Chiral Diene/Phosphine Hybrid Ligands: Synthesis & Applications

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Department of Chemistry
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Abstract

The Lautens group has recently developed a variety of novel multi-metal catalyzed synthetic methodologies involving chiral and achiral ligands. These types of systems are attractive in terms of efficiency as no reaction intermediates need to be isolated thus reducing waste, time and cost. In an attempt to expand this field, the focus of this work is on the synthesis of novel hybrid ligands containing a chiral diene and phosphine moiety for the purposes of Rh/Pd dual-metal catalysis. Achievements include the synthesis of a variety of hybrid ligands and progress towards the optimization of a one-pot one-step Rh/Pd dual-metal catalyzed reaction with these types of ligands. Specifically, this reaction involves the Rh-catalyzed asymmetric conjugate addition of boroxines to enones and a Pd-catalyzed Suzuki-Miyaura coupling reaction.
Acknowledgments

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<tbody>
<tr>
<td>acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>ad</td>
<td>1-adamantyl</td>
</tr>
<tr>
<td>t-amyl</td>
<td>2-methyl-2-butyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>ARO</td>
<td>asymmetric ring opening</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BOC</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>tert-butyllithium</td>
</tr>
<tr>
<td>CAM</td>
<td>cerium ammonium molybdate</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift, in parts per million</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dcype</td>
<td>1,2-bis(dicyclohexylphosphino)ethane</td>
</tr>
<tr>
<td>dioxane</td>
<td>1,4-dioxane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>dppb</td>
<td>1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,4-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppp</td>
<td>1,4-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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</table>
EtOAc  ethyl acetate
h  hour(s)
HBTU  \(N,N,N',N'-\text{tetramethyl-}O-(1H\text{-benzotriazol-}\ 1\text{-yl})\text{uronium hexafluorophosphate}\)
HPLC  high-performance liquid chromatography
HRMS  high-resolution mass spectrometry
IPr  1,3-\text{bis(diisopropyl)imidazol-2-ylidene}
i-Pr  isopropyl
IR  infrared
\(L\)  generic ligand
M  generic metal or molar concentration
Me  methyl
MeCN  acetonitrile
MeOH  methanol
MHz  megahertz
mp  melting point
MS  molecular sieves
Ms  methanesulfonyl
MVK  methyl vinyl ketone
ND  not determined
NMR  nuclear magnetic resonance
Ns  2- or 4-nitrobenzenesulfonyl
\(o\)  ortho
OAc  acetate
OMe  methoxy
\(p\)  para
Ph  phenyl
pin  pinacolyl
PPF-P\(^{1}\)Bu\(_{2}\)  \([\text{diphenylphosphinoferrocenyl}]\text{ethyl-di-}\text{tert-}\text{butyl-phosphine}\)
R  generic group
RCAA  rhodium-catalyzed asymmetric arylation
rt  room temperature
RuPhos  2-dicyclohexylphosphino-2',6'-diisoproxybiphenyl
sat.  saturated
Tf  trifluoromethanesulfonate
TFA  trifluoroacetic acid
TFP  tetrafluorophenyl
THF  tetrahydrofuran
TLC  thin-layer chromatography
TMS  tetramethylsilane
Ts  p-toluenesulfonyl
X  generic halide or generic group
XPhos  2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Chapter 1 – Introduction

1.1 Increasing Reaction Efficiency via Multi-Metal Catalysis

In recent years, multi-metal catalysis has become an increasingly important area of research as the use of more than one metal catalyst can allow for multiple synthetic transformations in a single reaction vessel. This type of synthetic methodology closely resembles enzymatic systems where multiple catalysts each execute a specific transformation with high selectivity in order to achieve a particular result. These types of systems are attractive in terms of efficiency as no reaction intermediates need to be isolated thus reducing waste, time and cost.

The Lautens group has recently developed a variety of novel multi-metal catalyzed methodologies involving chiral and achiral ligands. Ligands play an essential role in these reactions as they allow for excellent yields and high selectivity (chemo- and stereoselectivity). Rhodium/palladium catalysis with chiral diene and phosphine ligands is of particular interest to this group. Knowing that ligands can increase the reactivity and stereoselectivity of certain catalytic systems featuring more than one transition metal, synthesizing a hybrid ligand containing coordination sites for each transition metal may further increase the efficiency of synthesis. It is known that the optimization of these one-pot systems pose difficulties with respect to unproductive interactions between the two metals or the metals and the ligands. By combining two ligands into one rigid molecule, it would act to improve the reactivity of these one-pot systems as interference between rhodium and palladium is thought to be minimized. Specifically, the rigidity of the hybrid ligand would effectively separate both metals in order to prevent metal-metal interference. Also, in terms of ligand-metal mismatch, the rigidity of the hybrid ligand ensures that two different ligands cannot simultaneously bind to one metal. The focus of this work is on the synthesis of novel covalently bonded hybrid ligands containing a chiral diene and an achiral phosphine moiety for the purposes of Rh/Pd dual-metal catalysis. Subsequent work to this report would include ligands that are bonded through ionic or hydrogen bonding interactions. These hybrid ligand variations are thought to improve synthetic efficiency and reactivity in systems featuring one-pot domino catalysis.
1.2 Rhodium/Chiral Diene-Catalyzed Asymmetric Arylation

The conjugate addition of nucleophiles to acceptor-substituted double and triple bonds is a paramount transformation in organic synthesis, usually referred to as a Michael addition. Organocopper complexes have been widely used in the conjugate addition of enones. Other transition metals such as Ni and Pd have also been used to catalyze the conjugate addition of organozinc, -zirconium, -aluminum, -mercury compounds to enones. The beneficial aspects of these reactions are that they are known to generally be very high yielding and versatile. Problems do exist however, such as competitive 1,2-addition along with lack of enantioselective methodologies. However, it wasn’t until 1997 that Miyaura made progress towards an efficient rhodium-catalyzed conjugate addition of organoboron reagents to enones. This key discovery by Miyaura and co-workers featured the rhodium(I)-catalyzed conjugate addition of aryl- or 1-alkylboronic acids to cyclic and acyclic enones, which proceeded with high yields. This was attributed to a combination of (acac)Rh(CO)₂ and the phosphine ligand, diphenylphosphino butane (dppb) in an aqueous solvent such as DMF/H₂O (6:1), cyclohexane/H₂O (6:1) or MeOH/H₂O (6:1) (Scheme 1).

Scheme 1: Rhodium(I)-catalyzed conjugate addition of arylboronic acids to acyclic enones

This initial discovery proved to be extremely important in organic chemistry as it paved the way for the expansion of this methodology, ultimately leading to efficient enantioselective protocols. In terms of the initial ligand screening, various phosphine ligands gave good results for methyl vinyl ketone (MVK), as the product yields were more or less quantitative. However, the same

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reaction utilizing a less reactive substrate, 2-octen-4-one revealed the most efficient phosphine ligands in the following descending order: dppb>dppp>TFP>dppe, PPh$_3$ and AsPh$_3$. These results indicated that increasing the P–Rh–P bite angles accelerates the reaction. The features that render this methodology attractive when compared to copper catalyzed processes include neutral reaction conditions in the presence of water, no observation of the 1,2-addition byproducts, and excellent functional group tolerance. A few drawbacks were noted as well, including that ortho-substituted boronic acids tended to slow down the reaction due to steric effects and that a large excess of boronic acid had to be used due to protodeborylation as a side reaction.

In 1998 Hayashi and Miyaura described the first rhodium-catalyzed asymmetric arylation (RCAA) of aryloboronic acids to enones.$^3$ This protocol proceeds with both high yield and excellent enantioselectivity utilizing (S)-BINAP as the ligand (Scheme 2).

![Scheme 2: First rhodium-catalyzed asymmetric arylation (RCAA) of aryloboronic acids to enones](image)

These reaction conditions are compatible with both electron-donating and electron-withdrawing aryl boronic acids and both cyclic and trans-linear enones.

A detailed mechanistic pathway was proposed in 2002 by Hayashi and co-workers which was ultimately found to involve three Rh intermediates: hydroxorhodium, oxa-π-allylrhodium, and phenylrhodium species, all of which were observed in NMR spectroscopic studies.$^4$ First, the

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catalytically active rhodium-hydroxide species is generated from Rh(acac)(S)-BINAP (A, Scheme 3). This species then undergoes transmetallation with phenylboronic acid to generate phenylrhodium (B). The enone then inserts into the Rh–Ph bond in order to generate the oxa-π-allylrhodium species (C). Finally, hydrolysis delivers the asymmetric 1,4-addition product and regenerates the [Rh]-OH species.

Scheme 3: Mechanistic pathway proposed in 2002 by Hayashi and co-workers

It was confirmed that the rate determining step is transmetallation of the boronic acid to rhodium. These mechanistic studies led to the discovery of a more active rhodium catalyst, [Rh(OH)(binap)]₂, which catalyzes this transformation at lower temperatures leading to higher yields and enantioselectivities. Specifically, this is because the transmetallation step for the Rh(acac)(binap) catalyst requires temperatures as high as 80 °C in order to proceed at a reasonable rate. However, the hydroxide containing catalyst undergoes transmetallation quickly at just 25 °C. Following this report, ligand and base effects in the rhodium(I)-catalyzed 1,4-addition of arylboronic acids to enones were reinvestigated by Miyaura and co-workers. It was discovered that the [Rh(COD)OH] complex or the catalyst generated in situ from a [Rh(COD)Cl]

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complex was a highly efficient system when compared to Rh(acac) or RhCl complexes and their phosphine derivatives, allowing the reaction to proceed at temperatures even lower than room temperature. The addition of base greatly accelerated this reaction, especially KOH which displayed the largest increase. The authors commented that the base plays two roles in the mechanism. It acts to generate an active species for transmetallation when RhCl or Rh(acac) complexes are used as the catalyst precursors. Also, quaternization of arylboronic acids with a base facilitates transmetallation to the [Rh]-OH species. This methodology was generally very high yielding despite the fact that it was not enantioselective.

In 2003, Hayashi and co-workers reported the discovery of a new $C_2$-symmetric chiral chelating diene ligand for the purposes of rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents to $\alpha,\beta$-unsaturated ketones and esters (Scheme 4).^6

Scheme 4: Rhodium-diene complex catalyzed asymmetric arylation of $\alpha,\beta$-unsaturated ketones and esters

The enantioselectivities observed in this study were among the highest for this specific asymmetric transformation. Steric repulsions between the benzyl group on the diene and the carbonyl functionality are responsible for enantioface recognition of the enones by the $(R,R)-L^*$-rhodium complex. For both cyclic and linear enones coordination with the $\text{are}$-face is favorable, leading to formation of the $R$ enantiomer. This new diene catalytic complex possesses a much higher catalytic activity in comparison to the analogous chiral phosphine complexes when used in

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the reaction of phenyltrimethylstannane with 2-cyclohexenone, rendering the \((R,R)-L^*\) chiral diene the superior ligand choice for this transformation.

Concurrent to Hayashi’s initial report, Carreira and co-workers published their investigation of chiral dienes as ligands for catalytic iridium-mediated processes. They reported chiral \([2.2.2]\)-bicyclooctadienes as a new class of ligand, conveniently prepared from \((R)\)- or \((S)\)-carvone. These new ligands were featured in the Ir(I)-catalyzed kinetic resolution of allylic carbonates. Following this report, Carreira discovered that the new \([2.2.2]\)-diene ligands displayed high selectivity in Rh(I)-catalyzed conjugate addition reactions to a broadened range of substrates than Hayashi had illustrated in his initial report. This included substrates such as coumarin, 2-\((5H)\)-furanone, unsaturated amides and 3-penten-2-one, furnishing all of these additions in 88-98% ee (Scheme 5).

![Scheme 5: Rhodium-diene complex catalyzed asymmetric arylation to a broad class of substrates](image)

Since these initial discoveries by Hayashi and Carreira, there has been many different chiral dienes synthesized for the purposes of rhodium-catalyzed asymmetric arylation over the years. Some examples are displayed in figure 1.

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Figure 1: Different chiral dienes developed for rhodium-catalyzed asymmetric arylation

Of all of the examples presented, \( L7 \) is of particular interest due to its ester functionality. For the purposes of this project it can provide a synthetic pathway towards the generation of covalently linked diene/phosphine hybrid ligands and thus will be discussed in further detail.

In 2009, Hayashi and co-workers reported the rhodium-catalyzed asymmetric arylation of imines employing chiral diene ligands containing an ester group to produce diarylmethylamines in high yields and enantioselectivities (Scheme 6).\(^8\)

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Scheme 6: Rhodium-diene complex catalyzed asymmetric arylation of nosylimine

Through a ligand screen, it was found that ester group substituted bicyclo[2.2.2]octadienes were more powerful chiral ligands than those substituted with alkyl or aryl groups. Bulky aryl esters exhibited the highest levels of enantioselectivity in this study. The high performance ligand that the authors utilized in the substrate scope of the 1,2-asymmetric arylation of imines was also featured in the asymmetric 1,4-addition to α,β-unsaturated ketones (Scheme 7). A low catalyst loading of 0.3 mol % was effective for both cyclic and linear enones in their transformations to the corresponding β-aryl ketones.

Scheme 7: Rhodium-diene complex catalyzed asymmetric arylation of enones

It is worth mentioning that variations of these chiral dienes have also been reported. In 2011, Lam and co-workers reported the enantioselective rhodium-catalyzed arylation of β-substituted alkenyl-para-nitroarenes featuring a dibenzylamide-containing chiral diene ligand, L10 which proceeded with high yields and enantioselectivities (Scheme 8). It was found that placement of a

---

strongly electron-withdrawing group at the para-position led to addition products rather than Heck-type products. They also showcased the same addition reaction to an alkenyl-\(p\)-cyano-\(m\)-(trifluoromethyl)arene substrate.

Scheme 8: Enantioselective rhodium-catalyzed arylation of electron-deficient alkenylarenes

1.3 Multi-Metal Catalysis in the Lautens Group

It is important to highlight the recent work from the Lautens group using the ligands that have been developed by Hayashi and Miyaura for the purposes of Rh-catalyzed arylation. In 2011, Lautens and co-workers reported a one-pot methodology for the preparation of dihydroquinolines, which utilizes two different metals and two different phosphine ligands.\(^\text{10}\) This combination of a two-metal/two-ligand catalyst system, featuring a Rh-catalyzed alkyne arylation and Pd-catalyzed C–N coupling, was able to promote two out of three possible transformations in a “time-resolved” manner (Scheme 9). Specifically, a rhodium-catalyzed asymmetric arylation followed by a Pd-catalyzed C–N coupling are promoted while a possible Pd-catalyzed Suzuki-Miyaura coupling is avoided. Structural rigidity of the alkyne prevented the occurrence of the C–N coupling before the Rh-catalyzed arylation. NMR experiments indicated that palladium could bind with both phosphine ligands yet rhodium exclusively binds to BINAP. In the optimized reaction, no Suzuki-Miyaura products were observed as the intramolecular C–N coupling is faster than the Suzuki-Miyaura coupling. Both electron-rich and electron-poor aryl and heteroaryl boronic acids were tolerated giving good yields.

Scheme 9: Preliminary scope of domino reaction via Rh-catalyzed asymmetric arylation/Pd-catalyzed C–N coupling

Dual-metal catalysis has also been explored in terms of Rh-catalyzed asymmetric ring opening (ARO), a transformation that this group is well known for. In 2012, the one-pot synthesis of a biologically interesting chiral dihydrobenzofuran framework was described, combining Rh-catalyzed ARO with a Pd-catalyzed C–O coupling furnishing the product in good yield and enantioselectivity (Scheme 10).

Scheme 10: Asymmetric one-pot synthesis of dihydrobenzofuran via Rh-catalyzed ARO/Pd-catalyzed intramolecular C–O coupling sequence

In 2013, Lautens and co-workers developed a high yielding and enantioselective one-pot tandem Au/Rh-catalyzed synthesis of β-disubstituted ketones from racemic propargyl alcohols (Scheme 11).

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Scheme 11: One-Pot Au(I)/Rh(I) dual metal catalysis: boronic acid scope

This one-pot Au(I)/Rh(I) system involves an initial Au(I)-catalyzed Meyer-Schuster rearrangement to produce the enone intermediate, which is then followed by 1,4-addition to furnish the β-disubstituted ketone. An NHC ligand, IPr was utilized with the gold catalyst, while one of Hayashi’s chiral diene ligands, L7 was employed for the asymmetric arylation step.

The same year, another example involving Rh/Pd domino catalysis in a time-resolved manner was reported. This methodology features a Rh-catalyzed asymmetric arylation followed by an intramolecular C–O coupling, which combined 3-chloro-2-vinylpyridines with 2-hydroxy-phenylboronic esters in order to furnish biologically interesting aza-dihydrodibenzoxepines in good yields and excellent enantioselectivities (Scheme 12).\(^\text{13}\) The authors found that electron-poor vinyl pyridines displayed the highest performance in this transformation. A variety of chiral diene ligands were examined in order to produce the stereoselective version of the reaction. Most dienes screened gave good enantioselectivity, however the optimal results came from the dibenzylamide diene developed by Lam and co-workers. This was the first example of an asymmetric multicomponent, multi-metal reaction combining both a chiral diene and an achiral phosphine ligand in one-pot.

Scheme 12: Enantioselective domino reaction via Rh-catalyzed asymmetric arylation/Pd-catalyzed C–O coupling

Also in 2013, the efficient synthesis of biologically interesting dihydroquinolinones using a Rh/Pd/Cu catalyst system in a one-pot, two-step manner was achieved. This methodology featured a conjugate addition/amidation sequence, which furnished the desired products in good yields (Scheme 13).^{14}

Scheme 13: Two-step one-pot (MC)^2R scope featuring three transformations catalyzed Rh, Pd and Cu

This was the first triple metal-catalyzed synthesis in one reaction vessel. The authors note that the Cu-catlayzed amidation provides highly complementary reactivity towards the Pd-catalyzed reaction, as iodoanilines and iodohalobenzenes underwent Cu catalysis even in the presence of palladium.

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The following year, a domino reaction taking advantage of rhodium/palladium catalysis giving rise to potentially bio-active dihydroquinoline building blocks in high yields with excellent ee was reported.\textsuperscript{15} Chiral diene ligand, \textit{L8} developed by Hayashi was employed in the 1,4-conjugate arylation step, which was then followed by XPhos-Pd-G1 catalyzed C–N cross-coupling to furnish the final products (Scheme 14). The authors noted minimal interference of the bulky electron rich palladacycle developed by Buchwald with rhodium in the conjugate addition step. Also, the fast consumption of the phenylboronic acid minimized any potential Suzuki-Miyaura cross-coupling to the aryl chloride, demonstrating high control conferred by time resolution.

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{[Rh(L8)Cl]}_2 (2.5 \text{ mol \%}) \quad \text{XPhos-Pd-G1} (2.5 \text{ mol \%}) \\
\text{KOH (3.5 equiv.)} \\
\text{t-am-OH/MeOH} \\
110 \degree \text{C, 18 h}}
\end{array}
\end{array}
\end{equation}

\textbf{Scheme 14: One-Pot Rh/Pd dual metal catalysis: arylacrylamide scope}

The multicomponent synthesis of aza-dibenzoazepines \textit{via} Rh/Pd dual-metal catalysis was also reported in 2014.\textsuperscript{16} This three component multi-metal catalyzed domino process allows for greater diversity of the final product as opposed to similar methodologies developed by this group involving only two components and occurs in good yields (Scheme 15). The authors note that the \textit{ortho}-aminophenylboronic acid does not undergo 1,4-conjugate addition to the vinyl pyridine, so the order of the transformations is critical in order to obtain the desired product. In terms of the Pd-catalyzed amination, the authors found that using a 1:1 ratio of RuPhos and XPhos gave the best results. Further studies showed that XPhos was a critical component as yields were significantly lower when it was omitted. NMR studies indicated that this domino reaction occurs in a time resolved manner as the vinylpyridine substrate undergoes conjugate addition \textit{via} rhodium catalysis quite rapidly to produce the arylation product first, which then undergoes

intermolecular C–N coupling with the pyridyl chloride followed by the intramolecular amination. Electron-poor vinyl pyridines performed the best as they furnished the desired products in good yields. This was the first example of a three catalyst-three component domino reaction.

Scheme 15: Enantioselective domino reaction scope via Rh-catalyzed asymmetric arylation/Pd-catalyzed C–N coupling

Very recently, the Lautens group has developed a one-pot synthesis of enantioenriched 5,6-dihydrophenanthridine derivatives from o-bromo imines and boroxines by utilizing chiral diene, L7. This methodology begins with the rhodium-catalyzed 1,2-asymmetric arylation of an imine in order to generate a chiral o-bromobenzylamines species. This compound then undergoes a Pd-catalyzed homocoupling reaction via retro-carbopalladation in a one-pot manner. This set of transformations gives rapid access to biologically interesting 6-aryl-substituted 5,6-dihydrophenanthridine compounds in good yield and excellent enantioselectivity (Scheme 16).

Scheme 16: 1,2-Asymmetric arylation of imines & Pd-catalyzed homocoupling in one-pot: substrate scope

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1.4 Hybrid Ligands in the Literature

Before discussing the goals of this project, it is important to mention that there have been some examples of hybrid ligands in the literature containing phosphine-olefin, -nitrogen, -oxygen, -sulfur, or -NHC moieties (Figure 2). In terms of coordination, a phosphorus center acts to tune the steric and electronic properties and the other functionalities mentioned act to stabilize the Rh-complex. The olefins are used to diffuse the tight binding of phosphines to rhodium.

![Figure 2: Hybrid ligands in the literature for the purposes of Rh-catalysis](image)

Ligand $L_{11}$ was found to be useful in the rhodium-catalyzed asymmetric arylation of enones and displayed higher catalytic activity than a Rh/cod catalyst. In terms of the other ligands, $L_{12}$ did not induce any enantioselectivity while $L_{13}$, $L_{14}$ and $L_{15}$ were found to be very effective for RCAA. As mentioned, the phosphine moiety controls the major aspects of reactivity for the corresponding rhodium catalyst while the second functionality acts to stabilize the complex. With regards to the situation of a dual-metal catalyzed reaction, there are two ligands that confer the steric and electronic aspects of two catalysts for two different transformations. One could imagine linking these two ligands together, similarly to the hybrid ligands presented, except that there are two coordination sites that tune the steric and electronic properties for each catalyst.

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Chapter 2 – Results and Discussion

2.1. This Work: Hybrid Ligands for Rh/Pd Dual-Metal Catalysis

Based on the previous discoveries of the Lautens group and reports found in the literature describing chiral ligands, we envisioned a new class of ligand in order to further increase the efficiency of one-pot multi-metal catalysis protocols. In the presence of two metals and two ligands, there is potential for unfavorable interactions such as the mismatch of metal-ligand complexes which may be less active than the desired complexes. There is also potential for undesirable metal-metal interactions leading to detrimental affects for the subsequent reactions. With regards to the recent focus on rhodium/palladium dual-metal catalyzed reactions recently developed by the Lautens group, we envisioned the corresponding ligands that were required for these metals to be linked in a hybrid manner. Diene/phosphine hybrid ligands would essentially allow rhodium to coordinate to a chiral diene moiety while palladium coordinates to a phosphine (Figure 3).

![Diagram of hybrid ligands](image)

**Figure 3: Proposal for covalently or ionically bonded diene/phosphine hybrid ligands**

This idea could be executed via a covalent or ionic link between the two ligands. In the covalent linked case, the two fragments may be easily linked through an ester or amide bond, based on the ligands reported by Hayashi and Lam in their work on rhodium asymmetric arylation. By
employing an ionic linkage between the two ligands, it can further increase the optimization process of multi-metal catalysis as different ligands can be paired easily. A long term goal for this project includes the installation of electron-rich phosphines containing alkyl groups in order to facilitate oxidative addition to aryl chlorides and subsequently expand the scope of this system. Rigidity of both hybrid ligand models is important in order to prevent undesirable metal-ligand interactions. In 2011, Hayashi and co-workers reported the rhodium-catalyzed asymmetric cycloisomerization of 1,6-enynes employing a chiral diene and phosphine hybrid ligand which proceeded with excellent enantioselectivity (Scheme 17). In this case, the phosphine moiety is substituted ortho relative to the ester group and as a result, easily coordinates to the rhodium catalyst. In the proposed system for this work, the goal is to minimize rhodium-phosphine interactions as it may act to erode the enantioselectivity of the asymmetric arylation step.

Scheme 17: Rh-catalyzed asymmetric cycloisomerization of 1,6-enynes utilizing tridentate ligands

Rhodium should exclusively bind to the chiral diene in order to achieve high enantioselectivity and palladium should exclusively interact with the phosphine moiety in order to carry out a Pd-catalyzed transformation. To this end, the phosphine group should be placed as far away from the chiral diene as possible in a highly rigid system so as to minimize detrimental interactions between Rh and Pd along with Rh and the phosphine portion of the ligand.

2.2. Synthesis of Covalently Bonded Hybrid Ligands

2.2.1 Retrosynthetic Analysis of the Hybrid Ligand

When first devising a strategy for the synthesis of the hybrid ligand, there were two routes that came to mind. The first was that the phosphine moiety could be installed last via lithium halogen exchange followed by nucleophilic addition to chloro diphenylphosphine (A, Scheme 18). Alternatively, the two fragments (each containing one ligand) could be coupled together in the last step of the synthesis through a DCC coupling (B).

Scheme 18: Retrosynthetic analysis of the diene/phosphine hybrid ligand

When comparing these two options, route A is more attractive because it will be easy to diversify the phosphine functionality in order to generate a variety of these ligands with varying steric and electronic properties.

2.2.2 Synthesis of the Bromo-Containing Hybrid Ligand Precursor

Moving forward with this idea, a [4 + 2] cycloaddition of α-phellandrene with dienophile 6-bromonaphthalen-2-yl propiolate was initially attempted as it provided a short synthetic route to the desired bromo- compound (Scheme 19).
Scheme 19: Initial attempt for the synthesis of the hybrid ligand precursor

However, the Diels-Alder reaction proved to be unselective, affording a mixture of both the Diels-Alder and Alder-ene products. In order to try and obtain this desirable precursor, an alternative route was employed where the carboxylic acid chiral diene fragment could be coupled with 6-bromonaphthalen-2-ol. The synthesis of the diene fragment begins with the generation of the bicyclo[2.2.2]octadiene fragment through the [4 + 2] cycloaddition of α-phellandrene with dienophile 2-napthyl propiolate, with the latter species being generated from a DCC coupling between naphthalene-2-ol and propiolic acid (Scheme 20).

Scheme 20: Synthesis of Hayashi’s chiral naphthalene diene

The chiral diene carboxylic acid fragment was generated by subjecting the product from the [4 + 2] cycloaddition to a transesterification reaction to produce the methyl ester compound in excellent yield (Scheme 21).

Scheme 21: Chiral diene carboxylic acid fragment synthesis
The methyl ester compound is then hydrolyzed using sodium hydroxide to furnish the desired carboxylic acid compound in good yield. It is important to note direct hydrolysis of the starting material in scheme 21 is possible, however purification via silica gel flash column chromatography is difficult as the newly generated chiral diene and the 2-naphthol fragment co-elute under a variety of solvent systems. This two step procedure is more efficient than the direct hydrolysis, having screened a variety of solvent systems in an attempt to separate the two fragments.

Finally, a DCC coupling between the chiral diene carboxylic acid fragment with 6-bromonaphthalen-2-ol produced the bromo-substituted version of Hayashi’s naphthalene chiral diene ligand in 85% yield (Scheme 22).

Scheme 22: Ester linker ligand precursor synthesis: DCC coupling

Although this route requires more steps than the first, the desired precursor could be obtained. Using this particular alcohol fragment, the bromine is placed as far away from the diene moiety as possible, so subsequent phosphine installation will render the ligand incapable of simultaneously coordinating both binding groups.

With the precursor to the desired ligand in hand, it was first subjected to lithium halogen exchange using $n$-BuLi followed by addition of the phosphine electrophile. Unfortunately, the ester group did not survive the lithiation step. A second attempt was made using a Pd(0) source and di-1-adamantylphosphine (HPAd$_2$). This is a less ideal strategy when compared to the lithiation procedure because the phosphine coupling partner is not as versatile. However, under these conditions the ester group was also harmed. The resulting products can be seen below (Scheme 23).
2.2.3 Attempted Synthesis of Amide Linker Ligand

Although both attempts to install the phosphine at the end of the ligand synthesis failed, there was still hope that a more stable amide functionality could survive the lithiation step. The carboxylic acid chiral diene was subjected to an HBTU coupling with 6-bromonaphthalen-2-amine. This did not produce the desired product, rather the HBTU adduct in good yield. This was simply purified and coupled to the amine nucleophile under modified reaction conditions. This successfully produced the coupled amide ligand precursor in good yield (Scheme 24).

Scheme 24: Amide linker ligand synthesis: Amide bond formation featuring HBTU

It is important to note that other amide bond formation reactions were attempted as indicated in the table below (Table 1). A DCC coupling led to low yield with the majority of product being the anhydride formation between two chiral diene species. Acid chloride formation was also attempted twice using oxalyl chloride in combination with two different bases: triethylamine and a saturated aqueous solution of Na₂CO₃. However the yields for both were very low, 18% and 25% respectively. With the amide substrate in hand, the next step could be attempted.
## Table 1: Less successful amide coupling attempts

Upon subjecting this amide precursor to lithiation in order to install the phosphine, both methylated and free –NH substrates led to a mixture of recovered starting material and other unidentified byproducts (Scheme 25).

### Scheme 25: Amide linker ligand synthesis: phosphine installation attempts

Moving forward, a different route to phosphine instillation was envisioned. Although unfavorable in terms of synthetic ease, phosphine installation was attempted before the coupling of the two fragments as to not harm the linker functionality (Scheme 26). The amine fragment was first protected with a BOC group, which was then followed by N-methylation. A Grignard reaction
was then attempted in order to install the phosphine yet this approach also did not produce any desired product rather a complicated mixture containing some starting material.

Scheme 26: Amine fragment ligand synthesis: phosphine installation attempts

2.2.4 Synthesis of the Ester Linker Hybrid Ligand

Since no hybrid ligand was obtained at this point, the same synthetic approach of coupling the two fragments together at the end (route B, Scheme 18) was attempted for the ester linker version of the ligand. The fragment containing the phosphine is generated by subjecting 2-bromo-6-methoxynaphthalene to a Grignard reaction in order to install the phosphine (Scheme 27). This was then followed by demethylation of the methoxy group using aqueous HBr in order to reveal an alcohol group on the phosphine fragment in moderate yield over two steps. With the carboxylic acid and alcohol containing fragments in hand, a DCC coupling was performed in order to successfully furnish the desired ligand in good yield.

Scheme 27: Synthesis of ester linker ligand \textit{L17}

The same synthetic approach was used to synthesize the phenyl version of the ester linker ligand (Scheme 28).
Scheme 28: Ester linker ligand synthesis (phenyl version)

With two ester linker ligands successfully synthesized, their application to Rh/Pd dual-metal catalysis can now be probed.

2.2.5 Nickel Coupling Attempt and Future Considerations Towards the Amide Linker Ligand

The following reaction was attempted twice using the reported conditions by Han and co-workers (Scheme 29). However, both attempts failed. One explanation is that nickel may coordinate to the chiral diene moiety which can complicate the reaction. This nickel coupling should be attempted before the coupling to the diene fragment.

Scheme 29: Phosphine installation attempt via nickel catalysis

Although the amide linker ligand was not successfully obtained during the course of this work, there is a recent report published by Han and co-workers that is worth attempting in the future. This report features the nickel catalyzed coupling of phosphine oxides and t-butyl pivalates using dcype as a ligand (Scheme 30).

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2.3. Ion-Paired Ligands in the Literature

The synthesis of an ion-paired hybrid ligand was attempted during the course of this work. First, it is important to introduce the work that inspired this idea. In 2012, Ooi and co-workers introduced a new strategy for the design of chiral ligands for the purposes of asymmetric transition-metal catalysis. This new type of ligand featured an achiral cationic ammonium-phosphine ligand paired with a chiral binapholate anion and was found to be effective for the highly enantioselective Pd-catalyzed allylic alkylation of α-nitrocarboxylates (Scheme 31).

Scheme 30: Phosphine installation via nickel catalysis

Scheme 31: Substrate scope of asymmetric alkylation of benzofuranones with allylic carbonates

The next year, the authors reported their work using the same concept of ionically bonded ligands in order to realize a new methodology leading to a highly enantio- and diastereoselective [3 + 2] annulation reaction featuring 5-vinylloxazolidinones and activated trisubstituted alkenes (Scheme 32).

---

They successfully found a palladium complex containing a phosphine ligand paired with a chiral ammonium salt that generates three new stereocenters in a single step.

Scheme 32: Asymmetric construction of contiguous all-carbon quaternary stereocenters through palladium-catalyzed cycloaddition

Recently, Ooi and co-workers established their work on ion-paired chiral ligands for palladium-catalyzed enantioselective allylation of benzofuran-2(3H)-ones. This ligand featured a chiral phosphate in combination with an achiral or chiral ammonium phosphine (Scheme 33). In this work, the authors highlight modularity of multicomponent ligands as they allow for a library of structurally diverse catalysts, which would be beneficial in the optimization process.

Scheme 33: Substrate scope of asymmetric alkylation of benzofuranones with allylic carbonates


2.4. Attempted Synthesis of Ion-Paired Hybrid Ligands

Inspired by the work of Ooi, an attempt was made to synthesize an ion-paired hybrid ligand for the purposes of Rh/Pd dual-metal catalysis. Following the reported procedure, we tried to pair the same phosphine cation they used in their paper with the chiral diene we were interested in as the anion (Scheme 34). This was attempted three times and each time the integrations in the $^1$H NMR did not fit the desired structure. An X-ray crystal structure is necessary in order to be certain the correct salt has been synthesized.

![Scheme 34: Attempted synthesis of the ion-paired ligand](image)

2.5. Rh/Pd-Dual Metal Catalysis

2.5.1 Rh-Catalyzed 1,2-Asymmetric Arylation Followed by Cyclization via Pd-Catalyzed CO Insertion

Having synthesized the new hybrid ligand, it was then tested for its applications in Rh/Pd dual-metal catalysis. The first set of transformations planned was a 1,2-asymmetric arylation of an imine followed by a palladium-catalyzed cyclization via CO insertion in order to generate a 5-membered ring. The arylation step catalyzed by rhodium in combination with the new hybrid ligand was first tested in the absence of palladium to probe the ligand’s effectiveness towards the asymmetric arylation (Scheme 35).
Scheme 35: Rh-catalyzed arylation step only

The desired product was isolated with excellent yield and enantioselectivity, showing promise for this new hybrid ligand. The next step was to test the palladium-catalyzed cyclization step from the racemic arylation intermediate (Scheme 36). This transformation yielded 60% of the desired product with 40% recovery of the starting material. A control experiment was carried out where a rhodium catalyst was added to the conditions in scheme 36, and it produced quantitative yield of the final product. This raised suspicions about rhodium participating in the cyclization step. An experiment was then run involving just a rhodium catalyst with triphenylphosphine as the ligand (Scheme 37). A quantitative yield was obtained for this experiment, which shows that rhodium is capable of doing both of the desired transformations.

Scheme 36: Pd-catalyzed cyclization \textit{via} CO insertion step only

Scheme 37: Rh-catalyzed cyclization \textit{via} CO insertion control experiment
2.5.2 Changing the Substrate to Accommodate a Suzuki-Miyaura Coupling

In the search for a truly dual-metal catalyzed reaction, the palladium-catalyzed step needed to be changed to a reaction that is catalyzed exclusively by palladium rather than rhodium. We envisioned that a sequence involving a 1,2-asymmetric arylation of an imine and Suzuki-Miyaura reaction of an o-bromo imine using the same boron reagent might be possible. However, ortho-substituted bromo imines may not be as reactive in the Suzuki-Miyaura reaction due to steric reasons. By moving the bromine substituent to the para position relative to the imine functionality, it is less sterically encumbered which would help promote a Suzuki-Miyaura coupling reaction with boronic acids or boroxines (Scheme 38).

![Scheme 38: 1,2-arylation and Suzuki-Miyaura coupling sequence using boroxines](image)

2.5.3 Catalyst Loading Optimization for the 1,2-RCAA of the New Substrate

With the new substrate in hand, the new ligand was tested and the correct catalyst loading for the rhodium-catalyzed arylation step was investigated (Table 2). The following experiments were carried out using boroxines instead of boronic acids. This was because it was discovered that most of the boronic acids bought from commercial sources contained a significant amount of trimeric boroxine in addition to monomeric boronic acid. This unknown ratio of trimer to monomer species in the commercial bottles would cause an inaccurate amount of the boron nucleophile to be added to the reaction. It is more accurate to use pure boroxine as the vast majority of species being added to the reaction will be in the trimeric form. The boroxine can
then be hydrolyzed to the boronic acid monomers using water in the reaction. It was found that 5.5 mol % of the ligand $L_{17}$ and 5 mol % of the rhodium dimer species gave the best results in terms of yield and enantioselectivity. With the catalyst loading optimized for the first step, it is still important to see how this new hybrid ligand compares to Hayashi’s original ligand, $L_7$ as well as the control experiment employing free triphenylphosphine in combination with Hayashi’s ligand (Table 3).

![Chemical structure of L17]

<table>
<thead>
<tr>
<th>Entry</th>
<th>$L_{17}$ (x mol%)</th>
<th>$[\text{RhCl}((C_2H_4)_2]_2$ (n mol%)</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5</td>
<td>2.5</td>
<td>20</td>
<td>ND</td>
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</tr>
<tr>
<td>3</td>
<td>11</td>
<td>5</td>
<td>19</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not determined. Isolated yields given.

Table 2: Testing catalyst loading for Rh step only (no Pd)
<table>
<thead>
<tr>
<th>Entry</th>
<th>(L7) (5.5 mol%)</th>
<th>Yield [%]</th>
<th>ee [%]</th>
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<tbody>
<tr>
<td>1</td>
<td>(L7)</td>
<td>85</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>(L7/PPh_3) (5.5 mol%)</td>
<td>9</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not determined. Isolated yields given.

**Table 3: How does the new hybrid ligand measure up to Hayshi’s original ligand**

Fortunately, the new hybrid ligand \(L17\) displayed comparable yield and enantioselectivity to the original ligand \(L7\). In addition, the control experiment employing \(L7\) along with free triphenylphosphine in solution displayed a major deterioration in terms of yield. With this information in hand, there is initial promise that this new type of hybrid ligand provides benefit to this dual-metal catalyzed one-pot one-step reaction.

### 2.5.4 Initial Dual-Metal Attempts and Early Optimization Using \(L17\)

Moving forward, the next step was to try adding both rhodium and palladium to the same flask in order to carry out two separate transformations in a single reaction vessel (Scheme 39).

**Scheme 39: One-pot one-step (Rh and Pd)**

Unfortunately, after TLC analysis there was barely any conversion to product with the majority of species being starting material as well as aldehyde decomposition byproducts. A one-pot two-
step reaction was also tried where the vessel was opened after the completion of the rhodium step and palladium was then added in order to minimize potential metal-metal interference. This reaction also failed to produce the desired product. After these initial disappointing results, the catalyst loading was examined in further detail. Although, the ~1:2 ligand to metal ratio was optimal for the rhodium step, it was no longer effective when palladium was present in the reaction medium. This effect may be because there is enough rhodium to coordinate to both the diene and phosphine moieties, which effectively blocks palladium from coordinating with the ligand. Through some reaction optimization, it was found that by increasing the ligand loading to 11 mol % (increasing the ligand to palladium ratio from ~1:1 to ~2:1 and ligand to rhodium ratio to ~1:1) along with increasing the amount of KOH\(_{\text{aq}}\) to 80 mol % increased the rate of the palladium-catalyzed step (Scheme 40). This was the first instance that an isolable yield was obtained. Although the yield was low, the enantioselectivity was excellent. In this case both rhodium and palladium were premixed with the ligand, \textit{L17}.

![Scheme 40: First conditions where an isolable yield could be obtained](image)

2.5.5 Catalyst Premixing Studies and Control Experiments

Moving forward, the goal from this point was focused on yield improvement of this multicomponent reaction while retaining the level of enantioselectivity. Also, control experiments had to be run in order to ensure that all of the catalytic components were necessary for each individual transformation. Experimenting with the order of premixing of the metals with the ligands indicated that premixing both rhodium and palladium with \textit{L17} led to a slight increase in yield of the desired product 2 as compared to the case where just rhodium was premixed with the ligand (Table 4). When palladium was absent from the reaction, there was no Suzuki-Miyaura coupled product formed, indicating positive results that the palladium catalyst is necessary for the second transformation. Then, phosphine was omitted in order to probe its necessity as a ligand in the
reaction. In this case, there was also no Suzuki-Miyaura coupled product observed indicating that this ligand is necessary.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comment</th>
<th>$L$ (11 mol%)</th>
<th>Yield 1 [%]</th>
<th>Yield 2 [%]</th>
<th>ee 2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Premixing Rh, Pd &amp; $L_{17}$</td>
<td>$L_{17}$</td>
<td>ND</td>
<td>(20)</td>
<td>&gt;99</td>
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<td>12</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Omit Pd</td>
<td>$L_{17}$</td>
<td>33</td>
<td>0</td>
<td>-</td>
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<tr>
<td>4</td>
<td>Omit Phosphine</td>
<td>$L_{7}$</td>
<td>84</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

ND: not determined. Values in parenthesis indicate isolated yield. All other yields are $^1$H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

**Table 4: Control experiments: are all of the components necessary?**

**2.5.6 Reaction Optimization: Changing Amount and Nature of Boroxine**

The optimization process was now able to continue knowing that both metals and both components of the ligand were necessary for this one-pot transformation. There was a problem encountered with the decomposition of the starting material into an aldehyde byproduct. The $p$-bromobenzaldehyde species could also undergo Suzuki-Miyaura coupling. This not only led to more byproducts but also the boroxine was being over consumed. Moving forward, the boroxine loading was increased to 4 equivalents of boron as opposed to 2.2 equivalents in order to ensure that there was enough of the nucleophile in the reaction medium to produce the desired product. The boroxine was also changed from (PhBO)$_3$ to (4-MeOC$_6$H$_4$BO)$_3$. This was done because the intermediate 1 and product 2 were inseparable by TLC making the reaction difficult to monitor. Also, the important signals in the $^1$H NMR overlapped making it difficult to estimate yields by $^1$H NMR. The para-methoxy version of the boroxine was better for analytical purposes as the
intermediate and product were separable by TLC (as well as stained different colours using CAM stain [intermediate: brown, product: purple]). There also was not as much signal overlap present in the crude $^1$H NMR using para-methoxy boroxine.

**2.5.7 Reaction Optimization: Palladium Catalyst Studies**

With these improvement made, the reaction optimization continued with testing different palladium catalyst along with catalyst loading in order to improve the yield (Table 5). The first experiment involved premixing palladium and the ligand for 10 minutes at room temperature before the rhodium and ligand undergo premixing for 30 minutes at 60 °C. This led to a rather poor yield of 26% of the desired product 2. Then a different palladium source was tested, Pd(dba)$_2$, employing the same premixing procedure as was used for Pd(OAc)$_2$. A palladium (0) source does not need to be reduced by the phosphine ligands like a palladium (II) source does. This might make the hybrid ligand more effective for the Suzuki-Miyaura transformation as the phosphine groups on the ligand *L17* will not be oxidized. The results were very similar between the two palladium sources. In order to test if the premixing of palladium was beneficial, an experiment was done where palladium was added with the reagents instead of being premixed. This displayed a decrease in yield to 13% of the desired product, which indicates that premixing may help activate the palladium species. Increasing the catalyst loading of Pd(dba)$_2$ to 10 mol % without premixing gave very similar results to the case of using just 5 mol % in combination with premixing. Trying Pd$_2$(dba)$_3$ at a catalytic loading of 5 mol % of palladium yielded barely any product. Although the yield of the final product was still low at this point in the optimization process, it was evident that premixing palladium and the ligand before the premixing of rhodium and the ligand was benefitting the yield. Control experiments were then run to confirm that both metals were necessary. It was found that by omitting palladium from the reaction, only a trace amount of product was observed. A one-pot two-step reaction was attempted where the palladium was added to the reaction after the rhodium step was completed. Only trace amounts of product were observed in this case as well. The most important control experiment was run with the corresponding separate ligands in solution, *L7* and free triphenylphosphine. This result displayed a significant degradation in yield of both the intermediate and product. With this result in hand, the hybrid ligand *L17* still displays benefit to the efficiency of this one-pot transformation.
**Table 5: Reaction optimization testing different palladium sources and control experiments**

### 2.5.8 Testing the Phenyl Version of the Hybrid Ligand

At this point the phenyl version of the hybrid ligand, **L18** was tested using the best conditions from the previous catalyst screen. The yield of the product 2 was comparable to the yield obtained when using the naphthalene version of the hybrid ligand under the same reaction conditions. The enantiomeric excess was not determined (Scheme 41).
Scheme 41: Testing the phenyl version of the hybrid ligand

2.5.9 Changing the Rhodium Step and the Substrate Along with Base Screening

Since the imine substrate was prone to decomposition, it was decided to change the substrate to an enone for a 1,4-conjugate addition step, which was easily synthesized through an aldol reaction. This way the substrate cannot decompose thus avoiding byproduct formation. Further reaction optimization was carried out employing Pd(dba)$_2$ and stirring it at room temperature for 10 minutes with the hybrid ligand before the rhodium-ligand premixing for 30 minutes at 60 °C. This premixing procedure proved to be beneficial from the previous optimization study. A base screen was then conducted (Table 6).
Table 6: First base screen employing the new enone substrate

The standard conditions employing 80 mol % aqueous KOH displayed an initial 10% yield of the new product 2 with 78% of intermediate 1. The ee of the intermediate 1 was determined to be 95%. Increasing the amount of this base lead to worse results. Combining it with K$_2$CO$_3$ led to an increase in yield to 19%. Simply using 3 equivalents of K$_2$CO$_3$ or solid KOH, led to similar results. K$_3$PO$_4$ was the base that produced the highest yield of 21% in this base screen. However, it was decided to carry on with aqueous KOH since the mechanism for the arylation step requires a proton source for the hydrolysis step. Also, there was no drastic improvement in the yield at this stage so there must have been some other problem. A base screen would be revisited at a later stage in the optimization process.

2.5.10 Introducing Cesium Fluoride and Palladium Loading Studies

Through optimization studies, cesium fluoride seemed to provide benefit to the reaction. The amount of boroxine was increased to 4 equivalents due to the appearance of a byproduct (which
was later found to be the arylation of dba). Moving forward, the catalyst loading of palladium was examined in an attempt to make the second step more facile (Table 7). By lowering the catalyst loading to 2.5 mol % so that there are about 4 phosphine ligands to every palladium species, the yield improved significantly to 51% product. Lowering it even more to 1.25 mol % produced the same results as when the catalyst loading was 5 mol %.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(dba)₂ (x mol%)</th>
<th>Yield 1 [%]</th>
<th>Yield 2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>79</td>
<td>16</td>
</tr>
</tbody>
</table>

All yields are 'H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

**Table 7: Catalyst loading optimization**

### 2.5.11 Effect of Temperature Using Modified Catalyst Loading

Moving forward with the new additive and catalyst loading, different reaction temperatures were tested (Table 8). By stirring the reaction at room temperature for one hour and then heating it to 80 °C for 17 hours, the yield of the final product further improved to 61%. However, after stirring the reaction for one hour at room temperature the rhodium step did not go to completion under these conditions. Stirring at 40 °C for 15 minutes allowed the RCAA to go to completion and then the reaction was heated to 80 °C for the remainder of the reaction time. However, this temperature combination proved to diminish the yield of the final product.
Table 8: Testing temperature ranges employing new catalyst loading

2.5.12 Effect of Base Under Modified Temperature Regime

From this point, a few different bases were tested with the goal of improving the yield. Both K$_3$PO$_4$•H$_2$O and solid KOH (3 equiv. each) gave excellent yields (Table 9). However, upon determining the ee of the reaction it was found that it had degraded significantly to 48% and 35%, respectively. K$_3$PO$_4$ was found to have a similar yield to that of its monohydrate version, yet a higher ee of 64%.
Table 9: Base screen using new reaction temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield 1 [%]</th>
<th>Yield 2 [%]</th>
<th>ee 2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH (3 equiv.)</td>
<td>0</td>
<td>92</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>K₃PO₄•H₂O (3 equiv.)</td>
<td>trace</td>
<td>86</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>K₃PO₄ (3 equiv.)</td>
<td>15</td>
<td>(86)</td>
<td>64</td>
</tr>
</tbody>
</table>

Values in parenthesis indicate isolated yield. All other yields are ¹H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

2.5.13 Temperature Ramping and Effect on EE

Moving forward employing K₃PO₄ as the base, different temperature combinations were explored in an attempt to solve the enantioselectivity issues at hand. The initial thought was that there might be a chance that some of the conversion for the first step was happening at too high of a temperature in this instance, as the first step did not go to completion at room temperature regardless of the reaction time. Knowing this, the 40 °C (10 minutes) to 80 °C combination was tried in order for the first step to go to completion before heating to a higher temperature (Table 10). In this case, the yield dropped to 65% yet the enantioselectivity increased to 84%. A few other temperature combinations were attempted in order to obtain some more data points to see if there was a trend using the same reaction conditions. However, this led to some confusing results. Room temperature to 100 °C displayed a higher yield of 91% but the ee was 76%. This result was higher than the room temperature to 80 °C protocol (where the ee was 64%). Following the idea that the first step is going to completion at too high of a temperature, this result does not fit the expected trend. Next, 60 °C to 100 °C was tried to ensure that the RCAA was complete, as it was previously known that this temperature did give good enantioselectivity (ee 95%) in the very first base screen (Table 6). In this case the yield was 76% with an ee of 62%. Despite the confusing results, at this point a control experiment was run utilizing the separate ligands, L7 and
triphenylphosphine at the last temperature combination that was tested (60 °C to 100 °C). Indeed the yield of the product decreased significantly and the enantioselectivity decreased by 16%. Although the results were somewhat confusing in terms of this temperature evaluation, this control experiment result suggested that the hybrid ligand benefited the reaction in comparison to the case involving two separate ligands.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>L (11 mol %)</th>
<th>Temp. [°C]</th>
<th>Yield 1 [%]</th>
<th>Yield 2 [%]</th>
<th>ee 2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L17</td>
<td>40 (10 min) to 80</td>
<td>14</td>
<td>(65)</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>L17</td>
<td>rt (1 h) to 100</td>
<td>3</td>
<td>91</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>L17</td>
<td>60 (10 min) to 100</td>
<td>27</td>
<td>(76)</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>L7/PPh₃ (11 mol %)</td>
<td>60 (10 min) to 100</td>
<td>41</td>
<td>(36)</td>
<td>46</td>
</tr>
</tbody>
</table>

Values in parenthesis indicate isolated yield. All other yields are ¹H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

Table 10: Temperature screening

### 2.5.14 EE Investigation: Palladium Loading Experiments

Investigating the enantioselectivity issues further, the intermediate and product were isolated to check if their ee’s were the same (Table 11).
Table 11: Ee investigation: testing the effect of palladium loading

At the same temperature and reaction time as the original conditions, the ee’s of 1 and 2 were the same. Some other factor beyond temperature must be playing a role in the enantioselectivity process. The enantioselectivity was probed using 5 mol % vs. 2.5 mol % of palladium and a drop in yield was observed, yet the ee increased to 84%. Palladium may be affecting the enantioselectivity of the reaction in a way that is unclear.

2.5.15 EE Investigation: Control Experiments Omitting Palladium

Recall when 5 mol % palladium was used in combination with aqueous KOH, the ee was 95% while the yield was 78% (Table 6). Further control experiments showed when palladium was omitted from these conditions the ee was consistent at 94% (Table 12). When the base was changed to K₃PO₄ without using palladium the ee was 94%. This result suggests that the base is not the factor causing ee degradation. Next, an experiment was run involving cesium fluoride and K₃PO₄. The ee was 95% in this case indicating that cesium fluoride should not be causing any harm to the ee.
Table 12: Ee investigation: control experiments

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive</th>
<th>Yield 1 [%]</th>
<th>ee 1 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH$_{aq}$ (80 mol %)</td>
<td>-</td>
<td>(98)</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>K$_3$PO$_4$ (3 equiv.)</td>
<td>-</td>
<td>(78)</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>K$_3$PO$_4$ (3 equiv.)</td>
<td>CsF (2 equiv.)</td>
<td>(98)</td>
<td>95</td>
</tr>
</tbody>
</table>

Values in parenthesis indicate isolated yield.

2.5.16 EE Investigation: Probing the Effect of Dibenzylideneacetone (dba) on EE

As was previously noted during this study, dibenzylideneacetone (dba) was undergoing rhodium-catalyzed arylation. With this information in mind, it was thought there is a potential for dba to bind to rhodium and arylate the starting material. This could be the factor contributing to the enantioselectivity issues. To probe whether dba was causing ee degradation, an experiment was run where Pd(dba)$_2$ was not premixed before the rhodium and the chiral ligand. Instead, it was added after this premixing stage with the reagents (Table 13). This way, there is no free dba in solution that could potentially bind with rhodium during the catalytic premixing stage. It was found that the ee increased by 20% to a respectable 87%. These results indicated that dba may be binding to rhodium in solution along with the chiral diene species during the premixing stage. This also may explain some of the inconsistency of the results from the temperature screen as in some cases more dba may be bound to rhodium than others.
Changing the Palladium Source to Pd(OAc)$_2$

Moving forward, palladium (II) sources were screened in order to find a suitable palladium catalyst that does not contain dba as a ligand. Employing Pd(OAc)$_2$ as a palladium (II) source with the same catalyst loading of 2.5 mol %, initially gave a good yield of 71% along with a good enantioselectivity of 92% (Table 14). Conditions were tested where the base was dried using a heat gun under vacuum to remove any residual water. Although the yield was similar, the ee dropped to 83%, which was unexpected. The effect of cesium fluoride was tested when this additive was omitted (along with drying the K$_3$PO$_4$). The yield suffered while the enantioselectivity stayed similar in comparison to the previous reaction. This additive still seemed to be playing an effective role in terms of the yield. However, the enantioselectivities were still somewhat inconsistent and there was uncertainty about what was the cause of this issue. It was thought that moisture in the reaction medium might be the cause of these inconsistent results (as the humidity was high at this time). An experiment was run using a modified procedure in an attempt to keep the vessel as air and moisture free as possible. The rhodium catalyst was added last to the reaction via syringe. Although the yield was slightly lower, the ee was still good at 90%. When this experiment was repeated it led to very different results of only 30% yield and 13% ee. Unfortunately, the reaction was not reproducible as no experimental errors were noted. A scaled up reaction was then attempted (0.3 mmol instead of 0.15 mmol).
Relative to the experiment run using the original scale, the yield remained the same yet the ee was different. It was still believed that moisture was the potential cause for these discrepancies in ee. With this in mind a freeze pump thaw experiment was attempted in order to remove all possible moisture with hopes that this would resolve the enantioselectivity issues. Under these conditions, the yield decreased to 55% and the ee was 83%. Lastly, the original base was tested (aqueous KOH) instead of K$_3$PO$_4$. The enantioselectivity was good yet the yield decreased significantly to only 14% of the product 2. For some reason, this base is not very effective for the Suzuki-Miyaura coupling so K$_3$PO$_4$ was utilized in the optimization screen. Entry 5 in table 14 was performed by a visiting student, Cian Kingston. He found he could not reproduce the results of the author in this optimization screen.
**Table 14: Pd(OAc)$_2$ optimization table**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comment</th>
<th>Yield 1 [%]</th>
<th>Yield 2 [%]</th>
<th>ee 2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>ND</td>
<td>(71)</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>K$_3$PO$_4$ dried under vacuum</td>
<td>ND</td>
<td>(72)</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Omit CsF</td>
<td>ND</td>
<td>(43)</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Add Rh catalyst last</td>
<td>ND</td>
<td>(62)</td>
<td>90</td>
</tr>
<tr>
<td>5$^a$</td>
<td>Add Rh catalyst last</td>
<td>74</td>
<td>26, (23)</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>Add Rh catalyst last (repeat)</td>
<td>71</td>
<td>33, (30)</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>Add Rh catalyst last (0.3 mmol scale)</td>
<td>ND</td>
<td>(63)</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>Add Rh catalyst last + freeze pump thaw</td>
<td>ND</td>
<td>(55)</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>KOH$_{(aq)}$ (80 mol %) instead of K$_3$PO$_4$ (3 equiv.)</td>
<td>ND</td>
<td>(14)</td>
<td>91</td>
</tr>
</tbody>
</table>

$^a$performed by Cian Kingston. ND = not determined. Values in parenthesis indicate isolated yields. All other yields are $^1$H NMR yields using 1,3,5-trimethoxybenzene as an internal standard. “Add Rh catalyst last” includes drying of CsF and K$_3$PO$_4$ under vacuum.

### 2.5.18 Changing the Palladium Source to Pd(TFA)$_2$

A different palladium (II) catalyst was tested with the goal of obtaining more consistent results (Table 15). Employing the same procedure of adding the rhodium catalyst last along with 2.5 mol % of palladium, the results were not better than the best result using Pd(OAc)$_2$. The catalyst loading was then tested again relative to the latest reaction conditions and it was found that the
enantioselectivity increased to an excellent 94% when 5 mol % palladium was used yet the yield was moderate at 62%. This experiment was repeated, and unfortunately the ee decreased to 80% while the yield was similar. Again, there was a reproducibility issue associated with the enantioselectivity. Reverting back to the original procedure gave an increase in yield to 74% and a good ee of 88%. Also, by premixing the palladium with the ligand before the rhodium-ligand premixing produced the same ee as the previous reaction with a decreased yield of 58%. Knowing this, the original procedure was utilized through the remainder of the screening process as it consistently gave the highest yield out of all of the procedures tested between the two palladium sources thus far. The best result arose when the reaction was left over the weekend for 66 hours; 88% yield and 95% ee. Unfortunately, this result could not be repeated when the reaction was attempted again under apparently identical conditions. Again, suspicion was raised about the moisture content present in the reaction medium. One equivalent of water was added (relative to the enone starting material) to probe how the enantioselectivity compared to the best result. Both the yield and ee dropped, to 57% and 84% respectively. When cesium fluoride was omitted, the yield dropped to 54% and ee to 80%. At least in terms of yield, cesium fluoride seemed to still have a beneficial influence while adding water does not help improve the results of this methodology. Lastly, drying K$_3$PO$_4$ using a heat gun under vacuum did not help the reaction get back to the best results obtained. Entries 3 and 5 in table 15 were performed by a visiting student, Cian Kingston. He found that his results in this investigation were not reproducible relative to the author and to his own results as well.
\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{Br} & \quad \text{O} \\
\text{Br} & \quad \text{O} \\
\text{Br} & \quad \text{Ar} \\
\text{Br} & \quad \text{O} \\
\text{Br} & \quad \text{O} \\
\text{Br} & \quad \text{Ar} \\
\end{align*}
\]

![Chemical structure](image.png)

\[
\begin{align*}
(4\text{-MeOC}_6\text{H}_4\text{BO})_3 & \quad (4\text{ equiv. of } \text{B}) \\
[\text{RhCl(C}_2\text{H}_4]_2 & \quad (5\text{ mol%}) \\
L_{17} & \quad (11\text{ mol%}) \\
Pd(\text{TFA})_2 & \quad (x\text{ mol%}) \\
\text{K}_3\text{PO}_4 & \quad (3\text{ equiv.}) \\
\text{CsF} & \quad (2\text{ equiv.}) \\
\text{Toluene, 60 }^\circ\text{C, 18 h} \\
\end{align*}
\]

Ar = 4-MeOC₆H₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comment</th>
<th>(x mol%)</th>
<th>Yield 1 [%]</th>
<th>Yield 2 [%]</th>
<th>ee 2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Add Rh catalyst last</td>
<td>2.5</td>
<td>ND</td>
<td>(56)</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>Add Rh catalyst last</td>
<td>5</td>
<td>ND</td>
<td>(62)</td>
<td>94</td>
</tr>
<tr>
<td>3ᵃ</td>
<td>Add Rh catalyst last</td>
<td>5</td>
<td>ND</td>
<td>(49)</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>Add Rh catalyst last (repeat)</td>
<td>5</td>
<td>ND</td>
<td>(60)</td>
<td>80</td>
</tr>
<tr>
<td>5ᵃ</td>
<td>Add Rh catalyst last (repeat)</td>
<td>5</td>
<td>84</td>
<td>15, (14)</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>5</td>
<td>ND</td>
<td>(74)</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>Premixing Pd &amp; \textbf{L17} first</td>
<td>5</td>
<td>ND</td>
<td>(58)</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>66 h instead of 18 h</td>
<td>5</td>
<td>ND</td>
<td>(88)</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>66 h instead of 18 h (repeat)</td>
<td>5</td>
<td>ND</td>
<td>(42)</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>Add H₂O (1 equiv.)</td>
<td>5</td>
<td>ND</td>
<td>(57)</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>Omit CsF</td>
<td>5</td>
<td>ND</td>
<td>(54)</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>\text{K}_3\text{PO}_4 dried under vacuum</td>
<td>5</td>
<td>ND</td>
<td>(60)</td>
<td>87</td>
</tr>
</tbody>
</table>

ᵃperformed by Cian Kingston. ND = not determined. Values in parenthesis indicate isolated yields. All other yields are \(^1\text{H} \text{NMR yields using } 1,3,5\text{-trimethoxybenzene as an internal standard.} \) “Add Rh catalyst last” includes drying of CsF and \(\text{K}_3\text{PO}_4\) under vacuum.

**Table 15:** Optimization using Pd(\text{TFA})₂ as the catalyst for the Suzuki-Miyaura reaction
2.5.19 Investigating the Possibility of a Background Arylation

Facing the problem of irreproducible enantioselectivity, it was proposed that there may be a palladium-catalyzed background arylation occurring. An experiment was run omitting rhodium and the Suzuki-Miyaura coupled product was obtained in 61% yield (Scheme 42).

![Scheme 42](image)

Scheme 42: Investigating the possibility of a background arylation catalyzed by palladium

A close analysis of the crude mixture by $^1$H NMR showed 3 arylation peaks, barely evident: one from the arylated intermediate 1, one from the arylated product 2, and one is though to be the arylated dehalogenated product. However, they occurred in such small amounts that it was thought that palladium should have little to no interference with the enantioselectivity. Another experiment was run omitting the ligand so that there is more Pd(II) in the reaction medium than Pd(0), as it might promote the background arylation to a greater extent. TLC analysis showed that there was a lot of starting material remaining (as the phosphine ligand is required for the Suzuki-Miyaura coupling) and a small amount of Suzuki-Miyaura product. This was difficult to quantify
from the crude $^1$H NMR due to signal overlap. In this case, there was only one arylation peak evident in the crude $^1$H NMR which belonged to the arylated intermediate 3 in a small amount of 5% $^1$H NMR yield. With these results in hand, it is unlikely that a palladium-catalyzed arylation is causing the ee of the final product to decrease.

### 2.5.20 Trying to Reproduce Previous Results Using Pd(dba)$_2$

The Pd(dba)$_2$ conditions were revisited to test if there was a certain set of reaction conditions that could produce consistent results (Table 16). Trying to reproduce the initially promising result of 77% yield and 87% ee ended in failure.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comment</th>
<th>Yield A [%]</th>
<th>Yield B [%]</th>
<th>ee B [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Add Pd with reagents</td>
<td>ND</td>
<td>(77)</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Repeat Entry 1</td>
<td>23</td>
<td>58, (57)</td>
<td>46</td>
</tr>
</tbody>
</table>

ND = not determined. Values in the parenthesis indicate isolated yields. All other yields are $^1$H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

**Table 16: Attempt at reproducing previous results utilizing Pd(dba)$_2$**

### 2.5.21 Water Addition Experiments

Faced with these reproducibility issues, some mechanistic questions were raised. In the mechanism for the RCAA, it is unclear what reaction component is performing the hydrolysis as there is no water in the reaction. The first thought was that perhaps the 0.2 M HCl (added for the reaction quench) could act as the proton source and hydrolyze the rhodium enolate during the reaction work-up. However, when the reaction was quenched with D$_2$O instead of 0.2 M HCl, there was no deuterium incorporation observed by $^1$H NMR. In order to evaluate the effects of water, it was added in varying amounts to the reaction conditions at hand (Table 17).
Unfortunately, the only conclusion that can be made from this set of experiments is that water hinders the conversion from intermediate to product. There was no discernable trend for the enantioselectivities or even individual yields with regards to water content.

Table 17: Water addition experiments

<table>
<thead>
<tr>
<th>Entry</th>
<th>Water (x µL)</th>
<th>Yield A [%]</th>
<th>Yield B [%]</th>
<th>ee B [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>48</td>
<td>37, (36)</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>47</td>
<td>34, (32)</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>73</td>
<td>14, (5)</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
<td>39</td>
<td>33, (31)</td>
<td>70</td>
</tr>
</tbody>
</table>

Values in parenthesis indicate isolated yields. All other yields are ¹H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

2.5.22 L17 Palladacycle

It is evident that the reaction system at hand is quite complicated and extremely sensitive to some unknown variable. There is some uncertainty as to the structure of the catalyst in solution. In order to simplify the catalyst system, a palladacycle version of the ligand was synthesized from the corresponding G2 dimer according to a reported procedure. The goal was to have precisely one palladium species bound to one phosphine ligand. The palladium will only be released after all the reagents are added as it requires base to deprotonate the amine. This palladacycle approach

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might minimize any metal-metal interference or ligand-metal mismatch during the premixing stage. *L22* was tested under the conditions adopted thus far (Table 18).

![Diagram of L22]

**Entry** | **Comment** | **Yield 1** (%) | **Yield 2** (%) | **ee 2** (%)
---|---|---|---|---
1 | - | ND | 84, (64) | 20
2 | repeat | 9 | 81, (73) | 14
3 | repeat | ND | 82, ND | 46
4 | repeat | ND | ND, (62) | 67
5 | Cs$_2$CO$_3$ instead of K$_3$PO$_4$ | ND | 95, (84) | 20
6 | catalyst loading decreased by half | ND | 92, (77) | 68

ND = not determined. Values in parenthesis indicate isolated yields. All other yields are $^1$H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

**Table 18: L17 palladacycle optimization table using L22**

Although the yield seemed to improve compared to the case with free Pd(II) in solution ($^1$H NMR yields were consistently in the 80% range over three repeats of the experiment and no intermediate could be observed by TLC), the ee could not be reproduced over four trials. When Cs$_2$CO$_3$ was used in place of K$_3$PO$_4$ the yield was excellent yet the ee was poor at 20%. Next, the catalyst loading was investigated by decreasing it by half. The yield was comparable to the
regular catalyst loading while the ee was 68%, which was the best ee obtained in the screen. Although reproducibility was still an issue, in general \textit{L22} did perform better than the original hybrid ligand, \textit{L17} in terms of yield.

\subsection*{2.5.23 Control Experiments to Investigate EE}

Since the palladacycle version of the ligand did not lead to ee reproducibility, some control experiments were run with respect to the conditions utilizing the original naphthalene version of the hybrid ligand, \textit{L17}. The first experiment involved the preparation of a stock solution containing the premixed rhodium catalyst (twice the original size) and it was to be split between two identical pre-made reactions (Table 19). This method may be able to isolate the problem if it is occurring during the initial premixing stage and not during the reaction itself. However, the results from this experiment did not indicate that the problem was solely in the premixing stage as both the yields and ee’s did not match. We then attempted two sets of two-step one-pot reactions. The case where the RCAA proceeded first followed by the palladium-catalyzed Suzuki-Miyaura coupling produced both poor yield and ee of the final product. This was especially strange as previous control experiments without palladium showed that the ee was excellent with the use of this ligand (ee 95%) when palladium was omitted, regardless of the nature of the base used or whether cesium fluoride was present or not. In the absence of palladium, the rhodium step should occur in high yield and it was expected that the ee would be close to 95% in this case. The inverse case where the Suzuki-Miyaura coupling was run first overnight produced a low yield and a poor ee of 17%. Due to these confusing results, a final experiment was run where the isolated intermediate 1 with a known ee of 91% was subjected to the Suzuki-Miyaura coupling. The yield was not determined as some was lost during a fraction collection spill, however the compound that was saved displayed an ee of only 77%. These results suggest there must be some erosion happening to this stereocenter during the course of the reaction.
Table 19: Control experiments to investigate ee irreproducibility

2.6. Conclusion

In an attempt to expand the field of asymmetric multi-metal catalysis, preliminary work was carried out on the synthesis of novel covalently bonded hybrid ligands containing a diene and a phosphine moiety for the purposes of Rh/Pd dual-metal catalysis. In terms of the ligand synthesis, a successful route was achieved by implementing key steps from a reported procedure by Hayashi and co-workers (Scheme 43). This route gave access to a naphthalene version of the hybrid ligand, \textit{L17}. Other synthetic methods were explored but were found to be unsuccessful.
In terms of other hybrid ligands, attempts were made at obtaining both amide linker and ion-paired hybrid ligands. These attempts were not successful and require additional investigation.

Having synthesized hybrid ligand \( L17 \), it was applied to Rh/Pd dual metal catalysis. Although different substrates were tried, the main focus of this project features the Rh-catalyzed asymmetric 1,4-conjugate addition to an \( \alpha,\beta \)-unsaturated ketone followed by a Suzuki-Miyaura coupling in a one-pot one-step manner. The initial results gave a disappointing yield of 10% of the desired product 2. However, the intermediate 1 displayed an excellent enantioselectivity of 95%, which encouraged further optimization (Scheme 44).

**Scheme 43: Synthesis of hybrid ligand, \( L17 \)**

**Scheme 44: Initial results for the enone substrate**

Moving forward, the yield of the desired product 2 was improved through various base, reaction time and catalyst/catalytic loading modifications. The best result obtained during this study is depicted below in scheme 45.
Scheme 45: Best results obtained using the enone substrate

Control experiments were carried out featuring the corresponding separate ligands (Hayashi’s naphthalene version of the chiral diene and PPh₃). A significant erosion in both yield and ee were observed which indicate this hybrid ligand provides benefit to this methodology. This methodology was ultimately faced with reproducibility issues which prompted the synthesis of a palladacycle version of L17 in an attempt to simplify the catalyst system. Unfortunately the palladacycle did not render the results reproducible. Future work in terms of Rh/Pd dual-metal catalysis includes solving the existing reproducibility issues followed by the investigation of a substrate scope.
Chapter 3 – Supporting Information

3.1. General Considerations

**General Experimental Procedures:** Unless otherwise stated all reactions were carried out under argon atmosphere in glassware that was oven-dried. Reactions were monitored using thin-layer chromatography (TLC) using EMD Silica Gel 60 F254 plates. TLC visualization of the developed plates was performed using UV light (254 nm) or/and by staining with potassium permanganate (KMnO₄) or cerium ammonium molybdate (CAM) followed by heating of the plates with a heat gun. Compounds were purified via Silica Gel Flash Column Chromatography using SILICYCLE® SILIAFLASH P60, 40-63 µm silica gel.

**Materials:** Unless otherwise noted, starting materials and catalysts used were purchased from Sigma Aldrich, Alfa Aesar, Strem, or Combi-Blocks and used without further purification. Based used in the catalytic reactions (potassium carbonate, potassium hydroxide and potassium phosphate) were finely ground into powders and were stored in a desiccator. Toluene was freshly distilled over sodium under N₂ before use. Dichloromethane and acetonitrile were freshly distilled over calcium hydride under N₂ before use. Tetrahydrofuran was freshly distilled over sodium/benzophenone under N₂ before use. Imines, boroxines and enones were prepared according to literature procedures.

**Instrumentation:** NMR characterization data were recorded at 23 °C with a Bruker Advance III 400 MHz or a Varian VnmrS 400 NMR spectrometer. ¹H NMR spectra were internally referenced to TMS (δ = 0 ppm) or to the residual solvent signal (CDCl₃, δ = 7.26 ppm or C₆H₆, δ = 7.16 ppm). ¹³C NMR spectra were internally referenced to the residual solvent signal. ³¹P NMR spectra were not referenced. Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad),


coupling constant (Hz), integration. High Resolution Mass Spectra (HRMS) were obtained on a micromass 70S-250 spectrometer (EI) or an AB SciEX QSTAR® Mass Spectrometer (ESI) or a JEOL® AccuTOF medel JMS-T1000LC mass spectrometer equipped with IONICS® Direct Analysis in real time (DART) ion source at ADVANCED INSTRUMENTATION FOR MOLECULAR STRUCTURE (AIMS) in the Department of Chemistry at the University of Toronto. The HPLC system was a HP 1100 Series modular system from Agilent, operated by a Chem Station LC 3D software, v. 10.02. The details of column type and run conditions are described below in the characterization section.

3.2. Synthesis of Compounds in Section 2.2

6-bromonaphthalen-2-yl (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate

A round bottom flask was charged with 6-bromonaphthalen-2-ol (3.0 mmol, 669.2 mg), (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (2.5 mmol, 515.7 mg), DMAP (0.125 mmol, 15.2 mg), and DCM. This mixture was then cooled to 0 °C and stirred for 15 minutes. DCC (3.0 mmol, 619 mg) was then added slowly and the reaction was warmed to room temperature for 18 hours. The solution was then diluted with DCM and filtered through celite (washing with DCM). The crude mixture was then concentrated. Silica gel flash column chromatography (20:1 Hexane/EtOAc) gave the product (877.8 mg, 85%) as a white solid.

1H NMR (400 MHz, CDCl3) δ: 8.00 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.28 (dd, J = 8.9, 2.3 Hz, 1H), 5.89 (d, J = 6.0 Hz, 1H), 4.20 (dt, J = 6.1, 2.1 Hz, 1H), 3.54 – 3.43 (m, 1H), 1.87 (d, J = 1.7 Hz, 3H), 1.66 (ddd, J = 11.7, 8.8, 3.0 Hz, 1H), 1.34 – 1.24 (m, 1H), 1.21 – 1.10 (m, 1H), 1.10 – 0.99 (m, 4H), 0.86 (d, J = 6.4 Hz, 3H);

13C NMR (126 MHz, CDCl3) δ: 163.5, 149.1, 148.7, 143.4, 140.5, 132.4, 132.4, 129.9, 129.9, 129.3, 128.4, 124.4, 122.7, 119.5, 118.8, 47.9, 44.4, 39.8, 33.9, 31.6, 22.0, 21.5, 19.1;

IR (film) ν/cm⁻¹: 2960, 2910, 2399, 1712, 1610, 1589, 1471, 1354, 1238, 1192, 1143, 1062, 1008, 895, 669, 642;

HRMS (DART): m/z calculated for C23H24BrO2⁺ 411.0959, found 411.0954.
(1R,4R,7R)-N-(6-bromonaphthalen-2-yl)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxamide

A round bottom flask was charged with (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (0.2 mmol, 41.26 mg), HBTU (0.22 mmol, 83.43 mg), and DCM (4 mL). This mixture was then cooled to 0 °C and stirred for 10 minutes. 6-bromonaphthalen-2-amine (0.22 mmol, 48.86 mg) and triethylamine (0.22 mmol, 30.68 µL) were then added and the reaction was warmed to room temperature and stirred for 1 hour. The solution was then quenched with brine and extracted with EtOAc (3x). The organic layer was then washed with 1M HCl, sat. NaHCO$_3$, brine and dried with MgSO$_4$. The crude mixture was then filtered and concentrated. Silica gel flash column chromatography (2:1:7 DCM/EtOAc/Hexane) gave the HBTU adduct (55.9 mg, 86%) as a white solid. This adduct was then added to a round bottom flask along with 6-bromonaphthalen-2-amine (0.35 mmol, 76.83 mg) and acetonitrile (3.5 mL). This mixture was then heated to 50 °C for 16 hours. The reaction was then cooled to room temperature, quenched with brine and extracted with EtOAc (3x). The organic layer was then washed with 1M HCl, sat. NaHCO$_3$, brine and dried with MgSO$_4$. The crude mixture was then filtered and concentrated. Silica gel flash column chromatography (2:1:7 DCM/EtOAc/Hexane) gave the desired product (54.6 mg, 77%) as a red solid. $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.27 (d, $J = 2.1$ Hz, 1H), 7.90 (d, $J = 1.9$ Hz, 1H), 7.70 – 7.58 (m, 3H), 7.47 (ddd, $J = 17.6$, 8.8, 2.1 Hz, 2H), 7.01 (dd, $J = 6.2$, 1.9 Hz, 1H), 5.85 (dt, $J = 6.1$, 1.8 Hz, 1H), 4.19 (dt, $J = 6.1$, 2.1 Hz, 1H), 3.40 (dq, $J = 4.9$, 2.4 Hz, 1H), 1.84 (d, $J = 1.7$ Hz, 3H), 1.61 (ddd, $J = 11.7$, 8.8, 3.0 Hz, 1H), 1.27 (dddt, $J = 9.0$, 6.6, 4.8, 2.1 Hz, 1H), 1.12 (dddt, $J = 12.4$, 9.4, 6.3 Hz, 1H), 1.07 – 0.93 (m, 4H), 0.83 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 164.4, 145.7, 144.0, 139.1, 136.1, 132.5, 131.5, 129.9, 129.7, 129.4, 127.9, 124.2, 120.8, 118.7, 116.3, 48.0, 43.9, 40.2, 33.9, 31.9, 22.0, 21.5, 19.1; IR (film) ν/cm$^{-1}$: 3433, 2962, 2359, 2341, 2332, 1666, 1593, 1521, 1489, 1386; HRMS (DART): m/z calculated for C$_{23}$H$_{25}$BrNO$^+$ 410.1119, found 410.1117.
(1R,4R,7R)-N-(6-bromonaphthalen-2-yl)-7-isopropyl-N,5-dimethylbicyclo[2.2.2]octa-2,5-diene-2-carboxamide

A round bottom flask was charged with sodium hydride (60%) (0.4386 mmol, 17.54 mg) and THF (3 mL). This mixture was then cooled to 0 °C and stirred for 5 minutes. (1R,4R,7R)-N-(6-bromonaphthalen-2-yl)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxamide (0.2924 mmol, 120 mg) and THF (7 mL) were then added as a solution at 0 °C and the resulting mixture was then stirred for 30 minutes. Iodomethane (0.5848 mmol, 36 µL) was then added and the reaction was warmed to room temperature for 9 hours. The solution was then quenched with sat. NH₄Cl and ice followed by an extraction with EtOAc (3x). The organic layer was then washed with brine and dried with Na₂SO₄. The crude mixture was then filtered and concentrated. Silica gel flash column chromatography (4:1 Hexane/EtOAc) gave the desired product (118 mg, 95%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.98 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.63 – 7.51 (m, 2H), 7.38 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.7, 2.2 Hz, 1H), 6.25 (d, J = 8.1 Hz, 0H), 5.32 (d, J = 5.9 Hz, 1H), 3.53 (dt, J = 6.0, 2.0 Hz, 1H), 3.42 (s, 2H), 3.04 (dd, J = 6.2, 2.2 Hz, 1H), 1.59 (d, J = 1.6 Hz, 3H), 1.35 (ddd, J = 11.6, 8.8, 2.9 Hz, 1H), 1.04 (tdd, J = 9.2, 4.7, 2.1 Hz, 1H), 0.88 (dt, J = 16.1, 6.6 Hz, 1H), 0.81 – 0.72 (m, 4H), 0.66 (d, J = 6.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ: 169.2, 144.4, 142.8, 142.5, 140.2, 132.5, 131.9, 130.0, 129.7, 129.1, 127.8, 126.4, 124.8, 123.8, 119.9, 47.4, 43.3, 42.2, 37.8, 33.6, 31.8, 21.6, 21.1, 18.7; IR (film) ν/cm⁻¹: 2962, 2929, 2908, 2870, 2399, 1656, 1620, 1604, 1585, 1498, 1469, 1423, 1367, 1180, 623; HRMS (DART): m/z calculated for C₂₄H₂₇BrNO⁺ 424.1276, found 424.1288.

tert-butyl (6-bromonaphthalen-2-yl)carbamate

A round bottom flask was charged with 6-bromonaphthalen-2-amine (651 mg, 2.97 mmol), (Boc)₂O (5.94 mmol, 1.36 g), triethylamine (1 mL) and DCM (2 mL). The reaction was then stirred at room temperature for 9 hours. The solution was filtered through celite and washed with
EtOAc. The crude mixture was then filtered and concentrated. Silica gel flash column chromatography (8:1 Hexane/EtOAc) gave the desired product (702 mg, 73%) as a pink solid. Spectroscopic data are consistent with those reported in the literature.  

**tert-butyl (6-bromonaphthalen-2-yl)(methyl)carbamat**

\[
\text{HN} = C \text{Br}
\]

A round bottom flask was charged with sodium hydride (60%) (1.54 mmol, 61.6 mg) and THF (10 mL). This mixture was then cooled to 0 °C and stirred for 5 minutes. tert-butyl (6-bromonaphthalen-2-yl)carbamate (249.2 mg, 0.77 mmol) and THF (20 mL) were then added as a solution at 0 °C and the resulting mixture was then stirred for 30 minutes. Iodomethane (143.80 µL, 2.31 mmol) was then added and the reaction was warmed to room temperature for 16 hours. The solution was then quenched with sat. NH₄Cl and ice followed by an extraction with EtOAc (3x). The organic layer was then washed with brine and dried with Na₂SO₄. The crude mixture was then filtered and concentrated. Silica gel flash column chromatography (4:1 Hexane/EtOAc) gave the desired product (220.6 mg, 85%) as a white solid. Spectroscopic data are consistent with those reported in the literature.

**naphthalen-2-yl propiolate**

\[
\text{O} = C \text{CH} = C\text{H}
\]

A round bottom flask was charged with 2-naphthol (10.0 g, 69.4 mmol), DMAP (84.7 mg, 0.69 mmol) and DCM (150 mL). Propiolic acid (5.35g, 76.3 mmol) and DCC (15.7g, 76.3 mmol) were then added to this solution at 0 °C. The reaction was then warmed to room temperature and

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stirred for 4 hours. The precipitates were filtered off and the filtrate was concentrated. Silica gel flash column chromatography (40:1 Hexane/EtOAc) gave the desired product as a white solid (88%). Spectroscopic data are consistent with those reported in the literature.

**naphthalen-2-yl (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate**

A round bottom flask was charged with (R)-α-phellandrene (3.906 g, 28.6767 mmol), 2-naphthyl propiolate (5.12 g, 26.0958 mmol) and DCM (87 mL). Me₂AlCl was added to the solution slowly at -78 °C. The orange solution was allowed to sit in the cold bath and slowly warm to room temperature over 18 hours. The solution was then carefully poured into a vigorously stirred, ice-cooled aqueous solution of 1N HCl (150 mL). The mixture was filtered and washed with 50 mL of DCM. The filtrate was extracted using DCM (3x). The organic layers were washed with brine (150 mL) and then dried using MgSO₄, filtered and concentrated. Silica gel flash column chromatography (5:1 Hexane/EtOAc) gave the crude product, which was then diluted with 2 mL of DCM and an excess amount of hexanes. The opened flask was left at room temperature overnight. White needles precipitated and were collected by filtration, washing with cold hexane (67%). Spectroscopic data are consistent with those reported in the literature.

**methyl (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate**

A round bottom flask was charged with naphthalen-2-yl (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (1.0 g, 3.0 mmol), sodium methoxide (810 mg, 15.0 mmol) and MeOH (15 mL). The solution was stirred at room temperature for 24 hours. The mixture was then concentrated. Silica gel flash column chromatography (20:1 Hexane/EtOAc) gave the desired product (633.7 mg, 96%) as a colourless oil. Spectroscopic data are consistent with those reported in the literature.
(1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid

A round bottom flask was charged with methyl (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (598.6 mg, 2.717 mmol), MeOH (24 mL) and 1M NaOH (12 mL). The reaction was stirred for 6 hours at 50 °C. The mixture was then quenched with 1M HCl and the aqueous layer was extracted with DCM. The organic layers were then washed with brine, dried over Na₂SO₄, filtered and concentrated to afford the crude product. Silica gel flash column chromatography (8:1 Hexane/EtOAc) gave the purified product (419 mg, 75%) as a white solid. Spectroscopic data are consistent with those reported in the literature.³¹

(6-methoxynaphthalen-2-yl)diphenylphosphane

A two-necked round bottomed flask was charged with magnesium turnings (the turnings were cut up before use in order to expose the magnesium below the oxidized coat) (720 mg, 30 mmol) and heated with a heat gun under vacuum. The flask was allowed to cool to room temperature while under vacuum. A grain of I₂ and THF (10 mL) was then added to the flask now equipped with a reflux condenser. In a separate round bottom flask, 6-bromo-2-methoxynaphthalene (7.113 g, 30 mmol) was dissolved in THF (40 mL). This mixture was added to the magnesium turnings dropwise. After the exotherm subsided, this mixture was heated to 60 °C. Upon observation of the disappearance of the magnesium turnings, Ph₂PCl (8.1 mL, 45 mmol) was added dropwise at a slow rate over 10 minutes. The reaction was then left to stir for 16 hours at 60 °C. The mixture was then cooled to room temperature, quenched with ice and NH₄Cl, extracted using EtOAc (3x), washed with brine, dried under Na₂SO₄ and concentrated. The crude solid was recrystallized

from methanol affording the pure product as a white solid (5.13 g, 50%). Spectroscopic data are consistent with those reported in the literature.\textsuperscript{32}

\textbf{6-(diphenylphosphanyl)naphthalen-2-ol}

![Chemical structure](image)

A round bottom flask equipped with a reflux condenser was charged with (6-methoxynaphthalen-2-yl)diphenylphosphane (2.2 g, 6.4 mmol) and HBr\textsubscript{(aq)} (48\%) (10 mL). The reaction was refluxed at 100 °C for 4 hours. The reaction was then cooled to room temperature and the precipitate was collected by filtration, washed with water and dried affording the hydrobromide salt. This salt was then added to a solution of NaOH (0.38 g) dissolved in ethanol (20 mL) and left to stir until it completely dissolved. This solution was then treated with acetic acid until just acidic. Water was then added and the precipitate was collected by filtration. The crude product was recrystallized from methanol affording the pure compound (92\%)\textsuperscript{32} which was used without any further purification. Spectroscopic data are consistent with those reported in the literature.\textsuperscript{32}

\textbf{6-(diphenylphosphanyl)naphthalen-2-yl (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate}

![Chemical structure](image)

A round bottom flask was charged with 6-bromonaphthalen-2-ol (361.185 mg, 1.1 mmol), (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (206.28 mg, 1.0 mmol), DMAP (6.10 mg, 0.05 mmol), and DCM (10 mL). This mixture was then cooled to 0 °C and stirred for 15 minutes. DCC (247.59 mg, 1.2 mmol) was then added slowly and the reaction was warmed to room temperature for 5 hours. The solution was then diluted with DCM and filtered through celite (washing with DCM). The crude mixture was then concentrated. Silica gel

flash column chromatography (20:1 Hexane/EtOAc) gave the product (414.5 mg 80%) as a white solid. \( \text{mp} \) – 96-100 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.76 (dd, \( J = 16.2, 9.0 \) Hz, 3H), 7.61 – 7.55 (m, 2H), 7.41 – 7.30 (m, 11H), 7.26 – 7.22 (m, 1H), 5.89 (dd, \( J = 5.0, 3.1 \) Hz, 1H), 4.20 (dt, \( J = 6.1, 2.1 \) Hz, 1H), 3.49 (dq, \( J = 4.4, 2.4 \) Hz, 1H), 1.87 (d, \( J = 1.7 \) Hz, 3H), 1.66 (ddd, \( J = 11.6, 8.7, 2.9 \) Hz, 1H), 1.28 (d, \( J = 12.3 \) Hz, 1H), 1.20 – 1.10 (m, 1H), 1.08 – 0.99 (m, 4H), 0.86 (d, \( J = 6.5 \) Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 163.6, 149.5, 148.6, 143.4, 140.5, 137.1, 137.0, 134.5, 134.4, 134.1, 134.0, 133.8, 132.3, 132.2, 131.3, 131.2, 130.8, 130.7, 129.5, 128.9, 128.7, 128.6, 127.8, 127.8, 124.4, 122.0, 118.6, 47.9, 44.4, 39.8, 33.9, 31.6, 22.0, 21.5, 19.1; \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \( \delta \): -4.64; IR (film) \( \nu / \text{cm}^{-1} \): 2964, 2933, 2870, 2399, 1724, 1612, 1469, 1435, 1354, 1145, 1128, 1058; HRMS (DART): \( m/z \) calculated for C\(_{35}\)H\(_{34}\)O\(_2\)P\(_1\)\(^+\) 517.2296, found 517.2272; \([\alpha]^{20}_D\) +3.0 (c. 0.53, CHCl\(_3\)).

(4-methoxyphenyl)diphenylphosphane

A two-necked round bottomed flask was charged with magnesium turnings (the turnings were cut up before use in order to to expose the magnesium below the oxidized coat) (480 mg, 20 mmol) and heated with a heat gun under vacuum. The flask was allowed to cool to room temperature while under vacuum. A grain of I\(_2\) and THF (20 mL) was then added to the flask now equipped with a reflux condenser. In a separate round bottom flask, 1-bromo-4-methoxybenzene (2.5 mL, 20 mmol) was diluted in THF (10 mL). This mixture was added to the magnesium turnings dropwise. After the exotherm subsided, this mixture was heated to 60 °C. Upon observation of the disappearance of the magnesium turnings, Ph\(_2\)PCl (7.18 mL, 40 mmol) was added dropwise at a slow rate over 10 minutes. The reaction was then left to stir for 16 hours at 60 °C. The mixture was then cooled to room temperature, quenched with ice and NH\(_4\)Cl, extracted using EtOAc (3x), washed with brine, dried under Na\(_2\)SO\(_4\) and concentrated. The crude solid was recrystallized from methanol affording the pure product as a white solid (2.97 g, 51%). Spectroscopic data are consistent with those reported in the literature.\(^{33}\)

4-(diphenylphosphanyl)phenol

\[ \text{\begin{tikzpicture}
    \node[shape=circle,draw,fill=black] (A) at (0,0) {H};
    \node[shape=circle,draw,fill=black] (B) at (-1,0) {O};
    \node[shape=circle,draw,fill=black] (C) at (0,0) {O};
    \node[shape=circle,draw,fill=black] (D) at (1,0) {PPh_2};
\end{tikzpicture}} \]

A round bottom flask equipped with a reflux condenser was charged with (6-methoxynaphthalen-2-yl)diphenylphosphane (2.97 g, 10.2 mmol) and HBr\text{aq} (48\%) (20 mL). The reaction was refluxed at 100 °C for 4 hours. The reaction was then cooled to room temperature and the precipitate was collected by filtration, washed with water and dried affording the hydrobromide salt. This salt was then added to a solution of 1M NaOH (0.5 g) dissolved in ethanol (30 mL) and left to stir until it completely dissolved. This solution was then treated with acetic acid until just acidic. Water was then added and the precipitate was collected by filtration. The crude product was recrystallized from methanol followed by silica gel flash column chromatography (8:1 Hexane/EtOAc) affording the pure compound as a white solid (995 mg, 35%). Spectroscopic data are consistent with those reported in the literature.34

4-(diphenylphosphanyl)phenyl (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate

\[ \text{\begin{tikzpicture}
    \node[shape=circle,draw,fill=black] (E) at (0,0) {Me};
    \node[shape=circle,draw,fill=black] (F) at (0,-1) {O};
    \node[shape=circle,draw,fill=black] (G) at (0,0) {O};
    \node[shape=circle,draw,fill=black] (H) at (1,0) {PPh_2};
\end{tikzpicture}} \]

A round bottom flask was charged with 4-(diphenylphosphanyl)phenol (82.40 mg, 0.2916 mmol), (1R,4R,7R)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (54.7 mg, 0.2651 mmol), DMAP (1.61 mg, 0.0132 mmol), and DCM (4 mL). This mixture was then cooled to 0 °C and stirred for 15 minutes. DCC (65.63 mg, 0.3181 mmol) was then added slowly and the reaction was warmed to room temperature for 5 hours. The solution was then diluted with DCM and filtered through celite (washing with DCM). The crude mixture was then concentrated. Silica gel flash column chromatography (20:1 Hexane/EtOAc) gave the product (121 mg, 98%) as a colourless oil. \textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}) \( \delta: 7.53 \text{ (dd, } J = 6.3, 1.9 \text{ Hz, } 1\text{H}), 7.36 - 7.28 \text{ (m, } 11\text{H}), 7.13 - 7.05 \text{ (m, } 2\text{H}), 5.87 \text{ (ddd, } J = 6.0, 2.7, 1.2 \text{ Hz, } 1\text{H}), 4.16 \text{ (dt, } J = 6.0, 2.0 \text{ Hz, } 1\text{H}), 3.47
\]

(dtd, \( J = 6.4, 2.6, 1.9 \text{ Hz}, 1\text{H} \)), 1.85 (d, \( J = 1.7 \text{ Hz}, 3\text{H} \)), 1.63 (ddd, \( J = 11.7, 8.8, 3.0 \text{ Hz}, 1\text{H} \)), 1.30 – 1.20 (m, 2H), 1.13 (dp, \( J = 9.8, 6.5 \text{ Hz}, 1\text{H} \)), 1.06 – 0.98 (m, 4H), 0.84 (d, \( J = 6.5 \text{ Hz}, 3\text{H} \)); \(^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta \): 163.3, 151.7, 148.5, 143.4, 140.5, 137.3, 137.2, 135.1, 134.9, 134.2, 134.1, 133.8, 133.7, 128.9, 128.7, 128.6, 124.3, 122.0, 122.0, 47.9, 44.4, 39.8, 35.0, 33.9, 31.7, 31.6, 25.6, 24.8, 22.0, 21.4, 19.1; \(^{31}\text{P NMR} \) (162 MHz, CDCl\(_3\)) \( \delta \): -6.12; \( \text{IR (film)} \) \( \nu/cm^{-1} \): 3053, 2956, 2929, 2868, 2119, 1714, 1589, 1492, 1201, 1124, 1091, 1058, 1006, 974, 868, 742; \( \text{HRMS (DART)} \): \( m/z \) calculated for \( \text{C}_{31}\text{H}_{32}\text{O}_2\text{P}^+ \) 467.2139, found 467.2133.

**Palladacycle L22**

![Palladacycle L22](image)

A round bottom flask was charged with 6-(diphenylphosphanyl)naphthalen-2-yl (1\(R\),4\(R\),7\(R\))-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (32.8 mg, 0.063529 mmol), Chloro(2'-amino-1,1'-biphenyl-2-yl)palladium(II) dimer (20 mg, 0.03176 mmol) and acetone (1 mL). The solution was stirred for 2.5 hours and then was concentrated. The crude solid was then diluted with 1 drop of DCM and an excess amount of hexane. Concentrating this mixture afforded the pure product as a white solid (42 mg, 81%). \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \): 8.02 (dd, \( J = 13.5, 1.5 \text{ Hz}, 1\text{H} \)), 7.66 (d, \( J = 8.9 \text{ Hz}, 1\text{H} \)), 7.63 – 7.50 (m, 8H), 7.41 (ddd, \( J = 9.9, 8.6, 1.6 \text{ Hz}, 1\text{H} \)), 7.29 (dd, \( J = 10.4, 4.7 \text{ Hz}, 8\text{H} \)), 7.26 – 7.22 (m, 2H), 6.86 (td, \( J = 7.4, 1.1 \text{ Hz}, 1\text{H} \)), 6.53 (ddd, \( J = 7.3, 6.0, 1.2 \text{ Hz}, 1\text{H} \)), 6.40 (td, \( J = 7.5, 1.5 \text{ Hz}, 1\text{H} \)), 5.89 (dt, \( J = 6.0, 1.8 \text{ Hz}, 1\text{H} \)), 5.02 (d, \( J = 74.0 \text{ Hz}, 2\text{H} \)), 4.19 (dt, \( J = 6.1, 2.1 \text{ Hz}, 1\text{H} \)), 3.50 (dt, \( J = 6.4, 2.3 \text{ Hz}, 1\text{H} \)), 1.87 (d, \( J = 1.7 \text{ Hz}, 3\text{H} \)), 1.66 (ddd, \( J = 11.7, 8.8, 2.9 \text{ Hz}, 1\text{H} \)), 1.32 – 1.28 (m, 1\text{H})), 1.14 (qd, \( J = 6.5, 4.2 \text{ Hz}, 1\text{H} \)), 1.08 – 0.99 (m, 4H), 0.86 (d, \( J = 6.5 \text{ Hz}, 4\text{H} \)); \(^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \): 163.5, 150.6, 150.3, 148.7, 143.4, 140.4, 140.1, 138.5, 138.4, 138.3, 136.4, 136.3, 135.1, 135.1, 134.9, 134.8, 134.5, 134.5, 130.7, 130.6, 130.6, 130.2, 128.3, 128.2, 128.1, 127.9, 127.5, 127.4, 127.3, 127.2, 125.9, 125.8, 125.1, 124.4, 122.2, 120.6, 118.5, 47.9, 44.4, 39.8, 33.9, 31.6, 21.9, 21.5, 19.1; \(^{31}\text{P NMR} \) (162 MHz, CDCl\(_3\)) \( \delta \): 36.29; \( \text{IR (film)} \) \( \nu/cm^{-1} \): 3227, 3196, 2960, 2918, 2870, 2848, 2698, 2683,1722; \( \text{HRMS (ESI+)} \): \( m/z \) calculated for \( \text{C}_{47}\text{H}_{43}\text{NO}_2\text{PPd} \) 786.2082, found 786.2049.
3.3. Synthesis of Compounds in Section 2.5

General Procedure for dual-metal catalyzed reactions (palladium is pre-mixed): To a microwave vial was added the palladium precatalyst, L17 and toluene (0.5 mL). The vial was capped with a rubber septum, purged with argon for 2 minutes and stirred for 10 minutes at room temperature. The rhodium precatalyst was then added and the solution was capped with a rubber septum, purged with argon for 2 minutes and stirred at 60 °C for 30 minutes. The vial containing the catalyst was then cooled to room temperature under argon. The substrate (imine or enone) (0.15 mmol), boroxine (2.2 – 4 equiv. of [B]), cesium fluoride (2 equiv.), and base (if solid) (3 equiv.) were then weighed onto a single weigh paper in a layered fashion and added to the reaction followed by toluene (1 mL) (if KOH(aq) (40 or 80 mol %) was used it was added to the reaction after all the reagents using a microsyringe). The microwave vial was then quickly capped using a crimper and the vial containing all the reagents was purged under argon for 5 minutes. The balloon and outlet needle were then removed and the reaction was then run at the corresponding temperature and time. After the reaction time had elapsed, the reaction was then cooled to room temperature, opened and diluted with EtOAc (1 mL). Following this, the reaction was quenched with 0.2 M HCl (2.5 mL). The heterogeneous mixture was then vigorously mixed and an extraction was performed using EtOAc (3-4x). The organic layers were then dried over Na₂SO₄, filtered and concentrated. Silica gel flash column chromatography (10:1 Hexane/EtOAc) afforded the products.

General Procedure for dual-metal catalyzed reactions (palladium added with reagents): To a microwave vial was added the rhodium precatalyst, L17 and toluene (0.5 mL). The solution was capped with a rubber septum, purged with argon for 2 minutes and stirred at 60 °C for 30 minutes. The vial containing the rhodium catalyst was then cooled to room temperature under argon. The palladium precatalyst, substrate (imine or enone) (0.15 mmol), boroxine (2.2 – 4 equiv. of [B]), cesium fluoride (2 equiv.), and base (if solid) (3 equiv.) were then weighed onto a single weigh paper in a layered fashion and added to the reaction followed by toluene (1 mL) (if KOH(aq) (40 or 80 mol %) was used it was added to the reaction after all the reagents using a microsyringe). The microwave vial was then quickly capped using a crimper and the vial containing all the reagents was purged under argon for 5 minutes. The balloon and outlet needle were then removed and the reaction was then run at the corresponding temperature and time. After the reaction time had elapsed, the reaction was then cooled to room temperature, opened and diluted with EtOAc (1
mL). Following this, the reaction was quenched with 0.2 M HCl (2.5 mL). The heterogeneous mixture was then vigorously mixed and an extraction was performed using EtOAc (3-4x). The organic layers were then dried over Na₂SO₄, filtered and concentrated. Silica gel flash column chromatography (10:1 Hexane/EtOAc) afforded the products.

**General Procedure for dual-metal catalyzed reactions (Rh catalyst added last):** To a 2 dram vial was added the rhodium precatalysts, \textit{L}17 and toluene (0.5 mL). The solution was capped with a rubber septum, purged with argon for 2 minutes and stirred at 60 °C for 30 minutes. The vial containing the rhodium catalyst was then cooled to room temperature under argon. To a separate microwave vial, CsF (2 equiv) and base (3 equiv.) were added which was followed by drying these reagents under vacuum while heating with a heatgun. The palladium precatalyst, substrate (imine or enone) (0.15 mmol), and boroxine (4 equiv. of [B]) were then weighed onto a single weigh paper in a layered fashion and added to the microwave vial (if KOH (aq) (40 or 80 mol %) was used it was added to the reaction after all the reagents using a microsyringe). The microwave vial was then quickly capped using a crimper. The rhodium catalyst was then added to the mixture through the seal via syringe. Toluene (1 mL) was then added to the reaction and it was allowed to purge under argon for 5 minutes. The balloon and outlet needle were then removed and the reaction was then run at the corresponding temperature and time. After the reaction time had elapsed, the reaction was then cooled to room temperature, opened and diluted with EtOAc (1 mL). Following this, the reaction was quenched with 0.2 M HCl (2.5 mL). The heterogeneous mixture was then vigorously mixed and an extraction was performed using EtOAc (3-4x). The organic layers were then dried over Na₂SO₄, filtered and concentrated. Silica gel flash column chromatography (10:1 Hexane/EtOAc) afforded the products.

\textit{N-}((2-bromophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide

![Chemical structure](attachment:image.png)

To a microwave vial was added the rhodium precatalyst (5 mol %), \textit{L}17 (5.5 mol %) and toluene (0.5 mL). The solution was capped with a rubber septum, purged with argon for 2 minutes and stirred at 60 °C for 30 minutes. The vial containing the rhodium catalyst was then cooled to room
temperature under argon. The imine substrate (0.5 mmol), phenylboronic acid (1.1 equiv.), and toluene (1 mL) were then added to the reaction. KOH\textsubscript{(aq)} (40 mol %) was then added to the reaction using a microsyringe. The microwave vial was then quickly capped using a crimper and the vial containing all the reagents was purged under argon for at least 5 minutes. The balloon and outlet needle were then removed and the reaction was then run at the corresponding temperature and time. After the reaction time had elapsed, the reaction was then cooled to room temperature, opened and diluted with EtOAc (1 mL). Following this, the reaction was quenched with 0.2 M HCl (2.5 mL). The heterogeneous mixture was then vigorously mixed and an extraction was performed using EtOAc (3-4x). The organic layers were then dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. Silica gel flash column chromatography (10:1 Hexane/EtOAc) afforded the product as a white solid (85%, >99% ee). Spectroscopic data are consistent with those reported in the literature.\textsuperscript{35}

3-phenyl-2-tosylisoindolin-1-one

![3-phenyl-2-tosylisoindolin-1-one](image)

To a Schlenk flask was added \(N\)-((2-bromophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (0.5 mmol), Pd(OAc)\textsubscript{2} (5 mol%), PPh\textsubscript{3} (10 mol %) and K\textsubscript{2}CO\textsubscript{3} (2 equiv.). A carbon monoxide balloon was attached to the top of the flask \textit{via} an adaptor containing a inlet/outlet joint (ensuring this joint was closed). The Schlenk flask containing all the reagents was then evacuated under vacuum. After the vacuum was closed, the atmosphere was refilled with carbon monoxide by opening the previously installed joint attached to the CO balloon. Xylene (2 mL) was added and the reaction was then run at the corresponding temperature and time. After the reaction time had elapsed, the reaction was then cooled to room temperature, opened and diluted with EtOAc (1 mL). Following this, the reaction was quenched with 0.2 M HCl (2.5 mL). The heterogeneous mixture was then vigorously mixed and an extraction was performed using EtOAc (3-4x). The

organic layers were then dried over Na$_2$SO$_4$, filtered and concentrated. Silica gel flash column chromatography (10:1 Hexane/EtOAc) afforded the product as a white solid. Spectroscopic data are consistent with those reported in the literature.$^{35}$

$N$-((4-bromophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide

![Chemical structure]

**HPLC** (Chiralpak AD-H, n-hexane/2-propanol = 80/20, flow = 0.4 mL/min, detection at 254 nm). Spectroscopic data are consistent with those reported in the literature.$^{36}$

$N$-([1,1'-biphenyl]-4-yl(phenyl)methyl)-4-methylbenzenesulfonamide

![Chemical structure]

**HPLC** (Chiralpak AD-H, n-hexane/2-propanol = 90/10, flow = 0.4 mL/min, detection at 254 nm). Spectroscopic data are consistent with that reported in the literature.$^{37}$ The absolute configuration was assigned as $S$ from the comparison with the reported HPLC retention time for 99 % ee ($S$).$^{12}$

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\( \text{N-}((4\text{-bromophenyl})(4\text{-methoxyphenyl})\text{methyl})-4\text{-methylbenzenesulfonamide} \)

\[ \text{\includegraphics[width=0.2\textwidth]{molecule1.png}} \]

\( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \): 7.59 – 7.50 (m, 1H), 7.37 – 7.29 (m, 1H), 7.19 – 7.12 (m, 1H), 7.05 – 6.97 (m, 1H), 6.97 – 6.89 (m, 1H), 6.78 – 6.69 (m, 1H), 5.47 (d, \( J = 6.8 \text{ Hz} \), 1H), 4.99 (d, \( J = 6.8 \text{ Hz} \), 1H), 3.75 (s, 1H), 2.40 (s, 1H); \( ^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta \): 159.3, 143.5, 139.8, 137.3, 132.3, 131.6, 129.5, 129.1, 128.6, 127.3, 121.6, 114.2, 60.4, 55.4, 21.6; \( \text{IR (film) v/cm}^{-1} \): 3377, 3273, 2960, 2935, 2839, 2399, 1610, 1512, 1487, 1329, 1251, 1158, 1093, 1010, 925, 771, 669.

\( \text{N-}((4'\text{-methoxy-}[1,1'\text{-biphenyl}-4-yl])(4\text{-methoxyphenyl})\text{methyl})-4\text{-methylbenzenesulfonamide} \)

\[ \text{\includegraphics[width=0.2\textwidth]{molecule2.png}} \]

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \): 7.62 – 7.54 (m, 1H), 7.48 – 7.42 (m, 1H), 7.41 – 7.36 (m, 1H), 7.17 – 7.11 (m, 3H), 7.04 (dd, \( J = 8.9, 0.6 \text{ Hz} \), 1H), 6.96 (d, \( J = 8.9 \text{ Hz} \), 1H), 6.76 (d, \( J = 8.8 \text{ Hz} \), 1H), 5.55 (d, \( J = 6.8 \text{ Hz} \), 1H), 4.98 (d, \( J = 6.8 \text{ Hz} \), 1H), 3.85 (s, 3H), 3.76 (s, 3H), 2.37 (s, 1H); \( ^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta \): 159.3, 159.2, 143.3, 140.2, 139.1, 137.5, 133.1, 132.8, 129.5, 128.7, 128.1, 127.8, 127.4, 126.8, 114.3, 114.3, 114.1, 60.7, 55.5, 55.4, 21.6; \( \text{IR (film) v/cm}^{-1} \): 3286, 3273, 3248, 2964, 2848, 2721, 2332, 1595, 1157, 667; \( \text{HRMS (ESI+)} \): \( m/z \) calculated for \( \text{C}_{28}\text{H}_{27}\text{NaN}_{4}\text{O}_{4}\text{S} \) 496.1543, found 496.1553.
3-(4-bromophenyl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one

\[
\begin{align*}
\text{mp} &\quad 92-94 \, ^\circ\text{C}; \quad ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta: 8.00 - 7.85 \text{ (m, 1H), 7.62 - 7.50} \text{ (m, 0H), 7.49 - 7.41} \text{ (m, 1H), 7.40 - 7.35} \text{ (m, 1H), 7.19 - 7.09} \text{ (m, 2H), 6.85 - 6.79} \text{ (m, 1H), 4.74} \text{ (t, } J = 7.3 \text{ Hz, 1H), 3.76} \text{ (s, 1H), 3.67} \text{ (d, } J = 7.3 \text{ Hz, 1H);} \quad ^{13}\text{C NMR} \ (126 \text{ MHz, CDCl}_3) \delta: 197.9, 158.3, 143.6, 137.0, 135.8, 133.3, 131.7, 129.6, 128.8, 128.7, 128.1, 120.2, 114.1, 55.3, 44.8, 44.7; \quad \text{IR (film)} \\ &\quad \nu/cm^{-1}: 2956, 2933, 2914, 2837, 2399, 1687, 1610, 1597, 1581, 1512, 1487, 1448, 1303, 1249, 1215, 1178, 1074, 1010, 1035, 669, 621; \quad \text{HPLC} \quad (\text{Chiralpak AD-H, n-hexane/2-propanol} = 95/5, \text{ flow} = 0.4 \text{ mL/min, detection at 254 nm}).
\end{align*}
\]

3-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one

\[
\begin{align*}
\text{mp} &\quad 115-118 \, ^\circ\text{C}; \quad ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta: 7.99 - 7.91 \text{ (m, 2H), 7.59 - 7.52} \text{ (m, 1H), 7.50 - 7.41} \text{ (m, 6H), 7.32 - 7.28} \text{ (m, 2H), 7.23 - 7.17} \text{ (m, 2H), 6.98 - 6.92} \text{ (m, 2H), 6.86 - 6.80} \text{ (m, 2H), 4.81} \text{ (t, } J = 7.3 \text{ Hz, 1H), 3.83} \text{ (s, 3H), 3.76} \text{ (s, 3H), 3.74} \text{ (d, } J = 7.3 \text{ Hz, 2H);} \quad ^{13}\text{C NMR} \ (126 \text{ MHz, CDCl}_3) \delta: 198.2, 159.1, 158.2, 143.1, 138.9, 137.2, 136.4, 133.5, 133.2, 128.9, 128.7, 128.2, 128.1, 126.9, 114.2, 114.1, 55.4, 55.3, 45.0, 44.9; \quad \text{IR (film)} \\ &\quad \nu/cm^{-1}: 2956, 2935, 2910, 2837, 2399, 1680, 1610, 1581, 1512, 1498, 1464, 1247, 1215, 1178, 1041, 1114, 821, 815; \quad \text{HRMS (DART)}: \ m/z \text{ calculated for } \text{C}_{29}\text{H}_{30}\text{NO}_3 \text{ 440.2225, found 440.2237; HPLC} \quad (\text{Chiralpak AD-H, n-hexane/2-propanol} = 85/15, \text{ flow} = 0.4 \text{ mL/min, detection at 254 nm}). \quad \text{The absolute}
\end{align*}
\]
configuration was assigned as $S$ from the comparison with the reported HPLC retention time for 25 % ee ($S$).\textsuperscript{38}

\textsuperscript{38} Chen, G.; Xing, J.; Cao, P.; Liao, J. \textit{Tetrahedron} \textbf{2012}, \textit{68}(29), 5908-5911.
Chapter 4 – Spectra of New Compounds