl nucleophiles are not reported.

²⁹ Millet, R.; Alexakis, A. Synlett 2008, 1797.
Another type of desymmetrization of an allylic diol reaction comes from the Micalizio group.\textsuperscript{33} However, the amount of reagents used is far from catalytic and the reaction is racemic. Nevertheless, the reaction is valuable since it is the only method reported to prepare 1,2-cis substituted cyclopentenol 13.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{reaction_diagram.png}
\caption{Reaction scheme for desymmetrization of allylic diols.}
\end{figure}

At the time of writing (November 2009), the above survey represented the current state of research in AAS of allylic diols with “hard” nucleophiles. Beyond our own work, the best methodologies reported for enantiomeric desymmetrization of cyclopentenediols and butenediols reached a maximum of 78\% ee and 87\% ee, respectively. The remaining sections of the chapter will now describe our own results which led to highly enantioselective reactions—up to 99\% ee and 95\% ee for cyclic and linear systems, respectively.

### 2.3 Synthesis of Chiral \textit{trans}-2-Arylcyclopent-3-enols

Initial phases of this section were carried out by Dr. Timothy Chapman,\textsuperscript{34} based on a proposal from Dr. Chris Dockendorff.\textsuperscript{35} Only my contributions to this project are outlined, except when previous results supported discussion. Detailed accounts of this methodology are described in joint publications.\textsuperscript{36,37}

#### 2.3.1 Results & Discussion

**Synthesis of \textit{meso} substrates**

The symmetrical cyclopentenediol derivatives selected to test the feasibility of the reaction were prepared from readily available cyclopentadiene (1) according to a known protocol.\textsuperscript{38} The reaction takes advantage of a stereospecific [4+2] cycloaddition with singlet oxygen to

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{reaction_diagram.png}
\caption{Reaction scheme for desymmetrization of allylic diols.}
\end{figure}

\begin{align*}
\text{HO-} & \text{C} & \text{O} \\
\text{HO-} & \text{C} & \text{O} \\
\text{SiMe}_3 & & \text{SiMe}_3 \\
\text{(3 equiv)} & & \text{(3 equiv)} \\
i) \text{n-BuLi (2 equiv)} & \text{ii) Ti(O-i-Pr)_3Cl (3 equiv)} & \text{iii) cyclopentyl-MgCl (6 equiv)} \\
\text{iv) 1N HCl} & & \text{64\%} \\
\text{(a)-13} & \text{d.r. = 5:1 (rac.)} & \\
\end{align*}


\textsuperscript{34} Then a post-doctoral fellow in group. Present address: Sandoz Ltd, Bordon, UK.

\textsuperscript{35} Then a senior Ph.D. candidate in the group. Present address: Broad Medical Institute, Cambridge, MA, USA.


\textsuperscript{37} Menard, F.; Perez, D.; Sustac-Roman, D.; Chapman, T.M.; Dockendorff, C.; Lautens, M. \textit{Manuscript submitted.}

\textsuperscript{38} For synthesis of diol 2, see experimental section. The protocol was modified from: Kaneko, C.; Sugimoto, A.; Tanaka, S. \textit{Synthesis} \textbf{1974}, \textit{876}.
install two alcohols groups with a \textit{cis} relationship. In this reaction, the endoperoxide generated is unstable to isolation and is converted directly to diol 2 with thiourea acting as \textit{in situ} reductant. The original protocol called for high vacuum distillation of diol 2, yet we found that carrying the crude mixture directly to the bis-acylation with excess reagent was more convenient in terms of isolation.\(^{39}\) This sequence was followed several times to deliver from 8 g to 20 g of ethyl dicarbonate 3a (44–51%, Scheme 2-4). The yield was moderate, but the low cost of reagents and simplicity of operation make the approach acceptable.\(^{40}\)

![Scheme 2-4](image)

**Scheme 2–4** Synthesis of \textit{meso} cyclic allylic diol 2 and ethyl dicarbonate 3a.

The effect of different allylic leaving groups was eventually studied and different carbonates were needed. Various acylating agents were reacted with diol 2 (freshly obtained from dicarbonate 3a after basic methanolysis). For carbonates whose acylation precursors were not commercially accessible, the chloroformates were prepared from the corresponding alcohols as exemplified in Scheme 2-5. The chloroformates were reacted in slight excess (2.5 equiv.) with cyclopentenediol 2 to obtain the desired dicarbonates 3.\(^{41}\)

![Scheme 2-5](image)

**Scheme 2–5** Typical procedure for the preparation of dicarbonate substrates.

Initial trials from Section 2.2 showed a preference for formation of the 1,2-substituted product 4 (\textit{r.r.} = 2:1), albeit in modest yield. The primary goal was to find reaction conditions to increase conversion and regioselectivity of 2-phenylcyclopentenyl carbonate 4a, while maintaining good enantioselectivity.

**Initial discovery**

\(^{39}\) When distillation of diol 2 was attempted, it was found to crystallize on all glassware surfaces and joints, making for a tedious recovery, which did not improve significantly the overall yield of the sequence.\(^ {40}\) Alternatively, diol 2 is available from commercial sources; 489 CAD for 2.5 g from Aldrich.\(^ {41}\) Arnau, N.; Cortés, J.; Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. \textit{J. Heterocycl. Chem.} 1997, 34, 233.
Initial desymmetrization reactions were attempted with the meso diethyl dicarbonate 3a. Conditions that had proven successful in the asymmetric ring-opening reactions of oxa-bicyclic alkenes failed to produce any desired product with substrate 3a, and only unreacted starting material was observed (Table 2-1, entry 1).\(^4\) It was found that using [Rh(cod)OH]\(_2\)\(^4\) in combination with biaryl diphosphine ligand BINAP (L5)\(^4\) induced reaction of 3a (entry 2). The 1,2-trans substituted product 4a was obtained as the major product in a 2:1 ratio over the 1,4-trans substituted product 5a.\(^4\) Importantly, none of the diastereomeric cis isomers III or VIII were observed (Scheme 2-1). Despite low conversion of the starting material, we were encouraged by the clean reaction profile: only 4a, 5a, and unreacted starting material were present in the mixture. Other metal complexes like [Ir(cod)Cl]\(_2\) or cationic [Rh(cod)]\(_2\)OTf gave no reaction, or led to deboronation of the boronic acid. Increasing the reaction temperature, or using [Rh(cod)OH]\(_2\) in the absence of a phosphine ligand led mostly to deboronation.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>ligand</th>
<th>yield (%)(^a,b)</th>
<th>ratio 4:5(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)OH](_2)</td>
<td>t-Bu-Josiphos</td>
<td>0(^b)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)OH](_2)</td>
<td>(S)-BINAP</td>
<td>45</td>
<td>2 : 1</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(cod)Cl](_2)</td>
<td>(S)-BINAP</td>
<td>0(^b)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(cod)OH](_2)</td>
<td>None</td>
<td>10(^c)</td>
<td>20 : 1</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR analysis of crude mixture. \(^b\) Balance of material was recovered starting material. \(^c\) Deboronation observed. \(^d\) Results obtained by Dr. T. Chapman.

Carbonate products 4a and 5a could not be separated at this stage. However they were readily converted to the corresponding known alcohols 6 and 7 by simple methanolysis (Eqn 2-7). The resulting alcohols were easily separable by chromatography and their enantiomeric enrichment was determined by chiral HPLC. Thus, the chiral ligand BINAP provided 2-phenylcyclopent-3-enol (6) in 76% ee, along with 1,4-regioisomer 7 in 72% ee.

---


Absolute stereochemical assignment

At the time I initiated my studies, the P-PHOS family had been identified as a promising lead by Dr. Chapman. Thus Xylyl-P-PHOS (L2) was used to determine the absolute stereochemistry of the product (Scheme 2-6). The reaction was conducted with (R)-Xylyl-P-Phos to obtain the desymmetrized carbonates 4a and 5a in 84% in a 10:1 ratio. After solvolysis, the isomeric alcohols were readily separated by column chromatography to obtain the (+)-antipodes of 6 and 7 as measured by optical rotation. (R)-Xylyl-P-Phos was thus shown to yield phenylcyclopentenols 6 and 7 in 92% and 89% ee, respectively. Notably, these early results constituted the highest ee values observed so far for these products.

Scheme 2-6 Deprotection of carbonates 4 and 5 and enantiomeric ratio determination.

The absolute stereochemistry of alcohol (+)-6 was assigned by the Mosher ester method; thus its (+) and (−)-MTPA ester derivatives 8 and 9 were prepared (Scheme 2-7). Optical rotation measurements were also correlated with literature reports. Accordingly, the stereochemistry

of (1R,2S)-6 shown in Equation 2-7 arose from (S)-biaryl bisphospine ligands; that of (1R,4R)-7 was assigned by correlation.

Scheme 2-7 Determination of the absolute stereochemistry using Mosher esters, as induced by (R)-Xylyl-P-PHOS.

The above results provided a foundation to warrant more efforts to understand the reaction at hand. Whether the reaction was general still remained to be seen. Also, issues of regioselectivity and enantioselectivity needed to be solved for the reaction to be synthetically useful. The reaction was therefore systematically investigated to identify key factors that may help control selectivity.

2.3.2 Optimisation

Effect of solvent, base, and leaving group

After looking at the impact of the solvent, THF was selected as other solvents only led to decreased yields (Table 2-2, entries 1–6). Regioisomeric ratios were not affected by the solvent. It is noteworthy that, whereas enantioselectivity was constant for 4a, the solvent strongly influenced the ee of 1,4-product 5a (this aspect is discussed in more details in Section 2.5).

In contrast, changing the base had a marked effect on yield, product distribution, and on the enantioselectivity of 4a (entries 1, and 7–11). The absence of base showed the best results in terms of regioselectivity, but the yield was unsatisfactory (entry 8). Since the primary goal was to improve conversion, Cs₂CO₃ was used for further studies.
Substrates carrying different leaving groups were investigated in the asymmetric allylic substitution reaction, but ethyl carbonate still appeared to be the optimal for the desired reaction. The hexafluoroisopropyl carbonate leaving group (HFIP), which had proved successful for a related rhodium allylic substitution reported by Evans, gave only trace conversion under our conditions. We then turned our attention on the impact of the ligand in the hope of modulating the intrinsic reactivity of the rhodium catalyst.

The effect of additives was also examined with BINAP as ligand, but the results were not better. For example, dehydrating basic agents including BaO, MgO, and molecular sieves gave only lower yields and decreased selectivity. Adding water as co-solvent did not improve the results.

---

49 Among other leaving groups tested, most did not give desired product (carbonates: Me, Ph; acetate; benzoate; 4-nitrobenzoate; ethyl phosphonate), or only traces (HFIP carbonate); T. M. Chapman, unpublished results.

Effect of ligand

Biaryl bisphosphine ligands are the only class of ligands that showed any appreciable activity. Structures of the chiral ligands investigated in this chapter are depicted in Figure 2-3.

Figure 2–3 Selection of chiral ligands used in this chapter.

Electron-rich biaryl bisphosphines were key in favoring formation of 4a (Table 2-3). Two ligand families proved to be unique in giving trans-2-phenylcyclopentenyl carbonate (4a) with high regioselectivity: Chan’s P-PHOS ligands, and Genêt’s DIFLUORPHOS (entries 1–3). Fortunately, they also showed promising enantioselectivity, which might be improved upon further optimization.

Comparing the different members of the BINAP family, no clear trend could be inferred from steric factors (entries 5–7). The SEGPHOS family, however, gave good conversion and exceptional ee for both products 4 and 5, but yielded an almost equimolar mixture (entries 9 and 10). It is intriguing that replacing two hydrogens by two fluorine atoms on the catecholic methylene of the ligands, a site remote from the reacting groups, should display such a dramatic difference in regioselectivity between DIFLUORPHOS (L3) and SEGPHOS (L10). This aspect will be discussed in further details in the mechanistic section (Section 2-5).

From the ligands examined, it appears that bulky aryl groups on phosphorus help enantioselectivity. In the ligand classes of BINAP, P-PHOS, and SEGPHOS, the xylyl-substituted phosphanes gave enantiomeric excesses 4–6% higher than their phenyl-

53 We pursued our studies with P-PHOS ligands. Indeed, Synkem France, the company making DIFLUORPHOS, would only agree to sell us research quantities of their promising ligand at cost-prohibiting prices.
substituted analogues (entries 1 and 2; 5 and 7; 8 and 9). Among several other chiral ligands that were screened but are not shown, some returned only traces of products (i.e., Monophos, C$_2$-Ferriphos, KenPHOS), or did not react at all (i-Pr-PHOX, Me-DuPhos).

Using monodentate phosphines revealed that the regioselectivity can be totally diverted towards the 1,2-product when it is used in a 1:1 ratio to rhodium (not shown). However, the yield was far too low to be useful (< 10%). Using a 2:1 L:Rh ratio almost completely shut down the reaction.

Xylyl-SEGPHOS attracted our attention since it gave exceptional ee for both products, and gave good conversion (L11, entry 10). This result was later exploited in reactions aimed at synthesizing the complementary 1,4-product 5a (Section 2.4).

Table 2–3 Ligand Screening: Looking for Regioselectivity$^{a,b}$

<table>
<thead>
<tr>
<th>entry</th>
<th>Ln</th>
<th>ligand</th>
<th>yield (%)$^c$</th>
<th>ratio 4 : 5$^d$</th>
<th>ee 4 (%)$^e$</th>
<th>ee 5 (%)$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>P-PHOS</td>
<td>74</td>
<td>&gt;20 :1</td>
<td>82</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>Xyl-P-PHOS</td>
<td>65</td>
<td>13 : 1</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>DIFLUORPHOS</td>
<td>58</td>
<td>17 : 1</td>
<td>92</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>BINAP</td>
<td>45</td>
<td>2 : 1</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>Tol-BINAP</td>
<td>32</td>
<td>1 : 1</td>
<td>95</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>L7</td>
<td>Xyl-BINAP</td>
<td>59</td>
<td>2 : 1</td>
<td>82</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>L9</td>
<td>C$_3$-TunePhos</td>
<td>30</td>
<td>1.5 : 1</td>
<td>42</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>L10</td>
<td>SEGPHOS</td>
<td>60</td>
<td>2.3 : 1</td>
<td>92</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>L11</td>
<td>Xyl-SEGPHOS</td>
<td>76</td>
<td>1 : 1</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>L16</td>
<td>Cl-MeO-BIPHEP</td>
<td>60</td>
<td>1 : 1</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>L13</td>
<td>SOLPHOS</td>
<td>11</td>
<td>n.d.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>L20</td>
<td>QUINAP</td>
<td>3</td>
<td>n.d.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>L19</td>
<td>ChiraPhos</td>
<td>2</td>
<td>n.d.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>L18</td>
<td>t-Bu-JosiPhos</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Reactions performed using bicarbonate 3a (0.164 mmol), Rh catalyst (5 mol% dimer), ligand (10 mol%), Cs$_2$CO$_3$ (1.0 equiv), and ArB(OH)$_2$ (2.0 equiv) in THF (0.20 M) under Ar atmosphere. $^b$ Ligand screening conducted by T. M. Chapman. $^c$ Isolated yield. $^d$ Determined by $^1$H NMR analysis of crude mixture. $^e$ Determined by chiral HPLC analysis on deprotected alcohols.
Optimization of reaction conditions

With Xyl-P-PHOS showing excellent selectivity for the 1,2-product 4a, an optimization study was undertaken to improve the yield and enantioselectivity. A summary of the most significant results is shown in Table 2-4. A second look at the nature of the leaving group revealed that small alkyl carbonates worked equally well, whereas aryl carbonates led to a complete loss of regioselectivity (entries 1–3). The amount of Cs₂CO₃ was found to significantly impact the reaction, and 1.0 equivalent was optimal (entries 4 and 5). Increasing the equivalents of phenylboronic acid gave higher conversion, but at the expense of regioselectivity (entry 6). Increasing the ligand to catalyst ratio resulted in higher conversion and slightly better selectivity (entries 7 and 8). This positive effect is presumed to be due to the ready oxidation of the ligand L₂, therefore excess ligand may be resulting in higher concentration of active complex.³⁴ The lower ratio of 1.2:1 was preferred based on cost.

<table>
<thead>
<tr>
<th>entry</th>
<th>Variation from standard conditionsᵃ</th>
<th>yield (%)ᵇ</th>
<th>ratio 4:5ᶜ</th>
<th>ee 4 (%)ᵈ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Substrate: 3a (standard)</td>
<td>70</td>
<td>&gt;15 : 1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Substrate: 3c</td>
<td>74</td>
<td>&gt;15 : 1</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Substrate: 3d</td>
<td>41</td>
<td>1.2 : 1</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>0.5 equiv Cs₂CO₃</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5ᵉ</td>
<td>2.0 equiv Cs₂CO₃</td>
<td>73</td>
<td>7 : 1</td>
<td>84</td>
</tr>
<tr>
<td>6ᵉ</td>
<td>5.0 equiv PhB(OH)₂</td>
<td>79</td>
<td>3.5 : 1</td>
<td>90</td>
</tr>
<tr>
<td>7ᵉ</td>
<td>L:Rh = 2.0 : 1</td>
<td>79</td>
<td>&gt;20 : 1</td>
<td>92</td>
</tr>
<tr>
<td>8ᵉ</td>
<td>L:Rh = 1.2 : 1</td>
<td>70</td>
<td>&gt;20 : 1</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>L:Rh = 1.2 : 1; 7.5 mol% [Rh]₂</td>
<td>87</td>
<td>20 : 1</td>
<td>88</td>
</tr>
<tr>
<td>10ᵉ</td>
<td>P-PHOS, instead of Xyl-P-PHOS, L:Rh = 1.2:1</td>
<td>74</td>
<td>&gt;20 : 1</td>
<td>82</td>
</tr>
</tbody>
</table>

ᵃ Reaction conditions as described in Table 2-3.ᵇ Isolated yield.ᶜ Determined by ¹H NMR analysis of crude mixture.ᵈ Determined by chiral HPLC analysis on deprotected alcohols.ᵉ Experiment conducted by T. M. Chapman.

Indeed, ³¹P NMR analyses revealed that Xyl-P-PHOS is highly sensitive to oxidation in solution. Phosphine oxides of Xyl-P-PHOS: ³¹P NMR (thf-d₈) = 27.1 ppm for the dioxide; 25.3 and -14.2 for the monoxide; -12.5 ppm for the free diphosphine.
Increasing the amount of rhodium dimer led to significantly higher conversion but it was considered that a loading above the already high 5 mol% of dimer (10 mol% rhodium) was undesirable, so the catalyst loading was maintained at 5 mol% of dimer for further experiments. Finally, re-examining P-PHOS at a 1.2:1 Rh:L ratio showed better selectivity, but ee remained lower than Xyl-P-Phos (entry 10).

2.3.3 Scope and limitations of organoboronic acids

The enantioselective desymmetrization of allylic dicarbonate 3a proved to be efficient with a wide range of arylboronic acids (Table 2-5). Some trends were observed when comparing steric and electronic factors. First, meta-substituted arylboronic acids gave the best results in terms of combined yield and ee (entries 11–14). Then, within the para series, yields seem to correlate with electron density of the substituents as indicated by Hammet sigma constants, whereas ee did not seem affected (entries 2–9). In general, lower conversion with electron-rich arylboronic acids was accompanied by an increased amount of homocoupling products, which appeared detrimental to catalytic activity.

Arylboronic acids bearing ortho substituents showed a marked decrease in both conversion and selectivity (entries 15 and 16). Other limitations where no conversion occurred include: heteroaromatic boronic acids such as 4-pyridylboronic acid, 3-furylboronic acid, 3-thiophenylboronic acid and 2-furylboronic acid. Electron-poor 3-nitrophenylboronic acid gave only very low conversion (less than 10%). Also, sp³ nucleophiles such as methylboronic acid gave no reaction.

56 Control experiments showed that homocoupling of the boronic acid occurs as a background reaction under the reaction conditions.
Table 2–5 Scope of Arylboronic Acids

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>R</th>
<th>Hammet $\sigma$ cst</th>
<th>Yield (%)$^b$</th>
<th>ratio 4:5$^c$</th>
<th>ee 4 (%)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td></td>
<td>0.00</td>
<td>87</td>
<td>18 : 1</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>CF$_3$</td>
<td>0.54</td>
<td>86</td>
<td>13 : 1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>Ac</td>
<td>0.50</td>
<td>94</td>
<td>&gt;20 : 1</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>COOMe</td>
<td>0.39</td>
<td>95</td>
<td>&gt;20 : 1</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>Cl</td>
<td>0.23</td>
<td>53</td>
<td>13 : 1</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>Br</td>
<td>0.23</td>
<td>35</td>
<td>10 : 1</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>F</td>
<td>0.06</td>
<td>46</td>
<td>7 : 1</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Me</td>
<td>-0.17</td>
<td>70</td>
<td>20 : 1</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>OMe</td>
<td>-0.27</td>
<td>49</td>
<td>&gt;20 : 1</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>NH-Boc</td>
<td>-</td>
<td>32</td>
<td>&gt;20 : 1</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>21</td>
<td>Cl</td>
<td>0.37</td>
<td>87</td>
<td>10 : 1</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>22</td>
<td>OMe</td>
<td>0.12</td>
<td>63</td>
<td>&gt;20 : 1</td>
<td>92</td>
</tr>
<tr>
<td>13</td>
<td>23</td>
<td>Me</td>
<td>-0.07</td>
<td>78</td>
<td>20 : 1</td>
<td>92</td>
</tr>
<tr>
<td>14</td>
<td>24</td>
<td></td>
<td>-</td>
<td>78</td>
<td>&gt;20 : 1</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td></td>
<td>-</td>
<td>50</td>
<td>1 : 1</td>
<td>70</td>
</tr>
<tr>
<td>16</td>
<td>26</td>
<td></td>
<td>-</td>
<td>25</td>
<td>6 : 1</td>
<td>92</td>
</tr>
</tbody>
</table>

$^a$ Reactions performed using biscarbonate 3a (0.164 mmol), Rh catalyst (10 mol% dimer), ligand (10 mol%), Cs$_2$CO$_3$ (1.0 equiv), and ArB(OH)$_2$ (2.0 equiv) in THF (0.20 M) under Ar atmosphere. $^b$ Isolated yields of carbonates, average of at least two runs. $^c$ Determined by 1H NMR analysis of crude mixture. $^d$ Determined by chiral HPLC analysis on deprotected alcohols.
2.3.4 Alkenylboronic acids

We then turned to vinylboronic acids to try to address the unmet challenge exposed by Alexakis in a recent review of the field of Cu-catalyzed AAS.\(^{57}\) The authors pointed out that there is no general method to add vinylic nucleophiles to alkenes. Indeed, the few reported examples are limited to Rh-catalyzed conjugate additions\(^{58}\) and a unique recent report from Hoveyda using vinylaluminium reagents.\(^{59}\) Exploring the reactivity of vinylboronic acids in our catalytic system was a natural extension in view of their ready availability. The chiral products obtained after desymmetrization are synthetically attractive, as they bear two chemodifferentiated alkenes.\(^{60}\) These alkenes could serve as synthetic handles for further diastereoselective transformations.

\[
\begin{align*}
3a & \quad \text{EtO}_2\text{CO} & \quad \text{OCO}_2\text{Et} \\
+ & \quad \text{Ph} & \quad \text{BO} & \quad \text{O} & \quad \text{O} & \quad \text{Et} \\
\text{[Rh(cod)OH]}_2 & \quad \text{Xyl-P-PHOS} & \quad \text{THF, 50 °C} & \quad 16-20\text{h} \\
\text{28} & \quad \text{Ph} & \quad \text{OCO}_2\text{Et} \\
\text{20% (+80% 3a)}
\end{align*}
\]

Unfortunately, (E)-styrylboronic acid only led to traces of desired product 28. A variety of stable vinyl nucleophiles precursors were investigated, but the best results that could be obtained were with pinacolboronic ester 27 (Eqn 2-13). Despite much effort, the reaction seemed to plateau after two turnovers with 20% yield, independent of the alkenyl source. We hypothesize that the diene 28 formed may bind competitively to the rhodium catalyst. Figure 2-4 compares the putative catalyst inhibition by 28 to the known diene-Rh complex XIV.\(^{61}\)

![Potential product inhibition of catalyst due to diene 28 complexation (XV).](image)

---


2.4 Synthesis of Chiral \textit{trans}-4-Arylcyclopent-2-enols

The previous section showed that certain ligands gave product 5 in >95\% ee and that the desymmetrization reaction is quite sensitive to variations in conditions. A reaction that could deliver complementary products with a single set of starting materials and reagents would be powerful. Ideally, the ligand would dictate the regioisomer formed (Scheme 2–8). In the present section, we will detail how it is possible to tune the catalytic system so that it effects a regioselectivity reversal to favor the \textit{trans}-1,4-product 5.

Scheme 2–8 Can a ligand be found to divert the reaction towards 5?

2.4.1 Precedents for the synthesis of 4-substituted cyclopentenols

The enantioselective synthesis of 1,4-substituted cyclopentenols was very recently reported by the group of Alexakis using Cu-catalysis with a new family of chiral phosphine ligands, SimplePHOS. The reaction was described only with alkyl Grignard reagents. It is also significantly limited in terms of yield due to the process being a kinetic resolution (Eqn 2–14).

Alternatively, the group of Kobayashi has reported several catalytic methods to access a range of cyclopentenols. In most cases, their system uses copper catalysis with Grignard reagents to effect diastereoselective allylic substitutions. Although chiral products are formed, the starting material 11 are obtained by enzymatic resolution.

---

\textsuperscript{62} Millet, R.; Alexakis, A. \textit{Synlett} \textbf{2008}, 1797.

2.4.2 Results and Discussion

David Perez, a visiting student from France, contributed to this part of the project and worked under the author’s guidance. His efforts were instrumental in identifying the best solvent system, as well as for initial ligand screening. The present section reports mostly the author’s results, David’s contributions are acknowledged where appropriate.64

Ligand studies from Section 2.3 identified the electron-rich bisphosphine ligand Xyl-SEGPHOS65 as the least selective for the 1,2-product 4—the most promising for 5 (Eqn 2-16). More importantly, Xyl-SEGPHOS showed exceptional enantioselectivity for the 1,4-product 5 (98% ee), as well as improved ee for 4 (96% ee). Encouraged by these observations, we reinvestigated the reaction with the specific goal of finding conditions that would allow selective preparation of trans-1,4-arylcyclopentenols.

\[
\begin{align*}
3a + \text{Ph-B(OH)}_2 & \xrightarrow{[\text{Rh(cod)}][\text{OH}]} \text{Ln} \quad \text{Cs}_2\text{CO}_3, \text{THF}, 55 \degree \text{C} \\
& \quad \text{yield} \quad \text{regio} \quad \% \text{ee} \quad \frac{4a}{5a} \\
\text{Xyl-P-PHOS (L2)} & \quad 65\% \quad 13:1 \quad 88/98 \\
\text{Xyl-SEGPHOS (L7)} & \quad 76\% \quad 1:1 \quad 96/98
\end{align*}
\]

Effect of solvents on regioselectivity

The effect of solvent was examined using the SEGPHOS family of ligands. Dioxane and benzene gave similar results for the reaction, with benzene favoring slightly the desired regioisomer 5 (Table 9, entries 6 and 7; Table 10, entries 3 and 7). Non-coordinating solvents like benzene and toluene provided the highest ratio of desired 1,4-products as well as the highest ee for both regioisomers. Whereas toluene gave higher yields than benzene, benzene was still preferred for its superior solubility ability when boronic acids other than phenyl were used. Additives did not have a measurable impact. Some Lewis acids such as scandium(III) and zinc(II) triflate only slightly favored formation of the 1,2-product 4 (entries 5 and 6).

---

64 David Perez did a four months technician internship from the Institut Universitaire Technologique Paul-Sabatier, Castres, France.
Table 2–6 Effect of solvent and additive with SEGPHOS (L6)\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>yield (%)\textsuperscript{c}</th>
<th>ratio 4:5\textsuperscript{d}</th>
<th>% ee 4\textsuperscript{e}</th>
<th>% ee 5\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DME</td>
<td>-</td>
<td>44</td>
<td>1.4 : 1</td>
<td>91</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>-</td>
<td>42</td>
<td>1 : 1</td>
<td>94</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>Sc(OTf)\textsubscript{3}\textsuperscript{f}</td>
<td>50</td>
<td>1.4 : 1</td>
<td>91</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td>Zn(OTf)\textsubscript{2}\textsuperscript{f}</td>
<td>41</td>
<td>1.6 : 1</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>Dioxane</td>
<td>-</td>
<td>51</td>
<td>1 : 1.2</td>
<td>88</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>Benzene</td>
<td>-</td>
<td>44</td>
<td>1 : 1.5</td>
<td>94</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>-</td>
<td>69\textsuperscript{g}</td>
<td>1 : 1.5</td>
<td>96</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were performed using 3a (0.135 mmol), catalyst (10 mol\% in Rh), ligand (12 mol\%) and solvent (0.12 M). \textsuperscript{b} Experiments conducted by D. Perez. \textsuperscript{c} Isolated yield. \textsuperscript{d} Determined by \textsuperscript{1}H NMR of purified mixture. \textsuperscript{e} Determined by chiral HPLC analysis of deprotected alcohols (Chiracel OD-H). \textsuperscript{f} Used 20 mol\% additive. \textsuperscript{g} Average of 3 runs (56-81%).

**Influence of concentration**

Using a sterically demanding SEGPHOS ligand (L7), the concentration of the substrate was found to have a significant effect. Increasing the concentration from 0.12 M to \sim 0.5 M favored the desired 1,4-product 5 (Table 10, entries 8–10).\textsuperscript{66} Intriguingly, we also observed that the ee of the 1,2-product is affected by the concentration. A local maximum of concentration was observed at 0.47 M and was selected as the optimal concentration.

\textsuperscript{66} This key finding was a serendipitous discovery by David Perez. The solvent of a reaction evaporated overnight. Rather than discarding the black tar, he analyzed the mixture and the \textsuperscript{1}H NMR showed the best regioselectivity we observed at that point. This finding led us to look more carefully at the effect of concentration.
CHAPTER 2. ENANTIOSELECTIVE DESYMMETRIZATION OF ALKYL DIOLS

Table 2–7 Effect of Solvent and Concentration with Xyl-SEGPHOS (L7)\(^\text{a,b}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent (conc. M)</th>
<th>yield (%)(^\text{c})</th>
<th>4 : 5(^\text{d})</th>
<th>%ee 4a(^\text{e})</th>
<th>%ee 5a(^\text{e})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF (0.12)</td>
<td>26</td>
<td>1 : 1.2</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Dioxane (0.12)</td>
<td>n.d.</td>
<td>1.1 : 1</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Dioxane (0.31)</td>
<td>63</td>
<td>1.3 : 1</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>THF (0.31)(^\text{f})</td>
<td>85</td>
<td>1.3 : 1</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>THF (0.31)</td>
<td>56</td>
<td>1.5 : 1</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>Toluene (0.31)</td>
<td>70</td>
<td>1.5 : 1</td>
<td>88</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>Benzene (0.31)</td>
<td>66</td>
<td>1.7 : 1</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>Benzene (0.47)</td>
<td>80</td>
<td>2.0 : 1</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>Benzene (0.69)</td>
<td>70</td>
<td>1.8 : 1</td>
<td>96</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were performed using 3a (0.135 mmol), catalyst (8 mol% in Rh), ligand (12 mol%) and solvent (0.31 M).\(^\text{b}\) Experiments conducted by D. Perez.\(^\text{c}\) Isolated yield.\(^\text{d}\) Determined by \(^1\)H NMR of purified mixture.\(^\text{e}\) Determined by chiral HPLC analysis of deprotected alcohol (Chiracel OD-H).\(^\text{f}\) Used 20 mol% Zn(OTf)\(_2\) as additive.

Influence of leaving groups on enantioselectivity

The nature of the leaving group was investigated for it is thought to be non-innocent when released as nucleofuge. In the substitution reaction, a carbonate group is liberated and it can decarboxylate to release an alkoxide ion. The nucleofuge is presumed to be ultimately trapped by boron byproducts. Nevertheless, the alkoxide’s (or carbonate’s) potential to complex with the rhodium catalyst could not be neglected.

The nature of the carbonate had a strong influence on both yield and enantioselectivity, whereas regioselectivity was not affected significantly (Table 11, entries 4–6). When phenolic dicarbonate 3d was used, the yield indicated only one turnover (entry 6).\(^67\) It should also be noted, that ee of the 1,2-product 4 decreased dramatically (53% ee), while ee of the desired 1,4-products was affected, but remained high at 93% ee—providing support for the formation of the cyclopentenols occurring by divergent mechanisms. When the substrate bore isopropyl carbonates (3b), the yield was again poor, but enantioselectivity was the most affected parameter. In this case, ee of both regioisomers was highly eroded to 69 and 40% ee (entry 5).

\(^67\) This observation correlates with a statement made previously by Hayashi and coworkers, where they observed deactivation of the Rh catalyst by trace phenols present in the boronic acids reagents: Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida. K. J. Am. Chem. Soc., 2003, 125, 11508.
These results suggest the the released alkoxide may complex to Rh\(^{1}\) and hinder catalyst turnover. In addition, the size of the carbonate substituent may influence enantiotopic discrimination. Compared to isopropyl and phenyl carbonates, ethylcarbonate groups were still found to be best suited to provide 5 in high ee (Table 11, entries 4–6). The ethyl dicarbonate 3a was therefore kept as substrate of choice for the reaction of interest.

**Effect of the ligand on regiochemistry**

An optimization study was conducted, this time in benzene at a specific concentration. Again, only bidentates bisphosphanes were successful at giving the desymmetrized products 4 and 5. The most significant results of the ligand study are summarized in Table 2-9.

An interesting general trend is observed as regioselectivity seems to correlate with the electronic density of the phosphorus atoms.\(^{68}\) An incremental ratio drift can be seen towards the desired 1,4-substituted cyclopentene 5 from the pyridine-based P-PHOS family, which

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\(^{68}\) Correlation is also found with the bite angle of ligands. See Mechanistic Considerations section for more details.
was shown to be selective for 4 (entries 2–12). The ligand Cl-MeO-BIPHEP was selective for 5:4 ratio. The noted dependence on concentration observed with Xyl-SEGPHOS was also confirmed with Cl-MeO-BIPHEP (entries 8–10, and 12–14, respectively).

### Table 2-9 Effect of bisphosphane ligands on regioselectivity in THF

<table>
<thead>
<tr>
<th>entry</th>
<th>Ln</th>
<th>ligand</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>None</td>
<td>10</td>
<td>20:1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2&lt;sup&gt;i&lt;/sup&gt;</td>
<td>L1</td>
<td>P-PHOS</td>
<td>74</td>
<td>20:1</td>
<td>82</td>
<td>98</td>
</tr>
<tr>
<td>3&lt;sup&gt;i&lt;/sup&gt;</td>
<td>L2</td>
<td>Xyl-P-PHOS</td>
<td>87</td>
<td>18:1</td>
<td>92</td>
<td>n.d.</td>
</tr>
<tr>
<td>4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>L3</td>
<td>DIFLUORPHOS</td>
<td>58</td>
<td>17:1</td>
<td>92</td>
<td>n.d.</td>
</tr>
<tr>
<td>5&lt;sup&gt;g&lt;/sup&gt;</td>
<td>L7</td>
<td>Xyl-BINAP</td>
<td>43</td>
<td>12:1</td>
<td>12</td>
<td>n.d.</td>
</tr>
<tr>
<td>6&lt;sup&gt;g,k&lt;/sup&gt;</td>
<td>L5</td>
<td>BINAP</td>
<td>42</td>
<td>2.5:1</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>7&lt;sup&gt;f,k&lt;/sup&gt;</td>
<td>L10</td>
<td>SEGPHOS</td>
<td>60</td>
<td>2.3:1</td>
<td>92</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>L11</td>
<td>Xyl-SEGPHOS</td>
<td>26</td>
<td>1.2:1</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>9&lt;sup&gt;g&lt;/sup&gt;</td>
<td>L11</td>
<td>Xyl-SEGPHOS</td>
<td>56</td>
<td>1:1.4</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>L11</td>
<td>Xyl-SEGPHOS</td>
<td>80</td>
<td>1:2.0</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>11&lt;sup&gt;g,k&lt;/sup&gt;</td>
<td>L12</td>
<td>SYNPHOS</td>
<td>76</td>
<td>1:1.7</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>12&lt;sup&gt;f&lt;/sup&gt;</td>
<td>L16</td>
<td>Cl-MeO-BIPHEP</td>
<td>60</td>
<td>1:2.0</td>
<td>93</td>
<td>&gt;99</td>
</tr>
<tr>
<td>13&lt;sup&gt;g,k&lt;/sup&gt;</td>
<td>L16</td>
<td>Cl-MeO-BIPHEP</td>
<td>73</td>
<td>1:2.5</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>14&lt;sup&gt;h,k&lt;/sup&gt;</td>
<td>L16</td>
<td>Cl-MeO-BIPHEP</td>
<td>82</td>
<td>1:2.8</td>
<td>95</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed using 1a (0.135 mmol) with the listed catalyst (8 mol% in Rh), ligand (12 mol%) and solvent (0.12 M).<sup>b</sup> Isolated yield.<sup>c</sup> Determined by <sup>1</sup>H NMR of purified mixture.<sup>d</sup> Determined by chiral HPLC analysis of deprotected alcohols. Studies done by Tim Chapman (with Rh:L = 1:1).<sup>e</sup> In PhH (0.31 M).<sup>f</sup> In PhH (0.47 M).<sup>i</sup> In dioxane (0.47 M).<sup>j</sup> From ref. 3.<sup>k</sup> Experiments conducted by D. Perez.

Importantly, the electron-rich biphenyl-based ligands L10, L11, L12, and L16 consistently gave outstanding ee values for 5 (entries 7–13). It should also be noted that the ee of 1,2-substituted products 4 are notably higher with L10–L16 than those we found previously with Xyl-P-PHOS (L2). Despite our best efforts, the highest regioselectivity for 5 that could be achieved was 2.8:1 (entry 14). However, we believe the method is still very useful since, once the carbonate is cleaved, the parent alcohols 6 and 7 are easily separated by chromatography. Furthermore, results in Table 2-9 indicate that both cyclopentenols 6 and 7 can be prepared.

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with unprecedented enantioselectivity in a single operation from readily available starting materials (i.e., entry 10).

Cl-MeO-BIPHEP was selected as the optimal ligand to study the influence of the boronic acid on the regioselectivity of the reaction. While benzene is the solvent of choice to favor formation of 5, when boronic acids other than Ph-B(OH)$_2$ were used, problems of solubility arose. Experimentally, the reaction protocol requires premixing [Rh(cod)OH)$_2$ and the ligand in solvent at 60 °C for 15-20 min to form the active complex. The resulting red solution was cooled back to r.t., then 3a and the boronic acid were added concurrently as a stock solution.

Polar boronic acids would often not fully solubilize in benzene and could not be added this way. Attempts to solve this issue all resulted in decreasing the 5:4 ratio. For example, adding more solvent (which decreased the concentration), or using a more polar cosolvent such as THF, also decreased the concentration. Adding small amounts of THF to the stock solution did solubilize the reagents, but had a deleterious effect on regioselectivity – as is demonstrated in Table 13 for boronic acids bearing either EWG or EDG.

A practical modus operandi was found in changing the addition technique of reagents. Instead of adding them as a solution, the solids –catalyst, boronic acid, and base– were added all at once by rapidly opening the reaction vessel. For this protocol, the reaction vessel was changed from a 1 drachm vial to an elongated 15x130 mm pyrex test tube in order to keep the reaction under a blanket of argon gas while the solids were poured down the opened vessel. An argon purge followed the addition.

**Effect of the reaction temperature upon reagents addition**

As we surveyed more arylboronic acids, it became apparent that yields were generally low. Fortunately, a serendipitous discovery offered a solution to this issue. Adding the reagents while the premixed complex solution was still warm, at 60 °C, provided a strong improvement in yield. For instance, when para-trifluoromethylphenylboronic acid was reacted using BIPHEP as ligand, adding the substrate solution at 60 °C gave the substituted products in 87% yield—versus 18% when added at r.t. (Scheme 2-9).

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70 Because of a seminar beginning imminently, the author was impatient and did not allow the premixed complex solution to cool down to r.t. before adding the combined portion of solids to the reaction vessel. In view of the high yield obtained in this specific occasion, the cause was traced back to the addition occurring while the solution was still hot.
The regioselectivity was virtually identical, influence on regioselectivity hovered in the 1.4 to 2.0 to 1 range, favoring product. The electronic nature of the aryl nucleophile did not seem to influence the effect of electron density of the boronic acid was probed with SEGPHOS (Table 2-11). The new protocol (termed protocol B) was also tested with chiral ligands, since BIPHEP is achiral. Table 14 compares the two protocols for different arylboronic acids (A: addition at r.t.; B: addition at 60 °C). A two-fold increase in yield was observed.

**Table 2–10 Comparing Two Protocols with Chiral Ligands.**

<table>
<thead>
<tr>
<th>entry</th>
<th>4 / 5</th>
<th>R</th>
<th>protocol</th>
<th>yield (%)</th>
<th>Regio</th>
<th>% ee 4</th>
<th>% ee 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31 / 32</td>
<td>3-Me-4-MeO</td>
<td>A</td>
<td>35</td>
<td>1 : 1.4</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>31 / 32</td>
<td>3-Me-4-MeO</td>
<td>B</td>
<td>66</td>
<td>1 : 1.3</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>3*</td>
<td>22 / 33</td>
<td>3-MeO</td>
<td>A</td>
<td>42</td>
<td>1 : 0.75</td>
<td>nd</td>
<td>n.d.</td>
</tr>
<tr>
<td>4*</td>
<td>22 / 33</td>
<td>3-MeO</td>
<td>B</td>
<td>80</td>
<td>1 : 1.8</td>
<td>+89</td>
<td>+99</td>
</tr>
</tbody>
</table>

* Protocol A: Reactions were performed using 3a (0.135 mmol) with the catalyst (10 mol% in Rh), ligand (12 mol%) and solvent (0.47 M). Protocol B: Reactions were performed as for protocol A, but SM was added at 60 °C, followed by boronic acid and base added as solids in one portion.* Isolated yield. Determined by °H NMR of purified mixture.* Determined by chiral HPLC analysis of deprotected alcohols. (R)-SEGPHOS was used as ligand.

**Substituent effects of the aryl nucleophiles on regioselectivity**

The effect of electron density of the boronic acid was probed with SEGPHOS (Table 2-11). The electronic nature of the aryl nucleophile did not seem to influence the reaction significantly, as the regioselectivity hovered in the 1.4 to 2.0 to 1 range, favoring product 5, and yield were more or less constant.

Similarly, with BIPHEP, the electronic nature of aryl nucleophiles had a negligible influence on regioselectivity. For example, compare p-CF₃ and p-MeO on the aromatic moiety, the regioselectivity was virtually identical, i.e., at 1:1.5 and 1:1.4, respectively. The Hammett
constants of the two groups being very different suggests very little charge contribution at the transition state (+0.54 and -0.27, respectively). In addition, the yield did not seem to be affected by electron density as no clear trend was observed. Ortho substituents gave diminished yields (entries 15 and 16).

Table 2–11 Substituent Effect on Regioselectivity with Protocol B

<table>
<thead>
<tr>
<th>entry</th>
<th>ligands</th>
<th>products</th>
<th>R</th>
<th>Hammett α</th>
<th>yield (%)</th>
<th>1,2- : 1,4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-Xyl-SEGPHOS (L11)</td>
<td>4a / 5a</td>
<td>H</td>
<td>0</td>
<td>80</td>
<td>1 : 2.0</td>
</tr>
<tr>
<td>2*</td>
<td>(R)-Xyl-SEGPHOS (L11)</td>
<td>22 / 33</td>
<td>3-OMe</td>
<td>+0.12</td>
<td>64</td>
<td>1 : 1.4</td>
</tr>
<tr>
<td>3*</td>
<td>(R)-Xyl-SEGPHOS (L11)</td>
<td>14 / 34</td>
<td>4-COOME</td>
<td>+0.39</td>
<td>63</td>
<td>1 : 1.8</td>
</tr>
<tr>
<td>4</td>
<td>BIPHEP (L8)</td>
<td>12 / 30</td>
<td>4-CF₃</td>
<td>+0.54</td>
<td>87</td>
<td>1 : 1.5</td>
</tr>
<tr>
<td>5</td>
<td>BIPHEP (L8)</td>
<td>35 / 36</td>
<td>3-F-5-OMe</td>
<td>+0.46</td>
<td>75</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td>6</td>
<td>BIPHEP (L8)</td>
<td>14 / 34</td>
<td>4-COOME</td>
<td>+0.39</td>
<td>81</td>
<td>2 : 1.0</td>
</tr>
<tr>
<td>7</td>
<td>BIPHEP (L8)</td>
<td>37 / 38</td>
<td>3-Br</td>
<td>+0.39</td>
<td>83ʰ</td>
<td>1 : 1.6</td>
</tr>
<tr>
<td>8</td>
<td>BIPHEP (L8)</td>
<td>39 / 40</td>
<td>3-COOME</td>
<td>+0.32</td>
<td>71</td>
<td>1 : 1.0</td>
</tr>
<tr>
<td>9</td>
<td>BIPHEP (L8)</td>
<td>22 / 33</td>
<td>3-OMe</td>
<td>+0.12</td>
<td>70</td>
<td>1 : 1.0</td>
</tr>
<tr>
<td>10</td>
<td>BIPHEP (L8)</td>
<td>41 / 42</td>
<td>4-SMe</td>
<td>0</td>
<td>80</td>
<td>1 : 1.4</td>
</tr>
<tr>
<td>11</td>
<td>BIPHEP (L8)</td>
<td>43 / 44</td>
<td>3-Me-4-F</td>
<td>-0.01</td>
<td>68</td>
<td>1 : 1.4</td>
</tr>
<tr>
<td>12</td>
<td>BIPHEP (L8)</td>
<td>23 / 46</td>
<td>3-Me</td>
<td>-0.07</td>
<td>68</td>
<td>1 : 1.5</td>
</tr>
<tr>
<td>13</td>
<td>BIPHEP (L8)</td>
<td>19 / 47</td>
<td>4-OMe</td>
<td>-0.27</td>
<td>61ʰ</td>
<td>1 : 1.4</td>
</tr>
<tr>
<td>14</td>
<td>BIPHEP (L8)</td>
<td>31 / 32</td>
<td>3-Me-4-OMe</td>
<td>-0.34</td>
<td>67</td>
<td>1.1 : 1</td>
</tr>
<tr>
<td>15</td>
<td>BIPHEP (L8)</td>
<td>48 / 49</td>
<td>2-F-5-Me</td>
<td>-</td>
<td>15</td>
<td>1 : 2.0</td>
</tr>
<tr>
<td>16</td>
<td>BIPHEP (L8)</td>
<td>50 / 51</td>
<td>2-F</td>
<td>-</td>
<td>31ʰ</td>
<td>1 : 2.3</td>
</tr>
<tr>
<td>17</td>
<td>BIPHEP (L8)</td>
<td>52 / 53</td>
<td>3-Thiophen</td>
<td>-</td>
<td>27ʰ</td>
<td>1 : 2.2</td>
</tr>
</tbody>
</table>

* Protocol B: reactions were performed in a screw-cap test-tube using 3a (0.135 mmol) with Rh catalyst dimer (4 mol%), Ln (12 mol%) in solvent (0.47 M), under Ar; SM added at 60 °C, followed by boronic acid and base added as solids in one portion. * Heated at 80 °C. Reaction stirred for 45 days. Enol attack instead. New product observed. Concentration = 0.34 M, with added THF. Average of two runs.

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2.4.3 Scope of the reaction

With these optimized parameters in hand, the scope of the Rh-catalyzed enantioselective desymmetrization was investigated as a function of the boronic acid nucleophiles (Table 3). The most indicative results are summarized in Table 2-12.

With Cl-MeO-BIPHEP, the reaction tolerates a wide range arylboronic acids to give both regioisomeric arylcyclopentenols. Importantly, the 1,4-substitution products 5 are obtained with outstandingly robust enantioselectivity. The regioisomeric ratio is fairly constant at about 2:1 favoring the products 5. A limitation is observed with ortho substituted arylboronic acids. In these cases, the reactivity is likely hampered by steric factors as low yields are obtained, otherwise the regioselectivity and enantioselectivity is similar to the other examples.

Finally, the methodologies developed in this section and in Section 2.4 display a robust behaviour. The regioselectivity of the products can be tuned by simply changing the bisphosphine ligand and solvent system. The observations made along the optimization experiments provided the foundations for a discussion of the transformation’s mechanism in the following section.
Table 2–12 Scope of the Rh(I)-Catalyzed Enantioselective Desymmetrization

<table>
<thead>
<tr>
<th>entry</th>
<th>products 4 / 5</th>
<th>Ar</th>
<th>yield (%)(^b)</th>
<th>4 : 5 ratio(^c)</th>
<th>4 ee (%)(^d)</th>
<th>5 ee (%)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 / 30</td>
<td>Ar-CF(_3)</td>
<td>(81)</td>
<td>1 : 2.8</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>35 / 36</td>
<td>Ar-F</td>
<td>78</td>
<td>1 : 2.4</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>37 / 38</td>
<td>Ar-OH</td>
<td>89</td>
<td>1 : 2.3</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>22 / 33</td>
<td>Ar-CMe(_2)</td>
<td>80</td>
<td>1 : 1.8</td>
<td>89</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>4a / 5a</td>
<td>Ar</td>
<td>80</td>
<td>1 : 2.6</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>41 / 42</td>
<td>Ar-SMe</td>
<td>80</td>
<td>1 : 2.6</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>43 / 44</td>
<td>Ar-F</td>
<td>69</td>
<td>1 : 2.3</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>23 / 46</td>
<td>Ar-Me</td>
<td>100</td>
<td>1 : 2.2</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>31 / 32</td>
<td>Ar-OMe</td>
<td>66</td>
<td>1 : 1.3</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>48 / 49</td>
<td>Ar</td>
<td>15</td>
<td>1 : 2.0</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>11</td>
<td>50 / 51</td>
<td>Ar</td>
<td>16</td>
<td>1 : 1.6</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>52 / 53</td>
<td>Ar</td>
<td>21</td>
<td>1 : 2.0</td>
<td>89</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\) Protocol B: reactions were performed in a screw-cap test-tube using 3a (0.135 mmol) with Rh catalyst dimer (4 mol%), L16 (12 mol%) in solvent (0.47 M), under Ar; SM added at 60 °C, followed by boronic acid and base added as solids in one portion. \(^b\) Isolated yield. \(^c\) Determined by \(^1\)H NMR of purified mixture. \(^d\) Determined by chiral HPLC analysis of deprotected alcohols.
2.4.4 Limitations with Cyclic Diols Derivatives

The method developed above presents several limitations. A notable one is substrate scope. Despite repeated trials, the six-membered ring cyclohexenediol analogs did not show any reactivity. Only untouched starting material was recovered. We hypothesize that the diaxial conformation stereoelectronically required for an ionization pathway is too high in energy.\(^\text{72}\)

Any nucleophile with a nitrogen atom failed to react (nitriles, nitro groups, pyridylboronic acids), or lead to very low yields (4-NHBoc). Under the mild reaction conditions, the nitrogen containing groups may compete with the substrate alkene for binding, and may shut the reaction. In addition, vinylboronic acids showed almost no turnover.

\(^{72}\) Although the cyclohexene endoperoxide substrate is isolable and would intrinsically possess the required diaxial conformation of oxygens, it is notoriously unsafe to expose transition metals to endoperoxoites.
2.5 Mechanistic Considerations.

2.5.1 Proposed mechanism

Our working hypothesis for the mechanism of the reaction is depicted in Scheme 2-10. At least two catalytic cycles can be considered. The first involves a carborhodation of the alkene as the key step, whereas the second involves an oxidative addition of the Rh\textsuperscript{I} catalyst to generate Rh\textsuperscript{III} σ-ethyl intermediate. Our results suggest that both may be operative and competitive, depending on the ligands used.

The generation of the active catalyst is common to both proposed pathways. In the premixing phase, \([\text{Rh(cod)OH}]_2\) is heated in the presence of the bisphosphine ligand and the more labile cod is displaced by the chiral ligand to form A, which is presumably the active catalyst.\(^{73}\) Upon addition of the boronic acid, fast transmetalation of the aryl moiety from boron to rhodium occurs to form B. Binding the alkene of substrate 3 to the Rh center leads to C. The two proposed pathways diverge at this step.

\[\begin{align*}
\text{[Rh(cod)OH]}_2 + \text{L} & \rightarrow A \\
A + \text{Ar-B(OH)}_2 & \rightarrow B \\
B + \text{substrate} & \rightarrow C \\
C & \rightarrow D, E, F, \text{etc.}
\end{align*}\]

Scheme 2–10 Proposed catalytic cycles for the Rh-AAS proceeding via carborhodation and/or σ-ethyl divergent intermediates.

The carbo-rhodation pathway (i) contains a diastereo- and enantioselective insertion of the alkene into the Rh-Ar bond which would generate the key intermediate D. Subsequent anti-periplanar β-alkoxide elimination yields the 1,2-product 4. This mechanism is based on our previous work for Rh-catalyzed ring-opening of oxabicyclic molecules, which was discussed in Chapter 1.5. In the present case, desymmetrization of the cyclic dicarbonate yielded exclusively the trans products, whereas with the ring-opening reaction, cis products were observed exclusively. The relative stereochemistry in the products is set by the carboration occurring on the face of the olefin anti to the carbonate leaving groups.

The above mechanism cannot explain the formation of the 1,4-products 5. To account for the observed 1,4-product, we need to consider at least partial contribution from an alternative pathway.

The oxidative addition pathway (ii) proceeds with an enantioselective ionization of the rhodium(I) catalyst to generate a σ-enyl rhodium(III) complex intermediate F. The existence of σ-enyl intermediates was demonstrated by Evans and co-workers.74 They also showed that isomerization between regioisomers was slow. Once the 1,2-σ-enyl complex F is formed, it could reductively eliminate to yield the 1,2-substituted product 4, or equilibrate with the isomeric 1,4-σ-enyl complex G, from which a reductive elimination would lead to the 1,4-substituted product 5. Accordingly, the rate of F/G isomerization versus the rate of reductive elimination would be pivotal in determining the regioselectivity of the reaction.

The regioselectivity of the reaction on the relative rates of three steps: $k_1$, $k_2$, and $k_3/k_4$. The exclusive formation of the 1,2-products 4 will be observed if $k_1$ is greater than $k_2$. Alternatively, 4 will also be formed if conditions either disfavor equilibration of F to G, or force rapid reductive elimination, $k_3$ (e.g., by large steric demands on complex F). On the other hand, the challenge of Section 2.4 was to prepare selectively the 1,4-product 5. In this case, $k_2$ must be accelerated relative to $k_1$ to prevent “side-product” 4. Also, conditions must be found to stabilize the Rh(III) complexes F and G and to slow down reductive elimination $k_4$. Although, by analogy to Evans’s studies, it is assumed the regiosisomer G is thermodynamically favored over F, it is possible that in our case with the MeO-BIPHEP ligands, the average 4:5 ratio of 1:2 observed may in fact reflect the mixture of F:G at equilibrium.

2.5.2 Enantiodiscrimination

While screening ligands in the previous section, Table 2-3 revealed that both regioisomers 4 and 5 were formed in quite different ee. According to the proposed catalytic cycle leading to both regioisomers, it is expected that once the alkene of 3 has reacted with the Rh(I)-Ar catalyst, chirality has already been imparted to the molecule (i.e. stereochemistry at C-1 is fixed). Therefore, after ionization, no matter whether isomerization occurs or not, the ee measured for 4 and 5 should be the same. Yet, this was not the case, as certain ligands demonstrated; especially the BINAP family (Table 2-3, entries 5 to 7).

The fact that regioisomers are obtained with varying enantioselectivity hints at the possibility that the two mechanisms may be competitive. While the oxidative addition mechanism might be highly selective – affording cyclopentenols 4 and 5 in 99% ee, the less selective carbo-rhodation may compete to produce only 4 in low ee. Consequently, the ee measured for cyclopentenols 4 would be the weighed average of both pathways, where the gap in ee between 4 and 5 would give some measure of the relative rates between $k_1$ and $k_2$ (Scheme 2-11).

Interestingly, the SEGPHOS family of ligands displayed very similar ee levels for the two regioisomers (4a: 96% ee, and 5a: 98% ee). We interpreted this observation as SEGPHOS ligands potentially funnelling the reaction towards a single pathway—with the bonus attribute of being highly enantioselective. Thus, a ligand favoring an ionization process ($k_2$) is expected to display a better enantiodiscrimination.
2.5.3 Impact of the leaving group

As discussed in Section 2.3, we examined different carbonates at the optimization stage. We were surprised to see that the nature of the carbonate, anticipated to be remote from the reactive site, had a striking effect on the yield and enantioselectivity (Table 2-8). Looking more carefully at the impact of the liberated leaving group (LG) on the reaction suggests that it may both poison catalytic activity and disrupt the complex at the enantiodiscriminating step.

When the substrate bore isopropyl carbonates (3b), the yield was poor (20%), but enantioselectivity was the most affected parameter. In this case, the ee of both products was highly eroded to 69 and 40% ee.

An experiment was conducted to probe whether the alkoxide exerts a steric influence at the stage of alkene coordination, or due to complexation to rhodium center (Eqn 2-17). Ethyl dicarbonate 3a was submitted to the reaction conditions with one equivalent of propan-2-ol. The results revealed that both factors are at play in presence of propan-2-ol: the yield diminished to 21% compared to 60%, but ee remained high (92/96 vs 93/99% ee). Thus, it is possible that the alkoxide could complex to Rh and hinder catalyst turnover. Similarly, the size of the alcohol may perturb enantiotopic discrimination. This ethoxide ion may complex to rhodium and compete with substrate.

![Chemical diagram]

Two control experiments were conducted with BINAP as the ligand to test the effect of free alkoxide in the reaction (Eqn 2-18).\textsuperscript{75} Adding 0.5 equivalents of EtONa at the start of the reaction led to only 10% conversion. Similarly, adding 0.5 equivalents of t-BuOK showed no conversion at all. These experiments suggest that the production of an alkoxide during the course of the reaction may be detrimental to the conversion. Thus, as the reaction proceeds, even if decarboxylation is slow, it may generate enough alkoxide to impede reactivity. It follows that a solution to this problem might allow to decrease catalyst loading; a worthy goal.

\textsuperscript{75} The reaction conditions are overall basic and may not favor decarboxylation. Nevertheless, a large amount of boron reagents and by-products are present which may act as Lewis acids. Only a small concentration of alkoxide is required to shut down the catalytic activity.
given the high price of rhodium. Potential trapping agents were examined with the hope of sequestering the released ethoxide, but to no avail.\footnote{76}

\[
\begin{align*}
\text{EtO}_2\text{CO} & \xrightarrow{0.5 \text{ equiv}} \text{RO}^+\text{Na}^- & \text{[Rh(cod)OH]}_2 (10 \text{ mol\%}) \\
& \xrightarrow{(S)}\text{BINA}(12 \text{ mol\%}) & \text{Ph-B(OH)}_2 (2 \text{ equiv}) \\
& \text{Cs}_2\text{CO}_3 (1 \text{ equiv}) & \text{THF, } 50 \degree \text{C} \\
3\text{a} & \rightarrow 4\text{a} & \rightarrow 5\text{a} \\
\end{align*}
\]

Other leaving groups were therefore examined, which might be less nucleophilic towards the rhodium complex. Aware that such a complexation may not be the sole factor impeding the reaction,\footnote{77} this important parameter needed to be studied. As stated in section XX, ethyl carbonates were the best of surveyed leaving groups.

### 2.6 Synthetic Transformations

\textit{trans}\text{-3,4-Disubstituted piperidines} are important building blocks that are present in current drug candidates.\footnote{78} In particular, many tachykinin receptor antagonists possess a piperidine functionalized with a \textit{trans}\text{-3,4-substitution pattern} (Figure 2-6). A specific example is \textbf{56}, which is a patented analog of Aprepitant, an NK1 inhibitor from Merck (Scheme 2-12). We envisioned a synthesis of the chiral active molecule \(\textit{(R,S)}-\textbf{56}\) that avoids issues of chiral resolution and low diastereoselectivity encountered in Merck’s synthesis.\footnote{79}

![Figure 2-5](image)

\textbf{Figure 2-5} Drug candidates displaying the piperidine substitution motif accessible by the proposed method.

---

\footnote{76}{The trapping agents tested included TBSCI, 4A MS, MgO/BaO, and BF$_3$.}

\footnote{77}{Rhodium alkoxides are known to be effective catalysts in the transmetalation of boronic acids, although their activity is sensitive the metal-ligand system: Yoshida, K.; Ogasawara, M.; Hayashi, T. \textit{J. Org. Chem.} \textbf{2003}, 68, 1901.}


The synthesis the enantioenriched 3,5-trans disubstituted piperidine \((R,S)-56\) was effected by derivatizing \(6\) to an 3-arylpiperidine by simple transformations in 18% yield over three steps (Scheme 2-12). Piperidine 55 was obtained in 91% ee and intercepts the patented synthesis of \(56\). It constitutes a formal synthesis of the NK1 inhibitor, which was reported to be obtained in five further synthetic steps. Our synthesis circumvents the chiral resolution of an amine salt reported by the Merck synthesis; a costly one in terms of yield.

Aside from the formal synthesis of \(56\), the stereoselective synthesis of piperidines bearing the particular substitution pattern displayed in 55 cannot be accomplished easily using traditional methods. Thus, it further illustrates the value of the Rh-catalyzed AAS reaction developed above.

\[
\begin{align*}
\text{PhOH} & \xrightarrow{\text{TBSCI, imid.}} \text{PhOTBS} \\
(R,S)-6 & \xrightarrow{90\%} (R,S)-54 \\
& \xrightarrow{18\%, 3\text{ steps}} \text{TBSO}\text{PhN} \\
& \text{BnNH}_2, \text{dioxane, } \Delta \\
(R,S)-55 & \xrightarrow{\text{Ref. 78}} (R,S)-56
\end{align*}
\]

Scheme 2–12 Application of methodology to the formal synthesis of an NK1 inhibitor.

---

\(^{80}\) This formal synthesis was carried out by Daniela Sustac-Roman as part of her fourth year thesis project under the author’s guidance. The selection of this target and the route examined were proposed by the author.
2.7 Desymmetrization of Linear Allylic Diols

The previous sections described a catalytic system that adds hard C-nucleophiles to cyclic alkenes. In line with our goal to desymmetrize readily available substrates, but-2-ene-1,4-diol, was selected to test the generality of the reaction (VII, R = H; Scheme 2-13). This substrate lacks any latent ring-strain energy that can be exploited, and is arguably as close as unactivated an alkene one can get. In this section, we report a simple, useful protocol that effects the desymmetrization of allylic carbonates with arylboronic acids in high selectivity using a rhodium(I) catalyst and P-Phos as chiral ligand. A preliminary account of this project was published recently as an article in *Synthesis*.  

2.7.1 Introduction

Chiral small molecules are of interest for their use as building blocks in total synthesis and in medicinal chemistry. Extending the above rhodium-catalyzed methodology to linear allylic derivatives VII would give access to a wide array of versatile chirons XV (Scheme 2-13). These small chiral synths bear three differentiated functional groups for use as synthetic handles: a terminal alkene, a protected alcohol, and a substituted arene. Symmetrical linear butenediols derivatives VII are attractive because of their ease of preparation and commercial availability.

![Scheme 2-13](image)

The chiral branched homoallylic alcohols XVII would be very useful in synthesis. For example, they could be derivatized into hydroxyester XVIII by complete oxidation of the terminal alkene (Scheme 2-14). The chiral synths obtained would be aryl analog of the Roche ester, which has found widespread use in synthesis.

---

A simple literature search using the Sci-Finder database returned over 1000 molecules bearing the structural motif accessible by our proposed methodology. Figure 2-7 depicts three patented molecules displaying a range of biological activity. Our method would facilitate, if not shorten, the synthesis of these compounds in enantiomerically pure form.

**Literature precedents**

As discussed in Chapter 1, although a number of palladium-catalyzed asymmetric allylic substitutions (AAS) are known, only a few allow AAS with hard carbon nucleophiles. With linear substrates, exceptional results have been obtained with rhodium, iridium, and copper catalysts using unsymmetrical systems. However, no good method exist to desymmetrize allylic diols enantioselectively. Scheme 2-15 illustrates alternative methods available to prepare branched homoallylic alcohols XV in enantiomerically enriched fashion. Feringa and co-workers developed enantioselective Cu-catalyzed allylic alkylations performed on allylic bromides with a protected hydroxyl group using Taniaphos as chiral ligand (Eq. 2-3). Also, Murakami reported a substitutive arylation of cis-allylic diols.

---

catalyzed by rhodium(I) simultaneously to our efforts (Eq. 2-5 and 2-6). Their results showed a maximum of 83% ee, and thus set the bar for our studies. The present reaction is very similar in appearance to Murakami’s based on the products and the reagents. However, experimental evidence suggests that the two reactions proceed by different mechanisms.

Scheme 2–15 Alternative methods to prepare chiral branched homoallylic alcohols

2.7.2 Results and Discussion

The optimized conditions found for the desymmetrization of cyclic carbonates provided the starting point for the investigations. This section details the optimization of the reaction conditions, the reaction scope, and mechanistic aspects. Parts of this section’s results were carried out by Bing Yu, under mentorship of the author. Mr. Yu’s contributions are acknowledged where appropriate.

Survey of the reaction parameters

The reaction was initially tested with the conditions that had proved optimal for the cyclic system (Section 2.4). Thus, the catalyst [Rh(cod)OH]2 was used with Xyl-P-Phos to effect the desymmetrization of the linear allylic ethyl dicarbonate 58a (Table 2-13). The reaction gave 43% of a mixture of branched and linear substitution products, 59a and 60a, respectively. The desired branched product 59a was the major one and it was obtained in 81% ee (entry 1).

A preliminary survey of the reaction parameters was conducted. It showed that the reaction is very responsive to small changes of the ligands. Some ligands give good yield, others high regioselectivity, and others promising ee (entries 10, 4, and 1, respectively). It also showed that it is important to be aware of a racemic background reaction, since the reaction took place even without ligand (entries 5–7).

91 Bing M. Yu was a Master’s student at the time, and is presently a Research Associate at Novartis in Boston, MA. For further details about the optimization of the reaction, see: Yu. B. M. M.Sc. Thesis, University of Toronto, 2009, 110 pages.
After rounds of screening, P-PHOS (L2) was found to give 58a with the best combined yield and selectivity (Table 2-14). The regioselectivity depended strongly on the nature of the ligand. Specifically, P-PHOS and DIFLUORPHOS, ligands that are electron-donating by pi resonance, but electron-deficient by sigma induction, were best (entries 6 and 7). In contrast to cyclic substrates of Section 2.4, ligands with large groups on the phosphorus, i.e., Xyl-P-PHOS, gave lower selectivity compared to their phenyl analogs (entries 4 and 6). DIFLUORPHOS showed selectivities slightly higher than P-PHOS, but we pursued our studies with P-PHOS due to its availability. It should be noted that the reaction needs to be conducted under a strictly inert atmosphere.

92 P-PHOS is stable to air in the solid state; however, it is highly sensitive to oxygen once in solution.

---

**Table 2–13 Initial Results**

| Entry | Ligand          | Additives (eq.) | Solvent | Temp. (°C) | yield (%) | Regio B : L | % ee<sup>a</sup> <br> B |<br>---|-----------------|-----------------|---------|-----------|-----------|-------------|------------------|
| 1     | (R)-Xylyl-P-Phos | -               | THF     | 60        | 43        | 2.7 : 1    | 81               |
| 2     | (±)-BINAP       | -               | THF     | 60        | 18        | 2.5 : 1    | -                |
| 3     | (R)-Tol-BINAP   | -               | THF     | 50        | n.d.      | 2 : 1      | -22              |
| 4     | Degus. CatAsym 1| -               | THF     | 60        | 5         | 20 : 1     | n.d.             |
| 5     | None            | -               | THF     | 62        | 50        | 20 : 1     | -                |
| 6     | None            | No base         | THF     | 52        | 16        | 20 : 1     | -                |
| 7     | None            | No base         | THF + H<sub>2</sub>O<sup>a</sup> | 52 | tr. | - | - |
| 8     | (S)-Cl-MeO-BIPHEP | No base      | THF + H<sub>2</sub>O<sup>a</sup> | 52 | 58 | n.d. | +73 |
| 9     | (S)-Cl-MeO-BIPHEP | No base      | THF     | 52        | 18        | 2.1 : 1    | +71              |
| 10    | (S)-Cl-MeO-BIPHEP | -            | THF     | 52        | 68        | 1.5 : 1    | +62              |
| 11    | (S)-Cl-MeO-BIPHEP | -            | Dioxane | 58        | 34        | 1.8 : 1    | +62              |
| 12    | (S)-Cl-MeO-BIPHEP | -            | Dioxane + H<sub>2</sub>O<sup>a</sup> | 58 | 40 | 1.9 : 1 | +47 |
| 13    | (S)-Cl-MeO-BIPHEP | BHT + No base | Dioxane | 58        | 34        | 2.7 : 1    | +65              |

<sup>a</sup> Reaction were performed using 58a (0.135 mmol) with Rh catalyst dimer (5 mol%), Ligand (12 mol%), boronic acid (2 equiv), base (1 equiv), in solvent (0.20 M) under an Ar atmosphere. Isolated yield. Determined by <sup>1</sup>H NMR of purified mixture; B: branched; L: linear. Determined by chiral HPLC or GC analyses of deprotected 59a (K<sub>2</sub>CO<sub>3</sub>, MeOH, r.t., 3 h). Used a 10:1 mixture of solvent:water.
Effect of Lewis acid additives

The effect of additives was found to improve the conversion while maintaining the regio- and enantioselectivity. Although this was found by B. M. Yu, his results are presented in the text for completeness of discussion. Lewis acids that might activate the carbonate leaving groups were screened, and a substoichiometric amount of zinc triflate proved most effective (Table 2-15). Its presence was crucial in observing full conversion of the substrate. A variety of other Lewis acids showed no conversion to the desired products, i.e., TiCl₄, BF₃, AlCl₃ and TBSOTf. With an acceptable catalytic system in hand, we looked at the influence of the leaving group on the alcohols.


Table 2–15 Effect of Lewis Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Yield^b (%)</th>
<th>59 : 60</th>
<th>59 ee^d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>42</td>
<td>10 : 1</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf</td>
<td>65</td>
<td>17 : 1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>CuOTf</td>
<td>55</td>
<td>8 : 1</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Zn(OTf)₂</td>
<td>85</td>
<td>10 : 1</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>La(OTf)₃</td>
<td>76</td>
<td>10 : 1</td>
<td>88</td>
</tr>
</tbody>
</table>

^a Reaction were performed using 58a (0.135 mmol) with Rh catalyst dimer (5 mol%), Ligand (12 mol%), boronic acid (2 equiv), 1 equiv. Cs₂CO₃, 20 mol% Lewis acid in solvent (0.20 M) under an Ar atmosphere. ^b Isolated yield of carbonates. ^c Determined by ^d H NMR of purified mixture; B: branched; L: linear. ^e Determined by chiral HPLC or GC analyses of deprotected 59a (K₂CO₃, MeOH, r.t., 3 h). ^f Studies conducted by B. M. Yu.

Influence of the leaving group

A range of substrates were prepared by bis-acylation of (Z)-but-2-ene-1,4-diol. In a typical procedure, the diol was reacted with an excess of acylating agent 62 (Scheme 2-16). These simple reactions proceeded in excellent yields. Some acylating agents were prepared from the parent alcohols using triphosgene. A selection of bis-carbonates and diesters 58 were synthesized and tested.

Scheme 2–16 Synthesis of dicarbonates substrates.

To examine the influence of the leaving group, p-tolylboronic acid was used as nucleophile because its moderate but measurable reactivity would provide a reference point in seeking better conditions. Ethyl biscarbonate 58a remained the best substrate (Table 2-16). Substrates bearing weakly coordinating nucleofuges led to low regio- and enantioselectivity (entries 3 and 4), whereas more electron-rich leaving groups led to higher ee (entries 2 and 6). In view of the clean reaction profile, we settled on ethyl carbonates to explore the scope of the reaction. It should be noted that yields reflect incomplete conversion of starting material.
Indeed, 58a was always recovered along with the desired products (yields are >90% if based on recovered starting material).

### Table 2–16 Influence of the Leaving Group

<table>
<thead>
<tr>
<th>Entry</th>
<th>58x</th>
<th>R</th>
<th>Yield(^b) (%)</th>
<th>B : L(^c)</th>
<th>B ee(^d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>EtOCO-</td>
<td>59</td>
<td>&gt;20 : 1</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>i-PrOCO-</td>
<td>50</td>
<td>10 : 1</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>CF(_3)CH(_2)OCO-</td>
<td>76</td>
<td>1 : 1</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>PhOCO-</td>
<td>64</td>
<td>4 : 1</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>PhCO-</td>
<td>35</td>
<td>7 : 1</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>4-MeO-C(_6)H(_4)CO-</td>
<td>36</td>
<td>7 : 1</td>
<td>93</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: same as described in Table 2-15. \(^b\) Isolated yield of carbonates. \(^c\) Determined by \(^1\)H NMR of purified mixture; B: branched; L: linear. \(^d\) Determined by chiral HPLC or GC analyses of deprotected 63 (K\(_2\)CO\(_3\), MeOH, r.t., 3 h). \(^e\) Experiments conducted by B. M. Yu.

### 2.7.3 Scope of the reaction with arylboronic acids

A selection of arylboronic acids was tested in this reaction (Table 2-17). The reaction is highly enantioselective, and we observed that electron-rich aryl groups are best suited for this transformation in terms of regioselectivity. Substitution in the meta or para position on the boronic acid is also tolerated. However, ortho substituents did not react or led to significantly diminished yields when compared to their para isomers. Nucleophiles that did not react under these conditions included boronic acids bearing functional groups such as a protected amine, aldehyde, nitro, and bromide.
Table 2–17 **Scope of Boronic Acids***

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>X</th>
<th>Yieldb (%)</th>
<th>B : Lc</th>
<th>B ee(d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>59a</td>
<td>85</td>
<td>10 : 1</td>
<td>94</td>
</tr>
<tr>
<td>2e</td>
<td></td>
<td>63a</td>
<td>59</td>
<td>&gt;20 : 1</td>
<td>93</td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>65a</td>
<td>60</td>
<td>&gt;20 : 1</td>
<td>93</td>
</tr>
<tr>
<td>4e</td>
<td></td>
<td>66a</td>
<td>65</td>
<td>10 : 1</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>67a</td>
<td>66</td>
<td>4 : 1</td>
<td>67</td>
</tr>
<tr>
<td>6e</td>
<td></td>
<td>68a</td>
<td>68</td>
<td>7 : 1</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>69a</td>
<td>45</td>
<td>10 : 1</td>
<td>87</td>
</tr>
<tr>
<td>8e</td>
<td></td>
<td>70a</td>
<td>38</td>
<td>10 : 1</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>71a</td>
<td>66</td>
<td>4 : 1</td>
<td>70</td>
</tr>
<tr>
<td>10e</td>
<td></td>
<td>72a</td>
<td>32</td>
<td>&gt;20 : 1</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>73a</td>
<td>61</td>
<td>&gt;20 : 1</td>
<td>90</td>
</tr>
</tbody>
</table>

*a Reaction conditions: same as described in Table 2-15. b Isolated yield of carbonates. c Determined by 1H NMR of purified mixture; B: branched; L: linear. d Determined by chiral HPLC or GC analyses of deprotected 63 (K₂CO₃, MeOH, r.t., 3 h). e Experiments conducted by B. M. Yu.

### 2.7.4 Mechanistic discussion

Two proposed mechanistic scenarios are illustrated in Scheme 2-17. Our results suggest that pathway (a) may be dominant. This ionization mechanism is distinctly different from the one proposed by Murakami.⁹⁰ Pathway (a) involves an oxidative ionization of the catalyst to form a Rh(III) σ-enyl intermediate A, which can isomerize to B slowly, such as described by Nelson and Evans.⁷⁴ Reductive elimination from either A or B then yields products 59 or 60, respectively. Therefore, the product distribution may be dictated by the competing rates of
reductive elimination versus isomerization, and may depend on the species coordinated to the \( \sigma \)-enyl complex.

Alternatively, a carbometalation of the alkene leading to C, followed by simple elimination, cannot be ruled out (pathway b); although it would not explain formation of linear product 60. Notably, we did not observe byproduct 75, which was previously reported and can only occur by pathway (b). The only side product sometimes formed was 74, arising from isomerization of 60. Importantly, pathway (a) may not be accessible by Murakami’s protocol, based on stereoelectronic aspects. Indeed, they have shown through control experiments that a cyclic intermediate tying up both oxygens of C is necessary for their system, and the 7-membered ring thus formed does not allow the required alignment of allylic oxygens with the alkene to form Rh(III) complexes A or B. It may also explain why, in contrast to Murakami’s report, carbonates are suitable substrates.

The marked increase in yield when a metal-based Lewis acid is used may be due to activation of the leaving groups of 58a, thereby facilitating an ionization process (pathway a). We showed that the leaving groups are clearly involved, and their influence on regio and enantioselectivity suggests that nucleofuges may be bound to rhodium complexes A and B, and influence the relative rates of isomerization/reductive elimination. The fact that electron-rich leaving groups lead to higher ee and regioselectivity may provide experimental support for pathway (a).

NMR experiments were conducted to try to observe intermediates of the proposed catalytic cycles. In a simple experiment, starting material 58a was subjected to a
stoichiometric amount of [Rh(cod)OH]_2 in C_6D_{14}, and the mixture was heated at 60 °C for 30 min. The \(^1\)H NMR analysis of the sample showed a small, but observable concentration of what we assigned to be a Rh\(^{III}\)-\(\sigma\)-enyl complex A (76, Scheme 2-18). Importantly, van Leeuwen and co-workers have previously isolated a simpler Rh\(^{III}\)-\(\sigma\)-enyl complex and characterized it by X-ray.\(^93\) The vinylic and allylic \(^1\)H chemical shifts we observed match very closely those reported by van Leeuwen. Furthermore, when we repeated the experiment with a Xyl-P-PHOS as ligand, the characteristic \(^1\)H NMR signals were observed. These NMR studies help support an ionization pathway (a) involving a Rh\(^{III}\)-\(\sigma\)-enyl, as had been observed by Evans.

Scheme 2-18 Observation of rhodium(III) sigma-enyl species.

Exploring alternatives to bidentate phosphines

The scope of the reaction presented above shows that the reaction is far from perfect. The limitations under the given conditions include: the high sensitivity of the reaction to air contamination, unsatisfactory yield, low turnover, variable enantioselectivity, and modest regioselectivity. A more robust set of conditions is desirable.

In order to address the shortcomings of the P-PHOS/Zn(OTf)_2 system we examined the behavior of the reaction with ligands that are not necessarily bidentate. The significant background reaction without any ligand opened the door to more latitude in term of ligands, including monodentate phosphines and N-heterocyclic carbenes (NHC).

Table 2-18 shows the most significant results with a selection of phosphorus-based ligands. In all cases, a 1:1 ratio of ligand to Rh gave a higher yield than a 2:1 ratio. Although yields were poor, the regioselectivity was excellent for the desired branched product. The most encouraging results were observed with a phosphoramidite ligand (entry 7). These result suggest that leaving a coordination site open is beneficial. Moreover, chiral phosphor-

amidite may provide a cheaper alternative to the use of P-PHOS. It should be noted that a side-product was formed with certain ligands, and was identified as 3,4-diphenylbut-3-enyl ethyl 1-carbonate (entries 1–4). This product arises from a Heck-type coupling occurring between the product 63 and another molecule of boronic acid. This particular observation led to a secondary project fully detailed in Chapter 5.

N-Heterocyclic carbenes (NHCs) were also studied as monodentate ligands (Table 2–19). A rhodium(I) catalyst was prepared with a \( N,N \)-bismesitylimidazoylidene ligand IMes according to reported procedure.\(^{94} \) The Rh(IMes)(cod)Cl catalyst was active only if the halide anion was stripped with a silver salt source (entries 2 and 3). Again, regioselectivity was not an issue; only the branched product 59a could be detected by \(^1\)H NMR. A brief survey of the reaction conditions showed that water shuts down the reaction, and that a base is necessary (entries 5 and 7).

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### Table 2-19: Studies of the Regiochemistry of the Allylic Substitution with a Rh-NHC complex.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Additives</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Regio B : L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>-</td>
<td>Dioxane</td>
<td>18</td>
<td>50 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Rh(IMes)(cod)Cl</td>
<td>-</td>
<td>Dioxane</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Rh(IMes)(cod)Cl</td>
<td>AgSbF$_6$</td>
<td>Dioxane</td>
<td>&gt;10</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>Rh(IMes)(cod)Cl</td>
<td>AgBF$_4$</td>
<td>Dioxane</td>
<td>26</td>
<td>20 : 1</td>
</tr>
<tr>
<td>5</td>
<td>Rh(IMes)(cod)Cl</td>
<td>AgBF$_4$ + no base</td>
<td>Dioxane</td>
<td>&lt;10</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>Rh(IMes)(cod)Cl</td>
<td>AgBF$_4$ + Zn(OTf)$_2$</td>
<td>Dioxane</td>
<td>29</td>
<td>20 : 1</td>
</tr>
<tr>
<td>7</td>
<td>Rh(IMes)(cod)Cl</td>
<td>AgBF$_4$ + Et$_3$N</td>
<td>Dioxane + H$_2$O$^d$</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Rh(IMes)(cod)Cl</td>
<td>AgBF$_4$</td>
<td>Dioxane + DCM$^e$</td>
<td>26</td>
<td>20 : 1</td>
</tr>
<tr>
<td>9</td>
<td>Rh(IMes)(cod)Cl</td>
<td>AgBF$_4$</td>
<td>PhH</td>
<td>18</td>
<td>20 : 1</td>
</tr>
</tbody>
</table>

*Reaction were performed using 58a (0.135 mmol) with Rh catalyst (10 mol%), boronic acid (2 equiv), 1 equiv. base, 15 mol% silver salt in solvent (0.20 M) under an Ar atmosphere. $^b$ Isolated yield of carbonates. $^c$ Determined by $^1$H NMR of purified mixture; B: branched; L: linear. $^d$ Used a 10:1 mixture of dioxane:H$_2$O. $^e$ Used a 1:1 mixture of solvents.

Although the yields are not high, many factors suggest additional experiments are worth exploring with a Rh-NHC catalyst. Namely, the reaction's high regioselectivity, the reaction profile is clean, and there is potential for asymmetry with a chiral NHC. Moreover, a Rh-NHC system should make it possible to decrease catalyst loading due to the robustness of the complex. Rh(IMes)(COD)Cl is probably not optimal because the ancillary COD ligand may impede the reaction by competing with the substrate for binding. Thus, the rational design of a pre-catalyst should lead to a more active catalytic system. For reasons of time, further investigation of these encouraging results were left for a new student.
2.8 Conclusion

We reported a full study of the Rh(I)-catalyzed AAS of symmetrical allylic diols. A new catalytic method was established to add stable $sp^3$ C-nucleophiles to activated alkenes. A range of chiral homoallylic alcohols can be synthesized in unprecedented enantioselectivity from simple cyclic allylic diol derivatives. The above studies demonstrate that allylic biscarbonates are competent substrates, even though the alkenes lack bicyclic strain, thereby extending the generality of our previous work. The commercial availability of starting materials and reagents makes this protocol useful as it yields chiral building blocks in one step.

We found that the regioselectivity of the products can be tuned by simply changing the bisphosphine ligand and solvent system. For example, P-PHOS ligands favor the formation of homoallylic alcohol products with a 1,2-trans relationship, whereas Cl-MeO-BIPHEP favor the 1,4-trans regiosomeric products. Moreover, a route to chiral 3,4-trans substituted piperidines was demonstrated in five steps. The synthesis features the rhodium-catalyzed AAS as a key step to establish two neighbouring trans stereocenters in 91% ee.

Significant challenges remain with respect to the enantioselective addition of vinyl nucleophiles to cyclic allylic diol derivatives. Despite its strong potential synthetic utility, the catalytic enantioselective addition of vinylmetals to activated alkenes is still an underdeveloped class of transformations. Moreover, the addition to more substituted alkenes remains to be achieved.

2.9 Outlook

Following the above studies, we will aim to expand the reaction to more challenging substrates. Our strategy would provide a unique access to valuable building blocks for synthetic endeavours, e.g., medicinal chemistry. Scheme 2-19 depicts some substrates of interest. Extending the method to trisubstituted alkenes could give rise to two different products, both of which are chiral, and may lead to the formation of chiral quaternary center. Also, symmetrical dienyl dicarbonates offer interesting synthetic opportunities. Especially meso cyclohexadienylidio derivatives, since a sequential bis-substitution would proceed through the intermediacy of a second meso molecule and chirality would be effectively controlled in the second step. Thus it may be possible to add two distinct

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nucleophiles in one catalytic operation, provided that the substitution rates are different enough.

![Scheme 2–19 Proposed methodologies for future work.](image)

In the case of linear dicarbonates, preliminary results with monodentate ligands displayed the best regioselectivity so far (Section 2.8). It may be worth exploring the potential of chiral NHC ligands for the reaction, as this field is rapidly gaining interest. The major advantage here is the stability of NHC ligands compared to phosphine, which may allow to lower catalyst loadings – a highly desirable goal.
2.10 Experimental Section

General Experimental Procedures. All reactions were carried out under argon atmosphere, in flame-dried, single-neck, round-bottom flasks fitted with rubber septa, with magnetic stirring unless otherwise noted. No experiment was carried out in a glovebox, unless otherwise noted. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C at 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with Silicycle™ normal phase glass plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was accomplished with 254 nm UV light and/or by immersion in potassium permanganate (KMnO₄), or acidic aqueous-ethanolic vanillin solution, followed by brief heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.96

Materials. [Rh(cod)Cl]₂ was purchased from Strem Chemicals, Inc. and used as received. [Rh(cod)OH]₂ and Rh(Mes)(cod)Cl were prepared from [Rh(cod)Cl]₂ by literature procedures.97 98 Supplies of chiral bisphosphine ligands were generously provided by the following companies: Josiphos and the BIPHEP family from Solvias Inc., Segphos and its analogs from Takasago, and P-Phos families from Digital Chemical Specialty. Other chiral phosphine ligands were purchased from Strem Chemicals Inc. Boronic acids were obtained from Combi-Blocks or Aldrich and used without further purification without further purification, unless otherwise noted. Tetrahydrofuran and 1,4-dioxane were purified by distillation under N₂ followed by brief heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.96

Instrumentation. Proton nuclear magnetic resonance spectra (¹H NMR) spectra and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 23 °C with a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N-400 probe, a Varian 400 MHz NMR spectrometer equipped with ATB8123-400 probe, or a Bruker 400 Advance3 Nanobay (400 MHz) NMR spectrometer equipped with BBFO-ATM probe. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, CHDCl₃: δ 5.29, C₆D₆: δ 7.15, CD₂OD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0, CH₂Cl₂: δ 53.8, C₆D₆: δ 128.0, CD₂OD: δ 49.2). Data are

100 Alternatively, diol 2 is also commercial from a common suppliers.
represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, m = multiplet, br = broad), integration and coupling constant (J, Hz). Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment. High resolution mass spectra were obtained from a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured in a 10.0 cm cell with a Rudolph Autopol IV digital polarimeter equipped with a sodium lamp source (589 nm), and are reported as follows: [α]D T °C (c = g/100 mL, solvent). Reported readings are an average of at least two measurements for each sample. The 500 W flood lamps used in the substrate preparation were bought from a local hardware store, and UV filters were removed.

**Determination of the Enantiomeric Excesses by HPLC Analysis.** The enantiomeric excess (ee) of substituted products was determined after hydrolysis of the carbonate to the parent alcohols, followed by HPLC analysis of the crude reaction mixture (see following section for details). Unless otherwise noted, enantiomeric excesses of the deprotected products were determined using OD-H or AD-H columns from Chiralcel Technologies (fitted with a 1.0 cm guard column of the same chiral solid phase), flow rate 1.0 mL/min, 26°C, injection 5.0 uL of a ~1.5 mg/mL solution, typically using a gradient of i-PrOH:hexane solvent mixture: 2%, 0 to 10 min; 2–5% gradient, 10 to 20 min; 5–10% gradient, 20 to 25 min; 10%, 25–30 min (for initial finding of separation conditions).

Absolute stereochemistry of the products was assigned by MTPA ester derivatives¹⁰³ of 6, and by correlation of optical rotations with reported data of known compounds 6 and 7.¹⁰⁴

**2.10.1 Experimental Procedures**

**• General Procedure A**

Typical preparation of the 1,2-regioisomeric products. To a 1 dram vial equipped with a magnetic stir bar was added rhodium cyclooctadiene hydroxide, [Rh(cod)OH]₂ (3.7 mg, 0.0082 mmol), (S)-Xyl-P-PHOS (14.9 mg, 0.020 mmol) and Cs₂CO₃ (53 mg, 0.164 mmol). The vial was sealed and flushed with argon, then distilled THF (0.8 mL) was added and the mixture was stirred for 30 min on a 60 °C oil bath. *cis*-2-cyclopentene-1,4-diethyl carbonate 3a (40 mg, 0.164 mmol) and phenylboronic acid (40 mg, 0.32 mmol) were added together as a solution in distilled THF (0.8 mL) and the reaction mixture was heated on a 60°C oil bath. After 1 h, THF (5 mL) and hexanes (5 mL) were added to the reaction mixture and it was concentrated with silica gel, then applied to the top of a column of silica gel and purified by column chromatography (5 to 20% EtOAc/hexane as elution gradient). An inseparable

¹⁰³ See reference 12.
mixture of the mono-carbonates 4a and 5a was recovered as a colourless oil, 33 mg (87%). $^1$H NMR analysis revealed an isomer ratio of 92:8 for the 1,2-product 4a over the 1,4-product 5a. The enantiomeric excess was determined on the deprotected alcohols (see Procedure C).

**GENERAL PROCEDURE B**

Typical preparation favoring the 1,4-regioisomeric products. In a KIMAX 13x135 mm screw-cap tube equipped with a magnetic stir bar were weighed [Rh(cod)OH]$_2$ (7.4 mg, 0.0164 mmol) and (S)-Cl-MeO-BIPHEP (25.6 mg, 0.039 mmol). The tube was equipped with a screw-cap septum and flushed with argon, then benzene$^{105}$ (0.30 mL) was added and the mixture was stirred on a 60 °C oil bath for 15 min; to yellow solution turned to dark orange. Meanwhile, a solution of cis-2-cyclopentene-1,4-diethyl carbonate 3a (80 mg, 0.32 mmol) in 0.40 mL was prepared. The substrate solution was canulated to the premixed complex solution at 60°C; a slight darkening of the reddish solution occurred. Followed by phenylboronic acid (80 mg, 0.64 mmol) and Cs$_2$CO$_3$ (80 mg, 0.26 mmol) added together as solids, by rapidly opening the screw cap (by taking the tube out of the oil bath, unscrewing the septum and quick addition of solids while minimizing the vessel exposition to air; the long tube provides a thick inert atmosphere blanket over the reaction mixture upon solids addition). The reaction vessel was flushed with Ar at r.t. for 2-5 min, then put back to heat at 60 °C for 16 h. Reaction showed near full conversion by TLC (15% EtOAc/Hex; UV and vanillin stain; $R_f$ 3a 0.35, $R_f$ 4a+5a 0.62). To the dark brown reaction mixture was added 5 mL Et$_2$O (heavy ppt) and 10 mL saturated NH$_4$Cl aqueous solution. The decanted aqueous layer was extracted with 3x20 mL Et$_2$O; the combined organic phases were dried with brine and MgSO$_4$, then filtered, and concentrated under reduced pressure. The crude residue was applied to the top of a column of silica gel and purified by column chromatography (5 to 25% EtOAc/hexane as elution gradient). An inseparable mixture of the monocarbonates 4a and 5a was recovered as a colourless oil, 62 mg (82%). $^1$H NMR analysis revealed a 4 : 5 ratio of 1 : 2.8. The enantiomeric excess was determined on the deprotected alcohols (see Procedure C).

Note 1. (S)-biarylphosphines ligands (BINAP, MeO-BIPHEP, and P-PHOS analogs) all lead to the (–) enantiomers, which have the absolute stereochemistry represented in this paper. The use of the (R)-biarylphosphines yield the (+) enantiomers, having the opposite stereochemistry of that represented. We arbitrarily opted to represent the (1R, 2S)-stereochemistry for consistency and to avoid unnecessary complications for the reader.

Note 2. Racemic products were obtained following the same procedure with the achiral BIPHEP.

$^{105}$ Alternatively, toluene or dioxane can be used to obtain similar yields, however, the regioselectivity will not be optimimal for the formation of 5.
CHAPTER 2. ENANTIOSELECTIVE DESYMMETRIZATION OF ALLYLIC DIOLS

• **GENERAL PROCEDURE C.**

Typical deprotection of carbonates. The combined 1,2- and 1,4-monocarbonates 4 and 5 were dissolved in MeOH (0.02 M) and K$_2$CO$_3$ (10–14 equiv) was added. The white suspension was stirred at rt until complete conversion (usually < 3 h).\(^{106}\) One volume of NH$_4$Cl saturated aqueous solution was added and extracted three times with Et$_2$O. The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield the crude alcohols 6 and 7. The 1,2- and 1,4-regioisomers 6 and 7 were separated and purified by column chromatography on silica gel (10–25–40% gradient of EtOAc/hexane). The enantioenrichment of each regioisomer was measured on the isolated products, and compared to racemic samples.

• **TYPICAL PROCEDURE D:**

Bis-acylation of (Z)-butene-1,4-diol. (Z)-but-2-ene-1,4-diol (5.0 g, 56.7 mmol) was suspended in 280 mL DCM (oil, non miscible). The flask was capped with a septum, then purged with a stream of N$_2$, and cooled to 5 °C using an ice bath. Ethyl chloroformate (16.0 mL, 3.0 equiv) was added via syringe, followed by careful addition of pyridine (16.0 mL, 4.0 equiv), ensuring a controlled exotherm. From colorless, the solution turned to bright pink, with formation of white precipitate. The reaction was allowed to warm up to r.t. and was complete after 4 h by TLC (alternatively, longer stirring did not affect the reaction; i.e. overnight). The reaction was extracted successively with 200, 100, and 50 mL portions of saturated aq. NH$_4$Cl. The combined aqueous layer was extracted with 200 mL Et$_2$O. The combined organic layer was dried with brine, then MgSO$_4$, filtered and concentrated under reduced pressure to yield 17 g of an amber fluid crude oil. The crude was purified by silica gel chromatography using 10% EtOAc/pentane. $^{58a}$ was recovered as a colorless fluid oil, 13.2 g (99% yield).

• **TYPICAL PROCEDURE E:**

Asymmetric Allylic Substitution of Linear Allylic Dicarbonates. In a glove-box, [Rh(cod)OH]$_2$ (3.9 mg, 0.0086 mmol, 0.05 equiv), ligand (0.0206 mmol, 0.12 equiv), Cs$_2$CO$_3$ (56 mg, 0.172 mmol) and Zn(OTf)$_2$ (12.5 mg, 0.0344 mmol, 0.20 equiv) were weighed into an 8 mL oven-dried microwave tube. The tube was sealed with a septum and a crimp, and taken out of the glovebox. Dioxane was added (1.0 mL) and the resulting mixture was then

\(^{106}\) It was verified that longer reaction times did not affect the ee (up to 48h at rt).
stirred for 10-15 minutes at r.t. Meanwhile, the allylic carbonate (0.172 mmol) and the boronic acid (0.344 mmol) were weighed into a 4 mL vial. The vial was sealed, purged with argon, and 1.00 mL of dioxane was added. The substrate 58a and boronic acid solution was transferred via syringe to the sealed tube containing the premixed catalyst solution. The reaction mixture was then heated at 50 °C for 20 h. The reaction mixture was diluted with 10 mL of EtOAc, filtered through a silica pad (~2 g), and washed with ~50 mL EtOAc. The filtrate was concentrated under reduced pressure and purified by flash chromatography (5 to 15% EtOAc/pentane as elution gradient, depending on the Rf of the product). The branched and linear products, B and L, were isolated as an inseparable mixture. Regioselectivity was determined by 1H NMR analysis. Characterization was performed on the deprotected alcohols (see Typical Procedure F).

• Typical Procedure F:

Deprotection of linear homoallylic alcohols. In order to obtain the desired branched product, the mixture and Cs\textsubscript{2}CO\textsubscript{3} (10 equiv) were weighed into a 4 mL vial. Methanol (2 mL) was added and the solution was stirred at r.t. for 3 hours. The solvent was then concentrated under reduced pressure and the residue was retaken in 15 mL of EtOAc. The organic layer was washed with aqueous NH\textsubscript{4}Cl (saturated, 15 mL). The combined aqueous layer was extracted with Et\textsubscript{2}O (15 and 10 mL), and the combined organic layers were concentrated under reduced pressure. The crude oil was then purified via flash chromatography (10-25% EtOAc/pentane as elution gradient, depending on the Rf of the product) and isolated as colorless oil. Some compounds were found to be sensitive to silica in the alcohol form.

2.10.2 Characterization Data

cis-Cyclopent-4-ene-1,3-diol (2). Modified from a literature procedure,\textsuperscript{5} dry MeOH (1.84 L) was placed in a 3L 3-necked roundbottom flask fitted with a cold finger condenser. Thiourea (14 g, 184 mmol) and rose bengal (367.5 mg) were added to the reaction and the suspension was cooled down to 5 ºC. O\textsubscript{2} was bubbled through the solution, then the cold finger was filled with acetone and dry ice. Freshly distilled cyclopentadiene (20 mL, 244 mmol) was kept on ice, until the addition. Half of the cyclopentadiene was added to the flask under vigorous stirring, and irradiation was started immediately using two 500 W flood lamps. After 30 min, the remainder of the cyclopentadiene was added. After 4 h, O\textsubscript{2} bubbling and irradiation were stopped. On this scale, we found the distillation procedure reported to be highly inconvenient as the product crystallized on all surfaces; instead, the solvent was evaporated under reduced pressure and the remaining solid was dissolved and recrystallized sequentially in MeOH, THF and Et\textsubscript{2}O, until the 1H NMR analysis of the
filtrate looked clean. At that point, the product was a dark red paste (20.8 g, 85%), which was used as is for the next step, where the less polar dicarbonate is much easier to purify. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \&: 5.74 (s, 2H), 4.84 (dd, 2H, \(J = 7.8, 2.0\) Hz), 2.97-2.86 (m, 1H), 1.28-1.20 (m, 1H) ppm.

**Cyclopent-4-ene-1,3-diy diethyl dicarbonate (3a).** In a 1L 3-necked round-bottom flask, half of the crude diol 2 (5 g, 50 mmol) was poured in and suspended in dry DCM (50 mL). Half of the pyridine (210 mmol, 17 mL) was added to the flask. The remaining of the diol (50 mmol, 5 g) was added, along with more DCM (450 mL) and pyridine (17 mL, 210 mmol). The reaction was allowed to cool down to 5 °C, under a N\(_2\) atmosphere. Ethyl chloroformate (30 mL, 315 mmol) was added slowly, keeping the temperature constant between 5-10 °C. The reaction was allowed to warm up to room temperature and stirred until complete by TLC analysis. The reaction was washed with 

\[\text{1N aqueous HCl} \times 4\]

and the aqueous layers were extracted with EtOAc/Hex to give a clear, colourless oil (14 g, 55%). The combined organic layers were washed with brine, dried with MgSO\(_4\), filtered, and the solvent was evaporated under reduced pressure to give a yellow oil. The crude oil was loaded on a silica column and eluted with 10% EtOAc/Hex to give a clear, colourless oil (33.0 mg), showing a 18:1 ratio of \(5a\) and (1R, 2S) cyclopent-4-ene-1,3-diy diethyl dicarbonate (3a). According to General Procedure A; the inseparable regioisomers 4a and 5a were obtained as a colourless oil in 87% yield (33.0 mg), showing a 18:1 ratio of 4a by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols.

**1,2-regioisomer 4a:** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \&: 7.34-7.21 (5H, m), 5.94 (1H, ddd, \(J = 5.9, 4.1, 2.0\) Hz), 5.82 (1H, ddd, \(J = 5.8, 4.2, 2.0\) Hz), 5.04 (1H, dt, \(J = 6.6, 2.6\) Hz), 4.20 (2H, q, \(J = 7.1\) Hz), 4.00 (1H, br, s), 2.92 (1H, ddd, \(J = 17.8, 6.3, 4.0, 2.3\) Hz), 2.48 (1H, dddd, \(J = 17.8, 7.9, 5.1, 2.4\) Hz), 1.31 (3H, t, \(J = 7.1\) Hz). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \& 155.1, 141.3, 132.0, 129.6, 128.8, 128.7, 127.1, 85.2, 64.1, 57.8, 39.0, 14.5. IR (NaCl, neat film): 3061, 3030, 2983, 2850, 1743, 1451, 1374, 1261, 1170, 1105, 1012 cm\(^{-1}\).

**1,4-regioisomer 5a:** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \&: 7.37-7.23 (5H, m), 6.12 (1H, dd, \(J = 5.6, 2.0\) Hz), 6.01 (1H, dt, \(J = 5.5, 2.3\) Hz), 5.70 (1H, ddd, \(J = 7.1, 4.1, 2.0\) Hz), 4.13 (2H, q, \(J = 7.1\) Hz), 4.09-4.05 (1H, m), 2.46-2.36 (1H, m), 2.06 (1H, ddd, \(J = 13.0, 7.1, 5.9\) Hz), 1.25 (3H, t, \(J = 7.1\) Hz). 18

\[^{(1R,2S)-trans-2-phenylcyclopent-3-enol (6).}^1\] Deprotected and isolated as described in the **General Procedure C.** Colourless oil. The characterization data was fully concordant with that already reported in the literature.\(^{108,109}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \&: 7.31-7.14 (5H, m), 5.87 (1H, ddt, \(J = 6.2, 4.4, 2.2\) Hz), 5.75 (1H, ddd, \(J = 6.1, 4.2, 2.1\) Hz), 4.29-4.25 (1H, m), 3.74 (1H, ddd, \(J = 5.7, 4.0, 2.0\) Hz), 3.13 (3H, t, \(J = 7.5\) Hz), 1.25 (3H, t, \(J = 7.1\) Hz).


3.7, 1.8 Hz), 2.78 (1H, ddd, J = 16.9, 6.3, 3.9, 1.9 Hz), 2.35 (1H, dddd, J = 16.9, 6.1, 3.9, 1.8 Hz), 1.84 (1H, br. s, alcohol). 13C NMR (100 MHz, CDCl3): δ 142.6, 132.3, 129.5, 128.6, 127.3, 126.6, 80.9, 60.7, 41.3. IR (NaCl, neat film): 3328, 3061, 2922, 2854, 1650, 1557, 1537, 1492, 1453, 1052 cm−1. MS m/z (rel. intensity): 160 (M+, 84), 117 (50), 104 (100), 91 (70). HRMS (ESI)+: Calc’d for C11H12O [M+]: 160.0888; found = 160.0892. The ee was determined by HPLC analysis: 92% ee (Chiralcel OD-H, hexane/iPrOH = 99/1, 1.0 mL/min); tR = 31.1 min (15,2R) minor; tR = 38.2 min (1R,2S) major. [α]D26.39 = −228 (c 1.60, CHCl3, for 92% ee).110,111

(1R,4R)-trans-4-phenylcyclopent-2-enol (7). Deprotected and isolated as described in the General Procedure C. Colourless oil. The characterization data was fully concordant with that already reported in the literature.109 1H NMR (400 MHz, CDCl3): δ 7.25-7.05 (5H, m), 6.00-5.94 (2H, m), 5.00-4.96 (1H, m), 4.08 (1H, ddt, J = 5.9, 3.5, 1.9 Hz), 2.22 (1H, ddd, J = 14.0, 8.0, 2.7 Hz), 2.03 (1H, ddd, J = 14.0, 6.9, 5.5 Hz), 1.47 (1H, br. s).

(1R, 2S)-trans-2-(4′-Trifluoromethylphenyl)-cyclopent-3-enyl ethyl carbonate (12) and (1R,4R)-trans-4-(4′-Trifluoromethylphenyl)-cyclopent-2-enyl ethyl carbonate (30).

According to General Procedure A: the inseparable regioisomers 12 and 30 were obtained as a colourless oil in 86% yield (42 mg), showing a 13:1 ratio of 12:30 by 1H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols.

According to General Procedure B: the crude product was purified by column chromatography. The inseparable regioisomers were obtained as a colourless oil in 81% yield (80 mg), showing a 1:2.8 ratio of 12:30 by 1H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols.

1,2-regioisomer 12: 1H NMR (400 MHz, CDCl3): δ 7.56 (2H, d, J = 8.1 Hz), 7.34 (2H, d, J = 8.0 Hz), 5.99 (1H, ddd, J = 5.9, 4.2, 2.1 Hz), 5.80 (1H, ddd, J = 6.0, 4.3, 2.2 Hz), 5.01 (1H, dt, J = 6.7, 2.8 Hz), 4.21 (2H, q, J = 7.1 Hz), 4.07-4.03 (1H, br. s), 2.92 (1H, dddd, J = 17.9, 6.6, 4.1, 2.2 Hz), 2.56-2.48 (1H, m), 1.32 (3H, t, J = 7.1 Hz).

1,4-regioisomer 30: 1H NMR (400 MHz, CDCl3): δ 7.55 (2H, d, J = 8.2 Hz), 7.24 (2H, d, J = 8.7 Hz), 6.19-6.11 (2H, m), 5.76 (1H, ddd, J = 9.1, 4.0, 2.0 Hz), 4.25-4.16 (1H, m), 4.21 (2H, q, J = 7.1 Hz), 2.54-2.46 (1H, m), 2.11 (2H, ddd, J = 14.6, 7.1, 5.6 Hz), 1.31 (3H, t, J = 7.1 Hz).

(1R,2S)-trans-2-(4′-Trifluoromethylphenyl)-cyclopent-2-enol (12b).

Deprotected and isolated as described in General Procedure C. The alcohol was quantitatively isolated as a colourless oil. 1H NMR (400 MHz, CDCl3): δ 7.56 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.1 Hz) 5.95 (1H, ddd, J = 5.9, 4.3, 2.2 Hz), 5.77 (1H, ddd, J = 6.0, 4.2, 2.1 Hz), 4.28 (1H, dt, J = 6.9, 4.3 Hz), 3.85-3.82 (1H, m), 2.82 (1H, dddd, J = 17.0, 6.8, 3.9, 2.0 Hz), 2.40 (1H, dddd, J = 17.0, 6.1, 4.3, 1.9 Hz), 1.83 (1H, br. s, alcohol). 13C NMR (100 MHz, CDCl3): δ 146.7, 131.4, 130.4, 127.7, 125.5 (q, J = 3.8 Hz, CF3), 122.9, 80.8, 60.4, 41.5. IR (NaCl, neat film): 3324 (br.), 3061, 2922, 2850, 1618, 1418, 1328, 1163, 1126, 1070, 1018 cm−1. MS m/z (rel. intensity): 228 (M+, 98), 210 (30), 172 (100), 159 (52), 131 (20), 115 (19). HRMS (ESI)+: Calc’d for C12H12F3O [M+]: 228.07200; found = 228.076170. [α]D28.7 = +165 (c

The enantiomeric ligands (R)-Xyl-PHOS or (R)-BINAP gave the corresponding (+)-trans-cyclopentenol.

The absolute stereochemistry of 4a was assigned by the Mosher method on the MTPA ester derivative of 4a (2 equiv (S)-MTPA acid, 2 equiv DCC and 0.2 equiv DMAP were stirred in DCM at rt for 10h; quantitative yield). For details, see: Dale, J. A., Mosher, H. S. J. Am. Chem. Soc. 1973, 95, 512.

108 The enantiomeric ligands (R)-Xyl-PHOS or (R)-BINAP gave the corresponding (+)-trans-cyclopentenol.

111 The absolute stereochemistry of 4a was assigned by the Mosher method on the MTPA ester derivative of 4a (2 equiv (S)-MTPA acid, 2 equiv DCC and 0.2 equiv DMAP were stirred in DCM at rt for 10h; quantitative yield). For details, see: Dale, J. A., Mosher, H. S. J. Am. Chem. Soc. 1973, 95, 512.
0.80, CHCl₃) for an enantiomeric ratio was 96.4:3.6, as determined by HPLC analysis (Chiracel OD-H; tᵣ = 14.9 min (1S,2R) minor; tᵣ = 17.0 min (1R,2S) major.

**(1R,4R)-trans-4-(4'-Trifluoromethylphenyl)-cyclopent-2-enol (30b).**

Deprotected and isolated as described in General Procedure C. Colourless oil. ⁱH NMR (400 MHz, CDCl₃): δ 7.54 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.0 Hz), 6.09 (1H, dd, J = 5.7, 2.1 Hz), 6.03 (1H, ddd, J = 7.6, 2.2, 0.6 Hz), 5.09–5.03 (1H, m), 4.29–4.18 (1H, m), 2.32 (1H, ddd, J = 14.3, 8.0, 2.7 Hz), 2.08 (1H, ddd, J = 14.1, 6.9, 5.5 Hz), 1.57 (1H, brs). ¹³C NMR (100 MHz, CDCl₃): δ 149.1 (d, J = 15.5 Hz), 138.3 (2d), 135.1 (2d), 128.7, 127.6 (2d), 125.7 (q, J = 3.7 Hz, CF₃), 77.5, 49.9, 44.1. ¹⁹F NMR (375 MHz, CDCl₃): δ –62.8 (s, 3F). IR (NaCl, neat film): 3332 (br), 3057, 2967, 2936, 1619, 1416, 1254, 1163, 1122, 1068, 1017, 832, 790 cm⁻¹. MS (EI+) m/z (rel. intensity): 228.1 (M⁺, 8), 210 (100), 183 (12), 141 (89), 139 (16), 115 (45), 63 (17). HRMS (ESI): Calc’d for C₁₂H₁₅OF₃ [M⁺]: 228.0762; found = 228.0765. [α]D₉⁸.⁹ = +210 (c 1.35, CHCl₃) for an enantiomeric ratio was 99.5:0.5, as determined by HPLC analysis (Chiracel OD-H; tᵣ = 19.1 min (+), tᵣ = 20.6 min (−)).

**(1R, 2S)-trans-2-(4-Acetylphenyl)-cyclopent-3-enyl ethyl carbonate (13).**

According to General Procedure A. The inseparable regiosomers were obtained as a colourless oil in 94% yield (42 mg), showing a > 20:1 ratio of 4:5 by ¹H NMR spectroscopy. The regiosomers were submitted directly to the deprotection conditions and characterized as the free alcohols. *Major regioisomer 13:* ¹H NMR (400 MHz, CDCl₃): δ 7.91 (2H, d, J = 8.3 Hz), 7.32 (2H, d, J = 8.3 Hz), 5.98 (1H, ddd, J = 5.9, 4.2, 2.1 Hz), 5.80 (1H, ddd, J = 5.9, 4.0, 2.1 Hz), 5.03 (1H, dt, J = 6.7, 2.8 Hz), 4.20 (2H, q, J = 7.1 Hz), 4.05 (1H, m), 2.92 (1H, ddd, J = 17.9, 6.7, 2.0 Hz), 2.58 (3H, s), 2.52 (1H, ddd, J = 17.9, 5.1, 0 Hz), 1.31 (3H, t, J = 7.1 Hz).

**(1R,2S)-trans-2-(4-Acetylphenyl)-cyclopent-3-enol (13b).**

Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.91 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.4 Hz) 5.95 (1H, ddd, J = 5.9, 4.2, 2.0 Hz), 5.77 (1H, ddd, J = 6.0, 4.0, 2.0 Hz), 4.27-4.22 (1H, m), 3.84 (1H, br. s), 2.83 (1H, ddd, J = 17.0, 6.8, 2.2 Hz), 2.59 (3H, s), 2.41 (1H, ddd, J = 17.0, 6.2, 4.1, 2.2 Hz), 1.85 (1H, br. s, alcohol). ¹³C NMR (100 MHz, CDCl₃): δ 197.9, 148.5, 135.6, 131.4, 130.3, 128.7, 127.6, 80.7, 60.6, 41.5, 26.6. IR (NaCl, neat film): 3390 (br), 3056, 3003, 2920, 2844, 1682, 1606, 1560, 1417, 1361, 1273 cm⁻¹. MS m/z (rel. intensity): 202 (M⁺, 57), 187 (100), 173 (37), 159 (17), 131 (62), 115 (35), 91 (28). HRMS (ESI): Calc’d for C₁₂H₁₀O₃ [M⁺]: 202.0998; found = 202.0998. The ee was determined by HPLC analysis: 88% ee (Chiracel OD-H, hexane/iPrOH = 96/3, 1.0 mL/min); tᵣ = 39.4 min (1S,2R) minor; tᵣ = 49.2 min (1R,2S) major.

**(1R,4R)-trans-4-(4-Acetylphenyl)-cyclopent-2-enol (13c).**

Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.88 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.2 Hz) 6.09 (1H, ddd, J = 7.5, 5.3, 2.2 Hz), 6.04 (1H, ddd, J = 7.4, 5.7, 2.0 Hz), 5.09-5.04 (1H, m), 4.23-4.19 (1H, m), 2.58 (3H, s), 2.32 (1H, ddd, J = 14.3, 8.1, 2.6 Hz), 2.09 (1H, ddd, J = 13.8, 6.8, 4.5 Hz), 1.59 (1H, br. s, alcohol). ¹³C NMR (100 MHz, CDCl₃): δ 197.7, 150.5, 138.2, 135.5, 134.8, 128.8, 127.3, 110.0, 49.9, 43.8, 26.6.
(1R,2S)-trans-2-(4'-Methoxycarbonylphenyl)-cyclopent-3-enyl ethyl carbonate (14) and (1R,4R)-trans-4-(4'-Methoxycarbonylphenyl)-cyclopent-2-enyl ethyl carbonate (34).

According to General Procedure A. The inseparable regioisomers 14 and 34 were obtained as a colorless oil in 95% yield (45 mg), showing a >20:1 ratio of 14:34 by 1H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols.

L2-regioisomer 14: 1H NMR (400 MHz, CDCl3): δ 7.97 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.2 Hz), 5.98 (1H, ddd, J = 5.9, 4.2, 2.2 Hz), 5.80 (1H, ddd, J = 5.9, 4.0, 2.0 Hz), 5.04 (1H, ddd, J = 6.3, 2.5, 2.5 Hz), 4.20 (2H, q, J = 7.1 Hz), 4.00 (1H, br. s), 2.92 (1H, dddd, J = 17.8, 6.3, 4.0, 2.3 Hz), 2.41 (1H, dddd, J = 17.8, 7.9, 5.1, 2.3 Hz), 1.31 (3H, t, J = 7.1 Hz). 13C NMR (100 MHz, CDCl3): δ 166.9, 154.9, 146.4, 131.1, 130.1, 129.9, 128.9, 127.6, 84.6, 64.0, 57.6, 52.0, 38.7, 14.2. IR (NaCl, neat film): 3061, 2982, 2925, 2853, 1741, 1722, 1651, 1436, 1374, 1262 cm⁻¹.

(1R,2S)-trans-2-(4-Methoxycarbonylphenyl)-cyclopent-3-enol (14b).

Colourless oil. 1H NMR (400 MHz, CDCl3): δ 7.97 (2H, d, J = 8.2 Hz), 7.25 (2H, d, J = 8.3 Hz) 5.94 (1H, ddd, J = 6.2, 4.4, 2.2 Hz), 5.76 (1H, ddd, J = 6.3, 4.4, 2.2 Hz), 4.28 (1H, dt, J = 7.1, 1.4 Hz), 3.90 (3H, s), 3.85-3.82 (1H, m), 2.81 (1H, dddd, J = 17.1, 6.8, 3.7, 2.2 Hz), 2.39 (1H, dddd, J = 17.1, 5.9, 3.9, 2.2 Hz), 1.95 (1H, br. s, alcohol). 13C NMR (100 MHz, CDCl3): δ 167.0, 148.0, 131.5, 130.2, 129.9, 128.6, 127.3, 80.8, 60.7, 52.0, 41.5. IR (NaCl, neat film): 3418 (br.), 3054, 2998, 2949, 2845, 1717, 1651, 1609, 1436, 1282, 1179 cm⁻¹. MS m/z (rel. intensity): 218 (M⁺, 100), 200 (14), 187 (40), 162 (67), 131 (95), 115 (47). HRMS (ESI)⁺: Calc’d for C24H14O3 [M⁺]: 218.0943; found = 218.0947. The ee was determined by HPLC analysis: 90% ee (Chiralcel OD-H, hexane/iPrOH = 96/4, 1.0 mL/min); tᵣ = 19.5 min (15,2R) minor; tᵣ = 20.4 min (1R,2S) major. [α]D²⁴ = −354 (c 0.90, CHCl₃, for 90% ee).

(1R,2S)-trans-2-(4'-Chlorophenyl)-cyclopent-3-enyl ethyl carbonate (15).

According to General Procedure A: the inseparable regioisomers were obtained in 53% yield (23 mg), showing a 13:1 ratio of 4:5 by 1H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols.

L2-regioisomer 15: 1H NMR (400 MHz, CDCl3): δ 7.27 (2H, d, J = 8.8 Hz), 7.16 (2H, d, J = 8.3 Hz), 5.95 (1H, ddd, J = 5.9, 4.3, 2.0 Hz), 5.78 (1H, ddd, J = 5.9, 4.3, 2.0 Hz), 4.98 (1H, dt, J = 6.6, 2.8 Hz), 4.20 (2H, q, J = 7.1 Hz), 3.99-3.94 (1H, br. s), 2.89 (1H, dddd, J = 17.8, 6.6, 4.0, 2.2 Hz), 2.49 (1H, dddd, J = 17.8, 4.4, 2.8, 1.2, Hz), 1.32 (3H, t, J = 7.1 Hz).
(1R, 2S)-trans-2-(4’-Chlorophenyl)-cyclopent-3-enol (15b).
Deprotected and isolated as described in General Procedure C. Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.27 (2H, d, J = 8.4 Hz), 7.11 (2H, d, J = 8.2 Hz) 5.91 (1H, ddd, J = 5.9, 4.5, 2.2 Hz), 5.74 (1H, ddd, J = 6.0, 4.2, 2.1 Hz), 4.23 (1H, dt, J = 6.7, 4.2 Hz), 3.74 (1H, qn, J = 1.9 Hz), 2.80 (1H, dddd, J = 17.0, 6.8, 2.2, 1.9 Hz), 2.37 (1H, dddd, J = 17.3, 6.0, 4.2, 2.1 Hz), 1.84 (1H, br. s, alcohol). ¹³C NMR (100 MHz, CDCl₃): δ 141.0, 132.4, 131.8, 130.0, 128.7, 80.9, 60.0, 41.4. IR (NaCl, neat film): 3317 (br.), 3057, 2924, 2847, 1651, 1491, 1406, 1318, 1019 cm⁻¹. MS m/z (rel. intensity): 194 (M⁺, 75), 176 (13), 151 (26), 138 (100), 125 (40), 115 (39), 91 (18). HRMS (ESI⁺): Calc’d for C₁₃H₁₃ClO [M⁺]: 194.049843; found = 194.049690. The ee was determined by HPLC analysis: 90% ee (Chiralcel OD-H, hexane/iPrOH = 99/1, 1.0 mL/min), tᵣ = 32.7 min (1S,2R), tᵣ = 36.1 min (1R,2S). [α]°D = −187 (c 0.66, CHCl₃, for 87% ee).

(1R,4R)-trans-2-(4’-Chlorophenyl)-cyclopent-2-enol (15c).
Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.25 (2H, d, J = 8.0 Hz), 7.06 (2H, d, J = 8.6 Hz) 6.05 (1H, dt, J = 5.5, 2.1 Hz), 6.01 (1H, ddd, J = 5.6, 2.0, 0.6 Hz), 5.04 (1H, ddd, J = 7.0, 2.0, 0.7 Hz), 4.12 (1H, ddd, J = 7.4, 4.1, 2.0 Hz), 2.28 (1H, ddd, J = 14.2, 8.0, 2.6 Hz), 2.05 (1H, ddd, J = 14.2, 7.0, 5.5 Hz), 1.60 (1H, br. s, alcohol).

(1R,2S)-trans-2-(4’-Bromophenyl)-cyclopent-3-enyl ethyl carbonate (16).
According to General Procedure A: the inseparable regioisomers were obtained in 35% yield (18 mg), showing a 10:1 ratio of 4:5 by ¹H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. 1H-regioisomer 16: ¹H NMR (400 MHz, CDCl₃): δ 7.35 (2H, d, J = 8.4 Hz), 7.03 (2H, d, J = 8.3 Hz), 5.88 (1H, ddd, J = 6.2, 4.4, 2.3 Hz), 5.71 (1H, ddd, J = 5.9, 4.3, 2.0 Hz), 4.91 (1H, dt, J = 6.6, 2.8 Hz), 4.13 (2H, q, J = 7.1 Hz), 3.90-3.85 (1H, br. s), 2.82 (1H, dddd, J = 17.8, 6.6, 4.0, 2.2, Hz), 2.42 (1H, dddd, J = 17.8, 2.9, 2.0, 1.1, Hz), 1.24 (3H, t, J = 7.1 Hz).

(1R,2S)-trans-2-(4’-Bromophenyl)-cyclopent-3-enol (16b). Deprotected and isolated as described in General Procedure C. Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.40 (2H, m), 7.08-7.04 (2H, m) 5.91 (1H, ddd, J = 6.1, 4.4, 2.2 Hz), 5.74 (1H, ddd, J = 6.1, 3.2, 2.1 Hz), 4.23 (1H, dt, J = 6.6, 2.2 Hz), 3.73 (1H, qn, J = 1.9 Hz), 2.79 (1H, dddd, J = 16.9, 6.6, 3.9, 2.1 Hz), 2.37 (1H, dxs, J = 17.0, 2.0 Hz), 1.86 (1H, br. s, alcohol). ¹³C NMR (100 MHz, CDCl₃): δ 141.8, 132.0, 131.9, 130.3, 129.3, 120.6, 81.1, 60.3, 41.6. IR (NaCl, neat film): 3338 (br.), 3056, 2924, 2848, 1485, 1404, 1315, 1200, 1158, 1072, 1010 cm⁻¹. MS m/z (rel. intensity): 240 (M⁺, 71), 238 (M⁺, 73), 222 (6), 220 (6), 184 (98), 182 (100), 171 (26), 169 (27), 141 (24), 128 (51), 116 (68), 91 (28). HRMS (ESI⁺): Calc’d for C₁₃H₁₃BrO [M⁺]: 237.999326; found = 237.999879. The ee was determined by HPLC analysis: 86% ee (Chiralcel OD-H, hexane/iPrOH = 99/1, 1.0 mL/min); tᵣ = 35.7 min (1S,2R) minor; tᵣ = 40.2 min (1R,2S) major.

(1R, 4R)-trans-2-(4’-Bromophenyl)-cyclopent-2-enol (16c). Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.42-7.38 (2H, m), 7.03-6.98 (2H, m) 6.05 (1H, dt, J = 5.5, 2.1 Hz), 6.00 (1H, ddd, J = 5.6, 1.5 Hz), 5.07-5.01 (1H, m), 4.14-4.07 (1H, m), 2.28 (1H, ddd, J = 14.1, 8.0, 2.7 Hz), 2.04 (1H, ddd, J = 14.1, 7.0, 5.5 Hz), 1.51 (1H, br. s, alcohol).
(1R,2S)-trans-2-(4'-Fluorophenyl)-cyclopent-3-enyl ethyl carbonate (17).

According to General Procedure A: the inseparable regioisomers were obtained as a colourless oil in 46% yield (19 mg), showing a 7:1 ratio of 4:5 by ¹H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. ¹H NMR characterization data was fully concordant with that already reported in the literature.

**12-regioisomer 17:** ¹H NMR (400 MHz, CDCl₃): δ 7.16-7.08 (2H, m), 6.96-6.89 (2H, m), 5.87 (1H, ddd, J = 6.1, 4.2, 2.1 Hz), 5.72 (1H, ddd, J = 5.8, 4.5, 2.3 Hz), 4.91 (1H, dt, J = 6.6, 2.7 Hz), 4.13 (2H, q, J = 7.1 Hz), 3.93-3.89 (1H, br. s), 2.82 (1H, dddd, J = 17.8, 6.3, 4.0, 2.1 Hz), 2.41 (1H, dddd, J = 17.7, 5.2, 3.7, 2.7 Hz), 1.31 (3H, t, J = 7.1 Hz).

(1R,2S)-trans-2-(4'-Fluorophenyl)-cyclopent-3-enyl-3-enol (17b).

Deprotected and isolated as described in General Procedure C. Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.16-7.11 (2H, m), 7.02-6.96 (2H, m) 5.90 (1H, ddd, J = 6.0, 4.4, 2.3 Hz), 5.75 (1H, ddd, J = 6.2, 4.3, 2.1 Hz), 4.26-4.21 (1H, m), 3.75 (1H, sp, J = 1.9 Hz), 2.80 (1H, dddd, J = 16.9, 6.6, 4.4, 2.2 Hz), 2.37 (1H, dssx, J = 16.9, 2.1 Hz), 1.82 (1H, br. s, alcohol). ¹³C NMR (100 MHz, CDCl₃): δ 162.0 (J = 241 Hz), 138.4 (J = 3.3 Hz), 132.3, 129.9, 128.9 (J = 7.8 Hz), 115.5 (J = 20.9 Hz), 81.2, 60.1, 41.6. IR (NaCl, neat film): 3338 (br.), 3059, 2965, 2852, 1603, 1511, 1417, 1223, 1158, 1054, 950 cm⁻¹. MS m/z (rel. intensity): 178 (M⁺, 67), 135 (41), 122 (100), 109 (60), 57 (32). HRMS (ESI)⁺: Calc’d for C₁₁H₁₁FO [M⁺]: 178.079393; found = 178.079724. The ee was determined by HPLC analysis: 86% ee (Chiralcel OD-H, hexane/iPrOH = 99/1, 1.0 mL/min); tᵣ = 28.9 min (1S,2R) minor; tᵣ = 30.9 min (1R,2S) major.

(1R,4R)-trans-2-(4-Fluorophenyl)-cyclopent-2-enol (17c).

Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.10-7.06 (2H, m), 7.00-6.94 (2H, m) 6.05-6.00 (2H, m), 5.08-5.02 (1H, m), 4.15-4.11 (1H, m), 2.28 (1H, dddd, J = 14.3, 8.0, 2.8 Hz), 2.05 (1H, ddd, J = 14.0, 6.9, 5.3 Hz), 1.30 (1H, br. s, alcohol).

(1R,2S)-trans-2-(4'-Methylphenyl)-cyclopent-3-enyl ethyl carbonate (18).

According to General Procedure A: the inseparable regioisomers were obtained in 70% yield (28 mg), showing a 20:1 ratio of 4:5 by ¹H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols.

**12-regioisomer 18:** ¹H NMR (400 MHz, CDCl₃): δ 7.20-7.02 (4H, m), 5.91 (1H, ddd, J = 6.0, 4.1, 2.0 Hz), 5.79 (1H, ddd, J = 5.9, 4.2, 2.1 Hz), 5.00 (1H, dt, J = 6.1, 2.6 Hz), 4.19 (2H, q, J = 7.1 Hz), 3.96 (1H, br. s), 2.80 (1H, dddd, J = 17.7, 6.4, 4.0, 2.3 Hz), 2.47 (1H, br. d, J = 17.7 Hz), 2.32 (3H, s), 1.31 (3H, t, J = 7.1 Hz).

(1R,2S)-trans-2-(4'-Methylphenyl)-cyclopent-3-enyl-3-enol (18b).

Deprotected and isolated as described in General Procedure C. Colourless oil. The characterization data was fully concordant with that already reported in the literature. ¹H NMR (400 MHz, CDCl₃): δ 7.12 (2H, d, J = 7.9 Hz), 7.07 (2H, d, J = 7.9 Hz), 5.89 (1H, ddd, J = 6.1, 4.4, 2.1 Hz), 5.76 (1H, ddd, J = 6.2, 4.2, 2.1 Hz), 4.29-4.24 (1H, m), 3.73 (1H, sp, J = 1.9 Hz), 2.80 (1H, dddd, J = 16.9, 6.2, 4.2, 2.1 Hz), 2.36 (1H, dssx, J = 16.9, 1.9 Hz), 1.79 (1H, d, J = 5.5 Hz, alcohol). ¹³C NMR (100 MHz, CDCl₃): δ 142.5, 138.2, 132.4, 129.4, 128.5, 128.1, 127.4, 124.4, 81.0, 60.7, 41.3. IR (NaCl, neat film): 3342 (br.), 3052, 3022, 2920, 2865, 1650, 1492, 1456, 1272, 1159, 1054 cm⁻¹. The ee was determined by HPLC analysis: 84% ee (Chiralcel OD-H, hexane/iPrOH = 99/1, 1.0 mL/min); tᵣ = 23.0 min (1S,2R) minor; tᵣ = 28.5 min (1R,2S) major.
(1R,2S)-trans-2-(4’-Methoxyphenyl)-cyclopent-3-enyl ethyl carbonate (19).
According to General Procedure A: the inseparable regioisomers were obtained in 49% yield (21 mg), showing a > 20:1 ratio of 19:47 by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols.

1,2-regioisomer 19: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.14 (2\ H, d, J = 8.5\ Hz), 6.84 (2\ H, d, J = 8.8\ Hz), 5.92 (1H, ddd, \(J = 6.0, 4.1, 2.0\ Hz)), 5.80 (1H, ddd, \(J = 6.2, 4.3, 2.0\ Hz)), 4.99 (1H, dt, \(J = 6.6, 2.6\ Hz)), 4.20 (2H, q, \(J = 7.1\ Hz)), 3.95 (1H, br, s), 3.79 (3H, s), 2.89 (1H, ddd, \(J = 17.8, 6.3, 3.9, 2.2\ Hz)), 2.47 (1H, ddd, \(J = 17.8, 4.3, 2.7, 1.1\ Hz)), 1.31 (3H, t, \(J = 7.1\ Hz))

(1R,2S)-trans-2-(4’-Methoxyphenyl)-cyclopent-3-enol (19b).
Colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.10 (2\ H, d, J = 8.8\ Hz), 6.85 (2\ H, d, J = 8.7\ Hz), 5.88 (1H, ddd, \(J = 6.3, 4.4, 2.3\ Hz)), 5.76 (1H, ddd, \(J = 6.0, 4.2, 2.1\ Hz)), 4.24 (1H, dt, \(J = 6.7, 4.1\ Hz)), 3.79 (3H, s), 3.72 (1H, qn, \(J = 1.9\ Hz)), 2.79 (1H, ddd, \(J = 16.9, 6.7, 3.9, 1.8\ Hz)), 2.35 (1H, ddd, \(J = 16.9, 6.3, 4.2, 1.9\ Hz)), 1.85 (1H, br, s, alcohol). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 158.4, 134.5, 132.5, 129.2, 128.3, 81.0, 59.9, 55.3, 41.2\). IR (NaCl, neat film): \(3348\) (br.), \(3055, 3001, 2931, 2907, 2838, 1651, 1614, 1539, 1511, 1459, 1250, 1179\ cm\(^{-1}\)). MS m/z (rel. intensity): \(190 (M^+, 61), 172 (8), 147 (45), 134 (100), 121 (44), 115 (21), 91 (29)\). HRMS (ESI)\(^\dagger\): Calc’d for C\(_{19}\)H\(_{19}\)NO\(_3\)Na [M-\(Na^+\] : 298.1413; found = 298.1412.

(1R,4R)-trans-4-(4’-Methoxyphenyl)-cyclopent-2-enol (47b).
Colourless oil. The characterization data was fully concordant with that already reported in the literature.\(^{109}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.04 (2\ H, d, J = 8.8\ Hz), 6.83 (2\ H, d, J = 8.7\ Hz), 6.01 (1H, dt, \(J = 1.9, 1.6\ Hz)), 5.06-5.01 (1H, m), 4.12-4.08 (1H, m), 3.79 (3H, s), 2.26 (1H, ddd, \(J = 15.1, 8.0, 2.6\ Hz)), 2.06 (1H, ddd, \(J = 14.0, 6.9, 5.5\ Hz))

(1R,2S)-trans-2-(4’-[tert-Butoxycarbonylamino]-phenyl)-cyclopent-3-enyl ethyl carbonate (20).
According to General Procedure A: the inseparable regioisomers were obtained in 32% yield (18 mg), showing a > 20:1 ratio of 4:5 by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. 1,2-regioisomer 20: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.32-7.26 (2\ H, m), 7.15-7.11 (2\ H, m), 6.46 (1H, br, s, NHBoc), 5.91 (1H, ddd, \(J = 6.1, 4.2, 2.1\ Hz)), 5.78 (1H, ddd, \(J = 6.1, 4.2, 2.2\ Hz)), 4.99 (1H, dt, \(J = 6.6, 3.9\ Hz)), 4.19 (2H, q, \(J = 7.1\ Hz)), 3.95 (1H, br, s), 2.88 (1H, ddd, \(J = 17.7, 6.3, 5.0, 2.2\ Hz)), 2.46 (1H, br, d, \(J = 17.8\ Hz)), 1.51 (9H, s), 1.31 (3H, t, \(J = 7.1\ Hz))

(1R,2S)-trans-2-(4’-[tert-Butoxycarbonylamino]-phenyl)-cyclopent-3-enol (20b).
Colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.28 (2\ H, d, J = 8.4\ Hz), 7.10-7.07 (2\ H, m), 6.51 (1H, br, s, NHBoc), 5.88 (1H, ddd, \(J = 5.9, 4.4, 2.2\ Hz)), 5.74 (1H, ddd, \(J = 6.1, 4.2, 2.1\ Hz)), 4.25-4.20 (1H, m), 3.72-3.68 (1H, m), 2.77 (1H, ddd, \(J = 16.9, 6.5, 3.9, 1.9\ Hz)), 2.34 (1H, d sx, \(J = 16.9, 2.0\ Hz)), 2.02 (1H, br, s, alcohol), 1.51 (9H, s). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 153.1, 137.4, 137.1, 132.5, 129.7, 128.0, 119.2, 81.2, 80.7, 60.3, 41.5, 28.6\). IR (NaCl, neat film): \(3317\) (br.), \(3055, 2977, 2931, 2858, 1710, 1530, 1315, 1244, 1161, 1055\ cm\(^{-1}\)). MS m/z (rel. intensity): \(275 (M^+, 20), 219 (73), 163 (51), 132 (26), 119 (35), 57 (100)\). HRMS (ESI)\(^\dagger\): Calc’d for C\(_{19}\)H\(_{19}\)NO\(_3\)Na [M-\(Na^+\] : 298.1413; found =
298.1408. The ee was determined by HPLC analysis: 84% ee (Chiralcel OD-H, hexane/iPrOH = 97/3, 1.0 mL/min); \( t_R = 45.3 \text{ min} \) (1S,2R) minor; \( t_R = 49.0 \text{ min} \) (1R,2S) major.

(1R,2S)-trans-2-(3’-Chlorophenyl)-cyclopent-3-enyl ethyl carbonate (21). General Procedure A: the inseparable regioisomers were obtained in 87% yield (38 mg), showing a 10:1 ratio of 45 by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. \( \text{1,2-regioisomer 21: } \) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.26-7.11 \) (4H, m), 5.96 (1H, ddd, \( J = 6.1, 4.2, 2.1 \text{ Hz} \)), 5.77 (1H, ddd, \( J = 6.2, 4.3, 2.0 \text{ Hz} \)), 5.00 (1H, dt, \( J = 6.6, 2.8 \text{ Hz} \)), 4.20 (2H, q, \( J = 7.1 \text{ Hz} \)), 3.99-3.96 (1H, m), 2.91 (1H, dddd, \( J = 17.8, 6.4, 4.0, 2.3 \text{ Hz} \)), 2.53-2.45 (1H, m), 1.31 (3H, t, \( J = 7.1 \text{ Hz} \)).

(1R,2S)-trans-2-(3’-Chlorophenyl)-cyclopent-3-enol (21b). Colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.26-7.15 \) (3H, m), 7.08-7.05 (1H, m), 5.92 (1H, ddd, \( J = 6.3, 4.4, 2.2 \text{ Hz} \)), 5.74 (1H, ddd, \( J = 6.0, 4.4, 2.1 \text{ Hz} \)), 4.25 (1H, dt, \( J = 6.8, 4.1 \text{ Hz} \)), 3.73 (1H, sp, \( J = 1.9 \text{ Hz} \)), 2.80 (1H, dddd, \( J = 17.0, 6.8, 3.9, 1.7 \text{ Hz} \)), 2.37 (1H, dddd, \( J = 17.0, 6.5, 4.2, 2.1 \text{ Hz} \)), 2.07 (1H, br. s, alcohol). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 144.7, 134.4, 131.5, 130.2, 129.8, 127.4, 126.8, 125.6, 80.8, 60.3, 41.4. \) IR (NaCl, neat film): 3323 (br.), 3059, 2931, 2906, 2841, 1596, 1572, 1478, 1426, 1195, 1078 cm\(^{-1}\). \( \text{MS m/z (rel. intensity): } 194 (M^+, 100), 176 (20), 166 (32), 151 (25), 141 (47), 138 (91), 128 (44), 125 (42), 115 (49), 91 (21). \) HRMS (ESI): Calc’d for C\(_{13}\)H\(_{11}\)ClO \([M^+]: \) 194.049843; found = 194.049579. The ee was determined by HPLC analysis: 90% ee (Chiralcel OD-H, hexane/iPrOH = 99/1, 1.0 mL/min); \( t_R = 31.8 \text{ min} \) (1S,2R) minor; \( t_R = 40.4 \text{ min} \) (1R,2S) major.

(1R,4R)-trans-4-(3-Chlorophenyl)-cyclopent-2-enol (21c). Colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.26-7.16 \) (2H, m), 7.11-7.10 (1H, m), 7.03-7.00 (1H, m), 6.06 (1H, dt, \( J = 5.5, 2.2 \text{ Hz} \)), 6.00 (1H, dd, \( J = 5.6, 2.0 \text{ Hz} \)), 5.07-5.03 (1H, m), 4.12 (1H, dddd, \( J = 9.8, 7.6, 4.1, 2.0 \text{ Hz} \)), 2.29 (1H, dddd, \( J = 14.1, 8.0, 2.7 \text{ Hz} \)), 2.07 (1H, dddd, \( J = 14.2, 7.0, 5.5 \text{ Hz} \)), 1.58 (1H, br. s, alcohol). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 146.9, 138.3, 134.7, 134.4, 129.8, 127.2, 126.5, 125.3, 77.3, 49.6, 43.9. \)

(1R,2S)-trans-2-(3’-Methoxyphenyl)-cyclopent-3-enyl ethyl carbonate (22) and (1R,4R)-trans-4-(3’-Methoxyphenyl)-cyclopent-2-enyl ethyl carbonate (33). General Procedure A: the inseparable regioisomers were obtained in 63% yield (27 mg), showing a > 20:1 ratio of 22:33 by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. General Procedure B: the crude product was purified by column chromatography. The inseparable regioisomers were obtained as a colourless oil in 80% yield (69 mg), showing a 1:1.8 ratio of 22:33 by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. \( \text{1,2-regioisomer 22: } \) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.19-7.12 \) (1H, m), 6.77-6.69 (3H, m), 5.86 (1H, ddd, \( J = 5.9, 4.1, 2.0 \text{ Hz} \)), 5.73 (1H, ddd, \( J = 5.9, 4.2, 2.0 \text{ Hz} \)), 4.97 (1H, dt, \( J = 6.6, 2.8 \text{ Hz} \)), 4.12 (2H, q, \( J = 7.1 \text{ Hz} \)), 3.93-3.88 (1H, m), 3.72 (3H, s), 2.84 (1H, dddd, \( J = 17.8, 6.3, 4.0, 2.2 \text{ Hz} \)), 2.45-2.36 (1H, m), 1.24 (3H, t, \( J = 7.1 \text{ Hz} \)). \( \text{1,4-regioisomer 33: } \) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 6.80-6.65 \) (3H, m), 7.31-7.20 (1H, m), 6.18 (1H, dd, \( J = 5.6, 1.9 \text{ Hz} \)), 6.10-6.05
(1R,2S)-trans-2-(3'-Methoxyphenyl)-cyclopent-3-enol (22b).
Deprotected and isolated as described in General Procedure C. Colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.13 (1H, t, \(J = 7.4\) Hz), 6.70-6.62 (3H, m) 5.80 (1H, ddd, \(J = 6.0, 4.4, 2.2\) Hz), 5.67 (1H, ddd, \(J = 6.1, 4.1, 2.1\) Hz), 4.18 (1H, dt, \(J = 6.7, 4.2\) Hz), 3.70 (3H, s), 3.64 (1H, sp, \(J = 1.9\) Hz), 2.70 (1H, dddd, \(J = 16.9, 6.7, 3.9, 2.1\) Hz), 2.27 (1H, dsx, \(J = 16.9, 2.1\) Hz), 1.80 (1H, br. s, alcohol). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 160.1, 144.3, 132.2, 129.8, 128.7, 120.1, 113.2, 112.1, 81.2, 60.8, 55.3, 41.6. IR (NaCl, neat film): 3323 (br.), 3336 (br.), 3056, 3022, 2921, 2863, 1650, 1607, 1490, 1406, 1073, 1010 cm\(^{-1}\). MS m/z (rel. intensity): 190 (M\(^+\), 100), 172 (20), 162 (50), 147 (41), 134 (63), 129 (27), 121 (38), 115 (32), 91 (32).

(1R,4R)-trans-4-(3'-Methoxyphenyl)-cyclopent-2-enol (33b).
Colourless oil. The characterization data was fully concordant with that already reported in the literature.\(^{109}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.21 (2H, \(t, J = 7.9\) Hz), 6.77-6.67 (3H, m) 6.06-6.01 (2H, m), 5.08-5.02 (1H, m), 4.15-4.10 (1H, m), 3.79 (3H, s), 2.28 (1H, ddd, \(J = 14.1, 8.0, 2.8\) Hz), 2.11 (1H, dddd, \(J = 14.1, 6.9, 6.0\) Hz), 1.48 (1H, br. s). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 159.8, 146.5, 138.9, 134.1, 129.6, 119.5, 112.9, 111.5, 77.5, 55.2, 49.9, 44.0. IR (NaCl, neat film): 3333 (br), 3055, 3001, 2963, 2939, 2839, 1604, 1489, 1458, 1435, 1319, 1265, 1157, 1041, 1026, 771 cm\(^{-1}\). MS (EI) m/z (rel. intensity): 190.1 (M\(^+\), 30), 172 (100), 157 (47), 129 (33), 128 (38), 127 (29), 115 (18), 85 (21), 84 (30).

(1R,2S)-trans-2-(3'-Methylphenyl)-cyclopent-3-enol (23b).
and (1R,4R)-trans-4-(3'-Methylphenyl)-cyclopent-2-enyl ethyl carbonate (23).

(1R,2S)-trans-2-(3'-Methylphenyl)-cyclopent-3-enol (23b).

(1R,4R)-trans-4-(3'-Methylphenyl)-cyclopent-2-enyl ethyl carbonate (46).

(1R,2S)-trans-2-(3'-Methylphenyl)-cyclopent-3-enol (23b).

(1R,4R)-trans-4-(3'-Methylphenyl)-cyclopent-2-enyl ethyl carbonate (46).

(1R,2S)-trans-2-(3'-Methylphenyl)-cyclopent-3-enol (23b).

(1R,4R)-trans-4-(3'-Methylphenyl)-cyclopent-2-enyl ethyl carbonate (46).
1161, 1054 cm
. MS m/z (rel. intensity): 174 (M–H, 93), 156 (25), 146 (55), 131 (69), 128 (47), 118 (100), 115 (41), 105 (50), 91 (42). HRMS (ESI): Calc’d for C\textsubscript{15}H\textsubscript{24}O [M–H]: 210.104465; found = 210.105000. The ee was determined by HPLC analysis: 92% ee (Chiralcel OD-H, hexane/iPrOH = 98/2, 1.0 mL/min); t\(\text{R}\) = 16.3 min (1R,2S) minor; t\(\text{R}\) = 16.4 min (+), t\(\text{R}\) = 18.9 min (–).

\((1R,4R)\)-trans-4-(3'-Methylphenyl)-cyclopent-2-enol (46b). Deprotected and isolated as described in General Procedure C. Colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.18 (1H, t, \(J = 8.2\) Hz), 7.01 (1H, d, \(J = 7.7\) Hz), 6.95-6.92 (2H, m) 6.06-6.01 (2H, m), 5.07-5.03 (1H, m), 4.13-4.08 (1H, m), 2.33 (3H, s), 2.27 (1H, ddd, \(J = 14.1, 8.0, 2.6\) Hz), 2.10 (1H, ddd, \(J = 14.1, 7.0, 5.5\) Hz), 1.56 (1H, br. s, alcohol).

\((1R,2S)\)-trans-2-(2'-Naphthalenyl)-cyclopent-3-enyl ethyl carbonate (24).

General Procedure A. The crude product was purified by column chromatography (dry loaded). The inseparable regioisomers were obtained as a colourless oil in 78% yield (36 mg), showing a > 20:1 ratio of 4:5 by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. \(1\)-regioisomer 24: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.86-7.77 (3H, m), 7.62 (1H, s), 7.49-7.39 (3H, m), 6.01 (1H, ddd, \(J = 6.1, 4.0, 2.1\) Hz), 5.90 (1H, ddd, \(J = 5.8, 4.0, 2.0\) Hz), 5.12 (1H, dt, \(J = 6.0, 2.7\) Hz), 4.21 (2H, q, \(J = 7.1\) Hz), 4.19-4.16 (1H, m), 2.97 (1H, ddd, \(J = 17.8, 6.2, 4.4, 2.5\) Hz), 2.57-2.49 (1H, m), 1.32 (3H, t, \(J = 7.1\) Hz).

\((1R,2S)\)-trans-2-(2'-Naphthalenyl)-cyclopent-3-enol (24b). Deprotected and isolated as described in General Procedure C. The alcohol was quantitatively isolated as a colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.83-7.78 (3H, m), 7.62 (1H, s), 7.49-7.42 (2H, m), 7.33 (1H, dd, \(J = 8.5, 1.7\) Hz), 5.97 (1H, ddd, \(J = 6.0, 4.4, 2.2\) Hz), 5.87 (1H, ddd, \(J = 6.2, 4.2, 2.1\) Hz), 4.37 (1H, dt, \(J = 6.7, 4.1\) Hz), 3.94 (3H, sp, \(J = 1.9\) Hz), 2.86 (1H, ddd, \(J = 16.9, 6.3, 3.9, 2.0\) Hz), 2.42 (1H, ddd, \(J = 17.0, 6.0, 3.9, 2.0\) Hz), 1.99 (1H, br. s, alcohol). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 139.9, 133.5, 132.5, 132.2, 129.8, 128.3, 127.6, 126.1, 126.0, 125.5, 125.4, 80.8, 60.9, 41.4. IR (NaCl, neat film): 3028 (br.), 3054, 3017, 2925, 2854, 1650, 1633, 1506, 1456, 1271, 1216, 1050 cm\(^{-1}\). MS m/z (rel. intensity): 210 (M\(^+\), 100), 192 (24), 179 (46), 165 (58), 154 (96), 141 (48), 128 (36), 115 (19). HRMS (ESI): Calc’d for C\textsubscript{15}H\textsubscript{18}O [M\(^+\)]: 210.10445; found = 210.105000. The ee was determined by HPLC analysis: 90% ee (Chiralcel OD-H, hexane/iPrOH = 98/2, 1.0 mL/min); t\(\text{R}\) = 34.3 min (1S,2R) minor; t\(\text{R}\) = 51.8 min (1R,2S) major.
alcohol. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 142.1, 139.0, 134.3, 133.5, 132.3, 128.3, 127.6, 127.5, 126.1, 125.7, 125.4, 125.2, 77.6, 50.1, 44.0.

(1R,2S)-trans-2-(1'-Naphthalenyl)cyclopent-3-enyl ethyl carbonate (25). According to General Procedure A: the inseparable regioisomers were obtained in 50% yield (23 mg), showing a 1:1 ratio of 4:5 by $^1$H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. **L2-regioisomer 25**: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.18 (1H, d, $J = 8.2$ Hz), 7.87 (1H, dd, $J = 8.0$, 1.5 Hz), 7.76 (1H, d, $J = 8.2$ Hz), 7.56 (1H, dt, $J = 6.9$, 1.6 Hz), 7.50 (1H, dt, $J = 6.9$, 1.5 Hz), 7.40 (1H, t, $J = 8.2$ Hz), 7.26 (1H, s), 6.04 (1H, ddd, $J = 5.9$, 4.0, 2.0 Hz), 5.94 (1H, ddd, $J = 5.9$, 4.3, 2.0 Hz), 5.18 (1H, dt, $J = 6.5$, 2.4 Hz), 4.80 (1H, br. s), 4.18 (2H, q, $J = 7.1$ Hz), 2.97 (1H, dddd, $J = 17.9$, 6.4, 4.2, 2.1 Hz), 2.54 (1H, dddd, $J = 17.9$, 4.1, 2.6, 1.0 Hz), 1.31 (3H, t, $J = 7.1$ Hz).

(1R,2S)-trans-2-(1'-Naphthalenyl)cyclopent-3-enol (25b). Deprotected and isolated as described in General Procedure C. The alcohol was quantitatively isolated as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.33 (1H, d, $J = 8.4$ Hz), 7.88 (1H, d, $J = 7.9$ Hz), 7.75 (1H, d, $J = 8.2$ Hz), 7.58 (1H, dt, $J = 6.9$, 1.2 Hz), 7.52 (1H, dt, $J = 6.8$, 1.0 Hz), 7.39 (1H, t, $J = 8.0$ Hz), 7.22 (1H, d, $J = 8.0$ Hz), 6.06 (1H, ddd, $J = 5.7$, 4.1, 2.0 Hz), 5.95 (1H, ddd, $J = 5.8$, 4.2, 2.1 Hz), 4.60 (1H, br. s), 4.41-4.35 (1H, m), 2.81 (1H, dddd, $J = 17.3$, 6.3, 4.1, 2.0 Hz), 2.44 (1H, dm, $J = 17.3$ Hz), 2.02 (1H, br. s). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.9, 134.0, 132.1, 131.8, 130.3, 128.8, 127.2, 126.1, 125.6, 125.4, 123.9, 123.4, 79.6, 56.6, 41.7. IR (NaCl, neat film): 3347 (br.), 3050, 3010, 2927, 2843, 1595, 1511, 1431, 1396, 1287, 1207, 1066, 1033 cm$^{-1}$. HRMS (ESI)$^+$: Calc’d for C$_{15}$H$_{14}$O [M$^+$]: 210.104465; found = 210.105018. The ee was determined by HPLC analysis: 70% ee (Chiralcel OD-H, hexane/iPrOH = 98/2, 0.75 mL/min); $t_R$ = 48 min (1S,2R) minor; $t_R$ = 50.6 min (1R,2S) major.

(1R,4R)-trans-4-(1'-Naphthalenyl)cyclopent-2-enol (25c). Colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.07 (1H, d, $J = 7.2$ Hz), 7.88 (1H, d, $J = 7.9$ Hz), 7.74 (1H, d, $J = 8.2$ Hz), 7.57 (1H, dt, $J = 7.5$, 1.5 Hz), 7.51 (1H, dt, $J = 8.0$, 1.4 Hz), 7.41 (1H, t, $J = 7.2$ Hz), 7.34 (1H, d, $J = 6.8$ Hz), 6.16-6.13 (1H, m), 6.05-5.98 (1H, m), 5.15-5.10 (1H, m), 4.38 (1H, m), 3.13 (1H, dddd, $J = 17.4$, 8.9, 2.4 Hz), 2.65 (1H, dddd, $J = 17.4$, 4.0, 2.7, 1.5 Hz), 1.82 (1H, d, $J = 6.2$ Hz). MS m/z (rel. intensity): 210 (M$^+$, 100), 191 (40), 178 (27), 165 (87), 152 (57), 141 (47), 128 (55), 115 (17), 82 (45). HRMS (ESI)$^+$: Calc’d for C$_{15}$H$_{14}$O [M$^+$]: 210.104465; found = 210,105018.

(1R,2S)-trans-2-(Q'-Methylphenyl)cyclopent-3-enyl ethyl carbonate (26). According to General Procedure A: the inseparable regioisomers were obtained in 25% yield (10 mg), showing a 6:1 ratio of 4:5 by $^1$H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. **L2-regioisomer 26**: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.19-7.11 (3H, m), 7.03-6.98 (1H, m), 5.95 (1H, ddd, $J = 6.0$, 4.1, 2.0 Hz), 5.78 (1H, ddd, $J = 6.9$, 4.3, 2.0 Hz), 5.06 (1H, dt, $J = 6.5$, 2.6 Hz), 4.24-4.21 (1H, m), 4.18 (2H, q, $J = 7.1$ Hz), 2.94 (1H, dddd, $J = 17.8$, 6.4, 4.1, 2.2 Hz), 2.47 (1H, dddd, $J = 17.8$, 4.3, 2.6, 1.0 Hz), 2.40 (3H, s), 1.31 (3H, t, $J = 7.1$ Hz).
(1R,2S)-trans-2-(2'-Methylphenyl)-cyclopent-3-enol (26b). Colourless oil. The characterization data was fully concordant with that already reported.\(^{109}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.22-7.09 (3H, m), 7.03-6.98 (1H, m), 5.96 (1H, ddd, \(J = 6.1, 4.2, 2.0\) Hz), 5.77 (1H, ddd, \(J = 6.9, 4.1, 2.1\) Hz), 4.29-4.22 (1H, m), 4.04 (1H, br. s), 2.79 (1H, dddd, \(J = 17.8, 6.1, 4.2, 2.0\) Hz), 2.47 (3H, s), 2.34 (1H, br. d, \(J = 17.7\) Hz), 2.40 (3H, s), 1.79 (1H, br. s). \(\text{MS} m/z\) (rel. intensity): 174 (M\(^+\), 100), 156 (22), 131 (52), 128 (39), 118 (72), 115 (37), 105 (41), 91 (33). \(\text{HRMS}\) (ESI): Calc’d for C\(_{12}\)H\(_8\)O\(_2\) [M\(^+\)]: 174.104465; found = 174.104454. The ee was determined by HPLC analysis: 92% ee (Chiralcel OD-H, hexane/iPrOH = 98/2, 1.0 mL/min); \(t_r = 15.4\) min (15,2R) minor; \(t_r = 20.4\) min (1R,2S) major.

(1R,4R)-trans-4-(2'-Methylphenyl)-cyclopent-2-enyl ethyl carbonate (28). Colourless oil. The characterization data was fully concordant with that already reported.\(^{109}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.16-7.10 (3H, m), 7.00 (1H, dd, \(J = 6.3, 1.7\) Hz), 6.09-6.05 (2H, m), 5.03 (1H, br. s), 4.36 (1H, dt, \(J = 5.7, 1.7\) Hz), 2.36 (3H, s), 2.32 (1H, ddd, \(J = 14.2, 8.2, 2.6\) Hz), 1.98 (1H, ddd, \(J = 14.1, 6.8, 5.8\) Hz), 0.88 (1H, br. s).

\(\text{trans-2-(2'}-\text{Phenyl-1-vinyl)-cyclopent-3-enyl ethyl carbonate (28).}\)

According to General Procedure A: the inseparable regioisomers were obtained in 20% yield (9 mg), showing a 6:1 ratio of \(4:5\) by \(^1\)H NMR spectroscopy. \(\text{1,2-regioisomer 28:}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.31-7.10 (5H, m), 6.36 (1H, d, \(J = 16.0\) Hz), 6.13 (1H, dd, \(J = 15.9, 7.4\) Hz), 5.76 (1H, ddd, \(J = 6.1, 4.1, 2.1\) Hz), 5.66 (1H, ddd, \(J = 6.2, 4.4, 2.1\) Hz), 4.97 (1H, dt, \(J = 6.5, 2.8\) Hz), 4.13 (2H, q, \(J = 7.1\) Hz), 3.54-3.47 (1H, m), 2.81 (1H, dddd, \(J = 17.7, 6.6, 3.8, 2.2\) Hz), 2.39 (1H, dddd, \(J = 17.7, 4.0, 2.8, 1.1\) Hz), 1.24 (3H, t, \(J = 7.1\) Hz).

\(\text{(1R,4R)-trans-4-(4'}-\text{Trifluoromethyl-phenyl)-cyclopent-2-enyl ethyl carbonate (30): see product 12.}\)

\(\text{(1R,2S)-trans-2-(4'}-\text{Methoxy-3'-methylphenyl)-cyclopent-3-enyl ethyl carbonate (31) and (1R,4R)-trans-4-(4'}-\text{Methoxy-3'-methylphenyl)-cyclopent-2-enyl ethyl carbonate (32).}\)

According to General Procedure B; column chromatography gave the inseparable regioisomers as a colourless oil in 66% yield (60 mg), showing a 1:1.3 ratio of 31:32 by \(^1\)H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. Major \(\text{1,4-regioisomer 32:}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.03-6.97 (1H, m), 6.94-6.88 (1H, m), 6.74 (1H, d, \(J = 6.7\) Hz), 6.16 (1H, dd, \(J = 5.6, 2.0\) Hz), 6.05 (1H, dt, \(J = 5.6, 2.3\) Hz), 5.72 (1H, ddd, \(J = 6.9, 3.8, 2.1\) Hz), 4.20 (2H, q, \(J = 7.1\) Hz), 4.10-4.04 (1H, m), 3.81 (3H, s), 2.45 (1H, ddd, \(J = 14.5, 7.8, 2.0\) Hz), 2.20 (3H, m), 2.10 (1H, ddd, \(J = 14.6, 7.1, 5.8\) Hz), 1.31 (3H, t, \(J = 7.1\) Hz). \(\text{1,2-regioisomer 31:}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.03-6.97 (1H, m), 6.94-6.88 (1H, m), 6.76 (1H, d, \(J = 3.8\) Hz), 5.90 (1H, ddd, \(J = 5.9, 4.1, 2.1\) Hz), 5.81-5.76 (1H, m), 5.00 (1H, ddd, \(J = 6.6, 3.7, 2.7\) Hz), 4.16 (2H, q, \(J = 7.1\) Hz), 3.92 (1H, br.s), 3.81 (3H, s), 2.91 (1H, dddd, \(J = 17.7, 6.6, 4.0, 1.8\) Hz), 2.49-2.43 (1H, m), 2.20 (3H, s), 1.31 (3H, t, \(J = 7.1\) Hz).
trans-(1R,2S)-2-(4'-Methoxy-3'-methylphenyl)-cyclopent-3-enol (31b).

Colourless oil. [α]_D^{28.5} = +172 (c 1.00, CHCl₃) for an enantiomeric ratio was 89.7 : 10.3, as determined by HPLC analysis (Chiralcel OD-H; 235 nm; tₘ = 17.5 min (+), tₛ = 19.5 min (−)).

trans-(1R,2S)-2-(4'-Methoxy-3'-methylphenyl)-cyclopent-3-enol (31b).

Colourless oil. [α]_D^{28.6} = +228 (c 1.00, CHCl₃) for an enantiomeric ratio was 99.6 : 0.4, as determined by HPLC analysis (Chiralcel OD-H; 225 nm; tₘ = 18.1 min (+), tₛ = 19.3 min (−)).

trans-(1R,4R)-4-(4'-Methoxy-3'-methylphenyl)-cyclopent-2-enyl ethyl carbonate (33): see product 22.

trans-(1R,4R)-4-(4'-Methoxyphenethyl)-cyclopent-2-enyl ethyl carbonate (34): see product 14.

trans-(1R,2S)-2-(3'-Fluoro-5'-methylphenyl)-cyclopent-3-enyl ethyl carbonate (35)

and trans-(1R,4R)-4-(3'-Fluoro-5'-methoxyphenethyl)-cyclopent-2-enyl ethyl carbonate (36).

According to General Procedure B; column chromatography gave the inseparable regioisomers as a colourless oil in 78% yield (72 mg), showing a 1:2.4 ratio of 35:36 by ¹H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. Major 1,4-

regioisomer 36: ¹H NMR (400 MHz, CDCl₃): δ 6.59–6.40 (3H, m), 6.15 (1H, dd, J = 5.6, 1.8 Hz), 6.09 (1H, ddd, J = 5.6, 3.2, 2.2 Hz), 5.76–5.71 (1H, m), 4.20 (2H, q, J = 7.1 Hz), 4.13–4.05 (1H, m), 3.77 (3H, s), 2.45 (1H, ddd, J = 14.6, 7.8, 2.2 Hz), 2.11 (1H, ddd, J = 14.6, 7.1, 5.8 Hz), 1.31 (3H, t, J = 7.1 Hz). Minor 1,2-

regioisomer 35: ¹H NMR (400 MHz, CDCl₃): δ 6.59–6.40 (3H, m), 5.95 (1H, ddd, J = 5.9, 4.1, 2.1 Hz), 5.79–5.73 (1H, m), 5.02 (1H, dt, J = 6.6, 2.7 Hz), 4.20 (2H, q, J = 7.1 Hz), 3.94 (1H, br.s), 3.77 (3H, s), 2.90 (1H, dddd, J = 17.8, 6.6, 3.9, 1.8 Hz), 2.52–2.43 (1H, m), 1.31 (3H, t, J = 7.1 Hz).

trans-(1R,2S)-2-(3'-Fluoro-5'-methoxyphenethyl)-cyclopent-3-enyl (35b).

Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 6.55–6.43 (3H, m), 5.91 (1H, ddd, J = 12.2, 5.8, 2.4 Hz), 5.73 (1H, ddd, J = 8.0, 6.1, 1.9 Hz), 4.25 (1H, ddd, J = 8.2, 6.6, 3.1 Hz), 3.77 (3H, s), 3.74–3.68 (1H, m), 2.79 (1H, ddd, J = 17.0, 6.9, 2.1 Hz), 2.36 (1H, ddd, J = 17.0, 4.1, 2.2 Hz), 1.98 (1H, br. s). ¹³C NMR (100 MHz, CDCl₃): δ 163.8 (d, J = 245.0 Hz), 161.0 (d, J = 11.4 Hz), 145.8 (d, J = 8.9 Hz), 131.5, 130.2, 109.0 (d, J = 2.6 Hz), 106.4 (d, J = 21.7 Hz), 99.6 (d, J = 25.7 Hz), 80.7, 60.6 (d, J = 2.0
trans-(1R,4R)-4-(3'-Fluoro-5'-methoxyphenyl)-cyclopent-2-enol (36b).

Colourless oil. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 6.62\)–6.34 (3H, m), 5.97 (1H, ddd, \(J = 5.5, 3.3, 2.1\) Hz), 5.93 (1H, dd, \(J = 5.5, 2.0\) Hz), 4.97 (1H, ddd, \(J = 7.0, 4.6, 2.1\) Hz), 4.06–3.97 (1H, m), 3.70 (3H, s), 2.19 (1H, ddd, \(J = 14.1, 8.1, 2.7\) Hz), 2.00 (1H, ddd, \(J = 14.1, 8.7, 5.4\) Hz), 1.62 (1H, br. s). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta 163.8\) (d, \(J = 244.8\) Hz), 161.0 (d, \(J = 11.4\) Hz), 148.1 (d, \(J = 8.8\) Hz), 138.2, 134.7, 108.9 (d, \(J = 2.6\) Hz), 106.1 (d, \(J = 21.7\) Hz), 99.3 (d, \(J = 25.3\) Hz), 77.3, 55.5, 49.9 (d, \(J = 2.1\) Hz), 43.8. \(^{19}F\) NMR (375 MHz, CDCl\(_3\)): \(\delta -112.2\) (t, \(J = 9.7\) Hz, 1F). MS (EI\(^{+}\) m/z (rel. intensity): 208.1 (M\(^{+}\), 7), 190 (100), 175 (23), 147 (29), 146 (51), 133 (17), 127 (13), 86 (14), 84 (28). HRMS (EI\(^{+}\))": Calc’d for C\(_{13}\)H\(_{14}\)F [M\(^{+}\)]: 208.0900; found = 208.0905.

(1R,2S)-trans-2-(3'-Bromophenyl)-cyclopent-3-enyl ethyl carbonate (37).

According to General Procedure B: the inseparable regioisomers were obtained as a colourless oil in 89% yield (89 mg), showing a 1:2.3 ratio of 37/38 by \(^{1}H\) NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. Major 1,4-regioisomer 38: \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.39\)–7.03 (4H, m), 6.15 (1H, dd, \(J = 5.6, 1.7\) Hz), 6.10 (1H, ddd, \(J = 7.7, 5.6, 2.2\) Hz), 5.77–5.72 (1H, m), 4.20 (2H, q, \(J = 7.1\) Hz), 4.15–4.08 (1H, m), 2.46 (1H, dt, \(J = 6.8, 2.2\) Hz), 2.10 (1H, ddd, \(J = 14.7, 7.1, 5.9\) Hz), 1.31 (3H, t, \(J = 7.1\) Hz). Minor 1,2-regioisomer 37: \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.39\)–7.03 (4H, m), 5.96 (1H, ddd, \(J = 5.8, 4.0, 2.0\) Hz), 5.80–5.75 (1H, m), 5.00 (1H, ddd, \(J = 6.6, 2.6, 3.1\) Hz), 4.20 (2H, q, \(J = 7.1\) Hz), 3.96 (1H, br. s), 2.54–2.45 (1H, m), 2.91 (1H, ddd, \(J = 17.8, 6.3, 3.9, 2.1\) Hz), 1.31 (3H, t, \(J = 7.1\) Hz).

(1R,4R)-trans-4-(3'-Bromophenyl)-cyclopent-2-enol (37b).

Colourless oil. \([\alpha]_D^{270} = +181\) (c 1.00, CHCl\(_3\)) for an enantiomeric ratio was 99.5:0.5, as determined by HPLC analysis (Chiralcel OD-H; 225 nm; \(t_R = 20.4\) min (+), \(t_k = 21.6\) min (–)). \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.33\) (1H, dd, \(J = 6.1, 1.2\) Hz), 7.26 (1H, t, \(J = 2.2\) Hz), 7.15 (1H, t, \(J = 7.8\) Hz), 7.05 (1H, dd, \(J = 7.6, 1.2\) Hz), 6.08–6.05 (1H, m), 6.01 (1H, ddd, \(J = 4.7, 2.0\) Hz), 5.12–5.01 (1H, m), 4.16–4.08 (1H, m), 2.28 (1H, ddd, \(J = 14.1, 8.0, 2.6\) Hz), 2.07 (1H, ddd, \(J = 14.0, 7.0, 5.4\) Hz), 1.57 (1H, br. s). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta 146.6, 137.8, 134.3, 129.8, 129.7, 129.1, 125.6, 122.5, 77.9, 50.8, 45.2\). IR (NaCl, neat film): 3328 (br), 3057, 2930, 2876, 1592, 1476, 1424, 1350, 1110, 1072, 1052, 937, 791, 778, 743, 692 cm\(^{-1}\). MS (EI\(^{+}\) m/z (rel. intensity): 240 (M\(^{+}\), 6), 238 (16), 222 (72), 141 (100), 139 (23), 115 (67), 86 (22), 84 (27). HRMS (EI\(^{+}\))": Calc’d for C\(_{13}\)H\(_{13}\)BrO [M\(^{+}\)]: 237.9993; found = 237.9990.

(1R,2S)-trans-2-(3'-Bromophenyl)-cyclopent-3-enyl ethyl carbonate (38).

Deprotected and isolated as described in General Procedure C. Colourless oil. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.35\)–7.28 (2H, m), 7.15 (1H, t, \(J = 7.6\) Hz), 7.09 (1H, dd, \(J = 7.6, 1.4\) Hz), 5.90 (1H, ddd, \(J = 6.1, 4.3, 2.2\) Hz), 5.71 (1H, ddd, \(J = 6.1, 4.1, 2.0\) Hz), 4.28–4.19 (1H, m), 3.74–3.66 (1H, m), 2.77 (1H, ddd, \(J = 17.0, 3.0, 1.8\) Hz), 2.34 (1H, ddd, \(J = 17.0, 3.9, 1.8\) Hz), 2.08 (1H, br. s)

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta 144.4, 131.2, 130.0, 129.9, 129.8, 129.4, 125.8, 122.5, 81.4, 61.3, 42.8\). IR
(NaCl, neat film): 3331 (br), 3057, 2906, 2843, 1592, 1564, 1475, 1426, 1287, 1265, 1163, 1072, 1052, 996, 950, 780, 720 cm⁻¹. MS (EI) m/z (rel. intensity): 240 (M⁺, 14), 238 (17), 222 (33), 184 (40), 182 (44), 141 (65), 131 (75), 128 (44), 115 (100), 91 (14). HRMS (EI): Calc'd for C₉H₁₁BrO [M⁺]: 237.9993; found = 237.9996. [α]D₂⁶⁺ = +146 (c 1.00, CHCl₃) for an enantiomeric ratio was 96.8 : 3.2, as determined by HPLC analysis (Chiralcel OD-H; 225 nm; tR = 17.6 min (+), tR = 20.8 min (−)).

(1R,2S)-trans-2-(3'-Methoxycarbonylphenyl)-cyclopent-3-enyl ethyl carbonate (39) and (1R,4R)-trans-4-(3'-Methoxycarbonylphenyl)-cyclopent-2-enyl ethyl carbonate (40).

Prepared according to General Procedure B; only with racem ligands (problematic slow isomerisation to the cis-cyclopentene). Column chromatography gave inseparable regioisomers as a colourless oil in 71% yield (66 mg), showing a 1:1 ratio of 39:40 by ¹H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. ¹H NMR (400 MHz, CDCl₃): 6.79 (2H, m), 7.47–7.30 (2H, m), 7.25–7.18 (2H, m), 7.20 (1H, m), 6.93 (1H, m), 6.65 (1H, m), 6.59–6.38 (2H, m), 6.37–6.25 (1H, m), 6.22 (1H, m), 5.83–5.75 (1H, m), 5.73 (1H, m), 5.03 (1H, dt, J = 6.7, 2.8 Hz), 4.19 (2H, q, J = 7.1 Hz), 3.90 (3H, s), 2.99–2.88 (1H, m), 2.55–2.41 (1H, m), 1.31 (3H, t, J = 7.1 Hz).

trans-(1R,2S)-2-(3'-Methoxycarbonylphenyl)-cyclopent-3-enol (39b).

Colourless oil. ¹H NMR (400 MHz, CDCl₃): 6.79–7.88 (2H, m), 7.50–7.38 (2H, m), 5.97 (1H, dq, J = 6.4, 2.2 Hz), 5.80 (1H, dq, J = 6.0, 2.0 Hz), 4.34–4.28 (1H, m), 3.94 (3H, s), 3.87–3.84 (1H, m), 2.86 (1H, ddq, J = 17.0, 6.6, 2.1 Hz), 2.43 (1H, ddt, J = 17.0, 4.1, 2.1 Hz), 2.05 (1H, br.s), 1.31 (3H, t, J = 7.1 Hz).

trans-(1R,4R)-4-(3'-Methoxycarbonylphenyl)-cyclopent-2-enol (40b).

Colourless oil. ¹H NMR (400 MHz, CDCl₃): 6.78–7.81 (1H, dt, J = 7.3, 1.7 Hz), 7.74 (1H, t, J = 1.6 Hz), 7.29 (1H, t, J = 7.2 Hz), 7.25 (1H, dt, J = 7.6, 1.6 Hz), 6.00 (1H, dt, J = 5.2, 2.1 Hz), 5.98 (1H, dd, J = 5.8, 1.8 Hz), 5.03–4.97 (1H, m), 4.17–4.11 (1H, m), 3.84 (3H, s), 2.25 (1H, ddd, J = 14.2, 8.1, 2.6 Hz), 2.02 (1H, ddd, J = 14.2, 7.0, 5.6 Hz), 1.54 (1H, br.s). ¹³C NMR (75 MHz, CDCl₃): 84.167.1, 145.2, 138.5, 134.6, 131.7, 130.5, 128.6, 128.1, 127.7, 77.2, 52.1, 49.8, 44.0. HRMS (ESI)⁺: Calc’d for C₁₅H₁₄O₃ [M⁺]: 218.0943; found = 218.0946.

(1R,2S)-trans-2-(4'-Methylsulfanylphenyl)-cyclopent-3-enyl ethyl carbonate (41) and (1R,4R)-trans-4-(4'-Methylsulfanylphenyl)-cyclopent-2-enyl ethyl carbonate (42).

Prepared according to General Procedure B; column chromatography gave inseparable regioisomers as a colourless oil in 80% yield (72 mg), showing a 1:2.6 ratio of 41:42 by ¹H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. Major ¹H NMR (400 MHz, CDCl₃): 6.78–7.21 (2H, dd, J = 11.4, 1.6 Hz), 7.19 (2H, dd, J = 8.3, 1.8 Hz), 6.15 (1H, dd, J = 5.6, 1.9 Hz), 6.08 (1H, ddd, J = 5.5, 3.1, 2.3 Hz), 5.75 (1H, ddd, J = 7.0, 3.9, 2.1 Hz), 4.20 (2H, q, J = 7.1 Hz), 4.15–4.08 (1H, m), 2.46 (3H, s), 2.48–2.42 (1H, m), 2.09 (1H, ddd, J = 14.6, 7.1, 5.9 Hz), 1.31 (3H, t, J = 7.1 Hz).
trans-(1R,2S)-2-(4'-Methylsulfanylphenyl)-cyclopent-3-enol (41b).

Colourless oil. [α]D<sup>28.9</sup> = +205 (c 1.00, CHCl<sub>3</sub>) for an enantiomeric ratio was 95.6 : 4.4, as determined by HPLC analysis (Chiralcel OD-H; 262 nm; t<sub>R</sub> = 21.6 min (+), t<sub>R</sub> = 23.7 min (−)).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.22 (2H, dd, J = 8.4, 4.3, 2.2 Hz), 7.11 (1H, ddd, J = 8.2, 4.1, 2.2 Hz), 5.90 (1H, ddd, J = 5.8, 2.4, 2.2 Hz), 5.75 (1H, ddd, J = 5.9, 2.2, 2.0 Hz), 4.24 (1H, ddd, J = 6.6, 5.8, 4.3 Hz), 3.74–3.72 (1H, m), 2.80 (1H, ddd, J = 15.3, 6.8, 3.9, 2.2 Hz), 2.47 (3H, s), 2.37 (1H, ddd, J = 17.0, 6.1, 4.1, 2.0 Hz), 1.81 (1H, br.s).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 139.8, 136.6, 132.3, 129.9, 128.1 (2C), 127.4 (2C), 81.2, 60.4, 41.6, 16.4. IR (NaCl, neat film): 3348 (br), 3055, 3016, 2962, 2916, 2839, 1489, 1435, 1404, 1319, 1049, 949, 817, 732 cm<sup>−1</sup>. MS (EI<sup>+</sup>) m/z (rel. intensity): 206.1 (M<sup>+</sup>, 25), 188 (8), 150 (100), 129 (34), 128 (53), 116 (39), 115 (51), 91 (17), 89 (9). HRMS (EI<sup>+</sup>): Calc’d for C<sub>12</sub>H<sub>14</sub>OS [M<sup>+</sup>]: 206.0765; found = 206.0760.

trans-(1R,4R)-4-(4'-Methylsulfanylphenyl)-cyclopent-2-enol (42b).

Colourless oil. [α]D<sup>28.1</sup> = +298 (c 1.00, CHCl<sub>3</sub>) for an enantiomeric ratio was 99.5:0.5, as determined by HPLC analysis (Chiralcel OD-H; 262 nm; t<sub>R</sub> = 21.7 min (+), t<sub>R</sub> = 22.5 min (−)).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.20 (2H, dd, J = 9.4, 1.8 Hz), 7.05 (2H, dd, J = 8.2, 1.8 Hz), 6.06–5.97 (2H, m), 5.08–5.01 (1H, m), 4.15–4.05 (1H, m), 2.46 (3H, s), 2.27 (1H, ddd, J = 14.0, 8.0, 2.8 Hz), 2.06 (1H, ddd, J = 14.2, 7.2, 4.6 Hz), 1.66 (1H, br.s).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 142.1, 139.2, 136.2, 134.4, 127.8 (2C), 127.4 (2C), 77.6, 49.6, 44.3, 16.5. IR (NaCl, neat film): 3333 (br), 3055, 3016, 2962, 2931, 2885, 1489, 1435, 1411, 1319, 1026, 817, 732 cm<sup>−1</sup>. MS (EI<sup>+</sup>) m/z (rel. intensity): 206.1 (M<sup>+</sup>, 5), 150 (15), 142 (41), 128 (40), 115 (100), 102 (31), 89 (42), 63 (41). HRMS (EI<sup>+</sup>): Calc’d for C<sub>12</sub>H<sub>14</sub>OS [M<sup>+</sup>]: 206.0765; found = 206.0760.

(1R,2S)-trans-2-(4'-Fluoro-3'-methylphenyl)-cyclopent-3-enyl ethyl carbonate (43) and (1R,4R)-trans-4-(4'-Fluoro-3'-methylphenyl)-cyclopent-2-enyl ethyl carbonate (44).

General Procedure B: column chromatography gave the inseparable regioisomers as a colourless oil in 69% yield (60 mg), showing a 1:2.3 ratio of 43:44 by <sup>1</sup>H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. Major 1,4-regioisomer 44: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.03–6.96 (1H, m), 6.95–6.88 (2H, m), 6.14 (1H, dd, J = 5.6, 2.0 Hz), 6.07 (1H, dt, J = 5.6, 2.3 Hz), 5.74 (1H, dd, J = 6.9, 4.0, 2.1 Hz), 4.20 (2H, q, J = 7.1 Hz), 4.09 (1H, dddd, J = 7.8, 5.7, 4.2, 2.1 Hz), 2.45 (1H, ddd, J = 14.6, 7.9, 2.1 Hz), 2.24 (3H, s), 2.08 (1H, ddd, J = 14.6, 7.1, 1.3 Hz), 1.31 (3H, t, J = 7.1 Hz). Minor 1,2-regioisomer 43: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.03–6.96 (1H, m), 6.95–6.88 (2H, m), 5.93 (1H, ddd, J = 5.9, 4.2, 2.1 Hz), 5.78 (1H, dd, J = 4.3, 2.2 Hz), 4.99 (1H, dt, J = 6.6, 2.7 Hz), 4.20 (2H, q, J = 7.1 Hz), 3.40 (1H, br.s), 2.90 (1H, dddd, J = 17.8, 6.6, 4.0, 1.8 Hz), 2.51–2.44 (1H, m), 2.24 (3H, s), 1.31 (3H, t, J = 7.1 Hz).
trans-(1R,2S)-2-(4'-Fluoro-3'-methylphenyl)-cyclopent-3-enol (43b).

Colourless oil. [α]_D^{28.2} = +187 (c 0.50, CHCl₃) for an enantiomeric ratio was 97.1:2.9, as determined by HPLC analysis (Chiralcel OD-H; 215 nm; tₚ = 13.9 min (+), tᵦ = 15.4 min (-)).

¹H NMR (400 MHz, CDCl₃): δ 6.96 (1H, d, J = 8.0 Hz), 6.94–6.86 (2H, m), 5.87 (1H, dd, J = 5.9, 2.3 Hz), 5.71 (1H, dd, J = 6.0, 2.0 Hz), 4.20 (1H, dt, J = 6.6, 4.1 Hz), 3.70–3.64 (1H, m), 3.76 (1H, ddd, J = 16.9, 6.7, 2.0 Hz), 3.34 (1H, ddd, J = 16.8, 4.1, 2.1 Hz), 2.23 (3H, d, J = 2.0 Hz), 2.04 (1H, br.s).

¹³C NMR (100 MHz, CDCl₃): δ 160.0 (d, J = 243.1 Hz), 138.1 (d, J = 3.8 Hz), 132.4, 130.5 (d, J = 5.2 Hz), 129.7, 126.1 (d, J = 7.9 Hz), 125.0 (d, J = 17.2 Hz), 115.1 (d, J = 22.1 Hz), 81.2, 60.1, 41.5, 14.7. ¹⁹F NMR (375 MHz, CDCl₃): δ -121.4 (dd, J = 7.6, 1.9 Hz, 1F). IR (NaCl, neat film): 3337 (br), 3056, 3017, 2962, 2844, 1501, 1252, 1236, 1207, 1118, 1051, 949, 819, 756 cm⁻¹. MS (EI) m/z (rel. intensity): 192.1 (M⁺, 47), 174 (51), 159 (43), 146 (48), 136 (100), 133 (44), 123 (30), 109 (30). HRMS (EI): Calc’d for C₁₅H₁₃FO [M⁺]: 192.0950; found = 192.0950.

trans-(1R,4R)-4-(4'-Fluoro-3'-methylphenyl)-cyclopent-2-enol (44b).

Colourless oil. [α]_D^{28.1} = +204 (c 1.00, CHCl₃) for an enantiomeric ratio was 99.3 : 0.7, as determined by HPLC analysis (Chiralcel OD-H; 215 nm; tₚ = 16.5 min (+), tᵦ = 18.0 min (-)). ¹H NMR (400 MHz, CDCl₃): δ 6.95–6.86 (3H, m), 6.06–5.98 (2H, m), 5.09–5.00 (1H, m), 4.14–4.06 (1H, m), 2.27 (1H, ddd, J = 14.1, 8.0, 2.6 Hz), 2.24 (3H, d, J = 2.0 Hz) 2.05 (1H, ddd, J = 14.2, 6.8, 5.5 Hz), 1.58 (1H, br. s). ¹³C NMR (100 MHz, CDCl₃): δ 160.7 (d, J = 243.1 Hz), 140.3 (d, J = 3.7 Hz), 139.3, 134.2, 130.1 (d, J = 5.9 Hz), 125.9, 125.8, 115.1 (d, J = 22.4 Hz), 77.6, 49.3, 44.4, 14.7 (d, J = 3.8). ¹⁹F NMR (375 MHz, CDCl₃): δ -121.7 (dd, J = 13.3, 5.7 Hz, 1F). IR (NaCl, neat film): 3326 (br), 3055, 3018, 2962, 2927, 2891, 1501, 1325, 1245, 1205, 1118, 1028, 882, 790, 756 cm⁻¹. MS (EI) m/z (rel. intensity): 192.1 (M⁺, 5), 175 (15), 174 (100), 159 (82), 146 (29), 133 (54), 109 (11). HRMS (EI): Calc’d for C₁₅H₁₃OF [M⁺]: 192.0950; found = 192.0949.

(1R,4R)-trans-4-(3'-Methylphenyl)-cyclopent-2-enyl ethyl carbonate (46): see product 23.

(1R,4R)-trans-4-(4'-Methoxyphenyl)-cyclopent-2-enyl ethyl carbonate (47): see product 19.

trans-(1R,2S)-2-(2'-Fluoro-5'-methylphenyl)-cyclopent-3-enyl ethyl carbonate (48) and trans-(1R,4R)-4-(2'-Fluoro-5'-methylphenyl)-cyclopent-2-enyl ethyl carbonate (49).

According to General Procedure B: column chromatography gave inseparable regioisomers as a colourless oil in 15% yield (13 mg), showing a 1:2.0 ratio of 48:49 by ¹H and ¹⁹F NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. 1₄-regioisomer 49: ¹H NMR (400 MHz, CDCl₃), δ: 7.01–6.81 (3H, m), 6.16 (1H, dd, J = 5.6, 1.9 Hz), 6.09 (1H, dt, J = 5.6, 2.4 Hz), 5.76 (1H, ddd, J = 7.2, 4.6, 2.0 Hz), 4.44–4.36 (1H, m), 4.21 (2H, q, J = 7.1 Hz), 2.55–2.43 (1H, m), 2.27 (3H, s), 2.13 (1H, ddd, J = 14.5, 7.1, 5.9 Hz), 1.31 (3H, t, J = 7.1 Hz). ¹⁹F NMR (375 MHz, CDCl₃), δ: -124.3. 1₂-regioisomer 48: ¹H NMR (400 MHz, CDCl₃), δ: 7.01–6.81 (3H, m), 5.91 (1H, ddd, J = 6.0, 4.2, 2.0 Hz), 5.72 (1H, ddd, J = 6.0, 4.0, 2.1 Hz), 5.15 (1H, dt, J = 6.8, 2.8 Hz), 4.26–4.22 (1H, m), 4.21 (2H, q, J = 7.1 Hz), 2.97 (1H, ddd, J = 17.8, 6.9, 3.9, 2.4 Hz), 2.55–2.43 (1H, m), 2.27 (3H, s), 1.31 (3H, t, J = 7.1 Hz). ¹⁹F NMR (375 MHz, CDCl₃), δ: -123.3.
trans-(1R,2S)-2-(2’-Fluoro-5’-methylphenyl)-cyclopent-3-enol (48b).
Deprotected and isolated as described in General Procedure C. Colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$: 7.01–6.91 (2H, m), 6.85 (1H, dd, $J$ = 7.2, 1.9 Hz), 5.94 (1H, dq, $J$ = 6.3, 2.2 Hz), 5.73 (1H, dq, $J$ = 6.1, 2.1 Hz), 4.37–4.31 (1H, m), 4.05 (1H, br.s), 2.80 (1H, dddd, $J$ = 17.2, 6.4, 4.2, 2.1 Hz), 2.39 (1H, ddt, $J$ = 17.2, 3.6, 2.0 Hz), 2.27 (3H, s), 1.95 (1H, br.s). $^{19}$F NMR (375 MHz, CDCl$_3$): $\delta$ -123.8 (d, $J$ = 8.1 Hz). IR (NaCl, neat film): 3343 (br), 3051, 2988, 2924, 2849, 1721 (w), 1580, 1488, 1449, 1225, 1042, 951, 760 cm$^{-1}$.

trans-(1R,4R)-4-(2’-Fluoro-5’-methylphenyl)-cyclopent-2-enol (49b).
Colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$: 6.96 (1H, dd, $J$ = 7.6, 5.0, 2.2 Hz), 6.89 (1H, dd, $J$ = 7.3, 2.1 Hz), 6.06 (1H, dt, $J$ = 5.4, 2.1 Hz), 6.02 (1H, dd, $J$ = 5.7, 1.9 Hz), 5.08–5.00 (1H, m), 4.43–4.37 (1H, m), 2.29 (1H, ddd, $J$ = 14.1, 8.1, 2.7 Hz), 2.27 (3H, s), 2.10 (1H, ddd, $J$ = 14.1, 7.1, 5.5 Hz), 1.52 (1H, br.s). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$: 158.9 (d, $J$ = 242.3 Hz), 137.7, 134.5, 133.5 (d, $J$ = 3.6 Hz), 130.9 (d, $J$ = 14.7 Hz), 128.2 (d, $J$ = 14.7 Hz), 128.1, 115.1, 114.8, 77.4, 42.6, 20.7. $^{19}$F NMR (375 MHz, CDCl$_3$): $\delta$ -124.5. IR (NaCl, neat film): 3366 (br), 3061, 2965, 2934, 1581, 1491, 1452, 1349, 1225, 1112, 1026, 758 cm$^{-1}$.

trans-(1R,2S)-2-(2’-Fluorophenyl)-cyclopent-3-enyl ethyl carbonate (50) and trans-(1R,4R)-4-(2’-Fluorophenyl)-cyclopent-2-enyl ethyl carbonate (51).
According to General Procedure B: column chromatography gave inseparable regioisomers as a colourless oil in 16% yield (13 mg), showing a 1:1.3 ratio of 50:51 by $^1$H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. Major 1,4-regioisomer 51: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$: 7.24–7.16 (1H, m), 7.10–6.98 (3H, m), 6.18 (1H, dd, $J$ = 5.6, 2.0 Hz), 6.10 (1H, ddd, $J$ = 5.6, 3.2, 2.4 Hz), 5.74 (1H, ddd, $J$ = 7.9, 4.4, 2.3 Hz), 4.44 (1H, dddd, $J$ = 13.7, 7.9, 4.3, 2.2 Hz), 4.20 (2H, q, $J$ = 7.1 Hz), 2.53–2.47 (1H, m), 2.14 (1H, ddd, $J$ = 14.6, 7.2, 5.8 Hz), 1.31 (3H, t, $J$ = 7.1 Hz). Minor 1,2-regioisomer 50: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$: 7.24–7.16 (1H, m), 7.10–6.98 (3H, m), 5.93 (1H, ddd, $J$ = 5.9, 4.3, 2.2 Hz), 5.77 (1H, dd, $J$ = 4.1, 2.2 Hz), 5.16 (1H, dt, $J$ = 6.8, 2.9 Hz), 4.28 (1H, br.s), 4.20 (2H, q, $J$ = 7.1 Hz), 2.96 (1H, dddd, $J$ = 17.9, 6.8, 4.0, 2.1 Hz), 2.55–2.49 (1H, m), 1.31 (3H, t, $J$ = 7.1 Hz).

trans-(1R,2S)-2-(2-Fluorophenyl)-cyclopent-3-enol (50b).
Deprotected and isolated as described in General Procedure C. Colourless oil. [α]$_D^{28.8}$ = +150 (c 0.30, CHCl$_3$) for an enantiomeric ratio was 94.1 : 5.9, as determined by HPLC analysis (Chiralcel OD-H; 215 nm; $t_R$ = 14.1 min (+), $t_S$ = 16.3 min (−)). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$: 7.23–7.17 (1H, m), 7.10–7.02 (3H, m), 5.95 (1H, ddd, $J$ = 5.9, 4.4, 2.2 Hz), 5.75 (1H, ddd, $J$ = 5.9, 4.3, 2.2 Hz), 4.35 (1H, dt, $J$ = 6.6, 3.3 Hz), 4.10 (1H, br.s), 2.80 (1H, dddd, $J$ = 17.2, 6.7, 4.1, 2.1 Hz), 2.39 (1H, ddt, $J$ = 17.2, 3.6, 2.0 Hz), 1.97 (1H, br.s). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$: 161.2 (d, $J$ = 245.0 Hz), 130.7 (d, $J$ = 9.7 Hz), 129.4 (d, $J$ = 15.0 Hz), 128.4 (d, $J$ = 4.5 Hz), 128.3 (d, $J$ = 8.2 Hz), 124.3 (d, $J$ = 3.4 Hz), 115.6, 115.4, 79.8, 54.1 (d, $J$ = 1.5 Hz), 41.5. $^{19}$F NMR (375 MHz, CDCl$_3$): $\delta$: -118.3 (d, $J$ = 8.6 Hz, F). IR (NaCl, neat film): 3348 (br), 3055, 2993, 2924, 2847, 1720 (w), 1581, 1489, 1450, 1226, 1041, 949, 864, 756 cm$^{-1}$. MS (El$^+$) m/z (rel. intensity): 178.1 (M$^+$, 3), 146 (21), 135 (44), 133 (51), 122 (100), 115 (14), 109 (45), 75 (30), 63 (24). HRMS (El$^+$): Calc’d for C$_{11}$H$_{11}$FO [M$^+$]: 178.0794; found = 178.0800.
trans-(1R,4R)-4-(2-Fluorophenyl)-cyclopent-2-enol (51b). Colourless oil. $[\alpha]_D^{28.5} = +98$ (c 0.82, CHCl$_3$) for an enantiomeric ratio was 98.2 : 1.8, as determined by HPLC analysis (Chiralcel OD-H; 215 nm; $t_R = 17.6$ min (+), $t_S = 18.7$ min (−)). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.22–7.14 (1H, m), 7.10–6.97 (3H, m), 6.09–6.00 (2H, m), 5.08–5.01 (1H, m), 4.48–4.40 (1H, m), 2.31 (1H, ddd, $J = 14.1$, 8.1, 2.8 Hz), 2.11 (1H, ddd, $J = 13.8$, 6.8, 5.5 Hz), 1.58 (1H, br.s). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 161.0 (d, $J = 245.3$ Hz), 137.7, 134.8, 131.7 (d, $J = 14.7$ Hz), 128.1 (d, $J = 2.6$ Hz), 128.0, 124.4 (d, $J = 3.3$ Hz), 115.6, 115.4, 77.3, 42.8 (d, $J = 2.6$ Hz), 20.7. $^{19}$F NMR (375 MHz, CDCl$_3$): δ -119.0 to -119.1 (m, rotamers). IR (NaCl, neat film): 3317 (br), 2963, 2931, 1581, 1489, 1450, 1350, 1226, 1111, 1026, 756 cm$^{-1}$. MS (EI') m/z (rel. intensity): 178.1 (M$^+$, 20), 160 (100), 159 (72), 133 (75), 122 (19), 109 (34), 86 (24), 84 (44). HRMS (EI'): Calc'd for C$_{11}$H$_{12}$FO [M$^+$]: 178.0794; found = 178.0791.

trans-(1R,2S)-2-(Thiophen-3'-yl)-cyclopent-3-enyl ethyl carbonate (52) and trans-(1R,4R)-4-(Thiophen-3'-yl)-cyclopent-2-enyl ethyl carbonate (53).

According to General Procedure B; after column chromatography, the inseparable regioisomers were obtained as a colourless oil in 31% yield (24 mg), showing a 1.35 ratio of 52:53 by $^1$H NMR spectroscopy. The regioisomers were submitted directly to the deprotection conditions and characterized as the free alcohols. Major 1R,4R-regioisomer 53: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.22–6.98 (1H, m), 6.89–6.86 (1H, m), 6.81 (1H, dd, $J = 4.9$, 1.1 Hz), 6.14 (1H, dd, $J = 5.6$, 2.0 Hz), 5.96 (1H, dt, $J = 5.6$, 2.3 Hz), 5.67 (1H, ddd, $J = 7.1$, 4.1, 2.1 Hz), 4.21–4.14 (1H, m), 4.13 (2H, q, $J = 7.1$ Hz), 2.37 (1H, dd, $J = 14.5$, 7.8, 2.4 Hz), 2.10 (1H, ddd, $J = 14.1$, 7.1, 5.7 Hz), 1.24 (3H, t, $J = 7.1$ Hz). Minor 1R,2S-regioisomer 52: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.23–7.18 (1H, m), 6.97–6.91 (2H, m), 5.85–5.76 (2H, m), 4.99 (1H, dt, $J = 6.5$, 2.3 Hz), 4.13 (2H, q, $J = 7.1$ Hz), 4.00 (1H, br.s), 2.82 (1H, dddd, $J = 17.8$, 6.5, 3.8, 1.8 Hz), 2.45–2.36 (1H, m), 1.24 (3H, t, $J = 7.1$ Hz).

trans-(1R,2S)-2-(Thiophen-3'-yl)-cyclopent-3-enol (52b).

Colourless oil. $[\alpha]_D^{27.9} = +108$ (c 0.40, CHCl$_3$) for an enantiomeric ratio was 94.4 : 5.6, as determined by HPLC analysis (Chiralcel OD-H; 235 nm; $t_R = 19.4$ min (+), $t_S = 20.8$ min (−)). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.28 (1H, dd, $J = 4.9$, 3.0 Hz), 6.99–6.96 (1H, m), 6.95 (1H, dd, $J = 4.1$, 1.2 Hz), 5.87 (1H, ddd, $J = 5.9$, 4.1, 2.0 Hz), 5.82 (1H, ddd, $J = 5.9$, 4.0, 2.0 Hz), 4.31 (1H, dt, $J = 6.9$, 3.7 Hz), 3.89–3.84 (1H, m), 2.80 (1H, ddd, $J = 6.5$, 3.6, 1.8 Hz), 2.35 (1H, dtt, $J = 17.0$, 3.7, 1.8 Hz), 1.84 (1H, br.s). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 143.3, 133.2, 129.8, 127.3, 126.1, 120.3, 80.0, 56.1, 41.5. IR (NaCl, neat film): 3333 (br), 3101, 3055, 2916, 2847, 1527, 1411, 1319, 1257, 1157, 1049, 940, 841, 779, 748, 640 cm$^{-1}$. MS (EI') m/z (rel. intensity): 166.0 (M$^+$, 37), 148 (27), 147 (53), 138 (38), 135 (42), 123 (54), 110 (100), 97 (58), 91 (19), 84 (30), 77 (17). HRMS (EI'): Calc'd for C$_9$H$_{10}$OS [M$^+$]: 166.0452; found = 166.0452.

trans-(1R,4R)-4-(Thiophen-3'-yl)-cyclopent-2-enol (53b).

Colourless oil. $[\alpha]_D^{27.3} = +269$ (c 0.50, CHCl$_3$) for an enantiomeric ratio was 99.6 : 0.4, as determined by HPLC analysis (Chiralcel OD-H; 235 nm; $t_R = 22.7$ min (+), $t_S = 23.5$ min (−)). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.30–7.20 (1H, m), 6.97–6.82 (2H, m), 6.07 (1H, br.s), 5.99 (1H, br.s), 5.02 (1H, br.s), 4.22 (1H, br.s), 2.30–2.08 (2H, m), 1.58 (1H, br.s). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 145.5, 138.9, 133.9, 127.1, 126.1, 119.6, 77.5, 45.2, 43.2. IR (NaCl, neat film): 3317 (br), 3101, 3055, 2962, 2931, 2893, 1527, 1411, 1319, 1157, 1111, 1026, 779 cm$^{-1}$. MS (EI') m/z (rel. intensity): 166.0 (M$^+$, 32), 148 (99), 147 (91), 135
(IR,2S)-(tert-Butyldimethylsiloxy)-2-phenylcyclopent-3-ene (54). Based on a literature protocol,\textsuperscript{112} a solution of alcohol 6 (100 mg, 0.62 mmol) in dry DCM (10 mL) was stirred at 0 °C under N\textsubscript{2}. tert-Butyldimethylsilyl chloride (207 mg, 1.37 mmol) and imidazole (127 mg, 1.87 mmol) were added. The reaction was allowed to stir overnight at room temperature. Water (5 mL) was added and the layers were decanted. The aqueous layer was extracted with DCM (3x15 mL), the combined organic layers were washed with brine, dried with MgSO\textsubscript{4}, filtered, and the solvent was removed under reduced pressure to give an oil. The product was purified by column chromatography (10% EtOAc/Hex) to afford a colourless oil (152 mg, 90%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 7.43-7.28 (m, 5H), 5.90 (dddd, 1H, \(J = 16.2, 9.4, 7.0, 2.4\) Hz), 2.47 (ddddd, 1H, \(J = 16.4, 7.6, 5.5, 2.4\) Hz), 0.96 (s, 9H), 0.14 (s, 6H) ppm. \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\): 143.7, 132.7, 129.6, 127.8, 127.7, 126.6, 82.6, 60.6, 26.1, 26.0, 18.3, -4.7 ppm. IR (CHCl\textsubscript{3}) \(v\): 3060, 2956, 2929, 2857, 1471, 1361, 1252, 1113, 897 cm\textsuperscript{-1}. HRMS (EI\textsuperscript{+}): Calc’d for C\textsubscript{13}H\textsubscript{19}OSi [M\textsuperscript{+}]: 217.1049; found: 217.1051.

(2R,3R)-3-(tert-Butyldimethylsiloxy)-2-phenylpentane-1,5-diol. Modified from a literature protocol,\textsuperscript{113} 54 (162 mg, 1.12 mmol) was dissolved in dry DCM (36 mL) and MeOH (40 mL) and cooled down to -78 °C. A stream of ozone was bubbled through until solution turned blue, then N\textsubscript{2} was bubbled through until all the blue colour disappeared. Sodium borohydride (212 mg, 5.6 mmol) was added in four equal portions every 15 mins for the duration of one hour, while maintaining the bubbled through until all the blue colour disappeared. Sodium borohydride (212 mg, 5.6 mmol) was added in four equal portions every 15 mins for the duration of one hour, while maintaining the temperature at -78 °C. The reaction was left to stir at room temperature until complete by TLC analysis. The solvent was removed under reduced pressure; the residue was retaken in EtOAc (25 mL) and was washed with brine. The aqueous was extracted with EtOAc (5x25 mL), and the combined organic layers were dried with MgSO\textsubscript{4} filtered, and the solvent was removed under reduced pressure to give an oil, which was purified using column chromatography (50 to 100% EtOAc/Hex, then 5% MeOH/DCM) to give the diol as a white solid (100 mg, 55%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.27-7.17 (m, 5H), 4.14 (ddd, 1H, \(J = 9.8, 5.1, 1.6\) Hz), 4.03 (dd, 1H, \(J = 10.9, 7.4\) Hz), 3.86 (dd, 1H, \(J = 10.9, 7.4\) Hz), 3.60 (td, 2H, \(J = 7.4, 1.4\) Hz), 3.01 (ddd, 1H, \(J = 11.6, 7.3, 4.4\) Hz), 0.084 (s, 9H), 0.03 (s, 6H) ppm. \textsuperscript{13}CNMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 143.9, 133.8, 133.2, 131.7, 77.3, 68.2, 64.5, 57.4, 40.4, 30.6, 22.7, -0.5 ppm. IR (CHCl\textsubscript{3}) \(v\): 3338, 2956, 2925, 2883, 2852, 1473, 1251, 1098, 1031, 915 cm\textsuperscript{-1}. HRMS (EI\textsuperscript{+}): Calc’d for C\textsubscript{13}H\textsubscript{19}O\textsubscript{2}S\textsubscript{i} [M\textsuperscript{+}]: 235.1154; found 235.1165.

(2R,3R)-3-(tert-Butyldimethylsiloxy)-2-phenylpentane-1,5-diyl dimethanesulfonate. Following a literature protocol,\textsuperscript{114} the above diol (55 mg, 0.31 mmol) was dissolved in dry DCM (8 mL) under N\textsubscript{2} at

\textsuperscript{112} Knapp, S.; Yu, Y. Org. Lett. 2007, 9, 1359.


\textsuperscript{114} Marvin, C. C.; Voight, A. E.; Burke, D. S. Org. Lett. 2007, 9, 5357-5359.
0 °C. Triethylamine (0.18 mL, 1.3 mmol) and methanesulfonyl chloride (0.05 mL, 0.67 mmol) were added to the flask and the reaction was allowed to warm up to room temperature and stirred for 16 h. Water (30 mL) was added to quench the reaction, and the aqueous layer was extracted with DCM (5×20 mL). The combined organic layers were dried with MgSO$_4$, filtered, and the solvent was removed under reduced pressure to give 13 as a brown oil (135 mg, 100%) which was used without further purification in the next step.

(3S,4R)-1-benzyl-4-(tert-butyldimethylsilyloxy)-3-phenylpiperidine (55). The bissulfonate from the previous step (135 mg, 0.29 mmol) was dissolved in dry dioxane (15 mL). Benzylamine (0.473 mL, 4.34 mmol) and triethylamine (0.081 mL, 0.58 mmol) were added and the reaction was allowed to stir at 80 °C overnight. The reaction was washed with three times with 1 N HCl (50 mL, 30 mL and 20 mL). The organic layer was dried with MgSO$_4$, and the solvent was removed under reduced pressure to give a red oil, which was purified using column chromatography (40% EtOAc/Hex) to give piperidine 55 as a red oil (35 mg, 32%). $^1$H NMR (300 MHz, CDCl$_3$): δ = 7.84–7.64 (m, 10H), 4.12 (td, 1H, J = 9.8, 4.8 Hz), 4.04 (d, 2H, J = 2.8 Hz), 3.44 (dt, 2H, J = 11.4, 1.7 Hz), 3.32-3.24 (m, 2H), 2.78–2.60 (m, 2H), 2.43-2.19 (m, 2H), 1.18 (s, 9H), 0.33 (s, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 147.8, 134.6, 134.2, 133.8, 133.6, 132.6, 132.0, 80.0, 68.3, 64.0, 57.8, 56.7, 40.8, 31.2, 23.4, 0.9 ppm. IR (CHCl$_3$): ν: 3029, 2627, 2855, 2801, 1495, 1472, 1470, 1361, 1252, 1108, 835 cm$^{-1}$. HRMS (EI$^+$): Calc’d for C$_{24}$H$_{38}$NOSi [M]: 381.2488; found: 381.2469.

(Z)-But-2-ene-1,4-bis(ethylcarbonate) (58a).
Prepared according to Typical Procedure D, 58a was recovered as a colorless fluid oil, 13.2 g (99% yield). Characterization data matched that of literature reports.$^{115}$

(Z)-But-2-ene-1,4-bis(iso-propylcarbonate) (58b).
Prepared according to Typical Procedure D, with isopropylchloroformate. Colorless oil; quantitative yield. $^1$H NMR (400 MHz, CDCl$_3$): δ = 5.91–5.72 (m, 2H), 4.83–4.66 (m, 4H), 3.92 (m, 2H), 0.94 (d, J = 6.7 Hz, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 155.3, 128.2, 63.2, 28.0, 19.1. IR (NaCl, neat): 2965, 1747, 1471, 1400, 1381, 1377, 1371, 1244, 970 cm$^{-1}$. Compound was unstable under MS conditions.

(Z)-But-2-ene-1,4-bis(2’,2’-trifluoroethylcarbonate) (58c).
1,4-cis-butenediol (2.0 g, 0.023 mol) along with carbonyl-diimidazole (11.1 g, 0.0681 mol, 3 equiv) were weighed in a 150 mL round bottom flask. DCM (100 mL) was then added and the solution was stirred at r.t. for 3 h. The reaction was washed three times with 1 N HCl (50 mL, 30 mL and 20 mL). The organic layer was dried with MgSO$_4$, filtered, and the solvent was removed under reduced pressure to give a red oil, which was purified via flash chromatography (Hexane EtOAc: 90:10). Colorless oil; quantitative yield. $^1$H NMR (400 MHz, CDCl$_3$): δ = 5.86 (dd, J = 1.2, 4.1, 5.2 Hz, 2H), 4.82 (dd, J = 1.3, 4.1 Hz, 4H), 4.51 (q, J = 8.2 Hz, 4H). $^{19}$F NMR (376 MHz, CDCl$_3$): δ = -74.67 (t, J = 8.2 Hz, 1H). IR (NaCl, neat): 2983, 1770, 1454, 1417,

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1354, 1381, 1171, 1021, 968 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcd for C\(_{10}\)H\(_{10}\)O\(_6\) [M]\(^+\): 340.0382; found 340.0385.

(Z)-But-2-ene-1,4-bis(phenylcarbonate) (58d).
Prepared according to Typical Procedure D, with phenylchloroformate. Colorless oil; yield: 96%. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.42–7.35\) (m, 4H), 7.29–7.22 (m, 2H), 7.21–7.14 (m, 4H), 5.94 (t, \(J = 7.6\) Hz, 2H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 153.7, 151.2, 129.7, 128.2, 126.3, 121.2, 63.9\). IR (NaCl, neat): 3061, 2966, 1750, 1467, 1449, 1373, 1258, 1018, 920 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcd for C\(_{16}\)H\(_{16}\)O\(_6\)Na [MNa]\(^+\): 351.0839; found 351.0839.

(Z)-But-2-ene-1,4-bis(4-methoxybenzoate) (58f).
Prepared according to Typical Procedure D, with benzoyl chloride. Colorless crystals, mp 83–84 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.09–7.99\) (m, 4H), 7.59–7.52 (m, 2H), 7.43 (t, \(J = 7.7\) Hz, 4H), 5.98–5.89 (m, 2H), 5.00 (d, \(J = 5.2\) Hz, 4H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 166.6, 133.3, 130.2, 129.9, 128.6, 128.6, 60.8\). IR (NaCl, neat): 3061, 3034, 2966, 1748, 1601, 1448, 1346, 1267, 1107, 1095, 1070, 1024, 966, 940 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcd for C\(_{20}\)H\(_{20}\)O\(_6\) [MNa]\(^+\): 296.1049; found 296.1042.

2-Phenylbut-3-enyl ethylcarbonate (59a).
Prepared according to Typical Procedure E; the branched and linear products 59 and 60 were isolated as an inseparable mixture. Regioselectivity was determined by \(^1\)H NMR analysis. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 5.86–5.65\) (dt, \(J = 4.0, 1.2\) Hz, 2H), 4.82–4.62 (m, 4H), 4.17 (d, \(J = 5.3\) Hz, 4H), 1.27 (t, \(J = 7.1\) Hz, 6H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 155.1, 128.2, 64.3, 63.1, 14.4\). IR (NaCl, neat): 3007, 2986, 1750, 1467, 1449, 1373, 1258, 1018, 920 cm\(^{-1}\).

2-Phenylbut-3-en-1-ol (61).
Prepared according to Typical Procedure F; then solvolyzed according to Typical Procedure F. Isolated as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.37–7.29\) (m, 2H), 7.28–7.19 (m, 3H), 6.00 (ddd, \(J = 7.7, 10.4, 17.2\) Hz, 1H), 5.19 (m, 2H), 3.81 (ddd, \(J = 1.4, 7.1\) Hz, 2H), 3.52 (q, \(J = 7.3\) Hz, 1H), 1.55 (s, 1H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 140.8, 138.4, 129.0, 128.2, 127.2, 117.3, 66.3, 52.7\). IR (NaCl, neat): 3368, 3070, 2928, 2875, 1633, 1599, 1492, 1452, 1055, 955, 918 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcd for C\(_{10}\)H\(_{12}\)O [M]: 148.0888; found 148.0886. The ee was determined by HPLC analysis: 94% ee (Chiralcel AD, isocratic 0.5% i-ProH/Hexanes, 1.0 mL/min, 208 nm; \(t_\beta = 28.2\) min, \(t'_\beta = 32.4\) min). \([\alpha]^{25}_D\) \(= + 118.7\) (c = 0.62, CHCl\(_3\)).
2-(p-Tolyl)but-3-en-1-ol (and 63a).
Prepared according to Typical Procedure E; then solvolyzed according to Typical Procedure F. The carbonates were isolated in 59% yield and displayed a > 20:1 ratio for the branched product 63a by $^1$H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.21–7.06 (m, 4H), 5.99 (ddd, $J$ = 7.7, 10.5, 17.1 Hz, 1H), 5.24–5.12 (m, 2H), 3.80 ($t$, $J$ = 6.4 Hz, 2H), 3.50 ($q$, $J$ = 7.3 Hz, 1H), 2.33 (s, 3H), 1.46 (t, $J$ = 6.3 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.6, 137.7, 136.8, 129.7, 128.0, 117.0, 66.3, 52.3, 21.2. IR (NaCl, neat): 3366, 3020, 2872, 1739, 1638, 1510, 1460, 1412, 1040, 914 cm$^{-1}$. HRMS-ESI: $m/z$ calcld for $C_{11}H_{14}O$ [M$^+$]: 162.1045; found 162.1044. The ee was determined by HPLC analysis: 93% ee (Chiralcel AD-H, 0.9% i-PrOH/hexane, 0.3mL/min, 208 nm), $t_r$ = 74.9 min, $t'_r$ = 80.6 min) $[\alpha]_{D}^{25}$ = +140.5 (c = 0.61, CHCl$_3$).

2-(p-Methoxyphenyl)but-3-en-1ol (and 65a).
Prepared according to Typical Procedure E; then solvolyzed according to Typical Procedure F. The carbonates were isolated in 60% yield and displayed a > 20:1 ratio for the branched product 65a by $^1$H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.21–7.08 (m, 2H), 6.96–6.79 (m, 2H), 5.96 (ddd, $J$ = 7.6, 10.4, 17.2 Hz, 1H), 5.26–5.08 (m, 2H), 3.78 (s, 3H) 3.77 (d, $J$ = 7.12 Hz, 2H), 3.47 ($q$, $J$ = 7.3 Hz, 1H), 1.24 (t, $J$ = 7.1 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.8, 138.7, 132.7, 129.1, 117.0, 114.4, 66.3, 55.5, 51.8. IR (NaCl, neat): 3375, 3078, 2933, 1743, 1638, 1510, 1460, 1412, 1040, 918 cm$^{-1}$. HRMS-ESI: $m/z$ calcld for $C_{11}H_{14}O_2$ [M$^+$]: 178.0994; found 178.0994. The ee was determined by HPLC analysis: 93% ee (Chiralcel AD-H, 0.5% i-PrOH/hexane, 1.0 mL/min, 208 nm), $t_r$ = 81.7 min, $t'_r$ = 87.8 min). $[\alpha]_{D}^{25}$ = +83.7 (c = 0.64, CHCl$_3$).

2-(p-Chlorophenyl)but-3-en-1-ol (and 66a).
Prepared according to Typical Procedure E; then solvolyzed according to Typical Procedure F. The carbonates were isolated in 65% yield and displayed a 10:1 ratio for the branched product 66a by $^1$H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.35–7.27 (m, 2H), 7.21–7.14 (m, 2H), 5.97 (s, 1H), 5.20 (m, 2H), 3.81 (dd, $J$ = 6.6 Hz, 2H), 3.51 ($q$, $J$ = 7.2 Hz, 1H), 1.46 (t, $J$ = 6.3 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 139.1, 137.7, 133.2, 129.3, 128.9, 117.5, 65.9, 51.8. IR (NaCl, neat): 3365, 3082, 2928, 2878, 1637, 1491, 1406, 1093, 1057, 922 cm$^{-1}$. HRMS-ESI: $m/z$ calcld for $C_{11}H_{15}OCl$ [M$^+$]: 182.0498; found 182.0498. The ee was determined by gas chromatography analysis: 96% ee (Shuzimi column, 2 min 130°, then 130 to 200°C, 4 °C/ min). $t_r$ = 11.55 min, $t'_r$ = 11.63 min. $[\alpha]_{D}^{25}$ = −19.6(c = 0.76, CHCl$_3$).

2-(p-Fluorophenyl)but-3-en-1-ol (and 67a).
Prepared according to Typical Procedure E; then solvolyzed according to Typical Procedure F. The carbonates were isolated in 66% yield and displayed a 4:1 ratio for the branched product 67a by $^1$H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.18–7.08 (m, 2H), 7.01–6.89 (m, 2H), 5.90 (ddd, $J$ = 7.6, 10.4, 17.3 Hz, 1H), 5.20–5.05 (m, 2H), 3.74 (d, $J$ = 7.0 Hz, 2H), 3.45 ($q$, $J$ = 5.5, 10.9 Hz, 1H), 0.95 (t, $J$ = 7.9 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 163.2, 160.8, 138.2, 136.5, 129.6, 129.6, 117.5, 115.9, 115.6, 66.2, 66.2, 51.8. $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = −116.4 (tt, $J$ = 5.4, 8.7 Hz, 1H). IR (NaCl, neat): 3368, 3080, 2926, 2875, 1637, 1602, 1508, 1467, 1225, 1159, 1225.
1057, 1028, 922 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcld for \(\text{C}_{10}\text{H}_{15}\text{OF}\) [\(\text{M}^+\)]: 166.0794; found 166.0791. The ee was determined by HPLC analysis: 67% ee (Chiralcel AD-H, 0.9% \(i\)-PrOH/hexane, 0.5 mL/min, 208 nm, \(t_e = 47.5\) min, \(t_r = 50.1\) min). \([\alpha]^{25}_{D} = +54.8\) (c = 0.25, CHCl\(_3\)).

2-\((m,p\text{-Dimethoxyphenyl})\text{but}-3\text{-en}-1\text{-ol}\) (and 68a).

Prepared according to **Typical Procedure E**; then solvolyzed according to **Typical Procedure F**. The carbonates were isolated in 68% yield and displayed a 7:1 ratio for the branched product 68a by \(^1\)H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. **\(^1\)H NMR** (500 MHz, CDCl\(_3\)): \(\delta = 6.88\) (d, \(J = 8.3\) Hz, 1H), 6.83 (d, \(J = 8.2\) Hz, 1H), 6.79 (s, 1H), 6.10–5.94 (m, 1H), 6.03 (m, 1H), 5.23 (m, 2H), 3.91 (dd, \(J = 2.4, 7.1\) Hz, 2H), 3.85 (d, \(J = 7.2\) Hz, 3H), 3.85 (d, \(J = 7.2\) Hz, 3H), 3.52 (d, \(J = 7.3\), 1H). **\(^13\)C NMR** (125 MHz, CDCl\(_3\)): \(\delta = 169.2, 149.2, 148.0, 138.3, 133.0, 119.8, 116.9, 111.5, 111.24, 7.14, 6, 55.9, 52.0. IR (NaCl, neat): 3387, 2999, 2955, 1736, 1591, 1516, 1464, 1262, 1142, 1028 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcld for \(\text{C}_{12}\text{H}_{16}\text{O}_{2}\) [\(\text{M}^+\)]: 208.1099; found 208.1099. The ee was determined by HPLC analysis: 92% ee (Chiralcel AD-H, isocratic 1% \(i\)-PrOH/hexanes, 1.00 mL/min, 208 nm), \(t_e = 73.41\) min, \(t_r = 80.90\) min. \([\alpha]^{25}_{D} = +64.50\) (c = 0.11, CHCl\(_3\)).

2-\((p\text{-Methoxy-}m\text{-methylphenyl})\text{but}-3\text{-en}-1\text{-ol}\) (and 69a).

Prepared according to **Typical Procedure E**; then solvolyzed according to **Typical Procedure F**. The carbonates were isolated in 45% yield and displayed a 10:1 ratio for the branched product 69a by \(^1\)H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. **\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \(\delta = 7.06–6.97\) (m, 2H), 6.79 (d, \(J = 8.2\) Hz, 1H), 5.98 (ddd, \(J = 7.7, 10.5, 17.1\) Hz, 1H), 5.21–5.11 (m, 2H), 3.81 (s, 3H), 3.78 (d, \(J = 7.1\) Hz, 2H), 3.45 (q, \(J = 7.3\) Hz, 1H), 2.21 (s, 3H). **\(^13\)C NMR** (100 MHz, CDCl\(_3\)): \(\delta = 157.0, 138.8, 132.3, 130.4, 127.2, 126.3, 116.8, 110.4, 66.4, 55.6, 51.9, 16.5. IR (NaCl, neat): 3384, 3080, 2924, 1635, 1608, 1504, 1464, 1254, 1136, 1034, 916 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcld for \(\text{C}_{12}\text{H}_{16}\text{O}_{2}\) [\(\text{M}^+\)]: 192.1150; found 192.1155. The ee was determined by HPLC analysis: 88% ee (Chiralcel AD, isocratic 2% \(i\)-PrOH/hexanes, 1.00 mL/min, 208 nm), \(t_e = 24.4\) min, \(t_r = 26.7\) min. \([\alpha]^{25}_{D} = +116.40\) (c = 0.92, CHCl\(_3\)).

2-\((m\text{-Tolyl})\text{but}-3\text{-en}-1\text{-yl ethyl carbonato}\) (and 70a).

Prepared according to **Typical Procedure E**; then solvolyzed according to **Typical Procedure F**. The carbonates were isolated in 38% yield and displayed a 10:1 ratio for the branched product 70a by \(^1\)H NMR analysis. Colorless oil. **\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \(\delta = 7.21\) (m, 1H), 7.13 – 6.95 (m, 3H), 6.12 – 5.91 (m, 1H), 5.22 – 5.10 (m, 2H), 4.35 (dd, \(J = 3.6, 7.3\) Hz, 1H), 4.17 (m, 2H), 3.68 (q, \(J = 7.3\) Hz, 1H), 2.34 (s, 3H), 1.28 (t, \(J = 7.1\) Hz, 3H). **\(^13\)C NMR** (100 MHz, CDCl\(_3\)): \(\delta = 155.1, 139.8, 138.3, 137.5, 128.7, 128.5, 124.9, 116.8, 70.1, 64.0, 48.7, 21.4, 14.2. IR (NaCl, neat): 3080, 2982, 2920, 2872, 1745, 1607, 1466, 1396, 1259, 1115, 1009, 922, 877 cm\(^{-1}\). **HRMS-EI:** \(m/z\) calcld for \(\text{C}_{14}\text{H}_{18}\text{O}_{3}\text{Na}\) [\(\text{M}^+\)]: 257.1148; found 257.1143. The ee was determined by HPLC analysis: 88% ee (Chiralcel AD, isocratic 0.4% \(i\)-PrOH/hexanes, 1.00 mL/min, 208 nm), \(t_e = 34.8\) min, \(t_r = 42.1\) min. \([\alpha]^{25}_{D} = +24.8\) (c = 0.83, CHCl\(_3\)).
2-(m-Chlorophenyl)but-3-en-1-ol (and 71a).
Prepared according to Typical Procedure E; then solvolyzed according to Typical Procedure F. The carbonates were isolated in 66% yield and displayed a 4:1 ratio for the branched product 71a by \(^1\)H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.27-7.12\) (m, 3H), 7.09–7.02 (m, 1H), 5.90 (m, 1H), 5.22–5.08 (m, 2H), 3.76 (d, \(J = 7.0\) Hz, 2H), 3.44 (q, \(J = 7.1\) Hz, 14.4, 1H). \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 144.7, 138.3, 134.8, 130.2, 128.3, 127.6, 126.4, 117.9, 66.1, 52.3\). IR (NaCl, neat): 3335, 3080, 2926, 2874, 1637, 1597, 1510, 1396, 1259, 1167, 1035, 798 cm\(^{-1}\). HRMS-EI: \(m/z\) calcd for C\(_{11}\)H\(_{14}\)O [M]: 162.1045; found 162.1044. The ee was determined by HPLC analysis: 70% ee (Chiralcel AD-H, isocratic 0.9% i-PrOH/hexane, 0.30 mL/min, 208 nm), \(t_r = 84.9\) min, \(t' = 80.6\) min. \(\left[\alpha\right]^{25}_D = +80.7\) (c = 0.13, CHCl\(_3\)).

2-(Naphthalen-1’-yl)but-3-en-1-ol (and 72a).
Prepared according to Typical Procedure E; then solvolyzed according to Typical Procedure F. The carbonates were isolated in 32% yield and displayed a > 20:1 ratio for the branched product 72a by \(^1\)H NMR analysis. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.07\) (d, \(J = 8.8\) Hz, 1H), 7.83–7.78 (m, 1H), 7.70 (d, \(J = 8.0\) Hz, 1H), 7.51–7.31 (m, 4H), 6.08 (dd, \(J = 7.3, 10.7, 16.9\) Hz, 1H), 5.19 (m, 2H), 4.34 (dd, \(J = 7.2, 13.5\) Hz, 2H), 3.95 (qd, \(J = 6.7, 10.9\) Hz, 1H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 138.5, 136.6, 134.3, 132.0, 129.2, 127.7, 126.4, 125.9, 125.7, 124.6, 123.4, 117.7, 65.7, 47.3\). IR (NaCl, neat): 3363, 3047, 2926, 2874, 1637, 1597, 1510, 1396, 1259, 1167, 1035, 798 cm\(^{-1}\). HRMS-EI: \(m/z\) calcd for C\(_{14}\)H\(_{14}\)O [M]: 198.1045; found 198.1045. The ee was determined by HPLC analysis: 65% ee (Chiralcel AD, isocratic 2% i-PrOH/hexanes, 1.0 mL/min, 254 nm), \(t_r = 42.3\) min, \(t_s = 50.4\) min. \(\left[\alpha\right]^{25}_D = -11.3\) (c = 0.54, CHCl\(_3\)).

2-(Naphthalen-2’-yl)but-3-en-1-ol (and 73a).
Prepared according to Typical Procedure E; then solvolyzed according to Typical Procedure F. The carbonates were isolated in 61% yield and displayed a > 20:1 ratio for the branched product 73a by \(^1\)H NMR analysis. Colorless oil. The mixture was solvolyzed and the desired branched product was characterized as the free alcohol. Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.79-7.68\) (m, 3H), 7.62 (s, 1H), 7.45–7.34 (m, 2H), 7.30 (dd, \(J = 1.7, 8.5\) Hz, 1H), 4.03 (ddd, \(J = 7.5, 10.4, 17.2\) Hz, 1H), 5.26–5.05 (m, 2H), 4.01–3.75 (m, 2H), 3.64 (q, \(J = 7.2\) Hz, 1H), 1.20 (s, 1H). \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta = 138.1, 138.0, 133.5, 132.5, 128.4, 127.6, 127.6, 126.6, 126.1, 125.7, 117.3, 66.0, 52.6, 31.0\). IR (NaCl, neat): 3364, 3055, 2925, 2870, 1634, 1599, 1506, 1464, 1376, 1055, 1028, 914 cm\(^{-1}\). HRMS-EI: \(m/z\) calcd for C\(_{13}\)H\(_{12}\)O [M]: 198.1045; found 198.1045. The ee was determined by HPLC analysis: 90% ee (Chiralcel AD, isocratic 1.25% i-PrOH/hexane, 1.00 mL/min, 215 nm), \(t_r = 32.0\) min, \(t'_r = 37.5\) min. \(\left[\alpha\right]^{25}_D = +25.6\) (c = 0.46, CHCl\(_3\)).
CHAPTER 3

CHEMODIVERGENCE IN ENANTIOSELECTIVE
DESYMMETRIZATION OF BICYCLIC HYDRAZINES

Chiral molecules containing nitrogen-based functional groups are ubiquitous in biologically active compounds and in natural products. This chapter presents the discovery of two enantioselective reactions that give access to chiral functionalized hydrazine molecules. The initial efforts to develop an enantioselective synthesis of cyclopentenylamines revealed an unanticipated reductive arylation process. The latter reaction represents the first example of an intermolecular, asymmetric rhodium-mediated hydroarylation reaction of strained alkenes with boronic acids. Consequently, two classes of molecules are accessible using a single catalytic system by judicious selection of the reagents.

3.1 Introduction

Interest in desymmetrizations by asymmetric ring-opening reactions has grown significantly in recent years.\(^1\) As discussed in Section 1.4 and 1.5, efficient reactions have been developed for the desymmetrization of oxygenated compounds. In contrast, nitrogen-containing molecules have received much less attention.\(^2\) 2,3-Diazabicyclo[2.2.1]hept-5-enes of general structures I and II (herein referred to as ‘bicyclic hydrazines’ and ‘diazabicycles’) have recently emerged as easily synthesized meso bicyclic compounds that can be desymmetrized to form chiral cyclopentene products III (Figure 3-1). Bicyclic hydrazines I are attractive as

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key substrates due to their stability, ease of preparation, and because the hydrazine functionality in III is well recognized as an amine precursor.

![Figure 3-1](image_url) 2,3-Diazabicyclo[2.2.1]hept-5-enes used in organic synthesis to access functionalized cyclopentenes III.

Chiral cyclopentenylamines derived from III are of interest as they are precursors to the core of several bioactive synthetic molecules and natural products (e.g., pactamycin³ and agelastatin A,⁴ Figure 3-2). Accordingly, the relevance of these molecules has seeded efforts in a number of research groups towards the development of nucleophilic ring-opening reactions of I. This strategy is contextualized in the following section in the form of a brief literature survey.

![Figure 3-2](image_url) Biologically active compounds containing a substituted chiral cyclopentanamine core.

### 3.1.1 Precedents in the desymmetrization of bicyclic hydrazines

The desymmetrization of bicyclic hydrazines has been reviewed twice recently, illustrating the hefty body of work relying on this strategy over the last five years.⁵ ⁶ The nucleophilic ring-opening of compounds of type I and II can be categorized in two classes: with heteroatoms and carbon nucleophiles; each occurring by intermolecular or intramolecular modes.
**Desymmetrization by C–O or C–N bond formation**

**Intramolecular Ring-Opening.** The reactivity of bicyclic hydrazines was pioneered by Mackay, who studied thermal and reagent-promoted rearrangements in the 1970’s. The intramolecular ring-opening of bicyclic hydrazines is in fact a rearrangement where a bridged bicycle undergoes a formal allylic substitution to give a fused bicyclic heterocycle (Eqn. 3-1). In the process, a C–N bond is broken to be replaced by a C–O bond. Thermodynamic factors are invoked to drive the reaction towards a cis-1,2-N,O-substituted cyclopentene (e.g., bond strength and cyclic strain). Through rate studies, Mackay and coworkers determined that the acyl substituent on nitrogen controlled the reactivity and rate of isomerization. They also noted that the isomerization was highly accelerated by acidic conditions. Their work led to syntheses of oxadiazine products (Eqn. 3-1), as well as complex heterocycles (Eqn. 3-2).

![Diagram of intramolecular ring-opening](image)

This mode of reactivity was not applied to cyclopentadiene-based bicyclic hydrazines for another 25 years until Micouin and coworkers reported a similar Lewis acid-promoted intramolecular ring-opening. They reported that azaphilic Lewis acids such as SnCl₄ and Zn(OTf)₂ could promote the ring-opening in up to 82 % yield (Scheme 3-1). Micouin later developed a Brønsted acid-catalyzed method which worked well on large scale, and was applied to the synthesis of mannosidase inhibitors. The structure of the rearranged 5,6-fused heterocycle 2 was assigned in analogy to the report of Mackay.

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12 In the case depicted in Equation 3-2, the structure of the product was assigned as a 5,6-fused bicycle based on spectroscopic studies. This product arises from a 6-exo-trig cyclization of the γ carbamate C–O, followed by loss of tert-butyl group upon deprotonation (see Scheme 3-2 for an alternative mechanistic scenario).
Scheme 3–1  Micouin’s Lewis and Brønsted acid-catalyzed intramolecular ring-opening.

The Lewis acid promoted intramolecular ring-opening reported by Micouin was investigated by members of the Lautens group. The original intention was to functionalize the reported 5,6-fused heterocycles 2, but X-ray crystallography revealed that the products formed are in fact 5,5-cis-fused products 3. Our work led to structural revisions of previous reports.\(^\text{15}\)

Martins’ work eventually furnished a catalytic one-pot synthesis of N-arylaminooxazolidinones 4. A Cu\(^I\) salt was found to catalyze the molecular rearrangement and a subsequent coupling to aryl iodides.\(^\text{16}\)

Scheme 3–2  Lautens’ Lewis acid catalyzed rearrangement/C–N coupling sequence.

**Intermolecular Ring-Opening**. Micouin and coworkers also reported the intermolecular ring-opening with heteronucleophiles in what is formally a Pd-catalyzed allylic substitution.\(^\text{13}\)

Oxygen- and nitrogen-based nucleophiles possessing low \(pK_a\) could be added in good yields (mostly phenols and phthalimides). Notably, the palladium-catalyzed method gave the opposite regiochemistry of the acid-catalyzed process; forming 5 as a 1,4-cis substituted product rather than the 1,2-cis substitution pattern discussed above. The efforts of Micouin to find an enantioselective variant were met with limited success, as they obtained only moderate enantiomeric excesses (58% ee); though the ee could be upgraded upon crystallization (Eqn. 3-3).

\(^{15}\) It should be noted that despite our structural revision of 2 from Micouin as being 3, their subsequent synthetic transformations of 2 towards a mannosidase inhibitor are not affected (Scheme 3-1).

Desymmetrization by C–C bond formation

**sp³ Hybridized Nucleophiles.** Alkylmetal nucleophiles are the typical reagents used for alkyl chain addition. However, the selection of alkylmetals available commercially is rather limited, and usually requires strictly anhydrous reaction conditions. The high reactivity or difficulty of preparation of Grignard reagents (alkylmagnesiums) or alkylcuprates has led to the emergence of alkylzincs¹⁷ and, less often, alkylaluminums¹⁸ for enantioselective additions under copper catalysis.

Pineschi and coworkers have developed an enantioselective method to add alkylaluminum species to bicyclic hydrazines.¹⁹ They found that alkylzinc species afforded very low yields and virtually no enantioselectivity using a Cu²⁺/phosphoramidite catalyst system. When alkylaluminum species were used with the same catalyst system, excellent yields and moderate to good enantioselectivities were obtained (Scheme 3–3). Interestingly, Pineschi noted that the chirality of the amine functionality of the phosphoramidite override the chirality of the binaphthol unit, in contrast to what was previously found.¹⁷,¹⁸d Soon after this report, Alexakis and Micouin addressed this atypical mode of stereocontrol, and found that under Pineschi’s specific conditions (in chlorinated solvents), the alkylaluminum species reacts with the phosphoramidite ligand to form dialkylphosphoramidite-aluminate complex 7.²⁰ They also found that the unexpected dialkylphosphoramidite 7 is the active chiral ligand, thus affording comparable enantioselectivities to Pineschi’s report.

![Scheme 3–3 Enantioselective alkylaluminum ring-opening](image)

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**sp² and sp-Hybridized Nucleophiles.** The first intermolecular nucleophilic ring-opening of a bicyclic hydrazine was reported by Kaufmann et al. in 2002. In fact, the ring-opening of 1d was an unexpected side product during the development of an originally planned palladium-catalyzed hydroarylation reaction. Careful selection of the aryl iodides and bicyclic hydrazines afforded the ring-opening product 8 in up to 69% yield. The ring-opening pathway was favored by a fluoride ion. It was proposed that Heck-type carbometalation of the alkenes occurs, followed by fluoride-initiated E₂-type elimination of a palladium(II) fluoride complex (Scheme 3-4). This reaction enabled access to a new class of cyclopentene products and set the precedent for a variety of nucleophiles which can be added using metal catalysis.

![Scheme 3-4 Kaufmann’s discovery of a Pd-catalyzed ring-opening of bicyclic hydrazines.](image)

Building upon the findings of Kaufmann, Radhakrishnan has developed several methods for bicyclic hydrazine ring-opening with allyl, benzyl, azido, vinyl and aryl/heteroaryl nucleophiles. The methods reported by Radhakrishnan’s are typically catalyzed by palladium in the presence of a Lewis acid co-catalyst. Thus, they described the successful addition protocols for allyl nucleophiles, i.e., allylsilanes, allylstannanes, and allylindium reagents (Eqn. 3-4). The reaction displayed the broadest scope with stannyl nucleophiles. Indeed, the method could be extended to the addition of vinylstannanes, aryl- and heteroarylstannanes. Radhakrishnan was also the first to describe the use of arylboronic acids (Eqn. 3-5).

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While all of the above methods are useful, no report of a highly enantioselective variant had been made when we began this work. The aryl nucleophile additions are proposed to proceed through a Heck-type carbometalation to install the aryl group (IV, Scheme 3-5), the development of an enantioselective variant would require an enantiodetermining carbometalation as the key step. Group VIII metals (rhodium and iridium) generally afford higher selectivity in asymmetric carbometalation of alkenes when compared to the analogous palladium-catalyzed reactions. This advantage was no doubt recognized by Pineschi when simultaneously to our report, in 2006, they described the asymmetric ring-opening of bicycles such as 1a with arylboronic acid nucleophiles (Eqn. 3-6). While the best results were obtained with arylboronic acids, they demonstrated that triarylbromons, aryltrifluoroborates and arylzinc halides are also competent nucleophiles, albeit with low to moderate enantioselectivities.

Soon after the initial communication of the work described in this chapter, Pineschi reported the extension of the rhodium-catalyzed addition to alkynylboronate esters (Eqn. 3-7). As with the previous arylboronic acid addition, low to moderate yields and enantioselectivities were obtained (e.g., 67% and 66% ee).

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30 It is the author’s hypothesis that the poor results obtained by Pineschi et al. arise from an unfortunate optimization sequence. Pineschi reported having tested the parameters that we found were the best (solvent, ligands, catalysts, etc.), but they apparently were never combined in a single experiment. The low ee’s is likely due to the use of methanol as solvent; we observed that it usually gave poorer ee than other less coordinating solvents, potentially due to its capacity to coordinate Rh(I) complexes; disrupting the crucial chiral complex.
The extensive body of work on the ring-opening of bicyclic hydrazines demonstrates that they are useful compounds to generate a variety of cyclopentene products. Though numerous nucleophiles have been added to bicyclic hydrazines, the development of general enantioselective variants is a challenge that still remains to be addressed.

### 3.1.2 Research objectives

We recognized that the ring-opening of bicyclic hydrazines I provides products complementary to our preparation of chiral alcohols V from meso allylic bicarbonates (see Chapter 2). Moreover, this strategy yields products with trans stereochemistry and contrasts to methods previously developed in our group with oxa- or azabicycles, where the cis relationship was always observed (VI and VII, Scheme 3-6).\(^\text{32}\)

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Rh(I)-catalysis might provide a solution to the enantioselectivity challenge of the ring-opening of I (Scheme 3-7). We also viewed boronic acids as attractive stable C-nucleophiles.

Our proposal was strongly supported by the precedents of Radhakrishnan and coworkers who had shown that bicycles I can undergo a ring-opening to give hydrazinocyclopentenes III with boronic acids using Pd catalysts. Therefore, our initial efforts focused on finding conditions to provide a rapid synthesis of optically active trans-2-hydrazinoarylatedcyclopentenes III. Such substituted chiral scaffolds, as well as the parent amines VIII, are common in biologically significant molecules.33

3.2 Enantioselective Synthesis of trans-1,2-Arylcyclopentenyl Hydrazines

The proposed enantioselective ring-opening of bicyclic hydrazines eventually revealed a concommittant hydroarylation process. This reaction was found to occur by a mechanism different than the one proposed with Pd, thus opening new synthetic opportunities. This work was the subject of two publications. The first paper described a novel chemodivergent desymmetrization of bicyclic hydrazines.34 The following article reported an in-depth study about the importance of ligand control in an enantioselective 1,4-migration of rhodium catalyst.35

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3.2.1 Starting material synthesis

A variety of [2,2,1]-bicyclic hydrazines were conveniently prepared using Diels-Alder chemistry.\(^{36}\) Thus, freshly distilled cyclopentadiene underwent [4+2] cycloaddition with a range of acylated diazo compounds (Scheme 3-7). Bicyclic hydrazines 1a–1e were thus obtained on scales ranging from 1 g to 10 g; according to the availability of the required diazo reagents 11.

![Scheme 3-7 Preparation of bicyclic substrates by [4+2] cycloaddition.](image)

Some diazo compounds were obtained directly from commercial sources (11a–11c), but the others needed to be prepared by oxidation of the acylated hydrazine precursors. Two general methods were followed to oxidize the hydrazines, selected primarily for the safety of the protocols involved. Due to the instability of 11d, phthalazine 1d was prepared in a one-pot reaction with: cyclopentadiene, 1,2-dihydro-1,4-phthalazinedione and its \textit{in situ} oxidation to the diazoprecursor by lead tetraacetate in dichloromethane (Scheme 3-9).\(^{37}\) Alternatively, diazo 13 was prepared by a more convenient and safer protocol involving calcium hypochlorite.\(^{38}\) Once 13 was formed, cyclopentadiene was added \textit{in situ} to obtain 1e as a solid.

![Scheme 3–8 One-pot oxidation/cycloaddition of hydrazides.](image)


3.2.2 Results & Discussion

Initial findings

The conditions we found previously for the desymmetrizion of meso allylic biscarbonates provided a starting point to explore the enantioselective ring-opening of 1a.39 Preliminary results were promising: (R)-Xylyl-P-Phos40 generated the ring-opened cyclopentene 14a with good enantioselectivity (87% ee), and BINAP showed slightly higher yield (27%, Eqn. 3-8). Additional reaction parameters needed to be modified to reach both high conversion and enantioselectivity.

Assignment of stereochemistry

The relative stereochemical assignment of substituted cyclopentenes 14 was difficult because of the presence of multiple conformers and rotamers in NMR spectra (1H and 13C). Nevertheless, the relative stereochemistry was confirmed to be trans by X-ray crystallography of single crystals of phthalyl substituted 14d (Eqn. 3-9).41

The absolute and relative stereochemistry of Boc-protected 14c was also confirmed by sequential reductions of the alkene, the N–N bond, and deprotection to the free amine and comparison of the optical rotation to literature values (Scheme 3-10).42

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39 See chapter 2, reference 36a.
41 CCDC 661282 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data request/cif.
Scheme 3–9 Derivatization of ring-opened products to assign absolute sense of stereoinduction.

3.2.3 Optimization of the enantioselective ring-opening of [2.2.1] bicyclic hydrazines

Influence of solvent, water, base, and temperature

The ligand BINAP was kept constant throughout the initial screening experiments (Table 3-1). Amongst the solvents tested, THF and non-polar toluene or benzene gave the most promising results (entries 3–8, and 13–19). Ambient temperature was found to give the best compromise between yield and enantioselectivity (in THF: entries 4–8, and in toluene: entries 14–16). The presence of water as co-solvent was found to be necessary to improve conversion (entries 5 and 6). It is presumed that water is essential for regeneration of the catalyst. The presence of Cs$_2$CO$_3$ was found to be beneficial to the yield, regardless of the solvent tested. The base also improved ee’s by at least 10% (entries 3 and 4; 9 and 10; 13 and 14; 20 and 21).

### Table 3–1 Influence of reaction parameters on the ring-opening of 1a with BINAP.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>additive</th>
<th>base</th>
<th>Temp. (°C)</th>
<th>Yield [%]</th>
<th>Ee [%]</th>
</tr>
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<tbody>
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<td>1</td>
<td>MeCN</td>
<td>H₂O</td>
<td>-</td>
<td>60</td>
<td>Trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>60</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
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<td>H₂O</td>
<td>-</td>
<td>60</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
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<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>60</td>
<td>27</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
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<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>20</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
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<td>-</td>
<td>Cs₂CO₃</td>
<td>20</td>
<td>6</td>
<td>70</td>
</tr>
<tr>
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<td>THF</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>0</td>
<td>32</td>
<td>71</td>
</tr>
<tr>
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<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>-20</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
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<td>H₂O</td>
<td>-</td>
<td>60</td>
<td>35</td>
<td>51</td>
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<tr>
<td>10</td>
<td>Dioxane</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>60</td>
<td>20</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>Dioxane</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>0</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Dioxane</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>20</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>Toluene</td>
<td>H₂O</td>
<td>-</td>
<td>60</td>
<td>24</td>
<td>46</td>
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<tr>
<td>14</td>
<td>Toluene</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>60</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>15d</td>
<td>Toluene</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>20</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>16</td>
<td>Toluene</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>0</td>
<td>15</td>
<td>n.d.</td>
</tr>
<tr>
<td>17</td>
<td>Benzene</td>
<td>H₂O</td>
<td>-</td>
<td>20</td>
<td>45</td>
<td>75</td>
</tr>
<tr>
<td>18</td>
<td>Benzene</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>20</td>
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<td>73</td>
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<td>Benzene</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>0</td>
<td>70</td>
<td>n.d.</td>
</tr>
<tr>
<td>20</td>
<td>DCE</td>
<td>H₂O</td>
<td>-</td>
<td>20</td>
<td>10</td>
<td>22</td>
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<td>21</td>
<td>DCE</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>20</td>
<td>6</td>
<td>39</td>
</tr>
<tr>
<td>22</td>
<td>CHCl₃</td>
<td>H₂O</td>
<td>Cs₂CO₃</td>
<td>20</td>
<td>38</td>
<td>60</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1a (40 mg, 0.166 mmol), 2 equiv Ph(B(OH))₂, 5 mol% [Rh(cod)OH]₂, 12 mol% BINAP, 1 equiv. Cs₂CO₃ in 10:1 solvent/water mixture, stirred overnight. † Isolated yield. ‡ Determined by chiral HPLC analysis of isolated product. § Average of at least two experiments.
Screening of ligands

A strong ligand-dependence on reactivity was observed, as shown in Table 3-2. A range of ligands was examined using phenylboronic acid, but only bidentate \(P,P\)-ligands gave useful levels of enantioselectivity (Table 3-2). Good levels of enantioselectivity could be obtained with a subset of ligands, such as \(P\)-Phos and Difluorphos\(^{43}\) (entries 1-4). BINAP and its derivatives showed slightly lower selectivity, but marginally superior conversion (entries 5-8). Ferrocenyl diphosphine ligands showed high conversion, but modest enantioselectivity (entries 10-18). As we have observed in the past, tert-Bu-JOSIPHS (J002, Figure 3-3)\(^{44,45}\) seems to show unrivalled reactivity and enantioselectivity in Rh-catalyzed reactions with bicyclic systems.

---

**Figure 3-3** Ligands used in this chapter.


\(^{45}\) J001–J010 nomenclature (as well as W001–W008) is used throughout this chapter to match the commercial numbering of Solvias, thereby facilitating product retrieval, should there be need for future investigations.
Table 3–2  **Ligand screening for rhodium-catalyzed ring-opening of diazabicycles.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>ee 14a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Xylyl-P-Phos, L12</td>
<td>60</td>
<td>18</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Xylyl-P-Phos, L12</td>
<td>25</td>
<td>&lt; 10</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>P-Phos, L11</td>
<td>25</td>
<td>&lt; 10</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Difluorphos, L6</td>
<td>25</td>
<td>&lt; 10</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>BINAP, L1</td>
<td>60</td>
<td>15</td>
<td>n.d</td>
</tr>
<tr>
<td>6</td>
<td>BINAP, L1</td>
<td>25</td>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Tolyl-BINAP, L2</td>
<td>25</td>
<td>&lt; 10</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>Xylyl-BINAP, L3</td>
<td>0</td>
<td>&lt; 10</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>SegPhos, L7</td>
<td>25</td>
<td>&lt; 10</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>Josiphos, J001</td>
<td>25</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
<td>11</td>
<td>t-Bu-Josiphos, J002</td>
<td>25</td>
<td>78</td>
<td>69</td>
</tr>
<tr>
<td>12</td>
<td>t-Bu-Josiphos, J002</td>
<td>0</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td>J008</td>
<td>25</td>
<td>(70)</td>
<td>68</td>
</tr>
<tr>
<td>14</td>
<td>J009</td>
<td>25</td>
<td>(80)</td>
<td>-75</td>
</tr>
<tr>
<td>15</td>
<td>J011</td>
<td>25</td>
<td>(80)</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>J003</td>
<td>25</td>
<td>(50)</td>
<td>16</td>
</tr>
<tr>
<td>17</td>
<td>J005</td>
<td>25</td>
<td>&lt; 10</td>
<td>28</td>
</tr>
<tr>
<td>18</td>
<td>J006</td>
<td>25</td>
<td>(80)</td>
<td>80</td>
</tr>
<tr>
<td>19</td>
<td>J011</td>
<td>25</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

Reaction conditions: Rh catalyst (5 mol%), ligand (12 mol%), and base (2 equiv.) were premixed in THF:water (10:1); followed by a solution of 1a and PhB(OH)2 (2 equiv), and stirred at r.t. for 16 h under Ar. Yield of isolated products; “< 10” indicates that low conversion was observed by TLC; parentheses represent yield based on visual estimation of TLC analysis. Enantiomeric excess determined by chiral HPLC. Reaction performed using 1d. Compound 18a was a major side product.

Importantly, a byproduct was observed with Josiphos-based ligand J006, and was later identified as the reductive arylation product 18a (see Section 3.4).

The most promising ligands were examined more carefully in THF and toluene in an effort to increase yield and enantioselectivity (Table 3-3). Notably, t-Bu-Josiphos (J002) was unique in that the results were not affected by the presence of water, whereas water was deleterious with the other ligands (entries 1–12). Also, THF was found to give much higher yields than toluene with most ligands.
Table 3–3  Optimising conditions for promising ligands.

![Diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>L</th>
<th>Solvent</th>
<th>conversion (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>ee 14a (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-Tol-BINAP</td>
<td>L3</td>
<td>THF + H₂O (10:1)</td>
<td>10</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>(R)-Tol-BINAP</td>
<td>L3</td>
<td>THF</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>(R)-Tol-BINAP</td>
<td>L3</td>
<td>Toluene</td>
<td>40</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>(S)-P-Phos</td>
<td>L11</td>
<td>THF + H₂O (10:1)</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>(S)-P-Phos</td>
<td>L11</td>
<td>THF</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>(S)-P-Phos</td>
<td>L11</td>
<td>Toluene</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>(R)-DiFluorphos</td>
<td>L6</td>
<td>THF + H₂O (10:1)</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>(R)-DiFluorphos</td>
<td>L6</td>
<td>THF</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>(R)-DiFluorphos</td>
<td>L6</td>
<td>Toluene</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>(R)-SegPhos</td>
<td>L7</td>
<td>THF + H₂O (10:1)</td>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>11</td>
<td>(R)-Segphos</td>
<td>L7</td>
<td>THF</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td>(R)-Segphos</td>
<td>L7</td>
<td>Toluene</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>13</td>
<td>(R,S)-Josiphos 01</td>
<td>J001</td>
<td>Toluene</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>14</td>
<td>(R,S)-Josiphos 02</td>
<td>J002</td>
<td>THF + H₂O (10:1)</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>15</td>
<td>(R,S)-Josiphos 02</td>
<td>J002</td>
<td>THF</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>16</td>
<td>(R,S)-Josiphos 02</td>
<td>J002</td>
<td>Dioxane</td>
<td>95</td>
<td>70</td>
</tr>
<tr>
<td>17</td>
<td>(R,S)-Josiphos 02</td>
<td>J002</td>
<td>Toluene</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>18</td>
<td>(R,S)-Josiphos 06</td>
<td>J006</td>
<td>THF + H₂O (10:1)</td>
<td>100&lt;sup&gt;d&lt;/sup&gt;</td>
<td>67</td>
</tr>
<tr>
<td>19</td>
<td>(R,S)-Josiphos 06</td>
<td>J006</td>
<td>THF</td>
<td>100&lt;sup&gt;d&lt;/sup&gt;</td>
<td>66</td>
</tr>
<tr>
<td>20</td>
<td>(R,S)-Josiphos 06</td>
<td>J006</td>
<td>Toluene</td>
<td>50&lt;sup&gt;d&lt;/sup&gt;</td>
<td>69</td>
</tr>
<tr>
<td>21</td>
<td>(R,S)-Josiphos 09</td>
<td>J009</td>
<td>THF + H₂O (10:1)</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>22</td>
<td>(R,S)-Josiphos 09</td>
<td>J009</td>
<td>THF</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>23</td>
<td>(R,S)-Josiphos 09</td>
<td>J009</td>
<td>Toluene</td>
<td>80</td>
<td>73</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1a (40 mg, 0.166 mmol), 2 equiv PhB(OH)<sub>2</sub>, 5 mol% [Rh(cod)OH]<sub>2</sub>, 12 mol% ligand, 1 equiv. Cs₂CO₃ in 10:1 solvent/water mixture, stirred at r.t. overnight. <sup>b</sup> Visual estimation of conversion by TLC analysis. <sup>c</sup> Determined by chiral HPLC analysis of crude reaction mixture (filtered on SiO₂ plug). <sup>d</sup> Significant presence of product 18a by TLC analysis.

J002 was selected as ligand of choice for further studies. Although it did not give the highest ee, it was appealing for its robustness: (i) it tolerated water, (ii) its reaction profile was the cleanest (spot-to-spot reaction), and (iii) it displayed good reactivity in a variety of solvents without affecting its enantioinduction. Again, J006 was found to give rise to substantial amounts of a side-product (not quantified). We came back later to this intriguing reactivity, and exploited it in a hydroarylation process, as discussed in Section 3.5.
Impact of the arylboronic acid on enantioselectivity

A preliminary screen of boronic acids showed that t-Bu-Josiphos afforded excellent enantioselectivity with ortho-substituted boronic acids (Table 3-4). For example, with o-tolylboronic acid, 98% ee was reproducibly obtained (entries 5 and 6). Although the yield was low at an average of 45%, this result provided important information about the transition state of the reaction. Accordingly, we presumed that steric bulk close to the reacting site was necessary to impart good stereodifferentiation. In addition, the electron-density of the aromatic moiety seemed to display a reactivity/selectivity pattern. Arylboronic acids bearing an electron withdrawing group, i.e., CF₃, were less reactive than phenyl, but gave higher ee; whereas electron rich aryl groups gave high conversion and lower ee (cf. entries 1–3).

Table 3-4  Influence of the boronic acids.

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>R</th>
<th>Products</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,S)-t-Bu-Josiphos</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>19a</td>
<td>20</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>(R,S)-t-Bu-Josiphos</td>
<td>H</td>
<td>14a</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>(R,S)-t-Bu-Josiphos</td>
<td>3,4-(MeO)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>20a</td>
<td>89</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>(R,S)-t-Bu-Josiphos</td>
<td>2-Me-4-MeO</td>
<td>21a</td>
<td>28</td>
<td>90</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(R,S)-t-Bu-Josiphos</td>
<td>2-Me</td>
<td>22a</td>
<td>45</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>(S,R)-t-Bu-Josiphos</td>
<td>2-Me</td>
<td>22a</td>
<td>44</td>
<td>-98</td>
</tr>
<tr>
<td>7</td>
<td>(±)-t-Bu-Josiphos</td>
<td>2-Me</td>
<td>22a</td>
<td>56</td>
<td>±</td>
</tr>
<tr>
<td>8</td>
<td>(R,S)-t-Bu-Josiphos</td>
<td>2-COOMe</td>
<td>23a</td>
<td>20</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1a (40 mg, 0.166 mmol), 2 equiv PhB(OH)<sub>2</sub>, 5 mol% [Rh(cod)OH]<sub>2</sub>, 12 mol% ligand, 1 equiv. Cs₂CO₃ in 10:1 solvent/water mixture, stirred at r.t. overnight. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC analysis of crude reaction mixture (filtered on SiO₂ plug). <sup>d</sup> Average of two runs (42 and 47%).

Influence of the N-protecting groups

Different substituents on the substrate’s hydrazine were examined to see whether the reactivity could be improved. Also, having access to various protecting groups would allow greater synthetic versatility for the resulting cyclopentenes. It was reasoned that the nature of the substituents on the hydrazines might polarize the alkene, thus affecting the propensity of the bicycle to undergo ring-opening.

Three types of carbamates were tested (Cbz, Boc, Phthalyl) and they all gave similar results: good yields, but modest ee (Table 3-5, entries 1–5). Phthalhydrazide 1d however gave consistently excellent yield. The increase in yield suggests that improvement of the
leaving group ability of the hydrazide may prevent a competing 1,4-migration process from taking place (see Section 3.4).

Table 3–5 Influence of the hydrazine protecting group.

<table>
<thead>
<tr>
<th>entry</th>
<th>1</th>
<th>14</th>
<th>PG</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>ee 14 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>14a</td>
<td>COOEt</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>14b</td>
<td>COOBn</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1b</td>
<td>14b</td>
<td>COOBn</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>14c</td>
<td>Boc</td>
<td>85</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>14d</td>
<td>Phthalimide</td>
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<td>70</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1d</td>
<td>14d</td>
<td>Phthalimide</td>
<td>99±</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1 (0.166 mmol), 2 equiv PhB(OH)<sub>2</sub>, 5 mol% [Rh(cod)OH]<sub>2</sub>, 12 mol% ligand, 1 equiv. Cs<sub>2</sub>CO<sub>3</sub> in 10:1 solvent/water mixture, stirred at r.t. overnight. **Isolated yield.** <sup>d</sup> Determined by chiral HPLC analysis. **Racemic ligand used.**

Bis-Boc-protected diazabicycle 1c was selected as the substrate of choice primarily for the ease of deprotection and for practical reasons. 1c is a free-flowing powder, making for easy handling. Its preparation on scale is also convenient, involving simple filtration of the reaction mixture to obtain the substrate as analytically pure material.

Since our goal is to develop a practical method, it was important to investigate its robustness. We tested the reaction with Boc-protected substrate 1c and phenylboronic acid (Table 3-6). Using tert-Bu-Josiphos (J002) was found to actually require small amounts of water to give useful yields (entries 2–6 and 8). The absence of water led to diminished yields, without affecting enantioselectivity significantly. Surprisingly, a reaction conducted in an open vessel exposed to atmosphere gave results similar to reactions conducted in the same conditions under inert atmosphere (entries 4–6). Though yield are low, it illustrates that the Rh(I) catalyst of this reaction is less sensitive than other systems.<sup>46</sup> A reaction conducted on one mmol of substrate generated synthetically useful amounts of products (65%, entry 7).<sup>47</sup>

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<sup>46</sup> See Chapter 2 for examples; as well as the references cited in Section 2.1.
<sup>47</sup> The reaction conditions used for this experiment were not optimized. It can be anticipated that results would be better under the fully optimized reaction conditions shown in Table 3-7.
Table 3-6 Investigation of the robustness of the reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Comment</th>
<th>Yield (%) a,b</th>
<th>ee 14c (%) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)Cl]_2</td>
<td>THF/H_2O (10:1)</td>
<td>-</td>
<td>65</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)OH]_2</td>
<td>THF/H_2O (10:1)</td>
<td>-</td>
<td>98</td>
<td>67</td>
</tr>
<tr>
<td>3^eg</td>
<td>[Rh(cod)OH]_2</td>
<td>THF/H_2O (45:1)</td>
<td>-</td>
<td>72</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(cod)OH]_2</td>
<td>THF</td>
<td>N_2 atm.</td>
<td>24</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)OH]_2</td>
<td>THF</td>
<td>Ar atm.</td>
<td>37</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(cod)OH]_2</td>
<td>THF</td>
<td>in Air (open vessel)</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(cod)OH]_2</td>
<td>THF</td>
<td>1 mmol</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>8^d</td>
<td>[Rh(cod)OH]_2</td>
<td>Toluene/THF/H_2O</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>[Rh(cod)_2]OTf</td>
<td>THF</td>
<td>-</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)_2</td>
<td>THF</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Pd(CH_3CN)_2Cl_2</td>
<td>MeOH</td>
<td>-</td>
<td>84</td>
<td>1</td>
</tr>
<tr>
<td>12^g</td>
<td>Pd(CH_3CN)_2Cl_2</td>
<td>MeOH</td>
<td>-</td>
<td>10</td>
<td>42</td>
</tr>
</tbody>
</table>

a Reaction conditions: 1c (40 mg, 0.135 equiv), 2 equiv PhB(OH)_2, 10 mol% metal catalyst, 12 mol% ligand, 1 equiv. Cs_2CO_3 in 10:1 solvent/water mixture, stirred at r.t. overnight. b Isolated yield. c Determined by chiral HPLC analysis. d Racemic ligand used. e Hydroarylation side-product 18c observed. f Average of two runs (71 and 73% yields). g Used Tol-BINAP as ligand.

Entry 1 shows that chloride rhodium complex is catalytically competent for the reaction, but less efficient; alternatively, [Rh(cod)Cl]_2 did not give product without base and water, suggesting in situ formation of [Rh(cod)OH]_2 (not shown). In addition to rhodium catalysts, palladium was tested under conditions previously developed in ring-opening of bicyclic compounds (entries 11 and 12). The reaction proceeded to give yields similar to rhodium, and confirmed Rhadakrishnan's results (compare entries 2 and 11). However, the enantio-meric excess of the products was low.

---

48 Conditions for Pd catalyzed reaction were derived from: Lautens, M.; Dockendorff, C. Org. Lett. 2003, 5, 3695.
49 See references 24a, 25, and 27.
3.2.3 Scope of the boronic acids

The scope of the reaction was studied with the optimized conditions; that is, with Boc-protected bicyclic hydrazine 1c, [Rh(cod)OH]$_2$ as precatalyst, tert-Bu-Josiphos as chiral ligand, and tetrahydrofuran as solvent. Although no water was intentionally added to the reaction, strictly anhydrous conditions are not appropriate for this reaction. It appeared that simply weighing the reagents in air provides sufficient moisture for the reaction to take place efficiently. Table 3-7 summarizes the results using a wide range of aryl- and heteroaryl boronic acids. Some of the entries demonstrate the tolerance of the catalytic system to variations in the conditions.

Ortho-substituted boronic acids were ideal in this transformation, giving products with excellent enantioselectivity (ee > 96%, entries 1–15). The nature of the ortho substituent could be varied extensively, giving good yields with electron rich or neutral groups. It is apparent that steric bulk is important for generating good ee. Reaction conditions were mild and compatible with various functional groups (entries 12–21). As observed in Table 3-5, electron rich boronic acids generally led to higher yields and lower ee’s, whereas electron deficient systems proved less reactive and more selective (entries 16–21). With aryl groups not substituted in the 2-position, the enantioselectivity seemed to follow a trend where the electron rich aryl nucleophile gave the highest ee. A vinylboronic acid also ring-opened 1c in high yield but poor enantioselectivity, again reinforcing the hypothesis that steric hindrance is needed to help stereodifferentiation (trans-1,2-styrylboronic acid gave 33 with 99% yield, 44% ee). Unfortunately, the 1,1-styrylboronic acid analog did not give the desired product, and led to a complex mixture of unidentified products instead (entry 23). A limitation was observed with arylboron reagents bearing either bromide or iodide substituents. These arylhalides left the substrate untouched, and the catalyst rapidly changed colour in solution, presumably undergoing non-productive oxidative pathways.

Decreased yield of ring-opening product was caused, in most cases, by a competing C–H insertion leading to product 18, a mechanism that appeared to be more facile with electron deficient nucleophiles (see products 24, 27, 30, 18c, 36, and 37, Table 3-8). Nevertheless, the product ratio could be influenced to favour ring-opening by performing the reaction in a toluene/THF solvent system (c.f., entries 1 and 2; and 5 and 6).$^{50}$

---

$^{50}$ In cases where the boronic acid was insoluble in toluene, a few drops (~0.05 mL) of THF were added to the substrate solution until it became homogeneous. It should be noted that the reaction mixture was biphasic after addition of water.
Table 3–7  

Ring-opening of diazabicycles with substituted boronic acids.

![Schema](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>22c</td>
<td>32</td>
<td>97</td>
</tr>
<tr>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Me</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>3&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>24F</td>
<td>46</td>
<td>&gt;98</td>
</tr>
<tr>
<td>4&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td>53</td>
<td>99</td>
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<td>25</td>
<td>66</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6&lt;sup&gt;g&lt;/sup&gt;</td>
<td>78</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>26</td>
<td>68</td>
<td>99</td>
</tr>
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<td>8&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>21c</td>
<td>55</td>
<td>99</td>
</tr>
<tr>
<td>9&lt;sup&gt;f&lt;/sup&gt;</td>
<td>54</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>10&lt;sup&gt;d,g&lt;/sup&gt;</td>
<td>27</td>
<td>46</td>
<td>91</td>
</tr>
<tr>
<td>11&lt;sup&gt;f&lt;/sup&gt;</td>
<td>51</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>28Cl</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>13&lt;sup&gt;d&lt;/sup&gt;</td>
<td>29</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>14&lt;sup&gt;g&lt;/sup&gt;</td>
<td>99</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>&lt;5&lt;sup&gt;f&lt;/sup&gt;</td>
<td>96</td>
</tr>
<tr>
<td>16&lt;sup&gt;d&lt;/sup&gt;</td>
<td>31</td>
<td>58</td>
<td>86</td>
</tr>
<tr>
<td>17&lt;sup&gt;d,j&lt;/sup&gt;</td>
<td>19c</td>
<td>49</td>
<td>84</td>
</tr>
<tr>
<td>18&lt;sup&gt;g&lt;/sup&gt;</td>
<td>37</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>83</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>20&lt;sup&gt;l&lt;/sup&gt;</td>
<td>32</td>
<td>&lt;10</td>
<td>73</td>
</tr>
<tr>
<td>21</td>
<td>20c</td>
<td>80</td>
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</tr>
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<td>22</td>
<td>33</td>
<td>99</td>
<td>44</td>
</tr>
<tr>
<td>24&lt;sup&gt;d&lt;/sup&gt;</td>
<td>35</td>
<td>7</td>
<td>n.d.</td>
</tr>
<tr>
<td>25&lt;sup&gt;d,k&lt;/sup&gt;</td>
<td>36</td>
<td>Traces</td>
<td>n.d.</td>
</tr>
<tr>
<td>26&lt;sup&gt;f&lt;/sup&gt;</td>
<td>37</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>27&lt;sup&gt;f&lt;/sup&gt;</td>
<td>55</td>
<td>40</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1c (40 mg, 0.135 mmol), 2 equiv PhB(OH)<sub>2</sub>, 5 mol% [Rh(cod)OH]<sub>2</sub>, 12 mol% ligand, 1 equiv. Cs<sub>2</sub>CO<sub>3</sub> in THF, stirred at r.t. overnight.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by chiral HPLC analysis of isolated product.

<sup>d</sup> Average of at least two experiments.

<sup>e</sup> Toluene/THF/H<sub>2</sub>O (7:2:1).

<sup>f</sup> Hydroarylation side-product observed.

<sup>g</sup> Conducted in THF/H<sub>2</sub>O (15:1).

<sup>h</sup> Conducted in THF/H<sub>2</sub>O (100:1).

<sup>i</sup> 39% hydroarylation observed.

<sup>j</sup> Conducted at -78 ºC.

<sup>k</sup> Only hydroarylation observed.

**Limitations**

The conditions developed above were applied to the ring-opening of other cyclic hydrazines 41 and 43 (Eqns. 3-12 and 3-13). Unfortunately, none of the allylic substitution products 42 or 44 were observed. In the case of [2.2.2]-bicyclohydrazine derivative 41, 51 only starting

material was recovered, even when the reaction was heated to 100 °C for prolonged periods of time (in dioxane/water).

With heterocycle 43, the hope was to access the branched butenylhydrazide 44, a useful chiral building block. Alas, only isomerization of the alkene to diazacyclohexenyl product 45 was observed; even with the reactive 2-methoxy-5-chlorophenylboronic acid, which had been observed to favor allylic displacement due to the presence of a meta group minimizing a C–H insertion pathway. With heterocycle 43, the hope was to access the branched butenylhydrazide 44, a useful chiral building block. Alas, only isomerization of the alkene to diazacyclohexenyl product 45 was observed; even with the reactive 2-methoxy-5-chlorophenylboronic acid, which had been observed to favor allylic displacement due to the presence of a meta group minimizing a C–H insertion pathway.\(^\text{52}\) Rhodium(I)-catalyzed isomerization of alkenes to thermodynamically favored products is known.\(^\text{53}\)

3.2.4 Discovery of a reductive arylation process occurring via a 1,4-Rh migration

With heteroaryl nucleophiles, only traces of the expected ring-opened cyclopentenes were observed (entries 15, 25, and 26). In some cases, such as with 3-thiophenylboronic acid, a single product was isolated in high yield. This initially puzzling side-product was eventually identified as a hydroarylated bicycle, e.g. 38 (Eqn. 3-10). After characterization, these side-products could be found in varying proportions in several cases, e.g. entries 3, 4, 6, 8, 9–11, 15, 17, 25 and 26, Table 3-7.

---

\(^{52}\) See Table 3-7, entry 12.

Although the hydroarylation process had been reported earlier with palladium by Kaufmann, it had never been observed with arylboronic acids, or with rhodium.\textsuperscript{54} A reductive arylation reaction was revealed upon deuteration experiments with heteroaryl derivatives. For example, the reaction with pyrimidine derivative 39 in the presence of D\textsubscript{2}O afforded the reductive arylation product 40 in 96\% ee with almost complete deuterium incorporation at the ortho aromatic position (Eqn. 3-11).

\begin{align*}
\text{MeO} & \quad \text{N} \quad \text{N} \\
\text{B} & \quad \text{B} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{B} & \quad \text{B} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\end{align*} \\
(3-11) \\
\text{d-40, 69 \% yield} \\
[\alpha]_{D}^{25} \approx 25.5

Hydroarylation also occurred in cases where the arylboronic acids bore a sufficiently activated hydrogen in the 2-position. It is thought that the sigma inductive effect of neighbouring heteroatoms facilitates a C–H insertion reaction (see below, Sections 3.4 and 3.5). In addition, the fact that the enantioselectivity observed for hydroarylated products 30 and 36 matched that of ring-opened products 40 and 38, respectively, suggested that both products arise from a common mechanism, which is is discussed in the next section.

### 3.3 Mechanistic Considerations

This section describes a plausible mechanism accounting for the two types of products observed with [2.2.1]-bicyclic hydrazines. It is followed by studies supporting chemodivergent pathways, and thus provide the impetus to exploit the 1,4-metal migration process.

#### 3.3.1 Proposed catalytic cycle

The proposed mechanism for the rhodium-catalyzed formation of products F and G (i.e., 14 and 18, respectively) is illustrated in Scheme 3-11. Initially, the preformed active catalyst A undergoes a fast transmetalation to form the Ar–Rh\textsuperscript{I} complex B. The alkene of diazabicycle 1, activated by coordination to the metal center, inserts into the metal-carbon bond of B as the enantiodiscriminating step to give the key carbometalated intermediate C. Ring-opening of C

---

\textsuperscript{54} It should be noted that Pineschi and coworkers observed some unidentified byproducts which, in retrospect, may have been 18c. See reference 29 of this chapter.

\textsuperscript{55} The non-deuterated remainder of 39 may have formed by competing proto-demetallation with the boronic acid.

\textsuperscript{56} For a review on rhodium and palladium 1,4-shifts see: Ma, S.; Gu, Z. \textit{Angew. Chem. Int. Ed.} \textbf{2005}, \textit{44}, 7512.
can occur through anti-β-nitrogen elimination of the hydrazide leaving group to give the trans-cyclopentene 2 ($k_1$). Carborhodation of the alkene occurring on the more accessible exo face of the diazabicycle accounts for the trans diastereoselectivity observed in the ring-opened products 2. Alternatively, if the ortho-hydrogen is sufficiently activated, the RhI center of C can undergo an oxidative C–H insertion to give the RhIII complex D ($k_2$). Reductive elimination leads to the Rh-C(sp2) complex E, which is thermodynamically more stable than Rh-C(sp3) complex C. It results in a 1,4-migration of the Rh center. Subsequent proto-demetalation leads to the observed reductive arylation product 3, where the proton source is presumed to be the boronic acid.

A working hypothesis is that, if the C–H bond insertion rate is slow (i.e., not activated), a water molecule can fill the free coordination site in C, therefore preventing the formation of D. Thus, excess water in a less polar solvent system may favor the ring-opened products 2 (Table 3–7, entries 1 and 2).

![Scheme 3–10 Proposed catalytic cycle for the chemodivergent rhodium(I)-catalyzed desymmetrization of bicyclic hydrazines.](image)

The above mechanism invoking a common intermediate is proposed on the basis of the correlating enantioselectivity observed between the ring-opened hydrazines and the arylated diazabicycles (30 and 40, vs 19c and 47; Figure 3-5).
Equation 3-14 illustrates that 2-fluoroboronic acid seems to lie at the inflexion point of the competing reaction pathways, as both products 24 and 46 were obtained (53% and 45% yield, respectively). In this experiment, both products were again obtained with equal ee values.

Similar 1,4-migrations of rhodium have been reported previously: notably in a serial C–H activation sequence observed by Miura,\(^57\) and in cyclization reactions reported by Hayashi,\(^58\) Iwasawa,\(^59\) and Murakami.\(^60\) However, a process involving chemodivergence had never been reported.

---


3.3.2 Deuteration studies

It would be logical to think that arylated bicycles G arise from simple protonation of the carbometalated intermediate C. A simple way to test the validity of the proposed mechanism was to conduct the reaction in the presence of D$_2$O. Deuteration experiments supported formation of intermediate E. When conducting the reaction in a THF:D$_2$O mixture, deuterium incorporation was observed exclusively on the aromatic moiety (Scheme 3–12). These results were found to be consistent with several boronic acids.

Moreover, formation of hydridorhodium intermediate D is supported by the observation of deuterium transfer between the aromatic position and the diazabicycle. For example, when perdeuterated phenylboronic acid was used, 96% sequential deuterium transfer occurred on $sp^3$ carbons of bicyclic cores of 48 (Eqn. 3–15). This experiment was very important, in spite of the uselessness of complex product 48 generated: it showed that it is possible to create a new C–C bond at the ortho position of the aromatic group.

Our next efforts thus focused on exploiting the hydroarylation pathway. Altering the course of the reaction to obtain selectively products F or G required to study the factors influencing the reaction rates $k_1$ and $k_2$ (Scheme 3–11).
3.4 Enantioselective Hydroarylation of Bicyclic Hydrazines

This section explores the synthetic potential of a rhodium 1,4-migration. Investigations focused first on understanding the factors influencing the reaction divergence. The transformation could then be extended to substrates not necessarily bearing an activated C–H on the aryl moiety. Finally, a brief scope of the reaction is shown. The results presented herein arise from collaborative efforts from the author and Jane Panteleev. The project was conceived and initiated by the author; then J. Panteleev further investigated the opportunities offered by this new mode of reactivity.\(^\text{61}\)

3.4.1 Hydroarylation reaction proceeding by a 1,4-rhodium migration

The enantioselective reductive arylation products 18a were initially minor byproducts (Tables 3-2 and 3-3). However, the identification of sequential addition/C–H activation warranted more studies in view of its applicability to more sophisticated reactions; particularly in cascade sequences.\(^\text{62}\)

\[
\begin{align*}
\text{N}^\text{N} & \text{CO}_2\text{Et} \\
\text{N}^\text{N} & \text{CO}_2\text{Et} \\
\text{Ph-B(OH)}_2 & \\
& [\text{Rh(cod)OH]}_2 \\
& (R,S)-\text{Josiphos} \text{[006]} \\
\text{C}_2\text{CO}_3 & \\
\text{THF/H}_2\text{O} (10:1) \text{r.t., 16 h} \\
& 100\% \text{conversion} \\
& 14a \\
& 18a
\end{align*}
\]

This type of reductive arylation had been observed in the ring-opening of oxa- and azanorbornenes, by C. Dockendorff in our lab.\(^\text{63}\) However, it was deemed a nuisance; either because separation of the products was not possible, or due to the doubtful synthetic interest of the products (50, Scheme 3-13). In the case at hand, though, the possibility to cleave the N–N bond made the transformation much more attractive as it might allow to prepare highly functionalized diaminocyclopentenes, e.g. 51.

\(^{61}\) J.P.’s contributions are acknowledged where appropriate. For a full account of this work, see: Panteleev, J.; Menard, F., Lautens, M. Adv. Synth. Cat. 2008, 350, 2983.


\(^{63}\) Dockendorff, C. J.; PhD thesis, University of Toronto (Canada), 2006.
Scheme 3-12 Hydroarylation of diazabicycles offers a synthetic route to substituted cyclopentylidiamines.

Divergence of the Rh-catalyzed ring-opening towards a hydroarylation is surprising when one considers the reaction developed by Kaufmann with Pd, especially the example shown in Equation 3-16. In their case, a high yield of ring-opened products 10 was obtained, whereas our Rh-catalyzed system afforded almost exclusively the hydroarylation products 40 (Eqn. 3-17).

Consequently, the hydroarylation products formed under Rh-catalysis open up new synthetic opportunities because of the mechanism being markedly different than the one proposed with Pd. In previous work, we observed that organoboron reagents add to the alkene of diazabicycle I without ring opening. This difference in reactivity can perhaps be explained by the required oxidative step in the metal migration: with palladium, this would require a

---

(3-16)

---

(3-17)

---

Pd$^{II}$/Pd$^{IV}$ oxidation, whereas the analogous rhodium process involves a Rh$^{I}$/Rh$^{III}$ manifold, which should be much more accessible energetically under our mild conditions.

Reduction and deprotection of compounds V is known to prepare the parent diamines VI (Scheme 3-14). We anticipated that developing a reaction to access these products enantioselectively would be highly useful. Such substituted chiral scaffolds are common in biologically significant molecules.

Fundamentally, two questions needed to be answered: (1) can we extend the 1,4-migration of Rh to non-activated aryl groups? and (2) can we trap key intermediate E shown in Scheme 3-11 with electrophiles different that H$^+$? Our hypothesis was that we may find conditions to favor a Rh$^{I}$/Rh$^{III}$ oxidation pathway, thereby facilitating the oxidative insertion of rhodium(I) even with “non-activated” aryl groups.

3.4.2 Optimization to favor the 1,4-Rh migration

The results discussed above show that outside of ligand control, rhodium 1,4-migration can be favoured by utilizing $\sigma$-withdrawing groups on the aryl moiety to facilitate C–H insertion (Table 3-7), and using coordinating solvents to stabilize Rh(III) intermediate D (Table 3-3 and 3-4).

The chemoselectivity of the reaction was somewhat influenced by the solvent. Whereas the reductive arylation product was readily observed in THF (~20% yield), it either

---


disappeared or diminished significantly in reactions run in a THF/toluene mixture (Table 3-7, entries 1–6, 13 and 14). Such an outcome suggested that coordinating solvents may favour rhodium C–H insertion by stabilizing a Rh(III) complex, while non-coordinating solvents favour ring-opening. For example, running the reaction in a mixture of toluene/THF/water (7:2:1) gave the ring-opened product 22c as the sole product. In contrast, the hydroarylated product 22d was observed in 12% yield in pure THF/water (50:1); the remainder being unreacted 1c (Eqn 3-19). It should be mentioned that neither changes in concentration nor temperature influenced the product distribution.

\[
\begin{align*}
\text{N} & \quad \text{Boc} \\
& \quad \text{N} & \quad \text{Boc} \\
\text{1a} & \quad \text{o-Tol}-\text{B(OH)}_2 & \quad \text{[Rh(cod)OH]}_2 \quad \text{t-Bu-Josiphos J002} & \quad \text{Solvent, r.t., 16 h} & \quad \text{HN}^\text{Boc} \\
& \quad \text{N} & \quad \text{Boc} \\
\end{align*}
\]

Influence of ligands

Product 18c was initially observed during ligand screening (Table 3-3). The influence of ligand on the 14:18 product ratio was thus examined with ferrocenyl ligand series from a Solvias kit. A trend was noted between this ratio and the electronic density of the phosphorous atoms in the ligand (Table 3-9). Josiphos ligands bearing electron poor aromatic phosphines produced more reductive arylation product 18c (e.g., J015 and J008, entries 3 and 5). Conversely, electron rich ligands gave mainly ring-opening product 14c (J009 and J002, entries 1 and 2). The related ferrocenyl ligands, Walphos, were found to be better than Josiphos ligands at inducing 1,4-migration (entries 2 and 4). This observation suggests that the bite angle and the electronic density are important factors in the observed chemoselectivity. Walphos is an aryl-homologated Josiphos analog, with an accordingly larger bite angle (Figure 3-3).

Interestingly, two Walphos analogs bearing electron poor aryl groups, W005 and W008, gave the hydroarylation product 18a as the major product. This particular observation is of interest, as will be discussed in Section 3.5, because it occurred with PhB(OH)$_2$ as opposed to a heteroarylboronic acid bearing “activated” C–H bonds. This set of experiments revealed that toluene is also a competent solvent with t-Bu-Josiphos when water is present (entries 2 and 3).

\[\text{In cases where the boronic acid was insoluble in toluene, a few drops (~0.05 mL) of THF were added to the substrate solution until it became homogeneous. It should be noted that the reaction mixture was biphasic after addition of water.}\]
### Table 3–8 Chemodivergence between ring-opening and reductive arylation with variation in ligand.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>R¹</th>
<th>R²</th>
<th>Yield 14c (%)</th>
<th>Yield 18c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J009</td>
<td>Cy</td>
<td>t-Bu</td>
<td>84</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>J002</td>
<td></td>
<td>t-Bu</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>J015</td>
<td></td>
<td>t-Bu</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>W003</td>
<td></td>
<td>Cy</td>
<td>40</td>
<td>35</td>
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<tr>
<td>5</td>
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<td>8</td>
<td>W005</td>
<td></td>
<td></td>
<td>trace</td>
<td>51</td>
</tr>
</tbody>
</table>

*a Reaction conditions as described in Table 1. b All yields are isolated. c Mass balance was 48% of 48. d Mass balance was 61% of 48. e PhB(OH)₂ and diazabicycle 1d were added via syringe pump over 1 h.

Further examination of the Walphos ligand W001 revealed a multiple 1,4-migration cascade to give the byproduct 48 (Scheme 3-6). Formation of 48 can be explained by carborhodination/1,4-migration followed by a reaction with a second equivalent of diazabicycle, akin to the *merry-go-round* seen with norbornene under similar conditions. This observation gives insight in the stability of the intermediate E towards protolysis, as opposed to alkene coordination of the substrate. Formation of 48 could be decreased by slow addition of 1c (entry 7, Table 3-9). Formation of other disubstituted compounds, 56 and 57, occurred with 3-furylboronic acid and with Boc-protected 3-pyrrolylboronic acid. Intriguingly, 57 formed through a C–H insertion followed by ring-opening of a second equivalent of bicycle 1c.

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Influence of steric factors

The reductive arylation is sensitive to steric effects. In cases where a ortho-hydrogen was flanked with a hindering group in the meta-position, only the ring-opening reaction was observed (cf. 25 and 28, Scheme 3-15). It should be mentioned that in all cases where the ortho-hydrogen was accessible, hydroarylated products were observed in THF as solvent, but only in poor yield (2–15%).

A telling influence of steric effects was seen during deuterium quench experiments shown in equation 3-18 and 3-19. The reactions were performed in a THF/D$_2$O mixture, and deuterium incorporation was quantified in the reductive arylation products of the Boc-protected and the unprotected pyroles (53a and 53b, respectively). When the pyrrole bore a Boc group, 53b, deuteration occurred primarily at the C4 position of d-54b with J002, whereas in the unprotected example, 53a, deuterium was observed only at the C2 position of d-54a. Although the C2 position of pyroles 53 carries the more activated C–H bond, the rhodium insertion is hindered by steric bulk of the protecting group. This strong steric effect may explain the low level of reductive arylation in pyroles in comparison to other heterocycles (Scheme 3-16). It also confirms the steric influence of meta groups.

With tert-Bu-Josiphos (J002) deuterium was incorporated exclusively at the β position, while with Walphos W001 some deuteration was seen at the α position as well (Eqn. 3-19). This discrepancy demonstrates that, although similar, the two ligands have distinctly different steric demands.
CHAPTER 3. ENANTIOSELECTIVE DESYMMETRIZATION OF BICYCLIC HYDRAZINES 131

\[
1c + 5\% [\text{Rh(cod)OH}]_2 + 12\% \text{J002} \rightarrow \text{THF/D}_2\text{O} (10:1) \rightarrow \text{r.t., 16 h.} \rightarrow \text{53a} \rightarrow \text{53b} 
\]

\[
\text{53a} + 5\% [\text{Rh(cod)OH}]_2 + 12\% \text{J002 or W001} \rightarrow \text{THF/D}_2\text{O} (10:1) \rightarrow \text{r.t., 16 h.} \rightarrow \text{\text{53a} with different isotopes} 
\]
## 3.4.3 Scope of the Reaction

A number of reductive arylation products were synthesized with two selected ligands in an attempt to delineate the scope of this reaction (Table 3–10). Under the current conditions, the yields and enantioselectivity are still variable. It appears that enantioselectivity with Walphos ligands is governed by factors different than those for Josiphos. Although not ideal, the moderate selectivity ranging from 62 to 78% ee is encouraging (entries 1, 5, and 6). For pyrrolyl nucleophile, W005 was unique in affording modest, yet significant, amounts of arylated bicyclic hydrazone 54a (entry 6).

<table>
<thead>
<tr>
<th>Table 3–9 Enantioselective reductive arylation of diazabicycle 1d with substituted boronic acids.</th>
<th><img src="image.png" alt="Diagram" /></th>
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<tr>
<td>entry</td>
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</table>

<sup>a</sup> Reaction conditions: 1c (40 mg, 0.135 mmol), 2 equiv PhB(OH)<sub>2</sub>, 5 mol% [Rh(cod)OH]<sub>2</sub>, 12 mol% ligand in THF/H<sub>2</sub>O (50:1), stirred at r.t. overnight.  
<sup>b</sup> Isolated yield.  
<sup>c</sup> Determined by chiral HPLC analysis of isolated product.  
<sup>d</sup> Experiment performed by J.Panteleev.
3.5 Conclusions

In summary, a rhodium catalyzed chemodivergent desymmetrization of diazabicycles with boronic acids has been developed. Two chemodivergent processes have been discovered and optimized to give functionalized chiral carbocyclic hydrazides 14 and 18.

First, a highly enantioselective rhodium(I)-catalyzed ring-opening of bicyclic hydrazines was found to provide a rapid synthesis of chiral substituted cyclopentenyl hydrazines 14. This strategy complements our related approach to chiral cyclopentenols described in Chapter 2. Notably, the ring-opening is ideally suited for the addition of aryl boronic acids bearing ortho-substituents, thus is a good method to access valuable enantiopure building blocks. At the time of writing, these results represented the best enantioselectivity reported in the literature for the ring-opening of bicyclic hydrazines with hard $sp^2$ C-nucleophiles.

Additionally, a useful C–H activation pathway was identified which leads to hydroarylated diazabicycles 18, thereby setting the absolute stereochemistry at three carbons in one reaction. Moreover, enantioselectivity in such a 1,4-metal migration process was unprecedented. The hydroarylated products could be obtained with selectivity ranging from 62–99% ee, according to the ferrocenyl-based diphosphines ligands and the nature of the organoboron reagent used. Some level of ligand control could be exerted over the two competing reaction pathways. Whereas $t$-Bu-Josiphos afforded the highest yields of ring-opened products 14, electron deficient Walphos-type ligands favoured the 1,4-migration leading to 18, even with arylboronic acids bearing a non activated C–H bond in the 2-position. Alternative factors influencing chemoselectivity were shown to be electronics and steric of the boronic acids, the nature of the N-protecting group and the solvent used. Potential synthetic applications of the observed C–H insertion are exposed below.

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69 The 1,2,4- and 1,2,5- aromatic substitution patterns was found in 51 out of 128 drug candidate molecules surveyed, see: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Org. Biomol. Chem. 2006, 4, 2337.
3.6 Outlook

A new enantioselective 1,4-Rh migration process was identified and optimized in Sections 3.3 and 3.5. This unusual oxidative pathway allows for a potential selective electrophilic functionalization at the more hindered ortho-position of the aromatic ring to get IX in one transformation, a process not easily accomplished by other means (Scheme 3-18). For example, such a cascade sequence could be used to generate highly substituted chiral diamines X.

![Scheme 3–15](image)

Scheme 3–15 Trapping Rh(I)-aryl intermediate E after migration would allow to functionalize the ortho position of the aryl moiety.

Trapping intermediate E with electrophiles different than protons raises challenges in terms of reaction kinetics, because it requires E to react selectively with a external electrophile, at the same time as aryl-rhodium species B to react only with substrate I. Still, the feasibility of this strategy is supported by the observation of the multiple addition products 48, 56, and 57 (Eqn. 3-15 and Figure 3-6).

A way to simplify the system is to have an intramolecular electrophile tethered to the substrate in a position where it can react only once the migration has occurred. For example, an arylboron nucleophile could be used where the latent electrophile is prepositioned at the meta position XI (Scheme 3-19). In this proposed reaction, the Y group of XI is necessary to force C–H insertion at the desired ortho position, and is also required to get high ee. Moreover, ring-opening can be prevented by having the X groups of substrate XII different than the original hydrazide to favour migration. Using norbornadiene would also allow to eliminate a stereocenter and to regenerate an alkene in XIV for further transformations. The whole sequence would yield aryl compounds bearing a highly congested 1,2,3,4-substitution motif.
This part of the project is under investigation by J. Panteleev. She has performed preliminary studies that are very encouraging. For example, the proposed cascade reaction was found to occur to a high degree using arylboronic acid 59 and norbornadiene (Scheme 3-20). The tetracyclic lactone 61 was formed in 48% yield. Interestingly, cyclization of the aryl moiety took place at most hindered position of the alkene, thus resulting a polarity reversal compared to what is usually obtained from metal-catalyzed additions to conjugated systems (e.g., Michael addition). Future work from the Lautens lab will explore the new avenues offered by this cascade reaction.

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70 Panteleev, J. Unpublished results.
3.7 Experimental Section

General Experimental Procedures. Unless otherwise noted, reactions were carried out under argon atmosphere, in flame-dried, single-neck, round bottom flasks fitted with a rubber septum, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel canula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with Silicycle™ normal phase glass plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, or in potassium permanganate (KMnO₄), followed by heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.⁷¹

Materials. [Rh(cod)OH]₂ and Rh(IMes)(cod)Cl were conveniently prepared from [Rh(cod)Cl]₂ by literature procedures.⁷²,⁷³ Supplies of chiral bisphosphine ligands were generously provided by the following companies: Josiphos and Walphos families from Solvias Inc., (R)-Segphos from Takasago, and P-Phos families from Digital Chemical Specialty. Other chiral phosphine ligands were purchased from Strem Chemicals Inc. Unless otherwise indicated, boronic acids were obtained from Aldrich and used without further purification. Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under N₂ from Na/benzophenone immediately prior to use. Ether and dichloromethane were purified by the method of Pangborn et al.⁷⁴ Hexanes used for chromatography was purified by simple distillation before use. Diaza-bicyclo[2.2.1]hept-5-ene-dicarbamates 1a,⁷⁵ 1b,⁷⁶ 1c' and 1d⁷⁷ were prepared in quantitative yields by Diels-Alder reactions between cyclopentadiene and the corresponding azodicarbamates at r.t. according to literature procedures and characterization data was fully consistent with that previously reported.

Instrumentation. Proton nuclear magnetic resonance spectra (¹H NMR) spectra and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 23 °C with a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N probe, or a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe, or a Bruker 400 Advance3 Nanobay (400 MHz) NMR spectrometer equipped with BBFO-ATM probe. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, CHDCl₃: δ 5.29, C₂H₃OD: δ 7.15, CD₃HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0, CH₂Cl₂: δ

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53.8, C_6D_6: δ 128.0, CD_3OD: δ 49.2). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, m = multiplet, br = broad), and coupling constant (J, Hz). Doubling of signals due to carbamate rotamers was often observed: the word ‘and’ is used specifically to signify extra peaks arising from rotamers in the spectra. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High resolution mass spectra were obtained from a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured in a 10.0 cm cell with a Rudolph Autopol IV polarimeter digital polarimeter equipped with a sodium lamp source (589 nm), and are reported as follows: [α]D 7°C (c = g/100 mL, solvent).

Determination of the Enantiomeric Excesses by HPLC Analysis. The enantiomeric excess (ee) of the ring-opened products was determined by HPLC analysis after chromatographic purification on silica-gel (see following section for details). Unless otherwise noted, enantiomeric excesses of the bis-protected hydrazine products were determined using analytical chiral columns from Chiral Technologies Inc., (fitted with a matching 5.0 cm guard column), at 30 °C with 4.0 uL injections of sample solution of approximately 2 mg/mL. The HPLC system was a HP 1100 Series modular system from Agilent, operated by a ChemStation LC 3D software, v. 10.02.

Crystallographic Data: Crystal structure data for 14b can be retrieved from the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 66 1282. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_requests/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

3.7.1 Experimental Procedures

• Typical Procedure A:

Desymmetrization of diazabicyclo[2.2.1]heptenes by a Rh-catalyzed allylic substitution with organoboronic acids. In a representative example: to a 10 mL round-bottom flask equipped with a magnetic stir bar was added [Rh(cod)OH]_2 (3.1 mg, 0.0067 mmol), tert-Bu-JOSIPHOS (8.8 mg, 0.016 mmol). The vial was flushed with argon (balloon) and distilled THF (1.0 mL) was added. The clear orange solution was stirred at room temperature for 15-20 min, then 0.08 mL H_2O was added.79 Diazabicyclo[2.2.1]heptene dicarbamate 1c (40 mg, 0.135 mmol) and the arylboronic acid (0.20–0.27 mmol, 1.5–2.0 equiv) were added together as a solution80 in distilled THF (0.80 mL of a freshly prepared

79 In most cases, the reaction could be run without added water; moisture from either the atmosphere or the boronic acids was sufficient to carry out the reaction (equimolar water to boronic acid = 5 µL H_2O). Generally, no special precautions were taken since we wanted a robust process. However, a referee comment made us realize that the presence of a small amount of water is crucial for the reaction yield. To ensure reproducibility, we opted for the addition of a known amount of water, as described above.

80 If the alkene is added before the boronic acid, a slight erosion in ee occurs (4–9% ee).
stock solution) and the darkening reaction mixture allowed to react at r.t. (or 0 °C). After 16 h, TLC showed full consumption of 1c (20% EtOAc/Hex; acidic vanillin stain). The reaction mixture was filtered on a short silica gel pad (~2 g), washing with four portions of Et₂O. The filtrate was concentrated under reduced pressure, then was applied to the top of a column of silica gel and purified by column chromatography (5-10-20% EtOAc/hexane as elution gradient). The ring-opened hydrazine 14c was recovered as a colourless oil, 43 mg (85%). The enantiomeric excess was determined on the purified product (vide infra).

Note 1: NMR analysis displayed very broad peaks for all ring-opened products due to: (i) rotamers of the bis-carbamate hydrazine moiety, (ii) conformers equilibrium for some products, and (iii) atropisomers for some compounds bearing aromatic ortho-substituents. Resolution for both ¹H and ¹³C NMR spectra did not improve significantly when temperature was varied; most likely due to differential coalescence temperature of the multiple conformers. Doubling of signals was often observed: the word ‘and’ is used specifically to signify extra peaks arising from rotamers in the spectra.

Note 2: We arbitrarily opted to represent all ring-opened products with the (1R,2S)-stereochemistry in the paper for consistency and to avoid unnecessary complications for the readers. The depicted (−) enantiomers result from the use of (S₉₀,R)-tert-Bu-JOSIPHOS ligand. The use of (R₉₀,S)-tert-Bu-JOSIPHOS yielded the (+) enantiomers, having the opposite stereochemistry of that represented.

### 3.7.2 Characterization Data

**2,3-Diazabicyclo[2.2.1]hept-5-ene-N,N'-diethyl dicarboxylate (1a).**
Prepared according to a general procedure. To a freshly distilled cyclopentadiene (1.5–2.0 equiv) solution in CH₂Cl₂ kept at 0 °C, was added the azobis(carbamate) compound. The reaction was allowed to warm up to room temperature and stirred until full consumption of the azo starting material, as observed by TLC. The solvent was evaporated under reduced pressure. The crude clear oil was purified by silica-gel chromatography with EtOAc/hexanes as eluent (20-40% gradient). The diazabicycle was obtained quantitatively as a clear fluid oil. The characterization data was fully concordant with that already reported in the literature. ¹H NMR (400 MHz, CDCl₃): δ 6.51 (2H, br.s), 5.15 (2H, br.s), 4.25–4.15 (4H, m), 1.77–1.71 (2H, m), 1.28 (6H, t, J = 7.1 Hz).

**meso-2,3-Diazabicyclo[2.2.1]hept-5-ene-N,N'-dibenzyl dicarboxylate (1b).**
Prepared according to a general procedure. (note: the commercial azo precursor (CbzN)₂ quality was generally poor and needed a rapid purification by chromatography). The clear orange solution turned colorless. The diazabicycle was obtained quantitatively as a thick oil, which slowly solidified upon standing. Recrystallized in hexanes. The characterization data was fully concordant with that already reported in the literature. ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.28 (10H, m), 6.46 (2H, br.s), 5.27-5.14 (6H, m), 1.76-1.71 (2H, m).

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81 The reaction vessel must remain unopened, as the active catalyst in solution appears sensitive to oxygen traces.
2,3-Diazabicyclo[2.2.1]hept-5-ene-N,N'-di-tert-butyl dicarboxylate (1c).
To an ice-cooled solution of DtBAD in CH₂Cl₂ (10 g in 500 mL) was added neat cyclopentadiene (1.5 equiv). The clear orange solution was allowed to stir overnight at rt. After 16h, the colorless solution showed full conversion by TLC. The solvent was evaporated under reduced pressure to yield a white solid which had a strong Cp odor. The crude solid was recrystallized in 100 mL hexanes under vigorous stirring. After filtration on fritted funnel and drying, the diazabicycle was obtained as a white free-flowing powder (12.8 g, 99%). The characterization data was fully concordant with that already reported in the literature.¹³¹H NMR (400 MHz, CDCl₃): δ 8.27 (2H, dd, J = 1.6, 8.8 Hz), 7.75 (2H, ddd, J = 0.5, 3.7, 5.9 Hz), 6.72 (2H, t, J = 1.9 Hz), 5.94-5.92 (2H, m), 2.17 (1H, dt, J = 1.6, 8.8 Hz), 2.07 (1H, dt, J = 1.6, 8.8 Hz).

2,3-Diazabicyclo[2.2.1]hept-5-ene-N,N'-phthalazide (1d).
Prepared according to the procedure described for 1a, where cyclopentadiene was reacted with the azophthalazide in situ after its oxidation from the commercial phthalhydrazine. The diazabicycle was obtained as a white solid in 61% yield (5.95 g). The characterization data was fully concordant with that already reported in the literature.¹³¹H NMR (400 MHz, CDCl₃): δ 8.27 (2H, dd, J = 3.7, 5.9 Hz), 7.75 (2H, ddd, J = 0.5, 3.7, 5.9 Hz), 6.72 (2H, t, J = 1.9 Hz), 5.94-5.92 (2H, m), 2.17 (1H, dt, J = 1.6, 8.8 Hz), 2.07 (1H, dt, J = 1.6, 8.8 Hz).

trans-N,N'-[(2-Phenylcyclopent-3-enyl)-diethylhydrazine dicarboxylate (14a).
Using (S,R)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 96% yield (51 mg). The characterization data was fully concordant with that already reported in the literature.¹³¹H NMR (400 MHz, CDCl₃): δ 7.32-7.20 (5H, m), 6.40 and 6.20 (1H, coalescing br. s), 5.87 (1H, ddd, J = 2.0, 4.4, 6.0 Hz), 5.71 (1H, ddd, J = 2.0, 3.9, 6.0 Hz), 4.71 (1H, br. s), 4.23 (2H, dd, J = 7.1, 14.2 Hz), 4.15-3.95 (3H, br. m), 2.75-2.65 (1H, m), 2.63-2.49 (1H, m), 1.35-1.22 (3H, m), 1.17-0.92 (3H, m).¹³¹C NMR (100 MHz, CDCl₃): δ 157.2, 156.3, 143.5, 132.9 (2), 130.0 (2), 128.6, 127.7, 126.7, 67.5, 62.7, 62.4, 54.0, 35.4, 14.6, 14.4. The enantiomeric ratio was 87.5:12.5, as determined by HPLC analysis: (Chiralcel OD-H, gradient 1-7% iPrOH/hexane, 1.0 mL/min, 215 nm); tₑ = 16.4 min [minor], tₑ = 19.6 min [major]. Alternatively, the reaction could be carried out in toluene/water (9:1) to obtain 14a in 93% yield (49 mg), with the same enantioselectivity (76% ee). The absolute configuration was assigned by analogy with compound 14c.

trans-N,N'-[(2-Phenylcyclopent-3-enyl)-dibenzylhydrzone dicarboxylate (14b).
Prepared according to typical procedure A with 1b (40 mg, 0.109 mmol), (S,R)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 72% yield (35 mg). The characterization data was fully concordant with that already reported in the literature.¹³¹H NMR (400 MHz, CDCl₃): δ 7.38-7.20 (15H, m), 6.51 (1H, br.s), 5.84 (1H, br.s), 5.70 (1H, br.s), 5.19 (2H, br.s), 5.01 (2H, br.s), 4.80 (1H, br. s), 4.01 (1H, br.s), 2.76-2.50 (2H, m). The enantiomeric ratio was 90:10, as determined by HPLC analysis: (Chiralcel OD-H, gradient 1-7% iPrOH/hexane, 1.0 mL/min, 215 nm).

trans-N,N′-(2-Phenylcyclopent-3-enyl)-di-tert-butylhydrazine dicarboxylate (14c).

Using (5,R)-tert-BuJosiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 85% yield (43 mg). 1H NMR (400 MHz, CDCl3): δ 7.31-7.17 (5H, m), 6.26 and 6.06 (1H, coalescing br.s), 5.89-5.83 (1H, m), 5.74-5.66 (1H, br.m), 4.70 (1H, br.s), 3.95 (br.s), 2.72-2.51 (2H, br.m), 1.55-1.05 (18H, br.m). 13C NMR (100 MHz, CDCl3): δ 156.0, 155.1, 143.9, 132.9 (2), 130.2 (2), 128.6, 127.8, 126.6, 81.4 (2), 68.2 and 66.4 (br, rotamers), 54.0, 35.4, 28.4 (3), 28.2 (3). IR (NaCl, neat film): 3263 (br), 3056, 3025, 2977, 2930, 2865, 1744-1700 (br.), 1493, 1453, 1392, 1366, 1283, 1249, 1155, 1049, 952, 757, 699 cm⁻¹. MS (ESI): m/z (rel. intensity): 375.2 (MH⁺, 5), 319 (3), 297 (5), 263 (15), 219 (35), 143 (100), 128 (5). HRMS (ESI): calculated for C21H33N2O4 [MH⁺]: 375.2278; found = 375.2294. [α]D24,3 = -75 (c 1.33, CHCl₃) for 81:2:18.8 er, as determined by HPLC analysis: (Chiralcel AD, gradient 5-10% iPrOH/hexane, 0.80 mL/min, 220 nm); tR = 39.2 min [major], tR = 42.7 min [minor]. The absolute configuration was assigned by derivatization to (−)-17 and comparison to literature optical rotation values.

trans-4-Hydroxy-2-(2'-phenylcyclopent-3'-enyl)-2H-phthalazin-1-one (14d).

Using (R,S)-tert-BuJosiphos as chiral ligand, the phthalazide was obtained as a white solid in quantitative yield (53 mg, m.p.:135-138 °C). 1H NMR (400 MHz, CDCl3): δ 9.60 (1H, br.s), 8.42 (1H, d, J = 6.7 Hz), 8.06 (1H, d, J = 7.6 Hz), 7.79(1H, t, J = 7.2 Hz), 7.74 (1H, t, J = 7.6 Hz), 7.17-7.14 (2H, m), 7.10-7.05 (3H, m), 5.76-5.70 (2H, m), 5.65-5.60 (1H, m), 4.21-4.17 (1H, m), 2.87-2.77 (1H, dd, J = 8.9, 16.5 Hz), 2.57-2.47 (1H, m). 13C NMR (100 MHz, CDCl3): δ 158.9 (2), 151.6, 143.0, 133.2, 133.0, 132.6, 129.4, 128.7 (2), 127.8, 127.5 (2), 126.8, 124.9, 124.8, 64.5, 55.3, 37.6. IR (NaCl, neat film): 3058, 3026, 2930, 2853, 1617, 1573 (s), 1556 (s), 1493, 1385, 1263, 1178, 1091, 693 cm⁻¹. MS (EI): m/z (rel. intensity): 304 (M⁺, 4), 163 (84), 142 (100), 130 (17), 115 (15), 77 (8). HRMS (EI): calculated for C19H16N2O2 [M⁺]: 304.1212; found = 304.1205. [α]D24,3 = +112 (c 1.88, CHCl₃) for 85:15 er, as determined by HPLC analysis: (Chiralcel AD, elution gradient 0-10% iPrOH/hexane, 0.80 mL/min, 254 nm); tR = 49.6 min [major], tR = 52.9 min [minor]. The absolute configuration was assigned by analogy with compound 14c. The relative stereochemistry was determined by X-ray diffraction analysis of single crystals grown from an ether/2-propanol mixture.

(-)-(IR,2S)-2-Phenylcyclopentylamine. In a 10 mL RB flask was diluted diazabicycle 1c (104 mg, 0.277 mmol) in EtOH 95% (3.0 mL). The mixture was stirred for 16 h under a hydrogen atmosphere (balloon). The reaction mixture was filtered on celite, waqshed with methanol. Solvents were remove under reduced pressure, residual methanol was azeotroped with CH₂Cl₂. Recovered 111 mg crude colorless oil. If needed, the 1,2-substituted cyclopentane 15 could be purified by chromatography with 5-20% EtOAc/hexanes gradient. 1H NMR (400 MHz, CDCl3): δ 7.30-7.14 (5H, m), 6.06 and 5.81 (1H, br, rotamers), 4.68 and 4.53 (1H, br, rotamers),3.25 and 3.04 (1H, br, rotamers), 2.16-1.90 (2H, br.m), 1.90-1.58 (4H, br.m), 1.58-1.00 (18H, br.m).

The crude (Boc)₂-hydrazine 15 was retaken in CH₂Cl₂ (1.0 mL), transferred to a 10 mL flask, then trifluoroacetic acid (1.0 mL) was added at rt. The reaction was stirred for 4 h. After full consumption of starting material by TLC, the reaction mixture was transferred to a 25 mL flask with benzene and TFA was azeotroped under reduced pressure. 16 was recovered as a colorless ionic liquid (84 mg); [α]D25,4 =
-29.2 (c 1.25, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.18 (5H, m), 6.59 (4H, br.s., hydrazinium), 3.68-3.60 (1H, m), 3.19 (1H, dd, J = 17.6, 8.2 Hz), 2.30-2.15 (2H, m), 1.96-1.70 (4H, m). ¹³F NMR (375 MHz, CDCl₃): δ -76.02 (s).

The crude salt 16 was diluted in 2.5 mL EtOH in a 25 mL RB flask, to which was added Raney nickel 2800 in suspension in 0.80 mL EtOH (834 mg of slurry 50% in water, pre-washed with 2 x 2 mL water, 2 x 2 mL methanol, 1 x 2 mL EtOH). The reaction mixture was filtered on celite, waqshed with methanol. Solvents were removed under reduced pressure, residual methanol was azeotroped with CH₂Cl₂. Recovered 31 mg crude colorless oil (69% from 1ℓ). The characterization data for (+)-(1R,2S)-17 was fully concordant with that already reported in the literature.⁸³ [α]D⁰ = −36.5 (c 1.40, CHCl₃) for 81:19 er, as determined by HPLC analysis: (Chiralcel OD-H, isocratic 1% iPrOH/hexane, 0.75 mL/min).

**Di-tert-butyl 5-phenyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (18c).**

In a 10 mL round bottom flask, a solution of [Rh(cod)OH]₂ (2.3 mg, 0.005mM) and (R,R)-Walphos 001 (W001) (11.2 mg, 0.012mM) in THF (2 ml) and H₂O (0.5 ml) was stirred for 15 minutes. A solution of phenylboronic acid (24.4 mg, 0.2mM) and 1c (29.6 mg, 0.1 mM) in THF (1ml) was added to the reaction mixture using a syringe pump over the course of 1 hour. The solution was further stirred for 3 hours, after which the reaction mixture was extracted with ethyl acetate (2x) and concentrated. Flash column chromatography (pentanes:EtOAc - 9:1) yielded the titled compound in 69 % yield (26 mg) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.27-7.18 (m, 2H), 7.18-7.07 (m, 3H), 4.74-4.18 (m, 2H), 3.47-3.09 (m, 1H), 2.27-1.96 (m, 1H), 1.77-1.54 (m, 1H), 1.53-1.32 (m, 20H). ¹³C NMR (126 MHz, CDCl₃): 156.4 (m, 2), 141.7 and 140.9 (rotamers), 128.4 (2), 126.7 (2), 126.3, 81.1 (2), 65.9 and 64.93 (m, rotamers), 60.9 and 60.1 (m, rotamers), 45.9 and 44.5 (m, rotamers), 36.0 (m), 34.2 and 32.4 (rotamers), 27.99 (6). IR (NaCl, neat film): 3002, 2972, 1723, 1670, 1473, 1452, 1370, 1347, 1318, 1256, 1158, 1120, 1106, 853, 755 cm⁻¹. MS (ESI), m/z (rel. intensity): 397.2 (MNa⁺, 90), 375 (MH⁺, 30), 319 (45), 219 (100), 143 (25). HRMS (ESI): calculated for C₁₇H₁₇N₂O₂ [MH⁺]: 375.2278; found = 375.2296. HPLC analysis: (Chiralcel OD-H, isocratic 6% iPrOH/hexane, 0.80 mL/min, 225 nm); tᵣ = 8.8 min [minor], tᵣ = 11.3 min [major].

**trans-N,N’-[2-(4’-Trifluoromethylphenyl)-cyclopent-3-enyl]-diethylhydrazine dicarboxylate (19a).** Prepared according to typical procedure A with 1a (40 mg, 0.166 mmol). (S,S)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 20% yield (13 mg). ¹H NMR (400 MHz, CDCl₃): δ 7.55 (2H, d, J = 8.1 Hz), 7.46–7.35 (2H, m), 6.40 (1H, br.s), 5.91 (1H, dq, J = 6.1, 2.3 Hz), 5.69 (1H, dq, J = 6.1, 2.0 Hz), 4.81–4.69 (1H, m), 4.23 (2H, dd, J = 14.1, 7.0 Hz), 4.09 (1H, br.s), 4.11–3.93 (2H, m), 2.74-2.53 (2H, m), 1.34-0.60 (6H, br.m). The enantiomeric ratio was 91.5:8.5, as determined by HPLC analysis: (Chiralcel OD-H, gradient 1-7% iPrOH/hexane, 1.0 mL/min, 215 nm).

**trans-N,N’-[2-(4’-Trifluoromethylphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (19b).** Using (R,S)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 49% yield (29 mg). ¹H NMR (400 MHz, CDCl₃): δ 7.55 (2H, d, J = 7.7 Hz), 7.42 (2H, br.s), 6.21 (1H, br.s), 5.91 (1H, br.s), 5.69 (1H, br.s), 4.70 (1H, br.s), 4.06 (1H, br.s), 2.73-2.50 (2H, m), 1.60-1.01 (18H, br.m). ¹³C NMR (100 MHz, CDCl₃): δ 156.0, 154.9, 148.3, 132.0 (2), 130.9 (2), 128.9 (d, J = 31.9 Hz), 128.2, 125.5, 124.2, 123.2, 120.5, 119.4, 119.0, 116.9, 116.3, 108.1, 108.0, 107.6, 75.2, 65.9, 51.9, 45.7, 44.4, 36.5, 34.8, 32.9, 30.6, 27.7, 26.9.

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124.6 (d, J = 272 Hz), 81.6, 81.5, 68.3 and 65.9 (br, rotamers), 53.8, 35.6, 28.4 (3), 28.1 (3). **IR** (NaCl, neat film): 3261 (br), 3055, 3004, 2978, 2931, 2867, 1738-1681 (br.), 1477, 1392, 1367, 1326, 1249, 1161, 1068, 1018, 951, 851 cm⁻¹. **MS** (ESI), *m/z* (rel. intensity): 465.2 (MNa⁺, 12), 365 (4), 331 (13), 287 (100), 211 (24). **HRMS** (ESI): calculated for C₇₈H₁₄₃N₄O₂Na [MNa⁺]: 465.1971; found = 465.1980. [α]b₂₅ = -116 (c 1.45, CHCl₃) for 92.0 : 8.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 3% iPrOH/hexane, 0.75 mL/min, 225 nm); tR = 30.5 min [major], tR = 35.7 min [minor].

trans-N,N’-[2-(3’,4’-Dimethoxyphenyl)-cyclopent-3-eny]-diethylhydrazine dicarboxylic acid (21c). Prepared according to typical procedure A with 1a (40 mg, 0.166 mmol), (**S**,R)-**tert**-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 89% yield (56 mg). **H NMR** (400 MHz, CDCl₃): δ 6.90-6.70 (3H, m), 6.45 (1H, br.s), 5.85 (1H, dq, J = 6.1, 2.2 Hz), 5.70 (1H, ddd, J = 6.1, 4.0, 2.0 Hz), 4.72 (1H, br.s), 4.21 (2H, q, J = 7.1 Hz), 4.11-3.95 (2H, m), 3.95 (1H, br.s), 3.86 (3H, s), 3.84 (3H, s), 2.73-2.62 (1H, m), 2.59-2.49 (1H, m), 1.33-1.20 (3H, br.m), 1.18-0.98 (3H, br.m). The enantiomeric ratio was 80.5:19.5, as determined by HPLC analysis: (Chiralcel OD-H, gradient 1-7% iPrOH/hexane, 1.0 mL/min, 215 nm).

trans-N,N’-[2-(3’,4’-Dimethoxyphenyl)-cyclopent-3-eny]-di-**tert**-butyl-hydrazine dicarboxylic acid (20c). Using (**R**,S)-**tert**-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a white amorphous solid in 80% yield (47 mg). **H NMR** (400 MHz, CDCl₃): δ 6.94-6.70 (3H, m), 6.20 and 5.94 (1H, coalescing br.s), 5.87-5.82 (1H, m), 5.73-5.66 (1H, m), 4.68 (1H, br.s), 3.98-3.83 (1H, br.m), 3.87 (3H, s), 3.85 (3H, s), 2.73-2.47 (2H, m), 1.55-1.08 (18H, br.m). **C NMR** (100 MHz, CDCl₃): δ 156.0, 155.0, 149.2, 147.8, 136.6, 133.0, 130.0, 119.6, 114.4, 110.6, 81.3 (2), 68.4 and 66.2 (br, rotamers), 56.2, 56.0, 53.4, 35.3, 28.4 (3), 28.2 (3). **IR** (NaCl, neat film): 3319 (br), 3050, 2976, 2934, 2857, 1738 (br), 1707, 1590, 1515, 1454, 1393, 1367, 1249, 1157, 1028, 953, 756 cm⁻¹. **MS** (ESI), *m/z* (rel. intensity): 452.3 (MNa⁺, 13), 357 (8), 323 (71), 279 (100), 203 (96), 185 (31), 141 (42). **HRMS** (ESI): calculated for C₇₈H₁₄₃N₄O₂Na [MNa⁺]: 457.2309; found = 457.2323. [α]b₂₅ = +62.2 (c 1.40, CHCl₃) for 75.0:25.0 er, as determined by HPLC analysis: (Chiralcel OD-H, isocratic 4% iPrOH/hexane, 0.75 mL/min, 232 nm); tR = 11.1 min [major], tR = 12.5 min [minor].

trans-N,N’-[2-(2’-Methyl-4’-methoxyphenyl)-cyclopent-3-eny]-diethylhydrazine dicarboxylate (21a). Prepared according to typical procedure A with 1a (40 mg, 0.166 mmol), (**S**,R)-**tert**-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 28% yield (17 mg). **H NMR** (400 MHz, CDCl₃): δ 7.01 (1H, d, J = 8.2 Hz), 6.73-6.66 (2H, m), 6.51 (1H, br.s), 6.35 (1H, br.s), 5.86 (1H, dq, J = 6.1, 2.2 Hz), 5.67-5.62 (1H, m), 4.80-4.69 (1H, br.m), 4.28-4.01 (4H, br.m), 3.77 (3H, s), 2.80-2.69 (1H, m), 2.59-2.46 (1H, m), 2.33 (3H, s), 1.35-1.05 (6H, br.m). The enantiomeric ratio was 95:5, as determined by HPLC analysis: (Chiralcel OD-H, gradient 1-7% iPrOH/hexane, 1.0 mL/min, 215 nm).

trans-N,N’-[2-(2’-Methyl-4’-methoxyphenyl)-cyclopent-3-eny]-di-**tert**-butylhydrazine dicarboxylic acid (21e). Using (**R**,S)-**tert**-Bu-Josiphos as chiral ligand and dioxane as solvent, the bis-protected hydrazine was obtained as a colourless oil in 55% yield (31 mg). **H NMR** (400 MHz, CDCl₃): δ 7.03 (1H, d, J = 8.9 Hz), 6.72-6.67 (2H, m), 6.16 and 5.90 (1H, coalescing br.s), 5.88-5.84 (1H, m), 5.66-5.58 (1H, m), 4.70 (1H, br.s), 4.12 (1H, br.s), 3.77 (3H, s), 2.79-2.61 (1H, m), 2.61-2.49 (1H, m), 2.32 (3H, s), 1.61-1.11 (18H, br.m). **C NMR** (100 MHz, CDCl₃): δ 158.1, 156.1, 154.9, 137.4, 133.9, 133.4, 129.7, 128.2, 116.1, 111.6, 81.4 (2), 67.5 and 65.0 (br,
trans-N,N’-[2-(2’-Methylphenyl)-cyclopent-3-enyl]-diethylhydrazine dicarboxylate (22a).
Prepared according to typical procedure A with 1a (40 mg, 0.166 mmol), (S,R,R)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 45% yield (25 mg). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.21–7.08 (4H, m), 6.39–6.30 (1H, m), 5.89 (1H, dq, \(J = 6.5, 2.2\) Hz), 5.79–5.63 (1H, m), 4.79 (1H, br.s), 4.30–4.01 (5H, m), 2.81–2.71 (1H, m), 2.61–2.49 (1H, m), 2.36 (3H, s), 1.35–0.94 (6H, br.m). The enantiomeric ratio was 98.9:1.1, as determined by HPLC analysis: (Chiralcel AD, isocratic 10% iPrOH/hexane, 1.00 mL/min, 225 nm); \(t_R = 15.3\) min, \(t_k = 21.9\) min.

trans-N,N’-[2-(2’-Methylphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (22c). Using (S,R)-tert-Bu-Josiphos as chiral ligand, and a mixture of toluene/THF/water (7:2:1) as solvent, the bis-protected hydrazone was obtained as a colourless oil in 99% yield (52 mg). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.19–7.05 (4H, m), 6.17 and 5.93 (1H, coalescing br.s), 5.92–5.83 (1H, m), 5.64 (1H, br.s), 4.75 (1H, br.s), 4.26–4.07 (1H, m), 2.80–2.48 (2H, m), 2.35 (3H, s), 1.58–1.06 (18H, br.m). \(^13\)C NMR (100 MHz, CDCl\(_3\)): 161.3, 154.9, 141.7, 136.1, 133.1, 131.0, 130.5, 130.0, 127.2, 126.5, 81.4 (2), 67.6 and 64.2 (br, rotamers), 50.6, 35.9, 28.4 (3), 28.2 (3), 20.2. IR (NaCl, neat film): 3316 (br), 3055, 3003, 2977, 2929, 2866, 1740–1681 (br.), 1454, 1392, 1367, 1333, 1251, 1157, 1050, 951, 756 cm\(^{-1}\). MS ESI, \(m/z\) (rel. intensity): 419.2540; found = 419.2554. \([a]_D^{23.9} = -85.5\) (c 1.54, CHCl\(_3\)) for 99.3:0.7 er, as determined by HPLC analysis: (Chiralcel OD-H, gradient 1-7% iPrOH/hexane, 1.0 mL/min, 215 nm).

trans-N,N’-[2-(2’-Methoxycarbonylphenyl)-cyclopent-3-enyl]-diethylhydrazine dicarboxylate (23a).
Prepared according to typical procedure A with 1a (40 mg, 0.166 mmol), \((S,R,R,R)-tert-Bu-Josiphos\) as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 20% yield (12 mg). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.94 (1H, d, \(J = 8.2\) Hz), 7.39–7.25 (3H, m), 6.45 (1H, br.s), 5.88 (1H, dq, \(J = 6.2, 2.2\) Hz), 5.67 (1H, dq, \(J = 6.0, 2.0\) Hz), 4.79–4.69 (1H, m), 4.26–4.12 (2H, m), 4.07 (1H, br.s), 4.06–3.92 (2H, m), 3.87 (3H, s) 2.72–2.51 (2H, m), 1.33–0.91 (6H, br.m).
	rans-N,N’-[2-(2’-Fluorophenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (24). Using (S,R)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 43% yield (23 mg). Alternatively, the reaction could be carried out in toluene/THF/water (7:2:1) to obtain the ring-opened product in 53% yield (28 mg), with the same enantioselectivity. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.25–7.13 (2H, m), 7.08 (1H, dt, \(J = 1.0, 7.4\) Hz), 6.97 (1H, t, \(J = 9.6\) Hz), 6.27 and 6.03 (1H, coalescing br.s), 5.91–5.85 (1H, m), 5.67–5.60 (1H, br.m), 4.73 (1H, br.s), 4.25 (br.s), 2.80–2.47 (2H, br.m), 1.56–1.02 (18H, br.m). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 161.3 (d, \(J = 244\) Hz), 156.0, 154.9, 131.2, 130.3, 128.9, 128.2, 128.1, 124.6, 115.3 (d, \(J = 18.3\) Hz), 81.3 (2), 67.8 and 66.0 (br, rotamers), 46.0, 35.3, 28.4 (3), 28.1 (3). IR (NaCl, neat film): 3318 (br),
3058, 2977, 2932, 1738-1698 (br.), 1491, 1455, 1393, 1367, 1247, 1156, 1049, 950 cm⁻¹. **MS** (ESI): *m/z* (rel. intensity): 393.2 (MH⁺, 15), 281 (13), 237 (96), 161 (100). **HRMS** (ESI): calculated for C₁₃H₁₀FN₂O₄ [MH⁺]: 393.2184; found = 393.2198. [α]D⁺²⁵ = = -121 (c = 1.00, CHCl₃) for 99.8 : 0.2 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 8% iPrOH/hexane, 1.00 mL/min, 225 nm); *tₚ* = 19.5 min [minor], *tᵣ* = 30.8 min [major].

**trans-N,N′-[2-(2′-Methoxyphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (25).** Using (R,S)-tert-Bu-Josiphos as chiral ligand the bis-protected hydrazine was obtained as a colourless oil in 75% yield (41 mg). On a 1 mmol scale, 347 mg were obtained (86%, >99% ee). **¹H NMR** (400 MHz, CDCl₃): δ 7.21-7.15 (2H, m), 6.93 (1H, t, J = 7.2 Hz), 6.81 (1H, d, J = 8.1 Hz), 6.38 and 6.24 (1H, br, coalescing br.s), 5.90-5.84 (1H, m), 5.70-5.62 (1H, m), 4.75-4.47 (1H, br,m), 4.42-4.31 (1H, m), 3.82 (3H, s), 2.70-2.48 (2H, m), 1.57-1.00 (18H, br,m). **¹³C NMR** (100 MHz, CDCl₃): δ 165.7, 156.2, 155.8, 132.3, 128.8, 127.7, 121.3, 115.7, 110.4, 81.1 (2), 68.9 and 66.2 (br, rotamers), 55.8, 44.8 (br), 35.4 (br), 28.4 (3), 28.0 (3). **IR** (NaCl, neat film): 3326 (br), 3053, 2976, 2931, 2858, 1745, 1709, 1691, 1598, 1461, 1366, 1243, 1156, 1049, 1026, 951 cm⁻¹. **MS** (ESI): *m/z* (rel. intensity): 405.2 (MH⁺, 7), 293 (7), 249 (80), 205 (31), 173 (100), 131 (12), 107 (7). **HRMS** (ESI): calculated for C₂₅H₂₃N₂O₃ [MH⁺]: 405.2383; found = 405.2400. [α]D⁺²⁵ = = -51.0 (c 1.47, CHCl₃) for 99.7:0.3 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 10% iPrOH/hexane, 1.00 mL/min, 225 nm); *tₚ* = 7.3 min [minor], *tᵣ* = 9.1 min [major].

**trans-N,N′-[2-(2′-Naphthyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (26).** Using (R,S)-tert-Bu-Josiphos as chiral ligand as solvent, the bis-protected hydrazine was obtained as a colourless oil in 68% yield (39 mg). **¹H NMR** (400 MHz, CDCl₃): δ 8.19 (1H, br,s), 7.85 (1H, d, J = 9.1 Hz), 7.73 (1H, d, J = 8.3 Hz), 7.52-7.32 (4H, m), 6.25 (1H, 1H, br,s), 5.99-5.94 (1H, m), 5.86-5.80 (1H, m), 4.88 (1H, br,s), 4.73 (1H, br,s), 2.86-2.60 (2H, m), 1.59-0.80 (18H, br,m). **¹³C NMR** (100 MHz, CDCl₃): δ 165.6, 154.8, 139.7, 134.3, 133.2, 132.4, 130.2, 129.0, 127.3, 126.1, 125.7, 124.0 (3), 81.4 (2), 67.2 and 64.9 (br, rotamers), 50.7, 36.0, 28.4 (6). **IR** (NaCl, neat film): 3271 (br), 3049, 2977, 2927, 1739-1702 (br.), 1511, 1477, 1392, 1366, 1331, 1251, 1156, 1050, 1023, 950, 778 cm⁻¹. **MS** (ESI): *m/z* (rel. intensity): 425.2 (MH⁺, 7), 347 (11), 313 (41), 269 (100), 193 (91), 141 (27). **HRMS** (ESI): calculated for C₂₇H₂₁N₂O₃ [MH⁺]: 425.2434; found = 425.2422. [α]D⁺²⁵ = = +41.2 (c 1.40, CHCl₃) for 99.0 : 1.0 er, as determined by HPLC analysis: (Chiralcel AD, gradient 1-5% iPrOH/hexane, 1.0 mL/min, 225 nm); *tₚ* = 23.8 min [minor], *tᵣ* = 24.9 min [major].

**trans-N,N′-[2-(4′-Fluoro-2′-methoxyphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (27).** Using (R,S)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 54% yield (31 mg). **¹H NMR** (400 MHz, CDCl₃): δ 7.08 (1H, t, J = 7.0 Hz), 6.61 (1H, dt, J = 2.0, 8.3 Hz), 6.54 (1H, dd, J = 2.0, 10.9 Hz), 6.29 and 6.12 (1H, coalescing br.s), 5.88-5.82 (1H, m), 5.65-5.56 (1H, m), 4.65 and 4.55 (1H, coalescing br.s), 4.32-4.22 (1H, m), 3.78 (3H, s), 2.68-2.46 (2H, br,m), 1.60-1.04 (18H, br,m). **¹³C NMR** (100 MHz, CDCl₃): δ 162.6 (d, J = 244 Hz), 158.2, 156.1, 155.1 (br), 132.0, 130.8, 128.4, 127.6, 107.3 (d, J = 17.6 Hz), 98.8 (d, J = 25.7 Hz), 81.2 (2), 68.6 and 66.3 (br, rotamers), 56.1, 44.7 (br), 35.4, 28.4 (3), 28.1 (3). **IR** (NaCl, neat film): 3315 (br), 3052, 3002, 2976, 2932, 2869, 1748-1694 (br), 1603, 1502, 1456, 1393, 1367, 1331, 1277, 1255, 1152, 1103, 1033, 949, 834 cm⁻¹. **MS** (EI), *m/z* (rel. intensity): 423 (MH⁺, 3), 367 (5), 311 (15), 267 (18), 222 (24), 190 (100), 165 (39), 83 (24). [α]D⁺²⁵ = = +44.2 (c 1.00, CHCl₃) for 99.9 : 0.1 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 10% iPrOH/hexane, 1.0 mL/min, 272 nm); *tₚ* = 11.6 min [major], *tᵣ* = 16.0 min [minor].
trans-N,N'-[2-(5'-Chloro-2'-methoxyphenyl)-cyclopent-3-eny]-di-tert-butyl-hydrazine dicarboxylate (28). Using (S,R)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 96% yield (59 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.16-7.09 (2H, m), 6.72 (1H, d, $J = 8.6$ Hz), 6.30 and 6.14 (1H, coalescing br.s), 5.92-5.85 (1H, m), 5.65-5.56 (1H, m), 4.75-4.50 (1H, br.m), 4.37-4.28 (1H, m), 3.78 (3H, s), 2.72-2.49 (2H, m), 1.57-1.04 (18H, br.m). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.0, 155.1 (br), 134.0, 131.5, 131.4, 128.5, 127.9, 127.2, 126.2, 111.6, 81.2 (2), 68.6 and 66.1 (br, rotamers), 56.2, 44.8, 35.4, 28.4 (3), 28.1 (3). IR (NaCl, neat film): 3316 (br), 3050, 2972, 2929, 1750-1707 (br), 1489, 1463, 1392, 1366, 1330, 1243, 1155, 1127, 1024, 954 cm$^{-1}$. MS (ESI), $m/z$ (rel. intensity): 439.3 (MH$^+$, 15), 385 (3), 383 (10), 327 (45), 285 (30), 283 (100), 239 (9), 207 (6). HRMS (ESI): calculated for C$_{24}$H$_{22}$N$_2$O$_4$ [MH$^+$]: 439.1994; found = 439.2013. [$\alpha$]$_D$$^{23.5}$ = $-$101 (c 1.36, CHCl$_3$) for 99.4 : 0.6 er, as determined by HPLC analysis: (Chiralcel AD, isocatic 10% iPrOH/hexane, 1.0 mL/min, 235 nm); $t_R$ = 12.3 min [minor], $t_R$ = 20.4 min [major].

trans-N,N'-[2-(2'-Methoxy-3'-quinolino)-cyclopent-3-eny]-di-tert-butylhydrazine dicarboxylate (29). Using (R,S)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 91% yield (56 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88-7.77 (2H, m), 7.67 (1H, d, $J = 7.9$ Hz), 7.56 (1H, t, $J = 7.0$ Hz), 7.35 (1H, t, $J = 7.1$ Hz), 6.36 and 6.21 (1H, coalescing br.s), 5.96 (1H, br.s), 5.73 (1H, br.s), 4.83 and 4.69 (1H, coalescing br.s), 4.45-4.31 (1H, m), 4.09 (3H, s), 2.82-2.54 (2H, m), 1.67-0.90 (18H, br.m). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.7, 156.0, 155.0, 145.6, 135.1, 131.4, 128.9, 128.1, 127.2, 127.1, 125.9, 124.2 (2), 81.2 (2), 68.3 and 65.7 (br, rotamers), 53.9, 46.8, 35.8, 28.4 (3), 28.2 (3). IR (NaCl, neat film): 3293 (br), 3054, 3001, 2977, 2929, 2856, 1741-1701 (br.), 1624, 1473, 1443, 1401, 1366, 1256, 1155, 1016, 952, 756 cm$^{-1}$. MS (ESI), $m/z$ (rel. intensity): 456.3 (MH$^+$, 100), 400 (33), 344 (72), 300 (10). HRMS (ESI): calculated for C$_{23}$H$_{22}$N$_2$O$_4$ [MH$^+$]: 456.2492; found = 456.2504. [$\alpha$]$_D$$^{24.9}$ = +162 (c 1.31, CHCl$_3$) for 98 : 2 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 8% iPrOH/hexane, 1.0 mL/min, 225 nm); $t_R$ = 11.3 min [major], $t_R$ = 15.0 min [minor].

trans-N,N'-[2-(4'-Methoxycarbonylphenyl)-cyclopent-3-eny]-di-tert-butylhydrazine dicarboxylate (31). Using (S,R)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 58% yield (34 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.94 (2H, d, $J = 8.3$ Hz), 7.32 (2H, br.s), 6.24 (1H, br.s), 5.90-5.84 (1H, m), 5.69-5.63 (1H, m), 4.69 (1H, br.s), 4.09-3.97 (1H, br.m), 3.88 (3H, s), 2.70-2.49 (2H, m), 1.55-0.99 (18H, br.m). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.3, 156.0, 154.9, 149.6, 132.2 (2), 130.8, 129.9 (2), 128.5, 127.9, 81.6, 81.4, 67.8 and 66.0 (br, rotamers), 54.1, 52.2, 35.5, 28.4 (3), 28.2 (3). IR (NaCl, neat film): 3316 (br), 3051, 3004, 2977, 2931, 2857, 1744-1710 (br.), 1610, 1476, 1436, 1392, 1367, 1280, 1154, 1111, 1020, 951, 758 cm$^{-1}$. MS (ESI), $m/z$ (rel. intensity): 455.2 (MNa$^+$, 40), 355 (10), 277 (100), 245 (50), 201 (46), 169 (31). HRMS (ESI): calculated for C$_{23}$H$_{22}$N$_2$O$_4$Na [MNa$^+$]: 455.2152; found = 455.2170. The enantiomeric ratio was 92.8 : 7.2, as determined by HPLC analysis: (Chiralcel AD, isocratic 4% iPrOH/hexane, 0.75 mL/min, 225 nm); $t_R$ = 64.2 min [minor], $t_R$ = 71.8 min [major].
trans-N,N'-[(3'-Trimethylsilylphenyl)cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (32). Using (R,S)-tert-Bu-Josiphos as chiral ligand, and a THF/H₂O as solvent, the bis-protected hydrazine was obtained as a colourless oil in 83 % yield (37 mg). \(^1\)H NMR (400 MHz, CDCl₃): \(\delta 7.18-6.93\) (4H, m), 5.98 and 5.76 (1H, coalescing br.s), 5.66-5.57 (1H, m), 5.50-5.40 (1H, br.s), 4.57-4.40 (1H, br.m), 3.77-3.59 (1H, br.m), 2.50-2.26 (2H, br.m), 1.32-0.75 (18H, br.m), 0.00 (9H, s). \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta 156.9, 156.0, 143.6, 141.6, 133.9, 133.5, 132.6, 131.0, 129.3, 128.9, 83.4, 82.2, 69.4 and 66.9 (br, rotamers), 54.9, 36.3, 29.3 (3), 29.0 (3), 0.04 (3). IR (NaCl, neat film): 3319, 3039, 2978, 1738, 1697 (br.), 1477, 1454, 1367, 1336, 1249, 1157, 1049, 839, 771, 752 cm⁻¹. MS ESI, \(\text{m/z (rel. intensity)}\): 469 (MNa⁺, 60), 391 (12), 335 (10), 291 (100), 117 (5). HRMS (ESI⁺): calculated for \(\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_4\text{Na} [\text{MNa}⁺]: 469.2493; \text{found} = 469.2510. \text{[a]}_{D}^{23.2} = -119 (c 1.78, CHCl₃) for 78.5:21.5 er, as determined by HPLC analysis: (Chiralcel AD, 3% iPrOH/hexane, 0.75 mL/min, 225 nm); \(t_R = 20.7\) min [minor], \(t_R = 26.1\) min [major].

trans-N,N'-[(2'-Vinyl-(2'-phenyl)cyclopent-3-enyl)-di-tert-butylhydrazine dicarboxylate (33). Using (R,S)-tert-Bu-Josiphos as chiral ligand and THF/H₂O as solvent, the bis-protected hydrazine was obtained as a colourless oil in 99 % yield (39 mg). \(^1\)H NMR (400 MHz, CDCl₃): \(\delta 7.39-7.16\) (6H, m), 6.42 (2H, d, \(J = 15.9\) Hz), 6.20 and 5.93 (1H, coalescing br.m), 5.79-5.74 (1H, m), 5.67-5.60 (1H, m), 4.65 (1H, br.s), 3.56 (1H, br.s), 2.69-2.45 (2H, br.m), 1.52-1.35 (18H, br.m). \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta 155.9, 155.2, 137.7, 132.1, 131.9, 130.2, 129.9, 128.7 (2), 127.3, 126.4 (2), 81.5, 81.3, 65.5 and 64.3 (coalesc. br. rotamers), 51.7 (br), 35.4, 28.6 (6). IR (NaCl, neat film): 3313 (br), 3029, 2978, 2931, 2834, 1741, 1705 (br.), 1492, 1392, 1367, 1249, 1157, 1022, 964, 748 cm⁻¹. MS ESI, \(\text{m/z (rel. intensity)}\): 423.2 (MNa⁺, 100), 323 (28), 301 (20), 245 (50), 169 (20), 91 (15). HRMS (ESI⁺): calculated for \(\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4\text{Na} [\text{MNa}⁺]: 423.2254; \text{found} = 423.2258. \text{[a]}_{D}^{26.5} = -83.4 (c 1.17, CHCl₃) for 72.0:28.0 er, as determined by HPLC analysis: (Chiralcel OD, isocratic 4% iPrOH/hexane, 0.80 mL/min, 225 nm); \(t_R = 9.5\) min, \(t_R = 11.3\) min [major].

5-(3'-Thienophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate (38). Using (R,S)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 89% yield (46 mg). \(^1\)H NMR (400 MHz, CDCl₃): \(\delta 7.34-7.26\) (1H, m), 7.04-6.92 (2H, m), 4.74-4.30 (2H, br.m), 3.52-3.25 (1H, br.m), 2.51-2.12 (1H, br.m), 2.12-1.58 (3H, br.m), 1.58-1.40 (18H, br.m). \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta 157.1\) (br.), 155.7 (br), 143.5, 127.5, 126.5, 120.1, 81.7, 81.5, 65.6 and 64.7 (br, rotamers), 61.1 and 60.4 (br, rotamers), 42.3, 41.1, 36.6 (br, rotamers), 35.6 and 34.3 (br, rotamers), 28.4 (6). IR (NaCl, neat film): 3099, 3002, 2976, 2930, 2883, 1733 (br), 1696 (br.), 1590, 1475, 1457, 1367, 1339, 1256, 1161, 1140, 1048, 1011, 912, 774 cm⁻¹. MS (EI), \(\text{m/z (rel. intensity)}\): 380 (M⁺, 4), 280 (10), 251 (11), 224 (54), 149 (16), 113 (21), 69 (57), 57 (100). HRMS (EI): calculated for \(\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_{4}\text{S} [\text{M}⁺]: 380.1770; \text{found} = 380.1780. \text{[a]}_{D}^{24.6} = +22.2 (c 1.20, CHCl₃) for 81:19 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 5% iPrOH/hexane, 0.80 mL/min, 235 nm); \(t_R = 12.7\) min [minor], \(t_R = 16.7\) min [major].

5-(2'A'-Dimethoxypyrimidin-5-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate (40). Using (R,S)-tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 69% yield (41 mg). \(^1\)H NMR (400 MHz, CDCl₃): \(\delta 7.96\) (1H, s), 4.79-4.35 (2H, br.m), 4.02 (3H, s), 3.98 (3H, s), 3.41-3.19 (1H, br.m), 2.49-2.18 (1H, br.m), 1.72 (2H, br.s), 1.59 (1H, br.s), 1.63-1.39 (18H, br.m). \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta 169.4, 164.4, 157.1\) (br.), 154.6 (br), 154.1, 115.5, 81.7, 81.5, 63.4 and 61.9 (br, rotamers), 61.2 and 60.2 (br, rotamers), 54.9, 54.2, 38.1 and 37.1 (br, rotamers), 35.7, 35.0 and 34.1 (br, rotamers), 28.3 (6). IR
(NaCl, neat film): 3004, 2979, 2933, 2901, 1734 (br), 1699, 1601, 1567, 1473, 1404, 1368, 1333, 1301, 1257, 1156, 1140, 1106, 1075, 1016, 914, 860, 800, 757 cm⁻¹. **MS** (ESI), m/z (rel. intensity): 437 (MH⁺, 3), 307 (11), 280 (21), 236 (27), 167 (93), 69 (23), 57 (100). [α]D₂⁵⁻⁴ = -25.5 (c 1.37, CHCl₃) for 99.9:0.1 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 20% iPrOH/hexane, 1.0 mL/min, 220 nm); tᵣ = 7.1 min [minor], tᵣ = 15.4 min [major].

5-(6'-Deuterio-2',4'-dimethoxypyrimidin-5-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate (d-40). Modifications from 40: after premixing the catalyst in 0.80 mL THF, 0.80 mL D₂O was added. To the orange heterogeneous mixture was added the solution containing 1c and the boronic acid in THF (0.80 mL). The bis-protected hydrazine was obtained as a colourless oil in 69% yield (41 mg). **¹H NMR** (400 MHz, CDCl₃): Same as for 40, with the exception of the singlet at 7.96 ppm, which was significantly decreased (signal was 9% according to integration). **MS** (ESI), m/z (rel. intensity): 438.3 (MH⁺, 100), 382 (4), 338 (4), 282 (6), 238 (5). **HRMS** (ESI): calculated for C₂₆H₂₅N₂O₆: 438.2457; found = 438.2478.

5-(2'-Fluorophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate (46). Using (5,R)- tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 47% yield (25 mg). **¹H NMR** (400 MHz, CDCl₃): δ 7.30-7.17 (1H, m), 7.17-7.01 (3H, m), 4.90-4.33 (2H, br.m), 3.66-3.40 (1H, br.m), 2.60-1.91 (2H, br.m), 1.86-1.63 (2H, br.m), 1.63-1.19 (18H, br.m). **¹³C NMR** (100 MHz, CDCl₃): δ 161.2 (d, J = 247 Hz), 157.5 (br.), 155.6 (br), 129.7, 128.4, 127.0 (br), 124.3, 115.8 (d, J = 22 Hz), 81.7 (2), 64.9 and 63.9 and 62.9 (br, rotamers), 61.8 and 60.2 (br, rotamers), 39.7 and 39.1 and 38.7 (br, rotamers), 36.0 and 35.1 (br, rotamers), 32.7, 28.3 (6). **¹⁹F NMR** (376 MHz, CDCl₃): δ -114.9 and -115.7 (rotamers). **IR** (NaCl, neat film): 3069, 2978, 2932, 1733 (br), 1699 (br), 1491, 1455, 1367, 1336 (br), 1300, 1258, 1228, 1158, 1141, 1111, 1047, 1005, 970, 859, 757 cm⁻¹. **MS** (EI), m/z (rel. intensity): 392 (M⁺, 3), 263 (11), 236 (71), 192 (7), 161 (13), 113 (42), 69 (67), 57 (100). **HRMS** (EI): calculated for C₁₅H₁₃N₂O₄F [M⁺]: 392.2111; found = 392.2108. [α]D₁⁵⁶ = -38.5 (c 1.30, CHCl₃) for 99.0:1.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 8% iPrOH/hexane, 1.0 mL/min, 225 nm); tᵣ = 7.31 min [major], tᵣ = 11.1 min [minor].

5-(4'-Trifluoromethylphenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate (47). Using (R,S)- tert-Bu-Josiphos as chiral ligand, the bis-protected hydrazine was obtained as a colourless oil in 39% yield (23 mg). **¹H NMR** (400 MHz, CDCl₃): δ 7.60 (2H, d, J = 7.4 Hz), 7.33 (2H, d, J = 7.4 Hz), 4.83-4.30 (2H, br.m), 3.55 and 3.39 (1H, coalesc. br.m), 2.64-2.01 (2H, br.m), 1.92-1.63 (2H, br.m), 1.63-1.40 (18H, br.m). **¹³C NMR** (100 MHz, CDCl₃): δ 156.9 (br.), 155.1 (br), 146.0 (d, J = 72.1 Hz), 128.8 (q, J = 31.8 Hz),127.5 (2), 125.8 (2), 121.6 (d, J = 271.8 Hz), 81.9, 81.8 65.9 and 65.1 (br, rotamers), 61.3 and 60.5 (br, rotamers), 46.2 and 45.0 (br, rotamers), 36.8 and 35.9 (br, rotamers), 34.7 and 32.8 (br, rotamers), 28.4 (6). **IR** (NaCl, neat film): 3001, 2977, 2932, 2887, 1734 (br.), 1700 (br.), 1618, 1476, 1458, 1368, 1326, 1257, 1162, 1125, 1070, 969, 840, 770 cm⁻¹. **MS** (ESI), m/z (rel. intensity): 465.2 (MNa⁺, 24), 365 (6), 287 (100), 241 (3). **HRMS** (ESI): calculated for C₂₂H₂₅N₂O₄F₃Na [MNa⁺]: 465.1971; found = 465.40. [α]D₅⁵⁺ = +23.7 (c 1.65, CHCl₃) for 92.8 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 3% iPrOH/hexane, 0.75 mL/min, 225 nm); tᵣ = 14.7 min [minor], tᵣ = 17.2 min [major].
2,3-di-tert-butyl 5,5′-(1,2-phenylene)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate) (48). Using (R,R)-Walphos-001 (W001) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the hydrazine was obtained as a colourless oil in 61% yield (21 mg). 1H NMR (400 MHz, CDCl3): δ 7.17 (m, 2H), 7.08 (m, 2H), 4.57 (m, 4H), 3.41 (m, 2H), 2.42 (m, 2H), 1.93 (m, 2H), 1.75 (m, 2H), 1.60 (m, 2H), 1.46 (s, 9H), 1.43 (m, 9H). 13C NMR (126 MHz, CDCl3) δ 155.99 (m, 4), 141.15 (2), 126.50 (2), 125.19 (2), 81.32 (br, 4), 63.98 (2), 59.98 (m, 2), 41.18 (m, 2), 37.34 (m, 4), 28.15 (6), 27.93 (6). IR (NaCl, neat film): 3002, 2971, 1744, 1731, 1716, 1700, 1473, 1345, 1318, 1256, 1158, 829, 755 cm⁻¹. MS (ESI), m/z (rel. intensity): 693.4 (MNa⁺, 50), 671 (MH⁺, 15), 571 (100), 515.3 (15), 471 (13), 415 (12), 359 (45). HRMS (ESI): calculated for C38H35N3O9 [MH⁺]: 671.4014; found = 671.4033. [α]D°27.8 = +5.85 (c 1.50, CHCl3).

d°-48. Using (R,R)-Walphos-001 as chiral ligand, and a mixture of THF/H2O (10:1) as solvent, hydrazine was obtained as a colourless oil in 64% yield (22 mg). In order to quantify the extent of deuteration at the aliphatic positions the hydrazines were deprotected.

d°-1,2-di(2,3-diazabicyclo[2.2.1]heptan-5-yl)benzene.

Compound d°-48 (21 mg) was dissolved in DCM (0.15M) and cooled to 0 °C. Trifluoroacetic acid (0.15M, 214 µl) was added dropwise and the mixture was stirred for 30 minutes. TLC revealed full consumption of starting material. After evaporation of the liquids, the mixture was quenched with NaHCO₃ and extracted with EtOAc. The organic phase yielded the titled product as a colorless oil in 36% yield (5 mg). HNMR indicated the presence of 2 diastereomers in a ratio of 1:0.75. 1H NMR (400 MHz, CDCl3): δ 7.20 (s, 1H, major), 7.18 (s, 0.75H, minor), 5.30 (br. s, 1.5H, minor), 5.27 (br. s, 2H, major), 5.19 (s, 1.5H, minor), 5.18 (s, 2H, major), 2.55 (s, 1H, major), 2.53 (s, 1H, major), 2.42 (s, 0.75H, minor), 2.40 (s, 0.75H, minor), 1.69-1.62 (m, 3.5H, major+minor), 1.59-1.51 (m, 3.5H, major+minor), 1.45-1.37 (m, 3.5H, major+minor).

5-(1′H-pyrrol-3′-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl carboxylate (54a).

Using Walphos 005 as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colourless oil in 45% yield (16 mg). 1H NMR (400 MHz, CDCl3): δ 8.09 (1H, br.s), 6.68 (1H, m), 6.51 (1H, m), 6.02 (1H, m), 4.41 (2H, m), 3.21 (1H, m), 2.19 (1H, m), 1.71 (2H, d, J = 10.0 Hz), 1.43 (19H, m). 13C NMR (100 MHz, CDCl3): δ 156.8 (2), 125.3, 118.6, 115.0, 107.5, 81.6, 81.3, 66.6 and 65.5 (br, rotamers), 61.0 and 60.5 (br, rotamers), 39.7, 38.1, 34.9, 28.4 (6). IR (NaCl, neat film): 3348, 2977, 2925, 1725, 1687, 1475, 1396, 1284, 1248, 1158, 752 cm⁻¹. MS (ESI), m/z (rel. intensity): 364.2 (MH⁺, 30), 308 (55), 286 (25), 208 (100), 132 (30). HRMS (ESI): calculated for C19H30N3O4 [MH⁺]: 364.2230; found = 364.2244. [α]D°27.6 = +20.6 (c 0.713, CHCl3) for 89.0:11.0 er, as determined by HPLC analysis: (Chiralcel AD, isocratic 10 % iPrOH/hexane, 0.8 mL/min, 220 nm); tR = 10.4 min [minor], tR = 18.9 min [major].

5-1′-(tert-butoxycarbonyl)-pyrrol-3′-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl carboxylate (54b). Using (R,S)-t-Bu-Josiphos as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colourless oil in 30% yield (14 mg). 1H NMR (400 MHz, CDCl3): δ 7.17 (1H, s), 6.97 (1H, br.s), 6.09 (1H, br. s), 4.48 (2H, m), 3.18 (1H, m), 2.24 (1H, m), 1.71 (2H, d, J = 10.4 Hz), 1.58 (10H, br. s), 1.5 (18 H, br. s). 13C NMR (100 MHz, CDCl3): δ 156.7, 149.0, 129.0, 120.9, 116.4, 111.9, 83.9, 81.6, 81.3, 65.5 and 64.7 (br, rotamers), 61.0 and 60.4 (rotamers), 39.5 and 38.3 (rotamers), 35.3 and 34.9 (rotamers), 28.4(3),
Di-tert-butyl-1-[(2′-chlorophenyl)cyclopent-3-enyl]hydrazine-1,2-dicarboxylate (55).

Using (R,S)-tert-Bu-Josiphos as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colourless oil in 40% yield (16 mg). ¹H NMR (400 MHz, CDCl₃): δ 7.31 (1H, d, J = 7.6 Hz), 7.24 (2H, m), 7.15 (1H, m), 6.31 (1H, br. s), 5.90 (1H, m), 5.60 (1H, s), 4.71 (1H, m), 4.42 (1H, m), 2.64 (2H, m), 1.49 (9H, s), 1.47 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 155.0, 141.2, 133.8, 131.5, 131.3, 129.2, 128.6, 127.8, 127.3, 81.2 (2), 68.4 and 66.0 (br, rotamers), 49.2, 35.2, 28.4 (3), 28.3 (3). IR (NaCl, neat film): 2976, 2925, 1742, 1695, 1367, 1158 cm⁻¹.

trans-N,N′-[2′-(1′H-pyrrol-3′-yl)cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (59a).

Using (R,S)-t-Bu-Josiphos as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colourless oil in 15% yield (4 mg). For characterization purposes, 54a, was prepared through deprotection of 54c (TBAF 1.05 equiv in THF (0.25M) quantitative yield). ¹H NMR (400 MHz, CDCl₃): δ 8.47 (1H, br.s), 6.70 (1H, q, J = 2Hz), 6.65 (1H, br.s), 6.37 and 6.24 (1H, coalescing br.s), 6.10 (1H, s), 5.72 (2H, m), 4.75 (1H, m), 3.88 (1H, m), 2.56 (2H, m), 1.47 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 155.9, 155.3, 134.0, 128.5, 125.4, 118.2, 115.0, 107.4, 81.2 (2), 67.8 and 65.0 (br, rotamers), 46.1, 35.2, 28.4 (3), 28.3 (3). IR (NaCl, neat film): 3354, 2982, 2925, 1726, 1690, 1475, 1452, 1372, 1349, 1315, 1163, 755 cm⁻¹. MS (ESI), m/z (rel. intensity): 364 (MH⁺, 40), 308 (41), 286 (38), 264.6 (38), 252 (100), 133 (70). HRMS (ESI) calculated for C₈H₁₀N₂O₉ [MH⁺]: 364.2230; found = 364.2249. [α] D₂⁰⁺ = -77.05 (c 0.78, CHCl₃) for 99.5:0.5 er, as determined by HPLC analysis: (Chiralpak AD, isocratic 10% iPrOH/hexane, 0.8 mL/min, 225 nm); tᵣ = 14.0 min [major], tᵣ = 18.1 min [minor].

trans-N,N′-[N′-(tert-butoxycarbonyl)-pyrrol-3′-yl)cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate (59b).

Using (R,S)-t-Bu-Josiphos as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colourless oil in 68% yield (31mg). ¹H NMR (400 MHz, CDCl₃): δ 7.16 (1H, m), 7.02 (1H, s), 6.21 (1H, m), 6.16 (1H, m), 5.75 (1H, m), 5.68 (1H, m), 4.71 (1H, m), 3.83 (1H, m), 2.56 (2H, m), 1.56 (9H, s), 1.47 (9H, s), 1.39 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 155.9, 154.8, 149.2, 132.6, 129.4, 120.4, 116.5, 112.1, 83.3, 81.3, 81.0, 66.6 and 65.0 (rotamers), 46.2, 35.2, 28.3(3), 28.2(6). IR (NaCl, neat film): 3318 (br.), 2972, 2930, 1739, 1705, 1367, 1344 cm⁻¹. MS (ESI), m/z (rel. intensity): 464 (MH⁺, 25), 408(60), 352(100), 289(95), 176(55). HRMS (ESI) calculated for C₂₄H₃₈N₆O₁₆ [MH⁺]: 464.2755; found = 464.2756. [α] D₂⁰⁺⁺ = +52.3 (c 1.20, CHCl₃) for 68.0:32.0 er, as determined by HPLC analysis: (Chiralcecl AD, isocratic 15% iPrOH/hexane, 0.8 mL/min, 235 nm); tᵣ = 11.6 min [minor], tᵣ = 29.8 min [major].
1-(tert-Butoxycarbonyl)-3,4-bis[2,3-(di-tert-butoxycarbonyl)-2,3-diazabicyclo[2.2.1]heptan-5'-yl]-pyrrole (56). Using Walphos-001 (W001) as chiral ligand, and a mixture of THF/water (10:1) as solvent, the protected hydrazine was obtained as a colourless oil in 74% yield (28 mg). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.85 (br s, 2H), 4.72-4.30 (m, 4H), 3.30-2.86 (m, 2H), 2.56-2.15 (m, 2H), 1.88-1.65 (m, 2H), 1.56 (br s, 13H), 1.46 (br s, 36H). \(^1^3\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 157.7-155.2 (m, 2), 148.5, 128.6 (br), 115.4 (br), 83.9, 81.7-80.9 (m, 4), 63.7 (br, 2), 60.5 (br, 2), 38.3-33.9 (m, 6), 28.2 (br, 6), 28.1 (br, 6), 27.9 (3). IR (NaCl, neat film): 3032, 2972, 1734, 1695, 1475, 1449, 1375, 1346, 1279, 1256, 1158, 755 cm\(^{-1}\). MS (ESI), \(m/z\) (rel. intensity): 782.4 (MNa\(^+\), 35), 760 (25), 660 (100), 604 (15), 560 (5), 548 (4), 504 (3), 448 (30). HRMS (ESI): calculated for C\(_{39}\)H\(_{62}\)N\(_{10}\)O\(_{10}\) [MH\(^+\)]: 760.4491; found = 760.4522. [\(\alpha\)]\(_D\)\(^{27.8} \) = +4.23 (c 1.14, CHCl\(_3\)).

Di-tert-butyl 5-(2-(5,12-bis(tert-butoxycarbonyl)hydrazinyl)cyclopent-2-enyl)furan-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (57). Using (R,S)-t-Bu-Josiphos as chiral ligand, and a mixture of THF/water (10:1) as solvent, the hydrazine was obtained as a colourless oil in 68% yield (23 mg) as a mixture of 2 diastereomers (70:30). \(^1\)H NMR (Major, 500 MHz, CDCl\(_3\)): \(\delta\) 7.95 (br d, 1H, J = 50 Hz), 7.20 (br s, 1H), 6.16-5.99 (m, 1H), 5.81 (br s, 1H), 5.51 (br s, 1H), 5.17-4.48 (m, 1H), 4.65-4.66 (m, 1H), 4.47-4.20 (m, 1H), 4.17-4.02 (m, 1H), 3.30-2.99 (m, 1H), 2.71-2.42 (m, 1H), 2.04-1.89 (m, 1H), 1.83-1.60 (m, 1H), 1.53-1.07 (m, 38H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 157.4, 157.2, 156.4, 156.1, 155.5, 154.8, 154.4, 152.1, 151.9 (4 Boc groups, 2 diastereomers + rotamers), 141.5-140.6 (m), 131.8-130.5 (m), 130.0-128.5 (m), 121.4-119.3 (m), 109.8-108.9 (m), 82.3-81.1 (m), 80.9-79.9 (m), 66.3, 65.9, 64.7, 62.9, 60.9, 60.5, 45.7, 45.2, 44.2, 35.6-33.2 (m), 32.0, 28.5, 28.3, 28.1, 27.9, 27.6. IR (NaCl, neat film): 3297, 2977, 2930, 1747, 1724, 1690, 1667, 1504, 1380, 1346, 1251, 1153, 1127, 752 cm\(^{-1}\). MS (ESI), \(m/z\) (rel. intensity): 683.4 (MNa\(^+\), 30), 661.4 (MH\(^+\), 20), 561 (100), 505 (15), 461 (12), 349 (15), 105 (16). HRMS (ESI): calculated for C\(_{39}\)H\(_{52}\)N\(_{8}\)O\(_{6}\) [MH\(^+\)]: 661.3807; found = 661.3823. [\(\alpha\)]\(_D\)\(^{27.8} \) = +42.8 (c 0.851, CHCl\(_3\)).

5-(2'-Chlorophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate (58). Using (R,S)-t-Bu-Josiphos as chiral ligand, and a mixture of THF/water (10:1) as solvent, the bis-protected hydrazine was obtained as a colourless oil in 47% yield (19 mg). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.38 (1H, d, J=7.62Hz), 7.18 (3H, m), 4.88-4.41 (2H, m), 3.59 (1H, m), 2.49 (1H, m), 1.79 (2H, br s), 1.52 (10H, s), 1.49 (9H, s). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.6, 155.9 (2), 130.4, 120.3, 115.6, 113.4, 81.7 and 81.4 (2, rotamers), 65.2 and 64.5 (br, rotamers), 60.9 and 60.3 (rotamers), 39.4 and 38.2 (rotamers), 35.4 and 34.8 (rotamers), 28.4 (6). IR (NaCl, neat film): 2977, 2930, 1734, 1716, 1698, 1367, 1341, 1155 cm\(^{-1}\). MS (ESI), \(m/z\) (rel. intensity): 411 (MNa\(^+\), 5), 409 (MH\(^+\), 15), 255 (30), 253 (100), 177 (20). HRMS (ESI): calculated for C\(_{21}\)H\(_{29}\)N\(_{4}\)O\(_{4}\)Na [MNa\(^+\)]: 431.1708; found = 431.1712. [\(\alpha\)]\(_D\)\(^{27.1} \) = +36.4 (c 0.885, CHCl\(_3\)) for 99.4 : 0.6 er, as determined by HPLC analysis (Chiralcel AD, isocratic 4% iPrOH/hexane, 0.8 mL/min, 230 nm); \(t_r\) = 11.83 min [minor], \(t_R\) = 23.32 min [major].
CHAPTER 4

RHODIUM-CATALYZED ACYLATION OF ALKENES UNDER MILD CONDITIONS

This chapter discusses the use of rhodium catalysts to generate acyl anions catalytically with organoboron reagents in the presence of CO at ambient pressure and temperature. Specifically, this mode of reactivity is exploited to chemo- and diastereoselectively promote the desymmetrization of diazabicycles; constituting the first example of a formal allylic substitution with acyl anion as nucleophiles.\(^1\) The reactivity of other \(\pi\) acceptors towards acyl anions is also discussed, as well as the use of \(N\)-heterocyclic carbenes as ancillary ligands.

4.1 Introduction

Acylation reactions are the focus of a sustained interest as they now expand beyond the pioneering work done on hydroformylation.\(^2\) The insertion of carbon monoxide into metal-carbon bonds is well precedented with several metals, but rhodium is by far the most versatile in terms of reactivity.\(^3\) Two fundamental processes are typically involved in carbonylation reactions with transition metal catalysts. Either molecules of CO gas insert into

\(^1\) Portions of this chapter have been published as a communication: Menard, F.; Weise, C. F.; Lautens, M. Org. Lett. 2007, 9, 5365.


an organometallic bond, or the metal inserts into aldehydes or activated carboxyls (anhydrides and equivalents). Precedents about these two methods are reviewed below. Several transition metals are known to bind CO with high affinity including cobalt, manganese, rhodium, iridium, molybdenum, iron, ruthenium, and nickel.\(^7\)\(^9\) The following survey is limited to reactions catalyzed by Rh and Pd.

4.1.1 Carbonylation reactions by CO insertion

Carbon-carbon bond formation by carbonylation reactions using transition metal catalysts and CO almost invariably involves migratory insertion (I to II, Scheme 4-1).\(^8\) Migration of an organic nucleophile to a bound CO ligand can generate what is essentially an acyl anion, II. The process is driven by a free coordination site on complex II being filled by an incoming ligand L, and is often followed by reductive elimination.\(^9\)

![Scheme 4-1](attachment:image.png)

Scheme 4-1 Generic formation of acyl-metal species by CO insertion into organometallic bonds.

Palladium catalysis has been the most widely used organometallic method for carbonylation, at high pressures, and mainly in intramolecular cases.\(^2\)\(^b\) In cases where the acylmetal species III reacts with a neutral pi system (e.g. alkene or alkyne), acylmetalation can be followed by β-hydride elimination particularly with palladium (Eqn. 4-1),\(^10\) or by further acylation (Eqn. 4-2).\(^11\) However Pd-catalyzed methods often suffer from regioselectivity issues in intermolecular reactions.

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The related amino-carbonylation of aryl halides is an area that has generated tremendous interest within the synthetic community. Indeed, this strategy allows for a powerful direct amide formation; a recent example of which is depicted in Equation 4-3. For further details on this topic, the reader is directed towards major recent reviews of the field. The literature surveyed below is restricted to the carbonylation of alkenes and alkynes.

Hydroformylation. The seminal discovery of hydroformylation was made in 1938 at Ruhrchemie AG. The reaction affects the homologation of alkenes to aldehydes by the atom-economical addition of H₂ and CO (Eqn. 4-4). The original reaction was catalyzed by Co₂(CO)₈ and required elevated pressure and high temperatures. A major challenge still resides in controlling the regiochemistry of the process to obtain either the linear or branched products.

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The advent of new catalysts such as rhodium allowed lower CO/H₂ pressure from over 100 atm to 5–10 atm. Introducing phosphine ligands also resulted in a better control over the regioselectivity. The linear products are found to be favored in the presence of phosphine ligands on the rhodium complex. In view of its industrial importance, the mechanism for the Rh-catalyzed hydroformylation was extensively studied and its generally accepted cycle is shown in Scheme 4–1. The key regioselective step occurs at the hydrometallation of π-complex 1. Reversible insertion of CO into the Rh-alkyl bond of 3 gives the acylrhodium(I) species 4. After oxidative addition of H₂, reductive elimination of acylrhodium(III) yields the aldehyde and the active catalyst is recovered.

Scheme 4–2 Mechanism of Rh-catalyzed hydroformylation.

**Carbonylative cyclization reactions.** The extensive work accomplished on the Pauson-Khand reaction since its discovery in 1971, has established this formal [2+2+1] cycloaddition as the method of choice to prepare cyclopentenones. Developments in metal-catalyzed carbonylations have largely focused on intramolecular systems to circumvent regioselectivity issues that are often problematic. This strategy has led to useful synthetic methodologies by tethering of the unsaturated carbon reacting partners. For example, Wender and coworkers

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have exploited carbonylative cyclizations in [5+2+1] processes involving CO insertion to access complex medium-sized rings reactions (Eqn. 4–5).

Alternatively, intramolecular carbonylative cycloadditions with highly unsaturated substrates were studied by Brummond and coworkers using rhodium catalysts. For example, they recently reported a Rh(I)-catalyzed cyclocarbonylation reaction of allenol acetates to synthesize a variety of alkylidene cyclopentenones under mild reaction conditions (Eqn. 4–6).

In terms of intermolecular reactions, Scheme 4-2 illustrates a synthesis of coumarins by Larock and coworkers. The proposed reaction mechanism involves an arylpalladium complex that preferentially inserts an alkyne instead of CO to give the vinyl-palladium(II) species 7. Subsequent CO insertion generated the acylpalladium(II) species 8, followed by nucleophilic attack from the phenolic oxygen to force reductive elimination of the Pd(0) catalyst and to yield the desired coumarin. The isomeric product, where CO insertion would occur followed by intermolecular acylpalladation of the alkyne, was not observed. Larock states that in Pd-catalyzed carbonylation reactions, CO generally inserts preferentially to alkynes. Whereas this may be the case for Pd catalysis, it is not the typical reactivity

24 Negishi has published rates of various palladium catalyzed processes: CO insertion = intramolecular 5-exo or 6-exo-alkyne carbopalladation > intramolecular 5-exo-alkyne acyl palladation > trapping of an acyl palladium
for Rh(I) catalysis. Therefore, although the mechanism we propose in the next section would appear to be in line with the expected reactivity of Pd-catalyzed reactions, it is not usually observed with Rh catalysts.

![Scheme 4-3 Pd-catalyzed synthesis of coumarins.](image)

Chatani and coworkers recently reported a synthesis of indenones under Rh catalysis with alkynes with 2-bromoarylboronic acids\(^{25}\) carried out under a CO atmosphere (Scheme 4-3). They also proposed a mechanism involving carbometallation of the alkyne before acyl-metal formation, similar to Larock’s. Oxidation of Rh(I) to Rh(III) is needed to access the aryl nucleophile required to effect reductive elimination of the acyl-rhodium intermediate. The reaction proceeded under 1 atm of CO and required heating.

![Scheme 4-4 Rh-catalyzed synthesis of indenones and proposed mechanism.](image)

We wish to stress the mechanisms proposed by Larock and Chatani involve insertion of the alkyne into the metal-aryl bond prior to the insertion of CO. In other words, neither reactions propose an acyl-metal formation as the first step. This is significant in view the results that will be reported in the following sections.

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Artok and coworkers showed in their synthesis of 5-aryl-2(5H)-furanones 13 that the insertion of two molecules of CO is possible at high gas pressures (Scheme 4-4). The mechanism is analogous to the reaction reported by Negishi with palladium (Eqn. 4-2). The report displayed a very narrow scope. Nonetheless, the major difference between their proposed mechanism and the mechanisms of Larock and Chatani is the order in which the CO and the alkyne are inserted.

Carbonylative addition to α,β-unsaturated ketones. All the methods using CO gas introduced above added acyl-metal species to alkynes only. Scheme 4-6 illustrates the first example of addition of an acyl anion to α,β-unsaturated ketones to give 1,4-diketones 15 developed by Castanet and coworkers. However, the reaction was plagued with competing side-reactions. After transmetalation with a boronic acid, the Rh-aryl complex can reversibly insert CO to form an acylrhodium key intermediate. The acyl anion can add to an enone to give the 1,4-diketone 15 after protolysis. The competing reactions involve either direct addition of the Rh-aryl species to enone 14, and/or a reductive homocoupling leading to diarylketone 17 (which is a catalytically destructive pathway). Consequently, high pressures of CO must be used to minimize the kinetically favored 1,4-arylation 16.

Scheme 4-5 Rh-catalyzed synthesis of furanones.

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4.1.2 Generation of Rh–acyl species by oxidative insertion in carbonyls

An alternative way of generating Rh-acyl species is through oxidative insertion of a rhodium(I) center into a C–X bond of a carbonyl function to generate a key acylrhodium(III) intermediate (Eqn. 4-7). This strategy often requires a chelating group to prevent the otherwise favored decarbonylation. Typical chelating groups are electron donors, e.g., heteroatoms, alkenes, or alkynes.

Hydroarylation of alkynes. This strategy was used by Fu and Tanaka in stereoselective syntheses of cyclopentenones. An asymmetric version of the reaction was also developed by using of a chiral bisphosphine ligand to effect a parallel kinetic resolution yielding either cyclobutanones or cyclopentanone (Scheme 4–6). Insertion of Rh(I) in the aldehyde C–H bond gave an acyl-rhodium(III) species that subsequently added to the alkyne. Enantiomers of the racemic starting material are proposed to be resolved at the hydrometallated step through cis- or trans-hydrometallation pathways.

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Hydroacylation of olefins. An example of intermolecular acylation by C–H insertion in aldehydes was reported by Willis and coworkers (Eqn. 4–8). In this case, sulfide ethers served as chelating groups to prevent decarbonylation, and the neutral rhodium precatalyst was made cationic by using a silver salt. A wide range of alkenes were competent substrates; even unactivated ones such as oct-1-ene were hydroacylated in 61% yield.

A highly enantioselective intramolecular hydroacylation of olefins was recently developed by Dong and coworkers. The catalytic system displays high regioselectivity to afford medium-sized heterocyclic ketones (Eqn. 4–9). Heteroatoms such as oxygen or sulfur again proved necessary to chelate an acylrhodium(III) intermediate.

Tanaka developed a protocol to hydroacetylate conjugated alkenes intermolecularly. Several aliphatic aldehydes were shown to undergo a C–H activation without need for a appended chelating group on the aldehyde substrate (Eqn. 4–10). The reaction was limited to olefins.

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conjugated to amides groups. O-amide chelation is proposed to be crucial to the process; as amide carbonyls having a strong electron density on the oxygen by resonance. In this example, chelation is still necessary, but it takes place on the alkene instead of the alkyne reactant.

Perhaps one of the most unique examples of acylrhodium(III) use in intermolecular hydroacylation was reported by Krische and coworkers. A cationic Rh catalyst was shown to insert into C–O bonds of non symmetrical anhydrides; the acyl portion of which does not bear a chelating group (Eqn. 4-11). The methodology is a striking display of chemoselectivity: it is conducted under a H₂ atmosphere with a Rh(I) catalyst, yet none of the three alkenes in the reaction appeared to be reduced (i.e.; conjugated anhydride, styrene, or conjugated ketone). Deuteration experiments suggested that the acylation of styrene occurs before hydrogen gas activation. The method was limited to styrene or norbornene-type olefins.

Two elements are common in the above reactions: (i) they all involve a cationic Rh³ catalyst; and (ii) effecting the acyl-metallation of π acceptors always involves an oxidized Rh³ metal center. The question that intrigued us was whether using acylrhodium species at the Rh³ oxidation state was possible, and what kind of reactivity they might have.

### 4.2 Stereoselective Rhodium-Catalyzed Allylic Substitution with Acyl Anion Nucleophiles

As seen in the previous section, the generation of an acyl-rhodium species is usually achieved either by a metal insertion into aldehydes or anhydrides, or by the insertion of CO into an organometallic bond. The first approach generally requires a chelating group on the aldehyde reactant to prevent competing decarbonylation, which is an intrinsical drawback as the nature

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of the acyl group cannot be varied easily. The second approach usually necessitates high pressure apparatus, heating, or often both; harsh conditions are not always compatible with the substrates. Consequently, a catalytic protocol which could generate easily variable acyl anion equivalents under mild conditions would be very useful.

Parts of the results presented in this section were collected by Christian F. Weise, a visiting student from Leipzig University as part of his Diploma Thesis requirements. The author conceived the project, performed the experiments to prove the concept, and closely supervised Weise’s efforts to ensure a steady progress due to the field being competitive.

4.2.1 Reaction design and rationale

We envisaged to generate acyl-rhodium(I) intermediates catalytically by combining the strong affinity of Rh(I) catalyst for CO to its established ease of transmetallation with boronic acids. We then hypothesized that 22 might behave as an acyl anion nucleophile, and thus might trap intermolecular electrophiles (Scheme 4-8). This proposal contrasts conceptually with the Rh(1)/Rh(III) manifolds that require nucleophilic reactants to ensure reductive elimination and regenerate the Rh(I) catalyst (Scheme 4-8a,c).37 38

Scheme 4–8 Comparison of the proposed reaction to established carbonylation processes.

The use of acylrhodium(I) intermediates as nucleophilic components in intermolecular reactions was tested in the desymmetrization of meso alkenes as a proof of principle (Scheme

37 This concept was recently recognized by Castanet and Artok, see references 25 and 26.
39 See section 4.1.
Bicyclic hydrazines 23 were clearly established as competent substrates in Rh-catalyzed reactions in the previous chapter. However, in applying our Rh-catalyzed protocol under an atmosphere of CO gas, it was unclear whether the desired acylrhodation (pathway b) would occur preferentially to the established carborhodation (pathway a).

The feasibility of the reaction was expected to depend either upon the equilibrium constant between CO-insertion/extrusion of 21 and 22; and/or on the relative nucleophilicity of aryl- vs acylrhodium species. Thus, the reaction could follow two possible pathways. The first pathway would result in the same product 24 obtained under CO-free conditions. In the second pathway the acylrhodium species 22 would add to the alkene to give the CO insertion product 25 after β-nitrogen elimination.

Scheme 4–9 Proposed ring-opening of bicyclic hydrazines with acylrhodium species.

The proposed reaction with bicyclic hydrazines would provide a carbonyl-homologated variant of the products generated by the ring-opening method discussed in Chapter 3. In addition, substituted β-amino-ketones are versatile synthetic intermediates that are used in medicinal chemistry. The figure illustrates a range of compounds with biological activity that possess the 1,3-ketoamine motif accessible by our proposed method. More specifically, these compounds have shown activity for the therapy of proliferative diseases (e.g. epidermal growth factor receptor (EGF-R) protein tyrosine kinase family; 26 and 27), or they have analgesic/antidepressant central nervous system (CNS) activities, and are thus useful in treating pain and/or depression (28 and 29).

25 under Bayer-Villiger oxidation conditions would result in conformationally restricted beta-
amino acid analogs.\textsuperscript{43}

![Figure 4–1 Cyclopentylaminoketones with reported biological activity.](image)

### 4.2.2 Results and discussion

#### Discovery of a formal acylative allylic substitution reaction

The initial experiments involved reacting bicyclic hydrazine 31\textsubscript{a} with phenylboronic acid in
the presence of a rhodium(I) complex at amiant temperature, under a CO atmosphere.\textsuperscript{44} The
acylated cyclopentene 33\textsubscript{a} was obtained as the sole product in 68\% yield (Eqn. 4–12). The
absence of 32\textsubscript{a} was surprising given its ready formation in the absence of CO. Thus, the
outcome of the reaction is completely changed simply by using a CO gas balloon instead of
Ar. This observation suggests that when CO is present, it coordinates to Rh(I) preferentially
and that only when the acyl rhodium species is formed, is the alkene 31\textsubscript{a} allowed to bind and
react.

\[
\begin{align*}
\text{N-CO₂Et} & \quad \text{Ar-B(OH)₂ (2 equiv.)} \\
31\textsubscript{a} & \quad \text{[Rh(cod)OH]₂ (5 mol\%)} \\
& \quad \text{(S)-BINAP (12 mol\%)} \\
& \quad \text{Cs₂CO₃ (1 equiv)} \\
& \quad \text{Toluene/H₂O (10:1)} \\
& \quad \text{CO (1 atm), r.t.} \\
32\textsubscript{a} & \quad \text{not observed} \\
33\textsubscript{a} & \quad 68\%, 0\% ee
\end{align*}
\]

Only one diastereoisomer of the acylated product was detected by \textsuperscript{1}H NMR analysis. The
\textit{trans} stereochemistry was assigned by analogy to that of the confirmed 32 (despite several
crystallization attempts). The \textit{trans} stereochemistry presumably results from addition on the
alkene taking place on the \textit{exo} face of bicycle 31. The stereochemistry is also what one would
expect to result from thermodynamic conditions given the basic conditions of the reaction.

\textsuperscript{43} Barbe, G.; Charette, A. B. Personal communication.
\textsuperscript{44} Optimized conditions for the ring-opening reaction presented in Chapter 3, with the exception that a CO balloon
was used instead of an argon atmosphere.
Isomerization of the ketone substituent should give the trans product observed due to higher allylic strain ($A_{1,3}$) if the substituents were cis. Moreover, isomerization of the alkene to the conjugated enone was not observed in spite of the high acidity of the allylic proton in alpha position of a ketone in 33.

**Optimization of reaction conditions**

The most relevant optimization results are summarized in Table 4-1. It was found that a non-polar, non-coordinating solvent is needed in the presence of water to obtain high yields (entries 1–6). Rhodium is the metal of choice to effect the desired transformation, but the reaction is not sensitive to the rhodium source, as long as it is a neutral complex (entries 6–14). The presence of a phosphine ligand is not essential to the reaction (cf. entries 9 and 10), yet it was found to help turnover with boronic acid partners less reactive than phenyl. An explanation may be that the bidentate phosphine ligand creates a reservoir of inactive rhodium complex in solution. BINAP was thus kept as “additive” since it is now a widely used ligand. $[\text{Rh}(\text{CO})_2\text{acac}]$ was chosen as stable precatalyst with a 10:1 mixture of toluene and water as solvent mixture for further studies.

### Table 4–1 Optimization of the Ring-Opening with Benzoyl Anion

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$[\text{Rh}(\text{CO})_2\text{acac}]$</td>
<td>THF</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>2$^d$</td>
<td>$[\text{Rh}(\text{CO})_2\text{acac}]$</td>
<td>Dioxane</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>3$^d$</td>
<td>$[\text{Rh}(\text{CO})_2\text{acac}]$</td>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>$[\text{Rh}(\text{CO})_2\text{acac}]$</td>
<td>Toluene</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>$[\text{Rh}(\text{CO})_2\text{acac}]$</td>
<td>Benzene/$\text{H}_2\text{O}$</td>
<td>16</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>$[\text{Rh}(\text{CO})_2\text{acac}]$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>$[\text{Rh}(\text{CO})_2\text{Cl}_2]$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>$[\text{Rh}(\text{cod})\text{Cl}_2]$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>$[\text{Rh}(\text{cod})\text{OH}_2]$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>91</td>
</tr>
<tr>
<td>10$^c$</td>
<td>$[\text{Rh}(\text{cod})\text{OH}_2]$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>11$^d$</td>
<td>$[\text{Rh}(\text{cod})_2\text{OTf}]$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>12$^d$</td>
<td>$[\text{Ir}(\text{cod})\text{Cl}_2]$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>trace</td>
</tr>
<tr>
<td>13$^d$</td>
<td>$\text{Pd}_2(\text{dba})_3$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>14$^d$</td>
<td>$\text{Cu}(\text{OAc})_2$</td>
<td>Toluene/$\text{H}_2\text{O}$</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>
4.2.3 Scope and limitations

The influence of the hydrazine protecting groups was examined with substrates 31a–31d under the optimized reaction conditions. The nature of the carbamate protecting groups was found to be insignificant to the reaction outcome (Table 4–2). The reactions could easily be scaled to 1.0 mmol without any change in yield or reaction time. The reactions of 31a and 31c were run with up to 5.0 mmol and to 3.3 mmol, respectively (entries 2 and 4). By keeping the concentration of catalyst and ligand constant, but reducing the amount of solvent in the up-scaled reactions the loading of Rh could be dropped to 5 mol % without any difference in reactivity, and could probably be reduced more. Formation of rhodium black was often observed on the walls of the vials small scale reactions; but was not seen on larger scale reactions.

Table 4–2  Scope of Protecting Groups on Hydrazine Moiety.*

<table>
<thead>
<tr>
<th>entry</th>
<th>31</th>
<th>Z</th>
<th>product</th>
<th>yield (b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31a</td>
<td>COOEt</td>
<td>33a</td>
<td>92</td>
</tr>
<tr>
<td>2c</td>
<td>31a</td>
<td>COOEt</td>
<td>33a</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>31b</td>
<td>COO-t-Bu</td>
<td>33b</td>
<td>91</td>
</tr>
<tr>
<td>4c,d</td>
<td>31b</td>
<td>COO-t-Bu</td>
<td>33b</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>31c</td>
<td>COOBn</td>
<td>33c</td>
<td>93</td>
</tr>
<tr>
<td>6d</td>
<td>31d</td>
<td>COOCH₂CCl₃</td>
<td>33d</td>
<td>93</td>
</tr>
</tbody>
</table>

* Unless otherwise noted, all reactions were performed using 31 (0.135 mmol) with Rh catalyst (10 mol %), (R)- or rac-BINAP (12 mol %) in a 10:1 toluene/H₂O biphasic solvent mixture (0.07 M), under a CO gas atmosphere (balloon) for 20 h. b Isolated yield. c Reaction on 1 mmol scale. d Performed by C.F. Weise.

[^45]: See Section 3.2 for starting material preparation.
The rate of the reaction seemed to correlate with electron density of the alkene, as indicated by the $^1$H NMR chemical shifts of the vinylic protons. The relative reaction rates of product formation decreased in the order: $31\text{a} > 31\text{b} > 31\text{c} > 31\text{d}$, and the corresponding protons chemical shifts are $6.45 > 6.49 > 6.52 > 6.73$ ppm, respectively.\footnote{Measured by HPLC analysis of the reactions interrupted after 3 hours; Weise, C. F., \textit{Diploma Thesis}, Universität Leipzig, Leipzig, Germany, 2007, 91 p.}

Table 4-3 illustrates the scope of boronic acids with substrate $31\text{b}$ under the optimized reaction conditions. It was found that electron neutral and electron rich boronic acids gave the best results (83% to 96 %, entries 1–9). Steric hindrance in the \textit{ortho}-position lowered the yield (compare entries 5 and 6). Electron withdrawing groups on the aryl group led to decreased yield. For example, with strongly electron withdrawing groups like CF$_3$ or acetyl gave 57% and 38 %, respectively (entries 13 and 14). It is remarkable that even in low yielding reactions (e.g., entries 14 and 15), none of the potentially competing arylated product $32$ was observed.\footnote{Even after heating, the mass balance consisted mainly of unreacted starting material.}
### Table 4-3  Scope of the Acyl Rhodium(I)-Catalyzed Ring-Opening

![Acyl Rhodium(I) Catalysis](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>Ar</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33b</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>34</td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>35</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>37</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>38</td>
<td></td>
<td>94</td>
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<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>39</td>
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<tr>
<td>8</td>
<td>40</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>42</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>11&lt;sup&gt;d&lt;/sup&gt;</td>
<td>43</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>44</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td>45</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>14&lt;sup&gt;d&lt;/sup&gt;</td>
<td>46</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>15&lt;sup&gt;d&lt;/sup&gt;</td>
<td>47</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>16&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>48</td>
<td></td>
<td>63</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, all reactions were performed using 31b (0.135 mmol) with Rh catalyst (10 mol %), (R)- or rac-BINAP (12 mol %) in a 10:1 toluene/H<sub>2</sub>O biphasic solvent mixture (0.07 M), under a CO gas atmosphere (balloon) for 20 h. <sup>b</sup> Isolated yield. <sup>c</sup> Reaction on 1 mmol scale. <sup>d</sup> Performed by C.F. Weise. <sup>e</sup> Portion-wise addition of boronic acid, CsF was added (1.2 equiv).
In the case of trans-styrylboronic acid, the boronic acid was fully consumed after 20 h, but gave only 38% of 48, along with homocoupling product 49 (dibenzylidene acetone, Eqn. 4-13). Slow addition of the boronic acid minimized the competitive dba formation, but using additives was a more convenient procedure. Among the several additives examined, fluoride sources such as KF or CsF improved the yield by 20%, and addition of boronic acid in two portions combined with the use of CsF gave 63% yield (entry 16).

**Enantioselectivity**

Despite examining several phosphorus-based chiral ligands, attempts to render this reaction enantioselective did not lead to satisfactory results. This was surprising since the arylated ring-opened seco-product 32 was formed with significant enantiomeric enrichment under the same conditions (89:11 er, see section 3.2). The possibility of a competing ligand-free background reaction was examined by running the reaction in the absence of phosphine ligand. Indeed, the reaction was found to go to completion in the same time without BINAP (Eqn. 4-14). The rate of the phosphine-free catalyst is apparently much faster than that of a ligand-bound complex.

In their report on asymmetric hydroformylation on strained alkenes, Huang et al. commented in a footnote about the ready lability of phosphine ligands in presence of CO. In their case, the electron-rich and tight-biting ligand TangPhos was unique in affording enantiomerically

---

48 Such a synthesis of symmetrical ketones has been reported with organomercurials and rhodium under a CO atmosphere: Larock, R. C.; Hershberger, S. S. J. Org. Chem. 1980, 45, 3840.
enriched products; even then, bicyclic hydrazine 31c was hydroformylated in a modest 60% ee (Eqn. 4-15).\textsuperscript{49,50}

\[
\begin{align*}
\text{31c} & \quad [\text{Rh(CO)}_2\text{acac}] (0.5 \text{ mol\%}) \\
& \quad \text{TangPhos (0.6 mol\%)} \\
& \quad 500 \text{ psi CO/H}_2 (1:1) \\
& \quad \text{Toluene, 60 °C} \\
& \quad 99\% \text{ conversion}
\end{align*}
\]

Evidence of BINAP being readily dislodged by excess CO in solution at ambient temperature was confirmed by \textsuperscript{31}P NMR spectroscopic analyses in deuterated THF with complex [Rh(BINAP)acac]. In an NMR tube, the singlet at -13.9 ppm for free BINAP disappeared upon the addition of 1.2 eq [Rh(CO)\textsubscript{2}acac]. The same sample clearly showed free BINAP being released with a signal reappearing at -13.9 ppm after simple CO bubbling through the solution for one minute using a needle.

Opportunities to develop an enantioselective process with chiral phosphorus-based ligands are mitigated by these observations of bidentate phosphines being displaced by strong pi acids like CO. The alternative of using chiral N-heterocyclic carbenes as stronger sigma-donor ligands than phosphines is discussed in section 4.4.

\[
\begin{align*}
\text{50} & \quad \text{P-Rh-OH} \\
& \quad \text{OC}' \\
& \quad + \text{CO, C}_6\text{D}_6 \\
& \quad \text{BINA} \\
& \quad \text{51} & \quad \text{OC-Rh-OH} \\
& \quad \text{OC}' \\
& \quad \text{or} \\
& \quad \text{52} & \quad \text{HO-Rh-OH} \\
& \quad \text{OC}'
\end{align*}
\]

In summary, the catalytic generation of acyl anion equivalents was demonstrated in the desymmetrization of strained alkenes. The acylative ring-opening of bicyclic hydrazines allowed the rapid synthesis of trans-1,2-hydrazoneacyl cyclopentenes 33, which are not easily accessible stereoselectively by other means. The densely functionalized products obtained should prove to be of great value as building blocks in organic synthesis. This protocol obviates the typical use of high pressures of CO and high reaction temperatures.

Noteworthy features of the reaction are: the exclusive formation of the trans isomer of the acylated product; and the olefin of cyclopentene product does not isomerize to give the conjugated enone. The present ring-opening of the diaza compounds complements our previous work in the ring-opening of oxa or aza bicycles, which always gave the 1,2-cis ring-


\textsuperscript{50} Accordingly, it would be interesting to test how TangPhos would fare in our reaction since we use milder conditions.
opened products with carbon nucleophiles.\textsuperscript{51} The range of substrates 31a–31d allows to choose from a variety of orthogonal carbamate protecting groups. Current limitations that are yet to be overcome include the lack of enantioselectivity, and the poor reactivity of heteroarylboronic acids.

4.3 Addition of Acyl Anion to Other Strained Alkenes

The acyl addition to other strained alkenes was briefly investigated. For example, oxabicyclic substrate 53 was submitted to the optimized conditions with phenylboronic acid. Though the expected ring-opened hydroxyketone 54 was not observed, 89\% yield of naphthylketone 55 was isolated instead (Scheme 4-10). The naphthalene compound presumably arose from a facile dehydration of 54. This experiment showed that aromatic oxabicycles 53 are indeed competent substrates, but that the products formed are highly sensitive to elimination.

![Scheme 4–10 Carbonylation experiments with an oxabicyclic alkene substrate.](image)

Varying the rhodium source and the base gave the hydroacylated product 56 in 41\% yield, instead of ring-opened hydroxyketone 54. Again, this result demonstrates how subtle changes in reaction conditions can alter the reactivity of rhodium-catalyzed reactions. Importantly, the hydroacylated oxabicycle 56 displayed 40\% ee with BINAP as chiral ligand. These preliminary studies were conducted in the Lautens lab by Dr. Michael Langer, and still needs to be pursued further.

The last example is encouraging when compared to a very similar reaction reported by Bolm et al. (Eqn. 4-17).\textsuperscript{52} In their case, 20 mol\% of rhodium catalyst afforded the hydroacylated oxabicyclic ether 57. Though a chiral monodentate phosphoramidite was used,


no ee was observed in the product. The reaction required the presence of an ortho-phenol chelating group for the C–H insertion reaction involving a Rh(III) species.

Further studies are warranted to understand the factors involved in the Rh-catalyzed acylanion addition to oxabicyclic alkenes. Nonetheless, the above experiments indicate that chiral induction of the bisphosphine ligand is possible, and that exploring different ligands and reaction conditions may eventually lead to an enantioselective version of the reaction.

### 4.4 N-Heterocyclic Carbenes as Ligands in Rh-Catalyzed Carbonylation Reactions

This section demonstrates that N-heterocyclic carbenes (NHC) are competent ligands in rhodium-catalyzed carbonylation reactions and that they remain bound to the rhodium throughout the catalytic cycle. Detailed NMR studies are discussed that strongly support the proposed catalytic cycles. Finally, early results are presented indicating that chiral NHCs may provide a solution to enantioselectivity issues in catalytic carbonylation.

#### 4.4.1 NHC as strong sigma–donor ligand

The lack of enantioselectivity observed in section 4.2 is caused by the lability of phosphines ligands on the rhodium active catalyst in presence of CO (Eqn. 4-16). The combined sigma-donating ability and pi-acidity of CO make it a better ligand than phosphine ligands with Rh(I) complexes. We surmised that a ligand with stronger sigma-donation ability than phosphines might remain bound to the rhodium center throughout the catalytic cycle. N-heterocyclic carbenes (NHCs) are among the strongest sigma-donating ligands reported (Figure 4-2).\(^{53}\)

The discovery of transition metal complexes of NHCs was made by Wanzlick and Schönherr\textsuperscript{54} and by Oefele\textsuperscript{55} in 1968. But it was the isolation of the first free stable carbenes in 1991 by Arduengo\textsuperscript{56} that paved the way for NHCs to become universal ligands in organometallic chemistry and in catalysis. Whereas much attention has traditionally focused on phosphorus-based ligands in homogeneous catalysis for their ready electronic and steric modularity, NHCs have the advantage of being stable to oxidation and to tolerate a wide range of conditions. The main class of NHCs contains an imidazole core or its saturated version, \textit{i.e.} \textbf{58} and \textbf{59}, respectively (Figure 4-2). Two of the most popular NHCs are IMes (\textbf{60}) and the saturated imidazoline SIMes (\textbf{61}), owing to their general reactivity and ease of preparation.\textsuperscript{57} In particular, IMes has found widespread use as workhorse of the NHC family, akin to PPh\textsubscript{3} as being prototypical phosphine.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{N-Heterocyclic Carbenes (NHCs).}
\end{figure}

The idea of using NHC ligands in Rh-catalyzed carbonylation reactions was supported by a few key reports. First, rhodium(I)-NHC complexes bearing CO ligands have been isolated, thereby showing that coexistence of NHC and CO is possible.\textsuperscript{58} Second, rhodium-NHC complexes had been shown to be competent catalysts in reactions involving organoboron reagents (Eqn. 4-18).\textsuperscript{59,60}

\textsuperscript{55} Oefele, K. J. Organomet. Chem. 1968, 12, P42.
\textsuperscript{59} Ma, Y. D.; Song, C.; Ma, C. Q.; Sun, Z. J.; Chai, Q.; Andrus, M. B. Angew. Chem., Int. Ed. 2003, 42, 5871.
4.4.2 Results & Discussion

Initial trials. The complex Rh(IMes)(cod)Cl (63) was prepared according to a convenient and robust procedure reported by Evans et al. (Eqn. 4-19).\(^{61}\) Complex 63 was prepared using the commercial imidazolium salt 62. It is completely air-stable, and is even purified by column chromatography.

The reactivity of Rh(IMes)(cod)Cl was then tested in the carbonylative ring-opening of bicyclic hydrazine 31b. Table 4-4 compares experiments conducted with the rhodium-NHC catalyst to that using [Rh(cod)OH]₂ under the optimal conditions from section 4.2. The catalyst performed equally well in the presence of an NHC ligand, as it did without (entries 2, 3, 5 and 6). The observation that no reaction occurred in the absence of a silver salt (entries 4–6), suggested that the NHC ligand stays bound to the Rh(I) center; otherwise the same active species as for entry 3 would be expected to be generated. The presence of an hydroxide source was beneficial, as the yield dropped drastically in the absence of water as co-solvent (entries 7 and 8).

The nature of the silver salt did not significantly influence the reactivity (results not shown). AgBF₄ was chosen as the most convenient to use, being less hygroscopic than the antimony or triflate analogs.

---

The reaction also proceeded with excellent yield with an electron withdrawing arylboronic acid (64, Eqn. 4-20). The yield was much lower when a boronic ester was used instead of the parent acid (65 = 49%, as opposed to 99% for 64). It is noteworthy that using IMes as ligand significantly improved the yield of 44. Using BINAP as ligand had afforded 77% yield, whereas IMes gave 64 quantitatively (cf. Table 4-3, entry 12).

**4.4.3 Mechanistic investigations**

The above experiments showed that using an NHC as ligand was not detrimental to the reaction. Though they did not prove that the NHC was still bound to the Rh¹ active catalyst. Spectroscopic analyses were conducted with Rh-NHC complexes to try to observe the intermediates involved in the catalytic cycles. This valuable insight into the reaction mechanism could confirm—or infirm—mechanistic hypotheses made earlier in this chapter, as well as be used to design new catalytic manifolds.

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**Table 4–4 Ring-Opening with Benzoyl Anion Trials using an Rh-NHC Catalyst**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>additive</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 c</td>
<td>[Rh(cod)OH]₂</td>
<td>Benzene</td>
<td>-</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)OH]₂</td>
<td>Toluene/H₂O (10:1)</td>
<td>-</td>
<td>92</td>
</tr>
<tr>
<td>3 c</td>
<td>[Rh(cod)Cl]₂</td>
<td>Toluene/H₂O (10:1)</td>
<td>-</td>
<td>92</td>
</tr>
<tr>
<td>4 d</td>
<td>[Rh(cod)(IMes)Cl]</td>
<td>Toluene/H₂O (10:1)</td>
<td>AgBF₄</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)(IMes)Cl]</td>
<td>Toluene/H₂O (10:1)</td>
<td>AgBF₄</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(cod)(IMes)Cl]</td>
<td>Toluene/H₂O (10:1)</td>
<td>AgSbF₆</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(cod)(IMes)Cl]</td>
<td>Benzene/H₂O (10:1)</td>
<td>AgSbF₆</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>[Rh(cod)(IMes)Cl]</td>
<td>Benzene</td>
<td>AgSbF₆</td>
<td>19</td>
</tr>
</tbody>
</table>

* All reactions were performed using 31b (0.135 mmol) with the listed catalyst (10 mol % in Rh), PhB(OH)₂ (2.0 equiv), base (1 equiv), and solvent (0.07 M). * Isolated yield. * From Table 4-1. * Starting materials were recovered untouched.
The following NMR analyses of rhodium complexes in solution were typically stoichiometric, and involved stepwise addition of the reaction components directly to an NMR tube, in a deuterated solvent. Solution spectra were acquired for $^1$H, as well as $^{19}$F and $^{13}$C nuclei when relevant. For consistency, the spectra presented here were all acquired in deuterated benzene. When possible, intermediates were also prepared by different sequences to confirm the species observed, and were compared to literature examples of Rh–NHC complexes.62,63

Control experiments clearly demonstrated that the IMes remains bound to Rh in the presence of CO in solution. When a stream of CO gas was gently bubbled through a solution of Rh(IMes)(cod)Cl in C$_6$D$_6$, the solution rapidly underwent a discoloration, turning from clear yellow to very light yellow; a color change associated with release of 1,5-cyclooctadiene (COD) by CO gas. This solution was then condensed by simple rotavap evaporation to afford the air-stable Rh(IMes)(CO)$_2$Cl complex (66, Scheme 4-11).

Figure 4-3 displays $^1$H NMR spectra following this procedure. The reference spectrum of 63 in (a) shows the asymmetrical nature of the complex; whereas, after CO addition, free COD is released in the solution (b) (broad peaks at 5.5 and 2.2 ppm). The simplified spectrum (b) indicates that the CO ligands of complex 66 adopt a trans configuration. Removal of free COD confirmed the clean formation of 66, which possesses a highly symmetrical spectrum (c). Further bubbling of CO in a solution of 66 did not change the spectral signals, even upon heating at 60 °C for two hours.

62 See references 53, 56, 58, 59, 61, 62, 68, and 71 from this chapter.
Scheme 4-11 IMes remains bound to Rh in presence of CO (see Fig. 4-3).

Figure 4–3 $^1$H NMR spectra (C$_6$D$_6$, 25 °C) of rhodium complexes before (a) and after (b) CO bubbling to release COD. (c) Clean Rh(IMes)(CO)$_2$Cl formation by evaporation of volatiles.$^{64}$

The ability of a Rh–NHC complex to bind alkenes was also confirmed. Formation of CO-bound complex 66 was achieved as in the previous case, but instead of removing COD, an excess of silver salt (1.5 equiv.) was added to the solution to prepare the cationic rhodium complex 67, where only one alkene of COD is bound to the rhodium center (Scheme 4-12). This $\eta^2$-coordination of COD may result from the difference in binding affinity between COD and CO imparted by the trans effect.$^{65}$ $^1$H NMR analysis of this sequence is shown in Figure 4-4. After addition of the silver salt, two main observations are made in spectrum (c). First, the characteristic imidazolidene protons shifted from 6.1 to 6.6 ppm, which is interpreted to be caused by the decreased electronic density of the cationic Rh(I) center. Second, COD is not symmetrical, but still shows vinylic protons in the ‘free’ state at 5.55 ppm; which may may due to coordination of one alkene only. Moreover, the noticeable broadening of proton signals that are the closest to the metal suggest conformational mobility of the complex (e.g.,

$^{64}$ The electronic treatments involved in creating Figures 4-3 to 4-5 resulted in partial deformation of the spectral signals. Spectra of higher resolution are presented in the Appendix.

imidazolium protons at 6.6 and at ~4.0 ppm). The possible formation of cationic complex [Rh(IMes)(CO)$_3$]BF$_4$ instead of 67 was discounted as using AgBF$_4$ with pure complex 66, as prepared in Scheme 4-11, resulted in unidentifiable mixtures by proton NMR.\textsuperscript{66}

Scheme 4-12 Generation of a cationic rhodium(I) complex allows alkene coordination.

Figure 4-4 $^1$H NMR spectra of rhodium complexes in solution in C$_6$D$_6$. (a) Rh(IMes)(cod)Cl; (b) CO bubbling released COD. (c) Addition of AgBF$_4$ generates the cationic complex [Rh(IMes)(CO)$_2$(η$^2$-cod)]BF$_4$.\textsuperscript{64}

The transmetallation step of the boronic acid to generate the key acyl-rhodium intermediate 70 could not be identified directly spectroscopically. Scheme 4-13 depicts a stoichiometric sequence followed in one of these attempts. 4-Fluoroboronic acid (64) was selected for its characteristic peaks in the $^1$H NMR spectra (aromatic protons signals different than the mesityl ones); and because $^{19}$F NMR would allow for a sensitive alternative method of tracking aryl species in solution. The isolated complex 66 was dissolved with 1.1 equivalent of boronic acid 64, followed by excess AgBF$_4$. An aqueous basic solution was added to accelerate transmetallation, and the reaction mixture was followed by NMR to see whether 69 or 70 could be observed. After prolonged reaction time at ambient temperature, fluorobenzene was the major compound obtained, arising from deboronation of 64.

\textsuperscript{66} The possible intramolecular C–H activation of benzylic methyl groups of the mesityl by the unstabilized cationic Rh(I) complex may be the source of the observed complex mixture of products.
Figure 4-5 illustrates that without silver salt, at 25 °C, the neutral Rh-NHC complex 66 and the boronic acid 64 are perfectly stable in solution and do not interact (compare spectra a, b and c). Upon addition of AgBF₄, a cationic rhodium complex is generated, as indicated by the characteristic shift and broadening of the imidazolium protons. The species shown in spectrum d were stable and are very similar to Fig. 4-4 (c). The structure of the complex is tentatively assigned as 68, where the cationic metal center is stabilized by oxygen coordination from 64. When hydroxide was added as an aqueous base to this putative complex, the NMR analysis complexified rapidly, as shown by spectrum e, taken after 10 min at r.t. Two new triplets appeared at 6.9 and 8.1 ppm that belong to the 4-fluoroaryl moiety. It has not been possible to determine if these signals belong to aryl-rhodium 69 or acyl-rhodium 70 (or maybe both). Alternatively, ¹⁹F NMR spectra also showed two new peaks at -110.1 and -111.9 ppm potentially identifying 69 and 70 (whereas 64 displays a singlet at -106.1 ppm). Nevertheless, in the absence of an electrophilic partner, deboronation of 64 was easily traceable by ¹⁹F NMR, with the appearance of a singlet at -113.3 ppm belonging to 71. Deboronation occurred slowly at r.t., but was already observed by ¹⁹F NMR after 10 min (estimated to less than 10%). After a week at r.t., fluorobenzene was evident by ¹H NMR analysis as being the major product formed (spectrum f; g is pure 71 as reference). It should be noted that a control experiment involved treating 64 in the same conditions, but without Rh complex 66, did not generate 71, thus formation of aryl-rhodium complex 69 is implicit. Despite many efforts to characterize the proposed aryl-Rh 69, its generation is still circumstantial.

Scheme 4–13 Stepwise formation of rhodium intermediates in presence of the boronic acid.
Though acyl-rhodium intermediate 70 could not be observed directly, the information gathered on the species leading up to its putative formation are compelling. A last experiment was conducted by adding a diazabicycle substrate to the reaction mixture under parameters identical to spectroscopic studies (Scheme 4-14). Accordingly, pre-isolated Rh-IMes complex 66 was treated with the same protocol as in the above studies, with the exception that bicyclic hydrazine 31b was added after 10 min to the solution shown in Fig. 4-5 (e). The reaction was
allowed to stand overnight and it afforded a quantitative yield of the acylated ring-opened product 44.\textsuperscript{67}

Scheme 4–14 Formation of the acyl-rhodium(I) complex 70 relies on circumstantial evidence.

Proposed mechanism

Combining all the information presented above allows us to propose the following catalytic cycle illustrated in Scheme 4–15. With Rh(IMes)(cod)Cl (63) as pre-catalyst, the COD ancillary ligand is rapidly displaced by CO to give 66. Then the silver salt addition creates a cationic rhodium complex that is presumed to get stabilization from COD (67) or excess boronic acid (68, Scheme 4–13). A basic milieu accelerates transmetallation of the organoboron reagent to lead to aryl-rhodium(I) complex 69. The aryl group of 69 can reversibly migrate to a CO ligand (CO-insertion) to give the key acyl-rhodium(I) intermediate 70, thereby leaving a free coordination site for coordination of an alkene substrate (72). Acyl-rhodation of the substrate’s alkene followed by anti periplanar nitrogen elimination then affords the ring-opened product 33b, in a process analogous to that discussed previously in section 3.4.

Scheme 4–15 Proposed catalytic cycle with Rh(IMes)(cod)Cl as precatalyst in carbylation of 31b.

\textsuperscript{67} The same reaction was also conducted as a one-pot procedure and still gave quantitative yield of the same product, thereby ensuring that the stepwise protocol does not bias the system towards a certain pathway.
4.4.3 Enantioselectivity

Although the acylrhodium intermediate 70 could not be observed directly, the above NMR studies strongly suggest that the NHC ligand IMes is bound to the catalytically active metal center throughout the reaction. This information is crucial to develop an asymmetric variant, as the source of chirality should be involved at the enantio-discriminating step. Since the use of chiral phosphine ligands had afforded only racemic products (see Eqn. 4-14), we decided to investigate the reactivity of chiral NHC ligands. Though several classes of chiral NHCs have emerged in recent years, the area of asymmetric catalysis with chiral imidazolium ligands is still in its infancy. A selection of reported chiral NHCs is depicted in Figure 4-6.

The development of an enantioselective carbonylation reaction is the challenge currently being tackled in the Lautens group by Dr. Jason Bexrud. Early results have shown that ring-opened 33b could be obtained with up to 25% ee (Eqn. 4-21). Alternatively, when looking at the recent work with chiral NHCs, the highest ee seem to be obtained consistently with NHCs flanked with a chelating group (e.g. 77 and 78, Figure 4-6). Although more investigations are required to achieve synthetically useful levels of selectivity, these results strengthen the idea that chiral NHCs may address the asymmetry issue in carbonylation reactions.

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70 On-going studies at the time of writing.

In summary, *N*-heterocyclic carbenes (NHC) were demonstrated to be competent ligands in rhodium-catalyzed carbonylation reactions. They can effectively replace phosphine ligands, and lead to improved yields, which should allow us to reduce catalyst loadings—a highly desirable goal. NMR spectroscopic analyses of species in solution were conducted with the IMes ligand. Importantly, these investigations showed that the carbene remains bound to the rhodium center throughout the catalytic cycle, thereby strongly supporting the proposed mechanism. Finally, early experiments indicated that chiral NHCs may provide a solution to enantioselectivity issues in catalytic carbonylations. These findings are the focus of on-going research efforts in the group.

4.5 Regioselective Synthesis of Cyclopentenones

This sections describes the investigations probing the generality of the rhodium(I)-catalyzed acylation methodology. A synthesis of cyclopentenones is presented first, followed by early studies towards the extension of the acyl anion addition to other π-acceptors.

4.5.1 Design and discovery of a new method for the regioselective synthesis of cyclopentenones

Conceptually, using vinyl boronic acids opens up the potential use the acyl anion generation to generate *umpolung* reagents that can react in formal [3+2] cycloadditions. For example, reacting a vinylacyl anion intermediate 75 with alkynes could lead to substituted cyclopentenones (Scheme 4-16-a). This transformation is reminiscent of the well-established Pauson-Khand reaction. However, it is expected to afford the opposite regioisomers as the mechanism is fundamentally different (compare b and c, Scheme 4-16). Indeed, the order of steps involved would involve a polarity reversal of the reacting partners. The proposed method aims to address a recurrent problem of low regioselectivity in intermolecular cases of the Pauson-Khand reaction. An acyl rhodium species, similar to 75, has been generated by

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Chung using heterobimetallic nanoparticles; but involved a mechanism where the rhodium center would likely be in the III oxidation.\(^{73}\)

The mechanistic rationale behind the proposed transformation is illustrated in Scheme 4-17. The putative catalytic formation of the key acylrhodium species 75 is based upon the results obtained in section 4.2 (i.e., formation of styrylketone 48; entry 16, Table 4-3). Acyl-rhodation of an alkyne would lead to the vinylrhodium intermediate 77. Three pathways can be imagined that all lead to the same cyclopentenone 76. The first involves a vinyl-rhodium(I)
intermediate effecting a conjugate addition to the pendant enone to give enolate 78, followed by subsequent protonation.

Scheme 4–17 Possible mechanisms leading to cyclopentenone 76.

Alternatively, the vinyl-metal species 77 could undergo a Nazarov cyclization, followed by simple neutralization of the zwitterionic species 79. Finally, proto-demetalation of intermediate 77 would give dienone 80, which is prone to spontaneous Nazarov cyclization, thus forming the desired cyclopentenone 76. Distinguishing between these pathways would be difficult, but at least they should all funnel the reaction towards the same product.

The proposed reaction would also provide a valuable catalytic alternative to the stoichiometric [3+2] cyclization of chromium alkylidene complexes recently reported by Barluenga and coworkers (Eqn. 4–22). The yields for this reaction are modest when one considers that two metal complexes are required in over-stoichiometric amounts. In addition, the method makes it difficult to vary the vinyl moiety of chromium reagents 82.

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4.5.2 Results & Discussion

Initial trials consisted of reacting 1-phenylpropyne with styrylboronic acid under reaction conditions that had been found to give acylation in high yields (see section 4.2). The rhodium precatalyst \([\text{Rh(CO)}_2\text{Cl}_2]\) was used instead of the previous \([\text{Rh(cod)}\text{Cl}_2]\) to simplify the system, and to ensure cyclooctadiene would not be a competing substrate. Phenylpropyne was selected because it was easily traceable, and the \(^1\text{H NMR analysis of the reaction mixture allowed to follow and measure characteristic peaks of the known cyclopentenone 83.}\) Only traces of the desired 83 were present in the initial experiments. The mass balance consisted mostly of unreacted starting boronic acid, and small amounts of other unidentified vinylic products. Nevertheless, it showed that the transformation was feasible, and thus warranted more efforts to examine whether the reaction could be optimized.

Screening of reaction parameters

The influence of solvents was the first parameter investigated, since rhodium-catalyzed reactions are typically very sensitive to coordination effects and polarity. Table 4-5 compares various solvent systems obtained under standardized conditions with \([\text{Rh(CO)}_2\text{Cl}_2]\) as precatalyst. These experiments revealed that the reaction could produce three regioisomeric cyclopentenones. In addition, the ratio between the isomers was influenced by the solvent system used. Cyclopentenones 83 and 84 are formed by acyl-rhodation of the alkyne reactants occurring from opposite ends. 85 corresponds to a Pauson-Khand product and is therefore presumed to arise from protolysis of the boronic acid to give styrene, which would subsequently react in a typical Pauson-Khand reaction with 1-phenylpropyne.\(^{77}\)

A mixture of toluene and THF heated at 60 °C gave the highest yield of cyclopentenones, whereas pure THF appeared to give the best compromise in terms of yield and isomeric ratio for cyclopentenone 83. These two solvent systems were thus selected to examine the rhodium catalyst.


\(^{77}\) This assumption was supported by reacting styrene and 1-phenylpropyne in the reaction conditions, which afforded cyclopentenone 85, along with several other byproducts.
Table 4–5 Influence of Solvent on Regioselectivity.ª

<table>
<thead>
<tr>
<th>entry</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temp. (°C)</th>
<th>Yielda</th>
<th>Regio³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>H₂O</td>
<td>22</td>
<td>Trace</td>
<td>95 : 5 : 0</td>
</tr>
<tr>
<td>2</td>
<td>Toluene – THF (1:1)</td>
<td>-</td>
<td>22</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>Toluene – THF (1:1)</td>
<td>-</td>
<td>60</td>
<td>16</td>
<td>75 : 12 : 13</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>-</td>
<td>22</td>
<td>9</td>
<td>75 : 12 : 13</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td>-</td>
<td>22</td>
<td>7</td>
<td>67 : 33 : 0</td>
</tr>
<tr>
<td>6</td>
<td>Benzene</td>
<td>-</td>
<td>22</td>
<td>5</td>
<td>75 : 12 : 13</td>
</tr>
<tr>
<td>7</td>
<td>1,2-DCE</td>
<td>-</td>
<td>22</td>
<td>9</td>
<td>50 : 25 : 25</td>
</tr>
</tbody>
</table>

ª Reaction conditions: styrylboronic acid (0.270 mmol) and 1-phenylpropyne (0.267 mmol) with Rh catalyst (5 mol%), (R)- or rac-BINAP (12 mol%) in solvent (0.15 M), under a CO gas atmosphere (balloon) for 16 h. ³ Yield calculated by ¹H NMR integration relative to trimethoxybenzene internal standard. ³ Ratio calculated by ¹H NMR analysis.

The nature of the rhodium precatalyst strongly affected the isomers ratios. Table 4–6 summarizes the most relevant results from a catalyst screen. The highest yields were obtained with [Rh(CO)₂Cl]₂ and Rh(CO)₂acac, though Rh(CO)₂acac needed heating to 60 °C (entries 7 and 10, respectively). It appears that significant deboronation occurred with cationic catalysts, or at higher temperature, as Pauson-Khand isomer 85 was observed in almost equimolar ratio to the desired product (entries 5, 7, and 8). The cyclopentenone regioisomers 83, 75 84 and 85² were differentiated by ¹H NMR spectroscopy and the ratios were calculated using proton integration of the methylenic and allylic protons.

The above results are still preliminary. Nevertheless, they validate the proposed methodology. They also indicate that polar coordinating solvents may facilitate the process, and suggest that the reaction may be prone to halide effects. At the time of writing, cyclopentenone 83 had been obtained as the major regioisomer in 39% yield (Eqn. 4-24).

Future work will include completing the optimization of the reaction conditions and understanding the impact of the catalyst counterions. In the above preliminary studies, 1-phenylpropyne was used was selected for reaction development purposes; the next step will examine other alkyne partners (e.g., conjugated or polarized with electron withdrawing groups, Eqn. 4-25). The steric and electronic demands of both reacting partners also remain to

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be investigated. Finally, developing an enantioselective process is the ideal goal perhaps with chiral NHCs.  

\[ R_1 \equiv \text{Ar, Alk} \quad R_2 \equiv \text{Alk, Ar} \]

In summary, substituted cyclopentenones can be prepared by a multi-component reaction involving a key catalytic acyl-rhodium intermediate. The procedure is practical: it simply involves mixing the reagents under a CO atmosphere at ambient temperature and it tolerates water. The 2,3,4-trisubstituted cyclopentenones obtained are complementary regioisomers of the Pauson-Khand reaction. This is due to a mechanism involving a CO insertion early in the catalytic cycle and maintaining a Rh(I) catalyst throughout the reaction. Moreover, the reaction offers a catalytic alternative to Barluenga’s reaction using stoichiometric amounts of two metals (Cr and Ni). A clear advantage is that vinylboronic acids can be varied more easily than the equivalent Fisher carbene reagent needed with Barluenga’s protocol.

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4.6 Conclusions

In this chapter, the synthetic use of acyl anion generated catalytically was demonstrated with strained alkenes and alkynes, as summarized in Scheme 4-18. More specifically, the new carbonylation reaction was optimized for the desymmetrization of bicyclic hydrazines with a range of arylboronic acids to afford highly functionalized cyclopentenhydrazides 33. The synthetic value of the protocol includes the selective formation of two adjacent stereocenters of anti configuration. Chiral phosphines were shown to be labile, but the reaction proceeded equally well in presence of NHC ligands. Detailed spectroscopic analyses supported the proposed mechanistic scenarios. These investigations also indicated that NHCs, specifically IMes, remain bound to the rhodium catalyst throughout the reaction. Thus we are hopeful that the appropriate chiral NHC may allow to develop an enantioselective variant of the reaction (up to 25% ee have been observed so far).

The catalytic carbonylation could also be extended to alkynes to prepare trisubstituted cyclopentenones (Scheme 4–18). The major cyclopentenone isomer formed confirmed that the method is complementary to the Pauson-Khand reaction. Though much work remains to be done to optimize this reaction, its practical simplicity should make it a valuable procedure as all components can easily be modulated independently.

Scheme 4–18 Rh-catalyzed acylative reactions developed in this chapter: Desymmetrization of bicyclic hydrazines and synthesis of cyclopentenones.
4.7 Future work

Some results presented in this chapter pertain to projects still in their early stages. They served as proof of concept in order to delineate the breadth of scope of the Rh-catalyzed carbonylation. Potential extensions of these methodologies are outlined below as new avenues of research.

**Enantioselectivity.** Finding an enantioselective version of the above carbonylation reactions is one of the major tasks for the future. Work is already under way showing that chiral N-heterocyclic carbenes may offer a solution to this challenge. TangPhos is a bulky, electron-rich ligand that should also be examined in acylation reactions.

**Intramolecular carbonylation.** Intramolecular variant of the catalytic carbonylation reaction can also be imagined, taking inspiration from previous work in the Lautens group (Eqn. 4-26). The products obtained by this reaction would be difficult to make by other means. A related strategy using a Stetter reaction and aromatic aldehydes was also recently reported by Glorius.

\[
\text{Rh}^+ \text{catalyst} \quad \text{CO (1 atm)} \quad \text{products}
\]

**Acylation of Alkenes.** Extending the catalytic acyl anion addition to Michael acceptors would provide a powerful C–C bond forming reaction as it would allow to couple two components in a high oxidation state, thereby potentially reducing the number of steps in syntheses.

**Other 1,2-π Acceptors.** Isonitriles should also be investigated as electrophilic 1,2-acceptors (Scheme 4-19). Being isoelectronic to CO, isonitriles might result in formation of products bearing a 1,3-iminoamine motif in the ring-opening of bicyclic hydrazines (or 1,3-diamine after reduction). Alternatively, a novel ‘hydroimination’ pathway could be sought with reactive olefins that could give direct synthetic access to substituted arylimines 91.

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It would be interesting to examine the potential for the addition of acyl anion to carbonyl derivatives such as imines. For example, a diastereoselective reaction using sulfinimines as chiral auxiliary would circumvent a still elusive enantioselective reaction (Scheme 4-20). Indeed, the Rh(I)-catalyzed addition of boronic acids to chiral sulfimines was successfully demonstrated by Ellman and co-workers. The expected 1,2-ketoamines products might provide an alternative strategy for the rapid assembly of substituted α-amino acids analogs.

The direct acylation of other π-electrophiles would be interesting to examine. Especially highly reactive heteratomic π systems (Scheme 4-21). The reactivity of nitroso groups, for example, is intriguing as they might lead to hydroxamic acids, which are notoriously difficult to prepare, or to oxime esters. The reactivity of diazo groups was examined very briefly with styrylboronic acid. The acylated hydrazide was obtained in 15% yield and is testament of the feasibility of the transformation. These preliminary results were obtained by Dr. Nai-Wen Tseng, upon the author’s suggestion, but were not pursued further. This avenue of reactivity requires more systematic studies.

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Scheme 4–21 Proposed catalytic acylation addition to heteroatom π-electrophiles.
4.8 Experimental Section

General Experimental Procedures. Unless otherwise noted, reactions were carried out under argon atmosphere, in flame-dried, single-neck, round bottom flasks fitted with a rubber septum, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel canula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C at 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with Silicycle™ normal phase glass plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was done under a 254 nm UV light source and/or by immersion in potassium permanganate (KMnO₄), or acidic aqueous-ethanolic vanillin solution, followed by heating using a heat gun. Purification of reaction products was generally done by flash chromatography with Silicycle™ Ultra-Pure 230-400 mesh silica gel, as described by Still et al.

Materials. [Rh(CO)₂acac], [Rh(cod)Cl]₂, [Rh(CO)₂Cl]₂, were purchased from Strem Chemicals Inc. and used as received. [Rh(cod)OH]₂ and Rh(IMes)(cod)Cl were prepared from [Rh(cod)Cl]₂ by literature procedures. Supplies of (S,R)- and (R,S)-t-Bu-JOSIPHOS, and [Rh(cod)OTf] were generously provided by Solvias Inc. Other chiral phosphine ligands were purchased from Strem Chemicals Inc. Unless otherwise indicated, boronic acids were obtained from Aldrich and used without further purification. Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under N₂ from Na/benzophenone immediately prior to use. Ether and dichloromethane were purified by the method of Pangborn et al. Hexanes used for chromatographic purifications was distilled from calcium hydride. Diaza-bicyclo[2.2.1]hept-5-ene-dicarbamates 31a, 31b, and 31c were prepared in quantitative yields by Diels-Alder reactions between cyclopentadiene and the corresponding diazodicarbamates at r.t. according to literature procedures and characterization data was fully consistent with that reported in the literature.

Instrumentation. Proton nuclear magnetic resonance spectra (¹H NMR) spectra and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 23 °C with a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe, or a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a NaloracN-400 probe, or a Bruker 400 Advance3 Nanobay (400 MHz) NMR spectrometer equipped with BBFO-ATM probe. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CDCl₃: δ 7.26, CHDCl₃: δ 5.29, C₆D₆: δ 7.15, CD₂HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0, CH₂Cl₂: δ 53.8, C₆D₆: δ 128.0, CD₃OD: δ 49.2). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, m = multiplet, br = broad).

References:
92 For experimental details, consult Chapter 3.8.
integration and coupling constant ($J$, Hz). Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm$^{-1}$), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment. High resolution mass spectra were obtained from a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

4.8.1 Experimental Procedures

**General Procedure A:**

Rh(I)-Catalyzed Desymmetrization of Diazabicyclo[2.2.1]heptenes with Acyl Anions. To a 1 dram vial equipped with a magnetic stir bar was added $[\text{Rh(CO)}_2\text{acac}]$ (3.5 mg, 0.014 mmol), rac-BINAP (10.1 mg, 0.016 mmol). The vial was sealed and flushed with CO gas (balloon), then toluene (1.0 mL) and water (0.16 mL) were added and the mixture was stirred at room temperature for 15 min. Diazabicyclo[2.2.1]heptene dicarbamate 1b (40 mg, 0.135 mmol) and the arylboronic acid (0.16–0.27 mmol, 1.2–2.0 equiv) were added together as a solution in toluene (0.80–1.5 mL) and the reaction mixture was allowed to react at 20–25°C (in some cases, warming prior to addition was necessary to dissolve boronic acid). After 16-20 h, Et$_2$O (5 mL) was added to the reaction mixture and it was filtered on a short silica gel pad (~2 g), washed four portions of 5 mL of ether. The filtrate was concentrated under reduced pressure, then was applied to the top of a column of silica gel and purified by column chromatography (acetone:EtOAc:hexane 1:1:18 as elution gradient).

*Note 1:* NMR analysis displayed very broad peaks for all ring-opened products 33–48 due to rotamers of the bis-carbamate hydrazine moiety and conformers equilibrium for some products. Resolution for both $^1$H and $^{13}$C NMR spectra did not improve significantly when temperature was varied; most likely due to differential coalescence temperature of the multiple conformers. Doubling of signals was often observed; the word ‘and’ is used specifically to signify extra peaks arising from rotamers in the spectra.

4.8.2 Characterization Data

*meso-2,3-Diazabicyclo[2.2.1]hept-5-ene-N,N’-diethyl dicarboxylate (31a).*

Prepared according to a reported procedure. To a freshly distilled cyclopentadiene (1.5–2.0 equiv) solution in CH$_2$Cl$_2$ kept at 0°C, was added the azobis(carbamate) compound. The reaction was allowed to warm up to room temperature and stirred until full consumption of the azo starting material, as observed by TLC. The solvent was evaporated under reduced pressure. The crude clear oil was purified by silica-gel chromatography with EtOAc/hexanes as eluent (20-40% gradient). The diazabicycle was obtained quantitatively as a clear fluid oil. The characterization data was fully concordant with that already reported in the literature. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.51 (2H, br.s), 5.15 (2H, br.s), 4.25-4.15 (4H, m), 1.77-1.71 (2H, m), 1.28 (6H, t, $J$ = 7.1 Hz).
meso-2,3-Diazabicyclo[2.2.1]hept-5-ene-\(N, N\)-di-tert-butyl dicarboxylate (31b).
Prepared according to a reported procedure.\(^9\) To an ice-cooled solution of DtBAD in 
\(\text{CH}_2\text{Cl}_2\) (10 g in 500 mL) was added neat cyclopentadiene (1.5 equiv). The clear
orange solution was allowed to stir overnight at rt. After 16 h, the colorless solution showed full
conversion by TLC. The solvent was evaporated under reduced pressure to yield a white solid which
had a strong \(\text{Cp}\) odor. The crude solid was recrystallized in 100 mL hexanes under vigorous stirring.
After filtration on a fritted funnel and drying, the diazabicycle was obtained quantitatively as a thick oil, which slowly solidified upon standing. Recrystallized in hexanes. The characterization data was fully concordant with that already reported in the literature.\(^3\) \(^1\)H NMR (400 MHz, \(\text{CDCl}_3\)): \(\delta\) 6.51 (2H, br.s), 5.21 and 4.96 (2H, coalescing
br.s), 1.72-1.68 (2H, m), 1.57-1.42 (18H, m).

meso-2,3-Diazabicyclo[2.2.1]hept-5-ene-\(N, N\)-dibenzyl dicarboxylate (31c).
Prepared according to a reported procedure.\(^9\) \(\text{note}:\) the commercial azo precursor
(CbzN)\(_2\) quality was generally poor and needed a rapid purification by
chromatography). The clear orange solution turned colorless. The diazabicycle was obtained
quantitatively as a thick oil, which slowly solidified upon standing. Recrystallized in hexanes. The
coloration data was fully concordant with that already reported in the literature.\(^5\) \(^1\)H NMR (400 MHz, \(\text{CDCl}_3\)): \(\delta\) 7.35-7.28 (10H, m), 6.46 (2H, br.s), 5.27-5.14 (6H, m), 1.76-1.71 (2H, m).

**Bis(2,2,2-trichloroethyl) hydrazinodicarboxylate.**
Prepared according to a literature procedure,\(^93\) with the following modifications: the hydrazine dihydrochloride and 2.0 eq of \(\text{NEt}_3\) were used
(instead of 64 % hydrazine hydrate), to generate the hydrazine \(\text{situ}\). The product was obtained as a
colourless solid in 32 % (2.85 g) yield. The analytical data was consistent with that reported. \(^1\)H NMR (400 MHz, \(\text{CDCl}_3\)): \(\delta\) 7.10 (2H, br. s), 4.81 (4H, s) ppm. **MS ESI, m/z** (rel. intensity): 404.8 (M-\(\text{Na}^+\), 100).

**Bis(2,2,2-trichloroethyl) azodicarboxylate.**
Adapted from a literature procedure (equivalents of bromine adjusted to
required stoicheiometry).\(^94\) Bis(2,2,2-trichloroethyl) hydrazinodicarboxylate
(2.84 g, \(7.43 \text{ mmol}\)) was dissolved in 200 ml dry \(\text{DCM}\) under \(\text{N}_2\) atmosphere. Ahydrous pyridine (1.32
ml, 16.34 mmol) was added and the mixture cooled to 0°C. After 90 min \(\text{Br}_2\) (1.31 g, 8.17 mmol)
dissolved in 60 ml DCM was added dropwise. After addition the reaction mixture was allowed to stir
for another 90 min, then diluted with 500 ml DCM and washed with \(2 \times 150 \text{ ml} 5 \% \text{ HCl, 150 ml sat.}
\text{NaHCO}_3, 2 \times 150 \text{ ml H}_2\text{O and 150 ml brine. The solvent was removed under reduced pressure to give
93 % (2.64 g) as yellow needles. Mp 112-114 °C. The analytical data was consistent with that reported.\(^8\)
\(^1\)H NMR (400 MHz, \(\text{CDCl}_3\)): \(\delta\) = 5.06 (4H, s) ppm. \(^13\)C NMR (100 MHz, \(\text{CDCl}_3\)): \(\delta\) = 158.7, 93.4, 77.1
ppm.

**meso-Bis(2,2,2-trichloroethyl) 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (31d).**
Bis(2,2,2-trichloroethyl) azodicarboxylate (2.6 g, \(6.9 \text{ mmol}\)) was dissolved in 40 ml dry
\(\text{DCM}\) under \(\text{N}_2\) atmosphere and cooled to 0 °C. To the orange solution freshly distilled
cyclopentadiene (687 mg, 10.4 mmol) was added dropwise over 10 min. The reaction mixture turned

colourless upon addition indicating consumption of starting material. It was allowed to warm to r.t. while stirring overnight. Evaporation of the solvent under reduced pressure gave a viscous, colourless oil that was dissolved in 25 ml hot hexane. Upon cooling 74% (2.29 g) of a fine white powder precipitated. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 6.62$ (2H, br. s, CH=CH), 5.50 (2H, br. s, CHCH$_2$CH), 4.82 (4H, br. s, CH$_2$CCl$_3$), 1.88-1.86 (2H, m, CHCH$_2$CH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 156.3, 138.7-132.4$ (br. signal), 94.9, 66.0, 48.4 ppm. MS EI, m/z (rel. intensity): 446 (M$^+$, 10), 131 (30), 95 (32), 66 (100). HRMS (EI$^+$): calculated for C$_{14}$H$_{10}$Cl$_3$N$_2$O$_3$ [M$^+$]: 443.8771; found = 443.8765. MP 119-121°C.

**trans-(2-Benzoylcyclopent-3-eny)-N,N’-diethylhydrazine dicarboxylate (33a).**

Prepared according to Procedure A. The keto-hydrazine was obtained as a colourless foam in 92% yield (43 mg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.08$-7.95 (2H, m, ortho-CH ar.), 7.54 (1H, t, $J = 7.4$ Hz, para-CH ar.), 7.44 (2H, t, $J = 7.4$ Hz, meta-CH ar.), 6.65 (1H, br. s, R$_2$NH), 5.82-5.77 (1H, m, CH$_2$CHCH), 5.65-5.60 (1H, m, CH$_2$CHCH), 5.31 (1H, br. s, CH$_2$(CH(NRR$^-$))) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 199.6, 157.3, 155.9, 136.6, 133.4, 131.7, 128.9, 128.8 (3)$, 128.4, 62.8, 62.5, 60.2, 58.4, 36.5, 14.6, 14.5. IR (NaCl, neat film): 3296, 3059, 2983, 2933, 2869, 1755, 1742, 1724, 1689, 1677, 1665, 1596, 1480, 1410, 1173, 1130, 1061 cm$^{-1}$. MS ESI, m/z (rel. intensity): 369 (M-Na$^+$, 60), 347 (M-H$^+$, 21), 171 (40), 105 (100). HRMS (ESI$^+$): calculated for C$_{14}$H$_{13}$N$_2$O$_3$ [MH$^+$]: 347.1601; found = 347.1612.

**trans-(2-Benzoylcyclopent-3-eny)-N,N’-di-tert-butylhydrazine dicarboxylate (33b).**

Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 91% yield (50 mg). On a 1 mmol scale, 375 mg were obtained (93%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.57$ (1H, t, $J = 7.2$ Hz, para-CH ar.), 7.47 (2H, t, $J = 7.6$ Hz, meta-CH ar.), 6.30 (1H, br. s, R$_2$NH), 5.83 (1H, br. s, CH$_2$CHCH), 5.65 (1H, br.s, CH$_2$CHCH), 5.26 (1H, br. s, CH$_2$(CH(NRR$^-$))) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 199.8, 156.0, 154.5, 136.5, 133.0, 131.5, 128.8, 128.6, 128.2, 81.2, 60.2, 58.0, 36.3, 28.1. IR (NaCl, neat film): 3320, 3061, 2978, 2931, 1708 (br.), 1597, 1580, 1448, 1393, 1367, 1249, 1157, 1050 cm$^{-1}$. MS ESI, m/z (rel. intensity): 402 (M$^+$, 1), 246 (25), 202 (10), 186 (15), 171 (30), 141 (15), 105 (50), 97 (15), 77 (18), 57 (100). HRMS (ESI$^+$): calculated for C$_{23}$H$_{23}$N$_2$O$_5$ [MH$^+$]: 403.2232; found = 403.2237. The ee was determined by HPLC analysis: 0% ee (Chiralcel AD-H, hexane/iPrOH = 90/10, 1.2 mL/min, 242 nm); $t_R = 24.5$ min; $t_R = 29.2$ min.

**trans-(2-Benzoylcyclopent-3-eny)-N,N’-dibenzyldihydrazine dicarboxylate (33c).**

Prepared according to Procedure A. The keto-hydrazine was obtained as a colourless, viscous oil that became a waxy solid on standing; in 93% yield (60 mg). On a 1 mmol scale, 466 mg were obtained (99%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.01$ -7.99 (2H, m), 7.55-7.20 (14H, m), 6.88 (1H, br. s), 5.77 (1H, br. s, CH$_2$CHCH), 5.62 (1H, br.s, CH$_2$CHCH), 5.43-5.36 (1H, m, CH$_2$(CH(NRR$^-$))), 5.14-4.78 (5H, m, OCH$_2$Ph, CH(COAr)), 2.88-2.46 (2H, m, CH$_2$(CH(NRR$^-$)) diast.) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 199.0, 156.8, 155.4, 136.1, 135.6, 135.5, 133.1, 131.4, 128.7, 128.5, 128.8, 128.0, 127.8, 68.1, 67.79, 60.0, 58.1, 36.2 ppm. IR (NaCl, neat film): 3294, 3063, 3031, 2954, 2251, 1963, 1762-1656, 1596, 1497, 1455, 1409, 1171, 1133, 1050, 1004, 730, 697 cm$^{-1}$. MS ESI, m/z (rel. intensity): 509 (M-K$^-$, 7), 493 (M-Na$^-$, 72), 488 (M-NH$_3^+$, 10), 471 (M-H$^+$, 56), 171 (55), 105 (100), 91 (15). HRMS (ESI$^+$): calculated for C$_{25}$H$_{25}$N$_2$O$_5$ [M-H$^+$]: 471.1914; found = 471.1934.
trans-(2-Benzoyl-cyclopent-3-enyl)-N,N'-bis(2',2',2'-trichloroethyl)-hydrazine dicarboxylate (33d). Prepared according to Procedure A. The keto-hydrazine was obtained as a colourless foam in 93 % yield (69 mg). On a 1 mmol scale, 508 mg (92 %) were obtained. \[^1\text{H} \text{NMR}\] (400 MHz, CDCl\(_3\)): \(\delta = 8.02\) (2H, d, \(J = 10.0\) Hz, ortho-CH ar.), 7.59 (1H, \(J = 10.0\) Hz, meta-CH ar.), 7.10 (1H, br. s, R\(_2\)NH), 5.85-5.82 (1H, m, CH\(_2\)CHCH), 5.70-5.68 (1H, m, CH\(_2\)CHCH), 5.48 (1H, br. s, CH\(_2\)CH(NRR'))), 4.88-4.68 (5H, m, OCH\(_3\)Cl\(_2\), CH(COAr)), 2.99-2.89 (1H, m, CH\(_2\)CHCH diast.), 2.71-2.65 (1H, m, CH\(_2\)CHCH diast.). ppm. \[^{13}\text{C} \text{NMR}\] (100 MHz, CDCl\(_3\)): \(\delta = 198.1, 154.9\) (br), 136.0, 133.4, 131.4, 128.7, 128.2, 94.7, 75.7, 75.2, 60.6, 58.1 (br), 36.3 ppm. \textbf{IR} (NaCl, neat film): 3288, 3058, 3017, 2949, 1772-1731, 1677, 1596, 1505, 1446, 1410, 1286, 1211, 1139, 1105, 1048, 1001, 811, 728, cm\(^{-1}\). \textbf{MS} ESI, \(m/z\) (rel. intensity): 578 (M-Na\(^+\), 40), 553 (M-H\(^+\), 50), 171 (40), 105 (100) \textbf{HRMS} (ESI\(^{+}\)): calculated for C\(_{40}H_{38}Cl_8N_2O_8\) [M-H\(^+\)]: 550.9263; found = 550.9286.

\textbf{trans-[2-(4'-Methoxybenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butyl-hydrazine dicarboxylate (34).} Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 96% yield (56 mg). \[^1\text{H} \text{NMR}\] (400 MHz, CDCl\(_3\)): \(\delta = 8.06\) (2H, br. s), 6.94 (2H, \(J = 8.8\) Hz), 6.37 (1H, br. s, R\(_2\)NH), 5.82 (1H, br. s), 5.64 (1H, br. s), 5.23 (1H, br. s), 4.78 (1H, br. s), 3.87 (3H, s), 2.84-2.70 (1H, m), 2.65-2.52 (1H, m), 1.47 (9H, br. s), 1.37 (9H, br. s). \[^{13}\text{C} \text{NMR}\] (100 MHz, CDCl\(_3\)): \(\delta = 199.4, 163.5, 156.0, 154.5, 131.4, 131.1, 129.6, 128.5, 113.8, 81.5, 76.3, 55.5, 36.3, 28.1. \textbf{IR} (NaCl, neat film): 3316, 3058, 2978, 2934, 1737 1670 (br.), 1600, 1574, 1455, 1393, 1367, 1258, 1171, 1050, 1028, 837, 732 cm\(^{-1}\). \textbf{MS} ESI, \(m/z\) (rel. intensity): 471 (M-K\(^+\), 94), 455 (M-Na\(^+\)), 433 (M-H\(^+\), 6), 355 (17), 321 (45), 277 (16), 233 (40), 201 (50), 135 (71). \textbf{HRMS} (ESI\(^{+}\)): calculated for C\(_{42}H_{36}Cl_8N_3O_8\) [M-H\(^+\)]: 433.2333; found = 433.2347.

\textbf{trans-[2-(3'-Methoxybenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butyl-hydrazine dicarboxylate (35).} Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 84% yield (49 mg). \[^1\text{H} \text{NMR}\] (400 MHz, CDCl\(_3\)): \(\delta = 7.66-7.50\) (2H, br. m), 7.38 (1H, \(J = 8.0\) Hz), 7.11 (1H, dd, \(J = 8.0, 2.0\) Hz), 6.29 (1H, br. s, R\(_2\)NH), 5.86-5.79 (1H, br. m), 5.67-5.60 (1H, br. m), 5.24 (1H, br. s), 4.83 (1H, br. s), 3.86 (3H, s), 2.83-2.74 (1H, br. m), 2.64-2.52 (1H, br. m), 1.47 (9H, br. s), 1.36 (9H, br. s). \[^{13}\text{C} \text{NMR}\] (100 MHz, CDCl\(_3\)): \(\delta = 199.8, 160.0, 156.1, 154.5, 138.0, 131.5, 129.6, 128.3, 121.5, 120.0, 112.8, 81.3, 60.2, 58.0, 55.5, 36.3, 28.1. \textbf{IR} (NaCl, neat film): 3327, 3058, 2978, 2934, 1737-1683 (br.), 1597, 1582, 1488, 1393, 1367, 1260, 1157, 1049, 1025, 951, 753 cm\(^{-1}\). \textbf{MS} ESI, \(m/z\) (rel. intensity): 455 (M-Na\(^+\)), 433 (M-H\(^+\), 5), 355 (22), 321 (15), 277 (15), 233 (25), 201 (50), 135 (50). \textbf{HRMS} (ESI\(^{+}\)): calculated for C\(_{44}H_{36}Cl_8N_4O_8\) [M-Na\(^+\)]: 455.2152; found = 455.2143.

\textbf{trans-[2-(2'-Methyl-4'-methoxybenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butylhydrazine dicarboxylate (36).} Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 91% yield (55 mg). \[^1\text{H} \text{NMR}\] (400 MHz, CDCl\(_3\)): \(\delta = 7.88\) (1H, br. s), 6.78-6.74 (2H, m), 6.27 (1H, br. s, R\(_2\)NH), 5.82-5.78 (1H, m), 5.61 (1H, br. s), 5.23-5.16 (1H, m), 4.71 (1H, br. s), 3.84 (3H, s), 2.82-2.72 (1H, br. m), 2.61-2.51 (1H, br. m), 2.51 (3H, s), 1.47 (9H, br. s), 1.39 (9H, br. s). \[^{13}\text{C} \text{NMR}\] (100 MHz, CDCl\(_3\)): \(\delta = 201.3, 161.8, 155.9, 154.4, 142.3, 132.0, 131.2, 129.8, 128.5, 117.5, 110.5, 81.2, 60.0, 55.3, 36.3, 28.1, 22.3. \textbf{IR} (NaCl, neat film): 3323, 3060, 2977, 2932, 1734-1684 (br.), 1603, 1568, 1456, 1393, 1367, 1249, 1158, 1130, 1052, 950, 733 cm\(^{-1}\). \textbf{MS} ESI, \(m/z\) (rel. intensity): 485 (M-K\(^+\), 38), 469 (M-Na\(^+\), 100), 447 (M-H\(^+\), 8), 369 (10), 335 (45),
prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 84% yield (47 mg). ^1H NMR (400 MHz, CDCl₃): δ 7.74 (1H, br. s), 7.39-7.33 (1H, m), 7.29-7.21 (1H, m), 6.23 (1H, br. s, R₂NH), 5.83-5.78 (1H, m), 5.59 (1H, br. s), 5.27-5.18 (1H, m), 4.69 (1H, br. s), 2.82-2.72 (1H, m), 2.61-2.50 (1H, m), 2.45 (3H, s), 1.46 (9H, br. s), 1.40 (9H, br. s). ^13C NMR (100 MHz, CDCl₃): δ 203.4, 155.9, 154.4, 38.2, 137.9, 131.7, 131.5, 131.1, 128.6, 127.8, 125.6, 81.4, 60.7, 59.9, 36.3, 28.1, 21.1. IR (NaCl, neat film): 3323, 3062, 2979, 2931, 1732-1684 (br.), 1601, 1456, 1393, 1368, 1252, 1157, 1050, 949, 732 cm⁻¹. MS ESI, m/z (rel. intensity): 439 (M-Na⁺, 100), 417 (M-H⁺, 3), 339 (17), 217 (25), 185 (42), 119 (56). HRMS (ESI): calculated for C₂₅H₂₃N₂O₃Na [M-Na⁺]: 439.2203; found = 439.2225.

trans-[2-(3'-Methylbenzoyl)-cyclopent-3-enyl]-N,N-di-tert-butyldihydrazine dicarboxylate (38).
Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 94% yield (53 mg). ^1H NMR (400 MHz, CDCl₃): δ 7.91-7.73 (2H, br. m), 7.40-7.33 (2H, m), 6.30 (1H, br. s, R₂NH), 5.86-5.78 (1H, m), 5.64 (1H, br. s), 5.37-5.20 (1H, m), 4.80 (1H, br. s), 2.83-2.73 (1H, m), 2.65-2.51 (1H, m), 2.41 (3H, s), 1.47 (9H, br. s), 1.37 (9H, br. s). ^13C NMR (100 MHz, CDCl₃): δ 199.9, 160.0, 154.5, 138.4, 136.6, 133.8, 131.5, 129.3, 128.5, 125.3, 125.9, 81.5, 60.2, 57.9, 36.2, 28.1, 21.3. IR (NaCl, neat film): 3320, 3062, 2979, 2931, 1738-1682 (br.), 1604, 1588, 1456, 1392, 1367, 1250, 1160, 1050, 1025, 951, 732 cm⁻¹. MS ESI, m/z (rel. intensity): 439 (M-Na⁺, 100), 417 (M-H⁺, 2), 339 (15), 217 (31), 185 (43), 119 (60). HRMS (ESI): calculated for C₂₅H₂₃N₂O₃Na [M-Na⁺]: 439.2203; found = 439.2213.

trans-[2-(4'-Methylbenzoyl)-cyclopent-3-enyl]-N,N-di-tert-butyldihydrazine dicarboxylate (39).
Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 91% yield (51 mg). ^1H NMR (400 MHz, CDCl₃): δ 8.03-7.84 (2H, br. m), 7.26 (2H, d, J = 8.0 Hz), 6.31 (1H, br. s, R₂NH), 5.84-5.79 (1H, m), 5.70-5.62 (1H, br. m), 5.38-5.20 (1H, br. m), 4.79 (1H, br. s), 2.84-2.71 (1H, m), 2.67-2.51 (1H, m), 2.41 (3H, s), 1.47 (9H, br. s), 1.37 (9H, br. s). ^13C NMR (100 MHz, CDCl₃): δ 199.4, 156.0, 154.5, 143.8, 134.1, 131.5, 129.3, 128.9, 128.4, 81.3, 60.2, 57.9, 36.3, 28.1, 21.6. IR (NaCl, neat film): 3319, 3051, 2978, 2932, 1744-1682 (br.), 1607, 1572, 1456, 1393, 1367, 1252, 1157, 1051, 1025, 951, 732 cm⁻¹. MS ESI, m/z (rel. intensity): 439 (M-Na⁺, 100), 417 (M-H⁺, 20), 339 (22), 305 (50), 261 (35), 217 (50), 185 (70), 119 (92). HRMS (ESI): calculated for C₂₅H₂₃N₂O₃Na [M-H⁺]: 417.2383; found = 417.2388.

trans-[2-(2'-Naphthoyl)-cyclopent-3-enyl]-N,N-di-tert-butyldihydrazine dicarboxylate (40).
Prepared according to Procedure A. The keto-hydrazine was obtained as a colourless foam in 88% yield (54 mg). ^1H NMR (400 MHz, CDCl₃): δ 8.99-8.36 (1H, br. s), 8.09 (1H, d, J = 8.0 Hz), 7.99 (1H, d, J = 7.2 Hz), 7.88 (2H, t, J = 9.6 Hz), 7.57 (2H, dt, J = 6.9, 14.6 Hz), 6.42-6.00 (1H, coalesc. br. s), 5.96-5.80 (1H, br. s), 5.78-5.62 (1H, br. s), 5.57-5.18 (1H, coalesc. br. s), 5.01 (1H, br. s), 2.94-2.73 (1H, m), 2.72-2.47 (1H, m), 1.50 (9H, br. s), 1.31 (9H, br. s) ppm. ^13C NMR (100 MHz, CDCl₃): δ 200.0, 156.1, 154.5, 135.6, 133.9, 132.7, 131.6, 131.1, 129.8, 128.4, 127.7, 126.6, 124.4, 81.3, 60.4, 57.9, 36.3, 28.2, 28.0 ppm. IR (NaCl, neat film): 3320, 3060, 2978, 2932, 2253, 1713, 1627, 1596, 1504, 1472, 1392, 1367, 1250, 1157, 1050, 1024, 952.
trans-[2-(3'-Trimethylsilylbenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butylhydrazine dicarboxylate (41). Prepared according to Procedure A. The keto-hydrazine was obtained as a colorless viscous oil in 83% yield (53 mg). ¹H NMR (400 MHz, CDCl₃): δ 8.24 (1H, br. s), 7.71 (1H, d, J = 7.6 Hz), 7.45 (1H, t, J = 7.6 Hz), 6.28 (1H, coalesc. br. s), 5.86-5.80 (1H, m), 5.71-5.60 (1H, br. m), 5.33-5.20 (1H, br. m), 4.89 (1H, br. s), 2.89-2.70 (1H, m), 2.70-2.44 (1H, m), 1.47 (9H, br. s), 1.35 (9H, br. s), 0.30 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 200.4, 155.9, 155.0, 141.2, 137.9, 135.8, 133.5, 131.4, 129.2, 128.4, 127.9, 81.4, 60.5, 57.7, 36.2, 28.1, 28.0, 27.3 cm⁻¹. MS ESI, m/z (rel. intensity): 513 (M⁺, 15), 497 (M-Na⁺, 70), 475 (M-H⁺, 10), 363 (45), 319 (35), 275 (80), 243 (100), 177 (17). HRMS (ESI⁺): calculated for C₂₅H₂₅N₂O₃Si [M⁺]: 475.2622; found = 475.2643.

trans-[2-(3'-Vinylbenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butylhydrazine dicarboxylate (42). Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 83% yield (48 mg). ¹H NMR (400 MHz, CDCl₃): δ 8.18 (1H, br. s), 8.05-7.82 (1H, br. m), 7.60 (1H, d, J = 7.2 Hz), 7.43 (1H, t, J = 8.0 Hz), 6.76 (1H, dd, J = 17.8, 11.2 Hz), 6.29 (1H, br. s, R₂NH), 5.92-5.78 (2H, m), 5.71-5.60 (1H, br. m), 5.32 (1H, d, J = 11.2 Hz), 5.25 (1H, br. s), 4.88 (1H, br. s), 2.84-2.72 (1H, m), 2.67-2.50 (1H, m), 1.48 (9H, br. s), 1.36 (9H, br. s). ¹³C NMR (100 MHz, CDCl₃): δ 199.9, 156.0, 154.5, 138.1, 136.9, 136.0, 131.5, 130.6, 128.3, 128.1, 126.7, 115.2, 81.6, 60.3, 57.9, 36.3, 28.1, 28.0. IR (NaCl, neat film): 3324, 3059, 2978, 2932, 1736-1685 (br.), 1597, 1578, 1479, 1456, 1392, 1367, 1252, 1158, 1050, 1023, 949, 733 cm⁻¹. MS ESI, m/z (rel. intensity): 451 (M-Na⁺, 77), 429 (M-H⁺, 21), 317 (34), 273 (34), 229 (58), 197 (100), 131 (100). HRMS (ESI⁺): calculated for C₂₅H₂₅N₂O₃ [M⁺]: 429.2383; found = 429.2392.

trans-[2-(4'-Chlorobenzooyl)-cyclopent-3-enyl]-N,N'-di-tert-butylhydrazine dicarboxylate (43). Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 83% yield (48 mg). ¹H NMR (400 MHz, CDCl₃): δ 8.03 (2H, br. s), 7.44 (2H, d, J = 7.6 Hz), 6.27 (1H, br. s, R₂NH), 5.88-5.81 (1H, m), 5.66-5.57 (1H, br. m), 5.23 (1H, br. s), 4.80 (1H, br. s), 2.84-2.73 (1H, m), 2.66-2.48 (1H, m), 1.46 (9H, br. s), 1.38 (9H, br. s). ¹³C NMR (100 MHz, CDCl₃): δ 198.8, 156.1, 154.5, 139.6, 135.1, 131.8, 130.3, 128.8, 128.0, 81.7, 60.3, 58.0, 36.3, 28.19, 28.17. IR (NaCl, neat film): 3319, 3061, 2979, 2932, 1740-1675 (br.), 1588, 1570, 1490, 1437, 1394, 1368, 1251, 1157, 1092, 1051, 1010, 947, 735 cm⁻¹. MS ESI, m/z (rel. intensity): 459 (M-Na⁺, 100), 437 (M-H⁺, 9), 359 (26), 325 (64), 281 (55), 237 (85), 205 (92), 139 (83). HRMS (ESI⁺): calculated for C₂₂H₂₃N₂O₃NaCl [M-Na⁺]: 459.1657; found = 459.1634.
trans-[2-(4'-Fluorobenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butyldihydrazine dicarboxylate (44b). Prepared according to Procedure A. The keto-hydrazine was obtained as a colourless foam in 77% yield (44 mg). 1H NMR (400 MHz, CDCl3): δ 8.10-7.95 (2H, br. m), 7.14 (2H, d, J = 8.4 Hz), 6.29 (1H, br. s, R2NH), 5.86-5.81 (1H, m), 5.71-5.55 (1H, br. m), 5.37-5.17 (1H, br. m), 4.81 (1H, br. s), 2.85-2.72 (1H, m), 2.67-2.45 (1H, m), 1.47 (9H, br. s), 1.38 (9H, br. s). 13C NMR (100 MHz, CDCl3): δ 198.5, 165.8 (d, 1JCF = 253 Hz), 156.1, 154.4, 133.0, 131.6, 131.5, 128.1, 115.7 (d, 2JCF = 22 Hz), 81.4, 60.2, 57.9, 36.3, 28.1. IR (NaCl, neat film): 3319, 3060, 2978, 2928, 1732-1686 (br.), 1599, 1506, 1473, 1456, 1393, 1367, 1246, 1157, 1045, 1024, 953, 841, 758 cm⁻¹. MS ESI⁺, m/z (rel. intensity): 421 (M⁺, 1), 264 (30), 204 (20), 189 (24), 141 (19), 123 (46), 97 (16), 57 (100). HRMS (ESI⁺): calculated for C22H28N2O5F [M⁺]: 420.2061; found = 420.2050.

trans-[2-(4'-Trifluoromethylbenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butyldihydrazine dicarboxylate (45). Prepared according to Procedure A. The keto-hydrazine was obtained as a colourless viscous oil in 57% yield (36 mg). 1H NMR (400 MHz, CDCl3): δ 8.30-8.04 (2H, br. m), 7.74 (2H, d, J = 8.0 Hz), 6.32 (1H, br. s, R2NH), 5.90-5.83 (1H, m), 5.67-5.59 (1H, br. m), 5.36-5.18 (1H, br. m), 4.88 (1H, br. s), 2.83-2.72 (1H, m), 2.70-2.50 (1H, br. m), 1.48 (9H, br. s), 1.36 (9H, br. s). 13C NMR (100 MHz, CDCl3): δ 199.4, 156.1, 154.4, 139.3, 134.2 (q, 2JCF = 31 Hz), 131.9, 129.3, 127.8, 125.6, 123.7 (d, 1JCF = 271 Hz), 81.5, 60.2, 58.2, 36.3, 28.1, 28.0. IR (NaCl, neat film): 3321, 3064, 2980, 2933, 1730-1671 (br.), 1582, 1511, 1479, 1456, 1394, 1368, 1323, 1251, 1167, 1015, 949, 854, 734 cm⁻¹. MS ESI⁺, m/z (rel. intensity): 493 (M-Na⁺, 100), 471 (MH⁺, 5), 393 (13), 359 (38), 315 (44), 271 (79), 239 (60), 173 (31). HRMS (ESI⁺): calculated for C23H24N2O5F3 [MH⁺]: 471.2101; found = 471.2099.
	rans-[2-(3'-Nitrobenzoyl)-cyclopent-3-enyl]-N,N'-di-tert-butyldihydrazine dicarboxylate (46). Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 38% yield (23 mg). 1H NMR (400 MHz, CDCl3): δ 8.30-8.09 (2H, m), 8.03 (2H, d, J = 8.4 Hz), 6.32 (1H, br. s), 5.91-5.81 (1H, m), 5.73-5.56 (1H, m), 5.46-5.15 (1H, br. m), 4.87 (1H, br. s), 2.90-2.75 (1H, m), 2.75-2.55 (4H, m), 1.47 (9H, br. s), 1.37 (9H, br. s). 13C NMR (100 MHz, CDCl3): δ = 199.6, 197.6, 156.1, 154.4, 140.1, 139.8, 131.9, 129.1, 128.5, 127.8, 81.7, 60.1, 58.3, 36.3, 28.1, 26.9. IR (NaCl, neat film): 3318, 3060, 2979, 2932, 1745-1660 (br), 1569, 1478, 1456, 1394-1258, 1157, 1075, 1051, 1024, 1011, 955, 917, 734 cm⁻¹. MS ESI⁺, m/z (rel. intensity): 467 (M-Na⁺, 60), 455 (M-H⁺, 10), 333 (70), 289 (60), 245 (62), 213 (100), 147 (70). HRMS (ESI⁺): calculated for C22H22N2O4Na [M-Na⁺]: 467.2152; found = 467.2134.

trans-[2-(3'-Thiophenoyl)-cyclopent-3-enyl]-N,N'-di-tert-butyldihydrazine dicarboxylate (47). Prepared according to Procedure A. The keto-hydrazine was obtained as a light yellow, viscous oil in 39% yield (22 mg). 1H NMR (400 MHz, CDCl3): δ 8.49 (1H, br. s), 7.63 (1H, br. s), 7.31 (1H, br. s), 6.30 (1H, br. s, R2NH), 5.90-5.81 (1H, m), 5.74-5.60 (1H, br. m), 5.38-5.09 (1H, br. m), 4.66 (1H, br. s), 2.84-2.70 (1H, m), 2.69-2.46 (1H, br. m), 1.48 (9H, br. s), 1.35 (9H, br. s). 13C NMR (100 MHz, CDCl3): δ 194.8, 156.2, 154.4, 142.0, 133.8, 131.6, 128.4, 127.5, 126.1, 61.4, 60.8, 59.3, 36.3, 28.1, 28.0. IR (NaCl, neat film): 3311, 3092, 2978, 2932, 1731-1672 (br.), 1508, 1456, 1394, 1368, 1338, 1251, 1157, 1051, 1021, 951, 732 cm⁻¹. MS ESI⁺, m/z (rel. intensity): 431 (M-Na⁺, 100), 409 (M⁺, 9), 331 (15), 297 (50), 209 (55), 177 (65), 111 (88). HRMS (ESI⁺): calculated for C20H18N2O4S [MH⁺]: 409.1791; found = 409.1792.
trans-[2-(3’-Phenyl-acryloyl)-cyclopent-3-enyl]-N,N’-di-tert-butylhydrazine dicarboxylate (48).

When prepared according to Procedure A, the keto-hydrazine was obtained as a light yellow, viscous oil in 38% yield (22 mg). The yield was significantly increased by the presence of CsF (1.2 equiv) as a base and by portion-wise additions of the boronic acid (+0.5 equiv after 16 h); (63% yield, 36 mg). ^1H NMR (400 MHz, CDCl₃): δ 7.72 (1H, br. d, J = 15.6 Hz), 7.59-7.53 (1H, m), 7.39-7.31 (1H, m), 6.97 (1H, br. d, J = 15.6 Hz), 6.23 (1H, br. d, s, R₂NH), 5.86-5.81 (1H, m), 5.72-5.67 (1H, br. m), 5.18-5.10 (1H, br. m), 4.22 (1H, br. s), 2.79-2.69 (1H, m), 2.62-2.50 (1H, br. m), 1.48 (9H, br. s), 1.41 (9H, br. s). ^13C NMR (100 MHz, CDCl₃): δ 199.8, 156.0, 154.6, 143.5, 135.0, 131.6, 130.4, 128.9, 128.5, 128.1, 125.2, 81.7, 60.4, 36.2, 28.2. IR (NaCl, neat film): 3313, 3058, 2978, 2932, 1732, 1544, 1435, 1350, 1316, 1304, 1289, 1285, 1281, 1252, 817, 604, 362, 282. MS ESI, m/z (rel. intensity): 451 (M+[NH₄]+, 15), 351 (20), 317 (82), 273 (23), 229 (51), 197 (74), 131 (56). HRMS (ESI⁺): calculated for C₂₄H₁₇N₅O₃ [M⁺]: 429.2383; found = 429.2370.

Naphthalen-2-yl(phenyl)methaneone (55).

To a dram vial equipped with a magnetic stir bar was added [Rh(cod)OH]₂ (3.8 mg, 0.0083 mmol), (S)-BINAP (12.4 mg, 0.020 mmol), and Cs₂CO₃ (54 mg, 0.166 mmol). The vial was sealed and flushed with CO gas (balloon) for 15 min; the solid catalyst turned brown. Toluene was added (0.8 mL), followed by water (0.16 mL), and the mixture was stirred at room temperature for 30 min (dark opaque red-brown mixture). Benzooxacyclo[2.2.1]heptene 53 (24 mg, 0.166 mmol) and the phenylboronic acid (40 mg, 0.32 mmol) were added together as a solution in toluene (0.80 mL) and the reaction mixture was allowed to react at 20-25 °C under an atmosphere of CO (balloon). After 30 min, TLC analysis showed no reaction. The reaction mixture was then heated at 53 °C oil bath for additional 2.5 h, reaction turned to brown viscous opaque. TLC showed nearly full consumption of 53 (purple spot with vanillin, 25% EtOAc/Hex), and appearance of a major less polar yellow spot. The reaction mixture was extracted with 3 x 10 mL Et₂O, washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (10% Et₂O/hexane). Light yellow solid. Characterization matched reported data. ^1H NMR (CDCl₃, 500 MHz) δ: 8.28 (1H, s), 7.88 (2H, d, J = 1.6 Hz), 7.87–7.82 (2H, m), 7.81–7.76 (2H, m), 7.74 (1H, dd, J = 8.0, 1.7 Hz), 7.58–7.51 (2H, m), 7.51–7.37 (3H, m).

[Rh(IMes)(cod)Cl] (63). 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (342 mg, 1.0 mmol) was weighed into a 10 mL round-bottom flask, the vessel was then flushed with a gentle argon stream, then dichloromethane was added (~6.5 mL). Stirred until full dissolution (5 min; amber solution). Silver oxide (116 mg, 0.5 mmol) was added as a black solid in one portion to the stirring solution. Stirred at room temperature for an additional 2 h. Form dark gray, suspension turned to light brown. The light brown suspension was filtered directly into a solution of [Rh(cod)Cl]₂ (342 mg, 0.5 mmol) in dichloromethane (2.5 mL) using a pipet with celite and washing with 1.0 mL DCM. The clear orange solutions started forming an orange-yellow precipitate. The flask was purged with argon stream, and the solution was stirred at room temperature for ca. 18 hours. The solution was clear amber with grey precipitate (residual AgCl). The solvent was concentrated in vacuo to afford a crude solid (no precautions about atmosphere exposure). The residue was retaken in benzene and purified by flash chromatography (10–50% gradient elution with ether/pentane) afforded 63 (444 mg, 81%) as ochre-yellow crystals. Characterization data matched

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literature.\(^96\) MP 212–214 °C, uncorrected. \(^1H\) NMR (400 MHz, CDCl\(_3\)) δ: 7.06 (br.s, 2H), 7.01 (br.s, 2H), 6.95 (s, 2H), 4.50 (br.s, 2H), 3.29 (br.s, 2H), 2.39 (br.s, 12H), 2.11 (br.s, 6H), 1.92–1.73 (m, 4H), 1.62–1.46 (m, 4H). \(^13C\) NMR (100 MHz, C\(_6\)D\(_6\)) δ: 183.7 (d, \(J_{RhC} = 51.9\) Hz), 138.8, 137.7, 136.4, 134.4, 129.8, 128.2, 123.6, 96.2 (d, \(J_{RhC} = 7.6\) Hz), 67.9 (d, \(J_{RhC} = 14.5\) Hz, cod), 32.8 (cod), 28.5 (cod), 21.2, 19.9, 18.2. IR (neat) 3116, 3084, 2911, 2874, 2829, 1483, 1317, 1261, 848, 738, 708 cm\(^{-1}\).

\[\text{[Rh(IMes)(CO)\(_2\)Cl]}\] (66). [Rh(IMes)(cod)Cl] (63, 50 mg, 0.09 mmol) was dissolved in C\(_6\)D\(_6\) (10 mL) and CO was bubbled through the solution for 5–7 min. The solvent was evaporated twice on rotavap, the residue retaken in C\(_6\)D\(_6\). Complex 66 was obtained as a yellow solid; 43 mg (96%). Characterization data matched that of literature.\(^97\) \(^1H\) NMR (CDCl\(_3\), 500 MHz) δ: 7.11 (2H, s), 7.01 (4H, s), 2.37 (6H, s), 2.21 (12H, s). \(^13C\) NMR (CDCl\(_3\), 125 MHz) δ: 184.9 (\(J_{RhC} = 54\) Hz), 182.8 (\(J_{RhC} = 74\) Hz), 177.7 (\(J_{RhC} = 45\) Hz), 139.4, 135.3, 135.1, 129.3, 123.7, 21.2, 18.5.

\[\text{[Rh(IMes)(CO)\(_2\)(Ar)]}\] (69). A solution of 66 in C\(_6\)D\(_6\) (1.0 mL of a 0.018 mmol/mL) was transferred in a 0.5 dram vial, then purged with a CO stream. 4-Fluorophenylboronic acid was added and stirred until full dissolution, then AgBF\(_4\) was added rapidly as a solid and stirred vigourously under CO. The clear light yellow solution became turbid yellow, then cleared out as solids darkened and stuck to vessel walls. An aliquot of aqueous NaOH (20mg/0.20 mL of water) was syringed in. After 10 min stirring at r.t., a sample was withdrawn for NMR analysis. Afterwards, the sample was syringed back into the vessel, and the reaction allowed to stand for a week before a second NMR analysis of the mixture was done.

\[\text{[Rh(CO)\(_2\)acac]}\] (4.2 mg, 0.016 mmol) was weighed into a 1 dram vial equipped with a magnetic stir bar. The vial was sealed with a septum and parafilm and flushed with a CO stream (balloon) for 10 min. Toluene (1.0 mL) was added to dissolve the catalyst, stirred for 15 min at r.t. 1-Phenylpropyne (77 mg, 0.66 mmol) and (E)-2-styrylboronic acid (40 mg, 0.270 mmol) were added together as a solution in THF (0.80 mL). The reaction mixture was stirred at 25 °C under an atmosphere of CO (balloon) overnight (14-16 h). TLC analysis: 25% EtOAc/Hex, vanillin; desired spot \(R_f\) 0.45. The reaction mixture was filtered on silica plug in Pasteur pipet, washed with Et\(_2\)O. The crude residue was purified directly by column chromatography (loading in benzene, then elution with 5-10-25% Et\(_2\)O/hexane gradient). Recovered 5 mg of amorphous white solid displaying a 10:0:1 ratio of 83:84:85 according to \(^1H\) NMR analysis. (8%). Note: Running the reaction only in THF under the same parameters gave 39% as 3:1:1 isomeric mixture. \(^1H\) NMR (400 MHz, CDCl\(_3\)) 7.35-7.11 (10H, m), 4.54-4.50 (1H, m), 3.13 (1H, dd, \(J = 18.9, 7.2\) Hz), 2.53 (1H, dd, \(J = 18.9, 2.3\) Hz), 2.06 (3H, d, \(J = 1.8\) Hz). \(^13C\) NMR (100 MHz, CDCl\(_3\)) δ 208.9, 169.1, 142.3, 137.7, 135.2, 128.3, 128.9, 128.7, 128.0, 127.3, 126.6, 47.1, 45.1, 9.8. HRMS (EI): \(m/z\) calculated for C\(_{16}\)H\(_{10}\)O [M\(^+\)]: 248.1201; found = 248.1205.

\(^96\) Yu, X.-Y.; Patrick, B. O.; James, B. R. Organometallics 2006, 25, 2359.

CHAPTER 5

GENERAL CONCLUSIONS

From a synthetic perspective, a recurring theme of this thesis is the preparation of substituted 5-membered rings. The underlying foundation of the work reported herein, however, is the exploitation of Rh¹ catalysis to access new modes of reactivity. Rhodium catalysts were found to create C–C bonds stereoselectively by coupling boronic acids to alkenes or alkynes. Scheme 5-1 provides an overview of the various methodologies developed.

In Chapter 2, the enantioselective desymmetrization of allylic dicarbonates with arylboronic acids was shown to afford trans-aryl Ringolipentenols in excellent ee (up to 99% ee). Selectivity between 1,2- or 1,4-regioisomers could be controlled by using bisphosphines of different electronic density, and bite angle. Experimental evidence suggests that the reaction proceeds by formation of a rhodium(III) o-enyl complex. The reaction could also be extended to less reactive linear allylic dicarbonates by using a zinc(II) Lewis acid. This method allows to prepare homoallylic alcohols that are versatile building blocks with up to 97% ee.

The reactivity of bicyclic hydrazines was investigated in Chapter 3. Again, highly enantioselective desymmetrization reactions were found to occur with rhodium catalysts and arylboronic acids. The initial ring-opening of bicyclic hydrazines was found to give optimal yields and enantioselectivity with tert-Bu-Josiphos with ortho substituted arylboronic acids (96–99% ee). Though the trans-cyclopentenylhydrazines obtained are amine analogs of the alcohols obtained in Chapter 2, the mechanism of the reaction is different, as carbonboration is the key step of the ring-opening. During these studies, an alternative reaction pathway was identified that leads of hydroarylated bicyclic hydrazines. Deuteration experiments revealed a 1,4-migration of the rhodium catalyst when hydrogens of the aryl moiety were sufficiently activated, e.g., with heteroaryl groups. Further investigations led to the finding of Walphos, a ferrocenyl bidentate phosphate ligand, that could favor the hydroarylation reaction even for arylboronic acids not bearing “activated” hydrogens.

Finally, Chapter 4 described how boronic acids could be used to generate acylrhodium(I) intermediates under mild conditions; i.e., using a simple CO atmosphere at rt. As proof of concept, the acyl anions generated catalytically were shown to participate in ring-opening reactions with bicyclic hydrazines. The trans-1,2-ketocyclopentenylhydrazines
obtained are the ketone homologs of the ring-opened products from Chapter 3. Though this acylative ring-opening was very efficient (63–99% yields), the products could only prepared racemically due to the lability of phosphine ligands in the presence of CO. Mechanistic investigations revealed that N-heterocyclic carbenes (NHC) remain bound to the rhodium(I) center throughout the reaction. Preliminary results demonstrated that a chiral NHCs may provide a solution to the challenge of enantioselectivity in metal-catalyzed acylation methodologies. In addition, the reactivity of acylrhodium(I) species was briefly examined with alkynes. The combination of an alkyne, styrylboronic acid, and CO under rhodium(I) catalysis was found to yield cyclopentenones. The regioselectivity observed was found to be complementary to the Pauson-Khand reaction, because of the different mechanism involved. Further systematic studies are still needed to optimize this reaction.

Scheme 5–1 Overview of the reactions presented in this thesis.
Future work will focus on delineating the reactivity and scope of acylrhodium(I) intermediates generated catalytically. Further mechanistic investigations will aim to understand the conceptual ramifications of the strategy.

Toronto
March 12, 2010
APPENDIX A

SPECTRAL DATA OF NEW COMPOUNDS

— CHAPTER 2 —
(3a): *meso*-1,4-Diethylcyclopent-2-enedicarboxylate

\[ \text{\(1\text{H NMR} 300 MHz\ (CDCl_3, 25 \degree C):\)} \]

(3b): *meso*-1,4-Diisopropylcyclopent-2-enedicarboxylate

\[ \text{\(1\text{H NMR} 400 MHz\ (CDCl_3, 25 \degree C):\)} \]
(4a): \((1R, 2S)-\text{trans}-2\text{-phenylcyclopent-3-enyl-ethylcarbonate}\)
(6) : $\text{(1R, 2S)-trans-2-phenylcyclopent-3-enol}$

(7) : $\text{(1R, 4R)-trans-4-phenylcyclopent-2-enol}$
(12) : \((1R, \, 2S)-\text{trans}-2-(4\text{-Trifluoromethyl-phenyl})\text{-cyclopent-3-enyl ethylcarbonate.}\)

(13) : \((1R, \, 2S)-\text{trans}-2-(4\text{-Acetylphenyl})\text{-cyclopent-3-enyl ethylcarbonate.}\)
(12b) : \((1R, 2S)\)-trans-2-(4’-Trifluoromethylphenyl)-cyclopent-2-enol.
(13b) : \((1R, 2S)\)-trans-2-(4-Acetylphenyl)-cyclopent-3-enol.
(13c): (1R, 4R)-trans-4-(4-Acetylphenyl)-cyclopent-2-enol
(14): (1R, 2S)-trans-2-(4-Methoxycarbonyl-phenyl)-cyclopent-3-enyl ethyl-carbonate.
(14b) : (1R, 2S)-trans-2-(4-Methoxycarbonylphenyl)-cyclopent-3-enol.
(15): \((1R, 2S)\)-trans-2-(4-Chlorophenyl)-cyclopent-3-enyl ethylcarbonate.

(16): \((1R, 2S)\)-trans-2-(4-Bromophenyl)-cyclopent-3-enyl ethylcarbonate.
(15b): \((1R, 2S)-\text{trans-2-(4-Chlorophenyl)-cyclopent-3-enol}\).
(16b): (1R, 2S)-trans-2-(4-Bromophenyl)-cyclopent-3-enol.
(15c): \((1R, 4R)\)-trans-2-(4-Chlorophenyl)-cyclopent-2-enol.

(16c): \((1R, 4R)\)-trans-2-(4-Bromophenyl)-cyclopent-2-enol.
(17): \((1R, 2S)-\text{trans}-2-(4-\text{Fluorophenyl})-\text{cyclopent-3-enyl ethylcarbonate.}\)

(18): \((1R, 2S)-\text{trans}-2-(4-\text{Methylphenyl})-\text{cyclopent-3-enyl ethylcarbonate.}\)
(17b) : \((1R, 2S)-\text{trans}-2-(4-\text{Fluorophenyl})\)-cyclopent-3-enol.

\[
\text{NMR Spectra from Chapter 2}
\]
(17c) : (1R, 4R)-trans-2-(4-Fluorophenyl)-cyclopent-2-enol.
(18b): $(1R, 2S)$-trans-2-(4-Methylphenyl)-cyclopent-3-enol.
(19) : (1R, 2S)-trans-2-(4-Methoxyphenyl)-cyclopent-3-enyl ethylcarbonate.

(20) : (1R, 2S)-trans-2-(4-[t-Butoxycarbonylamino]-phenyl)-cyclopent-3-enyl ethylcarbonate.

(19b) : (1R, 2S)-trans-2-(4-Methoxyphenyl)-cyclopent-3-enol.
(20b) : (1R, 2S)-trans-2-(4-[t-Butoxycarbonylamino]-phenyl)-cyclopent-3-enol.
(21) : *(1R, 2S)-trans-2-(3-Chlorophenyl)-cyclopent-3-enyl ethylcarbonate.*

(22) : *(1R, 2S)-trans-2-(3-Methoxyphenyl)-cyclopent-3-enyl ethylcarbonate.*
(21b): (1R, 2S)-trans-2-(3-Chlorophenyl)-cyclopent-3-enol.
(21c): (1R, 4R)-trans-4-(3-Chlorophenyl)-cyclopent-2-enol.
(22b): (1R, 2S)-trans-2-(3-Methoxyphenyl)-cyclopent-3-enol.
(23) : \((1R, 2S)\)-trans-2-(3-Methylphenyl)-cyclopent-3-enyl ethylcarbonate.

(24) : \((1R, 2S)\)-trans-2-(2-Naphthalenyl)- cyclopent-3-enyl ethylcarbonate.
(23b): (1R, 2S)-trans-2-(3-Methylphenyl)-cyclopent-3-enol.
(24b) \((1R, 2S)\)-trans-2-(2-Naphthalenyl)-cyclopent-3-enol.

(26): (1R, 2S)-trans-2-(2-Methylphenyl)-cyclopent-3-enyl ethylcarbonate.
(25b): (1R, 2S)-trans-2-(1-Naphthalenyl)-cyclopent-3-enol.

(25c): (1R, 4R)-trans-4-(1-Naphthalenyl)-cyclopent-2-enol.
(26b): (1R, 2S)-trans-2-(2-Methylphenyl)-cyclopent-3-enol.

(28): (1R, 2S)-trans-2-(2-phenylvinyl)-cyclopent-3-enyl ethyl carbonate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):
(30b): *trans-(1R,4R)-4-(4-Trifluoromethylphenyl)-cyclopent-2-enol*.

**$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):**

![NMR spectrum of trans-(1R,4R)-4-(4-Trifluoromethylphenyl)-cyclopent-2-enol](image)

**$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):**

![NMR spectrum of trans-(1R,4R)-4-(4-Trifluoromethylphenyl)-cyclopent-2-enol](image)
(31b): *trans-*(1R,2S)-2-(4-Methoxy-3-methylphenyl)-cyclopent-3-enol.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(32b): trans-\((1R,4R)-4\)-(4-Methoxy-3-methylphenyl)-cyclopent-2-enol.

\[ \text{MeO} \]
\[ \text{Me} \]
\[ \text{OH} \]

\(^1\)H NMR 400 MHz (CDCl₃, 25 °C):

\(^{13}\)C NMR 100 MHz (CDCl₃, 25 °C):
(33b): trans-\((1R,4R)\)-4-(3-Methoxyphenyl)-cyclopent-2-enol.

\(^1\)H NMR 400 MHz (CDCl₃, 25 °C):

\(^{13}\)C NMR 100 MHz (CDCl₃, 25 °C):
(34b): \((1R, 4R)\)-trans-4-(4-Methoxycarbonylphenyl)-cyclopent-2-enol.
(35b): \textit{trans-}(1R,2S)-2-(3-Fluoro-5-methoxyphenyl)-cyclopent-3-enol.

\begin{center}
\includegraphics[width=0.3\textwidth]{structure.png}
\end{center}

\textbf{\textsuperscript{1}H NMR 400 MHz (CDCl$_3$, 25 \textdegree C)}:

\begin{center}
\includegraphics[width=0.8\textwidth]{hnmr.png}
\end{center}

\textbf{\textsuperscript{13}C NMR 100 MHz (CDCl$_3$, 25 \textdegree C)}:

\begin{center}
\includegraphics[width=0.8\textwidth]{cnmr.png}
\end{center}
(36b): trans-(1R,4R)-4-(3-Fluoro-5-methoxyphenyl)-cyclopent-2-enol.

\[
\text{OMe} \\
\text{F}
\]

$^1H$ NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}C$ NMR 100 MHz (CDCl$_3$, 25 °C):
(37b): trans-\((1R,2S)\)-2-(3-Bromophenyl)-cyclopent-3-enol.

\[ \text{trans-\((1R,2S)\)-2-(3-Bromophenyl)-cyclopent-3-enol.} \]

\[ \begin{align*}
\text{\textbf{1H NMR 400 MHz (CDCl}_3, \text{ 25 °C):}} \\
\text{\textbf{13C NMR 100 MHz (CDCl}_3, \text{ 25 °C):}}
\end{align*} \]
(38b): trans-(IR,4R)-4-(3-Bromophenyl)-cyclopent-2-enol.

\[ \begin{align*}
& \text{\textsuperscript{1}H NMR 400 MHz (CDCl\textsubscript{3}, 25 °C):} \\
& \text{\textsuperscript{13}C NMR 100 MHz (CDCl\textsubscript{3}, 25 °C):}
\end{align*} \]
(39b): \((1R, 2S)-\text{trans}-2-(3'-\text{Methoxycarbonylphenyl})\text{-cyclopent-3-enol}\).

\[\text{\textsuperscript{1}H NMR 400 MHz (CDCl}_3, 25 \, ^\circ\text{C):}\]

(40b): \((1R, 4R)-\text{trans}-4-(3'-\text{Methoxycarbonylphenyl})\text{-cyclopent-2-enol}\).

\[\text{\textsuperscript{1}H NMR 400 MHz (CDCl}_3, 25 \, ^\circ\text{C):}\]
(41b): *trans-(1R,2S)-2-(4-Methylsulfanylphenyl)-cyclopent-3-enol.*

**$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):**

**$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):**
(42b): *trans*-(1R,4R)-4-(4-Methylsulfanylphenyl)-cyclopent-2-enol.

**$^1$H NMR 400 MHz (CDCl₃, 25 °C):**

![NMR spectrum](image)

**$^{13}$C NMR 100 MHz (CDCl₃, 25 °C):**

![NMR spectrum](image)
(43b): trans-(1R,2S)-2-(4-Fluoro-3-methylphenyl)-cyclopent-3-enol.

\[ \text{OH} \]

\[ \text{Me} \]

\[ \text{F} \]

**\(^1\text{H NMR 400 MHz (CDCl}_3\), 25 °C}:**

![1H NMR spectrum](image1)

**\(^{13}\text{C NMR 100 MHz (CDCl}_3\), 25 °C}:**

![13C NMR spectrum](image2)
(44b): trans-\((1R,4R)-4-(4\text{-fluoro-3-methylphenyl})\text{-cyclopent-2-enol}\).

**\(^1\text{H NMR} 400 MHz (CDCl}_3, 25 \, ^\circ\text{C)}:**

![NMR Spectrum](image)

**\(^{13}\text{C NMR} 100 MHz (CDCl}_3, 25 \, ^\circ\text{C)}:**

![NMR Spectrum](image)

(47b): \((1R, 4R)\)-trans-4-(4-Methoxyphenyl)-cyclopent-2-enol.
(48b): *trans-(1R,2S)-2-(2'-Fluoro-5'-methylphenyl)-cyclopent-3-enol*

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):
(49-b) trans-(IR,AS)-4-(2'-Fluoro-5'-methylphenyl)-cyclopent-2-enol

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
trans-\((1R,2S)\)-2-(2-Fluorophenyl)-cyclopent-3-enol.

\[^1\text{H} \text{NMR} \ 400 \text{MHz} \ (\text{CDCl}_3, \ 25 ^\circ \text{C})\]:

\[^{13}\text{C} \text{NMR} \ 100 \text{MHz} \ (\text{CDCl}_3, \ 25 ^\circ \text{C})\]:
trans-(1R,4R)-4-(2-Fluorophenyl)-cyclopent-2-enol.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^13$C NMR 100 MHz (CDCl$_3$, 25 °C):
(52b): *trans-(1R,2S)-2-(Thiophen-3-yl)-cyclopent-3-enol.*

\[
\text{\textit{H NMR} 400 MHz (CDCl}_3, 25 ^\circ\text{C):}
\]

\[
\text{\textit{C NMR} 100 MHz (CDCl}_3, 25 ^\circ\text{C):}
\]
(53b): trans-(1R,4R)-4-(Thiophen-3-yl)cyclopent-2-enol.

\[
\text{\textsuperscript{1}H NMR 400 MHz (CDCl\textsubscript{3}, 25 °C):}
\]

\[
\text{\textsuperscript{13}C NMR 100 MHz (CDCl\textsubscript{3}, 25 °C):}
\]
(76) [(Xylyl-P-Phos)Rh (σ-enyl[CH₂CHCH₂OC₂Et])OH(OEt)]

$^1$H NMR 400 MHz (THF-$d_8$, 25 °C):

![NMR Spectrum](image1)

(77) [(cod)Rh (σ-enyl[CH₂CHCH₂OC₂Et])OH(OEt)]

$^1$H NMR 400 MHz (THF-$d_8$, 25 °C):

![NMR Spectrum](image2)
APPENDIX B

SPECTRAL DATA OF NEW COMPOUNDS

— CHAPTER 3 —
(1a) *meso*-2,3-Diazabicyclo[2.2.1]hept-5-ene-*N,N*-diethyl dicarboxylate

(1b) *meso*-2,3-Diazabicyclo[2.2.1]hept-5-ene-*N,N*-dibenzyl dicarboxylate
(1c): meso-2,3-Diazabicyclo[2.2.1]hept-5-ene-N,N'-di-tert-butyl dicarboxylate

(1d): meso-2,3-Diazabicyclo[2.2.1]hept-5-ene-N,N'-phthalazide
(14a): trans-$N,N'$-(2-Phenylcyclopent-3-enyl)-diethylhydrazine dicarboxylate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^1$C NMR 100 MHz (CDCl$_3$, 25 °C):
(14b): *trans*-N,N'-(2-Phenylcyclopent-3-enyl)-dibenzylhydrazine dicarboxylate.

**H NMR 400 MHz (CDCl₃, 25 °C):

![NMR Spectra](image-url)

(14c): *trans*-N,N'-(2-Phenylcyclopent-3-enyl)-di-tert-butylhydrazine dicarboxylate.

**H NMR 400 MHz (CDCl₃, 25 °C):

![NMR Spectra](image-url)

**C NMR 100 MHz (CDCl₃, 25 °C):

![NMR Spectra](image-url)
(14d): *trans*-4-Hydroxy-2-(2'-phenylcyclopent-3'-enyl)-2*H*-phthalazin-1-one.

**\(^1H\) NMR 400 MHz (CDCl\(_3\), 25 °C):**

[Image of NMR spectrum]

**\(^13C\) NMR 100 MHz (CDCl\(_3\), 25 °C):**

[Image of NMR spectrum]

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

(16): trans-(2-Phenylcyclopentyl)-hydrazinium trifluoroacetate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):
(18c) Di-tert-butyl 5-phenyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate

$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (100 MHz, CDCl$_3$)
(19a): *trans*-N,N'-[2-(4'-Trifluoromethylphenyl)-cyclopent-3-enyl]-dibenzylhydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):
(19c): trans-$N,N'$-[2-(4'-Trifluoromethylphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate.
(20a): trans-N,N’-[2-(3’,4’-Dimethoxyphenyl)-cyclopent-3-enyl]-dibenzylhydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):
(20c): trans-$N,N'$-[2-(3',4'-Dimethoxyphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(21a): \textit{trans-}N,N'\textit{-}[2-(4'\textit{-Methoxy-2'-methyl-phenyl})-cyclopent-3-enyl]-diethylhydrazine dicarboxylate.

$^1\text{H NMR}$ 400 MHz (CDCl$_3$, 25 °C):

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]
\[ \text{Me} \quad \text{OMe} \]

\(^1\text{H NMR} 400 \text{ MHz (CDCl}_3, 25 ^\circ \text{C):}\)

\[^{13}\text{C NMR} 100 \text{ MHz (CDCl}_3, 25 ^\circ \text{C):}\]
(22a) *trans*-N,N'-[2-(2'-Methylphenyl)-cyclopent-3-enyl]-diethylhydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):
(22c): trans-N,N’-[2-(2’-Methylphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate.

\[ \text{HN} \quad \text{Boc} \]

\[ \text{Me} \]

\[ \begin{array}{c}
\text{HN} \\
\text{Boc} \\
\text{Me}
\end{array} \]

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(23a): *trans*-N,N’-[2-(2’-Methoxycarbonylphenyl)-cyclopent-3-enyl]-diethylhydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):
(24): trans-\(N,N'\)-[2-(2'-Fluorophenyl)-cyclopent-3-enyl]-di-\(\text{tert}\)-butylhydrazine dicarboxylate

\(\text{HN} \quad \text{N} \quad \text{Boc} \quad \text{Boc} \quad \text{F} \)

\(\text{HN} \quad \text{N} \quad \text{Boc} \quad \text{Boc} \quad \text{F} \)

\(^1\text{H NMR} 400 \text{ MHz} (\text{CDCl}_3, 25 ^\circ \text{C})\):

\(^{13}\text{C NMR} 100 \text{ MHz} (\text{CDCl}_3, 25 ^\circ \text{C})\):
(25c): trans-$N,N'$-[2-(2'-Methoxyphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):

\[ \text{HN}^\text{Boc} \quad \text{N}^\text{Boc} \]

\[ ^1H \text{NMR} \ 400 \text{MHz (CDCl}_3, 25^\circ\text{C)):} \]

\[ ^{13}C \text{NMR} \ 100 \text{MHz (CDCl}_3, 25^\circ\text{C}): \]
(27): trans-N,N'-[2-(4'-Fluoro-2'-methoxyphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate.

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

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\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

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\[ \text{F} \quad \text{MeO} \]

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\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]

\[ \text{F} \quad \text{MeO} \]

\[ \text{HN} \quad \text{HN} \quad \text{Boc} \quad \text{Boc} \]
(28): trans-\(N,N^{\prime}\)-[2-(5′-Chloro-2′-methoxyphenyl)-cyclopent-3-enyl]-di-\(\textit{tert}\)-butylhydrazine dicarboxylate.

\[\text{HN Boc} \quad \text{Boc} \quad \text{Cl} \quad \text{MeO}^{-}\]

\(^1\text{H NMR} 400 \text{ MHz (CDCl}_3, 25 \degree \text{C}):\]

\(^{13}\text{C NMR} 100 \text{ MHz (CDCl}_3, 25 \degree \text{C}):\]

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(31): trans-N,N’-[2-(4’-Methoxycarbonylphenyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(38): 5-(3'-Thiophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-\textit{tert}-butyl dicarboxylate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(40): 5-(2′,4′-Dimethoxypyrimidin-5-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate.

**^1H NMR 400 MHz (CDCl₃, 25 °C):**

![NMR spectrum of 1H](image)

**^13C NMR 100 MHz (CDCl₃, 25 °C):**

![NMR spectrum of 13C](image)
(d-40): 5-(6'-Deuterio-2',4'-dimethoxypyrimidin-5-yl)-2,3-diazabicyclo-[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate.

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^13$C NMR 100 MHz (CDCl$_3$, 25 °C):
(46): 5-(2'-Fluorophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate.

\[ \text{NMR Spectra from Chapter 3} \quad 288 \]

\[ \text{\textsuperscript{1}H NMR 400 MHz (CDCl\textsubscript{3}, 25 °C):} \]

\[ \text{\textsuperscript{13}C NMR 100 MHz (CDCl\textsubscript{3}, 25 °C):} \]
(47): 5-(4'-Trifluoromethylphenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-di-tert-butyl dicarboxylate.

\[ \text{NMR Spectra from Chapter 3} \]

\( ^1H \text{ NMR} \) 400 MHz (CDCl\textsubscript{3}, 25 °C):

\( ^{13}C \text{ NMR} \) 100 MHz (CDCl\textsubscript{3}, 25 °C):
(48) 2,3-di-tert-butyl 5,5′-(1,2-phenylene)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate)

\[
\begin{align*}
\text{\textsuperscript{1}H NMR} & \quad (500 \text{ MHz, CDCl}_3) \\
\text{\textsuperscript{13}C NMR} & \quad (125 \text{ MHz, CDCl}_3)
\end{align*}
\]
(54a) di-tert-butyl 5-(1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate

\[ \text{NMR Spectra from Chapter 3} \]

\[ \text{\(^1H\) NMR (500 MHz, CDCl}_3\)} \]

\[ \text{\(^1C\) NMR (125 MHz, CDCl}_3\)} \]
(54b) di-tert-butyl 5-(1-(tert-butoxycarbonyl)-1H-pyrrol-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate

\[ \text{\textsuperscript{\emph{H}} NMR (500 MHz, CDCl\textsubscript{3})} \]

\[ \text{\textsuperscript{\emph{13}C NMR (125 MHz, CDCl\textsubscript{3})} \]
(55) di-tert-butyl 1-(2-(2-chlorophenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{)} & \\
\text{ppm (f1)} & \\
\text{C NMR (100 MHz, CDCl}_3\text{)} & \\
\text{ppm (f1)}
\end{align*}
\]
(59a) di-tert-butyl 1-(2H-pyrrol-3-yl)cyclopent-3-enylhydrazine-1,2-dicarboxylate

^1H NMR (500 MHz, CDCl₃)

^13C NMR (125 MHz, CDCl₃)
(59b) di-tert-butyl 1-(2-(1-(tert-butoxycarbonyl)-1H-pyrrolyl-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate

$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
(56) 2,3-di-tert-butyl 5,5’-(1-((tert-butoxycarbonyl)-1H-pyrrole-3,4-diyl)bis(2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate)

\[\text{NMR (500 MHz, CDCl}_3\text{)}\]

\[\text{C NMR (125 MHz, CDCl}_3\text{)}\]
(57) di-tert-butyl 5-(2-(5-(1,2-bis(tert-butoxycarbonyl)hydrazinyl)cyclopent-2-enyl)furan-3-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate

$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
(58) di-tert-butyl 5-(2-chlorophenyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate

\[ \text{NMR Spectra from Chapter 3} \]

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_3) \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) \]
APPENDIX C

SPECTRAL DATA OF NEW COMPOUNDS

— CHAPTER 4 —
(31a) *meso*-2,3-Diazabicyclo[2.2.1]hept-5-ene-\(N,N'\)-diethyl dicarboxylate

(31b) *meso*-2,3-Diazabicyclo[2.2.1]hept-5-ene-\(N,N'\)-di-\textit{tert}-butyl dicarboxylate
(31c) *meso*-2,3-Diazabicyclo[2.2.1]hept-5-ene-*N,N'*-dibenyl dicarboxylate

![Chemical Structure](image1)

(31d) *meso*-2,3-Diazabicyclo[2.2.1]hept-5-ene-*N'*-bis(2',2',2'-trichloroethyl)dicarboxylate

![Chemical Structure](image2)
(33a) *trans-N,N'-*(2-Benzoylcyclopent-3-enyl)-diethylhydrazine dicarboxylate*

\[
\text{\H NMR 400 MHz (CDCl}_3\text{, 25 °C):}
\]

\[
\text{\C NMR 100 MHz (CDCl}_3\text{, 25 °C):}
\]
(33b) *trans-N,N’-(2-Benzoylcyclopent-3-enyl)-di-tert-butylhydrazine dicarboxylate*

\[\begin{align*}
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}\]

**\(^1H\) NMR 400 MHz (CDCl\(_3\), 25 °C):**

![\(^1H\) NMR Spectrum]

**\(^{13}C\) NMR 100 MHz (CDCl\(_3\), 25 °C):**

![\(^{13}C\) NMR Spectrum]
(33c) *trans*-N,N'- (2-Benzoylcyclopent-3-enyl)-dibenzylhydrazine dicarboxylate

\[ \text{H NMR} 400 MHz (CDCl}_3, 25 \, ^\circ\text{C):} \]

\[ \text{ppm (f1)} \]

\[ \text{13C NMR} 100 MHz (CDCl}_3, 25 \, ^\circ\text{C):} \]

\[ \text{ppm (f1)} \]
(33d) trans-$N,N'$-(2-Benzoyl-cyclopent-3-enyl)-bis(2',2',2'-trichloroethyl)-hydrazine dicarboxylate

$^1$H NMR $400$ MHz (CDCl$_3$, $25 \degree$C):

$^{13}$C NMR $100$ MHz (CDCl$_3$, $25 \degree$C):
(34) *trans*-N,N’-[2-(4’-Methoxybenzoyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate

**1H NMR 400 MHz (CDCl3, 25 ℃):**

![1H NMR spectrum](image)

**13C NMR 100 MHz (CDCl3, 25 ℃):**

![13C NMR spectrum](image)
(35) trans-$N,N'$-[2-(3'-Methoxybenzoyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate

\[
\begin{align*}
\text{MeO-} & \\
\text{HN} & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(36) trans-\(N,N'\)-[2-(2'-Methyl-4'-methoxybenzoyl)-cyclopent-3-enyl]-di-\(tert\)-butylhydrazine dicarboxylate

\[ \text{MeO} \]

\( ^1H\) NMR 400 MHz (CDCl\(_3\), 25 °C):

\( ^{13}C\) NMR 100 MHz (CDCl\(_3\), 25 °C):
(37) *trans*-N,N’-[2-(2’-Methylbenzoyl)-cyclopent-3-enyl]-di-tert-butylhydrazine dicarboxylate

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{HN} & \\
\text{O} & \quad \text{O}
\end{align*}
\]

\[\text{1H NMR 400 MHz (CDCl}_3, 25 \, ^\circ\text{C)}:\]

\[\text{ppm (t1)}\]

\[\text{1C NMR 100 MHz (CDCl}_3, 25 \, ^\circ\text{C)}:\]

\[\text{ppm (t1)}\]
(38) *trans*-N,N’-[2-(3’-Methylbenzoyl)-cyclopent-3-enyl]-di-(*tert*-butyl)hydrazine dicarboxylate

**1H NMR 400 MHz (CDCl₃, 25 °C):**

![1H NMR spectrum](image)

**13C NMR 100 MHz (CDCl₃, 25 °C):**

![13C NMR spectrum](image)
(39) *trans*-N,N'-[2-(4'-Methylbenzoyl)-cyclopent-3-enyl]-di-(tert-butyl)hydrazine dicarboxylate

![Chemical Structure](image)

**^1H NMR 400 MHz (CDCl₃, 25 °C):**

![NMR Spectrum](image)

**^13C NMR 100 MHz (CDCl₃, 25 °C):**

![NMR Spectrum](image)
(40) trans-N,N'-[2-(2'-Naphthoyl)-cyclopent-3-enyl] di-(tert-butyl)hydrazine dicarboxylate

\[
\begin{align*}
\text{1H NMR } & 400 \text{ MHz (CDCl}_3, \text{ 25 }^{\circ}\text{C):}
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR } & 100 \text{ MHz (CDCl}_3, \text{ 25 }^{\circ}\text{C):}
\end{align*}
\]
(41): trans-$N,N'$-[2-(3'-Trimethylsilylbenzoyl)-cyclopent-3-enyl]-di-(tert-butyl)hydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(42) trans-$N,N'$$-$[2-(3'-Vinylbenzoyl)-cyclopent-3-enyl] di-(tert-butyI)hydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 $^\circ$C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 $^\circ$C):
(43) trans-\(N,N'\)-[2-(4'-Chlorobenzoyl)-cyclopent-3-enyl]-di-(tert-butyl)hydrazine dicarboxylate

\[
\begin{align*}
\text{\text{H NMR} } & 400 \text{ MHz (CDCl}_3, 25 ^\circ\text{C):} \\
\text{ppm (t1)} & \\
\text{8.0} & \text{7.0} & \text{6.0} & \text{5.0} & \text{4.0} & \text{3.0} & \text{2.0} & \text{1.0} & 0.0 \\
\text{13C NMR} & 100 \text{ MHz (CDCl}_3, 25 ^\circ\text{C):} \\
\text{ppm (t1)} & \\
\text{200} & \text{150} & \text{100} & 50 & 0 
\end{align*}
\]
(44) *trans*-N,N*- [2-(4'-Fluorobenzoyl)-cyclopent-3-enyl]-di-(tert-butyl)hydrazine dicarboxylate

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \\
\text{F} & 
\end{align*}
\]

\[1^1H\text{ NMR } 400 MHz (CDCl}_3, 25^\circ\text{C):}\]

\[\begin{array}{c}
\text{ppm (t1)}
\end{array}\]

\[\begin{array}{c}
8.0 & 7.0 & 6.0 & 5.0 & 4.0 & 3.0 & 2.0 & 1.0 & 0.0
\end{array}\]

\[1^3C\text{ NMR } 100 MHz (CDCl}_3, 25^\circ\text{C):}\]

\[\begin{array}{c}
\text{ppm (t1)}
\end{array}\]

\[\begin{array}{c}
1 & 150 & 100 & 50 & 0
\end{array}\]
(45) *trans*-N,N'-[2-(4'-Trifluoromethylbenzoyl)-cyclopent-3-enyl]-di-(tert-butyl)hydrazine dicarboxylate

**$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):**

**$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):**
(46): trans-$N,N'$-[2-(3'-Nitrobenzoyl)-cyclopent-3-enyl]-di-(tert-butyl)hydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(47) trans-$N,N'$-[2-(3'-Thiophenoyl)-cyclopent-3-enyl]-di-(tert-butyl)hydrazine dicarboxylate

$^1$H NMR 400 MHz (CDCl$_3$, 25 °C):

$^{13}$C NMR 100 MHz (CDCl$_3$, 25 °C):
(48) *trans*-\(N,N'\)-[2-(3'-(E)-Phenylacryloyl)-cyclopent-3-enyl]-di-(\textit{tert}-butyl)hydrazine dicarboxylate

\[
\begin{align*}
\text{H NMR} &\quad 400 \text{ MHz (CDCl}_3, 25 \^\circ\text{C):} \\
\text{ppm } (\text{t1}) &\quad 0.0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0
\end{align*}
\]

\[
\begin{align*}
\text{C NMR} &\quad 100 \text{ MHz (CDCl}_3, 25 \^\circ\text{C):} \\
\text{ppm } (\text{t1}) &\quad 0, 50, 100, 150, 200
\end{align*}
\]
(63): [Rh(IMes)(cod)Cl]

\[ ^1H \text{ NMR} \ 400 \text{ MHz} (\text{C}_6\text{D}_6, 25 \degree \text{C}) : \]

\[ ^1H \text{ NMR} \ 400 \text{ MHz} (\text{CDCl}_3, 25 \degree \text{C}) : \]
(66): $\text{[Rh(IMes)(CO)$_2$Cl]}$

$^1$H NMR 400 MHz ($\text{C}_6\text{D}_6$, 25 °C):

(67): Putative formation of $\text{[Rh(IMes)(CO)$_2$(cod)]BF}_4$

$^1$H NMR 400 MHz ($\text{C}_6\text{D}_6$, 25 °C):
(68): Putative formation of \([\text{Rh(IMes)(CO)}_2(\eta^1-O[p-\text{FC}_8\text{H}_4\text{B(OH)}_2])\text{BF}_4]\)

\(^1\text{H NMR} 400 \text{ MHz (C}_6\text{D}_6, 25 \degree \text{C}):\)

(69/70?): Putative formation of \([\text{Rh(IMes)(CO)}_2(p-\text{FC}_8\text{H}_4)]\) or \([\text{Rh(IMes)(CO)}(p-\text{FC}_8\text{H}_4\text{CO})]\)

\(^1\text{H NMR} 400 \text{ MHz (C}_6\text{D}_6, 25 \degree \text{C}):\)
(83): 2-Methyl-3,4-diphenylcyclopent-2-enone

$^1$H NMR 400 MHz (CD$_2$Cl$_2$, 25 °C):