Doctoral Thesis

Chiral olefins as novel ligands in asymmetric synthesis and the development of water and ammonia equivalents in iridium-catalyzed allylic substitution

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Chiral Olefins as Novel Ligands in Asymmetric Synthesis and the Development of Water and Ammonia Equivalents in Iridium-Catalyzed Allylic Substitution

A dissertation submitted to

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For the degree of

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Presented by

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Zürich 2007
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Publications

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Iridium-Catalyzed Synthesis of Primary Allylic Amines From Allylic Alcohols: Sulfamic Acid as Ammonia Equivalent.

Lyothier, L; Defieber, C.; Carreira, E. M.
Iridium-Catalyzed Enantioselective Synthesis of Allylic Alcohols: Silanolates as Hydroxide Equivalents.

Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M.
Asymmetric Synthesis of 3,3-Diarylpropanals with Chiral Diene-Rh Complexes.

Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M.
Catalytic Asymmetric Synthesis with Rh-Diene Complexes: 1,4-Addition of Arylboronic Acids to Unsaturated Esters.

Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M.
Chiral [2.2.2]-Dienes as Ligands for Rh(I) in Conjugate Additions of Boronic Acids to a Wide Range of Acceptors.

Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M.
Readily Available [2.2.2]-Bicyclooctadienes as New Chiral Ligands for Ir(I): Catalytic, Kinetic Resolution of Allylic Carbonates.

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Abstract

The straightforward synthesis of optically active pharmaceuticals is of prime importance, not only to improve efficiency in the production of drugs, but also to deliver safer and more active pharmaceuticals. Metal-catalyzed asymmetric processes offer one of the most efficient ways to introduce new stereogenic centers. Hence, the development of novel chiral ligands that can effectively induce asymmetry in reactions is crucial in modern organic synthesis.

While many known chiral ligands bind to a metal via heteroatoms, most notably phosphorus or nitrogen, chiral ligands that coordinate to metals via carbon atoms (chiral olefin units) have received little attention. However, there are stable, achiral metal complexes, i.e. \([\text{IrCl(cod)}]_2\) or \([\text{RhCl(C}_2\text{H}_4)]_2\) that possess olefins as ligands. Based on this precedence, the synthesis and application of the substituted chiral bicyclo[2.2.2]octadienes I and II were carried out.

![Figure I: Chiral Bicyclo[2.2.2]octadienes](image)

As a proof of concept, the ability of I to act as a ligand was demonstrated in an Ir\(^1\)-catalyzed kinetic resolution of allylic carbonates employing phenol as nucleophile. As shown in scheme I, high enantioselectivities could be obtained with this ligand.

![Scheme I: Ir/diene-catalyzed kinetic resolution of allylic carbonates](image)

A slight modification of the synthetic route allowed to introduce a substituent at the second olefin unit of the bicyclooctadiene scaffold (ligand II), thus creating a pseudo-\(C_2\)-symmetric environment for the coordinating metal.
The modular route permits the synthesis of a library of ligands which were employed in the \( \text{Rh}^1 \)-catalyzed conjugate addition of aryl and alkenyl boronic acids to a wide range of \( \alpha,\beta \)-unsaturated acceptors. Standard substrates such as acyclic and cyclic enones provided 1,4-adducts with high yields and selectivities within several hours. More importantly, traditionally problematic substrates including \( \alpha,\beta \)-unsaturated aldehydes and esters show good performance when chiral dienes II are used (Scheme II).

![Diagram](diagram.png)

**Scheme II**: \( \text{Rh/diene-catalyzed conjugate addition of arylboronic acids to } \alpha,\beta \)-unsaturated acceptors

A representative of this class of ligands, which we termed DOLEFIN, is now commercially available in both enantiomeric forms from Sigma-Aldrich (Figure II).

**Figure II**: Commercially available chiral bicyclo[2.2.2]octadienes

In a project aimed at broadening the scope of nucleophiles for iridium-catalyzed allylic substitutions, compounds that can act as water and ammonia equivalents were investigated. Silanolates such as TESOK serve as efficient hydroxide substitutes in
Ir/phosphoramidite catalyzed allylic displacement employing achiral, linear carbonates (Scheme III). The resulting silyl ethers are transformed during work-up to the corresponding alcohols in high yields and enantioselectivities. Alternatively, the use of TIPSOK or TBSOK generates stable silyl ethers that can be carried through multi-step reaction sequences.

Scheme III: Ir/phosphoramidite-catalyzed synthesis of chiral allylic alcohols

The development of a suitable ammonia equivalent is a more challenging problem. In this vein, the chemistry of sulfamic acid (H₂NSO₃H) was examined. Sulfamic acid is a crystalline, inexpensive solid that has found only limited applications in organic synthesis. It was surprising and beneficial to observe that racemic, branched alcohols can directly be employed in the transformation without any need for further activation (e.g. as carbonates). A commercially available iridium precursor in combination with a novel phosphoramidite-based phosphorous-olefin ligand is used as the catalyst system in the process (Scheme IV).

Scheme IV: Ir/phosphoramidite-catalyzed synthesis of allylic amines from allylic alcohols
Zusammenfassung


Die meisten etablierten Liganden koordinieren via Heteroatome (vor allem Phosphor und Stickstoff) an ein Metallzentrum. Die Synthese eines katalytisch aktiven Liganden, welcher über Kohlenstoffatome (chirale Olefineinheiten) an ein Metall bindet, wurde bisher noch nicht erreicht. Vielfach werden achirale Metall-Olefinkomplexe jedoch als stabile Katalysatorvorstufen verwandt (beispielsweise [IrCl(cod)]₂ oder [RhCl(cod)]₂). Basierend auf diesem Vorwissen wurden die chiralen, enantiomerenreinen, substituierten Bicyclo[2.2.2]octadiene I und II entwickelt, welche im Rahmen einer kurzen Reaktionssequenz ausgehend von (R)-(−)-Carvon hergestellt wurden.

Eine geringfügige Veränderung des Synthesewegs ermöglichte es, einen weiteren Substituenten am Bicyclooctadien-Gerüst einzuführen (Ligand II). Das koordinierende Metall befindet sich hierdurch in einer nahezu C₂-symmetrischen Umgebung.

Der modulare Charakter der Syntheseroute ermöglichte den Aufbau einer Klasse verschiedener Liganden, welche in der Rh¹-katalysierten konjugierten Addition von Arylboronsäuren an α,β-ungesättigte Akzeptoren eingesetzt wurden. Nicht nur Standardsubstrate wie acyclische oder cyclische Enone bilden 1,4-Addukte in hohen Ausbeuten und Selektivitäten bei kurzen Reaktionsdauern, auch traditionell schwierigere Substrate wie α,β-ungesättigte Aldehyde und Ester reagierten hochselektiv unter Verwendung von Liganden des Typs II (Schema II).

Ein Vertreter dieser Klasse, welchen wir DOLEFIN nannten, kann inzwischen von Sigma-Aldrich in beiden enantiomeren Formen bezogen werden (Abbildung II).

**Schema III: Ir/Phosphoramidit-katalysierte Synthese von chiralen Allylalkoholen**

Die Entwicklung eines geeigneten Ammoniakäquivalents in allylischen Substitutionen ist ein ungleich schwierigeres Problem. In diesem Zusammenhang wurde Sulfaminsäure untersucht; ein kristalliner, günstiger Feststoff, welcher bisher lediglich begrenzten Einsatz in der organischen Synthese gefunden hat. Überraschenderweise konnten racemische, verzweigte Allylalkohole direkt in Allylamine umgesetzt werden, ohne dass eine vorhergehende Aktivierung der Substrate (beispielsweise als Carbonat) notwendig war. Der Prozess nutzt eine käufliche Iridium-Katalysatorvorstufe sowie einen neuartigen Phosphoramidit-Olefin Liganden (Schema IV).
Schema IV: Ir/Phosphoramidit-katalysierte Synthese von Allylaminen aus Allyalkoholen
**List of Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>Å</td>
<td>Ångström</td>
</tr>
<tr>
<td>°C</td>
<td>degree celsius</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>Anal.</td>
<td>Elemental analysis</td>
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<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1’-bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>c-</td>
<td>cyclo</td>
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<td>cat.</td>
<td>catalyst</td>
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<tr>
<td>cm</td>
<td>centimeter</td>
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<td>cod</td>
<td>1,5-cyclooctadiene</td>
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<tr>
<td>coe</td>
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<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>conv.</td>
<td>conversion</td>
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<tr>
<td>cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in ppm</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N)-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization</td>
</tr>
<tr>
<td>ESI</td>
<td>electron spray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
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<td>EtOAc</td>
<td>ethyl acetate</td>
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<td>ETHZ</td>
<td>Eidgenössische Technische Hochschule Zürich</td>
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<tr>
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</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HR, HRES</td>
<td>high resolution</td>
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</table>
Hz  Hertz
IR  infra-red
i  iso
J  coupling constant in Hz
K  degree Kelvin
L  liter
LDA  lithium diisopropylamide
Lit.  Literature
LOC  Laboratorium für Organische Chemie
MALDI  matrix-assisted laser desorption ionization
NMR  nuclear magnetic resonance
m  multiplet
M  molecule ion
M  molar
mbar  millibar
Me  methyl
mg  milligram
MHz  Megahertz
min  minute
mL  milliliter
mmol  millimol
mp  melting point
MS  mass spectrometry
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>nbd</td>
<td>norbornadiene</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>n.d.</td>
<td>not determined</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>v</td>
<td>vibration frequency in cm$^{-1}$</td>
</tr>
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<tr>
<td>Ph</td>
<td>phenyl</td>
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<td>ppm</td>
<td>parts per million</td>
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<tr>
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<td>quartet</td>
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<tr>
<td>quant.</td>
<td>quantitative</td>
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<tr>
<td>recryst.</td>
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<td>triplet</td>
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<td>t</td>
<td>tert</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethyl silyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
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<td>trifluoro acetic acid</td>
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<td>triisopropyl silyl</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
</tbody>
</table>
1. Chiral Olefins as Ligands in Asymmetric Catalysis

1.1. Historical Perspective

Olefins have a rich history as ligands in organometallic chemistry. One of the first organometallic complexes ever reported is Zeise’s salt, a platinum complex coordinated to an ethylene molecule (Figure 1).

\[
\text{K}_2[\text{PtCl}_4] + \text{C}_2\text{H}_4 \xrightarrow{\text{dil. HCl, 60 bar}} \text{K}[\text{C}_2\text{H}_4\text{PtCl}_3] \cdot \text{H}_2\text{O} + \text{KCl}
\]

**Figure 1:** Neutron diffraction structure of \( \text{K}[\text{C}_2\text{H}_4\text{PtCl}_3] \) (Zeise’s salt)

Since 1827, a large number of olefin complexes mostly bound with late transition-metals such as Ni, Pd, Pt, Rh or Ir have been reported in the coordination chemistry literature. In the field of asymmetric catalysis, these complexes are of great importance due to the fact that they can be conveniently employed as catalyst precursors to perform ligand exchange reactions with chiral ligands. Most of the chiral ligands used in

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asymmetric catalysis are based on heteroatoms, most notably pnicogen atoms such as N or P. The lability of olefin ligands vis à vis the strong binding affinity of pnicogen-based ligands to transition metals ensures rapid and quantitative exchange reactions which allows in situ preparation of optically active catalyst systems.

![Figure 2: Selection of commercially available transition metal-olefin complexes](image)

Although some transition metal monoolefin complexes are commercially available (Figure 2, e.g. 2, 3 and 10), most of the complexes belong to the class of diolefin donor ligands. Diolefin units such as 1,5-cyclooctadiene (cod), norbornadiene (nbd) or dicyclopentadiene (dcp) can be found in a vast array of complexes. Especially noteworthy is Pd$_2$(dba)$_3$ 8, a convenient phosphine-free source of Pd(0), which is often employed as a precursor for cross-coupling reactions. The complex Pt$_2$(dvds)$_3$ 9, also known as Karstedt’s catalyst, serves as hydrosilylation catalyst on industrial scale.

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5 Various Pd/dba ratios are often quoted for these types of complexes. It should be noted that in solution these complexes are dimeric; the precise stoichiometry depends on whether the compound has been
In pioneering studies on molecular asymmetry of olefins, Cope et al. were able to prepare the first chiral olefin.\(^8\) \((E)-\text{cyclooctene} \text{ 11}\) displays planar chirality as a consequence of restricted rotation of the olefinic hydrogens through the hexamethylene chain (Figure 3).\(^9\)

Starting from Zeise’s salt 1, complexation with a chiral amine resulted in the formation of 12. Subsequent olefin exchange with \textit{rac-}(E)-cyclooctene\(^\text{10}\) led to a pair of diastereomeric Pt complexes 13 which were separated by fractional crystallization (Scheme 1). Treatment with KCN liberated the chiral olefin 11 which showed remarkable stability (racemization barrier for \((E)-\text{cyclooctene}: 35.6 \text{ kcal mol}^{-1}\))\(^\text{11}\).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{(E)-cyclooctene – a chiral olefin}
\end{figure}


Chiral Olefins as Ligands in Asymmetric Catalysis

4 Chiral Olefins as Ligands in Asymmetric Catalysis

**Scheme 1**: a) (+)-(R)-methylbenzylamine; b) 1. (±)-trans-cyclooctene, 2. fractional crystallization with 13 being the less soluble diastereomer; c) aq. KCN.

Compared with monoolefins, diolefin complexes generally exhibit greater stability towards decomposition. This feature can be exploited in order to synthesize diolefin complexes starting from monoolefin complexes. Characteristic to metal-bound olefins is their large spectroscopic shift due to the coordination, e.g., 100-150 cm\(^{-1}\) in IR (ν C=C) or ca. 1 ppm in \(^{1}\)H NMR compared with the free olefins. Ligand exchange reactions can thus be conveniently monitored by observing the corresponding olefin signals. 1,5-Cyclooctadiene is probably the most common diolefin ligand found in late transition-metal complexes. These tub-shaped complexes are generally stable because the bite angle \(\alpha\) of cod is close to 90°; suitable for forming tetrahedral, trigonal-bipyramidal or square-planar coordination modes. Dicyclopentadiene metal complexes are rarely encountered in organometallic literature, the bite angle of this ligand is somewhat larger compared to the cod analogues. For instance, whereas cod as ligand in [PdCl\(_2\)(cod)] shows a bite angle of 86.3°, dcp in [PdCl\(_2\)(dcp)] has 92.5°.\(^{12}\) Nevertheless, dcp metal complexes were among the first metal diene complexes to be isolated. In analogy to Cope’s cyclooctene resolution, Paiaro et al. showed in 1966 that it is possible to resolve endo-dicyclopentadiene with the help of [PtCl\(_2\)(dcp)] \(^{4}\) (Scheme 2).\(^{13}\) Reaction with methanol resulted in the stereospecific formation of the exo-6-methoxy derivative 14, with the metal binding on the endo face. Treatment with (S)-(1)-phenethylamine led to a mixture of diastereomeric complexes 15 which were resolved by fractional crystallization. Subsequent acid treatment removed the chiral amine and eliminated the

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methoxy group. The resulting optically pure \([\text{PtCl}_2(\text{dcp})]\) ent-
4 was treated with aqueous sodium cyanide to release \((+)-\text{endo-dicyclopentadiene} \ 16\).

\[
\text{rac-4} \quad \boxed{14} \quad 15 \quad \text{ent-14} \quad \text{ent-4} \quad 16
\]

Scheme 2: a) MeOH; b) 1. (S)-(1)-phenethylamine, 2. fractional crystallization with 15 being the less soluble diastereomer; c) HCl, MeOH; d) boiling HCl; e) NaCN.

Some diene ligands possess smaller bite angles. For example, in norbornadiene (nbd) complexes, the bite angle \(\alpha\) towards a coordinating metal comes as narrow as \(\alpha=70^\circ\). Norbornadiene compounds have a bridging carbon atom which links the two double bonds, and this ensures a suitable arrangement of the two double bonds for coordination with the metal. Another salient feature of this bicyclic system is that the central bridge suppresses delocalization and isomerization of the two double bonds to form the more stable conjugated system. In this vein, metal complexes with 1,4-cyclohexadiene are very sensitive, and these ligands tend to readily isomerize to 1,3-cyclohexadiene metal complexes. However, benzoquinone is known to form stable complexes with various metals because isomerization is not possible.\(^\text{14}\)

Naturally occurring dienes, including chiral dienes, are also capable of forming complexes with transition metals (Figure 4). In this respect, Lewis et al. were able to isolate \([\text{RhCl(diene}^*])_2\) dimers which are treated in situ with TiC\(_5\)H\(_5\) to obtain the corresponding \((\pi\text{-cyclopentadienyl})\) rhodium complexes as orange oils (diene* = \((R)-(+)\)-limonene 17, \((R)-(−)-\)phellandrene 18, \((S)-(+)\)-carvone 19).\(^\text{15}\) \(^1\)H-NMR spectroscopic measurements demonstrated that both double bonds are coordinated to the transition metal. Schurig et al. obtained an X-ray structure of \([\text{RhCp}(+)\text{-carvone}]\) which unambiguously established complexation to both olefin moieties.\(^\text{16}\) Salzer et al. were able


to prepare [RhCp(+)-nopadiene]], a complex containing a chiral diene derived from the monoterpene (-)-myrtenal.\textsuperscript{17}

![Figure 4: Chiral dienes used for Rh(I) and Ir(I) complexes](image)

Early investigations also aimed at designing and synthesizing non-natural chiral dienes and examining their metal binding capabilities (Figure 5). Noteworthy in this respect is the synthesis of Rh-complex 21, which contains a chiral analogue of cyclooctadiene.\textsuperscript{18} Panunzi et al. reported the synthesis and complexation of TOND (1,3,5,7-tetramethyl-2,6,9-trioxobicyclo[3.3.1]nona-3,7-diene) 22,\textsuperscript{19} a chiral diene which was resolved by formation of a diastereomeric Rh complex. Iron complexes incorporating a chiral bicyclo[2.2.2]octadiene 23\textsuperscript{20} as well as cyclohexa-1,3-diene 24\textsuperscript{21} were also disclosed.

![Figure 5: Chiral dienes for Rh(I) and Fe(0) complexes](image)

However, these studies were restricted within examination of the coordination chemistry and the associated reactivity of the metal-bound olefins. No investigations were carried out to explore the potential of these complexes as catalysts for asymmetric synthesis.

1.2. Theory of Metal-Olefin bonding

In theoretical terms, the metal-alkene bond can be understood with the help of a qualitative model first developed by Dewar, Chatt and Duncanson (DCD model, Figure 6). According to this model, a σ bond is formed by donation of a pair of electrons in the π₂p orbital on the olefin to an empty hybrid orbital on the metal. This is complemented by π back-donation of electron density from a filled hybrid orbital on the metal to the initially empty π*₂p (antibonding) orbital on the olefin. The σ bond inevitably causes an unfavorable build-up of negative charge on the metal; however, the π bond relieves this, giving a synergistic effect.

\[ \text{donation} \quad \text{back donation} \]

\[
\begin{array}{c}
\text{d-orbital} \\
\text{metal} \\
\text{π-orbital} \\
\text{olefin}
\end{array}
\quad
\begin{array}{c}
\text{d-orbital} \\
\text{metal} \\
\text{π*-orbital} \\
\text{olefin}
\end{array}
\]

Figure 6: Dewar-Chatt-Duncanson model of metal-olefin bonding

In 1995, Frenking et al. developed charge distribution analysis (CDA) which allows quantifying donation and back-donation contributions in the Dewar-Chatt-Duncanson model.

When applying CDA to the analysis of a metal-ligand complex, the following orbital contributions to the charge distributions are considered: a) mixing of the occupied orbitals of the ligand and the empty orbitals of the metal fragment leading to an electron-donation term \( d \), b) mixing of the unoccupied orbitals of the ligand with the filled orbitals of the metal fragment leading to back donation \( b \); c) interaction between the occupied orbitals of the ligand and the occupied orbitals of the metal fragment leading to the repulsive polarization \( r \). Finally, the non-classical term \( \Delta \) resulting from the mixing of

\[ \text{References} \]

unoccupied orbitals on the two fragments should be virtually zero in a donor-acceptor complex, because all interactions between the fragments should arise from the mixing of occupied and unoccupied orbitals. If it turns out not to be zero, the metal-ligand complex might not be appropriately described by the DCD model, $\Delta$ thus serves as a control term.

Using this computational method *Grützmacher* investigated a variety of gold-ligand complexes (Figure 7). The study unravels that back donation plays a significant role in metal-olefin and metal-alkyne complexes. Although there is back donation to $\sigma^*$ in complexes with conventional ligands such as amines or phosphines, the donation term exceeds back-donation.

![Charge Distribution Analysis in H-Au-L complexes](image)

*Figure 7: Charge Distribution Analysis in H-Au-L complexes*

It is also possible to exploit CDA analysis to examine substituent effects of an olefin on the coordination ability (Figure 8). Some interesting trends were observed. For olefins, particularly for the electron-poor acrylonitrile, the contribution from back donation becomes important. On the other hand, in phosphines, particularly for electron-rich phosphines, electron donation makes a significant contribution to the binding. The variation of the substituents $R$ has a larger dynamic range in phosphine complexes indicating that the electronic properties of a transition metal complex may be

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more easily controlled by changing the substituent via a coordinated phosphine than those in an olefin complex. DFT calculations also allow a reliable prediction of increased bond lengths and pyramidalization of the sp²-carbons that occurs upon complexation with a transition metal.

**CDA analysis of Pt-olefin and Pt-phosphine complexes**

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**Figure 8: CDA analysis of Pt-olefin and Pt-phosphine complexes**

As early as 1969, Hogeveen et al. examined the relative stabilities of various Rh-diene complexes and studied their relative rates of ligand exchange (Figure 9). The addition of an appropriate amount of a chelating diene to a solution of a rhodium complex of a different diene gives rise to a displacement reaction according to:

\[
2 \text{diene-A} + [\text{RhCl(diene-B)}]_2 \rightleftharpoons 2 \text{diene-B} + [\text{RhCl(diene-A)}]_2
\]

\[
K = \frac{[\text{diene-B}]^2 [\text{RhCl(diene-A)}]_2}{[\text{diene-A}]^2 [\text{RhCl(diene-B)}]_2}
\]

The extent of the displacement was measured by integration of suitable NMR signals of the four components in the reaction mixtures. Equilibration was generally rapid at room temperature. The numbers indicate the equilibrium constant K between the next nearest neighbors.

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The relative order in coordination stabilities is a result of a) the geometry of the diene and b) the nature of the substituents. The most stable complexes are those of bicyclo[2.2.1]hepta-2,5-diene 25 and bicyclo[2.2.2]octa-2,5-diene 26 which have a similar bite angle and no steric hindrance around the olefin moieties. Apart from the chelate effect which is exerted by the two olefin units located in close proximity, an additional factor of these strained scaffolds might be taken into account: As pyramidalization at the ligating carbon atoms occurs upon $\eta^2$-coordination with the metal, particularly strong bonds are formed. Quantum-chemical calculations of simple model complexes with specified pyramidalization angles revealed a significant metal-alkene bond strengthening relative to the planar alkene. The major electronic effect of double bond pyramidalization is to lower the energy of the $\pi^*$ LUMO, thus making it a better acceptor of electron density from the metal.

Endo-dicyclopentadiene 16 possesses drastically reduced binding affinity towards a metal. It is presumed that the non-parallel location of the diene system and the large distance (3.12 Å) between the two double bonds are responsible for the diminished affinity of 16. Compared to the rigid bicyclic structures in 25 and 26, cyclooctadiene 28 as well as cyclooctatetraene 32 are flexible molecules. Although their bite angles seem to be optimal for coordination with a metal, their coordination involves a considerable loss of entropy compared to the free diene, thus making complex formation unfavorable. However, the equal distance between the complexed double bonds in $[\text{RhCl(cod)}]_2$ and

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\[25 > 26 > 27 = 28 > 29\]

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\[29 > 16 > 30 > 31 > 32\]
the free diene (2.87 and 2.8 Å resp.) suggest that cod can bind relatively strongly to the metal despite the unfavorable entropy effect \(^{31}\). On the other hand, the instability of the cyclooctatetraene complex is probably due to the large distance between the non-conjugated double bonds (3.12 Å) combined with the unfavorable entropy effect. Generally, electron-withdrawing substituents stabilize metal-olefin complexes; the opposite is found for electron-donating substituents. This characteristic property can be rationalized with the DCD model (\textit{vide infra}). However, steric-destabilizing effects have to be superimposed on the electronic effects. Electron-donating substituents such as in 27 or 30 lead to destabilization compared to the unsubstituted 26. The lower stabilities of the symmetrically substituted dienes 29 and 31 are rather surprising taking into account the electron-withdrawing character of the carbomethoxy group. It may well be that the favorable electronic effect is entirely counterbalanced by a large steric hindrance of the substituents.

\textbf{1.3. Chiral Dienes as Ligands in Asymmetric Catalysis}

Independently and concurrently to our work on the development of chiral dienes as ligands for transition-metal catalyzed asymmetric processes, the group of \textit{Hayashi} made important contributions in the same area. In the following paragraphs the synthesis of the various ligand scaffolds will be briefly outlined.

In 2003 the synthesis of a chiral diene serving as a ligand in an asymmetric process was disclosed by \textit{Hayashi} (Scheme 3)\(^ {32}\). The ligand is based on a bicyclo[2.2.1]heptadiene scaffold, and it was used for the asymmetric rhodium-catalyzed 1,4-addition of arylboronic acids to a range of \(\alpha,\beta\)-unsaturated compounds to provide the corresponding adducts in high yields and enantioselectivities (see chapter 2 for a detailed overview on this reaction). The synthesis starts with catalytic asymmetric hydrosilylation of norbornadiene 25 in the presence of \textit{Pd/(R)-MeO-MOP} to provide optically active diol 34 in 99% ee.\(^ {33}\) Swern oxidation and acetal protection of one of the carbonyl groups gave acetal ketone 36. The alkenyl triflate formation followed by cross-coupling with BnMgBr

\begin{footnotesize}
\begin{itemize}
\item \footcite{Ibers, J. A.; Snyder, R. G. \textit{J. Am. Chem. Soc.} 1962, 84, 495.}
\item \footcite{Hayashi, T., Ueyama, K.; Tokunaga, N.; Yoshida, K. \textit{J. Am. Chem. Soc.} 2003, 125, 11508.}
\item \footcite{Uozomi, Y.; Lee, S.-Y.; Hayashi, T. \textit{Tetrahedron Lett.} 1992, 33, 7185.}
\end{itemize}
\end{footnotesize}
in the presence of PdCl₂(dppf) and its repetition for the other carbonyl group gave 

\[(IR,4R)-2,5\text{-dibenzylbicyclo[2.2.1]hepta-2,5-diene 41.}\]

![Scheme 3](image)

**Scheme 3:**

- a) 1. HSiCl₃ (2.5 equiv), [PdCl(π-C₃H₅)₂] (0.1 mol%), (R)-MeO-MOP (0.2 mol%), 2. KF, KHCO₃, H₂O₂, 78%;
- b) PDC (3.4 equiv), DMF, 73%;
- c) ethylene glycol (1 equiv), p-TsOH (cat.), 85%;
- d) 1. LDA (1.4 equiv), THF, 2. 2-PyNTf₂ (1.4 equiv), THF, 81%;
- e) BnMgBr (3.4 equiv), PdCl₂(dppf) (0.01 mol%), Et₂O, 97%;
- f) 2N HCl, THF, 94%;
- g) 1. LDA (1.5 equiv), THF, 2. 2-PyNTf₂ (1.5 equiv), THF, 70%;
- h) BnMgBr (5.5 equiv), PdCl₂(dppf) (0.01 mol%), Et₂O, 45%.

The sequential introduction of the side chains limits the synthetic efficiency of the route. A simultaneous introduction of both substituents was not viable at first due to difficulties encountered with isolation of bistriflate 42. However, recently an optimized process was disclosed which enabled simultaneous introduction of Me and Ph substituents (Scheme 4).³⁴

![Scheme 4](image)

**Scheme 4:**

- a) 1. 2-PyNTf₂ (2.4 equiv), KHMDS (2.3 equiv), THF, 85%;
- b) RMgBr (4 equiv), Fe(acac)₃ (5 mol%), THF/NMP, for R = Ph, 55%, R = Me, 50%.

A disadvantage of these bicyclo[2.2.1]heptadiene structures is their limited lifetime. A sample of Ph-nbd* 44 decomposed in CDCl₃ in less than 24 h. The origin of the instability is presumably due to the presence of a styrene moiety in a strained bicyclic[2.2.1] core. This effectively lowers the energy of the π*-orbital of the alkene rendering it highly reactive and prone to radical and acid-catalyzed decomposition. Although the phenyl substitution causes inherent instability of the ligand, this property is key for increasing the stability of the corresponding [RhCl(Ph-nbd*)]₂ complex.

An alternative ligand based on the bicyclo[2.2.2]octadiene scaffold was introduced in 2004 (Scheme 5).\textsuperscript{35} Enantiomerically pure \((IR,4R)\)-bicyclo[2.2.2]octa-2,5-dione 46 was obtained by optical resolution of racemic diketone 46 through fractional recrystallization of its hydrazone as the \((R)-5-\text{(1-phenylethyl)}\)semioxamazide. Ditriflate formation followed by cross-coupling with BnMgBr or PhMgBr gave the 2,5-disubstituted bicyclooctadienes \((R,R)\)-Ph-bod* 49 or \((R,R)\)-Bn-bod* 50, respectively. The major drawback of the synthesis is the low yield for the resolution of the key intermediate 47. Alternatively, this intermediate might be separated with the use of chiral preparative HPLC.\textsuperscript{36} Ligands 49 and 50 displayed excellent enantioselectivities in the 1,2-addition of arylboronic acids to imines.

The synthesis of a ligand based on a \([3.3.1]\) scaffold was published in 2005 (Scheme 6).\textsuperscript{37} Racemic diketone, bicyclo[3.3.1]nonane-2,6-dione 53, was prepared by treatment of dimethyl malonate 51 with paraformaldehyde (\textit{Weiss} reaction) and subsequent acid-promoted decarboxylation of intermediate 52.\textsuperscript{38} Treatment of 53 with a phenylcerium reagent followed by dehydration of the resulting diol 54 provided 2,6-diphenylsubstituted bicyclo[3.3.1]nona-2,6-diene 55. Resolution of 55 was carried out by use of a chiral stationary phase column.

\begin{align*}
\text{TMSO} & \rightarrow 45 \\
& \quad a) 1\text{-cyanovinyl acetate (1 equiv), 150 °C, 51\%}, b) 1. R*NHNH}_2, NaOAc (\text{cat.}), AcOH (\text{cat.}), 2. \text{resolution by recrystallization from MeOH, 12\%}, c) 1. 20\% H_2SO}_4, 2. \text{recrystallization from EtOH, 4.5\%}, d) \text{LDA (1.4 equiv), THF, 2. 2-PyNTf}_2 (1.4 \text{equiv}, \text{THF, 81\%}}, e) \text{BnMgBr (3.4 equiv), PdCl}_2(\text{dppf}) (0.01 \text{mol\%), Et}_2O, 97\%}.
\end{align*}

\textbf{Scheme 5:} a) 1-cyanovinyl acetate (1 equiv), 150 °C, 51%, b) 1. R*NHNH}_2, NaOAc (cat.), AcOH (cat.), 2. resolution by recrystallization from MeOH, 12%, c) 1. 20% H_2SO}_4, 2. recrystallization from EtOH, 4.5%, d) LDA (1.4 equiv), THF, 2. 2-PyNTf}_2 (1.4 equiv), THF, 81%, e) BnMgBr (3.4 equiv), PdCl}_2(dppf) (0.01 mol%), Et}_2O, 97%.

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\begin{align*}
\text{R = Ph} & \quad (R,R)\text{-Ph-bod* 49} \\
\text{R = CH}_2\text{Ph} & \quad (R,R)\text{-Bn-bod* 50}.
\end{align*}

\begin{align*}
\text{ent-46} & \rightarrow 47 \\
& \quad a) 1\text{-cyanovinyl acetate (1 equiv), 150 °C, 51\%}, b) 1. R*NHNH}_2, NaOAc (\text{cat.}), AcOH (\text{cat.}), 2. \text{resolution by recrystallization from MeOH, 12\%}, c) 1. 20\% H_2SO}_4, 2. \text{recrystallization from EtOH, 4.5\%}, d) \text{LDA (1.4 equiv), THF, 2. 2-PyNTf}_2 (1.4 \text{equiv}, \text{THF, 81\%}}, e) \text{BnMgBr (3.4 equiv), PdCl}_2(\text{dppf}) (0.01 \text{mol\%), Et}_2O, 97\%}.
\end{align*}

\begin{align*}
\text{ent-46} & \rightarrow 47 \\
& \quad a) 1\text{-cyanovinyl acetate (1 equiv), 150 °C, 51\%}, b) 1. R*NHNH}_2, NaOAc (\text{cat.}), AcOH (\text{cat.}), 2. \text{resolution by recrystallization from MeOH, 12\%}, c) 1. 20\% H_2SO}_4, 2. \text{recrystallization from EtOH, 4.5\%}, d) \text{LDA (1.4 equiv), THF, 2. 2-PyNTf}_2 (1.4 \text{equiv}, \text{THF, 81\%}}, e) \text{BnMgBr (3.4 equiv), PdCl}_2(dppf) (0.01 mol%), Et_2O, 97\%}.
\end{align*}

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Scheme 6: a) paraformaldehyde, piperidine, reflux, 56%; b) AcOH, H₂O, HCl, reflux, 67%; c) PhLi, CeCl₃, THF; d) POCl₃, pyridine, 95% (over 2 steps); e) resolution by chiral preparative HPLC.

A major challenge in the preparation of chiral dienes is enantiomer separation at one point in their synthesis. Whereas asymmetric catalysis, classical resolution of intermediates or chromatographic separation of enantiomers using a chiral stationary column provide solutions to this problem, Grützmacher employed a classical organometallic approach: the enantiomers are resolved by complexation to a chiral Rh-diamine complex and subsequent crystallization of the resulting diastereomeric complex (Scheme 7).³⁹

Scheme 7: a) BF₃·OEt₂ (1.5 equiv), TMSCH₂N₂ (1.5 equiv), CH₂Cl₂, 70%; b) CeCl₃ (1.4 equiv), PhMgBr, THF/Et₂O, 88%; c) CF₃CO₂H, 93%; d) 1. [RhCl(CO)₂]₂, CH₂Cl₂, 2. AgOTf, MeCN, 73%; e) (R)-(+)-1,1’-binaphthyl-2,2’-diamine (1 equiv), CH₂Cl₂, precipitation in EtOH/hexane at 4 °C, 32%; f) CF₃SO₃H, MeCN, 95%.

The synthesis of 62 started from commercially available dibenzosuberone 56. Ring-expansion by treatment with TMSCHN₂, subsequent addition of a phenylcerium reagent and dehydration provided 59. Complexation with Rh(I) and ligand exchange with optically pure (+)-1,1’-binaphthyl-2,2’-diamine yielded in a mixture of diastereomeric

complexes 61. Precipitation in a mixture of EtOH and hexanes resulted in the formation of diastereomerically pure 61 which could be liberated from the chiral diamine by treatment with triflic acid.

The same concept was adapted by Hayashi to resolve 1,5-disubstituted diphenyl-1,5-cyclooctadiene 64 (Scheme 8).40 Starting from 1,5-dibromo-1,5-cyclooctadiene 63 palladium-catalyzed cross-coupling with PhMgBr afforded the 1,5-diphenylcyclo-1,5-octadiene 64. Treatment of the diene with [RhCl(C₂H₄)₂]₂ in benzene brought about ligand substitution giving 65. Applying Grützmacher’s method, 65 was resolved in its diastereomerically pure complexes by coordination with (+)-1,1'-binaphthyl-2,2'-diamine and recrystallization to give 66. Acid treatment liberated the rhodium dimer 65 which was used as catalyst precursor. Applied in the rhodium-catalyzed 1,4-addition of phenylboronic acid to cyclohexenone, Hayashi found that the enantiomeric purity of the 1,4-adduct is strongly dependent on the progress of the reaction: the higher % ee at the lower conversion. For example, when the reaction was stopped after 20 min optically enriched product was obtained in 91% ee, but only 3% yield. After 6 hours reaction time the 1,4-adduct was isolated in 90% yield, but only 43% ee. A possible explanation invokes racemization of the catalyst under the reaction conditions, i.e. dissociation of the diene from rhodium and recoordination on the other enantioface.

Scheme 8: a) PhMgBr (4 equiv), PdCl₂(dppf) (2 mol%), Et₂O, 90%; b) [RhCl(C₂H₄)₂]₂ (1.2 equiv), benzene, 99%; c) 1. (R)-1,1'-binaphthyl-2,2'-diamine (1 equiv), AgBF₄ (1.1 equiv), CH₂Cl₂, 99%; 2. recrystallization from THF/benzene, 29% (58%); d) conc. HCl, MeCN, 96%; e) AgBF₄ (1.2 equiv), MeCN, 99%.

A comparison of X-ray structural data reveals some interesting properties of the different Rh-diene complexes (Figure 10). As expected, the rhodium-diene complexes based on the [2.2.1]- and [2.2.2]-bicyclic scaffold 68 and 69 show similar structural data. Both scaffolds have a bite angle for diene coordination of approximately 70°. This contrasts the [3.3.1]-bicyclononadiene based catalyst 70. The bite angle is 89°, much larger than those of the smaller ring scaffolds. Moreover, the distance from rhodium to the phenyl substituents on the olefin in 70 is slightly longer (Rh-C(l) = 3.13 Å) than that of 69 (Rh-C(l) = 3.05 Å). In complex 70, the two double bonds (Cα-Cβ) and Cα′-Cβ′) of bnd\(^*\) coordinated to the rhodium are not parallel to each other but twisted by 23°. As a result, the angles Cα-Rh-Cα′ (87°) and Cβ-Rh-Cβ′ (103°) are very different to each other. These coordination properties are very different from non-substituted cyclooctadiene complexes such as [RhCl(cod)]\(_2\) where two double bonds are oriented parallel. The twisted coordination is probably caused by the minimization of torsion in the bridging backbone. Conversely, the 1,4-cyclohexadiene framework of Ph-bod\(^*\) is highly symmetric, the two double bonds coordinated to rhodium almost parallel (1°).

An inspection of the 1,5-diphenylsubstituted cycloctadiene 65 reveals that the distance between rhodium and the carbon bonded to phenyl (Rh-Cα = 2.14 Å) is longer than that between rhodium and unsubstituted carbon (Rh-Cβ = 2.09 Å). Two double bonds are once again not parallel to each other, but slightly twisted by 9.4°.
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**Figure 10**: Comparison of various chiral diene-metal complexes

- **[RhCl(Bn-bnd*)]_2**
  - Rh-C1 = 3.16 Å, Rh-Cα = 2.12 Å, Rh-Cβ = 2.10 Å
  - ∠Cα-Rh-Cα' = 82°, ∠Cβ-Rh-Cβ' = 81°
  - ∠Ca-Cβ /Ca'-Cβ' = 1°, bite angle of the diene coordination = 70°

- **[RhCl(Ph-bnd*)]_2**
  - Rh-C1 = 3.05 Å, Rh-Cα = 2.13 Å, Rh-Cβ = 2.10 Å
  - ∠C1-Rh-C1' = 132°, ∠Cα-Rh-Cα' = 81°, ∠Cβ-Rh-Cβ' = 80°
  - ∠Ca-Cβ /Ca'-Cβ' = 1°, bite angle of the diene coordination = 72°

- **[RhCl(Tol-bnd*)]_2**
  - Rh-C1 = 3.13 Å, Rh-Cα = 2.19 Å, Rh-Cβ = 2.09 Å
  - ∠C1-Rh-C1' = 137°, ∠Cα-Rh-Cα' = 87°, ∠Cβ-Rh-Cβ' = 103°
  - ∠Ca-Cβ /Ca'-Cβ' = 23°, bite angle of the diene coordination = 89°

- **[RhCl(Ph-cod*)]_2**
  - Rh-C1 = 3.03 Å, Rh-Cα = 2.14 Å, Rh-Cβ = 2.09 Å
  - ∠C1-Rh-C1' = 149°, ∠Cα-Rh-Cα' = 93°, ∠Cβ-Rh-Cβ' = 93°
  - ∠Ca-Cβ /Ca'-Cβ' = 9.4°, bite angle of the diene coordination = 89°

- **[IrCl(Pdxcol)(MeCN)]**
  - Ir-Cα = 2.15 Å, Ir-Cβ = 2.11 Å
  - bite angle of the diene coordination = 88°
An innovative approach to make use of the well-known coordination chemistry of dibenzylideneacetone (dba) was reported by Trauner et al. in 2005 (Scheme 9). As a result of a modeling study, they reported on the synthesis of bicyclic bis(enone) 77 which forms stable complexes with Pd(0). The synthesis towards bicyclic ketone 75 was straightforward and involved enolate alkylation of cyclohexanone 72 followed by formation of a chiral imine which subsequently directed cuprate addition of methyl vinyl ketone. Hydrolysis of the imine and Robinson annulation gave rise to bicyclic ketone 75 which was treated with LDA and TMSCl to obtain 76. A bromination and dehydrobromination sequence provided bis(enone) 77 in good yield. The formation of an air- and moisture insensitive stable Pd(0) complex 78 could readily be accomplished. The stability of this complex was ascribed to the increased back-donation caused by the electron-withdrawing carbonyl-substituents at the olefin moieties. However, complex 78 showed no asymmetric induction in a Pd-catalyzed enyne cyclization.

![Scheme 9]

Scheme 9: a) LDA, THF, then MeI, 70%; b) 1. (R)-(−)-1-phenylethylamine (1.1 equiv), toluene, 2. methyl vinyl ketone (1.2 equiv), 3. MeOH, 10% aqueous KOH, 72% (over 3 steps); c) 1. Me₂CuLi, THF 2. 10% aqueous HCl, 61%; d) TMSCl, LHMDS, THF; e) 1. NBS, 2. CaCO₃, DMA, 160 °C, 36% (over 3 steps); f) Pd(OAc)₂, MeOH, 50 °C, 67%.

1.4. **Chiral Phosphine-Olefin Ligands in Asymmetric Catalysis**

Recently, the design, synthesis and application of phosphine-olefin hybrid ligands has emerged as a new promising class of ligands. Beneficial effects of different types of donors are thus combined in a single ligand framework: on the one hand, phosphorus ensures tight binding to the transition metal due to its increased coordination ability compared to an olefin (better σ-donor). On the other hand, an olefin inherits the unique opportunity to create a good chiral environment in close proximity to the transition metal.

![Scheme 10]

**Scheme 10**: a) Br₂, CCl₄, 2. KOH, MeOH, 95%; b) potassium (R)-menthylate (1.2 equiv), dioxane, 90%; c) NaBH₄, MeOH, 94%; d) thionylchloride (3 equiv); e) HPPPh₂ (1.2 equiv), 81% (over 2 steps); f) BH₃·Me₂S; g) column chromatography: (S,R)-79 (41%), (R,R)-79 (25%); morpholine.

A first representative ligand of this class was reported in 2004 by the group of **Grützmacher** (Scheme 10). Bromination and dehydrobromination of dibenzosuberone

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56 yielded in the formation of 79. Treatment with potassium menthylate and subsequent reduction of the ketone to the corresponding alcohol resulted in the formation of a 1:1 diastereomeric mixture of 80. A phosphorus donor was introduced by displacement with HPPh₂. The resulting four diastereomers 82 could be separated by column chromatography after protection of the phosphorus as a phosphine-borane complex. The resulting ligands could be applied in the context of an iridium-catalyzed hydrogenation reaction displaying moderate levels of enantioselectivity (ee range from 24 to 86%).

Scheme 11: a) 1. Br₂, CC1₄, 95%; 2. NaBH₄, MeOH, 99%; b) Pd(PPh₃)₄ (2.5 mol%), PhB(OH)₂ (1.2 equiv), Na₂CO₃, DME, EtOH, 97%; c) CF₃CO₂H, Ph₂PCl, 97%; d) 1. separation on a chiral preparative HPLC column, 2. HSiCl₃, toluene; e) [RhCl(C₂H₄)₂]₂, MeCN, 90%.

The synthesis of a hybrid phosphine-alkene ligand was significantly simplified by using a Suzuki cross-coupling approach (Scheme 11). Alcohol 84 underwent Arbuzov-like rearrangement to provide phosphine oxide 85. The enantiomers were resolved on chiral preparative HPLC columns. Reduction of 85 using HSiCl₃ gave ready access to the phosphine- and phenyl-substituted dibenzocycloheptatriene framework. Application using this ligand was found in Rh-catalyzed conjugate addition chemistry as well as Ir-catalyzed hydrogenation reactions demonstrating moderate levels of enantioselectivity (ee ranging from 30 to 67%).

In 2005 Hayashi also reported on the synthesis of a mixed phosphorus-olefin ligand (Scheme 12). Treatment of norbornene 88 with hypobromous acid led to selective formation of 89. A sequence of Swern oxidation, ketalisation and bromine-
phosphine oxide substitution gave rise to bicyclic phosphine oxide \( \text{92} \). The enantiomers were separated using chiral preparative HPLC columns. Enantiopure \( \text{92} \) was then deprotected and the ketone was converted to alkenyl triflate \( \text{94} \). Pd-catalyzed cross-coupling allowed the introduction of an aromatic substituent. Final reduction of the phosphine oxide using HSiCl\(_3\) resulted in the formation of the ligand \( \text{96} \), which has been successfully applied in a Rh-catalyzed enantioselective 1,4-addition to maleimides as well as a Pd-catalyzed enantioselective allylic alkylation.\(^{47}\) Recent kinetic studies using reaction calorimetry have shown that the Rh/\( \text{96} \) catalyst has a very high catalytic activity (considerably higher than the corresponding Rh/cod catalyst).\(^{48}\)

A recent publication from Kasák et al. discusses the synthesis of a different phosphine-olefin rhodium complex and its application in Rh-catalyzed 1,4-addition to enones (Scheme 13).\(^{49}\) Starting from dinaphthophosphepine \( \text{97} \), the side chain containing olefin functionality was selectively introduced after appropriate borane-protection of the phosphine moiety. Deprotection of the phosphine and complexation with Rh(I) afforded complex \( \text{102} \) whose X-Ray structure which unequivocally demonstrates binding via the olefin and the phosphorus atom. However, the rhodium catalyst only displayed moderate

selectivities compared to previously reported olefin-based ligands in the 1,4-addition reaction.

**Scheme 13:**
- a) BH$_3$·THF, 64%
- b) t-BuLi, PhC=CCH$_2$Br, 71%
- c) Et$_2$NH, THF, 86%
- d) [RhCl(C$_2$H$_4$)$_2$]
- e) AgBF$_4$, MeCN/THF

101
1.5. First Generation Synthesis of a Chiral Diene Ligand

In 2004 the Carreira group published a straightforward synthesis of a chiral diene which is a useful chiral ligand for the Ir(I)-catalyzed kinetic resolution of allylic carbonates (Scheme 14).51

\[
\begin{align*}
19 \xrightarrow{a)} \text{NBS, MeOH, CH}_2\text{Cl}_2, 91\% & \quad \text{b) t-BuOK, t-BuOH, THF, separation of epimers at C-5 in 104 using column chromatography, 40\%;} \\
103 \xrightarrow{b)} & \text{c) LDA, THF, then PhNTf}_2, 84\%;} \\
104 \xrightarrow{c)} & \text{d) Pd(PPh}_3)_4, \text{PhZnCl, 62\%.}}
\end{align*}
\]

Scheme 14: a) NBS, MeOH, CH₂Cl₂, 91%; b) t-BuOK, t-BuOH, THF, separation of epimers at C-5 in 104 using column chromatography, 40%; c) LDA, THF, then PhNTf₂, 84%; d) Pd(PPh₃)₄, PhZnCl, 62%.

Treatment of (R)-(−)-carvone 19 with NBS led to the selective formation of a bromonium ion which was trapped by addition of methanol.52 Thermodynamic enolisation of 103 with t-BuOK ensured a high-yielding cyclization to the bicyclic ketone 104.53 Further functionalization involved formation of an alkenyl triflate 105 which served as a convenient handle to perform palladium-catalyzed Negishi coupling as the last step.

Several attractive aspects of this synthetic route warrant special attention: Unlike all of the other chiral diene syntheses reported to date our synthesis sets the stereogenic centers by making use of the chiral pool reagent carvone.54 This commercially available, inexpensive55 terpene is accessible in both enantiomeric forms and thus allows convenient access to both enantiomers of the ligand. An additional salient feature is that chiral preparative HPLC or other types of resolution which severely limit the overall yield can be avoided. Straightforward scale-up of our synthetic route occurred without any problems. The ease of the individual steps allowed us to perform the synthesis in the

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50 The results described in this section were achieved in collaboration with Dr. C. Fischer and Dr. Takeyuki Suzuki. Their help is gratefully appreciated and acknowledged. Parts of these results are already described in: Fischer, C. Dissertation No. 15459, ETH Zürich, 2004.
52 Trapping with other alcohols (benzyl alcohol) allows introducing steric bulk at the top part of the ligand.
55 The Southern African Essential Oil Producers Asssociation quotes a price of EUR 19/kg for (-)-carvone. Seema International sells (+)-carvone for about $100/kg.
context of the AOCP I lab course by second-semester students without encountering difficulties.

In the cyclization step from 103 to 104, a roughly 1:1 mixture of epimers at C-5 was formed. For ease of interpretation of NMR data, these diastereomers were separated by column chromatography. However, both epimers can be further functionalized to give rise to diastereomeric chiral dienes which serve as equally effective ligand in transition-metal catalyzed reactions.

Another aspect that should be highlighted is the fact that the synthetic route is modular. Thus, in the last step a range of different aryl substituents can readily be introduced. In this vein, electron-rich and electron-poor substituted ligands were examined. For our purposes, sterically bulky ligands showed the highest catalytic performance (Figure 11).
1.6. Application of the Chiral Diene in an Iridium-Catalyzed Kinetic Resolution of Allylic Carbonates

1.6.1. Background Information

Asymmetric transition-metal catalyzed allylic substitution is one of the most important bond-forming reactions in organic synthesis. Not only the detailed mechanistic picture of this transformation (mostly investigated with Pd catalysts), but also related to its wide applicability in the context of total synthesis of biologically active compounds, have made this reaction the benchmark to test the efficiency of novel catalyst systems. However, the selectivity displayed in this reaction is a function of many factors, for instance the metal ion, ligands, nucleophiles and the substituents on the allyl system (Figure 12).

![Figure 12: Transition-metal catalyzed allylic substitution](image)

In this asymmetric catalysis, the studies have been primarily directed to find catalyst systems that favor the formation of branched, chiral products D in the substitution of linear, achiral products A and racemic, branched substrates B. With palladium complexes this transformation is so far only limited to special cases, whereas other metal complexes such as W- and Mo-based catalysts prefer the formation of

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branched products with high levels of regio- and enantioselectivities. It is generally assumed that in these cases the reactions proceed via π-allyl complexes which can isomerize via π−σ−π rearrangement or related processes in such a way that the sense of the stereogenic centre in the branched substrate is lost during the reaction.

Substitutions carried out with Rh, Fe, Ru or Ir complexes differ from the above as they generally proceed with a high degree of conservation of enantiomeric excess. It has been proposed that these reactions proceed via σ-allyl or π-allyl complexes which isomerize only slowly. In the context of Rh-catalyzed enantiospecific allylic substitutions, Evans invoked the presence of σ-enyl complexes F (Figure 13). The slow interconversion between F and ent-F compared to nucleophilic attack (k3 > k2) leads to a preservation of the original chiral information. Initial oxidative addition into the primary allylic system A furnishes the isomeric enyl E or ent-E. This intermediate is then influenced by its initial substitution and undergoes isomerization to F resp. ent-F in competition with nucleophilic attack. In the case of Rh and Ir, k2 is often faster than k3, which explains the observation that both linear A and branched allylic systems B lead to branched substitution patterns D.


65 Oxidative addition via a direct S,2 type process is unlikely based on Evans' observation that increased alkene substitution in a series of primary carbonates leads to decreased reactivity.
Figure 13: The origin of stereospecificity in Rh-catalyzed allylic substitution

Studying the X-ray structures and dynamic behavior of allyl-Ir$^{III}$ complexes Helmchen et al. were able to show that iridium complexes can also be best described as σ-enyl complexes, which is also reflected by their similar catalytic performance. Furthermore, it was possible to demonstrate that the iridium-catalyzed allylic substitution proceeds as a double inversion process. To this end, the reactions using substrates 110 and 112 were investigated (Scheme 15). These substrates do not allow a double inversion process because in 110 oxidative addition to Ir$^I$ and in 113 nucleophilic attack at the allyl-Ir$^{III}$ intermediate are both prevented by steric hindrance.

Scheme 15: Ir$^I$-catalyzed allylic substitution proceeds via double inversion

1.6.2. Preliminary Screening Studies

Due to our interest in iridium-catalyzed processes\(^{67}\) we opted for investigating the potential of the chiral dienes as ligands in iridium-catalyzed allylic substitutions. Starting from \([\text{IrCl(coe)}_2]_2\), a monoolefin-containing iridium complex, ligand exchange with 109 readily takes place in a variety of solvents and can be conveniently monitored by observing the peaks in the alkene region.\(^{68}\) At the outset of our studies, we chose to examine secondary non-symmetrical allylic carbonates in their reaction with a range of N- and O-based nucleophiles. Using phenol as a nucleophile, product formation was observed to be much slower than with amines and the reaction completion could not be achieved under these conditions (Scheme 16).

Upon isolation of phenyl ethers 117 the remaining carbonates 115 were also reisolated. To our surprise, both 115 and 117 showed considerable enantioenrichment. While extensive variations in product ee’s were observed throughout the screening reactions, the ee’s for the recovered starting carbonates were not only higher than those of the phenyl ether products but varied to a much lesser extent. It became apparent that this catalyst system would be suitable for a kinetic resolution of allylic carbonates.\(^{69}\)

\(^{68}\) For a detailed description of this experiment, see: Fischer, C.; Dissertation No. 15459, ETH Zürich, 2004.
In order to identify standard reaction conditions, a detailed screening study was initiated. Screening of three chiral diene ligands (107-109) and CH$_2$Cl$_2$, chlorobenzene and Et$_2$O set us in a position to determine ligand 109 and CH$_2$Cl$_2$ as optimal reaction parameters.

\[
\begin{align*}
1. & [\text{IrCl(coe)$_2$}]_2 (2.5 \text{ mol} \%), \\
& \text{ligand (6 mol\%),} \\
& \text{solvent, 8 h} \\
2. & \text{115,} \\
& \text{PhOH (0.5 equiv),} \\
& \text{solvent, 24 h}
\end{align*}
\]

<table>
<thead>
<tr>
<th></th>
<th>CH$_2$Cl$_2$</th>
<th>chlorobenzene</th>
<th>Et$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>107</td>
<td>34% yield</td>
<td>43% yield</td>
<td>35% yield</td>
</tr>
<tr>
<td></td>
<td>52% yield</td>
<td>45% yield</td>
<td>31% yield</td>
</tr>
<tr>
<td></td>
<td>86% ee</td>
<td>89% ee</td>
<td>62% ee</td>
</tr>
<tr>
<td></td>
<td>71% ee</td>
<td>66% ee</td>
<td>68% ee</td>
</tr>
<tr>
<td>109</td>
<td>32% yield</td>
<td>36% yield</td>
<td>42% yield</td>
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<td>49% yield</td>
<td>49% yield</td>
<td>22% yield</td>
</tr>
<tr>
<td></td>
<td>93% ee</td>
<td>90% ee</td>
<td>69% ee</td>
</tr>
<tr>
<td></td>
<td>66% ee</td>
<td>59% ee</td>
<td>65% ee</td>
</tr>
<tr>
<td>108</td>
<td>33% yield</td>
<td>43% yield</td>
<td>39% yield</td>
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<tr>
<td></td>
<td>54% yield</td>
<td>43% yield</td>
<td>28% yield</td>
</tr>
<tr>
<td></td>
<td>93% ee</td>
<td>45% ee</td>
<td>49% ee</td>
</tr>
<tr>
<td></td>
<td>55% ee</td>
<td>49% ee</td>
<td>69% ee</td>
</tr>
</tbody>
</table>

*Figure 14: Solvent and Ligand Optimization Study*

1.6.3. *Investigation of the Substrate Scope*

Once the optimal reaction conditions were identified we opted for investigation of the substrate scope of the kinetic resolution with a variety of allylic carbonates. The reaction is conveniently carried out at room temperature with 1.5 mol% [IrCl(coe)$_2$]$_2$ and 3.6 mol% ligand 109. A broad range of aryl- and alkyl-substituted allylic carbonates

With respect to the aromatic substrates, both electron-rich and electron-poor substitution patterns are tolerated (Table 1). However, the yields of certain allylic carbonates are low; this can be partially attributed to their limited stability on silica gel during purification.

**Table 1. Kinetic resolution of allylic carbonates**

<table>
<thead>
<tr>
<th>entry</th>
<th>carbonate</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Carbonate 1" /></td>
<td>32 (72)</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Carbonate 2" /></td>
<td>33 (81)</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Carbonate 3" /></td>
<td>28 (78)</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Carbonate 4" /></td>
<td>37 (87)</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Carbonate 5" /></td>
<td>38 (88)</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Carbonate 6" /></td>
<td>39 (87)</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Carbonate 7" /></td>
<td>34 (82)</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Carbonate 8" /></td>
<td>40 (90)</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Carbonate 9" /></td>
<td>37 (83)</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Only yields and ee values of the recovered carbonates are given. Yields and ee values of the allyl ether products can be found in the experimental section.
The combined yield of recovered optically active carbonate and optically active phenyl ether in parentheses, reaction time: 24 h. The selectivity factors were roughly calculated to be in general range between 5 and 15 for most substrates (with single entries as high as 30). Determined by chiral HPLC.

### 1.6.5. Proposed Mechanistic Cycle and Mode of Asymmetric Induction

The catalytic cycle for this transformation is assumed to be similar to other Ir(I)-catalyzed allylic displacement reactions and is shown in Figure 14. Upon coordination of the allylic carbonate 118 to the iridium-diene complex, a square-planar complex 119 is formed which subsequently is in a position to undergo oxidative addition to provide π-allyl complexes 120/121. It is assumed that these complexes are in slow π−σ−π equilibrium. Most likely, σ-enyl complexes as described by Evans et al. are involved. Attack by an external nucleophile leads to complex 122 which liberates product 123. The resulting complex 124 is either identical to 119 if the undefined donor ligand (L) is another allylic carbonate. Otherwise, ligand exchange from 124 with allylic carbonate 118 will close the cycle to return complex 119.
The stereodetermining step in the cycle for the kinetic resolution is assumed to be the ionization reaction from complex 119 to 120. It is reasonable to assume that the coordination of the allylic carbonate is reversible and has no influence on the outcome of the reaction. The differences in the two transition states of the ionization account for the selective ionization of one enantiomer (which ultimately results in product formation) whereas the other remains untouched. Based on these hypotheses, the following working model was developed (Figure 15).

**Figure 14:** Catalytic Cycle proposed for the Ir-catalyzed allylic substitution

**Figure 15:** Working Model for the Stereoinduction in the Kinetic Resolution of Allylic Carbonates.
The two transition states depicted show the secondary stereocenter undergoing ionization below the plane defined by the iridium centre and the midpoint of the two double bonds, with the aryl blocking the upper face. An arrangement wherein the benzylic position is placed adjacent to the aryl substituent of the ligand is unlikely due to steric repulsion. For appropriate $\pi \rightarrow \sigma^*$ orbital overlap, the leaving carbonate has to be oriented antiperiplanar to the alkene C=C double bond. In transition state 126, steric interactions arise between the R group of the carbonate and the chiral diene ligand. It is this destabilizing interaction that is believed to be responsible for the rate differences in the ionization of the two enantiomers, ultimately leading to an enantioenrichment of the (R)-isomer.

1.7. Investigation towards a Dynamic Kinetic Resolution

1.7.1. Background Information

Kinetic resolution processes have the inherit disadvantage that the maximum theoretical yield is limited to 50%. In order to turn our transformation into a dynamic process, two key prerequisites must be established for high enantioselectivity to be obtained in the formation of D commencing with rac-B (Figure 13). A close inspection of figure 13 reveals that a) the chiral ligand must impart a sufficiently large difference in the rates of nucleophilic attack of the involved diastereomeric complexes; b) the rate of isomerization between the $\pi$-allyl intermediates must be fast compared to nucleophilic attack, that is, Curtin-Hammett conditions must be established ($k_1 \gg k_3$).

In a series of investigations, Togni demonstrated that additional halide ions can increase the rate of isomerization of $\pi$-allyl intermediates and thus lead to beneficial

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effects for enantioselectivity (Scheme 17).\textsuperscript{74} Upon examining symmetrical chalcone-derived substrates, such as 127, Togni argued that in the absence of coordinating counter ions, equilibration between \textit{endo-syn-syn} and the more stable \textit{exo-syn-syn} π-allyl palladium intermediates is slow. Upon addition of such ions, interconversion becomes rapid compared to the nucleophilic attack and thus leading to significantly higher enantioselectivities (with added PF₆⁻: 68% ee; with added F⁻: >99.5% ee).\textsuperscript{75}

\begin{center}
\textbf{Scheme 17:} Counterion effects on π-allyl complex isomerization
\end{center}

Trost et al. examined the case of unsymmetrical substrate 130 using \textit{p}-methoxyphenol as nucleophile (Scheme 18).\textsuperscript{76} In this case, addition of halide ions also proved to be beneficial on regio- and enantioselectivity. Various salt additives were examined and it was found that the reaction with chloride ions as additive displayed best regio- and enantioselectivity. Other factors that influence the selectivity of these transformations include the counter ion associated with the halide additives, the reaction concentration as well as the choice of solvent. All of these factors were found to influence the generation of the \textit{Curtin-Hammett} conditions.


\textsuperscript{76} Trost, B.M.; Toste, F. D. \textit{J. Am. Chem. Soc.} 1999, 121, 4545.
Chiral Olefins as Ligands in Asymmetric Catalysis

Scheme 18: Trost’s study on the influence of halide ions

Besides the obvious mechanistic insights gained in such optimization studies towards a catalytic asymmetric process our interest in improving the reaction conditions were also fueled by the fact that the chiral diaryl ether unit is found in a number of prominent pharmaceuticals (Figure 16). For instance, the reaction can be used to set the stereogenic centers in blockbuster drugs such as duloxetine\textsuperscript{77} and fluoxetine.\textsuperscript{78,79}

![Chemical structures with captions](image)

Figure 16: Selection of pharmaceutically active structures incorporating the diaryl ether unit

1.7.2. Effect of Additives

In this respect, o-cresol 134, p-trifluoromethylphenol 136, and o-methoxyphenol 138 were investigated as nucleophiles using the protocol developed for the kinetic resolution process. It became apparent that the reactivity is correlated to the pK\textsubscript{a} value of the corresponding phenol. Thus, p-trifluoromethylphenol possessing the most acidic


proton shows the fastest reaction rate in the process, whereas \( \alpha \)-methoxyphenol only reacts sluggishly (Scheme 19).

![Scheme 19: Kinetic Resolution with a set of nucleophiles](image)

For the optimization towards a dynamic kinetic resolution, \( \alpha \)-cresol 134 was chosen as a nucleophile, partially due to its electron-neutral nature. Additionally, it was of interest if the increased steric bulk exerted by the ortho-substitution would be tolerated in the process (Scheme 20). Using equal amounts of substrates the allylic phenyl ether 135 was isolated in 57% yield and 52% ee after 24 h reaction time. Addition of inorganic halides such as LiF or LiCl did not result in an increase of reactivity, a fact that might be attributed to their low solubility in \( \text{CH}_2\text{Cl}_2 \). By contrast, organic fluoride sources such as TBAF or TASF resulted in a marked increase of yield along with a significantly reduced reaction time (generally full conversion was reached after 5 h). Unfortunately, the increased reaction rate was paralleled by a sharp decrease in enantioselectivity. It is worthy of note, however, that the addition of small amounts (3 mol%) of tetrahexylammonium bromide (THABr) or iodide (THAI) drove the reaction to completion within 90 minutes at room temperature.
Scheme 20: Investigation into the additive effect

This brief investigation into halide additives did not allow us to improve enantioselectivity in the formation of the phenyl ether. Presumably, the resulting Ir(diene)-allyl complexes do not create a chiral environment which is sufficiently stereodifferentiating for nucleophilic attack. However, a marked increase in reaction rate was observed, a fact that might be exploited in the synthesis of achiral, branched secondary and/or tertiary electron-rich phenyl ethers, products difficult to achieve otherwise.
1.8. Conclusion

In summary, chiral dienes based on a [2.2.2]-bicyclooctadiene scaffold were developed. The straightforward synthetic route starts from carvone as a commercially available, inexpensive terpene. The synthesis does not rely on optical resolution of intermediates or separation of enantiomers via chiral HPLC techniques, but the synthesis is based on the use of an chiral pool reagent to establish configurations. Scale-up of the synthesis is thus considerably facilitated compared to chiral dienes published by other groups.

The chiral dienes were successfully employed as ligands in an Ir(I)-catalyzed kinetic resolution of allylic carbonates employing phenol as a nucleophile. The reaction served as a proof of concept demonstrating the ability of chiral dienes to act as ligands and to induce asymmetry in a process. Preliminary efforts towards developing a dynamic kinetic resolution to obtain chiral allylic phenyl ethers only proceeded with limited success. However, direct access to synthetically more useful building blocks, chiral allylic alcohols, were achieved via a different process outlined in chapter 5.
2. **Rhodium/Diene-Catalyzed Conjugate Addition of Organoboronic Acids to α,β-Unsaturated Carbonyl Compounds**

2.1. **Background Information**

*Initial Studies*

Nucleophilic addition of organometallic reagents to electron-deficient compounds is fundamentally important in organic synthesis. Organomagnesium and organolithium derivatives are most frequently used because they are readily available and highly reactive. However, these organometallic reagents can tolerate only a few electrophilic groups. Protection of functional groups can be avoided by the use of milder nucleophiles. In this respect, the combination of rhodium catalysts and organoboronic acids has emerged recently as a powerful and ideal catalytic system in carbon-carbon bond forming reactions. In 1997, Miyaura published a pioneering paper in which the conjugate addition of aryl- and alkenyl boronic acids to α,β-unsaturated ketones was shown to proceed under catalysis by a rhodium complex (Scheme 21). It was demonstrated that organoboronic acids are not reactive towards enones in the absence of a rhodium catalyst. The stability of organoboronic acids in the presence of oxygen and moisture ensures ease of handling during the reaction.

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80 The results described in this section were achieved in collaboration with Dr. Jean-François Paquin and Sonia Serna in the context of her three-month internship in the Carreira group. Their help is gratefully appreciated and acknowledged. Partially, results of this section have been published in the following communication: Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. Org. Lett. 2004, 6, 3873. It should be noted that due to a drawing error in Scheme 1, the enantiomeric series of ligands are displayed in this communication.


82 Due to their application in Suzuki reactions, more than 700 boronic acid derivatives are commercially available, see: www.sigma-aldrich.com/boronpd


In 1998, Hayashi and Miyaura reported the first example of rhodium-catalyzed asymmetric conjugate addition. High enantioselectivities were obtained for a range of substrates when (S)-BINAP was employed as a chiral bisphosphine (Scheme 22).

**Employed Chiral Ligands**

Since the initial report different ligands were applied to catalyze this process, some of which are displayed in figure 17. Traditional ligands such as DIOP, CHIRAPHOS, phosphinooxazolines or ferroceny-based bisphosphines only gave moderate enantioselectivities. Tomioka’s L-proline based amidomonophosphine-based ligand 143, however, showed similar catalytic behavior to BINAP. Reetz demonstrated the applicability of a family of bisphosphonite ligands 144 in this reaction, a concept that was expanded by Feringa using phosphoramidite-based ligands. Interesting ligand

---

structures such as the dicyclophe imidazolium carbene-based ligand 145 or the norbornane-derived bisphosphine DIPHONANE also showed excellent catalytic performance in this reaction. A recent disclosure made use of the P-chiral ligand QUINOX-P to provide 1,4-adducts in high yields and enantioselectivities (Figure 17).  

Figure 17: Employed Ligands for the Rh-catalyzed 1,4-Addition of Arylboronic Acids

Mechanism of the Rh-Catalyzed 1,4-Addition to α,β-Unsaturated Compounds

The mechanism of this process was thoroughly investigated by Hayashi et al. using NMR spectroscopic studies (Figure 18). The reaction has three main intermediates: hydroxorhodium 146, phenylrhodium 147, and oxa-π-allylrhodium 148.

---

complexes that are related in the catalytic cycle as follows: A) transmetallation of a phenyl group from boron to hydroxorhodium 146, giving phenylrhodium 147, B) insertion of the substrates (e.g. 2-cyclohexenone 141) into the phenyl-rhodium bond of 147, forming oxa-π-allylrhodium 148 and C) hydrolysis of 148, giving the conjugate addition product 142 and regenerating hydroxorhodium 146.

![Catalytic cycle for the rhodium-catalyzed conjugate addition](image)

**Figure 18: Catalytic cycle for the rhodium-catalyzed conjugate addition**

**Optimization of the Reaction Conditions, Addition of a Base**

Improved reaction conditions could be obtained when [Rh(OH)(BINAP)]2 149, an acetylacetonato-free rhodium complex, was tested as a catalyst. The increased activity enabled Hayashi to lower the reaction temperature of the process. For example, the addition of phenylboronic acid to 2-cyclohexenone is catalyzed by 149 at 35 °C to give a quantitative yield of 142 with 99% ee. In the original procedure an excess of boronic acid had to be used (up to 5 equivalents) to avoid competing protodeboronation at the high reaction temperatures. Thus, lowering of the reaction temperature also enabled the suppression of this side reaction; consequently the amount of boronic acid could be reduced.

The catalytically active rhodium complex [Rh(OH)(BINAP)]2 can also be prepared *in situ* by mixing a rhodium halide and an inorganic base, e.g. the combination of [RhCl(BINAP)]2 and KOH. The role of inorganic bases is to convert rhodium halide into hydroxorhodium. Miyaura reported an additional effect of the bases in accelerating the reaction. Reactions performed with a combination of hydroxorhodium and a base
were faster than those with only hydroxorhodium. The role of the base was considered to be quaternization of the boronic acid, to facilitate its transmetalation to the hydroxorhodium or assistance of hydrolysis of a rhodium enolate intermediate.

**Importance of Dienes as Ligands**

In 2001 Miyaura reported that a rhodium complex coordinated with 1,5-cyclooctadiene is a highly active catalyst for the rhodium-catalyzed conjugate addition (Scheme 23).

![Scheme 23: Cyclooctadiene acts as ligand](image)

Importantly, Rh(I)-cyclooctene, -ethylenne, and -norbornadiene complexes are not effective in catalyzing the reaction. Intrigued by these preliminary results, further investigations were started in order to improve turnover numbers. With as little as 0.0002 mol% Rh catalyst, 75% of the 1,4-adduct 151 could be isolated after 36 hours reaction time (Scheme 24).

![Scheme 24: Investigation into catalytic efficiency](image)

These impressive results highlight the importance of dienes as ligands. Furthermore, they indicate that the generation of a chiral Rh/phosphine catalyst by

---

mixing a rhodium-cod precursor with a chiral phosphine ligand may cause lower enantioselectivity if the ligand exchange is incomplete. An optically active diene would thus be an optimal ligand for this transformation.

Indeed Hayashi was able to show in a recent study that high turnover numbers can also be achieved using chiral diene 50 as a ligand.\textsuperscript{95} In this respect, it was possible to significantly reduce the catalyst loading to 0.005-0.10 mol\% (TOF up to 14 000 h\textsuperscript{-1}) without loss of enantioselectivity.

**Stereochemical Model**

Concerning the stereochemical course of the reaction, Hayashi\textsuperscript{96} proposed the following model which takes the following steric interactions into account: the rhodium complex combined with the chiral bicyclo[2.2.2]octa-2,5-diene 50 of (R,R) absolute configuration constructs an effective C\textsubscript{2}-symmetric environment with the substituents R located at upper left and lower right positions (Figure 19). Upon addition of a phenylrhodium species to an enone in the catalytic cycle, the olefinic double bond of the enone coordinates to the rhodium in a manner which avoids steric repulsions between the substituent on the diene ligand and the carbonyl moiety of the enone. The alkyl substituent at the \(\beta\)-position is not a decisive factor on controlling the enantioface of olefin coordination. Consequently, both cyclic and acyclic substrates undergo phenylrhodation from their Re-face giving the 1,4-arylation product with the observed absolute configuration. Due to the topological similarities of Hayashi’s ligand, this model can be readily extended to our catalyst system in order to rationalize the stereochemical outcome of all reactions described in the subsequent sections.


Figure 19: Stereochemical Model for the Rh/Diene-Catalyzed 1,4-Addition to α,β-unsaturated Compounds
2.2. Investigation of First Generation Chiral Dienes

Once we had shown that our diene ligand could be successfully employed in an asymmetric transformation, we turned our attention to other catalytic processes. Independently and concurrently, Hayashi reported the synthesis and application of a chiral bicyclo[2.2.1]heptadiene in a Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to enones. Intrigued by these results, we wondered if our chiral diene could be employed in the same transformation. However, initial results revealed that our original ligand performed poorly in the 1,4-addition of phenylboronic acid to cyclohexenone (Scheme 25).

As depicted in Scheme 25, standard ligand 109 displayed satisfactory reactivity but only modest enantioselectivity. At the outset of our investigations, we opted for optimization by electronic variation of the substituents attached to the aryl group of the ligand. Thus, ligands 152 with an electron-donating dimethylamino-substituent showed similar reactivity, but enantioselectivity is within the same range as 109. Electron-deficient ligand 153 performed even worse, yielding 3-phenylcyclohexenone in 92% yield, albeit in only 52% ee.

Scheme 25: Rh(I)-catalyzed addition of phenylboronic acid to cyclohexenone

2.3. Second Generation Synthesis of the Chiral Diene Ligand

Due to the only moderate success we encountered when using chiral dienes 109, 152, and 153, we aimed for improving our ligand template. An initial idea was based on the following hypothesis: if the metal coordinates to the olefin units of the bicyclic scaffold, an increased pseudo-C₂ symmetric chiral environment might be created by placing a second substituent at the other olefin moiety diametrically opposed to the first substituent. A salient feature of this idea was that it could be readily implemented by a slight modification of the initially designed synthetic route (Scheme 26).⁹⁸

![Scheme 26: Second-generation synthesis of a family of chiral dienes](image)

There are two key differences with respect to our earlier route: an initial addition/transposition sequence with carvone (19 → 154) and subsequent alkylation of the [2.2.2]-ketone (155 → 156). Although a separable mixture of C-8 diastereomers was obtained for 155, the derived Rh(I) complexes for both again led to identical results.⁹⁹ This novel ligand synthesis allowed for easy scale-up.

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⁹⁹ The numbering in bicyclic scaffold 156 corresponds to IUPAC nomenclature.
2.4. **Rhodium/Diene-Catalyzed 1,4-Addition of Arylboronic Acids to \( \alpha,\beta \)-Unsaturated Carbonyl Compounds**

2.4.1. **Optimization Studies**

With access to a family of ligands (Scheme 27), several variations were screened in the test reaction of \( \text{PhB(OH)}_2 \) and 2-cyclohexenone under conditions previously reported by Hayashi (Scheme 28).

![Scheme 27](image)

In general the C-2/C-5 disubstituted systems (161 and 164) afforded adducts in higher selectivity (up to 91% ee) when compared to the original ligand 109 (Scheme 25, 67% ee). For bicyclo[2.2.2]octadienes substituted at C-2 with a phenyl group, variation at C-5 was examined. In this series, the presence of a C=C in the substituents at C-5 led to improvement in selectivity (compare 161 at 88% ee with 164 at 91% ee). This effect was not present if the olefin was absent (167 at 82% ee and 161 at 88% ee) or was attenuated with a more flexible spacer (170 at 93% ee). Interestingly, a study of the Rh\textsuperscript{164} complex by \(^1\text{H} \) NMR spectroscopy indicated coordination by all three double bonds, with potential implications for the enantiodetermining step.
Rh-Catalyzed 1,4-Addition of Organoboronic Acids to $\alpha,\beta$-Unsaturated Compounds

\[
\text{PhB(OH)}_2
\]

\[
\text{[Rh(C}_2\text{H}_4\text{)Cl}_2 (1.5 \text{ mol\%})}
\]

\[
\text{ligand (3.3 mol\%)}
\]

\[
\text{KOH (0.5 \text{ equiv})}
\]

\[
\text{dioxane/H}_2\text{O}
\]

\[
25^\circ\text{C}
\]

\[
\text{MeO}
\]

\[
\text{Ph'}
\]

\[
\text{Me}
\]

\[
\text{Ph}
\]

\[
\text{161}
\]

\[
91\% \text{ yield}
\]

\[
88\% \text{ ee}
\]

\[
\text{91\% yield}
\]

\[
91\% \text{ ee}
\]

\[
85\% \text{ yield}
\]

\[
82\% \text{ ee}
\]

\[
93\% \text{ ee}
\]

\[
\text{Scheme 28: Influence of the various ligands}
\]

Several attempts to crystallize a rhodium-diene complex were carried out, albeit to no avail. Nevertheless, we speculated based on model studies that the phenyl substituent at C-2 might be slightly tilted relative to the olefin unit in the bicyclic scaffold because a planar arrangement would result in serious steric interactions between the ortho-hydrogen atoms of the phenyl substituent and the methyl group at C-1. However, such a torsional strain might prevent the metal from accepting a proper overlap with the olefin and thus result in an overall stability decrease of the metal diene complex. Consequently, we aimed at increasing the available space at C-1 by exchanging the phenyl substituent by an isobutyl group. Such a modification could be readily accomplished according to scheme 29.

\[
\text{R-(-)-carvone}
\]

\[
19
\]

\[
\text{R} = \text{allyl}
\]

\[
\text{R} = \text{benzyl}
\]

\[
\text{171}
\]

\[
\text{+ diastereomer}
\]

\[
172
\]

\[
\text{R} = \text{allyl}
\]

\[
\text{R} = \text{benzyl}
\]

\[
\text{173}
\]

\[
\text{174}
\]

\[
\text{175}
\]

\[
\text{176}
\]

\[
\text{177}
\]

\[
\text{178}
\]

\[
\text{Scheme 29: a) 1. } \text{iBuLi, Et}_2\text{O, 2. PCC, silica gel, CH}_2\text{Cl}_2, 52\% \text{ (over 2 steps); b) 1. NBS, CH}_2\text{Cl}_2, \text{MeOH, 2. } \text{t-BuOK, t-BuOH, THF, 54\% (over 2 steps); c) LDA, RBr, THF, } -78^\circ\text{C, 173 = 87\%, 176 = 76\%; d) LiNEt}_2, \text{PhNTf}_2, \text{THF, } -78^\circ\text{C; e) HCO}_2\text{H, Bu}_3\text{N, Pd(OAc)}_2, \text{PPh}_3, \text{DMF, 60 }^\circ\text{C, 175 = 62\%, 178 = 57\% (over 2 steps).}
\]
Indeed, our hypothesis turned out to be correct as enantioselectivity in the standard reaction between cyclohex-2-en-1-one and phenylboronic acid increased to 95% while maintaining high yield (87% yield) when using ligand 175.

Ligand 178 turned out to be the ligand of choice not only for the addition of aryl boronic acids to $\alpha,\beta$-unsaturated aldehydes but also for ester addition reactions (see chapter 3 and 4). The synthesis of this ligand for both enantiomers was carried out on multi-gram scale (about 7 g, 23 mmol of each enantiomer) and was prepared without difficulty. The ligand which we termed DOLEFIN can now be purchased from Sigma-Aldrich (Figure 20).

![Figure 20: Commercially available Chiral Diene Ligands](image)

In parallel to developing the synthetic route to the disubstituted second-generation dienes, we additionally modified our initially disclosed route to a monosubstituted ligand (Scheme 30).

Guided by the same thought of replacing a potentially inflexible phenyl substituent at the olefin unit by a more flexible one, we introduced a set of electronically differing benzyl substituents. Starting from common intermediate 104, a sequence of

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100 The scale-up of the synthesis was carried out in collaboration with Sandro Mollet in the context of his “Semesterarbeit” in the Carreira group. His help is gratefully acknowledged and appreciated.

101 The name DOLEFIN should reflect the following unique properties: It is a diolefin donor which is disubstituted in diametrically opposite positions of the bicyclic scaffold.

102 Prices for 100 mg (+) or (-)-DOLEFIN = CHF 194, February 2007.
enolate alkylation, vinyl triflate formation and subsequent triflate reduction provided straightforward access to monosubstituted ligands 181, 184, and 187.

However, exploration of their performance in the standard addition reaction between cyclohex-2-en-1-one and phenylboronic acid only met with limited success. All ligands displayed poor reactivity and enantioselectivities were inferior to their disubstituted counterparts (Scheme 31). Nevertheless, two important conclusions were drawn from these experiments: a) a disubstituted pattern is important for efficient chiral recognition and stereoselectivity of the reaction, b) electronic variation at the olefin units seems to have only a minor effect on the catalytic performance.

Scheme 31: Investigation of monosubstituted ligands

Having identified 175 as the optimal ligand for performing 1,4-additions to α,β-unsaturated compounds, we became interested in investigating the individual roles of the three olefin moieties found in the ligand and their significance regarding the reaction outcome. The synthesis of ligand 191 wherein one olefin unit in the bicyclic scaffold is eliminated is displayed in scheme 32. Common intermediate 104 was submitted to hydrogenation conditions before the usual sequence of enolate alkylation, vinyl triflate formation and triflate reduction provided ligand 191 (Scheme 32).

Scheme 32: a) H₂, Pd/C, EtOH, 92%; b) LDA, allyl bromide, THF, -78 °C, 57%; c) LiNEt₂, PhNTf₂, THF, -78 °C, 69%; d) HCO₂H, Bu₃N, Pd(OAc)₂, PPh₃, DMF, 60 °C, 45%.
To investigate the specific role of the iso-butyl side arm, allyl-substituted ligand 194 was synthesized from 104 in three steps (Scheme 33).

Scheme 33: a) LDA, allyl bromide, THF, -78 °C, 79%; b) LiNEt₂, PhN Tf₂, THF, 66%; c) HCO₂H, Bu₃N, Pd(OAc)₂, PPh₃, DMF, 60 °C, 45%.

Interestingly, the use of 191 failed to give any significant amount of product; by contrast 194 furnished the 1,4-adduct in 93% yield, but only 58% ee (Scheme 34). Again the presence of two diametrically opposed substituents was shown to be a prerequisite for obtaining high stereoselectivity.

Scheme 34: Influence of Ligand Substitutions

2.4.2. Investigation of the Substrate Scope

We then proceeded to examine the addition reaction for a range of acceptors utilizing the optimal ligand 175 (Table 2). Conjugate additions to cyclopentenone have historically proven difficult to effect in high selectivities under a variety of conditions. It is important to note that the selectivities we obtained for 3-phenylcyclopentanone (97% ee, entry 2; when the addition is carried out with a ligand containing R¹ = phenyl, R² = allyl, the same adduct is obtained in 98% ee) represent, to the best of our knowledge, the highest observed to date using any of the available methods (including Cu- and-Zn-based
addition reactions). When cyclopentenones were subjected to additions with both substituted phenyl- as well as 2-styrylboronic acids, adducts were isolated in 90-97% ee and 91-98% yield (entry 1-4). Additions to cyclohexenone afforded products in high selectivity (94-97% ee) and 83-96% yield, employing 4-, 3-, and 2-substituted phenylboronic acids (entries 5-9). The use of 2-substituted phenylboronic acids had not been previously examined in these reactions with diene ligands. In previous reports involving chiral dienes as ligands, acceptors such as 2-(5H)-furanone (entry 11), coumarin (entry 12), acyclic 3-penten-2-one (entry 13) or unsaturated amides (entry 15) were not examined. Using Rh(I)·175 these additions are all executed successfully (88-98% ee).

Table 2. Reactions of acceptors and boronic acids catalyzed by Rh(I)-chiral diene 175.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>boronic acid</th>
<th>yield (%) (^a)</th>
<th>ee (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{C}<em>5\text{H}</em>{10})</td>
<td>((\text{HO})_2\text{B} \text{Ph}^+)</td>
<td>91</td>
<td>94° (R)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{HC} = \text{CH})</td>
<td>((\text{PhBO})_3)</td>
<td>95</td>
<td>97 (S)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{C}<em>5\text{H}</em>{10})</td>
<td>((\text{HO})_2\text{B} \text{Cl}^+)</td>
<td>98(^d)</td>
<td>95° (R)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{HC} = \text{CH})</td>
<td>((\text{HO})_2\text{B} \text{Ph}^+)</td>
<td>97</td>
<td>90° (R)</td>
</tr>
<tr>
<td>5</td>
<td>(\text{C}<em>6\text{H}</em>{12})</td>
<td>((\text{HO})_2\text{B} \text{Ph}^+)</td>
<td>83</td>
<td>96 (S)</td>
</tr>
<tr>
<td>6</td>
<td>(\text{C}<em>6\text{H}</em>{12})</td>
<td>((\text{HO})_2\text{B} \text{OMe}^+)</td>
<td>85(^d)</td>
<td>96° (R)</td>
</tr>
</tbody>
</table>

54 Rh-Catalyzed 1,4-Addition of Organoboronic Acids to α,β-Unsaturated Compounds

7
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{MeO}^+ \\
\end{align*}
\]
93\(^d\) 94 (S)

8
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
96\(^d\) 97 (S)

9
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{F} \\
\end{align*}
\]
94\(^d\) 97 (S)

10
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
81 95\(^e\) (R)

11
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
80 90 (S)

12
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
43\(^d\) 98 (S)

13
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
78 89 (R)

14
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
68 90 (S)

15
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
98\(^d\) 93 (R)

16
\[
\begin{align*}
\text{(HO)₂B} & \quad \text{Me} \\
\end{align*}
\]
93 88 (R)

\(^a\) Isolated yield after chromatography; \(^b\) Determined by chiral HPLC; \(^c\) Reaction carried out with the opposite enantiomer of the ligand to facilitate analysis by chiral HPLC; \(^d\) Conducted at 50 °C.

2.5. Conclusion

In summary, the successful use of a chiral bicyclo[2.2.2]octadiene ligand in the Rh(I) catalyzed addition of aryl- and styrylboronic acids to a variety of acceptors was documented for the first time. Included in the set of substrates that were investigated are unsaturated lactones, an acyclic amide, and a simple ketone, none of which had been previously examined with diene ligands. Within this ligand family, interesting and unexpected observations were found that result from the introduction of a third olefin moiety, underscoring the dramatic effects that can ensue with relatively minor structural modifications of the scaffold. In particular, this study established the versatility of the [2.2.2]-ligands derived from (R)- or (S)-carvone using a new synthetic sequence, which finally allowed us to considerably expand the substrate scope of the process (chapter 3 and 4). Furthermore, the chiral pool approach of the synthetic route set us in a position to
significantly scale-up the synthesis and ultimately commercialize the ligand in both enantiomeric forms. Owing to the ready accessibility of these ligands, widespread application for a diverse set of transformations can already be found in the literature.\textsuperscript{104}

3. Rhodium/Diene-Catalyzed Addition of Arylboronic Acids to α,β-Unsaturated Aldehydes

3.1. Background Information

Having established that chiral diene 175 is a suitable ligand for the induction of selectivity in α,β-unsaturated carbonyl compounds, our interest shifted towards the expansion of this methodology to a more challenging substrate class: α,β-unsaturated aldehydes. Although scattered reports for the rhodium-catalyzed 1,4-addition to aldehydes are found in the literature, a broad investigation was still missing at the outset of our studies. In fact, there were only two reports of the addition of arylboronic acids to unsaturated aldehydes by Miyaura, however the products are either achiral or obtained in modest yield (3-alkyl-3-arylpropanal). The lack of precedence is likely due to the fact that several competing reaction pathways are possible and thus prevent the reaction to occur in a straightforward fashion (Figure 21).

![Figure 21: Possible Reaction Pathways](image)

Any effort in developing a general conjugate addition reaction to unsaturated aldehydes could be thwarted by 1,2-addition either in competition with 1,4-addition (a vs b) or subsequent to the formation of 196 (a then c) to give 197 (Figure 21). 1,2-additions

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105 The results achieved in this section were achieved in collaboration with Dr. Jean-François Paquin and Dr. Corey R. J. Stephenson. Their help is gratefully appreciated and acknowledged.


109 The use of Rh complexes incorporating chiral phosphines such as BINAP has not been investigated with cinnamaldehyde derivatives; BINAP has been examined in only two cases involving the enantioselective addition to β-alkyl-α,β-unsaturated aldehydes, see Itooka, R.; Iguchi, Y.; Miyaura, N. J. Org. Chem. 2003, 68, 6000.
of organoboronic acids to aldehydes are well known, however, it was only until recently that the first chiral approaches were reported.\textsuperscript{110}

Moreover, it is noteworthy that we limited our study to the synthesis of 3,3-diarylpropanals. Compounds incorporating diarylmethine stereogenic centers are found in a number of natural products\textsuperscript{111} as well as some notable pharmaceuticals\textsuperscript{112} as illustrated in figure 22.

\begin{center}
\includegraphics[width=\textwidth]{figure22.png}
\end{center}

\textit{Figure 22: Natural Products and Pharmaceuticals with a Diarylmethine Stereogenic Center}

The stereoselective preparation of these building blocks is difficult to achieve otherwise, particularly when little differentiates the two arènes electronically or sterically. The current state of the art for the preparation of nonracemic 3,3-diarylpropanals is the

\textsuperscript{110} For a complete listing of references, confer chapter 3.4.


amine-catalyzed addition of aromatic nucleophiles to 3-substituted acrolein derivatives (Scheme 35).

![Scheme 35: MacMillan's approach to the synthesis of 3,3-diarylpropanals](image)

While this approach performs well with electron-rich nucleophiles, electron-poor aromatics do not furnish 1,4-adducts because they are insufficiently reactive. The Rh(I)-catalyzed conjugate addition of arylboronic acids is less sensitive to the electronic nature of the arene nucleophile and thus offers the promise of a general solution for the synthesis of this important class of compounds.

### 3.2. Optimization of the Reaction Conditions

At the outset of our investigations, the addition of 4-methoxybenzeneboronic acid 202 to cinnamaldehyde 201 was used as a test reaction to optimize enantioselectivity via systematic variation of the pseudo-C2 symmetric ligand scaffold (Scheme 36). In the presence of parent ligand 164, adduct 203 was isolated in 43% yield and 47% ee along with < 5% of the product resulting from 1,2-addition (path b, figure 21). A modest increase to 60% ee was observed with Bn-substituted ligand 161. When the phenyl moiety of 164 was replaced with isobutyl (ligand 175), a significant amplification in the enantioselectivity to 83% ee was observed. The use of ligand 178, a hybrid of 161 and 175, afforded the desired product in 92% ee. In each case, we were able to recover approximately 10% of cinnamaldehyde 201 along with 20-25% of the corresponding double addition product (a then c, figure 21). This observation is consistent with the greater propensity of the system to perform conjugate addition over 1,2-addition. It also provided us with further impetus to study the reaction with the aim of precluding 1,2-addition to 201 and/or 203.

---

Scheme 36: Influence of various diene ligands on the stereochemical outcome

In further efforts to optimize the yields, we observed that the use of alcohol solvents had a dramatic influence on the outcome of the reaction. Thus, in a mixture of 10:1 EtOH/H2O with ligand 178, the desired aldehyde 203 could be isolated in 68% yield and 92% ee. In MeOH, it was possible to reduce side reactions to an even greater extent, so that aldehyde 203 was isolated in 80% yield and 92% ee. Phosphorus-based ligands such as BINAP 204 and phosphoramidite 205 furnished adduct 202 in 33% yield/89% ee and 19% yield/56% ee, respectively (Scheme 37).

Scheme 37: Comparison with other ligands

---

114 This solvent effect was first observed by Miyaura in the context of Rh-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated ketones: Ueda, M.; Miyaura, N. J. Org. Chem. 2000, 65, 4450.
3.3. Investigation of the Substrate Scope

While examining the scope of this transformation, the addition of both electron-rich (Table 3, entry 1), as well as electron-poor boronic acids (entries 2-6) proceeded smoothly with various enals in 63-90% yield with little variation in the enantioselectivity (89-93% ee).

Table 3. Conjugate Addition Reactions catalyzed by Rh(I)*(-)-DOLEFIN 178

<table>
<thead>
<tr>
<th>entry</th>
<th>enal</th>
<th>Ar2B(OH)2</th>
<th>yield (%)a</th>
<th>ee (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>MeO</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>F</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Me</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>CO2Me</td>
<td>70</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>CF3</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>MeO</td>
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<td>93</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>MeO</td>
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<td>92</td>
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<tr>
<td>8</td>
<td></td>
<td>F</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>OMe</td>
<td>76</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>OMe</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Bn</td>
<td>63</td>
<td>93</td>
</tr>
</tbody>
</table>

*a* Isolated yield after chromatography; *b* Determined by chiral HPLC after reduction of the aldehyde.
Both enantiomers of a given building block were obtained with the same enantiomer of the ligand (-)-DOLEFIN 178 by varying the donor and acceptor (entries 1 and 7, and entries 2 and 8). In addition, the functional group tolerance of this catalytic system allowed the use of a wide range of substituents. The resulting adducts could be used subsequently in the diversity-oriented synthesis of pharmaceutical libraries.

3.4. Rhodium-Catalyzed Asymmetric 1,2-Addition of Arylboronic Acids to Aldehydes

We next sought to expand the scope of the transformation to 1,2-addition of arylboronic acids to aldehydes. Although there were a number of reports on 1,4-addition, efficient asymmetric 1,2-addition was underdeveloped. A landmark contribution in this field is the study by Miyaura et al. disclosed in 1998 (Scheme 38). Using 2-(diphenylphosphanyl)-2'-methoxy-1,1'-binaphthyl ((S)-MOP) ligand, they demonstrated the 1,2-addition of phenylboronic acid to 1-naphthaldehyde in 78% yield and 41% ee.

\[
\begin{align*}
\text{CHO} & \quad \begin{array}{c}
\text{B(OH)}_2 \\
1.0 \text{ equiv} \\
206
\end{array} \\
\begin{array}{c}
\text{[Rh(acac)(C}_2\text{H}_4)_2] (3 \text{ mol}%) \\
\text{(S)-MOP (6 mol%)}
\end{array} \\
\text{DME/H}_2\text{O (1:1)} \\
60 \degree \text{C, 36 h}} \\
\rightarrow \quad \begin{array}{c}
\text{OH} \\
207
\end{array}
\end{align*}
\]

Scheme 38: Miyaura’s initial study

To examine if chiral dienes would be suitable ligands for this transformation, our initial investigations were directed towards adopting Miyaura’s conditions. No product was obtained when chiral diene 164 was used instead of (S)-MOP under Miyaura’s conditions. However, it was possible to isolate the 1,2-adduct in 48% yield and 35% ee when our conditions for the 1,4-addition to \(\alpha,\beta\)-unsaturated aldehydes were applied with the exception of using dioxane/H\_2O as reaction solvent (Scheme 39).

---


Some features of this process deserve further comments. To ensure a quantitative ligand exchange it is important to use $[\text{RhCl(C}_2\text{H}_4)_2]$ as ligand precursor, other precursors such as $[\text{Rh(acac)}(\text{C}_2\text{H}_4)_2]$ do not convert the substrate. Although having identified a lead, the reaction still proceeded very slowly (48% conversion in 42 h) and did not reach completion. In order to accelerate the addition reaction, a solvent screen was carried out (Scheme 40).

As in the case of the 1,4-additions to aldehydes, alcoholic solvents provide the best results. The use of ethanol as solvent led to a significant rate acceleration of the
reaction resulting in 70% conversion and 28% ee after 18 h reaction time. Subsequent investigations were aimed at examining various EtOH/H2O ratios. As depicted in scheme 40, the use of a 10:1 ratio led to 70% conversion of 1-naphthaldehyde 206. However, changes of the EtOH/H2O ratio to 4:1 and 1:1 did not affect the reaction outcome. Temperature change (50 °C vs. 23 °C) also displayed no major influence on conversion and ee. A rapid screening of different sources of nucleophiles provided no further improvement. Whereas the use of a boronate ester (PhB(OCH2)2CH2) proceeded with the same efficiency as phenylboronic acid, phenyl trifluoroborate salts (PhBF3K), only led to 17% conversion. The enantioselectivity remained constant and did not depend on the source of organoboron compound.

Having identified EtOH as the best solvent for this transformation, we next sought to improve the stereoselectivity of this transformation. A variety of chiral dienes were tested using conditions outlined in scheme 41.

Unfortunately, no major increase in ee was observed in screening the various chiral dienes. The best results were obtained with ligand 161, substituted with a phenyl and a benzyl-substituent (100% conversion, 36% ee). A solvent change to 1,4-dioxane brought a slight increase in enantioselectivity (76% conversion, 40% ee). However, major changes in the ligand architecture would probably be necessary to increase the enantioselectivity to a synthetically relevant level.
3.5. Application of the Methodology in the Synthesis of (R)-(+) Tolterodine

In order to showcase the applicability of our method, we decided to pursue the synthesis of a pharmaceutically active compound incorporating a stereogenic diarylmethine center.

(R)-(+) Tolterodine (Dextrol® or Detrusitol®) 208 is a competitive muscarine receptor antagonist used in the treatment of urinary bladder disorders such as incontinence. In 1997, the drug was launched by Pharmacia & Upjohn and marketed worldwide as the (R,R)-tartaric salt. The annual consumption increase is estimated about 20%, the bulk production in the 15 most industrialized countries in the world was 450 kg in 1999. In addition to resolution of racemic tolterodine and diastereoselective auxiliary-based approaches, several catalytic asymmetric routes were reported to access this molecule. Catalytic asymmetric hydrogenation of 1,1-diarylsubstituted olefins requires formation of a single double bond configuration and is therefore not a trivial problem. In 2002, Botteghi et al. disclosed a route which relied on asymmetric hydroformylation with Rh/Binaphos as catalyst, however enantioselectivity did not exceed 8% ee. Andersson published an improved route which is outlined in scheme 42.

Rh-Catalyzed Addition of Arylboronic Acids to α,β-Unsaturated Aldehydes

Scheme 42: a) (S)-Me-CBS (5 mol%), BH₃·THF, THF, -20 °C, 2 h, 91%, 97% ee; b) Et₃N, DABCO (20 mol%), THF, 60 °C, 4 h, 90% yield, 94% ee; c) m-CPBA, TsOH·H₂O, MS 4Å, CH₂Cl₂, 4 °C, 92%, 94% ee.

It relies on a Corey-Bakshi-Shibata reduction of indenone 209 followed by base-induced [1,5]-suprafacial sigmatropic rearrangement of the corresponding 3-arylidenediol 210. Dihydrochromen-2-one 212 accessed by Baeyer-Villiger oxidation of 211 was further functionalized (5 steps) to provide 208 with an overall yield of 30% and 99% ee.

Our approach to 208 started with commercially available phenol 213. After protection as benzyl ether, a Heck reaction provided α,β-unsaturated aldehyde 214, which underwent Rh-diene-catalyzed 1,4-addition with phenylboronic acid to provide 216 in 78% yield and 90% ee (Scheme 43).

Scheme 43: a) NaH, BnBr, DMF, 99%; b) diethyl acrolein acetal (3 equiv), n-Bu₄NOAc (2 equiv), K₂CO₃ (1.5 equiv), KCl (1 equiv), Pd(OAc)₂ (3 mol%), DMF, 90 °C, 8 h, 41% (91% brsm); c) PhB(OH)₂ (1.5 equiv), KOH (0.5 equiv), [RhCl(C₂H₅)₂] (1.5 mol%), (-)-DOLEFIN 178 (3.3 mol%), MeOH/H₂O (10:1), 50 °C, 5 h, 78%, 90% ee.

Aldehyde 216 is an intermediate of Botteghi’s synthesis and can be transformed into tolterodine by debenzylation and reductive amination. In addition to the ease of converting 216 into the desired product, the aldehyde functionality constitutes a promising synthetic handle for derivatisation (addition, decarbonylation, etc.) which allows the exploration of analogues of the drug.

Parallel to our studies, Hayashi independently developed a synthetic approach to (R)-tolterodine based on an asymmetric catalytic 1,4-addition of arylboronic acids to coumarins (Scheme 44).123

The conjugate addition was carried out with a number of differently substituted aryl boronic acids to give ready access to a family of 4-aryldihydrochromen-2-ones, however the reaction required the use of 10 equiv of boronic acid.

3.6. Conclusion

In summary, the application of Rh(I)-diene based catalysts in the conjugate addition of arylboronic acids to substituted cinnamaldehydes provided access to valuable optically enriched 3,3-diarylpropanals in 63-90% yield and 89-93% ee. The successful fine tuning of the enantioselectivity in this process was made possible by our modular synthesis of bicyclo[2.2.2]octadiene ligands beginning with natural carvone. This approach offers a tactical advantage over existing methodology in that electron-poor nucleophiles function with equal efficiency as their electron-rich counterparts. The methodology was successfully applied to the synthesis of (R)-(+)-tolterodine. By contrast, the Rh(I)-diene catalyzed addition of phenylboronic acid to naphthaldehyde only proceeded with moderate enantioselectivity (best case: 99% conversion, 40% ee).
4. Rhodium/Diene-Catalyzed Addition of Arylboronic Acids to \( \alpha,\beta \)-Unsaturated Esters\(^{124,125} \)

The use of cinnamic acid esters\(^{126} \) as acceptors is advantageous because of the wide variety of commercially available unsaturated acids as well as the increased stability of the esters, which makes them easily handled starting materials. Of additional importance was the fact that the conjugate addition of arylboronic acids to cinnamate ester acceptors catalyzed by metal-diene complexes was previously unreported.

4.1. Optimization of the Reaction Conditions

We examined the Rh-catalyzed addition of 4-methoxybenzeneboronic acid 202 to ethyl cinnamate 218 in the presence of diene ligand 164 under the conditions developed for the conjugate addition of arylboronic acids to enones. As expected, the reactivity of the esters was considerably attenuated compared to the corresponding enals (18 h vs. 75 min reaction time). We were able to isolate the desired 3,3-diarylpropanoate 221 in 72% yield, albeit in only 19% ee (table in scheme 45, entry 1). The enantioselectivity was improved to 65% ee using the isobutyl substituted ligand ent-175 (entry 2). Increasing the size of the ester substituent (R = Bn) provided a small increase in enantioselectivity (71% ee). The combination of the isobutyl-substituted ligand 175 and tert-butyl ester 220 provided 223 in substantially improved enantioselectivity (entry 4, 89% ee). Under optimal conditions, \( \beta \)-butyl cinnamate 220\(^{127} \) was converted to diarylpropanoate 223 in the presence of the \([\text{RhCl(C}_2\text{H}_4\text{)}_2]\)_2 and ligand 178 (3 mol% Rh) in excellent yield and enantioselectivity (entry 6, 85% yield, 93% ee).

\(^{124} \) The results achieved in this section were achieved in collaboration with Dr. Jean-François Paquin and Dr. Corey R. J. Stephenson. Their help is gratefully appreciated and acknowledged.


4.2. Investigation of the Substrate Scope

In the Rh-catalyzed conjugate addition reaction to \( t \)-butyl cinnamate \( \text{220} \), we observed that both electron-rich (table 4, entry 1) and electron-poor boronic acids (entries 2-3) afforded the desired adducts in 69-85% yield and 92-93% ee. By switching the aryl acceptor and donor, we could easily prepare both enantiomers of a given product (cf. entries 1 and 4) using a single enantiomer of ligand \( \text{178} \). In addition, a wide variety of substituted cinnamate esters could be used as acceptors in the conjugate addition reaction. Aromatics substituted with electron-donating (entry 4) and electron-withdrawing groups (entries 5-8) provided the 3,3-diarylpropanoates in 78-95% yield and 92-94% ee. Interestingly, the nitro-substituted cinnamate (entries 7-8) was a good substrate for this conjugate addition reaction, while the corresponding aldehyde was not.
**Table 4. Conjugate Addition Reactions catalyzed by Rh(I)•(-)-DOLEFIN 178**

<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>Ar$_2$B(OH)$_2$</th>
<th>yield (%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>76</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>95</td>
<td>91</td>
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<tr>
<td>5</td>
<td></td>
<td></td>
<td>95</td>
<td>94$^c$</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>93</td>
<td>93</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after chromatography; $^b$ Determined by chiral HPLC. $^c$ This value was estimated because the signals could not be completely resolved in the chiral HPLC.

We also examined a number of heterocyclic acceptors to broaden the scope of the conjugate addition reaction. In all cases, the heterocycle-substituted enoates reacted more slowly than the cinnamate derivatives, often requiring reaction times of 12-18 h (Table 5). In some cases, 1,4-dioxane proved to be a better solvent than MeOH (entries 3-6). Furayl-substituted acceptors reacted with both electron-rich and electron-poor boronic acids to give the desired adducts in 62-68% yield and 91-92% ee (entries 1-2). Both regioisomeric thienyl-substitued acceptors afforded adducts in 65-68% yield and 89-91% ee (entries 3-4). We were pleased to observe that the pyridyl-substituted enoate was converted to the 1,4-addition product in 70% yield and 93% ee (entry 5). In our previous study, the corresponding enal did not afford any 1,4-addition product. Finally, the
indolyl-substituted enoate provided the conjugate addition product in excellent yield and enantioselectivity (entry 6, 90%, 94% ee).

Table 5: Conjugate Addition Reactions catalyzed by Rh(I)*(-)-DOLEFIN to Heterocyclic Acceptors

<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>Ar\textsuperscript{2}B(OH)\textsubscript{2}</th>
<th>yield(%)\textsuperscript{a}</th>
<th>ee(%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="ester" /></td>
<td><img src="image2.png" alt="boronic acid" /></td>
<td>62</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="ester" /></td>
<td><img src="image4.png" alt="boronic acid" /></td>
<td>68</td>
<td>91</td>
</tr>
<tr>
<td>3\textsuperscript{c}</td>
<td><img src="image5.png" alt="ester" /></td>
<td><img src="image6.png" alt="boronic acid" /></td>
<td>65</td>
<td>91</td>
</tr>
<tr>
<td>4\textsuperscript{c}</td>
<td><img src="image7.png" alt="ester" /></td>
<td><img src="image8.png" alt="boronic acid" /></td>
<td>68</td>
<td>89</td>
</tr>
<tr>
<td>5\textsuperscript{c}</td>
<td><img src="image9.png" alt="ester" /></td>
<td><img src="image10.png" alt="boronic acid" /></td>
<td>70</td>
<td>93</td>
</tr>
<tr>
<td>6\textsuperscript{c}</td>
<td><img src="image11.png" alt="ester" /></td>
<td><img src="image12.png" alt="boronic acid" /></td>
<td>90</td>
<td>94</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield after chromatography; \textsuperscript{b} Determined by chiral HPLC; \textsuperscript{c} The solvent for these reactions was 1,4-dioxane.

In order to extend the utility of this methodology, we decided to take advantage of the functional groups present in the conjugate addition products for subsequent synthetic elaboration. In particular, the adduct of phenylboronic acid and \(\alpha\)-NO\textsubscript{2}\-substituted cinnamate ester provided the opportunity to prepare optically enriched dihydroquinolin-2-ones from the 1,4-adducts.\textsuperscript{128} Thus, subjection of 224 (table 4, entry 7) to hydrogenation (\(\text{H}_2\), Pd/C in MeOH) afforded the amino ester; this could be converted to the desired lactam 225 by treatment with AcOH in THF (Scheme 46).

A one-step protocol involving hydrogenation of \( \text{224} \) in the presence of 1 equiv AcOH furnished \( \text{225} \) in 96% yield.\(^\text{129}\)

### 4.3. Conclusion

In summary, the functional utility of chiral Rh-diene complexes in the preparation of 3,3-diarylpropanoates in good yields and enantioselectivities has successfully been demonstrated. The Rh-catalyzed addition of arylboronic acids was also used to prepare 3-aryl-3-heteroaryl-propanoates in 62-90% yield and 89-94% ee. This process is attractive because of the ready availability of the starting materials (esters and boronic acids) and its success with a wide variety of donors and acceptors. In addition, we have established the applicability of this reaction via the simple, one-pot synthesis of optically enriched dihydroquinolin-2-one \( \text{225} \).

\(^{129}\) The hydrogenation was accelerated in the presence of AcOH (ca. 2 h compared to 24 h).
5. **Iridium-Catalyzed Synthesis of Chiral Allylic Alcohols: Silanolates as Nucleophiles**

5.1. Background Information

Our initially reported process to demonstrate the utilization of chiral dienes in asymmetric synthesis involves the kinetic resolution of allylic carbonates, which gave rise to enantioenriched allylic ethers and carbonates. Due to the nature of this process, however, the efficiency is limited to a maximum 50% yield. Therefore, we aimed at developing a more efficient transformation for the synthesis of chiral allylic alcohols, and resorted to Ir-catalyzed allylic substitution. Recently the field of Ir-catalyzed asymmetric allylic substitution has blossomed into a highly active field of research, with seminal contributions by the research groups of Hartwig, Helmchen and Alexakis (Scheme 47).

\[
\text{Nu} \quad \text{Indium catalysis} \quad 1 \quad \text{Nu} \quad \text{regioisomer}
\]

Scheme 47: Iridium-catalyzed allylic substitution (LG = leaving group, Nu = C-, N- or O-Nucleophile)

As a consequence, a range of different C-, N- and O-nucleophiles can now be conveniently employed in this process. Since the early investigations by Takeuchi and Helmchen a significant breakthrough in this field was achieved by Hartwig whose base-induced catalyst activation significantly improved the rates and ultimately the reaction scope of the process.

For instance, the range of tolerated nucleophiles in Ir-catalyzed asymmetric alkylation reactions goes far beyond the initially employed traditional malonates.

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130 The results described in this section were achieved in collaboration with Dr. Isabelle Lyothier. Furthermore, Koni Marti contributed to the progress of the project in the context of his “Semesterarbeit” in the Carreira group. Their help is gratefully acknowledged and appreciated.


and now includes β-keto Weinreb amides\textsuperscript{136} \textbf{226}, β-ketoesters\textsuperscript{137} \textbf{227}, aliphatic nitro compounds\textsuperscript{138} \textbf{228}, diphenylamino glycinate\textsuperscript{139} \textbf{229} and TMS enol ethers\textsuperscript{140} \textbf{230} (Scheme 48).

![Chemical Structures]

\textbf{Scheme 48: Various C-nucleophiles employed in Ir-catalyzed allylic substitution}

Chiral phosphoramidites are popular ligands to induce asymmetry in this process because their modular nature allows for rapid fine-tuning to improve stereoselectivity (Figure 23).\textsuperscript{141}

![Chemical Structures]

\textbf{Figure 23: Chiral ligands employed in Ir-catalyzed allylic substitution}

As illustrated in scheme 49 the most common way to prepare phosphoramidites is via derivatization of compounds derived from BINOL. Phosphoramidites can usually be handled for short periods without special precaution. The following routes are often applied for the preparation of these ligands:

a) Pathway A: Reaction of neat PCl\textsubscript{3} with a binaphthol or biphenol leads to a chlorophosphite which can be treated with a lithiated secondary amine to provide a phosphoramidite. The scope of this method is very broad.

b) Pathway B: An alternative route involves reaction of PCl₃ with a secondary amine followed by treatment of the product with the binaphthol or biphenol to give the phosphoramidite. From a practical point of view, it is important to note that this procedure can also be carried out with the hydrochloride of a secondary amine.

![Scheme 49: Preparation of Phosphoramidites](image)

In 2002 Helmchen et al. made an interesting observation in the course of preparing a putative (allyl)Ir-intermediate. Surprisingly, the standard catalyst system [IrCl(cod)]₂/P(OPh)₃ did not react with typical substrates such as allylic acetates. However, a reaction occurred upon addition of the nucleophile. The catalytically active complex was generated by addition of the precomplex 236 with dimethyl sodiomalonate. The resultant complex 237 is formed via orthometallation (IrIV), elimination of HCl (IrIII) and addition of P(OPh)₃ (Scheme 50).

![Scheme 50: Catalyst formation via base-induced C-H Activation](image)

Shortly thereafter, Hartwig obtained a crystal structure of the activated cyclometallated complex 239 (Scheme 51). This base-induced C-H activation turned out to be an important method of catalyst activation, that results not only in an increase in the

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143 This complex has been characterized earlier in another context: Bedford, R. B.; Castillon, S.; Chaloner, P. A.; Claver, C.; Fernandez, E.; Hitchcock, P. B.; Ruiz, A. Organometallics 1996, 15, 3990.
rate of the reaction but also significantly expanded the substrate scope of this Ir-catalyzed reaction (Scheme 51).\textsuperscript{144}

\begin{align*}
&\text{Ir-Catalyzed Synthesis of Chiral Allylic Alcohols using Silanolates} \\
&\text{rate of the reaction but also significantly expanded the substrate scope of this Ir-catalyzed reaction (Scheme 51).} \\
&\begin{aligned}
&\text{Successful application of phosphoramidites requires close attention to catalyst preparation and reaction conditions because ligands can be altered by C-H activation at aryl or CH}_3 \text{ groups. The following procedure was developed and finds wide application: Mixing of [IrCl(cod)]}_2 \text{ and a chiral ligand } L^* \text{ in a 1:2 ratio. A complex [IrCl(cod)L}]_2 \text{ is formed, simply by breaking up chloro bridges. This complex is further activated by treatment of the mixture with a base (TBD}^{145} \text{, DABCO}^{146} \text{ or } n\text{-propylamine) which results in the formation of complex 239 by } \text{in situ } C\text{-H activation at the } CH}_3 \text{ group (Scheme 51). Complex 239 is a coordinatively saturated (18 VE) Ir}\text{ complex; dissociation of } L \text{ is thus needed in order to get a reactive species.}
\end{aligned}
\end{align*}

A modified catalyst activation protocol for allylic alkylation was reported by Helmchen: Treatment of [IrCl(cod)]\textsubscript{2}, a chiral phosphoramidite, THT (tetrahydrothiophene, an auxiliary ligand), in THF with the base TBD for 2 hours, then addition of the allylic substrate and subsequently of Cu\textsubscript{I}, leads to a protocol which provides excellent yields, regio- and enantioselectivities. However, it should be noted that this procedure was not applicable to allylic amination due to the coordination of Cu\textsuperscript{I} to the amine. However, as a result of screening studies, salts of soft cations (such as Pb\textsuperscript{II} salts) in conjunction with a base led to significantly faster reaction rates.

\begin{align*}
&\text{5.2. Phenoxides as O-Nucleophiles} \\
&\text{In 2003 Hartwig employed phenoxides as nucleophiles in the context of an Ir/phosphoramidite catalyzed allylic etherification.}^{147} \text{ In these early experiments the}
\end{align*}

\begin{itemize}
\item TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.
\item DABCO = 1,4-diazabicyclo[2.2.2]octane.
\end{itemize}
activation of the catalyst was not carried out deliberately. However, cyclometallation, most likely, occurred in situ; if not induced by the phenoxide, then by the alkoxide ion generated from the leaving group. Selectivities and yields were found to strongly depend on the base used to generate the phenoxide. Alkali phenoxides gave much better results than ammonium phenoxides (generated by addition of NEt₃, table 6, entry 1). Use of sodium phenoxide in combination with a methyl carbonate gave rise to a transesterification as side reaction (entry 2). Better results were obtained with ethyl carbonates (entry 3) or lithium phenoxides (entry 4). Typically, carbonates with R¹ = aryl gave better results than those with R¹ = alkyl (entry 5). The solvent was found to influence the reaction rate and selectivity; the best results were obtained with THF.

**Table 6: Allylic Substitutions with Phenoxides as Nucleophiles**

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>M</th>
<th>time [h]</th>
<th>yield [%]</th>
<th>242 : 243</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>NEt₃H</td>
<td>15</td>
<td>76</td>
<td>93 : 7</td>
<td>84</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>Na</td>
<td>22</td>
<td>40</td>
<td>97 : 3</td>
<td>92</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>Ph</td>
<td>Et</td>
<td>H</td>
<td>Na</td>
<td>35</td>
<td>76</td>
<td>99 : 1</td>
<td>94</td>
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<tr>
<td>4</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>Li</td>
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<td>86</td>
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<td>96</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>n-Pr</td>
<td>Me</td>
<td>p-OMe</td>
<td>Li</td>
<td>14</td>
<td>73</td>
<td>90 : 10</td>
<td>85</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>n-Pr</td>
<td>Me</td>
<td>p-OMe</td>
<td>Li</td>
<td>14</td>
<td>95</td>
<td>93 : 7</td>
<td>94</td>
</tr>
</tbody>
</table>

*a* Yield of 242 + 243. *b* Reaction temperature: 23 °C. *c* Catalyst activation by heating at 50 °C with n-propylamine for 20 min.

When the activation procedure was employed, distinct improvements in yield and selectivities were observed (entries 5 and 6).¹⁴⁸ Within the phenoxide, donor substituents including halogen were tolerated. Sterically hindered lithium phenoxides were remarkably reactive. Phenoxides with moderately strong electron-withdrawing substituents gave good results when their sodium salts in combination with ethyl carbonates were used. However, 4-nitro and 4-cyano phenoxides failed to react. It should

---

be further noted that intramolecular versions have also been developed in the meantime.¹⁴⁹

### 5.3. Alkoxides as O-Nucleophiles

Alkali alkoxides are notoriously difficult nucleophiles in this process. Superior results were obtained in allylic substitutions with Zn-alkoxides (achiral catalysts) by Roberts and Lee¹⁵⁰ and Cu-alkoxides (achiral Rh-catalyst with chiral substrates) by Evans and Leahy.¹⁵¹ Shu and Hartwig successfully employed these compounds in the allylic substitution with Ir/phosphoramidite catalysts (Table 7).¹⁵²

<table>
<thead>
<tr>
<th>Table 7: Allylic Substitutions with Aliphatic Alkoxides as Nucleophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure]</td>
</tr>
<tr>
<td>entry</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

### 5.4. Hydroxylamine Derivatives as O-Nucleophile

In interesting studies involving hydroxylamine as ambident nucleophile, Takemoto has shown that whereas N-benzyl-hydroxylamine behaves as N-nucleophile in the Ir-catalyzed allylic substitution, N-Boc-hydroxylamine gives mixtures of the N- and O-substituted product, both in the Ir- and the Pd-catalyzed allylic substitution (Scheme 52).¹⁵³

---

¹⁵³ Miyabe, H.; Takemoto, Y. *Synlett* **2005**, *1641*. 
Scheme 52: Ambident character of hydroxylamine derivatives

Takemoto was able to demonstrate the use of hydroxamic acid derivatives as O-nucleophiles. The use of [IrCl(cod)]2/Ph-pybox in combination with allylic phosphates provided adducts in good regio- and enantioselectivity (Scheme 53). The addition of a base proved to be beneficial, with Ba(OH)2·H2O and CsOH·H2O showing the best performance.

Scheme 53: Hydroxamic Acid as O-Nucleophile

Extending the screening studies, it was also possible to employ oximes as suitable O-nucleophiles (Scheme 54). However, only allylic phosphates containing an electron-rich aryl substituent have been reported so far.

Scheme 54: Oximes as O-Nucleophile

5.5. Silanlates as O-Nucleophiles

We have documented the use of chiral dienes as ligands in an Ir-catalyzed kinetic resolution of branched allylic carbonates using phenol as nucleophile. In our continuing interest in this area we have been searching to further expand the scope of nucleophiles that can be employed, with particular attention on the development of a process that employs water, or its equivalent, to give rise directly to allylic alcohols. This process became important to us for two reasons: (1) the Ir-catalyzed allylic displacement reaction to give the secondary alcohol directly has not, to the best of our knowledge been reported,\textsuperscript{155} despite the fact that (2) the resulting allylic alcohol adducts are amenable to further elaboration. The methods reported to date that could in principle give rise to the free benzylic/allylic alcohols via an allylation process involve the use of the copper salt of benzyl alcohol.\textsuperscript{156}

![Image of potential selectivity problems during deprotection](image)

\textit{Figure 24: Potential Selectivity problems during Deprotection}

However, the chemoselective removal of the O-benzyl ether protecting group (I in Figure 24) from the products is difficult because of the presence of the C=C (II in Figure 24) as well as the potential for undesired hydrogenolytic cleavage of the benzylic/allylic C-O bond that defines the stereogenic center (III in Figure 24).

5.6. Optimization of the Process

At the outset of our investigations, tert-butyl cinnamyl carbonate 255 was employed as a test substrate. The reaction of 255 was examined with water in the presence of the catalyst derived from Feringa's phosphoramidite ligand 232 and Ir(I). It


is important to stress that it is necessary to use the same kind of activation than previously described by Hartwig. Despite repeated attempts with this reaction, no secondary alcohol was observed. At this point a number of hydroxide-equivalents were screened, with specific interest in silanols, which appeared to be a particularly attractive class of nucleophiles. Silanols are considerably more acidic than the corresponding alcohols (H₂O (pKₐ = 3.12), t-BuOH (pKₐ = 3.22), TIPSOH (pKₐ = 24.4) in DMSO). These reagents can thus be considered as water surrogates, because silyl ether cleavage is known to proceed under a variety of mild conditions.

| Table 8: Investigation into the Ir-catalyzed allylic etherification |

Unfortunately, neither commercially available TMSOK nor triethylsilanol led to the formation of any adducts (Table 8, entries 1-2). However, when using the corresponding potassium salt of the latter a lead result was obtained: the secondary silyl ether was formed in 39% yield, in 96% ee (entry 3). The modest yield was attributed to the poor regioselectivity (ratio 256 : 257 = 3:1). In order to optimize the process, a


\[ \text{160 When employing TESOLi or TESONa, the reaction only proceeded with low conversion (17% resp. 44%). This might be partially attributed to the low solubility of these reactants in CH₂Cl₂.} \]
range of different leaving groups were screened, albeit to no avail. Cinnamyl acetate led only to formation of the undesired linear product 257, and cinnamyl carbonates with small alkyl groups underwent alcoholate exchange in competition with etherification.

Gratifyingly, as part of a subsequent screening of reaction conditions, excellent results arose in changing the reaction solvent to CH₂Cl₂ (entry 5). It is interesting to note that the Ir-catalyzed enantioselective allylations to date have been largely conducted in THF. The pronounced solvent effect we observe may be relevant in other processes of interest.¹⁶¹

5.7. Investigation of the Substrate Scope

In the context of our preliminary investigations, we noted that various silanlates could be utilized, including tert-BuMe₂SiOK and i-Pr₃SiOK (Scheme 55), with the products formed in 98 and 99% ee, respectively. Although the triisopropylsilanolate gave somewhat lower regioselectivity (branched : linear = 86:14) the t-butyldimethylsilanolate gave TBS ether 259 in high regioselectivity (branched : linear = 97:3). The fact that both unhindered, labile (TES) and hindered, robust (TBS and TIPS) silyl ethers can be generated is significant. This convenience permits access to free, optically active secondary alcohols (when using TES) as well as stable silyl ethers (TBS, TIPS) that can be carried through multi-step reaction sequences.

Scheme 55: Various Silanolate Salts can be employed

¹⁶¹ Trost observed an increase of regioselectivity in a Pd-catalyzed allylic etherification when changing to more polar solvents, with CH₃CN being optimal in his studies: Trost, B. M.; Toste, F. D. J. Am. Chem. Soc. 1999, 121, 4545.
Once the standard conditions were identified, our efforts were focused on examining the substrate scope (Table 9). Various electron-poor (entries 2-4) and electron-rich (entries 5-6) aryl-substituted allylic carbonates can be employed as the starting materials for the transformation. The subsequent silyl ether cleavage proceeds uneventfully to yield chiral alcohols in 64-88% yield and with 92-98% ee. Notably, the cleavage is conveniently carried out using TBAF in THF. However, a simple deprotection of the crude material involving 30% aq. NaOH in MeOH also allows straightforward access to chiral allylic alcohols. The process tolerates substrates with additional functional groups (acetals, cf. entries 6-7) without showing any deleterious impact on yield or enantioselectivity. In addition, the reaction can be carried out with heterocyclic-substituted allylic carbonates. Thus, thiophene- (entries 8 and 9) and furane-substituted (entries 10 and 11) allylic alcohols can be obtained in good yields and excellent enantioselectivities (97-99% ee). The use of a dienyl carbonate proceeds in a highly regio- and enantioselective fashion (entry 12). The method is tolerant of alkyl-substituted allylic carbonates (entry 13). At the current level of investigation α-branched aliphatic allylic carbonates displayed diminished reactivity.

Table 9: Investigation into the Substrate Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
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<td>![product image]</td>
<td>88b</td>
<td>97</td>
</tr>
<tr>
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<td>![product image]</td>
<td>74b</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>![substrate image]</td>
<td>![product image]</td>
<td>78b</td>
<td>98</td>
</tr>
<tr>
<td>Entry</td>
<td>Structure 1</td>
<td>Structure 2</td>
<td>Yield</td>
<td>ee (%)</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------</td>
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<td>--------</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image2.png" alt="Structure" /></td>
<td>64&lt;sup&gt;c&lt;/sup&gt;</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td><img src="image3.png" alt="Structure" /></td>
<td><img src="image4.png" alt="Structure" /></td>
<td>75&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95</td>
</tr>
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<td>6</td>
<td><img src="image5.png" alt="Structure" /></td>
<td><img src="image6.png" alt="Structure" /></td>
<td>72&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Structure" /></td>
<td><img src="image8.png" alt="Structure" /></td>
<td>70&lt;sup&gt;c&lt;/sup&gt;</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td><img src="image9.png" alt="Structure" /></td>
<td><img src="image10.png" alt="Structure" /></td>
<td>62&lt;sup&gt;b&lt;/sup&gt;</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
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<td>67&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>10</td>
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<td>97</td>
</tr>
<tr>
<td>11</td>
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<td><img src="image16.png" alt="Structure" /></td>
<td>60&lt;sup&gt;c&lt;/sup&gt;</td>
<td>99</td>
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<td><img src="image18.png" alt="Structure" /></td>
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<td><img src="image20.png" alt="Structure" /></td>
<td>65&lt;sup&gt;d&lt;/sup&gt;</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after purification by chromatography; the regioselectivity was found to be >99:1 in favor of the branched product. <sup>b</sup> Silyl ether cleavage was carried out by using 30% aq NaOH in MeOH. <sup>c</sup> Cleavage of the silyl ether was carried out using TBAF. <sup>d</sup> Isolated as the silyl ether because of volatility problems of the corresponding alcohol. <sup>e</sup> The ee value was determined by HPLC or GC on chiral stationary phases; the absolute configuration was established as (S) for entry 1.

### 5.8. Conclusion

In conclusion, a highly regio- and enantioselective Ir-catalyzed allylic etherification of achiral allylic carbonates is described that makes use of potassium silanolates as nucleophiles. In the process a wide range of aryl- and alkyl-substituted carbonates served as substrates. Subsequent mild silyl ether cleavage of the TES adducts gave rapid and reliable access to chiral allylic alcohols in high yields and enantioselectivities. Stable silyl ethers (TBS, TIPS) which can be carried through multi-
step reaction sequences were also formed in excellent yields and enantioselectivities. The fact that optically active allylic alcohols are conveniently accessed with this methodology opens up new avenues for the process involving Ir-catalysis in complex molecule synthesis. Additionally, the use of silanolates may be of interest in other carbon-oxygen bond forming reactions.
6. **Iridium-Catalyzed Synthesis of Primary Allylic Amines from Allylic Alcohols: Sulfamic Acid as an Ammonia Equivalent**

6.1. **Background**

Special attention has been directed to the development of an iridium-catalyzed allylic amination protocol due to the importance of chiral amines as high value-added building blocks in organic syntheses. In the following sections a brief overview of the various employed nucleophiles will be given.

6.2. **Aliphatic Amines as N-Nucleophiles**

In 2002 Hartwig reported the first Ir/phosphoramidite catalyzed allylic amination. Obviously, aliphatic amines, for example benzylamine and pyrrolidine, which were mainly used as nucleophiles in exploratory experiments, are sufficiently basic to induce cyclometallation. However, bulky aliphatic amines and anilines did not work to a synthetically sufficient level, therefore catalyst activation was necessary. Some results of aminations examined by the groups of Hartwig, Helmchen and Alexakis are collected in table 10. Generally, the monoallylated branched product was the major product. The results were slightly better with ligand 233 than with ligand 232. In the cases where R₁ = Ph or alkenyl (entries 1-6) enantiomeric excess was high. Reactions of carbonates with an electron-withdrawing (entry 7) or potentially coordinating (entry 8) ortho-substituent in the aryl group proceeded with considerably reduced degrees of selectivity. Substrates with R₁ = alkyl yielded products with high enantio- but reduced regioselectivity (entries 9, 10). With the bulky Ph₂CH, the standard amination gave only...
11% conversion (entry 12), the activated catalyst gave the product with excellent selectivity in 85% yield.

**Table 10: Ir-catalysed aminations with alkylamines**

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>L*</th>
<th>time [h]</th>
<th>yield</th>
<th>263 : 264 : 265</th>
<th>ee [%]</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Ph</td>
<td>Bn</td>
<td>232</td>
<td>10</td>
<td>84</td>
<td>98 : 1 : 1</td>
<td>95</td>
<td>164</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Bn</td>
<td>233</td>
<td>n.d.</td>
<td>88</td>
<td>98 : 2</td>
<td>97</td>
<td>166a</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>PMB</td>
<td>232</td>
<td>18</td>
<td>80</td>
<td>99 : 0 : 1</td>
<td>94</td>
<td>164</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>n-C₆H₁₁</td>
<td>232</td>
<td>9</td>
<td>88</td>
<td>98 : 2</td>
<td>96</td>
<td>164</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>n-C₆H₁₁</td>
<td>233</td>
<td>n.d.</td>
<td>89</td>
<td>98 : 2</td>
<td>98</td>
<td>166a</td>
</tr>
<tr>
<td>6</td>
<td>PhCH=CH</td>
<td>Bn</td>
<td>232</td>
<td>24</td>
<td>61</td>
<td>99 : 1</td>
<td>97</td>
<td>166a</td>
</tr>
<tr>
<td>7</td>
<td>p-(NO₂)C₆H₄</td>
<td>Bn</td>
<td>232</td>
<td>12</td>
<td>67</td>
<td>83 : 13 : 4</td>
<td>86</td>
<td>164</td>
</tr>
<tr>
<td>8</td>
<td>o-(MeO)C₆H₄</td>
<td>Bn</td>
<td>232</td>
<td>16</td>
<td>77</td>
<td>95 : 4 : 1</td>
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<td>9</td>
<td>n-Pr</td>
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<td>233</td>
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<td>84 : 16</td>
<td>96</td>
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<tr>
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<td>PhCH₂CH₂</td>
<td>Bn</td>
<td>233</td>
<td>0.7</td>
<td>59</td>
<td>84 : 16</td>
<td>96</td>
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<td>12</td>
<td>Ph</td>
<td>Ph₂CH</td>
<td>232</td>
<td>10</td>
<td>11c</td>
<td>-</td>
<td>-</td>
<td>144</td>
</tr>
<tr>
<td>13d</td>
<td>Ph</td>
<td>Ph₂CH</td>
<td>232</td>
<td>10</td>
<td>85</td>
<td>97 : 3</td>
<td>98</td>
<td>144</td>
</tr>
<tr>
<td>14b,e</td>
<td>PhCH₂CH₂</td>
<td>Bn</td>
<td>232</td>
<td>72</td>
<td>0c</td>
<td>-</td>
<td>-</td>
<td>149</td>
</tr>
<tr>
<td>15b,e</td>
<td>PhCH₂CH₂</td>
<td>Bn</td>
<td>232</td>
<td>72</td>
<td>67</td>
<td>81 : 19</td>
<td>95</td>
<td>149</td>
</tr>
</tbody>
</table>

*a Isolated yield of branched product. b The catalyst was activated with TBD. c Conversion. d 1 mol% [IrCl(cod)]₂ was used as catalyst. e 0.4 mol% catalyst. f Addition of 0.4 mol% Pb(NO₃)₂ and tetrahydrothiophene.

### 6.3. Aromatic Amines as N-Nucleophiles

Anilines are not sufficiently basic to induce cyclometallation. Accordingly, catalyst activation by treatment with base (usually n-propylamine or DABCO) was employed.¹⁶⁷ A remarkable feature of these reactions is the uniformly high regioselectivity, even with R¹ being a sp³-substituent such as n-Pr (Table 11). Enantiomeric excess was excellent when using the sterically demanding ligand 234.

It is noteworthy that it was possible to significantly simplify the original catalyst system.\(^1\) In an extension on the mechanistic studies aimed at elucidation of potential catalytic intermediates, Hartwig demonstrated that replacement of the distal chiral phenethyl substituent with a large achiral cycloalkyl group led to a catalyst that reacts with rates that are similar to those of the original catalyst (Figure 25). Even more important, it was possible to substitute the BINOL backbone by an achiral biphenolate backbone and thus reduce the complexity of the original system to a single resolved stereocenter while maintaining reaction rates, selectivities and yields.

It is remarkable that generally only linear, achiral carbonates 261 gave rise to high enantioselectivities. To overcome this intrinsic limitation, Hartwig recently developed a sequential allylic isomerization-substitution process that utilized easily prepared branched, racemic substrates 265 (Scheme 56).\(^{169}\)

Palladium-catalyzed isomerization is followed by the usual amination or etherification process to provide adducts in high yields and enantioselectivities.

### 6.4. Suitable Ammonia Equivalents

Most of the protocols outlined above use anilines or benzylamines as nucleophiles. Whereas secondary and tertiary amines can be accessed in excellent yields and stereoselectivities, the preparation of primary chiral amines requires difficult deprotection steps. In a similar fashion as our work with silanolates, we focused again on developing a synthetic equivalent that would give rapid and easy access to chiral allylic

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amines. A number of research groups already developed such ammonia equivalents in the context of this process.

6.4.1. Hydroxylamines as N-Nucleophiles

Takemoto et al. employed hydroxylamines as N-nucleophiles (Scheme 57). Phosphates rather than carbonates, which did not react, were used as substrates. The addition of CsOH-H$_2$O or Ba(OH)$_2$-H$_2$O had to be added in order to improve regio- and enantioselectivity.

\[
\begin{align*}
\text{[IrCl(cod)$_2$]} & \quad \text{(4 mol\%)} \\
\text{P(0)(OEt)$_2$ H} & \\
\text{Ph} & \quad \text{247} \\
\text{267} & \quad \text{267} \\
\text{Bz} & \quad \text{OBn} \\
\text{Bz} & \quad \text{OBn} \\
\text{N} & \quad \text{N} \\
\text{Ar} = \text{p-CIC}_6\text{H}_4 & \\
\text{b/l} = 70:30, 87\% \text{ ee (75\%)} \\
\text{Ar} = \text{a-Naphthyl} & \\
\text{b/l} = >95:5, 96\% \text{ ee (95\%)} \\
\text{CsOH-H}_2\text{O (1 equiv)} & \\
\text{CH}_2\text{Cl}_2, -20 \, ^\circ\text{C} & \\
\text{Ar} & \\
\text{Ph-pybox} & \quad \text{249} \\
\end{align*}
\]

Scheme 57: Takemoto’s hydroxylamine equivalent

6.4.2. N-Sulfonyl and N,N-Diacylamines as N-Nucleophiles

Helmchen introduced o- and p-nitrophenylsulfonylamines as ammonia equivalents (Scheme 58).$^{170}$ They are sufficiently acidic to react without additional base, the internal methoxide which is liberated from the leaving group presumably acts as a base.

\[
\begin{align*}
\text{Ph} & \quad \text{270} \\
\text{OCCO}_2\text{Me} & \quad \text{+ Nu} \\
\text{[IrCl(cod)$_2$]} & \quad \text{(2 mol\%)} \\
\text{232 (4 mol\%)} & \\
\text{THF, 23 \, ^\circ\text{C}} & \\
\text{Nu} & \quad \text{271} \\
\text{H}_2\text{N} & \quad \text{SO} & \quad \text{H}_2\text{N} \\
\text{NO}_2 & \quad \text{O} & \quad \text{H} \\
\text{Boc}$ & \quad \text{N} & \quad \text{Boc} \\
\text{Na} & \\
\text{92\%, 96\% ee} & \quad \text{95\%, 98\% ee} & \quad \text{80\%, 97\% ee} & \quad \text{96\%, 98\% ee} \\
\text{90:10 b/l} & \quad \text{96:4 b/l} & \quad \text{97:3 b/l} & \quad \text{98:2 b/l} \\
\end{align*}
\]

Scheme 58: Allylic aminations with sulfonylamides and N,N-diacylamines

Whereas carboxamides cannot be employed in this process so far, substitutions with \(N,N\)-diacylamines, for example \(\text{HN(Boc)}_2\), and \(\text{HN(Boc)(CHO)}\), furnished excellent yields and selectivities. The reaction with \(\text{HN(Boc)}_2\) was very slow, however, complete conversion was obtained with the sodium salt \(\text{NaN(Boc)}_2\).

6.5. Sulfamic Acid as Ammonia Equivalent

In order to increase practicality and atom-economy\(^\text{171}\) of the iridium-catalyzed allylic amination to give primary amines we have investigated the chemistry of sulfamic acid (\(\text{H}_2\text{NSO}_3\text{H}\)) and specifically its capacity to serve as an ammonia equivalent.\(^\text{172}\) Sulfamic acid is a crystalline, inexpensive solid that has found only limited applications in organic synthesis, primarily as an acid catalyst.\(^\text{173}\) Traditionally, it has been used as hypochlorous acid scavenger in Lindgren oxidations.\(^\text{174}\) The compound finds widespread use in electroplating industry, as acid detergent, for chlorine stabilization in swimming pools and other applications. However, sulfamic acid has never been employed as a nitrogen source in a process, despite its many obvious and potential advantages.

At the outset of the investigations, \textit{tert}-butyl cinnamyl carbonate 255 was examined as a test substrate in its reaction with sulfamic acid in the presence of a catalyst derived from \textit{Feringa’s} phophoramidite ligand 232 and \textit{Ir(I)} (Figure 25). However, all experiments conducted in THF, \(\text{CH}_2\text{Cl}_2\), \(\text{CH}_3\text{CN}\), \(\text{EtOH}\), \(\text{MeOH}\) or acetone were hampered by the low solubility of sulfamic acid, leading to recovery of starting material 255.

![Figure 25: Employed Substrates](image_url)

\(^{172}\) For reviews on the chemistry of sulfamic acid, see: a) Benson, G. A.; Spillane, W. J. \textit{Chem. Rev.} 1980, 80, 151; b) Wang, B. \textit{Synlett} 2005, 1342. Sulfamic acid can be purchased from a number of commercial suppliers, e.g. Fluka Switzerland, 2007, 5 kg à CHF 94 = $ 78.
Although in dipolar aprotic solvents such as DMF, DMA or DMSO sulfamic acid is soluble, no conversion to the targeted amine product or its derivatives (ie. secondary sulfamate) was observed.

The first set of promising results were noted with branched tert-butyl carbonate 272 as substrate in DMF (15% conversion). Of greater significance, however, was the subsequent surprising observation that alcohol 273 could be employed directly under otherwise identical conditions (15% conversion). This key finding and the subsequent spectroscopic investigations were central to the further optimization of the process. In transition-metal catalyzed allylic substitution reactions, activated allylic substrates, e.g. halides, esters, carbonates or carbamates are usually required to facilitate the formation of the necessary allyl-metal intermediate.\textsuperscript{175} Alternatively, added metal reagents (Et$_3$B) or catalysts (Bi(III)), can provide for \textit{in situ} activation of a free alcohol.\textsuperscript{176} A recent paper by Shibasaki nicely illustrates the possibility of activating allylic and propargylic alcohols with catalytic amounts of Bi(OTf)$_3$. The substitution was then directly carried out by a number of nucleophiles including sulfonamides, carbamates and carboxamides.\textsuperscript{177}

\begin{equation}
\begin{aligned}
\text{Ph} & \equiv \text{OH} \\
\text{Ph} + \text{TsNH}_2 & \xrightarrow{\text{Bi(OTf)}_3 (2 \text{ mol}%) \\
& \text{KPF}_6 (2 \text{ mol})} \xrightarrow{1,4\text{-dioxane}, 0.2 \text{ h}, 23 \text{ °C} \\
& \text{drierite (CaSO}_4) \text{]} \xrightarrow{1.5 \text{ equiv}} \text{Ph} \equiv \text{NHTs} \\
\text{274} & \rightarrow \text{275} \text{ 96% yield}
\end{aligned}
\end{equation}

\textbf{Scheme 58: Shibasaki’s bismuth-catalyzed direct catalytic substitution}

The potential development of a process involving the direct use of allylic alcohols was an unexpected boon. Moreover, a process in which a single reagent serves as both the ammonia source and \textit{in situ} hydroxy activator has not been previously reported in transition-metal mediated processes.


In further experimentation, the influence of various ligands was examined. The nitrogen-based pybox ligand 249 only displayed decreased reactivity (5% conversion). Whereas the amination did not proceed with PPh$_3$ and P(NMe$_2$)$_3$ (< 5% conversion), a conversion of 25% was obtained with P(OPh)$_3$. Encouraged by this result and exploiting the modular structure of phosphoramidites, attention was focused on the achiral variant of the phosphoramidite ligand 276 (Figure 26).

![Figure 26: Investigated phosphoramidite ligands](image)

Using 1.5 mol% [Ir(cod)Cl]$_2$, 3 mol% 276, we obtained 30% conversion of 273 (DMF, 24 h, 23 °C). Based on our interest in alkenes as ligands in transition-metal catalysis, olefin ligands were investigated in the substitution process. Ligand 277 can easily be synthesized starting from inexpensive 2,2'-biphenol, PCl$_3$ and 5$H$-dibenzo[b,f]azepine. Our efforts were rewarded by a remarkably clean reaction (>99% conversion, DMF, 24 h, 23 °C). When saturated analogue ligand 278 was employed, alcohol 273 is only converted to 20%. We speculate that the presence of the olefin in 277 may at the very least serve to stabilize any of the various intermediate complexes that are part of the catalytic cycle. In this respect, the bent structure of 5$H$-dibenzo[b,f]azepine reduces the amount of conjugation and renders the olefin unit more susceptible to coordination with a transition metal. The central azepine in 5$H$-dibenzo[b,f]azepine is known to adopt a boat conformation.

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179 For bidentate phosphorus-olefin ligands used in asymmetric catalysis, compare chapter 1.4.

180 In the course of the reaction with ligand 275, the color of the reaction mixture changes from initially light yellow to dark brown. TLC indicates partial ligand decomposition.

It is worth noting that the Ir-catalyzed transformation proceeds with complete regioselectivity. Furthermore, neither di- nor triallylated amines could be observed in the unpurified reaction mixture.

With an optimal protocol in hand, the reaction scope was investigated (Table 12). A convenient way to isolate the amine products is precipitation as their hydrochloride salts. However, a salient feature of the process described herein results from the use of an ammonia equivalent, wherein subsequent one-pot protection as benzamide (entry 2), Boc-carbamate (entry 3) or trifluoroacetamide (entry 4) is feasible and, in fact, can facilitate isolation for certain small molecular-weight substances produced on small scale. Various substituents are accepted in the substrate including phenyl- (entry 5), cylohexyl- (entry 6) as well as benzyloxymethyl-substituted allylic amines (entry 7). Additionally, the isolation of hexa-1,5-dien-3-amine hydrochloride (entry 8) proceeded with 75% yield without any double bond isomerization.

Table 12: Investigation into the substrate scope

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
</table>
| 1     | \begin{align*} & \text{benzyl (entry 5)} \\
|       | \text{cylohexyl (entry 6)} |
| 2     | \begin{align*} & \text{benzyl (entry 5)} \\
|       | \text{cylohexyl (entry 6)} |
| 3     | \begin{align*} & \text{benzyl (entry 5)} \\
|       | \text{cylohexyl (entry 6)} |


This contrasts regioselectivity problems (Sn2 vs. Sn2') in Mitsunobu-type conversion of allyl derivatives, for a study see: Mulzer, J.; Funk, G. Synthesis, 1995, 101.
6.6. Spectroscopic Investigations

To obtain further insight in this interesting process, the course of the reaction was followed using time-dependent \(^1\)H-NMR spectroscopy in d\(^7\)-DMF, monitoring the signal corresponding to H-3 of our test alcohol 273. As was observed during preparative scale experiments NMR studies revealed that clean transformation of 273 (\(\delta\) (H-3) 4.04 ppm) into the corresponding amine 279 (\(\delta\) (H-3) 3.88 ppm) occurred within 3 h (Figure 27). In a separate experiment, we investigated the influence of excess sulfamic acid (2 equiv). At first, the desired amine 279 is generated after 2 h as evidenced by the appearance of the corresponding signal of the amine at \(\delta\) (H-3) 3.88 ppm; when the reaction is allowed to continue over 8 h amine 279 is observed to undergo partial conversion into another product with a characteristic signal at \(\delta\) 4.46 ppm. In order to assign a structure for this species, we conducted additional experiments in d\(^7\)-DMF: Treatment of alcohol 273 with two equivalents of sulfamic acid leads after 8 h to the quantitative formation of sulfate ester 280 (\(\delta\) (H-3) 4.72 ppm) which is consistent to what is known in literature.
Ir-Catalyzed Synthesis of Allylic Amines using Sulfamic Acid

Figure 27: Selected Results from Spectroscopic Experiments in d<sup>5</sup>-DMF

The more potent commercially available sulfating agent sulfur trioxide-N,N-dimethylformamide performs sulfation in an analogous way to deliver 280 (δ (H-3) 4.72 ppm) already after 1 h. When amine 279 is treated under the same conditions, sulfamate 281 could be obtained along with side products after 9 h. These spectroscopic observations allow us to draw the following conclusions: (1) When an excess of sulfamic acid is employed, the initially produced amine 279 partially undergoes sulfamation using the second equivalent of sulfamic acid to form 281. It is important to note that this sulfamation only starts after 273 has been entirely transformed to 279. (2) In the iridium-catalyzed process no signals due to 280 are observed throughout the course of the reaction. Given the long reaction time (8 h) required to perform the sulfation with sulfamic acid, it is unlikely that sulfate ester 280 serves as activated intermediate in the iridium-catalyzed reaction. (3) Moreover, the absence of 281 in the catalytic process leads us to suspect that sulfamic acid is not acting as nucleophile.

Based on these observations we have generated a working model (Figure 28). It has been suggested in the literature that N,N-dimethylformamide undergoes condensation with sulfamic acid<sup>184</sup> to form Vilsmeier-like intermediate 282.<sup>185</sup> We speculate that this reactive intermediate is generated and subsequently reacts with the allylic alcohol to form 283.<sup>186</sup> This in situ activated species is then in a position to participate in oxidative addition with the iridium complex.<sup>187</sup> The resulting iridium-allyl species 284 is

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<sup>185</sup> DMF-SO<sub>3</sub> can be viewed as Vilsmeier adduct: Wolfrom, M. L.; Shen Han, T. M. J. Am. Chem. Soc. 1959, 81, 1764.

<sup>186</sup> For a recent example of activation of alcohols with Vilsmeier reagents: Kawano, Y.; Kenko, N.; Mukaiyama, T. Chem. Lett. 2005, 34, 1612.

<sup>187</sup> For the transition metal-catalyzed oxidative addition of allylic imidates: Schenck, T. G.; Bosnich, B. J. Am. Chem. Soc. 1985, 107, 2058.
sufficiently electrophilic to participate in nucleophilic attack by NH₃, liberating the primary allylic amine product that is isolated.

![Proposed Working Model](image)

**Figure 28: Proposed Working Model**

### 6.7. Initial Experiments aimed at the Development of an Asymmetric, Catalytic Process

We were interested in applying the unique aspects of sulfamic acid chemistry we have noted to a catalytic asymmetric process. The following experiment was carried out to investigate if the allylation proceeds in an enantiospecific way: Treatment of (R)-phenylprop-2-en-1-ol 285 with one equivalent sulfamic acid and catalysis by Ir(I)/phosphoramidite 277 led after 24 h at 23 °C to the formation of the corresponding amine which was isolated as its corresponding benzamide 286. However during the course of the reaction enantioselectivity decreased from 88% to 44%.

![Scheme 58: Allylic Amination with an enantioenriched Allylic Alcohol](image)

**Scheme 58: Allylic Amination with an enantioenriched Allylic Alcohol**
The modular structure of phosphoramidite ligand 277 allows incorporation of a wide range of chiral diol backbones. For instance, integration of (S)-BINOL instead of 2,2’-biphenol yielded a chiral ligand 289 in combination with Ir(I) can be used in the reaction of 1-cyclohexylprop-2-en-1-ol 287 to provide (S)-1-cyclohexylprop-2-en-1-amine hydrochloride 288 in 70% yield and 70% ee (Scheme 59). It was possible to upgrade the ee to a synthetically useful level (93% ee) by digeration of the hydrochloride salt. Although this is still far from optimal, it represents the first example of direct generation of a primary optically active allylic amine from an allylic alcohol.

![Scheme 59: Catalytic, Asymmetric Synthesis of Allylic Amines](image)

6.8. Conclusion

In conclusion, we demonstrate for the first time the direct iridium-catalyzed conversion of an allylic alcohol to an allylic amine with the use of sulfamic acid. Neither separate prior activation nor a protecting group is required to perform this transformation, which render the process attractive economically and ecologically. Preliminary results towards the development of an asymmetric process are promising. Further mechanistic investigations as well as fine-tuning of ligands are underway and will be reported in due course. The fact that sulfamic acid can serve as an ammonia equivalent is intriguing, and may have applications in other transformations involving OH to NH2 conversion.
7. Conclusion and Outlook

In the first part of this work, we described our efforts towards the synthesis of a family of novel chiral ligands employing olefins as donor moieties. Their catalytic performance was explored in a number of different transition-metal catalyzed processes.

In the first synthesis, a chiral bicycloocta[2.2.2]diene was prepared in four steps starting from (R)-(−)-carvone. This scaffold served as an efficient chiral ligand in an Ir-catalyzed kinetic resolution of allylic carbonates. The ligand geometry was optimized in order to reach high enantioselectivities in Rh-catalyzed asymmetric conjugate addition reactions of aryl- and alkenylboronic acids to various α,β-unsaturated acceptors. It is important to note that not only standard substrates such as cyclic or acyclic enones, but also more challenging synthetically useful substrates such as α,β-unsaturated aldehydes and esters yielded 1,4-adducts in high yields and stereoselectivities. We have demonstrated that chiral olefins can serve as valuable ligands in asymmetric catalysis, complementing traditional heteroatom-based ligands.

Further developments in this area will strongly dependent on the ease of accessibility of these ligands. As classical resolution or separation of enantiomers by HPLC using chiral stationary phases impose severe constraints to the scale-up of the ligand synthesis, the most straightforward and practical approach to access chiral dienes might be to start with compounds obtained from the chiral pool. In this respect, the synthesis of 294 might be worthwhile to be highlighted (Scheme 60):

![Scheme 60: Straightforward access to a novel chiral olefin scaffold](image)

D-isomannide 290 can be transformed via a) oxidation, b) vinyl triflate formation and c) transition-metal catalyzed aryl coupling to a chiral, nonracemic diene 294. D-Isomannide is a commercially available, inexpensive carbohydrate derivative.

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easily accessible by acid treatment of D-mannitol.\textsuperscript{189,190} Preliminary simple modeling studies predict that the olefin units in \textbf{294} are well-oriented to provide for stable coordination with a metal center. The straightforward and modular access to \textbf{294} should enable the formation of a library of diene ligands.

A number of processes deserve investigation with chiral diene ligands. In this respect, a recent report by Tilley on the Pt-catalyzed hydroamination might serve as an example.\textsuperscript{191} In this transformation, a variety of olefins (also non-activated olefins such as \textbf{298}) react with weakly basic amines and sulfonamides as nucleophiles (Scheme 61).

\begin{center}
\textbf{Scheme 61:} Tilley's Pt-catalyzed hydroamination reaction
\end{center}

In a number of mechanistic experiments which aimed at elucidating the active form of the catalyst, Tilley identified \([\text{Pt}(\text{cod})(\text{alkene})_2](\text{OTf})_2\). Importantly, it was possible to show that cyclooctadiene remains bound to Pt during the course of catalysis. This observation might have important implications for the development of an asymmetric version of the process. Substitution of the cyclooctadiene by a chiral diene in the ligand precursor might thus be a suitable way to introduce stereoselectivity.

In the second part of this thesis, novel water and ammonia equivalents were examined as nucleophiles in Ir-catalyzed allylic displacement reactions. The use of silanolates gave rise to chiral allylic alcohols in high yields and stereoselectivities. More importantly, we documented the use of sulfamic acid as an ammonia equivalent. The role


of this reagent was not only limited to its function as a source of nitrogen, but it also
served in combination with the solvent DMF as an \textit{in situ} activator for hydroxyl groups.
Consequently, allylic alcohols were directly employed without any need for further
activation; a fact that significantly increased the practicality of the process.

Considering other fields of application for sulfamic acid, a number of
transformations that involve OH to NH$_2$ transformation might be thought of. In this
respect, \textit{Marshall} reported a method for the synthesis of nonracemic propargylic amines
starting from propargylic mesylates (Scheme 62).\textsuperscript{192}

\textbf{Scheme 62: Marshall’s transformation of a propargylic mesylate into a propargylic amine}

The Pd-catalyzed reaction proceeds with retention of configuration, presumably
via an allenyl Pd intermediate. It might be worthwhile investigating this reaction
provided sulfamic acid can serve as effective nucleophile. Moreover, it would represent
an exquisite testing ground to examine if the mode of activation found for allylic alcohols
finds an analogy in the propargylic alcohols.

Furthermore, it might be interesting to investigate the ability of sulfamic acid as
nucleophile in similar hydroamination reactions as described above. \textit{Togni} pointed out,
that a catalytic hydroamination that proceeds via olefin activation at the metal center
necessitates a nitrogen base that is a weak donor, such that it does not compete with the
olefin for metal binding.\textsuperscript{193} However, the amine must be nucleophilic enough to attack a
carbon atom of the metal-olefin complex. These conflicting requirements appear to limit
the range of substrates that may currently be used in hydroamination. Taken into account
the low basicity of sulfamic acid, it might be well suited as an ammonia equivalent in
hydroamination reactions.

8. Experimental Section

8.1. General Methods

All reactions were carried out in oven dried glassware under an atmosphere of argon or nitrogen unless otherwise stated. For the reactions, THF, Et₂O, CH₃CN, toluene and CH₂Cl₂ were purified by distillation and dried by passage over two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; Macherey und Nagel; activated under a flow of N₂ at 300° over night; solvent drying system) under an argon atmosphere (H₂O content < 30 ppm, Karl-Fischer titration). 1,4-dioxane (Acros, 99.5%, extra dry over molecular sieves) and N,N-Dimethylformamide (Fluka, > 99.5%, stored over molecular sieves) were employed. Et₃N and pyridine were distilled under nitrogen from KOH. All chemicals were purchased from Acros, Aldrich, Fluka, Merck or Lancaster and used as such unless otherwise stated. Silanols were obtained from Lancaster, sulfamic acid was received from Fluka (>99.3%, lot number: 1097230). [RhCl(C₅H₄)₂]₂, [RhCl(cod)]₂, [IrCl(cod)]₂ were bought from Strem Chemicals. [IrCl(coe)₂]₂ was prepared according to the following literature procedures from IrCl₃: R. H. Crabtree, J. M. Quirk, Synth. React. Inorg. Met.-Org. Chem. 1982, 12, 407. Deuterated solvents were obtained from Armar Chemicals, Döttingen, Switzerland in the indicated purity grade.

Chromatographic purification was performed as flash chromatography with 0.3-0.5 bar pressure using Brunschwig silica 32-63, 60Å. Technical grade solvents were employed, which were distilled prior to use. Chromatographic purification of the allylic amines was performed using alumina Woelm N, Akt. 1 using CH₂Cl₂/methanol as eluent.

TLC was performed on Merck silica gel 60 F₂₅₄ TLC glass plates and visualized with UV light or permanganate stain.

Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected.

¹H-NMR spectra were recorded on a VARIAN Mercury 300 MHz or a Gemini 300 MHz spectrometer in chloroform-d, CD₃OD and d⁷-DMF. All signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal methanol signal at 3.30 ppm, the internal DMF signal at 8.01 ppm as standard. The data is being reported as (s = singlet, d
= doublet, t = triplet, q = quadruplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration).

$^{13}$C-NMR spectra were recorded with $^1$H-decoupling on a VARIAN Mercury 75 MHz spectrometer in chloroform-d, CD$_3$OD and d$^7$-DMF. All signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal methanol signal at 49.0 ppm

$^{19}$F-NMR spectra were recorded with $^1$H-decoupling on a VARIAN Mercury 282 MHz spectrometer in the indicated deuterated solvent.

$^{31}$P-NMR spectra were recorded with $^1$H-decoupling on a VARIAN Mercury 121 MHz spectrometer in the indicated deuterated solvent.

Infrared spectra were recorded on a Perkin Elmer Spectrophotometer RX-I FT-IR as thin film or neat on a Varian 800 FT-IR Scimlar Series spectrophotometer.

Optical rotations were measured on a JASCO DIP-1000 digital polarimeter in 10 cm, 2 mL cells, the concentration in g/100 mL and the solvent is given in parentheses.

HPLC analyses were carried out on a Merck Hitachi D-7000 system with Daicel columns in hexanes/PrOH mixtures. Conditions, retention times and columns used are given in parentheses.

Gas chromatographic measurements were performed on a HP 6890 Series gas chromatography system using a Supelco fused silica column β-Dex 120 (length: 30 m, diameter: 0.25 cm, film thickness: 0.25 μm), hydrogen as carrier gas and a FID detector.

High resolution mass spectrometric measurements were performed by the mass spectrometry service of the Laboratorium für Organische Chemie at the ETH Zürich on a Finnigan TSQ 7000 ESI spectrometer for low resolution measurements. An IonSpec Ultima HR FT-ICR MS MALDI was employed for high resolution measurements using the DHB-tl (2,5-Dihydroxybenzoic acid-two layers) method at 4.7 Tesla. Alternatively, an Ion Spec ESI-FT-ICR spectrometer at 4.7 Tesla or a EI-HIRES Micromass Autospel-Ultima spectrometer at 70 eV were employed.

Elemental analysis was performed by the Mikroelementaranalytisches Laboratorium der ETH Zürich.
8.2. Kinetic Resolution of Allylic Carbonates – Chiral Bicyclo[2.2.2]octadienes as Novel Ligands in Asymmetric Synthesis

8.2.1. Synthesis of the Ligands

GP1: Ligand Synthesis

A stirred solution of the aryl bromide (1.0 mmol, 2.5 equiv) in 3 mL dry THF under argon at -78 °C was treated with 1.3 mL tBuLi (2.0 mmol, 5 equiv) [1.5M in pentane], and then with a solution of 136 mg ZnCl₂ (1.0 mmol, 2.5 equiv) in 1 mL dry THF. The mixture was allowed to warm to room temperature. A premixed solution of (1S,4R,8R)-8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl trifluoromethane sulfonate (105) (125 mg, 0.40 mmol, 1 equiv) and Pd(PPh₃)₄ (23 mg, 0.02 mmol, 0.05 equiv) in 2 mL dry THF were added dropwise to the colorless reaction mixture. The resulting red-brown solution was stirred for 8 h at room temperature. Saturated aqueous ammonium chloride (3 mL) followed by water (2 mL) and Et₂O (5 mL) were added, and the organic layer was separated. The aqueous layer was extracted three times with 5 mL Et₂O. The combined organic layers were dried over Na₂SO₄, and the solvent was removed in vacuo. The crude oils were purified by flash chromatography using pentane/diethylether (30:1) as eluent.

\[(R)-5-(2-Bromo-1-methoxy-1-methyl-ethyl)-2-methylcyclohex-2-en-1-one (103)\]

Under argon, R-(-)-carvone 19 (15.0 g, 0.10 mol, 1 equiv) was placed in a 250 mL flask. Upon cooling to 0 °C 60 mL methanol and 90 mL CH₂Cl₂ were added. The colorless solution was stirred for 10 min, then N-bromosuccinimide (21.4 g, 0.12 mol, 1.2 equiv) was added in three portions over 90 min. The last aliquot did not completely dissolve and gave a yellow suspension. After warming to 23 °C, the reaction was allowed to stir for 16 h. The yellow solution was diluted with 200 mL CH₂Cl₂ and 2 % aqueous NaOH solution as well as brine. The organic layer was dried over Na₂SO₄. Solvent evaporation gave a
yellow oil, which was purified by column chromatography on silica gel (hexanes/EtOAc 6:1). The title compound 103 (23.9 g, 0.09 mmol, 91%) was received as a diastereomeric mixture which was not separated.

\(^{1}\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 6.78-6.76 (m, 1H), 3.50-3.38 (m, 2H), 3.24 and 3.23 (s, 3H), 2.58-2.20 (m, 5H), 1.78 (s, 3H), 1.26 (s, 3H).


\((1S, 4S, 5R)-5\)-methoxy-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (104A) and \((1S, 4S, 5S)-5\)-methoxy-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (104B)

A solution containing (R)-5-(2-Bromo-1-methoxy-1-methyl-ethyl)-2-methylcyclohex-2-en-1-one (103) (23.3 g, 89.2 mmol, 1.0 equiv) in 200 mL freshly distilled t-BuOH and 250 mL THF was cooled to 0 °C. The orange solution was stirred for 10 min, then t-BuOK (11.8 g, 105 mmol, 1.17 equiv) was slowly added in three portions over 30 min. Immediate color change to dark brown/black was observed along with the formation of a precipitate. After 10 min at 0 °C the reaction mixture was allowed to warm to 23 °C and stirred for 8 h. Acidic brine (3% HCl) was added to the brown suspension and the mixture was extracted three times with Et\(_2\)O. The combined organic layers were washed with brine and dried over Na\(_2\)SO\(_4\). Solvent evaporation gave a brown oil which was purified by chromatography on silica gel (hexanes/EtOAc 6:1) with 104A (6.42 g, 35.7 mmol, 40%) eluting first followed by 104B (4.01 g, 22.3 mmol, 25%).

104A: \(^{1}\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 6.41 (t, \(J = 7.5\) Hz, 1H), 5.81 (d, \(J = 8.1\) Hz, 1H), 3.15 (s, 3H), 2.88 (m, 1H), 2.50 (dd, \(J = 18.0\), 3.3 Hz, 1H), 1.84 (dt, \(J = 18.3\), 3.3 Hz, 1H), 1.73 (dd, \(J = 13.5\), 3.3 Hz, 1H), 1.42 (dd, \(J = 13.8\), 3.3 Hz, 1H), 1.23 (s, 3H), 1.12 (s, 3H);
**104B:** $^1$H NMR (CDCl$_3$, 300 MHz) δ 6.42 (t, $J = 8.1$ Hz, 1H), 5.88 (d, $J = 8.1$ Hz, 1H), 3.13 (s, 3H), 2.97 (m, 1H), 2.05 (m, 2H), 1.61 (ABq, $J = 15.0$ Hz, 2H), 1.32 (s, 3H), 1.14 (s, 3H).


**(1S,4R,8R)-8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl trifluoromethane sulfonate (105)**

![Structural formula](image-url)

Under argon, iPr$_2$NH (3.22 mL, 24.6 mmol, 1.5 equiv) was placed in a 250 mL flask and 100 mL THF was added. The solution was cooled to -78 °C and nBuLi [2.5M in hexanes] (10.0 mL, 25.0 mmol, 1.5 equiv) was added dropwise. The light yellow solution was stirred for 20 minutes before (1S,5R,4R)-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (104A) (2.96 g, 16.4 mmol, 1.0 equiv) in 10 mL THF was added. The yellow reaction mixture was stirred for one hour at -78 °C. N-Phenylbistriflimide (8.9 g, 75 mmol, 4.6 equiv) was added in one portion and the reaction stirred for 8 h gradually allowing it to warm to room temperature. The orange solution was quenched with water and the THF was removed in vacuo. CH$_2$Cl$_2$ was added and the aqueous layer extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. Solvent evaporation gave an orange oil which was purified by column chromatography to give the title compound 105 (4.31 g, 13.8 mmol, 84%) as a yellowish oil.

$[\alpha]_D^{17} = +1.8$ (c = 1.12, CHCl$_3$);
Experimental Section

$^1$H NMR (CDCl₃, 300 MHz) δ 6.30 (t, J = 6.5 Hz, 1H), 6.14-6.08 (m, 2H), 3.59 (dt, J = 6.5, 1.6 Hz, 1H), 3.16 (s, 3H), 1.78 (d, J = 12.1 Hz 1H), 1.46 (s, 3H), 1.29 (d, J = 12.1 Hz, 1H), 1.27 (s, 3H);

$^{13}$C NMR (CDCl₃, 75 MHz) δ 155.5, 139.9, 133.7, 119.7, 83.7, 49.9, 49.2, 47.4, 44.6, 24.5, 17.5;

$^{19}$F NMR (CDCl₃, 282 MHz) δ -73.2;

IR (thin film) 3062, 2976, 2939, 2829, 1720, 1655, 1605, 1459, 1444, 1420, 1372, 1348, 1313, 1280, 1247, 1212, 1142, 1109, 1082, 1068, 1053, 914, 875, 844, 789, 738, 693, 608 cm⁻¹;

Anal. Calcd for C₁₂H₁₅F₃O₄S: C, 46.15; H, 4.84. Found: C, 46.12; H, 5.00.

(1S,4R,5R)-5-methoxy-1,5-dimethyl-2-phenylbicyclo[2.2.2]octa-2,7-diene (106)

(1S,4R,8R)-8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl trifluoromethane sulfonate (105) (220 mg, 0.70 mmol, 1 equiv) and Pd(PPh₃)₄ (40.0 mg, 35.2 µmol, 0.05 equiv) were placed in a 25 mL flask. After addition of 10 mL THF, a red solution was obtained. PhZnBr [0.5M solution in THF] (5.0 mL, 2.5 mmol, 3.6 equiv) was added to this solution and the resulting dark mixture was stirred for 8 h at room temperature. Then NH₄Cl solution was added and the layers were separated. The aqueous layer was twice extracted with Et₂O and the combined layers washed with brine. The organic layer was dried over Na₂SO₄, the solvents evaporated and the residue purified by flash chromatography. The title compound 106 (105 mg, 0.44 mmol, 62%) was isolated as a colorless oil.

$\left[\alpha\right]_{D}^{25} = -35.7$ (c = 1.12, CHCl₃);

$^1$H NMR (CDCl₃, 300 MHz) δ 7.32-7.23 (m, 3H), 7.15-7.12 (m, 2H), 6.40-6.36 (m, 1H), 6.18-6.14 (m, 2H), 3.63 (dt, J = 5.9, 1.1 Hz, 1H), 3.21 (s, 3H), 1.63 (d, J = 11.8 Hz, 1H), (one H under the 2 methyl groups), 1.32 (s, 3H), 1.30 (s, 3H);
Experimental Section

\[^{13}\text{C} \text{ NMR (CDCl}_3, \text{ 75 MHz)}\] \(\delta\) 150.0, 141.8, 139.8, 134.2, 131.6, 128.7, 127.8, 126.6, 84.3, 50.8, 50.1, 47.9, 45.6, 25.0, 22.0;

\textbf{IR (thin film)} 3053, 2963, 2930, 2823, 1603, 1492, 1454, 1367, 1346, 1239, 1198, 1126, 1100, 1074, 904, 837, 762, 740, 702, 685 cm\(^{-1}\);

\textbf{MS(EI)} m/z (relative intensity): 239.9 (63\%), 107.0 (100\%), 77.0 (50\%);

\textbf{Anal.} Calcd for C\(_{17}\)H\(_{20}\)O: C, 84.96; H, 8.39. Found: C, 84.85; H, 8.28.

(1S,4R,5R)-2-(biphenyl-4-yl)-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene (107)

\[
\begin{array}{c}
\text{Me} & \text{OMe} \\
\text{Me} & \text{Ph} \\
\end{array}
\]

Compound 107 was synthesized according to GP1. 67 mg (21 mmol, 53\%) ligand was obtained as clear, colorless oil.

\([\alpha]_D^5 = -49.5 \text{ (c = 0.46, CHCl}_3)\);

\[^1\text{H} \text{ NMR (CDCl}_3, \text{ 300 MHz)}\] \(\delta\) 7.62-7.58 (m, 2H), 7.55-7.50 (m, 2H), 7.46-7.40 (m, 2H), 7.36-7.30 (m, 1H), 7.24-7.20 (m, 2H), 6.39 (d, \(J = 6.8\) Hz, 1H), 6.22 (d, \(J = 5.9\) Hz, 1H), 6.20 (dd, \(J = 7.3, 1.2\) Hz, 1H), 3.65 (dt, \(J = 6.2, 1.2\) Hz, 1H), 3.22 (s, 3H), 1.65 (d, \(J = 11.8\) Hz, 1H), 1.38 (s, 3H), (one H under the 2 methyl groups), 1.31 (s, 3H);

\[^{13}\text{C} \text{ NMR (CDCl}_3, \text{ 75 MHz)}\] \(\delta\) 149.3, 141.6, 140.9, 139.2, 138.5, 133.9, 131.6, 128.8, 128.6, 127.0, 126.9, 126.3, 84.2, 50.7, 50.0, 47.8, 45.5, 24.9, 21.9;

\textbf{IR (thin film)} 3052, 2962, 2929, 2822, 1720, 1597, 1486, 1453, 1367, 1345, 1236, 1198, 1126, 1100, 1074, 108, 828, 767, 724, 712, 697 cm\(^{-1}\);

\textbf{HRMS} calcd for C\(_{23}\)H\(_{24}\)ONa (M + Na\(^+\)) 339.1725, found 339.1725.
Compound 108 was synthesized according to GP1. 70.0 mg (21.0 mmol, 53%) ligand was obtained as clear, colorless oil.

\[ \alpha \] = -50.3 (c = 1.03, CHCl₃);

\(^1\)H NMR (CDCl₃, 300 MHz) δ 7.36-7.31 (m, 2H), 7.12-7.00 (m, 5H), 6.95-6.92 (m, 2H), 6.37 (t, \( J = 6.8 \) Hz, 1H), 6.18-6.14 (m, 2H), 3.63 (dt, \( J = 5.9, 1.2 \) Hz, 1H), 3.21 (s, 3H), 1.61 (d, \( J = 11.8 \) Hz, 1H), 1.34 (s, 3H), (one H under the 2 methyl groups), 1.30 (s, 3H);

\(^{13}\)C NMR (CDCl₃, 75 MHz) δ 155.7, 149.1, 141.5, 134.5, 133.9, 131.4, 129.7, 129.6, 123.0, 118.7, 118.1, 84.2, 50.6, 50.0, 47.8, 45.5, 24.9, 21.9;

IR (thin film) 3040, 2962, 2929, 2823, 1721, 1589, 1502, 1489, 1455, 1367, 1345, 1236, 1199, 1166, 1100, 1074, 1016, 904, 870, 831, 775, 754, 733, 712, 692 cm\(^{-1}\);

HRMS calcd for C\(_{23}\)H\(_{24}\)O\(_2\)Na (M + Na\(^{+}\)) 355.1674, found 339.1664.

Compound 109 was synthesized according to GP1. 67 mg (21 mmol, 53%) ligand was obtained as a clear, colorless oil which crystallized upon standing.

\[ \alpha \] = -33.1 (c = 1.01, CHCl₃);
mp = 47 °C;

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.32-7.28 (m, 2H), 7.10-7.06 (m, 2H), 6.37 (t, $J$ = 6.5 Hz, 1H), 6.16-6.13 (m, 2H), 3.61 (dt, $J$ = 6.1, 1.2 Hz, 1H), 3.20 (s, 3H), 1.62 (d, $J$ = 11.8 Hz, 1H), 1.34 (s, 3H), (one H under the 2 methyl groups), 1.32 (s, 9H), 1.30 (s, 3H);

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 149.5, 149.0, 141.6, 136.4, 133.8, 131.0, 128.0, 124.4, 84.1, 50.6, 50.0, 47.7, 45.5, 34.5, 31.4, 24.9, 21.9;

IR (thin film) 3050, 2962, 2870, 2822, 1907, 1596, 1507, 1456, 1456, 1365, 1346, 1310, 1269, 1238, 1199, 1175, 1126, 1100, 1075, 1021, 931, 904, 844, 826, 746, 706, 652 cm$^{-1}$;


8.2.2. Kinetic Resolution of Allylic Carbonates

GP2: Kinetic resolution of allylic carbonates

Under argon, [IrCl(coe)$_2$]$_2$ (6.7 mg, 7.5 µmol, 1.5 mol%) and ligand 109 (5.3 mg, 18 µmol, 3.6 mol%) were placed in a 10 mL Schlenk flask. 2 mL freshly degassed CH$_2$Cl$_2$ were added and the orange solution stirred at 23 °C for 8 h (ligand exchange can be monitored by $^1$H NMR spectroscopy). The allylic carbonate (0.5 mmol, 1.0 equiv) and 1 mL of a 0.25 M solution of phenol in CH$_2$Cl$_2$ (0.25 mmol, 0.50 equiv) were added and the solution stirred for 24 h at 23 °C. The orange to brown solution was evaporated and the residue directly subjected to column chromatography. The recovered allylic carbonates were obtained as clear oils.

(R)-(+)−1-Phenyl-prop-2-enyl-methyl carbonate (Table 1, entry 1)

![Reaction scheme](image)

1-Phenyl-prop-2-enyl-methyl carbonate (96 mg, 0.50 mmol) was resolved under the conditions described in GP2. (R)-(+)−1-phenyl-prop-2-enyl-methyl carbonate (31 mg, 0.16 mmol, 32%) was obtained after purification by chromatography in 93% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), t$_r$ 14.8 (minor) t$_r$ 18.4 (major). The allylic displacement product (S)-(+)−
phenoxy-allyl-benzene (42 mg, 0.18 mmol, 40%) was obtained in 66% ee as determined by HPLC analysis (Chiralcel OD-H, 1% iPrOH in hexanes, flow 0.6 mL/min, 220 nm), t_r 15.0 (major) t_r 20.8 (minor).

(R)-(+)-l-phenyl-prop-2-enyl-methyl carbonate
\[ \alpha^2_D = +20.6 \ (c = 0.8, \text{CHCl}_3) \];

\( ^1\text{H NMR (CDCl}_3, \ 300 \text{ MHz)} \delta 7.38-7.31 \ (m, 5H), 6.10-5.98 \ (m, 2H), 5.39 -5.25 \ (m, 2H), 3.78 \ (s, 3H). \)


(S)-(+)‐phenoxy-allyl-benzene
\[ \alpha^4_D = +3.3 \ (c = 1.1, \text{CHCl}_3, \text{ determined for a 53% ee sample}); \]

\( ^1\text{H NMR (CDCl}_3, \ 300 \text{ MHz)} \delta 7.43-7.19 \ (m, 7H), 6.95-6.89 \ (m, 3H), 6.16-6.05 \ (m, 1H), 5.64 (d, J = 5.6 Hz, 1H), 5.35 (d, J = 16.9 Hz, 1H), 5.26 (d, J = 10.5 Hz, 1H). \)


(+)-1-(2'-Naphthyl)-prop-2-enyl methyl carbonate (Table 1, entry 2)

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{OCO}_2\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\end{align*}
\]

1-(2'-Naphthyl)-prop-2-enyl methyl carbonate (121 mg, 0.50 mmol) was resolved under the conditions described in GP2. (+)-1-(2'-naphthyl)-prop-2-enyl methyl carbonate (40 mg, 0.17 mmol, 33%) was obtained after purification by chromatography in 94% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), t_r 7.5 (major) t_r 10.0 (minor). The allylic displacement product (+)-2-(1-
phenoxy-allyl)-naphthalene (62 mg, 0.24 mmol, 48%) was obtained in 80% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t<sub>r</sub> 22.7 (minor) t<sub>r</sub> 23.8 (major).

(+)-l-(2'-naphthyl)-prop-2-enyl methyl carbonate

\[ [\alpha]_D^{20} = +50.7 \text{ (c} = 1.0, \text{ CHCl}_3); \]

1<sup>H</sup> NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.86-7.82 (m, 4H), 7.51-7.46 (m, 3H), 6.26 (d, J = 5.9 Hz, 1H), 6.17-6.06 (m, 1H), 5.43-5.30 (m, 2H), 3.79 (s, 3H).


(+)-2-(1-phenoxy-allyl)-naphthalene

\[ [\alpha]_D^{27} = +1.8 \text{ (c} = 1.54, \text{ CHCl}_3, \text{ determined for a 41% ee sample);} \]

1<sup>H</sup> NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.87-7.81 (m, 4H), 7.55-7.46 (m, 3H), 7.25-7.19 (m, 2H), 7.01-6.88 (m, 3H), 6.24-6.13 (m, 3H), 5.80 (d, J = 5.6 Hz, 1H), 5.43-5.27 (m, 2H).

13<sup>C</sup> NMR (CDCl<sub>3</sub>, 75 MHz) δ 157.7, 137.7, 137.4, 133.2, 129.2, 128.4, 127.9, 127.6, 126.1, 125.9, 125.4, 124.4, 120.9, 116.6, 116.1, 80.9;

IR (thin film) 3058, 1597, 1493, 1229 cm<sup>-1</sup>;

HRMS (El) calcd. for C<sub>19</sub>H<sub>16</sub>O (M<sup>+</sup>) 260.1201, found 260.1202.

(R)-(+-)-1-(1'-Naphthyl)-prop-2-enyl methyl carbonate (Table 1, entry 3)

1-(1'-Naphthyl)-prop-2-enyl methyl carbonate (121 mg, 0.50 mmol) was resolved under the conditions described in GP2. (R)-(+-)-1-(1'-naphthyl)-prop-2-enyl methyl carbonate (34 mg, 0.14 mmol, 28%) was obtained after purification by chromatography in 90% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), t<sub>r</sub> 6.8 (major) t<sub>r</sub> 9.9 (minor). The allylic displacement product (+)-1-(1-
naphthyl)-1-phenoxy-2-propene (65 mg, 0.25 mmol, 50%) was obtained in 73% ee as
determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min,
220 nm), t₁ 13.1 (major) t₂ 21.3 (minor).

(R)-(+)-1-(1'-naphthyl)-prop-2-enylmethyl carbonate

\[ \alpha_{D}^{0} = +33.2 \] (c = 1.2, CHCl₃);

\(^1\)H NMR (CDCl₃, 300 MHz) δ 8.14-7.83 (m, 3H), 7.62-7.45 (m, 4H), 6.80 (d, J = 5.3
Hz, 1H), 6.27-6.16 (m, 1H), 5.41-5.29 (m, 2H), 3.79 (s, 3H).

For other spectroscopic data see: Lehmann, J.; Lloyd-Jones, G. C. Tetrahedron 1995, 51,
8863. The absolute configuration was determined by comparison of the HPLC retention
time after transformation to the corresponding saturated alcohol. For reference see: Dai,

(+)-1-(1'-naphthyl)-1-phenoxy-2-propene

\[ \alpha_{D}^{0} = +48.9 \] (c = 1.0, CHCl₃);

\(^1\)H NMR (CDCl₃, 300 MHz) δ 8.16-7.43 (m, 7H), 7.23-6.87 (m, 5H), 6.35-6.24 (m, 2H),
5.40 (d, J = 16.8 Hz, 1H), 5.31 (d, J = 10.3 Hz, 1H).

\(^13\)C NMR (CDCl₃, 75 MHz) δ 158.2, 137.2, 135.6, 134.3, 130.9, 129.7, 129.3, 128.9,
126.6, 126.0, 125.9, 125.1, 123.7, 121.3, 117.5, 116.2, 78.1;
IR (thin film) 1597, 1493, 1229 cm⁻¹;
HRMS (EI) calcd. for C₁₉H₁₆O (M⁺) 260.1201, found 260.1201.

(+)-1-(3'-Methoxyphenyl)-prop-2-enylmethyl carbonate (Table 1, entry 4)

1-(3'-Methoxyphenyl)-prop-2-enylmethyl carbonate (111 mg, 0.50 mmol) was resolved
under the conditions described in GP2. (+)-1-(3'-methoxyphenyl)-prop-2-enyl-methyl
carbonate (41 mg, 0.19 mmol, 37%) was obtained after purification by chromatography
in 97% ee as determined by HPLC analysis (Chiralcel OD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), t<sub>r</sub> 7.9 (minor) t<sub>r</sub> 8.8 (major). The allylic displacement product (+)-1-methoxy-3-(1-phenoxy-allyl)-benzene (65 mg, 0.27 mmol, 54%) was obtained in 77% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t<sub>r</sub> 21.2 (major) t<sub>r</sub> 24.9 (minor).

(+)-1-(3'-methoxyphenyl)-prop-2-enyl-methyl carbonate

\([\alpha\]_<D>^5 = +38.0 (c = 1.0, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.31-7.25 (m, 1H), 6.98-6.84 (m, 3H), 6.09-5.97 (m, 2H), 5.40-5.25 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 159.5, 154.7, 139.6, 135.5, 129.5, 119.1, 117.3, 113.8, 112.3, 79.9, 55.1, 54.7;

IR (thin film) 3005, 2958, 2837, 1751, 1644, 1602, 1588, 1491, 1456, 1441, 1341, 1262, 1193, 1166, 1086, 1050, 979, 938, 883, 791, 699 cm<sup>-1</sup>;

MS (EI) m/z (relative intensity): 223.3 (5.0%), 222.3 (40.4%), 147.3 (56.8%), 146.3 (100%);

Anal. Calcd for C<sub>12</sub>H<sub>14</sub>O<sub>4</sub>: C, 64.85; H, 6.35. Found: C, 64.66; H, 6.37.

(+)-1-methoxy-3-(1-phenoxy-allyl)-benzene

\([\alpha\]_<D>^7 = +5.9 (c = 1.0, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.31-7.21 (m, 3H), 7.02-6.80 (m, 5H), 6.10 (ddd, J = 5.9, 10.2, 17.1 Hz, 1H), 5.61 (d, J = 5.9 Hz, 1H), 5.32 (dd, J = 10.3, 17.1 Hz, 2H), 3.80 (s, 3H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 159.7, 157.7, 141.7, 137.7, 129.6, 129.2, 120.9, 118.8, 116.5, 116.0, 113.1, 112.0, 80.7, 55.3;

IR (thin film) 1598, 1586, 1493, 1455, 1436, 1318, 1266, 1234, 1178, 1157, 1031, 988, 928, 881, 836, 753, 691 cm<sup>-1</sup>;

HRMS (EI) calcd. for C<sub>10</sub>H<sub>11</sub>O ([M-OPh]<sup>+</sup>) 147.0810, found 147.0810.

(+)-1-(4’-Bromophenyl)-prop-2-enyl-methyl carbonate (Table 1, entry 5)

1-(4’-Bromophenyl)-prop-2-enyl-methyl carbonate (136 mg, 0.50 mmol) was resolved under the conditions described in GP2. (+)-1-(4’-bromophenyl)-prop-2-enyl-methyl carbonate (52 mg, 0.19 mmol, 38%) was obtained after purification by chromatography in 97% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), tR 5.6 (major) tR 7.1 (minor). The allylic displacement product (+)-1-bromo-4-(1-phenoxy-allyl)-benzene (73 mg, 0.25 mmol, 50%) was obtained in 87% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), tR 9.3 (minor) tR 11.8 (major).

(+)-1-(4’-bromophenyl)-prop-2-enyl-methyl carbonate

[α]D5 = +32.3 (c = 1.0, CHCl3);

1H NMR (CDCl3, 300 MHz) δ 7.50 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.04-5.93 (m, 2H), 5.38-5.26 (m, 2H), 3.78 (s, 3H).


(+)-1-bromo-4-(1-phenoxy-allyl)-benzene

[α]D7 = +0.3 (c = 1.11, CHCl3, determined for a 67% ee sample);

1H NMR (CDCl3, 300 MHz) δ 7.51-7.46 (m, 2H), 7.31-7.20 (m, 4H), 6.95-6.90 (m, 3H), 6.11-6.00 (m, 1H), 5.59 (d, J = 6.2 Hz, 1H), 5.37-5.25 (m, 2H);

13C NMR (CDCl3, 75 MHz) δ 157.4, 139.0, 137.3, 131.6, 129.3, 128.2, 121.6, 121.1, 116.9, 116.0, 80.1;

IR (thin film) 3039, 1597, 1489, 1234, 1010 cm⁻¹;

Experimental Section

(R)-(+) -1-(4'-Chlorophenyl)-prop-2-enyl methyl carbonate (Table 1, entry 6)

![Chemical Structure](image)

1-(4'-Chlorophenyl)-prop-2-enyl methyl carbonate (113 mg, 0.50 mmol) was resolved under the conditions described in GP2. (R)-(+) -1-(4'-chlorophenyl)-prop-2-enyl methyl carbonate (44 mg, 0.20 mmol, 39%) was obtained after purification by chromatography in 91% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), t_r 5.3 (major), t_r 6.6 (minor). The allylic displacement product (+)-1-(p-chlorophenyl)-1-phenoxy-2-propene (59 mg, 0.24 mmol, 48%) was obtained in 87% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t_r 9.3 (minor) t_r 12.2 (major).

(R)-(+) -1-(4'-chlorophenyl)-prop-2-enyl methyl carbonate

\[ [\alpha]_D^5 = +38.2 \text{ (c = 1.0, CHCl}_3) \]

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.36-7.29 (m, 4H), 6.05-5.94 (m, 2H), 5.36-5.27 (m, 2H), 3.78 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.7, 136.6, 135.2, 134.2, 128.7, 128.4, 117.8, 79.3, 54.9;

IR (thin film) 1751, 1493, 1442, 1265 cm$^{-1}$;

MS (EI) m/z (relative intensity): 226.0 (11.7%), 150.0 (59.4%), 115.0 (100%);

Anal. Calc. For C$_{11}$H$_{11}$ClO$_3$: C, 58.29; H, 4.89. Found: C, 58.02, H, 4.96.


(+)-1-(p-chlorophenyl)-1-phenoxy-2-propene

\[ [\alpha]_D^5 = +2.7 \text{ (c = 1.1, CHCl}_3) \]
**Experimental Section**

\[ ^1H\) NMR (300 MHz, CDCl\(_3\)) \delta 7.37-7.31 (m, 4H), 7.24-7.21 (m, 2H), 6.96-6.90 (m, 3H), 6.06 (dd, \(J = 17.1, 10.6, 5.9\) Hz, 1H), 5.61 (d, \(J = 5.9\) Hz), 5.34 (d, \(J = 17.1\) Hz, 1H), 5.27 (d, \(J = 10.6\) Hz, 1H);

\[ ^13C\) NMR (75 MHz, CDCl\(_3\)) \delta 157.9, 138.9, 137.8, 133.8, 129.6, 129.1, 128.2, 121.5, 117.2, 116.4, 80.3;

**IR (thin film)** 1598, 1492, 1235, 1015 cm\(^{-1}\);

**MS** (EI) m/z (relative intensity): 244.0 (1%), 151.0 (100%).

**HRMS** (EI) calcd. for C\(_{15}\)H\(_{13}\)C\(_{14}\O\) (M\(^+\)) 244.0655, found 244.0656.

\(\text{(+)-l-(4’-Fluorophenyl)-prop-2-enyl methyl carbonate (Table 1, entry 7)}\)

\[ \begin{align*}
\text{F} & \quad \text{O} \quad \text{CO}_2\text{Me} \\
\text{C} & \quad \text{O} \quad \text{Me} \\
\text{p-C}_6\text{H}_4 & \quad \text{(-Bu)}
\end{align*} \]

\(\text{Me} \quad \text{OMe} \)

\(\text{Me} \quad \text{OMe} \)

\(\text{109} \quad (3.6 \text{ mol%}) \)

\(\text{[IrCl(coc)]}_2 \quad (1.5 \text{ mol%}) \)

\(\text{CH}_2\text{Cl}_2, 25 ^\circ\text{C} \)

1-(4’-Fluorophenyl)-prop-2-enyl methyl carbonate (105 mg, 0.50 mmol) was resolved under the conditions described in GP2. \(\text{(+) -1-(4’-fluorophenyl)-prop-2-enyl methyl carbonate (36 mg, 0.17 mmol, 68%) was obtained after purification by chromatography in 85% ee as determined by HPLC analysis (Chiralcel OD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), \(t_r \) 10.4 (minor) \(t_r \) 12.2 (major). The allylic displacement product \(\text{(+) -1-fluoro-4-(1-phenoxy-allyl)-benzene (55 mg, 0.24 mmol, 48%) was obtained in 53% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), \(t_r \) 11.4 (minor) \(t_r \) 14.7 (major).} \)

\(\text{(+)-l-(4’-Fluorophenyl)-prop-2-enyl methyl carbonate} \)

\[ [\alpha]_D^{20} = +30.4 \text{ (c = 1.0, CHCl}_3); \]

\[ ^1H\) NMR (CDCl\(_3\), 300 MHz) \delta 7.38-7.33 (m, 2H), 7.09-7.02 (m, 2H), 6.07-5.95 (m, 2H), 5.38-5.26 (m, 2H), 3.78 (s, 3H);

\[ ^13C\) NMR (CDCl\(_3\), 75 MHz) \delta 164.1, 160.9, 154.8, 135.4, 134.0 (2C), 129.0, 128.9, 117.5, 115.6, 115.3, 79.4, 54.9;

\[ ^19F\) NMR (CDCl\(_3\), 282 MHz) \delta -113.0; \]
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**IR (thin film)** 2959, 1750, 1605, 1443, 1266, 1226, 1160, 976, 927, 837, 789 cm\(^{-1}\);

**MS(EI)**  m/z (relative intensity): 211.1 (1.3%), 210.1 (10.4%), 135.1 (63.2%), 134.1 (100%), 133.0 (72.5%);

**Anal.** Calcd for C\(_{11}\)H\(_{11}\)O\(_3\)F: C, 62.85; H, 5.27. Found: C, 62.67; H, 5.40.

**(+)-1-fluoro-4-(1-phenoxy-allyl)-benzene**

[\(\alpha\)\(_D\)]\(^{20}\) = +4.5 (c = 1.15, CHCl\(_3\));

**\(^1\)H NMR** (CDCl\(_3\), 300 MHz) \(\delta\) 7.42-7.37 (m, 2H), 7.27-7.22 (m, 2H), 7.08-7.02 (m, 2H), 6.96-6.91 (m, 3H), 6.08 (ddd, \(J\) = 5.9, 10.6, 17.1 Hz, 1H), 5.63 (d, \(J\) = 5.9 Hz, 1H), 5.37-5.26 (m, 2H);

**\(^{13}\)C NMR** (CDCl\(_3\), 75 MHz) \(\delta\) 157.5, 137.6, 129.2, 128.3, 128.2, 121.0, 116.7, 116.1, 115.6, 115.3;

**\(^{19}\)F NMR** (CDCl\(_3\), 282 MHz) \(\delta\) -114.1;

**IR (thin film)** 1598, 1509, 1493, 1417, 1297, 1224, 1172, 1157, 1095, 1078, 1030, 1014, 988, 931, 837, 793, 753, 691 cm\(^{-1}\);

**HRMS (EI)** calcd. for C\(_9\)H\(_8\)F ([M-OPh]\(^+\)) 135.0610, found 135.0617.

**Anal.** Calcd for C\(_{15}\)H\(_{13}\)OF: C, 78.93; H, 5.74. Found: C, 78.91; H, 5.72.

**(+)-1-(3’-Bromophenyl)-prop-2-enyl methyl carbonate (Table 1, entry 8)**

\[
\begin{align*}
\text{Br} & \quad \text{OCO}_2\text{Me} \\
\text{OH} & \quad \text{CH}_2\text{Cl}_2, 25^\circ \text{C}
\end{align*}
\]

1-(3’-Bromophenyl)-prop-2-enyl methyl carbonate (135 mg, 0.50 mmol) was resolved under the conditions described in GP2. (+)-1-(3’-bromophenyl)-prop-2-enyl methyl carbonate (55 mg, 0.20 mmol, 40%) was obtained after purification by chromatography in 88% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm), \(t\) \(_1\) 8.8 (major) \(t\) \(_2\) 10.8 (minor). The allylic displacement product (+)-1-bromo-3-(1-phenoxy-allyl)-benzene (72 mg, 0.25 mmol, 50%) was obtained in 80% ee.
as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t² 9.8 (minor) t, 11.4 (major).

\((\pm)-1-(3\text{'-bromophenyl})-prop-2-enyl methyl carbonate\)

\[ \alpha^\circ_{\text{D}} +25.8 \quad (c = 1.02, \text{CHCl}_3); \]

\(^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta 7.53-7.43 \text{ (m, 1H), 7.32-7.21 (m, 3H), 6.04-5.92 (m, 2H),} \]

\[5.40-5.28 \text{ (m, 2H), 3.80 (s, 3H);} \]

\(^{13}\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta 155.1, 140.8, 135.4, 131.7, 130.4, 130.3, 125.9, 122.9, \]

\[118.4, 79.5, 55.2; \]

\text{IR (thin film) 2956, 1751, 1572, 1477, 1442, 1262, 1220, 1196, 1073, 978, 931 cm}^{-1}; \]

\text{MS(EI) m/z (relative intensity): 271 (13.4%), 195 (40%), 116 (100%), 104 (16%);} \]

\text{Anal. Calcd for C}_{11}\text{H}_{10}\text{O}_3\text{Br: C, 48.73; H, 4.09. Found: C, 48.57; H, 3.94.}\]

\((\pm)-1\text{-bromo-3-(1-phenoxy-allyl)-benzene}\)

\[ \alpha^\circ_{\text{D}} +5.4 \quad (c = 0.99, \text{CHCl}_3, \text{determined for a 66% ee sample}); \]

\(^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta 7.58-7.57 \text{ (m, 1H), 7.44-7.20 (m, 3H), 6.96-6.91 (m, 3H),} \]

\[6.11-5.99 \text{ (m, 1H), 5.59 (d, J = 5.9 Hz, 1H), 5.40-5.27 (m, 2H);} \]

\(^{13}\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta 157.4, 142.4, 137.2, 130.8, 130.1, 129.5, 129.3, 125.1, \]

\[122.7, 121.2, 117.1, 116.1, 80.1; \]

\text{IR (thin film) 3062, 1596, 1494, 1234 cm}^{-1}; \]

\text{Anal. Calcd for C}_{15}\text{H}_{13}\text{OBr: C, 62.30; H, 4.53. Found: C, 62.11; H, 4.57.}\]

\((\pm)-1-(4\text{'-Trifluoromethylphenyl})-prop-2-enyl methyl carbonate (Table 1, entry 9)\)

\(1-(4\text{'-Trifluoromethylphenyl})-prop-2-enyl methyl carbonate (130 mg, 0.50 \text{ mmol}) \text{ was resolved under the conditions described in GP2.} \(\pm\)-1-(4\text{'-trifluoromethylphenyl})-prop-2-enyl methyl carbonate (48 mg, 0.19 \text{ mmol, 37%} \text{ was obtained after purification by} \)
chromatography in 96% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm) t₁ 4.7 (major) t₂ 6.0 (minor). The allylic displacement product (+)-1-(1-phenoxy-allyl)-4-trifluoromethyl-benzene (64 mg, 0.23 mmol, 46%) was obtained in 82% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t₁ 6.7 (major) t₂ 7.2 (minor).

(+)-1-(4′-trifluoromethylphenyl)-prop-2-enyl methyl carbonate

\[ \alpha^\circ \] = \+12.5 (c = 1.0, CHCl₃);

\[^1\text{H} \text{ NMR (CDCl₃, 300 MHz)} \] δ 7.63 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 6.12 (d, J = 6.2 Hz, 1H), 6.06-5.94 (m, 1H), 5.40-5.30 (m, 2H), 3.80 (s, 3H).


(+)-1-(1-phenoxy-allyl)-4-trifluoromethyl-benzene

\[ \alpha^\circ \] = \+10.6 (c = 1.12, CHCl₃, determined for a 64% ee sample);

\[^1\text{H} \text{ NMR (CDCl₃, 300 MHz)} \] δ 7.62 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.27-7.22 (m, 2H), 6.97-6.91 (m, 3H), 6.13-6.01 (m, 1H), 5.68 (d, J = 5.9 Hz, 1H), 5.40-5.28 (m, 2H);

\[^{13}\text{C} \text{ NMR (CDCl₃, 75 MHz)} \] δ 157.7, 144.4, 137.5, 129.7, 127.1, 125.9, 125.8, 121.6, 117.6, 116.3, 80.4;

\text{IR (thin film)} 3042, 1598, 1494, 1220 cm⁻¹;

\text{Anal. Calcd for C}_{16}\text{H}_{13}\text{OF}_3: \text{C}, 69.06; \text{H}, 4.71. \text{Found: C}, 69.02; \text{H}, 4.87.

(+)-1-(4′-Nitrophenyl)-prop-2-enyl methyl carbonate (Table 1, entry 10)

\[ \text{1-(4′-Nitrophenyl)-prop-2-enyl methyl carbonate (119 mg, 0.50 mmol) was resolved under the conditions described in GP2.} \]
carbonate (54 mg, 0.23 mmol, 45%) was obtained after purification by chromatography in 95% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm) \( t_r 35.6 \) (minor) \( t_r 38.6 \) (major). The allylic displacement product (+)-1-nitro-4-(1- phenoxy-allyl)-benzene (62 mg, 0.25 mmol, 49%) was obtained in 86% ee as determined by HPLC analysis (Chiralcel OJ-H, 2% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), \( t_r 39.6 \) (major) \( t_r 49.8 \) (minor).

\((-\)-1-(4’-nitrophenyl)-prop-2-enyl methyl carbonate\)

\( [\alpha]_D^{20} = +14.8 \ (c = 1.04; \text{CHCl}_3); \)

\(^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta 8.22-8.18 \ (m, 2H), 7.55-7.51 \ (m, 2H), 6.13 \ (d, J = 6.2 Hz, 1H), 6.03-5.92 \ (m, 1H), 5.41-5.32 \ (m, 2H), 3.78 \ (s, 3H); \)

\(^{13}\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta 154.5, 147.5, 145.2, 134.4, 127.5, 123.7, 118.8, 78.8, 55.1; \)

\text{IR (thin film)} 3084, 3014, 2957, 2915, 2557, 2211, 1750, 1643, 1608, 1523, 1495, 1443, 1350, 1259, 1200, 1110, 1015, 981, 949, 855, 833, 790, 755, 743, 704 \text{ cm}^{-1}; \)

\text{MS(El)} m/z (relative intensity): 237.1 (0.4%), 116.0 (2.1%), 115.0 (19.4%), 15.0 (100%); \)

\text{Anal. Calcd for C}_{11}\text{H}_{11}\text{NO}_3: \text{C}, 55.70; \text{H}, 4.67; \text{N}, 5.90. \text{Found: C}, 55.98; \text{H}, 4.81; \text{N}, 6.04. \)

\((-\)-1-nitro-4-(1-phenoxy-allyl)-benzene\)

\( [\alpha]_D^{20} = +21.9 \ (c = 1.07, \text{CHCl}_3); \)

\(^1\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz}) \delta 8.25-8.20 \ (m, 2H), 7.62-7.58 \ (m, 2H), 7.29-7.22 \ (m, 2H), 6.98-6.89 \ (m, 3H), 6.06 \ (ddd, J = 5.9, 10.3, 17.1 \text{ Hz, 1H}), 5.73 \ (d, J = 5.9 \text{ Hz, 1H}), 5.38 \ (dd, J = 10.3, 17.1 \text{ Hz, 2H}); \)

\(^{13}\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz}) \delta 157.1, 147.3, 136.6, 129.4, 127.2, 123.8, 121.5, 117.9, 116.0, 79.9; \)

\text{IR (thin film)} 1597, 1522, 1493, 1347, 1231, 1172, 1108, 1178, 1033, 1016, 989, 934, 854, 752, 709, 691 \text{ cm}^{-1}; \)

\text{HRMS (El) calcd. for C}_{9}\text{H}_8\text{NO}_2 ([M-OPh]^+) 162.0555, found 162.0561. \)
**Experimental Section**

**Anal.** Calcd for C₁₅H₁₃NO₃: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.54; H, 5.15; N, 5.46.

(+)-1-(4’-Methoxycarbonyloxyphenyl)-prop-2-enyl methyl carbonate (Table 1, entry 11)

1-(4’-Methoxycarbonyloxyphenyl)-prop-2-enyl methyl carbonate (125 mg, 0.50 mmol) was resolved under the conditions described in GP2. (+)-1-(4’-methoxycarbonyloxyphenyl)-prop-2-enyl methyl carbonate (57 mg, 0.23 mmol, 46%) was obtained after purification by chromatography in 80% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm) tₘ 14.7 (major) tₗ 10.1 (minor). The allylic displacement product (+)-4-(1-phenoxy-allyl)-benzoic acid methyl ester (60 mg, 0.23 mmol, 45%) was obtained in 92% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), tₘ 14.7 (major) tₗ 17.9 (minor).

(+)-1-(4’-methoxycarbonyloxyphenyl)-prop-2-enyl methyl carbonate

\[ [\alpha]_D^{25} = +13.3 \text{ (c = 0.99, CHCl₃)}; \]

\[ ^1H \text{ NMR (CDCl₃, 300 MHz) } \delta 8.02 (d, J = 8.1 \text{ Hz, 2H}), 7.42 (d, J = 8.1 \text{ Hz, 2H}), 6.10 (d, J = 6.2 \text{ Hz, 1H}), 6.04-5.93 (m, 1H), 5.37-5.27 (m, 2H), 3.89 (s, 3H), 3.77 (s, 3H); \]

\[ ^{13}C \text{ NMR (CDCl₃, 75 MHz) } \delta 166.4, 154.7, 143.1, 135.0, 130.0, 129.8, 126.7, 118.2, 79.5, 55.0, 52.2; \]

\[ \text{IR (thin film) } 3004, 2949, 2841, 2361, 2198, 2080, 1931, 1750, 1723, 1642, 1610, 1574, 1510, 1438, 1411, 1343, 1193, 1180, 1107, 1017, 976, 944, 926, 863, 813, 787, 772, 709 \text{ cm}^{-1}; \]

\[ \text{MS(El) } m/z \text{ (relative intensity): } 250 (22\%), 219 (23\%), 174 (100\%), 143 (99\%), 115 (99\%); \]
**Anal.** Calcd for C\textsubscript{13}H\textsubscript{14}O\textsubscript{5}: C, 62.39; H, 5.64. Found: C, 62.19; H, 5.66.

\((-\)-4-(1-phenoxy-allyl)-benzoic acid methyl ester

\([\alpha]_D^\circ +8.7 \; (c = 0.7, \text{CHCl}_3, \text{determined for a 78% ee sample});

\(^1\text{H NMR (CDCl}_3, 300 \text{ MHz}) \; \delta \; 8.05-8.01 \; (m, 2H), \; 7.51-7.48 \; (m, 2H), \; 7.26-7.21 \; (m, 2H), \; 6.96-6.91 \; (m, 3H), \; 6.13-6.02 \; (m, 1H), \; 5.68 \; (d, \; J = 5.9 \; \text{Hz, 1H}), \; 5.40-5.28 \; (m, 2H), \; 3.91 \; (s, 3H);

\(^{13}\text{C NMR (CDCl}_3, 75 \text{ MHz}) \; \delta \; 167.0, \; 157.8, \; 145.5, \; 137.5, \; 130.2, \; 129.8, \; 129.6, \; 126.7, \; 121.5, \; 117.4, \; 116.4, \; 80.6, \; 52.4;

\text{IR (thin film)} \; 2951, \; 1723, \; 1597, \; 1493, \; 1279, \; 1234 \; \text{cm}^{-1};

**Anal.** Calcd for C\textsubscript{17}H\textsubscript{16}O\textsubscript{3}: C, 76.10; H, 6.01. Found: C, 75.94; H, 6.19.

\((\,+\)-1-(3'-Methylphenyl)-prop-2-enyl methyl carbonate (Table 1, entry 12)

\[ + \]

1-(3'-Methylphenyl)-prop-2-enyl methyl carbonate (103 mg, 0.500 mmol) was resolved under the conditions described in GP2. (+)-1-(3'-methylphenyl)-prop-2-enyl methyl carbonate (40 mg, 0.20 mmol, 39%) was obtained after purification by chromatography in 80% ee as determined by HPLC analysis (Chiralcel OD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm) t\(_r\) 4.9 (minor) t\(_r\) 5.6 (major). The allylic displacement product (+)-1-methyl-3-(1-phenoxy-allyl)-benzene (59 mg, 0.27 mmol, 53%) was obtained in 45% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t\(_r\) 14.6 (minor) t\(_r\) 16.8 (major).

\((\,+\)-1-(3’-methylphenyl)-prop-2-enyl methyl carbonate

\([\alpha]_D^\circ +29.4 \; (c = 1.0, \text{CHCl}_3);

\(^1\text{H NMR (CDCl}_3, 300 \text{ MHz}) \; \delta \; 7.30-7.14 \; (m, 4H), \; 6.10-6.00 \; (m, 2H), \; 5.42-5.26 \; (m, 2H), \; 3.79 \; (s, 3H), \; 2.38 \; (s, 3H);
**Experimental Section**

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 154.8, 138.1, 135.7, 129.0, 128.3, 127.5, 123.9, 117.1, 80.1, 54.7, 21.4;

**IR (thin film)** 3023, 2957, 2862, 1751, 1644, 1490, 1442, 1380, 1341, 1262, 1160, 1086, 973, 934, 885, 791, 703 cm$^{-1}$;

**MS(EI)** (relative intensity): 206.3 (33.9%), 131.3 (47.8%), 130.3 (100.0%), 129.3 (49.4%);

**Anal.** Calcd for C$_{12}$H$_{14}$O$_3$: C, 69.89; H, 6.84. Found: C, 69.79; H, 6.82.

(+)-1-methyl-3-(1-phenoxy-allyl)-benzene

$[\alpha]_D^2$ +2.9 (c = 1.04, CHCl$_3$);

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.26-7.20 (m, 5H), 7.11-7.09 (m, 1H), 6.96-6.89 (m, 3H), 6.09 (ddd, $J$ = 5.9, 10.6, 17.1 Hz, 1H), 5.60 (d, $J$ = 6.2 Hz, 1H), 5.35 (td, $J$ = 1.3, 17.1 Hz, 1H), 5.25 (td, $J$ = 1.3, 10.6 Hz, 1H), 2.36 (s, 3H);

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 157.8, 139.9, 138.2, 137.9, 129.2, 128.5, 128.4, 127.1, 123.6, 120.8, 116.3, 116.1, 80.8, 21.6;

**IR (thin film)** 1597, 1494, 1236, 1173, 1078, 1030, 987, 927, 883, 791, 752, 704, 690, 668 cm$^{-1}$;

**HRMS (EI)** calcd. for C$_{10}$H$_{11}$ ([M-OPh]$^+$) 131.0861, found 131.0868;

**Anal.** Calcd for C$_{16}$H$_{16}$O: C, 85.68; H, 7.19. Found: C, 85.73; H, 7.22.

(+)-1-(4'-Methylphenyl)-prop-2-enyl methyl carbonate (Table 1, entry 13)

(+)-1-(4'-Methylphenyl)-prop-2-enyl methyl carbonate (103 mg, 0.50 mmol) was resolved under the conditions described in GP2. (+)-1-(4'-methylphenyl)-prop-2-enyl methyl carbonate (33 mg, 0.14 mmol, 28%) was obtained after purification by chromatography in 87% ee as determined by HPLC analysis (Chiralpak AD-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm) $t_r$ 8.7 (minor) $t_r$ 11.2 (major). The allylic displacement product (+)-...
1-(p-tolyl)-1-phenoxy-2-propene (56 mg, 0.25 mmol, 50%) was obtained in 75% ee as determined by HPLC analysis (Chiralcel OD-H, 0.2% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t, 6.6 (minor) t, 7.7 (major).

(+)-1-(4’-methylphenyl)-prop-2-enyl methyl carbonate

$\left[\alpha\right]_D^5 = +39.8$ (c = 1.0, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28-7.15 (m, 4H), 6.09-5.97 (m, 2H), 5.37-5.23 (m, 2H), 3.77 (s, 3H), 2.34 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.9, 138.2, 135.8, 135.2, 129.2, 127.0, 117.1, 80.2, 54.8, 21.3;

IR (thin film) 1750, 1442, 1263 cm$^{-1}$;

MS(EI) (relative intensity): 206 (27%), 130 (100%), 115 (80%); 91 (50%);


(-)-1-(p-tolyl)-1-phenoxy-2-propene

$\left[\alpha\right]_D^4 = -3.0$ (c = 1.1, CHCl$_3$);

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.31-7.15 (m, 6H), 6.95-6.88 (m, 3H), 6.09 (ddd, $J = 5.9$, 10.3, 17.4 Hz, 1H), 5.61 (d, $J = 6.2$ Hz, 1H), 5.33 (d, $J = 17.4$ Hz, 1H), 5.24 (d, $J = 10.3$ Hz, 1H), 2.33 (s, 3H);

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 158.2, 138.4, 137.8, 137.4, 129.6, 129.6, 126.8, 121.2, 116.5, 116.4, 80.9, 21.4;

IR (thin film) 1598, 1493, 1236, 1031 cm$^{-1}$;

MS(EI) (relative intensity): 224 (7%), 131 (100%);

HRMS (EI) calcd. for C$_{16}$H$_{16}$O (M$^+$) 224.1201, found 224.1197;

(+)-1-Cyclohexylprop-2-enyl methyl carbonate (Table 1, entry 14)

\[
\begin{align*}
\text{Me}^\text{OMe} & \quad \text{O} \quad \text{Me} \\
\text{OCO}_2\text{Me} & \quad \text{Me} \\
\text{p-C}_6\text{H}_4\text{-Bu} & \quad \text{OPh}
\end{align*}
\]

$\text{[IrCl(coe)$_2$]}_2$ (1.5 mol%) \quad CH$_2$Cl$_2$, 25 $^\circ$C
Experimental Section

1-Cyclohexylprop-2-enyl methyl carbonate (99 mg, 0.50 mmol) was resolved under the conditions described in GP2. (+)-1-cyclohexylprop-2-enyl methyl carbonate (30 mg, 0.15 mmol, 30%) was obtained after purification by chromatography in >98% ee as determined by GC analysis (Supelco Beta-Dex 120, Fused Silica Capillary Column 30m x 0.25mm x 0.25μm film thickness), t<sub>r</sub> 47.1 (minor) t<sub>r</sub> 47.8 (major). The allylic displacement product (+)-(1-cyclohexyl-allyloxy)-benzene (41 mg, 0.19 mmol, 38%) was obtained in 72% ee as determined by HPLC analysis (Chiralpak AD-H, 0.1% iPrOH in hexanes, flow 0.4 mL/min, 220 nm), t<sub>r</sub> 10.7 (minor) t<sub>r</sub> 11.2 (major).

(+)-1-cyclohexylprop-2-enyl methyl carbonate

\[ [\alpha]_0^{28} = +2.9 \ (c = 0.52, \text{CHCl}_3) \]

<br>\[ ^1H \text{ NMR (CDCl}_3, 300 \text{ MHz}) \delta 5.83-5.72 (m, 1H), 5.31-5.21 (m, 2H), 4.84 (t, J = 6.9 Hz, 1H), 3.77 (s, 3H, Me), 1.82-1.53 (m, 6H), 1.30-0.94 (m, 5H); \]

\[ ^13C \text{ NMR (CDCl}_3, 75 \text{ MHz}) \delta 155.1, 134.3, 117.9, 83.1, 54.4, 41.4, 28.4, 28.3, 26.2, 25.8, 25.8; \]

IR (thin film) 2930, 2855, 1750, 1442, 1268, 962, 942, 890, 792 cm\(^{-1}\);

Anal. Calcd for C\(_{11}\)H\(_{18}\)O\(_3\): C, 66.64; H, 9.15. Found: C, 66.54; H, 8.98.


(+)-(1-cyclohexyl-allyloxy)-benzene

\[ [\alpha]_0^{28} = +10.3 \ (c = 0.55, \text{CHCl}_3) \]

<br>\[ ^1H \text{ NMR (CDCl}_3, 300 \text{ MHz}) \delta 7.28-7.21 (m, 2H), 6.93-6.88 (m, 3H), 5.88-5.77 (m, 1H), 5.26-5.18 (m, 2H), 4.34 (t, J = 6.2 Hz, 1H), 1.95 (d, J = 13.1 Hz, 1H), 1.79-1.60 (m, 5H), 1.35-1.04 (m, 5H); \]

\[ ^13C \text{ NMR (CDCl}_3, 75 \text{ MHz}) \delta 158.6, 136.5, 129.1, 120.4, 117.2, 116.0, 83.5, 42.7, 28.9, 28.8, 26.6, 26.2; \]

IR (thin film) 2927, 2853, 1646, 1597, 1494, 1450, 1420, 1300, 1287, 1240, 1171, 1152, 1097, 1077, 1028, 990, 924, 895, 880, 821, 752, 690 cm\(^{-1}\);

HRMS (EI) calcd. for C\(_{15}\)H\(_{20}\)O (M\(^+\)) 216.1514, found 216.1521;
(+)-1-Benzylxprop-2-enyl methyl carbonate (Table 1, entry 15)

[Image of chemical reaction]

1-Benzylxprop-2-enyl methyl carbonate (118 mg, 0.50 mmol) was resolved under the conditions described in GP2. (+)-1-benzylxprop-2-enyl methyl carbonate (38 mg, 0.16 mmol, 32%) was obtained after purification by chromatography in 84% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexane, flow 1.2 mL/min, 220 nm) t<sub>r</sub> 24.0 (minor) t<sub>r</sub> 27.2 (major). The allylic displacement product (-)-(1-benzylxy-allyloxy)-benzene (57 mg, 0.23 mmol, 45%) was obtained in 61% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), t<sub>r</sub> 17.4 (major) t<sub>r</sub> 18.9 (minor).

(+)-1-benzylxprop-2-enyl methyl carbonate

[α]<sub>D</sub> = +3.5 (c = 1.0, CHCl₃);

<sup>1</sup>H NMR (CDCl₃, 300 MHz) δ 7.36-7.29 (m, 5H), 5.90-5.78 (m, 1H), 5.43-5.27 (m, 3H), 4.58 (s, 2H), 3.79 (s, 3H), 3.61-3.56 (m, 2H).


(-)-(1-benzylxy-allyloxy)-benzene

[α]<sub>D</sub> = -6.0 (c = 1.15, CHCl₃);

<sup>1</sup>H NMR (CDCl₃, 300 MHz) δ 7.36-7.23 (m, 7H), 6.97-6.91 (m, 3H), 5.91 (ddd, J = 5.6, 10.6, 17.4 Hz, 1H), 5.38 (d, J = 17.4 Hz, 1H), 5.28 (td, J = 1.3, 10.6 Hz, 1H), 4.90-4.84 (m, 1H), 4.69-4.60 (m, 2H), 3.77-3.64 (m, 2H);

<sup>13</sup>C NMR (CDCl₃, 75 MHz) δ 157.9, 138.0, 134.7, 129.2, 128.3, 127.6, 127.6, 120.9, 117.8, 116.0, 78.1, 73.5, 72.5;

IR (thin film) 1598, 1494, 1454, 1363, 1291, 1240, 1091, 1028, 990, 752, 692 cm⁻¹;

HRMS (EI) calcd. for C₁₀H₁₃O ([M-OPh]<sup>⁺</sup>) 161.0966, found 161.0968;
8.2.3. Studies directed towards a Dynamic Kinetic Resolution

GP3: Kinetic Resolution with different phenol nucleophiles:

Under argon, $\text{[IrCl(coe)$_2$]}_2$ (6.7 mg, 7.5 µmol, 1.5 mol%) and ligand 109 (5.3 mg, 18 µmol, 3.6 mol%) were placed in a 10 mL Schlenk flask. 2 mL freshly degassed CH$_2$Cl$_2$ were added and the orange solution stirred at 23 °C for 8 h (ligand exchange can be monitored by $^1$H NMR spectroscopy). Racemic methyl 1-phenylallyl carbonate 115 (96 mg, 0.5 mmol, 1.0 equiv) and 1 mL of a 0.25 M solution of the indicated phenol in CH$_2$Cl$_2$ (0.25 mmol, 0.50 equiv) were added and the solution stirred for 24 h at 23 °C. The orange to brown solution was evaporated and the residue directly subjected to column chromatography. The recovered allylic carbonates were obtained as clear oils.

(+)-1-phenyl-1-(2-methylphenoxy)-2-propene (135)

Racemic methyl 1-phenylallyl carbonate 115 (96 mg, 0.50 mmol) was resolved under the conditions described in GP3. (+)-methyl 1-phenylallyl carbonate (44 mg, 0.23 mmol, 46%) was obtained after purification by chromatography in 72% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm) $t_r$ 17.6 (minor) $t_m$ 20.9 (major). The allylic displacement product (+)-(1-phenyl-1-(2-methylphenoxy)-2-propene (44 mg, 0.19 mmol, 39%) was obtained in 87% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm), $t_r$ 8.1 (major) $t_m$ 9.6 (minor).

(+)-(1-phenyl-1-(2-methylphenoxy)-2-propene

$[\alpha]_D^{27} +4.9$ (c 1.0, CHCl$_3$);
$^1$H NMR (300 MHz, CDCl$_3$) δ 7.26-7.43 (m, 5H), 7.14 (d, $J = 7.3$ Hz, 1H), 7.04 (dd, $J = 7.3$, 7.3 Hz, 1H), 6.82 (dd, $J = 7.3$, 7.3 Hz, 1H), 6.78 (d, $J = 7.3$ Hz, 1H), 6.09 (ddd, $J = 17.1$, 10.5, 5.8 Hz, 1H), 5.64 (d, $J = 5.8$ Hz, 1H), 5.37 (d, $J = 17.1$ Hz, 1H), 5.23 (d, $J = 10.5$ Hz, 1H), 2.32 (s, 3H).


$(+)$-1-(1-phenylallyloxy)-4-(trifluoromethyl)benzene (137)

Racemic methyl 1-phenylallyl carbonate 115 (96 mg, 0.50 mmol) was resolved under the conditions described in GP3. $(+)$-methyl 1-phenylallyl carbonate (36 mg, 0.19 mmol, 37%) was obtained after purification by chromatography in 63% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 1.2 mL/min, 220 nm) $t_r$ 14.9 (minor) $t_r$ 18.3 (major). The allylic displacement product $(+)$-1-(1-phenylallyloxy)-4-(trifluoromethyl)benzene 137 (71 mg, 0.25 mmol, 50%) was obtained in 62% ee as determined by HPLC analysis (Chiralcel OJ-H, 1% iPrOH in hexanes, flow 0.7 mL/min, 220 nm), $t_r$ 20.5 (major) $t_r$ 27.0 (minor).

$(+)$-1-(1-phenylallyloxy)-4-(trifluoromethyl)benzene

$[\alpha]_D^{27} +5.6$ (c 1.0, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.25-7.60 (m, 5H), 7.49 (d, $J = 8.7$ Hz, 2H), 7.01 (d, $J = 8.7$ Hz, 2H), 6.11 (ddd, $J = 17.2$, 10.4, 5.9 Hz, 1H), 5.69 (d, $J = 5.9$ Hz, 1H), 5.37 (d, $J = 17.2$ Hz, 1H), 5.30 (d, $J = 10.4$ Hz, 1H).

GP 4: Studies towards a Dynamic Kinetic Resolution

Under argon, [IrCl(coe)₂]₂ (6.7 mg, 7.5 μmol, 1.5 mol%) and ligand 109 (5.3 mg, 18 μmol, 3.6 mol%) were placed in a 10 mL Schlenk flask. 2 mL freshly degassed CH₂Cl₂ were added and the orange solution stirred at 23 °C for 8 h (ligand exchange can be monitored by ¹H NMR spectroscopy). Racemic methyl 1-phenylallyl carbonate 115 (96 mg, 0.5 mmol, 1.0 equiv), o-kresol 134 (below indicated amount) and an additive (below indicated amount) were added and the solution stirred for 24 h at 23 °C. The orange to brown solution was evaporated and the residue directly subjected to column chromatography.

Following GP4 54 mg (0.5 mmol, 1 equiv) o-kresol 134 and no additive were employed to obtain 65 mg (0.29 mmol, 57%) 135 in 52% ee after 24 h reaction time. Additionally, 19 mg (0.10 mmol, 20%) 115 were recovered in 88% ee.

Following GP4 65 mg (0.6 mmol, 1.2 equiv) o-kresol 134 and 13 mg (0.5 mmol, 1 equiv) LiF as additive were employed to obtain 63 mg (0.28 mmol, 56%) 135 in 36% ee after 24 h reaction time. Additionally, 11 mg (0.06 mmol, 12%) 115 were recovered in 92% ee.
Following GP4 65 mg (0.6 mmol, 1.2 equiv) o-kresol 134 and 21 mg (0.5 mmol, 1 equiv) LiCl as additive were employed to obtain 62 mg (0.28 mmol, 55%) 135 in 11% ee after 24 h reaction time. Additionally, 17 mg (0.09 mmol, 18%) 115 can be recovered in 15% ee.

Following GP4 108 mg (1.0 mmol, 2 equiv) o-kresol 134 and 158 mg (0.5 mmol, 1 equiv) n-tetrabutylammoniumfluoride trihydrate as additive were employed to obtain 66 mg (0.30 mmol, 59%) 135 in 31% ee after 24 h reaction time.

Following GP4 216 mg (2.0 mmol, 4 equiv) o-kresol 134 and 158 mg (0.5 mmol, 1 equiv) n-tetrabutylammoniumfluoride trihydrate as additive were employed to obtain 103 mg (0.46 mmol, 92%) 135 in 35% ee after 10 h reaction time.
Following GP4 108 mg (1.0 mmol, 2 equiv) o-kresol 134 and 138 mg (0.5 mmol, 1 equiv) tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) as additive are employed to obtain 98 mg (0.44 mmol, 87%) 135 in 24% ee after 4 h reaction time.

\[
\begin{align*}
\text{Me} & \quad \text{OCO}_2\text{Me} \quad \text{OH} \\
1 \text{ equiv} & \quad 115 \\
2 \text{ equiv} & \quad 134 \\
\text{[IrCl[(coe)]_2} (1.5 \text{ mol\%}) & \quad \text{TASF (0.04 equiv)} \\
\text{CH}_2\text{Cl}_2, 23 \degree \text{C}, 8 \text{ h} & \quad 115 \\
& \quad 135
\end{align*}
\]

Following GP4 108 mg (1.0 mmol, 2 equiv) o-kresol 134 and 5.5 mg (20 µmol, 0.04 equiv) tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) as additive are employed to obtain 76 mg (0.34 mmol, 67%) 135 in 36% ee after 8 h reaction time.

\[
\begin{align*}
\text{Me} & \quad \text{OCO}_2\text{Me} \quad \text{OH} \\
1 \text{ equiv} & \quad 115 \\
2 \text{ equiv} & \quad 134 \\
\text{[IrCl[(coe)]_2} (1.5 \text{ mol\%}) & \quad \text{Cs}_2\text{CO}_3 (1 \text{ equiv}) \\
\text{CH}_2\text{Cl}_2, 23 \degree \text{C}, 6 \text{ h} & \quad 115 \\
& \quad 135
\end{align*}
\]

Following GP4 108 mg (1.0 mmol, 2 equiv) o-kresol 134 and 163 mg (0.5 mmol, 1 equiv) Cs₂CO₃ as additive are employed to obtain 98 mg (0.44 mmol, 88%) 135 in 13% ee after 6 h reaction time.

\[
\begin{align*}
\text{Me} & \quad \text{OCO}_2\text{Me} \quad \text{OH} \\
1 \text{ equiv} & \quad 115 \\
2 \text{ equiv} & \quad 134 \\
\text{[IrCl[(coe)]_2} (1.5 \text{ mol\%}) & \quad \text{THABr (0.3 equiv)} \\
\text{CH}_2\text{Cl}_2, 23 \degree \text{C}, 3 \text{ h} & \quad 115 \\
& \quad 135
\end{align*}
\]

Following GP4 108 mg (1.0 mmol, 2 equiv) o-kresol 134 and 65 mg (0.15 mmol, 0.3 equiv) tetrahexylammonium bromide (THABr) as additive are employed to obtain 105 mg (0.48 mmol, 93%) 135 in 28% ee after 3 h reaction time.
Following GP4 108 mg (1.0 mmol, 2 equiv) o-kresol 134 and 72 mg (0.15 mmol, 0.3 equiv) tetrahexylammonium iodide (THAI) as additive are employed to obtain 107 mg (0.48 mmol, 95%) 135 in 22% ee after 2 h reaction time.

Following GP4 108 mg (1.0 mmol, 2 equiv) o-kresol 134 and 7.2 mg (15 µmol, 0.03 equiv) tetrahexylammonium iodide (THAI) as additive are employed to obtain 112 mg (0.5 mmol, 99%) 135 in 29% ee after 2 h reaction time.

8.3. Second Generation Chiral Bicyclo[2.2.2]octadienes

(+)-(S)-5-isopropenyl-2-methyl-3-phenylcyclohex-2-en-1-one (157).

To a pre-cooled solution (0 °C) of phenylmagnesium bromide in dry THF (80 mL, 80 mmol, 2 equiv) was added a solution of R-(-)-carvone 19 (6.0 g, 40 mmol, 1 equiv) in 20 mL THF over a period of 30 min. The reaction mixture was stirred at 23 °C for 6 h and then quenched by the addition of 30 mL sat. aq. NH₄Cl solution at 0 °C. Approximately two thirds of the solution was concentrated under reduced pressure, the resulting mixture was diluted with 50 mL Et₂O. The organic phase was separated and the aqueous phase was extracted three times with 40 mL Et₂O. The combined organic phases were washed
with brine and dried over Na₂SO₄. Evaporation of the solvents under reduced pressure furnished the crude tertiary alcohol (9.1 g, 40 mmol, 99% crude yield) as pale yellow oil which was used without any further purification for the next step.

To a pre-cooled suspension (0 °C) of PCC (12.8 g, 60 mmol, 1.5 equiv) and silica gel (13 g) in 50 mL dry CH₂Cl₂ was added a solution of the crude tertiary alcohol (9.1 g, 40 mmol, 1 equiv) in 50 mL dry CH₂Cl₂. The reaction mixture turned immediately black, stirring was continued at 23 °C for 6 h. The entire reaction mixture was then loaded on a silica gel column and eluted with more CH₂Cl₂ (to remove silica-bound chromium species). The solvent was evaporated and the residue was further purified over SiO₂ using hexanes/EtOAc (4:1) as eluent. The title compound 157 (7.0 g, 31 mmol, 77%) was isolated as yellow oil.

H NMR (300 MHz, CDCl₃) δ 7.62-7.16 (m, 5H), 4.82 (br s, 2H), 3.01-2.41 (m, 5H), 1.76 (br s, 6H).


(1R,4R,8S)-8-methoxy-1,8-dimethyl-6-phenylbicyclo[2.2.2]oct-5-en-2-one (158A) and (1R,4R,8R)-8-methoxy-1,8-dimethyl-6-phenylbicyclo[2.2.2]oct-5-en-2-one (158B)

To a solution of 157 (7.0 g, 31 mmol, 1 equiv) in CH₂Cl₂ (35 mL) and MeOH (25 mL) at -10 °C was added NBS (6.6 g, 37 mmol, 1.2 equiv) in small portions over 1 h and the reaction was allowed to warm to 23 °C overnight. The reaction was diluted with CH₂Cl₂ and washed with 1M aqueous NaOH. The aqueous layer was extracted with CH₂Cl₂ (3×), the combined organic layers washed with brine, dried over Na₂SO₄, and the solvent evaporated. The crude product was purified by flash chromatography using hexanes/EtOAc (85:15) to give the intermediate bromo compound (diastereomeric mixture, 9.5 g, 28 mmol, 91%) as yellow oil.
\textbf{Experimental Section}

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta 7.60-7.10 \) (m, 5H), 3.48 (s, 2H), 3.26 (s, 3H), 2.64 (br s, 3H), 2.40 and 2.60 (AB q, \(J = 15 \text{ Hz}, 2\)H), 1.72 (s, 3H), 1.31 (s, 3H).

For further spectroscopic details and separation conditions at this stage see: Srikrishna, A.; Hemamalini, P. \textit{Tetrahedron} \textbf{1992}, \textit{48}, 9337.

To a solution of \(t\)-BuOK (4.8 g, 42 mmol, 1.5 equiv) in \(t\)-BuOH (43 mL) at 0 °C was added a solution of the intermediate bromo compound (9.5 g, 28 mmol, 1 equiv, diastereomeric mixture) in THF (43 mL). The reaction mixture was warmed to room temperature and stirred 28 h. Et\textsubscript{2}O (75 mL) was added and the solution was washed with 0.5 M aqueous HCl (3x), brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and the solvent was evaporated. Purification of the crude by flash chromatography using hexanes/EtOAc (5:1) gave 158A (2.21 g, 8.62 mmol, 31%, solidified upon standing), 158B (1.58 g, 6.16 mmol, 22%) along with a mixed fraction (1.63 g, 6.36 mmol, 22%), as colorless oils (5.42 g, 21 mmol, 75%).

\textit{Analytical Data for 158A}:

\([\alpha]_D^{26} +224.8 \) (c 2.46, CHCl\textsubscript{3});

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta 7.35-7.20 \) (m, 3H), 7.10-7.00 (m, 2H), 6.34 (d, \(J = 6.9 \) Hz, 1H), 3.24 (s, 3H), 3.03 (td, \(J = 6.9, 2.6 \) Hz, 1H), 2.68 (d of \(1/2 \) AB q, \(J = 18.2, 2.0 \) Hz, 1H), 2.06 (d of \(1/2 \) AB q, \(J = 18.2, 3.3 \) Hz, 1H), 1.90 and 1.68 (AB q, \(J = 14 \text{ Hz}, 2\)H), 1.38 (s, 3H), 1.05 (s, 3H).

\textit{Analytical Data for 158B}:

\([\alpha]_D^{26} +169.4 \) (c 0.71, CHCl\textsubscript{3});

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta 7.45-7.09 \) (m, 5H), 6.34 (d, \(J = 6.4 \) Hz, 1H), 3.23 (s, 3H), 3.10-3.08 (m, 1H), 2.25 (d, \(J = 2.8 \) Hz, 1H), 1.95 and 1.63 (AB q, \(J = 14 \text{ Hz}, 2\)H), 1.42 (s, 3H), 1.06 (s, 3H).

GP5: Enolate Alkylation of the Bicyclic Ketone Intermediate 158A
To a solution of i-Pr₂NH (1.58 mmol, 1.5 equiv) in THF (5 mL) and DMPU (500 μL) at 0 °C was added n-BuLi (1.58 mmol, 1.5 equiv, 1.6 M/hexanes) dropwise and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and 158A (1.06 mmol, 1 equiv) was added. After 1 h at -78 °C, freshly distilled alkyl bromide (1.58 mmol, 1.5 equiv) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred another 5 h. The reaction was diluted with Et₂O and a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with Et₂O (3×), the combined organic layer washed with brine, dried over Na₂SO₄, and the solvent evaporated. Purification of the crude by flash chromatography was carried out using hexanes/EtOAc.

GP6: Formation of the Vinyl Triflate Intermediate
To a solution of Et₂NH (3.5 mmol, 4 equiv) in THF (3.5 mL) and DMPU (350 μL) at 0 °C was added n-BuLi (3.5 mmol, 4 equiv, 1.6 M/hexanes) dropwise and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and the bicyclic ketone obtained from GP5 (0.88 mmol, 1 equiv) was added. After 1 h at -78 °C, a solution of PhNTf₂ (3.5 mmol, 4 equiv) in THF (1 mL) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred overnight. The reaction was diluted with Et₂O and a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with Et₂O (3×), the combined organic layer washed with brine, dried over Na₂SO₄, and the solvent evaporated. The crude product was purified by flash chromatography using n-pentane/Et₂O (10:1) to give the triflate.

GP7: Reduction of the Vinyl Triflate Intermediate
To a solution of Pd(OAc)₂ (0.085 mmol, 0.1 equiv), Ph₃P (0.17 mmol, 0.2 equiv), and n-Bu₃N (2.55 mmol, 3 equiv) in DMF (4 mL) was added the triflate obtained from GP6 (0.85 mmol, 1 equiv). The solution was stirred 5 min at room temperature, HCO₂H (1.70 mmol, 2 equiv) was added, and the resulting solution was heated to 60 °C for 2 h. The reaction mixture was diluted with Et₂O, washed with 2M aqueous HCl (3×), the combined organic layers washed with brine, dried over Na₂SO₄, and the solvent
evaporated. Purification of the crude material was carried out by flash chromatography using *n*-pentane/Et₂O.

\[(1R,3R,4S,5S)-3\text{-benzyl-5-methoxy-1,5-dimethyl-7-phenylbicyclo[2.2.2]oct-7-en-2-one} \ (159)\]

\[
\text{MeC}^\text{Me} \text{Ph} \text{Ph} \]

Prepared according to GP5 on a 0.41 mmol scale. 115 mg (0.33 mmol, 81%) \(159\) were isolated as colorless oil.

\[
\left[\alpha\right]_D^{29} -2.7 \ (c \ 0.53, \ \text{CHCl}_3); \\
^1\text{H NMR (300 MHz, CDCl}_3\) \ \delta \ 7.19-7.32 \ (m, 8H), 7.03-7.06 \ (m, 2H), 6.23 \ (d, J = 6.9 Hz, 1H), 3.34-3.38 \ (m, 1H), 2.91 \ (s, 3H), 2.87 \ (m, 1H), 2.81 \ (dd, J = 6.9 Hz, J = 1.9 Hz, 1H), 2.30-2.39 \ (m, 1H), 1.90 \ (d, J = 14.0 Hz, 1H), 1.70 \ (d, J = 13.7 Hz, 1H), 1.27 \ (s, 3H), 1.08 \ (s, 3H); \\
^1\text{C NMR (75 MHz, CDCl}_3\) \ \delta \ 211.7, 144.2, 139.9, 138.1, 131.8, 128.7, 128.4, 128.2, 127.9, 127.3, 126.2, 78.7, 53.0, 49.2, 47.7, 44.8, 43.2, 37.6, 25.1, 16.7; \\
\text{IR (neat) } \nu = 3026, 2970, 2933, 2826, 1715, 1452, 1085, 1071, 1055, 762, 744 \ \text{cm}^{-1}; \\
\text{HRMS-EI calcd for } \text{C}_{24}\text{H}_{26}\text{O}_2 [M]^+ 346.1933, \ \text{found } 346.1927.\]

\[(1R,4S,8S)-3\text{-benzyl-8-methoxy-1,8-dimethyl-6-phenylbicyclo[2.2.2]octa-2,5-dien-2-yltrifluoromethanesulfonate} \ (160)\]

\[
\text{MeO}^\text{TF} \text{Ph} \text{Ph} \\
\text{O} \text{Me} \text{Ph} \]

Prepared according to GP6 on a 0.13 mmol scale. 35 mg (0.07 mmol, 55%) \(160\) were isolated as colorless oil.

\[
\left[\alpha\right]_D^{34} -174.5 \ (c \ 0.69, \ \text{CHCl}_3); \\
^1\text{H NMR (300 MHz, CDCl}_3\) \ \delta \ 7.21-7.34 \ (m, 6H), 7.12-7.15 \ (m, 4H), 6.00 \ (d, J = 6.5 Hz, 1H), 4.12 \ (d, J = 15.6 Hz, 1H), 3.32 \ (d, J = 16.5 Hz, 1H), 3.31 \ (d, J = 6.2 Hz, 1H),
3.20 (s, 3H), 1.95 (d, J = 12.5 Hz, 1H), 1.48 (d, J = 12.1 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 185.2, 150.9, 140.6, 137.5, 135.2, 130.9, 129.0, 128.4, 128.3, 127.9, 127.2, 126.3, 83.3, 51.0, 50.7, 50.5, 47.3, 35.8, 24.8, 17.7;

IR (neat) ν = 2968, 2938, 2824, 1686, 1599, 1400, 1207, 1136, 1086, 1063, 1046, 865, 764 cm$^{-1}$;

Anal. Calcd for C$_{25}$H$_{25}$F$_3$O$_4$S: C, 62.75; H, 5.27. Found: C, 63.02; H, 5.27.

**(1S,4S,8S)-5-benzyl-8-methoxy-1,8-dimethyl-2-phenylbicyclo[2.2.2]octa-2,5-diene**

(161)

![Diagram of (1S,4S,8S)-5-benzyl-8-methoxy-1,8-dimethyl-2-phenylbicyclo[2.2.2]octa-2,5-diene](image)

Prepared according to GP7 on a 0.05 mmol scale. 14 mg (0.04 mmol, 86%) 161 were isolated as colorless oil.

$[^\alpha]$_D$^{33}$ -150.4 (c 0.73, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.06-7.33 (m, 10H), 6.01 (d, J = 6.2 Hz, 1H), 5.79 (s, 1H), 3.72 (d, J = 15.9 Hz, 1H), 3.47 (d, J = 15.9 Hz, 1H), 3.35 (dd, J = 6.5 Hz, J = 1.9 Hz, 1H), 3.24 (s, 3H), 1.55 (d, J = 11.8 Hz, 1H), 1.44 (d, J = 11.8 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.7, 146.8, 139.4, 133.2, 131.4, 129.1, 128.1, 127.9, 127.6, 126.5, 125.8, 84.0, 51.1, 50.8, 50.3, 45.1, 41.0, 25.1, 22.0;

IR (neat) ν = 3020, 2961, 2823, 1601, 1493, 1452, 1366, 1213, 1117, 1071, 751 cm$^{-1}$;

HRMS-ESI calcd for C$_{24}$H$_{25}$NaO $[\text{MNa}]^+$ 353.1876, found 353.1881.

**(1R,3R,4S,5S)-3-allyl-5-methoxy-1,5-dimethyl-7-phenylbicyclo[2.2.2]oct-7-en-2-one**

(162)

![Diagram of (1R,3R,4S,5S)-3-allyl-5-methoxy-1,5-dimethyl-7-phenylbicyclo[2.2.2]oct-7-en-2-one](image)
Prepared according to GP5 on a 0.39 mmol scale. 97 mg (0.33 mmol, 84%) 162 were isolated as colorless oil.

$[^{\alpha}]D^{31} 115.3$ (c 1.74, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.46-7.54 (m, 3H), 7.23-7.26 (m, 2H), 6.44 (d, $J = 6.9$ Hz, 1H), 5.95-6.08 (m, 1H), 5.23-5.29 (m, 2H), 3.41 (s, 3H), 3.17 (d, $J = 6.9$ Hz, 1H), 2.86-2.92 (m, 2H), 2.07-2.18 (m, 1H), 2.12 (d, $J = 14.0$ Hz, 1H), 1.89 (d, $J = 14.0$ Hz, 1H), 1.56 (s, 3H), 1.25 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 212.0, 143.9, 138.1, 136.4, 132.0, 128.1, 127.8, 127.2, 116.5, 78.6, 53.0, 49.6, 47.2, 44.1, 42.5, 36.2, 25.2, 16.7;

IR (neat) $\nu$ = 3016, 2970, 2943, 2933, 1737, 1442, 1366, 1228, 1216, 1075, 912 cm$^{-1}$;

HRMS-ESI calcld for C$_{20}$H$_{24}$O$_2$ [M]+ 296.1776, found 296.1772.

Anal. Calcd for C$_{20}$H$_{24}$O$_2$: C, 81.04; H, 8.16. Found: C, 81.15; H, 8.30;

(1R,4S,8S)-3-allyl-8-methoxy-1,8-dimethyl-6-phenylbicyclo[2.2.2]octa-2,5-dien-2-yltrifluoromethanesulfonate (163)

Prepared according to GP6 on a 0.33 mmol scale. 64 mg (0.15 mmol, 45%) 163 were isolated as colorless oil.

$[^{\alpha}]D^{34} -126.3$ (c 1.42, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.25-7.35 (m, 3H), 7.10-7.13 (m, 2H), 6.12 (d, $J = 6.5$ Hz, 1H), 5.71-5.85 (m, 1H), 5.06-5.13 (m, 2H), 3.53 (d, $J = 6.2$ Hz, 1H), 3.32-3.48 (m, 1H), 3.22 (s, 3H), 2.78-2.85 (m, 1H), 1.90 (d, $J = 12.4$ Hz, 1H), 1.47 (d, $J = 12.1$ Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 151.3, 148.1, 137.5, 134.6, 133.7, 130.6, 128.2, 127.8, 127.1, 117.1, 83.3, 51.2, 50.5, 50.4, 47.3, 34.2, 24.9, 17.4;

IR (neat) $\nu$ = 2976, 2828, 1686, 1639, 1400, 1206, 1137, 1088, 1046, 860 cm$^{-1}$;

HRMS-ESI calcld for C$_{21}$H$_{21}$F$_3$NaO$_4$S [MNa]$^+$ 451.1161, found 451.1163.
Experimental Section

**Anal.** Calcd for C_{21}H_{23}F_{3}O_{4}S: C, 58.87; H, 5.41. Found: C, 58.68; H, 5.63.

(1S,4S,8S)-5-allyl-8-methoxy-1,8-dimethyl-2-phenylbicyclo[2.2.2]octa-2,5-diene (164)

Prepared according to GP7 on a 0.15 mmol scale. 24 mg (0.09 mmol, 60%) 164 were isolated as colorless oil.

$[\alpha]_{D}^{33} -150.3$ (c 0.84, CHCl₃);

$^1$H NMR (300 MHz, CDCl₃) δ 7.21-7.32 (m, 3H), 7.06-7.09 (m, 2H), 6.09 (d, $J = 6.5$ Hz, 1H), 5.79-5.93 (m, 2H), 5.03-5.10 (m, 2H), 3.43 (dd, $J = 6.5$ Hz, $J = 1.9$ Hz, 1H), 3.23 (s, 3H), 2.88-3.23 (m, 2H), 1.53 (d, $J = 12.1$ Hz, 1H), 1.43 (d, $J = 11.8$ Hz, 1H), 1.34 (s, 3H), 1.29 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl₃) δ 152.0, 146.1, 139.4, 135.9, 132.3, 131.1, 127.8, 127.6, 126.4, 115.9, 83.9, 51.2, 50.7, 50.3, 45.1, 39.1, 25.1, 22.0;

IR (neat) ν = 3040, 2961, 2822, 1637, 1597, 1454, 1366, 1191, 910, 756 cm⁻¹;

HRMS-ESI calcd for C_{20}H_{24}NaO [MNa]⁺ 303.1719, found 303.1716;

**Anal.** Calcd for C_{20}H_{24}O: C, 85.67; H, 8.63. Found: C, 85.41; H, 8.76.

(1R,3R,4S,5S)-5-methoxy-1,5-dimethyl-7-phenyl-3-propylbicyclo[2.2.2]oct-7-en-2-one (165)

Prepared according to GP5 on a 0.42 mmol scale. 98 mg (0.33 mmol, 79%) 165 were isolated as colorless oil.

$[\alpha]_{D}^{31} 157.6$ (c 1.70, CHCl₃);

$^1$H NMR (300 MHz, CDCl₃) δ 7.24-7.30 (m, 3H), 7.01-7.04 (m, 2H), 6.22 (d, $J = 7.2$ Hz, 1H), 3.21 (s, 3H), 2.95 (dd, $J = 6.9$ Hz, $J = 1.9$ Hz, 1H), 2.55-2.60 (m, 1H), 1.87 (d, $J$
13.7 Hz, 1H), 1.77-1.84 (m, 1H), 1.66 (d, J = 13.7 Hz, 1H), 1.33-1.49 (m, 2H), 1.35 (s, 3H), 1.17-1.24 (m, 1H), 1.03 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 213.5, 144.0, 138.1, 132.1, 128.2, 127.9, 127.2, 78.7, 52.8, 49.5, 47.1, 44.8, 42.6, 34.0, 25.2, 21.0, 16.6, 14.1;

IR (neat) ν = 2957, 2932, 2871, 2826, 1714, 1451, 1144, 1069, 853, 764 cm$^{-1}$;

HRMS-EI calcd for C$_{20}$H$_{24}$O$_2$ [M]+ 298.1933, found 298.1931;

Anal. Calcd for C$_{20}$H$_{26}$O$_2$: C, 80.50; H, 8.78. Found: C, 80.38; H, 9.05.

(1R,4S,8S)-8-methoxy-1,8-dimethyl-6-phenyl-3-propylbicyclo[2.2.2]octa-2,5-dien-2-yltrifluoromethanesulfonate (166)

![Chemical structure image]

Prepared according to GP6 on a 0.25 mmol scale. 43 mg (0.10 mmol, 40%) 166 were isolated as colorless oil.

$[^{34}]$D +55.0 (c 1.26, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.26-7.34 (m, 3H), 7.08-7.11 (m, 2H), 6.12 (d, J = 6.5 Hz, 1H), 3.52 (d, J = 6.2 Hz, 1H), 3.21 (s, 3H), 2.44-2.54 (m, 1H), 2.02-2.12 (m, 1H), 1.90 (d, J = 12.1 Hz, 1H), 1.41-1.60 (m, 2H), 1.42 (d, J = 12.1 Hz, 1H), 1.39 (s, 3H), 1.29 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.5, 147.5, 137.6, 137.2, 130.6, 129.8, 128.2, 127.8, 127.1, 83.2, 51.5, 50.4, 49.7, 47.1, 42.7, 31.7, 25.0, 20.4, 17.5, 14.0;

IR (neat) ν = 2969, 1443, 1399, 1385, 1206, 1137, 1091, 1062, 1045, 862 cm$^{-1}$;

HRMS-EI calcd for C$_{17}$H$_{17}$F$_3$O$_3$S [M-C$_4$H$_8$O]$^+$ 358.0850, found 358.0847 (Retro-Diels-Alder product).
Experimental Section

(1S,4S,8S)-8-methoxy-1,8-dimethyl-2-phenyl-5-propylbicyclo[2.2.2]octa-2,5-diene (167)

Prepared according to GP7 on a 0.10 mmol scale. 24 mg (0.08 mmol, 84%) 167 were isolated as colorless oil. 

$\left[\alpha\right]_D^{33} -71.5 (c 0.65, \text{CHCl}_3)$; 

$^1H$ NMR (300 MHz, CDCl$_3$) $\delta$ 7.23-7.32 (m, 3H), 7.05-7.08 (m, 2H), 6.08 (d, $J = 6.5$ Hz, 1H), 5.76 (s, 1H), 5.42 (dd, $J = 6.5$ Hz, $J = 1.9$ Hz, 1H), 3.23 (s, 3H), 2.17-2.23 (m, 2H), 1.41-1.55 (m, 2H), 1.52 (d, $J = 11.8$ Hz, 1H), 1.43 (d, $J = 12.1$ Hz, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 0.88 (t, $J = 7.5$ Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.1, 148.1, 139.5, 131.2, 131.0, 127.8, 127.6, 126.4, 83.8, 51.5, 50.3, 44.9, 36.7, 25.1, 22.0, 20.5, 14.0; 

IR (neat) $\nu$ = 3039, 2956, 2928, 2870, 2823, 1596, 1454, 1366, 1196, 1158, 1120, 1071, 865, 847 cm$^{-1}$; 

HRMS-ESI calcd for C$_{20}$H$_{26}$NaO $[\text{MNa}]^+$ 305.1876, found 305.1873.

(1R,3R,4S,5S)-3-(but-3-enyl)-5-methoxy-1,5-dimethyl-7-phenylbicyclo[2.2.2]oct-7-en-2-one (168)

Prepared according to GP5 on a 0.42 mmol scale. 75 mg (0.24 mmol, 57%) 168 were isolated as colorless oil. 

$\left[\alpha\right]_D^{31} 147.5 (c 1.74, \text{CHCl}_3)$; 

$^1H$ NMR (300 MHz, CDCl$_3$) $\delta$ 7.26-7.32 (m, 3H), 7.02-7.06 (m, 2H), 6.25 (d, $J = 6.9$ Hz, 1H), 5.77-5.86 (m, 1H), 5.00-5.09 (m, 2H), 3.22 (s, 3H), 2.97 (dd, $J = 6.9$ Hz, $J = 1.9$ Hz, 1H), 2.58-2.63 (m, 1H), 2.14-2.22 (m, 2H), 1.92-1.96 (m, 1H), 1.88 (d, $J = 14.0$ Hz, 1H), 1.67 (d, $J = 13.7$ Hz, 1H), 1.37 (s, 3H), 1.18-1.40 (m, 1H), 1.04 (s, 3H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 213.6, 152.9, 144.4, 138.4, 132.2, 128.4, 128.1, 127.5, 115.3, 78.9, 53.0, 49.8, 47.4, 45.0, 42.4, 32.2, 31.3, 25.4, 16.8;

IR (neat) $\nu$ = 3016, 2970, 2942, 1737, 1441, 1366, 1228, 1216, 1068, 910, 760 cm$^{-1}$;

HRMS-EI calcd for C$_{21}$H$_{26}$O$_2$ [M]$^+$ 310.1933, found 310.1929;

Anal. Calcd for C$_{21}$H$_{26}$O$_2$: C, 81.25; H, 8.44. Found: C, 81.18; H, 8.35.

(1R,4S,8S)-3-(but-3-enyl)-8-methoxy-1,8-dimethyl-6-phenylbicyclo[2.2.2]octa-2,5-dien-2-yltrifluoromethanesulfonate (169)

Prepared according to GP6 on a 0.13 mmol scale. 26 mg (0.06 mmol, 46%) 169 were isolated as colorless oil.

$[\alpha]_D^{34}$-70.9 (c 1.44, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26-7.35 (m, 3H), 7.07-7.11 (m, 2H), 6.11 (d, $J$ = 6.2 Hz, 1H), 5.78-5.83 (m, 1H), 4.96-5.07 (m, 2H), 3.53 (d, $J$ = 6.2 Hz, 1H), 3.21 (s, 3H), 2.58-2.64 (m, 1H), 2.16-2.30 (m, 3H), 1.90 (d, $J$ = 12.1 Hz, 1H), 1.42 (d, $J$ = 12.1 Hz, 1H), 1.39 (s, 3H), 1.29 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 151.4, 147.6, 137.6, 137.5, 136.6, 130.6, 128.2, 127.8, 127.1, 115.1, 83.2, 51.8, 50.4, 49.6, 47.1, 31.3, 29.3, 25.0, 17.4;

IR (neat) $\nu$ = 2976, 2827, 1684, 1641, 1399, 1205, 1138, 1087, 1046, 861 cm$^{-1}$;

HRMS-ESI calcd for C$_{22}$H$_{25}$F$_3$NaO$_4$S [MNa]$^+$ 465.1318, found 465.1325;


(1S,4S,8S)-5-(but-3-enyl)-8-methoxy-1,8-dimethyl-2-phenylbicyclo[2.2.2]-octa-2,5-diene (170)
Prepared according to GP7 on a 0.06 mmol scale. 15 mg (0.05 mmol, 86%) 170 were isolated as colorless oil.

$[\alpha]_D^{30}$ -53.4 (c 0.19, CHCl₃);

$^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.23-7.31 (m, 3H), 7.04-7.11 (m, 2H), 6.08 (d, $J = 6.3$ Hz, 1H), 5.78-5.90 (m, 2H), 4.93-5.05 (m, 2H), 3.44 (dd, $J = 6.7$ Hz, $J = 1.9$ Hz, 1H), 3.22 (s, 3H), 2.22-2.34 (m, 3H), 1.38-1.50 (m, 3H), 1.33 (s, 3H), 1.28 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 147.6, 139.5, 138.5, 131.2, 131.1, 128.2, 127.8, 127.6, 126.4, 114.4, 83.8, 51.8, 50.6, 50.3, 45.0, 34.1, 31.7, 25.2, 22.1;

IR (neat) $\nu$ = 2927, 1457, 1213, 1073, 864 cm$^{-1}$;

HRMS-ESI calc'd for C$_{21}$H$_{26}$NaO $[MNa]^{+}$ 317.1876, found 317.1871.

(S)-3-isobutyl-5-isopropenyl-2-methylcyclohex-2-en-1-one (171).

A solution of (R)-(−)-carvone 19 (3.13 mL, 19.9 mmol), Li (693 mg, 99.8 mmol), isobutylbromide (8.69 mL, 79.9 mmol) in THF (150 mL) was sonicated for 1.5 h. The reaction mixture was cooled to 0 °C and quenched slowly with a saturated aqueous NH$_4$Cl solution followed by cold water. The THF was removed and the residual aqueous layer was extracted with Et$_2$O (3×). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and the solvent was evaporated. The crude alcohol was used for the next step without further purification. To a suspension/solution of PCC (8.40 g, 38.9 mmol) and silica gel (8.40 g) in CH$_2$Cl$_2$ (35 mL) was added a solution the crude alcohol in CH$_2$Cl$_2$ (35 mL). After stirring for 3 h, the reaction mixture was filtered through a pad of silica gel using CH$_2$Cl$_2$ as eluent to give the crude product. The latter was purified by flash chromatography using hexanes/EtOAc (10:1) to give 171 (2.15 g, 52% from (R)-(−)-carvone) as a colorless oil.

$[\alpha]_D^{27}$ 59.7 (c 0.95, CHCl₃);
**Experimental Section**

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.76-4.72 (m, 2H), 2.57-2.50 (m, 2H), 2.33-2.24 (m, 2H), 2.17-2.14 (m, 1H), 1.94-1.81 (m, 1H), 1.74 (s, 3H), 1.71 (s, 3H), 0.91 (d, $J$ = 6.6 Hz, 3H), 0.88 (d, $J$ = 6.6 Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.1, 157.1, 146.7, 131.1, 110.1, 44.3, 42.7, 41.5, 36.5, 27.5, 23.0, 22.5, 20.6, 11.2;

IR (neat) $\nu$ = 2956, 2869, 1667, 1627, 1463, 1381, 1165, 1129, 1081, 891 cm$^{-1}$;

HRMS-EI calcd for C$_{14}$H$_{22}$O $[M]^+$ 206.1671, found 206.1666;

Anal. Calcd for C$_{14}$H$_{22}$O: C, 81.50; H, 10.75. Found: C, 81.24; H, 10.67.

$(1R,4R,8J)$-6-isobutyl-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-one (172A) and $(1R,4S,8R)$-6-isobutyl-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-one (172B)

![Chemical Structures](image1.png)

To a solution of 171 (2.11 g, 10.2 mmol) in CH$_2$Cl$_2$ (11 mL) and MeOH (7 mL) at -10 °C was added NBS (2.18 g, 12.3 mmol) in small portions over 1 h and the reaction was allowed to warm to 23 °C overnight. The reaction was diluted with CH$_2$Cl$_2$ and washed with 1M aqueous NaOH. The aqueous layer was extracted with CH$_2$Cl$_2$ (3×), the combined organic layers washed with brine, dried over Na$_2$SO$_4$, and the solvent evaporated. The crude product was purified by flash chromatography using hexanes/EtOAc (85:15) to give the intermediate bromo compound (2.17 g, 68%) as a colorless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.48-3.37 (m, 2H), 3.21 (m, 3H), 2.58-2.08 (m, 7H), 2.00-1.83 (m, 1H), 1.74 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.2, 199.0, 158.0, 156.9, 131.3, 131.1, 75.9, 75.7, 49.5, 49.4, 44.4, 44.3, 40.0, 39.9, 38.7, 37.9, 36.7, 36.5, 32.1, 31.2, 27.4 (2), 22.9 (2), 22.3, 18.1, 17.8, 11.0.

IR (neat) $\nu$ = 2955, 2688, 1663, 1629, 1459 cm$^{-1}$;

To a solution of $t$-BuOK (1.18 g, 10.5 mmol) in $t$-BuOH (10.5 mL) at 0 °C was added a solution of the bromo compound in THF (11 mL). The reaction mixture was warmed to
room temperature and stirred 28 h. Et₂O (75 mL) was added and the solution was washed with 0.5 M aqueous HCl (3×), brine, dried over Na₂SO₄, and the solvent was evaporated. Purification of the crude by flash chromatography using hexanes/EtOAc (5:1) gave 172A (336 mg), 172B (133 mg) along with mixed fraction (845 mg), as colorless oils (1.31 g, 79%).

**Analytical Data for 172A**

[α]D²⁸ +320.76 (c 1.37, CHCl₃);

**¹H NMR (300 MHz, CDCl₃)** δ 6.04 (d, 1H, J = 6.9 Hz), 3.14 (s, 3H), 2.84-2.80 (m, 1H), 2.50 (dd, J = 18.1, 2.0 Hz, 1H), 1.93-1.76 (m, 3H), 1.70 (d, J = 13.8 Hz, 1H), 1.65-1.54 (m, 1H), 1.43 (d, J = 13.8 Hz, 1H), 1.23 (s, 3H), 1.10 (s, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.79 (d, J = 6.5 Hz, 3H);

**¹³C NMR (75 MHz, CDCl₃)** δ 213.1, 142.5, 129.8, 78.1, 52.7, 49.5, 46.7, 40.6, 40.2, 34.8, 26.7, 24.8, 22.6, 22.3, 14.8;

**IR (neat)** ν = 2954, 2869, 2826, 1722, 1464, 1368, 1144, 1083, 1068 cm⁻¹;

**HRMS-EI** calcd for C₁₅H₂₄O₂ [M]⁺ 236.1776, found 236.1772;

**Anal.** Calcd for C₁₅H₂₄O₂: C, 76.23; H, 10.23. Found: C, 76.04; H, 10.12.

**GP8: Enolate Alkylation of the Bicyclic Ketone Intermediate 172A**

To a solution of i-Pr₂NH (1.58 mmol, 1.5 equiv) in THF (5 mL) and DMPU (500 μL) at 0 °C was added n-BuLi (1.58 mmol, 1.5 equiv, 1.6 M/hexanes) dropwise and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and 172A (1.06 mmol, 1 equiv) was added. After 1 h at -78 °C, freshly distilled alkyl bromide (1.58 mmol, 1.5 equiv) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred another 5 h. The reaction was diluted with Et₂O and a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with Et₂O (3×), the combined organic layer washed with brine, dried over Na₂SO₄, and the solvent evaporated. Purification of the crude by flash chromatography was carried out using hexanes/EtOAc.
**GP9: Formation of the Vinyl Triflate Intermediate and Subsequent Reduction**

To a solution of Et₂NH (3.5 mmol, 4 equiv) in THF (3.5 mL) and DMPU (350 μL) at 0 °C was added n-BuLi (3.5 mmol, 4 equiv, 1.6 M/hexanes) dropwise and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and the bicyclic ketone obtained from GP5 (0.88 mmol, 1 equiv) was added. After 1 h at -78 °C, a solution of PhNTf₂ (3.5 mmol, 4 equiv) in THF (1 mL) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred overnight. The reaction was diluted with Et₂O and a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with Et₂O (3×), the combined organic layer washed with brine, dried over Na₂SO₄, and the solvent evaporated. The crude product was purified by flash chromatography using n-pentane/Et₂O (10:1) to give the triflate. The crude product was purified by flash chromatography using n-pentane/Et₂O to give the triflate contaminated with PhNTf₂ side-products. This mixture was used in the next step without further purification. However, an analytically pure sample could be obtained as colorless oil by additional flash chromatography.

To a solution of Pd(OAc)₂ (0.085 mmol, 0.1 equiv), Ph₃P (0.17 mmol, 0.2 equiv), and n-Bu₃N (2.55 mmol, 3 equiv) in DMF (4 mL) was added the triflate (0.85 mmol, 1 equiv). The solution was stirred 5 min at room temperature, HCO₂H (1.70 mmol, 2 equiv) was added, and the resulting solution was heated to 60 °C for 2 h. The reaction mixture was diluted with Et₂O, washed with 2M aqueous HCl (3×), the combined organic layers washed with brine, dried over Na₂SO₄, and the solvent evaporated. Purification of the crude material was carried out by flash chromatography using n-pentane/Et₂O.

**173**

Prepared according to GP8 on a 1.06 mmol scale. 254 mg (0.92 mmol, 87%) 173 were isolated as colorless oil.
Experimental Section

[α]D$^\circ$ 189.0 (c 0.93, CHCl₃);

$^1$H NMR (300 MHz, CDCl₃) δ 5.96 (d, J = 6.8 Hz, 1H), 5.83-5.70 (m, 1H), 5.04-4.98 (m, 2H), 3.12 (s, 3H), 2.78 (dd, J = 6.8, 1.7 Hz, 1H), 2.64-2.48 (m, 2H), 1.87-1.60 (m, 5H), 1.46 (d, J = 13.8 Hz, 1H), 1.22 (s, 3H), 1.12 (s, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl₃) δ 212.5, 141.1, 136.6, 128.4, 116.1, 78.3, 52.9, 49.4, 46.7, 43.5, 42.4, 39.9, 36.1, 26.9, 24.9, 22.8, 22.6, 15.0;

IR (neat) v = 2954, 2862, 2812, 1717, 1639, 1460, 1368, 1072, 912 cm$^{-1}$;

HRMS-EI calcd for C$_{18}$H$_{28}$O$_2$ [M]$^+$ 276.2089, found 276.2084.

Anal. Calcd for C$_{18}$H$_{28}$O$_2$: C, 78.21; H, 10.21. Found: C, 78.26; H, 10.43.

(1S,4S,8S)-5-allyl-2-isobutyl-8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-diene (175)

Prepared according to GP9 on a 0.88 mmol scale. 348 mg of the triflate 174 contaminated with PhNTf$_2$ side-products were obtained which were directly subjected to reduction conditions as described in GP9 to finally obtain 175 (142 mg, 0.55 mmol, 62% from 173) as colorless liquid.

Analytical data of 174:

[α]$_D$$^\circ$ 46.2 (c 0.50, CHCl₃);

$^1$H NMR (300 MHz, CDCl₃) δ 5.83 (d, J = 6.3 Hz, 1H), 5.78-5.63 (m, 1H), 5.09-4.99 (m, 2H), 3.35 (d, J = 6.3 Hz, 1H), 3.31-3.22 (m, 1H), 3.15 (s, 3H), 2.72 (dd, J = 15.7, 7.6 Hz, 1H), 2.01-1.84 (m, 2H), 1.79-1.68 (m, 2H), 1.41 (s, 3H), 1.25 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl₃) δ 149.3, 148.4, 134.3, 133.9, 126.9, 118.5 (q, J = 320 Hz), 117.0, 50.7, 50.3, 49.7, 46.9, 39.1, 33.9, 26.2, 24.7, 22.8, 22.6, 15.5.

IR (neat) v = 2957, 1445, 1402, 1245, 1210, 1140, 1093, 1063, 1027, 862 cm$^{-1}$;
Analytical Data of 175:

$[\alpha]_D^{33}$ -83.2 (c 0.93, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.87-5.74 (m, 2H), 5.67 (d, $J = 1.4$ Hz, 1H), 5.04-4.98 (m, 2H), 3.27 (dd, $J = 6.4$, 1.9 Hz, 1H), 3.18 (s, 3H), 3.19-2.96 (m, 1H), 2.89-2.81 (m, 1H), 1.91 (dd, $J = 6.8$, 1.4 Hz, 2H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 149.8, 145.8, 136.1, 132.1, 126.8, 115.6, 83.5, 50.7, 50.2, 50.1, 44.9, 39.6, 39.0, 26.6, 25.0, 22.9, 22.8, 20.3;

IR (neat) $\nu$ = 3037, 2955, 2823, 1638, 1461, 1366, 1120, 1072, 910 cm$^{-1}$;

HRMS-EI calcd for C$_{18}$H$_{28}$O $[M]^+$ 260.2140, found 260.2138;

Anal. Calcd for C$_{18}$H$_{28}$O: C, 83.02; H, 10.84. Found: C, 83.27; H, 11.00.

(1R,3R,4S,5S)-3-benzyl-7-isobutyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (176)

Prepared according to GP8 on a 1.69 mmol scale. 420 mg (1.28 mmol, 76%) 176 were isolated as colorless oil.

$[\alpha]_D^{30}$ +96.2 (c 0.45, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.32-7.26 (m, 2H), 7.22-7.17 (m, 3H), 6.00 (d, $J = 6.9$ Hz, 1H), 3.28 (dd, $J = 13.5$, 3.9 Hz, 1H), 2.83 (s, 3H), 2.75 (dd, $J = 11.7$, 3.9, 1.5 Hz, 1H), 2.58 (dd, $J = 6.9$, 1.8 Hz, 1H), 2.19 (dd, $J = 13.8$, 11.4 Hz, 1H), 1.97-1.84 (m, 2H), 1.74 (d, $J = 13.8$ Hz, 1H), 1.76-1.62 (m, 1H), 1.50 (d, $J = 13.8$ Hz, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 212.6, 141.6, 140.2, 128.8, 128.4, 126.1, 78.2, 53.0, 48.9, 47.3, 44.7, 42.5, 40.0, 37.4, 26.9, 24.8, 22.8, 22.6, 15.0;

IR (neat) $\nu$ = 3027, 2952, 2868, 2826, 1714, 1454, 1140, 1086, 1070 cm$^{-1}$;

HRMS-EI calcd for C$_{22}$H$_{30}$O$_2$ $[M]^+$ 326.2241, found 326.2241.
Experimental Section

(1S,4S,8S)-5-benzyl-2-isobutyl-8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-diene (178)

Prepared according to GP9 on a 1.20 mmol scale. 460 mg of the triflate 177 contaminated with PhNTf2 side-products were obtained which were directly subjected to reduction conditions as described in GP9 to finally obtain 178 (210 mg, 0.68 mmol, 57% from 175) as colorless liquid.

$\text{[a]}^\circ_{D} = -96.3$ (c 0.70, CHCl3);

$^1\text{H NMR (300 MHz, CDCl}_3$) $\delta$ 7.28-7.10 (m, 5H), 5.71 (d, $J = 6.3$ Hz, 1H), 5.64 (bs, 1H), 3.65 (d, $J = 15.9$ Hz, 1H), 3.40 (dd, $J = 15.6$, 1.8 Hz, 1H), 3.20 (s, 3H), 3.18 (dd, $J = 6.3$, 1.8 Hz, 1H), 1.93, 1.90 (AB of ABMX, $J_{AB} = 15.3$ Hz, $J_{BM} = 7.2$ Hz, $J_{BM} = 6.6$ Hz, $J_{AX} = J_{AX} = 1.5$ Hz, 2H), 1.70 (sep, $J = 6.6$ Hz, 1H), 1.42 (d, $J = 12.0$ Hz, 1H), 1.34 (s, 3H), 1.20 (d, $J = 12.0$ Hz, 1H), 1.20 (s, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H);

$^{13}\text{C NMR (75.5 MHz, CDCl}_3$) $\delta$ 149.3, 146.4, 139.6, 132.9, 129.0, 127.9, 127.1, 125.6, 83.6, 50.5, 50.3, 50.2, 44.8, 40.9, 39.6, 26.7, 24.9, 22.9, 22.8, 20.3;

IR (neat) $\nu$ = 3028, 2953, 2823, 1495, 1453, 1366, 1181, 1118, 1071, 1052 cm$^{-1}$;

HRMS-EI calcd for C$_{22}$H$_{30}$O [M]$^+$ 310.2292, found 310.2289.

GP10: Enolate Alkylation of the Bicyclic Ketone Intermediate 104

To a solution of $i$-Pr$_2$NH (2.5 mmol, 1.5 equiv) in THF (5 mL) and DMPU (500 µL) at 0 °C was added $n$-BuLi (2.5 mmol, 1.5 equiv, 1.6 M/hexanes) dropwise and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and 104 (1.66 mmol, 1 equiv) was added. After 1 h at -78 °C, freshly distilled alkyl bromide (2.5 mmol, 1.5 equiv) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred another 8 h. The reaction was diluted with Et$_2$O and a saturated aqueous solution of NH$_4$Cl was added. The aqueous layer was extracted with Et$_2$O (3 ×), the combined organic layer washed with brine, dried over Na$_2$SO$_4$, and the solvent evaporated. Purification of the crude by flash chromatography was carried out using hexanes/EtOAc.
**GP11: Formation of the Vinyl Triflate Intermediate**

To a solution of Et₂NH (5.0 mmol, 5 equiv) in THF (2.5 mL) and DMPU (250 μL) at 0 °C was added n-BuLi (5.0 mmol, 5 equiv, 1.6 M/hexanes) dropwise and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and the bicyclic ketone obtained from GP10 (1.0 mmol, 1 equiv) was added. After 1 h at -78 °C, a solution of PhNTf₂ (5.0 mmol, 5 equiv) in THF (1 mL) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred overnight. The reaction was diluted with Et₂O and a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with Et₂O (3×), the combined organic layer washed with brine, dried over Na₂SO₄, and the solvent evaporated. The crude product was purified by flash chromatography using n-pentane/Et₂O (10:1) to give the triflate.

**GP12: Reduction of the Vinyl Triflate Intermediate**

To a solution of Pd(OAc)₂ (19.3 μmol, 0.1 equiv), Ph₃P (38.7 μmol, 0.2 equiv), and n-Bu₃N (0.58 mmol, 3 equiv) in DMF (0.8 mL) was added the triflate obtained from GP11 (0.19 mmol, 1 equiv). The solution was stirred 5 min at room temperature, HCO₂H (0.38 mmol, 2 equiv) was added, and the resulting solution was heated to 60 °C for 2 h. The reaction mixture was diluted with Et₂O, washed with 2M aqueous HCl (3×), the combined organic layers washed with brine, dried over Na₂SO₄, and the solvent evaporated. Purification of the crude material was carried out by flash chromatography using n-pentane/Et₂O.

*(1S,3S,4R,5R)-3-benzyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (179)*

Prepared according to GP10 on a 1.66 mmol scale. 305 mg (1.13 mmol, 68%) 179 were isolated as colorless oil.

\[ [\alpha]_{D}^{28} = -153.4 (c 0.62, CHCl₃); \]
**Experimental Section**

**1H NMR (300 MHz, CDCl₃)** δ 7.31-7.15 (m, 5H), 6.37-6.32 (m, 1H), 5.85-5.82 (m, 1H), 3.25 (dd, J = 13.7, 1.0 Hz, 1H), 2.85 (s, 3H), 2.77 (ddd, J = 11.6, 4.0, 1.7 Hz, 1H), 2.62 (td, J = 6.6, 1.6 Hz, 1H), 2.18 (dd, J = 13.7, 11.6 Hz, 1H), 1.76 (d, J = 13.7 Hz, 1H), 1.48 (d, J = 13.7 Hz, 1H), 1.19 (s, 3H), 1.15 (s, 3H), 1.01 (d, J = 6.6 Hz, 1H);

**13C NMR (75 MHz, CDCl₃)** δ 212.2, 139.9, 134.4, 133.4, 128.6, 128.3, 126.1, 78.8, 50.4, 49.0, 46.5, 44.7, 43.4, 37.3, 24.8, 20.8, 17.4;

**IR (neat)** ν = 2960, 2930, 1720, 1450, 1371, 1273, 1086, 1072, 701 cm⁻¹;

**HRMS-EI** calcd for C₁₈H₂₂O₂ [M]+ 270.1620, found 270.1617.

(1S,4R,5R)-3-benzyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-dien-2-yl trifluoromethanesulfonate (180)

![Chemical Structure](image)

Prepared according to GP11 on a 1.0 mmol scale. 148 mg (0.37 mmol, 37%) **180** were isolated as colorless oil.

[α]D³³ +45.6 (c 0.44, CHCl₃);

**1H NMR (300 MHz, CDCl₃)** δ 7.31-7.21 (m, 3H), 7.18-7.06 (m, 2H), 6.16-6.08 (m, 2H), 4.04 (d, J = 16.0 Hz, 1H), 3.26 (d, J = 16.0 Hz, 1H), 3.20 (dd, J = 5.8, 2.0 Hz, 1H), 3.16 (s, 3H), 1.92 (d, J = 12.1 Hz, 1H), 1.53 (s, 3H), 1.25 (d, J = 12.1 Hz, 1H), 1.19 (s, 3H);

**13C NMR (75 MHz, CDCl₃)** δ 148.5, 140.7, 137.9, 134.9, 134.0, 129.3, 128.7, 128.5, 120.9, 83.8, 51.8, 50.5, 40.1, 44.9, 35.9, 24.7, 18.2;

**IR (neat)** ν = 2936, 1496, 1400, 1205, 1137, 1077, 1062, 1045, 903, 868, 851, 721 cm⁻¹;


(1S,4R,5R)-3-benzyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene (181)

![Chemical Structure](image)
Prepared according to GP12 on a 0.17 mmol scale. 34 mg (0.13 mmol, 79%) 181 were isolated as colorless oil.

$[\alpha]_D^{28} +64.7 (c 0.20, \text{CHCl}_3)$;

$^1\text{H NMR (300 MHz, CDCl}_3$) $\delta$ 7.29-7.09 (m, 5H), 6.18-6.14 (m, 2H), 6.04 (dd, $J = 7.2$, 1.1 Hz, 1H), 5.67 (s, 1H), 3.65 (d, $J = 15.8$ Hz, 1H), 3.40 (dd, $J = 15.7$, 1.9 Hz, 1H), 3.29-3.26 (m, 1H), 3.19 (s, 3H), 1.43 (d, $J = 12.0$ Hz, 1H), 1.40 (s, 3H), 1.19 (d, $J = 12.0$ Hz, 1H), 1.19 (s, 3H);

$^{13}\text{C NMR (75 MHz, CDCl}_3$) $\delta$ 146.6, 141.2, 139.6, 133.6, 132.4, 129.1, 128.1, 125.8, 84.1, 51.0, 50.2, 49.6, 42.6, 41.0, 24.7, 22.2;

IR (neat) $\nu = 2952, 1597, 1494, 1102, 1071 \text{ cm}^{-1}$;

HRMS-ESI calcd for C$_{18}$H$_{22}$NaO $[\text{MNa}]^+$ 277.1563, found 277.1560.

(1S,3S,4R,5R)-5-methoxy-3-(4-methoxybenzyl)-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (182)

Prepared according to GP10 on a 1.66 mmol scale. 158 mg (0.53 mmol, 32%) 182 were isolated as colorless oil.

$[\alpha]_D^{29} -130.2 (c 0.57, \text{CHCl}_3)$;

$^1\text{H NMR (300 MHz, CDCl}_3$) $\delta$ 7.09 (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 6.35 (dd, $J = 7.7$, 6.8 Hz, 1H), 5.85-5.82 (m, 1H), 3.79 (s, 3H), 3.19 (dd, $J = 13.9$, 4.1 Hz, 1H), 2.89 (s, 3H), 2.73 (ddd, $J = 11.6$, 4.1, 1.7 Hz, 1H), 2.64 (td, $J = 6.7$, 1.6 Hz, 1H), 2.15 (dd, $J = 13.9$, 11.6 Hz, 1H), 1.77 (d, $J = 13.7$ Hz, 1H), 1.49 (d, $J = 13.7$ Hz, 1H), 1.20 (s, 3H), 1.17 (s, 3H);

$^{13}\text{C NMR (75 MHz, CDCl}_3$) $\delta$ 212.4, 157.9, 134.5, 133.5, 131.9, 129.5, 113.8, 78.9, 55.3, 50.6, 49.2, 46.6, 44.9, 43.5, 36.4, 24.8, 17.5;

IR (neat) $\nu = 2929, 2831, 1716, 1612, 1512, 1453, 1247, 1178, 1082, 1035, 691 \text{ cm}^{-1}$;

HRMS-ESI calcd for C$_{19}$H$_{24}$O$_3$ [M]$^+$ 300.1725, found 300.1721.
(1S,4R,5R)-5-methoxy-3-(4-methoxybenzyl)-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene (184)

Prepared according to GP9 on a 0.36 mmol scale. 57 mg of the triflate 183 contaminated with PhNTf₂ side-products were obtained which were directly subjected to reduction conditions as described in GP9 to finally obtain 184 (22 mg, 0.08 mmol, 19% from 182) as colorless liquid. Several trials to purify 183 were undertaken but to no avail. 

\[ \alpha \]_D

+56.8 (c 0.20, CHCl₃);

\(^1\)H NMR (300 MHz, CDCl₃)  7.02 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.19-6.14 (m, 1H), 6.05 (dd, J = 7.2, 1.1 Hz, 1H), 5.67 (s, 1H), 3.79 (s, 3H), 3.58 (d, J = 16.0 Hz, 1H), 3.34 (dd, J = 16.0, 2.0 Hz, 1H), 3.27 (td, J = 6.3, 1.5 Hz, 1H), 3.19 (s, 3H), 1.42 (d, J = 12.0 Hz, 1H), 1.39 (s, 3H), 1.19 (d, J = 12.0 Hz, 1H), 1.19 (s, 3H);

\(^13\)C NMR (75 MHz, CDCl₃)  157.8, 147.0, 141.3, 133.6, 132.2, 131.6, 130.0, 113.5, 84.1, 55.2, 51.0, 50.2, 49.7, 42.6, 40.1, 24.7, 22.2;

IR (neat)  \( \nu \)  = 2952, 2927, 1612, 1511, 1456, 1246, 1176, 1106, 1071, 1038, 805 cm⁻¹;

HRMS-EI calcd for C₁₉H₂₄O₂ [M+ ] 284.3927, found 284.3925.

(1S,3S,4R,5R)-3-(4-fluorobenzyl)-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (185)

Prepared according to GP10 on a 1.66 mmol scale. 268 mg (0.93 mmol, 56%) 185 were isolated as colorless oil.

\[ \alpha \]_D

-142.6 (c 0.44, CHCl₃);

\(^1\)H NMR (300 MHz, CDCl₃)  7.15-7.10 (m, 2H), 7.01-6.95 (m, 2H), 6.33 (dd, J = 7.7, 6.8 Hz, 1H), 5.85-5.82 (m, 1H), 3.20 (dd, J = 13.9, 4.0 Hz, 1H), 2.89 (s, 3H), 2.74 (ddd, J
Experimental Section

= 11.4, 4.0, 1.7 Hz, 1H), 2.60 (td, J = 6.7, 1.6 Hz, 1H), 2.20 (dd, J = 13.7, 11.4 Hz, 1H),
1.77 (d, J = 13.7 Hz, 1H), 1.48 (d, J = 13.7 Hz, 1H), 1.19 (s, 3H), 1.17 (s, 3H);

13C NMR (75 MHz, CDCl3) δ 212.0, 161.3 (d, J_{CF} = 243.6 Hz), 135.5, 134.3, 133.5,
129.9, 115.1 (d, J_{CF} = 21.2 Hz), 78.8, 50.6, 49.1, 46.2, 44.8, 43.6, 36.5, 24.8, 17.4;
IR (neat) v = 2929, 1718, 1509, 1220, 1081, 772 cm⁻¹;
HRMS-EI calcd for C_{18}H_{21}FO_{2} [M⁺] 288.1526, found 288.1523.

(1S,4R,5R)-3-(4-fluorobenzyl)-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-dien-2-yl
trifluoromethanesulfonate (186)

Prepared according to GP11 on a 0.83 mmol scale. 96 mg (0.23 mmol, 27%) 186 were
isolated as colorless oil.

[α]D° +43.8 (c 0.46, CHCl₃);

1H NMR (300 MHz, CDCl₃) δ 7.06-6.93 (m, 5H), 6.15-6.08 (m, 2H), 3.98 (d, J = 16.0
Hz, 1H), 3.24 (d, J = 16.0 Hz, 1H), 3.18-3.16 (m, 1H), 3.16 (s, 3H), 1.91 (d, J = 11.8 Hz,
1H), 1.24 (d, J = 11.8 Hz, 1H), 1.19 (s, 3H);
13C NMR (75 MHz, CDCl₃) δ 161.4 (d, J_{CF} = 243.9 Hz), 148.0, 140.4, 134.5, 133.4,
133.1, 130.3, 118.4 (q, J_{CF} = 319.3 Hz), 115.2 (d, J_{CF} = 21.2 Hz), 83.5, 51.8, 50.3,
48.5, 44.7, 35.0, 24.6, 18.0;
IR (neat) v = 2937, 1519, 1400, 1205, 1137, 851 cm⁻¹;
HRMS-ESI calcd for C_{19}H_{20}NaO_{4}F_{4}S [MNa⁺] 443.0916, found 443.0904.
Anal. Calcd for C_{19}H_{20}NaO_{4}F_{4}S: C, 54.28; H, 4.79. Found: C, 54.40; H, 4.81.

(1S,4R,5R)-3-(4-fluorobenzyl)-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene
(187)
Prepared according to GP12 on a 0.19 mmol scale. 32 mg (0.12 mmol, 63%) 187 were isolated as colorless oil.

\[ [\alpha]_D^{27} +56.3 \ (c 0.37, \text{CHCl}_3); \]

**1H NMR (300 MHz, CDCl₃)** δ 7.08-7.04 (m, 2H), 6.97-6.91 (m, 2H), 6.16 (t, \( J = 6.7 \text{ Hz}, \ 1H \)), 6.06-6.04 (m, 1H), 5.64 (s, 1H), 3.59 (d, \( J = 15.9 \text{ Hz}, \ 1H \)), 3.37 (dd, \( J = 15.8, 1.6 \text{ Hz}, \ 1H \)), 3.25-3.23 (m, 1H), 3.19 (s, 3H), 1.43 (d, \( J = 12.0 \text{ Hz}, \ 1H \)), 1.40 (s, 3H), 1.20 (s, 3H), 1.18 (d, \( J = 12.0 \text{ Hz}, \ 1H \));

**13C NMR (75 MHz, CDCl₃)** δ 161.1 (d, \( J_{C-F} = 242.7 \text{ Hz} \)), 146.5, 141.2, 135.1, 133.4, 132.4, 130.3, 114.8 (d, \( J_{C-F} = 21.1 \text{ Hz} \)), 84.1, 51.3, 50.2, 49.4, 42.7, 40.3, 24.8, 22.3;

**IR (neat)** ν = 2952, 1600, 1508, 1220, 1070, 810 cm⁻¹;

**HRMS-ESI** calcd for C₁₈H₂₁FNaO [MNa]⁺ 295.1469, found 295.1464;


*(1R,4R,5R)-5-methoxy-1,5-dimethylbicyclo[2.2.2]octan-2-one (188)*

Ketone 104 (153 mg, 0.85 mmol) was dissolved in 10 mL EtOH. Pd/C was added and the flask was evacuated and purged three times with argon. A ballon with H₂ (1 atm) was put on top of the reaction vessel. The reaction mixture was stirred overnight at 23 °C. After filtering through a plug of silica gel, the solvent was evaporated to isolate analytically pure 188 (142 mg, 0.78 mmol, 92%).

\[ [\alpha]_D^{30} 1.5 \ (c 1.02, \text{CHCl}_3); \]

**1H NMR (300 MHz, CDCl₃)** δ 3.13 (s, 3H), 2.62 (dt, \( J = 18.6 \text{ Hz}, \ J = 2.9 \text{ Hz}, \ 1H \)), 2.18 (t, \( J = 2.9 \text{ Hz}, \ 1H \)), 1.98 (dd, \( J = 18.6 \text{ Hz}, \ J = 2.8 \text{ Hz}, \ 1H \)), 1.50-1.86 (m, 6H), 1.33 (s, 3H), 0.91 (s, 3H);

**13C NMR (75 MHz, CDCl₃)** δ 216.4, 75.2, 48.9, 47.1, 44.0, 39.7, 36.6, 29.9, 23.2, 22.3, 19.9;

**IR (film)** ν = 2927, 2826, 1721, 1454, 1375, 1220, 1174, 1085, 772 cm⁻¹;

**HRMS-EI** calcd for C₁₁H₁₈O₂ [M⁺] 182.1307, found 182.1302.
(1R,3S,4R,5R)-3-allyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-2-en-2-one (189)

| ![Structure](image)

To a solution of i-Pr₂NH (564 mg, 5.56 mmol, 1.5 equiv) in THF (10 mL) and DMPU (1 mL) at 0 °C was added n-BuLi (3.5 mL, 5.56 mmol, 1.5 equiv, 1.6 M/hexanes) dropwise and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and 188 (677 mg, 3.71 mmol, 1 equiv) was added. After 1 h at -78 °C, freshly distilled allyl bromide (671 mg, 5.56 mmol, 1.5 equiv) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred another 8 h. The reaction was diluted with Et₂O and a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with Et₂O (3 ×), the combined organic layer washed with brine, dried over Na₂SO₄, and the solvent evaporated. Purification of the crude by flash chromatography was carried out using hexanes/EtOAc (8:1). The title compound 189 (469 mg, 2.11 mmol, 57%) was isolated as colorless liquid.

[α]D²⁴ 5.3 (c 0.57, CHCl₃);

¹H NMR (300 MHz, CDCl₃) δ 5.69-5.82 (m, 1H), 5.00-5.13 (m, 2H), 3.10 (s, 3H), 2.64-2.72 (m, 2H), 1.86-2.09 (m, 2H), 1.40-1.79 (m, 6H), 1.36 (s, 3H), 0.90 (s, 3H);

¹³C NMR (75 MHz, CDCl₃) δ 218.0, 136.7, 116.4, 75.3, 48.7, 46.7, 45.4, 44.5, 38.0, 31.5, 30.6, 23.7, 19.9, 17.2;

IR (film) ν = 2927, 1718, 1640, 1457, 1375, 1067 cm⁻¹;

HRMS-ESI calcd for C₁₄H₂₂NaO₂ [MNa]⁺ 245.1512, found 245.1509.

(1R,4R,5R)-3-allyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-2-en-2-yl trifluoromethanesulfonate (190)

| ![Structure](image)

To a solution of Et₂NH (597 mg, 8.05 mmol, 4 equiv) in THF (10 mL) and DMPU (1 mL) at 0 °C was added n-BuLi (5.0 mL, 8.05 mmol, 4 equiv, 1.6 M/hexanes) dropwise
and the reaction was stirred 10 min at 0 °C. The solution was cooled to -78 °C and ketone 189 (448 mg, 2.01 mmol, 1 equiv) was added. After 1 h at -78 °C, a solution of PhNTf₂ (2.88 g, 8.05 mmol, 4 equiv) in THF (1 mL) was added. The reaction was stirred for 1 h at -78 °C and warmed to 23 °C and stirred overnight. The reaction was diluted with Et₂O and a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with Et₂O (3×), the combined organic layer washed with brine, dried over Na₂SO₄, and the solvent evaporated. The crude product was purified by flash chromatography using n-pentane/Et₂O (20:1) to give triflate 190 (495 mg, 1.30 mmol, 69%) as colorless liquid.

[α]D²⁶ 64.7 (c 0.78, CHCl₃);

¹H NMR (300 MHz, CDCl₃) δ 5.63-5.79 (m, 1H), 5.07-5.18 (m, 2H), 3.28-3.50 (m, 1H), 3.24 (dt, J = 5.7 Hz, J = 1.5 Hz, 1H), 3.09 (s, 3H), 2.79 (m, 1H), 2.71 (t, J = 2.8 Hz, 1H), 1.64-1.73 (m, 2H), 1.42-1.53 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.17-1.34 (m, 2H);

¹³C NMR (75 MHz, CDCl₃) δ 143.7, 133.9, 133.2, 117.4, 78.7, 50.8, 49.0, 45.0, 42.7, 34.5, 32.8, 23.2, 22.7, 20.2;

IR (film) ν = 2943, 2823, 1401, 1209, 1140, 881 cm⁻¹;

HRMS-ESI calcd for C₁₅H₂₁F₃O₄S [MNa]+ 377.1005, found 377.1000;


(1R,4R,5R)-3-allyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-2-ene (191)

To a solution of Pd(OAc)₂ (13 mg, 52 µmol, 0.1 equiv), Ph₃P (27 mg, 104 µmol, 0.2 equiv), and n-Bu₃N (289 mg, 1.56 mmol, 3 equiv) in DMF (0.5 mL) was added the triflate 190 (184 mg, 0.52 mmol, 1 equiv). The solution was stirred 5 min at room temperature, HCO₂H (12 mg, 0.25 mmol, 2 equiv) was added, and the resulting solution was heated to 60 °C for 2 h. The reaction mixture was diluted with Et₂O, washed with 2M aqueous HCl (3×), the combined organic layers washed with brine, dried over Na₂SO₄, and the solvent evaporated. Purification of the crude material was carried out by
flash chromatography using n-pentane/Et2O. The title compound 191 (48 mg, 0.23 mmol, 45\%) was isolated as colorless liquid.

[\alpha]_D^{28} 95.4 (c 0.67, CHCl3);

\( ^1H \) NMR (300 MHz, CDCl3) \( \delta \) 5.78-5.89 (m, 1H), 5.58 (s, 1H), 5.00-5.12 (m, 2H), 3.14 (s, 3H), 1.84-2.09 (m, 2H), 1.57-1.68 (m, 1H), 1.29 (s, 3H), 1.09-1.35 (m, 5H), 1.08 (s, 3H);

\( ^{13}C \) NMR (75 MHz, CDCl3) \( \delta \) 143.6, 136.1, 129.1, 115.7, 79.1, 50.9, 49.2, 42.6, 40.1, 35.6, 32.3, 25.2, 23.8, 23.6;

IR (film) \( \nu = 2947, 1637, 1456, 1369, 1120, 1075, 994 \text{ cm}^{-1}; \)

HRMS-ESI calcd for C14H22NaO [MNa]+ 229.1563, found 245.1559;

Anal. Calcd for C14H22O: C, 81.50; H, 10.75. Found: C, 81.23; H, 10.72.

(1S,3S,4R,5R)-3-allyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]oct-7-en-2-one (192)

Prepared according to GP10 on a 1.10 mmol scale. 193 mg (0.88 mmol, 79\%) 192 were isolated as colorless oil.

[\alpha]_D^{25} -275.5 (c 0.78, CHCl3);

\( ^1H \) NMR (300 MHz, CDCl3) \( \delta \) 6.34 (t, \( J = 6.8 \) Hz, 1H), 5.70-5.84 (m, 2H), 5.00-5.06 (m, 2H), 3.16 (s, 3H), 2.86 (d, \( J = 6.8 \) Hz, 1H), 2.53-2.62 (m, 2H), 1.78 (d, \( J = 13.7 \) Hz, 1H), 1.75-1.81 (m, 1H), 1.47 (d, \( J = 13.7 \) Hz, 1H), 1.25 (s, 3H), 1.17 (s, 3H);

\( ^{13}C \) NMR (75 MHz, CDCl3) \( \delta \) 212.5, 136.5, 134.6, 133.2, 116.3, 78.9, 50.5, 49.5, 45.9, 44.4, 42.4, 36.0, 25.0, 17.4;

IR (film) \( \nu = 2972, 2930, 1720, 1640, 1449, 1080 \text{ cm}^{-1}; \)

HRMS-EI calcd for C14H20O [M]+ 220.1463, found 220.1460.
(1S,4R,5R)-3-allyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-dien-2-yltrifluoromethanesulfonate (193)

Prepared according to GP11 on a 0.52 mmol scale. 121 mg (0.34 mmol, 66%) 193 were isolated as colorless oil.

\[\alpha\]_D^{27} 44.4 (c 0.65, CHCl₃);

\(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 6.27 (t, J = 6.2 Hz, 1H), 6.10 (dd, J = 7.2 Hz, J = 1.6 Hz, 1H), 5.64-5.77 (m, 1H), 5.00-5.10 (m, 2H), 3.42 (dd, J = 6.2 Hz, J = 1.6 Hz, 1H), 3.23-3.31 (m, 1H), 3.16 (s, 3H), 2.71-2.78 (m, 1H), 1.84 (d, J = 11.8 Hz, 1H), 1.47 (s, 3H), 1.25 (s, 3H), 1.23 (d, J = 11.8 Hz, 1H);

\(^13\)C NMR (75 MHz, CDCl₃) \(\delta\) 147.8, 140.7, 133.9, 133.7, 133.3, 120.5, 117.1, 83.5, 51.7, 50.3, 48.6, 44.7, 34.1, 24.7, 17.9;

IR (film) \(v\) = 2928, 2931, 2825, 1403, 1210, 1141, 869 cm\(^{-1}\);


(1S,4R,5R)-3-allyl-5-methoxy-1,5-dimethylbicyclo[2.2.2]octa-2,7-diene (194)

Prepared according to GP12 on a 0.45 mmol scale. 42 mg (0.20 mmol, 45%) 194 were isolated as colorless oil.

\[\alpha\]_D^{33} 64.3 (c 0.45, CHCl₃);

\(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 6.26 (t, J = 6.9 Hz, 1H), 6.07 (d, J = 7.2 Hz, 1H), 5.72-5.87 (m, 2H), 5.00-5.06 (m, 2H), 3.36 (dd, J = 6.2 Hz, J = 1.5 Hz, 1H), 3.18 (s, 3H), 2.81-3.17 (m, 2H), 1.40 (s, 3H), 1.40 (d, J = 11.8 Hz, 1H), 1.22 (s, 3H), 1.19 (d, J = 11.8 Hz, 1H),
**13C NMR (75 MHz, CDCl₃)** δ 145.9, 141.7, 136.0, 133.4, 131.7, 115.9, 84.0, 51.2, 50.2, 49.5, 42.6, 39.1, 24.7, 22.2;
**IR (film)** ν = 2954, 2926, 2823, 1456, 1365, 1331, 1101, 1072 cm⁻¹;
**Anal.** Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C, 82.37; H, 9.81.

### 8.4. Rh/Diene-catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to α,β-Unsaturated Compounds

**Effect of ligand substitution on selectivity**

![Reaction Scheme](image)

**GP13: Rh/Diene-catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid to Cyclohex-2-en-1-one**

To [RhCl(C₂H₄)₂]₂ (1.8 mg, 4.6 µmol, 1.5 mol%) and the chiral diene ligand (9.9 µmol, 3.3 mol%) in a Schlenk was added anhydrous 1,4-dioxane (1 mL). The resulting solution was stirred for 15 min, and KOH (100 µL, 0.15 mmol, 0.5 equiv, 1.5 M solution in H₂O) was added. After stirring for 15 min, phenylboronic acid 138 (73 mg, 0.6 mmol, 2 equiv) was added followed by freshly distilled cyclohex-2-en-1-one 141 (29 mg, 0.3 mmol, 1 equiv). The reaction was stirred at 23 °C (unless otherwise indicated) until completion by TLC. Saturated aqueous NH₄Cl was added, and the aqueous layer was extracted with Et₂O (3×). The combined organic layers were washed with brine, dried over MgSO₄, and the solvent was evaporated to give the crude. 3-Phenylcyclohexanone 142 was obtained as a colorless liquid after purification by flash chromatography using hexanes/EtOAc (5:1). The enantioselectivity was determined by HPLC on a chiral stationary phase (AD-H, 254 nm, hexanes/i-PrOH = 98:2, flow rate 0.5 ml/min).

**1H NMR (300 MHz, CDCl₃)** δ 7.38-7.24 (m, 5H), 3.08-3.00 (m, 1H), 2.65-2.36 (m, 4H), 2.21-1.84 (m, 2H), 1.83-1.78 (m, 2H).
All other spectroscopic data were in agreement with the literature: Denmark, S. E.; Amishiro, N. *J. Org. Chem.* **2003**, *68*, 6997.

- Using ligand 109, 47 mg (0.28 mmol, 89%) of 142 were isolated in 67% ee.
- Using ligand 152, 44 mg (0.26 mmol, 85%) of 142 were isolated in 72% ee.
- Using ligand 153, 48 mg (0.28 mmol, 92%) of 142 were isolated in 52% ee.
- Using ligand 161, 48 mg (0.27 mmol, 91%) of 142 were isolated in 88% ee.
- Using ligand 164, 48 mg (0.27 mmol, 91%) of 142 were isolated in 91% ee.
- Using ligand 167, 44 mg (0.26 mmol, 85%) of 142 were isolated in 82% ee.
- Using ligand 170, 33 mg (0.19 mmol, 63%) of 142 were isolated in 93% ee.
- Using ligand 175, 45 mg (0.26 mmol, 87%) of 142 were isolated in 93% ee.
- Using ligand 181, 35 mg (0.20 mmol, 67%) of 142 were isolated in 58% ee.
- Using ligand 184, 37 mg (0.21 mmol, 71%) of 142 were isolated in 62% ee.
- Using ligand 187, 76 mg (0.44 mmol, 87%) of 142 were isolated in 63% ee.
- Using ligand 191, the 1,4-addition proceeded with <10% conversion.
- Using ligand 194, 49 mg (0.28 mmol, 93%) of 142 were isolated in 58% ee.

**Investigation into the Substrate Scope**

**GP14: Rh/Diene-catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to α,β-Unsaturated Compounds**

To [Rh(C2H4)2Cl] (1.8 mg, 4.6 μmol, 1.5 mol%) and 175 or *ent*-175 (2.4 mg, 9.9 μmol, 3.3 mol%) in a Schlenk flask (10 mL) was added dioxane (1 mL). The resulting solution was stirred for 15 min, and KOH (100 μL, 0.15 mmol, 0.5 equiv, 1.5 M solution in H2O) was added. After stirring for 15 min, the aryl- or alkenylboronic acid (0.60 mmol, 2 equiv) was added followed by the α,β-unsaturated compound (0.30 mmol, 1 equiv) and the reaction was either stirred at 23 °C or heated at 50 °C until completion by TLC (reaction temperature as indicated below). Saturated aqueous NH4Cl was added, and the aqueous layer was extracted with Et2O (3×). The combined organic layers were washed with brine, dried over MgSO4, and the solvent was evaporated to give the crude. The desired 1,4-adduct was obtained after purification by flash chromatography.
(R)-3-phenylcyclopentanone (Table 2, entry 1)

Following GP14 at 25 °C on a 0.30 mmol scale using 2-cyclopentenone and phenylboronic acid, the desired product (44 mg, 91%) was isolated by flash chromatography using hexanes/EtOAc (5:1). The enantioselectivity was 94% ee (Chiralcel OB-H, 254 nm, hexanes/iPrOH = 99:1, flow rate 1.0 ml/min).

$\alpha^\circ_3 24.2 (c 0.49, \text{CHCl}_3)$.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38-7.24 (m, 5H), 3.48-3.39 (m, 1H), 2.72-2.65 (m, 1H), 2.52-2.27 (m, 4H), 2.06-1.95 (1H).

All other spectroscopic data were in agreement with the literature: Denmark, S. E.; Amishiro, N. J. Org. Chem. 2003, 68, 6997.

(S)-3-phenylcyclopentanone (Table 2, entry 2)

Following GP14 at 25 °C on a 0.30 mmol scale using 2-cyclopentenone and phenylboric anhydride, the desired product (46 mg, 95%) was isolated by flash chromatography using hexanes/EtOAc (5:1). The enantioselectivity was 97% ee (Chiralcel OB-H, 254 nm, hexanes/iPrOH = 99:1, flow rate 1.0 ml/min).
(R)-3-(3-chlorophenyl)cyclopentanone (Table 2, entry 3)

Following GP14 at 50 °C on a 0.34 mmol scale using 2-cyclopentenone and 3-chlorophenylboronic acid, the desired product (65 mg, 98%) was isolated by flash chromatography using 20% Et₂O/hexane. The enantioselectivity was 95% ee (Chiralcel OB-H, 254 nm, hexanes/iPrOH = 98:2, flow rate 1.0 ml/min). 

\[\alpha\]D\text{33} 57.9 (c 0.95, CHCl₃).

\(^1\)H NMR (300 MHz, CDCl₃) δ 7.30-7.22 (m, 3H), 7.15-7.13 (m, 1H), 3.40 (tt, J= 11.0, 6.8 Hz, 1H), 2.71-2.64 (m, 1H), 2.51-2.41 (m, 2H), 2.36-2.26 (m, 2H), 1.92-2.03 (m, 1H).

All other spectroscopic data were in agreement with the literature: Itooka, R.; Iguchi, Y.; Miyaura, N. J. Org. Chem. 2003, 68, 6000.

(R)-3-[(E)-2-phenylvinyl]cyclopentanone (Table 2, entry 4)

Following GP14 at 25 °C on a 0.30 mmol scale using 2-cyclopentenone and trans-2-phenylvinylboronic acid, the desired product (53 mg, 97%) was isolated by flash chromatography using hexanes/EtOAc (4:1). The enantioselectivity was 90% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 99:1, flow rate 1.0 ml/min).

\[\alpha\]D\text{33} 70.7 (c 0.49, CHCl₃).

\(^1\)H NMR (300 MHz, CDCl₃) δ 7.36 (d, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 6.22 (dd, J = 15.9, 7.3 Hz, 1H), 3.06-2.98 (m,
1H), 2.49 (dd, J = 18.2, 7.5 Hz, 1H), 2.42-2.35 (m, 1H), 2.30-2.19 (m, 2H), 2.13 (ddd, J = 18.2, 10.4, 1.2 Hz, 1H), 1.86-1.79 (m, 1H).

All other spectroscopic data were in agreement with the literature: Otomaru, Y.; Hayashi, T. Tetrahedron: Asymmetry 2004, 15, 2647.

(S)-3-phenylcyclohexanone (Table 2, entry 5)

Following GP14 at 25 °C on a 0.33 mmol scale using 2-cyclohexenone and 2-phenyl-1,3,2-dioxaboriane, the desired product (48 mg, 83%) was isolated by flash chromatography using 20% Et₂O/hexanes. The enantioselectivity was 96% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate 0.5 ml/min).

\[ \alpha \] D \ 27 -18.6 (c 1.045, CHCl₃)

\( ^1H \) NMR (300 MHz, CDCl₃) δ 7.38-7.24 (m, 5H), 3.08-3.00 (m, 1H), 2.65-2.36 (m, 4H), 2.21-1.84 (m, 2H), 1.83-1.78 (m, 2H).

All other spectroscopic data were in agreement with the literature: Denmark, S. E.; Amishiro, N. J. Org. Chem. 2003, 68, 6997.

(R)-3-(4-methoxyphenyl)cyclohexanone (Table 2, entry 6)

Following GP14 at 50 °C on a 0.34 mmol scale using 2-cyclohexenone and 4-methoxyphenylboronic acid, the desired product (57 mg, 85%) was isolated by flash...
Experimental Section

chromatography using 25% Et$_2$O/hexanes. The enantioselectivity was 96% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate 0.5 ml/min).

$\alpha$$_{D}$$^{33}$ 13.6 (c 1.15, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.14 (dt, $J$ = 8.7, 2.5 Hz, 2H), 6.87 (dt, $J$ = 8.7, 2.5 Hz, 2H), 3.80 (s, 2H), 2.97 (tt, $J$ = 11.8, 3.9 Hz, 1H), 2.60-2.33 (m, 4H), 2.20-2.01 (m, 2H), 1.87-1.70 (m, 2H).

All other spectroscopic data were in agreement with the literature: Itooka, R.; Iguchi, Y.; Miyaura, N. J. Org. Chem. 2003, 68, 6000.

(S)-3-(2-methoxyphenyl)cyclohexanone (Table 2, entry 7)

Following GP14 at 50 °C on a 0.34 mmol scale using 2-cyclohexenone and 2-methoxyphenylboronic acid, the desired product (69 mg, 93%) was isolated by flash chromatography using 20% Et$_2$O/hexanes. The enantioselectivity was 94% ee (Chiralcel OD, 254 nm, hexanes/iPrOH = 95:5, flow rate 1.0 ml/min).

$\alpha$$_{D}$$^{32}$ -36.3 (c 1.02, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.23-7.20 (m, 2H), 6.84-6.82 (m, 2H), 3.76 (s, 3H), 3.72 (m, 1H), 2.58-2.10 (m, 4H), 2.10-1.68 (m, 4H).

All other spectroscopic data were in agreement with the literature: Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. Org. Lett. 2003, 5, 681.
(S)-3-(4-acetylphenyl)cyclohexanone (Table 2, entry 8)

Following GP14 at 50 °C on a 0.38 mmol scale using 2-cyclohexenone and 4-acetylphenylboronic acid, the desired product (79 mg, 96%) was isolated by flash chromatography using 30% EtOAc/hexanes. The enantioselectivity was 97% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 90:10, flow rate 0.5 ml/min).

$$[\alpha]_D^{32} = -7.8 \quad (c \ 1.02, \ CHCl_3);$$

$^1H$ NMR (300 MHz, CDCl$_3$) $\delta$ 7.87 (m, 2H), 7.26 (m, 2H), 3.02 (m, 1H), 2.59-2.28 (m, 7H), 2.15-2.01 (m, 2H), 1.86-1.70 (m, 2H);

$^{13}C$ NMR (75 MHz, CDCl$_3$) $\delta$ 210.0, 197.4, 149.5, 135.6, 128.7, 126.7, 48.4, 44.6, 41.1, 32.5, 26.6, 25.5;

IR (neat) $\nu = 2940, 1737, 1717, 1667, 1365, 1268, 1226, 1217, 960, 827$ cm$^{-1};$

MS-ESI (m/z) 239 [M + Na]$^+.$

(S)-3-(2-fluorophenyl)cyclohexanone (Table 2, entry 9)

Following GP14 at 50 °C on a 0.36 mmol scale using 2-cyclohexenone and 2-fluorophenylboronic acid, the desired product (69 mg, 94%) was isolated by flash chromatography using 20% Et$_2$O/hexanes. The enantioselectivity was 97% ee (Chiralcel OD, 254 nm, hexanes/iPrOH = 99.5:0.5, flow rate 1.0 ml/min).

$$[\alpha]_D^{32} = -12.2 \quad (c \ 1.40, \ CHCl_3).$$
Experimental Section

\[ \text{H NMR (300 MHz, CDCl}_3\] \( \delta \) 7.20-6.95 (m, 4H), 3.27 (m, 1H), 2.45-2.27 (m, 4H), 2.12-1.98 (m, 2H), 1.92-1.70 (m, 2H).

All other spectroscopic data were in agreement with the literature: Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* 2003, 5, 681.

**(R)-3-phenylcycloheptanone (Table 2, entry 10)**

Following GP14 at 25 °C on a 0.30 mmol scale using 2-cycloheptenone and phenylboronic acid, the desired product (49 mg, 81%) was isolated by flash chromatography using hexanes/EtOAc (5:1). The enantioselectivity was 95% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate 0.5 ml/min).

\[ \alpha \]_D^33 116.8 (c 0.35, CHCl_3).

\[ \text{H NMR (300 MHz, CDCl}_3\] \( \delta \) 7.32-7.28 (m, 2H), 7.22-7.17 (m, 3H), 2.97-2.87 (m, 2H), 2.69-2.58 (m, 3H), 2.11-1.97 (m, 3H), 1.79-1.67 (m, 2H), 1.56-1.45 (m, 1H).

All other spectroscopic data were in agreement with the literature: Denmark, S. E.; Amishiro, N. *J. Org. Chem.* 2003, 68, 6997.

**(S)-4-phenyldihydro-2(3H)-furanone (Table 2, entry 11)**

Following GP14 at 25 °C on a 0.36 mmol scale using 2-(5H)-furanone and phenylboronic acid, the desired product (39 mg, 80%) was isolated by flash chromatography using hexanes/EtOAc (4:1). The enantioselectivity was 90% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate 1.0 ml/min).
[α]_D^{33} 45.8 (c 0.76, CHCl₃);

^1^H NMR (300 MHz, CDCl₃) δ 7.08-7.00 (m, 5H), 4.64 (t, J = 8.5 Hz, 1H), 4.19 (t, J = 8.5 Hz, 1H), 3.76 (q, J = 8.5 Hz, 1H), 2.84 (dd, J = 17.7, 8.4 Hz, 1H), 2.61 (dd, J = 17.4, 9.0 Hz, 1H).

All other spectroscopic data were in agreement with the literature: Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. Org. Lett. 2003, 5, 681.

(4S)-4-phenyl-2-chromanone (Table 2, entry 12)

Following GP14 at 50 °C on a 0.30 mmol scale using coumarin and phenylboronic acid, the desired product (29 mg, 43%) was isolated by flash chromatography using hexanes/EtOAc (7:1). The enantioselectivity was 98% ee (Chiralcel OJ-H, 254 nm, hexanes/iPrOH = 97:3, flow rate 1.0 ml/min).

[α]_D^{33} 37.4 (c 0.74, CHCl₃);

^1^H NMR (300 MHz, CDCl₃) δ 7.37-7.33 (m, 2H), 7.32-7.27 (m, 2H), 7.17-7.13 (m, 3H), 7.08 (dt, J = 7.4, 1.2 Hz, 1H), 6.98 (d, J = 1.1 Hz, 1H), 4.35 (dd, J = 7.8, 6.1 Hz, 1H), 3.08 (dd, J = 14.3, 6.1 Hz, 1H), 3.03 (dd, J = 14.3, 7.8 Hz).

All other spectroscopic data was in agreement with the literature: Chen, G.; Tokunaga, N.; Hayashi, T. Org. Lett. 2005, 7, 2285.

(4R,5E)-4-methyl-6-phenyl-5-hexen-2-one (Table 2, entry 13)
Following GP14 at 25 °C on a 0.26 mmol scale using 3-penten-2-one and trans-2-phenylvinylboronic acid, the desired product (37 mg, 78%) was isolated by flash chromatography using hexanes/EtOAc (5:1). The enantioselectivity was 89% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 99:1, flow rate 0.8 ml/min).

\[ [\alpha]_D^{24} -58.4 (c 0.85, \text{CHCl}_3); \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3) \delta 7.36-6.94 (m, 5H), 6.28 (d, J = 15.0 \text{ Hz, } 1H), 5.96 (dd, J = 15.0, 7.0 \text{ Hz, } 1H), 2.83 (septet, J = 7.0 \text{ Hz, } 1H), 2.41 (m, 2H), 2.04 (s, 3H), 1.10 (d, J = 7.0 \text{ Hz, } 3H). \]

All other spectroscopic data were in agreement with the literature: Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* 1986, 51, 723.

**(S)-4-(4-methoxyphenyl)-4-phenyl-2-butanone (Table 2, entry 14)**

Following GP14 at 25 °C on a 0.30 mmol scale using trans-4-phenyl-3-buten-2-one and 4-methoxyphenylboronic acid, the desired product (52 mg, 68%) was isolated by flash chromatography using hexanes/EtOAc (5:1). The enantioselectivity was 90% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate 1.0 ml/min).

\[ [\alpha]_D^{33} -0.6 (c 0.72, \text{CHCl}_3); \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3) \delta 7.29-7.11 (m, 7H), 6.95 (d, J = 6.6 \text{ Hz, } 2H), 4.53 (t, J = 7.6 \text{ Hz, } 1H), 3.73 (s, 3H), 3.13 (d, J = 7.6 \text{ Hz, } 2H), 2.04 (s, 3H). \]

All other spectroscopic data were in agreement with the literature. Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* 2002, 58, 91.
(R)-N,N-3-triphenylbutanamide (Table 2, entry 15)

Following GP14 at 50 °C on a 0.30 mmol scale using (2E)-N,N-diphenyl-2-butenamide and phenylboronic acid, the desired product (93 mg, 98%) was isolated by flash chromatography using hexanes/EtOAc (7:1). The enantioselectivity was 93% ee (OD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate 1.0 ml/min).

\[[\alpha]_D^{32} = -71.4 \text{ (c 0.64, CHCl}_3)\];

\( ^1\text{H NMR (300 MHz, CDCl}_3 \) \( \delta 7.31-7.01 \text{ (m, 15H), 3.40-3.18 \ (m, 1H), 2.44-2.61 \ (m, 2H), 1.29 \ (d, 3H, J = 7.2 Hz)}; \)

\( ^{13}\text{C NMR (75 MHz, CDCl}_3 \) \( \delta 171.7, 145.7, 142.7, 128.3, 127.1, 126.2, 43.6, 37.3, 21.6; \)

\( \text{IR (neat) } \nu = 3060, 3027, 2962, 1666, 1591, 1489, 1451, 1363, 1292 \text{ cm}^{-1}; \)

(3R)-Methyl 3-phenylbutanoate (Table 2, entry 16)

Following GP14 at 25 °C on a 0.30 mmol scale using methyl crotonate and phenylboronic acid, the desired product (50 mg, 93%) was isolated by flash chromatography using hexanes/EtOAc (10:1). The enantioselectivity was 88% ee (Chiralcel OB-H, 254 nm, hexanes/iPrOH = 99:1, flow rate 1.0 ml/min).

\[[\alpha]_D^{33} = -18.9 \text{ (c 0.72, CHCl}_3)\];

\( ^1\text{H NMR (300 MHz, CDCl}_3 \) \( \delta 7.29-7.33 \text{ (m, 5H), 3.30 \ (s, 3H), 2.66 \ (dd, J = 15.1, 6.9 Hz, 1H), 2.58 \ (dd, J = 15.1, 8.2, Hz, 1H), 1.33 \ (d, J = 7.0 Hz, 3H)}. \)
All other spectroscopic data were in agreement with the literature: Tang, W.; Wang, W.; Zhang, X. Angew. Chem. Int. Ed. 2003, 42, 943.

8.5. Rh/Diene-catalyzed 1,4-Addition of Arylboronic Acids to Cinnamaldehyde Derivatives

Optimization of Reaction Conditions

\[
\begin{align*}
\text{Ph} &= \text{Me} \quad \text{[RhCl(C_2H_4)\textsubscript{2}]\textsubscript{2} (1 \text{ mol\%})} \\
\text{CHO} + \text{B(OH)\textsubscript{2}} &\quad \text{KOH (0.5 equiv)} \\
\text{solvent/H_2O (10/1)} &\quad \text{50 °C, 75 min}
\end{align*}
\]

GP15: Rh/Diene-Catalyzed Asymmetric 1,4-Addition of 4-Methoxyphenylboronic Acid to Cinnamaldehyde

To \([\text{RhCl(C_2H_4)\textsubscript{2}]\textsubscript{2}} (1.8 \text{ mg, 4.6 \mu mol, 1.5 mol\%})\) in a Schlenk flask (10 mL) was added a solution of the chiral ligand (9.9 \mu mol, 3.3 mol\%) in the solvent (either 1,4-dioxane or MeOH) (1 mL). The resulting solution was stirred for 15 min, and KOH (100 \mu L, 0.15 mmol, 0.5 equiv, 1.5 M solution in \text{H}_2\text{O}) was added. After stirring for 15 min, 4-MeOC\textsubscript{6}H\textsubscript{4}B(OH)\textsubscript{2} (91 mg, 0.6 mmol, 2 equiv) was added followed by trans-cinnamaldehyde (40 mg, 0.3 mmol, 1 equiv) and the reaction was stirred at 50 °C for 75 min. Saturated NH\textsubscript{4}Cl was added, and the aqueous layer was extracted with Et\textsubscript{2}O (3\times). The combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, and the solvent was evaporated to give the crude. The desired product (S)-3-(4-methoxyphenyl)-3-phenylpropanal 203 was isolated by flash chromatography using hexanes/EtOAc (5:1). The enantioselectivity of the corresponding alcohol (obtained by reduction with NaBH\textsubscript{4}) was determined by HPLC employing the following conditions: Chiralpak AD-H, 254 nm, hexanes/iPrOH = 92:8, flow rate = 1.0 mL/min, t\textsubscript{r} (major) = 15.4 min, t\textsubscript{r} (minor) = 17.5 min.

- Using ligand 164 and 1,4-dioxane as solvent, 31 mg (0.13 mmol, 43%) of the 1,4-adduct 203 were isolated with 47% ee.
• Using ligand 161 and 1,4-dioxane as solvent, 32 mg (0.14 mmol, 45%) of the 1,4-adduct 203 were isolated with 60% ee.

• Using ligand 175 and 1,4-dioxane as solvent, 36 mg (0.15 mmol, 50%) of the 1,4-adduct 203 were isolated with 83% ee.

• Using ligand 178 and 1,4-dioxane as solvent, 31 mg (0.13 mmol, 43%) of the 1,4-adduct 203 were isolated with 92% ee.

• Using ligand 178 and ethanol as solvent, 36 mg (0.20 mmol, 68%) of the 1,4-adduct 203 were isolated with 92% ee.

• Using ligand 178 and methanol as solvent, 58 mg (0.24 mmol, 80%) of the 1,4-adduct 203 were isolated with 92% ee.

• Using ligand 204 and methanol as solvent, 24 mg (0.10 mmol, 33%) of the 1,4-adduct 203 were isolated with 89% ee.

• Using ligand 205 and methanol as solvent, 14 mg (0.06 mmol, 19%) of the 1,4-adduct 203 were isolated with 56% ee.

Investigation into the Substrate Scope

GP16: Enantioselective Rh/Diene-Catalyzed 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Enals

To [Rh(C2H4)Cl]2 (1.8 mg, 4.6 μmol, 1.5 mol%) in a Schlenk flask (10 mL) was added a solution of 178 (3.1 mg, 9.9 μmol, 3.3 mol%) in MeOH (1 mL). The resulting solution was stirred for 15 min, and KOH (100 μL, 0.15 mmol, 0.5 equiv, 1.5 M solution in H2O) was added. After stirring for 15 min, the arylboronic acid (0.6 mmol, 2 equiv) was added followed by the α,β-unsaturated aldehyde (0.3 mmol, 1 equiv) and the reaction was stirred at 50 °C for 75 min. Saturated NH4Cl was added, and the aqueous layer was extracted with Et2O (3×). The combined organic layers were washed with brine, dried over MgSO4, and the solvent was evaporated to give the crude.
(S)-3-(4-methoxyphenyl)-3-phenylpropanal (Table 3, entry 1).

Following GP16 on a 0.30 mmol scale using trans-cinnamaldehyde and 4-methoxyphenylboronic acid (2.0 equiv) with a reaction time of 75 min, the desired product (58 mg, 80%, colorless liquid) was isolated by flash chromatography using hexane/EtOAc (5:1). The enantioselectivity of the corresponding alcohol (obtained by reduction with NaBH₄) was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 92:8, flow rate = 1.0 mL/min, tₑ (major) = 15.4 min, tₑ (minor) = 17.5 min).

[α]D₃₀⁺4.6 (c 0.68, CHCl₃);

¹H NMR (300 MHz, CDCl₃) δ 9.73 (t, 1H, J = 2.1 Hz), 7.32-7.13 (m, 7H), 6.83 (m, 2H), 4.57 (t, 1H, J = 7.8 Hz), 3.77 (s, 3H), 3.13 (dd, 2H, J = 7.8, 2.1 Hz);

¹³C NMR (75.5 MHz, CDCl₃) δ 201.2, 158.2, 143.6, 135.3, 128.7, 127.6, 126.6, 114.1, 55.2, 49.5, 44.2;

IR (neat) ν = 3027, 2929, 2835, 2725, 1720, 1509, 1247, 1177, 1031, 698 cm⁻¹;

HRMS-EI calcd for C₁₆H₁₆O₂ [M]⁺ 240.1150, found 240.1140.

(S)-3-(4-Fluorophenyl)-3-phenylpropanal (Table 3, entry 2)

Following GP16 on a 0.34 mmol scale using trans-cinnamaldehyde and 4-fluorophenylboronic acid (2.0 equiv) with a reaction time of 75 min, the desired product (70 mg, 90%, colorless liquid) was isolated by flash chromatography using 15% Et₂O/hexane. The enantioselectivity of the corresponding alcohol was 93% ee (Chiralcel
Experimental Section

OJ-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, t_\text{r} (major) = 13.3 min, t_\text{r} (minor) = 19.9 min.

[\alpha]_D^{20} +1.8 (c 0.48, CHC13);

$^1$H NMR (300 MHz, CDCl$_3$) δ 9.74 (t, 1H, J = 1.8 Hz), 7.33-7.17 (m, 7H), 6.98 (m, 2H), 4.62 (t, 1H, J = 7.8 Hz), 3.16 (dd, 2H, J = 7.8, 1.8 Hz);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 200.4, 161.4 (d, $^1$JC-F = 244.7 Hz), 142.9, 138.8, 129.1 (d, $^3$JC-F = 8.5 Hz), 128.7, 127.5, 126.7, 115.4 (d, $^2$JC-F = 21.4 Hz), 49.6, 44.2;

IR (neat) ν = 3029, 2924, 2827, 2726, 1721, 1603, 1507, 1211, 698 cm$^{-1}$;

HRMS-EI calcd for C$_{15}$H$_{13}$FO [M]$^+$ 228.0950, found 228.0947.

(S)-3-(4-Acetylphenyl)-3-phenylpropanal (Table 3, entry 3)

Following GP16 on a 0.3 mmol scale using trans-cinnamaldehyde and 4-acetylphenylboronic acid (1.5 equiv) with a reaction time of 120 min, the desired product (59 mg, 78%) was isolated by flash chromatography using 3:1 hexane/EtOAc. The enantioselectivity of the corresponding alcohol was 92% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, t_\text{r} (minor) = 27.6 min, t_\text{r} (major) = 32.5 min).

mp = 68-69 °C;

[\alpha]_D^{20} +6.0 (c 1.06, CHCl3);

$^1$H NMR (300 MHz, CDCl$_3$) δ 9.73-9.74 (m, 1H), 7.87 (d, 2H, J = 8.1 Hz), 7.18-7.32 (m, 7H), 4.67 (t, 1H, J = 7.5 Hz), 3.20 (dd, 2H, J = 7.5, 1.6 Hz), 2.54 (s, 3H);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 199.9, 197.3, 148.5, 142.2, 135.5, 128.8, 128.7, 127.8, 127.6, 126.9, 49.1, 44.8, 26.7;

IR (thin film) ν = 3028, 2827, 2726, 1722, 1680, 1606, 1494, 1452, 1414, 1359, 1269, 1183, 1014, 958 cm$^{-1}$;
HRMS-EI calcd for C_{17}H_{16}O_2 [M]^+ 252.1150, found 252.1145.

(S)-Methyl 3-((S)-2-formyl-1-phenylethyl)benzoate (Table 3, entry 4)

Following GP16 on a 0.33 mmol scale using *trans*-cinnamaldehyde and 3-methoxycarbonylphenylboronic acid (2.0 equiv) with a reaction time of 22 h, the desired product (62 mg, 70%, colorless liquid) was isolated by flash chromatography using 30% Et₂O/hexane. The enantioselectivity of the corresponding alcohol was 89% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, tᵣ(major) = 43.9 min, tᵣ(minor) = 63.0 min).

[α]D^30 +17.6 (c 0.43, CHCl₃);

^1^H NMR (300 MHz, CDCl₃) δ 9.75 (t, 1H, J = 1.8 Hz), 7.95 (t, 1H, J = 1.8 Hz), 7.88 (dt, 1H, J = 7.5, 1.8 Hz), 7.44-7.18 (m, 7H), 4.68 (t, 1H, J = 7.8 Hz), 3.90 (s, 3H), 3.22 (dd, 2H, J = 7.8, 1.8 Hz);

^1^C NMR (75.5 MHz, CDCl₃) δ 200.1, 166.7, 143.5, 142.5, 132.4, 130.4, 128.7, 128.4, 127.9, 127.5, 126.8, 52.2, 49.3, 44.7;

IR (neat) ν = 3027, 2951, 2726, 1716, 1280, 1196, 749, 702, 667 cm⁻¹;

HRMS-EI calcd for C_{17}H_{16}O_3 [M]^+ 268.1099, found 268.1094.

(S)-3-Phenyl-3-(3-(trifluoromethyl)phenyl)propanal (Table 3, entry 5)
Following GP16 on a 0.38 mmol scale using trans-cinnamaldehyde and 3-trifluoromethylphenylboronic acid (2.0 equiv) with a reaction time of 2.5 h, the desired product (89 mg, 85%, colorless liquid) was isolated by flash chromatography using 1:5 Et$_2$O/pentane. The enantioselectivity of the corresponding alcohol was 90% ee (Chiralcel OJ-H, 254 nm, hexanes/iPrOH = 99:1, flow rate = 1.0 mL/min, $t_r$ (minor) = 40.4 min, $t_r$ (major) = 43.8 min).

$[\alpha]_D^{31} +2.8$ (c 0.7, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.76 (t, 1H, $J = 1.5$ Hz), 7.49-7.21 (m, 9H), 4.70 (t, 1H, $J = 7.5$ Hz), 3.22 (dt, 2H, $J = 7.5$, 1.5 Hz);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 200.0, 144.3, 142.2, 131.2, 131.0 (q, $^2$J$_{C-F} = 31.4$ Hz), 129.2, 128.9, 127.7, 127.6 (q, $^1$J$_{C-F} = 272$ Hz), 127.0, 124.3 (q, $^3$J$_{C-F} = 3.8$ Hz), 123.6 (q, $^3$J$_{C-F} = 3.8$ Hz), 49.2, 44.5;

IR (neat) $\nu$ = 3066, 3029, 2927, 2827, 2727, 1724, 1326, 1118, 698 cm$^{-1}$;

HRMS-EI calcd for C$_{16}$H$_{13}$F$_3$O $[M]^+$ 278.0918, found 278.0909.

(R)-3-(4-Acetylphenyl)-3-(4-methoxyphenyl)propanal (Table 3, entry 6)

Following GP16 on a 0.3 mmol scale using trans-methoxycinnamaldehyde and 4-acetylphenylboronic acid (1.5 equiv) with a reaction time of 75 min, the desired product (66 mg, 78%) was isolated by flash chromatography using 2:1 hexane/EtOAc. The enantioselectivity of the corresponding alcohol was 93% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, $t_r$ (major) = 39.2 min , $t_r$ (minor) = 44.7 min).

$[\alpha]_D^{34} +4.6$ (c 0.72, CHCl$_3$);
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$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.74 (t, 1H, $J = 1.7$ Hz), 7.88 (d, 2H, $J = 8.4$ Hz), 7.31 (d, 2H, $J = 8.4$ Hz), 7.13 (d, 2H, $J = 8.7$ Hz), 6.84 (d, 2H, $J = 8.7$ Hz), 4.64 (t, 1H, $J = 7.5$ Hz), 3.77 (s, 3H), 3.17 (dd, 2H, $J = 7.5$, 1.7 Hz), 2.56 (s, 3H);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 200.1, 197.3, 158.3, 148.9, 135.4, 134.2, 128.7, 128.5, 128.4, 127.7, 114.2, 55.3, 49.3, 44.0, 26.7;

IR (thin film) $\nu = 2835, 1722, 1680, 1606, 1512, 1413, 1359, 1303, 1269, 1180, 1033$ cm$^{-1}$;

HRMS-EI calcd for C$_{18}$H$_{18}$O$_3$ [M]$^+$ 282.1256, found 282.1252.

$(R)$-3-(4-methoxyphenyl)-3-phenylpropanal (Table 3, entry 7)

Following GP16 on a 0.34 mmol scale using $trans$-4-methoxycinnamaldehyde and phenylboronic acid (1.2 equiv) with a reaction time of 75 min, the desired product (57 mg, 70%, colorless liquid) was isolated by flash chromatography using 20% Et$_2$O/hexane. The enantioselectivity of the corresponding alcohol was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 92:8, flow rate = 1.0 mL/min, $t_r$ (major) = 17.5 min).

$[\alpha]_D^{22} -4.2$ (c 0.53, CHCl$_3$);

The spectroscopic data were identical to 202.

$(R)$-3-(4-Fluorophenyl)-3-phenylpropanal (Table 3, entry 8)

Following GP16 on a 0.34 mmol scale using $trans$-4-methoxycinnamaldehyde and phenylboronic acid (1.2 equiv) with a reaction time of 75 min, the desired product (57 mg, 70%, colorless liquid) was isolated by flash chromatography using 20% Et$_2$O/hexane. The enantioselectivity of the corresponding alcohol was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 92:8, flow rate = 1.0 mL/min, $t_r$ (major) = 17.5 min).

$[\alpha]_D^{22} -4.2$ (c 0.53, CHCl$_3$);

The spectroscopic data were identical to 202.
Following GP16 on a 0.3 mmol scale using trans-4-fluorocinnamaldehyde (prepared according to: Battistuzzi, G.; Cacchi, S.; Fabrizi, G. Org. Lett. 2003, 5, 777) and phenylboronic acid (1.5 equiv) with a reaction time of 75 min, the desired product (60 mg, 87%) was isolated by flash chromatography using hexane/EtOAc (5:1). The enantioselectivity of the corresponding alcohol was 91% ee (Chiralcel OJ-H, 254 nm, hexanes/iPrOH = 95:5, flow rate = 0.5 mL/min, $t_r$ (minor) = 58.4 min, $t_r$ (major) = 77.0 min).

$[\alpha]_D^{29} -2.3$ (c 0.55, CHCl$_3$);
The spectroscopic data were identical to those of its enantiomer (Table 3, entry 2).

**(R)-3-(2-Methoxyphenyl)-3-phenylpropanal (Table 3, entry 9)**

\[
\text{MeCl} \xrightarrow{\text{PhB(OH)$_2$}} \text{Me} / \text{i-Bu} \xrightarrow{\text{[Rh(C$_2$H$_4$)$_2$Cl]$_2$ (1.5 mol%) KOH (0.5 equiv)}} \xrightarrow{\text{MeOH/H$_2$O (10/1)}} \text{PhCHO}
\]

Following GP16 on a 0.38 mmol scale using trans-2-methoxycinnamaldehyde and phenylboronic acid (1.2 equiv) with a reaction time of 4 h, the desired product (69 mg, 76%, colorless liquid) was isolated by flash chromatography using 15% Et$_2$O/hexane. The enantioselectivity of the corresponding alcohol was 91% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, $t_r$ (minor) = 11.0 min, $t_r$ (major) = 14.7 min.

$[\alpha]_D^{32} +47.3$ (c 0.58, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) δ 9.71 (t, 1H, $J = 2.1$ Hz), 7.32-7.17 (m, 6H), 7.05 (dd, 1H, $J = 7.8, 1.8$ Hz), 6.89 (m, 2H), 5.04 (t, 1H, $J = 7.8$ Hz), 3.81 (s, 3H), 3.11 (ddd, 2H, $J = 7.8, 2.1, 0.6$ Hz);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 201.6, 156.4, 142.6, 131.4, 128.3, 128.0, 127.9, 127.7, 126.3, 120.6, 110.6, 55.4, 48.5, 38.3;

IR (neat) ν = 3027, 2937, 2836, 2723, 1720, 1489, 1240, 1026, 751, 698 cm$^{-1}$;

HRMS-EI calcd for C$_{16}$H$_{16}$O$_2$ [M$^+$] 240.1150, found 240.1145.
(R)-3-(2-(Benzyloxy)-5-methylphenyl)-3-phenylpropanal 215 (Table 3, entry 10)

Following GP16 on a 0.3 mmol scale using (E)-3-(2-Benzylloxy)-5-methylphenyl)acrylaldehyde 214 and phenylboronic acid (1.5 equiv) with a reaction time of 75 min, the desired product (77 mg, 78%) was isolated by flash chromatography using 10:1 hexane/EtOAc. The enantioselectivity of the corresponding alcohol was 90% ee (Chiralcel OJ-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, \( t_r \) (minor) = 12.9 min, \( t_r \) (major) = 14.8 min).

\([\alpha]_D^{34} +17.0 \ (c \ 1.02, \ CHCl_3)\);

mp = 80-81 °C;

IR (thin film) \( \nu = 3028, 1723, 1601, 1499, 1452, 1381, 1239, 1126, 1023 \ cm^{-1} \);

\(^1H\) NMR (300 MHz, CDCl\(_3\)) \( \delta \ 9.68 \ (t, \ 1H, \ J = 2.2 \ Hz), \ 7.16-7.37 \ (m, \ 10H), \ 6.94-6.99 \ (m, \ 2H), \ 6.80 \ (d, \ 1H, \ J = 8.2 \ Hz), \ 5.00-5.06 \ (m, \ 3H), \ 3.08-3.12 \ (m, \ 2H), \ 2.25 \ (s, \ 3H); \)

\(^{13}C\) NMR (75.5 MHz, CDCl\(_3\)) \( \delta \ 202.1, \ 153.9, \ 143.2, \ 137.3, \ 131.7, \ 130.4, \ 129.1, \ 128.7, \ 128.6, \ 128.3, \ 128.1, \ 127.6, \ 126.6, \ 112.3, \ 70.5, \ 48.7, \ 38.8, \ 20.9; \)

HRMS-EI calcd for C\(_{23}\)H\(_{22}\)O\(_2\) [M]\(^+\) 330.1620, found 330.1615.

(R)-3-(Furan-2-yl)-3-phenylpropanal (Table 3, entry 11)

Following GP16 on a 0.3 mmol scale using \( \trans \)-3-(2-furyl)-acroleine and phenylboronic acid (1.5 equiv) with a reaction time of 75 min, the desired product (38 mg, 63%) was isolated by flash chromatography using 5:1 hexane/EtOAc. The enantioselectivity of the
corresponding alcohol was 93% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, t<sub>r</sub> (minor) = 11.8 min, t<sub>r</sub> (major) = 12.8 min).

[α]<sup>D</sup><sub>34</sub> -45.4 (c 0.34, CHCl<sub>3</sub>);

1H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.74-9.75 (m, 1H), 7.22-7.35 (m, 6H), 6.28-6.30 (m, 1H), 6.03-6.04 (m, 1H), 4.63 (t, 1H, J = 7.5 Hz), 3.16-3.25 (m, 1H), 2.96-3.05 (m, 1H);

13C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 200.1, 155.7, 141.7, 140.8, 128.6, 128.5, 127.5, 110.1, 106.1, 48.3, 39.2;

IR (thin film) ν = 1724, 1506, 1454, 1144, 1010 cm<sup>-1</sup>;


8.6. Rh/Diene-Catalyzed Asymmetric 1,2-Addition of Arylboronic Acids to Aldehydes

Solvent Screening

GP17: Enantioselective Rh/Diene 164-Catalyzed 1,2-Addition of Phenylboronic Acid to 1-Naphthaldehyde

To [RhCl(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>] (1.8 mg, 4.6 μmol, 1.5 mol%) in a Schlenk flask (10 mL) was added a solution of the chiral diene ligand 164 (2.8 mg, 9.9 μmol, 3.3 mol%) in the below indicated solvent (1 mL). The resulting solution was stirred for 15 min, and KOH (100 μL, 0.15 mmol, 0.5 equiv, 1.5 M solution in H<sub>2</sub>O) was added. After stirring for 15 min, phenylboronic acid 138 (73 mg, 0.6 mmol, 2 equiv) was added followed by 1-naphthaldehyde 206 (47 mg, 0.3 mmol, 1 equiv) and the reaction was stirred at 50 °C for the time indicated below. Saturated NH<sub>4</sub>Cl was added, and the aqueous layer was extracted with Et<sub>2</sub>O (3×). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and the solvent was evaporated to give the crude. The conversion was
determined by $^1$H NMR spectroscopy of an aliquot taken from the unpurified reaction mixture. The desired product (S)-naphthalen-1-yl(phenyl)methanol 207 was isolated by flash chromatography using 20% Et$_2$O in hexanes. The enantioselectivity was determined by HPLC employing the following conditions: Chiralcel OD, 254 nm, hexanes/iPrOH = 80:20, flow rate = 1.0 mL/min, $t_r$ (major) = 8.5 min, $t_r$ (minor) = 17.3 min.

- Using 1,4-dioxane/H$_2$O as solvent system, a conversion of 35% was measured after 42 h reaction time. The 1,2-adduct 207 was isolated in 35% ee.
- Using 1,2-dimethoxyethane/H$_2$O as solvent system, a conversion of 14% was measured after 18 h reaction time. The 1,2-adduct 207 was isolated in 17% ee.
- Using ethanol/H$_2$O as solvent system, a conversion of 70% was measured after 18 h reaction time. The 1,2-adduct 207 was isolated in 28% ee.
- Using acetonitrile/H$_2$O as solvent system, a conversion of <3% was measured after 19 h reaction time. Enantioselectivity of 207 was not determined.
- Using $N,N$-dimethylformamide/H$_2$O as solvent system, no conversion was measured after 19 h reaction time. Enantioselectivity of 207 was not determined.
- Using toluene/H$_2$O as solvent system, a conversion of 30% was measured after 18 h reaction time. The 1,2-adduct 207 was isolated in 18% ee.
- Using 1,2-dichloroethane/H$_2$O as solvent system, a conversion of 21% was measured after 18 h reaction time. The 1,2-adduct 207 was isolated in 27% ee.
- Using methanol/H$_2$O as solvent system, a conversion of 66% was measured after 19 h reaction time. The 1,2-adduct 207 was isolated in 21% ee.
- Using iso-propanol/H$_2$O as solvent system, a conversion of 50% was measured after 19 h reaction time. The 1,2-adduct 207 was isolated in 33% ee.

**Ligand Screening with various Chiral Dienes**

\[
\begin{array}{c}
\text{CHO} \\
1 \text{ equiv 206}
\end{array} + 
\begin{array}{c}
\text{B(OH)}_2 \\
2 \text{ equiv 138}
\end{array} \rightarrow 
\begin{array}{c}
\text{HO} \\
207
\end{array}
\]

$[\text{RhCl(C}_2\text{H}_4)_2]_2$ (1.5 mol%) chiral diene (3.3 mol%) EtOH/H$_2$O (10:1) KOH (0.5 equiv) 50°C, 19 h
GP18: Enantioselective Rh/Diene-Catalyzed 1,4-Addition of Phenylboronic Acid to 1-Naphthaldehyde

To [RhCl(C₂H₄)₂]₂ (1.8 mg, 4.6 μmol, 1.5 mol%) in a Schlenk flask (10 mL) was added a solution of the chiral diene ligand indicated below (9.9 μmol, 3.3 mol%) in EtOH (1 mL). The resulting solution was stirred for 15 min, and KOH (100 μL, 0.15 mmol, 0.5 equiv, 1.5 M solution in H₂O) was added. After stirring for 15 min, phenylboronic acid 138 (73 mg, 0.6 mmol, 2 equiv) was added followed by 1-naphthaldehyde 206 (47 mg, 0.3 mmol, 1 equiv) and the reaction was stirred at 50 °C for 19 h. Saturated NH₄Cl was added, and the aqueous layer was extracted with Et₂O (3×). The combined organic layers were washed with brine, dried over MgSO₄, and the solvent was evaporated to give the crude. The conversion was determined by ¹H NMR spectroscopy of an aliquot taken from the unpurified reaction mixture. The desired product (S)-naphthalen-1-yl(phenyl)methanol 207 was isolated by flash chromatography using 20% Et₂O in hexanes. The enantioselectivity was determined by HPLC employing the following conditions: Chiralcel OD, 254 nm, hexanes/iPrOH = 80:20, flow rate = 1.0 mL/min, tᵣ(major) = 8.5 min, tᵣ(minor) = 17.3 min.

- Using ligand 109, a conversion of 97% was measured. The 1,2-adduct 207 was isolated in 10% ee.
- Using ligand 164, a conversion of 83% was measured. The 1,2-adduct 207 was isolated in 28% ee.
- Using ligand 161, a conversion of 100% was measured. The 1,2-adduct 207 was isolated in 36% ee. Using 1,4-dioxane/H₂O instead of EtOH/H₂O as solvent system under otherwise identical reaction conditions, 76% conversion were measured. The 1,2-adduct 207 was then isolated in 40% ee.
- Using ligand 175, a conversion of 68% was measured. The 1,2-adduct 207 was isolated in 14% ee.
8.7 Formal Synthesis of (R)-(−)-Tolterodine 208

1-((2-bromo-4-methylphenoxy)methyl)benzene 214

A solution of 2-bromo-4-methylphenol 213 (604 μL, 5 mmol, 1 equiv) in 12 mL anhydrous DMF was added to a slurry of sodium hydride (144 mg, 6 mmol, 1.2 equiv) in 12 mL anhydrous DMF over 10 min. Anhydrous THF was added to dissipate the resulting solid. After 1 h of stirring, benzyl bromide (714 μL, 6 mmol, 1.2 equiv) in THF was added and the mixture was stirred at 23 °C for 15 h. The mixture was then diluted with ether, washed with brine and dried over Na₂SO₄. Concentration resulted in the formation of a yellow oil that solidified upon standing. The residue was purified by chromatography using hexanes/EtOAc (15:1) as eluent to give the title compound 214 (1.37 g, 5 mmol, 99%) as white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.45 (m, 2H), 7.35 (m, 3H), 6.99 (m, 1H), 6.79 (d, J = 8.2 Hz, 1H), 5.10 (s, 2H), 2.24 (s, 3H).


(E)-3-(2-(Benzyloxy)-5-methylphenyl)acrylaldehyde 215

To a stirred solution of 1-((2-bromo-4-methylphenoxy)methyl)benzene 214 (456 mg, 1.65 mmol) in DMF (7 mL) was added acrolein diethyl acetal (757 μL, 4.94 mmol), n-Bu₄NOAc (993 mg, 3.30 mmol), K₂CO₃ (342 mg, 2.48 mmol), KCl (123 mg, 1.65 mmol, and Pd(OAc)₂ (37 mg, 0.17 mmol). The mixture was stirred for 2.5 h at 90 °C. After the mixture was cooled, 2 N HCl was slowly added and the resulting black reaction mixture was stirred at room temperature for 10 min. The black solution was diluted with ether and washed three times with water. The organic layer was dried over Na₂SO₄, and
concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexane/EtOAc (10:1), yielding 170 mg (0.67 mmol, 41%) of the title compound 215 as a slightly yellow, odorous powder. 251 mg (0.91 mmol, 55%) of the starting 1-((2-bromo-4-methylphenoxy)methyl)benzene 214 could be recovered.

\[ \text{mp} = 68-69 \, ^\circ \text{C}; \]

\[ ^1\text{H NMR (300 MHz, CDCl}_3 \] \( \delta \) 9.67 (d, 1H, \( J = 7.8 \) Hz), 7.88 (d, 1H, \( J = 16.2 \) Hz), 7.35-7.44 (m, 6H), 7.18 (dd, 1H, \( J = 1.9 \) Hz, 8.4 Hz), 6.90 (d, 1H, \( J = 8.4 \) Hz), 6.76 (dd, 1H, \( J = 7.8 \) Hz, 16.2 Hz), 5.15 (s, 2H), 2.31 (s, 3H);

\[ ^{13}\text{C NMR (75.5 MHz, CDCl}_3 \] \( \delta \) 194.8, 155.6, 148.3, 136.7, 133.5, 130.7, 129.2, 129.0, 128.9, 128.4, 127.6, 123.3, 113.1, 70.9, 20.7;

\[ \text{IR (thin film)} \quad v = 3031, 2863, 1673, 1620, 1609, 1577, 1494, 1453, 1314, 1289, 1245, 1237, 1008 \, \text{cm}^{-1}; \]

\[ \text{HRMS-EI calcd for C}_{17}\text{H}_{16}\text{O}_2 252.1150, \text{found 252.1146.} \]

The transformation of (E)-3-(2-(Benzyloxy)-5-methylphenyl)acrylaldehyde 215 to (R)-3-(2-(Benzyloxy)-5-methylphenyl)-3-phenylpropanal 216 was already described above.

8.8. **Rh/Diene-Catalyzed Enantioselective 1,4-Addition of Arylboronic Acids to \( \alpha,\beta \)-Unsaturated Esters**

**GP19: Preparation of \( t \)-Butyl Esters**

To a solution of the \( \alpha,\beta \)-unsaturated acid (5.2 mmol, 1 equiv) in dry THF (25 mL) was added Boc\(_2\)O (2.26 g, 10.4 mmol, 2 equiv) and DMAP (190 mg, 1.55 mmol, 0.3 equiv). The reaction mixture was stirred for 72 h at 23 \( ^\circ \text{C} \) and concentrated. The residue was purified by chromatography on SiO\(_2\) (85:15, pentane/Et\(_2\)O).

\[ \text{tert-Butyl 3-(2-nitrophenyl)acrylate} \]

\[ HOOC\underbrace{\text{C}=\text{C}}_{\text{Bu}}\text{NO}_2 \]
Prepared according to GP 19 employing 2-nitrocinnamic acid (1 g, 5.18 mmol) to give (1.29 g, 5.18 mmol, 99%) of a light yellow solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.03-7.98 (m, 2 H), 7.64-7.63 (m, 2 H), 7.56-7.48 (m, 1 H), 6.30 (d, 1 H, $J = 15.6$ Hz), 1.54 (s, 9 H);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 164.8, 148.1, 138.5, 133.2, 130.6, 129.9, 128.9, 125.1, 124.7, 81.1, 28.2;

IR (neat) ν = 2979, 2933, 1711, 1638, 1572, 1526, 1366, 1345, 1326, 1295, 1289, 1153 cm$^{-1}$;


tert-Butyl 3-(thiophen-3-yl)acrylate

Prepared according to GP 19 employing ($E$)-3-(thiophen-3-yl)acrylic acid (0.80 g, 5.18 mmol) to give (1.09 g, 5.18 mmol, 99%) of a yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.57 (d, 1H, $J = 15.9$ Hz), 7.46 (m, 1H), 7.35-7.26 (m, 2H), 6.19 (d, 1H, $J = 15.9$ Hz), 1.53 (s, 9H);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 166.4, 137.6, 137.0, 127.4, 126.7, 125.1, 119.8, 80.4, 28.3;

IR (neat) ν = 3099, 2976, 2932, 1699, 1632, 1366, 1309, 1279, 1141, 976, 854, 782 cm$^{-1}$;

HRMS-EI calcd for C$_{11}$H$_{14}$O$_2$S [M]$^+$ 210.0715, found 210.0710.

tert-Butyl-3-(thiophen-2-yl)acrylate

Prepared according to GP 19 employing ($E$)-3-(thiophen-2-yl)acrylic acid (0.80 g, 5.18 mmol) to give (1.09 g, 5.18 mmol, 99%) of a yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, 1H, $J = 15.6$ Hz), 7.33 (m, 1H), 7.22 (m, 2H), 7.05-7.02 (m, 1H), 6.17 (d, 1H, $J = 15.6$ Hz), 1.52 (s, 9H);

$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 166.0, 139.7, 135.9, 130.3, 127.8, 118.9, 80.4, 28.1;
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**IR** (neat) \( \nu = 3106, 2977, 2931, 1703, 1391, 1367, 1310, 1283, 1230, 1208, 971, 852 \text{ cm}^{-1}; \\
**HRMS-EI** calcd for \( C_{11}H_{14}O_{2}S \) [M]⁺ 210.0715, found 210.0712.

**tert-Butyl 3-(3-tert-butoxy-3-oxoprop-1-enyl)-1H-indole-1-carboxylate**

Prepared according to GP 19 employing (E)-3-(1H-indol-3-yl)acrylic acid (0.97 g, 5.18 mmol) and Boc₂O (4.52 g, 20.7 mmol, 4 equiv) to give (1.78 g, 5.18 mmol, 99%) of a colorless solid.

\( mp = 111-112 \, ^\circ C; \)

\(^1H\) NMR (300 MHz, CDCl₃) \( \delta \) 8.19 (d, 1H, \( J = 7.8 \) Hz), 7.86-7.83 (m, 2H), 7.73 (dd, 1H, \( J = 16.2, 0.6 \) Hz), 7.41-7.29 (m, 2H), 6.47 (d, 1H, \( J = 16.2 \) Hz), 1.68 (s, 9H), 1.53 (s, 9H);

\(^13C\) NMR (75.5 MHz, CDCl₃) \( \delta \) 166.6, 149.0, 136.1, 135.1, 128.1, 127.9, 125.1, 123.4, 120.2, 119.4, 116.8, 115.4, 84.5, 80.4, 28.4, 28.3;

**IR** (neat) \( \nu = 3140, 2978, 2932, 1740, 1704, 1636, 1452, 1367, 1258, 1256, 1146, 1094, 913, 743 \text{ cm}^{-1}; \\
**HRMS-MALDI** calcd for \([C_{20}H_{25}NO_{4}Na]⁺\) 366.1676, found 366.1669.

**Ligand Screening and Reaction Optimization**

**GP20: Rh/Diene-Catalyzed 1,4-Addition of 4-Methoxyphenylboronic Acid to \( \alpha,\beta\)-Unsaturated Esters**

To [Rh(C₂H₄)₂Cl]₂ (1.8 mg, 4.6 \( \mu \)mol, 1.5 mol%) in a Schlenk flask (10 mL) was added a solution of the chiral diene (9.9 \( \mu \)mol, 3.3 mol%) in 1,4-dioxane or methanol (1 mL). The resulting solution was stirred for 15 min, and KOH (100 \( \mu \)L, 0.15 mmol, 0.5 equiv, 1.5 M solution in H₂O) was added. After stirring for 15 min, 4-MeOC₆H₄B(OH)₂ (91 mg, 0.60 mmol, 2 equiv) was added followed by the \( \alpha,\beta\)-unsaturated ester (0.30 mmol, 1 equiv) and the reaction was stirred at 50 °C for the indicated time. Saturated NH₄Cl was added, and the aqueous layer was extracted with Et₂O (3 ×). The combined organic layers were
washed with brine, dried over MgSO₄, and the solvent was evaporated to give the crude. The desired product was isolated by flash chromatography using Et₂O/hexane as eluent.

\[ (S)\text{-Ethyl 3-(4-methoxyphenyl)-3-phenylpropanoate (221)} \]

Following GP 20 in 1,4-dioxane on 0.29 mmol scale using ethyl cinnamate 218, 4-methoxyphenylboronic acid 202 and ligand 164 with a reaction time of 18 h, the desired product (59 mg, 72%) was isolated by flash chromatography using 15% Et₂O/hexane as a colorless liquid. The enantioselectivity was 19% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 95:5, flow rate = 1.0 mL/min, \( t_r \) (minor) = 7.13 min, \( t_r \) (major) = 8.34 min).

IR (neat) \( \nu = 3030, 2980, 2835, 1730, 1510, 1246, 1031, 699, 667 \text{ cm}^{-1} \);

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \( \delta 7.31-7.15 \text{ (m, 7H), 6.83 \text{ (m, 2H), 4.53 \text{ (t, 1H, } J = 8.1 \text{ Hz), 4.05 \text{ (q, 2H, } J = 7.2 \text{ Hz), 3.77 \text{ (s, 3H), 3.04 \text{ (d, 2H, } J = 8.1 \text{ Hz), 1.13 \text{ (t, 3H, } J = 7.2 \text{ Hz);}} \]

\[ ^13C \text{ NMR (75.5 MHz, CDCl}_3 \] \( \delta 172.1, 158.3, 144.1, 135.8, 128.8, 128.7, 127.8, 126.6, 114.1, 60.6, 55.4, 46.5, 41.2, 14.3; \]


\[ (R)\text{-Ethyl 3-(4-methoxyphenyl)-3-phenylpropanoate (ent-221)} \]
Following GP 20 in 1,4-dioxane on 0.33 mmol scale using ethyl cinnamate 218, 4-methoxyphenylboronic acid 202 and ligand ent-175 with a reaction time of 17 h, the desired product (93 mg, 99%) was isolated by flash chromatography using 15% Et₂O/hexane as a colorless liquid. The enantioselectivity was -65% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 95:5, flow rate = 1.0 mL/min, tᵣ (major) = 7.15 min, tᵣ (minor) = 8.47 min).

(S)-Benzyl 3-(4-methoxyphenyl)-3-phenylpropanoate (222)

Following GP 20 in 1,4-dioxane on 0.31 mmol scale using benzyl cinnamate 219, 4-methoxyphenylboronic acid and ligand 175 with a reaction time of 18 h, the desired product (91 mg, 85%) was isolated by flash chromatography using 15% Et₂O/hexane as a colorless solid. The enantioselectivity was 71% ee (Chiracel OD-H, 254 nm, hexanes/iPrOH = 90:10, flow rate = 1.0 mL/min, tᵣ (minor) = 9.18 min, tᵣ (major) = 10.49 min).

mp = 79-80 °C;

¹H NMR (300 MHz, CDCl₃) δ 7.32-7.14 (m, 12H), 6.82 (m, 2H), 5.03 (s, 2H), 4.54 (t, 1H, J = 8.1 Hz), 3.78 (s, 3H), 3.09 (d, 2H, J = 8.1 Hz);

¹³C NMR (75.5 MHz, CDCl₃) δ 171.9, 158.4, 143.9, 136.0, 135.7, 128.8, 128.7, 128.6, 128.3, 127.8, 126.7, 114.1, 66.5, 55.4, 46.5, 41.2;

IR (neat) ν = 3031, 2960, 2909, 2837, 1727, 1246, 1147, 732, 693, 667 cm⁻¹;

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**(S)-tert-Butyl 3-(4-methoxyphenyl)-3-phenylpropanoate (223)**

![Chemical Structure](image)

Following GP20 in 1,4-dioxane on 0.29 mmol scale using t-butyl cinnamate 220, 4-methoxyphenylboronic acid (2.0 equiv), and ligand 175 with a reaction time of 16 h, the desired product (65 mg, 72%) was isolated by flash chromatography using 10% Et₂O/hexane as a colorless solid. The enantioselectivity was 89% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 0.35 mL/min, tᵣ (major) = 23.55 min, tᵣ (minor) = 25.73 min).

**mp** = 70-71 °C;

**¹H NMR (300 MHz, CDCl₃)** δ 7.30-7.15 (m, 7H), 6.82 (m, 2H), 4.44 (t, 1H, J = 8.4 Hz), 3.77 (s, 3H), 2.94 (d, 2H, J = 8.4 Hz), 1.29 (s, 3H);

**¹³C NMR (75.5 MHz, CDCl₃)** δ 171.4, 158.3, 144.1, 136.0, 128.9, 128.6, 127.9, 126.5, 114.0, 80.6, 55.4, 46.8, 42.5, 28.1;

**IR (neat)** ν = 3030, 3005, 2969, 2932, 2838, 1714, 1512, 1139, 1029, 667 cm⁻¹;

**HRMS-EI** calcd for C₂₀H₂₄O₃ [M]⁺ 312.1725, found 312.1722.

**(S)-tert-Butyl 3-(4-methoxyphenyl)-3-phenylpropanoate (223)**

Following GP20 in 1,4-dioxane on 0.31 mmol scale using t-butyl cinnamate 220, 4-methoxyphenyl boronic acid and ligand 178 with a reaction time of 17 h, the desired product (86 mg, 89%) was isolated by flash chromatography using 10% Et₂O/hexane as a
colorless solid. The enantioselectivity was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 0.35 mL/min, t_r (major) = 24.29 min, t_r (minor) = 26.56 min).

Investigation in the Substrate Scope

GP21: Rh/Diene-Catalyzed 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Esters

To [Rh(C2H4)Cl]2 (1.8 mg, 4.6 μmol, 1.5 mol%) in a Schlenk flask (10 mL) was added a solution of 178 (3.1 mg, 9.9 μmol, 3.3 mol%) in 1,4-dioxane or MeOH (1 mL). The resulting solution was stirred for 15 min, and KOH (100 μL, 0.15 mmol, 0.5 equiv, 1.5 M solution in H2O) was added. After stirring for 15 min, the arylboronic acid (0.6 mmol, 2 equiv) was added followed by the α,β-unsaturated ester (0.3 mmol, 1 equiv) and the reaction was stirred at 50 °C for the indicated time. Saturated NH4Cl was added, and the aqueous layer was extracted with Et2O (3×). The combined organic layers were washed with brine, dried over MgSO4, and the solvent was evaporated to give the crude. The desired product was isolated by flash chromatography using Et2O/hexanes as eluent.

(S)-tert-Butyl 3-(4-methoxyphenyl)-3-phenylpropanoate (223, Table 4, entry 1)

Following GP21 in MeOH on 0.34 mmol scale using t-butyl cinnamate 220, 4-methoxyphenylboronic acid (2.0 equiv), and ligand 178 with a reaction time of 75 min, the desired product (90 mg, 85%) was isolated by flash chromatography using 15% Et2O/hexanes as a colorless liquid. The enantioselectivity was 93% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 0.35 mL/min, t_r (major) = 24.25 min, t_r (minor) = 26.63 min). [α]D26 +1.6 (c 0.96, MeOH).
(S)-tert-Butyl 3-(4-acetylphenyl)-3-phenylpropanoate (Table 4, entry 2)

Following GP21 in MeOH on 0.3 mmol scale using tert-butyl cinnamate, 4-acetylphenylboronic acid (1.5 equiv), and ligand 178 with a reaction time of 75 min, the desired product (74 mg, 76%) was isolated by flash chromatography using hexanes/EtOAc 7:1 as a colorless solid. The enantioselectivity was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 1.0 mL/min, t_r (major) = 19.7 min, t_r (minor) = 21.5 min).

[α]_D^24 +7.5 (c 1.03, CHCl₃);

[^1]H NMR (300 MHz, CDCl₃) δ 7.88 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.32-7.17 (m, 5H), 4.54 (t, 1H, J = 8.1 Hz), 2.98 (d, 2H, J = 8.1 Hz), 2.56 (s, 3H), 1.28 (s, 9H);

[^13]C NMR (75.5 MHz, CDCl₃) δ 197.5, 170.5, 149.0, 142.6, 135.4, 128.6, 127.9, 127.6, 126.7, 80.8, 47.4, 41.7, 28.0, 26.7;

IR (neat) ν = 3028, 3005, 2979, 2931, 1720, 1680, 1597, 1495, 1365, 1261, 1145, 1116, 957, 850 cm⁻¹;


(S)-tert-Butyl 3-(3-trifluoromethylphenyl)-3-phenylpropanoate (Table 4, entry 3)

Following GP21 in MeOH on 0.39 mmol scale using tert-butyl cinnamate, 3-trifluoromethylphenylboronic acid (2.5 equiv), and ligand 178 with a reaction time of 24 h, the desired product (94 mg, 69%) was isolated by flash chromatography using 5%
EtOAc/hexane as a colorless oil. The enantioselectivity was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 1.0 mL/min, t<sub>r</sub> (major) = 4.44 min, t<sub>r</sub> (minor) = 5.69 min).

\[ \alpha \] <sub>D</sub> 29 = 5.4 (c 0.8, MeOH),

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.53 (bs, 1 H), 7.47-7.35 (m, 3 H), 7.32-7.18 (m, 5 H), 4.55 (t, 1 H, J = 8.1 Hz), 2.98 (d, 2 H, J = 8.4 Hz), 1.28 (s, 9 H);

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 170.6, 144.6, 142.7, 131.4 (q, \( J_{CF} = 1.1 \) Hz), 130.8 (q, \( J_{CF} = 31.9 \) Hz), 128.9, 128.7, 127.7, 126.8, 124.4 (q, \( J_{CF} = 3.8 \) Hz), 124.1 (q, \( J_{CF} = 272 \) Hz), 123.4 (q, \( J_{CF} = 4.0 \) Hz);

IR (neat) ν = 3066, 3030, 2979, 2933, 1706, 1444, 1366, 1327, 1160, 1119, 1075 cm<sup>-1</sup>;


(R)-tert-Butyl 3-(4-methoxyphenyl)-3-phenylpropanoate (ent-222, Table 4, entry 4)

Following GP21 in MeOH on 0.39 mmol scale using i-butyl 4-methoxycinnamate, phenylboronic acid (2.0 equiv), and ligand 178 with a reaction time of 18.5 h, the desired product (115 mg, 95%) was isolated by flash chromatography using 10% EtOAc/hexane as a light yellow oil. The enantioselectivity was 91% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 0.35 mL/min, t<sub>r</sub> (minor) = 24.16 min, t<sub>r</sub> (major) = 26.14 min). [\( \alpha \)]<sub>D</sub> 31 = -0.92 (c 0.86, MeOH). The spectral data were identical to 223.
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(R)-tert-Butyl 3-(3-fluorophenyl)-3-phenylpropanoate (Table 4, entry 5)

Following GP21 in MeOH on 0.39 mmol scale using tert-butyl 3-fluorocinnamate, phenylboronic acid (2.0 equiv), and ligand 178 with a reaction time of 1.5 h, the desired product (111 mg, 95%) was isolated by flash chromatography using 5% EtOAc/hexane as a colorless oil. The enantioselectivity was 94% ee (Chiralcel OJ-H, 254 nm, hexanes/iPrOH = 99:1, flow rate = 0.50 mL/min, t<sub>r</sub> (minor) = 32.37 min, t<sub>r</sub> (major) = 34.37 min).

[α]<sub>D</sub> = 25° 7.1 (c 1.2, C<sub>6</sub>H<sub>6</sub>);

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.33-7.18 (m, 6H), 7.04 (br d, 1H, J = 7.5 Hz), 6.96 (dt, 1H, J = 10.2, 2.4 Hz), 6.88 (td, 1H, J = 8.7, 2.4, 0.9 Hz), 4.49 (t, 1H, J = 8.4 Hz), 2.96 (d, 2H, J = 8.4 Hz), 1.30 (s, 9H);

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 170.6, 162.7 (d, <sup>3</sup>JC-F = 244.8 Hz), 146.1 (d, <sup>3</sup>JC-F = 6.7 Hz), 142.8, 129.8 (d, <sup>3</sup>JC-F = 8.5 Hz), 128.5, 127.6, 126.6, 123.3 (d, <sup>4</sup>JC-F = 2.4 Hz), 114.6 (d, <sup>2</sup>JC-F = 21.4 Hz), 113.3 (d, <sup>2</sup>JC-F = 21.4 Hz), 80.7, 47.2, 41.9, 27.9;

IR (neat) ν = 3066, 3030, 2977, 2929, 1725, 1366, 1247, 1141, 699 cm<sup>-1</sup>;

HRMS-EI calcd for C<sub>19</sub>H<sub>21</sub>F<sub>2</sub>O<sub>2</sub> [M]+ 300.1526, found 300.1522.

(R)-tert-Butyl 3-(3-fluorophenyl)-3-(4-methoxyphenyl)propanoate (Table 4, entry 6)

Following GP21 in MeOH on 0.39 mmol scale using tert-butyl 3-fluorocinnamate, 4-methoxyphenylboronic acid (2.0 equiv), and ligand 178 with a reaction time of 2 h, the
desired product (120 mg, 93%) was isolated by flash chromatography using 5% EtOAc/hexane as a colorless oil. The enantioselectivity was 93% ee (Chiralcel OJ-H, 254 nm, hexanes/iPrOH = 99:1, flow rate = 0.50 mL/min, t_r (minor) = 28.57 min, t_r (major) = 33.79 min).

\[ \alpha \]_D^{28} = -2.4 (c 0.84, C_6H_6);
mp = 67-68 °C;

\(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 7.27-7.12 (m, 3H), 7.03-6.80 (m, 5H), 4.43 (t, 1H, J = 8.1 Hz), 3.77 (S, 3H), 2.91 (d, 2H, J = 8.1 Hz), 1.30 (s, 9H);

\(^13\)C NMR (75.5 MHz, CDCl_3) \( \delta \) 170.7, 162.7 (d, \(^3\)J_C-F = 245.4 Hz), 158.1, 146.5 (d, \(^3\)J_C-F = 6.7 Hz), 134.9, 129.7 (d, \(^3\)J_C-F = 7.9 Hz), 128.5, 123.2 (d, \(^4\)J_C-F = 2.5 Hz), 114.5 (d, \(^3\)J_C-F = 21.4 Hz), 113.8, 113.1 (d, \(^2\)J_C-F = 21.4 Hz), 80.6, 55.2, 46.4, 42.1, 27.9;

IR (neat) \( \nu = \) 3064, 2982, 2934, 2838, 1711, 1512, 1247, 1139, 1026, 687 cm\(^{-1}\);


(R)-tert-Butyl 3-(2-nitrophenyl)-3-phenylpropanoate (Table 4, entry 7)

![Chemical structure](image)

Following GP21 in MeOH on 0.40 mmol scale using \( t \)-butyl 2-nitrocinnamate, phenylboronic acid (2.0 equiv), and ligand 178 with a reaction time of 75 min, the desired product (102 mg, 78%) was isolated by flash chromatography using 10% EtOAc/hexane as a colorless oil. The enantioselectivity was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 99:1, flow rate = 0.50 mL/min, t_r (minor) = 29.43 min, t_r (major) = 39.13 min).

\[ \alpha \]_D^{27} = +13.3 (c 0.42, CHCl_3);

\(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 7.77 (dd, 1 H, J = 8.1, 1.2 Hz), 7.56-7.44 (m, 2 H), 7.36-7.17 (m, 6 H), 5.15 (t, 1 H, J = 8.4 Hz), 3.07-2.93 (m, 2 H), 1.26 (s, 9 H);
\(^{13}\text{C} \text{ NMR (75.5 MHz, CDCl}_3\) \: \delta 170.0, 149.8, 141.6, 137.5, 132.5, 129.3, 128.6, 127.8, 127.3, 126.9, 124.4, 80.9, 42.0, 41.1, 27.7; \\
\text{IR (neat)} \: \nu = 3306, 3026, 2970, 1725, 1524, 1354, 1256, 1148 \text{ cm}^{-1}; \\
\text{HRMS-EI} \text{ calcd for C}_{15}\text{H}_{12}\text{NO}_3 [M-OC}_4\text{H}_9]^+ 254.0817, \text{ found 254.0813.} \\

(R)-tert-Butyl 3-(4-methoxyphenyl)-3-(2-nitrophenyl)propanoate (Table 4, entry 8)

\[ \begin{align*}
\text{MeO} & - \text{Me} \\
\text{OMe} & - \text{Me} \\
\text{Ph} & - \text{iBu}^+/ (3.3 \text{ mol%}) \\
\text{OMe} & - \text{CO}_2\text{f-Bu}
\end{align*} \]

Following GP21 in MeOH on 0.39 mmol scale using \(-\text{butyl 2-nitrocinnamate, 4-}
\text{methoxyphenylboronic acid (3.0 equiv), and ligand 178 with a reaction time of 75 min,}
the desired product (117 mg, 84\%) was isolated by flash chromatography using 10\%
\text{EtOAc/hexane as a light yellow oil. The enantioselectivity was 92\% ee (Chiralpak AD-H,}
254 nm, hexanes/iPrOH = 98:2, flow rate = 0.5 mL/min, t\text{r (minor)} = 39.29 \text{ min, t\text{r (major)}}
= 53.89 \text{ min}).

\[\alpha\] \text{D}^{29} +35.1 (c 0.94, \text{MeOH}); \\
\text{H NMR (300 MHz, CDCl}_3\) \: \delta 7.79-7.76 (m, 1 H), 7.56-7.44 (m, 2 H), 7.37-7.31 (m, 1 H), 7.21-7.17 (m, 2 H), 6.86-6.81 (m, 2 H), 5.10 (t, 1 H, \text{J = 8.1 Hz}), 3.77 (s, 3 H), 3.05-2.90 (m, 2 H), 1.28 (s, 9 H); \\
\text{C NMR (75.5 MHz, CDCl}_3\) \: \delta 170.1, 158.4, 149.8, 137.9, 133.7, 132.5, 129.2, 128.8, 127.2, 124.4, 113.9, 80.9, 55.2, 42.2, 40.4, 27.7; \\
\text{IR (neat)} \: \nu = 2977, 1728, 1610, 1527, 1512, 1355, 1252, 1151, 1034 \text{ cm}^{-1}; \\
\text{HRMS-EI} \text{ calcd for C}_{16}\text{H}_{15}\text{NO}_5 [M-\text{C}_4\text{H}_8]^+ 301.0945, \text{ found 301.0946.}
(R)-tert-Butyl 3-(furan-2-yl)-3-(4-methoxyphenyl)propanoate (Table 5, entry 1)

Following GP21 in MeOH on 0.37 mmol scale using t-butyl 3-(furan-2-yl)acrylate, 4-methoxyphenylboronic acid (2.0 equiv), and ligand 178 with a reaction time of 14 h, the desired product (68 mg, 62%) was isolated by flash chromatography using 10% EtOAc/hexane as a colorless oil. The enantioselectivity was 92% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 99:1, flow rate = 0.50 mL/min, t_r (major) = 18.17 min, t_r (minor) = 23.64 min).

[α]D27 = -38.2 (c 0.66, CHCl3);

1H NMR (300 MHz, CDCl3) δ 7.30 (dd, 1H, J = 1.8, 0.6 Hz), 7.18 (m, 2H), 6.84 (m, 2H), 6.27 (dd, 1H, J = 3.3, 1.8 Hz), 6.02 (dt, 1H, J = 3.3, 0.6 Hz), 4.44 (t, 1H, J = 8.1 Hz), 3.78 (s, 3H), 2.98 (dd, 1H, J = 15.0, 8.1 Hz), 2.77 (dd, 1H, J = 15.0, 8.1 Hz), 1.33 (s, 9H);

13C NMR (75.5 MHz, CDCl3) δ 170.9, 158.7, 157.0, 141.7, 133.5, 129.0, 114.0, 110.2, 105.6, 80.8, 55.4, 41.3, 41.1, 28.1;

IR (neat) ν = 2976, 2932, 2836, 1727, 1511, 1246, 1145, 730 cm⁻¹;


(R)-tert-Butyl 3-(4-acetylphenyl)-3-(furan-2-yl)propanoate (Table 5, entry 2)

Following GP21 in MeOH on 0.39 mmol scale using t-butyl 3-(furan-2-yl)acrylate, 4-acetylphenylboronic acid (2.0 equiv), and ligand 178 with a reaction time of 14 h, the
desired product (82 mg, 68%) was isolated by flash chromatography using 10% then 20% EtOAc/hexane as a colorless oil. The enantioselectivity was 91% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 1.0 mL/min, t_r (major) = 15.58 min, t_r (minor) = 20.35 min).

\[ \alpha \]_D^20 = –41.3 (c 0.8, CHCl_3);

_1^H NMR (300 MHz, CDCl_3) \delta 7.92 (m, 2H), 7.35 (m, 2H), 7.31 (dd, 1H, J = 1.8, 0.9 Hz), 6.28 (dd, 1H, J = 3.3, 1.8 Hz), 6.06 (dt, 1H, J = 3.3, 0.9 Hz), 4.55 (br t, 1H, J = 8.1 Hz), 3.01 (dd, 1H, J = 15.3, 7.5 Hz), 2.83 (dd, 1H, J = 15.3, 8.3 Hz), 2.57 (s, 3H), 1.32 (s, 9H);

_1^C NMR (75.5 MHz, CDCl_3) \delta 197.5, 170.0, 155.3, 146.5, 141.7, 135.8, 128.5, 128.0, 110.1, 105.9, 80.9, 41.6, 40.5, 28.0, 26.7;

IR (neat) \nu = 3006, 2977, 2933, 1726, 1682, 1265, 1146, 734 cm\(^{-1}\);

HRMS-EI calcd for C_{19}H_{22}O_4 [M-C_4H_9]^+ 257.0814, found 257.0806.

(R)-tert-Butyl 3-(4-acetylphenyl)-3-(thiophen-2-yl)propanoate (Table 5, entry 3)

Following GP21 in 1,4-dioxane on 0.39 mmol scale using tert-butyl-3-(thiophen-2-yl)acrylate, 4-acetylphenylboronic acid (1.5 equiv), and ligand 178 with a reaction time of 14 h, the desired product (64 mg, 65%) was isolated by flash chromatography using hexanes/EtOAc 10:1 as a colorless oil. The enantioselectivity was 91% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 96:4, flow rate = 0.5 mL/min, t_r (minor) = 18.9 min, t_r (major) = 20.1 min).

\[ \alpha \]_D^20 = –14.5 (c 0.95, CHCl_3);

_1^H NMR (300 MHz, CDCl_3) \delta 7.90 (d, 2H, J = 8.1 Hz), 7.38 (d, 2H, J = 8.1 Hz), 7.17-7.14 (m, 1H), 6.91 (m, 1H), 6.83 (m, 1H), 4.76 (t, 1H, J = 8.1 Hz), 3.01 (dd, 1H, J = 15.3, 7.5 Hz), 2.83 (dd, 1H, J = 15.3, 8.3 Hz), 2.57 (s, 3H), 1.30 (s, 9H);
13C NMR (75.5 MHz, CDCl3) δ 197.5, 169.9, 148.4, 146.4, 135.7, 128.6, 127.8, 126.6, 124.2, 124.1, 81.6, 43.0, 42.9, 28.0, 26.7;
IR (neat) ν = 2976, 1727, 1686, 1606, 1366, 1267, 1147, 956, 843 cm⁻¹;

(R)-tert-Butyl 3-(4-acetylphenyl)-3-(thiophen-3-yl)propanoate (Table 5, entry 4)

Following GP21 in 1,4-dioxane on 0.30 mmol scale using tert-butyl 3-(thiophen-3-yl)acrylate, 4-acetylphenylboronic acid (1.5 equiv), and ligand 178 with a reaction time of 14 h, the desired product (67 mg, 68%) was isolated by flash chromatography using hexane/EtOAc (3:1) as a colorless oil. The enantioselectivity was 89% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 98:2, flow rate = 1.0 mL/min, tᵣ (major) = 22.4 min, tᵣ (minor) = 25.4 min).

[α]D34 = −37.2 (c 1.0, CHCl₃);
1H NMR (300 MHz, CDCl₃) δ 7.89 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.27 (m, 1H), 7.01 (m, 1H), 6.88 (m, 1H), 4.59 (t, 1H, J = 8.1 Hz), 3.04-2.86 (m, 2H), 2.58 (s, 3H), 1.30 (s, 9H);
13C NMR (75.5 MHz, CDCl3) δ 197.5, 170.4, 148.7, 143.3, 135.5, 128.6, 127.9, 127.3, 125.9, 120.6, 80.9, 43.2, 42.2, 28.0, 26.7;
IR (neat) ν = 3103, 2976, 2929, 1723, 1681, 1606, 1366, 1357, 1265, 1141, 956, 830, 779 cm⁻¹;
(R)-tert-Butyl 3-(4-methoxyphenyl)-3-(pyridin-3-yl)propanoate (Table 5, entry 5)

Following the GP21 in 1,4-dioxane on 0.30 mmol scale using tert-butyl 3-(pyridin-3-yl)acrylate, 4-methoxyphenylboronic acid (2 equiv), and ligand 178 with a reaction time of 14 h, the desired product (66 mg, 70%) was isolated by flash chromatography using hexane/EtOAc (2:1) as a colorless powder. The enantioselectivity was 93% ee (Chiralcel OD-H, 254 nm, hexanes/iPrOH = 92:8, flow rate = 0.5 mL/min, t_r (major) = 19.4 min, t_r (minor) = 21.2 min).

$\left[\alpha\right]_D^{34} +6.8$ (c 1.095, CHCl_3);

mp = 57-58 °C;

$^1$H NMR (300 MHz, CDCl_3) $\delta$ 8.54 (d, 1H, $J = 2.2$ Hz), 8.45 (m, 1H), 7.51 (m, 1H), 7.20 (m, 1H), 7.15 (d, 2H, $J = 8.7$ Hz), 6.84 (d, 2H, $J = 8.7$ Hz), 4.45 (t, 1H, $J = 8.1$ Hz), 3.77 (s, 3H), 2.94 (d, 2H, $J = 8.1$ Hz), 1.29 (s, 9H);

$^{13}$C NMR (75.5 MHz, CDCl_3) $\delta$ 170.4, 158.2, 149.3, 147.8, 135.0, 134.4, 128.5, 123.3, 114.0, 80.9, 55.3, 44.3, 41.9, 28.0;

IR (neat) $\nu = 2977, 2932, 2835, 1725, 1610, 1512, 1367, 1250, 1178, 1146, 1030, 833, 713$ cm$^{-1}$;

HRMS-EI calcd for C_{19}H_{23}NO_3 [M]$^+$ 313.1678, found 313.1677.

(R)-tert-Butyl 3-(3-tert-butoxy-1-(4-methoxyphenyl)-3-oxopropyl)-1H-indole-1-carboxylate (Table 5, entry 6)

$^1$H NMR (300 MHz, CDCl_3) $\delta$ 8.54 (d, 1H, $J = 2.2$ Hz), 8.45 (m, 1H), 7.51 (m, 1H), 7.20 (m, 1H), 7.15 (d, 2H, $J = 8.7$ Hz), 6.84 (d, 2H, $J = 8.7$ Hz), 4.45 (t, 1H, $J = 8.1$ Hz), 3.77 (s, 3H), 2.94 (d, 2H, $J = 8.1$ Hz), 1.29 (s, 9H);

$^{13}$C NMR (75.5 MHz, CDCl_3) $\delta$ 170.4, 158.2, 149.3, 147.8, 135.0, 134.4, 128.5, 123.3, 114.0, 80.9, 55.3, 44.3, 41.9, 28.0;

IR (neat) $\nu = 2977, 2932, 2835, 1725, 1610, 1512, 1367, 1250, 1178, 1146, 1030, 833, 713$ cm$^{-1}$;

HRMS-EI calcd for C_{19}H_{23}NO_3 [M]$^+$ 313.1678, found 313.1677.
Following GP21 in 1,4-dioxane on 0.20 mmol scale using tert-butyl 3-(3-tert-butoxy-3-oxoprop-1-enyl)-1H-indole-1-carboxylate, 4-methoxyphenylboronic acid (3.0 equiv), [Rh(C₂H₄)₂Cl]₂ (2.25 mol%), and 178 (5.0 mol%) with a reaction time of 14 h, the desired product (81 mg, 90%) was isolated by flash chromatography using hexane/EtOAc (15:1) as a colorless oil. The enantioselectivity was 94% ee (Chiralpak AD-H, 254 nm, hexanes/iPrOH = 99:1, flow rate = 1.0 mL/min, t₁ (major) = 9.9 min, t₂ (minor) = 16.6 min).

[α]D₃⁴ -81.5 (c 0.435, CHCl₃);

¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, 1H, J = 8.0 Hz), 7.47 (s, 1H), 7.31-7.19 (m, 2H), 7.22 (d, 2H, J = 8.8 Hz), 7.10 (m, 1H), 6.80 (d, 2H, J = 8.8 Hz), 4.60 (t, 1H, J = 7.7 Hz), 3.76 (s, 3H), 3.02 (dd, 1H, J = 15.3, 7.7 Hz), 2.85 (dd, 1H, J = 15.3, 7.7 Hz), 1.67 (s, 9H), 1.33 (s, 9H);

¹³C NMR (75.5 MHz, CDCl₃) δ 170.9, 158.1, 149.7, 135.6, 134.5, 129.7, 128.7, 124.3, 123.4, 122.3, 122.0, 119.8, 115.1, 113.8, 83.5, 80.6, 55.3, 42.4, 38.5, 28.4, 28.1;

IR (neat) v = 2977, 2932, 2835, 1731, 1610, 1511, 1453, 1369, 1253, 1157, 1092, 1036, 912, 746 cm⁻¹;

HRMS-MALDI calcd for C₂₇H₃₃NO₅Na [M]⁺ 474.2251, found 474.2244.

(R)-4-Phenyl-3,4-dihydroquinolin-2(1H)-one (225)

A mixture of 224 (75 mg, 0.23 mmol) and Pd/C (24 mg, 0.023 mmol, 10 wt% Pd on C) under Ar was suspended in MeOH (2.0 mL) and treated with AcOH (13 µL, 0.23 mmol). The flask was evacuated and purged with H₂ (1 atm) and the reaction was vigorously stirred for 1.5 h. The H₂ balloon was removed and the reaction was stirred under Ar for 14 h, filtered through Celite and concentrated. The residue was purified by chromatography on SiO₂ (1:1, hexanes/EtOAc) to give 225 (49 mg, 96%) as a colorless solid.

[α]D₂⁷ -48.8 (c 0.79, CHCl₃);
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^1H NMR (300 MHz, CDCl₃) δ 9.11 (bs, 1 H), 7.37-7.19 (m, 6 H), 6.99-6.89 (m, 3 H), 4.31 (t, 1 H, J = 7.5 Hz), 3.02-2.88 (m, 2 H);

^13C NMR (75.5 MHz, CDCl₃) δ 170.8, 141.3, 136.9, 128.8, 128.2, 127.9, 127.7, 127.1, 126.5, 123.2, 115.6, 42.0, 38.5;

IR (neat) ν = 3208, 3059, 2914, 1679, 1593, 1486, 1374, 1260 cm⁻¹;


8.9. Iridium-Catalyzed Synthesis of Chiral Allylic Alcohols: Silanlates as Hydroxide Equivalents

GP 22: Synthesis of potassium silanlates

A solution of trialkylsilanol (5 mmol, 1 equiv) in Et₂O (5 mL) was added dropwise to a suspension of KH (7.5 mmol, 1.5 equiv) in Et₂O (10 mL) at RT. The reaction mixture was stirred for 1 h, then filtered through cotton wool and concentrated in vacuo. Potassium silanlates could be stored under argon in a refrigerator for prolonged period of time.

Reaction Optimization

GP 23: GP24: Ir/Phosphoramidite-Catalyzed Synthesis of Silyl Ethers from tert-Butylcarbonates and Silanlates:

A Schlenk under argon was charged with [Ir(cod)Cl]₂ (20.2 mg, 30 μmol, 3 mol%) and (S)-(+)-(3,5-Dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)bis[(1S)-1-phenylethyl]amine 232 (32.4 mg, 60 μmol, 6 mol%). THF (0.7 mL) and n-propylamine (0.7 mL) were added, and the reaction mixture was stirred at 50 °C for 30 min. The solution was allowed to cool to 23 °C, and the volatiles were removed under high vacuum (30 min). A solution of the potassium silanolate (1.0 mmol, 2 equiv) in the indicated solvent (2 mL) was added, followed by tert-butyl cinnamyl carbonate 255 (0.5
mmol, 1 equiv) in CH2Cl2 (2 mL), and the reaction mixture was stirred at 23 °C for 1 to 2 days. The crude mixture was partitioned between H2O (20 mL) and Et2O (20 mL). The aqueous layer was re-extracted with Et2O (3 × 15 mL). The combined organic layers were dried (Na2SO4) and concentrated under reduced pressure to afford the crude silyl ether, which was purified by flash column chromatography using Et2O in pentane as eluent.

**[(S)-triethyl(1-phenylallyloxy)silane (Table 8, entry 5)]**

Following GP23 using tert-butyl cinnamyl carbonate and potassium triethylsilanolate, the desired product was isolated as colorless oil (100.2 mg, 81%). The enantioselectivity was established after silyl ether cleavage using TBAF in THF: 97% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, t<sub>r</sub> (major) = 26.3 min, t<sub>r</sub> (minor) = 33.1 min).

[α]<sup>25</sup> = -31.2 (c 1.0, CHCl3);

**<sup>1</sup>H NMR (300 MHz, CDCl3)** δ 7.37-7.23 (m, 5H), 6.00-5.88 (m, 1H), 5.28 (d, J = 17.0 Hz, 1H), 5.16 (d, J = 5.9 Hz, 1H), 5.08 (d, J = 10.1 Hz, 1H), 0.95-0.89 (m, 9H), 0.65-0.57 (m, 6H).

All other spectroscopic data were in agreement with the literature: Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* 2005, 127, 14194.

**[(S)-tert-butyldimethyl(1-phenylallyloxy)silane (259)]**

Following GP23 using tert-butyl cinnamyl carbonate and potassium tert-butyldimethylsilanolate, the desired product was isolated as colorless oil (98.1 mg, 79%). The enantioselectivity was established after silyl ether cleavage using TBAF in THF:
98% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, t_r (major) = 26.3 min, t_r (minor) = 33.1 min).

$[\alpha]_D^{25} -34.7$ (c 1.0, CHCl₃);

$^1$H NMR (300 MHz, CDCl₃) δ 7.37-7.24 (m, 5H), 6.00-5.87 (m, 1H), 5.30 (d, J = 17.0 Hz, 1H), 5.18 (d, J = 5.7 Hz, 1H), 5.08 (d, J = 10.2 Hz, 1H), 0.94 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H).


(S)-triisopropyl(1-phenylallyloxy)silane (260)

Following GP 23 using tert-butyl cinnamyl carbonate and potassium triisopropylsilanolate, the desired product was isolated as colorless oil (92.9 mg, 64%). The enantioselectivity was established after silyl ether cleavage using TBAF in THF: 99% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, t_r (major) = 26.3 min, t_r (minor) = 33.1 min).

$[\alpha]_D^{25} -32.0$ (c 0.5, CHCl₃);

$^1$H NMR (300 MHz, CDCl₃) δ 7.38-7.24 (m, 5H), 6.00-5.88 (m, 1H), 5.32-5.25 (m, 2H), 5.07-5.03 (m, 1H), 1.07-0.99 (m, 21H);

$^{13}$C NMR (75 MHz, CDCl₃) δ 144.2, 142.2, 128.1, 127.0, 126.0, 112.8, 76.1, 18.0, 12.3;

IR (thin film) ν 2943, 2866, 1463, 1129, 1062, 882, 698 cm⁻¹;

Anal. calcd for C₁₈H₃₀OSi: C, 74.42; H, 10.41; found C, 74.21; H, 10.52.

GP24: Ir/Phosphoramidite-Catalyzed Synthesis of Allylic Alcohols from tert-Butyl carbonates and Potassium Silanolates and Subsequent Silyl Ether Cleavage:

A Schlenk under argon was charged with [Ir(cod)Cl]₂ (10.1 mg, 15 µmol, 3 mol%) and (S)-(+-)(3,5-Dioxa-4- phosphacyclohepta[2,1-a;3,4-a’]dianaphthalen-4-yl)bis[(1S)-1-phenylethyl]amine 232 (16.2 mg, 30 µmol, 6 mol%). THF (0.5 mL) and n-propylamine
(0.5 mL) were added, and the reaction mixture was stirred at 50 °C for 30 min. The solution was allowed to cool to RT, and the volatiles were removed under high vacuum (30 min). A solution of potassium triethylsilanolate (170 mg, 1.0 mmol, 2 equiv) in CH₂Cl₂ (2 mL) was added, followed by the tert-butyl carbonate (0.5 mmol, 1 equiv) in CH₂Cl₂ (2 mL), and the reaction mixture was stirred at 23 °C. After the reaction was complete (usually 14 h), as determined by TLC, the crude mixture was partitioned between H₂O (20 mL) and CH₂Cl₂ (20 mL). The aqueous layer was re-extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude silyl ether. The ratio of regioisomers was determined by ¹H NMR analysis of the crude sample.

**GP24a: Silyl ether cleavage using TBAF in THF**

The crude mixture was taken up in THF (5 mL), cooled to 0 °C, and treated with TBAF (1 M in THF, 1 mL, 2 equiv). The reaction mixture was stirred for 2 h, then partitioned between H₂O (50 mL) and CH₂Cl₂ (20 mL). The aqueous layer was re-extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude allylic alcohol. Purification by flash column chromatography (10% Et₂O in hexanes or pentane) afforded the desired product. Some allylic alcohols are volatile.

**GP24b: Silyl ether cleavage using 30% aq. NaOH in methanol**

The crude mixture was taken up in methanol (3 mL), cooled to 0 °C, and treated with 0.3 mL 30% aqueous sodium hydroxide. The reaction mixture was stirred for 4 h, then partitioned between H₂O (50 mL) and Et₂O (20 mL). The aqueous layer was re-extracted with Et₂O (3 × 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude allylic alcohol. Purification by flash column chromatography (10% Et₂O in hexanes or pentane) afforded the desired product. Some allylic alcohols are volatile.
(S)-1-phenylprop-2-en-1-ol (Table 9, entry 1)

Following GP24 and GP24b using tert-butyl cinnamyl carbonate and potassium triethylsilanolate, the desired product was isolated as colorless oil (59 mg, 88%). The enantioselectivity was 97% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, $t_\text{r}$(major) = 26.3 min, $t_\text{r}$(minor) = 33.1 min).

$[\alpha]_D^{25}$ -5.9 (c 1.73, PhH);

$^1$H NMR (300 MHz, CDCl$_3$) δ.

All other spectroscopic data were in agreement with the literature: Davis, F. A.; Stringer, O. D.; McCauley Jr., J. P. Tetrahedron 1985, 41, 4747.

(S)-1-(4-chlorophenyl)prop-2-en-1-ol (Table 9, entry 2)

Following GP24 and GP24b using (E)-tert-butyl 3-(4-chlorophenyl)allyl carbonate and potassium triethyl silanolate, the desired product was isolated as a colorless oil (62.4 mg, 74%). The enantioselectivity was 98% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 95:5, flow rate 1 ml/min, $t_\text{r}$(major) = 12.3 min, $t_\text{r}$(minor) = 13.6 min).

$[\alpha]_D^{26}$ +15.3 (c 1.0, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.34-7.27 (m, 4H), 6.15-5.92 (m, 1H), 5.34 (d, J = 17.1 Hz, 1H), 5.23-5.16 (m, 2H), 2.05 (br s, 1H).

All other spectroscopic data were in agreement with the literature: Lehmann, J.; Lloyd-Jones, G. C. Tetrahedron 1995, 51, 8863.
(S)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (Table 9, entry 3)

Following GP24 and GP24b using (E)-tert-butyl 3-(4-(trifluoromethyl)phenyl)allyl carbonate and potassium triethylsilanolate, the desired product was isolated as a colorless oil (78.8 mg, 78%). The enantioselectivity was 98% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, tr (major) = 16.5 min, tr (minor) = 18.3 min).

$[\alpha]_D^{35} +11.7$ (c 0.3, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.63-7.58 (m, 2H), 7.50-7.45 (m, 2H), 6.06-5.92 (m, 1H), 5.36 (d, $J = 17.1$ Hz, 1H), 5.27-5.20 (m, 2H), 2.29 (br s, 1H).

All other spectroscopic data were in agreement with the literature: Lehmann, J.; Lloyd-Jones, G. C. Tetrahedron 1995, 51, 8863.

(S)-1-(3-fluorophenyl)prop-2-en-1-ol (Table 9, entry 4)

Following GP24 and GP24a using (E)-tert-butyl 3-(3-fluorophenyl)allyl carbonate and potassium triethyl silanolate, the desired product was isolated as a colorless oil (48.7 mg, 64%). The enantioselectivity was 98% ee (GC, Supelco $\beta$-dex 120, 95 °C isotherm, 2 mL H$_2$ / min, split ratio 40:1, tr (minor) = 29.6 min, tr (major) = 30.5 min).

$[\alpha]_D^{35} +12.1$ (c 0.56, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.25 (m, 1H), 7.12-7.03 (m, 1H), 7.00-6.91 (m, 1H), 6.03-5.90 (m, 1H), 5.31 (d, $J = 17.1$ Hz, 1H), 5.19 (d, $J = 10.3$ Hz, 1H), 5.15-5.10 (m, 1H), 2.88 (br s, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 162.7 (d, $J = 245.2$ Hz), 144.9 (d, $J = 6.9$ Hz), 139.5, 129.8 (d, $J = 8.1$ Hz), 121.7 (d, $J = 2.6$ Hz), 115.6, 114.3 (d, $J = 21.1$ Hz), 113.1 (d, $J = 22.1$ Hz), 74.6;
Experimental Section

IR (thin film) ν 3339, 1615, 1590, 1448, 1247, 928, 631 cm⁻¹;

HR-EI-MS m/z calcd for C₉H₈FO [M-H]⁺ 151.0554, found 151.0557.

(S)-1-(4-methoxyphenyl)prop-2-en-1-ol (Table 9, entry 5)

Following GP24 and GP24b using (E)-tert-butyl 3-(4-(methoxy)phenyl)allyl carbonate and potassium triethyl silanolate, the desired product was isolated as a colorless oil (61.6 mg, 75%). The enantioselectivity was 95% ee (Chiralcel OD-H, 220 nm, hexanes/iPrOH = 90:10, flow rate 0.7 ml/min, tᵣ(minor) = 10.9 min, tᵣ(major) = 12.5 min).

[α]D²⁶ -6.04 (c 1.0, CHCl₃);

¹H NMR (300 MHz, CDCl₃) δ 7.32-7.27 (m, 2H), 6.91-6.87 (m, 2H), 6.11-5.98 (m, 1H), 5.34 (d, J = 17.1 Hz, 1H), 5.21-5.15 (m, 2H), 3.80 (s, 3H), 1.91 (br s, 1H).

All other spectroscopic data were in agreement with the literature: Evans, P. A.; Leahy, D. K. J. Am. Chem. Soc. 2003, 125, 8974.

(S)-1-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (Table 9, entry 6)

Following GP24 and GP24b using (E)-3-(benzo[d][1,3]dioxol-5-yl)allyl tert-butyl carbonate and potassium triethylsilanolate, the desired product was isolated as a colorless oil (64.1 mg, 72%). The enantioselectivity was 92% ee (Chiralcel OD-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, tᵣ(minor) = 27.5 min, tᵣ(major) = 34.0 min).

[α]D³⁵ +1.01 (c 0.5, CHCl₃);

¹H NMR (300 MHz, CDCl₃) δ 6.88-6.75 (m, 3H), 6.07-5.95 (m, 1H), 5.94 (s, 2H), 5.34 (dd, J = 17.1, 1.4 Hz, 1H), 5.19 (dd, J = 10.3, 1.3 Hz, 1H), 1.93 (br s, 1H).
All other spectroscopic data were in agreement with the literature: Laabs, S., Muench, W.; Bats, J. W.; Nubbemeyer, U. *Tetrahedron* 2002, 58, 1317.

**(S)-1-(3-(diethoxymethyl)phenyl)prop-2-en-1-ol (Table 9, entry 7)**

Following GP24 and GP24a using (E)-tert-butyl 3-(3-(diethoxymethyl)phenyl)allyl carbonate and potassium triethylsilanolate, the desired product was isolated as a colorless oil (82.7 mg, 70%). The enantioselectivity was 98% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, t_r (major) = 15.9 min, t_r (minor) = 21.4 min).

$[\alpha]_D^{25} -0.46$ (c 1, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40-7.26 (m, 4H), 6.02-5.96 (m, 1H), 5.42 (s, 1H), 5.26 (d, $J$ = 17.1 Hz, 1H), 5.13-5.08 (m, 2H), 3.58-3.43 (m, 4H), 2.65 (br s, 1H), 1.17 (t, $J$ = 7.1 Hz, 6 H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.6, 140.1, 139.1, 128.3, 126.2, 125.8, 124.6, 114.9, 101.4, 75.1, 61.1, 15.3;

IR (thin film) $\nu$ 3408, 2976, 2879, 1334, 1050, 910, 631 cm$^{-1}$;

HR-EI-MS $m/z$ calced for C$_{12}$H$_{15}$O$_2$ [M-OEt]$^+$ 191.1067 found 191.1068.

**(S)-1-(thiophen-2-yl)prop-2-en-1-ol (Table 9, entry 8)**

Following GP24 and GP24b using (E)-tert-butyl 3-(thiophen-2-yl)allyl carbonate and potassium triethylsilanolate, the desired product was isolated as a slightly yellow oil (43.5 mg, 62%). The enantioselectivity was 99% ee (Chiralcel OD-H, 220 nm, hexanes/iPrOH = 99:1, flow rate 1 ml/min, t_r (minor) = 27.1 min, t_r (major) = 29.0 min).

$[\alpha]_D^{26} +18.4$ (c 0.5, CHCl$_3$);
**Experimental Section**

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.26 (m, 1H), 7.02-6.96 (m, 2H), 6.19-6.06 (m, 1H), 5.45-5.35 (m, 2H), 5.26 (d, \(J = 10.3\) Hz, 1H), 2.19 (br s, 1H).

All other spectroscopic data were in agreement with the literature: Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, *127*, 6172.

**(S)-1-(thiophen-3-yl)prop-2-en-1-ol (Table 9, entry 9)**

Following GP24 and GP24a using (E)-tert-buty 3-(thiophen-3-yl)allyl carbonate and potassium triethylsilanolate, the desired product was isolated as a slightly yellow oil (47.0 mg, 67%). The enantioselectivity was 98% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 98:2, flow rate 1 ml/min, \(t_r\) (minor) = 27.5 min, \(t_r\) (major) = 36.9 min).

\([\alpha]_D^{25} +13.4\) (c 0.5, CHCl\(_3\));

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.26 (m, 1H), 7.20-7.15 (m, 1H), 7.04 (dd, \(J = 5.0, 1.0\) Hz, 1H), 6.09-5.96 (m, 1H), 5.30 (dd, \(J = 17.1, 1.0\) Hz, 1H), 5.20-5.15 (m, 2H), 3.23 (br s, 1H).

All other spectroscopic data were in agreement with the literature: Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, *127*, 6172.

**(S)-1-(furan-2-yl)prop-2-en-1-ol (Table 9, entry 10)**

Following GP24 and GP24a using (E)-tert-butyl 3-(furan-2-yl)allyl carbonate and potassium triethylsilanolate, the desired product was isolated as a slightly orange oil (31.0 mg, 50%). The enantioselectivity was 97% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 95:5, flow rate 1 ml/min, \(t_r\) (major) = 12.9 min, \(t_r\) (minor) = 14.6 min).

\([\alpha]_D^{26} +1.14\) (c 0.5, CHCl\(_3\));
\[ ^1\text{H NMR} (300\text{ MHz, CDCl}_3) \delta 7.40 (s, 1H), 6.33 (s, 1H), 6.26 (s, 1H), 6.19-6.06 (m, 1H), 5.43 (d, J = 17.2 Hz, 1H), 5.32-5.21 (m, 2H), 2.12 (d, J = 4.3 Hz, 1H). \]

All other spectroscopic data were in agreement with the literature: Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. J. Org. Chem. 1989, 54, 2085.

\[(S)-1-(furan-3-yl)prop-2-en-1-ol\] (Table 9, entry 11)

\[
\begin{align*}
\text{1 equiv} & \quad \text{OCO}_2\text{t-Bu} \\
\text{TESOK} & \quad \text{CH}_2\text{Cl}_2, 23^\circ\text{C} \\
\text{2 equiv} & \quad \text{2} \text{TBAF, THF}
\end{align*}
\]

Following GP24 and GP24a using \((E)\)-\text{tert}-butyl 3-(furan-3-yl)allyl carbonate and potassium triethylsilanolate, the desired product was isolated as a colorless oil (37.2 mg, 60%). The enantioselectivity was 99% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 95:5, flow rate 1 ml/min, \(t_r\) (major) = 11.6 min, \(t_r\) (minor) = 12.9 min).

\([\alpha]_D^{26} 9.2 \text{ (c 0.5, CHCl}_3)\);

\[ ^1\text{H NMR} (300\text{ MHz, CDCl}_3) \delta 7.39 (s, 2H), 6.40 (s, 1H), 6.12-5.99 (m, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.23-5.10 (m, 2H), 2.01 (d, J = 4.6 Hz, 1H). \]

All other spectroscopic data were in agreement with the literature: Ito, M.; Kitahara, S.; Ikariya, T. J. Am. Chem. Soc. 2005, 127, 6172.

\[(S,E)-1-phenylpenta-1,4-dien-3-ol\] (Table 9, entry 12)

\[
\begin{align*}
\text{Ph} & \quad \text{OCO}_2\text{t-Bu} \\
\text{TESOK} & \quad \text{CH}_2\text{Cl}_2, 23^\circ\text{C} \\
\text{2 equiv} & \quad \text{2} \text{equiv} \\
\text{2 equiv} & \quad \text{30\% aq, NaOH, MeOH}
\end{align*}
\]

Following GP24 and GP24b using \text{tert}-butyl \((2E,4E)\)-5-phenylpenta-2,4-dienyl carbonate and potassium triethylsilanolate, the desired product was isolated as a colorless oil (52.1 mg, 65%). The enantioselectivity was 97% ee (Chiralcel OJ-H, 220 nm, hexanes/iPrOH = 93:7, flow rate 0.8 ml/min, \(t_r\) (major) = 15.5 min, \(t_r\) (minor) = 20.3 min).

\([\alpha]_D^{35} 34.1 \text{ (c 0.3, CHCl}_3)\);
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42-7.16 (m, 5H), 6.62 (dd, $J = 15.9$, 0.9 Hz, 1H), 6.25 (dd, $J = 15.9$, 6.4 Hz, 1H), 6.05-5.92 (m, 1H), 5.35 (dt, $J = 17.2$, 1.4 Hz, 1H), 5.21 (dt, $J = 10.4$, 1.3 Hz, 1H), 4.85-4.77 (m, 1H).

All other spectroscopic data were in agreement with the literature: Burgess, K.; Jennings, L. D. J. Am. Chem. Soc. 1991, 113, 6129.

(*)-(hex-1-en-3-yloxy)triethylsilane (Table 9, entry 13)

Following GP23 using (E)-tert-butyl hex-2-enyl carbonate and potassium triethyl silanolate, the desired product was isolated after 2 days reaction time at 23 °C. Purification by flash column chromatography (1% Et$_2$O in pentane) afforded the desired product as colorless oil (139.4 mg, 65%).

$[\alpha]_D^{26} = -4.6$ (c 2.0, CHCl$_3$);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.86-5.73 (m, 1H), 5.13 (d, $J = 17.1$ Hz, 1H), 5.01 (dd, $J = 10.3$, 1.0 Hz, 1H), 4.10-4.01 (m, 1H), 1.60-1.29 (m, 4H), 0.98-0.89 (m, 12H), 0.64-0.53 (m, 6H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.8, 113.4, 73.7, 40.5, 18.6, 14.2, 7.0, 5.1;

IR (thin film) $\nu$ 2957, 2877, 1459, 1097, 1005, 920 cm$^{-1}$;

Anal. calcd for C$_{12}$H$_{26}$OSi: C, 67.22; H, 12.22; found C, 67.08; H, 11.96.

To measure the ee of the product, it was converted to the corresponding benzoyl ester (according to a literature procedure: Martin, V. S.; Ode, J. M.; Palazon, J. M.; Soler, M. A. Tetrahedron: Asymmetry 1992, 3, 573) by cleavage of the TES ether and treatment with benzoyl chloride.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06 (m, 2H), 7.50 (m, 3H), 5.90 (m, 1H), 5.53 (m, 1H), 5.28 (m, 2H), 1.75 (m, 2H), 1.45 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H). HPLC analysis indicated that the enantiomeric excess of the ester was 95% (Chiralcel OB, 220 nm, hexanes, flow rate 0.8 ml/min, $t_r$(minor) = 9.40 min, $t_r$(major) = 11.8 min).
8.10. *Iridium-Catalyzed Synthesis of Primary Allylic Amines From Allylic Alcohols: Sulfamic Acid as an Ammonia Equivalent*

**GP25: Synthesis of the Phosphoramidites 277, 278, 286**

A Schlenk flask under argon was charged with the diol (1 equiv), PCl₃ (15 equiv) and a catalytic amount of N-methylpyrrolidone (0.03 equiv) were added and the reaction mixture was heated at 50 °C during 30 min. The initially heterogeneous mixture turned into a brownish homogenous solution. After cooling to 23 °C, the excess PCl₃ was evaporated in vacuo, 1 mL toluene was added to azeotropically remove remaining PCl₃. The resulting phosphochloridite (air-and moisture-sensitive!) was redissolved in 25 mL THF.

In a separate Schlenk flask under argon, the amine (1.2 equiv) dissolved in 25 mL THF was deprotonated at -78 °C by the slow addition of n-BuLi (1.1 equiv, 1.6M solution in hexanes). The resulting deep blue solution was continued to stir at -78 °C for 1 hour before the phosphochloridite solution was slowly transferred via cannula. The resulting mixture was stirred at -78°C, then warmed to 23°C and continued to stir during 8 h. After completion of the reaction, as determined by TLC, the solvents were evaporated in vacuo. Purification of the residue by flash chromatography on silica gel using hexanes/toluene as eluent afforded the desired product as a white foam.

((3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,j]azepine 277

Prepared according to GP25 using 2.23 g (12.0 mmol) 2,2'-biphenol. Yield: 1.35 g (3.31 mmol, 28%) (off-white powder). Keep under inert atmosphere for long-term storage. **mp 159 °C**;
$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.38 (m, 2H), 7.22-7.27 (m, 4H), 7.10-7.20 (m, 8H), 6.98-7.08 (m, 2H), 6.96 (s, 2H);
$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 150.6, 142.4, 135.8, 131.3, 130.4, 130.3, 129.4, 128.9, 128.8, 128.7, 126.4, 124.2, 121.9;
$^{31}$P-NMR (121 MHz, CDCl$_3$) 137.9;
IR (neat) v 3062, 3025, 1486, 1434, 1196, 1095, 984, 890, 848, 759, 746;
HR-MALDI-MS $m/z$ calcd for C$_{26}$H$_{18}$N$_2$O$_2$P $[M+H]^+$ 408.1148, found 408.1149.

(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-10,11-dihydro-dibenzo-[b,f]azepine 278

Prepared according to GP25 using 834 mg (4.48 mmol) 2,2’-biphenol. Yield: 568 mg (1.39 mmol, 31%) (off-white powder). Keep under inert atmosphere for long-term storage.
mp 145 °C;
$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.43-7.6.94 (m, 16H), 3.77-3.61 (m, 2H), 3.01-2.93 (m, 2H);
$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 150.5, 142.3, 136.8, 130.2, 130.0, 129.9, 128.8, 127.9, 126.5, 126.2, 124.2, 121.2, 31.6;
$^{31}$P-NMR (121 MHz, CDCl$_3$) 136.4;
IR (neat) v 3061, 3029, 1486, 1436, 1184, 1094, 990, 880, 842, 699;
HR-MALDI-MS $m/z$ calcd for C$_{26}$H$_{20}$N$_2$O$_2$P $[M+H]^+$ 410.1304 found 410.1303.
(S)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-dibenza-[b,f]-azepine 286

Prepared according to GP25 using 300 mg (1.05 mmol) (S)-BINOL. Yield: 239 mg (0.47 mmol, 45%) (off-white powder). Keep under inert atmosphere for long-term storage.

mp 246 °C;

$\alpha$D$^25 +313.6$ (c 1.07, CHCl3);

$^1$H-NMR (500 MHz, CDCl3) δ 7.96 (d, $J = 8.8$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.73 (d, $J = 8.1$ Hz, 1 H), 7.60 (dd, $J = 8.8$, 0.7 Hz, 1H), 7.41 (d, $J = 8.7$ Hz, 1 H), 7.38-7.31 (m, 2H), 7.23-7.13 (m, 2H), 7.19-7.13 (m, 6H), 7.11-7.07 (m, 1H), 6.96 (d, $J = 11.6$ Hz, 1H), 6.92-6.87 (m, 2H), 6.84 (dd, $J = 8.8$, 0.5 Hz, 1H), 6.53-6.49 (m, 2H);

$^{13}$C-NMR (125 MHz, CDCl3) δ 149.9, 149.9, 148.7, 143.0, 142.8, 142.5, 135.4, 135.2, 132.8, 132.1, 131.5, 131.4, 131.3, 130.2, 130.1, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 128.3, 127.8, 126.8, 126.7, 126.1, 126.0, 125.6, 124.8, 124.2, 122.1, 121.5, 121.1;

$^{31}$P-NMR (121 MHz, CDCl3) 138.0;

IR (neat) ν 3057, 3023, 1590, 1484, 1236, 1201, 1070, 979, 938, 800, 767;

HR-MALDI-MS m/z calcd for C$_{34}$H$_{22}$N$_2$O$_2$P [M+H]$^+$ 508.1461, found 508.1463.

GP 26: Substrate, Solvent, Ligand Screening

A Schlenk flask under argon was charged with [IrCl(cod)]$_2$ (10.1 mg, 15 µmol, 3 mol %) and the corresponding ligand (30 µmol, 6 mol %). 2 mL (0.25 M) solvent were added and the reaction mixture was stirred at 23 °C for 15 min. The allylic carbonate resp. alcohol (0.50 mmol, 1 equiv) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 equiv). The resulting reaction mixture was stirred at 23 °C for 24 hours. Conversion was checked by disappearance of the starting material on TLC and/or by measuring $^1$H-NMR of an aliquot taken from the reaction mixture. In cases, in which the conversion was above 50%, triethylamine (202 mg, 2.00 mmol, 4 equiv) and
freshly distilled benzoyl chloride (141 mg, 1.00 mmol, 2 equiv) were added to the reaction mixture and stirring was continued during 4 hours at 23 °C. Subsequently, the reaction mixture was partitioned between 10 mL CH₂Cl₂ and 10 mL H₂O. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude allylic benzamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded the desired benzamide.

**GP27: Iridium-Catalyzed Allylic Amination with Sulfamic Acid**

A Schlenk flask under argon was charged with [IrCl(cod)]₂ (10 mg, 15 μmol, 1.5 mol %) and ligand (3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en-)dibenzo[6,7]azepine 277 (12 mg, 30 μmol, 3 mol %). 2 mL N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. The allylic alcohol (1.00 mmol, 1 equiv) was added via syringe followed by the addition of solid sulfamic acid (97 mg, 1.00 mmol, 1 equiv). The resulting reaction mixture was heated to 50°C. After completion of the reaction (usually 6-7 h), as determined by TLC, the solvent was evaporated at high vacuum. The resulting brown residue was dissolved in 10 mL CH₂Cl₂ and 10 ml sat. aqueous NaHCO₃ solution and stirred for 10 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude allylic amine. The ratio of regioisomers was determined by ¹H NMR analysis of the unpurified sample. Purification of the residue by flash chromatography on basic or neutral alumina using CH₂Cl₂/MeOH as eluent afforded the desired amine. As some amines proved to be unstable and/or volatile, they were precipitated by addition of 2M HCl in Et₂O and stored as their hydrochloride salts.

**5-Phenylpent-1-en-3-amine hydrochloride (Table 12, entry 1)**

```
[IrCl(cod)]₂(1.5 mol%) + H₃N⁺SO₃⁻ (1 equiv) → [IrCl(cod)]₂(1.5 mol%) + H₃N⁺SO₃⁻ (1 equiv) → PhCH=CHCH₂CH₃ + H₂O
```

Prepared according to GP27. Off-white solid. Yield: 162 mg (0.82 mmol, 82%).
mp 168 °C;

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.67 (br. s, 3H), 7.31-7.19 (m, 5H), 5.93 (ddd, $J$ = 17.3, 10.5, 7.7 Hz, 1H), 5.47 (d, $J$ = 17.3 Hz, 1H), 5.36 (d, $J$ = 10.5 Hz), 3.74 (br. s, 1H), 2.82-2.64 (m, 2H), 2.32-2.04 (m, 2H);

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 139.8, 132.9, 128.4, 128.3, 126.2, 121.2, 54.1, 34.7, 31.4;

IR (neat) $\nu$ 2882 (br), 2045, 1601, 1511, 1453, 988, 936, 765, 745;

HR-ESI-MS $m/z$ calcd for C$_{11}$H$_{13}$ [M-NH$_3$]$^+$ 145.1012, found 145.1012.

Anal. calcd for C$_{11}$H$_{16}$NCl: C, 66.83; H, 8.16; N, 7.08 found C, 66.54; H, 8.09; N, 6.81.

$^{N}$-(5-phenylpent-1-en-3-yl)-benzamide (Table 12, entry 2)

A Schlenk flask under argon was charged with [IrCl(cod)]$_2$ (10 mg, 15 µmol, 3 mol %) and ligand (3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']diphenyl-4-en)-dibenzo[h,f]azepine 277 (12 mg, 30 µmol, 6 mol %). 2 mL N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. 5-phenylpent-1-en-3-ol 273 (81 mg, 0.50 mmol, 1 equiv) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 equiv). The resulting reaction mixture was heated to 50°C. Conversion was checked by disappearance of the starting material on TLC and/or by measuring $^1$H-NMR of an aliquot taken from the reaction mixture. After completion of the reaction (usually 3-4 h), triethylamine (202 mg, 2.00 mmol, 4 equiv) and freshly distilled benzoylchloride (141 mg, 1.00 mmol, 2 equiv) were added to the reaction mixture and stirring was continued during 4 hours at 23 °C. Subsequently, the reaction mixture was partitioned between 10 mL CH$_2$Cl$_2$ and 10 mL H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the crude allylic benzamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded $^{N}$-(5-phenylpent-1-en-3-yl)-benzamide (97 mg, 0.37 mmol, 73%) as an off-white solid.
Experimental Section

mp 131 °C;

$^1$H-NMR (300 MHz, CDCl$_3$) δ 7.71-7.68 (m, 2H), 7.52-7.37 (m, 3H), 7.31-7.17 (m, 5H), 6.11 (d, $J = 8.2$ Hz, 1H), 5.90 (ddd, $J = 17.2$, 10.4, 5.6 Hz, 1H), 5.24 (dd, $J = 17.2$, 1.2 Hz, 1H), 5.18 (dd, $J = 10.4$, 1.2 Hz, 1H), 4.76 (br. quintet, 1H), 2.75 (t, $J = 2.9$ Hz, 2H), 2.10-1.90 (m, 2H);

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ 166.7, 141.5, 138.0, 134.5, 131.4, 128.5, 128.4, 126.8, 126.0, 115.4, 51.6, 36.3, 32.1;

IR (neat) v 3326, 2946, 2979, 2862, 1633, 1526, 1487, 1334, 1292, 920, 748, 698;

HR-MALDI-MS m/z calcd for C$_{18}$H$_{19}$NO [M+H]$^+$ 266.1539, found 266.1538.

tert-Butyl 5-phenylpent-1-en-3-ylcarbamate (Table 12, entry 3)

A Schlenk flask under argon was charged with [IrCl(cod)]$_2$ (10 mg, 15 µmol, 3 mol %) and ligand (3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,f]azepine 277 (12 mg, 30 µmol, 6 mol %). 2 mL N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. 5-phenylpent-1-en-3-ol 273 (81 mg, 0.50 mmol, 1 equiv) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 equiv). The resulting reaction mixture was heated to 50°C. Conversion was checked by disappearance of the starting material on TLC and/or by measuring $^1$H-NMR of an aliquot taken from the reaction mixture. After completion of the reaction (usually 3-4 h), the reaction mixture was carefully concentrated and cooled to 23 °C. The resulting brownish oil was redissolved in 3 mL CH$_2$Cl$_2$ and at 0 °C, 202 mg (1.00 mmol, 2 equiv) Boc$_2$O and a catalytic amount (ca. 10 mg) of the phase transfer reagent n-Bu$_4$HSO$_4$ was added. At 0 °C, the reaction mixture was treated with 3 mL of a 0.5 M aqueous NaOH solution and warmed to 23 °C during 6 hours. Subsequently, the reaction mixture was partitioned between 10 mL CH$_2$Cl$_2$ and 10 mL H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the crude Boc-protected
amine. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded tert-Butyl 5-phenylpent-1-en-3-ylcarbamate (93 mg, 0.36 mmol, 71%) as an off-white solid.

mp 53 °C;

$^1$H-NMR (300 MHz, CDCl$_3$) δ 7.17-7.31 (m, 5H), 5.79 (ddd, $J = 16.5$, 10.3, 5.6 Hz, 1H), 5.10-5.21 (m, 2H), 4.49 (br. s, 1H), 4.16 (br. s, 1H), 2.62-2.96 (m, 2H), 1.78-1.89 (m, 2H), 1.46 (s, 9H);

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ 155.2, 141.5, 138.6, 128.3, 128.2, 125.8, 114.6, 79.3, 52.6, 37.0, 32.2, 28.6;

IR (neat) v 3364, 3028, 2979, 2945, 1681, 1517, 1330, 1243, 1172, 1045, 1030, 926, 752, 701;

HR-ESI-MS $m/z$ calcd for C$_{16}$H$_{23}$N$_2$O$_2$Na [MNa]$^+$ 284.1621, found 284.1623.

2,2,2-Trifluoro-N-(5-phenylpent-1-en-3-yl)-acetamide (Table 12, entry 4)

A Schlenk flask under argon was charged with [IrCl(cod)]$_2$ (10 mg, 15 µmol, 3 mol %) and ligand (3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']diphenyl-4-en)-dibenzo[h,f]azepine 277 (12 mg, 30 µmol, 6 mol %). 2 mL N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. 5-phenylpent-1-en-3-ol 273 (81 mg, 0.50 mmol, 1 equiv) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 equiv). The resulting reaction mixture was heated to 50°C. Conversion was checked by disappearance of the starting material on TLC and/or by measuring $^1$H-NMR of an aliquot taken from the reaction mixture. After completion of the reaction (usually 3-4 h), the reaction mixture was carefully concentrated and cooled to 23 °C. The resulting brownish oil was redissolved in 2 mL CH$_2$Cl$_2$ and at 0 °C, 315 mg trifluoroacetic anhydride (1.50 mmol, 3 equiv) and 276 mg solid, anhydrous K$_2$CO$_3$ (2.00 mmol, 4 equiv) were added. The reaction mixture was continued to stir during 8 hours at 23 °C. Subsequently, it was partitioned between 10 mL CH$_2$Cl$_2$ and 10 mL H$_2$O. The
aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the crude trifluoroacetamide. Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded 2,2,2-trifluoro-N-(5-phenylpent-1-en-3-yl)-acetamide (91 mg, 0.36 mmol, 71%) as a yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$) δ 7.13-7.99 (m, 5H), 6.14 (br. s, 1H), 5.79 (ddd, $J$ = 17.0, 10.7, 6.0 Hz, 1H), 5.19-5.25 (m, 2H), 4.46-4.55 (br. quintet, 1H), 2.67 (t, $J$ = 7.8 Hz, 2H), 1.89-2.01 (m, 2H);

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ 156.5 (q, $J$ = 36.9 Hz), 140.6, 135.9, 128.6, 128.3, 126.3, 117.0, 115.8 (q, $J$ = 288.3 Hz), 52.1, 35.7, 31.9;

$^{19}$F-NMR (282 MHz, CDCl$_3$) -75.7;

IR (neat) ν 3293, 3088, 2928, 1698, 1554, 1206, 1181, 747, 724, 698;

HR-ESI-MS $m/z$ calcd for C$_{13}$H$_{14}$NOF$_3$Na$^+[MNa]^+$ 280.0919, found 280.0919.

1-Phenylprop-2-en-1-amine hydrochloride (Table 12, entry 5)

Prepared according to GP27. Off-white solid. Yield: 132 mg (0.78 mmol, 78%);

$^1$H-NMR (300 MHz, CD$_3$OD) δ 7.43-7.57 (m, 5H), 6.19 (ddd, $J$ = 17.3, 10.6, 6.5 Hz, 1H), 5.51 (dd, $J$ = 10.6, 1.0 Hz, 1H), 5.44 (dd, $J$ = 17.3, 1.3 Hz, 1H), 5.04 (d, $J$ = 6.5, 1H), 4.55 (br. s, 3H).

For other spectroscopic data see: A. Zwierzak, A. Napieraj, Synthesis, 1999, 930.

1-Cyclohexylprop-2-en-1-amine hydrochloride (Table 12, entry 6)

Prepared according to GP27. White flakes. Yield: 132 mg (0.75 mmol, 75%);
mp 231 °C;

$^1$H-NMR (300 MHz, CDCl$_3$) δ 8.54 (br. s, 3H), 5.91-5.79 (ddd, J = 17.3, 9.6, 6.9 Hz, 1H), 5.42 (d, J = 17.3 Hz, 1H), 5.37 (d, J = 9.6 Hz, 1H); 3.51-3.46 (m, 1H), 1.89-1.61 (m, 6H), 1.45-1.03 (m, 5H);

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ 131.9, 121.0, 59.5, 40.3, 29.1, 28.1, 25.6;

IR (neat) ν 3274, 2921, 2851, 1629, 1600, 1510, 1447, 993, 933, 918, 687;

HR-ESI-MS m/z calcd for C$_{11}$H$_{13}$ [MH-NH$_3$]$^+$ 145.1012, found 145.1012.

1-(Benzyloxy)but-3-en-2-amine hydrochloride (Table 12, entry 7)

\[
\begin{align*}
\text{BnO-} & \quad \text{OH} \quad \text{+ H}_3\text{N-SO}_3^- \\
\text{1 equiv} & \quad \text{1 equiv} \\
\text{DMF, 50 °C, 3 h} & \quad \text{[IrCl(cod)]}_2 (1.5 \text{ mol%}) \text{ phosphoramidite 277 (3 mol%)} \\
\text{BnO-} & \quad \text{NH}_3 \text{Cl} \\
\end{align*}
\]

Prepared according to GP27. White powder. Yield: 152 mg (0.71 mmol, 71%);

$^1$H-NMR (300 MHz, CD$_3$OD) δ 7.39-7.26 (m, 5H), 5.88 (m, 1H), 5.41 (d, J = 17.4 Hz, 1H), 5.37 (d, J = 11.2 Hz, 1H), 4.59 (s, 2H), 3.87 (m, 1H), 3.64 (dd, J = 10.1, 3.9 Hz, 1H), 3.49 (dd, J = 10.1, 7.8 Hz, 1H).


Hexa-1,5-dien-3-amine hydrochloride (Table 12, entry 8)

\[
\begin{align*}
\text{OH} & \quad \text{+ H}_3\text{N-SO}_3^- \\
\text{1 equiv} & \quad \text{1 equiv} \\
\text{DMF, 50 °C, 3 h} & \quad \text{[IrCl(cod)]}_2 (1.5 \text{ mol%}) \text{ phosphoramidite 277 (3 mol%)} \\
\text{NH}_3 \text{Cl} & \quad \\
\end{align*}
\]

Prepared according to GP27. Off-white solid. Yield: 101 mg (0.75 mmol, 75%);

$^1$H-NMR (300 MHz, D$_2$O) δ 5.64-5.86 (m, 2H), 5.14-5.34 (m, 4H), 3.81 (q, J = 6.7 Hz, 1H), 2.31-2.46 (m, 2H).

**Test for Enantiospecificity: (R)-N-Benzoyl-l-phenyl-2-propenylamine (286)**

\[
\begin{align*}
\text{OH} & \quad + \quad H_3N-SO_3^- \\
285 & \quad \text{1 equiv} & \quad 1 \equiv \text{equiv} \\
\text{1. [IrCl(coe)₂]₂ (3 mol\%)} & \quad \text{phosphoramidite 277 (6 mol\%)} \\
\text{DMF, 23 °C, 24 h} & \quad \text{2. BzCl, Et₃N, CH₂Cl₂} \\
\text{NHBz} & \quad 286
\end{align*}
\]

A Schlenk flask under argon was charged with [IrCl(coe)₂]₂ (13.1 mg, 15 μmol, 3 mol %) and ligand (3,5-Dioxo-4-phospha-cyclohepta[2,1-a;3,4-a']diphenyl-4-en)-dibenzo[b,f]azepine 277 (12 mg, 30 μmol, 6 mol %). 2 mL N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. Optically active (R)-1-phenylprop-2-en-1-ol 285 (67 mg, 0.50 mmol, 1 equiv, 88% ee) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 equiv). The resulting reaction mixture was stirred at 23°C for 24 hours. After completion of the reaction (checked by TLC), triethylamine (202 mg, 2.00 mmol, 4 equiv) and freshly distilled benzoylchloride (141 mg, 1.00 mmol, 2 equiv) were added to the reaction mixture and stirring was continued during 4 hours at 23 °C. Subsequently, the reaction mixture was partitioned between 10 mL CH₂Cl₂ and 10 mL H₂O. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude allylic benzamide.

Purification of the residue by flash chromatography on silica gel using hexanes/EtOAc as eluent afforded (R)-N-benzoyl-1-phenyl-2-propenylamine 286 (84 mg, 0.36 mmol, 71%) as an off-white solid. The enantioselectivity was 44% ee (Chiralpak AD-H, 220 mm, hexanes/iPrOH = 95:5, flow rate 1.0 ml/min, tₘ (minor) = 23.9 min, tₘ (major) = 40.9 min).

\(^1\text{H-NMR (300 MHz, CDCl}_3\) δ 7.79-7.28 (m, 10H), 6.74 (d, J = 7.5 Hz, 1H), 6.08 (ddd, J = 15.7, 10.0, 5.5 Hz, 1H), 5.85-5.78 (m, 1H), 5.30 (m, 1H), 5.25 (d, J = 11.5 Hz, 1H).

(S)-1-Cyclohexylprop-2-en-1-amine hydrochloride (288)

A Schlenk flask under argon was charged with [IrCl(coe)₂]₂ (13.1 mg, 15 µmol, 3 mol %) and ligand (S)-(+-)(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-dibenzo-[b,f]-azepine 289 (16.2 mg, 30 µmol, 6 mol %). 2 mL N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. Racemic 1-cyclohexylprop-2-en-1-ol 287 (70 mg, 0.50 mmol, 1 equiv) was added via syringe followed by the addition of solid sulfamic acid (49 mg, 0.50 mmol, 1 equiv). The resulting reaction mixture was stirred at 23°C for 24 hours. After completion of the reaction, as determined by TLC, the solvent was carefully evaporated at high vacuum. The resulting brown residue was dissolved in 10 mL CH₂Cl₂ and 10 mL saturated aqueous NaHCO₃ solution and stirred for 10 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the crude allylic amine. The ratio of regioisomers was determined by ¹H NMR analysis of the unpurified sample. Purification of the residue by flash chromatography on neutral alumina using CH₂Cl₂/MeOH as eluent afforded the desired amine which was immediately treated with 2M HCl in diethylether. The corresponding hydrochloride salt 288 precipitated as a white solid in 70 % yield (61 mg, 0.35 mmol).

Determination of the absolute configuration

To determine the absolute configuration, 50 mg (0.28 mmol, 1 equiv) of the amine hydrochloride 288 were suspended in 1 mL Et₂O and treated with 0.5 mL (10 equiv) 6 M KOH. After stirring at 23 °C for 30 min, the mixture was partitioned between Et₂O and
H₂O. The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with brine and dried over MgSO₄. The mixture was carefully (!) concentrated under reduced pressure to obtain a brownish oil that was immediately dissolved in 2 mL CH₂Cl₂ and treated with 115 mg (1.14 mmol, 4 equiv) triethylamine and 103 mg (0.57 mmol, 2 equiv) freshly distilled trichloroacetyl chloride. After 3 h stirring at 23 °C, the reaction mixture was partitioned between CH₂Cl₂ and H₂O. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were washed with brine and dried over MgSO₄. Concentration of the mixture under reduced pressure yielded in a brownish residue that was subjected to chromatography on silica gel (30:1 hexanes/EtOAc) to obtain 36 mg (0.13 mmol, 45%) 2,2,2-trichloro-N-(1-cyclohexylallyl)-acetamide as a colorless solid. The optical rotation was measured: [α]₀°₂⁵⁻26.5 (c 0.45, CHCl₃); Comparison to the literature [α]₀°₂⁵⁺30.7 (c 0.42, CHCl₃) (Anderson, C. E.; Overman, L. E. J. Am. Chem. Soc. 2003, 125, 12412) allowed to establish the absolute configuration for the product as: (S)-2,2,2-Trichloro-N-(1-cyclohexylallyl)acetamide.

¹H-NMR (300 MHz, CDCl₃) δ 6.58 (br s, 1H), 5.79 (ddd, J = 17.1, 10.5, 6.0 Hz, 1H), 5.19-5.25 (m, 2H), 4.27 (dd, J = 14.8, 6.2 Hz, 1H), 1.65-1.81 (m, 5H), 1.51-1.60 (m, 1H), 0.95-1.30 (m, 5H).

For other spectroscopic data see: (Anderson, C. E.; Overman, L. E. J. Am. Chem. Soc. 2003, 125, 12412)

**Determination of enantioselectivity**

For determination of the enantioselectivity, the allylic amination procedure described above was repeated but it differed in the workup: Thus, the resulting amine was directly protected by the addition of triethylamine (202 mg, 2.00 mmol, 4 equiv) and freshly distilled benzoylchloride (141 mg, 1.00 mmol, 2 equiv). The mixture was stirred at 23 °C for 3 hours, then partitioned between CH₂Cl₂ and H₂O. The aqueous phase was extracted
three times with CH₂Cl₂. The combined organic layers were washed with brine and dried over MgSO₄. Concentration of the solvents under reduced pressure and purification of the residue by silica gel chromatography yielded a white solid.

[α]D²⁵ -35.1 (c 0.53, CHCl₃); N-(1-cyclohexylallyl)-benzamide was obtained (67 mg, 0.28 mmol, 55% yield) after chromatographical purification in 70% ee as determined by HPLC analysis (Chiralcel OD-H, 95:5 hexanes/i-PrOH, flow: 1 mL/min, 220 nm), t₂ 22.6 (minor) t₂ 27.4 (minor).

When the hydrochloride salt obtained from the allylic amination was triturated with Et₂O, enantioselectivity could be upgraded to 93% ee. Enantioselectivity was determined after derivatisation to the corresponding benzamide in an analogous way.


**Detailed description of the spectroscopic experiments.**

**A) Iridium-catalyzed allylic amination using 1 equivalent sulfamic acid**

\[
\text{[Ir(cod)Cl]₂} + \text{5-Phenylpent-1-en-3-ol} + \text{H₃N-SO₃}^- \rightarrow \text{N-(1-cyclohexylallyl)-benzamide} + \text{HMDSO}^+ \quad \text{(1)}
\]

A Schlenk flask under argon was charged with [Ir(cod)Cl₂] (10 mg, 15 μmol, 1.5 mol %) and ligand (3,5-Dioxo-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,h]azepine 277 (12 mg, 30 μmol, 3 mol %). 1.5 mL d⁷-DMF, 50 °C, 3 h

100% conversion

\[
\delta (H-3) 3.88 ppm \quad 279
\]

A Schlenk flask under argon was charged with [Ir(cod)Cl₂] (10 mg, 15 μmol, 1.5 mol %) and ligand (3,5-Dioxo-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[b,h]azepine 277 (12 mg, 30 μmol, 3 mol %). 1.5 mL d⁷-DMF, 50 °C, 3 h

100% conversion

\[
\delta (H-3) 3.88 ppm \quad 279
\]
5-Phenylpent-1-en-3-ol (273):

$^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 7.32-7.17 (m, 5H), 5.92 (ddd, $J = 17.4$, 10.4, 6.1 Hz, 1H), 5.26 (d, $J = 17.4$ Hz, 1H), 5.15 (d, $J = 10.4$ Hz, 1H), 4.14 (br quintet, $J = 5.9$ Hz, 1H), 2.81-2.64 (m, 2H), 1.86 (q, $J = 7.5$ Hz, 2H), 1.49 (d, $J = 4.0$ Hz, 1H).


$^1$H-NMR (d$_7$-DMF, 300 MHz) $\delta$ 7.31-7.14 (m, 5H), 5.91 (ddd, $J = 17.4$, 10.4, 5.6 Hz, 1H), 5.20 (d, $J = 17.4$ Hz, 1H), 5.02 (d, $J = 10.4$ Hz), 4.83 (d, $J = 4.7$ Hz), 4.04 (br. quintet, $J = 5.6$ Hz, 1H), 2.78-2.60 (m, 2H), 1.78-1.71 (m, 2H).

Spectrum measured after 22 min
spectrum measured after 1 h 30 min

spectrum measured after 2 h 30 min

spectrum measured after 3 h
Experimental Section

spectrum measured after 20 h (no further change)

B) Iridium-catalyzed allylic amination using 2 equivalents sulfamic acid

A Schlenk flask under argon was charged with [IrCl(cod)]$_2$ (10 mg, 15 µmol, 1.5 mol %) and ligand (3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]diphenyl-4-en)-dibenzo[h,j]azepine 277 (12 mg, 30 µmol, 3 mol %). 1.5 ml d$_7$-N,N-dimethylformamide were added and the reaction mixture was stirred at 23 °C for 15 min. 5-Phenylpent-1-en-3-ol 273 (81 mg, 0.50 mmol, 1 equiv) was added via syringe followed by the addition of solid sulfamic acid (97 mg, 1.00 mmol, 2 equiv). The resulting reaction mixture was heated to 50°C. At regular intervals, aliquots à 100 µL were taken from the reaction mixture and $^1$H-NMR spectra were measured. In the spectra the relevant range (δ 6.49-3.21 ppm) is depicted.
spectrum measured after 1 hour

spectrum measured after 2 hours 30 min

spectrum measured after 4 hours
Experimental Section

spectrum measured after 9 hours

spectrum measured after 12 hours

spectrum measured after 23 hours
C) Sulfation of alcohol 273 using 2 equivalents sulfamic acid

\[
\text{PhCH} = \text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH} + \text{H}_2\text{N}-\text{SO}_3 \xrightarrow{\text{d}-\text{DMF, 50 °C, 8 h}} \text{PhCH} = \text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{SO}_3\text{NH}_4^+ \tag{2}
\]

A Schlenk flask under argon was charged with 5-Phenylpent-1-en-3-ol 273 (81 mg, 0.50 mmol, 1 equiv). 0.7 mL d7-N,N-dimethylformamide were added followed by the addition of solid sulfamic acid (97 mg, 1.00 mmol, 2 equiv). The resulting homogenous reaction mixture was heated to 50 °C. At regular intervals, aliquots 100 μL were taken from the reaction mixture and 1H-NMR spectra were measured. In the spectra the relevant range (δ 6.49-3.21 ppm) is depicted.
spectrum measured after 3 hours

spectrum measured after 5 hours

spectrum measured after 6 hours
**D) Sulfation of alcohol 273 using 2 equivalents SO$_3$-DMF**

A Schlenk flask under argon was charged with 5-Phenylpent-1-en-3-ol 273 (81 mg, 0.50 mmol, 1 equiv). 0.7 mL d$_7$-$\text{N},\text{N}$-dimethylformamide were added followed by the addition of solid SO$_3$-DMF (153 mg, 1.00 mmol, 1 equiv). The resulting homogenous reaction mixture was heated to 50°C. After one hour reaction time, an aliquot à 100 µl was taken from the reaction mixture and a $^1$H-NMR spectrum was measured.
E) Sulfamation of the amine 279 with 2 equiv SO₃-DMF

\[
\begin{align*}
\text{H} & \quad \text{NH}_3 \\
\text{H} & \quad \text{NH}_3 \\
& \quad + \quad \text{SO}_3 \cdot \text{DMF} \\
\text{H} & \quad \text{NHOSO}_3\text{H} \\
\end{align*}
\]

A Schlenk flask under argon was charged with 5-Phenylpent-1-en-3-amine 279 (81 mg, 1.00 mmol, 1 equiv). 0.7 ml d⁷-Ν,Ν-dimethylformamide were added followed by the addition of solid SO₃-DMF (153 mg, 0.50 mmol, 1 equiv). The resulting homogenous reaction mixture was heated to 50°C. At regular intervals, aliquots à 100 µL were taken from the reaction mixture and ¹H-NMR spectra were measured. In the spectra the relevant range (δ 6.49-3.21 ppm) is depicted. The analysis was complicated due to the formation of various side products.

[Graph showing the ¹H-NMR spectrum measured after 1 hour 30 min]
spectrum measured after 20 hours
Curriculum Vitae

Born December 21, 1977 in Karlsruhe, Germany.

1984-1988  Primary School, Bad Bergzabern, Germany
1988-1997  Gymnasium Bad Bergzabern, Germany
30 June, 1997  Abitur (final degree), Gymnasium Bad Bergzabern, Germany
10/ 1998 – 04/2003  Undergraduate studies in chemistry, ETH Zurich
10/ 1999  First pre-diploma, ETH Zurich
10/ 2000  Second pre-diploma, ETH Zurich
02/ 2001 – 07/ 2001  Erasmus Exchange Program in Ecole Polytechnique, Palaiseau, France
Advanced laboratory course in organometallic chemistry in the group of Prof. François Mathey, Ecole Polytechnique, Palaiseau
07/ 2001 – 09/ 2001  Work on the synthesis of novel heterocyclophanes in the group of Prof. Pascal Le Floch, Ecole Polytechnique, Palaiseau
10/ 2001 – 02/ 2002  Advanced laboratory course in organic chemistry in the group of Prof. Dieter Seebach, ETH Zurich
03/2002 – 05/2002  Work on optimisation of an asymmetric transfer hydrogenation process under the supervision of Dr. Kai Exner, BASF AG, Ludwigshafen/Rhein, Germany
17 April, 2003  Diploma, ETH Zurich, Switzerland

During my Ph.D. studies, I was teaching assistant for two introductory-level organic chemistry courses, four times teaching assistant for organic chemistry exercises and lectures as well as responsible for the supervision of two undergraduate students in the context of their “Semesterarbeit”.

Zürich, April 2007  Christian Defieber
Appendix: NMR Spectra of New Compounds
Appendix

MeO

Me

Me

ppm (f1)

ppm (f2)

200 150 100 50 0
O

Ph

(\text{f})

(\text{D Co})

ppm (fT)

ppm (fT)

ppm (fT)

ppm (fT)
Appendix

![Chemical Structures]

- Ph₂N−C=O−Me
- MeO−C=O−Me

![NMR Spectra]

- ppm scale for each spectrum, ranging from 0 to 200
- Specific resonances at different ppm values for each compound
Appendix
Appendix

Ph
CF₃
CHO

10 0 ppm

200 ppm

0 ppm
Appendix A63

\[
\begin{align*}
&\text{Me} - \text{O} \\
&\text{CO}_2\text{-t-Bu}
\end{align*}
\]

ppm

\[
\begin{align*}
&\text{ppm (FT)}
\end{align*}
\]
1H-NMR Ligand L3

13C-NMR ligand L3
31P-NMR ligand L3

1H-NMR ligand L4
31P-NMR ligand L4
$^{1}H$-NMR ligand L5

$^{13}C$-NMR ligand L5
31P-NMR ligand L5