Expanding Rh-Catalyzed Nucleophile Additions to Electron-Deficient Dienes

by

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ABSTRACT

The metal-catalyzed addition of nucleophiles to electron-deficient alkenes represents one of the most useful tools for the construction of carbon-carbon and carbon-heteroatom bonds. Of the methods that have been developed, the Rh-catalyzed conjugate addition of aryl and alkenyl boronic acids to electron-deficient dienes is considered one of the most useful platforms for installing a stereocenter β to an electron-withdrawing group. While this area has seen a tremendous amount of development over the last 25 years, the Rh-catalyzed addition to structurally related electron-deficient dienes remains comparatively underdeveloped. This thesis describes the development of new methods for the stereoselective functionalization of electron-deficient dienes, initiated by nucleophilic addition to the δ-position of the diene.

PREFACE

The research conducted for this thesis was performed in collaboration with Prof. Rylan Lundgren

The direct formic acid mediated *Z*-selective reductive coupling of dienes and aldehydes via Rh-catalyzed δ-conjugate addition of a Rh-hydride described in Chapter 2 was published as Christopher Cooze, Raphael Dada, Rylan J. Lundgren *Angew. Chem. Int. Ed.* **2019**, *58*, 12246–12251. Reaction optimization and scope studies are my original work. Raphael Dada assisted with substrate synthesis, scope, and mechanistic studies.

The diastereo-, enantio-, and *Z*-selective α,δ-difunctionalization of electron-deficient dienes initiated by Rh-catalyzed conjugate addition described in Chapter 3 was published as Christopher J. C. Cooze, Wesley McNutt, Markus D. Shoetz, Bohdan Sosunovych, Svetlana Grigoryan, Rylan J. Lundgren *J. Am. Chem. Soc.* **2021**, *143*, 10770-10777. Reaction optimization, scope and mechanistic studies are my original work. Wesley McNutt assisted with most of the scope, some mechanistic studies and performed all product derivatizations. Markus D. Shoetz assisted with substrate synthesis and initial scope examples under my direct supervision. Bohdan Sosunovych assisted with initial reaction optimization. Svetlana Grigoryan assisted in substrate synthesis related to the mechanistic studies.

The enantio-, and *Z*-selective δ-arylation of aryl dienes via the Rh-catalyzed δ conjugate addition of aryl boronic acids described in Chapter 4 is currently being developed. Reaction discovery, optimization and preliminary scope studies are my original work.

DEDICATION

To my family and friends, those who are with us, and those who are watching over us.

ACKNOWLEDGMENTS

First and foremost, I would like to thank Prof. Rylan Lundgren for his invaluable guidance and support over the last five years of this journey. Although a lot has changed since I joined the group, the fundamental support and advice you provide has not waivered. Thank you for having confidence in my ability, through the good times and the bad, thank you for pushing me to be the best version of myself.

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I would also like to thank my undergraduate supervisor, Dr. Sunil Pansare for all the support during my time in the group and in the time since, many of my accomplishments would not be possible without your valuable reference letters.

To my parents, stepparents, and sisters, thank you for your continued support over the years, without you as a safety net to fall back on, this thesis would not be possible.

To my lifelong friends, thank you for being there when I needed you and for helping me to work through challenging times during my studies.

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LIST OF ABBREVIATION AND SYMBOLS USED

Å	Ångstrom
Ac	acetyl
acac	acetylacetone
aq.	aqueous
Ar	generic aryl moiety
binap	(2,2'-bis(diphenylphosphino)-1,1'-binapthyl
Bn	benzyl
bod	[2.2.2]-bicyclooctadiene
cod	1,5-cyclooctadiene
coe	cyclooctene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	N,N-diisopropylethylamine
DMF	Dimethylformamide
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalents
Fc	ferrocene
FMO	frontier molecular orbitals
Fsp^3	Fraction of sp3 character
HPLC	high performance liquid chromatography
HRMS	high resolution mass-spectroscopy

*i*Pr	*iso*-propyl
L	generic ligand
LUMO	lowest unoccupied molecular orbitals
[M]	generic metal complex
MeOH	methanol
nbd	norbornadiene
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
PG	protecting group
Ph	phenyl
pin	pinacol
PTSA	*para*-toluenesufonic acid
R	generic group
rt	room temperature
SPINOL	1,1'-spirobiindane-7,7'-diol
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
tfb	tetrafluorobenzobarrelene
TLC	thin layer chromatography
TS	transition state
VTN	variable time normalization

Chapter 1 – Introduction

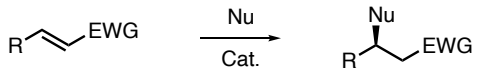
1.1 General Introduction

Drug discovery and development is among the most important translational science activity that contributes to human health and well-being.[1] Organic synthesis is an integral part of this but often represents the most time intensive aspect of drug discovery projects.[2-4] Medicinal chemistry and drug design campaigns continue to benefit from the discovery of new reaction manifolds and pathways.[2] For example, the Buchwald and Hartwig Groups discovered a Pd-catalyzed method to access aromatic amines directly from aryl (pseudo)halides and cheap amine feedstocks during the late 1990s. This revolutionary discovery has changed the way that aromatic amines are synthesized on a variety of scales.[5] 19 years after the discovery of the Buchwald–Hartwig amination, it was reported that ~10% of all medicinal chemistry papers published in 2014 had used the reaction at least once.[6] This example, along with other new synthetic methodologies, some of which have won Nobel prizes,[7-9] demonstrates that methodologies developed in an academic laboratory can spark the pharmaceutical industry to make, and explore privileged structures that were previously difficult to access.[2, 10]

The development of reactions with control over the three-dimensional configuration of a molecule are of particular importance due to their structure being more "natural product like".[11] Natural products often act as highly specific, small molecule protein-binding agents. The complex three-dimensional display of chiral functional groups is crucial for exhibiting specificity in protein binding and in differentiating between closely related proteins.[12] Since many drugs are natural products or derivatives thereof, it is important to be capable of creating more topologically complex, drug like molecule libraries, which may increase the chance of discovering new bioactive compounds.[11] One way to monitor the complexity of

compounds relates to two metrics: first is the fraction of sp^3 character (Fsp^3) as well as a count for the number of stereogenic in a molecule.[13] Methodologies that lead to an increase in these two metrics are more likely to lead to successful identification of clinical candidates.

Stereoselective reactions have enabled access to molecules with increased structural complexity. Stereoselective addition to prochiral substrates have been an attractive approach since they install at least one new stereogenic center as well as rehybridizing both carbons from sp^2 to sp^3. One class of prochiral substrates used for stereoselective reactions are alkenes. While there are a wide range of stereoselective addition reactions to alkenes,[14-18] one of most reliable methods for the stereoselective nucleophilic addition to alkenes is the conjugate addition reaction. Conjugate addition reactions involve the nucleophilic addition to an electron-deficient alkene, which installs the nucleophile β to an electron-withdrawing group (**Fig. 1–1**). This reaction class represents one of the most useful transformations in organic chemistry to increase molecular complexity through the selective elaboration of the three-dimensional space.[19-20]



organometallic Nu = RMgBr, ZnR_3, AlR_3, $RB(OH)_2$, etc.

nonorganometallic Nu = R_2CH, ROH, R_2NH

Fig. 1–1 The conjugate addition reaction

Following the seminal report of conjugate additions in 1887 by Arthur Michael,[21-22] many combinations of conjugate donors (nucleophiles) and acceptors (electrophiles) have been reported. With respect to the conjugate acceptor, a wide range of electron-withdrawing groups have been applied to this reaction. Generally speaking, it is expected that the rate in,

which these conjugate acceptors react should be influenced by the polarity of the alkene in the conjugate acceptor.[23] Some common acceptors used for these reactions include alkenes activated by nitro groups, esters, ketones, amides, and sulfonyls. The reactivity of the conjugate acceptor is generally observed to be parallel to the activating group's ability to stabilize an adjacent carbanion (**Fig. 1–2**).[24]

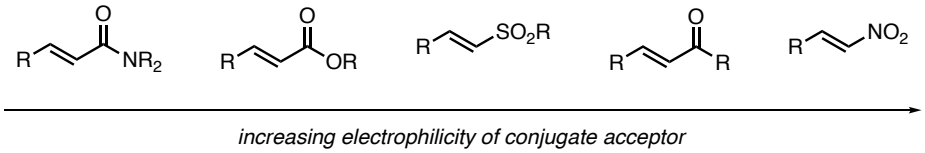


Fig. 1–2 Examples of conjugate acceptors

The conjugate donor can be divided into three groups. The first type of donors are carbanions stabilized by two π-electron-withdrawing groups (**Fig. 1–3a**). These types of substrates were the first to be used and are the most acidic of the donors used for conjugate addition reactions. Contradictory to other areas of carbanion chemistry these soft nucleophiles react successfully with a range of conjugate acceptors and due to their relatively high acidity, very mild conditions are typically employed. The second class of donors are carbanions stabilized by one π-electron-withdrawing group (**Fig. 1–3b**). These substrates typically require strong base to activate and can form both *E* and *Z* enolates, therefore control over the enolate geometry is important for the stereochemical outcome of the reaction. The third type of donors are carbanions without π-electron-withdrawing groups (**Fig. 1–3c**). These conjugate donors can be divided into two classes; organometallic donors, which are essentially masked carbanions, such as organocuprates[25] or enolate equivalents in the form of enamines. The discovery that organocuprates provide conjugate addition products

predominantly over direct nucleophilic attack to a carbonyl group, revived the field of organocopper reagents. The observation that the *in-situ* generation of enol equivalents in the form of enamines via the condensation of amines with ketones or aldehydes initiated a new field of organocatalytic reactions.[26] Overall, conjugate addition reactions have endured widespread use in organic synthesis with many different classes of conjugate donors and conjugate acceptors in both inter-[23] and intramolecular[27] reactions.

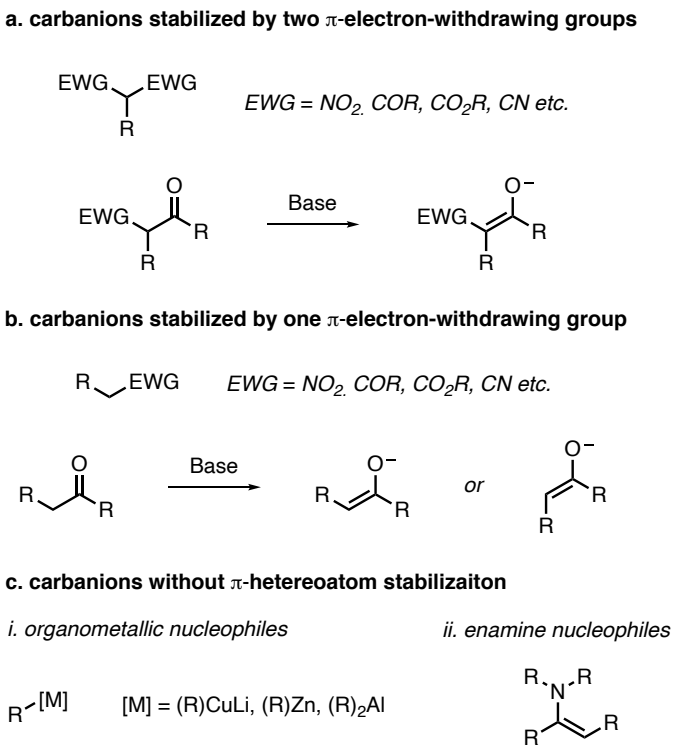


Fig. 1–3 Examples of conjugate donors

The enantioselective conjugate addition reaction has received a lot of attention with numerous reports of organocatalytic[28-29] as well as metal-catalyzed[20, 29] reactions for the enantioselective formation of both carbon-carbon and carbon-heteroatom bonds. From a mechanistic point of view, the organocatalytic conjugate addition can be achieved using four

different strategies.[26] Enantiopure organocatalysts provide a chiral environment, which can activate the conjugate donor, acceptor, or both components simultaneously through weak interactions, such as hydrogen-bonding or ion-pairing,[30] or by stronger interactions such as covalent bonding (**Fig. 1–4**). Enantioselective phase-transfer catalysis demonstrates that weak interactions such as ion pairing can be used to perform facially selective additions to prochiral conjugate acceptors (**Fig. 1–4a**).[31-33] Such ion pairs are formed by deprotonation of the conjugate donor with a chiral base; the resulting chiral cation provides a chiral environment for the enantioselective addition of the conjugate donor, which can undergo a facially selective addition to the conjugate acceptor. A second strategy for enantioselective organocatalytic conjugate additions involves the electrophilic activation of conjugate acceptors with chiral Lewis acids, which contain hydrogen-bond donors (**Fig. 1–4b**).[34-35] These hydrogen-bond donors activate the conjugate acceptor by decreasing its electron density, further activating the acceptor towards a conjugate addition reaction, while providing a chiral environment to direct the addition. A third strategy involves the covalent activation of either the conjugate acceptor or donor. The catalyst can reversibly form a chiral enamine to activate the conjugate donor (**Fig. 1–4c**), or a chiral iminium ion to activate the conjugate acceptor (**Fig. 1–4d**). A fourth strategy involves the use of chiral bifunctional organocatalysts (**Fig. 1–4e**). These catalysts can activate the acceptor and donor simultaneously through a combination of hydrogen-bonding catalysis and chiral ion-pairs. The hydrogen-bonding reagent is typically attached to a chiral base, which upon deprotonation of the conjugate donor, forms an ion pair. The proximity of the donor and acceptor allows for the enantioselective addition to provide enantioenriched products.

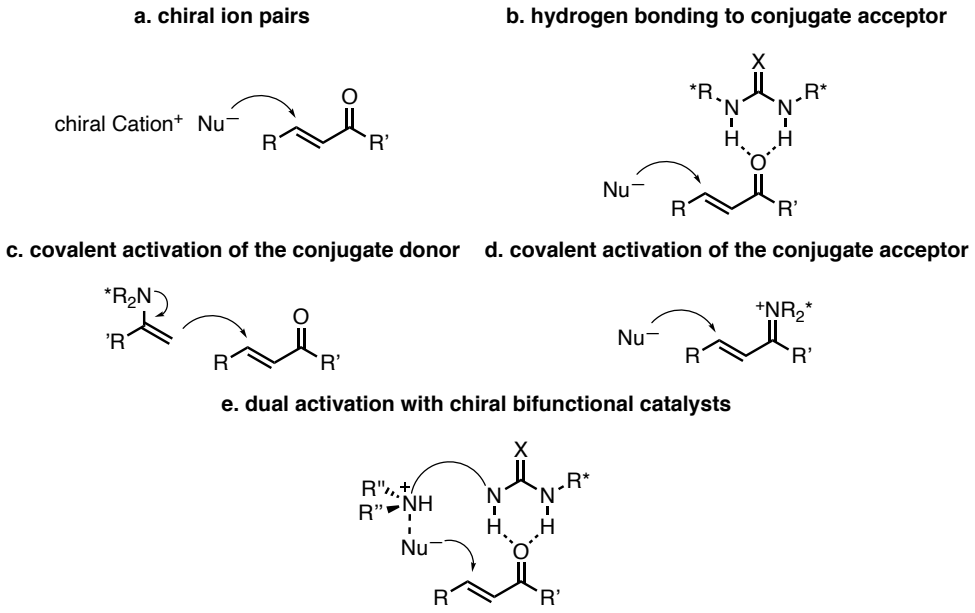


Fig. 1–4 Organocatalytic activation of conjugate acceptors and donors

While organocatalytic conjugate addition have been the subject of many studies, the focus of this thesis will revolve around metal-catalyzed enantioselective conjugate addition reactions. Such reactions can be made enantioselective with three different approaches.[36] The first strategy is the diastereoselective conjugate addition, which uses a conjugate acceptor activated by a chiral auxiliary that directs the addition of the nucleophile to a single face of the acceptor. Subsequent removal of the chiral auxiliary results in the enantioenriched conjugate addition products. The second strategy is the use of stoichiometric chiral organometallic reagents to perform an enantioselective conjugate addition. A well known example of this involves the use of chiral organocuprates to direct the enantioselective addition.[37] The final and most attractive strategy is to use catalytic amounts of both metal-catalyst and chiral ligand to achieve a catalytic enantioselective conjugate addition.

One of the most useful catalytic enantioselective conjugate addition reactions is the Rh-catalyzed β aryl- or alkenylation of organoboron compounds, which uses chiral Rh-

complexes to add aryl or alkenyl boronic acid nucleophiles to a wide range of electron-deficient alkenes (**Fig. 1–1**).[38] This reaction is attractive since the organoboronic acid compounds used in these reactions are commercially available and stable under ambient conditions allowing them to be used in weakly basic aqueous media.[39] Additionally, there is essentially no background reactivity of the boronic acids with electron-deficient alkenes compared to other organometallic reagents used in other catalytic enantioselective conjugate additions. Such background reactions lead to the undesired formation of regioisomers through ipso-addition or, racemic background reactions of the desired transformation (β-addition), which reduces the selectivity of the process. Lastly, due to the wide variety and availability of chiral ligands, many different catalyst systems are available to catalyze the reaction.[40]

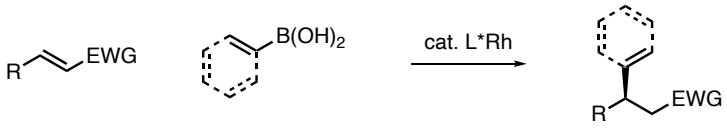


Fig. 1–5 The enantioselective Rh-catalyzed conjugate addition reaction

1.2 Rh-Catalyzed Enantioselective Conjugate Additions

1.2.1 Discovery and Brief History

The Rh-catalyzed conjugate addition of aryl boronic acids was initially discovered as a racemic reaction.[41] Miyaura and co-workers were inspired by a report from Uemura[42] involving the addition of phenyl group from sodium tetraphenyl borate to enones via Pd catalysis. The reaction was proposed to proceed through the oxidative addition of the C–B bond to the Pd(0) species; however, Miyaura postulated that an alternative mechanism

involving the transmetalation to transition metals may allow a similar catalytic transformation using organoboronic acids. With this hypothesis, they developed a protocol using $Rh(acac)(CO)_2$ as the Rh source and 1,4-bis(diphenylphosphino)butane (dppb) as the ligand with aryl boronic acids, to generate a Rh-aryl intermediate through transmetalation of the aryl boronic acid, which then undergoes an alkene insertion reaction to afford products with a new stereocenter β to an electron-withdrawing group. They demonstrated this reaction on multiple different conjugate acceptors under three different aqueous solvent mixtures. One example is shown in **Fig. 1–6**, where a quantitative yield of **1-3** is achieved.

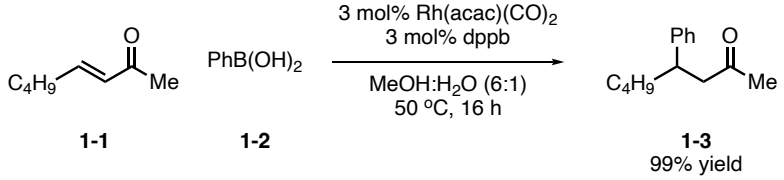


Fig. 1–6 Discovery of Rh-catalyzed conjugate additions of aryl boronic acids

A year later they reported the first enantioselective Rh-catalyzed reaction with the use of (*S*)-binap as the chiral ligand (**Fig. 1–7**).[39] CO ligands were replaced with more labile ethylene ligands, which leads to in irreversible formation of the Rh(acac)(*S*)-binap complex and drastically increased catalytic activity. Dioxane was the preferred solvent, and the temperature was increased to 50 ºC from 100 ºC. Many different enones underwent successful conjugate addition, for examples cyclic enones (**1-4**, **1-5**) and linear enones (**1-6**) gave high yields and *ee*'s. Vinyl boronic acid (**1-7**) also gave high *ee*'s but with lower yields.

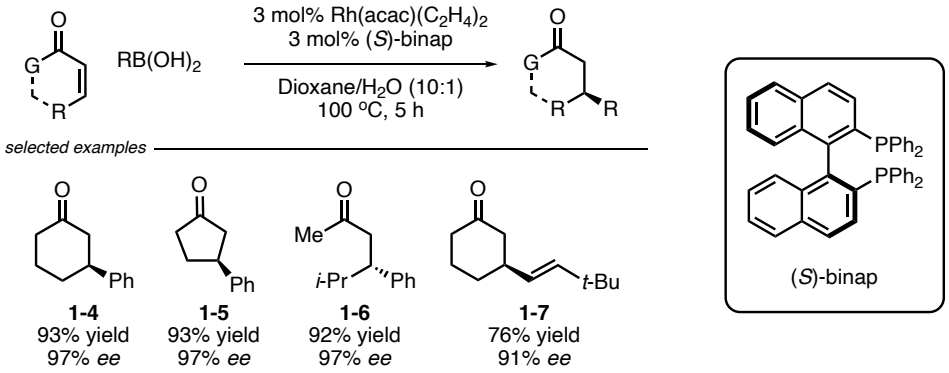


Fig. 1–7 The first enantioselective Rh-catalyzed conjugate addition

In 2001, Miyaura and co-workers published a report that cyclooctadiene (cod) could be used as a catalyst. The use of $[Rh(cod)Cl]_2$ catalysts drastically increases the catalytic activity,[43] which prompted an in depth analysis of the factors leading to successful Rh-catalyzed conjugate addition reaction.[44-45] It was established that $[Rh(cod)Cl]_2$ was a much more active catalyst compared to [Rh(acac)(cod)], achieving similar yields at 50 °C where the latter requires 90 °C. Looking at base effects with $[Rh(cod)Cl]_2$ they found the addition of one equivalent of KOH increased the reaction rate significantly achieving high yields at 0 °C while catalyst loading could be used in as low as 0.0002 mol% to achieve 375 000 turnovers. These discoveries inspired efforts towards improving the efficiency of the analogous enantioselective reaction. Rh-catalysts with cod as the ancillary ligand were avoided since $[Rh(cod)Cl]_2$ is much more active and would lead to background racemic reactions, reducing the enantioselectivity of the process. They found that [Rh(*R*-binap)(nbd)]BF_4 with Et_3N as the base could achieve the enantioselective reaction at room temperature across many substrates achieving between 56% and 99% yields and 83% to 99% *ee*'s, which was a significant improvement on the first-generation system.

The observation that $[Rh(cod)Cl]_2$ drastically increased catalytic activity prompted the Hayashi Group to investigate the possibility that Rh-catalysts ligated by chiral dienes could catalyzed the enantioselective Rh-catalyzed conjugate addition. In 2003 they reported the first Rh/chiral diene catalyzed enantioselective reaction with the use of a chiral norbornadiene (nbd) ligand (**Fig. 1–8**).[44] The system displayed the highest catalytic activity of any previous Rh-catalyzed enantioselective conjugate addition, and the enantioselectivities were among the highest observed with most substrates being above 90% *ee*. Comparing this reaction to the first-generation system with $Rh(acac)(C_2H_4)_2$/(*S*)-binap it should be noted that these reactions were completed much faster at lower temperatures while still providing excellent yields and *ee*'s.

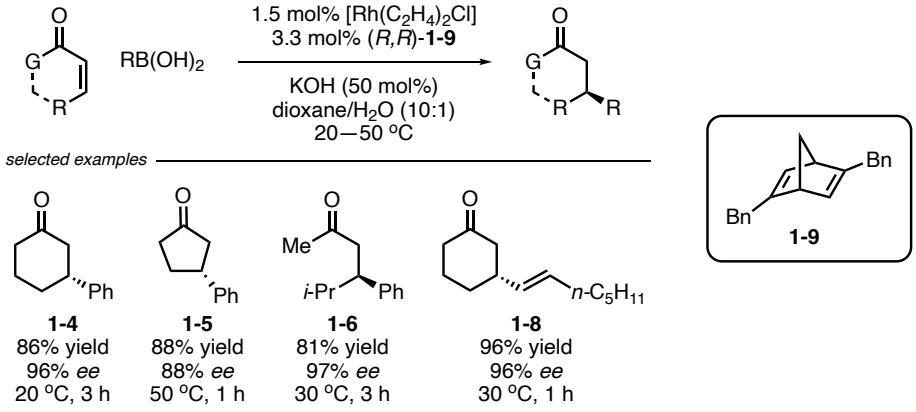


Fig. 1–8 First reported use of chiral dienes as ligands for enantioselective catalysis

The discovery that Rh-complexes ligated by chiral norbornadiene (nbd) can catalyze the enantioselective Rh-catalyzed conjugate additions led to the development of many different chiral diene ligands. These ligand systems were demonstrated across multiple different conjugate acceptors and Csp^2 organoboron species.[46] New ligands that are

developed are typically benchmarked with the enantioselective Rh-catalyzed conjugate addition of phenyl boronic acid to 2-cyclohexenone, however they have been shown to promote different types of reactions, such as the addition of aryl boronic acids to imines and ketones to provide access to enantioenriched diarylmethyl amines[47] or diarylmethanols.[48] The increased catalytic activity of Rh-chiral diene catalysts when compared to Rh-chiral phosphine systems allows for the enantioselective arylative cyclization reactions of alkynals,[49] alkynes with traditional conjugate acceptors,[50] as well as for an intramolecular [4+2] cycloaddition[51] with remarkable chemo- and enantioselectivities initiated by the arylation of the alkyne.

A few examples of some common chiral diene ligands that have been developed since the first example shown by Hayashi (see **Fig. 1–9**). Of the diene ligands shown, the enantiopure forms of the ligands can be accessed through two different strategies. Bicyclo[2.2.2]octa-2,5-dienes (bod)[52] and tetrafluorobenzobarrelene (tfb) ligands[48] are synthesized through cycloaddition chemistry to provide access to the corresponding diketones. These processes require kinetic or chromatographic resolution to access the enantiopure compounds. Conversion of the enantiopure diketones to enol triflates provides a cross-coupling handle for further diversification. In contrast, the Rawal-type ligands can be accessed via a chiral pool strategy from α-phellandrene and an aluminum catalyzed cycloaddition with methyl propiloate[53] while Carreira-type ligands can be accessed from the ®-carvone in four steps.[54]

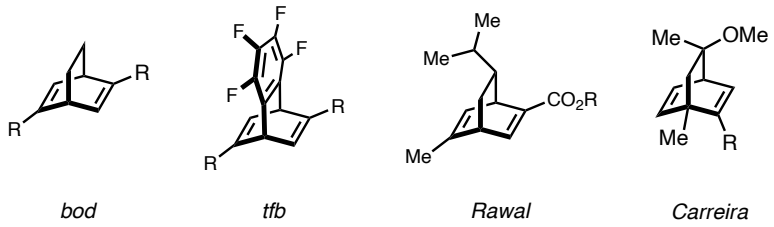


Fig. 1–9 Examples of chiral dienes developed since Hayashi's initial discovery

Since the initial discovery of the enantioselective Rh-catalyzed conjugate addition of aryl and alkenyl boronic acids, a wide variety of chiral phosphine and chiral dienes have been employed across many different classes of conjugate acceptors.[38, 55]

1.2.2 Catalytic Cycle

The catalytic cycle of the Rh-catalyzed conjugate addition is well understood.[56] Typically, Rh–Cl catalyst precursors are used as the precatalyst for the reaction, either as catalyst precursor salts, or they are generated by mixing the chiral ligand with $[Rh(C_2H_4)_2Cl]_2$, which irreversible forms the chiral Rh–Cl catalyst. This species must undergo a salt metathesis to access the active Rh–OH catalyst, which occurs either through direct reaction with added hydroxide bases, or by reaction of the added base with water, generating hydroxide *in-situ*. This Rh–OH species can undergo transmetalation with aryl boronic acids or esters, generating a Rh-aryl species. Upon facially selective coordination (*vide infra*) and insertion of the alkene into the Rh-aryl bond, a Rh-enolate is generated. Protonolysis of the Rh-enolate with water provides the product with a stereocenter β to the electron-withdrawing group while regenerating the active Rh–OH catalyst.

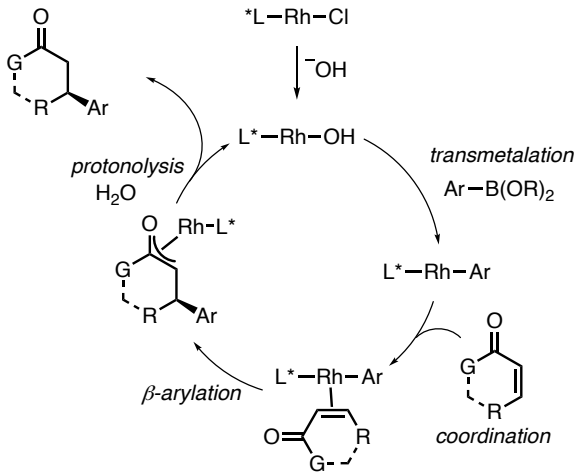


Fig. 1–10 Mechanism of the Rh-catalyzed enantioselective conjugate addition

1.2.3 Model for Enantioselectivity

The first model for enantioselectivity of the Rh-catalyzed enantioselective conjugate addition with chiral phosphines was proposed in 1998 (**Fig. 1–11**).[39] After transmetalation occurs to form **1-13**, **1-10** coordinates selectively to the empty coordination site on the *si* face of **1-10**. This coordination minimizes sterics when compared to the coordination of the *re* face where the molecule would clash with the phenyl group. Insertion of the alkene into the Rh–Ph bond from the *si* face of the alkene followed by protonolysis provides (*S*)-**1-4**.

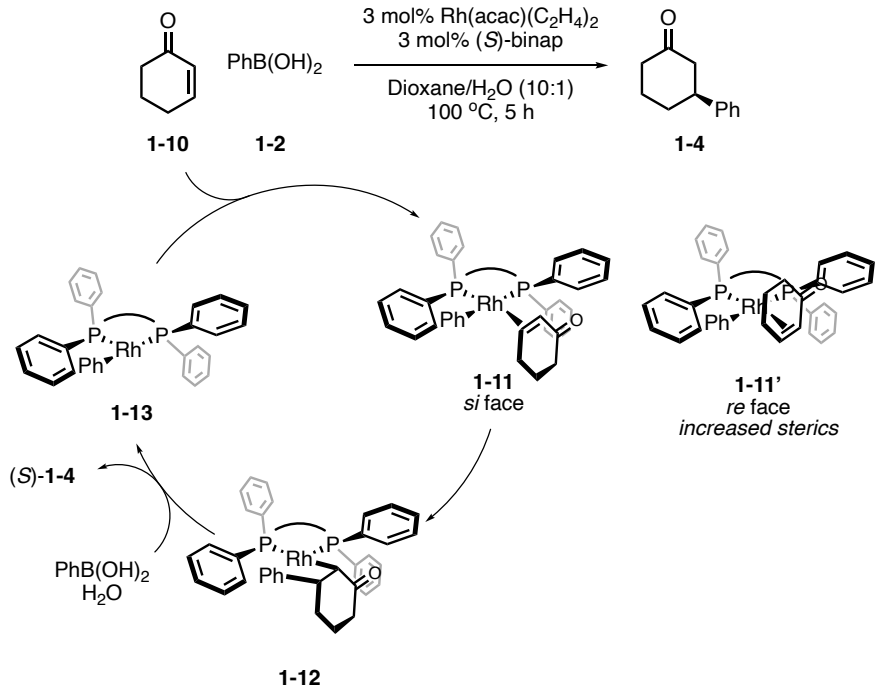


Fig. 1–11 Stereochemical model for Rh-(*S*)-binap catalyzed reactions

A similar model was also proposed for the enantioselective Rh-catalyzed conjugate addition using chiral diene ligands (**Fig. 1–12**).[45] The same principles apply as above, after transmetalation, and *re* face coordination of **1-10** to minimize steric clash with the R group and insertion of the alkene into the Rh–Ph on the *re* face of the alkene followed by protonolysis of the Rh enolate, the product formed is **1-4**.

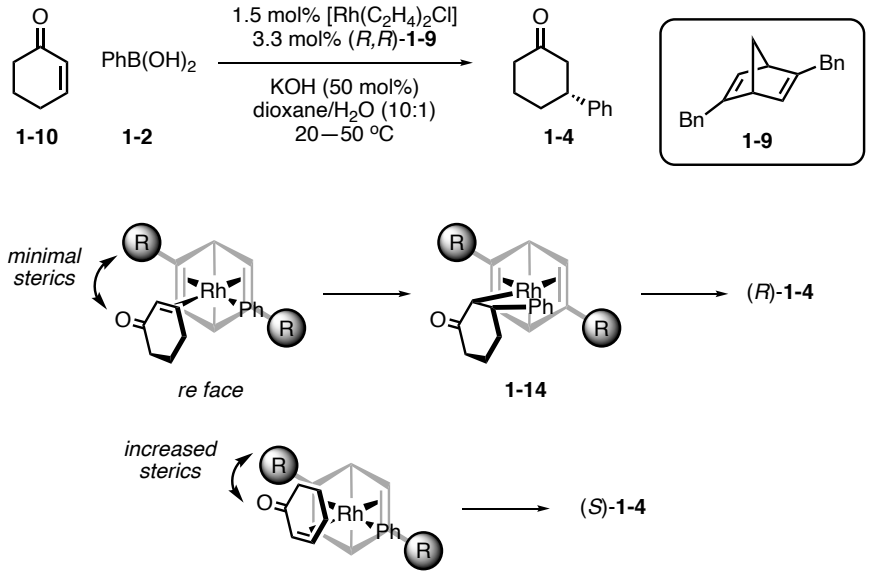


Fig. 1–12 Stereochemical model for Rh-(*R*,*R*)-Bn-nbd catalyzed reactions

It is worth noting, that the absolute stereochemistry of the arylation step, is dependent on the geometry of the alkene of the conjugate acceptor. For example, if (*E*)-**1-15**, and (*Z*)-**1-15** are used as substrates in the reaction catalyzed by *R*,*R*-Bn-nbd, the absolute stereochemistry of the product is the opposite for each example. Both substrates coordinate to minimize the steric clash of the ketone group with the R group on the ligand. Therefore, the geometry of the alkene has no influence on the preferred coordination mode with respect to the activating group, however the opposite geometry of the alkene switches the designation such that it is now coordinated on the *si* face of (*E*)-**1-15** instead of the *re* face, providing the opposite absolute stereochemical outcome (**Fig. 1–13**).

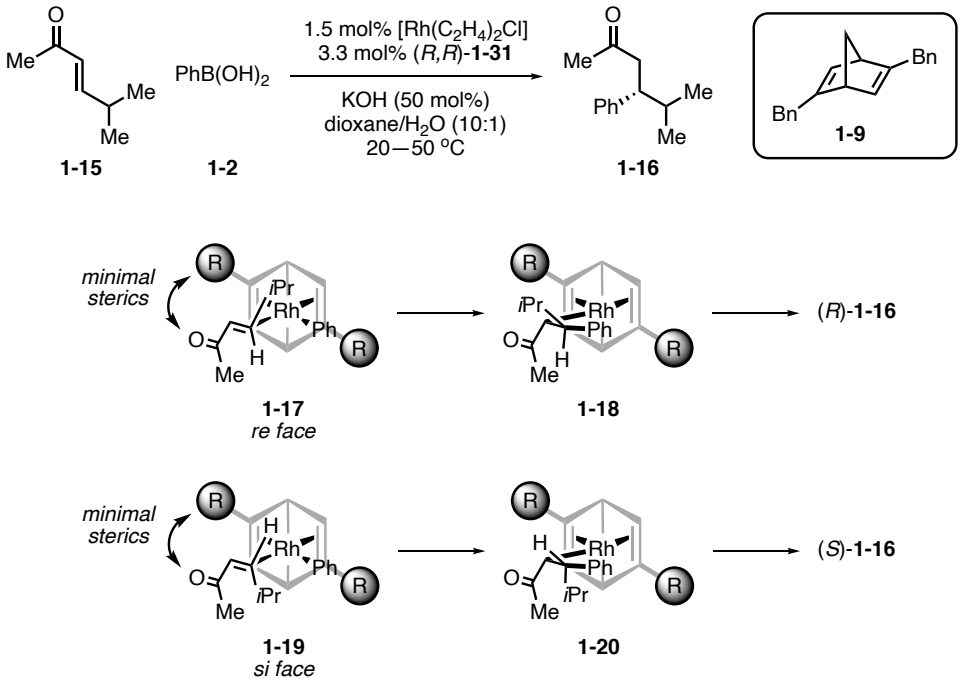


Fig. 1–13 Stereochemical model for Rh(*R*,*R*)-Bn-nbd catalyzed reactions with *E* and *Z*-alkenes

1.2.4 Organoboron Reagents

The prototypical organoboron reagent for Rh-catalyzed conjugate additions are aryl or alkenyl boronic acids. These are favourable due to their air and moisture stability, as well as their wide availability.[39] Boroxines (**1-21**) or boronic esters (e.g. **1-22**, **1-23**) can be employed in conjugate addition reactions. These reagents may be favourable in cases where the corresponding boronic acid undergoes fast, competitive protodeborylation. Boroxine or boronic esters are proposed to undergo *in-situ* hydrolysis to slowly liberate boronic acids. The rates of conjugate addition are directly related to the rate of hydrolysis of the corresponding organoboron reagent (**Fig. 1–14**).[55]

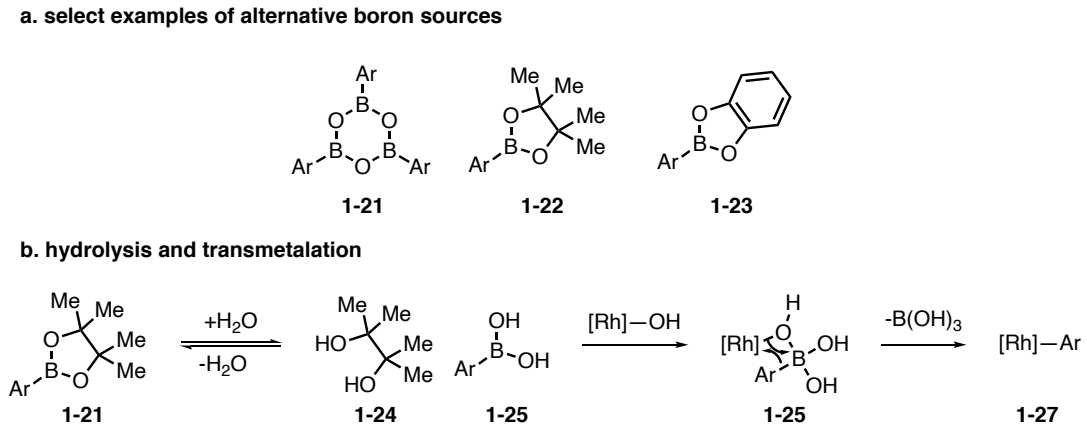


Fig. 1–14 Alternate organoboron sources and their reactivity

Aryl 9-BBN reagents can be used as alternatives to boronic acid derivatives in Rh-catalyzed conjugate additions. They are used under anhydrous conditions and give access to chiral boron enolates. After insertion to generate the Rh-enolate, subsequent transmetalation of another equivalent of aryl 9-BBN reagent provides boron enolate **1-29**, which can be further functionalized by external electrophiles to give products in high enantioselectivity (**Fig. 1–15**).[57] Using aryl 9-BBN reagents as nucleophiles in the Rh-catalyzed conjugate addition remains underdeveloped, likely due to the challenge of preparing the reagents, which are unstable to air and moisture.

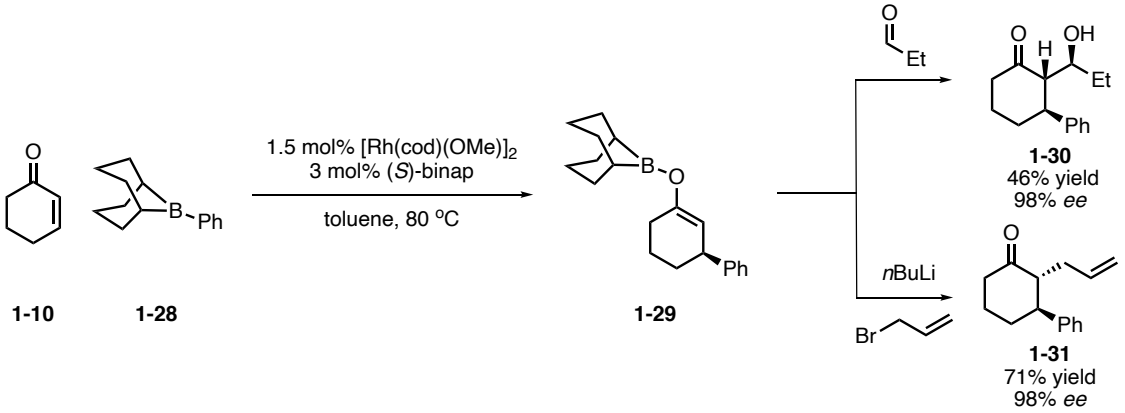


Fig. 1–15 Aryl 9-BBN reagents to form chiral boron enolates

1.2.5 Other Transmetalating Species

Although most Rh-catalyzed conjugate addition reactions use organoboron reagents, the reaction is not limited to their use and other organometallic reagents can be employed. These include organosilicon, zirconium, zinc, tin, titanium and aluminum.[19] These reagents differ in their reactivity, availability, and stability and can provide useful alternatives to organoboron reagents. Generally, transmetalating reagents that are based on metalloids that are significantly more electropositive than boron (e.g., titanium, zinc, aluminum, and zirconium) display greater reactivity in the Rh-catalyzed conjugate addition and can typically be conducted at lower temperatures than what is required for the corresponding organoboron reagent. However, these reagents require an additional preparative step and are less stable than organoboron compounds such that reactions must be performed under anhydrous, inert-atmosphere conditions.

1.2.6 Applications in Natural Product and Drug Synthesis

The Rh-catalyzed enantioselective conjugate addition reaction has been used in the synthesis of complex molecules and intermediates in drug discovery on a variety of scales.[58] In 2017 Bristol Myers Squibb published the kilogram scale the synthesis of (S)-3-isopropenyl-cyclo-hexan-1-one (**1-33**), which was part of an ongoing drug discovery program.[59] Through a lengthy optimization of solvent, base, boron source, ligand and Rh-precatalyst they were able to synthesize 581 kg of **1-33** in 99.4% *ee* and 86% yield (**Fig. 1–16**).

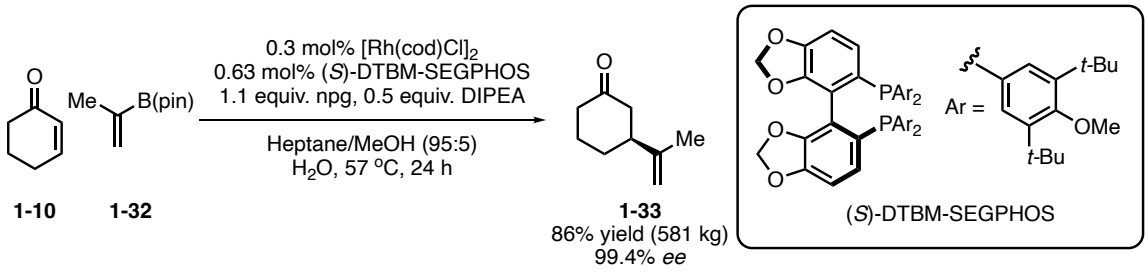


Fig. 1–16 BMS' synthesis of intermediate **1-33** for a drug development program

The Rh-catalyzed enantioselective conjugate addition has also been elegantly applied to the synthesis of amino acid derivatives. In 2019 the Wu group published an efficient method to synthesize phenylalanine derivatives (**Fig. 1–17a**). In the example shown, O, and N, protected phenylalanine (**1-36**) was prepared in 99% yield and a 92% *ee*.[60] In 2021, Merck published a report that used the Rh-catalyzed enantioselective conjugate addition in the synthesis of *trans*-3-substituted proline derivatives (**Fig. 1–17b**).[61] In the example shown, they are able to produce **1-39** on a gram scale with 83% yield, 95% *ee* and 20:1 *dr*.

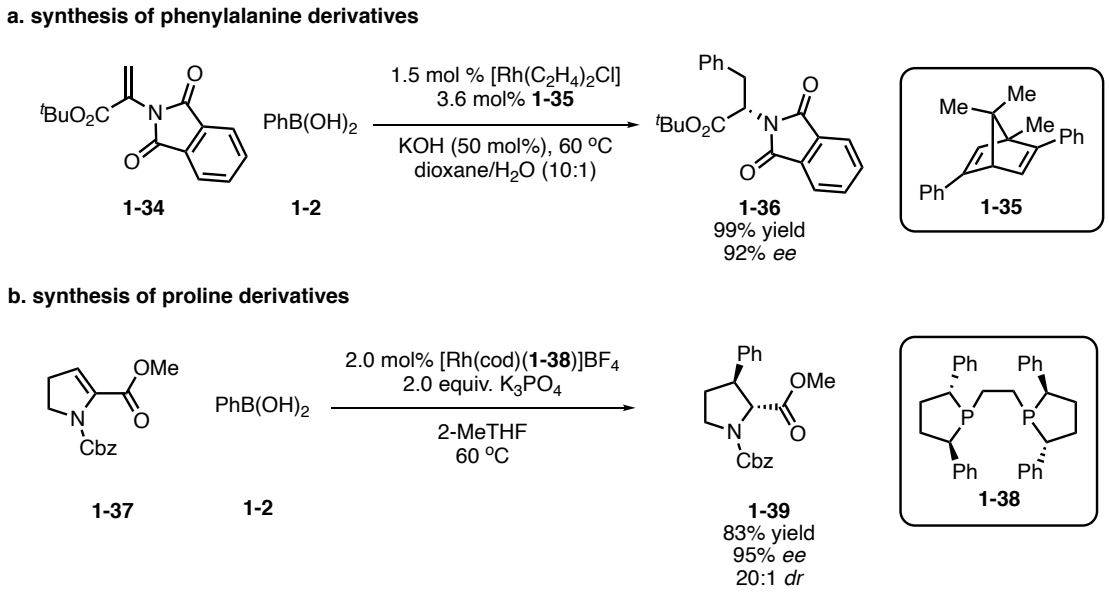


Fig. 1–17 Applications of the Rh-catalyzed conjugate addition reaction

1.2.7 Multi-Component Reactions triggered by a Rh-Catalyzed Conjugate Addition

The Rh-catalyzed conjugate addition reaction generates Rh-enolate intermediates, and in select cases Rh-enolates have been trapped in multicomponent reactions. Rh-catalyzed conjugate additions with aryl boronic acids requires the use of protic cosolvents, which generally leads to fast protonolysis of the Rh-enolate intermediate generated. The inherent instability of the Rh-enolates makes the interception of this intermediate with an external electrophile difficult (**Fig. 1–18**). These limitations can be addressed with the use of two general strategies, first the use of alternative nucleophiles, under anhydrous conditions, or by using conjugate acceptors that contain tethered electrophiles where the high local concentration of the electrophile can override the inherent instability of the Rh-enolate towards protonation.

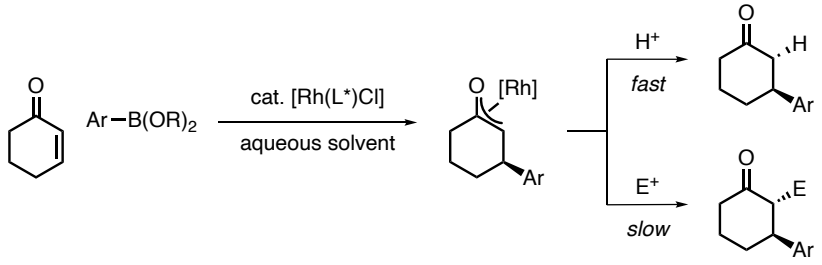


Fig. 1–18 Limitations of Rh-catalyzed conjugate addition in multi-component reactions

Hayashi and co-workers have shown that the use of many different alternative nucleophiles under anhydrous conditions can lead to an enolate intermediate that is stable and can subsequently trap electrophiles in solution (**Fig. 1–19**). They have shown that the use of aryl 9-BBN reagents can lead to a successful trapping of aldehydes through a chiral Rh-enolate to provide the multicomponent product in 44% yield, with low *dr* and 94% *ee* of

the major, *syn* diastereomer (**Fig. 1–19a**).[62] They have also shown that with the use of cyclohexenone as a conjugate acceptor with aryl Ti-reagents can lead to the formation of a stable Ti-enolate, which can undergo functionalization to achieve multi-component reactions (**Fig. 1–19b**).[63] This general strategy has been applied to other nucleophiles, including aryl 9-BBN,[57] aryl Zn-reagents,[64] and alkenyl Zr-nucleophiles.[65]

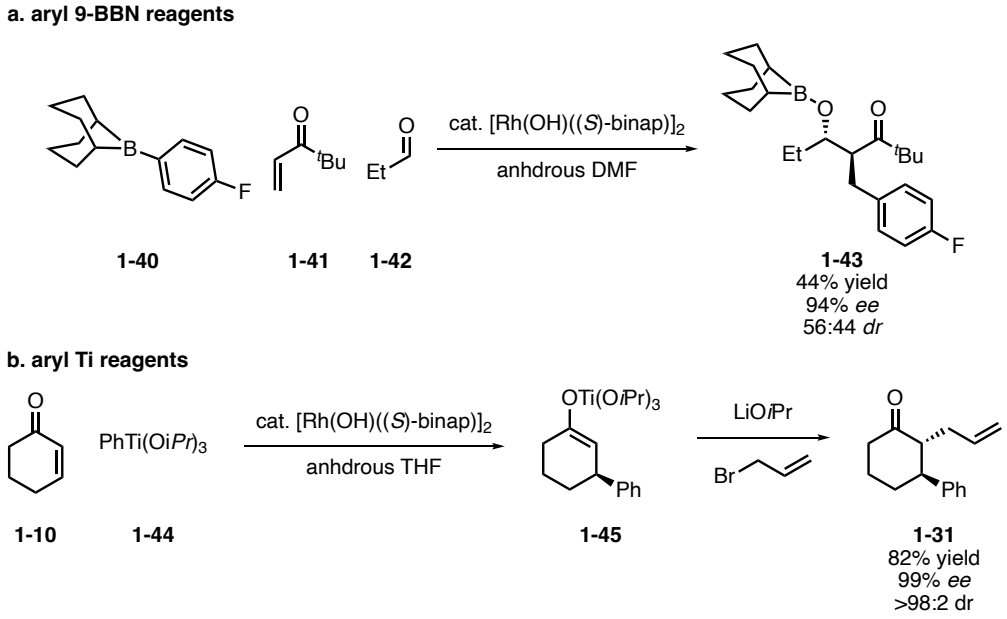


Fig. 1–19 Anhydrous conditions with alternative electrophiles

Krische and co-workers demonstrated an enantio- and diastereoselective carbometallative aldol condensation initiated by a Rh-catalyzed conjugate addition (**Fig. 1–20**).[66] Due to the close proximity of the tethered electrophile, trapping of the Rh-enolate can now outpace undesired protonation allowing for the intramolecular trapping of the tethered ketone to achieve a intramolecular aldol reaction providing products like **1-47**, which contain three contiguous stereocenters. Other strategies (not depicted here) include conjugate addition followed by a Mannich reaction[67] and a subsequent conjugate addition.[68] These

examples are conducted with $[Rh(cod)Cl]_2$ to achieve a diastereoselective cyclization with >80:20 *dr* depending on the combinations of substrates.

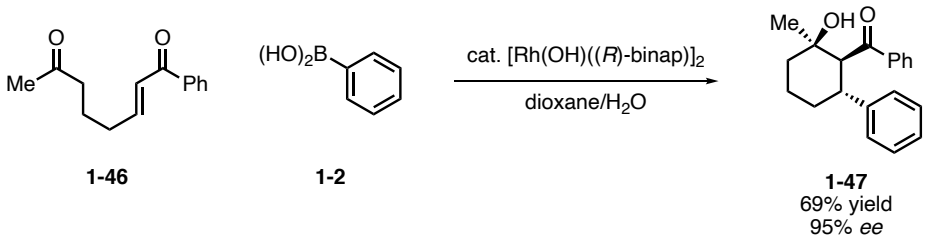


Fig. 1–20 Rh-catalyzed enantioselective conjugate addition followed by an intramolecular aldol cyclization

1.3 Conjugate Addition to Electron-Deficient Dienes

The conjugate addition to electron-deficient alkenes represents one of the most versatile carbon-carbon bond forming reactions used by organic chemists.[19-20] Compared to alkenes, conjugate addition reactions with structurally related electron-deficient dienes are comparatively underdeveloped likely due to several additional challenges.[69-70] First electron-deficient dienes have an additional reactive site when compared to traditional conjugate acceptors, so control over regioselectivity (ipso (1,2) vs. β (1,4) vs. δ (1,6)) can be an issue. For example, alkyl lithium reagents will provide products from the direct attack on the carbonyl to achieve a 1,2 addition (**1-49**), Grignard reagents tend to be more selective for the β position to achieve a 1,4 addition (**1-50**) predominantly but still provide 1,2 addition products. The use of Fe-catalysts with Grignard reagents and organocuprates provide access to δ products to achieve a 1,6 addition (**1-51** or **1-52**).[71] For additions that can be directed to the δ position, more selectivity issues can arise where control over the regioselectivity of the trapped electrophile (typically H^+) can be problematic as the electrophile can be trapped at

the α- or γ-positions (**1-51** vs. **1-52**). Finally, control over the geometry of the resulting alkene unit is also challenging, most processes provide the thermodynamically more stable *E* alkene, while access to the less stable *Z* alkenes is more limited (*vide infra*).

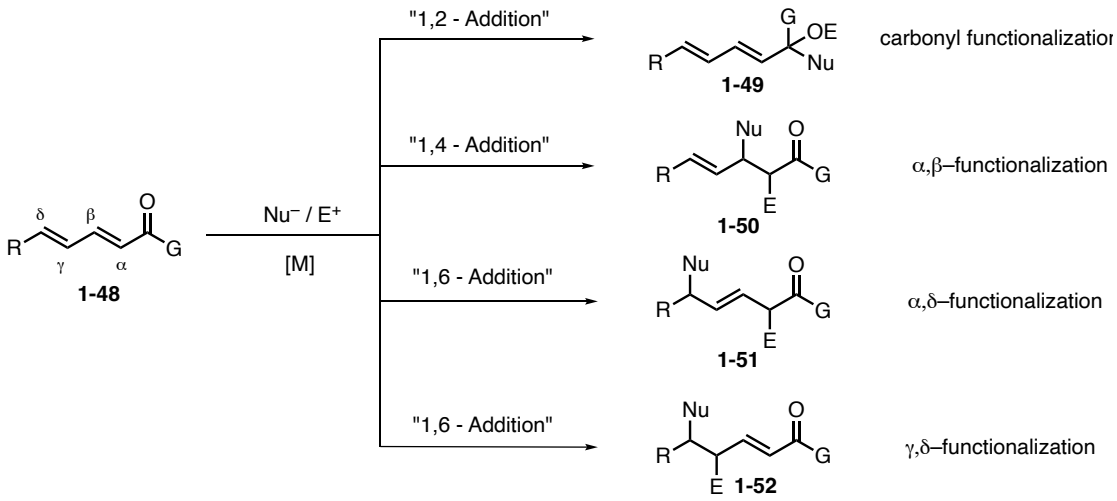


Fig. 1–21 Challenges of conjugate additions to electron-deficient dienes

The Csákÿ Group demonstrated that conjugate additions to ethyl sorbate using $[Rh(cod)Cl]_2$ as the catalyst under typical Rh-catalyzed conjugate addition conditions leads to imperfect regioselectivity. (**Fig. 1–22**).[72] In the best case scenario they obtained an 82:18 mixture of δ (**1-54**) and β products (**1-55**), small changes to the structure of the boronic acid had large, negative impacts and lead to selectivities as low as 70:30.

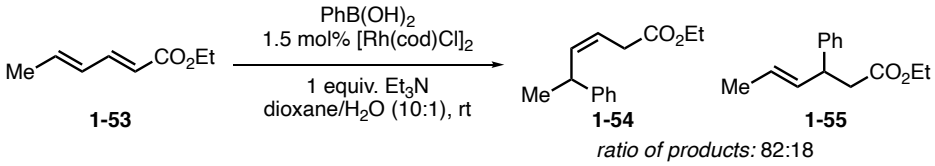


Fig. 1–22 Regioselectivity of the $[Rh(cod)Cl]_2$ catalyzed conjugate addition to ethyl sorbate

Nishimura and co-workers developed an $[Ir(cod)Cl]_2$ catalyzed reaction of dieneones and aryl boroxines.[73] Although they were able to develop reaction conditions to achieve complete δ selectivity, complete control over the resulting alkene geometry (**1-57** vs. **1-58**) and position (**1-59**) was not achieved. This reaction feature resulted in the isolation of products after hydrogenation of the alkene unit removing the possibility for subsequent alkene functionalization. They have also accomplished enantioselective examples, which suffer from the same selectivity issues.[74-75]

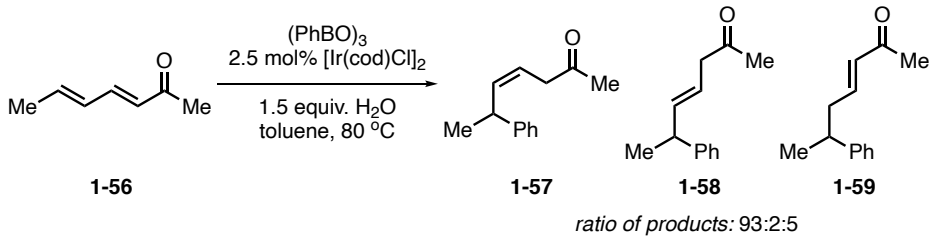


Fig. 1–23 Imperfect alkene position and geometry control in δ-selective conjugate additions

1.3.1 δ-Selective Conjugate Additions to Electron-Deficient Dienes

Even with the regio- and stereoselectivity challenges, there have been a few examples of successful δ additions to electron-deficient dienes. These examples are limited to Fe-catalyzed arylations,[76-78] vinylations[77] and alkylations.[79] Cu-catalyzed alkylations,[80-83] allylations,[84-85] and propargylations[84] and Co-catalyzed alkynylations.[86]

Urabe has shown a variety of Fe-catalyzed reactions provide *Z*-δ-β,γ- unsaturated products (**Fig. 1–24**) using aryl and vinyl Grignard reagents,[76-77] methyl (**1-63**) or cyclopropyl (**1-64**) Grignard reagents[79] with dienyl esters (**1-60**, **1-63**) and amides (**1-61**). They have also demonstrated the addition of aryl Grignard reagents to dienes activated by

sulphonyl groups (**1-62**).[78] The *Z*-selectivity is proposed to be due to the *s-cis* cordination of the diene substrate to the Fe catalyst after transmetalation of the Grignard reagent. Insertion of the R group to the δ-position then forms an extended Mg-enolate, which does not undergo *Z* to *E* isomerization. An acidic aqueous workup then provides the *Z*-δ-β,γ- unsaturated products.

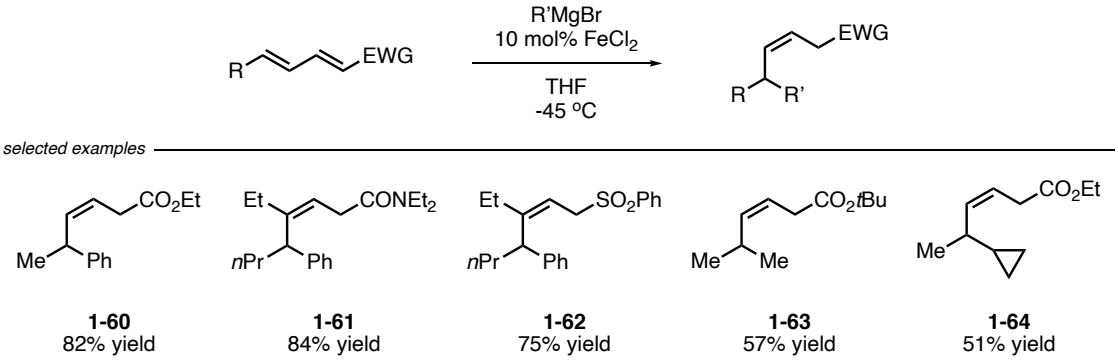


Fig. 1–24 Fe-catalyzed *Z*- and δ-selective addition to electron-deficient dienes

Cu-catalyzed enantio- and δ-selective alkylations have been demonstrated with alkyl Grignard reagents for the addition to dienes activated by esters[80] and amides.[81] They have also been performed with alkyl Zn reagents for the addition to dienes activated by nitro groups[82] and ketones[83] (**Fig. 1–25**). These reactions are proposed to form a Cu(III) σ complex where the diene is metalated at the β-position, subsequent migration of Cu to the δ-position of the diene followed by reductive elimination forms an extended Zn/Mg-enolate. An acidic workup then yields the δ-*E*-β,γ-unsaturated products. In the case of dienes activated by a nitro group (**1-70**), a Zn-nitronate is formed and upon acidic workup provides and α,β-unsaturated ketone through a Nef reaction (**1-72**).

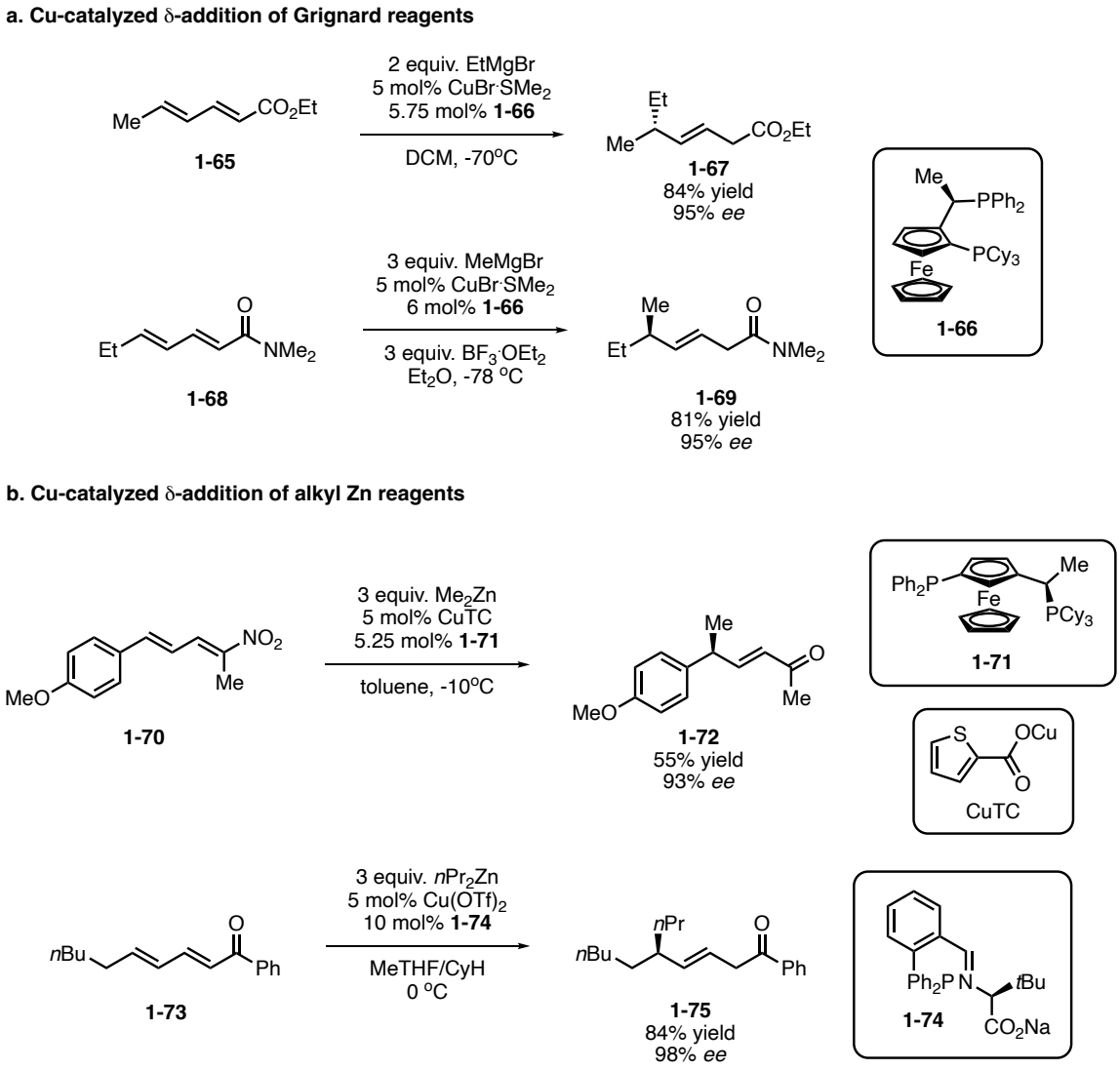


Fig. 1–25 Cu-catalyzed *E*- and δ-selective alkylations of electron-deficient dienes

Hoveyda has demonstrated that Cu(NHC) catalysts can catalyze the enantioselective δ-allyl[84-85] and propargylation[84] of dienes activated by diethyl malonate (**1-76**) (**Fig. 1–26**). These reactions are proposed to occur through the coordination of a Cu(I)-allenyl or allyl species to the α,β-alkene of the diene, subsequent rearrangement installing a propargyl or allyl group (respectively) in the δ-position of diene provides an extended Cu-enolate.

Transmetalation with sodium phenoxide provides an extended Na-enolate, acidic workup provides δ-*E*-β,γ-unsaturated products.

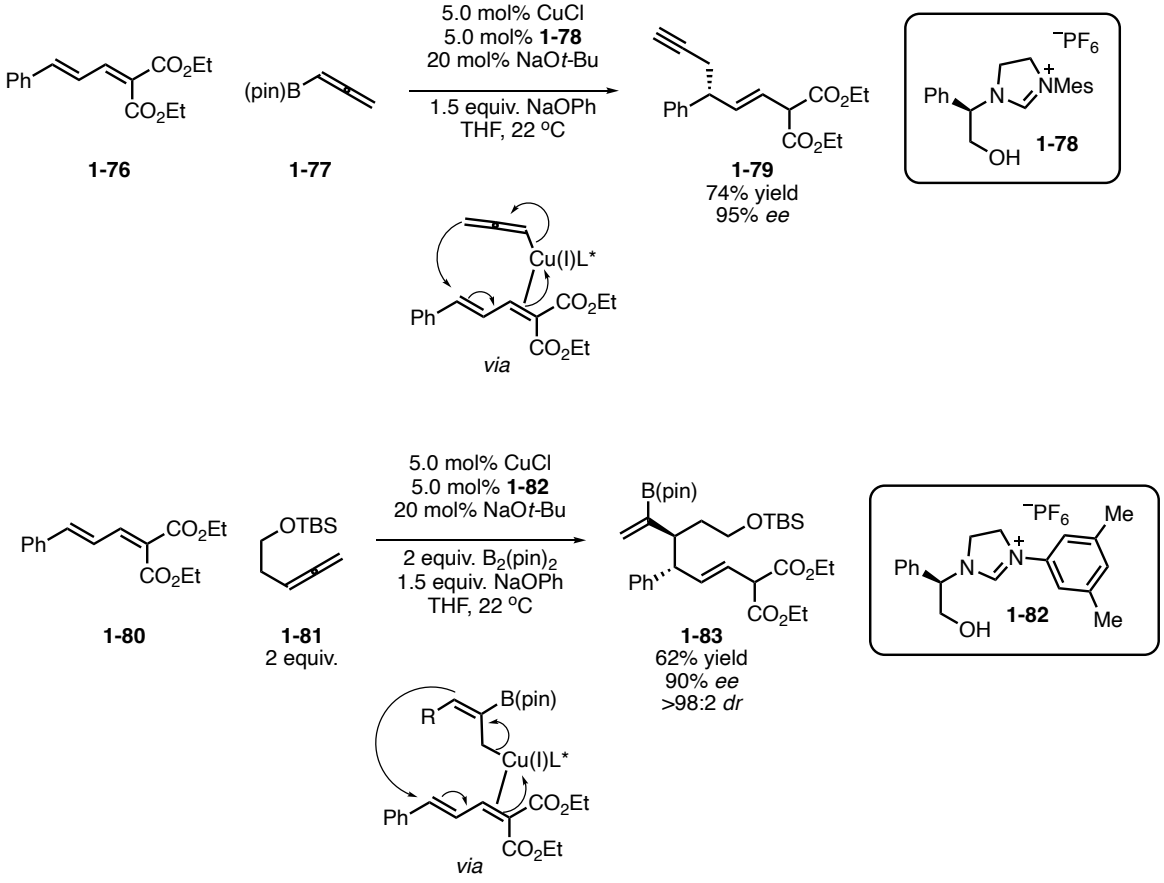


Fig. 1–26 Hoveyda's Cu-catalyzed δ-allyl and propargylation

Finally, Hayashi and Nishimura have shown that Co-bisphosphine catalysts can catalyzed the δ-addition of triispropyl acetylene to dienes activated by esters and amides providing δ-*E*-α,β-unsaturated products (**1-87**) (**Fig. 1–27**).[86] This reaction is proposed to occur via a *s-cis* coordination of the diene to a Co(I)-alkyne complex. Insertion into the δ-position forms a Co-allyl complex, which upon protonation forms **1-87**.

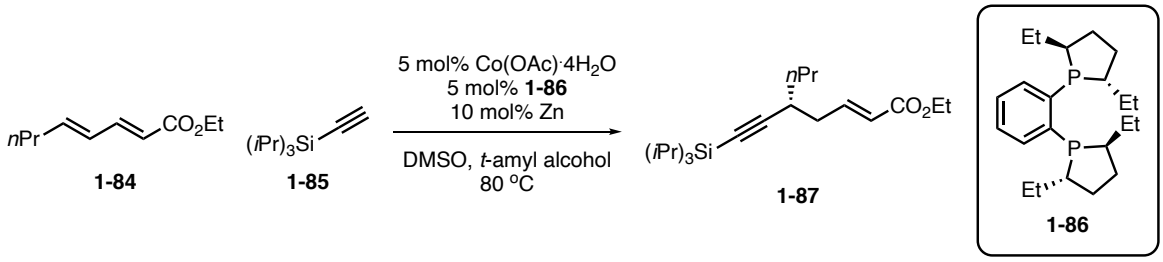


Fig. 1–27 Co-catalyzed δ-alkynylation of TIPS acetylene

Metal-catalyzed conjugate addition reactions are highly selective and there is a wide range of catalysts that can be used for stereoselective additions to simple substrates, generating molecules with new Csp^3 stereocenters. Additions to diene substrates provide an avenue for preparing structurally complicated molecules; however, their multiple sites of reactivity provide complications, resulting in the underdevelopment of such reactions for synthetically useful applications. This thesis will provide an overview of Rh-catalyzed stereoselective transformations to diene molecules with high selectivity for the nucleophilic insertion at the δ-position of the diene. The Rh-intermediates generated upon addition can undergo subsequent trapping of electrophiles providing access to complex, three dimensional molecules from simple, prochiral starting materials.

1.4 Thesis Overview

This thesis describes the discovery, optimization, and application of new Rh-catalyzed δ-additions to electron-deficient dienes. Mechanistic studies of the processes were conducted with particular focus on understanding the difference in selectivity compared to previous reported β-additions.

Chapter 2 describes the development of a *Z*-selective Rh-catalyzed, formic acid mediated reductive coupling of dienes and aldehydes. This process involves the δ-insertion of a Rh-hydride species followed by subsequent trapping of aldehyde electrophiles. It displays a much wider tolerance to other Rh-hydride catalyzed processes due to the use of formic acid as a mild reductant.

Chapter 3 describes the diastereo-, enantio-, and *Z*-selective α,δ-difunctionalization of electron-deficient dienes, which is initiated by a Rh-catalyzed conjugate addition. Mechanistic studies show that the intermediate Rh-allyl species is uniquely primed for aldehyde allyl rhodation and resistant to protonation when compared to the Rh-catalyzed conjugate addition to electron-deficient alkenes.

Chapter 4 describes the Rh-catalyzed enantio-, and *Z*-selective δ-arylation of electron-deficient dienes, which are activated by an aryl group. A wide range of electronics has been demonstrated and the knowledge learned from previous mechanistic studies (Chapter 3) proved to be invaluable in the development of the process.

Chapter 5 provides a brief overview of the research objectives accomplished in this thesis as well as providing some possibilities for future work, that is inspired by the findings in this thesis.

Chapter 2 – Direct Formic Acid Mediated *Z*-Selective Reductive Coupling of Dienes and Aldehydes via Rh-Catalyzed δ-Conjugate Addition of a Rh-Hydride

2.1 Introduction

Metal-catalyzed conjugate additions to electron-deficient alkenes represents one of the most useful synthetic tools for the construction of carbon-carbon or carbon-heteroatom bonds.[20] Stoichiometric main-group element hydride donors in the presence of a transition metal-catalyst can be employed to form a nucleophilic metal hydride to achieve a conjugate hydride addition. The hydride is inserted β to the electron-withdrawing group while typically generating a metal enolate.[87-89] If the generated intermediate is protonated, formal hydrogenation of the electron-deficient alkene is achieved. This approach is advantageous compared to reduction processes that use H_2 due to the high chemoselectivity for the reduction of electron-deficient alkenes without the reaction of other unsaturated groups.[90]

The metal intermediate that is generated from a conjugate hydride insertion, generally an enolate, can also be intercepted by electrophiles in a catalytic reductive coupling process (**Fig. 2–1**). These reactions have been traditionally dominated by the trapping of aldehydes and imines or by intramolecular aldol reactions.[91]

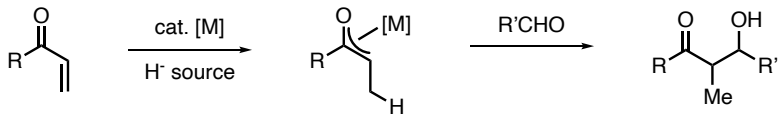


Fig. 2–1 Catalytic reductive coupling of electron-deficient alkenes with aldehydes

Early reductive coupling methods required stoichiometric main-group hydride sources such as trialkyl silanes (R_3SiH) or pyrophoric, organometallic reagents such as alkyl boranes (BEt_3) or alkyl zincs ($ZnEt_2$).[92-93] These reagents produce stoichiometric organometallic waste while also limiting functional group compatibility with protic or reducible functional groups. The use of milder reductants in these reactions was realized, by Krische, who demonstrated that inexpensive feedstocks such as H_2, isopropanol, or formic acid could be used in tandem with a metal-catalyst to dramatically broaden the scope and utility of metal-catalyzed reductive coupling reactions (**Fig. 2–2**).[92-99]

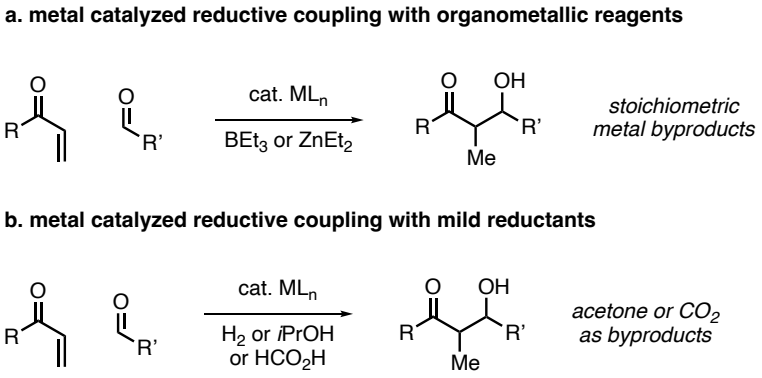


Fig. 2–2 Strategies for metal-catalyzed reductive coupling

The use of dienes and alkynes as substrates for reductive coupling reactions[100-101] for the allylation of carbonyl compounds has seen less development in comparison with alkenes. These reactions provide products with a pendant alkene, which can be used for further stereoselective functionalizations. The geometry of the resulting alkene affects the properties of the molecule and controls the stereochemical outcome of stereoselective functionalization reactions,[102] therefore reactions with control over the geometry of the newly formed alkene

are crucial. Despite efforts,[92] addition reactions that use dienes or alkynes as pronucleophiles to access the less thermodynamically stable *Z*-alkene product remains rare.[96]

In 2004, Mori and co-workers reported a Ni-catalyzed reductive coupling of dimethyl phenyl silyl dienes with various aromatic aldehydes (**Fig. 2–3**).[103] They designed reaction conditions that successfully control the stereoselectivity of the newly formed alkene unit by employing different solvents, ligands, and hydride sources to achieve either *E*- or *Z*-selective reductive coupling. For the *Z*-selective process, an *in situ* formed Ni(NHC) (NHC = **2-3**) catalyst with Et_3SiH as the hydride source was used. A plausible mechanism to explain the *Z*-selectivity involves the oxidative cyclization of the diene and aldehyde with Ni(0) forming oxanickelacycle **2-5**, which is in equilibrium with π-allyl-nickel complex **2-6** and oxanickelacycle **2-7**. Subsequent σ-bond metathesis between **2-7** and the hydrosilane gives *Z*-allylnickel hydride complex **2-8**. Reductive elimination of **2-8** reforms the active Ni(0) catalyst while forming **2-9**, which liberates the product **2-4** upon acidic workup. In 2007 Sato and co-workers reported the enantioselectively version of the reaction using a chiral NHC ligand to provide *Z*-homoallylic alcohols from silyl dienes, as well as aryl substituted dienes with products formed with a wide range of enantioselectivities (50 – 97%).[104]

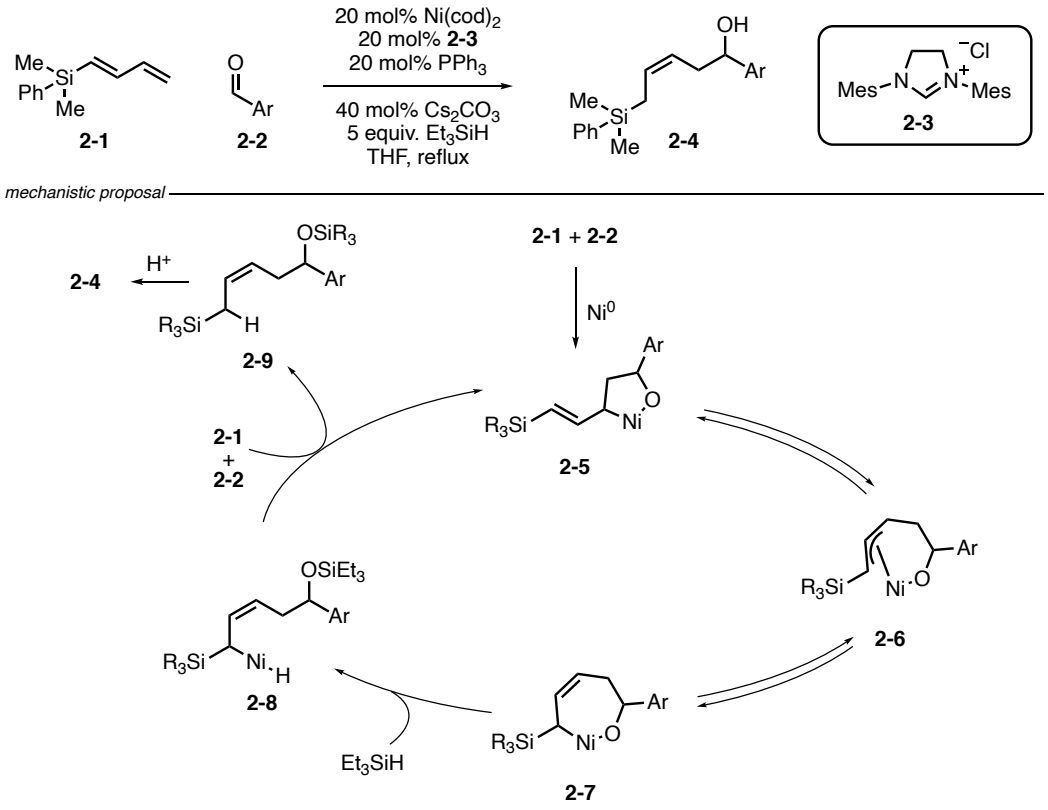


Fig. 2–3 Mori and co-workers Ni-catalyzed *Z*-selective reductive coupling

The *Z*-selective reductive coupling of aldehydes and dienes has been achieved with Rh-based catalysts. These methods rely on stoichiometric BEt_3 as the hydride source to generate the required Rh-hydride precluding the use of protic or reducible functional groups.[105-106] This catalyst system was first reported in 2009 by Inoue and co-workers, however only one *Z*-alkene product was reported (**2-12**).[105] A similar catalytic system was applied to non-conjugated dienes, which involved Rh chain walking isomerism to access the same types of products.[106] The proposed mechanism of these transformations is depicted in **Fig. 2–4** using diene **2-10** for simplicity. BEt_3 reacts with the Rh–OH to form Rh–Et species, which readily undergoes β-hydride elimination to generate a Rh-hydride along with the evolution of ethylene. Alkene insertion into the Rh-hydride places the hydride in the δ-position of the

diene, while forming the nucleophilic Rh–allyl species **2-13**. This species undergoes aldehyde allylrhodation through a Zimmerman-Traxler transition state[107] (**2-14**) to provide *Z-syn* homoallylic alcohol **2-12**. The products formed from chain walking isomerization with unconjugated dienes undergo a similar mechanism after generating **2-10** from alkene insertion followed by π-σ-π isomerization and β-hydride elimination. The remaining steps are the same to provide access to *Z-syn* homoallylic alcohols like **2-12**.

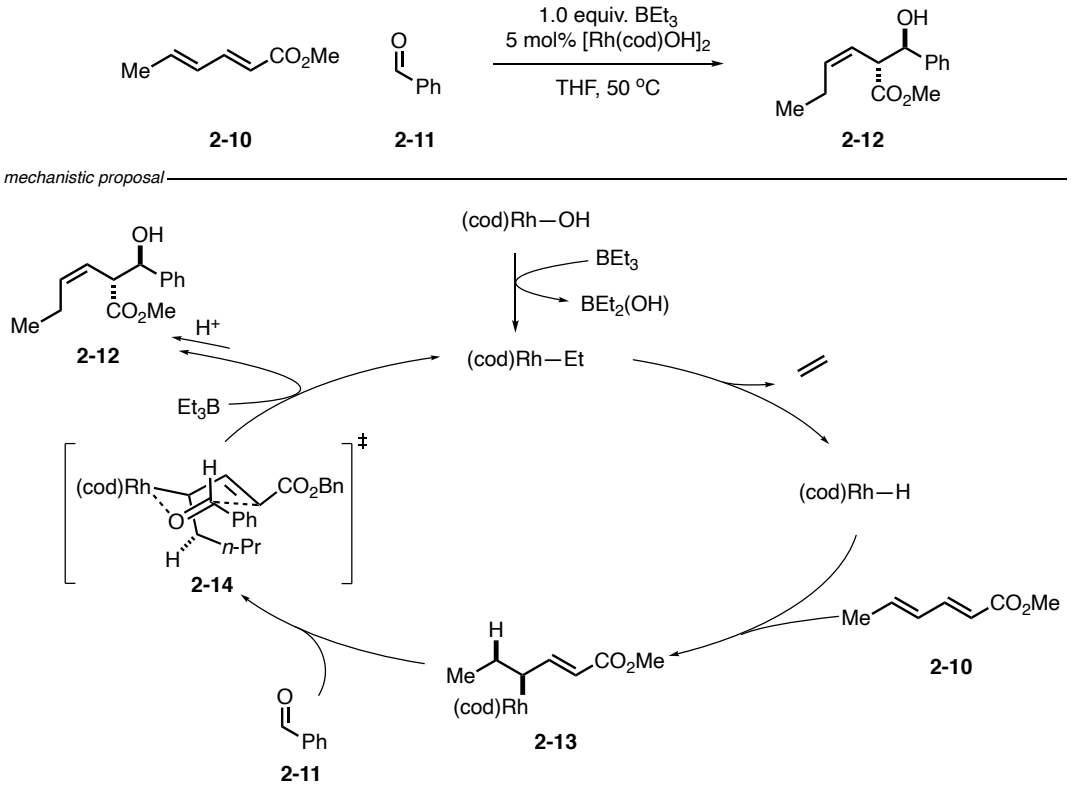


Fig. 2–4 *Z*-selective reductive coupling of dienes and aldehydes

The lack of generality in *Z*-selective diene additions highlights the difficulty in controlling both regio- and stereoselectivity in catalytic diene functionalizations,[84] particularly in reactions that generate the less thermodynamically stable product isomers.[108-

[115] From a mechanistic perspective, improving reductive chemoselectivity while inhibiting chain-walking isomerization in diene-aldehyde coupling can potentially be realized by using a milder reducing agent and tailoring the reactivity of the Rh-intermediates involved in the reaction pathway. Specifically, if both diene insertion into the Rh-hydride and electrophilic capture of the resultant Rh-allyl species outpace undesired isomerization, β-hydride elimination, or other reductive processes, a direct and selective coupling process could be accomplished.

Our group developed a method for the *Z*-selective Rh-catalyzed, formate-mediated 1,6-reduction of electron-deficient dienes in 2018 (**Fig. 2–5**).[116] To aid in the understanding of the process, deuterium labeling experiments with DCO_2H show that the diene inserts into the Rh-deuteride placing the deuteride in the δ-position. Diene geometry studies suggested that the *s*-cis coordination of the diene to a Rh-hydride (**2-17**) generated from formic acid was necessary to facilitate a stereoselective process. This species was then proposed to undergo a δ-hydride insertion to form a Rh-enolate (**2-18).** Protonation of the proposed Rh-enolate provides access to *Z*-β,γ-unsaturated products **2-16**. Based on this methodology, we then questioned whether this pathway could be diverted to enable reductive coupling to access products with a carbon-based electrophile rather than simply undergoing electrophilic protonation. When this methodology was under development, the reductive coupling of nonconjugated dienes through chain-walking isomerism was reported by Lam and co-workers.[106]

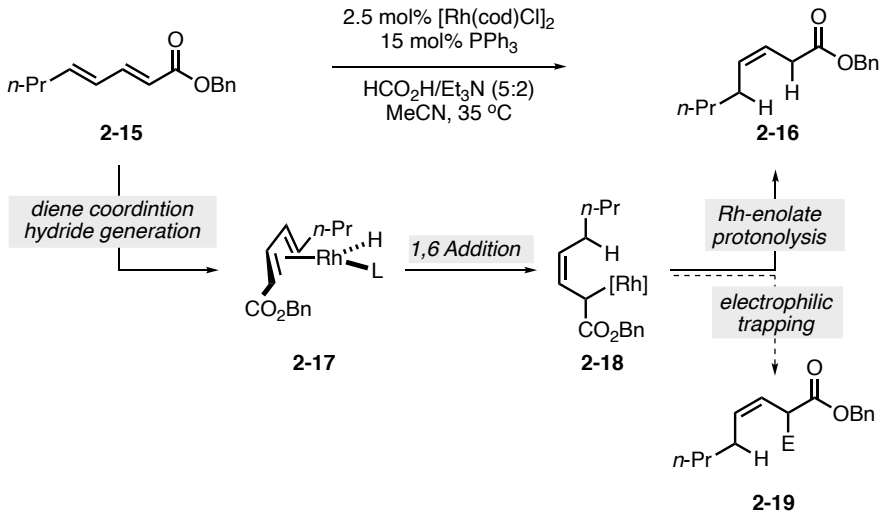


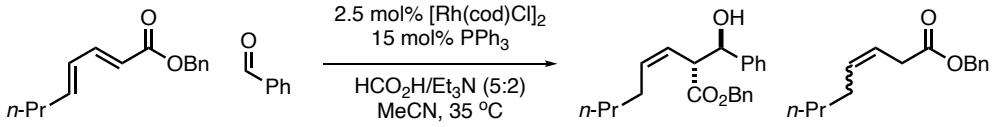
Fig. 2–5 Rh-catalyzed *Z*-selective 1,6-semi-reduction of dienes

Chapter 2 describes the development of a Rh-catalyzed, formate-mediated *Z*-selective reductive coupling of electron-deficient dienes with aldehydes to provide access to *Z-syn* homoallylic alcohols typically with complete *Z*-selectivity and >95:5 diastereomeric ratio.

2.2 Development of Direct Formic Acid Mediated *Z*-selective Reductive Coupling of Dienes and Aldehydes via Rh-Catalyzed δ-Conjugate addition of a Rh-Hydride

Starting from the reaction conditions developed for the *Z*-selective 1,6-reduction while screening different electrophiles using diene **2-15**, the addition of three equivalents of benzaldehyde provided an initial hit of 17% (**Fig. 2–6**). We hypothesized that the nature and loading of the base could affect the ratio of product to undesired reduction side products (**2-21**). Increasing the basicity of the reaction mixture has negligible impact on the yield of **2-20** (entry 1) however, using a more sterically hindered base such as DIPEA instead of Et_3N increased the yield of **2-20** (entry 2). At this point the reaction was still very slow, while forming undesired reduction products as the major product of the reaction. Reducing the

amount of PPh_3 had a positive effect on the formation of **2-20** although formic acid was consumed before complete conversion of **2-15** was achieved (entry 3). The use of excess formic acid with two equivalents of DIPEA resulted in the full conversion of **2-15** while providing **2-20** in 77% yield (entry 4). Reducing the amount of base to DIPEA to 1 equivalent had a negative impact on the selectivity of the reaction (entry 5) therefore conditions from entry 4 were selected as the standard conditions for more general optimization studies. In all cases, the remainder of diene mass balance corresponds to the formation of reduction products (**2-21**).



2-15 | **2-11** 3 equiv. | *reduction conditions* | **2-20** 17% yield | **2-21**

entry	deviation from above	conv. (%)	yield (%)	**2-21** (%)
1	1:2 HCO_2H/Et_3N	92	21	77
2	1:2 HCO_2H/DIPEA	91	37	61
3	1:2 HCO_2H/DIPEA; 5 mol% PPh_3	88	67	18
4	**1.2:2 HCO_2H/DIPEA; 5 mol% PPh_3**	**>98**	**77**	**18**
5	1.2:1 HCO_2H/DIPEA; 5 mol% PPh_3	>98	62	35

0.2 mmol scale, 0.2 M, 19-48 h; yields, selectivity, and conversions determined by calibrated ^1H NMR using internal standards, *Z*/*E* >95:5 *dr* >98:2; **2-21** assigned based on previous literatature reports (reference 116)

Fig. 2–6 Discovery and initial optimization of the Rh-catalyzed *Z*-selective reductive coupling

With standard conditions in hand, our focus turned to assessing how the different reaction parameters effect the formation of **2-20** (**Fig. 2–7**) The use of other Rh-based catalysts, including Wilkinson's catalyst or $[Rh(coe)_2Cl]_2$, as well as $[Ir(cod)Cl]_2$ consumed

diene without significant product formation, while other transition-metal complexes (Ru-, Pd-, and Cu- based) were completely inactive under the standard conditions. 1,5-cycloctadiene (cod) is essential for the reactivity and inactive $[Rh(coe)_2Cl]_2$ provides similar yields and reactivity compared to the use of $[Rh(cod)Cl]_2$ when 10% cod is added to the catalyst mixture. Catalyst loadings as low as 0.25 mol% $[Rh(cod)Cl]_2$ can be used to achieve yields comparable to the standard reaction when additional cod is added. DIPEA is required to achieve good selectivity while other less sterically hindered organic bases do not perform well. 2,6-Lutidine consumes diene unproductively while not forming any product. Triethylamine and DBU suffer from low selectivity while inorganic bases such as Cs_2CO_3 only provide a mixture of reduction products. The use of PPh_3 is not essential but removing it from the reaction mixture appears to result in catalyst decomposition and reduced selectivities (*vide infra*). Using one equivalent of aldehyde erodes selectivity and attempts to use sodium formate instead of formic acid provided low conversions and yield. The relative stereochemistry of **2-20** was determined through reduction of the ester followed by acetonization to provide **2-20'**.[105] The coupling constant between H_a and H_b was determined to be 2.8 Hz, indicating a *syn*-arrangement of the protons, indicating that **2-20** is formed as the *syn* diastereomer.[117]

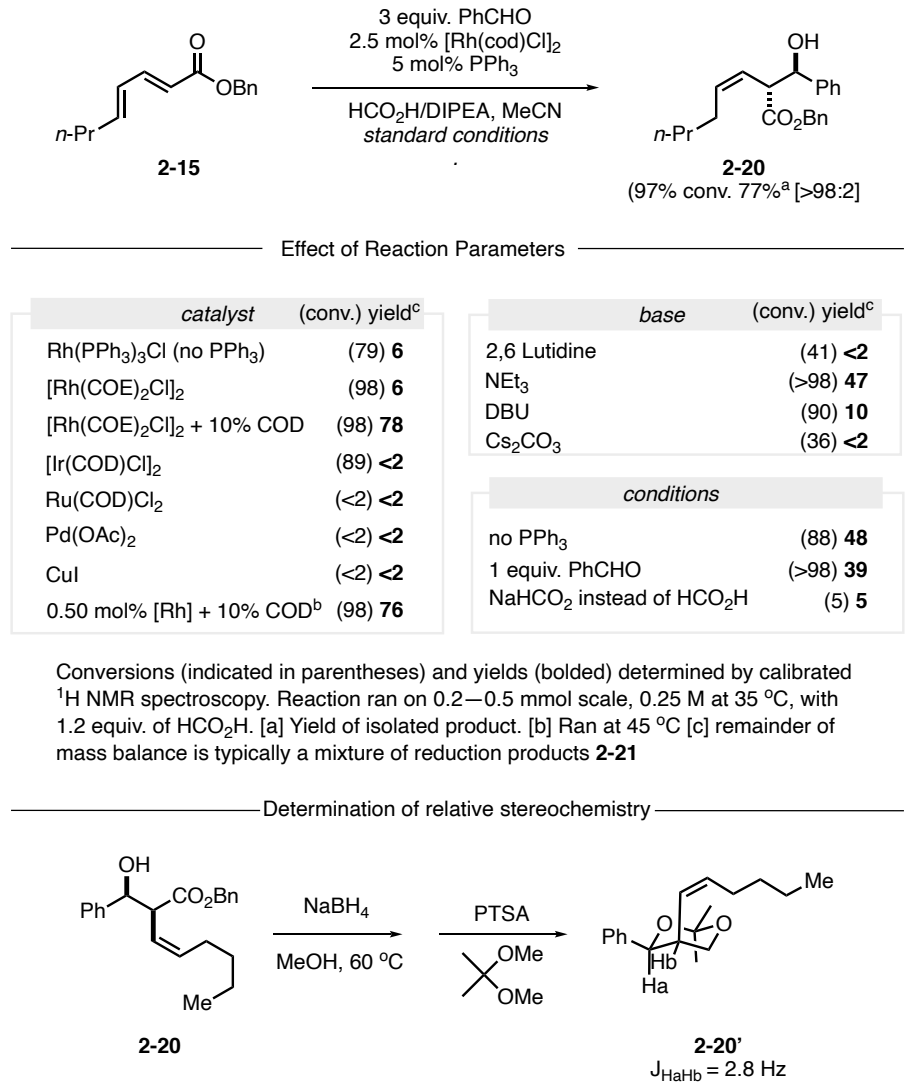
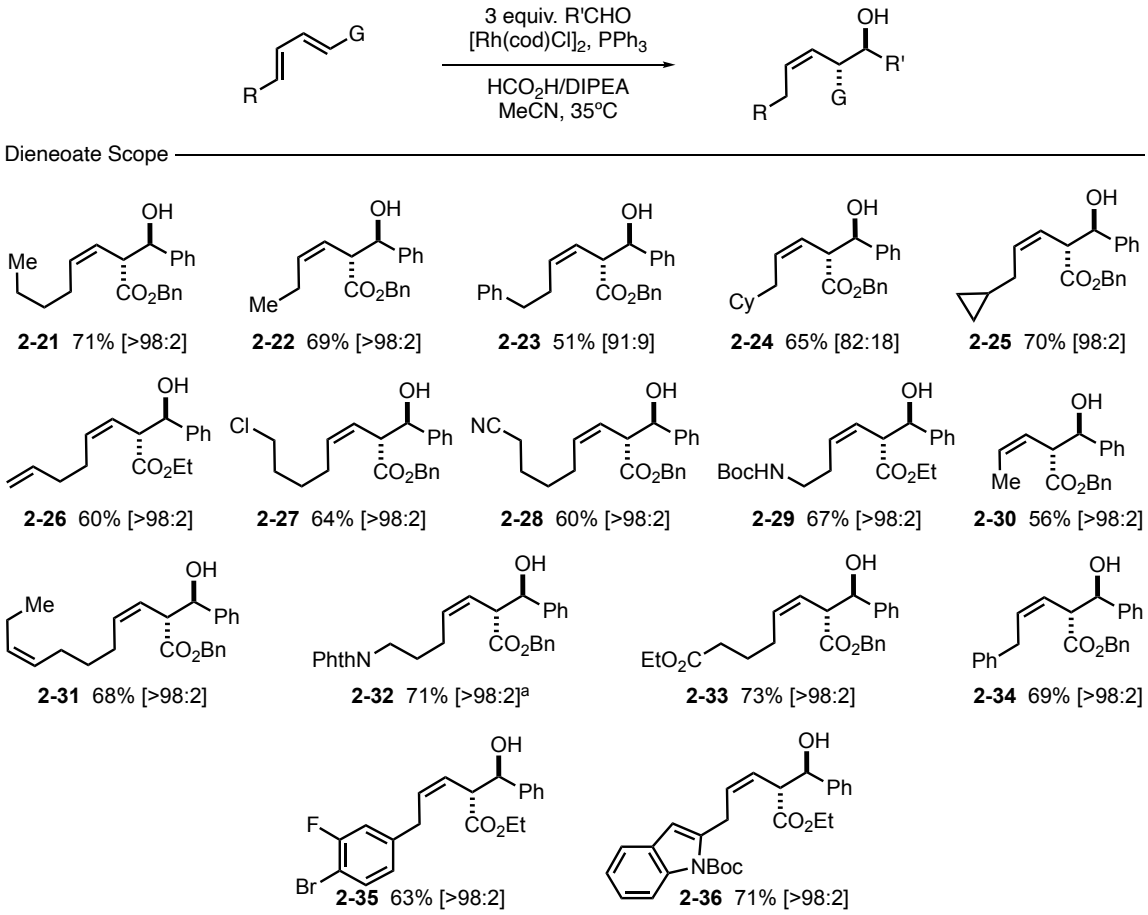


Fig. 2–7 Effect of reaction parameters on the *Z*-selective reductive coupling and determination of relative stereochemistry

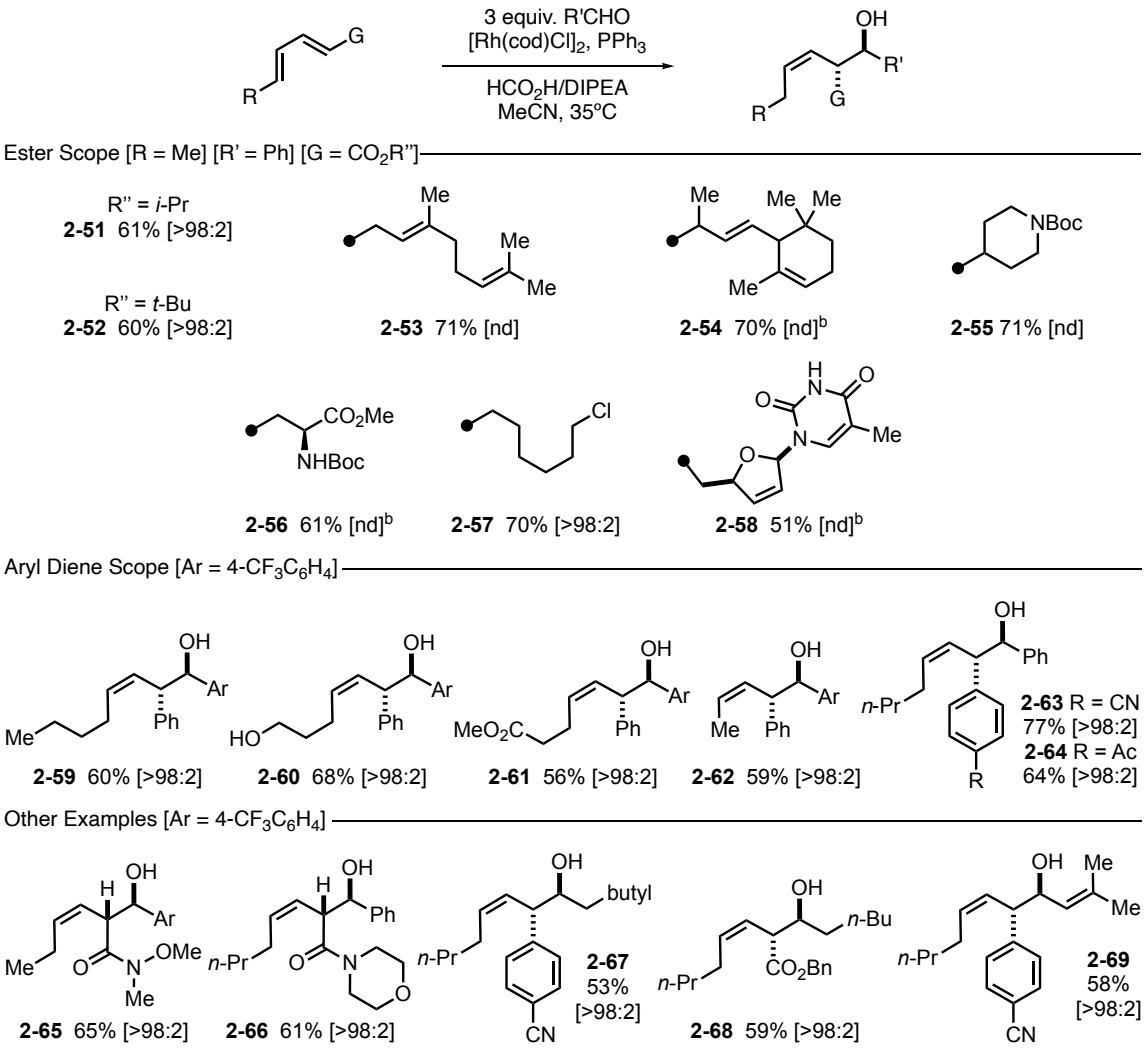
With optimized conditions confirmed, our focus turned to demonstrating the functional group compatibility of the reaction with potentially reactive functional groups. **Table 2–1** provides an overview of the dieneoate and aryl aldehyde scope for the Rh-catalyzed, formate-mediated reductive coupling. Alkyl-substituted dieneoates, including those with bulky groups (**2-24**, **2-25**) isolated alkene units (**2-26**, **2-31**), halogen (**2-27**), nitrile

(**2-28**), carbamates and imides (**2-29**, **2-32**), ester (**2-33**) and (hetero)aryl (**2-34**, **2-35**, **2-36**) substitution undergo reductive coupling to give products with good to moderate yields with uniformly high *syn*- and *Z*-selectivity. The aryl aldehyde partner can take on a range of electronic properties (**2-37**, **2-38**), more electrophilic aldehydes react selectively in competition studies, when 3 equivalents of *p*-anisaldehyde and 4-nitro benzaldehyde are added to the same reaction, **2-50** was observed as the lone coupling product. Other aryl aldehydes containing boronic ester (**2-39**), aryl halide (**2-40**, **2-41**, **2-42**, **2-45**) or reducible functional group such as nitrile (**2-44**), ketone (**2-46**), or nitro (**2-50**), as well as heterocyclic groups (**2-47**, **2-45**) react smoothly with uniformly high yields and diastereoselectivities. **Table 2–2** provides an overview of the scope of the ester groups, aryl dienes and some miscellaneous examples. The reaction accommodates a range of ester groups including *i*Pr (**2-51**), *t*Bu (**2-52**), and more complex alkene groups (**2-53**, **2-54**), carbamate (**2-55**, **2-56**), alkyl chloride (**2-57**), or polyfunctionalized groups (**2-58**). Interestingly, when attempting to form **2-35** under reduced catalyst loading conditions, 15% of the opposite regioisomer (trapping α to the aryl group) of product was observed. This prompted us to expand the scope of the diene partner to dienes activated by an aryl group. These dienes are reductively coupled with similar efficiency and selectivity including those with a tethered alcohol (**2-60**) or ester (**2-61**) groups. Aryl groups activated by nitriles (**2-63**) and ketone groups (**2-64**) provide increased yields over compounds activated by phenyl groups, which require more electrophilic 4-CF_3 benzaldehyde to improve reductive coupling yields (**2-50**, **2-60**, **2-61**, **2-62**). Finally, weinreb (**2-65**), and morpholine dienyl amides are viable substrates, as are alkyl (**2-67**, **2-68**) and α,β-unsaturated aldehydes (**2-69**).



Yields are of isolated materials under standard conditions (**Fig. 1—6**). See Section **3.3** for examples with lower [Rh] loading and minor modifications dependent on substrate. The *syn dr* values are given in square brackets.

Table 2–1 Dieneoate and aryl aldehyde scope of the Rh-catalyzed *Z*-selective reductive coupling



Yields are of isolated materials under standard conditions (**Fig. 1—6**). See Section **3.3** for examples with lower [Rh] loading and minor modifications dependent on substrate. The *syn dr* values are given in square brackets. *dr* with chiral esteres is ~ 1:1. [n.d.] = *dr* value of the crude reaction mixture could not be determined.

Table 2–2 Ester, aryl diene, and miscellaneous scope examples of the Rh-catalyzed *Z*-selective reductive coupling

Next, our focus turned to elucidating the mechanistic features that allow the use of a broad range of diene and aldehyde partners with functional groups that would be incompatible with more aggressive reducing conditions. First, the stereochemistry of the diene starting material (*E,E*-, *Z,E*-, or *E,Z*-) had minimal impact on the reaction outcomes and rate of reaction (**Fig. 2–8)**. The results of this experiment contradict those in the

previously develop 1,6-reduction,[116] which suggests that the reaction could be operating under a different mechanism. Control reactions with products from the *Z*-selective 1,6-reduction (**2-72**) under reductive coupling conditions provides no product and low conversion, ruling out a stepwise reaction to first generate the reduced product followed by a diastereoselective aldol process.

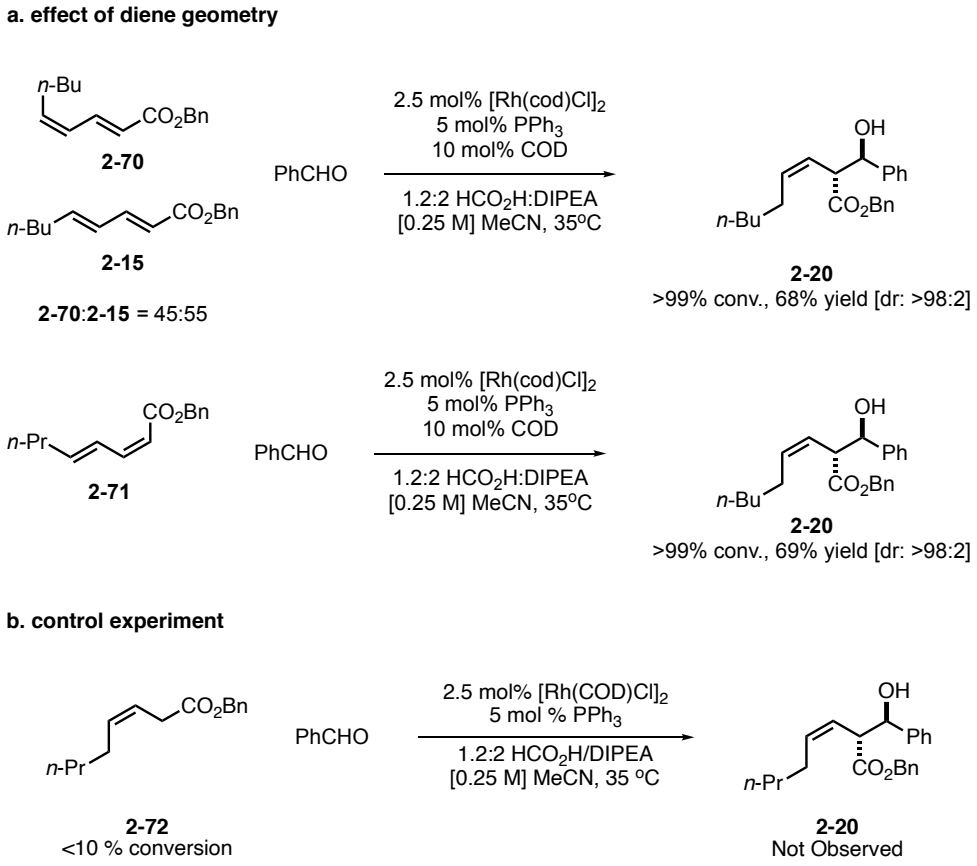


Fig. 2–8 Preliminary mechanistic studies on the Rh-catalyzed *Z*-selective reductive coupling

The formic acid mediated reductive coupling process yields products of direct aldehyde allylrhodation without isomerization (**Fig. 2–9)**. For example, dienyl ester **2-73**

provides a single coupling product (**2-33**) in 73% yield, chain walking and addition adjacent to the remote ester (**2-33'**) was not observed. Even when there is a clear thermodynamic driving force for isomerization, like in the cases of the ester tethered aryl diene **2-74**, only direct-coupled product **2-61** was observed while the chain walking product **2-61'** was not observed.

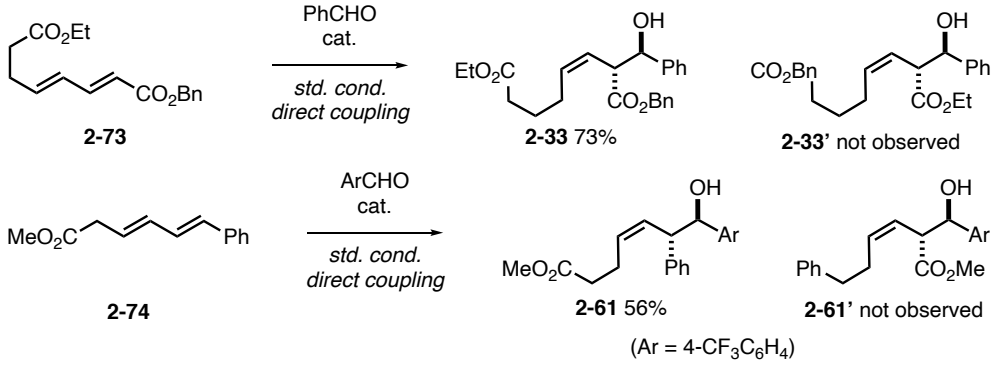


Fig. 2–9 Isomerization test on the Rh-catalyzed *Z*-selective reductive coupling: <5% chain walking

The role of catalyst components was elucidated by mechanistic studies. Variable time normalization (VTN), performed by a senior graduate student, demonstrated that the reaction is essentially zero order in aldehyde and formate, positive order in Rh and cod while being negative order in diene and PPh_3. These observations can be rationalized by proposing that the diene substrate, cod, and PPh_3 ligate Rh in various species that undergo ligand exchange processes. Rh species exist as off-cycle intermediates and the active species that enters the catalytic cycle is likely solvated $Rh(cod)^+$. The generation of this species by ligand dissociation is proposed to be rate determining. PPh_3 and additional cod are essential at low catalyst loading (**Fig. 2–10a**). The above observations prompted an in-depth study on the

effect of the Rh:PPh_3 ratio on reaction rates (**Fig. 2–10b**). The rate of reaction increased when the PPh_3 loading was halved. (**Fig. 2–10b**, left, grey trace). The reaction with no PPh_3 has similar initial rates as the standard reaction however catalyst decomposition and precipitation erode selectivity resulting in lower yields (**Fig. 2–10**, left, red trace). These observations prompted a kinetic study comparing the relative rates at different Rh:PPh_3 ratios (**Fig. 2–10**, right). Relative rates were estimated by following reaction progress to ~95% conversion (except for 2 equiv. PPh_3, which did not reach high conversion). These rates were then plotted as a function of relative rates compared to the standard reaction. It was determined that at high PPh_3 loadings, the reaction is very sluggish due to the majority of the Rh being sequestered off cycle by the phosphine ligand. Reactions ran with low/no PPh_3 result in catalyst death and eroded selectivity. The optimal rate of reaction occurs at 1:0.35 Rh:PPh_3.

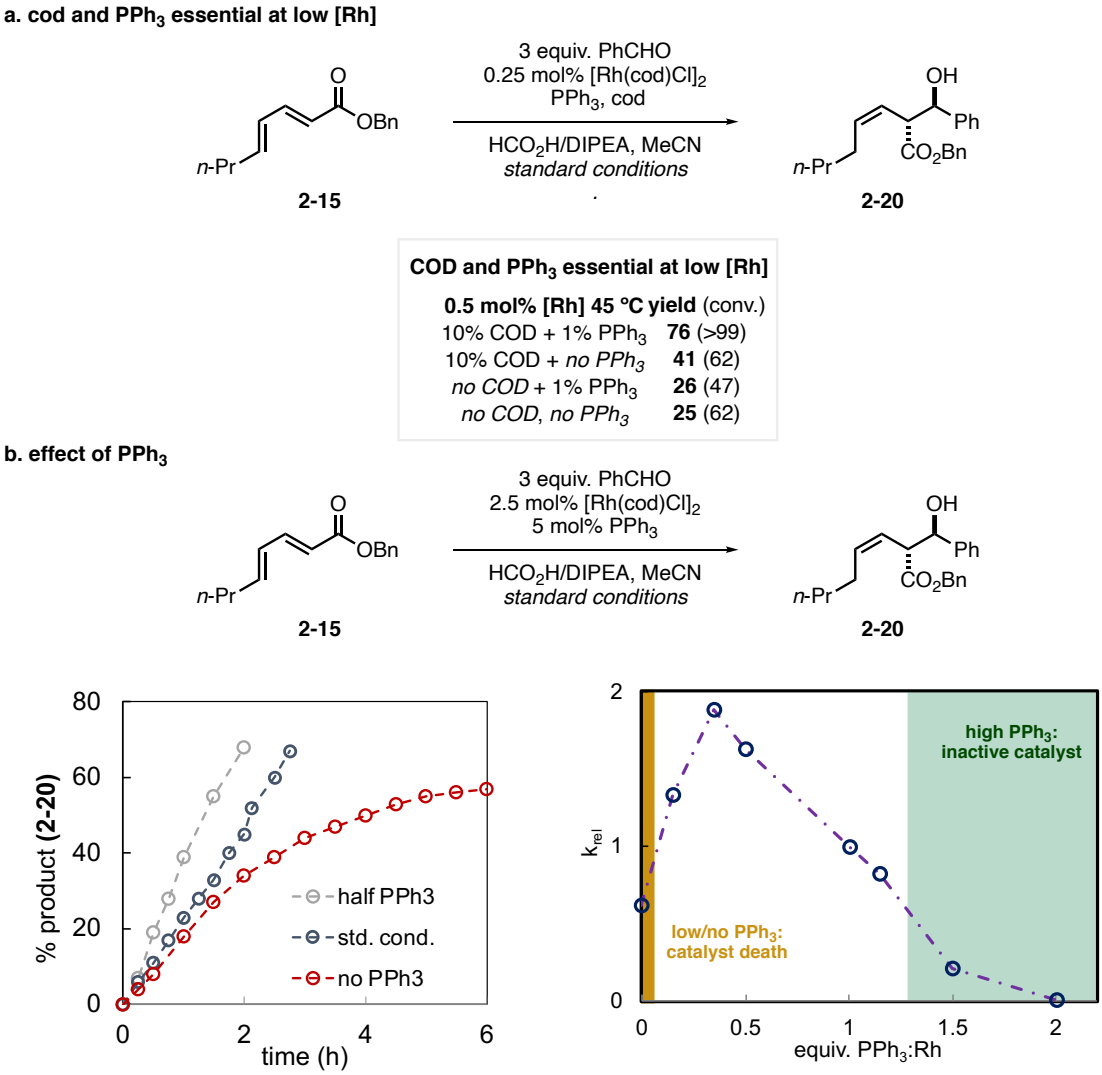


Fig. 2–10 Role of catalyst components in the Rh-catalyzed *Z*-selective reductive coupling

Experiments using formic acid-d_1 (DCO_2H) gave results consistent with *syn* hydrorhodation while installing the deuteride in the δ-position with 86% incorporation. No D label was found anywhere else in the molecule, however, some D was incorporated into cod (**Fig. 2–11**), suggesting that while the diene substrate (**2-15**) does not undergo reversible insertion/β-hydride elimination the ancillary diene ligand can; further demonstrating the importance of the cod ligand framework on the catalysis. The validity of ancillary diene

ligated Rh intermediates being involved in the catalytic cycle was confirmed by the observation of modest enantio-induction (up to 30% ee) by use of structurally related chiral diene ligands in place of cod.

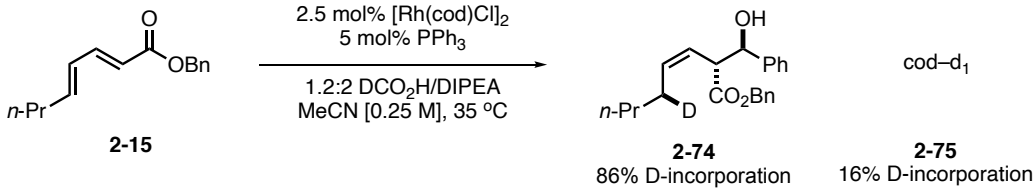


Fig. 2–11 Deuterium labeling study for the Rh-catalyzed *Z*-selective reductive coupling

A potential mechanistic cycle is provided in **Fig. 2–12**. After rate-determining ligand dissociation to form the active catalyst $Rh(cod)^+$ formic acid coordinates to Rh. Subsequent β-hydride elimination then forms the Rh-hydride. Diene coordination and insertion into the Rh–H bond generates a Rh-allyl with the hydride inserted into the δ-position. This intermediate undergoes aldehyde allylrhodation faster than undesirable isomerization events through a Zimmerman Traxler transition state (**Fig. 2–12b**) where the alkyl group is oriented in a pseudoaxial position to minimize steric interaction with the cod ligand, reinforcing the high *Z*-selectivity. The Rh-alkoxide generated is then protonated by $H–DIPEA^+$ or formic acid to provide the product while releasing Rh to re-enter the catalytic cycle or be ligated by free ligand to repeat the cycle.

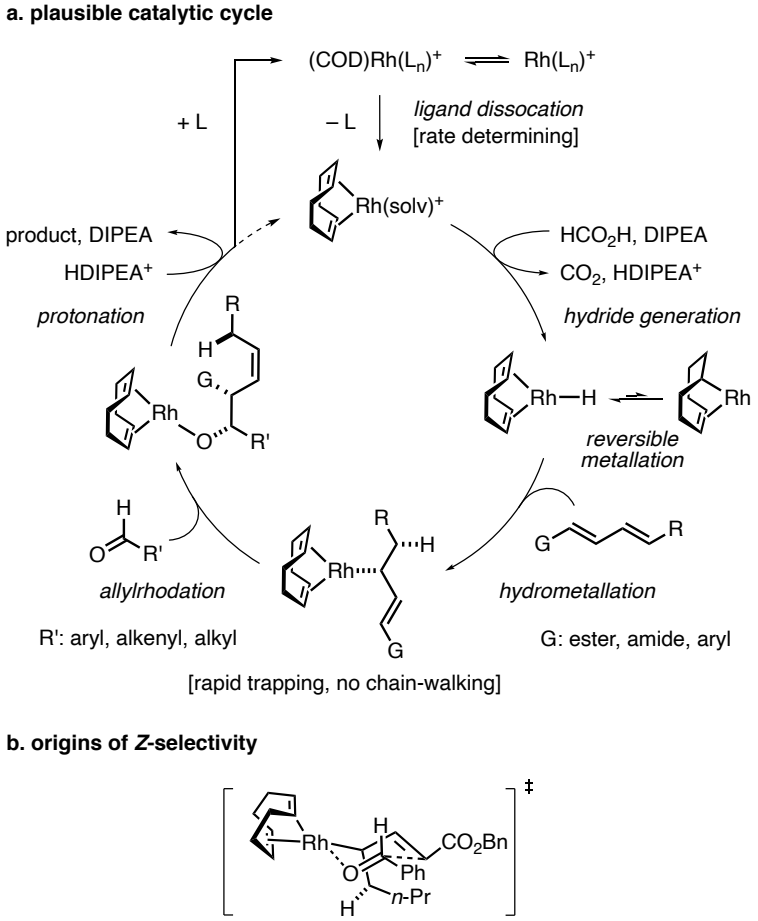


Fig. 2–12 Proposed catalytic cycle for the Rh-catalyzed *Z*-selective reductive coupling

2.3 Conclusion

The direct Rh-catalyzed, formic acid mediated reductive coupling of dienes and aldehydes provides a direct route to *Z-syn* homoallylic alcohols. The use of formic acid as a mild reductant allows for the expansion of substrate scope when compared to previously reported reductive couplings that use BEt_3 as the hydride source where protic and reducible functionalities were not tolerated. The absence of chain-walking isomerism is proposed to be facilitated by comparatively slow liberation of active catalyst species followed by rapid insertion into the Rh-hydride and fast aldehyde trapping. The identification of the Rh-allyl

intermediate allowed the use of carbon-based nucleophiles to achieve diene a difunctionalization reaction (Chapter 3).

2.4 Procedures and Characterization

General Considerations

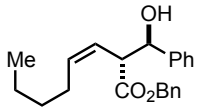
Unless noted, all reactions were conducted under inert atmosphere employing standard schlenk technique or using a N_2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed as described by Still and co-workers[118] (SiliaFlash P60, 40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using dibenzylether as an internal standard. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied. *Z*-alkene stereochemistry is confirmed through ^{1}H ROESY1D. Compound **2-15**[116] was prepared according to the literature. Compound **2-21** assigned based on previous literature report on the basis of ^{1}H NMR.[116]

General Procedure A: In an atmosphere controlled glovebox, $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.025 equiv.) and PPh_3 (6.6 mg, 0.025 mmol, 0.050 equiv.) were weighed into separate one dram vials. To the vial containing $[Rh(COD)Cl]_2$ was added MeCN (1 mL) and the solution was transferred into the vial containing PPh_3. MeCN (0.4 mL) was used to wash the remaining Rh solution into the vial containing the PPh_3 catalyst mixture. To a separate one dram vial was weighed diene (0.50 mmol, 1.0 equiv.) followed by aldehyde (1.50 mmol, 3.0 equiv.) and finally internal standard (dibenzyl ether). To this mixture was transferred the catalyst solution using MeCN (0.3 mL) to rinse the remaining solution into the reaction mixture. Diisopropylethylamine (174 μL, 1.0 mmol, 2.0 equiv.) was added followed by a freshly prepared 2 M formic acid solution (0.30 mL, 0.60 mmol, 1.2 equiv). A stir bar was added into the mixture, the vial was capped with a PTFE-lined cap, taken out of the glovebox, and placed in an aluminum block heated to 35 °C. The reaction progress was monitored periodically via ^1H NMR. Once the reaction reached >95% conversion, the solution was diluted with toluene to quench, concentrated and purified by silica gel chromatography. The use of a glovebox is not required, see example **2a**. The remaining mass balance of diene is typically the 1,6-reduction product generated as a mixture of *E*- and *Z*-isomers.

General Procedure B [reduced catalyst loadings with additional COD]: In an atmosphere controlled glovebox, $[Rh(COD)Cl]_2$ (5.2 mg, 0.0105 mmol) and PPh_3 (5.5 mg, 0.021 mmol) were weighed into separate one dram vials. To the vial containing $[Rh(COD)Cl]_2$ was added MeCN (4.2 mL) and the solution was transferred into the vial containing PPh_3. MeCN (2.94 mL) was used to wash the remaining Rh solution into the vial containing the PPh_3 catalyst mixture. To four separate one dram vial was weighed diene (0.50

mmol, 1.0 equiv.) followed by aldehyde (1.50 mmol, 3.0 equiv.) and 1,5-cyclooctadiene (5.4 mg, 0.050 mmol, 0.10 equiv.) and finally internal standard (dibenzyl ether). To these mixtures were transferred the catalyst solution (1.4 mL). Diisopropylethylamine (174 μL, 1.0 mmol, 2.0 equiv.) was added followed by a freshly prepared 1 M formic acid solution (0.60 mL, 0.60 mmol, 1.2 equiv). A stir bar was added into the mixture, the vial was capped with a PTFE-lined cap, taken out of the glovebox and placed in an aluminum block heated to 35 °C. The reaction progress was monitored periodically via ^{1}H NMR.

General Procedure C [additional COD]: In an atmosphere controlled glovebox, $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.025 equiv.) and PPh_3 (6.6 mg, 0.025 mmol, 0.050 equiv.) were weighed into separate one dram vials. To the vial containing $[Rh(COD)Cl]_2$ was added MeCN (1 mL) and the solution was transferred into the vial containing PPh_3. MeCN (0.4 mL) was used to wash the remaining Rh solution into the vial containing the PPh_3 catalyst mixture. To a separate one dram vial was weighed diene (0.50 mmol, 1.0 equiv.) followed by aldehyde (1.5 mmol, 3.0 equiv.) and 1,5-cyclooctadiene (5.4 mg, 0.050 mmol, 0.10 equiv.) and finally internal standard (dibenzyl ether). To this mixture was transferred the catalyst solution using MeCN (0.3 mL) to rinse the remaining solution into the reaction mixture. Diisopropylethylamine (174 μL, 1.0 mmol, 2.0 equiv.) was added followed by a freshly prepared 2 M formic acid solution (0.30 mL, 0.60 mmol, 1.2 equiv.). A stir bar was added into the mixture, the vial was capped with a PTFE-lined cap, taken out of the glovebox and placed in an aluminum block heated to 35 °C. The reaction progress was monitored periodically via ^{1}H NMR. Once the reaction reached >95% conversion, the solution was diluted with toluene to quench, concentrated and purified by silica gel chromatography.



2-20 Prepared according to the General Procedure A from the corresponding diene (115.2 mg, 0.500 mmol) and benzaldehyde (153 μL, 1.50 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 95%, crude yield: 76%, *dr*: >98:2. Isolated in 71% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

Gram Scale Reaction: In an atmosphere controlled glovebox, $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.0025 equiv.) and PPh_3 (6.6 mg, 0.025 mmol, 0.0050 equiv.) were weighed into separate one dram vials. To the vial containing $[Rh(COD)Cl]_2$ was added MeCN (1 mL) and the solution was transferred into the vial containing PPh_3. MeCN (1 mL) was used to wash the remaining Rh solution into the vial containing the PPh_3 catalyst mixture. To an 8 dram vial was weighed diene (1.15 g, 5.0 mmol, 1.0 equiv.) followed by benzaldehyde (1.60 g, 15 mmol, 3 equiv.) and 1,5-cyclooctadiene (54.1 mg, 0.5 mmol, 0.1 equiv.). To this mixture was transferred the catalyst solution using MeCN (1 mL) to rinse the remaining solution into the reaction mixture. MeCN (11 mL) is added to the reaction mixture. Diisopropylethylamine (1.75 mL, 10 mmol, 2 equiv.) was added followed by a freshly prepared 1 M formic acid solution (6 mL, 6 mmol, 1.2 equiv). A stir bar was added into the mixture, the vial was capped with a PTFE-lined cap, taken out of the glovebox and placed in an aluminum block heated to 35 °C for 48h. ^{1}H NMR conversion: 95%, crude yield: 74%, *dr*: >98:2. Isolated in 71% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

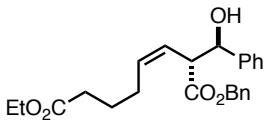
Prepared according to General Procedure C under air (no glovebox used) from the corresponding diene (115.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.50 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 77%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 – 7.28 (m, 7H), 7.28 – 7.24 (m, 1H), 7.18 – 7.16 (m, 2H), 5.73 – 5.67 (m, 1H), 5.64 – 5.58 (m, 1H), 5.07 – 5.00 (m, 3H), 3.71 (ddd, *J* = 9.8, 5.8, 0.8 Hz, 1H) 2.82 (d, *J* = 2.1 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.89 – 1.82 (m, 1H), 1.23 – 1.07 (m, 4H), 0.81 (t, *J* = 7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 140.9, 136.8, 135.6, 128.5, 128.3, 128.1, 127.8, 126.5, 122.1, 74.4, 52.3, 66.6, 52.3, 31.4, 27.4, 22.3, 13.9;

HRMS (ESI): calcd for $C_{22}H_{26}O_3Na$ $[M+Na]^+$ 361.1774. Found 361.1769;

IR: ν (cm^{-1}) 3504, 3064, 3032, 2956, 2929, 2871, 2859, 1951, 1880, 1731, 1604, 1454, 1312, 1160.



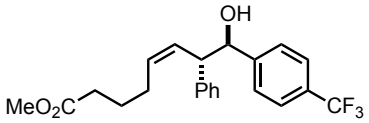
2-33 Prepared according to the General Procedure C from the corresponding diene (144.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 80%, *dr*: >98:2. Isolated in 73% yield as a yellow oil after purification by column chromatography (17:5 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.22 (m, 8H), 7.20–7.14 (m, 2H), 5.71–6.61 (m, 2H), 5.08–4.99 (m, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.69 (dd, *J* = 9.2, 5.9 Hz, 1H), 2.98 (d, *J* = 3.1 Hz, 1H), 2.13 (t, *J* = 7.6 Hz, 2H), 2.05 – 1.85 (m, 2H), 1.61 – 1.43 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 172.6, 140.9, 135.5, 135.0, 128.5, 128.3, 128.3, 128.1, 127.4, 126.4, 123.5, 74.3, 66.7, 52.3, 33.6, 26.9, 24.4, 14.3;

HRMS (ESI): calcd for $C_{24}H_{28}O_5Na$ $[M+Na]^+$ 419.1829. Found 419.1937;

IR: ν (cm^{-1}) 3501, 3064, 3032, 2980, 2939, 2906, 2872, 1958, 1887, 1730, 1604, 1496, 1454, 1311, 1153.



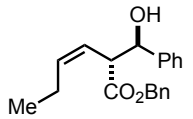
2-61 Prepared according to a modified General Procedure A (additional 0.5 equiv. HCO_2H added upon consumption of first 1.2 equiv.) from the corresponding diene (40 mg, 0.2 mmol) and 4-(trifluoromethyl)benzaldehyde (104 mg, 0.6 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 59%, *dr*: >98:2. Isolated in 56% yield as a light-yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.15 (m, 5H), 7.08 – 7.06 (m, 2H), 5.96 – 5.91 (m, 1H), 5.63 – 5.58 (m, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 3.91 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.62 (s, 3H), 2.67 (bs, 1H), 2.47 – 2.39 (m, 1H), 2.34 – 2.21 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 146.2, 140.6, 131.5, 129.6, 128.6, 128.2, 126.9, 126.8, 126.3 (q, *J* = 271.2 Hz), 124.8 (q, *J* = 7.5, 3.6 Hz), 77.5, 52.4, 51.7, 33.3, 22.9;

HRMS (ESI): cacld for $C_{21}H_{21}O_3F_3Na$ $[M+Na]^+$ 401.1335. Found 401.1344;

IR: ν (cm^{-1}) 3472, 3064, 3028, 2953, 2922, 1923, 1735, 1619, 1493, 1438, 1323, 1161.



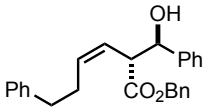
2-22 Prepared according to the General Procedure A from the corresponding diene (101.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 74%, *dr*: >98:2. Isolated in 69% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.29 (m, 7H), 7.27 – 7.24 (m, 1H), 7.19 – 7.15 (m, 2H), 5.73 – 5.67 (m, 1H), 5.62 – 5.56 (m, 1H), 5.08 – 4.95 (m, 3H), 3.73 (ddd, *J* = 9.9 Hz, 6.0, 0.9 Hz, 1H), 2.85 (d, *J* = 2.6 Hz, 1H), 1.97 (m, 1H), 1.86 (m, 1H) , 0.81 (t, *J* = 7.6 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 140.9, 138.1, 135.6, 128.5, 128.3, 128.3, 128.1, 127.9, 126.5, 121.7, 74.3, 66.6, 52.3, 21.0, 13.8;

HRMS (ESI): calcd for $C_{20}H_{22}O_3Na$ $[M+Na]^+$: 333.1565. Found 333.1465;

IR: ν (cm^{-1}) 3501, 3089, 3064, 3032, 2964, 2934, 2874, 1953, 1730, 1604, 1497, 1454, 1160.



2-23 Prepared according to the General Procedure from the corresponding diene (139 mg, 0.5 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 53%, *dr*: >98:2. Isolated in 52% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

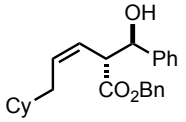
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 – 7.27 (m, 8H), 7.25 – 7.22 (m, 3H), 7.18 – 7.14 (m, 2H), 7.05 (d, *J* = 7.2, 2H), 5.74 – 5.69 (m, 1H), 5.66 – 5.62 (m, 1H), 5.05 – 4.99 (m, 3H),

3.67 (dd, *J* = 9.8, 5.8 Hz, 1H), 2.77 (d, *J* = 2.7 Hz, 1H), 2.52 – 2.46 (m, 1H), 2.42 – 2.36 (m, 1H), 2.30 – 2.13 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 141.4, 140.8, 135.5, 135.3, 128.5, 128.4, 128.3(2), 128.2, 128.1, 127.8, 126.4, 125.9, 122.9, 74.2, 66.6, 52.2, 35.3, 29.5;

HRMS (ESI): calcd for $C_{26}H_{26}O_3Na$ $[M+Na]^+$ 409.1774. Found 409.1774;

IR: ν (cm^{-1}) 3503, 3086, 3064, 3028, 2935, 2858, 1951, 1880, 1729, 1603, 1496, 1453, 1158.



2-24 Prepared according to the General Procedure A from the corresponding diene (135.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 74%, *dr*: 82:18. Isolated in 65% yield as white solid after purification by column chromatography (10:1 Hexane/EtOAc).

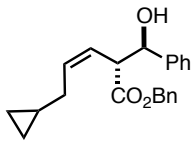
^{1}H NMR ($CDCl_3$, 400 MHz) ***syn* diastereomer:** δ 7.37 – 7.22 (m, 8H), 7.20 – 7.15 (m, 2H), 5.76 – 5.60 (m, 2H), 5.07 – 5.01 (m, 3H), 3.70 (dd, *J* = 9.7, 5.9 Hz, 1H), 2.88 (d, *J* = 2.4 Hz, 1H), 1.90 – 1.71 (m, 2H), 1.65 – 1.43 (m, 5H), 1.18 – 1.01 (m, 4H), 0.83 – 0.67 (m, 2H); ***anti* diastereomer (selected signals):** δ 3.62 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.99 (d, *J* = 2.4 Hz, 1H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.8, 140.8, 135.6, 135.4, 128.5, 128.3, 128.2, 128.1, 127.8, 126.5, 122.8, 74.4, 66.6, 52.6, 37,9, 35.4, 33.1, 32.9, 26.5, 26.3, 26.3;

HRMS (ESI): calcd for $C_{25}H_{30}O_3Na$ $[M+Na]^+$: 401.2087. Found 401.2087;

MP: 51 - 54 °C;

IR: ν (cm^{-1}) 3506, 3092, 3064, 3032, 2923, 2850, 1730, 1497, 1450, 1311, 1159**.**



2-25 Prepared according to the General Procedure A from the corresponding diene (114.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 76%, *dr*: 98:2. Isolated in 71% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

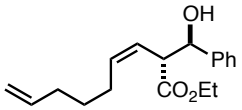
Prepared according to General Procedure B from the corresponding diene (114.2 mg, 0.50 mmol, 1 equiv.) and benzaldehyde (159.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 81%, *dr*: 98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 – 7.27 (m, 7H), 7.27 – 7.23 (m, 1H), 7.18 – 7.14 (m, 2H), 5.84 – 5.78 (m, 1H), 5.67 – 5.61 (m, 1H), 5.06 – 5.00 (m, 3H), 3.68 (dd, *J* = 9.9, 6.1 Hz, 1H), 2.82 (d, 2.8 Hz, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 0.58 – 0.49 (m, 1H), 0.38 – 0.30 (m, 2H), 0.01 – -0.09 (m, 2H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.6, 140.8, 135.7, 135.5, 128.5, 128.3, 128.3, 128.1, 127.9, 126.5, 122.3, 74.3, 66.6, 52.4, 32.3, 10.4, 4.2, 4.1;

HRMS (ESI): calcd for $C_{22}H_{24}O_3Na$ $[M+Na]^+$ 359.1618. Found 359.1620;

IR: ν (cm^{-1}) 3509, 3065, 3032, 3002, 2963, 2893, 1951, 1881, 1730, 1497, 1454, 1315, 1160**.**



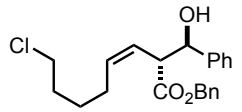
2-26 Prepared according to the General Procedure A from the corresponding diene (16 mg, 0.09 mmol) and benzaldehyde (27 μL, 0.26 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 65%, *dr*: >98:2. Isolated in 60% yield as a yellow oil after purification by column chromatography (4:1 Pentane/Et_2O).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 – 7.29 (m, 4H), 7.27 – 7.23 (m, 1H), 5.76 – 5.58 (m, 3H), 5.04 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.97 – 4.91 (m, 2H), 4.06 (qd, *J* = 7.2, 1.5 Hz, 2H), 3.62 (dd, *J* = 9.5, 5.4 Hz, 1H), 2.97 (d, *J* = 2.4 Hz, 1H), 1.99 – 1.81 (m, 4H), 1.34 – 1.20 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 140.9, 138.5, 135.9, 128.1, 127.7, 126.4, 122.5, 114.6, 74.2, 60.9, 52.1, 33.2, 28.3, 27.0, 14.0;

HRMS (ESI): calcd for $C_{18}H_{24}O_3Na$ $[M+Na]^+$ 311.1618. Found 311.1617;

IR: ν (cm^{-1}) 3500, 3065, 3034, 2979, 2931, 2858, 1940, 1729, 1640, 1453, 1176,1028.



2-27 Prepared according to the General Procedure A from the corresponding diene (132 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 65%, *dr*: >98:2. Isolated in 64% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

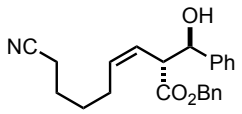
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 – 7.26 (m, 8H), 7.20 – 7.18 (m, 2H), 5.68 – 5.62 (m, 2H), 5.09 (dd, *J* = 5.4, 2.6 Hz, 1H), 5.08 – 5.05 (m, 2H), 3.67 (dd, *J* = 9.2, 5.4 Hz, 1H),

3.38 (t, *J* = 6.9 Hz, 2H), 2.90 (d, *J* = 2.6 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.87 – 1.80 (m, 1H), 1.60 – 1.51 (m, 2H), 1.36 – 1.22 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 140.8, 135.6, 135.5, 128.5, 128.3, 128.2, 128.1, 127.8, 126.4, 122.7, 74.2, 66.7, 52.1, 44.8, 31.9, 26.8, 26.3;

HRMS (ESI): calcd for $C_{22}H_{25}O_3ClNa$ $[M+Na]^+$ 395.1384. Found 395.1383;

IR: ν (cm^{-1}) 3506, 3088, 3064, 3031, 2939, 2865, 1953, 1857, 1729, 1604, 1496, 1454, 1161**.**



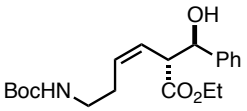
2-28 Prepared according to the General Procedure from the corresponding diene (115 mg, 0.45 mmol) and benzaldehyde (137 μL, 1.4 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >96%, crude yield: 62%, *dr*: >98:2. Isolated in 60% yield as a yellow oil after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 – 7.26 (m, 8H), 7.22 – 7.20 (m, 2H), 5.70 – 5.66 (m, 1H), 5.64 – 5.59 (m, 1H), 5.12 (d, *J* = 5.1, Hz, 1H), 5.06 (s, 2H), 3.67 (dd, *J* = 9.6, 5.1 Hz, 1H), 2.90 (bs, 1H), 2.14 (t, *J* = 7.0 Hz, 2H) 1.98 – 1.91 (m, 1H), 1.86 – 1.79 (m, 1H), 1.43 – 1.22 (m, 4H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 140.8, 135.4, 134.8, 128.6, 128.4, 128.3, 128.2, 127.8, 126.3, 123.0, 119.5, 74.1, 66.7, 52.0, 27.9, 26.6, 24.6, 16.9;

HRMS (ESI): calcd for $C_{22}H_{25}O_3ClNa$ $[M+Na]^+$ 386.1727. Found 386.1722;

IR: ν (cm^{-1}) 3491, 3088, 3063, 3031, 2939, 2866, 2246, 1956, 1884, 1729, 1496, 1454, 1153**.**



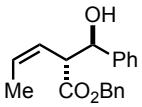
2-29 Prepared according to the General Procedure from the corresponding diene (134 mg, 0.5 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 68%, *dr*: >98:2. Isolated in 67% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 – 7.30 (m, 4H), 7.27 – 7.24 (m, 1H), 5.66 – 5.60 (m, 2H), 5.05 (dd, *J* = 5.5, 2.4 Hz, 1H), 4.56 (bs, 1H), 4.09 – 4.01 (qd, *J* = 7.2, 2.9 Hz, 2H), 3.62 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.05 (d, *J* = 2.4 Hz, 1H), 3.0 – 2.96 (m, 2H), 2.00 – 1.85 (m, 2H), 1.44 (s, 9H), 1.34 – 1.27 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 156.0, 141.0, 135.0, 128.2, 127.8, 126.4, 123.3, 79.0, 74.3, 60.9, 52.1, 39.7, 29.2, 28.4, 24.7, 14.0;

HRMS (ESI): calcd for $C_{22}H_{25}O_3ClNa$ $[M+Na]^+$ 400.2094. Found 400.2091;

IR: ν (cm^{-1}) 3387, 3063, 3033, 2978, 2934, 1957, 1713, 1692, 1521, 1453, 1366, 1172**.**



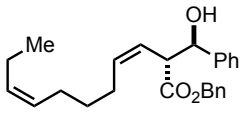
2-30 Prepared according to General Procedure C from the corresponding diene (128.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.) ^{1}H NMR diene conversion: >99%, crude yield: 57%, *dr*: >98:2. Isolated in 56% yield as a yellow-brown oil after purification by column chromatography (17:3 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.36 – 7.25 (m, 8H), 7.19 – 7.15 (m, 2H), 5.83 – 5.77 (m, 1H), 5.68 – 5.62 (m, 1H), 5.08 – 5.00 (m, 3H), 3.74 (ddd, *J* = 9.9, 6.0, 0.8 Hz, 1H), 2.84 (d, *J* = 2.6 Hz, 1H), 1.50 (dd, *J* = 6.9, 1.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.7, 140.9, 135.6, 130.7, 128.5, 128.3(2), 128.1, 127.9, 126.5, 123.4, 74.9, 66.6, 52.0, 13.2;

HRMS (ESI): calcd for $C_{19}H_{20}O_3Na$ $[M+Na]^+$ 319.1305. Found 319.1304;

IR: ν (cm^{-1}) 3505, 3089, 3064, 3032, 2941, 2920, 2891, 1953, 1882, 1729, 1497, 1454, 1156**.**



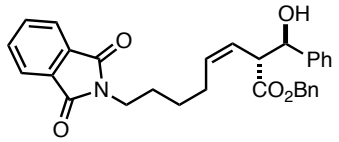
2-31 Prepared according to the General Procedure A from the corresponding diene (128.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 68%, *dr*: >98:2. Isolated in 68% yield as a yellow-brown oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.28 (m, 7H), 7.27 – 7.23 (m, 1H), 7.19 – 7.16 (m, 2H), 5.73 – 5.67 (m, 1H), 5.65 – 5.59 (m, 1H), 5.37 – 5.31 (m, 1H), 5.25 – 5.20 (m, 1H), 5.08 – 5.00 (m, 3H), 3.70 (ddd, *J* = 9.8, 5.8, 0.7 Hz, 1H), 2.87 (d, *J* = 2.6 Hz, 1H), 2.02 – 1.81 (m, 6H), 1.30 – 1.22 (m, 1H), 1.22 – 1.14 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.8, 140.8, 136.4, 135.5, 132.0, 128.6, 128.6, 128.3, 128.1, 127.8, 126.5, 122.4, 122.3, 74.4, 66.6, 52.3, 29.3, 27.3, 26.7, 20.5, 14.4;

HRMS (ESI): calcd for $C_{25}H_{30}O_3Na$ $[M+Na]^+$ 401.2088. Found 401.2088;

IRν (cm^{-1}) 3507, 3089, 3064, 3032, 3005, 2961, 2931, 2872, 2859, 1951, 1879, 1731, 1497, 1454, 1158**.**



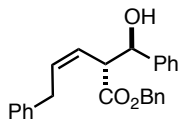
2-32 Prepared according to the General Procedure A from the corresponding diene (187.8 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 76%, *dr*: >98:2. Isolated in 71% yield as a brown solid after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.85 – 7.81 (m, 2H), 7.72 – 7.68 (m, 2H), 7.34 – 7.23 (m, 7H), 7.21 – 7.15 (m, 3H), 5.67 – 5.60 (m, 2H), 5.08 – 5.00 (m, 3H), 3.73 – 3.69 (m, 1H), 3.61 – 3.53 (m, 2H), 2.98 (d, *J* = 2.7 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.93 – 1.86 (m, 1H), 1.54 – 1.44 (m, 1H), 1.28 – 1.20 (m, 1H), 1.17 – 1.10 (m, 1H);

^{13}C NMR $CDCl_3$, 175 MHz) δ 172.8, 168.5, 140.9, 135.7, 135.6, 133.9, 132.2, 128.6, 128.2, 128.1, 127.8, 126.4, 123.2, 122.7, 74.3, 66.6, 52.2, 37.7, 28.0, 27.1, 26.2;

HRMS (ESI): calcd for $C_{30}H_{29}NO_5Na$ $[M+Na]^+$ 506.1938. Found 506.1941;

IR: ν (cm^{-1}) 3500, 3089, 3063, 3031, 2940, 2862, 1769, 1710, 1613, 1496, 1454, 1437, 1397**.**



2-34 Prepared according to the General Procedure A from the corresponding diene (132.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene

conversion: 96%, crude yield: 74%, *dr*: >98:2. Isolated in 69% yield as a yellow solid after purification by column chromatography (10:1 Hexane/EtOAc).

Prepared according to General Procedure B from the corresponding diene (132.2 mg, 0.50 mmol, 1.0 equiv.) and benzaldehyde (159.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 87%, *dr*: >98:2.

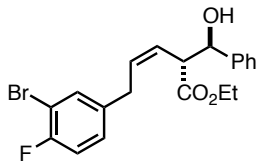
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.39 – 7.28 (m, 8H), 7.23 – 7.13 (m, 5H), 6.96 – 6.92 (m, 2H), 5.86 – 5.81 (m, 1H), 5.80 – 5.76 (m, 1H), 5.16 (d, *J* = 5.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 3.85 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.27 (dd, *J* = 16.1, 7.7 Hz, 1H), 2.17 (dd, *J* = 16.1, 7.7 Hz, 1H) 3.02 (d, *J* = 2.3 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 140.8, 139.7, 135.5, 134.6, 128.6, 128.4, 128.4, 128.4, 128.3, 128.1, 127.9, 126.4, 126.1, 122.9, 74.2, 66.8, 52.0, 33.8;

HRMS (ESI): calcd for $C_{25}H_{24}O_3Na$ $[M+Na]^+$ 295.1618. Found 295.1618;

MP: 60 – 63 °C;

IR: ν (cm^{-1}) 3496, 3089, 3062, 3029, 2916, 1953, 1888, 1729, 1601, 1495, 1453, 1313, 1158**.**



2-35 Prepared according to the General Procedure A from the corresponding diene (149 mg, 0.5 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 63%, *dr*: >98:2. Isolated in 63% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

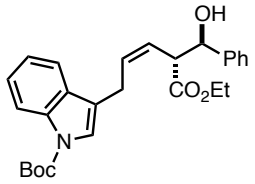
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.28 (m, 5H), 7.14 (dd, *J* = 6.5, 2.0 Hz, 1H), 6.9 (t, *J* = 8.4 Hz, 1H), 6.79 – 6.76 (m, 1H), 5.81 – 5.77 (m, 1H), 5.74 – 5.69 (m, 1H), 5.17 (dd, *J* = 4.6, 2.4 Hz, 1H), 4.15 – 4.10 (m, 2H), 3.69 (dd, *J* = 9.9, 4.6 Hz, 1H), 3.18 (dd, *J* = 15.7, 7.3 Hz, 1H), 3.08 (d, *J* = 2.4 Hz, 1H), 3.05 (dd, *J* = 15.7, 7.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 158.5, 156.6, 140.8, 137.1, 133.1, 133.0, 128.8 (d, *J* = 7.0 Hz) 128.3, 127.9, 126.2, 123.7, 116.2, 73.9, 61.2, 51.7, 32.6, 14.1;

^{19}F NMR ($CDCl_3$, 468 MHz) δ -111.5 (m);

HRMS (ESI): calcd for $C_{20}H_{20}O_3BrFNa$ $[M+Na]^+$ 429.0472. Found 429.0477;

IR: ν (cm^{-1}) 3488, 3062, 3032, 2939, 2981, 2937, 2904, 1959, 1893, 1728, 1598, 1494, 1451, 1244**.**



2-36 Prepared according to the General Procedure A from the corresponding diene (170.7 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 73%, *dr*: >98:2. Isolated in 71% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

Prepared according to General Procedure B from the corresponding diene (170.7 mg, 0.50 mmol) and benzaldehyde (159.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 90%, *dr*: >98:2.

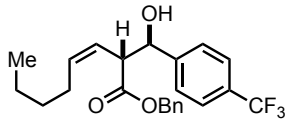
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, *J* = 6.1 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.36 (m, 5H), 7.23 – 7.13 (m, 2H), 5.93 – 5.86 (m, 1H), 5.80 (app tt, *J* = 10.0, 1.7 Hz, 1H), 5.17 (d, *J*

= 5.0 Hz, 1H), 4.12 (qd, *J* = 7.2, 2.2 Hz, 2H), 3.81 (ddd, *J* = 10.0, 5.1, 0.7 Hz, 1H), 3.31 (ddd, *J* = 16.6, 7.3, 1.7 Hz, 1H), 3.18 – 3.10 (m, 2H), 1.66 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 149.7, 140.9, 132.9, 130.3, 128.3, 127.8, 126.4, 124.4, 123.6, 122.7, 122.3, 119.0, 118.9, 115.2, 83.4, 74.2, 61.1, 52.0, 28.3, 23.4, 14.1;

HRMS (ESI): calcd for $C_{27}H_{31}NO_5Na$ $[M+Na]^+$ 472.2094. Found 472.2093;

IR: ν (cm^{-1}) 3508, 3087, 3057, 3030, 2979, 2933, 1941, 1730, 1608, 1452, 1369, 1159**.**



2-37 Prepared according to the General Procedure A from the corresponding diene (92 mg, 0.40 mmol) and 4-(trifluoromethyl)-benzaldehyde (208.9 mg, 1.2 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 90%, *dr*: >98:2. Isolated in 81% yield as a brown solid after purification by column chromatography (10:1 Hexane/EtOAc).

Prepared according to General Procedure B from the corresponding diene (115.2 mg, 0.50 mmol, 1 equiv.) and 4-(trifluoromethyl)-benzaldehyde (261.3 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 77%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.31 (m, 3H), 7.22 – 7.18 (m, 2H), 5.72 – 5.67 (m, 1H), 5.58 (app t, *J* = 10.4 Hz, 1H), 5.11 (dd, *J* = 4.9, 1.2 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 5.04 (d, *J* = 12.3 Hz, 1H), 3.67 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.11 (d, *J* = 2.4 Hz, 1H), 1.92 (m, 1H), 1.79 (m, 1H), 1.20 – 1.01 (m, 4H), 0.78 (t, *J* = 7.1 Hz, 3H);

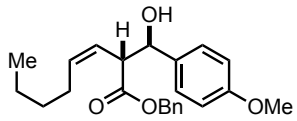
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 144.8, 137.3, 135.3, 129.9 (q, *J* = 32.3 Hz) 128.6, 128.5, 128.2, 126.8, 125.1 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.9 Hz), 121.2, 73.6, 66.9, 51.8, 31.3, 27.4, 22.2, 13.8;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.5 (s);

HRMS (ESI): calcd for $C_{23}H_{25}F_3O_3Na$ $[M+Na]^+$ 429.1648. Found 429.1648;

MP: 49 - 51 °C;

IR: ν (cm^{-1}) 3484, 3062, 3035, 2961, 2929, 2901, 2859, 1929, 1716, 1618, 1454, 1328, 1167**.**



2-38 Prepared according to the General Procedure A from the corresponding diene (115.3 mg, 0.50 mmol) and 4-methoxybenzaldehyde (204.3 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 52%, *dr*: >98:2. Isolated in 51% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

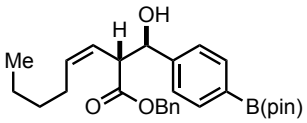
Prepared according to General Procedure B from the corresponding diene (115.2 mg, 0.50 mmol) and 4-methoxybenzaldehyde (204.2 mg, 1.5 mmol, 3 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 65%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ ($CDCl_3$, 700 MHz) δ 7.33 – 7.28 (m, 3H), 7.26 – 7.23 (m, 2H), 7.17 – 7.14 (m, 1H), 6.84 – 6.30 (m, 2H), 5.74 – 5.69 (m, 1H), 5.61 (app tt, *J* = 10.5, 1.4 Hz, 1H), 5.04 (d, *J* = 12.6 Hz, 1H), 4.99 (d, *J* = 12.6 Hz, 1H), 4.96 (dd, *J* = 6.3 Hz, 2.8 Hz, 1H), 3.79 (s, 3H), 3.67 (ddd, *J* = 10.0, 6.4, 0.7 Hz, 1H), 2.74 (d, *J* = 2.8 Hz, 1H) 2.03 – 1.96 (m, 1H), 1.95 – 1.88 (m, 1H), 1.27 – 1.14 (m, 4H), 0.82 (t, *J* = 7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.6, 159.3, 136.7, 135.6, 133.0, 128.5, 128.2, 128.1, 127.7, 122.6, 113.7, 74.1, 66.5, 55.3, 52.6, 31.4, 27.5, 22.3, 13.9;

HRMS (ESI): calcd for $C_{23}H_{28}O_4Na$ $[M+Na]^+$ 391.188. Found 391.1883;

IR: ν (cm^{-1}) 3503, 3064, 3032, 3010, 2956, 2930, 2871, 2858, 2837, 1887, 1730, 1612, 1513, 1248, 1172**.**



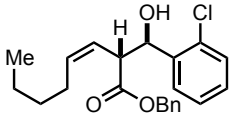
2-39 Prepared according to the General Procedure A from the corresponding diene (115 mg, 0.50 mmol) and 4-formylphenylboronic acid, pinacol ester (348 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >96%, crude yield: 75%, *dr*: >98:2. Isolated in 75% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.33 – 7.29 (m, 5H), 7.17 – 7.15 (m, 2H), 5.69 – 5.64 (m, 1H), 5.61 – 5.56 (m, 1H), 5.08 – 5.00 (m, 3H), 3.69 (dd, *J* = 9.7, 5.4 Hz, 1H), 2.92 (d, 2.6 Hz, 1H), 1.96 – 1.89 (m, 1H), 1.84 – 1.77 (m, 1H), 1.34 (s, 12H) 1.15 – 1.05 (m, 4H), 0.78 (t, *J* = 7.2, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 143.9, 136.7, 135.5, 134.7, 128.5, 128.3, 128.2, 128.0, 125.7, 121.8, 83.7, 74.3, 66.6, 52.0, 31.3, 27.4, 24.9, 22.5, 13.9;

HRMS (ESI): calcd for $C_{28}H_{37}O_5BNa$ $[M+Na]^+$ 487.2626. Found 487.2625;

IR: ν (cm^{-1}) 3483, 3090, 3068, 3033, 2977, 2957, 2930, 2871, 1941, 1731, 1613, 1498, 1456, 1361, 1145**.**



2-40 Prepared according to the General Procedure A from the corresponding diene (92 mg, 0.40 mmol) and 2-chlorobenzaldehyde (168.7 mg, 1.2 mmol, 3.0 equiv.). ^{1}H NMR

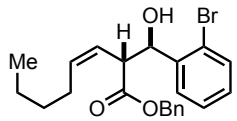
diene conversion: >99%, crude yield: 70%, *dr*: >98:2. Isolated in 69% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.53 (dd, *J* = 7.5, 1.7, 1H), 7.38 – 7.26 (m, 6H), 7.25 (td, *J* = 7.5, 1.2 Hz, 1H), 7.18 (td, *J* = 7.5, 1.7 Hz, 1H), 6.62 – 5.53 (m, 3H), 5.22 – 5.16 (m, 2H), 3.94 (dd, *J* = 9.6, 2.9 Hz, 1H), 3.45 (d, 2.6 Hz, 1H), 1.76 – 1.70 (m, 1H), 1.56 – 1.50 (m, 1H), 1.06 – 0.97 (m, 3H), 0.85 – 0.78 (m, 1H), 0.72 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 138.0, 136.7, 135.7, 131.4, 129.0, 128.8, 128.6, 128.6, 128.3, 127.9, 126.6, 120.2, 70.5, 66.8, 47.6, 31.1, 27.1, 22.1, 13.8;

HRMS (ESI): calcd for $C_{22}H_{25}ClO_3Na$ $[M+Na]^+$ 395.1384. Found 395.1393;

IR: ν (cm^{-1}) 3513, 3067, 3033, 2957, 2929, 2871, 2859, 1949, 1719, 1455, 1170**.**



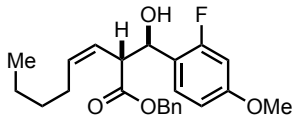
2-41 Prepared according to the General Procedure A from the corresponding diene (115 mg, 0.50 mmol) and 2-bromobenzaldehyde (278 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 60%, *dr*: >98:2. Isolated in 58% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.37 – 7.26 (m, 6H), 7.10 (td, *J* = 7.8, 1.7 Hz, 1H), 5.61 – 5.52 (m, 3H), 5.19 (s, 2H), 3.97 (dd, *J* = 9.4, 2.7 Hz, 1H), 3.44 (d, *J* = 2.7 Hz, 1H), 1.74 – 1.67 (m, 1H), 1.52 – 1.47 (m, 1H), 1.05 – 0.95 (m, 3H), 0.83 – 0.76 (m, 1H), 0.71 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.0, 139.4, 136.7, 135.6, 132.3, 129.1, 128.9, 128.6, 128.2, 127.8, 127.1, 121.4, 120.1, 72.6, 66.8, 47.5, 31.0, 27.1, 22.0, 13.8;

HRMS (ESI): calcd for $C_{22}H_{25}BrO_3Na$ $[M+Na]^+$ 439.0879. Found 439.0886;

IR: ν (cm^{-1}) 3501, 3065, 3032, 2956, 2929, 2871, 2858, 1950, 1718, 1455, 1439 1169**.**



2-42 Prepared according to the General Procedure A from the corresponding diene (115.3 mg, 0.50 mmol) and 2-fluoro-4-methoxy-benzaldehyde (231.3 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 84%, *dr*: >98:2. Isolated in 72% yield as a yellow oil after purification by column chromatography (17:3 Hexane/EtOAc).

Prepared according to General Procedure B from the corresponding diene (115.2 mg, 0.50 mmol) and 2-fluoro-4-methoxybenzaldehyde (231.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 81%, *dr*: >98:2.

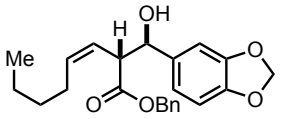
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.36 – 7.29 (m, 4H), 7.26 – 7.23 (m, 2H), 6.65 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.54 (dd, *J* = 12.4, 2.4 Hz, 1H), 5.67 – 5.62 (m, 1H), 5.61 – 5.55 (m, 1H), 5.34 – 5.31 (m, 1H), 5.13 – 5.07 (m, 2H), 3.80 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.77 (s, 3H), 3.11 (d, *J* = 3.1 Hz, 1H), 1,95 – 1.88 (m, 1H), 1.83 – 1.76 (m, 1H), 1.20 – 1.09 (m, 3H), 1.08 – 1.01 (m, 1H), 0.79 (t, *J* = 7.1Hz);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 173.2, 160.4 (d, *J* = 11.1 Hz), 160.2 (d, *J* = 245.4 Hz), 136.7, 135.6, 129.0 (d, *J* = 6.4 Hz), 128.5, 128.2, 128.0, 121.5, 119.8, 109.6 (d, *J* = 2.8 Hz), 101.3 (d, *J* = 25.6), 68.2 (d, *J* = 1.4 Hz), 66.7, 55.5, 49.9, 31.3, 27.2, 22.2, 13.9;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -177.1 (dd, *J* = 12.4, 8.9 Hz);

HRMS (ESI): calcd for $C_{23}H_{27}FO_4Na$ $[M+Na]^+$ 409.1786. Found 409.1785;

IR: ν (cm^{-1}) 3501, 3066, 3032, 2956, 2931, 2871, 2858, 1731, 1627, 1508, 1465, 1154**.**



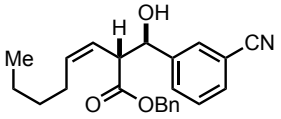
2-43 Prepared according to the General Procedure A from the corresponding diene (115.3 mg, 0.50 mmol) and piperonal (225.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 59%, *dr*: >98:2. Isolated in 57% yield as a yellow oil after purification by column chromatography (17:3 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.29 (m, 3H), 7.19 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.86 (d, *J* = 1.6 Hz, 1H), 6.77 – 6.74 (m, 1H), 6.72 – 6.69 (m, 1H), 5.92 (q, *J* = 3.8, 1.5 Hz, 2H), 5.75 – 5.70 (m, 1H), 5.59 (app tt, *J* = 10.5, 1.5 Hz, 1H), 5.06 (d, *J* = 12.6 Hz, 1H), 5.01 (d, *J* = 12.6 Hz, 1H), 4.93 (dd, *J* = 6.3, 2.2 Hz, 1H), 3.65 (ddd, *J* = 10, 4.2 Hz, 1H), 2.78 (d, *J* = 2.1 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.96 – 1.89 (m, 1H), 1.28 – 1.15 (m, 4H), 0.83 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.6, 147.6, 147.2, 136.9, 135.6, 134.9, 128.5, 128.3, 128.1, 122.4, 120.0, 108.0, 107.1, 101.0, 74.2, 66.6, 52.6, 31.4, 27.5, 22.3, 13.9;

HRMS (ESI): calcd for $C_{23}H_{26}O_5Na$ $[M+H]^+$ 405.1672. Found 405.1674;

IR: ν (cm^{-1}) 3507, 3089, 3070, 3030, 3015, 2956, 2930, 2872, 2778, 1728, 1502, 1488, 1244, 1154**.**



2-44 Prepared according to the General Procedure A from the corresponding diene (92.0 mg, 0.40 mmol) and 3-cyanobenzaldehyde (157 mg, 1.2 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 90%, crude yield: 79%, *dr*: >98:2. Isolated in 75% yield as a yellow oil after purification by column chromatography (4:1 Pentane/Et_2O).

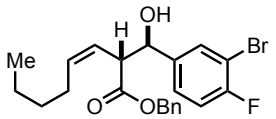
Prepared according to General Procedure B from the corresponding diene (115.2 mg, 0.50 mmol) and 3-cyanobenzaldehyde (196.7 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 83%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 (t, *J* = 1.7 Hz, 1H), 7.27 (dt, *J* = 7.9, 1.7 Hz, 2H), 7.13 – 7.05 (m, 4H), 6.99 – 6.96 (m, 2H), 5.46 – 5.41 (m, 1H), 5.32 – 5.27 (m, 1H), 4.86 – 4.80 (m, 3H), 3.38 (dd, *J* = 10.0, 5.1 Hz, 1H), 1.98 (d, *J* = 2.3 Hz, 1H), 1.68 – 1.61 (m, 1H), 1.54 – 1.47 (m, 1H), 0.95 – 0.84 (m, 3H), 0.83 – 0.76 (m, 1H), 0.53 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 142.4, 137.5, 135.3, 131.4, 130.9, 130.2, 128.9, 128.7, 128.5, 128.2, 120.8, 118.8, 112.3, 73.1, 66.9, 51.5, 31.2, 27.4, 22.2, 13.9;

HRMS (ESI): calcd for $C_{23}H_{25}NO_3Na$ $[M+Na]^+$ 386.1727. Found 386.1727;

IR: ν (cm^{-1}) 3475, 3086, 3063, 3029, 2956, 2928, 2871, 2859, 2227, 1916, 1763, 1606, 1502, 1453, 1188, 1156**.**



2-45 Prepared according to the General Procedure A from the corresponding diene (115.3 mg, 0.50 mmol) and 3-bromo-4-fluoro-benzaldehyde (304.5 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 81%, *dr*: >98:2. Isolated in 75% yield as a yellow oil after purification by column chromatography (17:3 Hexane/EtOAc).

Prepared according to General Procedure B from the corresponding diene (115.2 mg, 0.50 mmol) and 3-bromo-4-fluorobenzaldehyde (304.5 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 77%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.55 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.36 – 7.30 (m, 3H), 7.23 – 7.19 (m, 3H), 7.00 (t, *J* = 8.4 Hz, 1H), 5.74 – 5.69 (m, 1H), 5.56 (app tt, *J* = 10.5, 1.4

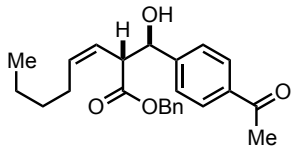
Hz, 1H), 5.12 – 4.02 (m, 2H), 5.00 (dd, *J* = 5.5, 2.4 Hz, 1H), 3.62 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.04 (d, *J* = 2.3 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.88 – 1.81 (m, 1H), 1.24 – 1.09 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H);

^{19}F NMR ($CDCl_3$, 467 MHz) δ -108.9 (m);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.7, 158.5 (d, *J* = 246.2 Hz), 138.2 (d, *J* = 3.7 Hz), 137.4, 135.3, 131.6, 128.6, 128.4, 128.2, 127.1 (d, *J* = 7.4 Hz), 121.3, 116.1 (d, *J* = 22.2 Hz), 108.8 (d, *J* = 21.2 Hz), 73.0, 66.8, 52.0, 31.3, 27.5, 22.3, 13.9;

HRMS (ESI): calcd for $C_{22}H_{24}BrFO_3Na$ $[M+Na]^+$ 457.0785. Found 457.0785;

IR: ν (cm^{-1}) 3468, 3062, 3030, 2981, 2932, 2906, 2872, 1885, 1730, 1494, 1245, 1178**.**



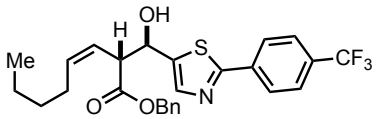
2-46 Prepared according to the General Procedure A from the corresponding diene (115 mg, 0.50 mmol) and 3-acetylbenzaldehyde (222 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 84%, *dr*: >98:2. Isolated in 79% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (s, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.30 (m, 3H), 7.21 – 7.19 (m, 2H), 5.71 – 5.66 (m, 1H), 5.62 – 5.57 (m, 1H), 5.14 (dd, *J* = 5.2, 2.3 Hz, 1H), 5.07 (d, *J* = 12.3 Hz, 2H), 3.70 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.12 (d, *J* = 2.4 Hz, 1H), 2.57 (s, 3H), 1.93 – 1.87 (m, 1H), 1.81 – 1.75 (m, 1H), 1.18 – 1.02 (m, 4H), 0.77 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9, 172.8 141.4, 137.1, 137.0, 135.4, 131.2, 128.6, 128.5, 128.3, 128.1, 127.7, 126.3, 121.3, 73.7, 66.7, 51.8, 31.2, 27.4, 26.7, 22.2, 13.8;

HRMS (ESI): calcd for $C_{24}H_{28}O_4Na$ $[M+Na]^+$ 403.1880. Found 403.1876;

IR: ν (cm^{-1}) 3486, 2956, 2930, 2871, 2858, 2228, 1716, 1606, 1502, 1466, 1378, 1111.



2-47 Prepared according to the General Procedure A from the corresponding diene (83 mg, 0.36 mmol) and 2-(4-(trifluoromethyl)phenyl)thiazole-5-carbaldehyde (278 mg, 1.1 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 45%, *dr*: >98:2. Isolated in 44% yield as a brown solid after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.71 – 7.68 (m, 3H), 7.32 – 7.24 (m, 5H), 5.84 – 5.78 (m, 1H), 5.64 – 5.59 (m, 1H), 5.39 (dd, *J* = 5.2, 3.5 Hz, 1H), 5.12 (d, *J* = 8.0 Hz, 2H), 3.78 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.32 (d, *J* = 3.0 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.29 – 1.18 (m, 5H), 0.81 (t, *J* = 7.1 Hz, 3H);

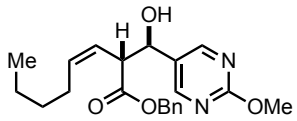
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 166.3, 141.2, 140.2, 138.1, 135.1, 131.6 (q, *J* = 32.6 Hz), 128.6, 128.4, 128.2, 126.6, 126.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.0 Hz) 120.9, 68.9, 67.1, 51.9, 31.3, 27.6, 22.3, 13.9;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -63.0 (s);

HRMS (ESI): calcd for $C_{26}H_{27}O_3F_3NSNa$ $[M+Na]^+$ 490.1658 Found 490.1659;

MP: 51 - 52 °C;

IR: ν (cm^{-1}) 3482, 3094, 3064, 3034, 2958, 2930, 2873, 2860, 1731, 1616, 1455, 1325, 1168**.**



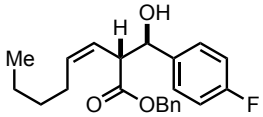
2-48 Prepared according to the General Procedure A from the corresponding diene (115 mg, 0.5 mmol) and 2-methoxypyrimidine-5-carbaldehyde (207 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 49%, *dr*: >98:2. Isolated in 45% yield as a colourless oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.45 (s, 2H), 7.36 – 7.31 (m, 3H), 7.25 – 7.23 (m, 2H), 5.78 – 5.72 (m, 1H), 5.59 – 5.54 (m, 1H), 5.13 – 5.06 (m, 3H), 3.99 (s, 3H), 3.63 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.23 (s, 1H), 1.97 – 1.92 (m, 1H), 1.86 – 1.80 (m, 1H), 1.25 – 1.12 (m, 4H), 0.80 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 165.4, 157.8, 137.8, 135.2, 128.6, 128.5, 128.1, 127.1, 120.6, 70.1, 67.0, 54.9, 51.2, 31.2, 27.4, 22.2, 13.8;

HRMS (ESI): calcd for $C_{21}H_{26}O_4N_2Na$ $[M+Na]^+$ 393.1785 Found 393.1789;

IR: ν (cm^{-1}) 3287, 3092, 3068, 3031, 2957, 2929, 2872, 2859, 1730, 1599, 1566, 1476, 1408, 1326, 1159.



2-49 Prepared according to the General Procedure A from the corresponding diene (115.3 mg, 0.50 mmol) and 4-fluoro-benzaldehyde (186 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 75%, *dr*: >98:2. Isolated in 74% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

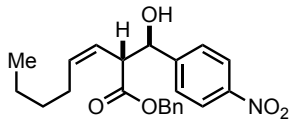
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 – 7.27 (m, 5H), 7.20 – 7.17 (m, 2H), 6.96 (t, *J* = 8.6 Hz, 2H), 5.71 (td, *J* = 10.7, 7.5 Hz, 1H), 5.57 (tt, *J* = 10.7, 1.6 Hz, 1H), 5.08 – 5.00 (m, 3H), 3.65 (ddd, *J* = 10.0, 5.9, 0.8 Hz, 1H), 2.92 (d, *J* = 2.3 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.89 – 1.83 (m, 1H), 1.24 – 1.10 (m, 1H), 0.81 (t, *J* =7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.7, 162.4 (d, *J* = 245.3 Hz), 137.0, 136.6 (d, *J* = 2.9 Hz), 135.4, 128.6, 128.3 (d, *J* = 14.9 Hz), 128.1, 128.1, 121.9, 115.1, 115.0, 73.7, 52.3, 31.4, 27.4, 22.3, 13.9.

^{19}F NMR ($CDCl_3$, 376 MHz) δ –114.74 (m).

HRMS (ESI): calcd for $C_{22}H_{25}FO_3Na$ $[M+Na]^+$ 356.1788. Found 379.1681;

IR: ν (cm^{-1}) 3499, 3066, 3033, 2957, 2929, 2872, 2859, 1891, 1729, 1605, 1511, 1456, 1222, 1157**.**



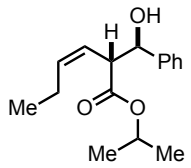
2-50 Prepared according to the General Procedure A from the corresponding diene (115 mg, 0.5 mmol) and 4-nitrobenzaldehyde (227 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 90%, crude yield: 78%, *dr*: >98:2. Isolated in 74% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.31 (m, 3H), 7.23 – 7.21 (m, 2H), 5.72 – 5.67 (m, 1H), 5.58 – 5.53 (m, 1H), 5.16 (dd, *J* = 5.1, 2.3 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 2H), 3.66 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.25 (d, *J* = 2.3 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.81 – 1.74 (m, 1H), 1.20 – 1.04 (m, 4H), 0.78 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 148.0, 147.4, 137.5, 135.2, 128.6, 128.5, 128.3, 127.2, 123.3, 120.8, 73.2, 66.9, 51.5, 31.2, 27.4, 22.2, 13.8;

HRMS (ESI): calcd for $C_{24}H_{28}O_4Na$ $[M+Na]^+$ 406.1625. Found 406.1624;

IR: ν (cm^{-1}) 3518, 3111, 3067, 3032, 2957, 2930, 2871, 2859, 1952, 1727, 1605, 1519, 1455, 1345, 1165**.**



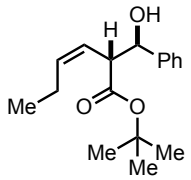
2-51 Prepared according to the General Procedure A from the corresponding diene (77.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 71%, *dr*: >98:2. Isolated in 61% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz), 7.37 – 7.24 (m, 2H), 7.33 – 7.29 (m, 2H), 7.27 – 7.23 (m, 1H), 5.71 – 5.65 (m, 1H), 5.56 (app tt, *J* = 10.5, 1.5 Hz, 1H), 4.99 (dd, *J* = 6.1, 2.2 Hz, 1H), 5.00 (sep, *J* = 6.4 Hz, 1H), 3.60 (ddd, *J* = 10.0, 6.0, 0.8 Hz, 1H), 2.95 (d, *J* = 2.1 Hz, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.84 (t, *J* = 7.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.5, 140.9, 137.9, 128.2, 127.8, 126.6, 122.1, 74.4, 68.3, 52.3, 21.6, 21.0, 13.8;

HRMS (ESI): calcd for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1461. Found 285.1458;

IR: ν (cm^{-1}) 3490, 3089, 3063, 3031, 2979, 2935, 2876, 1726, 1454, 1374, 1178, 1107**.**



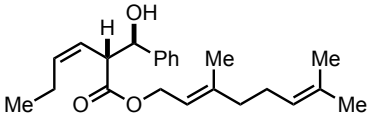
2-52 Prepared according to the General Procedure A from the corresponding diene (84.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 62%, *dr*: >98:2. Isolated in 60% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz), δ 7.36 (app d, *J* = 7.4 Hz, 2H), 7.31 (app t, *J* = 7.4 Hz, 2H), 7.25 (app tt, *J* = 7.4, 2.0 Hz, 1H), 5.70 – 5.64 (m, 1H), 5.54 (app tt, *J* = 10.5, 2.1 Hz, 1H), 4.97 (dd, *J* = 5.9, 2.2 Hz, 1H), 3.55 (ddd, *J* = 9.8 Hz, 5.9 Hz, 0.9 Hz, 1H), 3.02 (d, *J* = 2.2 Hz, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.33 (s, 9H), 0.84 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.4, 141.0, 137.6, 128.1, 127.7, 126.7, 122.3, 81.3, 74.4, 52.8, 27.9, 21.0, 13.9;

HRMS (ESI): calcd for $C_{17}H_{24}O_2Na$ $[M+Na]^+$ 299.1618. Found 299.1622;

IR: ν (cm^{-1}) 3497, 3088, 3064, 3030, 3007, 2976, 2934, 2875, 1950, 1725, 1455, 1368, 1150**.**



2-53 Prepared according to the General Procedure A from the corresponding diene (99.3 mg, 0.40 mmol) and benzaldehyde (122 μL, 1.2 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 90%, crude yield: 73%, *dr*: >98:2. Isolated in 71% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

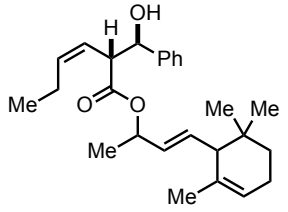
Prepared according to General Procedure B from the corresponding diene (124.2 mg, 0.50 mmol, 1.0 equiv.) and benzaldehyde (159 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 77%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700MHz) δ 7.36 – 7.33 (m, 2H), 7.31 (app t, *J* = 7.7 Hz, 2H), 7.24 (tt, *J* = 7.7, 1.9 Hz, 1H)**,** 5.70 – 5.64 (m, 1H), 5.56 (tt, *J* = 11.2, 1.4 Hz, 1H), 5.21 – 5.17 (m, 1H), 5.09 – 5.05 (m, 1H), 5.03 (dd, *J* = 5.6, 2.3 Hz, 1H), 5.53 (d, *J* = 7.1 Hz, 2H), 3.64 (ddd, *J* = 9.9, 5.7, 0.9 Hz, 1H), 2.97 (d, *J* = 2.4 Hz, 1H), 2.10 – 2.05 (m, 2H), 2.03 – 1.93 (m, 3H), 1.84 (m, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.64 (d, *J* = 1.4 Hz, 3H), 1.60 (brs, 3H), 0.81 (t, *J* = 7.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 173.1, 142.6, 140.9, 137.9, 131.9, 128.2, 127.8, 126.5, 123.7, 121.7, 117.9, 74.3, 61.8, 52.1, 39.5, 26.3, 25.7, 21.0, 17.7, 16.5, 13.8;

HRMS (ESI): calcd for $C_{23}H_{23}O_3Na$ $[M+Na]^+$ 379.2. Found 379.2;

IR: ν (cm^{-1}) 3513, 3091, 3064, 3031, 3006, 2961, 2931, 2873, 1948, 1731, 1497, 1454, 1311, 1154**.**



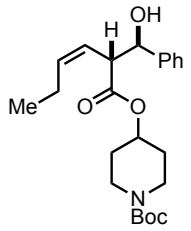
2-54 Prepared according to the General Procedure A from the corresponding diene (144.2 mg, 0.50 mmol, 1 equiv.) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 76%. Isolated as a 1:1:1:1 mixture of diastereomers in 70% yield as a thick yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 (app t, *J* = 7.0 Hz, 8H), 7.31 (app t, *J* = 7.0 Hz, 8H), 7.25 (app td, *J* = 7.6, 1.4 Hz, 4H), 5.68 – 5.63 (m, 4H), 5.57 – 5.51 (m, 4H), 5.49 – 5.22 (m, 16H), 5.04 – 5.00 (m, 4H), 3.64 – 3.59 (m, 4H), 3.64 – 3.59 (m, 4H), 3.05 – 3.00 (m, 4H), 2.05 (d, *J* = 9.5 Hz, 4H), 2.01 – 1.93 (m, 3H), 1.91 – 1.80 (m, 1H), 1.55 – 1.51 (m, 1H), 1.42 – 1.33 (m, 1H), 1.25 (dd, *J* = 6.4, 1.9 Hz, 4H), 1.19 – 1.09 (m, 12H), 0.87 – 0.84 (m, 12H), 0.82 – 0.78 (m, 12H), 0.77 – 0.74 (m, 12H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.4(2), 172.3(2), 140.9(3), 137.9(2), 137.8(2), 134.4(2), 134.0(2), 133.6(2), 130.7(2), 130.6, 130.5, 128.2, 127.8, 127.7, 126.5(3), 121.9, 121.8, 121.7(2), 121.3(2), 121.2, 74.2, 74.1, 71.9, 71.8, 71.7, 71.6, 54.0, 53.9(2), 52.2, 52.1(2), 32.0(2), 31.78, 31.6(2), 27.4(2), 27.0(3), 23.1, 22.9, 22.8(2), 21.0, 20.3(2), 13.8;

HRMS (ESI): calcd for $C_{26}H_{36}O_3Na$ $[M+Na]^+$ 419.2557. Found 419.2560;

IR: ν (cm^{-1}) 3513, 3064, 3030, 2963, 2930, 2873, 1728, 1494, 1453, 1376, 1173**.**



2-55 Prepared according to the General Procedure A from the corresponding diene (156.7 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 93%, crude yield: 76%, *dr*: >98:2. Isolated in 71% yield as a yellow oil after purification by column chromatography (3:1 Hexane/EtOAc).

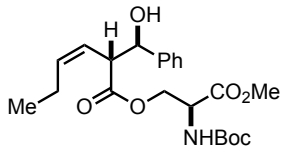
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 – 7.19 (m, 5H), 5.72 – 5.63 (m, 1H), 5.54 (app tt, *J* = 10.8, 1.5 Hz, 1H), 4.96 (dd, *J* = 6.4, 2.1 Hz, 1H), 4.81 (sept, *J* = 3.8 Hz, 1H), 3.63 (ddd,

J = 9.8, 6.4, 0.7 Hz, 1H), 3.51 (ddd, *J* = 11.2, 7.4, 4.0 Hz, 1H), 3.40 (11.3, 7.4, 4.0 Hz, 1H), 3.26 – 3.10 (m, 2H), 2.76 (d, *J* = 1.8 Hz, 1H), 2.07 – 1.85 (m, 2H), 1.75 – 1.65 (m, 1H), 1.64 – 1.55 (m, 1H), 1.53 – 1.43 (m, 1H), 1.43 (s, 9H), 1.38 – 1.28 (m, 1H), 0.85 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.0, 154.8, 141.2, 137.9, 128.2, 127.9, 126.7, 122.4, 79.7, 74.6, 70.1, 52.6, 40.8, 30.4, 28.5, 21.1, 13.8;

HRMS (ESI): calcd for $C_{23}H_{33}NO_5N_a$ $[M+Na]^+$ 426.2251. Found 426.2250;

IR: ν (cm^{-1}) 3447, 3062, 3010, 2969, 2933, 2874, 1728, 1696, 1453, 1366, 1168, 1026**.**



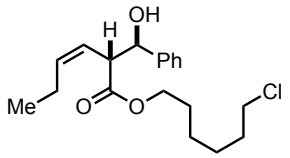
2-56 Prepared according to the General Procedure A from the corresponding diene (156.7 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 96%, crude yield: 65%. Isolated as a 1:1 mixture of diastereomers in 61% yield as a yellow oil after purification by column chromatography (3:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 – 7.30 (m, 8H), 7.29 – 7.24 (m, 2H), 5.69 – 5.64 (m, 2H), 5.57 – 5.50 (m, 2H), 5.20 – 5.01 (m, 4H), 4.55 – 4.48 (m, 2H), 4.35 (d, *J* = 3.6 Hz, 2H), 4.32 (d, *J* = 3.6 Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.67 – 3.61 (m, 2H), 2.94 (s, 1H). 2.85 (s, 1H), 1.96 – 1.87 (m, 2H), 1.84 – 1.75 (m, 2H), 1.45 (s, 18H), 0.79 (t, *J* = 7.7 Hz, 6H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.3(2), 170.1(2), 155.1(2), 140.8, 138.0, 137.9, 128.2, 127.9, 127.8, 126.3, 121.3, 121.1, 80.4, 74.1(2), 64.7, 64.5, 52.9, 52.8, 52.7, 52.0, 51.9, 38.3, 20.9, 13.7(2);

HRMS (ESI): calcd for $C_{22}H_{31}NO_7Na$ $[M+Na]^+$ 444.1993. Found 444.1997;

IR: ν (cm^{-1}) 3438, 2978, 2935, 2876, 1742, 1719, 1502, 1454, 1367, 1300, 1163**.**



2-57 Prepared according to the General Procedure A from the corresponding diene (115.4 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 80%, *dr*: >98:2. Isolated in 70% yield as a yellow oil after purification by column chromatography (17:3 Hexane/EtOAc).

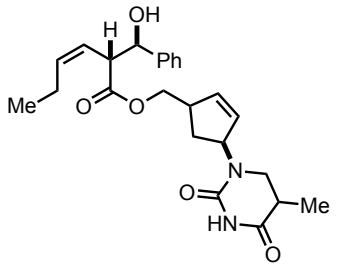
Prepared according to General Procedure B from the corresponding diene (115.4 mg, 0.50 mmol) and benzaldehyde (159.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 80%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.36 – 7.35 (m, 2H), 7.32 (app t, *J* = 7.1 Hz, 2H) 7.26 (app tt, *J* = 7.1, 1.5 Hz, 1H), 5.72 – 5.66 (m, 1H), 5.56 (app tt, *J* = 10.5 Hz, 1.4 Hz, 1H), 5.02 (dd, *J* = 5.9, 2.3 Hz, 1H), 4.03 – 3.96 (m, 2H), 3.64 (ddd, *J* = 10.1, 5.9, 0.8 Hz, 1H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.90 (d, *J* = 2.7 Hz, 1H), 1.99 (m, 1H), 1.88 (m, 1H), 1.76 – 1.71 (m, 2H), 1.54 – 1.47 (m, 2H), 1.40 (quin, *J* = 7.6 Hz, 2H), 1.23 (quin, *J* = 7.5 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 173.1, 141.0, 138.0, 128.2, 127.8, 126.5, 121.9, 74.3, 64.3, 52.2, 44.9, 32.4, 28.3, 26.5, 25.1, 21.0, 13.9;

HRMS (ESI): calcd for $C_{19}H_{27}ClO_3Na$ $[M+Na]^+$ 361.1541. Found 361.1541;

IR: ν (cm^{-1}) 3500, 3087, 3063, 3029, 2959, 2936, 2871, 1951, 1728, 1454, 1318, 1168**.**



2-58 Prepared according to the General Procedure A from the corresponding diene (166 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 60%, *dr*: >98:2. Isolated as a 1:1 mixture of diastereomers in 51% yield as a white solid after purification by column chromatography (20:1 DCM/MeOH).

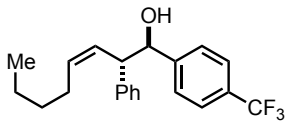
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.17 (s, 2H), 7.35 – 7.30 (m, 8H), 7.29 – 7.26 (m, 2H), 7.04 – 7.03 (m, 1H), 6.99 -6.98 (m, 1H), 6.92 – 6.91 (m, 1H), 6.88 – 6.87 (m, 1H), 6.08 (dt, *J* = 6.0, 1.6 Hz , 1H), 5.88 (dt, *J* = 6.0, 1.6 Hz, 1H) 5.86 – 5.84 (m, 1H), 5.77 – 5.66 (m, 3H), 5.58 – 5.53 (m, 2H), 5.02 (dd, *J* = 6.1, 2.1 Hz, 1H), 4.97 (dd, *J* = 7.0, 2.1 Hz, 1H), 4.87 – 4.84 (m, 2H), 4.37 (dd, *J* = 12.2, 4.9 Hz, 1H) 4.22 (dd, *J* = 11.9, 5.7 Hz, 1H), 4.10 (dd, *J* = 11.9, 4.2 Hz 1H), 4.03 (dd, *J* = 12.2, 3.7 Hz 1H), 3.68 – 3.63 (m, 2H), 2.68 (d, *J* = 2.6 Hz, 1H), 2.57 (d, *J* = 2.3 Hz, 1H), 2.03 – 1.83 (m, 10H), 0.88 (t, *J* = 7.4 Hz, 3H); 0.82 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ **Isomer 1** 172.4, 172.1, 163.3, 163.2, 150.4, 140.9, 140.6, 138.6, 138.3, 135.1, 135.0, 133.1, 132.8, 128.4, 128.3, 128.1, 128.0, 127.1, 127.0, 126.5, 126.4, 121.9, 121.5, 111.3, 111.1, 90.0, 89.8, 83.9, 83.8, 74.5, 65.3, 64.9, 52.8, 52.3, 21.1, 21.0, 13.8, 13.7, 12.7, 12.6;

HRMS (ESI): calcd for $C_{23}H_{26}N_2O_6Na$ $[M+Na]^+$ 449.1683. Found 449.1680;

MP: 46 – 47 °C;

IR: ν (cm^{-1}) 3441, 3191, 3061, 3038, 2963, 2934, 2875, 1690, 1467, 1399, 1248, 1157, 1107, 1082.



2-59 Prepared according to a modified General Procedure A (2.2 equiv. HCO_2H and 4.4 equiv. DIPEA) from the corresponding diene (34 mg, 0.2 mmol) and 4-(trifluoromethyl)benzaldehyde (105 mg, 0.6 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >96%, crude yield: 64%, *dr*: >98:2. Isolated in 60% yield as colourless oil after purification by column chromatography (4:1 Hexane/EtOAc).

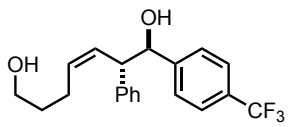
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.16 (m, 5H), 7.09 (d, *J* = 7.2 Hz, 2H), 5.86 – 5.82 (m, 1H), 5.71 – 5.66 (m, 1H), 4.88 (d, *J* = 7.2 Hz, 1H), 3.83 (dd, *J* = 10.1, 7.2 Hz, 1H), 2.31 (bs, 1H), 2.02 – 1.98 (m, 2H), 1.24 – 1.18 (m, 4H), 0.82 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.0, 140.9, 134.9, 129.5 (q, *J* = 32.4 Hz), 128.6, 128.2, 127.3, 126.9, 126.8, 124.8 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 271.0 Hz) 52.4, 31.5, 27.3, 22.2, 13.8;

^{19}F NMR ($CDCl_3$, 468 MHz) δ -62.4 (s);

HRMS (EI): cacld for $C_{21}H_{23}F_3ONa$ $[M\text{-}H_2O]^+$ 330.1595. Found 330.1600;

IR: ν (cm^{-1}) 3454, 3063, 3028, 2959, 2930, 2873, 2859, 1620, 1453, 1326, 1165, 1126, 1068**.**



2-60 Prepared according to General Procedure A from the corresponding diene (35 mg, 0.2 mmol) and 4-(trifluoromethyl)benzaldehyde (104 mg, 0.6 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 94%, crude yield: 70%, *dr*: >98:2. Isolated in 68% yield as a white solid after purification by column chromatography (1:3 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.21 (m, 4H), 7.18 – 7.15 (m, 1H), 7.07 – 7.06 (m, 2H), 5.95 – 5.90 (m, 1H), 5.69 – 5.64 (m, 1H), 4.88 (d, *J* = 7.6 Hz, 1H), 3.88 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.59 – 3.51 (m, 2H), 2.26 – 2.18 (m, 1H), 2.14 – 2.07 (m, 1H), 1.60 – 1.49 (m, 3H), 1.41 (bs, 1H);

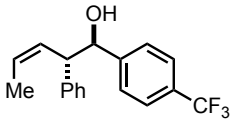
^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.1, 140.8, 133.2, 129.4 (q, *J* = 31.4 Hz), 128.8, 128.6, 128.2, 126.9, 126.8, 124.8 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 270.2 Hz) 77.6, 61.8, 52.3, 31.7, 23.8;

^{19}F NMR ($CDCl_3$, 468 MHz) δ -62.4 (s);

HRMS (ESI): cacld for $C_{20}H_{21}O_2F_3Na$ $[M+Na]^+$ 373.1386. Found 373.1383;

MP: 73 - 75 °C;

IR: ν (cm^{-1}) 3358, 3086, 3064, 3028, 2938, 2881, 1619, 1452, 1326, 1124, 1068.



2-62 Prepared according to a modified General Procedure A (2.2 equiv. HCO_2H and 4.4 equiv. DIPEA) from the corresponding diene (65 mg, 0.50 mmol) and 4-(trifluoromethyl)-benzaldehyde (261 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 64%, *dr*: >98:2. Isolated in 62% yield as colourless oil after purification by column chromatography (4:1 Hexane/EtOAc).

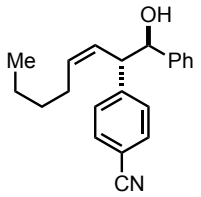
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.16 (m, 5H), 7.09 (d, *J* = 8.3 Hz, 2H), 5.90 – 5.86 (m, 1H), 5.82 – 5.76 (m, 1H), 4.88 (d, *J* = 7.3 Hz, 1H), 3.86 (dd, *J* = 9.7, 7.3 Hz, 1H), 2.31 (d, *J* = 2.0 Hz, 1H), 1.60 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.9, 140.6, 129.5 (q, *J* = 31.2 Hz) 128.8, 128.6(2), 128.2, 126.9, 126.8, 124.8 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 271.1 Hz) 77.5, 52.1, 13.2;

^{19}F NMR ($CDCl_3$, 468 MHz) δ -62.4 (s);

HRMS (EI): cacld for $C_{18}H_{17}F_3ONa$ $[M\text{-}H_2O]^+$ 288.1125. Found 288.1131;

IR: ν (cm^{-1}) 3467, 3088, 3062, 3029, 2925, 2857, 1620, 1493, 1453, 1326, 1124, 1067, 1017.



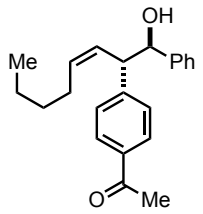
2-63 Prepared according to General Procedure C from the corresponding diene (98.7 mg, 0.5 mmol, 1.0 equiv.) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 95%, crude yield: 81%, *dr* >98:2. Isolated in a 77% yield as a yellow oil after purification by column chromatography (17:3 Hexanes/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.25 – 7.20 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H) , 7.14 – 7.10 (m, 2H), 5.85 – 5.79 (m, 1H), 5.72 (tdd, *J* = 10.9, 7.3, 0.8 Hz, 1H), 4.18 (d, *J* = 7.3 Hz, 1H), 3.92 (dd, *J* = 9.7, 7.3 Hz, 1H), 2.20 (br s, 1H), 2.05 – 1.93 (m, 2H), 1.28 – 1.16 (m, 4H), 0.83 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$. 125 MHz) δ 147.3, 141.4, 135.3, 132.1, 129.2, 128.2, 127.9, 127.0, 126.6, 118.9, 110.3, 77.9, 52.5, 31.4, 27.4, 22.3, 13.9;

HRMS (ESI): calcd for $C_{21}H_{23}NONa$ $[M+Na]^+$ 328. 1672. Found 328.1668;

IR: ν (cm^{-1}) 3504, 3089, 3066 2956, 2930, 2876, 2859, 2228, 1920, 1609, 1505, 1464, 1375, 1174**.**



2-64 Prepared according to General Procedure C from the corresponding diene (93.2 mg, 0.5 mmol, 1 equiv.) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 96%, crude yield: 67%, *dr* >98:2. Isolated in a 64% yield as a white solid after purification by column chromatography (4:1 Hexanes/EtOAc).

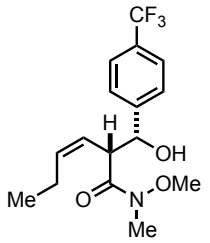
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.24 – 7.13 (m, 7H), 5.87 – 5.80 (m, 1H), 5.70 (tdd, *J* = 10.8, 7.2, 0.7 Hz, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 3.94 (dd, *J* = 9.9, 7.2 Hz, 1H), 2.54 (s, 3H), 2.26 (s, 1H), 2.12 – 1.98 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 147.3, 141.7, 136.4, 135.4, 128.6, 128.5, 128.1, 127.7, 127.1, 126.6, 77.9, 52.5, 26.6, 21.1, 13.9;

HRMS (EI): calcd for $C_{20}H_{22}O_2Na$ $[M+Na]^+$ 317.1512. Found 317.1513;

MP: 108 - 111 ºC;

IR: ν (cm^{-1}) 3404, 3091, 3058, 3015, 2965, 2932, 2873, 1667, 1604, 1448, 1358, 1278, 1058**.**



2-65 Prepared according to General Procedure A at room temperature from the corresponding diene (77.6 mg, 0.5 mmol) and 4-(trifluoromethyl)-benzaldehyde (261.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 65%, *dr*: >98:2. Isolated in 59% yield as colourless oil after purification by column chromatography (3:2 Hexane/EtOAc).

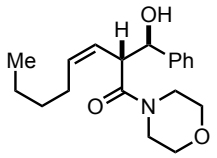
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 5.61 – 5.47 (m, 2H), 5.18 (d, *J* = 2.8 Hz, 1H), 4.46 (s, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 3.58 (s, 3H), 3.19 (s, 3H) 1.78 – 1.64 (m, 1H), 1.51 – 1.40 (m, 1H), 0.56 (t, *J* = 7.6, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 145/4, 137.8, 129.6 (q, *J* = 32.7 Hz), 126.9, 124.9 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 271.8), 120.7, 73.9, 61.3, 46.7, 32.0, 20.9, 13.2;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.5 (s);

HRMS (ESI): cacld for $C_{16}H_{20}F_3NO_3Na$ $[M+Na]^+$ 354.1287. Found 354.1289;

IR: ν (cm^{-1}) 3436, 3020, 2970, 2938, 2877, 1733, 1635, 1414, 1326, 1164, 1124, 1068,



2-66 Prepared according to General Procedure A from the corresponding diene amide (104 mg, 0.5 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene

conversion: >99%, crude yield: 66%, *dr*: >98:2. Isolated in 66% yield as a yellow solid after purification by column chromatography (1:1 Hexane/EtOAc).

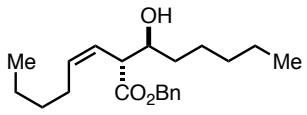
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.28 (m, 4H), 7.24 – 7.22 (m, 1H), 5.95 -5.52 (m, 2H), 5.15 (d, *J* = 3.6 Hz, 1H), 4.42 (s, 1H), 3.68 (dt, *J* = 13.3, 4.4 Hz, 1H), 3.62 – 3.59 (m, 3H), 3.53 – 3.46 (m, 2H), 3.38 – 3.35 (m, 1H), 3.31 – 3.28 (m, 1H), 3.24 – 3.22 (m, 1H), 1.63 – 1.60 (m, 1H), 1.39 – 1.36 (m, 1H), 1.10 – 1.00 (m, 3H), 0.85 – 0.82 (m, 1H), 0.76 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 172.7, 141.2, 135.5, 128.0, 127.4, 126.4, 122.0, 74.6, 66.7, 66.3, 48.3, 45.9, 42.1, 31.1, 27.4, 22.4, 13.8;

HRMS (ESI): cacld for $C_{19}H_{27}NO_3Na$ $[M+Na]^+$ 340.1883. Found 340.1882;

MP: 47 - 48 °C;

IR: ν (cm^{-1}) 3424, 3062, 3019, 2957, 2926, 2857, 1622, 1452, 1434, 1225, 1115**.**



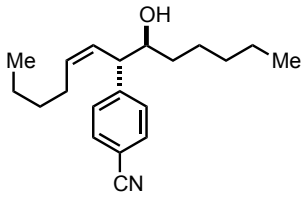
2-67 Prepared according to General Procedure A from the corresponding diene (115 mg, 0.5 mmol) and hexanal (369 μL, 3.0 mmol, 6.0 equiv.) using $[Rh(COD)_2]BF_4$ (10.2 mg, 0.025 mmol, 0.05 equiv.). ^{1}H NMR diene conversion: >97%, crude yield: 63%, *dr*: >98:2. Isolated in 59% yield as a light-yellow oil after purification by column chromatography (10:1 Pentane/Et_2O).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.30 (m, 5H), 5.75 – 5.70 (m, 1H), 5.57 -5.52 (m, 1H), 5.14 (s, 2H), 3.93 – 3.89 (m, 1H), 3.44 (ddd, *J* = 10.1, 4.5, 0.7 Hz, 1H), 2.60 (d, *J* = 3.2 Hz, 1H), 2.14 – 2.02 (m, 2H), 1.47 – 1.41 (m, 1H), 1.36 – 1.20 (m, 11H), 0.89 – 0.85 (m, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 136.1, 135.7, 128.5, 128.3, 128.1, 122.1, 71.7, 66.5, 49.5, 34.1, 31.7, 31.6, 27.6, 25.4, 22.6, 22.3, 14.0, 13.9;

HRMS (ESI): cacld for $C_{21}H_{32}O_3Na$ $[M+Na]^+$ 355.2243. Found 355.2243;

IR: ν (cm^{-1}) 3469, 3090, 3066, 3032, 2955, 2931, 2871, 2859, 1947, 1732, 1456, 1307, 1161**.**



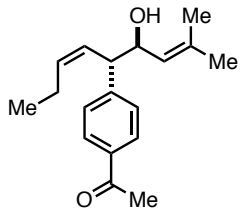
2-68 Prepared according to a modified General Procedure A (extra 0.5 equiv. HCO_2H after consumption of initial 1.2 equiv.) from the corresponding diene (40 mg, 0.2 mmol) and trans-2-hexenal (148 μL, 1.2 mmol, 6.0 equiv.). ^{1}H NMR diene conversion: 92%, crude yield: 55%, *dr*: >98:2. Isolated in 53% yield as a colourless oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.72 – 5.66 (m, 2H), 3.77 – 3.75 (m, 1H), 3.64 (dd, *J* = 8.6, 6.4 Hz, 1H), 2.11 – 2.08 (m, 2H), 1.68 (bs, 1H), 1.56 – 1.43 (m, 1H), 1.36 – 1.17 (m, 11H), 0.85 (t, *J* = 7.0 Hz, 6H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 148.4, 134.8, 132.4, 128.9, 127.2, 118.9, 110.3, 74.7, 50.3, 34.6, 31.7, 31.5, 27.5, 25.5, 22.6, 22.3, 14.0, 13.9;

HRMS (ESI): cacld for $C_{20}H_{29}NONa$ $[M+Na]^+$ 322.2141. Found 322.2142;

IR: ν (cm^{-1}) 3479, 3017, 2956, 2930, 2876, 2858, 2228, 1920, 1606, 1502, 1465, 1378, 1176**.**



2-69 Prepared according to a modified General Procedure A (extra 0.5 equiv. HCO_2H after consumption of initial 1.2 equiv.) from the corresponding diene (93.2 mg, 0.5 mmol) and 3-methyl-2-butenal (252.4 mg, 3.0 mmol, 6.0 equiv.) ^{1}H NMR diene conversion: >99%, crude yield: 56%, *dr*: 96:4. Isolated in 52% yield as a light-yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.78 – 5.65 (m, 2H), 5.11 (d, *J* = 8.7 Hz, 1H), 5.51 (t, *J* = 7.6 Hz, 1H), 3.73 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.58 (s, 3H), 2.21 – 1.98 (m, 2H), 1.62 (s, 3H), 1.48 (s, 3H), 0.94 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9, 147.8, 136.9, 135.9, 135.4, 128.7, 128.6, 127.5, 125.1, 71.6, 50.5, 26.6, 25.8, 21.1, 18.3, 14.0

HRMS (ESI): calcd for $C_{18}H_{24}O_2Na$ $[M+Na]^+$ 295.1669. Found 295.1663;

IR: ν (cm^{-1}) 3451, 3080, 2966, 2931, 2874, 1681,1605, 1569, 1416, 1359, 1270.

Chapter 3 – Diastereo-, Enantio-, and Z-Selective α,δ-Difunctionalization of Electron-Deficient Dienes Initiated by Rh-Catalyzed Conjugate Addition

3.1 Introduction

Transition-metal-catalyzed enantioselective conjugate addition reactions are among the most well-studies and reliable methods for the stereocontrolled formation of carbon–carbon bonds (**Fig. 3–1a**).[20, 38, 119-121] These reactions have been used in natural product synthesis, medicinal chemistry campaigns, and even the large scale preparation of enantioenriched small molecules (see Section 1.2.7 for recent examples).[58, 60-61, 122-125] As discussed in the introduction of this thesis, the Rh-catalyzed conjugate arylation of electron-deficient alkenes using boronic acid-derived nucleophiles arguably provides the most accommodating platform to generate β-arylated stereocenters, achieving high selectivity profiles across a structurally diverse classes of substrates under weakly basic conditions.[38, 120]

Compared to alkenes, electron-deficient dienes have been understudied in enantioselective arylations (**Fig. 3–1b**). These substrates can undergo metal-catalyzed conjugate additions to generate a new stereocenter δ to an electron-withdrawing group. The resulting alkene unit in these products is primed for subsequent functionalization, making this an ideal entry point into preparation of acyclic molecules with multiple stereocenters. Achieving positional selectivity for nucleophile addition (β vs. δ) while forming products with high regiocontrol of the resulting alkene unit (*E* vs. *Z*, α,β- vs. β,γ-unsaturation) with acyclic diene substrates remains a challenge (**Fig. 3–1b**). Examples of enantioselective δ-addition to dienes are restricted to Cu-catalyzed alkylations[80-83] and allylations,[84-85, 126] and Co-catalyzed alkynylations;[86] these processes provide access to the more thermodynamically

favoured *E*, alkene. The enantioselective δ-arylation of carbonyl activated dienes has been achieved with aryl boroxines using Ir-based catalysts, although the products of the reactions are typically isolated after isomerization to the α,β-unsaturated species or hydrogenation of the alkene.[74-75] Given the lack of general methods for the preparation of acyclic molecules with multiple stereocenters in a single step,[127-128] the development of new processes that leverage the mechanistic steps of metal-catalyzed conjugate additions in multicomponent reactions would be valuable.

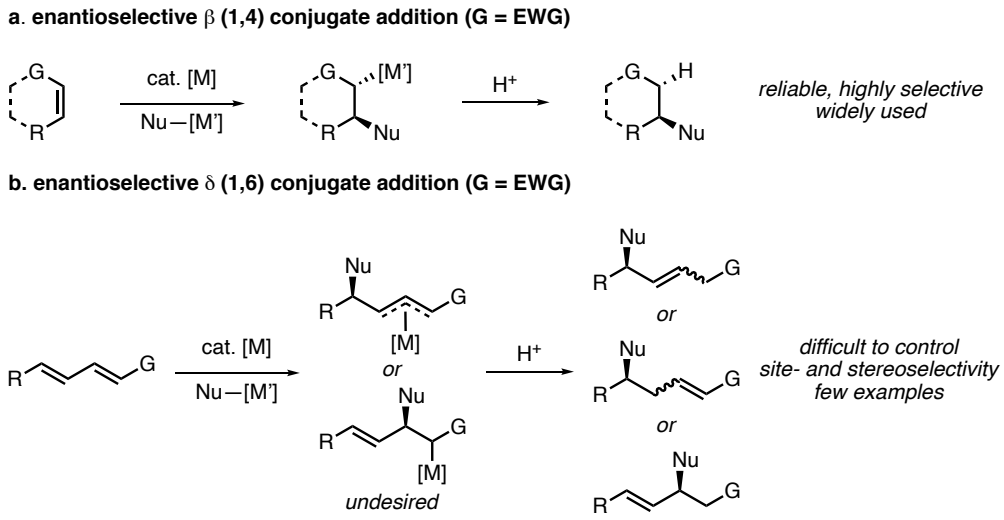


Fig. 3–1 Overview of metal-catalyzed, enantioselective conjugate addition of carbon nucleophiles to electron-deficient π-systems

Metal-catalyzed conjugate addition reactions generate nucleophilic intermediates after the initial addition step (**Fig. 3–2**). These species are usually protonated to generate the hydroarylation products (**Fig. 3–1a**). In certain systems, it has been reported that the nucleophilic metal intermediate generated in the enantioselective conjugate addition reaction, typically an enolate, can be intercepted by nonproton electrophiles to generate products with

up to three contiguous stereocenters depending on the nature of the intercepted electrophile. (**Fig. 3–2**, if E^+ is prochiral, products contain three contiguous stereocenters). This approach is typically restricted to cyclic conjugate addition acceptors like cycloenones or to intramolecular reactions with tethered electrophiles.[38, 66-67, 121, 129-132] In the case of intermolecular Rh-catalyzed α,β-difunctionalization, the use of Ti-aryl[65] or 9-BBN-aryl reagents[57, 62] under nonprotic conditions instead of aryl boronic acid derivatives is required to suppress rapid protonation of enolate intermediates.[133]

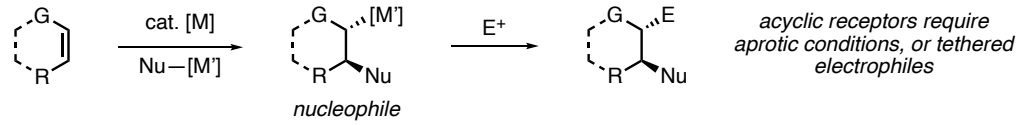


Fig. 3–2 Three-component reactions through β-addition

Interception of the nucleophilic metal-allyl intermediate generated by δ-addition to a 1,3-diene with an external electrophile, like an aldehyde, would allow the preparation of acyclic products with three, nonadjacent stereocenters (**Fig. 3–3a**). Although many enantioselective diene functionalization reactions are known, most provide access to products with one or two stereocenteres,[77, 104, 110, 134-139] only one known example provides access to three stereocenters (**Fig. 3–3a**).[140] In this report, Sato and co-workers used silylboranes under Ni-catalyzed conditions with a chiral phosphoramidite ligand to achieve an enantioselective γ,δ-difunctionalization leading to the formation of chiral α-substitutes silanes. As an alternative to reactions triggered by conjugate addition, Gong and co-workers have demonstrated that combinations of $Pd(OAc)_2$ and chiral spinol derived phosphoric acid catalysts enable the *Z*- and enantioselective α,δ-difunctionalization (**Fig. 3–3b**).[110] These

reactions are proposed to proceed via an arylation/borylation/aledhyde allylboration pathway and are restricted to the use of terminally unsubstituted dienes as substrates.

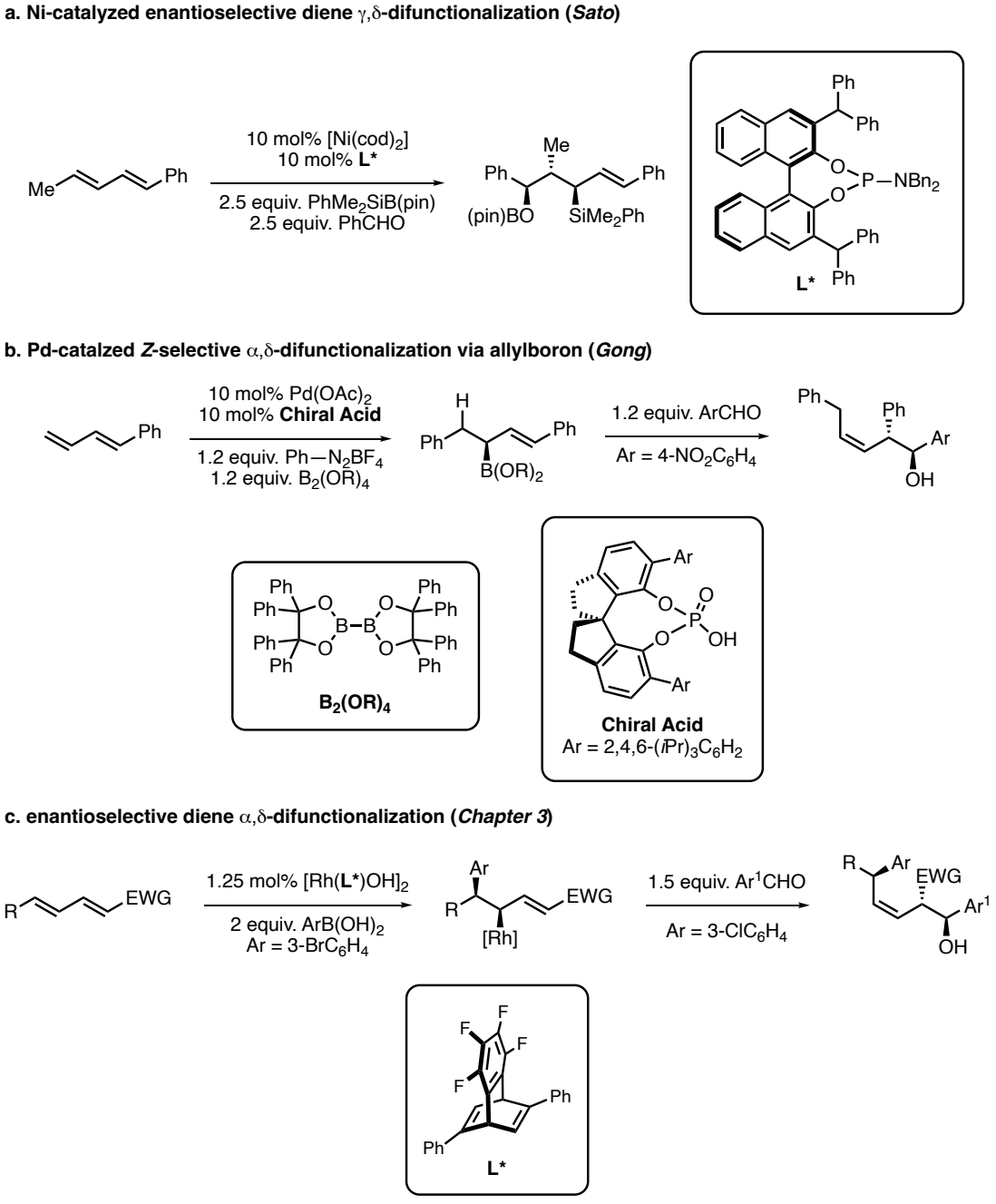


Fig. 3–3 Enantioselective diene difunctionalization reactions generating two or more stereocenters

As discussed in Chapter 2, we developed a racemic *Z*-selective reductive coupling of electron-deficient dienes and aldehydes[141] and questioned whether the Rh-allyl intermediate generated in an enantioselective δ-arylation could be trapped in a similar way. We were originally inspired by reactions reported by Csákÿ and co-workers,[72] where they show that the use of $Rh(cod)^+$ type catalysts for the Rh-catalyzed conjugate addition of aryl boronic acids to ethyl sorbate. They propose the formation of a similar, Rh-allyl intermediate proposed in our reductive coupling methodology, when the arylation occurs at the δ-position of the diene. We hypothesized that using similar conditions to those reported by Csákÿ, we could develop a Rh-catalyzed α,δ-difunctionalization, triggered by a Rh-catalyzed vinylogous conjugate addition.

With the hopes of potentially realizing an enantioselective three component coupling there were many mechanistic aspects to consider. **Fig. 3–4** provides the proposed mechanistic features of the process. The target process is a combination of the enantioselective Rh-catalyzed conjugate addition mechanism[56] followed by aldehyde trapping similar to our proposed mechanism for reductive coupling of diene and aldehydes.[141] Achieving a stereoselective diene α,δ-difunctionalization triggered by conjugate arylation would require high selectivity at several mechanistic steps. First, upon transmetalation to form **3-1**, direct aldehyde arylation[48] and undesirable protonation must be avoided. Second, arylation must be selective for the δ-position of the diene to form Rh-allyl **3-2** and avoid undesired β-arylation.[72] Even when the desired intermediate **3-2** is formed, aldehyde trapping must outpace undesirable π-σ-π allyl face-swapping, which would erode diastereoselectivity, chain walking isomerization[106, 142-143] and protonation to provide products of hydroarylation.

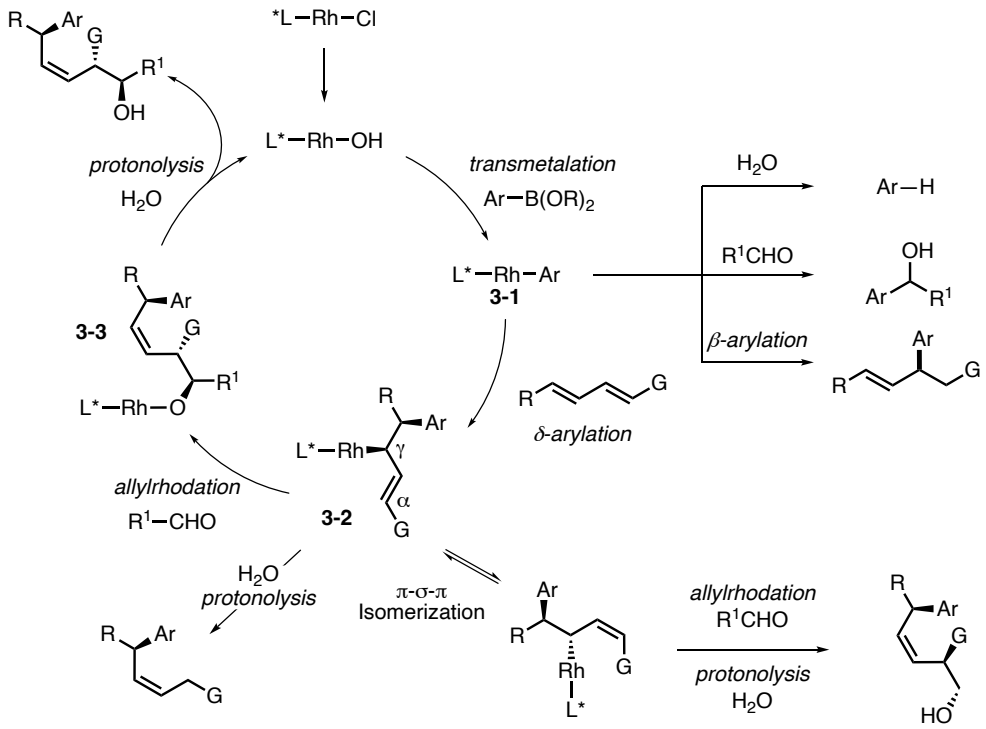
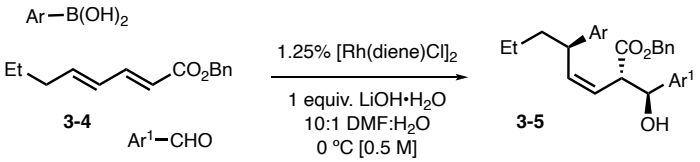


Fig. 3–4 Mechanistic framework for the Rh-catalyzed enantioselective α,δ-difunctionalization of dienes

Chapter 3 describes the Rh-catalyzed enantioselective α,δ-difunctionalization enabled by Rh-catalysts with chiral tetrafluorobenzobarrelene ligands. This process is initiated by a δ-arylation of organoboronic acid nucleophiles followed by the *Z-syn* selective α-trapping of aldehydes. The three-component reaction products can be readily converted into linear compounds with five contiguous stereocenters. Mechanistic studies show that Rh-allyl intermediates generated by a δ-arylation of dienes are uniquely suited for stereoselective interception with nonproton electrophiles, contrasting the reactivity of related Rh-enolate intermediates.

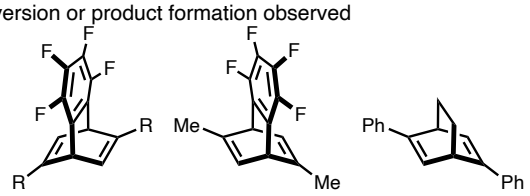
3.2 Development of Diastereo-, Enantio-, and *Z*-Selective α,δ-Difunctionalization of Electron-Deficient Dienes Initiated by Rh-Catalyzed Conjugate Addition

With the aim of developing a three-component coupling reaction initiated through a metal-catalyzed δ-arylation, we started with conditions reported by Csákÿ and co-workers, which uses $[Rh(cod)Cl]_2$ as the catalyst to achieve the *Z*-selective δ-arylation of ethyl sorbate derivatives.[72] Using diene **3-4** with 3-bromophenylboronic acid and three equivalents of 3-chlorobenzaldehyde 10% yield of *rac*-**3-5** was obtained. After several optimization experiments, it became evident that simply changing reaction conditions with $[Rh(cod)Cl]_2$ (boronic acid derivatives, base, solvent, concentration, temperature) would not provide improved positional selectivity (δ over β). A series of of $[M(chiral\ diene)Cl]_2$ catalysts were synthesized and tested in hopes of improving the inherent positional selectivity and developing an enantioselective process.[38] **Table 3–1** provides an overview of the catalysts screened under the best conditions identified under the optimized $[Rh(cod)Cl]_2$ conditions. Using a Rh-complex supported by Nishimura's chiral tetraflurobenzobarrelene ligand (Ph-tfb),[48] we were pleased to see that **3-5** was generated in 98% yield, 98% *ee* and 97:3 *dr* (**3-5**:sum of others) with exclusive *Z*-selectivity (entry 1). Other structurally related tfb ligands provided lower yields and enantioselectivities while not fully consuming **3-4** due to undesired protonation of the Rh-aryl dominating over diene insertion into the Rh-aryl bond (entries 3, 6). Structually related Ph-bod proved to be inferior to Ph-tfb providing 15% yield of the desired product with a 21% *ee* (entry 2). Rawal type ligands provided low yields while consuming aryl boronic acid unproductively (entries 4, 5, 7). Ir-complexed of Ph-tfb and Me-tfb did not provide any conversion of **3-4**, even when heated to 50 °C.



entry	Catalyst	conv (%)[a]	yield (%)	*dr*	*ee (%)*
1	**[Rh((*R,R*)-Ph-tfb)Cl]$_2$**	**>98**	**>98**	**[97:3]**	**98**
2	[Rh((*S,S*)-Ph-BOD)Cl]$_2$	25	15	[>98:2]	-21
3	[Rh((*R,R*)-Bn-tfb)Cl]$_2$	33	28	[97:3]	89
4	[Rh(*R,R,R*-L1)Cl]$_2$	12	9	[>98:2]	76
5	[Rh(*R,R,R*-L2)Cl]$_2$	25	22	[>98:2]	53
6	[Rh((*S,S*)-Me-tfb)Cl]$_2$	23	20	[98:2]	-94
7	[Rh(*R,R,R*-L3)Cl]$_2$	25	3	-	36
8	[Ir((*S,S*)-Me-tfb)Cl]$_2$[b]	0	0	-	-
9	[Ir((*R,R*)-Ph-tfb)Cl]$_2$[b]	0	0	-	-

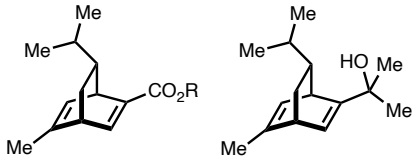
0.1—0.25 mmol scale, 5h, **3-4**:aldehyde:ArB(OH)$_2$ = 1:1.5:2, 5h
Ar = 3-BrC$_6$H$_4$, Ar^1 = 3-ClC$_6$H$_4$; yields and *dr* determined by ^{1}H NMR; *ee* determined by chiral HPLC; [a] complete consumption of ArB(OH)$_2$ [b] Reaction heated to 50 degrees after 5 h, no conversion or product formation observed



R = Ph (Ph-tfb)
R = Bn (Bn-tfb)

Me-tfb

Ph-bod



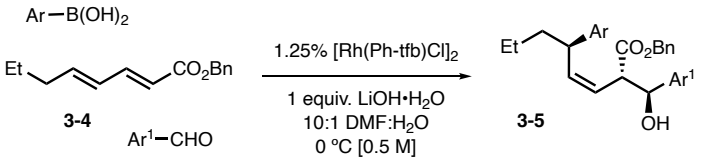
R = Napthyl = L1
R = Methyl = L2

L3

Table 3–1 Catalyst screen for the enantioselective Rh-catalyzed α,δ-difunctionalization

With optimal conditions in hand, our focus turned to assessing how different reaction parameters effect the formation of **3-5**. **Table 3–2** provides an overview of these experiments. Arylboronic acids or pinacol esters could be used as the arylating reagent with minimal effect on reaction outcome (entry 2). A 10:1 mixture of DMF/water was the optimal solvent, although DMF could be replaced with ethereal solvents like dioxane at the expense of reaction rate (entry 3). Water is required for the reaction; no product is observed without it

(entry 4). Reactions conducted at reduced concentration, aldehyde loading, and increased temperatures result in a reduced *dr* (entry 5, from 97:3 to 90:10), likely because to the Rh-allyl intermediate is long-lived enough to undergo π-σ-π isomerization with allyl face swapping (*vide infra*). The catalyst loading could be reduced to 1 mol% total Rh/Ph-tfb with similar yields and selectivities (entries 6,7).



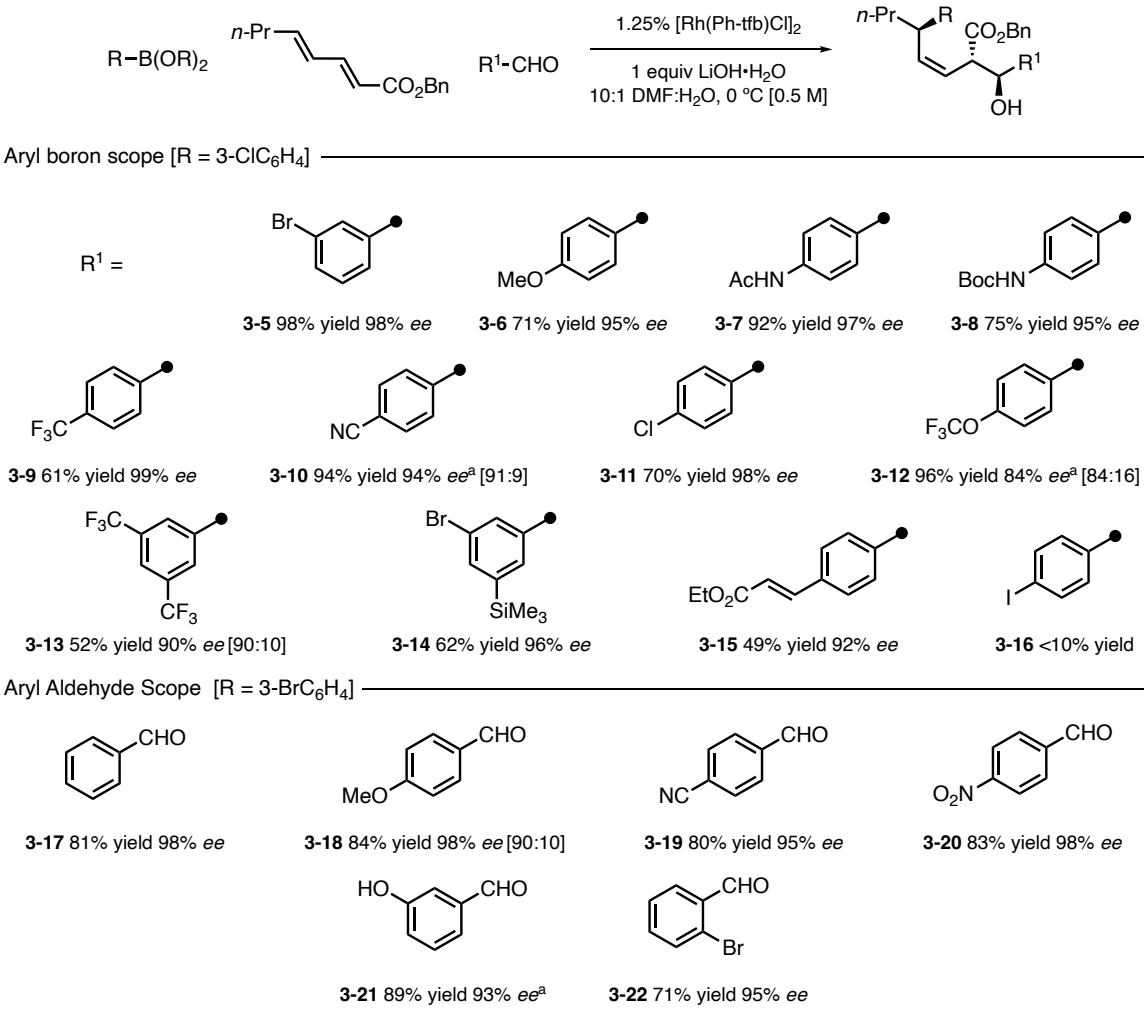
entry	deviation from above	yield (%)	**ee (%)**	dr
1	**none**	**>98**	**98**	**97:3**
2	Ar–B(pin) instead of Ar–B(OH)$_2$	95	98	96:4
3	dioxane instead of DMF	63	97	98:2
4	no H_2O instead of 10%	<2	nd	nd
5	0.2 M, 1 equiv Ar^1–CHO instead of 1.5[b]	84	95	90:10
6	0.5% [Rh(Ph-tfb)Cl]$_2$ instead of 1.25%[b]	89	97	83:17
7	**0.5% [Rh(Ph-tfb)Cl]$_2$ instead of 1.25%[c]**	**>98**	**98**	**97:3**
8	[Ir(Ph-tfb)Cl]$_2$ instead of [Rh(Ph-tfb)Cl]$_2$	<2	nd	nd

0.1–0.25 mmol scale, **1**:aldehyde:ArB(OH)$_2$ = 1:1.5:2; 5 h, Ar = 3-BrC_6H_4, Ar^1 = 3-ClC_6H_4;yields and *dr* determined by ^{1}H NMR, ee determined by chiral HPLC. [a]unless noted using [Rh(Ph-tfb)Cl]$_2$; [b] at rt; [c] 9 h

Table 3–2 Impact of reaction conditions on the enantioselective Rh-catalyzed α,δ-difunctionalization

The Rh-catalyzed diene α,δ-difunctionalization process enables access to chiral *Z*-homoallylic alcohols with three stereocenters. **Table 3–3** provides an overview of the scope for the nucleophilic and electrophilic partners in the reaction. For both electron-rich (**3-6**, **3-7**, **3-8**) and electron-poor (**3-9**, **3-10**, **3-13**) aryl boron nucleophiles, the product diastereo- and enantioselectivities remain high (≥90:10 *dr*, ≥90% *ee*, ≥50 % yield). Potentially reactive functional groups like aryl halides (**3-5**, **3-11**, **3-14**), NH-groups (**3-7**, **3-8**), nitrile (**3-10**), aryl silane (**3-14**), and aryl acrylate (**3-15**) are tolerated on the aryl boron group. The aryl aldehyde

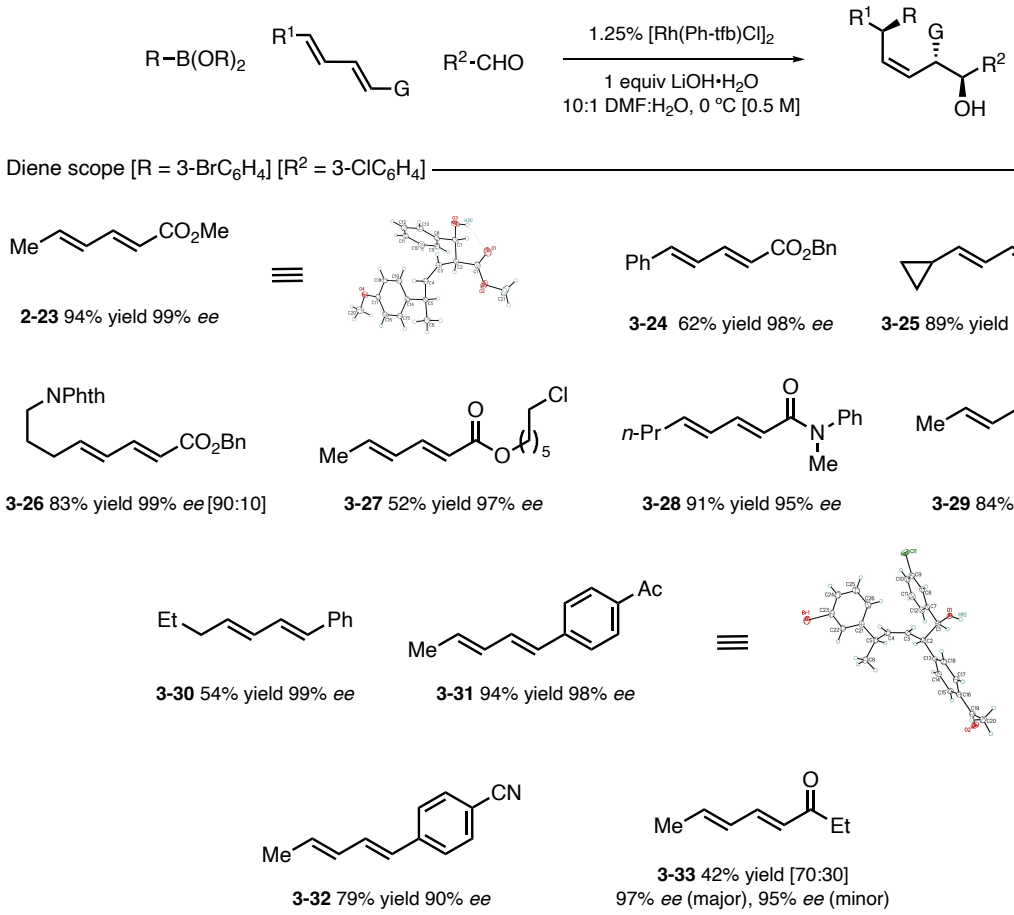
partner can feature electron-donating group (**3-18**) or electron-withdrawing groups (**3-19**, **3-20**) as well as phenol (**3-21**) or ortho bromo substitution (**3-22**). Less electrophilic aldehydes provide products with lower *dr* due to increased lifetime of the Rh–allyl species (**3-3**).



Unless noted yields are of isolated materials under standard conditions (**Fig. 3—6**). Unless noted, *dr* > 95:5, lower values are indicated in square brackets, *Z*:*E* > 98:2. Diene:aldehyde:RB(OR')$_2$ = 1:1.5:2. *dr* = **3-5**:sum of others
[a] Yield and *dr* determined by calibrated ^{1}H NMR; *ee* determined by chiral HPLC.

Table 3–3 Scope of aryl boron and aryl aldehyde partners for the enantioselective Rh-catalyzed α,δ-difunctionalization

The dieneoate partner (**Table 3–4**) can feature either alkyl or aryl groups at the δ-position (**3-23** – **3-26**). Variation in the diene's ester substituent had little impact on selectivity (Me (**3-23**), Bn (**3-24** – **3-26**), long chain alkyl (**3-27**) all provide ≥95% *ee*) with uniformly high yields and selectivities observed. Dieneamides, including those featuring the Weinreb amides, engage in the reaction to give products as nearly single diastereomers in ≥95% *ee* (**3-28**, **3-29**). A dienyl ketone substrate underwent α,δ-difunctionalization with reduced diastereoselectivity (70:30) to give **3-33** but with high enantioselectivity for both products (97% *ee* major, 95% *ee* minor).



Unless noted yields are of isolated materials under standard conditions (**Fig. 3—6**). Unless noted, *dr* > 95:5, lower values are indicated in square brackets, *Z*:*E* > 98:2. Diene:aldehyde:RB(OR')$_2$ = 1:1.5:2. *dr* = **3-5**:sum of others

[a] Yield and *dr* determined by calibrated ^{1}H NMR; *ee* determined by chiral HPLC

Table 3–4 Diene scope and miscellaneous examples for the enantioselective Rh-catalyzed α,δ-difunctionalization

The enantioselective diene addition process can be used to access other classes of products, including those featuring 1,4-(*E*,*Z*)-dienes using alkenyl boronic ester nucleophiles

(**3-34**), 1,5-dienes using α,β-unsaturated aldehyde partners (**3-35**), and dialkyl *Z*-homoallylic alcohols using alkyl aldehydes (**3-36**). When δ-unsubstituted aryl diene is used as a reaction partner (R^1 = H), the sense of enantio-addition arising from the δ-arylation step is relayed to the aldehyde allylrhodation step to give products with two stereocenters in 95% *ee*, remote from the initial arylation site (**3-37**).[110] Collectively, these scope studies demonstrate that under suitable conditions, enantioselective Rh-catalyzed conjugate additions can be relayed to electrophile trapping by Rh-allyl intermediates with high fidelity to generate stereochemically rich, acyclic molecules.

To better understand the origin of high chemo- and stereoselectivity in the Rh-catalyzed diene α,δ-difunctionalization reaction, mechanistic analysis was conducted. The stereochemistry of the products agree with the established sense of metal/(Ph-tfb)-catalyzed conjugate addition to electron-poor dienes[74] and Rh(cod)-catalyzed reductive aldehyde allylation.[106, 141, 144] Coordination to minimize steric clashing between the R-group of the diene substrate and aryl ligand on Rh as well as position the electron-withdrawing group (G) in the open pocket created by the chiral diene ligand sets the stereochemistry at the δ-position (**Fig. 3–5**; the sense of addition is the reverse for β-arylations). The *Z-syn* selectivity is consistent with a six-membered ring Zimmerman-Traxler transition state[107] involving Rh-allyl nucleophile **3-2** and the incoming aldehyde (**Fig. 3–5**, **3-39**).[106, 141, 144] The minor diastereomer generated in the reaction, formed in ~2 to 10% depending on the combination of substrates, is the *Z-syn* addition product arising from the allyl face swapping of intermediate **3-2** to Rh- allyl **3-2'**. This was determined by reduction and acetonization of a 75:25 mixture of diastereomers, both **3-39** and **3-39'** display equivalent, 2.5 Hz coupling constant, indicating that they are both *syn* products.[117] Formation of the minor diastereomer

increased when using less effective catalyst, when the initial aldehyde concentration is lowered, or when less electrophilic aldehydes are used. This suggest that if trapping of **3-2** is too slow, allyl isomerization occurs to generate **3-2'** and aldehyde allylrhodation via transition state **3-39'** provides the minor diastereomer. Moderate to high *Z-syn* diastereoselectivity is observed with an achiral catalyst like $[Rh(cod)Cl]_2$,[141] suggesting that the chiral diene ligands do not significantly impact the selectivity at this step. The reaction demonstrates a brief induction period, which arises from the initial conversion of $[Rh(Ph\text{-}tfb)Cl]_2$ to the active $[Rh(Ph\text{-}tfb)(OH)]_2$ catalyst (**Fig. 3–6a**).[38] When using $[Rh(Ph\text{-}tfb)(OH)]_2$, LiOH is not required but its presence increases reactions rates (**Fig. 3–6b**).[44]

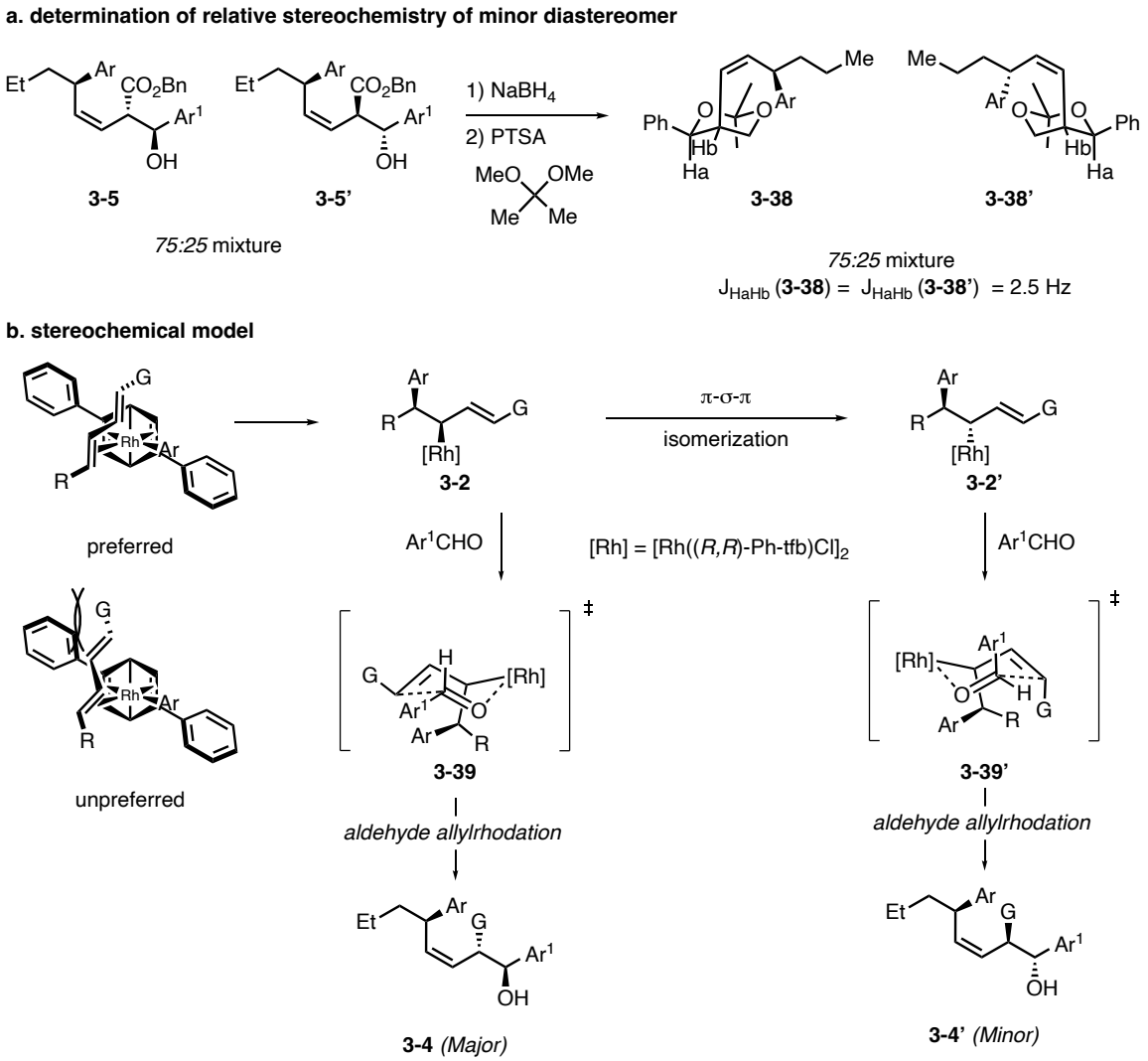


Fig. 3–5 Determination of relative stereochemistry of minor diastereomer and stereochemical model for the enantioselective Rh-catalyzed α,δ-difunctionalization

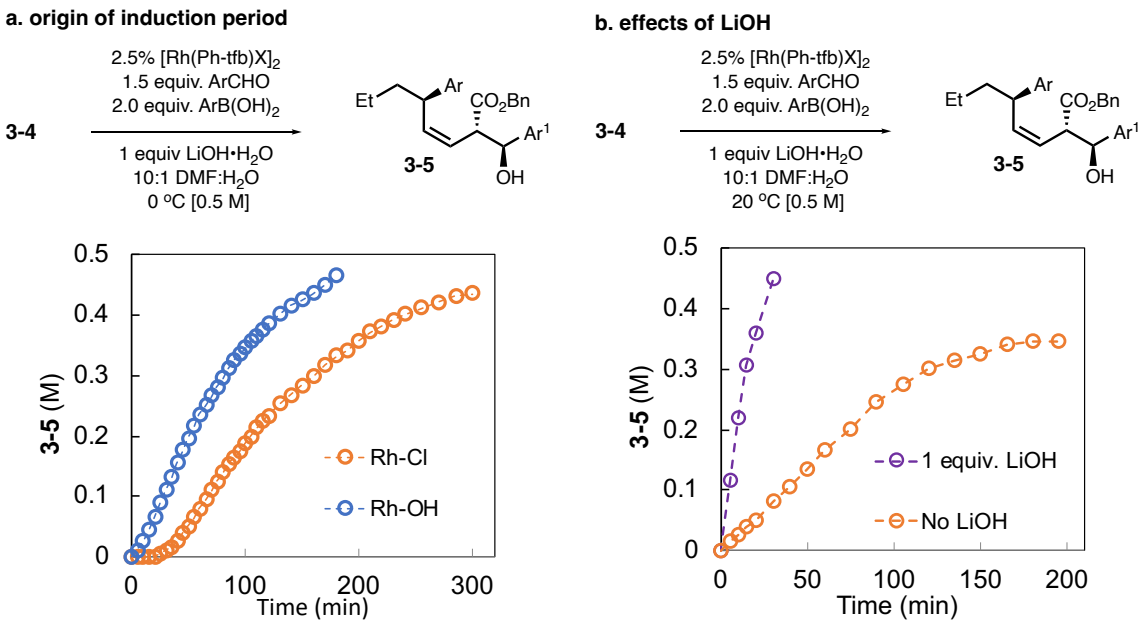


Fig. 3–6 Impact of Rh-precatalyst and LiOH

Variable time normalization (VTN) analysis, a method developed by Burés[145-146] was used to determine the order in each reactant of the reaction. VTN involves graphically comparing the reaction concentration profiles of experiments that differ in the initial concentration of a single reactant. Usually, the time axis is replaced by a time integral of the concentration of the reactant being investigated raised to an arbitrary power. Two reaction concentration profiles with different initial concentration of a single reactant, plotted on the same graph, will overlay when the arbitrary power matches the order of the reaction in that reactant or catalyst. The reaction order in each substrate can change during the course of some reactions, especially for those involving catalysis where catalyst deactivation can occur, which can lead to non-integer values for the order in some substrates.[146] VTN of the Rh-catalyzed diene α,δ-difunctionalization, using [Rh(Ph-tfb)(OH)]$_2$ as the catalyst show the reaction to be approximately first order in Rh (**Fig. 3–7**) as well as aldehyde (**Fig. 3–8**),

approximately zero order in diene and partial positive order in aryl boronic acid (**Fig. 3–8**). These observations suggest that aldehyde allylrhodation from Rh-allyl **3-2** is the rate determining step.

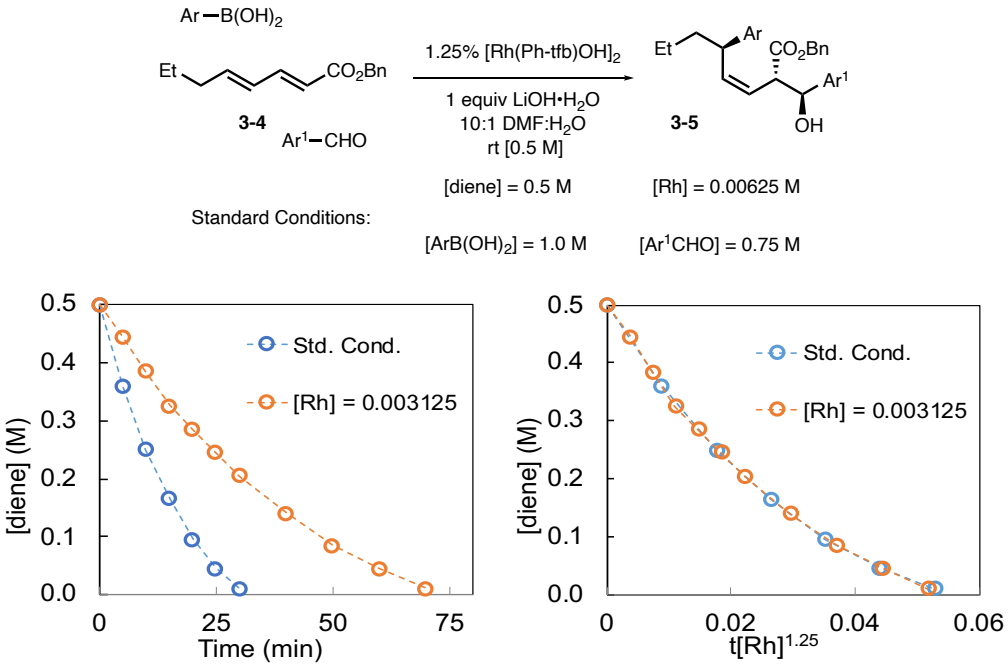


Fig. 3–7 Variable time normalization to determine reaction order in catalyst

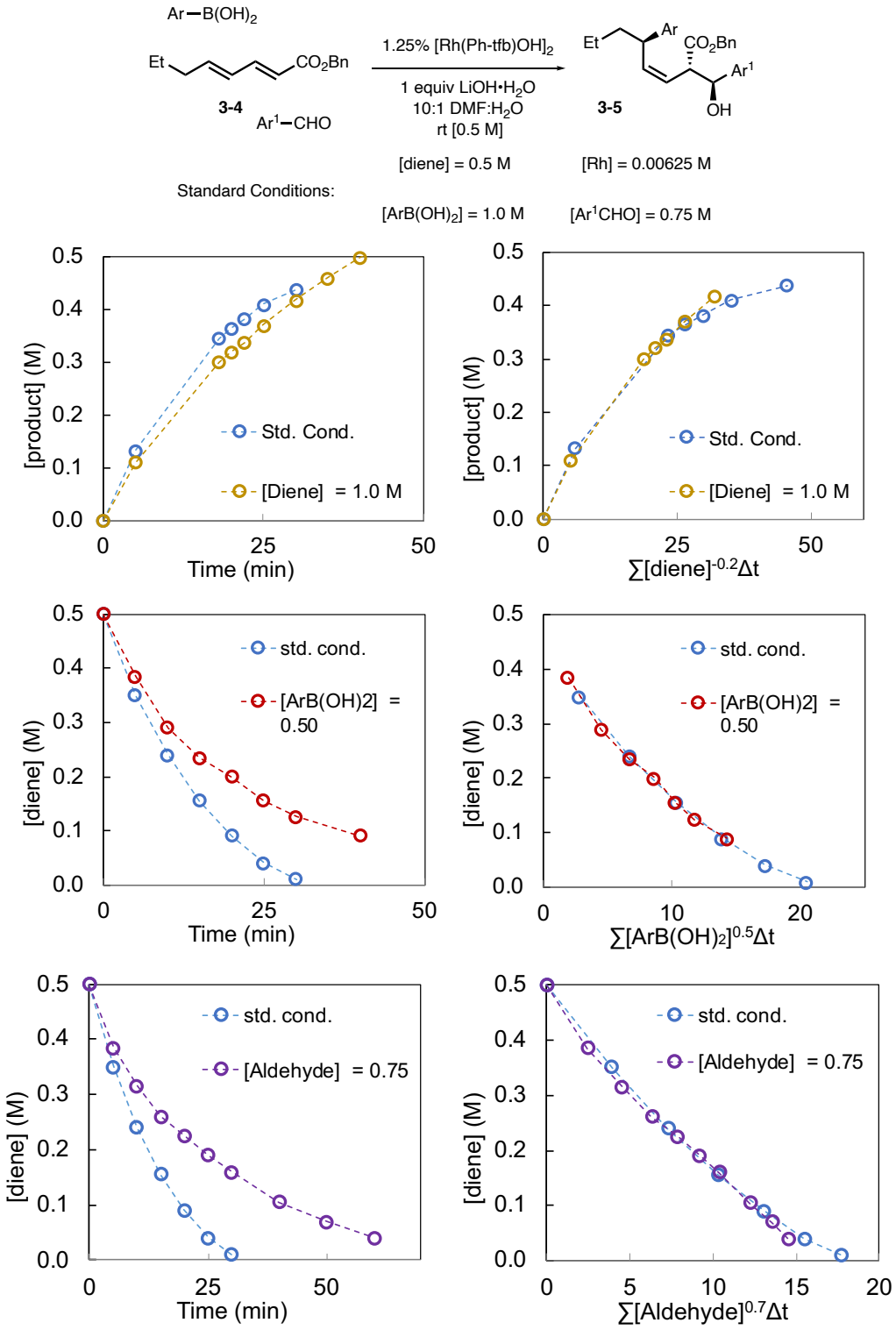


Fig. 3–8 Variable time normalization to determine reaction order in reactants for the enantioselective Rh-catalyzed α,δ-difunctionalization

The Rh-allyl intermediate is uniquely selective for aldehyde trapping over protonation despite the high concentration of water present in the reaction (5 M). To probe this behaviour, a series of competition and rate experiments were conducted. In absence of aldehyde, diene **3-4** undergoes addition and protonation to generate δ-hydroarylation product **3-40** (assigned based on closest literature example)[72] in 90% yield, >98:2 *Z*:*E* and 95% *ee* (**Fig. 3–9**). The hydroarylation reaction is ~ 20 times slower than the α,δ-difunctionalization with aldehyde electrophiles. Given the similar mechanistic pathway, Rh-allyl protonolysis is likely also the slow step in direct δ-arylation of dienes.

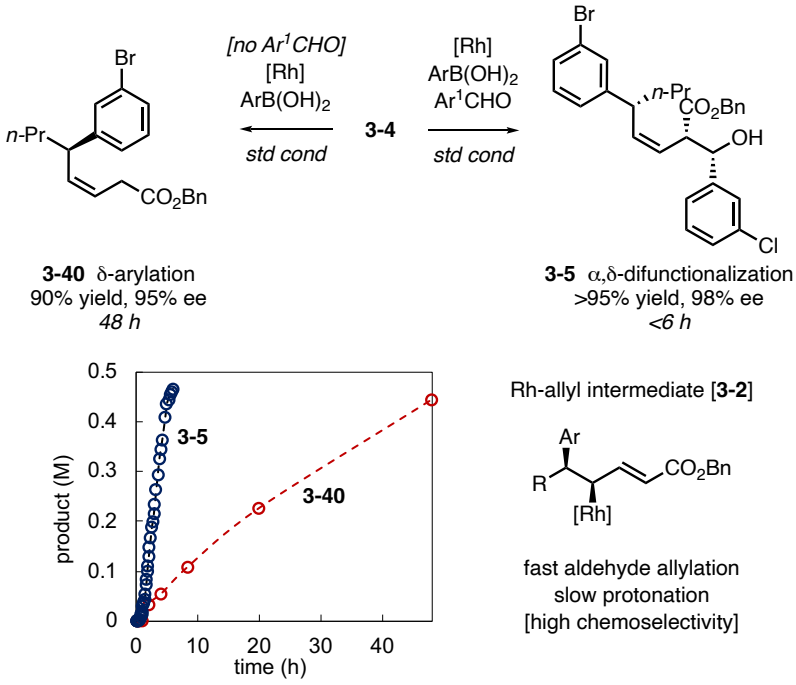
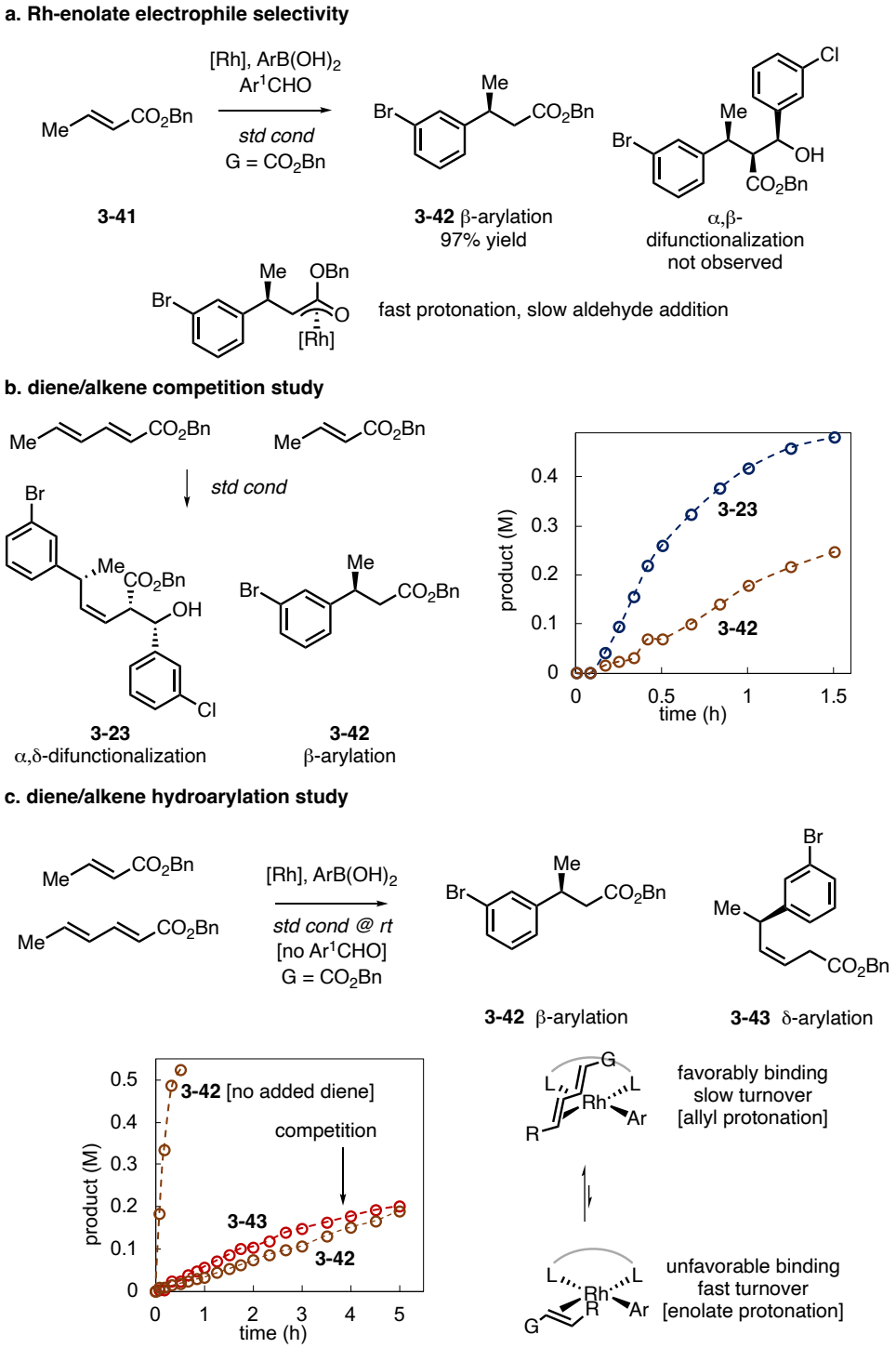


Fig. 3–9 Rh-allyl electrophile selectivity for the enantioselective Rh-catalyzed α,δ-difunctionalization

Contrasting the reactivity of dienes, simple α,β-unsaturated esters such as **3-41** do not undergo addition to aldehyde under the standard conditions (**Fig. 3–10a**). The Rh-enolate derived from the β-arylation of alkene **3-41** undergoes fast protonation to give **3-42** (assigned based on closest literature example)[147] in 97% yield after 2.5 h. In competition studies between alkene and diene, products from diene difunctionalization (**3-23**) are formed at a faster rate than products from alkene arylation (**3-42**) (**Fig. 3–10b**). In the absence of aldehyde, diene δ-arylation product is formed at similar rates to alkene β-arylation (**Fig. 3–10**). This is despite large differences in rates for independent experiments, where near quantitative alkene β-arylation occurs in less than 30 min, at room temperature. The slowing of alkene β-arylation rates in the presence of diene can be rationalize by diene substrate preferentially binding to the Rh-catalyst, effectively inhibiting the β-arylation pathway.



The work described in this figure was performed by Wesley McNutt. Yields determined by calibrated ^{1}H NMR, **3-42**, and **3-43** were not isolated, Yields of **3-42** and **3-43** were based on the closest literature examples. (**3-42**, reference 147), (**3-43**, reference 72)

Fig. 3–10 Rh-enolate electrophile selectivity and diene alkene competition study for the enantioselective Rh-catalyzed α,δ-difunctionalization

Geometrical isomers of standard (***E,E***)-**3-4** are less productive substrates in α,δ-difunctionalization (**Fig. 3–11**). (***Z,E***)-**3-4** slowly generates the same product stereoisomer as (***E,E***)-**3-4** with reduced diastereoselectivity, while (***E,Z***)-**3-4** and (***Z,Z***)-**3-4** are resistant to δ-arylation. Under the reaction conditions, (***Z,E***)-**3-4** is converted to (***E,E***)-**3-4** in a process catalyzed by Rh. The rates of product formation for both (***E,E***)-**3-4** (**Fig. 3–11**, left, blue trace) and (***Z,E***)-**3-4** (**Fig. 3–11**, left, orange) are very different, and when ~ equimolar mixtures of each are used (**Fig. 3–11**, left, purple trace) initial rates of product formation are similar to the standard reaction until all (***E,E***)-**3-4** is consumed and then the rate of product formation resembles the rates of product formation with (***Z,E***)-**3-4** alone. The progress of this reaction is shown on the left, where essentially no (***Z,E***)-**3-4** reacts until (***E,E***)-**3-4** is consumed at which point (***Z,E***)-**3-4** starts to be consumed. Note the slight increase in *E,E*-diene product formation at later time points in the reaction. We view this arising from *Z*-to-*E* isomerization where the *E,E*-diene undergoes slow enough difunctionalization (due to lower concentrations of aryl boronic acid and aldehyde) such that it can be observed. Improved yields when using (***Z,E***)-**3-4** could be achieved by modifying the conditions to increase isomerization (2.5 mol % $[Rh(Ph\text{-}tfb)Cl]_2$ at 20 ºC) and by using a more slowly reacting pinacol ester in place of boronic acid as the nucleophile. Under modified conditions, 66% yield of **3-5** was obtained in 97% *ee* and 82:18 *dr* from (***Z,E***)-**3-4**, showing that crude mixtures of diene products typically obtained by carbonyl olefination or cross-coupling commonly obtained in ~80:20 *E*,*E*/*Z*,*E* mixtures, can be used without the removal of the *Z*,*E* isomer.

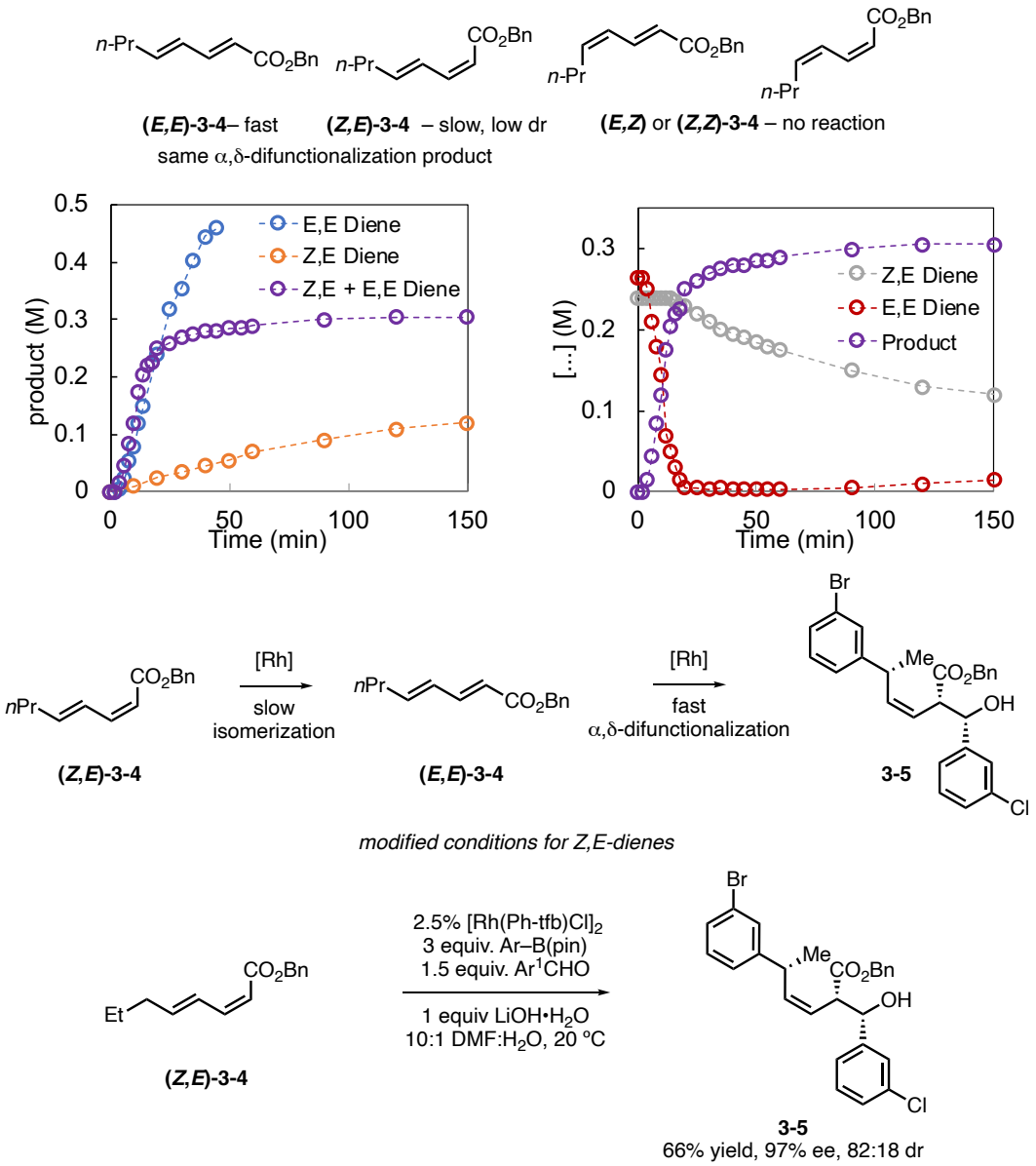


Fig. 3–11 Impact of diene geometry on the enantioselective Rh-catalyzed α,δ-difunctionalization

Taken together, these mechanistic studies show that (Ph-tfb)Rh-allyl species are well suited to engage nonproton electrophiles in multicomponent reactions triggered by δ-arylation. By tailoring the reaction conditions (i.e., relatively high concentration and slight excess of aldehyde), diastereoselective coupling to aldehyde outpaces Rh-allyl η^1-η^3-η^1

isomerization, ultimately leading to the formation of one stereoisomer from the 16 possible outcomes. The reactivity of Rh-allyl species is in contrast with that of the Rh-enolate intermediates for which electrophile trapping is stymied by rapid protonolysis.

3.3 Conclusion

The metal-catalyzed conjugate arylation represents a reliable and practical reaction platform for the generation of stereocenters at positions remote from a carbonyl or arene activating group. The work described in this chapter shows that Rh-catalysts ligated by chiral tetrafluorobenzobarrelene ligands can catalyzed the enantioselective δ-arylation of several classes of electron-poor dienes to generate Rh-allyl intermediates, which are coupled with aldehydes in high chemo- and stereoselectivity. The products contain three stereocenters separated by a *Z*-alkene unit that would be tedious to prepare using a stepwise approach. A more general understanding of the reactivity of the Rh-allyl intermediates formed by Rh-catalyzed δ-arylation should allow this approach to be used with alternative electrophilic partners.

3.4 Procedures and Characterization

General Considerations

Unless noted, all reactions were conducted under inert atmosphere employing standard Schlenk technique or using a N_2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed as described by Still and co-workers[148] (SiliaFlash P60, 40–63 μm, 60Å silica gel, Silicycle) or by automated flash chromatography (Isolera,

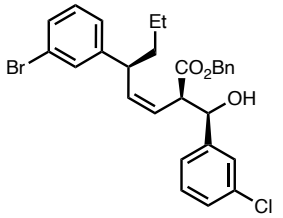
HP-SIL silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250 μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. Preparatory HPLC was accomplished via an Agilent 1260 Infinity system under reverse-phase conditions. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian VNMRS 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal ($CDCl_3$: δH = 7.26 ppm, δC = 77.06 ppm) (DMSO-d_6: δH = 2.49 ppm, δC = 39.50). Chiral HPLC analysis was accomplished on a normal-phase Agilent 1260 system with Daicel CHIRALPAK IA, IB, IC, or IG columns (4.6 x 150mm, 5 mm particle size), or Regis Whelk O1 column (4.6 x 25 mm, 5 mm particle size) with UV detection using a standard diod-array-detector. FTIR spectra was obtained using a Thermo Nicolet 8700, with attached Continuum FTIR Microscope. Optical rotation data was obtained using a Perkin Elmer 241 Polarimeter at 589 nm at 25 °C, using a 10 cm path-length cell. Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using dibenzyl ether as an internal standard. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied. Compound **3-4**[116] was prepared according to the literature. Compounds **3-40**,[72] **3-42**,[147] and **3-43**[72] were assigned based on the closest literature examples on the basis of ^{1}H NMR.

General Procedure: In an atmosphere controlled glovebox, [Rh((*S,S*)-Ph-tfb)Cl]$_2$ or [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) was weighed into a 1 dram vial. Into a separate 1 dram vial was weighed out diene (0.30 mmol, 1.0 equiv.) followed by

aldehyde (0.45 mmol, 1.5 equiv.), aryl boronic acid or ester (0.60 mmol, 2.0 equiv.) and internal standard (dibenzyl ether). DMF (145 mL) was added and the solution was transferred to the vial containing the catalyst using DMF to rinse (2 x 200 mL). To a 0.5 dram vial was weighed $LiOH{\cdot}H_2O$ (0.3 mmol, 12.6 mg, 1.0 equiv.) and was subsequently transferred to the vial containing the reaction mixture. A stir bar was added into the vial that was then sealed with a PTFE-lined septa cap, taken out of the glovebox and placed in an aluminum block cooled to 0 °C in an ice bath. H_2O (55 mL) was added at 0 °C. The reaction was stirred at 0 °C and reaction progress was monitored periodically via ^1H NMR (typically at 600 or 700 MHz) by removing 1–5 mL and diluting with $CDCl_3$. Reported terminal NMR yields were obtained in a similar manner. Once the reaction reached >95% conversion of diene, the solution was diluted with 60 mL of EtOAc, washed with 1M HCl (20 mL), water (3x20 mL), and brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel chromatography. Diastereomeric ratios given as [major:sum of others] determined by ^1H NMR. The predominant minor diastereomer arising from π-σ-π facial isomerization was confirmed by derivatization of a reaction that was modified to give poor dr, see section IX for experimental details. The trace minor diastereomers present in some reactions (5–10%) were assigned by analogy.

General Procedure (no glovebox) In air, diene (46.1 mg, 0.2 mmol, 1.0 equiv.), 3-bromophenylboronic acid (80.3 mg, 0.40 mmol, 2.0 equiv.), and LiOH (8.4 mg, 0.2 mmol, 1.0 equiv.) were weighed into 1 dram vial. The vial was sealed with a PTFE cap and next evacuated and refilled with N_2 three times. Next, 3-chlorobenzaldehyde (34 μL, 0.3 mmol, 1.5 equiv.) followed by dibenzyl ether (internal standard) were added to the vial by microliter

syringe. [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (2.6 mg, 0.0025 mmol, 0.013 equiv.) was weighed into a 1 dram vial, sealed with PTFE line cap and evacuated and backfilled three times with N_2. DMF (360 μL) was added to the vial containing catalyst and the solution was transferred to the 1 dram vial contain substrate. The reaction mixture was allowed to become completely homogenous, then was cooled to 0 °C, after which water (36 μL) was added and the reaction was stirred at 0 °C. This procedure provided identical results to those using a glovebox for the synthesis of **2**.



3-5 Prepared according to the General Procedure with [Rh((*S,S*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (169.8 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, NMR yield: >99%, *dr*: ≥95:5. Isolated in 98% yield *dr:* ≥95:5, *ee:* 98*%,* as a colourless oil after purification by column chromatography (3% to 24% EtOAc in hexanes). No glovebox procedure ^{1}H NMR diene conversion: >99%, NMR yield: >99%, *dr*: ≥95:5.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.33 (m, 3H), 7.30 – 7.21 (m, 5H), 7.13 – 7.01 (m, 5H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.78 (t, *J* = 10.3, 1H), 5.68 (t, *J* = 10.3, 1H), 5.12 (s, 2H), 5.03 (dd, *J* = 4.5, 2.5 Hz, 1H), 3.67 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.30 (dt, *J* = 9.9, 7.5 Hz, 1H), 2.98 (d, *J* = 2.5 Hz, 1H), 1.58 – 1.42 (m, 2H), 1.22 – 1.02 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H);

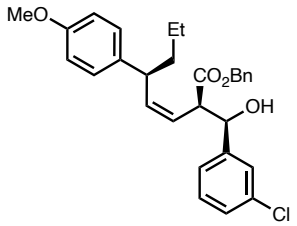
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 146.7, 142.4, 139.4, 135.2, 134.1, 130.1, 130.0, 129.4, 129.3, 128.7, 128.5, 128.4, 128.0, 126.3, 125.8, 124.3, 122.6, 121.7, 73.3, 67.1, 51.9, 43.4, 39.2, 20.5, 13.9;

HRMS (ESI): calcd for $C_{28}H_{28}BrClO_3Na$ $[M+Na]^+$ 549.0803. Found 549.0803;

IR ν (cm^{-1}) 3506, 3066, 3032, 3006, 2956, 2931, 2871, 2836, 2062, 1950, 1878, 1728, 1610, 1511, 1456, 1283, 1249, 1178, 1167, 1036, 827, 787, 750, 696;

Chiral HPLC: Chiralpak IG column (2.5% IPA in hexanes, 1.5 mL/min), t_r = 5.3 min (minor), t_r = 5.7 min (major);

$[\alpha]_D^{25}$ 151.97 (c = 1.30, $CHCl_3$).



3-6 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv. from the corresponding diene (69.4 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 4-methoxyphenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, NMR yield: >99%, *dr*: 92:8. Isolated in 71% yield, *dr*: ≥95:5 *ee*: 95% as a colourless oil after purification by column chromatography (2% to 18% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.32 (m, 3H), 7.27 – 7.21 (m, 3H) 7.16 – 7.13 (m, 1H), 7.11 – 7.05 (m, 2H), 6.85 (m, 2H), 6.75 (m, 2H), 5.81 (t, *J* = 10.5, 1H), 5.62 (t, *J* = 10.5, 1H), 5.08 (s, 2H), 4.95 (dd, *J* = 5.5, 2.6 Hz, 1H), 3.78 (s, 3H), 3.74 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.38 (dt, *J* = 10.2, 7.5 Hz, 1H), 2.84 (d, *J* = 2.6 Hz, 1H), 1.62 – 1.45 (m, 2H), 1.24 – 1.05 (m, 2H), 0.79 (t, *J* = 7.5, 3H);

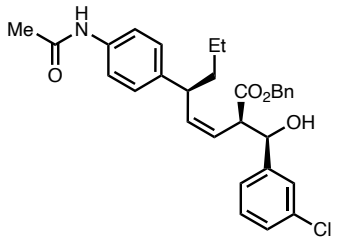
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 157.9, 142.7, 141.1, 136.4, 135.3, 134.2, 129.5, 128.6, 128.5, 128.3, 128.01, 127.95, 126.5, 124.6, 120.9, 114.0, 73.6, 66.9, 55.3, 52.3, 42.9, 39.0, 20.6, 14.0;

HRMS (ESI): calcd for $C_{29}H_{31}ClNaO_4$ $[M+Na]^+$ 501.1803. Found 501.1803;

IR ν (cm^{-1}) 3506, 3066, 3032, 3006, 2956, 2931, 2871, 2836, 2062, 1950, 1878, 1728, 1610, 1511, 1464, 1378, 1303, 1249, 1178, 1166, 1036, 827, 787, 750, 696;

Chiral HPLC: Chiralpak IG column (2.5% IPA in hexanes, 1.5 mL/min), t_r = 5.0 min (major), t_r = 5.9 min (minor);

$[\alpha]_D^{25}$ 205.23 (c = 0.41, $CHCl_3$).



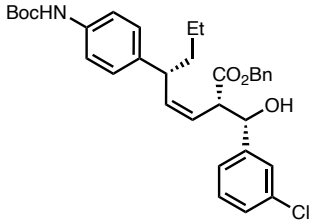
3-7 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (68.5 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 4-acetylaminophenylboronic acid (98.4 mg, 0.55 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 99%, NMR yield: 99%, *dr*: ≥95:5. Isolated in 92% yield, *dr*: ≥95:5, *ee*: 97% as a colourless oil after purification by column chromatography (10% to 80% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.04 (m, 11H), 6.87 (d, *J* = 9.2 Hz, 2H), 5.80 (t, *J* = 10.2 Hz, 1H), 5.63 (t, *J* = 10.2 Hz, 1H), 5.08 (s, 2H), 4.96 (d, *J* = 5.5, 1H), 3.71 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.37 (dt, *J* = 9.5, 7.6 Hz, 1H), 2.95 (s, 1H), 2.15 (s, 3H), 1.65 – 1.44 (m, 2H), 1.23 – 1.03 (m, 2H), 0.78 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 168.2, 142.6, 140.5, 140.3, 135.9, 135.3, 134.1, 129.5, 128.6, 128.5, 128.3, 127.9, 126.4, 124.5, 121.2, 120.2, 73.5, 67.0, 52.2, 43.1, 38.9, 24.6, 20.5, 14.0;

HRMS (ESI): calcd for $C_{30}H_{32}ClNO_4Na$ $[M+Na]^+$ 528.1912 Found 528.1916;

IR ν (cm^{-1}) 3307, 3198, 3125, 3066, 3033, 2957, 2930, 2871, 1727, 1667, 1601, 1534, 1514, 1413, 1373, 1318, 1265, 1217, 1163, 755, 697;



Chiral HPLC: ChiralPak IA column (10% IPA in hexanes, 1.5 mL/min), t_r = 12.0 min (minor), t_r = 22.6 min (major);

$[\alpha]_D^{25}$ 174.93 (c = 0.50, $CHCl_3$).

3-8 Prepared according to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (7.8 mg, 0.0076 mmol, 0.026 equiv.) from the corresponding diene (69.2 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 4-(*tert*-butoxycarbonylamino) phenylboronic acid (143.5 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 96%, NMR yield: 88%, *dr*: 95:5. Isolated in 75% yield, *dr*: ≥95:5, *ee*: 95% as a colourless oil after purification by column chromatography (5% to 40% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.32 (m, 3H), 7.25 – 7.22 (m, 3H), 7.21 – 7.12 (m, 3H), 7.09 (t, *J* = 7.5 Hz, 1H) 7.07 – 7.04 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.38 (bs, 1H), 5.81 (t, *J* = 10.5 Hz, 1H), 5.62 (t, *J* = 10.5 Hz, 1H), 5.08 (s, 2H), 4.95 (dd, *J* = 5.2, 2.4 Hz,

1H), 3.72 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.36 (dt, *J* = 9.5, 7.8 Hz, 1H), 2.86 (d, *J* = 2.4 Hz, 1H), 1.60 – 1.44 (m, 11H), 1.21 – 1.04 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H);

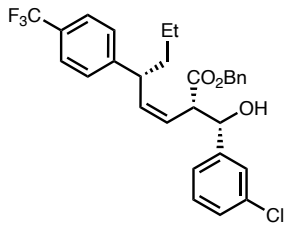
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 152.8, 142.6, 140.8, 139.0, 136.4, 135.3, 134.1, 129.5, 128.6, 128.4, 128.3, 127.9, 127.6, 126.4, 124.5, 121.0, 118.8, 80.4, 73.5, 66.9, 52.2, 43.1, 39.0, 28.4, 20.5, 14.0;

HRMS (ESI): calcd for $C_{33}H_{38}ClNNaO_5$ $[M+Na]^+$ 586.2331 Found 586.233;

IR ν (cm^{-1}) 3423, 3350, 3068, 3034, 3007, 2958, 2931, 2872, 1713, 1613, 1596, 1576, 1523, 1478, 1456, 1414, 1393, 1368, 1315, 1239, 1161, 1098, 1054, 1028, 1017, 1001, 902, 860, 833, 779, 754, 697;

Chiral HPLC: ChiralPak IC column (5% IPA in hexanes, 1.5 mL/min), t_r = 9.5 min (minor), t_r = 12.7 min (major);

$[\alpha]_D^{25}$ –176.96 (c = 1.12, $CHCl_3$).



3-9 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 4-trifluoromethyl phenylboronic acid (114.0 mg, 0.6 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, NMR yield: 99%, *dr*: ≥95:5. Isolated in 61% yield, *dr*: ≥95:5, *ee*: 99% colourless oil after purification by column chromatography (3% to 26% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.33 (m, 3H), 7.30 – 7.27 (m, 2H), 7.23 – 7.21 (m, 1H), 7.07 – 7.02 (m, 1H), 7.01 – 6.98 (m, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.79 (t, *J* = 10.3 Hz, 1H), 5.73 (t, *J* = 10.2 Hz, 1H), 5.13 (s, 2H), 5.05 (dd, *J* = 4.3, 1.9 Hz, 1H), 3.66 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.40 (dt, *J* = 9.3, 7.5 Hz, 1H), 3.05 (d, *J* = 2.3 Hz, 1H), 1.60 – 1.45 (m, 2H), 1.23 – 1.02 (m, 2H), 0.77 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 148.3, 142.4, 139.1, 135.2, 134.2, 129.4, 128.7, 128.6, 128.4, 127.9, 127.3, 126.3, 125.4 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 270 Hz), *124*.2, 121.7, 73.2, 67.2, 51.8, 43.5, 39.1, 20.5, 13.9;

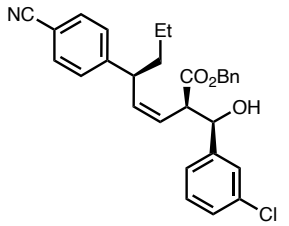
^{19}F NMR($CDCl_3$, 400 MHz) δ –62.4;

HRMS (ESI): calcd for $C_{29}H_{28}ClF_3NaO_3$ $[M+Na]^+$ 539.1571 Found 539.1567;

IR ν (cm^{-1}) 3503, 3068, 3034, 2958, 2932, 2873, 1719, 1618, 1599, 1576, 1498, 1456, 1421, 1379, 1327, 1215, 1165, 1123, 1069, 1017, 1000, 905, 864, 836, 783, 751, 697;

Chiral HPLC: ChiralPak IA column (1.8%IPA in hexanes, 0.4 mL/min), t_r = 25.8 min (minor), t_r = 27.6 min (major);

$[\alpha]_D^{25}$ –155.99 (c = 0.82, $CHCl_3$).



3-10 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.3 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 4-cyanophenylboronic acid pinacol ester (137.5 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 99%, NMR yield: 94%,

dr: 91:9. Isolated in 36% yield, *dr*: 92:8, *ee*: 94% as a colourless oil after purification by preparatory thin-layer chromatography (15% EtOAc in hexanes, 1000 μm).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 – 7.42 (m, 2H), 7.39 – 7.34 (m, 3H), 7.30 – 7.27 (m, 2H), 7.20 – 7.18 (m, 1H), 7.10 – 7.07 (m, 1H), 7.04 – 7.01 (m, 2H), 6.93 – 6.90 (m, 2H), 5.75 (m, *2*H), 5.13 (s, 2H), 5.07 (dd, *J* = 3.9, 2.5 Hz, 1H), 3.62 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.37 (td, *J* = 8.5, 6.8 Hz, 1H), 3.8 (d, *J* = 2.5 Hz, 1H), 1.58 – 1.43 (m, 2H), 1.21 – 1.00 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H);

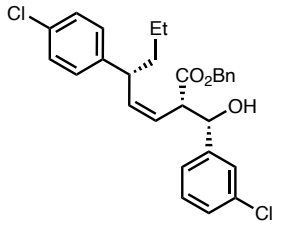
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 149.8, 142.5, 138.4, 135.2, 134.2, 132.3, 129.4, 128.7, 128.6, 128.4, 127.9, 127.8, 126.3, 124.2, 122.2, 119.0, 109.9, 73.1, 67.2, 51.7, 43.7, 38.8, 20.5, 13.9;

HRMS (ESI): calcd for $C_{29}H_{28}ClNNaO_3$ $[M+Na]^+$ 496.165 Found 496.165;

IR ν (cm^{-1}) 3502, 3067, 3033, 2958, 2931, 2871, 2228, 1729, 1606, 1575, 1456, 1166, 1078, 1000, 783, 750, 698;

Chiral HPLC: ChiralPak IC column (5% IPA in hexanes, 1.25 mL/min), t_r = 21.6 min (minor), t_r = 27.2 min (major);

$[\alpha]_D^{25}$ –189.23 (c = 1.01, $CHCl_3$).



3-11 Prepared according to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 4-chlorophenylboronic acid (93.8

mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 97%, NMR yield: 97%, *dr*: ≥95:5. Isolated in 70% yield, *dr*: ≥95:5, *ee*: 98% as a colourless oil after purification by column chromatography (3% to 26% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.30 (m, 4H), 7.27 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.15 – 7.11 (m, 3H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.02 (dt, *J* = 7.6, 1.5 Hz, 1H), 6.82 – 6.77 (m, 2H), 5.77 (t, *J* = 10.2 Hz, 1H), 5.67 (t, *J* = 10.2 Hz, 1H), 5.11 (s, 2H), 5.02 (dd, *J* = 4.7, 1.9 Hz, 1H), 3.67 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.34 (dt, *J* = 9.6, 7.7 Hz, 1H), 2.99 (d, *J* = 2.4 Hz, 1H), 1.58 – 1.43 (m, 2H), 1.22 – 1.02 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H);

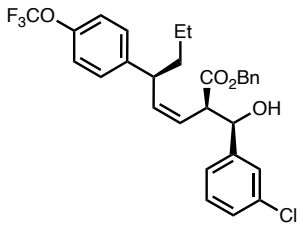
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 142.7, 142.5, 139.8, 135.2, 134.2, 131.7, 129.5, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 126.4, 124.3, 121.4, 73.3, 67.1, 51.9, 43.0, 39.0, 20.5, 14.0;

HRMS (ESI): calcd for $C_{28}H_{28}Cl_2NaO_3$ $[M+Na]^+$ 505.1308 Found 505.1307;

IR ν (cm^{-1}) 3496, 3066, 3032, 2957, 2930, 2871, 1950, 1892, 1716, 1598, 1575, 1491, 1456, 1432, 1410, 1378, 1314, 1264, 1215, 1166, 1128, 1092, 1014, 1001, 897, 857, 823, 780, 752, 696;

Chiral HPLC: ChiralPak IB column (1.8%IPA in hexanes, 0.4 mL/min), t_r = 20.3 min (minor), t_r = 21.1 min (major);

$[\alpha]_D^{25}$ –178.00 (c = 1.27, $CHCl_3$).



3-12 Prepared according to the General Procedure with [Rh((*S,S*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), 3-

chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 4-trifluoromethoxyphenylboronic acid (123.6 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 96%, NMR yield: 96%, *dr*: 84:16. Isolated in 14% yield, *dr*: 92:8, *ee*: 84% as a colourless oil after purification by preparatory thin-layer chromatography (12% EtOAc in hexanes, 1000 μm). The reduced isolated yield in this case is due to overlap with the diaryl methanol product.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.32 (m, 3H), 7.30 – 7.23 (m, 3H) 7.11 – 7.05 (m, 1H), 7.05 – 6.99 (m, 4H), 6.89 – 6.84 (m, 2H), 5.77 (t, *J* = 10.5 Hz, 1H), 5.69 (t, *J* = 10.5 Hz, 1H), 5.12 (s, 2H), 5.05 (dd, *J* = 4.6, 2.5 Hz, 1H), 3.69 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.26 (dt, J = 8.6, 7.5 Hz, 1H), 3.04 (d, *J* = 2.5 Hz, 1H), 1.59 – 1.41 (m, 2H), 1.23 – 1.01 (m, 2H), 0.78 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 147.4, 142.9, 142.5, 139.6, 135.2, 134.2, 129.4, 128.7, 128.6, 128.4, 128.2, 127.9, 126.4, 124.3, 121.3, 120.9, 73.3, 67.1, 51.9, 43.0, 39.1, 20.5, 14.0;

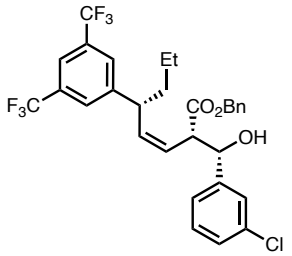
^{19}F NMR ($CDCl_3$, 400 MHz) δ –57.9;

HRMS (ESI): calcd for $C_{29}H_{28}ClF_3NaO_4$ $[M+Na]^+$ 555.152 Found 555.152;

IR ν (cm^{-1}) 3499, 3070, 3034, 2959, 2932, 2873, 1719, 1598, 1576, 1508, 1456, 1263, 1223, 1166, 1019, 751, 697;

Chiral HPLC: Regis Whelk O1 column (2% IPA in hexanes, 0.5 mL/min), t_r = 40.2 min (minor), t_r = 42.4 min (major);

$[\alpha]_D^{25}$ 142.90 (c = 2.01, $CHCl_3$).



3-13 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (7.8 mg, 0.0076 mmol, 0.026 equiv.) from the corresponding diene (69.0 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 3,5-bis(trifluoromethyl)phenylboronic acid pinacol ester (206.7 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 80%, NMR yield: 68%, *dr*: 90:10. Isolated in 52% yield, *dr*: 90:10, *ee*: 90%, as a pale yellow oil after purification by column chromatography (3% to 24% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (s, 1H), 7.41 – 7.32 (m, 5H), 7.31 – 7.27 (m, 2H), 7.18 (s, 1H), 7.03 – 6.96 (m, 3H), 5.84 – 5.76 (m, 2H), 5.14 (d, *J* = 2.1 Hz, 2H), 5.09 (dd, *J* = 4.2, 2.3 Hz, 1H), 3.63 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.42 (td, *J* = 8.7, 6.4 Hz, 1H), 3.02 (d, *J* = 2.5 Hz, 1H), 1.58 – 1.44 (m, 2H), 1.23 – 0.99 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 147.0, 142.4, 137.4, 135.2, 134.1, 131.6 (q, *J* = 33.3 Hz), 129.3, 128.7, 128.6, 128.4, 127.9, 127.1 (q, *J* = 4.0 Hz), 126.2, 123.9, 123.1, 120.3 (sept, *J* = 3.8 Hz), 73.1, 67.3, 51.8, 43.3, 39.6, 20.5, 3.8;

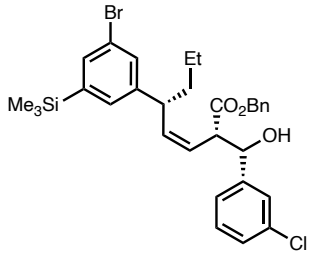
^{19}F NMR ($CDCl_3$, 400 MHz) δ –62.7;

HRMS (ESI): calcd for $C_{30}H_{27}ClF_6NaO_3$ $[M+Na]^+$ 607.1445 Found 607.1444;

IR ν (cm^{-1}) 3499, 3070, 3036, 2961, 2934, 2874, 1721, 1375, 1279, 1172, 1134, 786, 704, 683;

Chiral HPLC: ChiralPak IB column (2% IPA in hexanes, 1.5 mL/min), t_r = 4.9 min (major), t_r = 5.5 min (minor);

$[\alpha]_D^{25}$ –105.55 (c 1.41, $CHCl_3$);



3-14 Prepared according to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (71.1 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 3-bromo-5-trimethylsilylphenylboronic acid (220.7 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 76%, NMR yield: 76%, *dr*: 94:6. Isolated in 62% yield, *dr*: ≥95:5, *ee*: 96% as a slight orange oil after purification by column chromatography (2% to 18% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.380 (m, 1H), 7.377 – 7.31 (m, 3H); 7.26 – 7.22 (m, 3H), 7.13 – 7.08 (m, 2H), 7.06 (t, *J* = 7.7 Hz, 1H), 7.04 – 7.00 (m, 1H), 5.83 (t, *J* = 10.4 Hz, 1H), 5.67 (t, *J* = 10.4 Hz, 1H), 5.09 (s, 2H), 4.97 (dd, *J* = 5.4, 2.1 Hz, 1H), 3.70 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.35 (dt, *J* = 9.7, 7.6 Hz, 1H), 2.82 (d, *J* = 2.6 Hz, 1H), 1.60 – 1.45 (m, 2H), 1.23 – 1.03 (m, 2H), 0.79 (t, *J* = 7.5 Hz, 3H), 0.26 (s, 9H);

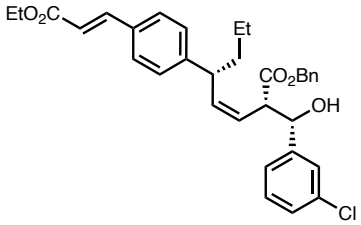
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 146.1, 143.8, 142.5, 139.6, 135.3, 134.1, 133.8, 130.5, 130.4, 129.4, 128.6, 128.5, 128.3, 128.0, 126.4, 124.3, 123.0, 122.1, 73.5, 67.0, 52.3, 43.6, 39.4, 20.6, 14.0, -1.1;

HRMS (ESI): calcd for $C_{31}H_{36}BrClNaO_3Si$ $[M+Na]^+$ 621.1198 Found 621.1201;

IR ν (cm^{-1}) 3500, 3063, 3034, 2956, 2931, 2899, 2871, 1945, 1871, 1728, 1598, 1578, 1552, 1498, 1456, 1434, 1397, 1378, 1315, 1249, 1215, 1196, 1164, 1109, 1078, 993, 892, 839, 782, 752, 695;

Chiral HPLC: Regis Whelk O1 column (2% IPA in hexanes, 1.5 mL/min), t_r = 17.0 min (major), t_r = 18.5 min (minor);

$[\alpha]_D^{25}$ –157.15 (c 1.03, $CHCl_3$).



3-15 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and ethyl 4-boronocinnamate (132.3 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 98%, NMR yield: 65%, *dr*: 92:8. Isolated in 49% yield, *dr*: ≥95:5, *ee*: 93% as a pale yellow oil after purification by column chromatography (5% to 40% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (d, *J* = 16.0 Hz, 1H), 7.38 – 7.32 (m, 5H), 7.29 – 7.25 (m, 2H), 7.22 (s, 1H), 7.10 – 7.05 (m, 1H), 7.04 – 7.00 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 16.0 Hz, 1H), 5.80 (t, *J* = 10.6 Hz, 1H), 5.68 (t, *J* = 10.6 Hz, 1H), 5.11 (s, 2H), 5.01 (dd, *J* = 4.5, 2.3 Hz, 1H), 4.27 (q, *J* = 7.3 Hz, 2H), 3.69 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.39 (dt, *J* = 9.2, 7.6 Hz, 1H), 2.98 (d, *J* = 2.4 Hz, 1H), 1.62 – 1.45 (m, 2H), 1.35 (t, *J* = 7.3 Hz, 3H), 1.24 – 1.03 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H);

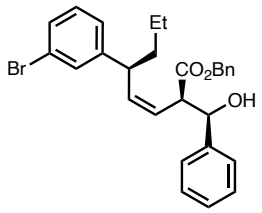
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 167.2, 146.8, 144.5, 142.5, 139.7, 135.3, 134.2, 132.4, 129.4, 128.7, 128.5, 128.4, 128.3, 127.9, 127.6, 126.4, 124.4, 121.5, 117.6, 73.3, 67.1, 60.5, 52.0, 43.6, 38.9, 20.6, 14.4, 14.0;

HRMS (ESI): calcd for $C_{33}H_{35}ClNaO_5$ $[M+Na]^+$ 569.2065 Found 569.2056;

IR ν (cm^{-1}) 3473, 3066, 3030, 2957, 2932, 2872, 1712, 1635, 1607, 1574, 1511, 1498, 1456, 1421, 1394, 1368, 1321, 1311, 1269, 1208, 1174, 1097, 1078, 1038, 1018, 985, 885, 867, 828, 779, 752, 697;

Chiral HPLC: ChiralPak IA column (5%IPA in hexanes, 1.5 mL/min), t_r = 13.1 min (major), t_r = 15.1 min (minor);

$[\alpha]_D^{25}$ –236.35 (c =1.01, $CHCl_3$).



3-17 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), benzaldehyde (45.7 □L, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 95%, crude yield: 88%, *dr*: 88:12. Isolated in 81% yield, *dr*: ≥95:5, *ee*: 98% as a colourless oil after purification by column chromatography (3% to 30% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 – 7.19 (m, 11H), 7.08 (t, *J* = 1.9 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.81 (dt, *J* = 7.7, 1.3 Hz, 1H), 5.77 – 5.68 (m, 2H), 5.08 (s, 2H), 5.04 (dd,

J = 5.3, 2.5 Hz, 1H), 3.74 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.34 (q, *J* = 8.1 Hz, 1H), 2.79 (d, *J* = 2.5 Hz, 1H), 1.60 – 1.40 (m, 2H), 1.22 – 1.01 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H);

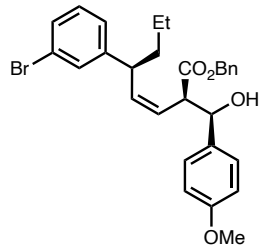
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 146.7, 140.5, 139.2, 135.4, 130.2, 130.0 129.2, 128.6, 128.4, 128.3(2), 128.0, 126.2, 126.0, 122.6, 122.3, 74.1, 66.9, 52.4, 43.4, 38.8, 20.5, 14.0;

HRMS (ESI): calcd for $C_{28}H_{29}BrO_3Na$ $[M+Na]^+$ 515.1192. Found 515.1193;

IR ν (cm^{-1}) 3516, 3063, 3032, 2957, 2930, 2872, 1948, 1875, 1809, 1729, 1592, 1567, 1454, 1398, 1310, 1162, 997;

Chiral HPLC: Regis Whelk O1 column (5% IPA in hexanes, 1.5 mL/min), t_r = 15.0 min (minor), t_r = 19.4 min (major);

$[\alpha]_D^{25}$ 138.6 (c = 0.59, $CHCl_3$).



3-18 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), *p*-anisaldehyde (109.5 μL, 0.90 mmol, 3.0 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 100%, crude yield: 88%, *dr*: 90:10. Isolated in 84% yield, *dr*: 93:7, *ee*: 98% as a colourless oil after purification by column chromatography (5% to 40% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20– 7.12 (m, 9H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.82 (dt, *J* = 7.7, 1.4 Hz, 1H), 6.74 – 6.70 (m, 2H), 5.79 – 5.68 (m, 2H), 5.07 (d, *J* = 12.3 Hz, 1H),

5.07 (d, J = 12.3 Hz, 1H), 4.97 (dd, J = 5.7, 2.0 Hz, 1H), 3.76 (s, 3H), 3.71 (dd, J = 9.7, 5.7 Hz, 1H), 3.41 – 3.35 (m, 1H), 2.69 (d, J = 2.0 Hz, 1H), 1.62 – 1.44 (m, 2H), 1.24 – 1.03 (m, 2H), 0.79 (t, J = 7.3, 3H);

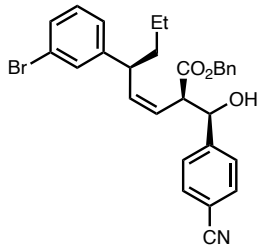
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 159.2, 146.8, 139.1, 135.5, 132.6, 130.2, 130.0, 129.2, 128.6, 128.4, 128.3, 127.4, 126.1, 122.7, 122.5, 113.6, 73.8, 66.8, 55.2, 52.6, 43.4, 38.9, 20.5, 14.0;

HRMS (ESI): calcd for $C_{29}H_{31}BrO_4Na$ $[M+Na]^+$ 545.1298. Found 545.1294;

IR ν (cm^{-1}) 3514, 3033, 2956, 2931, 2871, 2062, 1949, 1887, 1729, 1612, 1514, 1464, 1304, 1249, 1172, 1033, 997;

Chiral HPLC: Regis Whelk O1 column (20% IPA in hexanes, 1.5 mL/min), t_r = 9.0 min (minor), t_r = 12.5 min (major);

$[\alpha]_D^{25}$158.5 (c = 0.68, $CHCl_3$).



3-19 Prepared according to the General Procedure with [Rh((*S,S*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.)from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), 4-cyanobenzaldehyde (59.0 mg, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 90%, crude yield: 87%, *dr*: 90:10. Isolated in 80% yield, *dr*: ≥95:5 *ee*: 95% as a pale yellow oil after purification by column chromatography (3% to 30% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41– 7.34 (m, 5H), 7.32– 7.27 (m, 3H), 7.25 – 7.20 (m, 2H), 7.03 (t, *J* = 7.8, 1H), 6.99 (t, *J* = 1.8 Hz, 1H), 6.70 (dt, *J* = 7.8, 1.4 Hz, 1H), 5.80 – 5.75 (m, 1H), 5.70 – 5.65 (m, 1H), 5.15 (s, 2H), 5.12 (dd, *J* = 4.0, 2.4 Hz, 1H), 3.64 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.29 – 3.22 (m, 2H), 1.55 – 1.39 (m, 2H), 1.19 – 0.98 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 3H);

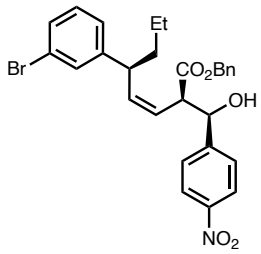
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 146.7, 145.4, 139.5, 135.1, 131.8, 130.1(2), 129.4, 128.7, 128.5, 126.6, 125.6, 122.6, 121.2, 118.7, 111.5, 72.9, 67.3, 51.3, 43.3, 39.5, 20.5, 13.9;

HRMS (ESI): calcd for $C_{29}H_{28}BrNO_3Na$ $[M+Na]^+$ 540.1145. Found 540.1137;

IR ν (cm^{-1}) 3484, 3064, 3033, 2957, 2931, 2871, 2229, 1951, 1873, 1813, 1728, 1609, 1567, 1456, 1311, 1215, 1167, 1074, 1019, 997;

Chiral HPLC: ChiralPak IG column (4% IPA in hexanes, 1.0 mL/min), t_r = 27.0 min (minor), t_r = 29.7 min (major);

$[\alpha]_D^{25}$ 139.3 (c = 0.60, $CHCl_3$).



3-20 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.)from the corresponding diene (69.1 mg, 0.30 mmol, 1.0 equiv.), 4-nitrobenzaldehyde (68.0 mg, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 96%, crude yield: 90%,

dr: 95:5. Isolated in 83% yield, *dr*: ≥95:5, *ee*: 98% as a colourless oil after purification by column chromatography (5% to 40% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.38 – 7.34 (m, 3H), 7.32 – 7.28 (m, 2H), 7.28 – 7.24 (m, 2H), 7.21 (ddd, *J* = 7.9, 2.9, 1.0 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.97 (t, *J* = 10.4 Hz, 1H), 5.70 (t, *J* = 10.4 Hz, 1H), 5.18 (dd, *J* = 3.5, 2.4 Hz, 1H), 5.16 (s, 2H), 3.65 (dd, *J* = 10.4, 3.8 Hz, 1H), 3.36 (d, *J* = 2.4 Hz, 1H), 3.25 (q, *J* = 8.2 Hz, 1H), 1.53 – 1.37 (m, 2H), 1.20 – 0.97 (m, 2H), 0.76 (t, *J* = 7.4 Hz, 3H);

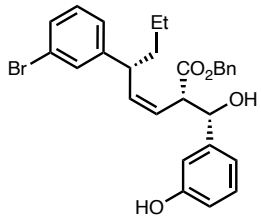
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 147.3, 147.2, 146.7, 139.5, 135.1, 130.0(2), 129.3, 128.7(2), 128.5, 127.0, 125.5, 123.2, 122.6, 121.1, 72.8, 67.4, 51.2, 43.3, 39.7, 20.6, 13.9;

HRMS (ESI): calcd for $C_{28}H_{28}BrNO_5Na$ $[M+Na]^+$ 560.1043. Found 560.1057;

IR ν (cm^{-1}) 3523, 3066, 3033, 2957, 2930, 2871, 1937, 1871, 1720, 1606, 1520, 1347, 1262, 1169, 1073;

Chiral HPLC: ChiralPak IB column (5% IPA in hexanes, 1.5 mL/min), t_r = 9.0 min (minor), t_r = 13.1 min (major);

$[\alpha]_D^{25}$ 135.0 (c = 0.45, $CHCl_3$).



3-21 Prepared according to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (68.9 mg, 0.30 mmol, 1.0 equiv.), 3-hydroxybenzaldehyde (55 μL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid

(122.4 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 92%, NMR yield: 89%, *dr*: 92:8. Isolated in 34% yield, *dr*: ≥95:5, *ee*: 93% as a colourless oil after purification by preparatory thin-layer silica chromatography (5% to 40% EtOAc in hexanes, 1000 μm).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.33 (m, 3H), 7.28 – 7.24 (m, 3H), 7.09 (t, *J* = 1.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.69 – 6.67 (m, 1H), 6.65 (ddd, *J* = 8.0, 2.6, 0.9 Hz, 1H), 5.76 (t, *J* = 10.4 Hz, 1H), 5.68 (t, *J* = 10.4 Hz, 1H), 5.10 (s, 2H), 4.99 (d, *J* = 5.4 Hz, 1H), 4.65 (bs, 1H), 3.71 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.34 (dt, *J* = 9.6, 7.6 Hz, 1H), 2.82 (bs, 1H), 1.60 – 1.44 (m, 2H), 1.22 – 1.03 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H);

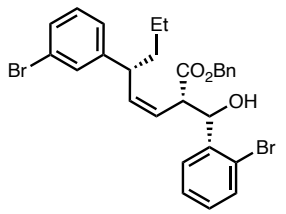
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 155.5, 146.8, 142.4, 139.2, 135.4, 130.2, 130.1, 129.5, 129.2, 128.6, 128.5, 128.4, 126.0, 122.5, 122.2, 118.6, 115.0, 113.1, 73.7, 66.9, 52.2, 43.5, 38.9, 20.5, 14.0;

HRMS (ESI): calcd for $C_{28}H_{29}BrNaO_4$ $[M+Na]^+$ 507.1176 Found 507.1179;

IR ν (cm^{-1}) 3408, 3063, 3033, 2957, 2930, 2871, 1713, 1593, 1567, 1475, 1456, 1427, 1378, 1312, 1267, 1217, 1163, 1074, 1049, 998, 876, 780, 749, 697;

Chiral HPLC: Regis Whelk O1 column (7.5 %IPA in hexanes, 1.5 mL/min), t_r = 16.7 min (major), t_r = 18.8 min (minor);

$[\alpha]_D^{25}$ –165.74 (c = 0.72, $CHCl_3$).



3-22 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (69.1 mg, 0.30 mmol, 1.00 equiv.),

2-bromobenzaldehyde (52.5 μL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (121.2 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 95%, NMR yield: 97%, *dr*: ≥95:5. Isolated in 15% yield, *dr*: ≥95:5, *ee*: 95% as a colourless oil after purification by preparatory TLC (1000 μm, (15% EtOAc/Hexanes).

Separation of these products are also amenable to preparatory HPLC. To showcase this **3-22** was again prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (1.3 mg, 0.0013 mmol, 0.013 equiv.) from the corresponding diene (23.0 mg, 0.10 mmol, 1.0 equiv.), 2-bromobenzaldehyde (17.5 μL, 0.15 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (40.2 mg, 0.20 mmol, 2.0 equiv.). Isolated in 71% yield, *dr*: 98:2, *ee*: 95% as a colourless oil after purification by non-optimized preparatory HPLC (Agilent 1260 Infinity prep system; Eclipse XDB-C8, 21.2x150 mm, 7 μm; 10 mL/min, 50 – 80% MeCN:H_2O [2 min gradient], 80 – 100% MeCN:H_2O [38 min gradient], t_r = 16.7 min).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.33 (m, 4H), 7.31 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.16 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H), 7.71 (t, *J* = 10.5 Hz, 1H), 5.65 (t, *J* = 10.5 Hz, 1H), 5.50 (t, *J* = 1.9 Hz, 1H), 5.23 (q, *J* = 12.1 Hz, 2H), 4.01 (dd, *J* = 10.4, 2.5 Hz, 1H), 3.48 (d, *J* = 2.5 Hz, 1H), 3.11 (dt, *J* = 9.2, 7.4 Hz, 1H), 1.49 – 1.34 (m, 2H), 1.16 – 0.82 (m, 2H), 0.73 (t, *J* = 7.3 Hz, 3H);

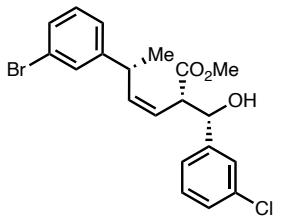
^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 146.7, 138.9, 138.7, 135.5, 132.2, 129.9, 129.8, 129.1, 128.9, 128.7, 128.6, 128.5, 128.2, 127.0, 125.6, 122.3, 120.9, 120.7, 72.4, 67.1, 47.6, 43.2, 39.5, 20.5, 13.9;

HRMS (ESI): calcd for $C_{28}H_{28}Br_2NaO_3$ $[M+Na]^+$ 593.0297 Found 593.0305;

IR ν (cm^{-1}) 3502, 3064, 3033, 2946, 2929, 2871, 1717, 1592, 1568, 1498, 1471, 1456, 1440, 1378, 1299, 1263, 1215, 1170, 1123, 1074, 1022, 997, 908, 823, 782, 747, 696, 658;

Chiral HPLC: Regis Whelk O1 column (5% IPA in hexanes), t_r = 10.2 min (major), t_r = 13.6 min (major);

$[\alpha]_D^{25}$ –132.7 (c = 0.34, $CHCl_3$)



3-23 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (37.9 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.50 equiv.) and 3-bromophenylboronic acid (120.5 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, NMR yield: 96%, *dr*: ≥95:5. Isolated in 94% yield *dr:* ≥95:5, *ee:* 99*%,* as a colourless oil after purification by column chromatography (3% to 30% EtOAc in hexanes). Compound **20'**, the benzyl ester variant of this product, used in competition studies with benzyl crotonate, displayed similar characteristic NMR features.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.14 (m, 2H), 7.13 – 7.09 (m, 1H), 7.07 – 7.02 (m, 2H), 6.74 (d, *J* = 7.7 Hz, 1H), 5.73 (t, *J* = 10.2 Hz, 1H), 5.63 (t, *J* = 10.2 Hz, 1H), 5.10 (dd, *J* = 4.0, 2.3 Hz, 1H), 3.72 (s, 3H), 3.68 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.51 (qd, *J* = 7.0, 2.6 Hz, 1H), 3.17 (d, *J* = 2.3 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 3H);

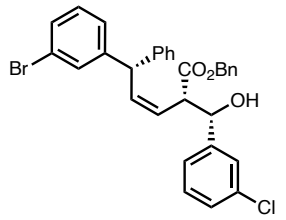
^{13}C NMR ($CDCl_3$, 125 Hz) δ 173.5, 147.3, 142.6, 140.2, 134.2, 130.0, 129.7, 129.5, 129.3, 128.0, 126.3, 125.5, 124.2, 122.6, 120.4, 73.0. 52.4, 51.3, 37.4, 21.6;

HRMS (ESI): calcd for $C_{20}H_{20}BrClNO_3Na$ $[M+H]^+$ 445.0177. Found 445.0174;

IR ν (cm^{-1}) 3501, 3065, 3022, 2965, 2929, 2875, 2377, 1722, 1594, 1568, 1476, 1452, 1434, 1371, 1184, 1099, 1015, 919, 781, 694;

Chiral HPLC: Regis Whelk O1 column (1% IPA in hexanes, 1.5 mL/min), t_r = 18.6 min (major), t_r = 21.3 min (minor);

$[\alpha]_D^{25}$ –212.88 (c = 0.54, $CHCl_3$).



3-24 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (79.3 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 mL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 74%, *dr*: 90:10. Isolated in 65% yield, *dr*: ≥95:5 *ee*: 98% as a colourless oil after purification by column chromatography (3% to 30% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 6.91 (m, 17H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.04 (t, *J* = 10.6 Hz, 1H), 5.85 (td, *J* = 10.6, 1.0 Hz, 1H), 5.18 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.09 (d, *J* = 12.3 Hz, 1H), 5.01 (d, *J* = 12.3 Hz, 1H), 4.67 (d, *J* = 10.1 Hz, 1H), 3.76 (dd, *J* = 10.4, 3.8 Hz, 1H), 3.28 (d, *J* = 2.6 Hz, 1H);

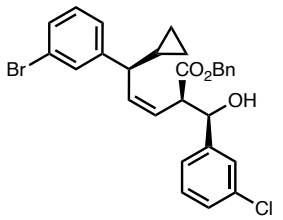
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 145.5, 142.6, 142.5, 137.4, 135.1, 134.3, 131.0, 130.0, 129.5(2), 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 126.7, 126.6, 126.3, 125.2, 122.6, 122.0, 73.0, 67.2, 51.3, 48.4;

HRMS (ESI): calcd for $C_{31}H_{26}BrClO_3Na$ $[M+Na]^+$ 583.0646. Found 583.0644.

IR ν (cm^{-1}) 3508, 3063, 3030, 1949, 1876, 1805, 1720, 1591, 1568, 1493, 1315, 1167;

Chiral HPLC: Regis Whelk O1 column (5% IPA in hexanes, 1.5 mL/min), t_r = 25.8 (minor), t_r = 37.4 min (major);

$[\alpha]_D^{25}$ –57.86 (c = 0.63, $CHCl_3$).



3-25 Prepared according to the General Procedure with [Rh((*S,S*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (68.5 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 mL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 100%, crude yield: 98%, *dr*: 90:10. Isolated in 89% yield, *dr*: 93:7, *ee*: 98% as a colourless oil after purification by column chromatography (3% to 30% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 6.99 (m, 12H), 6.76 (d, *J* = 7.7 Hz, 1H), 5.82 (t, *J* = 10.5 Hz, 1H), 5.73 (t, *J* = 10.5 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.04 (dd, *J* = 4.6, 2.4 Hz, 1H), 3.58 (dd, *J* = 4.6, 10.3 Hz, 1H), 3.02 (d, *J* = 2.4 Hz, 1H), 2.76 (dd, *J* = 9.1, 9.1, Hz, 1H), 0.96 – 0.87 (m, 1H), 0.50 – 0.34 (m, 2H), 0.19 – 0.08 (m, 2H);

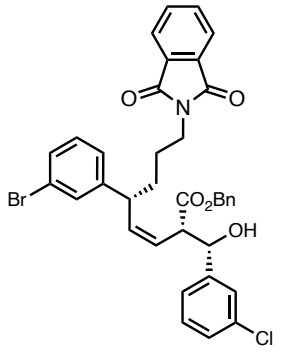
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 146.0, 142.4, 137.8, 135.1, 134.2, 130.1, 129.9, 129.5, 128.7, 128.6, 128.4, 128.1, 126.3, 126.0, 124.3, 122.5, 121.5, 73.3, 67.1, 51.8, 47.0, 16.7, 4.3. 3.8;

HRMS (ESI): calcd for $C_{28}H_{26}BrClO_3Na$ $[M+Na]^+$ 547.0646. Found 547.0646;

IR ν (cm^{-1}) 3510, 3066, 3032, 3003, 1943, 1871, 1807, 1724, 1593, 1568, 1498, 1164;

Chiral HPLC: ChiralPak IB column (2% IPA in hexanes, 1.5 mL/min), t_r = 8.0 min (minor), t_r = 23.6 min (major);

$[\alpha]_D^{25}$ 132,97 (c = 0.62, $CHCl_3$).



3-26 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (112.6 mg, 0.25 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (43 μL, 0.38 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (100.7 mg, 0.50 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 90%, NMR yield: 95%, *dr*: 90:10. Isolated in 83% yield, *dr*: 94:6, *ee*: 99% as a colourless oil after purification by column chromatography (3% to 30% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.37 – 7.21 (m, 7H), 7.14 – 7.00 (m, 5H), 6.81 (d, *J* = 7.5 Hz, 1H), 5.79 (t, *J* = 10.7 Hz, 1H), 5.72 (t, *J* = 10.7 Hz, 1H), 5.13 – 5.04 (m, 3H), 3.73 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.43 – 3.35 (m, 1H), 3.07, (d, *J* = 2.7 Hz, 1H), 1.65 – 1.45 (m, 4H);

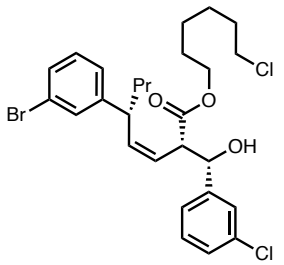
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 168.4, 146.0, 142.3, 138.5, 135.2, 134.0, 133.9, 132.0, 130.1, 130.0, 129.5, 129.3, 128.6, 128.5, 128.2, 127.9, 126.3, 125.7, 124.2, 123.2, 122.6, 122.3, 73.2, 67.0, 51.7, 42.8, 37.4, 33.8, 26.1;

HRMS (ESI): calcd for $C_{36}H_{31}BrClNO_5Na$ $[M+Na]^+$ 694.0966. Found 694.0978;

IR ν (cm^{-1}) 3503, 3063, 3031, 2936, 2859, 1949, 1770, 1210, 1593, 1568, 1467, 1455, 1436, 1397, 1371, 1335, 1188, 1168, 1073, 1033, 997, 779, 721;

Chiral HPLC: Determined on ChiralPak IC column (7.5% IPA in hexanes, 1.25 mL/min), t_r = 15.4 min (minor), t_r = 20.2 min (major);

$[\alpha]_D^{25}$ –91.55 (c = 0.60, $CHCl_3$).



3-27 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (68.5 mg, 0.25 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (43 μL, 0.38 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (100.7 mg, 0.50 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 95%, NMR yield: 95%, *dr*: 94:6. Isolated in 52% yield, *dr*: ≥95:5, *ee*: 97% as a colourless oil after purification by column chromatography (3% to 30% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.26 (m, 2H), 7.21 – 7.12 (m, 3H), 7.08 – 7.04 (m, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 5.74 (t, *J* = 10.3 Hz, 1H), 5.63 (t, *J* = 10.3 Hz, 1H), 5.07 (d, *J* = 4.5 Hz, 1H), 4.11 (t, *J* = 6.7 Hz, 2H), 3.67 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.58 – 3.51 (m, 3H), 3.17 (bs, 1H), 1.78 (dq, *J* = 8.3, 6.8 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.50 – 1.42 (m, 2H), 1.36 – 1.25 (m, 5H);

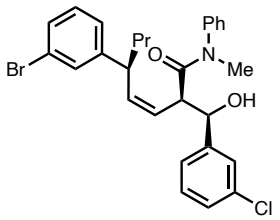
^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 147.3, 142.7, 140.2, 134.2, 130.0, 129.7, 129.5, 129.3, 128.0, 126.4, 125.5, 124.3, 122.6, 120.8, 73.1, 65.2, 51.6, 44.9, 37.4, 32.4, 28.4, 26.5, 25.2, 21.7;

HRMS (ESI): calcd for $C_{25}H_{29}BrCl_2NaO_3$ $[M+Na]^+$ 549.0569 Found 549.0564;

IR ν (cm^{-1}) 3504, 3063, 3022, 2959, 2937, 2863, 1942, 1871, 1716, 1595, 1568, 1475, 1429, 1399, 1315, 1178, 1099, 1074, 997, 920, 884, 782, 730, 695;

Chiral HPLC: Regis Whelk O1 column (3% IPA in hexanes, 1.5 mL/min), t_r = 13.0 min (minor), t_r = 14.3 min (major);

$[\alpha]_D^{25}$ –176.59 (c = 0.67, $CHCl_3$).



3-28 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (68.8 mg, 0.3 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 mL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.6 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 95%, crude yield: 93%, *dr*: ≥95:5. Isolated in 91% yield, *dr*: ≥95:5, *ee*: 95% as a colourless oil after purification by column chromatography (5% to 40% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 – 7.43 (m, 3H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.15 – 6.40 (br s, 2H) 7.14 – 7.06 (m, 2H), 7.05 (t, *J* = 1.8 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.90 (dt, *J* = 7.8, 1.4 Hz, 1H), 6.68 (t, *J* = 1.8 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.83 – 5.68 (m, 2H), 4.85 (d, *J* = 6.0 Hz, 1H), 3.49 (dd, *J* = 10.0, 6.1 Hz, 1H), 3.20 (s, 3H), 2.99 (br s, 1H), 2.49 (dt, *J* = 8.6, 6.4 Hz, 1H), 1.46 – 1.30 (m, 2H), 1.04 – 0.89 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H);

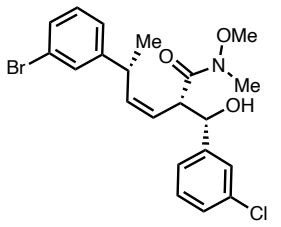
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 146.9, 143.2, 143.0, 138.7, 134.1, 130.1(2), 130.0, 129.3, 129.2, 128.5, 127.8, 127.5, 126.3, 125.7, 124.5, 124.2, 122.5, 74.3, 50.0, 43.7, 39.8, 37.5, 20.4, 14.1;

HRMS (ESI): calcd for $C_{28}H_{29}BrClNO_2Na$ $[M+Na]^+$ 548.0962. Found 548.0961.

IR ν (cm^{-1}) 3210, 3063, 2957, 1953, 1886, 1802, 1634, 1594, 1568, 1496, 1386;

Chiral HPLC: ChiralPak IG column (5% IPA in hexanes, 1.5 mL/min), t_r = 8.2 min (minor), t_r = 9.3 min (major);

$[\alpha]_D^{25}$ 171.00 (c = 0.52, $CHCl_3$).



3-29 Prepared according to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (46.6 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.50 equiv.) and 3-bromophenylboronic acid (120.5 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, NMR yield: 90%, *dr*: ≥95:5. Isolated in 84% yield *dr:* ≥95:5, *ee:* 98*%,* as a colourless oil after purification by column chromatography (7% to 60% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 – 7.24 (m, 2H), 7.15 – 7.01 (m, 5H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.76 (t, *J* = 10.4 Hz, 1H), 5.65 (t, *J* = 10.4 Hz, 1H), 5.03 (d, *J* = 4.0 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.65 (s, 3H), 3.39 (qd, *J* = 6.9, 2.9 Hz, 1H), 3.20 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H);

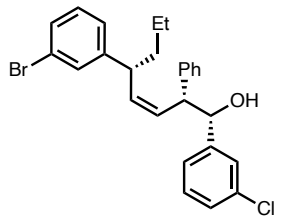
^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 147.6, 143.1, 139.4, 134.1, 130.0, 129.6, 129.3, 129.2, 127.8, 126.3, 125.4, 124.4, 122.5, 121.1, 73.9, 61.6, 47.1, 37.7, 32.1, 22.3;

HRMS (ESI): calcd for $C_{21}H_{24}BrClO_3$ $[M+H]^+$ 452.0623. Found 452.0622;

IR ν (cm^{-1}) 3428, 3064, 3016, 3968, 2935, 2873, 2823, 1634, 1595, 1568, 1476, 1426, 1387, 1287, 1195, 996, 887, 824, 771, 694;

Chiral HPLC: Chiralpak IC column (10% IPA in hexanes, 1.5 mL/min), t_r = 8.2 (minor), t_r = 13.6 min (major);

$[\alpha]_D^{25}$ –126.76 (c = 0.56, $CHCl_3$).



3-30 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (33.8 mg, 0.20 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (34 μL, 0.30 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (81.1 mg, 0.40 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 60%, NMR yield: 55%, *dr*: 94:6. Isolated in 54% yield, *dr*: ≥95:5, *ee*: >99% as an orange oil after purification by column chromatography (2% to 20% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1H), 7.30 – 7.20 (m, 4H), 7.16 – 7.10 (m, 5H), 7.06 (dt, *J* = 7.5, 0.7 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 5.94 (t, *J* = 10.5 Hz, 1H), 5.75 (t, *J* = 10.5 Hz, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 3.85 (dd, *J* = 10.2, 6.8 Hz, 1H), 3.45 (dt, *J* = 9.6, 7.5 Hz, 1H), 2.01 (bs, 1H), 1.59 – 1.50 (m, 1H), 1.48 – 1.39 (m, 1H), 1.14 – 0.93 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H);

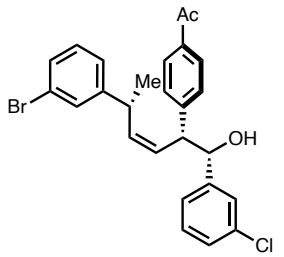
^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.4, 143.9, 140.9, 137.1, 133.9, 130.3, 130.2, 129.3, 129.1, 128.7, 128.3, 127.9, 127.6, 126.9, 126.4, 126.1, 124.6, 122.7, 77.3, 52.5, 43.3, 39.0, 20.4, 13.9;

HRMS (ESI): calcd for $C_{26}H_{26}BrClNaO$ $[M+Na]^+$ 491.0748 Found 491.0729;

IR ν (cm^{-1}) 3550, 3453, 3062, 3027, 2957, 2929, 2871, 1944, 1870, 1800, 1743, 1594, 1568, 1595, 1475, 1453, 1428, 1379, 1298, 1189, 1098, 1073, 997, 972, 883, 784, 772, 753, 697;

Chiral HPLC: ChiralPak IB column (2% IPA in hexanes, 1.5 mL/min), t_r = 8.1 min (minor), t_r = 9.2 min (major);

$[\alpha]_D^{25}$ –211.27 (c = 0.55, $CHCl_3$).



3-31 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (56.0 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (121.3 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 97%, NMR yield: 95%, *dr*: 95:5. Isolated in 94% yield, *dr*: ≥95:5, *ee*: 98% as an off-white solid after purification by column chromatography (7% to 60% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 – 7.86 (m, 2H), 7.33 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.24 (t, *J* = 1.8 Hz, 1H), 7.19 – 7.12 (m, 3H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 5.91 (td, *J* = 10.4, 0.9 Hz, 1H), 5.76

(td, J = 10.4, 0.8 Hz, 1H), 4.84 (d, J = 6.2 Hz, 1H), 3.95 (dd, J = 10.0, 6.3 Hz, 1H), 3.61 (dq, J = 9.4, 7.0 Hz, 1H), 2.58 (s, 3H), 2.04 (bs, 1H), 1.14 (d, J = 7.0 Hz, 3H);

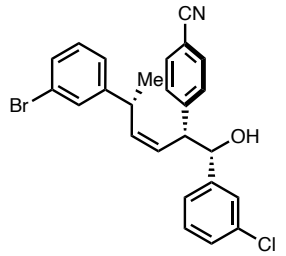
^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7, 147.8, 146.8, 143.8, 138.4, 135.9, 134.2, 130.2, 129.9, 129.40, 129.37, 128.7, 128.5, 127.9, 126.4, 126.3, 125.6, 124.6, 122.7, 99.4, 52.1, 37.5, 26.6, 21.8;

HRMS (ESI): calcd for $C_{26}H_{24}BrClNaO_2$ $[M+Na]^+$ 505.054 Found 505.054;

IR ν (cm^{-1}) 3447, 3063, 3014, 2966, 2926, 2873, 1678, 1605, 1568, 1475, 1416, 1359, 1304, 1271, 1187, 1098, 1073, 1016, 997, 959, 870, 825, 772, 721, 695;

Chiral HPLC: ChiralPak IB column (5% IPA in hexanes, 1.5 mL/min), t_r = 12.5 min (major), t_r = 16.4 min (minor);

$[\alpha]_D^{25}$ –191.10 (c = 0.60, $CHCl_3$).



3-32 Prepared according to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (47.0 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (122.2 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >98%, NMR yield: 79%, *dr*: 91:9. Isolated in 25% yield, *dr*: ≥95:5, *ee*: 90% as a colourless oil after purification by preparatory thin-layer silica chromatography (30% Et_2O in pentane, 1000 μm).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 – 7.54 (m, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.26 – 7.23 (m, 3H), 7.22 – 7.20 (m, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.09 – 7.05 (m, 2H), 6.99 (d, J =

7.5 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.02 (tdd, *J* = 10.6, 1.6, 1.0 Hz, 1H), 5.83 (dtd, *J* = 10.6, 7.3, 0.9 Hz, 1H), 4.89 (d, *J* = 6.3 Hz, 1H), 3.95 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.25 (d, *J* = 7.5 Hz, 2H), 2.16 (bs, 1H);

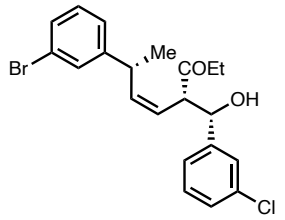
^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.7, 143.7, 141.9, 134.4, 132.4, 132.2, 131.3, 130.1, 129.5, 129.4, 129.2, 128.2, 128.1, 126.9, 126.5, 124.6, 122.6, 118.7, 110.9, 77.1, 52.1, 34.5;

HRMS (ESI): calcd for $C_{24}H_{19}BrClNNaO$ $[M+Na]^+$ 474.0231 Found 474.0239;

IR ν (cm^{-1}) 3472, 3064, 3018, 2913, 2229, 1939, 1606, 1596, 1569, 1502, 1474, 1429, 1332, 1297, 1193, 1098, 1071, 1021, 998, 971, 925, 870, 830, 774, 696;

Chiral HPLC: ChiralPak IB column (5% IPA in hexanes, 1.5 mL/min), t_r = 16.9 min (major), t_r = 20.2 min (minor);

$[\alpha]_D^{25}$ –20.71 (c = 0.64, $CHCl_3$).



3-33 Prepared according to to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding (4*E*,6*E*)-octa-4,6-dien-3-one (37.5 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (121.8 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >98%, NMR yield: 67%, *dr*: 58:42. Isolated in 42% yield, *dr*: 70:30, *ee*: 97% as a colourless oil after purification by column chromatography (3% to 30% EtOAc in hexanes).

Major Diastereomer:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.35 (m, 1H), 7.32 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.30 – 7.22 (m, 4H), 7.20 (dtd, *J* = 7.2, 1.7, 0.6 Hz, 1H), 5.80 (t, *J* = 10.5 Hz, 1H), 5.52 (td, *J* = 10.5, 1.1 Hz, 1H), 5.16 (d, *J* = 3.5 Hz, 1H), 3.66 (dd, *J* = 10.8, 3.7 Hz, 1H), 3.38 (bs, 1H), 3.23 (dq, *J* = 9.5, 7.2 Hz, 1H), 2.21 (dq, *J* = 18.2, 7.2 Hz, 1H), 2.08 (dq, *J* = 18.2, 7.2 Hz, 1H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.6, 148.0, 143.5, 140.4, 134.3, 130.3, 130.0, 129.51, 129.46, 127.7, 126.5, 125.4, 124.4, 121.5, 72.9, 58.1, 37.7, 35.8, 22.2, 7.4;

Minor Diastereomer (selected signals)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.66 – 6.63 (m, 1H), 5.78 (t, *J* = 5.8 Hz, 1H), 5.57 (td, *J* = 10.8 Hz, 1H), 5.12 (d, *J* = 3.6 Hz, 1H), 3.73 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.47 (dq, *J* = 10.1, 7.1 Hz, 1H), 3.25 (bs, 1H), 2.58 (dq, *J* = 18.2, 7.3 Hz, 1H), 2.39 (dq, *J* = 18.2, 7.3 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H);

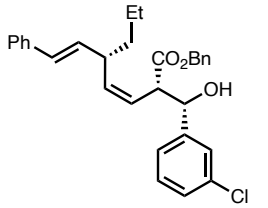
^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.3, 147.0, 143.1, 140.3, 134.2, 37.5, 22.0, 7.5;

HRMS (ESI): calcd for $C_{21}H_{22}BrClNaO_2$ $[M+Na]^+$ 443.0384 Found 443.0384;

IR ν (cm^{-1}) 3474, 3064, 3015, 2973, 2936, 2879, 1704, 1594, 1568, 1475, 1427, 1193, 1074, 773;

Chiral HPLC: ChiralPak IG column (5% EtOAc in hexanes, 1.5 mL/min), t_r = 11.6 min (major), t_r = 13.3 min (minor), t_r = 13.3 min (minor of diastereomer), t_r = 15.9 min (major of diastereomer);

$[\alpha]_D^{25}$ –55.43 (c = 1.22, $CHCl_3$)



3-34 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (7.9 mg, 0.0076 mmol, 0.026 equiv.) from the corresponding diene (69.2 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 μL, 0.45 mmol, 1.5 equiv.) and *trans*-2-phenylvinylboronic acid (88.8 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 90%, NMR yield: 63%, *dr*: 81:19. Isolated in 39% yield, *dr*: ≥95:5, *ee*: 86% as a colourless oil after purification by preparatory thin-layer silica chromatography (15% EtOAc in hexanes, 1000 μm).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.32 (m, 4H), 7.30 – 7.27 (m, 2H), 7.25 – 7.16 (m, 5H), 7.14 (dt, *J* = 6.9, 2.0 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.01 (d, *J* = 16.2 Hz, 1H), 5.79 (dd, *J* = 16.2, 7.4 Hz, 1H), 5.67 (t, *J* = 10.3 Hz, 1H), 5.58 (t, *J* = 10.3 Hz, 1H), 5.10 (s, 2H), 5.07 (dd, *J* = 5.1, 2.4 Hz, 1H), 3.72 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.12 (d, *J* = 2.4 Hz, 1H), 3.03 – 2.95 (m, 1H), 1.46 – 1.14 (m, 4H), 0.80 (t, *J* = 7.4 Hz, 3H);

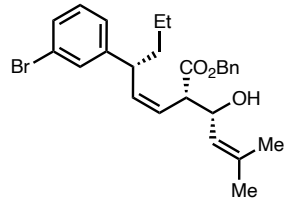
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 142.7, 139.0, 137.4, 135.3, 134.2, 132.2, 129.5, 129.2, 128.6, 128.5, 128.4, 128.3, 128.0, 127.1, 126.5, 126.2, 124.5, 121.3, 73.4, 67.0, 52.0, 41.2, 37.5, 20.3, 14.1;

HRMS (ESI): calcd for $C_{30}H_{31}ClNaO_3$ $[M+Na]^+$ 497.1854 Found 497.1867;

IR ν (cm^{-1}) 3512, 3063, 3027, 2956, 2929, 2871, 1948, 1873, 1728, 1653, 1599, 1576, 1497, 1478, 1456, 1432, 1378, 1214, 1214, 1165, 1099, 1077, 1029, 1001, 966, 899, 783, 749, 695;

Chiral HPLC: ChiralPak IC column (1.5% IPA in hexanes, 1.0 mL/min), t_r = 7.6 min (major), t_r = 7.9 min (minor);

$[\alpha]_D^{25}$ –198.65 (c = 0.73, $CHCl_3$).



3-35 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (7.8 mg, 0.0076 mmol, 0.026 equiv.) with durene (in place of Bn_2O as ISTD) from the corresponding diene (69.4 mg, 0.30 mmol, 1.00 equiv.), 3,3-dimethyl acrylaldehyde (42 μL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (120.4 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 96%, NMR yield: 80%, *dr*: 87:13. Isolated in 45% yield, *dr*: ≥95:5, *ee*: 97% as a colourless oil after purification by preparatory thin-layer chromatography (15% EtOAc in hexanes, 1000 μm).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.28 (m, 7H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.11 (dt, *J* = 7.7, 1.5 Hz, 1H), 5.81 (t, *J* = 10.5 Hz, 1H), 5.65 (t, *J* = 10.5 Hz, 1H), 5.17 (A of ABq, *J* = 12.3 Hz, 1H), 5.13 (B of ABq, *J* = 12.3 Hz, 1H), 5.05 (dsept, *J* = 9.0, 1.3 Hz, 1H), 4.58 (ddd, *J* = 9.0, 5.2, 3.2 Hz, 1H), 3.57 – 3.48 (m, 2H), 2.25 (d, *J* = 3.2 Hz, 1H), 1.66 – 1.51 (m, 8H), 1.29 – 1.08 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H);

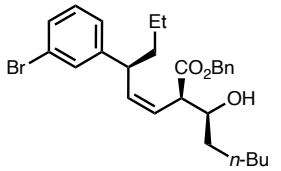
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 147.3, 138.5, 137.5, 135.7, 130.4, 130.1, 129.3, 128.6, 128.4, 128.3, 126.1, 123.7, 123.1, 122.7, 68.9, 66.7, 50.7, 43.5, 39.1, 25.8, 20.6, 18.3, 14.0;

HRMS (ESI): calcd for $C_{26}H_{31}BrO_3$ $[M+Na]^+$ 493.1349 Found 493.1355;

IR ν (cm^{-1}) 3508, 3065, 3033, 2957, 2930, 2871, 2729, 1951, 1868, 1732, 1592, 1567, 1498, 1475, 1455, 1427, 1377, 1310, 1262, 1216, 1160, 1074, 997, 907, 882, 841, 781, 747, 696;

Chiral HPLC: ChiralPak IB column (2% IPA in hexanes, 1.5 mL/min), t_r = 4.1 min (minor), t_r = 4.6 min (major);

$[\alpha]_D^{25}$ –180.96 (c = 0.54, $CHCl_3$).



3-36 Prepared according to the General Procedure with [Rh((*S,S*)-Ph-tfb)Cl]$_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (68.5 mg, 0.30 mmol, 1.0 equiv.), hexanal (45 mg, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid (120.5 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: 93%, NMR yield: 84%, *dr*: 93:7. Isolated in 77% yield, *dr*: ≥95:5, *ee*: 98% as a ruddy oil after purification by column chromatography (3% to 26% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.28 (m, 7H), 718 – 7.03 (m, 2H), 5.84 (t, *J* = 10.4 Hz, 1H), 5.66 (t, *J* = 10.4 Hz, 1H), 5.17 (s, 2H), 3.88 (dq, *J* = 8.1, 3.7 Hz, 1H), 3.52 (dt, *J* = 9.4, 7.7 Hz, 1H), 3.45 (dd, *J* = 10.3, 3.6 Hz, 1H), 2.54 (d, *J* = 3.6 Hz, 1H), 1.65 – 1.46 (m, 2H), 1.37 – 1.03 (m, 10H), 0.82 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H);

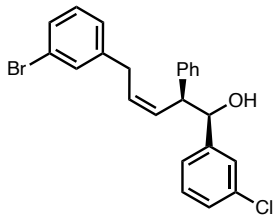
^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 147.4, 138.5, 135.6, 130.4, 130.1, 129.3, 128.7, 128.5, 128.4, 126.1, 122.8, 122.7, 71.8, 66.8, 49.6, 43.5, 39.5, 34.1, 31.7, 25.3, 22.5, 20.5, 14.1, 14.0;

HRMS (ESI): calcd for $C_{27}H_{35}BrO_3Na$ $[M+Na]^+$ 509.1662 Found 509.1668;

IR ν (cm^{-1}) 3533, 3065, 3033, 2956, 2931, 2871, 1728, 1592, 1567, 1456, 1305, 1217, 1164, 1074, 997, 781, 747, 696;

Chiral HPLC: Regis Whelk O1 column (3% IPA in hexanes, 1.5 mL/min), t_r = 7.3 min (major), t_r = 8.9 min (minor);

$[\alpha]_D^{25}$ 161.47 (c = 0.84, $CHCl_3$).



3-37 Prepared according to the General Procedure with $[Rh((S,S)\text{-Ph-tfb})Cl]_2$ (3.9 mg, 0.0038 mmol, 0.013 equiv.) from the corresponding diene (39.1 mg, 0.30 mmol, 1.0 equiv.), 3-chlorobenzaldehyde (51 mL, 0.45 mmol, 1.5 equiv.) and 3-bromophenylboronic acid pinacol ester (170 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 80%, *dr*: 95:5 Isolated in 69% yield, *dr*: ≥95:5, *ee*: 95% as a colourless oil after purification by column chromatography (2% to 18% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 – 7.01 (m, 12H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.05 (tt, *J* = 10.8, 1.6 Hz, 1H), 5.77 (td, *J* = 10.8, 7.5 Hz, 1H), 4.89 (dd, *J* = 6.6, 2.2 Hz, 1H), 3.92 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.28 (d, *J* = 7.4 Hz, 2H), 2.17 (d, *J* = 2.2 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.1, 142.4, 140.9, 134.1, 131.4, 131.2, 130.0, 129.3, 129.2, 129.1, 128.7, 128.3, 127.7, 127.0(2), 126.6, 124.7, 122.5, 77.4, 52.1, 33.5;

HRMS (ESI): calcd for $C_{23}H_{20}BrClONa$ $[M+Na]^+$ 449.0274. Found 449.0278.

IR ν (cm^{-1}) 3446, 3082, 3026, 2910, 1846, 1873, 1803, 1748, 1693, 1696, 1568, 1493, 1097;

Chiral HPLC: Regis Whelk O1 column (2% IPA in hexanes, 1.0 mL/min), t_r = 15.0 min (major), t_r = 18.6 min (minor);

$[\alpha]_D^{25}$ 16.10 (c = 1.20, $CHCl_3$).

Chapter 4 – Enantio-, and *Z*-Selective δ-Arylation of Aryl Dienes via a Rh-Catalyzed Vinylogous Conjugate Addition of Aryl Boronic Acids

4.1 Introduction

As outlined in Chapters 1 and 3, the Rh-catalyzed conjugate addition of Csp^2 organoboronic acids to electron-deficient alkenes is one of the most reliable methods for the installation of a stereocenter β to an electron-withdrawing group.[55, 142] These reactions have been demonstrated with numerous classes of alkenes activated by an electron-withdrawing group; however, the enantioselective addition to alkenes without strong electron-withdrawing groups, such as ketones, esters, or amides, is not well developed.

The underdevelopment of Rh-catalyzed conjugate additions to alkenes without strong electron-withdrawing groups can be partially attributed to the energies of the LUMO frontier molecular orbitals (FMOs) of electrophilic alkenes with different classes of substituents (**Fig. 4–1**).[149] When compared to ethylene, the LUMO of alkenes substituted by an electron-withdrawing group is lower in energy, while the LUMO of alkenes substituted by an electron-donating group is higher in energy. Extending the conjugation of an alkene has a similar effect to adding an electron-withdrawing group, lowering the energy of the LUMO to a lesser extent. Classic conjugate acceptors (i.e., electron-deficient alkenes) are activated towards conjugate addition since the LUMO is lower in energy and the largest LUMO orbital coefficients are located at the β carbon. Alkenes substituted by electron-donating groups are unactivated (or deactivated) since the LUMO is higher in energy, while the largest LUMO orbital coefficients are located at the internal, α carbon.

An understudied class of molecules towards conjugate addition reactions are alkenes substituted by groups with extended conjugation. For the purposes of this chapter, this class

will be generalized to alkenes substituted by aryl groups. While aryl substituted alkenes are typically considered unactivated towards nucleophilic addition, the extended conjugation lowers the LUMO compared to unactivated alkenes while the largest LUMO orbital coefficients are located at the β carbon. Although this class of alkenes has a LUMO that is typically higher in energy compared to classic electron-deficient conjugate acceptors, they are still activated relative to alkenes substituted by electron-donating groups and are potential substrates for conjugate addition type reactions.

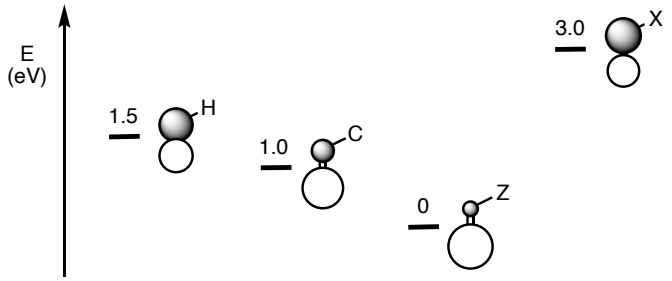


Fig. 4–1 LUMO estimates of substituted alkenes. Energies are representative values from each class of alkene. (C = $CHCH_2$, Ph, etc.; Z = CHO, CN, etc.; X = R, OR, NR_2, etc.) (1 eV = 96.5 kJ)[149-150]

For alkenes that are activated by aryl groups, the energy of their LUMO FMOs can be lowered by the addition of an electron-withdrawing substituent. The degree in which these groups lower the energy of the FMOs depends on their ability to remove electron density from the system. This can be correlated to the σ Hammett constant for the corresponding substituent. The higher the value of σ, the more effective the substituent is at removing electron density from the system.[151] If the substituent is in the *para*-position of the arene,

then σ_p values should be used as the reference point. Likewise, if the substituent is in the *meta*-position, then σ_m values should be used.

Unactivated and moderately activated alkenes represent understudied substrates in Rh-catalyzed conjugate additions. This is largely due to the relative instability of the generated Rh-alkyl intermediate generated after Rh-aryl insertion. In these cases, β-hydride elimination is favoured over protonation providing Heck-type products rather than hydroarylation products. This was first demonstrated by Lautens and co-workers when trying to achieve the Rh-catalyzed conjugate addition to styrene derivatives.[152] It was reported that the must feature more electron-deficient arenes such as 2-pyrazine, 2- or 4-pyridyl arenes while substrates without this activation provided Heck-type products. (**Fig. 4–2**).

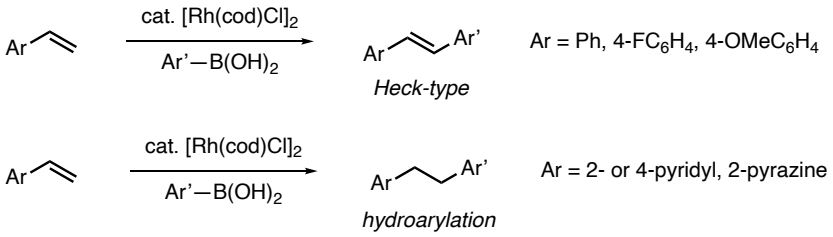


Fig. 4–2 Rh-catalyzed addition of aryl boronic acids to styrene derivatives

There are three known reports of Rh-catalyzed hydroarylation of alkenes not activated by strong electron-withdrawing groups. Lautens and co-workers reported the enantioselective Rh-catalyzed addition of aryl boronic acids to bicyclic hydrazine compounds. After insertion of the alkene into the Rh-aryl, which was generated through transmetalation of the aryl boronic acid, a 1,4-Rh-shift (determined through D-labelling studies) forms a Rh-aryl intermediate. Rh-aryl protonolysis then provides hydroarylation products (**Fig. 4–3a**, top).[153] They also reported the Rh-catalyzed arylation of unactivated

sulfonyl protected allylic amines with aryl boronic acids (**Fig. 4–3a**, bottom). The presence of a sulfonyl protecting group was required to stabilize the resulting Rh-alkyl and prevent undesirable β-hydride elimination.[154] Nishimura reported the enantioselective Rh-catalyzed addition of aryl boronic acids to 2*H*-chromenes, which upon *syn*-arylrhodation, undergo a 1,4-Rh shift from a Rh-benzyl species to a Rh-aryl. Subsequent protonolysis of the generated Rh-aryl provided enantioenriched 3-arylchromane derivatives. In each of the above three examples, the Rh-alkyl intermediates cannot undergo β-hydride elimination due to the absence of either open coordination sites on Rh or due to the lack of accessible β hydrogens in the required *syn*-coplanar arrangement.

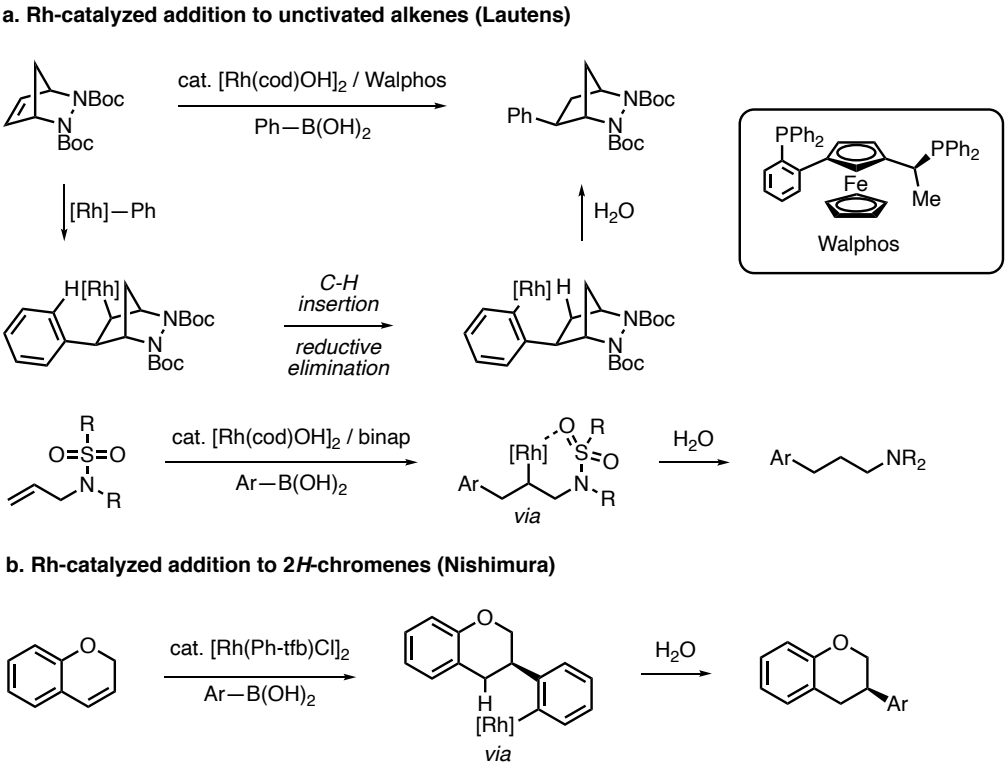


Fig. 4–3 Rh-catalyzed addition of aryl boronic acids to unactivated alkenes

The enantioselective Rh-catalyzed β-arylation of styrenes has been reported in cases where electron-deficient aryl groups are used. In 2010, Lam and co-workers demonstrated that azaarene alkenes undergo enantioselective Rh-catalyzed addition with aryl boronic acids (**Fig. 4–4**).[155] A variety of N-heterocycles provide good yields and enantioselectivities when using a Rh-catalyst ligated by a Rawal-type chiral diene with an amide derived from chiral *trans*-1,2-diaminocyclohexane (**4-1**). Substrates are limited to N-heterocycles containing a nitrogen at the 2-position of the arene. The authors hypothesized that this nitrogen coordinates to Rh in the Rh-benzyl intermediate stabilizing it while occupying the empty coordination site of Rh, preventing β-hydride elimination. In a follow up study, a Rh-catalyst ligated by a Rawal-type chiral diene with an amide derived from 2,4,6-triisopropylanaline, under otherwise identical conditions, provided higher enantioselectivities. For example, **4-2** was isolated in 76% yield, and 98% *ee*, and **4-3** was isolated in similar yields (73%), with increased enantioselectivity (98% *ee*).[156]

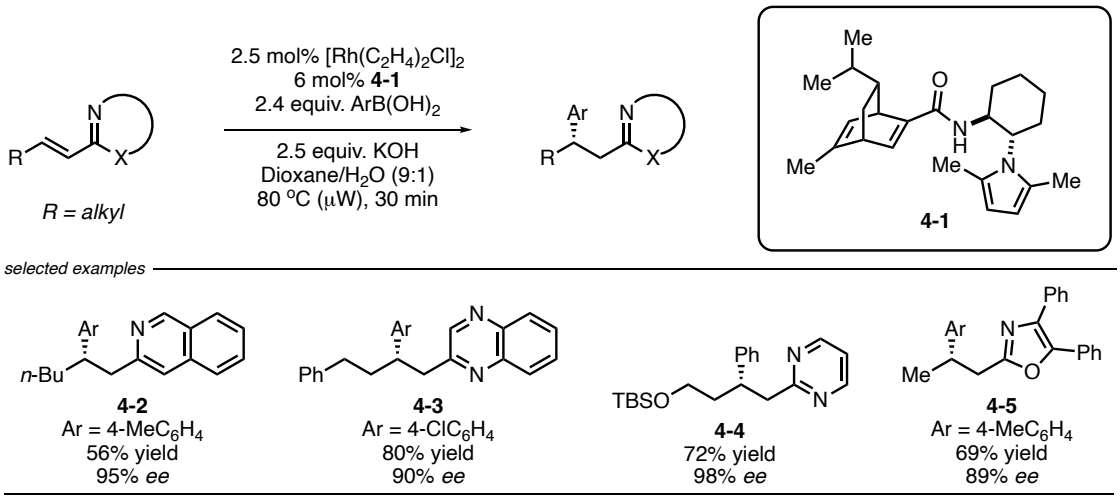
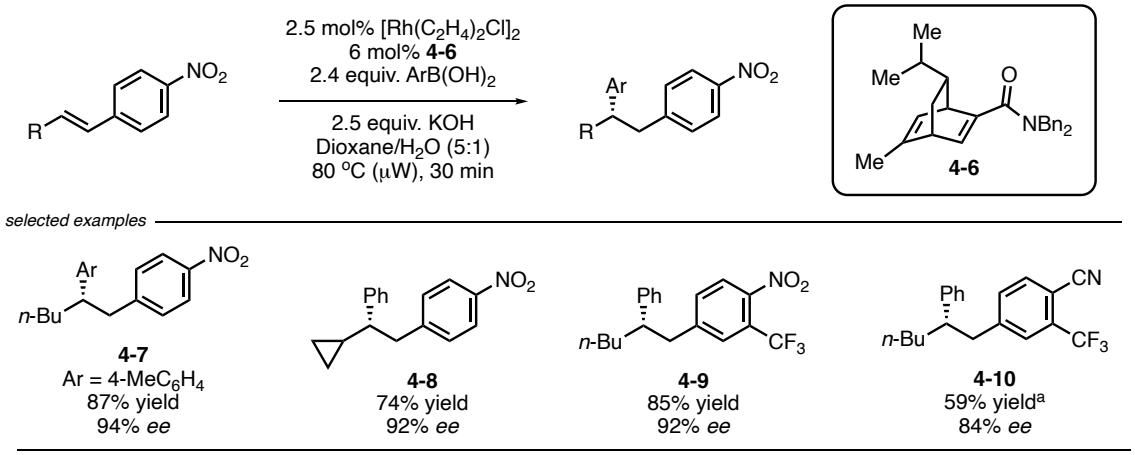


Fig. 4–4 First enantioselective Rh-catalyzed addition of aryl boronic acids to azaarene activated alkenes

The Lam Group also reported that styrene derivatives activated by *para*-nitro groups (NO_2 $\sigma_p = 0.78$)[151] can serve as substrates in the enantioselective Rh-catalyzed conjugate addition using aryl boronic acids (**Fig. 4–5**).[157] Using similar conditions to those reported for azaarene activated alkenes with a Rh-catalyst ligated by a Rawal-type chiral diene ligand containing an amide derived from dibenzyl amine (**4-6**), they achieved high yields and enantioselectivities across a variety of 4-nitro activated styrenes substituted by simple alkyl groups. It was found that substrates substituted with other *para*-electron-withdrawing groups, such as acetyl ($\sigma_p = 0.50$),[151] nitrile ($\sigma_p = 0.66$),[151] or methanesulfonyl ($\sigma_p = 0.59$),[151] were inactive towards arylation, providing low conversions and yields of the desired products, or any products arising from β-arylation (e.g. Heck-type products).[152] Only one example of non-*para*-nitro substituted arenes (**4-10**, CN $\sigma_p = 0.66$)[151] provided moderate yields but with low *ee*, high catalyst loading, longer reaction times, and a *meta*-CF_3 ($\sigma_m = 0.43$) group to provide additional electronic activation.



[a] Reaction ran with 10 mol% total [Rh] and 12 mol% **4-6** for 1.5 h

Fig. 4–5 Rh-Catalyzed addition of aryl boronic acids to *para*-nitro styrenes

As described in Chapter 3,[158] aryl 1,3-dienes were successfully used in the α,δ-difunctionalization. This was a rare example of an enantioselective Rh-catalyzed conjugate arylation process of a substrate with an aryl activating group. We questioned whether it would be possible to develop an enantio-, and *Z*-selective hydroarylation of aryl dienes by protonolysis of the Rh-allyl intermediate rather than undergoing allylrhodation with aldehydes (**Fig. 4–6**).

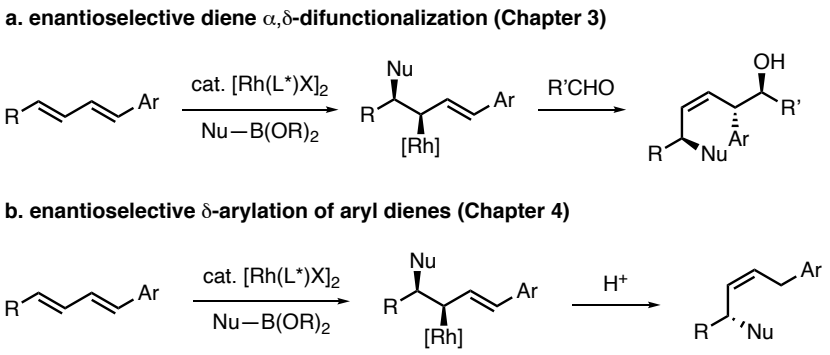


Fig. 4–6 Proposed enantio- and *Z*-selective hydroarylation of aryl dienes based on previously developed α,δ-difunctionalizations.

The enantioselective δ-arylation of dienes activated by ketones, esters or amides has been reported by Nishimura and Hayashi using Ir tetrafluorobenzobarrelene based catalysts.[74-75] As discussed in Chapter 1, these reactions provide mixtures of geometrical and positional alkene isomers resulting in products being isolated after hydrogenation or isomerization of the mixture.

The only other example of addition of aryl boron nucleophiles to aryl dienes is the enantioselective Ni-catalyzed addition of aryl boronic esters to aryl dienes reported by Meek and co-workers (**Fig. 4–7**).[159] Using [Ni(allyl)Br]$_2$ and phosphoramidite ligand **4-11** in

ethanol the enantioselective γ-arylation of a variety of electron rich and poor aryl 1,3-dienes was achieved. The proposed origin of the γ-selectivity comes from an initial Ni-hydride insertion, which is generated through either the oxidative addition of ethanol or by ligand-to-ligand proton transfer, into the δ-position. This generates a Ni-allyl with Ni at the γ-position. Transmetalation with aryl boron reagents followed by reductive elimination affords the γ-arylated product while regenerating the Ni(0) catalyst. To the best of our knowledge, there are no methods that install an aryl group δ to an aryl diene.

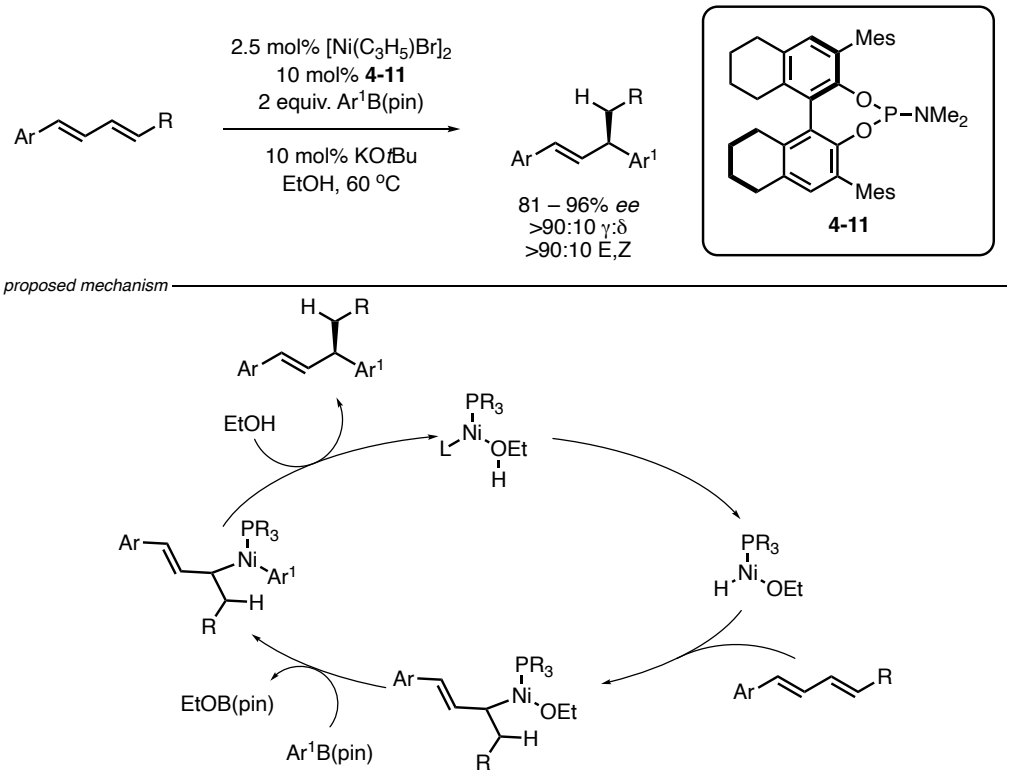


Fig. 4–7 Ni-catalyzed γ-arylation of aryl dienes

A proposed mechanistic cycle for the Rh-catalyzed *Z*-selective δ-hydroarylation of aryl dienes is shown in **Fig. 4–8**. After transmetalation of the aryl boronic acid to form Rh-

aryl **4-12**, insertion of the diene into the Rh-aryl placing the aryl group in the δ-position would provide Rh-allyl **4-13**. Based on mechanistic studies outlined in Chapter 3, the protonolysis of this intermediate will likely be the rate determining step for these reactions. More activated substrates such as dienyl esters undergo protonation ~ 20 times slower than aldehyde trapping. Therefore, the protonolysis of aryl dienes could be less favourable due to the decreased nucleophilicity of the Rh-allyl intermediate. The slow protonolysis of **4-13** could result in the formation of side products arising from allyl isomerization or β-hydride elimination.

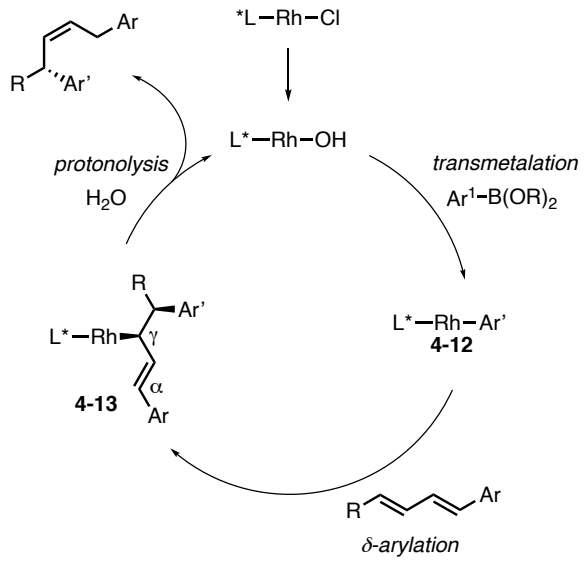


Fig. 4–8 Proposed mechanistic features of Rh-catalyzed δ-arylation of aryl dienes

Chapter 4 describes the Rh-catalyzed enantio-, and *Z*-selective δ-arylation of aryl dienes enabled by Rh-catalysts with chiral tetrafluorobenzobarrelene (tfb) ligands. This process is hindered by slow rates, presumably due to the rate determining protonolysis. This

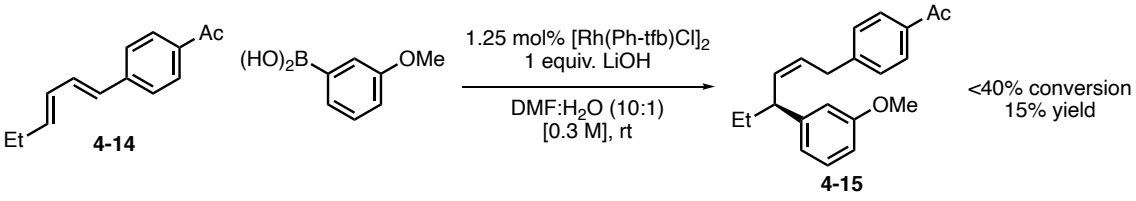
is overcome by using alcohols as the solvent, increasing the rate of this elementary step. Reaction optimization, preliminary scope, and mechanistic studies will be discussed.

4.2 Development of the Enantio-, and *Z*-Selective δ-Arylation of Aryl dienes via a Rh-Catalyzed Vinylogous Conjugate Addition of Aryl Boronic Acids

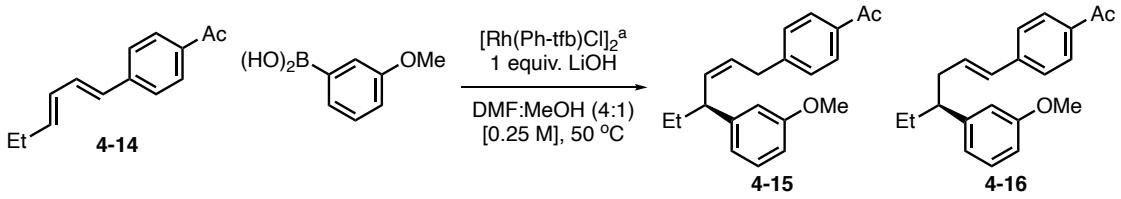
Starting from the conditions developed for the α,δ-difunctionalization,[158] using an aryl diene activated by a 4-acetyl group ($\sigma_p = 0.50$)[151] (**4-14**) and 3-methoxy phenylboronic acid (**4-15**) at room temperature, the target hydroarylation product **4-15** was generated in 15% yield (**Fig. 4–9a**). Other proton sources such as MeOH and trifluoroethanol performed similarly under these conditions. Taking a step back to consider how the reaction conditions could affect the rate of protonolysis of the Rh-allyl intermediate, MeOH and H_2O were separately examined as the proton source. The concentration of these proton sources was increased relative to DMF (4:1 instead of 10:1), and rection temperature was increased to 50 ºC (**Fig. 4–9**). The complete conversion of **4-14** occurred, forming 78% of **4-15** in >98:2 *Z*:*E*, and 89% *ee* when MeOH was used as the proton source (entry 1). H_2O resulted in lower conversions and yields while forming more side products when compared to MeOH (entry 2). Under both conditions the formation of an inseparable side product, which was tentatively assigned to be styrene derivative **4-16** (assigned based on closest literature example)[160] poses significant problems in isolation of the desired *Z*-akene product. This product likely forms through base catalyzed isomerization of the desired product. In attempts to reduce the amount of isomerization product, different solvent mixtures and bases were screened. LiOH was found to be the optimal base, and can be used in sub-stoichiometric amounts, however; using less does not reduce the amount of **4-16** that is formed (entry 3). Other bases, such as K_2CO_3

and Et_3N increased the rate of protodeborylation resulting in incomplete conversion of **4-14** and reduced yields of **4-15** (entries 4, 5). Other solvents typically used for conjugate addition reactions performed similarly to DMF, with reduced enantioselectivities while still forming **4-16** (entries 7, 8). Other structurally related tfb catalysts such as Me-tfb, and Bn-tfb provided lower conversions, yields, and enantioselectivities (entries 9, 10). The use of Fc-tfb (Fc = ferrocene) improved reactivity achieving full conversion of **4-14** in half the time with similar yields, but with reduced *ee* (entry 11). A follow-up solvent screen with $[Rh(Fc\text{-}tfb)Cl]_2$ and only MeOH (i.e., no co-solvent) at room temperature increased the yield (93%) and *ee* (90%) while eliminating the formation of undesired **4-16** (entry 12).

a. initial attempts at the Rh-catalyzed δ-arylation of aryl dienes



b. initial optimization of the Rh-catalyzed δ-arylation of aryl dienes



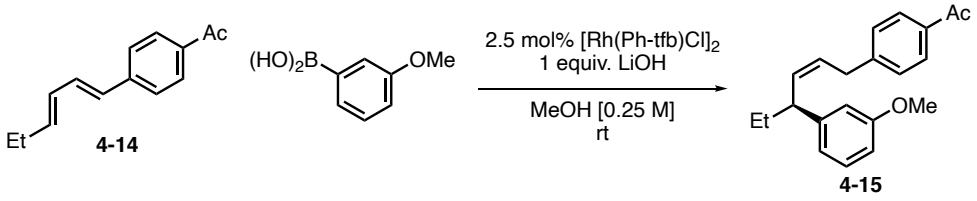
entry	deviation from above	conv (%)	yield (%)[b]	*ee (%)*[c]
1	**none**	**>98**	**78**	**89**
2	H_2O Instead of MeOH	88	42	nd
3	0.5 equiv. LiOH instead of 1	>98	75	nd
4	K_2CO_3 instead of LiOH	44[d]	38	nd
5	0.5 equiv. K_2CO_3 instead of LiOH	41[d]	32	nd
6	Et_3N instead of LiOH	20[d]	12	nd
7	Toluene instead of DMF	>98	74	86
8	Dioxane instead of DMF	86[d]	62	86
9	$[Rh(Me\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	78[d]	44	70
10	$[Rh(Bn\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	53[d]	25	73
11	$[Rh(Fc\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	>98	80	83
12	**same as 11, with 100% MeOH, @ rt**	**>98**	**93[e]**	**90**

0.05 mmol scale, **4-14**:$ArB(OH)_2$ = 1:2, [a] 1.25 or 2.5 mol%, [b]remainder of diene mass balance corresponds to the formation of **4-16**, [c] determined after hydrogenation with Pd/C in EtOAc with chiral HPLC [d] complete consumption of $ArB(OH)_2$ [e] no formation of **4-16**; **4-16** tentatively assignment is based on the closest literature example (reference 160)

Fig. 4–9 Reaction discovery and initial optimization of the Rh-catalyzed δ-arylation of aryl dienes

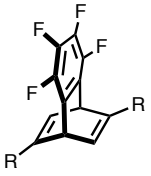
With the identification of a better solvent for the reaction, an additional catalyst screen was performed under these conditions to probe whether other Rh-precatalysts could provide increased enantioselectivity. **Table 4–1** provides an overview of the catalyst screening experiments. Ph-tfb was chosen as the optimal catalyst, forming **4-15** with 78% yield and 94% *ee* (entry 1), Fc-tfb is more reactive than Ph-tfb and provides increased yields,

however; the enantioselectivity was 91% (entry 2). Other related tfb ligands resulted in fast protodeborylation, decreasing conversions and yields (entries 3, 4). Structurally related Ph-bod provided lower yield with 77% *ee* (entry 5). Rawal-type methyl ester diene ligand was not a competent ligand for this reaction. Using Ir-based precatalyst $[Ir(Ph\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$ resulted in a lower conversion of **4-14**, a mixture of products, and only 18% yield and 75% *ee* of **4-15**.

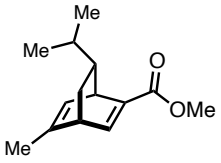


entry	deviation from above	conv (%)	yield (%)	*ee (%)*[a]
1	**none**	**>98**	**78**	**94**
2	$[Rh(Fc\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	>98	93	91
3	$[Rh(Me\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	13[b]	4	nd
4	$[Rh(Bn\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	31[b]	16	nd
5	$[Rh(Ph\text{-}bod)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	82	55	77
6	$[Rh(\mathbf{L1})Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	40	18	71
7	$[Ir(Ph\text{-}tfb)Cl]_2$ instead of $[Rh(Ph\text{-}tfb)Cl]_2$	50	18	75

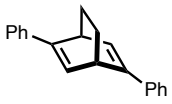
0.1 mmol scale, **4-14**:$ArB(OH)_2$ = 1:2, [a] determined after hydrogenaton with $RhPPh_3Cl$ in MeOH with chiral HPLC



R = Ph (Ph-tfb)
R = Bn (Bn-tfb)
R = Me (Me-tfb)
R = Fc (Fc-tfb)



L1

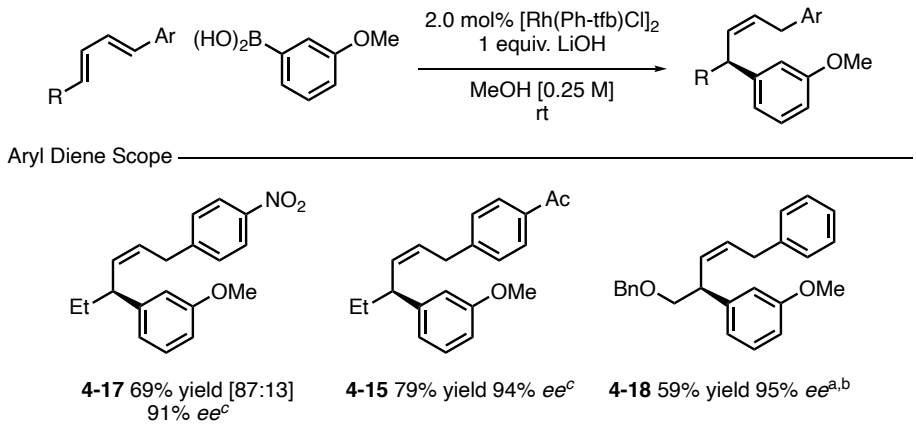


Ph-bod

Table 4–1 Catalyst screen for the Rh-catalyzed δ-arylation of aryl dienes

The preliminary scope of the reaction with respect to the electronics of the aryl group has been explored. **Table 4–2** provides an overview of aryl dienes with different levels of electronic activation under otherwise standard conditions. Aryl dienes activated by a 4-nitro

group ($\sigma_p = 0.78$)[151] provided hydroarylation product in 69% yield and 91% *ee*. This was the only substrate with less than excellent *Z*:*E* selectivity (**4-17**, *Z*:E = 87:13). The standard 4-acetyl functionalized product (**4-15**) was isolated in 79% yield with 94% *ee*. An aryl diene substrate activated by a simple phenyl group ($\sigma_p = 0$)[151] provided 59% yield with 95% *ee* when the reaction was run at 40 ºC (**4-18**). This increase in temperature resulted in the formation of 7% of the undesired styrene side product. Elimination of this side product may occur if this substrate is used with the more reactive $[Rh(Fc\text{-}tfb)Cl]_2$ catalyst at lower temperature. The OBn-group at the 5-position of this substrate may play a role in reactivity and alternative substrates will be explored to confirm the impact of arene electronic on the rates and selectivities of the hydroarylation process. Products substituted with ethyl groups in the δ-position require hydrogenation for determination of *ee* by chiral HPLC.



Unless noted yields are of isolated materials under standard conditions. Unless noted *Z*:*E*>98:2, lower values are indicated in square brackets. Diene:$ArB(OH)_2$ = 1:2. [a]reaction ran at 40 °C, [b]contains 7% styrene, [c]determined after hydrogenation with $Rh(PPh_3)_3Cl$

Table 4–2 Aryl diene scope of the Rh-catalyzed δ-arylation of aryl dienes.

In the absence of mechanistic studies, the optimization and scope examples provide insight into the mechanism. First, MeOH outperforms H_2O as a proton source, which could suggest that an inner sphere protonation is occurring since MeOH is more Lewis basic and would have more favourable coordination to the Lewis acidic Rh species in a 6-membered ring transition state. Comparing the conversion rates of the three scope examples, the most activated 4-nitro substrate (σ_p = 0.78)[151] reacts the fastest while the least electronically activated phenyl substrate (σ_p = 0)[151] reacts the slowest and requires an increase in reaction temperature. The nucleophilicity of each Rh-allyl species is expected to have the opposite trend, where the Rh-allyl generated from the 4-nitro substrate is the least nucleophilic and the Rh-allyl generated from the phenyl substrate is the most nucleophilic. Finally, if we consider how the substrate changes the Lewis acidity of Rh in the Rh-allyl intermediates, Rh-allyl generated from the 4-nitro substrate would result in the Rh being the most Lewis acidic, while the Rh-allyl generated from the phenyl substrate would result in the Rh with lower Lewis acidity (**Fig. 4–10**). Assuming the rate determining step of the process is the protonation of the Rh-allyl intermediate,[158] it would be expected that if an outer sphere mechanism was operative, the rates of reaction would increase with increased nucleophilicity. If the mechanism involves an inner sphere protonation, the rate of reaction could increase with the increased Lewis acidity of the Rh-allyl intermediate. This is expected due to more favourable binding of the Lewis basic MeOH. The high *Z*-selectivity observed, where the alkyl group is oriented in a pseudoaxial position, to minimize steric interaction with the Ph-tfb ligand (**Fig. 4–11**, **4-19**) supports an inner sphere mechanism. The reduced *Z*-selectivity observed in the case of the 4-nitro aryl diene is attributed to the increased Lewis acidity of the Rh species. This increased Lewis acidity increases the strength of the Lewis

acid-base interaction between MeOH and Rh. Due to the reduced distance between these two species in the 6-membered ring transition state, the ring-flipped product becomes more favourable, resulting in reduced *Z*-selectivity (**Fig. 4–11**, **4-19'**).

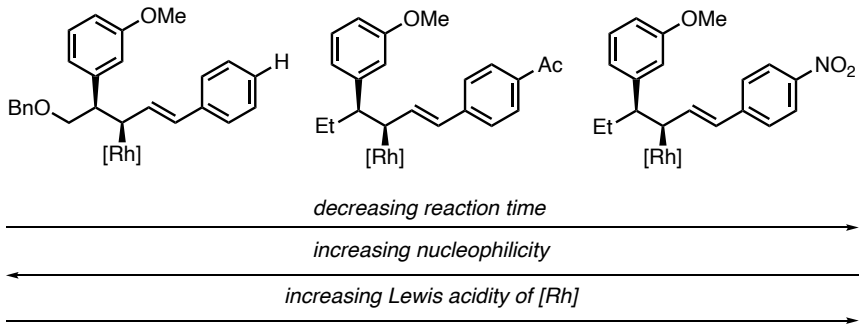


Fig. 4–10 Rate of reaction vs. nucleophilicity of Rh-allyl vs. Lewis acidity of [Rh]

Taken together, the above observations tentatively support an inner sphere protonolysis mechanism. A plausible complete mechanism is provided in **Fig. 4–11**. First, the Rh–Cl catalyst is converted to the active Rh–OMe catalyst, this species then undergoes transmetalation to form Rh-aryl **4-12**. Coordination and insertion of the diene into the Rh-aryl places the Ar' group in the δ-position and forms the Rh-allyl intermediate **4-13**. Upon coordination of MeOH in a 6-membered ring transition state (**4-19** or **4-19'**), protonolysis occurs to give the *Z*-δ-arylated product from **4-19** or *E*-δ-arylated product from **4-19'**.

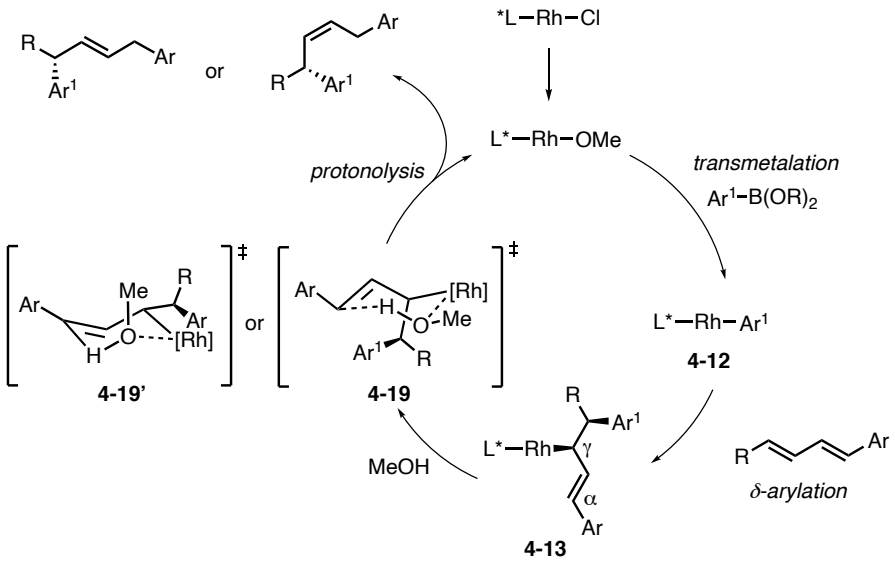


Fig. 4–11 Plausible mechanism of Rh-catalyzed δ-arylation of aryl dienes.

4.3 Conclusion and Future Work

The enantioselective δ-arylation of aryl dienes provides the first example of a Rh-catalyzed hydroarylation of aryl dienes. This reaction provides access to functionalized arenes with a *Z*-alkene, which would be difficult to prepare using established methodologies. This unit is primed for further stereoselective functionalizations to provide functionalized arenes with up to three contiguous stereocenters. Future work includes studying the range of electronics of the aryl activating group, as well as studying how the structure and electronics of the boronic acid affects rates and selectivities the process. Mechanistic studies to establish more concrete evidence for the mechanistic aspects of the process and product derivatizations to demonstrate the utility of the reaction are also necessary.

4.4 Procedures and Characterization

General Considerations

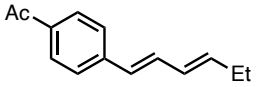
Unless noted, all reactions were conducted under inert atmosphere employing standard Schlenk technique or using a N_2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed as described by Still and co-workers[118] (SiliaFlash P60, 40–63 μm, 60Å silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250 μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. Preparatory HPLC was accomplished via an Agilent 1260 Infinity system under reverse-phase conditions. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian VNMRS 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal ($CDCl_3$:dH = 7.26 ppm, dC = 77.06 ppm) (DMSO-d_6: dH = 2.49 ppm, dC = 39.50). Chiral HPLC analysis was accomplished on a normal-phase Agilent 1260 system with Daicel CHIRALPAK IA, IB, IC, or IG columns (4.6 x 150mm, 5 mm particle size), or Regis Whelk O1 column (4.6 x 25 mm, 5 mm particle size) with UV detection using a standard diod-array-detector. FTIR spectra was obtained using a Thermo Nicolet 8700, with attached Continuum FTIR Microscope. Optical rotation data was obtained using a Perkin Elmer 241 Polarimeter at 589 nm at 25 °C, using a 10 cm path-length cell. Unless otherwise noted, quantitative ^{1}H NMR yields were determined from crude reaction mixtures using dibenzyl ether as an internal standard. Absolute stereochemistry is assigned by analogy to previous iteration of chemistry.[158] The *Z*-configuration of the products

were determined through 1D-ROESY. Compound **4-16**[160] was tentatively assigned based on the closest literature example on the basis of ^{1}H NMR.

General Procedure A: In an atmosphere controlled glovebox, [Rh((*S,S*)-Ph-tfb)Cl]$_2$ or [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (6.2 mg, 0.006 mmol, 0.02 equiv.) was weighed into a 1 dram vial. Diene (0.30 mmol, 1.0 equiv.), aryl boronic acid (0.60 mmol, 2.0 equiv.), and internal standard (dibenzyl ether or trimethoxy benzene) were weighed into a separate 1 dram vial. MeOH (800 μL) was added to the vial containing substrates, and the solution was transferred to the vial containing the catalyst using MeOH to rinse (2 x 200 μL). LiOH·H_2O (0.300 mmol, 12.6 mg, 1.0 equiv.) was weighed into a 0.5 dram vial and transferred to the reaction mixture. A stir bar was added into the mixture, the vial was capped with a PTFE-lined cap, taken out of the glovebox, and placed in an aluminum block at room temperature. The reaction was stirred at room temperature and reaction progress was monitored periodically via ^{1}H NMR by removing 5 μL and diluting with $CDCl_3$. Once the reaction reached >95% conversion, the solution was diluted with 60 mL of EtOAc, washed with 1M KOH (20 mL), and brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel chromatography.

General Procedure B: [product hydrogenation for HPLC analysis] In an atmosphere controlled glovebox, to a vial containing approx. 0.1 mmol of appropriate product was added $Rh(PPh_3)_3Cl$ (4.6 mg, 0.005 mmol, 0.05 equiv.) followed by MeOH (1.0 mL). A stir bar was added into the mixture, the vial was capped with a PTFE-lined cap, taken out of the glovebox, and placed in an aluminum block at room temperature. A balloon of H_2 (1 atm) was added to the vial, the vial was flushed with H_2 and allowed to stir at room temperature overnight under

a balloon of H_2. The reaction mixture is filtered through celite with EtOAc as the eluent, and then through a short silica gel plug with 20% EtOAc in hexanes. This product was used directly for HPLC analysis unless further derivatization is required.

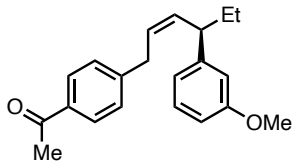


4-14 Prepared according to literature procedure[161] from corresponding alkyne (3.80 g, 19 mmol, 1.0 equiv.) Isolated in 87% yield, *EE*:*ZE* = 88:12 as a yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.86 (dd, *J* = 15.8, 10.6 Hz, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.25 – 6.19 (m, 1H), 5.99 – 5.93 (m, 1H), 2.57 (s, 3H), 2.22 – 2.16 (m, 2H) 1.08 – 1.04 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.4, 142.5, 139.6, 135.5, 132.3, 130.7, 129.3, 128.8, 126.1, 26.5, 26.0, 13.4;

HRMS (EI) calcd for $C_{14}H_{16}O$ $[M]^+$ 200.1196. Found 200.1202.



4-15 Prepared according to General Procedure A with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (6.2 mg, 0.006 mmol, 0.02 equiv.) from the corresponding diene (60.1 mg, 0.30 mmol, 1.0 equiv.), and 3-methoxyphenylboronic acid (91.2 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 88%, *Z*:*E* >98:2. Isolated in 79% yield, *Z:E* >98:2 as a colourless oil after purification by column chromatography (5% to 10% EtOAc in hexanes). 94% *ee* after derivatization according to General Procedure B.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.19 (m, 3H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.77 – 6.72 (m, 2H), 5.70 (tt, *J* = 10.7, 1.4 Hz, 1H), 5.59 (td, J = 10.7, 7.2

Hz, 1H), 3.79 (s, 3H), 3.57 – 3.46 (m, 3H), 2.57 (s, 3H), 1.83 – 1.73 (m, 1H), 1.73 – 1.63 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H);

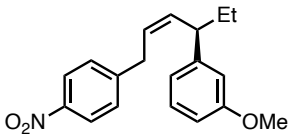
^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9, 159.8, 146.9, 146.7, 135.3, 135.2, 129.5, 128.6 (2), 127.1, 119.9, 113.5, 111.1, 55.2, 45.4, 33.9, 29.9, 26.6, 12.3;

HRMS (EI): calcd for $C_{21}H_{24}O_2$ $[M]^+$ 308.1771. Found 308.1775

IR ν (cm^{-1}) 3005, 2960, 2930, 2872, 2835, 1683, 1606, 1584, 1486, 1413, 1357, 1267, 1181, 1153, 1045, 957, 814, 779;

Chiral HPLC: Chiralpak IC column (1% IPA in hexanes, 1.5mL/min). t_r = 18.1 min (major), t_r = 20.3 min (minor);

$[\alpha]_D^{25}$ –108.59 (c = 0.56, $CHCl_3$)



4-17 Prepared according to the General Procedure with [Rh((*R,R*)-Ph-tfb)Cl]$_2$ (6.2 mg, 0.006 mmol, 0.02 equiv.) from the corresponding diene (61.0 mg, 0.30 mmol, 1.0 equiv.), and 3-methoxyphenylboronic acid (91.2 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 76%. *Z*:*E* = 89:11. Isolated in 69% yield, *Z:E* = 87:13 as a yellow oil after purification by column chromatography (1% to 3% EtOAc in hexanes). 91% *ee* after derivatization according to General Procedure B and nitro group reduction.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, J = 8.7 Hz, 2H), 7.27 – 7.19 (m, 3H), 6.83 – 6.71 (m, 3H), 5.75 (tt, J = 10.2, 1.6 Hz, 1H), 5.58 (dtd, J = 10.2, 7.5, 1.1 Hz, 1H), 3.79 (s, 3H), 3.57 – 3.46 (m, 3H), 1.84 – 1.63 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H)

Visible resonances of E isomer: δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 5.69 (ddt, *J* = 15.2, 7.9, 1.3 Hz, 1H), 3.45 (d, *J* = 6.6 Hz, 2H), 3.13 (q, *J* = 7.5 Hz, 1H), 0.86 (t, *J* = 7.5 Hz, 3H);

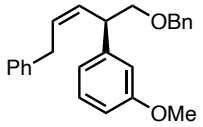
^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 148.6, 146.7, 136.1, 129.6, 129.2 (2), 126.3, 123.7, 119.8, 113.6, 111.0, 55.2, 45.5, 33.8. 30.0, 12.2;

HRMS (EI): calcd for $C_{19}H_{21}NO_3$ $[M]^+$ 311.1516. Found 311.1517.

IR ν (cm^{-1}) 3007, 2961, 2930, 2872, 2836, 1599, 1583, 1517, 1491, 1453, 1435, 1344, 1260, 1153, 1109, 1045, 1015, 971, 815, 741, 698;

Chiral HPLC: Chiralpak IG column (1% IPA in hexanes, 1.5mL/min). t_r = 14.0 min (major), t_r = 15.6 min (minor);

$[\alpha]_D^{25}$ –88.71 (c = 0.52, $CHCl_3$)



4-18 Prepared according to the General Procedure with $[Rh((R,R)\text{-Ph-tfb})Cl]_2$ (6.2 mg, 0.006 mmol, 0.02 equiv.) from the corresponding diene (75.1 mg, 0.30 mmol, 1.0 equiv.), and 3-methoxyphenylboronic acid (91.2 mg, 0.60 mmol, 2.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 60%. *Z*:*E* >98:2. Isolated in 59% yield, *Z:E* >98:2, *ee:* 95%, as a colourless oil after purification by column chromatography (1% to 3% EtOAc in hexanes).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.14 (m, 9H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.81 (dd, *J* = 2.9, 1.9 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.9 Hz, 1H), 5.76 – 5.68 (m, 2H), 4.53 (d, *J* = 2.3 Hz, 2H), 4.04 (dt, *J* = 7.5, 6.1 Hz. 1H), 3.77 (s, 3H) 3.71 (dd, *J* = 9.4, 6.5 Hz, 1H), 3.66 (dd, *J* = 9.4, 7.7 Hz, 1H) 3.49 (dd, *J* = 16.0, 7.1 Hz, 1H), (dd, *J* = 16.0, 7.1 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 144.0, 140.6, 138.4, 131.0, 130.1, 129.5, 128.5(2), 128.4(2), 127.6, 126.0, 120.2, 113.8, 111.8, 74.6, 73.1, 55.2, 44.1, 34.0;

HRMS (EI): calcd for $C_{25}H_{26}O_2$ $[M]^+$ 358.1927. Found 358.1927.

Chiral HPLC: Chiralpak IB column (1% EtOAc in hexanes, 1.5mL/min). t_r = 12.5 min (major), t_r = 13.3 min (minor);

Chapter 5 – Conclusions and Future Work

5.1 Conclusions

The metal-catalyzed addition of nucleophiles to electron-deficient dienes represents an underutilized tool for the generation of stereochemically complex molecules from simple, readily accessible starting materials. The work discussed in this thesis describes the development of new Rh-catalyzed δ-selective nucleophilic additions to electron-deficient dienes that generates a nucleophilic Rh-allyl intermediate that can be intercepted by nonproton electrophiles. After reactions were discovered and optimized, detailed mechanistic studies provided the foundation for the development of new Rh-catalyzed diene functionalization reactions.

The *Z*-selective reductive coupling of electron-deficient dienes with aldehydes generates *Z*-*syn*-homoallylic alcohols while using formic acid as a mild reductant (Chapter 2). This methodology represents an advancement from previous reported Rh-catalyzed reductive couplings of dienes[105-106] where pyrophoric BEt_3 is used as the terminal reductant. The highly reactive BEt_3 limits the functional group compatibility with respect to protic and reducible functionalities. The use of formic acid allows substrates with reactive functional groups that are not compatible with reactions that use highly polarized organometallic reagents as terminal reductants. Mechanistic studies indicate that the slow liberation of active catalyst and formation of the Rh-hydride followed by comparatively fast diene insertion and aldehyde trapping allow for the direct trapping of the Rh-allyl intermediate without undesirable isomerization events. The identification of the Rh-allyl intermediate has allowed

the expansion of this methodology to the addition of carbon-based nucleophiles rather than hydride nucleophiles.

The enantio-, diastereo-, and *Z*-selective α,δ-difunctionalization of electron-deficient dienes initiated by a Rh-catalyzed vinylogous conjugate addition of aryl boronic acids provides access to highly stereodefined enantioenriched *Z-syn*-homoallylic alcohols (Chapter 3). The increased catalytic activity of Rh-catalysts ligated by tetrafluorobenzobarrelene ligands allows for a wide range of electron-deficient dienes to be viable substrates for the process. The products contain three stereocenters separated by a *Z*-alkene unit that would be difficult to prepare in a stepwise approach. Stereoselective functionalization of the *Z*-alkene allows for the formation of linear products with up to five contiguous stereocenters. The mechanistic features of this reaction were leveraged to achieve high chemo- and stereoselectivity, particularly a relatively high reaction concentration and slight excess of aldehyde is required to outpace undesired Rh-allyl isomerization, that erodes the diastereoselectivity of the process. The Rh-allyl intermediate generated is uniquely suited for aldehyde allylrhodation and resistant to protonation. A more general understanding of the reactivity of Rh-allyl intermediates formed from δ-conjugate arylation should allow the use of alternative electrophiles in multicomponent reactions.

The *Z*-selective Rh-catalyzed δ-arylation of dienes activated by an aryl group provides enantioenriched arene products (Chapter 4). This reaction represents the first Rh-catalyzed conjugate addition to alkenes activated by an aryl group without strong activating groups. The use of more Lewis basic MeOH rather than H_2O allows for the inner-sphere protonation of the Rh-allyl intermediate, contrasting the reactivity of the Rh-allyl intermediate under conditions suited for α,δ-difunctionalization.

5.2 Future Work

The work described in this thesis provides the foundation for future exploration of new Rh-catalyzed δ-selective addition of nucleophiles to electron-deficient dienes. The most promising reaction platform for expansion of these methodologies is the further expansion of electrophiles to intercept a Rh-allyl intermediate generated through a Rh-catalyzed δ-arylation.

The work described in chapter 3 on the Rh-catalyzed α,δ- difunctionalization is currently limited to the trapping of aldehydes to generate *Z-syn*-homoallylic alcohols. Extension of this methodology to intercept the Rh-allyl nucleophile with alternative electrophiles providing alternate types of stereodefined *Z*-alkenes would be valuable. Other carbonyl-based electrophiles such as imines would complement the current methodology to form stereodefined *Z*-homoallylic amines. Imines with a wide range of protecting groups could be compatible under the rection conditions but the size of the protecting group and the electrophilicity of the imine must be tuned to undergo trapping with the Rh-allyl intermediate (**Fig. 5–1**).

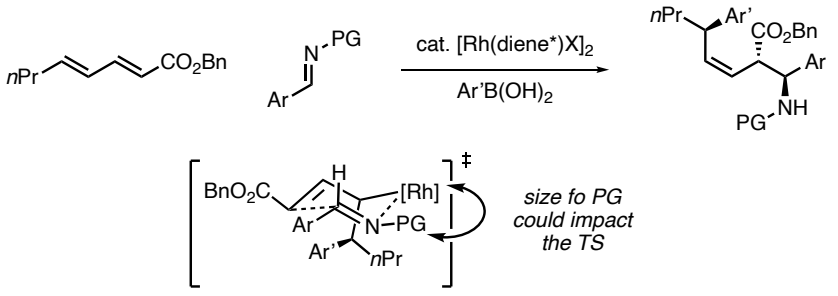


Fig. 5–1 Rh-catalyzed α,δ-difunctionalization with imines to provide enantioenriched *Z*-homoallylic amines

Another attractive electrophile that could potentially be intercepted by the proposed nucleophilic Rh-allyl intermediate is electrophilic allyl compounds derived from Ir- or Pd-catalyst systems. The generation of electrophilic allyl species derived from Ir[162] and Pd[163] are well precedented and have a variety of catalytic systems that utilize them in enantioselective catalysis. A dual Rh/Ir catalytic system could be employed to control the stereochemistry at the δ-position of the diene with different enantiomers of the Rh-diene catalyst while controlling the allyl stereocenters with the choice or the Pd or Ir catalyst allowing for the selective formation of compounds with three stereocenters (**Fig. 5–2**).

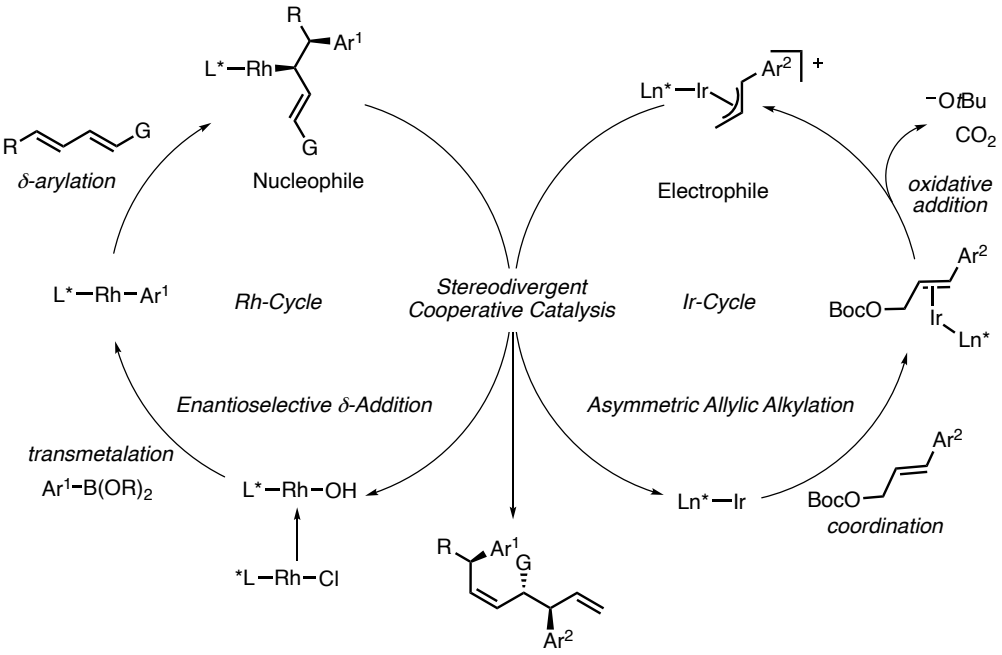


Fig. 5–2 Mechanistic proposal for Rh/Ir stereodivergent cooperative catalysis of nucleophilic Rh-allyl intermediates with electrophilic Ir-ally intermediates

Other aspects of the Rh-catalyzed α,δ-difunctionalization that could be leveraged into future projects involves the regiocontrol of a Rh-catalyzed conjugate addition to *E*,*Z*-dienes.

When using the *E*,*Z* geometrical isomer of the standard diene for mechanistic studies in the Rh-catalyzed α,δ-difunctionalization, it was observed that the addition occurs at the β-position with high regioselectivity, which contrasts with the exclusive δ-selectivity observed when the *E*,*E* geometrical isomer is used. The regioselectivity of the nucleophilic addition to electron-deficient dienes represents a significant challenge in the functionalization of dienes, therefore the demonstration of a geometry controlled, *Z*-retentive β-arylation of *E*,*Z* dienes would be a valuable contribution to the electron-deficient diene functionalization literature (**Fig. 5–3**, top). This geometry control could also be extended to the α,δ-difunctionalization of *E*,*E*,*Z* trienes to provide access a skipped *Z*,*Z* dienes (Fig. 5–3, bottom).

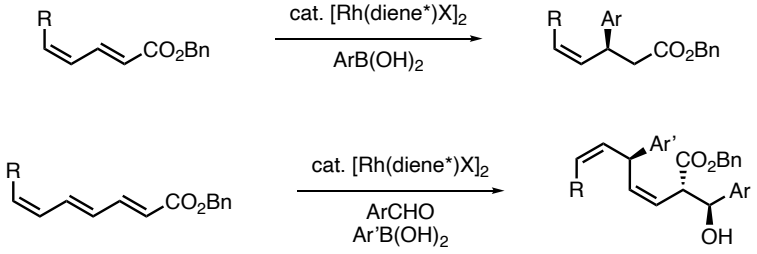


Fig. 5–3 *Z*-retentive arylations of *E*,*Z* and *E*,*E*,*Z* dienes.

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