Development of Rhodium Catalyzed Formic Acid Mediated *Z*-Selective Alkene Synthesis from Electron Deficient Dienes

by

Raphael Oluwagbemiga Dada

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry
University of Alberta

ABSTRACT

Z-Alkenes are important functional moieties in biological molecules and serve as versatile units for chemical transformations in synthetic chemistry. Synthetic strategies to readily generate these less thermodynamically stable alkenes with high regio-, chemo- and stereocontrol remain challenging, as these methods require stoichiometric main-group activators or are poorly tolerant of reactive functional groups. Selective hydride addition to electron deficient dienes and their use as pronucleophiles in reductive coupling processes can serve as an alternative to the already existing strategies. This thesis describes the development of a new chemo-, regio-, and stereoselective synthesis of *Z*-alkenes from electron deficient dienes mediated by formic acid using Rh-catalysis.

PREFACE

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

The Rh-catalyzed formic acid mediated *Z*-selective reduction of electron deficient dienes described in Chapter 2 was published as Raphael Dada, Zhongyu Wei, Ruohua Gui and Rylan J. Lundgren *Angew. Chem. Int. Ed*. **2018**, *57*, 3981–3984. Reaction discovery, optimization, mechanistic, kinetic and scope studies are my original work. Zhongyu Wei assisted with optimization for dienamides, scope studies including complex substrates examples, and product derivatization. Ruohua Gui conducted effect of diene geometry experiments.

The *Z*-selective Rh-catalyzed reductive coupling of electron deficient dienes and aldehydes mediated by formic acid described in Chapter 3 was published as Christopher Cooze, Raphael Dada and Rylan J. Lundgren *Angew. Chem. Int. Ed*. **2019**, *58*, 12246–12251. Kinetic studies, product derivatization, synthesis of intermediate to glucagon receptor antagonist, part of scope and mechanistic studies are my original work. Reaction discovery, optimization, mechanistic and scope studies were conducted by Christopher Cooze.

The *Z*-selective Rh-catalyzed reductive coupling of electron deficient dienes and imines mediated by formic acid described in Chapter 4 is currently being developed. Reaction discovery, optimization and scope studies are my original work. Ruohua Gui conducted preliminary reaction optimization. Lars Ross assisted with regioselectivity determination.

DEDICATION

This thesis is dedicated to the loving memory of my father, Ebenezer Olujimi Dada. Your fatherly love and encouragements are greatly missed.

ACKNOWLEDGEMENTS

I thank the Almighty God in whom "we live, move and have our being" (Acts 17:28). Thanks to God for the strength and grace through graduate school. Indeed, a man can receive nothing except it be given him from heaven.

A special thank you to Dr. Rylan J. Lundgren. The grooming and mentoring over the last five years have been phenomenal. Thank you for all the personal commitments to my growth. You didn't give-up on me and for that I will forever be grateful. All the drillings in your office are memories I will treasure for the rest of my life. Did you ever notice why I never refer to you by your first name as others?

To members of the Lundgren group, past and present, you all are greatly appreciated. Thanks to Bryce Thomas for training me in the lab and coming to my rescue when the computer I brought from home crashed. I still wonder why you opted for chemistry instead of computer science with your dexterity with machines. Sharing the lab with you and Jenner Lakusta at the beginning of my graduate studies was a rewarding period in terms of knowing short-cuts to locating things in the lab. I'd like to specifically thank Zhongyu Wei, Christopher Cooze, Ruohuo Gui and Lars Ross for your help on our projects. To high school (WISEST) students; Amy Wohlgemuth and Clara Vicera, undergraduate Toni Dimaano, it was fulfilling to be your mentor during your stay with the Lundgren group. To exceptional Patrick Moon, Duanyang Kong, Erica Lui, Wes McNutt, Odey Bsharat, Mike Doyle, Qiqige Qiqige, Alex Gabbey, Markus Schoetz, Anis Fahandej-Sadi, Shengkang Yin, Heather Halperin, Ping Shen and Wenyu "Mac" Qian, it was great

having you as group mates and thank you for always offering to test the waters at our group outings in terms of ordering food first so I know what food is best for my taste buds.

My gratitude also goes to members of my supervisory committee, Prof. Derrick Clive and Prof. Steve Bergens for their constant support and advice these past years. To the mass-spectrometry facilities staffs, Dr. Randy Whittal, Dr. Angelina Morales-Izquierdo, Jing Zheng, Bela Reiz; NMR facilities staffs, Dr. Ryan McKay, Mark Miskolzie, and Nupur Dabral; analytical and instrumentation facilities staffs, Wayne Moffat and Jennifer Jones; machine shop staffs, Dirk Kelm, Vincent Bizon, Paul Crothers and Dieter Starke; and Glassbower Jason Dibbs, thank you for all the assistance in the past five years. Special thanks to Paul Crothers for the help in getting a new guitar and the gift of a combo. To every of my friends in the department especially the BSOC 2019 organizing committee members, chemical stores staffs, chemistry general office staffs especially Esther Moibi and Beverly Bochon, thank you for being so wonderful. Special thanks to Dr. Yoram Apelblat, Dr. Hayley Wan and Connor Part for guidance on how to be a better TA.

Finally, a special gratitude to my wife, Oluwatobi Dada. Thank you for your unwavering support and understanding for all the times I had to be late coming home. Especially during the time of writing this thesis, for offering to come pick me up from the department in the middle of the night. I promise to continue to love you and our wonderful kids, Morireoluwa and Morayooluwa always. To my mum and siblings, God bless you always for always being supportive.

Table of Contents

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND SYMBOLS USED

p-ABSA	4-acetamidobenzenesulfonyl azide
atm	atmosphere
Ar	generic aryl moiety
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bpin	pinacol boronic ester
$B_2(pin)_2$	bis(pinacolato)diboron
*n*BuLi	butyllithium
°C	degrees Celsius
[cat]	generic catalyzed
COD	1,5-cyclooctadiene
COE	cyclooctene
Cy	cyclohexyl
δ	chemical shift
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dCypp	1,3-bis(dicyclohexylphosphino)propane
DIPEA	diisopropylethylamine

DMF	*N*,*N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
EDCl	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
Hex	hexane (mixture of isomers)
HOSA	hydroxylamine-*O*-sulfonic acid
HRMS	high resolution mass-spectroscopy
*i*Pr	*iso*-propyl
L	generic ligand
LDA	lithium diisopropylamide
LiAH	lithium aluminium hydride
[M]	generic metal complex
Me	methyl
MeCN	acetonitrile
Moc	methyloxycarbonyl
MTBE	methyl *tert*-butyl ether
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NEt_3	triethylamine

NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
*n*Pr	propyl
OAc	acetate
Ph	phenyl
ppm	parts per million
PTFE	polytetrafluoroethylene
R	generic group
rt	room temperature
*t*Bu	*tert*-butyl
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Tf	trifluoromethanesulfonate
Ts	4-toluenesulfonyl
UV	ultraviolet
wt	weight
X	generic halide

Chapter 1 – Introduction

1.1 General Introduction

Alkenes are an important functional group in organic chemistry and serve as useful building blocks in chemical synthesis. Feedstock alkenes derived from petrochemicals are converted to many commodity and fine chemicals such as carboxylic acids, ketones, aldehydes, alcohols, and amines by oxidation or hydrofunctionalization.[1-6] New stereogenic centers can be generated by enantioselective catalysis utilizing processes such as asymmetric hydrogenation or oxidation of alkenes.[7-10] These are among the most widely-relied upon techniques in enantioselective synthesis. Due to their wide spanning use, improved synthetic methods for the preparation of alkenes will have a positive impact on many areas of applied organic synthesis including drug discovery, manufacturing and fine chemical synthesis.

1,2-Disubstituted and more highly substituted alkenes can exist as two possible stereoisomers; *E*-alkene or *Z*-alkene isomers. To specify the geometry of the alkene, Cahn-Ingold-Prelog (CIP) priority rules can be used.[11] By the CIP priority rules, atoms at the ends of the double bond can be ranked based on the atomic number. If the atom with the highest ranking are on the same side of the double bond, the alkene geometry is defined as *Z*-alkene. If on opposite sides, the alkene has an *E*-geometry. The same principle applies to 1,2-disubstituted alkenes with other substituent groups by comparing the atomic number at the earliest difference.

The *E*/*Z* geometry adopted by an alkene often has a direct and significant impact on the physical property, chemical reactivity, and in some cases biological activity of alkene containing molecules as outlined in **Fig. 1-1**.[12] Synthetic methods to generate

alkenes can often result in a mixture of *E*- and *Z*-isomers. Separation of these mixtures can be challenging due to similar boiling points and affinity for stationary phases used for chromatography. Thus, stereocontrol in alkene synthesis remains an important goal in synthetic chemistry.

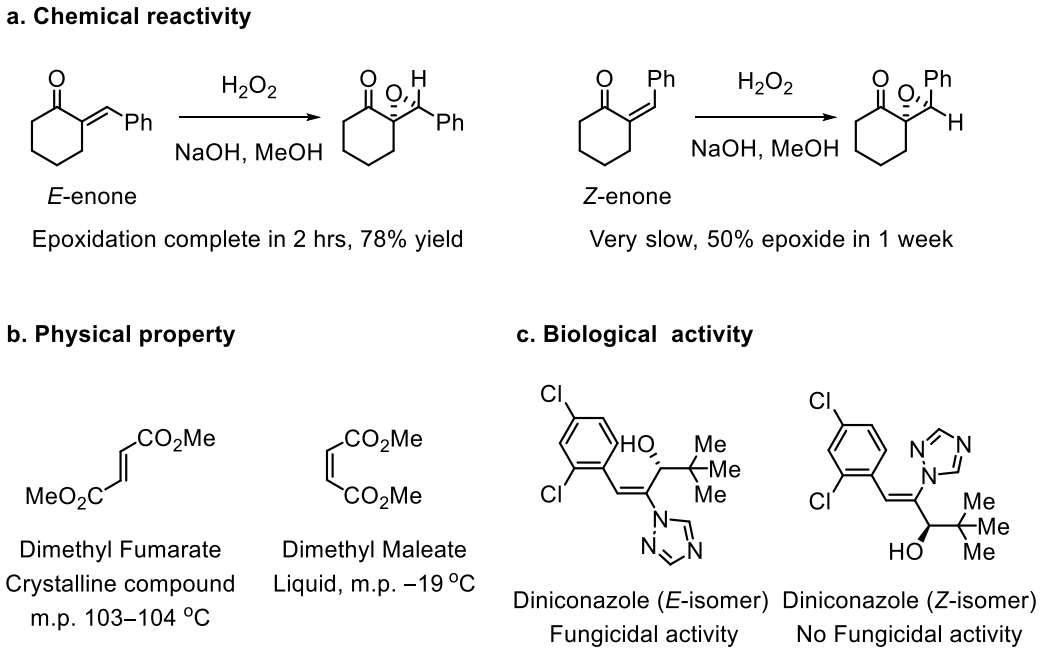


Fig. 1-1 Impact of geometry on properties of alkenes.

1.2 Stereoselective Synthesis of *Z*-Alkenes

The synthetic methods available for the preparation of 1,2-disubstituted *Z*-alkenes are fewer compared to the synthesis of 1,2-disubstituted *E*-alkenes because *E*-alkenes are more thermodynamically stable. Heat of hydrogenation of alkenes can be used to measure the stability of the carbon–carbon double bond. As outlined in **Fig. 1-2**, the heat of hydrogenation of *E*-but-2-ene (–115.5 $kJmol^{-1}$) is more than the heat of hydrogenation of

Z-but-2-ene (–119.6 kJmol^{-1}). The more positive the heat of hydrogenation indicates a more stable alkene. This is the general case for most simple 1,2-disubstituted alkenes.

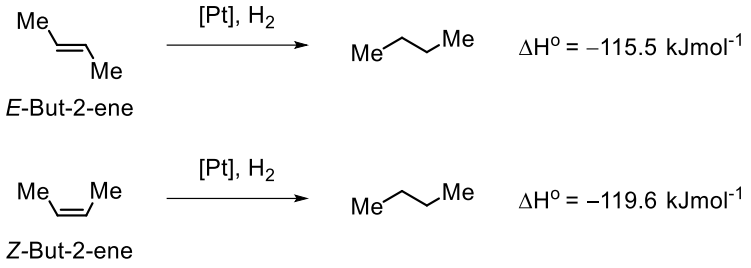


Fig. 1-2 Heat of hydrogenation of *E*- and *Z*- but-2-ene.

Many existing methods for the stereoselective synthesis of *Z*-alkenes make use of modified protocols of available alkene forming reactions. These methods include carbonyl olefination, olefin metathesis, cross coupling reactions, and alkyne semi-reduction.[13] Stereocontrol often arises from modifying the nature of the starting material, the use of high energy reagents, application of specially designed catalysts, and/or modification of reaction conditions and workup procedures to favor kinetic pathways for the formation of *Z*-alkenes. In the context of this thesis, a brief overview of the most well-established methods to synthesize *Z*-alkenes is presented. A brief rationalization for stereoselectivity is provided along with some commentary on strengths and limitations.

1.2.1 Carbonyl Olefination

Carbonyl olefination is a synthetic method to make alkenes with high positional selectivity. It involves the reaction between aldehydes or ketones and phosphorus, silicon or sulfur containing olefination reagents to form a carbon–carbon double bond as shown

in **Fig. 1-3**.[14] The high regio- and stereoselectivity that can be achieved with carbonyl olefination has found applications in the synthesis of *Z*-alkenes. *Z*-Selective carbonyl olefination reactions include Wittig, Still-Gennari modified Horner-Wadsworth-Emmons and Peterson olefination reactions.

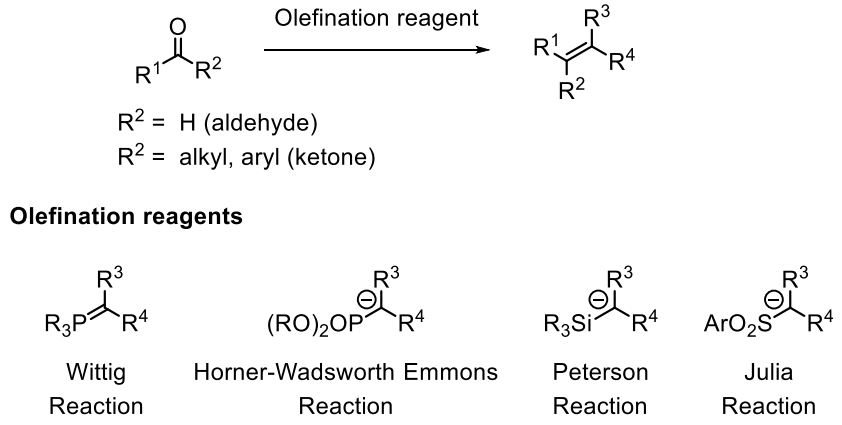


Fig. 1-3 General carbonyl olefination methods.

1.2.1.1 Wittig Reaction

Wittig olefination, a basis for a portion of the 1979 Nobel Prize in Chemistry, is the reaction of an aldehyde or ketone with a phosphorus ylide to synthesize a new alkene with the generation of phosphine oxide as the side product.[14-16] The Wittig reaction proceeds through the formation of an intermediate oxaphosphetane followed by stereospecific *syn*-elimination of the oxaphosphetane to give an alkene.[15, 16] Stereoselectivity of the reaction depends among other factors on the stability of the phosphorus ylide as outlined in **Fig. 1-4**.[17] The use of an unstabilized ylide gives *Z*-alkenes and *E*-alkenes are predominantly formed when a stabilized ylide is used.

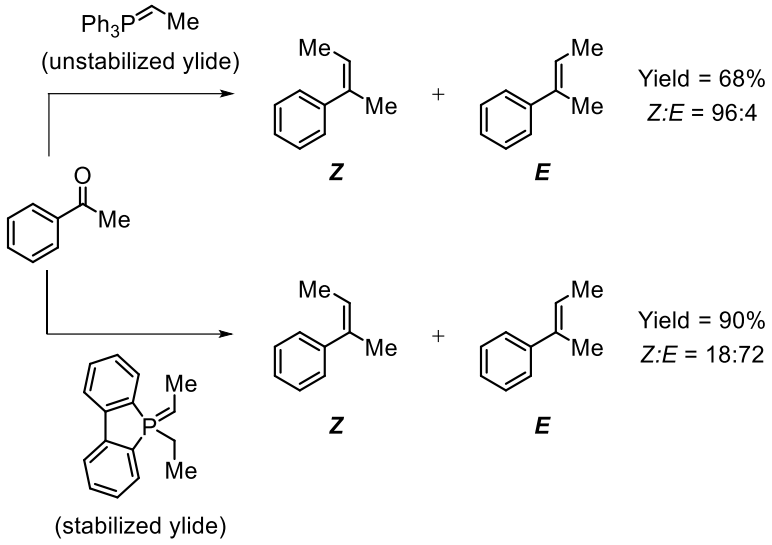


Fig. 1-4 Selectivity profile in Wittig reactions based on the stability of the ylide.

The stereoselectivity between *E*- and *Z*- product isomers is determined by the stereochemistry of the intermediate oxaphosphetane. Formation of the less stable *syn*-oxaphosphetane is preferred under kinetic conditions and it is promoted by use of unstabilized ylides (alkyl-substituted ylides), primary aliphatic aldehydes and unsymmetric ketones such as aryl-alkyl-ketones. The ylide and the carbonyl compound approach each other at a right angle such that steric repulsion between large substituents are minimized. Although, less stable, the *syn*-oxaphosphetane is formed quickly and stereospecific *syn*-elimination of the *syn*-oxaphosphetane produces the *Z*-alkene (**Fig. 1-5)**.[14] In the cases where the oxaphosphetane is stabilized by an electron-withdrawing group, for example when R^2 is an ester, the *E*-alkene product is generated.

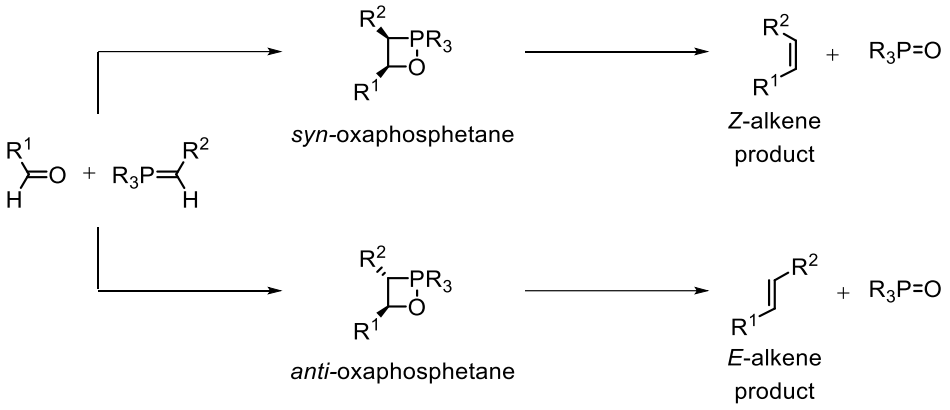


Fig. 1-5 Stereoselectivity of the Wittig reaction.

The Wittig olefination has proven to be one of the important methods for the stereoselective synthesis of *Z*-alkenes in natural products syntheses.[18] But the generation of stoichiometric amounts of phosphine oxide waste and the requirement of a strong base in the preparation of the phosphonium ylides remain major challenges. Reactive aldehyde functional groups are a requirement for the reaction in processes that generate 1,2-disubstituted products, a requirement which can complicate synthesis.

1.2.1.2 Horner-Wadsworth-Emmons (HWE) Reaction – Still-Gennari Modification

The Horner-Wadsworth-Emmons (HWE) reaction is the reaction of an aldehyde or ketone with a dialkyl phosphonate in the presence of a strong base to make predominantly *E*-alkenes.[19, 20] Compared to the classical Wittig stabilized ylides, the dialkyl phosphonates are more reactive and are applied in the olefination of sterically hindered ketones. The HWE reaction is particularly useful in the synthesis of α,β-unsaturated esters and ketones due to the requirement of the presence of an electron

withdrawing group to stabilize the dialkyl phosphonate carbanion. The dialkyl phosphate by-product is water soluble and can be easily removed by aqueous extraction.

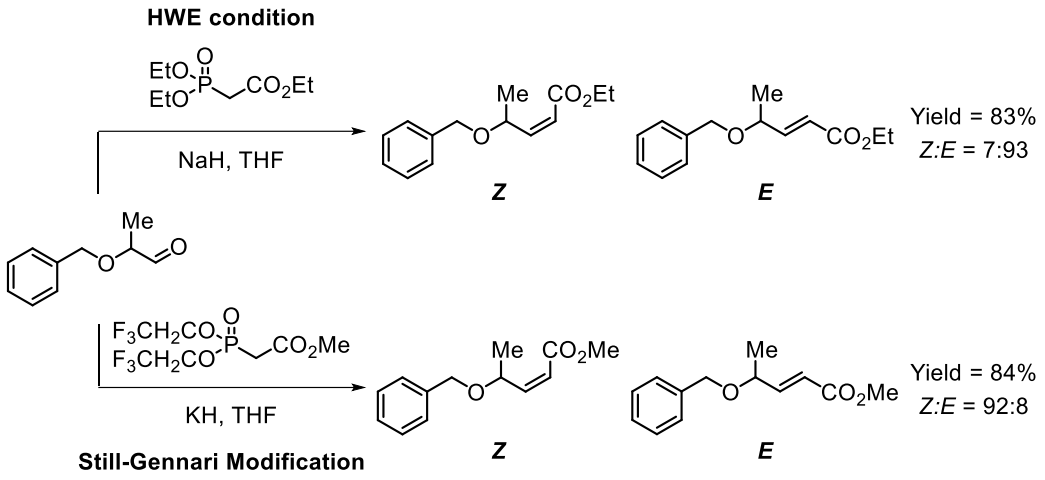


Fig. 1-6 Still-Gennari modification of the Horner-Wadsworth-Emmons reaction.

In a bid to improve the *Z*-selectivity of the HWE reaction to a synthetically useful level, the use of electrophilic bis(trifluoroethyl) phosphonate in the presence of a strong base has been employed in the Still-Gennari modified-HWE reaction **(Fig. 1-6)**.[21] The use of the electrophilic bis(trifluoroethyl) phosphonate improves the kinetic control of the reaction towards the formation of *Z*-alkenes by increasing the rate of elimination of the oxaphosphetane relative to equilibration with the initial aldol adduct. The kinetic selectivity of the initial addition step favors formation of a *syn*-oxaphosphetane in a way similar to use of unstabilized ylide in Wittig reaction. As the elimination step is fast and irreversible, the kinetic selectivity in the initial addition step, that favors formation of *syn*-oxaphosphetane to generate the *Z*-alkene product is maintained (**Fig. 1-7)**. The use of diarylphosphonate as the olefination reagent in the presence of Triton B

(trimethylbenzylammonium hydroxide) or sodium hydride as the base to generate *Z*-alkenes has also been reported by Ando.[22, 23] The preference for the generation of the *Z*-alkene is promoted by the steric hindrance of the aryl group in the diarylphosphonate to favor the kinetic pathway in the generation of the *syn*-oxaphosphetane intermediate.

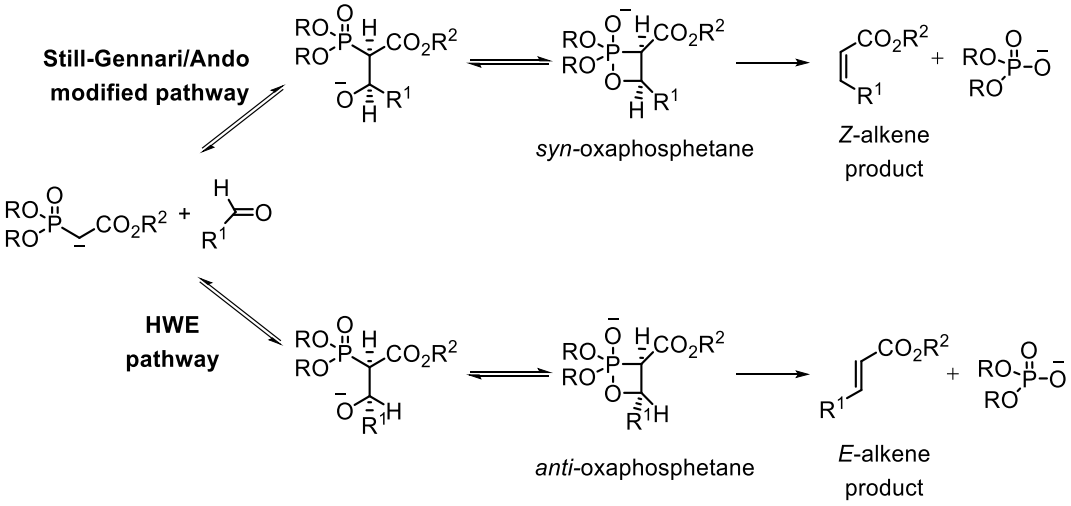


Fig. 1-7 Stereoselectivity in Still-Gennari modified HWE reaction.

1.2.1.3 Peterson Olefination

The preparation of alkenes by reacting a carbonyl compound with an α-silyl carbanion is known as the Peterson olefination.[24] The first step of the reaction is the addition of the α-silyl carbanion to the carbonyl compound to generate an intermediate β-hydroxysilane. The intermediate is formed as a mixture of diastereomers. Each diastereomer can be isolated and the formation of an alkene stereoisomer can be obtained by performing two different eliminations on the diastereomers as shown in **Fig. 1-8**. The elimination step can either be base or acid promoted depending on the stereochemistry of the β-hydroxysilane and on the expected alkene stereoisomer. *Z*-Alkenes are obtained from acid promoted

elimination of the *anti*-β-hydroxysilane and base promoted elimination of the *syn*-β-hydroxysilane. The ability to perform either acid or base promoted eliminations on different diastereomers to obtain a single alkene stereoisomer improves the yield and is a major advantage of the Peterson olefination reaction.

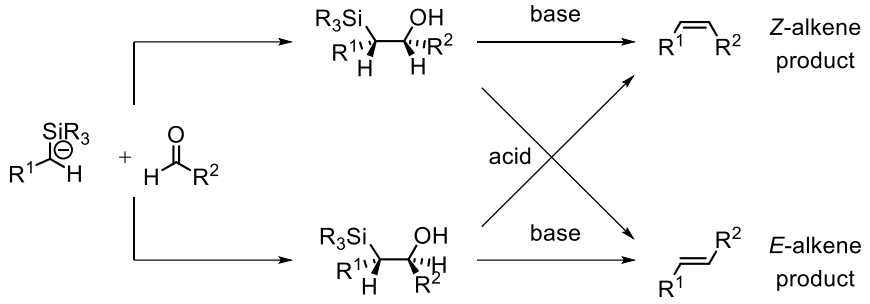


Fig. 1-8 Peterson olefination reaction.

Stereoselectivity can be understood from the mechanism of the elimination step (**Fig. 1-9)**. Acid-promoted elimination of the *anti*-β-hydroxysilane proceeds through protonation of the hydroxyl group followed by dehydration and desilylation via an *anti*-elimination step to form a *Z*-alkene. Stereocontrol to obtain a *Z*-alkene from the *syn*-β-hydroxysilane can be achieved by a base promoted elimination step in a *syn*- manner. After deprotonation of the hydroxyl group, elimination can proceed by 1,3-migration of the silyl group followed by elimination of trimethylsiloxide. Another possible route is the formation of 1,2-oxasiletanide followed by elimination of the trimethylsiloxide. The improved yield due to different elimination conditions to obtain the *Z*-alkenes from different diastereomers, high stereoselectivity of the elimination step and higher reactivity of the α-silyl carbanions towards carbonyl compounds compared to phosphorus olefination reagents are major benefits of the Peterson olefination reaction. Acid or base promoted elimination conditions

may promote other side reactions such as double bond isomerization. In addition, incompatibility with certain functional groups like protic functionalities under these acid- or base- promoted elimination conditions present some drawbacks in the Peterson olefination reaction.[25]

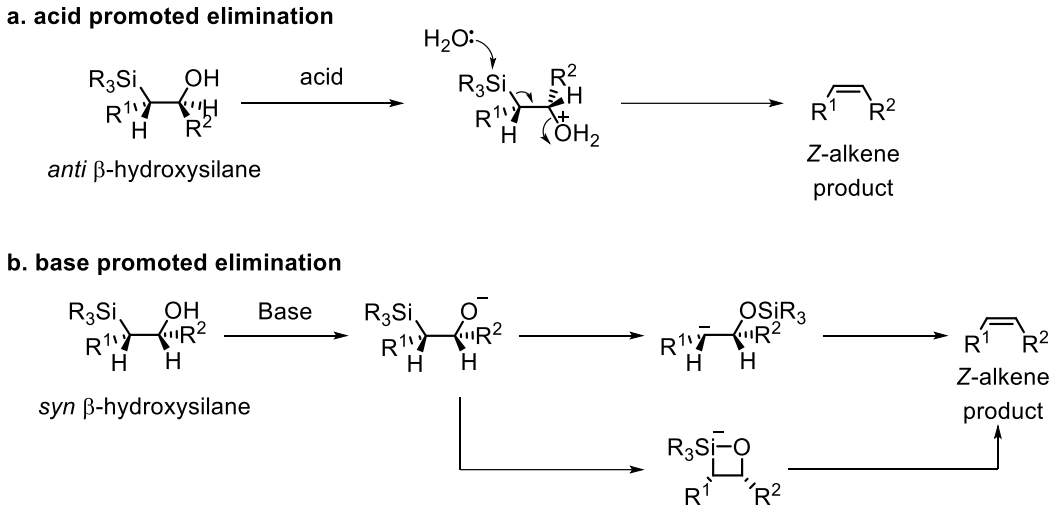


Fig. 1-9 Proposed mechanism for *Z*-selective elimination step of the Peterson reaction.

1.2.2. Alkyne Semi-Reduction

Alkyne semi-reduction is the hydrogenation of alkynes to form alkenes. The ability to stop the reaction once the alkene product is generated and prevent over reduction to the corresponding alkane is a key requirement to the success of the reduction process. 1,2-Disubstituted *E*- or *Z*-alkenes can be prepared by the stereoselective addition of a molar equivalent of hydrogen to an internal alkyne. The reaction can be catalyzed using heterogenous or homogenous catalysis.[26-28]

The most widely used catalyst for the stereoselective semi-reduction of internal alkynes to form 1,2-disubstituted *Z*-alkenes is Lindlar catalyst.[29] Lindlar's catalyst is a

heterogenous catalyst containing palladium (5–10 wt%) deposited on calcium carbonate, poisoned with a lead co-catalyst (lead acetate or lead oxide) and quinoline. The poisoning reduces catalyst activity to prevent further reduction of the *Z*-alkene product to the corresponding alkane.[29] Other stereoselective semi-reduction of alkynes to *Z*-alkenes using Ni, Rh, Pd, Cr, Zn, Ru and Ti catalyses have been reported.[27] The selectivity observed in these systems depends on kinetic factors and lack of catalyst interaction with the alkene product.[3]

The alkyne semi-reduction mechanism using Lindlar's catalyst is similar to the heterogeneous Pd-catalyzed hydrogenation of alkenes outlined in **Fig. 1-10**. The alkyne semi-hydrogenation is stereospecific and occurs through a *syn*-addition to give the corresponding *Z*-alkene. Semi-reduction with Lindlar's catalyst suffers from a number of drawbacks such as the partial isomerization of the *Z*-alkene product to the *E*-alkene and problems with reproducibility.[26] Careful optimization and control of reaction parameters are typically required to achieve high yields and selectivity in Lindlar-type alkyne hydrogenations.

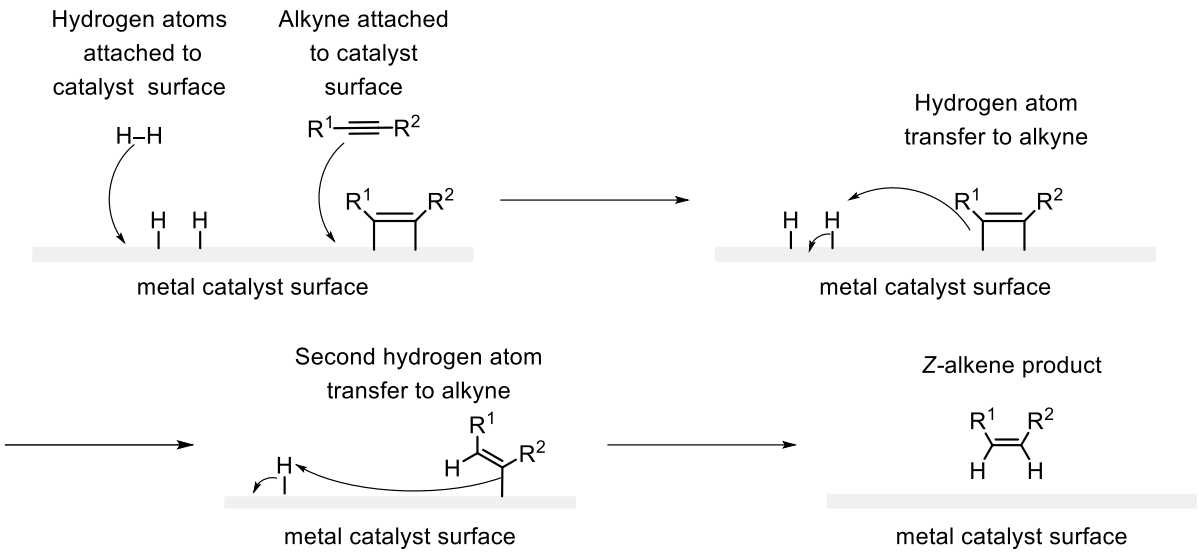


Fig. 1-10 Heterogeneous catalytic *Z*-selective hydrogenation of alkyne.

The homogeneous hydrogenation of alkynes has also been studied in detail. A representative example is discussed below. Elsevier and co-workers reported the stereoselective hydrogenation of alkynes using a homogenous zerovalent palladium catalyst supported by diamine ligands.[27] Under mild reaction conditions, a wide variety of alkynes can be reduced to the corresponding alkenes with high *Z*-selectivity. The rigidity of the diamine ligand enables correct orientation for the palladium to coordinate to the alkyne. Stronger coordination of the alkyne to the palladium center lowers the amount of alkene complex thereby lowering the over-reduction of the alkene product generated.[3, 27] The reaction proceeds via an alkyne coordination, followed by a stereodefined *syn*-hydropalladation of the alkyne. Subsequent reductive elimination generates the Z-alkene product (**Fig. 1-11**).

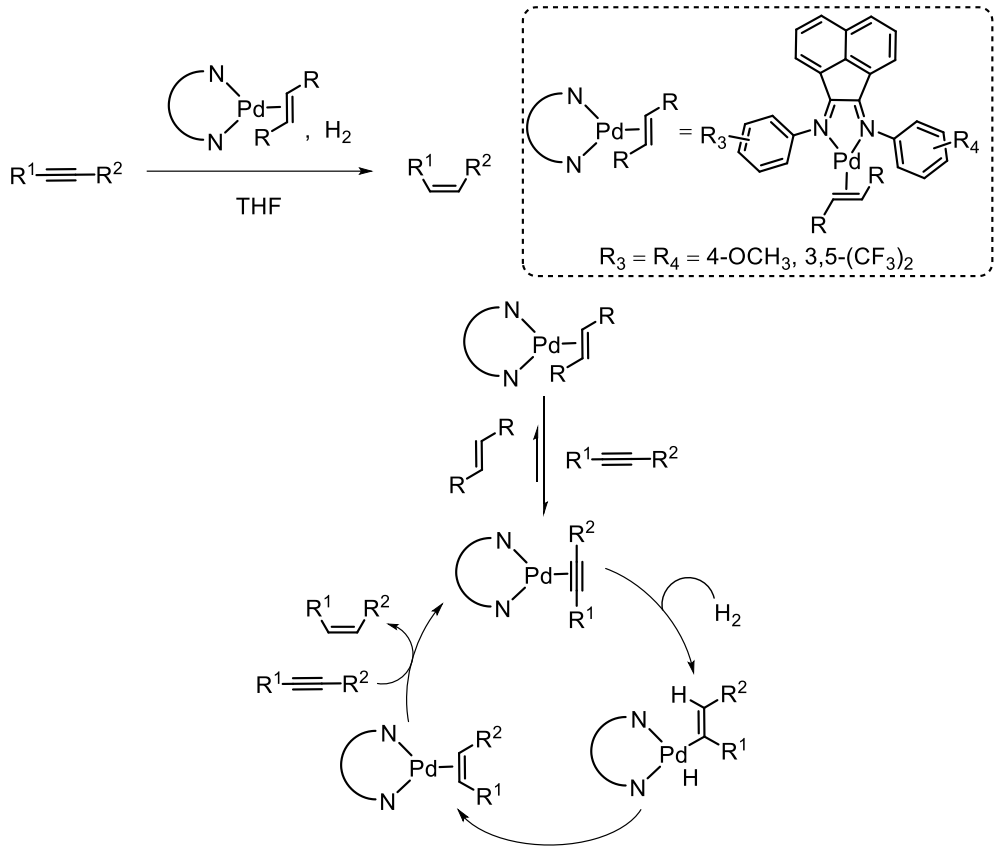


Fig. 1-11 Mechanism of the Pd^0 catalyzed *Z*-selective hydrogenation of alkynes.

1.2.3 Cross Coupling Reactions

Cross coupling reactions between an organohalide and organometallic reagents in the presence of a metal catalyst is a powerful tool for the formation of new carbon–carbon bonds in organic synthesis.[30,31] Transition metal catalysts such as Pd, Ni, Cu and Fe (among others) and organometallic reagents like organo- boron, magnesium, silicon, zinc, and tin species have been employed to effect cross coupling reactions.[30] Stereoselective cross coupling reactions to make either *E*- or *Z*-alkenes involve the use of an alkenyl metal species or alkenyl halide to be coupled with the corresponding organic halide or organometallic reagent respectively.

As the cross coupling step is usually stereospecific, the stereochemistry of the starting alkenyl metal species or alkenyl halide has to be established before the cross-coupling reaction (**Fig. 1-12a**).[32] As an example, cross coupling between a *Z*-alkenyl halide and an organometallic reagent proceeds through an oxidative addition of the *Z*-alkenyl halide at the metal. The oxidative addition is followed by transmetallation of the organometallic reagent, then reductive elimination to generate the product (**Fig. 1-12b)**.

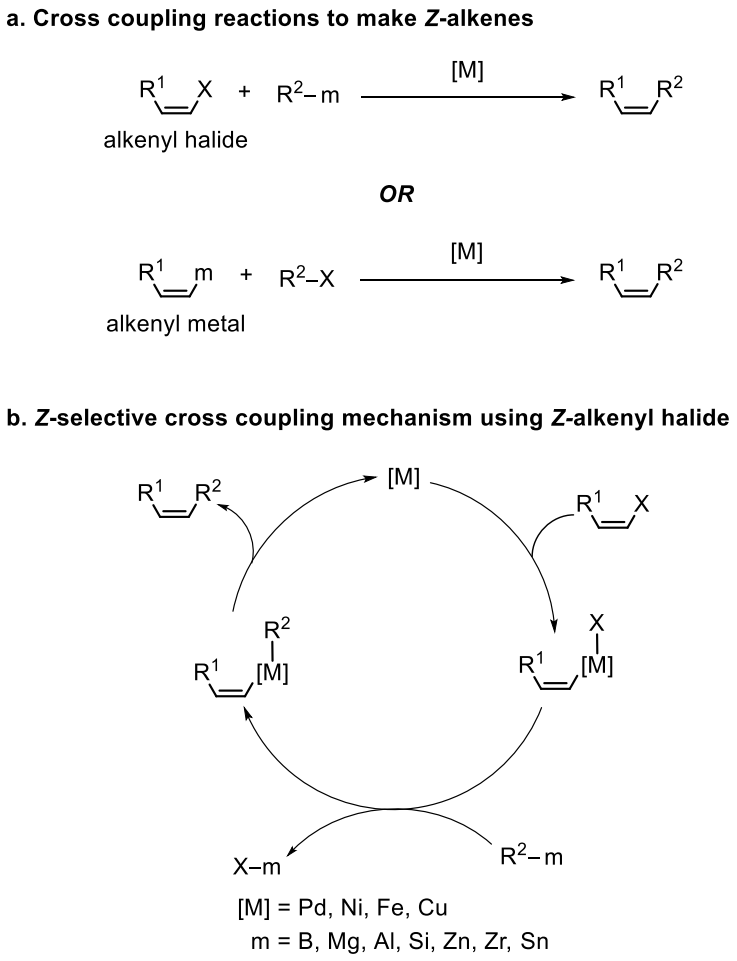


Fig. 1-12 General catalytic cycle for *Z*-selective cross coupling reaction.

Z-Selective cross coupling reactions for the synthesis of 1,2-disubstituted *Z*-alkenes uses either *Z*-alkenyl metal species or *Z*-alkenyl halides to be coupled with an organic halide or organometallic reagent respectively as the starting reagents. These *Z*-alkenyl species can be prepared from terminal alkynes through hydrometallation[33] and hydrohalogenation[34] reactions. For example, *Z*-alkenyl bromides have been synthesized via the hydroboration of terminal alkynes with catecholborane. The *trans*-alkenylcatecholboronic ester intermediate generated undergoes a *trans*-bromination and a subsequent *trans*-elimination to make a *Z*-alkenyl bromide (**Fig. 1-13a)**.[35] Rh-catalyzed hydroboration of terminal alkynes to make *Z*-alkenyl pinacolboronic esters has also been reported (**Fig. 1-13b)**.[36] Intramolecular Suzuki cross coupling reaction to synthesize *Z*-alkenes has been demonstrated in the synthesis of a 12-membered macrolactone intermediate in the natural product synthesis of oximidine II.[37] It involved a Pd-catalyzed cross coupling reaction between a *Z,Z*-dienyl bromide and an *E*-alkenyl potassium trifluoroborate to form an *E,Z,Z* conjugated triene as shown in **Fig. 1-13c**. With several available methods for cross coupling reactions, chemoselectivity is a major challenge in the presence of similar functionalities that can react under the same condition.

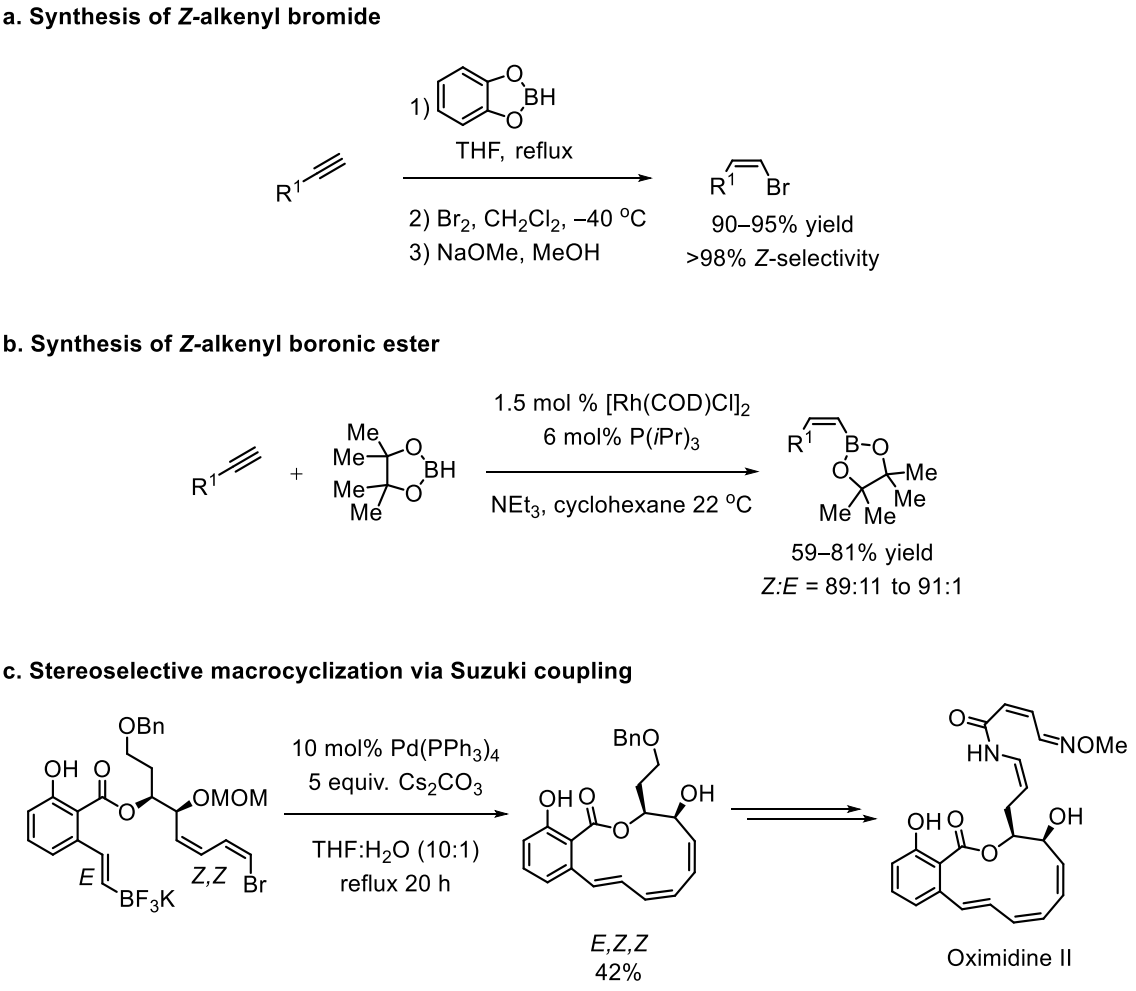


Fig. 1-13 Synthesis of *Z*-alkenyl bromide, *Z*-alkenyl pinacolboronic ester and application in *Z*-selective intramolecular cross coupling reaction.

1.2.4 Olefin Metathesis

The redistribution of the substituents of alkenes to generate a new alkene can be achieved through different classes of olefin metathesis such as cross, ring-opening and ring closing olefin metathesis reactions. Generally, olefin metathesis proceeds through a cycloaddition between an alkene and a metal alkylidene to form a metallacyclobutane. Cycloreversion of the metallacyclobutane either goes through a productive generation of a

new metal alkylidene and ethylene or the non-productive starting alkene and metal alkylidene generation. If productive, the new metal alkylidene center can react with a new olefin to generate the olefin metathesis product and the initial metal alkylidene as shown in **Fig. 1-14**.[38, 39] Several catalysts based on molybdenum (Mo), tungsten (W), and ruthenium (Ru) centers have been developed over the years to improve the Nobel Prize winning reaction.[39, 40] Given that the process is typically reversible at each mechanistic step, the product distributions obtained by olefin metathesis reactions are close to the thermodynamic ratio, and thus give *E*-1,2-disubstituted products.

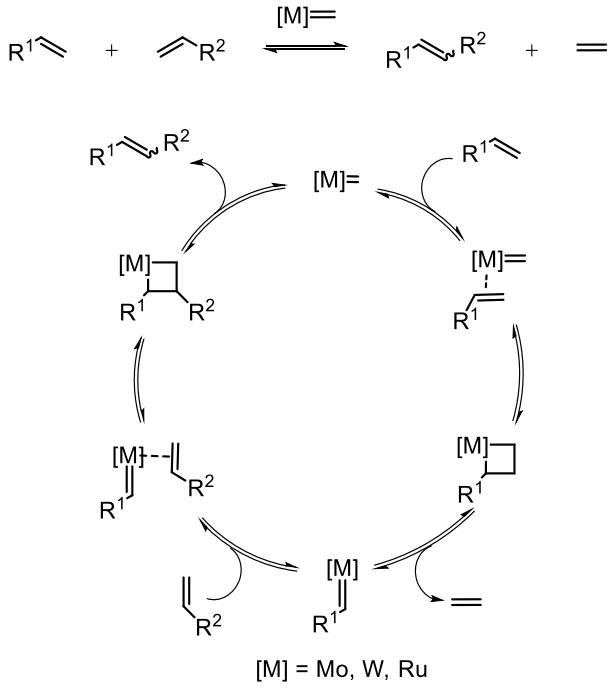


Fig. 1-14 General mechanism of olefin metathesis.

Based on an understanding of the structure and stability of substituted metallacyclobutanes, catalyst designs for *Z*-selective olefin metathesis has been developed (**Fig. 1-15**).[38] Initiated by Schrock and Hoveyda, the use of W and Mo monoaryloxide

pyrrolide (MAP) complexes has been applied in *Z*-selective cross-metathesis (CM) and ring-opening/cross-metathesis (ROCM) reactions.[40-44] Recently, ruthenium catalysts with cyclometalated *N*-heterocyclic carbene (NHC) ligands have also been reported by Grubbs and co-workers to be efficient *Z*-selective olefin cross metathesis catalysts.[38, 45]

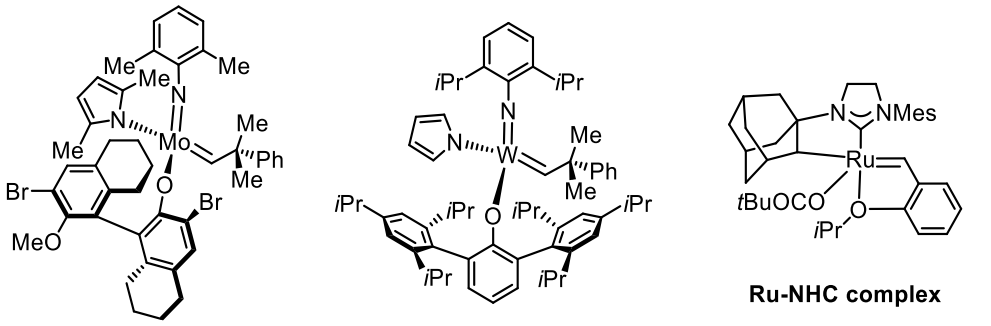


Fig. 1-15 Representative examples of *Z*-selective olefin metathesis catalysts.

The origin of *Z*-selectivity could be explained with the **Mo-MAP** complex as outlined in **Fig. 1-16**.[42] Large size differences between the freely rotating but bulky aryloxide and small imido group is a key factor. The large size difference favors the approach of the incoming alkene with substituents directed towards the imido ligand and reaction with the *syn*-alkylidene to form a *cis*-metallacyclobutane. Cycloreversion of the *cis*-metallacyclobutane forms the *Z*-alkene with the regeneration of the *syn*-alkylidene which goes back into the catalytic cycle. Ru-based catalyst systems operate by a similar principle, where a rigid, bulky ligand enforces the approach and cycloaddition of an incoming alkene such that its R-group lies along the same face of metallocyclobutane as the R-group of the Ru-alkylidene.[38] With the progress recorded in the *Z*-selective olefin metathesis, designing the catalysts for specific types of metathesis reaction – cross metathesis, ring-

opening/cross-metathesis, ring closing metathesis, is still required. In addition, the catalysts are usually substrate specific, thus making the catalysts design more difficult and this limits the generality of the *Z*-selective olefin metathesis process. The use of a *Z*-selective olefin metathesis catalyst for a particular type of metathesis reaction would lead to undesired products when used for another type of metathesis reaction.[42]

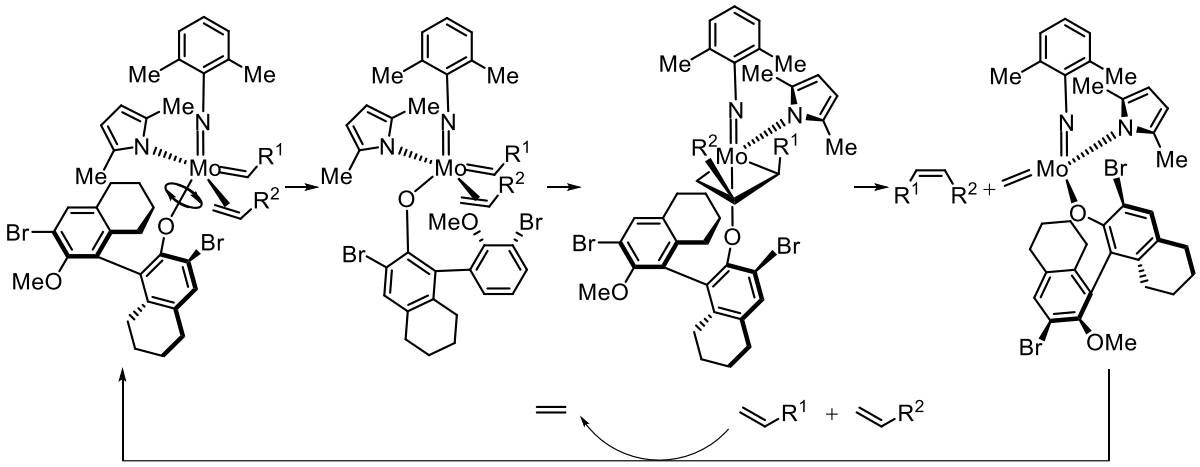


Fig. 1-16 Mechanism of Mo-catalyzed *Z*-selective olefin cross metathesis.

1.3 Conjugate Addition Reaction

The addition of a nucleophile to an electron deficient alkene is generally referred to as conjugate addition.[46] As a useful method in the synthesis of carbon–carbon and carbon–heteroatom bonds; transition metal- and organocatalyzed enantioselective conjugate addition processes have been developed and used in complex molecule synthesis.[47-49] Transition metal catalysts based on Cu, Rh, Fe, Ni, Zn, Ru, Ir and Pd catalysts are common catalysts used in conjugate addition reactions.[47] The use of organocatalysts such as cinchona-derived phase transfer catalysts and secondary or primary amine organocatalysts have also been reported.[48, 50, 51] Conjugate addition reactions have,

in limited cases, been developed to prepare *Z*-alkenes from dienes. Due to the importance of this topic to the thesis, a general overview of conjugate addition chemistry will be provided along with a discussion of known protocols to generate *Z*-alkenes by the technique.

Thanks to decades of research, a wide array of nucleophiles have found application in conjugate addition reactions including organometallic nucleophiles such as organo-magnesium, zinc, aluminum, boron, silicon, zirconium, tin, copper and lithium reagents.[46, 52] Non-organometallic nucleophiles like malonates, 1,3-dicarbonyls, nitroalkanes, aldehydes, ketones, amino acid derivatives and heteronucleophiles can also be used.[46] Electron deficient alkenes such as carbonyl-, cyano-, sulfonyl- and nitro- activated monoenes, dienes or trienes are suitable for conjugate addition.[53] Depending on the number of double bonds in the electron deficient alkene and other factors such as whether the bonds are in conjugation or not, addition can proceed through either 1,2- 1,4- or 1,6- addition pathways (**Fig. 1-17)**.

Selectivity (stereo- and regiocontrol) is an important goal in conjugate addition reactions because, different sites are prone to nucleophilic attack and can lead to different stereo- and regioisomers. In an electron deficient diene for example (**Fig. 1-17)**, conjugate addition is more problematic because, the extension of the π-system results in another site for nucleophilic attack.[46, 47] In this case, formation of the 1,4-conjugate addition product is favored compared to the 1,6-conjugate addition product because of the higher reactivity at the β-position compared to the δ-position. The δ-position is less prone to nucleophilic attack because of the poor electronic propagation through the conjugated system. To achieve selectivity control in conjugate addition reactions, steric crowding at the less

favored position to prevent nucleophilic attack or the designing of an activation mode to make the favored position more electropositive and prone to nucleophilic attack are the main strategies. These can be achieved through substrate or catalysts control.[46, 54]

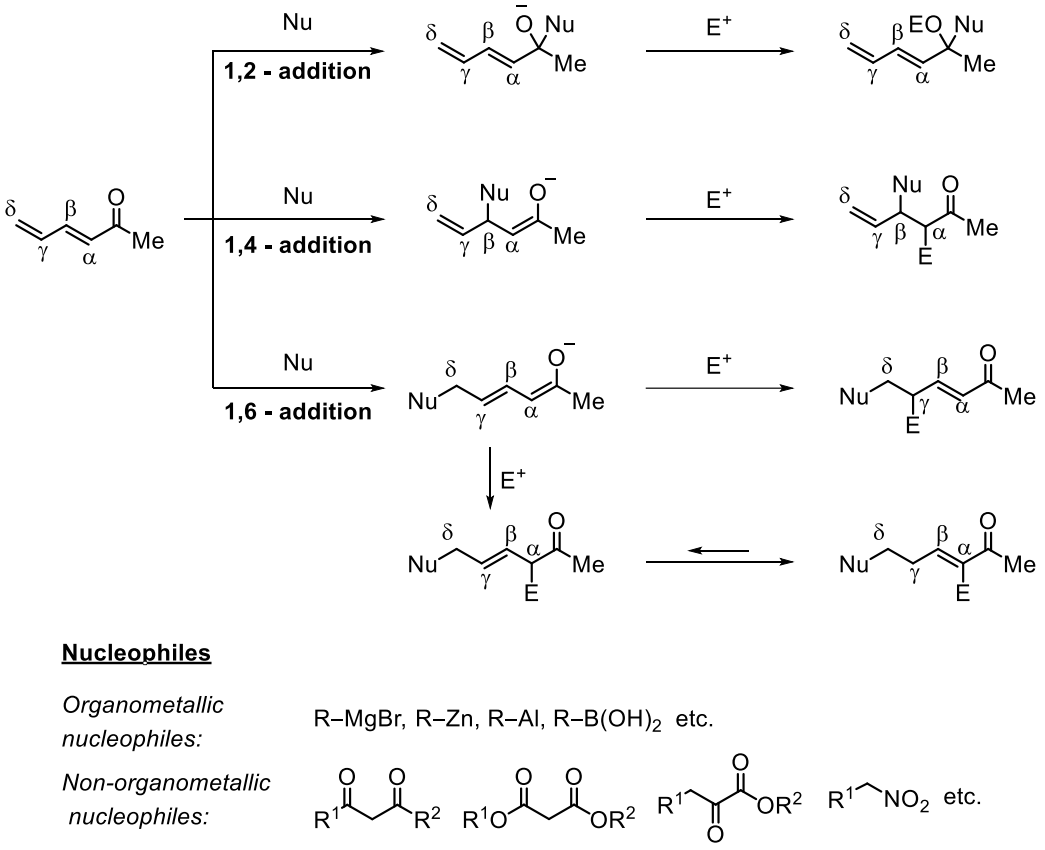
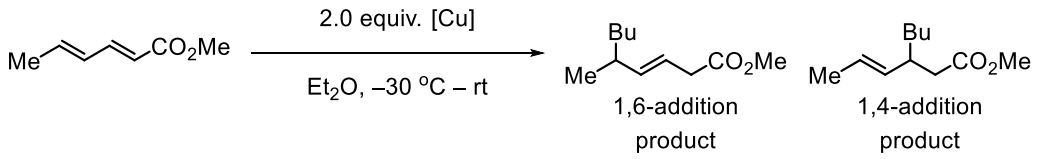


Fig. 1-17 Nucleophilic conjugate addition to electron deficient diene.

Terminal polarization of the activated diene to make the δ-position more electrophilic, favors the addition of the nucleophile at the δ-position. Factors to achieve addition at the δ-position include steric effects, electronic effects and the nature of the added nucleophile (**Fig. 1-18**).[47] Yamamoto and co-workers reported the use of different copper reagents, BuCu•BF_3 (Yamamoto cuprate) and Bu_2CuLi (Gilman

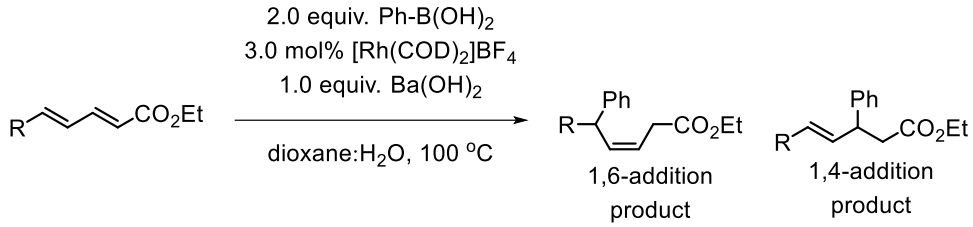
reagent) to achieve regiocontrol in conjugate additions (**Fig. 1-18a)**.[55] The electron density tuning in the copper reagents afforded 1,6-conjugate addition and 1,4-conjugate additions respectively. The use of substituent groups to prefer one type of addition over the other has been reported by Csákÿ and co-workers (**Fig. 1-18b)**.[56] 1,6-Conjugate addition generally proceeds through the formation of an extended enolate which can then be trapped by an electrophile or protonated at the α or γ positions (**Fig. 1-17)**.

a. Regiocontrol using copper reagents



	Selectivity	
	1,6-addition product	1,4-addition product
$BuCu.BF_3$ = 44% yield	7	92
Bu_2CuLi = 82% yield	100	0

b. Regiocontrol using substituent group



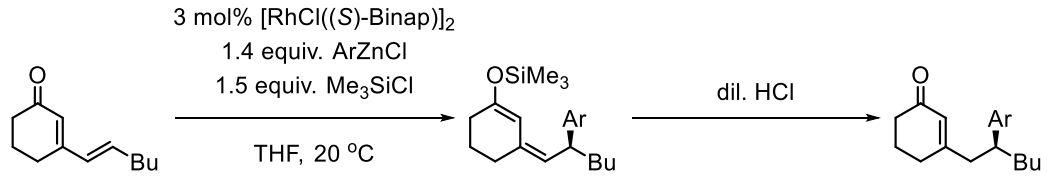
	Selectivity	
	1,6-addition product	1,4-addition product
R = Me, 90% yield	82	18
R = Ph, 85% yield	20	80

Fig. 1-18 Regiocontrol in conjugate addition.

Transition metal catalyzed 1,6-conjugate addition is dominated by Rh and Cu catalysts. Other transition metal catalysts for 1,6-conjugate addition include Fe, Ir, Ru, Ni, Pd and Al based catalysts.[57-64] While the 1,6-conjugate addition of alkyl groups to electron deficient dienes utilizing organo- lithium, magnesium and zinc reagents is mostly catalyzed by Cu or Al,[47] the 1,6-conjugate additions of aryl or alkenyl groups are catalyzed by Rh, Ir or Pd in the presence of organo- boron, tin, titanium and silicon reagents.[56, 57] These methods are useful in the asymmetric synthesis of new carbon–carbon bonds. An example of a Rh-catalyzed asymmetric 1,6-conjugate addition of arylzinc reagent in the presence of a Lewis acid to make 2,4 dien-1-one is outlined in **Fig. 1-19a**.[65] 1,6-Conjugate addition reactions catalyzed by organocatalysts have also been reported.[48, 66]

Transition metal catalyzed stereoselective 1,6-conjugate addition to synthesize *Z*-alkenes using silyl,[67, 68] boronic acid[54] and Grignard[69] reagents has been reported. *Z*-Selective Rh-catalyzed 1,6-conjugate addition of arylboronic acids reported by Csákÿ and co-workers (**Fig. 1-19b)** proceeds through the transmetalation of the aryl boronic acid reagent with the Rh-catalyst to generate the arylrhodium species. The arylrhodium species insert into the γ,δ-double bond of the dienoate followed by π–allyl isomerization to generate an oxo-π-allylrhodium complex. Subsequent acid hydrolysis generates the β,δ-unsaturated ester.

a. Rh-catalyzed asymmetric 1,6-conjugate addition of arylzinc reagent



b. Rh-catalyzed *Z*-Selective 1,6 conjugate addition of arylboronic acid

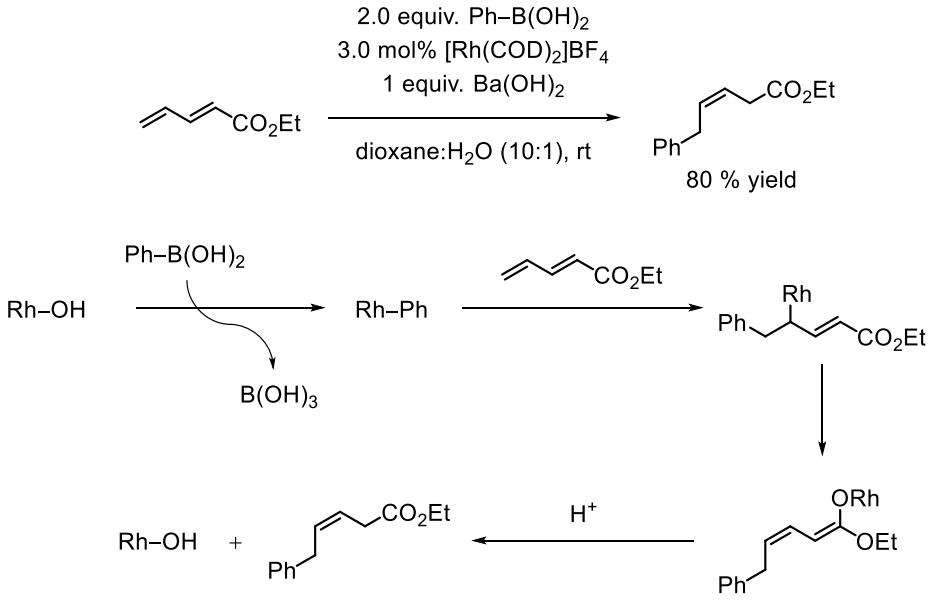


Fig. 1-19 Rh-catalyzed 1,6-conjugate addition reaction.

Z-Selective hydride addition to electron deficient dienes such as methyl sorbate, sorbic acid and sorbic alcohol catalyzed by Cr and Ru is shown in **Fig. 1-20**.[26, 70, 71] Regio- and stereocontrol is dictated by the diene coordination in an η^4 *s-cis* fashion to the metal center to allow for a rapid hydride delivery to form the *Z*-alkenes. *Z*-Selective hydride addition to sorbic acid or sorbic alcohol is particularly useful as it can be used to access a high value fragrance, *Z*-hex-3-en-1-ol sold as 'leaf alcohol'. The selectivity of the process is essential because the *E*-hex-3-en-1-ol has a very terrible odour.

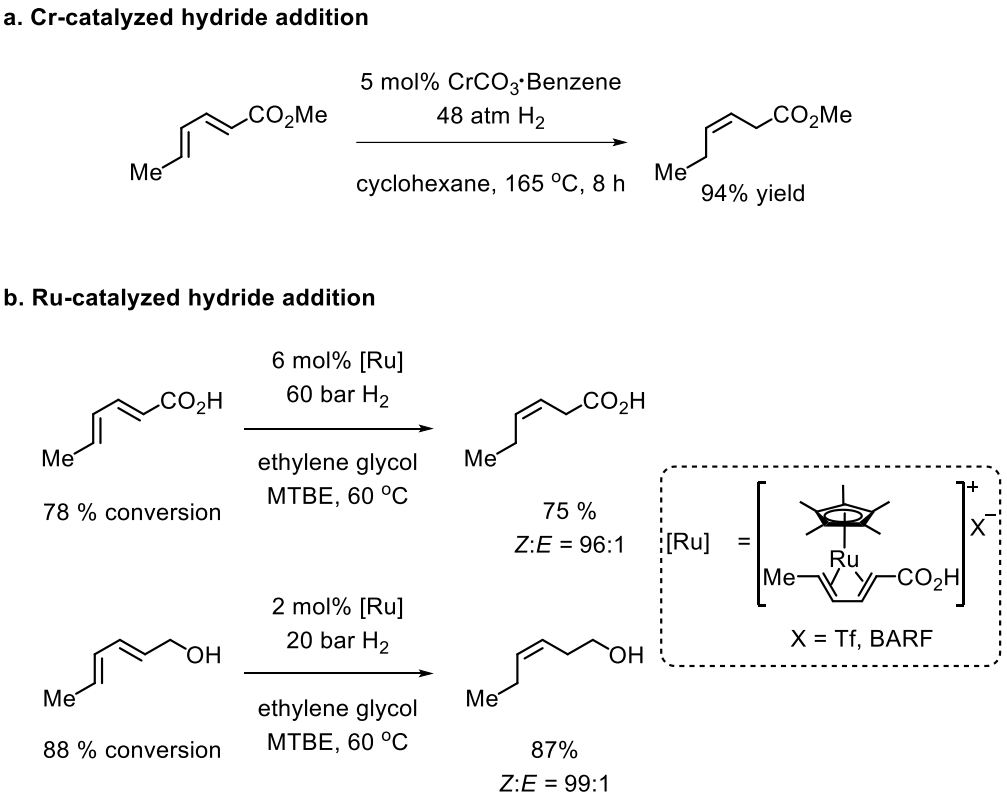


Fig. 1-20 *Z*-selective conjugate hydride addition.

The use of electron deficient dienes as pronucleophiles to generate allylmetal nucleophiles for use in reductive coupling reactions with electrophiles has been expanding in recent years.[72, 73] Reductive coupling reactions involving catalytically generated metal allyl species derived from electron deficient dienes and electrophiles that employ organo-boron, silicon and zinc reagents as the hydride source have been reported.[74-76] The use of cheap and readily available hydride sources such as molecular hydrogen, isopropanol and formic acid in reductive coupling processes improve safety and reduce selectivity challenges associated with the use of organometallic reagents.[73, 74, 76-81] Carbonyl compounds, imines and their derivatives are useful electrophilic partners in these reductive coupling processes promoted by Ni, Ru, Rh, Ir, Ti and Cu catalyses.[72] The reductive

coupling proceeds through the metal hydride insertion into the electron deficient diene to generate an allylmetal species which is subsequently trapped by an electrophile to generate the alkene product (**Fig. 1-21)**.

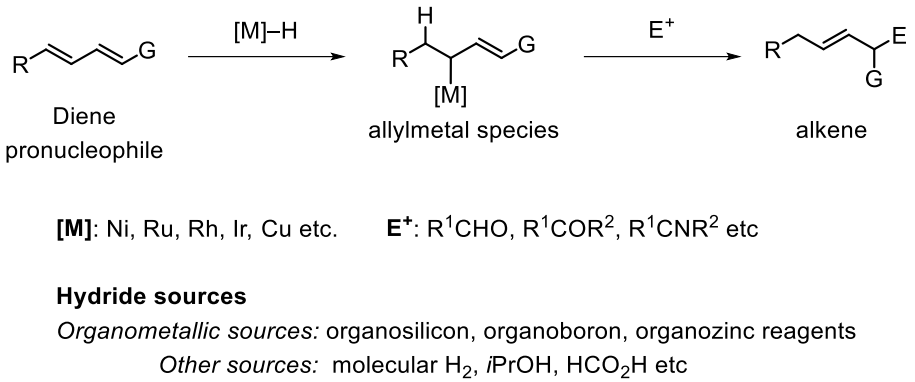
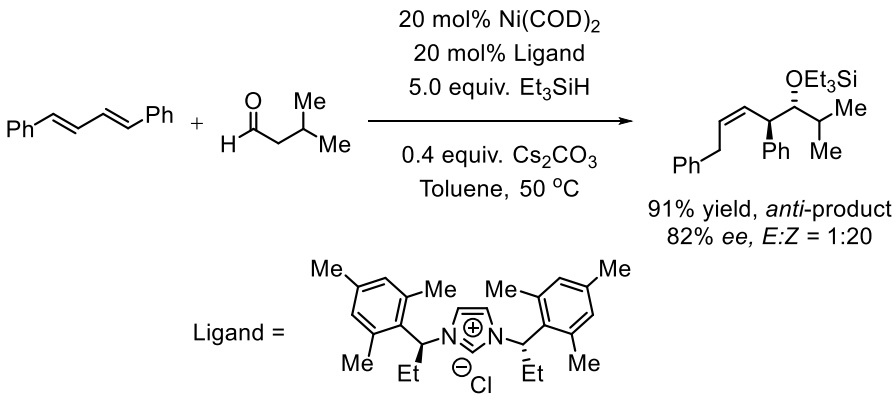


Fig. 1-21 General scheme for reductive coupling using an electron deficient diene as pronucleophile.

Stereoselective reductive coupling utilizing electron deficient dienes as pronucleophiles with aldehyde electrophiles and catalyzed by Ni and Rh to generate *Z*-alkenes is outlined in **Fig. 1-22**.[82, 83] The hydride sources in these cases are triethylsilane for the Ni-catalyzed reductive coupling and triethylborane for the Rh-catalyzed reductive coupling processes. An example to generate *Z*-alkenes via a Rh-catalyzed reductive coupling of methyl sorbate and benzaldehyde is shown in **Fig. 1-22b.** Rh–H generated from Rh–OH and the triethylborane adds to the conjugated diene to form an allylrhodium intermediate which is trapped by benzaldehyde via a transition state with minimal unfavorable non-bonding interactions with the ligand to form *Z*-homoallylic alcohol.[82] *Z*-Selective reductive coupling of conjugated dienes with aldehydes and imines through allyl metal chain walking has been pioneered by Lam and co-workers.[84, 85]

a. Ni-catalyzed *Z*-selective reductive coupling



b. Rh-catalyzed *Z*-selective reductive coupling

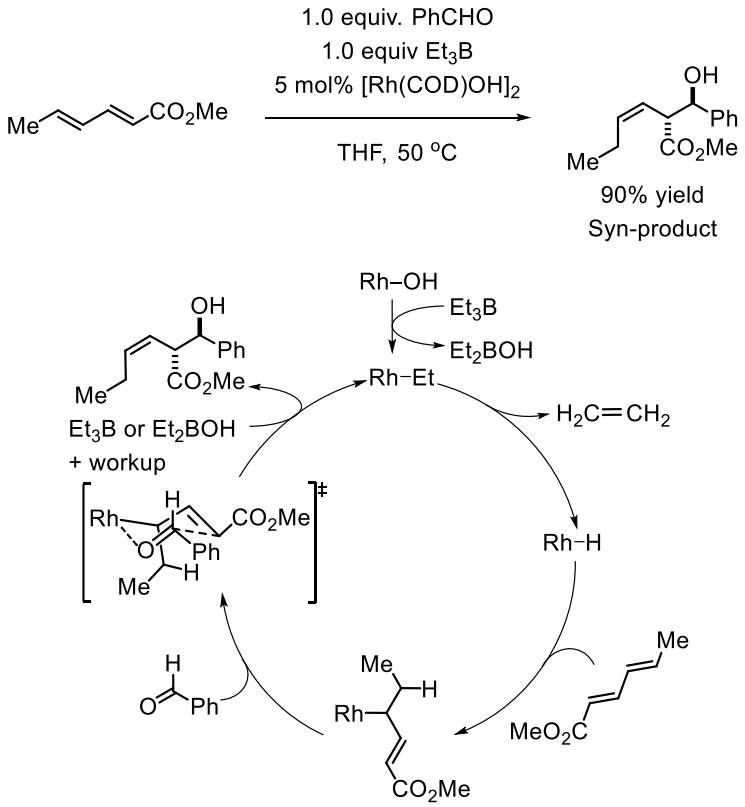


Fig. 1-22 *Z*-selective reductive coupling of diene and aldehyde.

With some limitations to the established methods to prepare *Z*-alkenes especially tolerance to unsaturated functionalities, a new method, complimentary to these existing protocols is desirable. Reductive processes for *Z*-alkene preparation involving catalytic transformation of electron deficient dienes using cheap hydride sources with tolerance to reducible functionalities including unsaturated groups could offer an alternative pathway.

1.4 Overview of Thesis

The description of the discovery and development of new catalytic methods to synthesize *Z*-alkenes from electron deficient dienes is provided. Mechanistic studies to understand the origin of *Z*-selectivity are carried out. A particular emphasis was placed on identifying reaction processes and conditions that demonstrated chemoselectivity for *Z*-selective reductive functionalization in the presence of other potentially reducible or reactive functional groups.

Chapter 2 discusses the development of *Z*-selective formate-mediated 1,6 reduction of electron deficient dienes. Mechanistic studies suggest that chemo- and regioselectivity are controlled by substrate coordination to the Rh-catalyst for selective hydride delivery. Tolerance to unsaturated functionalities and electrophilic groups was also demonstrated.

Chapter 3 discusses the Rh-catalyzed, *Z*-selective reductive coupling of dienes and aldehydes to access *Z*-homoallylic alcohols. The effect of catalyst components was understood through mechanistic experiments and kinetic analysis. The use of cyclooctadiene ligand was found to be essential for the reductive coupling process and triphenylphosphine ligand promotes catalyst lifetime. An understanding of ligand effects

in Rh-catalyzed reactions of dienes has enabled related enantioselective processes to be developed (see Chapter 5).

Chapter 4 provides detail on the development of the *Z*-selective reductive coupling of dienes and imines to access homoallylic amines. Optimization of the process shows that substrate electronic and steric factors play a major role in the regioselectivity of the reductive coupling.

Chapter 5 gives a brief summary of the key achievements of the thesis, unanswered questions, and an overview of future work that has been inspired by the findings of the thesis.

CHAPTER 2 - Rh-Catalyzed Formic Acid Mediated Z-Selective 1,6-Reduction of Electron Deficient Dienes

2.1 Introduction

A large number of bioactive molecules contain *Z*-alkene units (**Fig. 2-1**), and stereospecific transformations of *Z*-alkenes are commonly used to develop molecular complexity.[86-91] Thus, the synthesis of less thermodynamically stable alkenes is an important goal.

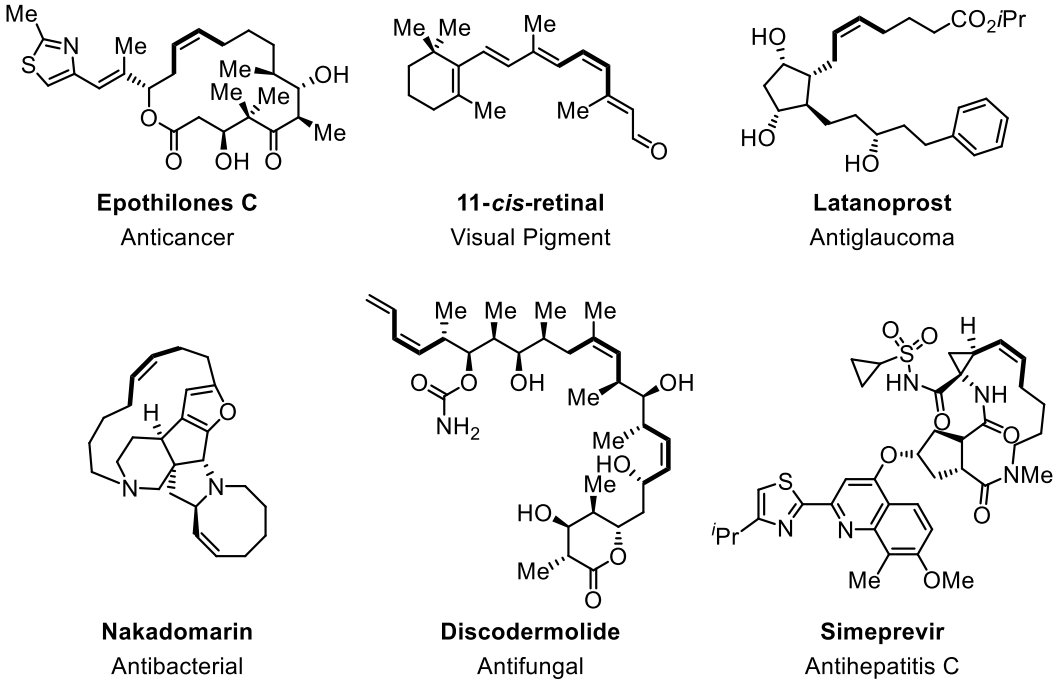


Fig. 2-1 Examples of bioactive compounds containing Z-alkenes.

An array of methods to generate *Z*-alkenes with high stereoselectivity,[13, 38] while maintaining control over chemo- and regioselectivity when employing unprotected, polyfunctionalized substrates remains a challenge. *Z*-Selective carbonyl olefination reactions using phosphorus-, silicon- or sulfur-containing precursors have enabled the

preparation of *Z*-olefins in a myriad of settings.[14] These processes are usually non-catalytic and the requirement for stoichiometric generation of main-group element ylides (typically P- or Si- units) intermediates over an additional synthetic step limits efficiency. Furthermore, the strongly basic reaction conditions are often incompatible with protic or electrophilic functionality.[13] Alternative methods for *Z*-olefin synthesis include *Z*-selective alkyne reductions[26-29] and alkene metathesis reactions.[40-44, 92] Despite their remarkable and growing utility, alkyne semi-reduction and *Z*-selective metathesis reactions can exhibit poor chemoselectivity on targets bearing multiple alkyne or olefin units. There remains a need for complementary catalytic approaches to *Z*-olefin synthesis in the presence of other carbon–carbon π-bonds and protic or electrophilic groups.

Catalyst-controlled addition of nucleophiles to carbonyl-activated dienes is a pivotal method to generate functionalized olefins.[47, 48, 56, 93] In select cases, these transformations enable highly regioselective 1,6-addition to deliver γ-substituted *E*-alkenes.[53, 94-97] By contrast, *Z*-selective 1,6-additions to electron deficient dienes remain rare.[54, 67-69] The addition of hydrogen or hydride equivalents to extended Michael acceptors to generate *Z*-olefin products is limited to Cr-promoted reactions (**Fig. 2-2a**) requiring forcing conditions (typically ≥150 °C).[70, 98] The Cr-promoted 1,6-hydride addition employs the use of chromium tricarbonyl arene complex catalyst and proceeds through a solvent activation step to generate the chromium tricarbonyl solvent complex via the loss of the arene ligand. The chromium tricarbonyl solvent complex is the active catalyst and can be described as a twelve-electron complex with three vacant coordination sites due to a weak coordination of the solvent to chromium.[26] The mechanism can proceed through two possible routes; the hydride route or the diene route. The hydride route involves the

oxidative addition of dihydrogen to generate the Cr–hydride complex which subsequently coordinates to the diene in an η^4 fashion to generate the chromium hydride diene complex leading to a rapid hydride transfer to the diene to generate the *Z*-alkene. The alternate diene route proceeds through the coordination of the diene in an η^4 fashion to the active catalyst followed by the molecular hydrogen activation. Kinetic studies at high hydrogen pressure and elevated temperature demonstrate the hydride route to be more operative and the oxidative addition is the rate determining step. The regio- and stereocontrol within these processes is proposed to be dictated by the generation of a conformationally rigid η^4 *s-cis* diene coordination to the chromium center to allow for a selective hydride delivery to generate the product. The 1,6-*cis* reduction of sorbic acid has been documented with Cp*Ru-based catalysts (**Fig. 2-2b**), however careful monitoring of the reaction is required to prevent substrate over-reduction and isomerization.[71]

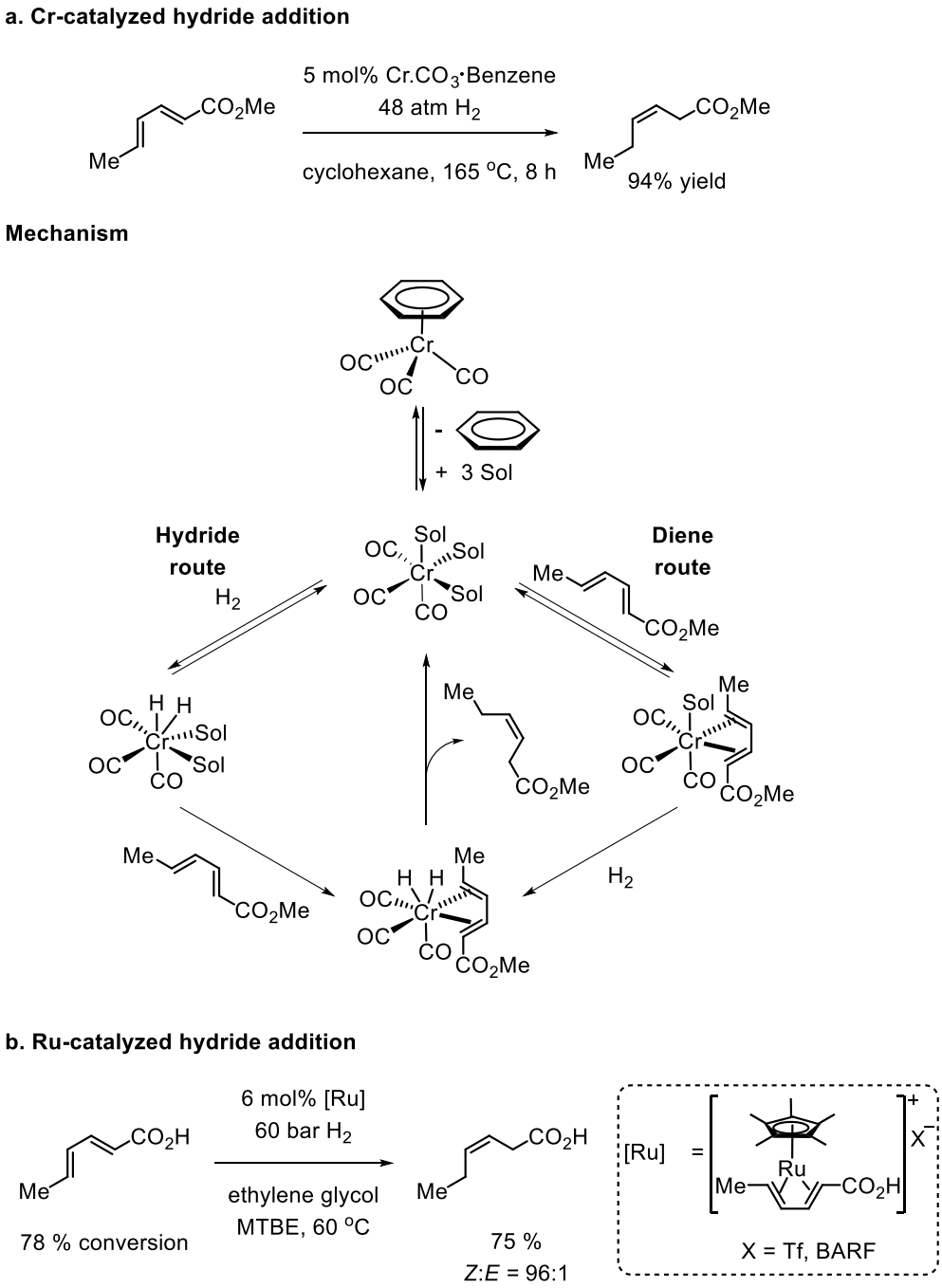


Fig. 2-2 *Z*-Selective catalytic 1,6-hydride addition to electron deficient dienes.

This chapter describes the Rh-catalyzed formate-mediated reduction of electron deficient dienes to generate *Z*-olefins.[99, 100] Substrate coordination and hydride delivery from a Rh-catalyst is shown to dictate a chemo- and regioselective process. Other

unsaturated groups such as non-activated olefins or dienes, α,β-unsaturated esters, internal alkynes and a host of electrophilic groups are tolerated (**Fig. 2-3**). The process offers a new opportunity to prepare polyfunctionalized *Z*-olefins in complex substrate environments without protecting groups. A mechanistic analysis of the process shows carefully controlled addition of hydride equivalence is required to achieve high selectivity as the first-formed reduction product is prone to isomerization and further reduction.

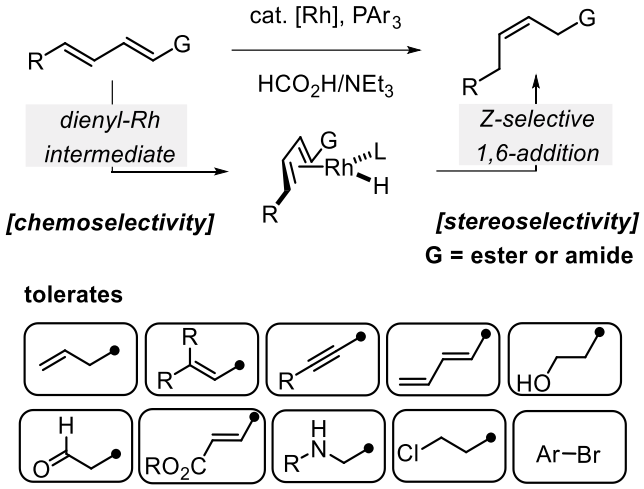
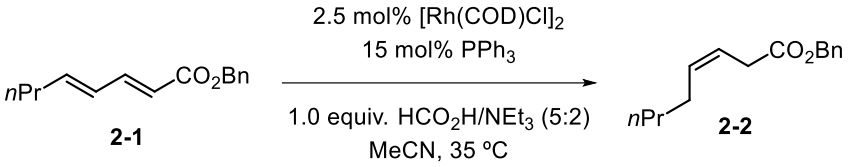


Fig. 2-3 Rh-catalyzed hydride addition to generate *Z*-olefins.

2.2 Development of Chemoselective Synthesis of *Z*-Olefins through Rh-Catalyzed Formate Mediated 1,6-Reduction of Electron Deficient Dienes

After surveying a broad range of reaction conditions and catalysts, it was found that 2.5 mol% $[Rh(COD)Cl]_2$ and 15 mol% PPh_3 in the presence of formic acid/NEt_3 in acetonitrile provided the desired mono-reduced olefin **2-2** in 80% yield with 96:4 *Z/E* selectivity using the model dienoate substrate **2-1** (**Table 2-1**, entry 1). The nature of the pre-catalyst was important; $RhCl(PPh_3)_3$, alternative Rh/PPh_3 stoichiometries, or the use of

other ligands resulted in reduction with moderate to low *E*-selectivity (**Table 2-1**, entries 2-8). The poor reactivity observed when other phosphine ligands instead of triphenylphosphine were used may be related to the difficulty to generate Rh–H for the reduction in the presence of these ligands (**Table 2-1**, entries 4-8). This may be due to electronic properties, steric properties or possible coordination of substituents on the phosphine to rhodium. Other metals, including Ir, Cu, and Pd did not generate the *Z*-olefin product (**Table 2-1,** entries 9-11). When alternative reductants were used, including H_2, diphenylsilane (Ph_2SiH_2), or pinacolborane (HB(pin)), poor product yields were observed (**Table 2-1,** entries 12-14). Reactions conducted with lower catalysts loadings (0.5 mol% $[Rh(COD)Cl]_2$) at 50 °C resulted in similar product yields and selectivities (**Table 2-1,** entry 15). In the productive Rh-catalyzed reductions, the remaining mass balance is typically 5–10% α,β-unsaturated ester that could arise from either direct reduction at the more remote olefin position or from isomerization of product **2-2**.



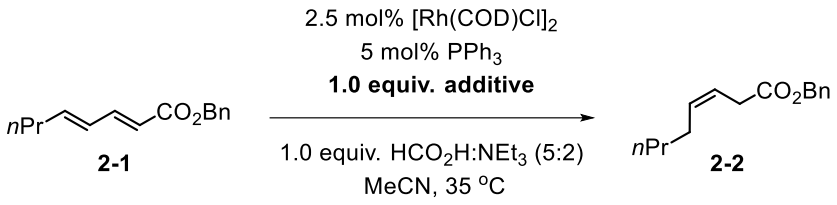
entry	deviation from above	conv. (%)	yield (%) [*Z*/*E*]
1	none	91	**80 [96:4]**
2	$Rh(PPh)_3Cl$ (no PPh_3)	94	41 [31:69]
3	1:1 Rh:PPh_3 instead of 1:3	93	40 [28:72]
4	no PPh_3	93	52 [25:75]
5	$P(OPh)_3$ instead of PPh_3	59	47 [50:50]
6[a]	Dppe instead of PPh_3	7	7 [nd]
7[a]	$[(2\text{-MeO-}C_6H_4)]_3P$ instead of PPh_3	52	22 [29:71]
8[a]	$[(3,5\text{-}CF_3\text{-}C_6H_3)]_3P$ instead of PPh_3	<5	4 [nd]
9	$[Ir(COD)Cl]_2$	24	<2
10	CuI	<2	<2
11	$Pd(OAc)_2$	20	<2
12	H_2 (1 atm) instead of HCO_2H/NEt_3	37	5 [nd]
13	Ph_2SiH_2 instead of HCO_2H/NEt_3	54	7 [57:43]
14	HB(pin) instead of HCO_2H/NEt_3	54	14 [86:14]
15[b]	0.5 mol% $[Rh(COD)Cl]_2$, 3 mol% PPh_3	89	79 [96:4]

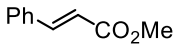
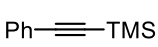
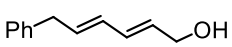
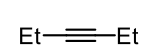
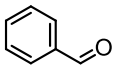
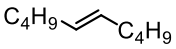
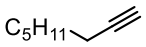
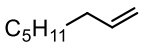
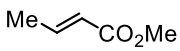
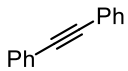
0.2 mmol scale, 1.0 equiv. HCO_2H, 0.2 M, yields and conversions determined by calibrated ^1H NMR spectroscopy using dibenzyl ether as internal standard. a) 1.2 equiv. HCO_2H/NEt_3 (5:2). b) at 50 ºC, 48h.

Table 2-1 Effect of selected reaction parameters on the Rh-catalyzed *Z*-selective 1,6-reduction of dienyl esters.

A preliminary mechanistic hypothesis for the Rh-catalyzed reaction to account for the observed selectivity involves the chelation-controlled 1,6-reduction of the diene substrate. Over-reduction or isomerization was not observed under the standard reaction conditions, suggesting the ability to conduct chemoselective hydride additions. It was reasoned that electron-rich olefins, polar unsaturates, and suitably substituted alkynes should not be reduced at rates competitive with bidentate extended Michael acceptors. To rapidly test the hypothesis, a functional group tolerance screen with an array of unsaturated substrates was conducted (**Table 2-2**).[101] In these experiments, one equivalent of an unsaturated substrate was added to a standard Rh-catalyzed reduction using substrate **2-2**.

Product yields and consumption of the added substrate were monitored by nuclear magnetic resonance (NMR) spectroscopy and gas chromatography (GC). Under standard reaction conditions, aryl/silyl and dialkyl alkynes (**Table 2-2** entries 2 and 3), internal and terminal olefins (**Table 2-2** entries 4 and 5), α,β-unsaturated esters (**Table 2-2** entries 6 and 7), electron-rich dienes and aldehydes (**Table 2-2** entries 8 and 9) were tolerated (>70% product formation, <20% additive consumption). Of the array of substrate classes examined, only terminal and diaryl alkynes (**Table 2-2** entries 10 to 12) were found to be incompatible. These groups both poisoned dienoate reduction and were partially consumed.



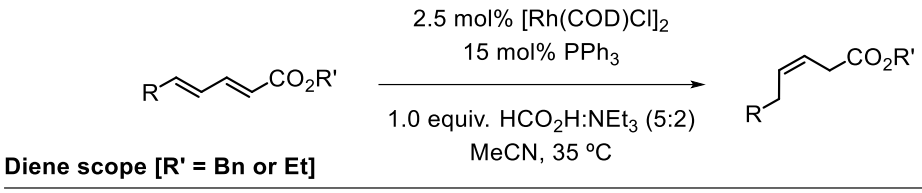
entry	Additive	yield of 2-2 (%)	Additive remaining (%)	entry	Additive	yield of 2-2 (%)	Additive remaining (%)
1	none	82 ✓	none	7		74 ✓	98 ✓
2		76 ✓	92 ✓	8		72 ✓	85 ✓
3		70 ✓	84 ✓	9		74 ✓	>99 ✓
4		70 ✓	100 ✓	10		22 ✗	65 ✗
5		77 ✓	85 ✓	11		3 ✗	67 ✗
6		76 ✓	90 ✓	12		56 ✗	63 ✗

Reactions performed on 0.20 mmol scale according to the general procedure, with an additional 1.0 equivalent of additive. Yields and conversions determined by calibrated ^{1}H NMR spectroscopy using dibenzyl ether as internal standard. General assessment of product yield and additive recovery based on :Yield:100 – 70%(good ✓), 69 – 0% (poor ✗). n.d. not determined; Additive Conversion: <20 % good(✓) >20% (poor ✗).

Table 2-2 Functional group tolerance screen for Rh-catalyzed *Z*-selective 1,6-reduction of electron deficient diene.

The substrate scope of the Rh-catalyzed *Z*-selective 1,6-reduction of dienoates was evaluated (**Table 2-3 and Table 2-4**). Calibrated ^{1}H NMR yields, conversions and selectivites along with isolated yields are shown for the examples in **Table 2-3** and **2-4** to provide information on both the inherent reactivity of each substrate. Isolated yields of pure (>95%) *Z*-reduction products were achieved by using silver-impregnated silica gel. Aliphatic and aryl groups at the terminal position of the dienoate led to product formation

in similarly high selectivities (**2-2** to **2-8**), including unsubstituted (**2-5**) and cyclopropyl (**2-4**) substituted species. Substrates bearing electron-rich (**2-9**) or electron-poor (**2-10**) heterocycles, electrophilic ketone (**2-11**) and aldehyde (**2-12**) functionalities, as well as amines (**2-13**,), alkyl chlorides (**2-15**), and alkyl nitriles (**2-16**) gave *Z*-alkene products in good yield and typically >95:5 *Z:E* selectivity. The formate-mediated reduction method allowed for the preparation of *Z*-alkene containing molecules that contain pendent carbon–carbon unsaturation, including terminal alkenes (**2-18**), internal alkenes (**2-19**), α,β-unsaturated esters (**2-20**), and alkynes (**2-14**). These types of stereochemically defined polyunsaturated products would be difficult to obtain directly via established catalytic semi-reduction or metathesis reactions. The process can be scaled to deliver gram-quantities of product (**2-7**, 1.2 g, 69% yield).



Diene scope [R' = Bn or Et]

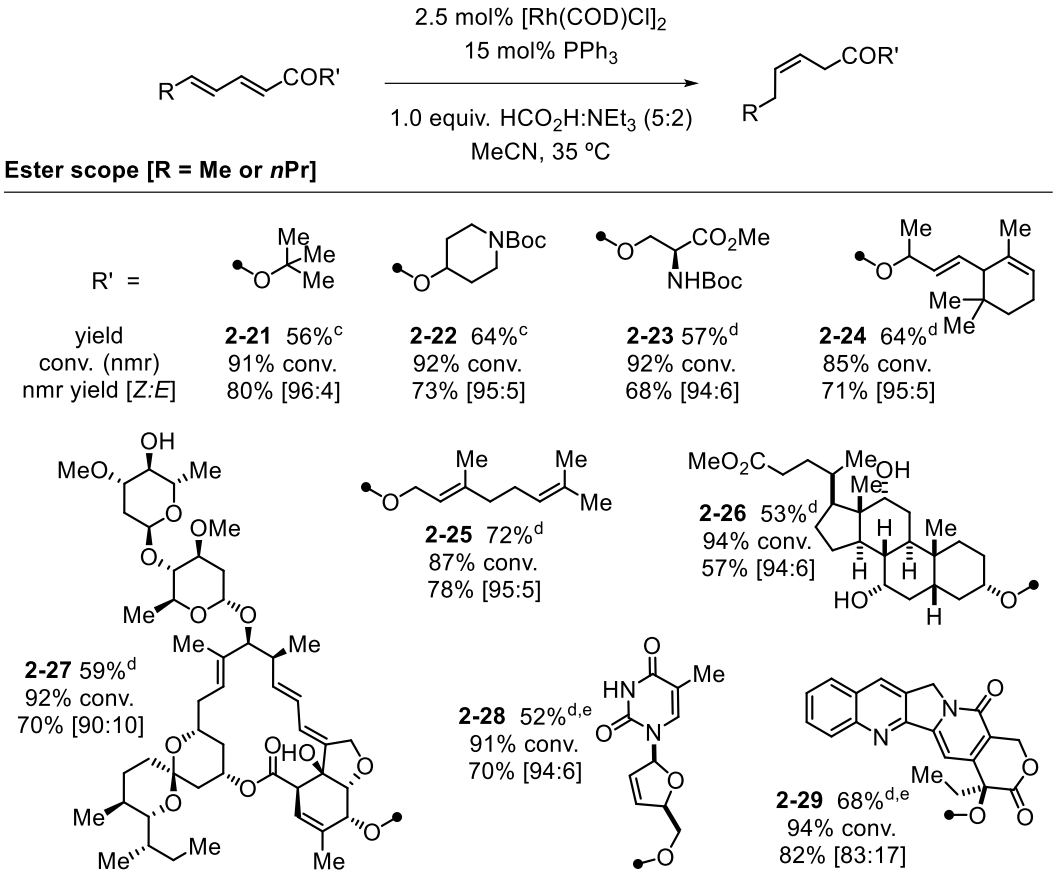
R =	Me	Me		H
yield conv. (nmr) nmr yield [*Z*:*E*]	**2-2** 74%[a] 91% conv. 80% [96:4]	**2-3** 75%[a] 95% conv. 82% [96:4]	**2-4** 67%[a] 92% conv. 72% [97:3]	**2-5** 69%[a] 94% conv. 80% [90:10]
2-6 65%[a] 91% conv. 81% [85:15]	**2-7** 75%[a] 93% conv. 81% [96:4] [gram scale: 1.2g, 69%]	**2-8** 74%[a] 95% conv. 79% [96:4]	**2-9** 73%[b] 90% conv. 77% [96:4]	**2-10** 61%[b] 83% conv. 68% [96:4]
2-11 62%[b] 90% conv. 75% [95:5]	**2-12** 66%[b] 90% conv. 73% [96:4]	**2-13** 69%[a] 93% conv. 78% [97:3]	**2-14** 71%[b] 93% conv. 74% [97:3]	**2-15** 78%[a] 91% conv. 82% [98:2]
2-16 70%[a] 85% conv. 77% [98:2]	***2-17*** *71%*[b] 93% conv. 74% [97:3]	***2-18*** *62%*[b] 86% conv. 71% [93:7]	**2-19** 74%[b] 86% conv. 79% [97:3]	**2-20** 67%[b] 74% conv. 72% [nd]

a) R' = Bn. b) R' = Et.

Table 2-3 Diene scope of the Rh-catalyzed formate-mediated *Z*-selective 1,6-reduction of electron deficient dienes.

The ester group of the dienoate can be varied from benzyl or ethyl groups to a bulky *tert*-butyl group (**2-21**); amine-containing moieties, including a protected amino acid derivative (**2-22**, **2-23**); and esters containing multiple alkene units (**2-24**, **2-25**). The functional group tolerance of the reaction was also examined with derivatives of bioactive molecules. Dienyl esters of the hydroxylated sterol methyl cholate (**2-26**), polyketide ivermectin (**2-27**), nucleoside analog stavudine (**2-28**), and quinoline alkaloid

camptothecin (**2-29**) could be reduced with acceptable yields and minimal complication from the array of chemical functionality present. Complex substrates like **2-25** to **2-29** would pose considerable difficulty in established *Z*-olefin forming processes (**Table 2-4)**.

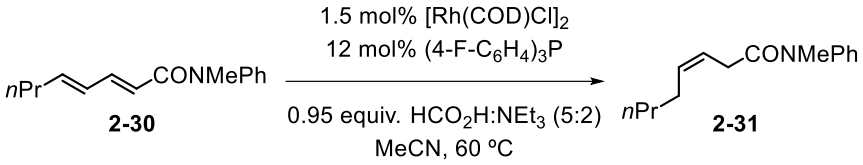


c) R = *n*Pr. d) R = Me. e) 5 mol% $[Rh(COD)Cl]_2$, 30 mol% PPh_3, 4:1 MeCN:DMSO.

Table 2-4 Ester scope of the Rh-catalyzed formate-mediated *Z*-selective 1,6-reduction of electron deficient dienes.

Under slightly modified conditions, it was found that dienamide **2-30** could be reduced with 1.5 mol% $[Rh(COD)Cl]_2$ and 12 mol% $(4\text{-F-}C_6H_4)_3P$ in the presence of formic acid/NEt_3 in acetonitrile to provide the desired mono-reduced olefin **2-31** in 61%

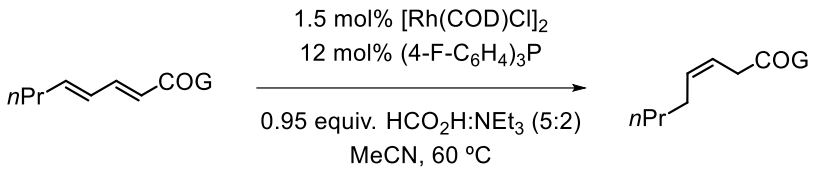
yield with 92:8 *Z/E* selectivity (**Table 2-5**, entry 1). The use of 0.95 equiv. formic acid/NEt_3 was to maintan the stereo- and regioselectivity of the reaction. Lowering the temperature and use of other phosphine ligands gave reduced yield and low *Z/E* selectivity (**Table 2-5**, entries 2 and 3). Chiral biphosphine ligand, *R*-BINAP shuts down the reaction (**Table 2-5**, entry 6). Increasing the catalyst loading and changing the Rh/(4-F-$C_6H_4)_3P$ stoichiometry gave similar yield and selectivity (**Table 2-5**, entries 7 and 8). With the modified condition, a series of amidyl dienes (**Table 2-6)**, including the Weinreb amide (**2-34**) were reduced with good selectivity (**2-31** to **2-34**).



entry	deviation from above	conv. (%)	yield (%) [*Z*/*E*]
1	none	90	61 [92:8]
2	35 ºC	82	47 [91:9]
3	rt	70	35 [86:14]
4	PPh_3 instead of (4-F-$C_6H_4)_3P$	89	55 [84:16]
5	(4-MeOPh)$_3$P instead of (4-F-$C_6H_4)_3P$	100	27 [60:40]
6	*R*-BINAP instead of (4-F-$C_6H_4)_3P$	0	0
7	2.5 mol% [Rh(COD)Cl]$_2$, 15 mol% (4-F-$C_6H_4)_3P$	88	63 [89:11]
8	1.5 mol% [Rh(COD)Cl]$_2$, 15 mol% (4-F-$C_6H_4)_3P$	87	57 [89:11]

0.2 mmol scale, 0.95 equiv. HCO_2H, 0.2 M;, 48h; yields, selectivities and conversions determined by calibrated ^1H NMR spectroscopy using dibenzyl ether as internal standard.

Table 2-5 Effect of selected reaction parameters on the Rh-catalyzed *Z*-selective 1,6-reduction of dienamide.



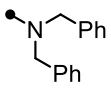
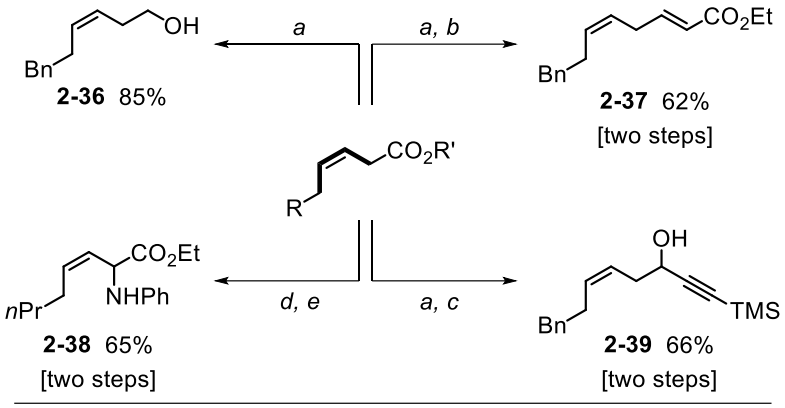
G =				
yield	**2-31** 51%	**2-32** 59%	**2-33** 51%	**2-34** 69%
conv. (nmr)	93% conv.	93% conv.	90% conv.	86% conv.
nmr yield [*Z*/*E*]	61% [92:8]	63% [95:5]	61% [94:6]	78% [nd]

Table 2-6 Dienamide scope of the Rh-catalyzed formate-mediated *Z*-selective 1,6-reduction of electron deficient dienes.

The β-carbonyl containing *Z*-olefins are useful precursors to a range of other product classes (**Fig. 2-4**). *Z*-Homoallylic alcohols (**2-36**) could be obtained by $LiAlH_4$ mediated ester reduction. Skipped *Z*,*E*-dienes (**2-37**) were prepared by oxidation of the alcohol in **2-36** by DMP followed by HWE olefination of the resulting aldehyde. Propargylic *Z*-1,5-enyne (**2-39**) was prepared in a similar manner except the crude aldehyde was trapped with Li-TMS acetylene. *Z*-α-Amino esters (**2-38**) could be obtained by conversion of **2-2** to the corresponding α-diazo ester with *p*-ABSA and treatment with catalytic $Rh_2(OAc)_4$ and aniline. Collectively, these results help demonstrate the products obtained by Rh-catalyzed formate mediated reduction can serve as a starting point for more complex *Z*-alkene containing molecules.



a) $LiAlH_4$. b) DMP then triethyl phosphonoacetate. c) DMP then Li-TMS acetylene. d) *p*-ABSA, DBU. e) $Rh_2(OAc)_4$, $PhNH_2$. DMP = Dess Martin periodinane. TMS = trimethylsilyl, *p*ABSA = 4-acetamidobenzenesulfonyl azide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Fig. 2-4 Product derivatizations to generate other *Z*-alkene containing molecules.

Mechanistic experiments were conducted to help rationalize the high selectivity for *Z*-1,6-addition catalyzed by Rh(COD)Cl/PPh_3 mixtures. Reduction of dienoate **2-1** with D-labelled formic acid at the formyl position under otherwise standard conditions leads to exclusive hydride addition to the remote δ-position. Formic acid labelled at the carboxylic site results in labelling at the α-carbonyl position (**Fig. 2-6a**). D-Incorporation at other sites was not detected. Rationalization for incomplete D-incorporation at the δ-position could involve Rh–D/H exchange with non-formic acid hydrogens, although in subsequent studies of related processes we observed D-incorporation into the COD ligand (see Chapter 3). Nonetheless, labelling studies suggested a mechanism in which Rh–H conjugate addition is followed by protonolysis of a Rh-enolate.

Reaction progress kinetic analysis (RPKA) has served as a tool to elucidate reaction mechanisms using a minimal number of experiments.[102] By changing the concentration of each reactant and monitoring the effect these changes have on the reaction rate over a

conversion period, graphical rate equations derived from simple mathematical data manipulation can show how these changes compare to the standard reaction condition. The comparison can be used to determine reaction order and rate in a reactant which is useful in the understanding of the reaction mechanism. Variable time normalization (VTN) analysis, a method developed by Burés[103] was used to determine the order in each reactant of the *Z*-selective reduction of activated dienes. VTN involves graphically comparing the reaction concentration profiles of experiments that differ in the initial concentration of a reactant. Usually, the time axis (abscissa) is replaced by the 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 reactant, plotted on the same graph, will overlay when the arbitrary power equals the order of the reaction in that reactant. VTN analysis of the reduction revealed the process to be positive order in catalyst mixture and formic acid, and partial negative order in substrate (**Fig. 2-5)**. Formation of an off-cycle $Rh(dienoate)_2^+$ species could explain the observed negative order in substrate; excess phosphine may be beneficial in formation of $Rh(PPh_3)(dienoate)^+$ from such intermediates. Generation of the Rh–H intermediate from a substrate-bound precursor is a potential rate determining step that fits with the kinetic data.

High selectivity for *Z*-1,6-reduction is maintained throughout the reaction under standard conditions across a range of substrates (**Fig. 2-6b**). However, when excess formate (added as formic acid/triethylamine) is provided (**Fig. 2-6c**), both olefin isomerization and reduction to the saturated ester (purple trace) is observed after diene substrate **2-1** (black trace) is consumed (**Fig. 2-6c**). The consumption of *Z*-product **2-2** (red trace) is rapid, highlighting its relative instability compared to *E*-reduction isomer. Reintroduction of 50%

of the diene **2-1** inhibits these side reactions via the regeneration of a productive $Rh(PPh_3)(dienoate)^+$ complex and olefin **2-2** is smoothly generated again with minimal side-product formation.

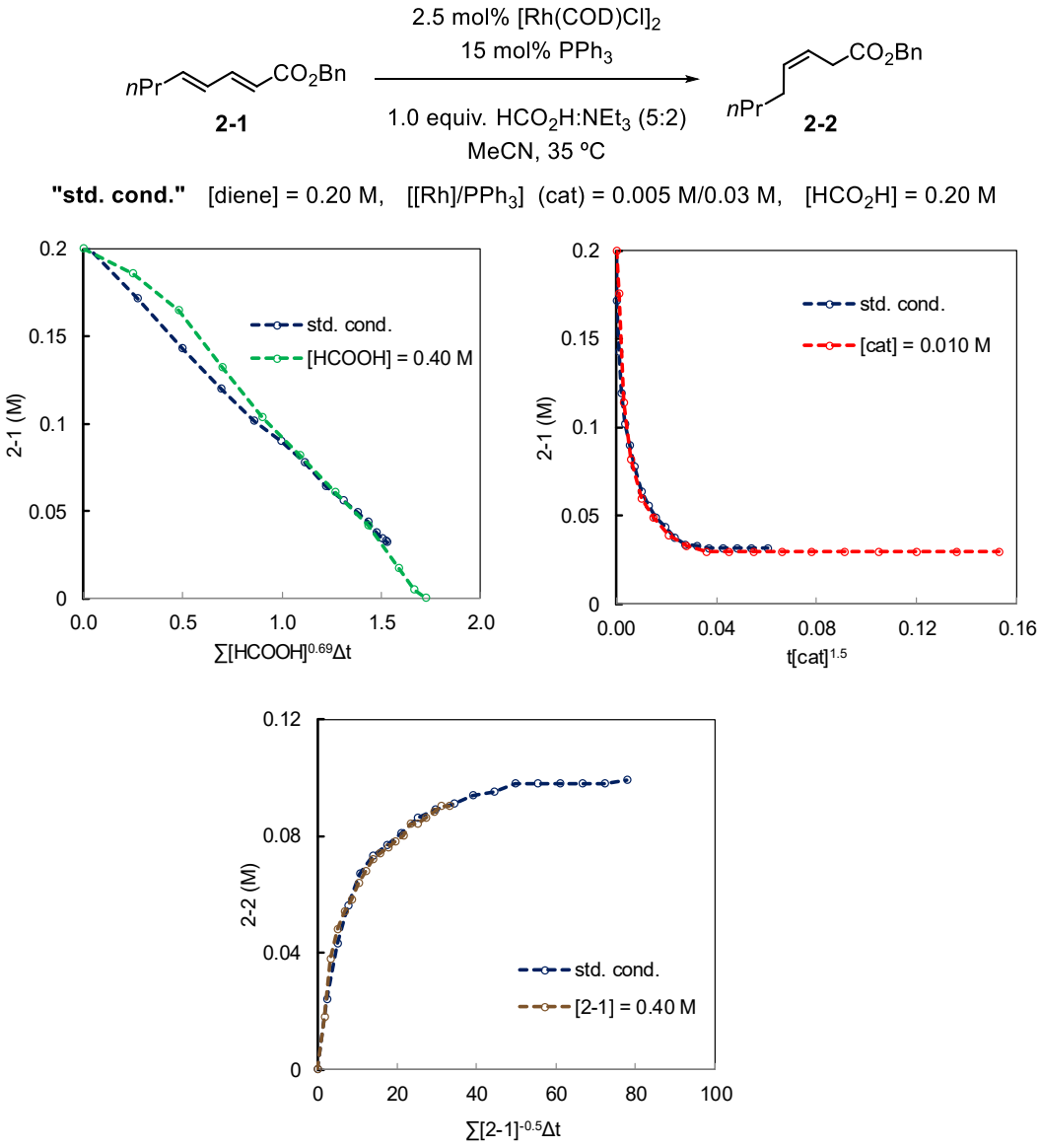
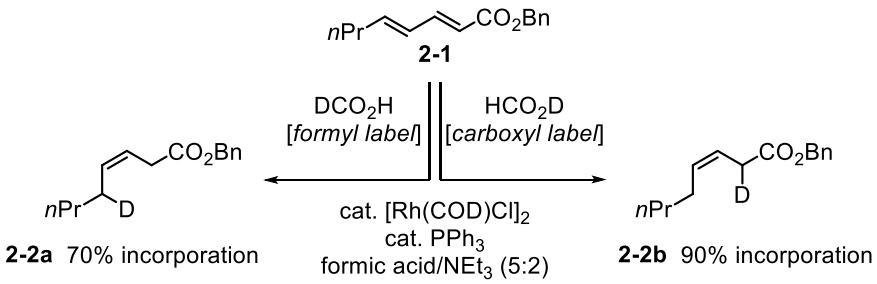
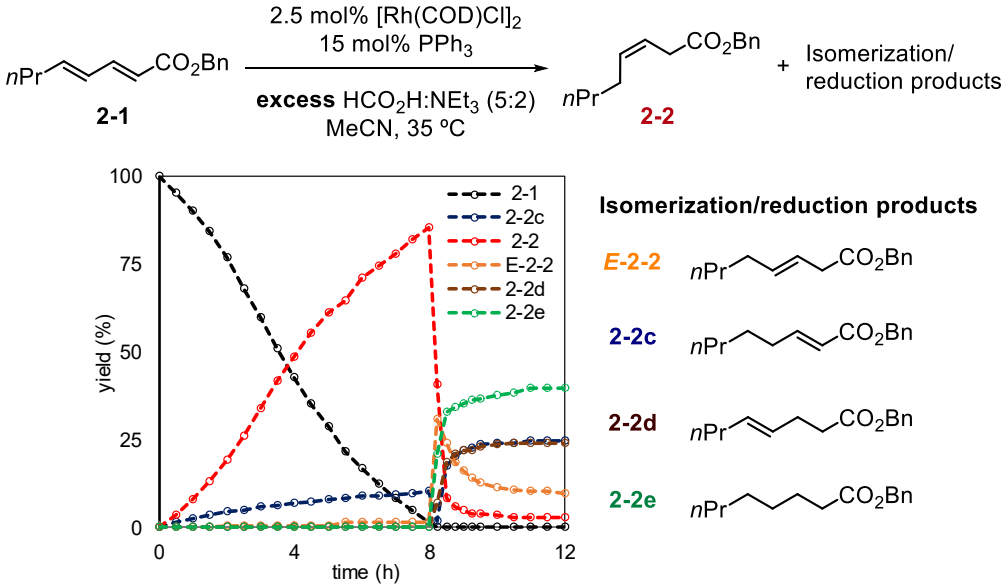


Fig. 2-5 Reaction progress kinetic analysis/variable time normalization plot.

a. Formic acid D-labelling studies



b. Kinetic profile of reaction with excess formic acid



c. Reaction profile with excess formic acid and re-introduction of diene

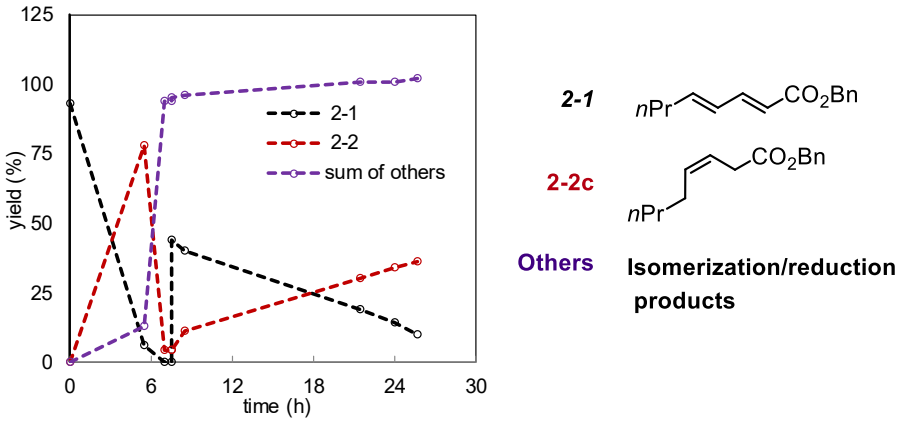


Fig. 2-6 Mechanistic and kinetic studies.

A mechanism to explain the observed selectivity involves coordination of the electron-poor diene moiety **2-1** to a Rh(I) species **2-41** to generate a square planar $Rh(PPh_3)(dienoate)^+$ complex **2-42**. The $Rh(PPh_3)(dienoate)^+$ complex **2-42,** undergoes selective hydride addition through intermediate complexes **2-43** and **2-44** to generate Rh-enolate species **2-45**. The chelation-driven, *Z*-selective Rh-enolate species **2-45** generated is readily protonated to deliver the non-conjugated *Z*-alkene. (**Fig. 2-7**).

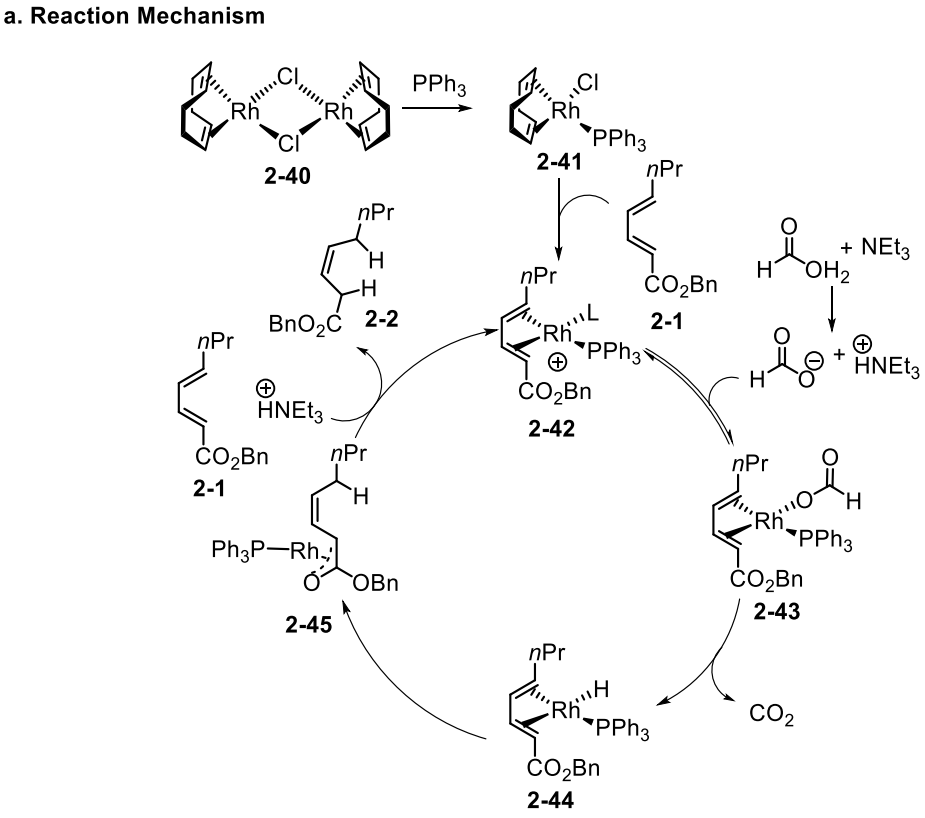


Fig. 2-7 Proposed mechanism for the Rh-catalyzed formate-mediated *Z*-selective 1,6-reduction of electron deficient dienes.

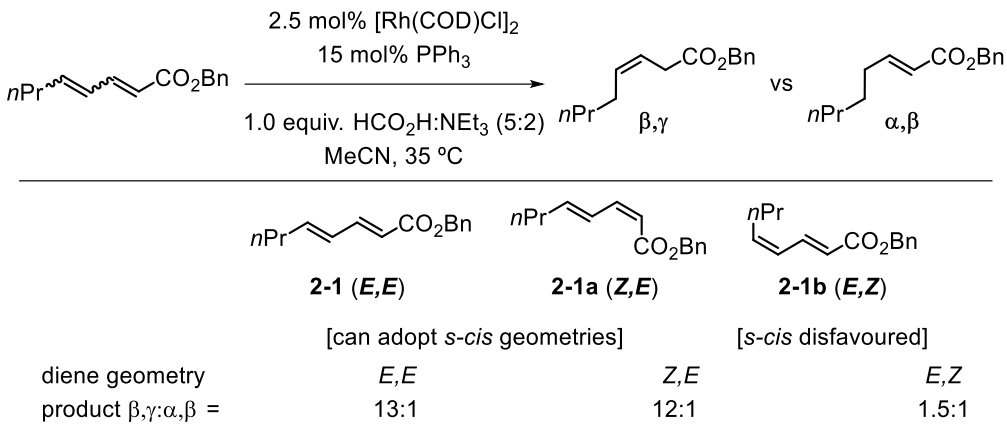


Fig. 2-8 Effect of diene geometry on regioselectivity of Rh-catalyzed formate-mediated *Z*-selective 1,6-reduction of electron deficient dienes.

The ability to selectively generate a diene coordinated Rh-hydride under the optimized conditions appears to be key for an efficient transformation.[82, 84] In line with the argument, both **2-1** (*E,E)* and **2-1a** (*Z,E)*-dienoates that can readily adopt *s-cis* conformations undergo 1,6-reduction with high regioselectivity (>10:1 for the β,γ-product). **2-1b** (*E,Z)*-dienoate that would experience significant steric repulsion in an *s-cis* configuration from the *Z*-positioned alkyl group is reduced with low selectivity (**Fig. 2-8)**. Under the standard condition, certain substrates with phenyl alkyne units such as phenyl propargyl sorbate (**2-46**), allyl sorbate (**2-47**), substitution at the α- (**2-48**) and δ-position (**2-49**) of the dienoate, conjugated triene (**2-50**), dienoic acid (**2-51**), secondary dienamide (**2-52**), *N*-methyl pyrazole substituted dienoate (**2-53**) and other complex bioactive derivatives (**2-54**) showed less reactivity (**Fig. 2-9)**. The lesser reactivity is attributed among other factors to the presence of stronger coordination of the Rh to more reactive functionalities (**2-46)**, steric factors which prevents the formation of a Rh–diene square planar complex required for the chemo- and regioselectivity of the reaction (**2-48** and **2-49**), the presence of

extended conjugation resulting in the presence of other electrophilic sites (**2-50**) and solubility issues with the substrate (**2-54**).

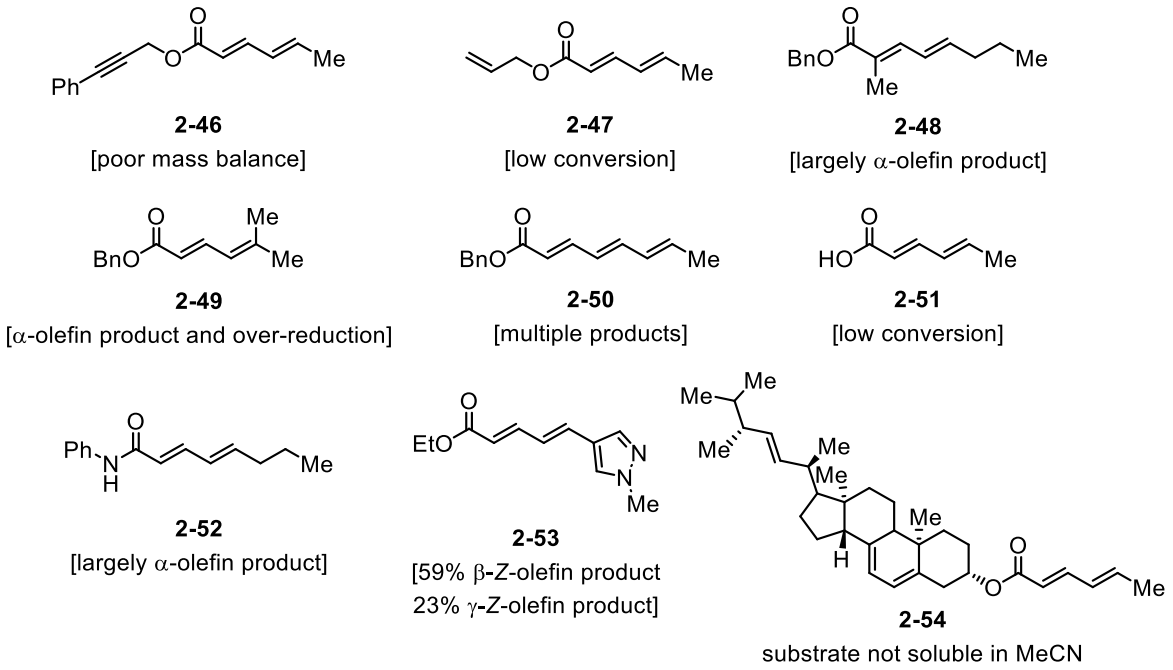


Fig. 2-9 Less successful substrates.

2.3 Summary and Conclusions

In summary, a simple Rh(I)/phosphine catalyst system enables the formate-mediated *Z*-selective reduction of electron deficient dienes via a 1,6-addition process. Mechanistic studies suggest the 1,6-addition process is key to enabling chemoselective diene reductions in the presence of alternative olefin and alkyne units, overcoming difficulties associated with existing catalytic methods. We envision the general concept to extend to related *Z*-selective diene hydrofunctionalization reactions.

2.4 Procedures and Characterization

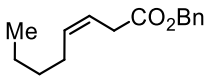
General Consideration: Unless noted, all reactions were conducted under an inert atmosphere employing standard Schlenk techniques or by the use of an N_2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed as described by Still and co-workers[104] (SiliaFlash 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. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied. Reaction progress kinetic analysis experiments were conducted by removing small aliquots of reaction mixtures containing an internal standard, diluting with $CDCl_3$ and analyzing by ^1H NMR (700 MHz).

General Procedure A [ester scope]: In an atmosphere-controlled glovebox, PPh_3 (19.7 mg, 0.075 mmol, 0.15 equiv.) and $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.025 equiv.) were weighed into separate one dram vials. To the $[Rh(COD)Cl]_2$ was added MeCN (1.0 mL) and the solution was transferred into the vial containing the PPh_3. MeCN (2 × 0.25 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the PPh_3 to make catalyst mixture. To a one dram vial was weighed diene (0.5 mmol, 1 equiv.), followed by addition of the catalyst solution. Additional MeCN (2 x 0.25 mL) was used to wash the remaining catalyst solution into the diene containing vial. Formic acid/triethylamine (5:2, 43.2 mg, 0.5 mmol, 1.0 equiv.), was weighed into a half dram vial and then transferred into the vial containing the reaction mixture. The formic acid/triethylamine containing vial was

washed into the solution with MeCN (2 x 0.25 mL). A stir bar was added into the mixture, the vial was capped with a PTFE-line cap, taken out of the glovebox and placed in an aluminum block heated to 35 ºC and the mixture was stirred. The reaction progress was monitored periodically by NMR and quenched once ~90% conversion of the diene was observed. [Note: If 1.00 equiv. of formic acid is employed, the reaction can proceed for prolonged periods without isomerization and over-reduction, and the reaction is not time-sensitive. The use of excess formic acid can result in *Z*-olefin isomerization and over-reduction.] The solution was filtered through silica to quench the reaction, concentrated *in vacuo* and purified by silica gel chromatography. Confirmation of *Z*-olefin geometry was established by comparison of ^{1}H NMR shifts, coupling constants to reported compounds and through-space NMR correlation experiments establishing the proximity of protons at C2 and C5.

General Procedure B [amide scope] In an atmosphere controlled glovebox, tri(4-fluoro-phenyl)phosphine (19.0 mg, 0.0600 mmol, 0.12 equiv.) and $[Rh(COD)Cl]_2$ (3.8 mg, 0.00750 mmol, 0.015 equiv.) were weighted into separate one dram vial. To the $[Rh(COD)Cl]_2$ was added MeCN (0.50 mL), shaken to dissolve and the solution was transferred to the vial containing the phosphine. Additional MeCN (0.50 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the phosphine to make the $[Rh(COD)Cl]_2$/phosphine solution. To a one dram vial was added dienamide (0.50 mmol, 1.0 equiv.), followed by the catalyst solution. Additional MeCN (0.50 mL) was used to wash the remaining catalyst solution into the dienamide solution. To a separate one dram vial was added formic acid/triethylamine (5:2; 41.0 mg, 0.475 mmol, 0.95 equiv.) and MeCN (0.50 mL). The solution was then added to the reaction mixture. Additional MeCN

(0.50 mL) was used to wash the remaining formic acid solution into the mixture, followed by a teflon coated magnetic stir bar. The vial was capped with a PTFE-lined cap, taken out of the glovebox, placed in an aluminum block heated to 60 °C and stirred overnight. Upon the completion of the reaction, the mixture was concentrated *in vacuo* and purified by chromatography.

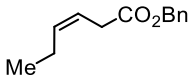


2-2 Prepared according to the General Procedure A from the corresponding diene (115.2 mg, 0.50 mmol). Crude diene conversion: 91%, crude product yield: 80% [96:4 *Z:E*]. Isolated in 74% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 – 7.31 (m, 5H), 5.61 – 5.55 (m, 2H), 5.13 (s, 2H), 3.14 (d, J = 5.6 Hz, 2H), 2.04 (q, J = 6.6 Hz, 2H), 1.36 – 1.29 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.9, 136.0, 133.7, 128.6, 128.2 (2), 120.6, 66.4, 33.0, 31.4, 27.1, 22.3, 13.9;

HRMS (**EI**): calcd for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463. Found 232.1461.



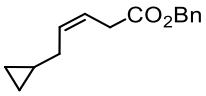
2-3 Prepared according to the General Procedure A from the corresponding diene (101.1 mg, 0.50 mmol). Crude diene conversion: 95%, crude product yield: 82% [96:4

Z:E]. Isolated in 75% yield as a colorless oil after purification by column chromatography (20:1 Hex/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 – 7.31 (m, 5H), 5.61 – 5.52 (m, 2H), 5.13 (s, 2H), 3.14 (d, *J* = 6.8 Hz, 2H), 2.06 (q, *J* = 7.6 Hz, 2H), 0.97 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.9, 136.0, 135.3, 128.6, 128.2 (2), 120.0, 66.4, 32.9, 20.7, 13.9;

HRMS (**EI**): calcd for $C_{13}H_{16}O_2$ $[M]^+$ 204.1150. Found 204.1150.

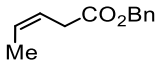


2-4 Prepared according to the General Procedure A from the corresponding diene (114.1 mg, 0.50 mmol). Crude diene conversion: 92%, crude product yield: 72% [97:3 *Z:E*]. Isolated in 67% yield as a colorless oil after purification by column chromatography (20:1 Hex/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 – 7.32 (m, 5H), 5.69 – 5.66 (m, 1H), 5.62 – 5.58 (m, 1H), 5.13 (s, 2H), 3.13 (d, *J* = 6.9 Hz, 2H), 1.98 (t, *J* = 6.9 Hz, 2H), 0.73 – 0.70 (m, 1H), 0.41 (q, *J* = 6.1 Hz, 2H), 0.06 (q, *J* = 5.8 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.8, 135.8, 132.6, 128.6, 128.2(2), 120.7, 66.4, 33.1, 32.0, 10.5, 4.1;

HRMS (**ESI**): calcd for $C_{15}H_{18}O_2Na$ $[M+Na]^+$ 253.1199. Found 253.1201.

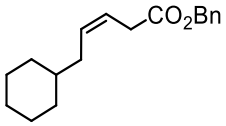


2-5 Prepared according to the General Procedure A from the corresponding diene (94.0 mg, 0.50 mmol). Crude diene conversion: 94%, crude product yield: 80% [90:10 *Z:E*]. Isolated in 69% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.32 (m, 5H), 5.69 – 5.65 (m, 1H), 5.63 – 5.59 (m, 1H), 5.13 (s, 2H), 3.15 (d, *J* = 7.0 Hz, 2H), 1.64 (d, *J* = 6.7 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.8, 136.0, 128.6, 128.3, 128.2, 127.7, 121.6, 66.4, 32.7, 13.0;

HRMS (**EI**): calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994. Found 190.0994.

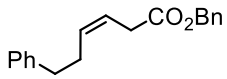


2-6 Prepared according to the General Procedure A from the corresponding diene (135.2 mg, 0.50 mmol). Crude diene conversion: 91%, crude product yield: 81% [85:15 *Z:E*]. Isolated in 65% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.31 (m, 5H), 5.63 – 5.59 (m, 2H), 5.13 (s, 2H), 3.14 (d, *J* = 6.7 Hz, 2H), 1.93 (t, *J* = 7.6 Hz, 2H), 1.70-1.62 (m, 5H), 1.32 – 1.10 (m, 4H), 0.93-0.85 (m, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.9, 136.0, 132.2, 128.5, 128.2 (2), 121.2, 66.4, 38.0, 35.2, 33.1, 26.5, 26.3;

HRMS (**EI**): calcd for $C_{18}H_{24}O_2$ $[M]^+$ 272.1776. Found 272.1770.



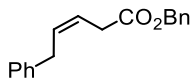
2-7 Prepared according to the General Procedure A from the corresponding diene (139.1 mg, 0.50 mmol). Crude diene conversion: 93%, crude product yield: 81% [96:4 *Z:E*]. Isolated in 75% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O), using Ag/SiO_2.

Gram-scale reaction Procedure: In an atmosphere controlled glovebox, PPh_3 (192 mg, 0.73 mmol 0.12 equiv.) and $[Rh(COD)Cl]_2$ (60.1 mg, 0.120 mmol, 0.02 equiv.) were weighed into separate four dram vials. To the vial containing $[Rh(COD)Cl]_2$ was added MeCN (10.5 mL) and the solution was transferred into the vial containing the PPh_3. MeCN (2 x 2.5 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the PPh_3 to make catalyst mixture. To a 50 mL round bottom flask was weighed diene (1.70 g, 6.10 mmol, 1.00 equiv.), followed by the addition of catalyst solution. Additional MeCN (2 x 5.0 mL) was used to wash the remaining catalyst solution into the diene containing flask. Formic acid/triethylamine (5:2, 527 mg, 6.10 mmol, 1.00 equiv.), was weighed into a four dram vial and then transferred into the flask containing the reaction mixture. The formic acid containing vial was washed into the solution with MeCN (2 x 2.5 mL). A stir bar was added into the mixture, the round bottom flask was capped with a rubber septum, taken out of the glovebox and placed in an aluminum block heated to 40 ^oC and stirred. The reaction progress was monitored by NMR and quenched once ~95% conversion (29 h) of the diene was observed. The solution was filtered through silica to quench the reaction, concentrated *in vacuo* and purified by silica gel chromatography.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.32 (m, 5H), 7.28 – 7.25 (m, 2H), 7.19 – 7.15 (m, 3H), 5.63 – 5.60 (m, 2H), 5.11 (s, 2H), 3.06 (d, *J* = 6.3 Hz, 2H), 2.67 (t, J = 8.3 Hz, 2H), 2.39 – 2.34 (m, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.7, 141.6, 136.0, 132.4, 128.6, 128.5, 128.4, 128.3, 128.2, 125.9, 121.5, 66.5, 35.5, 33.0, 29.4;

HRMS (**EI**): calcd for $C_{19}H_{20}O_2$ $[M]^+$ 280.1463. Found 280.1460.

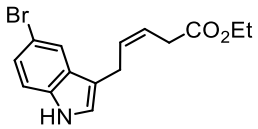


2-8 Prepared according to the General Procedure A from the corresponding diene (132.1 mg, 0.50 mmol). Crude diene conversion: 95%, crude product yield: 79% [96:4 *Z:E*]. Isolated in 74% yield as a colorless oil after purification by silica column chromatography (20:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.34 (m, 5H), 7.30 – 7.27 (m, 2H), 7.22 – 7.17 (m, 3H), 5.82 – 5.73 (m, 2H), 5.16 (s, 2H), 3.42 (d, *J* = 7.5 Hz, 2H), 3.27 (d, *J* = 6.6 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.5, 140.0, 135.8, 131.8, 128.6, 128.5, 128.3 (2), 128.2, 126.1, 121.7, 66.5, 33.6, 33.0;

HRMS (**ESI**): calcd for $C_{18}H_{18}O_2Na$ $[M+Na]^+$ 289.1199. Found 289.1194.



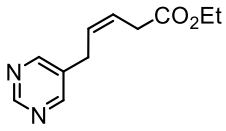
2-9 Prepared according to the General Procedure A from the corresponding diene (96.0 mg, 0.30 mmol). Crude diene conversion: 90%, crude product yield: 77% [96:4 *Z:E*].

Isolated in 73% yield as a light-yellow oil after purification by column chromatography (4:1 Hex/EtOAc gradient) using SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (br s, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.23 (m, 1H), 7.00 (m, 1H), 5.91 – 5.85 (m, 1H), 5.78 – 5.73 (m 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.49 (d, *J* = 7.2 Hz, 2H), 3.26 – 3.24 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.9, 135.1, 131.1, 129.1, 125.0, 122.8, 122.1, 121.6, 114.4, 112.7, 112.6, 60.8, 33.1, 23.3, 14.3;

HRMS (**EI**): calcd for $C_{15}H_{16}BrNO_2$ $[M]^+$: 323.0344. Found 323.0346.

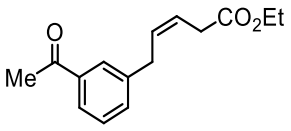


2-10 Prepared according to the General Procedure A from the corresponding diene (102.0 mg, 0.50 mmol). Crude diene conversion: 83%, crude product yield: 68% [96:4 *Z:E*]. Isolated in 61% yield (contains ~4% *E*-product) as a colorless oil after purification by column chromatography (1:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.08 (s, 1H), 8.58 (s, 2H), 5.85 – 5.81 (m, 1H), 5.74 – 5.69 (m, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 3.42 (d, *J* = 7.2 Hz, 2H), 3.19 (d, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1, Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.1, 157.1, 156.7, 133.3, 128.7, 124.3, 61.0, 33.1, 28.4, 14.2;

HRMS (**EI**): calcd for $C_{11}H_{14}O_2N_2$ $[M]^+$ 206.1055 Found 206.1054.

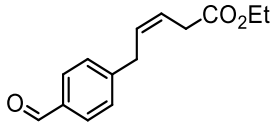


2-11 Prepared according to the General Procedure A from the corresponding diene (73.2 mg, 0.30 mmol). Crude diene conversion: 90%, crude product yield: 75% [95:5 *Z:E*]. Isolated in 62% yield as a colorless oil after purification by column chromatography (4:1 Hex/EtOAc gradient) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 – 7.80 (m, 2H), 7.42 – 7.40 (m, 2H), 5.80 – 5.79 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.50 – 3.48 (m, 2H), 3.22 – 3.20 (m, 2H), 2.61 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 101 MHz) δ 198.3, 171.6, 140.8, 137.5, 133.2, 130.9, 128.8, 128.2, 126.4, 122.8, 60.9, 33.5, 33.2, 26.7, 14.3;

HRMS (**EI**): calcd for $C_{15}H_{18}O_3$ $[M]^+$: 246.1260. Found 246.1259.

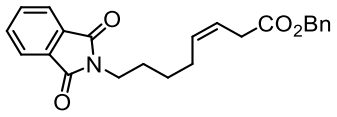


2-12 Prepared according to the General Procedure A from the corresponding diene (69.1 mg, 0.30 mmol). Crude diene conversion: 90%, crude product yield: 73% [96:4 *Z:E*]. Isolated in 66% yield as a colorless oil after purification by column chromatography (4:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.98 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 5.81 – 5.73 (m, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.50 (d, *J* = 5.5 Hz, 2H), 3.19 (d, *J* = 5.5 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.0, 171.5, 147.5, 134.8, 130.2, 130.1, 129.1, 123.2, 60.9, 33.9, 33.2, 14.2;

HRMS (**EI**): calcd for $C_{14}H_{16}O_3$ $[M]^+$: 232.1099. Found 232.1097.

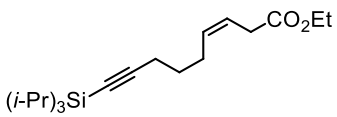


2-13 Prepared according to the General Procedure A from the corresponding diene (187.6 mg, 0.50 mmol). Crude diene conversion: 93%, crude product yield: 78% [97:3 *Z:E*]. Isolated in 69% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 – 7.81 (m, 2H), 7.72 – 7.69 (m, 2H), 7.38 – 7.30 (m, 5H), 5.60 – 5.54 (m, 2H), 5.12 (s, 2H), 3.67 (t, *J* = 7.5 Hz, 2H), 3.14 (d, *J* = 6.1 Hz, 2H), 2.09 (q, *J* = 7.4 Hz, 2H), 1.68 (qu, *J* = 7.5 Hz, 2H), 1.41 (qu, *J* = 7.5 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.7, 168.4, 135.9, 133.9, 132.8, 132.2, 128.5, 128.3 (2), 123.2, 121.3, 66.4, 37.8, 33.0, 28.1, 26.9, 26.4;

HRMS (**ESI**): calcd for $C_{23}H_{23}NO_4Na$ $[M+Na]^+$ 400.1519. Found 400.1514.



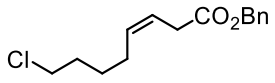
2-14 Prepared according to the General Procedure A from the corresponding dienyne (90.0 mg, 0.27 mmol). Crude dienyne conversion: 93%, crude product yield: 74% [97:3 *Z:E*]. To facilitate product isolation, the unreacted starting material and conjugated side-products were arylated by the following procedure. To the crude mixture in a vial under N_2

atmosphere was added 4-methoxyphenylboronic acid (41.00 mg, 0.27 mmol, 1.00 equiv.), $[Rh(COD)Cl]_2$ (1.33 mg, 0.0027 mmol, 0.01 equiv.) in dioxane (0.20 M) and KOH solution (1.50 M, 1.00 equiv.). The vial was then placed in an aluminum block heated to 35 ºC and stirred. The reaction progress was monitored by NMR and quenched as soon as remaining starting material and conjugated ester were consumed. Isolated in 64% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.63 – 5.54 (m, 2H), 4.13 (q, *J* = 7.4 Hz, 2H), 3.11 (d, *J* = 6.4 Hz, 2H), 2.27 – 2.24 (m, 2H), 2.21 – 2.16 (m, 2H), 1.63 – 1.57 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.08 – 0.98 (m, 21H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.0, 132.2, 122.0, 108.7, 60.6, 33.0, 28.8, 26.4, 19.3, 18.6, 18.3, 18.1, 14.2, 11.3;

HRMS (**EI**): calcd for $C_{20}H_{36}O_2Si$ $[M]^+$ 321.2250. Found 321.2251.

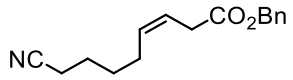


2-15 Prepared according to the General Procedure A from the corresponding diene (132.1 mg, 0.50 mmol). Crude diene conversion: 91%, crude product yield: 82% [98:2 *Z:E*]. Isolated in 78% yield as a colorless oil after purification by column chromatography (10:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.32 (m, 5H), 5.61 – 5.56 (m, 2H), 5.13 (s, 2H), 3.50 (t, *J* = 7.6 Hz, 2H), 3.14 (d, *J* = 6.8 Hz, 2H), 2.08 (q, *J* = 7.6 Hz, 2H), 1.78 – 1.73 (m, 2H), 1.54 – 1.50 (m, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.6, 135.9, 132.8, 128.6, 128.3, 128.2, 121.4, 66.5, 44.9, 33.0, 32.0, 26.7, 26.5;

HRMS (**EI**): calcd for $C_{15}H_{19}ClO_2$ $[M]^+$ 266.1074. Found 266.1076.

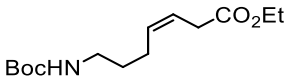


2-16 Prepared according to the General Procedure A from the corresponding diene (127.5 mg, 0.50 mmol). Crude diene conversion: 85%, crude product yield: 77% [98:2 *Z:E*]. Isolated in 70% yield as a light-yellow oil after purification by column chromatography (4:1 Hex/EtOAc gradient), using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.34 (m, 5H), 5.68 – 5.54 (m, 2H), 5.15 (s, 2H), 3.16 (t, J = 7.0 Hz, 2H), 2.32 (t, J = 7.0 Hz, 2H), 2.11 (q, J = 7.0 Hz, 2H), 1.67 – 1.62 (m, 2H), 1.57 – 1.53 (m, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.5, 135.9, 132.3, 128.6, 128.4, 128.3, 121.8, 119.6, 66.6, 33.1, 28.2, 26.6, 24.9, 17.1;

HRMS (**EI**): calcd for $C_{16}H_{19}NO_2$ $[M]^+$ 257.1416. Found 257.1414.

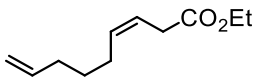


2-17 Prepared according to the General Procedure A from the corresponding diene (187.6 mg, 0.50 mmol). Crude diene conversion: 93%, crude product yield: 74% [97:3 *Z:E*]. Isolated in 71% yield as a colorless oil after purification by column chromatography (4:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60 – 5.53 (m, 2H), 4.62 (bs, 1H), 4.14 (q, J = 7.5 Hz, 2H), 3.13 – 3.06 (m, 4H), 2.08 (q, J = 6.9 Hz, 2H), 1.57 (qu, J = 7.3 Hz, 2H), 1.44 (s, 9H), 1.25 (t, J = 7.1, Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.9, 156.0, 132.3, 121.8, 60.7, 40.0, 33.0, 29.7, 29.5, 28.4, 24.6, 14.2;

HRMS (ESI): calcd for $C_{14}H_{25}NO_4Na$ $[M+Na]^+$ 294.1676. Found 294.1668.

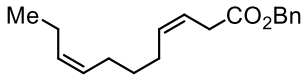


2-18 Prepared according to the General Procedure A from the corresponding triene (72.0 mg, 0.40 mmol). Crude triene conversion: 86%, crude product yield: 71% [*Z:E* = 97:3]%. Isolated in 62% yield as a colorless oil after purification by column chromatography (20:1 Hex/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.83 – 5.78 (m, 1H), 5.58 – 5.56 (m, 2H), 5.02 – 4.94 (m, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.08 (d, *J* = 5.0 Hz, 2H), 2.08 – 2.04 (m, 4H), 1.50 – 1.46 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 138.6, 133.0, 121.3, 114.7, 60.6, 33.3, 33.1, 28.5, 26.8, 14.3;

HRMS (EI): calcd for $C_{11}H_{18}O_2$ $[M]^+$: 182.1307. Found 182.1305.



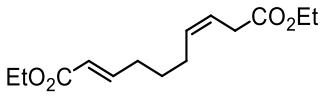
2-19 Prepared according to the General Procedure A from the corresponding triene (65.5 mg, 0.25 mmol). Crude triene conversion: 86%, crude product yield: 79% [97:3 *Z:E*]. To facilitate product isolation, the unreacted starting material and conjugated side-products were arylated by the following procedure. To the crude mixture in a vial under N_2 atmosphere was added 4-methoxyphenylboronic acid (75.97 mg, 0.50 mmol, 1.00 equiv.),

[Rh(COD)Cl]$_2$ (1.23 mg, 0.0025 mmol, 0.005 equiv.) in dioxane (0.20 M) and KOH solution (1.50 M, 0.5 equiv.). The vial was then placed in an aluminum block heated to 35 ^{o}C and stirred. The reaction progress was monitored by NMR and quenched as soon as remaining starting material and conjugated ester were consumed. Isolated in 74% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et$_2$O) using Ag/SiO$_2$.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.31 (m, 5H), 5.62 – 5.55 (m, 2H), 5.47 – 5.27 (m, 2H), 5.13 (s, 2H), 3.14 (d, *J* = 4.8 Hz, 2H), 2.07-1.97 (m, 6H), 1.42 (qu, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.8, 135.9, 133.4, 132.1, 128.6(2), 128.2(2), 120.9, 66.4, 33.0, 29.3, 27.0, 26.6, 20.5, 14.3;

HRMS (**EI**): calcd for $C_{18}H_{24}O_2$ $[M]^+$ 272.1776. Found 272.1774.

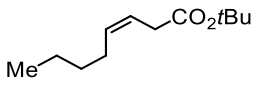


2-20 Prepared according to the General Procedure A from the corresponding triene (50.5 mg, 0.20 mmol). Crude triene conversion: 93%, crude product yield: 72% [96:4 *Z:E*]. Isolated in 62% yield as a colorless oil after purification by column chromatography (4:1 Pentane/Et$_2$O) using Ag/SiO$_2$.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.96 – 6.89 (m, 1H), 5.81 (d, *J* = 15.5 Hz, 1H), 5.61 – 5.52 (m, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.05 (d, *J* = 7.0 Hz, 2H), 2.22 – 2.18 (m, 2H), 2.09 – 2.06 (m, 2H), 1.56 – 1.52 (m, 2H), 1.27 (t, *J* = 7.5 Hz, 3H), 1.25 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 166.6, 148.7, 132.3, 121.8, 121.7, 60.6, 60.2, 33.1, 31.6, 27.6, 26.8, 14.3, 14.2;

HRMS (EI): calcd for $C_{14}H_{22}O_4$ $[M]^+$: 254.1518. Found 254.1515.

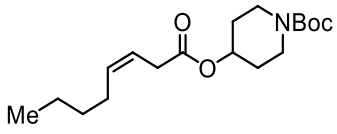


2-21 Prepared according to the General Procedure A from the corresponding diene (98.1 mg, 0.50 mmol). Crude diene conversion: 91%, crude product yield: 80% [96:4 *Z:E*]. Isolated in 56% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.54 – 5.53 (m, 2H), 2.99 (d, J = 6.3 Hz, 2H), 2.04 (q, J = 7.7 Hz, 2H), 1.45 (s, 9H), 1.35-1.32 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.5, 138.1, 121.4, 80.4, 34.4, 31.6, 28.1, 27.2, 22.3, 14.0;

HRMS (**ESI**): calcd for $C_{12}H_{22}O_2Na$ $[M+Na]^+$ 221.1512. Found 221.1514.

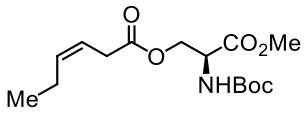


2-22 Prepared according to the General Procedure A from the corresponding diene (161.7 mg, 0.50 mmol). Crude diene conversion: 92%, crude product yield: 73% [95:5 *Z:E*]. Isolated as a colorless oil in 64% yield after purification by column chromatography (4:1 Hex/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.56 – 5.53 (m, 2H), 4.93 – 4.92 (m, 1H), 3.69 – 3.66 (m, 2H), 3.26 – 3.20 (m, 2H), 3.08 (d, *J* = 6.0 Hz, 2H), 2.05 – 2.02 (m, 2H), 1.85 – 1.81 (m, 2H), 1.61 – 1.58 (m, 2H), 1.45 (s, 9H), 1.35 – 1.30 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 154.8, 133.7, 120.7, 79.7, 69.9, 41.0 (br), 33.3, 31.5, 30.6, 28.5, 27.1, 22.3, 14.0;

HRMS (ESI): calcd for $C_{18}H_{31}NNaO_4$ $[M + Na]^+$: 348.2145. Found 348.2145.

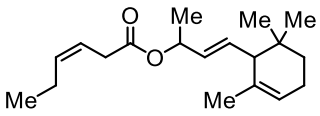


2-23 Prepared according to the General Procedure A from the corresponding diene (62.6 mg, 0.20 mmol). Crude diene conversion: 92%, crude product yield: 68% [94:6 *Z:E*]. Isolated as a colorless oil in 57% yield after purification by chromatography (4:1 Hex/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.61 – 5.56 (m, 1H), 5.49 – 5.44 (m, 1H), 5.28 – 5.26 (m, 1H), 4.58 – 4.56 (m, 1H), 4.47 – 4.44 (m, 1H), 4.34 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.76 (s, 3H), 3.08 (d, *J* = 7.0 Hz, 2H), 2.06 – 2.01 (m, 2H), 1.45 (s, 9H), 0.98 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 170.3, 155.2, 135.5, 119.6, 80.4, 64.5, 53.0, 52.8, 32.6, 28.3, 20.8, 13.9;

HRMS (ESI): calcd for $C_{15}H_{25}NNaO_6$ $[M + Na]^+$: 338.1574. Found 338.1570.

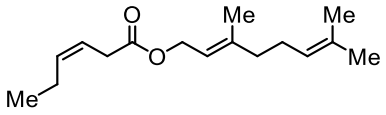


2-24 Prepared according to the General Procedure A from the corresponding tetraene (144.1 mg, 0.50 mmol). Crude tetraene conversion: 85%, crude product yield: 71% [95:5 *Z:E*]. To facilitate product isolation, the unreacted starting material and conjugated side-products were arylated by the following procedure. To the crude mixture in a vial under N_2 atmosphere was added 4-methoxyphenylboronic acid (76.0 mg, 0.50 mmol, 1.00 equiv.), $[Rh(COD)Cl]_2$ (1.2 mg, 0.0025 mmol, 0.005 equiv.) in dioxane (0.20 M) and KOH solution (1.50 M, 0.5 equiv.). The vial was then placed in an aluminum block heated to 35 ºC and stirred. The reaction progress was monitored by NMR and quenched as soon as remaining starting material conjugated ester were consumed. Isolated in 64% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.57 – 5.32 (m, 6H), 3.05 (d, *J* = 6.4 Hz, 2H), 2.08 – 1.98 (m, 5H), 1.55 (s, 3H), 1.43 – 1.36 (m, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.18 – 1.13 (m, 1H), 0.97 (t, *J* = 7.9 Hz, 3H), 0.87 (s, 3H), 0.79 (s, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.2, 135.0, 133.9, 133.7, 131.1, 121.2, 120.4, 71.2, 53.9, 33.3, 31.9, 31.6, 27.4, 27.0, 23.0, 22.8, 20.7, 20.5, 13.9;

HRMS (**EI**): calcd for $C_{19}H_{30}O_2$ $[M]^+$ 234.1620. Found 234.1620.



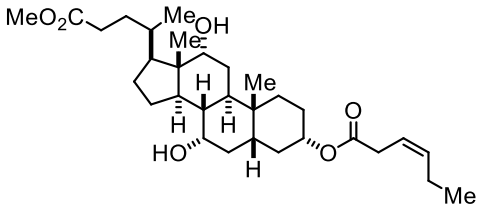
2-25 Prepared according to the General Procedure A from the corresponding tetraene (124.1 mg, 0.50 mmol). Crude diene conversion: 87%, crude product yield: 78% [95:5

Z:E]. Isolated in 72% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.59 – 5.50 (m, 2H), 5.34 (t, *J* = 7.2 Hz, 1H), 5.08 (t, *J* = 7.1 Hz, 1H), 4.61 (d, *J* = 7.2 Hz, 2H), 3.09 (d, *J* = 6.5 Hz, 2H), 2.11 – 2.02 (m, 6H), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 0.97 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.1, 142.3, 135.1, 131.9, 123.8, 120.3, 118.3, 61.6, 39.6, 33.0, 26.3, 25.7, 20.8, 17.7, 16.5, 14.0;

HRMS (**EI**): calcd for $C_{16}H_{26}O_2$ $[M]^+$ 250.1933. Found 250.1933.

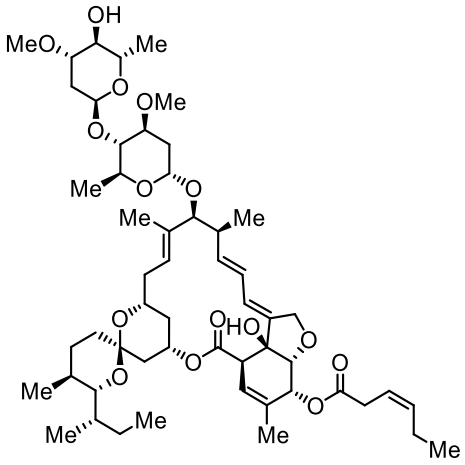


2-26 Prepared according to the General Procedure A from corresponding methyl cholate-derived dienyl ester (103.3 mg, 0.20 mmol). Crude diene conversion: 94%, crude product yield: 58% [95:5 *Z:E*]. Isolated as a white solid in 53% yield after purification by column chromatography (1:2 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60 – 5.49 (m, 2H), 4.62 – 4.55 (m, 1H), 3.99 (s, 1H), 3.86 (s, 1H), 3.67 (s, 3H), 2.98 (d, *J* = 6.0 Hz, 2H), 2.42 – 2.17 (m, 4H), 2.11 – 2.02 (m, 2H), 2.00 – 1.03 (m, 24H), 1.00 – 0.97 (m, 6H), 0.91 (s, 3H), 0.70 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 171.9, 136.0, 120.9, 74.4, 72.9, 68.2, 51.5, 47.2, 46.6, 42.1, 41.2, 39.6, 38.5, 35.2, 35.1, 34.9, 34.7, 34.3, 31.1, 30.9, 28.4, 27.4, 26.8, 26.6, 25.5, 23.1, 22.6, 17.4, 13.5, 12.6;

HRMS (ESI): calcd for $C_{31}H_{54}NO_6$ $[M + NH_4]^+$: 536.3946. Found 536.3954.

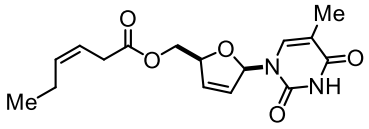


2-27 Prepared according to the General Procedure A from the corresponding ivermectin-derived dienyl ester (96.9 mg, 0.10 mmol). Crude diene conversion: 92%, crude product yield: 70% [90:10 *Z:E*]. Isolated in 59% yield as a white solid after purification by chromatography (1:3 Pentane/Et_2O) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.85 – 5.83 (m, 1H), 5.77 – 5.67 (m, 2H), 5.63 – 5.54 (m, 4H), 5.39 (d, *J* = 4.0 Hz, 1H), 5.37 – 5.30 (m, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.78 (d, *J* = 3.5 Hz, 1H), 4.67 – 4.55 (m, 2H), 4.08 (d, *J* = 6.0 Hz, 1H), 4.03 (s, 1H), 3.94 (s, 1H), 3.86 – 3.74 (m, 2H), 3.70 – 3.60 (m, 2H), 3.51 – 3.45 (m, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.36 – 3.34 (m, 1H), 3.26 – 3.15 (m, 5H), 2.53 – 2.45 (m, 2H), 2.35 – 2.20 (m, 4H), 2.09 – 1.98 (m, 3H), 1.78 – 1.16 (m, 27H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.86 – 0.78 (m, 7H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 171.7, 139.5, 138.0, 135.4, 135.1, 133.6, 124.7, 120.7, 120.3, 120.0, 118.4, 98.6, 97.5, 94.8, 81.8, 80.6, 80.5, 79.4, 78.2, 77.4, 76.8, 76.2, 70.3, 68.9, 68.3, 68.2, 67.3, 56.6, 56.5, 45.7, 41.3, 39.8, 36.9, 35.8, 35.5, 34.6, 34.2(2), 32.6, 31.3, 31.0, 28.1, 27.4, 20.8, 20.3, 19.6, 18.5, 17.7, 17.5, 15.2, 13.9, 12.5, 12.1;

HRMS (ESI): calcd for $C_{54}H_{82}NaO_{15}$ $[M + Na]^+$: 993.5546. Found 993.5547.



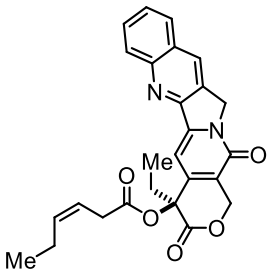
2-28 In an atmosphere controlled glovebox, PPh_3 (15.7 mg, 0.06 mmol, 0.30 equiv.) and $[Rh(COD)Cl]_2$ (4.90 mg, 0.01 mmol, 0.05 equiv.) were weighted into separate one dram vial. To the $[Rh(COD)Cl]_2$ was added MeCN (0.40 mL), shaken to dissolve and the solution was transferred to the vial containing the phosphine. Additional MeCN (0.40 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the phosphine to make the catalyst solution. To a one dram vial was added diene (63.6 mg, 0.20 mmol, 1.0 equiv.), followed by the catalyst solution. Additional MeCN (0.40 mL) was used to wash the remaining catalyst solution into the substrate containing vial. To another one dram vial was added formic acid/triethylamine (5:2; 51.9 mg, 0.60 mmol, 3.0 equiv.) and MeCN (0.20 mL). The solution was then added to the reaction mixture. Additional MeCN (0.20 mL) was used to wash the remaining formic acid solution into the mixture. DMSO (0.40 mL) was added to the mixture as co-solvent, followed by a teflon coated magnetic stir bar. The vial was capped with a PTFE-lined cap, taken out of the glovebox, placed in an aluminum block heated to 35 °C and stirred overnight. Upon the completion of the reaction, the mixture was diluted by EtOAc (10 mL), extracted with water (3 × 10 mL), concentrated *in vacuo* and purified by chromatography. Crude diene conversion: 91%, crude product yield: 70% [94:6 *Z:E*]. Isolated in 52% yield as a white solid after purification by column chromatography (20:1 DCM/MeOH) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (br, 1H), 7.21 – 7.20 (m, 1H), 7.00 – 6.99 (m, 1H), 6.29 – 6.27 (m, 1H), 5.92 – 5.90 (m, 1H), 5.64 – 5.58 (m, 1H), 5.52 – 5.46 (m, 1H),

5.07 – 5.04 (m, 1H), 4.42 (dd, J = 10.0, 4.5 Hz, 1H), 4.25 (dd, J = 12.0, 3.5 Hz, 1H), 3.11 (d, J = 7.0 Hz, 2H), 2.04 – 2.03 (m, 2H), 1.93 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 163.3, 150.5, 135.8, 135.4, 133.3, 127.4, 119.3, 111.1, 89.9, 84.2, 65.0, 32.6, 20.9, 13.9, 12.6;

HRMS (ESI): calcd for $C_{16}H_{19}N_2O_5$ [M - H]$^-$: 319.1299. Found 319.1298.



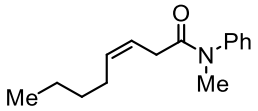
2-29 In an atmosphere controlled glovebox, PPh_3 (7.9 mg, 0.030 mmol, 0.30 equiv.) and $[Rh(COD)Cl]_2$ (2.5 mg, 0.005 mmol, 0.05 equiv.) were weighted into separate one dram vial. To the $[Rh(COD)Cl]_2$ was added MeCN (0.20 mL), shaken to dissolve and the solution was transferred to the vial containing the phosphine. Additional MeCN (0.20 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the phosphine to make the catalyst solution. To a one dram vial was added substrate (44.2 mg, 0.10 mmol, 1.0 equiv.), followed by the catalyst solution. Additional MeCN (0.20 mL) was used to wash the remaining catalyst solution into the reaction vial. To another one dram vial was added formic acid/triethylamine (5:2; 17.3 mg, 0.20 mmol, 2.0 equiv.) and MeCN (0.10 mL). The solution was then added to the reaction mixture. Additional MeCN (0.10 mL) was used to wash the remaining formic acid into the mixture. DMSO (0.20 mL) was added to the mixture as co-solvent, followed by a teflon coated magnetic stir bar. The vial was capped with a PTFE-lined cap, taken out of the glovebox, placed in an aluminum block heated to

35 °C and stirred overnight. Upon the completion of the reaction, the mixture was diluted by EtOAc (10 mL), extracted with water (3 × 10 mL), concentrated *in vacuo* and purified by chromatography. Crude diene conversion: 94%, crude product yield: 82% [83:17 *Z:E*]. Isolated in 50% yield as a white solid after purification by column chromatography (20:1 DCM/MeOH), using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.39 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.85 – 7.83 (m, 1H), 7.68 – 7.66 (m, 1H), 7.21 (s, 1H), 5.67 (d, *J* = 17.5 Hz, 1H), 5.65 – 5.63 (m, 1H), 5.53 – 5.50 (m, 1H), 5.41 (d, *J* = 17.5 Hz, 1H), 5.32 – 5.25 (m, 2H), 3.27 (d, *J* = 7.0 Hz, 2H), 2.31 – 2.04 (m, 4H), 1.00 – 0.97 (m, 6H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 170.9, 167.5, 157.4, 152.5, 149.0, 146.3, 145.9, 136.3, 131.2, 130.7, 129.7, 128.5, 128.3, 128.2, 128.1, 120.4, 118.9, 96.0, 76.0, 67.1, 50.0, 32.5, 31.9, 20.9, 13.9, 7.6;

HRMS (ESI): calcd for $C_{26}H_{24}N_2NaO_5$ $[M + Na]^+$: 467.1577. Found 467.1582.

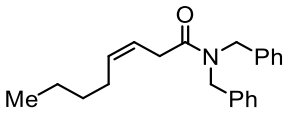


2-31 Prepared according to the General Procedure B from the corresponding diene (114.7 mg, 0.50 mmol). Crude diene conversion: 93%, crude product yield: 61% [92:8 *Z:E*]. Isolated in 51% yield as a colorless oil after purification by column chromatography (4:1 Hex/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 – 7.40 (m, 2H), 7.35 – 7.32 (m, 1H), 7.20 – 7.18(m, 2H), 5.51-5.43 (m, 2H), 3.27 (s, 3H), 2.88 (d, *J* = 5.0 Hz, 2H), 1.74 – 1.70 (m, 2H), 1.22 – 1.17 (m, 4H), 0.82 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 144.2, 132.5, 129.7, 127.7, 127.4, 122.4, 37.4, 33.2, 31.4, 27.0, 22.3, 13.9;

HRMS (EI): calcd for $C_{15}H_{21}NO$ $[M]^+$: 231.1623. Found 231.1623.

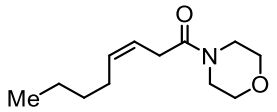


2-32 Prepared according to the General Procedure B from the corresponding diene (164.8 mg, 0.52 mmol). Crude diene conversion: 93%, crude product yield: 63% [95:5 *Z:E*]. Isolated in 59% yield as a colorless oil after purification by chromatography (4:1 Hex/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.36 (m, 2H), 7.33 – 7.30 (m, 3H), 7.28 – 7.25 (m, 1H), 7.22 (d, J = 7.0 Hz, 2H), 7.16 (d, J = 7.0 Hz, 2H), 5.68 – 5.63 (m, 1H), 5.60 – 5.55 (m, 1H), 4.61 (s, 2H), 4.45 (s, 2H), 3.22 (d, J = 6.5 Hz, 2H), 1.98 – 1.93 (m, 2H), 1.32 – 1.23 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 137.5, 136.6, 133.1, 129.0, 128.6, 128.4, 127.7, 127.4, 126.4, 122.0, 50.0, 48.3, 32.7, 31.5, 27.3, 22.4, 13.9;

HRMS (EI): calcd for $C_{22}H_{27}NO$ $[M]^+$: 321.2093. Found 321.2090.



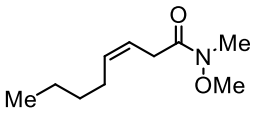
2-33 Prepared according to the General Procedure B from the corresponding diene (104.7 mg, 0.50 mmol). Crude diene conversion: 90%, crude product yield: 61% [94:6

Z:E]. Isolated in 51% yield as a colorless oil after purification by chromatography (4:1 Hexane/EtOAc), using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60 – 5.52 (m, 2H), 3.67 – 3.65 (m, 4H), 3.62 (d, *J* = 5.0 Hz, 2H), 3.47 – 3.45 (m, 2H), 3.13 – 3.11 (m, 2H), 2.08 – 2.03 (m, 2H), 1.38 – 1.31 (m, 4H), 0.90 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 133.1, 121.5, 67.0, 66.7, 46.2, 42.1, 32.6, 31.5, 27.3, 22.4, 14.0;

HRMS (EI): calcd for $C_{12}H_{21}NO_2$ $[M]^+$: 211.1572. Found 211.1575.

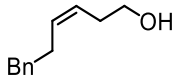


2-34 Prepared according to the General Procedure B from the corresponding diene (91.6 mg, 0.50 mmol). Crude diene conversion: 86%, crude product yield: 78%, selectivity not determined due to overlap of ^{1}H NMR signals. Isolated in 69% yield as a colorless oil after purification by chromatography (4:1 Hexane/EtOAc) using Ag/SiO_2.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60 – 5.57 (m, 2H), 3.70 (s, 3H), 3.22 (d, *J* = 4.5 Hz, 2H), 3.19 (s, 3H), 2.09 – 2.05 (m, 2H), 1.38 – 1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 133.1, 121.5, 61.3, 32.4, 31.6, 31.1, 27.3, 22.4, 14.0;

HRMS (EI): calcd for $C_{10}H_{19}NO_2$ $[M]^+$: 185.1416. Found 185.1418.

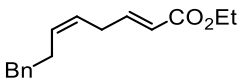


2-36 LiAH (0.18 g, 4.9 mmol, 1.4 equiv.) was added to a 50 mL round bottom flask charged with a stir bar. The flask was purged with 3 times N_2, Et_2O (20 mL, 0.2 M) was added and the reaction mixture was cooled to 0 °C. *Z*-olefin **2f** (1.0 g, 3.6 mmol, 1.0 equiv.) was added dropwise and the mixture was stirred for 2 h at room temperature. Upon completion of the reaction, the solution was re-cooled to 0 °C and diluted with Et_2O. Water (0.18 mL), 2 M NaOH (0.36 mL), additional water (0.54 mL) were added slowly in sequence. The mixture was warmed to room temperature and stirred for 15 min. Na_2SO_4 was then added. The mixture was further stirred for 15 min and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (Ag/SiO_2, 3:1 EtOAc/Hexane). Isolated in 85% yield as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.27 (m, 2H), 7.20 – 7.18 (m, 3H), 5.62 – 5.57 (m, 1H), 5.42 – 5.37 (m, 1H), 3.56 (dt, *J* = 6.5, 6.0 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.43 – 2.38 (m, 2H), 2.28 – 2.23 (m, 2H), 1.20 (t, *J* = 5.5 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.8, 132.2, 128.6, 128.3, 126.1, 125.9, 62.2, 35.9, 30.8, 29.3;

HRMS (EI): calcd for $C_{12}H_{16}O$ $[M]^+$: 176.1201. Found 176.1203.



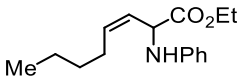
2-37 DMP (0.64 g, 1.5 mmol, 1.0 equiv.) was added to a 50 mL round bottom flask charged with a stir bar. The flask was purged with N_2 and CH_2Cl_2 (15 mL, 0.1 M) followed by **4a** (0.26 g, 1.5 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at room

temperature for 2 h. Upon completion of the reaction, the solution was filtered through a pad of silica, rinsed with Hexane/EtOAc (1:1), concentrated *in vacuo*. Isolated in 82% yield as a colorless oil and used in next step without further purification. NaH (4.8 mg, 0.12 mmol, 1.2 equiv.) was added to a one dram vial charged with a stir bar. The flask was purged with N_2, THF (1 mL, 0.1 M) was added and the solution was cooled to 0 °C. Triethyl phosphonoacetate (24 µl, 0.12 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred for 10 min and the aldehyde prepared above (17 mg, 0.10 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Upon completion of the reaction, the mixture was concentrated *in vacuo* and purified by flash chromatography (10:1 Hexane/EtOAc). Isolated in 89% yield as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 – 7.26 (m, 2H), 7.20 – 7.17 (m, 3H), 6.87 (dt, *J* = 16.0, 6.0 Hz, 1H), 5.77 (d, *J* = 15.5 Hz, 1H), 5.61 – 5.55 (m, 1H), 5.43 – 5.38 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 2.89 (dd, *J* = 7.5, 7.0 Hz, 2H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.36 (dt, *J* = 7.5, 7.5 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7, 147.0, 141.7, 131.6, 128.5, 128.4, 126.0, 125.0, 121.5, 60.2, 35.7, 29.9, 29.2, 14.3;

HRMS (EI): calcd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463. Found 244.1462.



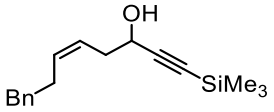
2-38 *p*-ABSA (2.0 g, 8.4 mmol, 2.0 equiv.) was added to a 50 mL round bottom flask charged with a stir bar. The flask was purged with N_2, MeCN (20 mL, 0.2 M) and **2a** (0.72 g, 4.2 mmol, 1.0 equiv.) were added sequentially. The reaction mixture was cooled to 0 °C and DBU (1.3 mL, 8.4 mmol, 2.0 equiv.) was added dropwise. The mixture was stirred at

room temperature for 3.5 h. Upon completion of the reaction, the solution was filtered through a pad of silica, rinsed with Pentane/Et_2O (1:1), concentrated *in vacuo*. Isolated in 81% yield as an orange oil and used in next step without further purification. A four dram vial charged with a stir bar was purged with N_2, aniline (0.21 mL, 2.3 mmol, 5.0 equiv.), the diazo ester prepared above (90 mg, 0.46 mmol, 1.0 equiv.) and benzene (3 mL) were added sequentially. $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol, 0.022 equiv.) was then added in a solution of benzene (2 mL). The reaction mixture was heated at reflux for 10 min. Upon the completion of the reaction, the mixture was concentrated *in vacuo*. Isolated in 80% yield after purification by chromatography (10:1 Hexane/EtOAc) as a yellow oil (65% over two steps).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dd, *J* = 8.8, 7.4 Hz, 2H), 6.73 (dd, *J* = 14.0, 7.3 Hz, 1H), 6.60 (dd, *J* = 8.7, 1.1 Hz, 2H), 5.74 – 5.69 (m, 1H), 5.32 – 5.27 (m, 1H), 4.82 (dd, *J* = 14.7, 6.8 Hz, 1H), 4.37 (d, *J* = 5.9 Hz, 1H), 4.23 – 4.17 (m, 2H), 2.32 – 2.27 (m, 2H), 1.47-1.35 (m, 4H), 1.26 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 146.4, 136.2, 129.3, 126.1, 118.3, 113.6, 61.5, 54.9, 31.5, 28.0, 22.5, 14.2, 14.0;

HRMS (EI): calcd for $C_{16}H_{23}NO_2$ $[M]^+$: 261.1729. Found 261.1725.



2-39 A four dram vial charged with a stir bar was purged with N_2, ethynyltrimethylsilane (15 mg, 0.1 mmol, 1.5 equiv.) and THF (1 mL, 0.1 M) were added and the solution was cooled to –78 °C. *n*BuLi (2.5 M in hexane, 60 μL, 1.5 equiv.) was

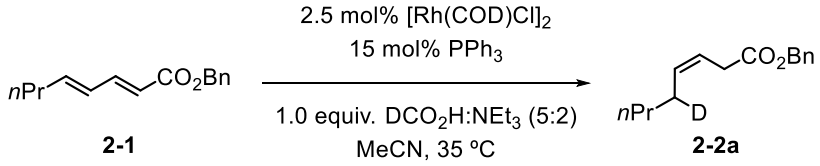
added dropwise. The mixture was stirred for 1 h and the aldehyde prepared above (17 mg, 0.10 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at – 78 °C for 2 h. Upon completion of the reaction, the mixture was quenched with saturated aqueous solution of NH_4Cl (1 ml) and the aqueous layer was extracted with EtOAc (3 × 1.0 mL). The organic layers were combined, concentrated *in vacuo* and purified by column chromatography (4:1 Hexane/EtOAc). Isolated in 94% yield as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.27 (m, 2H), 7.20 – 7.17 (m, 3H), 5.67 – 5.62 (m, 1H), 5.52 – 5.47 (m, 1H), 4.29 (dt, *J* = 6.5, 6.0 Hz, 1H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.43 – 2.39 (m, 4H), 1.72 (d, *J* = 7.5, 6.0 Hz, 1H), 0.17 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.8, 132.9, 128.5, 128.4, 125.9, 124.3, 106.2, 89.6, 62.4, 35.8, 35.7, 29.4, -0.1;

HRMS (EI): calcd for $C_{17}H_{24}OSi$ $[M]^+$: 272.1596. Found 272.1596.

2.5 Formic Acid D-Labelling Studies



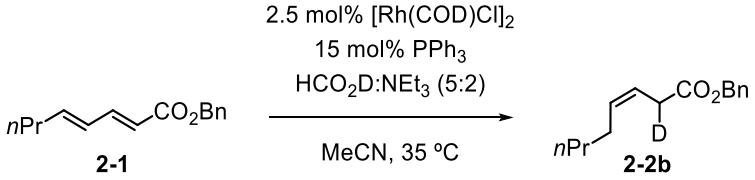
2-1 **2-2a**

2-2a Crude yield of *Z*-product: 77%, 70% D-incorporation at C5, <10% D-incorporation at C2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 – 7.31 (m, 5H), 5.60 – 5.55 (m, 2H), 5.13 (s, 2H), 3.14 (d, *J* = 5.6 Hz, 2H), 2.05 – 2.00 (m, 1H), 1.36 – 1.27 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.9, 136.0, 133.7, 128.6, 128.2 (2), 120.6, 66.4, 33.0, 31.4, 27.1, 26.8 (t, J_{CD} = 19.1 Hz), 22.3, 13.9;

HRMS (**EI**): calcd for $C_{15}H_{19}DO_2$ $[M]^+$: 233.1526. Found 233.1527.



2-2b Crude yield of *Z*-product: 72%, 90% D-incorporation at C2, <10% D-incorporation at C5.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 – 7.31 (m, 5H), 5.61 – 5.55 (m, 2H), 5.13 (s, 2H), 3.15 – 3.12 (m, 1H), 2.04 (q, J = 6.8 Hz, 2H), 1.36 – 1.28 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.9, 136.0, 133.7, 128.6, 128.2 (2), 120.5, 66.4, 33.0, 32.8 (t, J_{CD} = 19.8 Hz), 31.5, 27.1, 22.3, 13.9;

HRMS (**EI**): calcd for $C_{15}H_{19}DO_2$ $[M]^+$: 233.1526. Found 233.1526.

2.6 Preparation of Substrates (representative examples): The synthetic routes towards the preparation of the substrates were not optimized.

General Procedure A for Wittig Olefination Triphenylphosphoranylidene ester (1.0 equiv.) was added into a round bottom flask charged with a stir bar. The flask was purged with N_2, toluene (0.20 M) and aldehyde (1.0 equiv.) were added sequentially and the reaction mixture was heated to 90 °C for 10 h. Upon completion of the reaction, the solvent was removed *in vacuo* and hexane (0.25 M) was added with further stirring for

about 20 min. The precipitate was filtered off, concentrated *in vacuo* and purified by column chromatography.

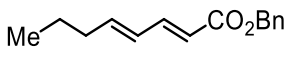
General Procedure B for Wittig Olefination To a flask charged with stir bar purged with N_2 was added aldehyde (1.0 equiv.) and dry DCM (1.00 M). Triphenylphosphoranylidene ester (1.2 equiv.) was then added in one portion and the mixture was stirred overnight at room temperature and monitored by TLC until completion. The solvent was removed *in vacuo* and hexane (0.25 M) was added with further stirring for about 20 min. The precipitate was filtered off, concentrated *in vacuo* and purified by column chromatography.

General Procedure for DCC Coupling To a flask charged with stir bar and purged with N_2 was added carboxylic acid (1.0 equiv.), DCM (0.40 M), alcohol (1.00 equiv.) and DMAP (0.05 equiv.). The solution was cooled to 0 °C and DCC (1.0 equiv.) was added portion-wise over 5 minutes. The mixture was warmed to room temperature and stirred overnight. The mixture was filtered through silica using DCM as eluent, concentrated *in vacuo* and purified by column chromatography.

General Procedure for Suzuki Coupling To a flask charged with stir bar and purged with N_2 was added alkenyl bromide (1.0 equiv.), toluene (12 mL/mmol), EtOH (4 mL/mmol) and H_2O (4 mL/mmol). The corresponding alkenylboronic ester (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol%) and Na_2CO_3 (2.0 equiv.) were added and refluxed at 100 °C for 24 h. The mixture was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ (10 mL/mmol) and then with aqueous NH_4Cl solution (10 mL/mmol). The organic phase was dried with Na_2SO_4, concentrated *in vacuo* and purified by column chromatography.

General Procedure for Horner-Wadsworth-Emmons Olefination To a flask charged with stir bar and purged with N_2 was added triethyl-4-phosphonocrotonate (1.3 equiv.) and anhydrous THF. The resulting solution was cooled to -78 °C and LDA (0.75 M in THF, 1.3 equiv.) was added dropwise over 2 min. The mixture was stirred for a further 1 hour at –78 °C and a solution of aldehyde (1.0 equiv.) in THF (0.20 M) was added dropwise over 3 min. The solution was warmed to room temperature with further stirring for 3 h before being quenched with saturated aqueous NH_4Cl solution. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography.

General Procedure for Amide Coupling Amine (5.0 mmol, 1.0 equiv.), EDCl (6.0 mmol, 1.2 equiv.) and DMAP (0.5 mmol, 0.1 equiv.) were added to a 50 ml round bottom flask charged with a stir bar. The flask was purged with nitrogen and dichloromethane (20 ml, 0.25 M) and triethylamine (7.5 mmol, 1.5 equiv.) were added sequentially and the mixture was maintained at 0 °C. Then acid (0.84 g, 6.0 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature overnight. Upon completion of the reaction, the mixture was washed with 1 M HCl (2 × 10 mL), 1 M NaOH (2 × 10 mL), water (1 × 10 mL). The organic layer was dried with Na_2SO_4, concentrated *in vacuo* and purified by column chromatography.



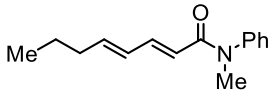
2-1 Prepared according to the General Procedure A for Wittig Olefination from (carbobenzyloxymethylene)triphenylphosphorane (9.70 mmol, 4.00 g, 1.0 equiv.) and

trans-2-hexenal (9.70 mmol, 1.13 mL, 1.0 equiv.). Isolated in 90% yield as a colorless oil after purification by column chromatography (20:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.39 – 7.29 (m, 6H), 6.20 – 6.11 (m, 2H), 5.84 (d, *J* = 15.3 Hz, 1H), 5.19 (s, 2H), 2.15 (q, *J* = 7.1 Hz, 2H), 1.46 (sext, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.1, 145.7, 144.9, 136.3, 128.5(2), 128.2, 128.1, 118.9, 66.0, 35.0, 21.9, 13.7;

HRMS (EI): calcd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307. Found 230.1302.

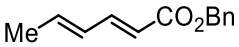


2-30 Prepared according to the General Procedure B for Wittig Olefination from *N*-methyl-*N*-phenyl-2-(triphenylphosphoranylidene)acetamide (8.2 g, 20 mmol, 1.0 equiv.) and *trans*-2-hexenal (2.3 mL, 20 mmol, 1.0 equiv.). Isolated in 55% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 – 7.39 (m, 2H), 7.34 – 7.33 (m, 1H), 7.26 (dd, *J* = 15.4, 11.2 Hz, 1H), 7.19 – 7.17 (m, 2H), 6.03 – 5.98 (m, 2H), 5.72 (d, *J* = 15.4 Hz, 1H), 3.35 (s, 3H), 2.09 – 2.04 (m, 2H), 1.44 – 1.37 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6, 143.9, 142.9, 142.4, 129.6, 128.9, 127.4(2), 119.8, 37.5, 35.0, 22.0, 13.7;

HRMS (EI): calcd for $C_{15}H_{19}NO$ $[M]^+$: 229.1467. Found 229.1470.

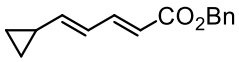


2-56 Prepared according to the General Procedure for DCC Coupling from sorbic acid (17.8 mmol, 2.00 g, 1.00 equiv.) and benzyl alcohol (17.8 mmol, 1.85 mL, 1.00 equiv.) Isolated in 88% yield as a light yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.27 (m, 6H), 6.23 – 6.12 (m, 2H), 5.83 (d, *J* = 15.3 Hz, 1H), 5.19 (s, 2H), 1.85 (d, *J* = 6.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.1, 145.5, 139.6, 136.2, 129.8, 128.5, 128.2, 128.1, 118.6, 66.0, 18.6;

HRMS (EI): calcd for $C_{13}H_{14}O_2$ $[M]^+$: 202.0994. Found 202.0996.

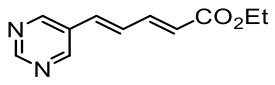


2-57 Prepared according to the General Procedure for Suzuki Coupling from 2-cyclopropylvinylpinacolborane (4.70 mmol, 906 mg, 1.25 equiv.) and benzyl-3-bromoprop-2-enoate (3.70 mmol, 896 mg, 1.00 equiv.). Isolated in 82% yield as a light yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR (CDCl3, 500 MHz) δ 7.39 – 7.31 (m, 5H), 7.27 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.26 (dd, *J* = 14.5, 10.8 Hz, 1H) 5.80 (d, *J* = 15.9 Hz, 1H), 5.62 (dd, *J* = 14.5, 10.3 Hz, 1H), 5.18 (s, 2H), 1.54 – 1.47 (m, 1H), 0.88 (q, *J* = 6.8 Hz, 2H), 0.54 (q, *J* = 6.8 Hz, 2H);

^{13}C NMR (CDCl3, 126 MHz) δ 167.2, 149.2, 145.4, 136.3, 128.5, 128.1(2), 125.8, 117.5, 65.9, 14.9, 8.4;

HRMS (EI): calcd for C15H16O2 [M]+: 228.1150, found 228.1155.

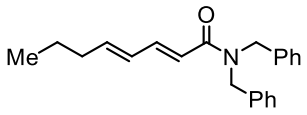


2-58 Prepared according to the General Procedure for Horner-Wadsworth-Emmons Olefination from triethyl 4-phosphonocrotonate (8.40 mmol, 2.10 g, 1.30 equiv.) and pyrimidine-5-carbaldehyde (6.50 mmol, 700 mg, 1.00 equiv.). Isolated in 41% yield as light brown flakes after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR (CDCl3, 500 MHz) δ 9.14 (s, 1H), 8.85 (bs, 2H), 7.43 (dd, *J* = 14.9 Hz, 11.2 Hz, 1H), 7.00 (dd, *J* = 15.4 Hz, 11.2 Hz, 1H), 6.81 (d, *J* = 15.9 Hz, 1H), 6.10 (d, *J* = 15.1 Hz, 1H), 4.25 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.4, Hz, 3H);

^{13}C NMR (CDCl3, 126 MHz) δ 166.5, 158.1, 154.7, 142.7, 132.1, 130.0, 124.2, 60.7, 14.3;

HRMS (EI): calcd for $C_{11}H_{12}O_2N_2$ $[M]^+$: 204.0899. Found 204.0903.



2-59 Prepared according to the General Procedure for Amide Coupling from octa-2,4-dienoic acid and dibenzylamine (0.99 g, 5 mmol, 1.0 equiv.). Isolated in 84% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a light-yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (dd, *J* = 14.5, 10.0 Hz, 1H), 7.38 – 7.25 (m, 8H), 7.18 (d, *J* = 7.5 Hz, 2H), 6.26 (d, *J* = 15.0 Hz, 1H), 6.18 – 6.08 (m, 2H), 4.66 (s, 2H), 4.51 (s, 2H), 2.14 – 2.10 (m, 2H), 1.46 – 1.42 (m, 2H), 0.90 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 144.4, 143.4, 137.5, 136.8, 128.9(2), 128.6, 128.3, 127.6, 127.3, 126.5, 118.1, 49.9, 48.6, 35.0, 22.0, 13.7;

HRMS (EI): calcd for $C_{22}H_{25}NO$ $[M]^+$: 319.1936. Found 319.1936.

CHAPTER 3 - Rh-Catalyzed *Z*-Homoallylic Alcohol Synthesis via Reductive Coupling of Electron Deficient Dienes and Aldehydes

3.1 Introduction

The addition of carbon-based nucleophiles to carbonyl units is one of the most fundamental reactions in synthetic organic chemistry. Since organometallic reagents often require an additional preparative step to obtain and exhibit limited functional group compatibility,[105] reductive coupling strategies that use olefins as pronucleophiles can streamline synthetic routes that involve carbonyl alkylation.[106, 107]

Early olefin-aldehyde reductive coupling protocols employed aggressive reducing agents like alkyl borane or alkyl zinc reagents to generate the metal hydride intermediate required for nucleophile formation.[107-110] The nucleophile formed can then be trapped by an aldehyde to generate the reductive coupling product. In the presence of diethyl zinc and Wilkinson's catalyst ($RhCl(PPh_3)_3$), Ando and co-workers reported the reductive coupling of α,β-unsaturated esters with aldehydes and ketones to synthesize β-hydroxyesters (**Fig. 3-1**).[107] Transmetalation between the diethyl zinc reagent and Wilkinson's catalyst forms a Rh-ethyl species which undergoes a β-hydride elimination to generate rhodium hydride, Rh–H and eliminate ethylene. The alkene inserts into the Rh–H forming a Rh-enolate which upon transmetalation with ethylzinc chloride forms a Zn-enolate. Subsequent trapping of the Zn-enolate by a carbonyl compound generates the β-hydroxyester product in a reductive aldol-type reaction. These organometallic reagents are highly pyrophoric and require careful handling.

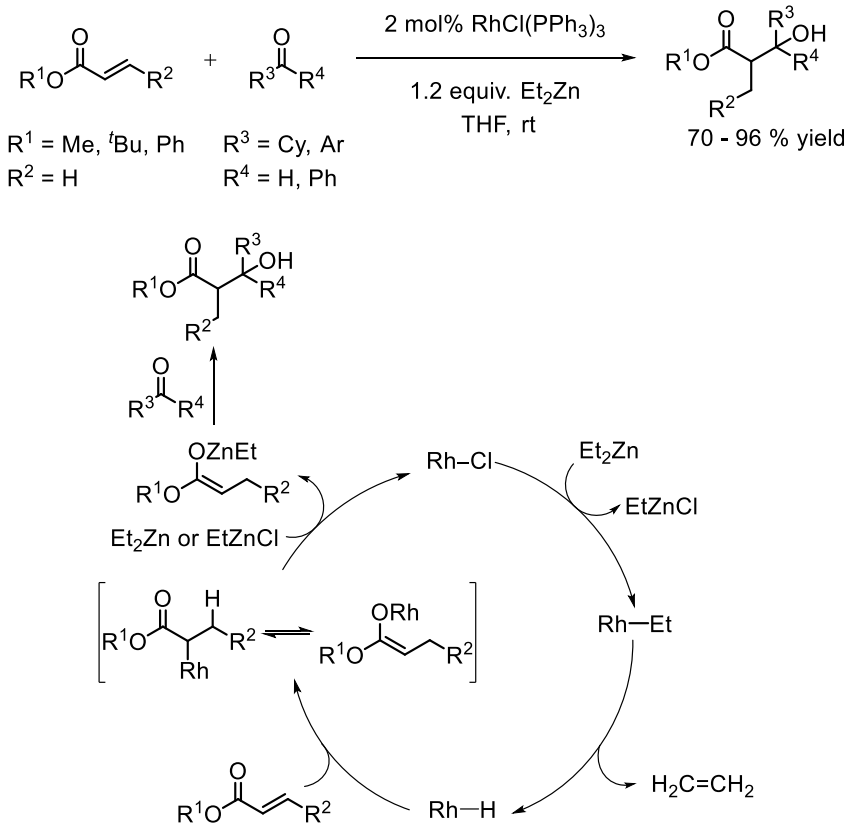


Fig. 3-1 Rh-catalyzed olefin-carbonyl reductive coupling with alkyl zinc reagent.

More recently, the use of milder reductants, such as molecular hydrogen or isopropanol, in combination with suitable transition metal catalysts has been pioneered by the group of Krische to dramatically broaden the scope and utility of olefin-based carbonyl additions.[72, 73, 111, 112] These methods proceed through a hydride transfer from the reductants to generate a metal hydride necessary for the reaction. The metal hydride generation involves either the activation of the molecular hydrogen followed by proton abstraction by a base (**Fig. 3-2a)** or dehydrogenation in the case of an alcohol. In the Rh-catalyzed carbon–carbon bond formation between α,β-unsaturated enones and aldehydes using molecular hydrogen as terminal reductant reported by Krische and co-workers (**Fig. 3-2b)**,[112] Rh–H was generated from molecular hydrogen and [Rh(COD)$_2$]OTf in the presence

of potassium acetate as a base additive. The activation of the molecular hydrogen via oxidative addition by $[Rh(COD)_2]OTf$ generates a rhodium dihydride which upon a proton abstraction by the base additive generates the Rh–H as outlined in **Scheme 3-2a**. The use of these milder reductants is realtively cheap and safe compared to use of organo- zinc or boron reagents.

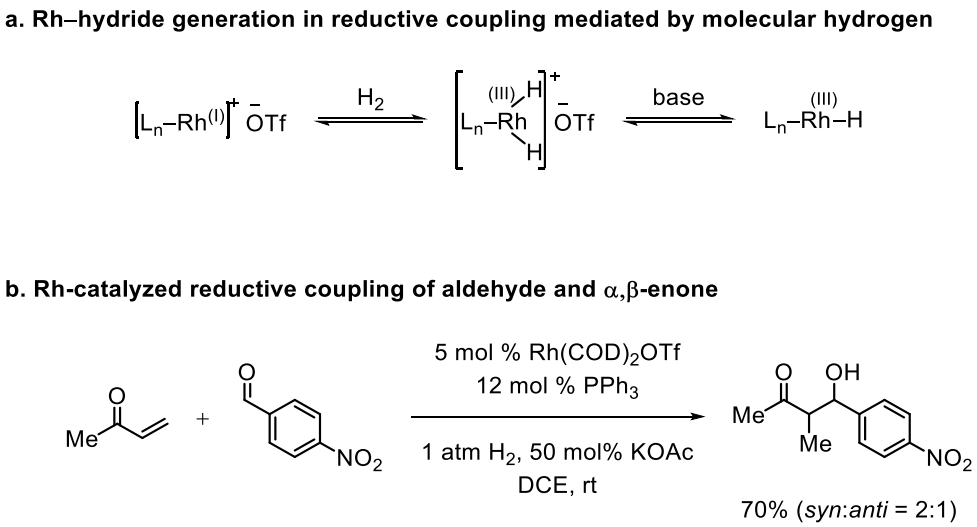


Fig. 3-2 Rh-catalyzed reductive coupling reaction mediated by molecular hydrogen.

Despite advances in catalytic carbonyl reductive coupling processes,[113-123] addition reactions involving diene or alkyne pro-nucleophiles that generate less thermodynamically stable *Z*-olefin products remain rare.[77, 83, 124, 125] These processes include the Ni-catalyzed reductive coupling of dienes and aldehydes in the presence of *N*-heterocyclic carbene (NHC) ligands which dictates stereoselectivity in the synthesis of *Z*-homoallylic silylethers.[83, 124] Stereoselective reductive coupling reactions between alkyne and primary alcohol catalyzed by Ru and Ir proceed through an allene-carbonyl oxidative addition and hydride shift enabled π-allyl formation respectively to generate *Z*-homoallylic alcohol

selectively.[77, 125] The *Z*-selective coupling of aldehydes and dienes can be promoted by Rh-based catalysts, however the requirement for stoichiometric Et_3B to generate a Rh–H intermediate limits chemoselectivity (**Fig. 3-3**).[82, 85] The proposed mechanism involve the generation of Rh–H via β-hydride elimination from Rh–ethyl complex (L_nRh–Et) obtained from $[Rh(COD)OH]_2$ and Et_3B. Alkene insertion into the Rh–H of the diene results in the formation of an allylrhodium species. Respective σ–π–σ isomerization, β-hydride elimination and alkene insertion resulting in an overall 1,4-hydride shift generates another allyrhodium species with α-unsaturation to the ester group. The overall hydride shift in the reaction depends on the length of the carbon chain between the ester group and the diene moiety. Nucleophilic allylation of the allylrhodium species in the presence of benzaldehyde through the transition state with minimal non-bonding interaction of the ethyl group with the cyclooctadiene ligand provides a rhodium alkoxide. Transmetalation of the rhodium alkoxide in the presence of organoboron reagents results in a boron alkoxide intermediate which upon work-up generates the *Z*-homoallylic alcohol product. Under these conditions, products derived from chain-walking isomerization are observed,[85] restricting access to a narrow range of product classes.[84, 85, 126-128] The lack of generality in *Z*-selective diene additions highlights the difficulty in controlling both site- and stereoselectivity in catalytic diene functionalization,[96] particularly in those reactions that generate thermodynamically less favorable product isomers.[129-136]

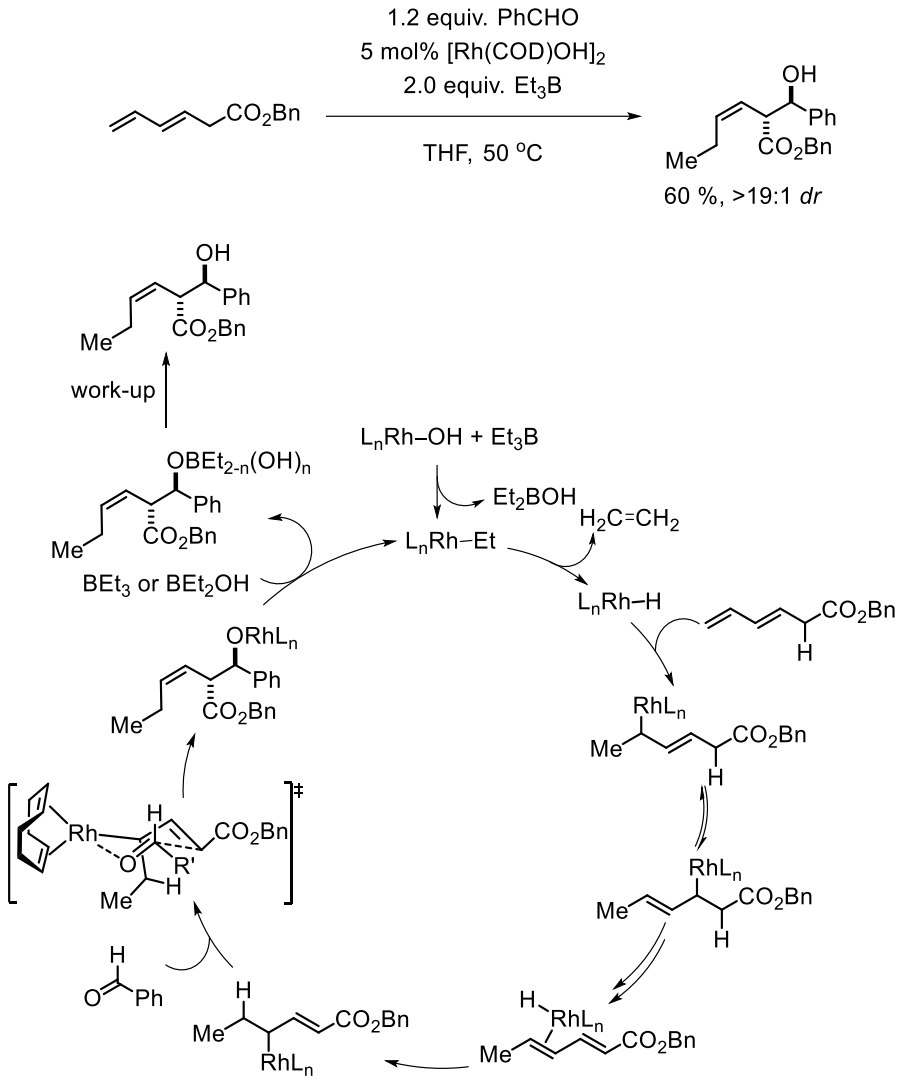


Fig. 3-3 *Z*-selective reductive coupling of diene and aldehyde via allymetal chain walking.

From a mechanistic perspective, improving reductive chemoselectivity while inhibiting chain-walking events in diene-aldehyde coupling can potentially be realized by tailoring the reactivity of the Rh-intermediates involved in the reaction pathway. Specifically, if both diene insertion into the Rh–H catalyst and electrophilic capture of the resultant Rh–allyl outpace undesirable isomerization, β-hydride elimination, or other

reductive processes, a direct and selective coupling process should be possible. As presented in Chapter 2, formic acid acts as reducing agent for the *Z*-selective 1,6-reduction of dienyl esters.[137] The diversion of the pathway to enable reductive coupling was questioned. Formic acid has been used as a reductant for metal catalyzed carbon–carbon bond forming carbonyl allylation and vinylation processes, and thus it seemed like a reasonable hypothesis to extend formic acid mediated reduction processes to reductive couplings.[75, 76, 79]

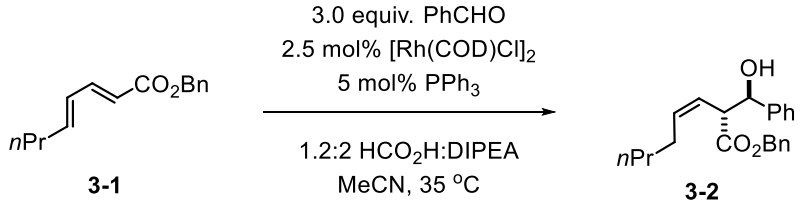
Chapter 3 demonstrates that mixtures of Rh-precatalysts, 1,5-cyclooctadiene (COD), and PPh_3 mediate the isomerization-free, stereoselective addition of diene-derived nucleophiles to aldehyde. The process delivers substituted *Z*-homoallylic alcohols with typically >95:5 *syn*- and *Z*-selectivity without interference from other reducible functionality. The role of each of the catalyst components is delineated through kinetic studies. Generation of the catalytically active Rh-species is the overall rate determining step and helps to impart high selectivity at reduced catalysts loadings.

3.2 Development of Direct Formic Acid Mediated *Z*-Selective Reductive Coupling of Electron Deficient Dienes and Aldehydes

A wide range of experimental conditions was surveyed to ultimately find that dienoate **3-1** can be reductively coupled to benzaldehyde using formic acid/diisopropylethylamine (DIPEA) in the presence of $[Rh(COD)Cl]_2$ and PPh_3 to generate *Z*-homoallylic alcohol **3-2** as a single isomer in good yield (>98:2 *syn*/*anti* and *Z*/*E*, 77% yield). **Fig. 3-4a** provides an overview of important reaction parameters. The use of other Rh-based catalysts, including Wilkinson's catalyst or $[Rh(COE)Cl]_2$, as well as

$[Ir(COD)Cl]_2$ (**Fig. 3-4a** entries 2 to 3) consumed diene without significant product formation, while other transition metal complexes (Ru-, Pd-, and Cu-based) were completely inactive (**Fig. 3-4a** entries 5 to 8). Catalyst loadings as low as 0.25 mol% $[Rh(COD)Cl]_2$ (**Fig. 3-4a** entry 9) gave good yields when additional COD was added. DIPEA was essential to observe good yields of reductive coupling product relative to diene transfer hydrogenation. The stereochemistry of *Z*-homoallylic alcohol **3-2** was assigned as the *syn*, *Z*- form based on literature precedent[82] by using the spectra data of the acetonide obtained via the $NaBH_4$ reduction of **3-2** followed by acetonization of the intermediate 1,3-diol using acetone dimethyl acetal (**Fig. 3-4b)**.

a. Optimization table



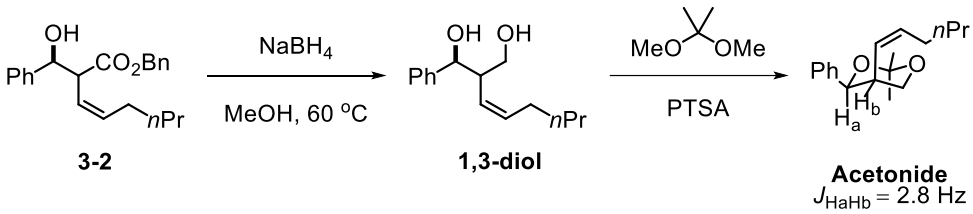
3-1 **3-2**

(97% conv.) **77%[a] [>98:2]**

entry	deviation from above	conv. (%)	yield (%)
1	none	97	77
2	$Rh(PPh)_3Cl$ (no PPh_3)	79	6
3	$[Rh(COE)_2Cl]_2$ instead of $[Rh(COD)Cl]_2$	98	6
4	$[Ir(COD)Cl]_2$ instead of $[Rh(COD)Cl]_2$	89	<2
5	$Ru(COD)Cl_2$ instead of $[Rh(COD)Cl]_2$	<2	<2
6	$RuCp^*(MeCN)_3PF_6$ instead of $[Rh(COD)Cl]_2$	<2	<2
7	$Pd(OAc)_2$ instead of $[Rh(COD)Cl]_2$	<2	<2
8	CuI instead of $[Rh(COD)Cl]_2$	<2	<2
9	0.25 mol% [Rh] + 10% COD[b]	98	76
10	NEt_3 instead of DIPEA	>98	47
11	DBU instead of DIPEA	90	10
12	Cs_2CO_3 instead of DIPEA	36	<2
13	no PPh_3	88	48
14	1 equiv PhCHO	>98	39
15	$NaHCO_3$ instead of HCO_2H	5	5

0.2 mmol scale, 0.25 M at 35 °C, with 1.2 equiv. HCO_2H. Conversions and yields determined by calibrated ^1H NMR spectroscopy using dibenzyl ether as internal standard, 14 - 18 h. a) Yield of isolated product. b) Run at 45 °C.

b. Stereochemistry of product determination



3-2 **1,3-diol** **Acetonide**

J_{HaHb} = 2.8 Hz

Fig. 3-4 Optimization table and stereochemistry determination.

The stereochemistry of the diene starting material (*E,E*, *Z,E* or *E,Z*) had minimal impact on reaction outcomes (**Fig. 3-5a**), allowing for the use of crude substrate mixtures obtained from standard diene syntheses. A pathway in which reduced diene could act as a nucleophile in a Rh-catalyzed or base-mediated aldol reaction after reduction was ruled out

with control experiments (**Fig. 3-5b**). The addition of base-generated nucleophiles, similar to those that are formed by hydrorhodation in this study, have been reported to add to aldehydes with low diastereoselectivity.[138]

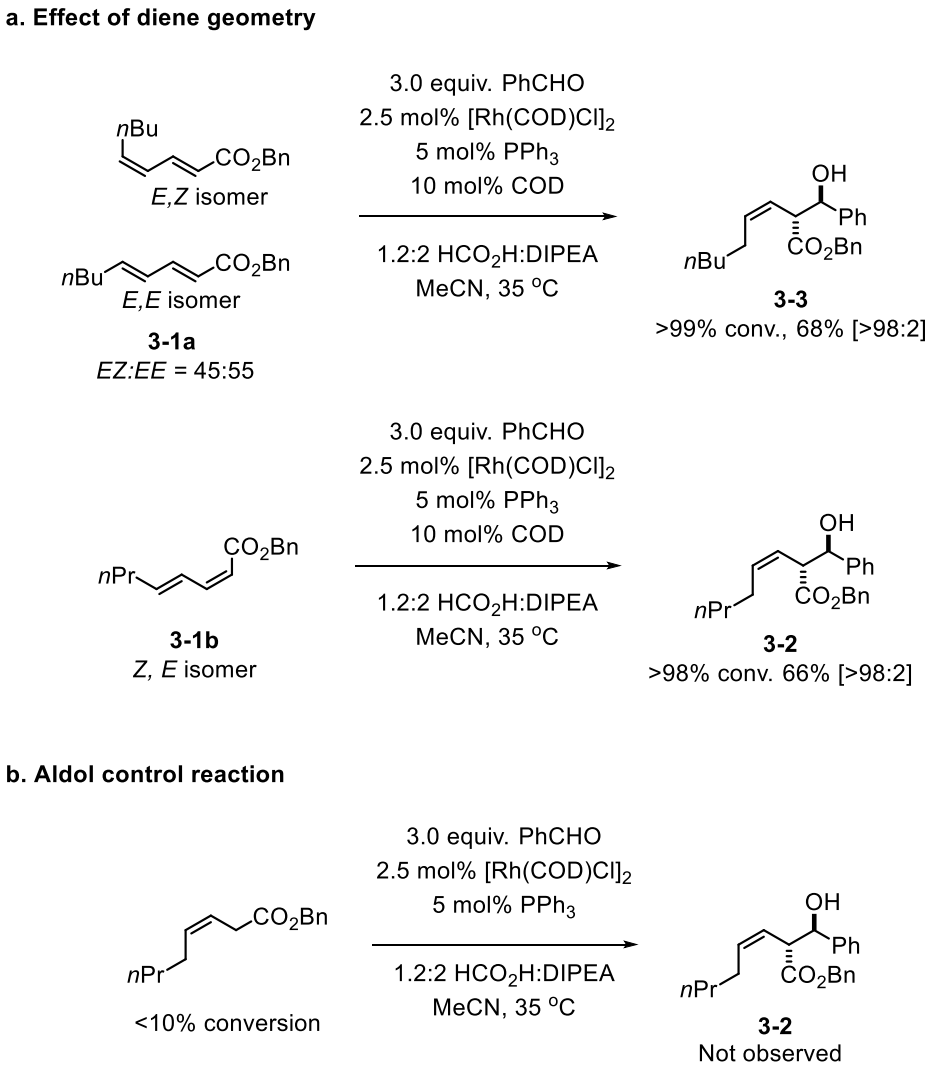
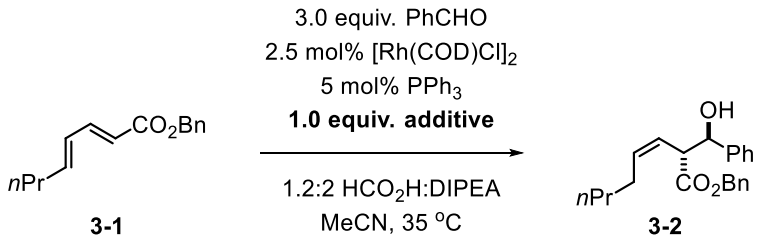
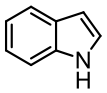
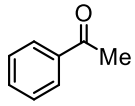
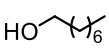
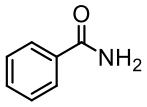
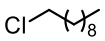
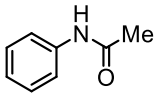
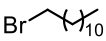
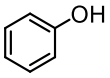
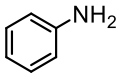
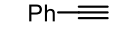
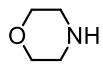
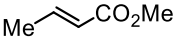
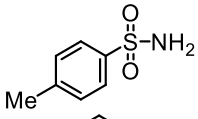
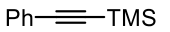
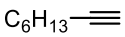
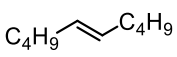
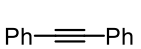
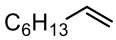
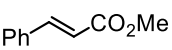
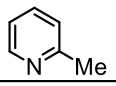
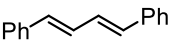
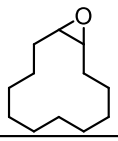


Fig. 3-5 Effect of diene geometry and control reaction to disprove alternative reaction pathway.



3-1 **3-2**

entry	Additive	yield of 1a (%)	Additive remaining (%)	entry	Additive	yield of 1a (%)	Additive remaining (%)
1	none	77 ✓	none	14		65 ✓	99 ✓
2		69 ✓	98 ✓	15		68 ✓	99 ✓
3		66 ✓	99 ✓	16		68 ✓	>99 ✓
4		70 ✓	100 ✓	17		33 ✗	68 ✗
5		62 ✓	99 ✓	18		28 ✗	62 ✗
6		64 ✓	96 ✓	19		3 ✗	10 ✗
7		54 ▬	97 ✓	20		56 ▬	70 ✗
8		66 ✓	61 ✗	21		20 ✗	76 ✗
9		35 ✗	94 ✓	22		20 ✗	45 ✗
10		63 ✓	97 ✓	23		6 ✗	n.d
11		66 ✓	98 ✓	24		62 ✓	68 ✗
12	H_2O	63 ✓	nd	25		70 ✓	85 ✓
13		52 ▬	97 ✓	26		68 ✓	99 ✓
				27		71 ✓	97 ✓

Reactions performed on 0.20 mmol scale according to the general procedure, with an additional 1.0 equivalent of additive. Yields determined by caliberated ^{1}H NMR spectroscopy using dibenzyl ether as internal standard. General accessment of product yield and additive recovery based on: Yield: 100 – 60% (good ✓), 60 – 50% (mediocre ▬), 50 – 0% (poor ✗). [n.d] = not determined; Additive Conversion: <15% (good ✓) >15% (poor ✗). *dr* >98:2 in all cases.

Table 3-1 Functional group compatibility screen.

The reductive chemoselectivity of the reaction was assessed by a comprehensive functional group compatibility screen (**Table 3-1**),[101] via the addition of an equivalent of substrates with reactive functional groups as additive to the standard Rh-catalyzed reductive coupling reaction using substrate **3-1**. Related carbonyl groups- ketones, esters, amides (**Table 3-1** entries 2, 3, 4 and 25), activated and unactivated olefins or dienes (**Table 3-1** entries 10, 11 and 26), alkyl halides (**Table 3-1** entry 16), epoxides (**Table 3-1** entry 27), and protic NH- and OH- groups (**Table 3-1** entries 5, 6, 7, 15) are well tolerated (>60% product yield with one equivalent of additive and >85% recovery of additive). Of the functional groups screened, only alkynes and alkyl bromides were impacted under the standard reaction conditions (**Table 3-1** entries 17 to 19 and 21 to 24).

The formic acid mediated coupling process yielded products of direct aldehyde *Z*-allylrhodation without isomerization (**Fig. 3-6**). For example, diester **3-4** underwent reaction to give a single coupling product **3-5** in 73% yield, chain-walking and addition adjacent to the remote ester was not observed. Even where there is a clear thermodynamic driving force for isomerization, like in the cases of ester-tethered aryldiene **3-6**, only direct coupling product **3-7** is obtained, contrasting approaches with alternative reducing agents.[85]

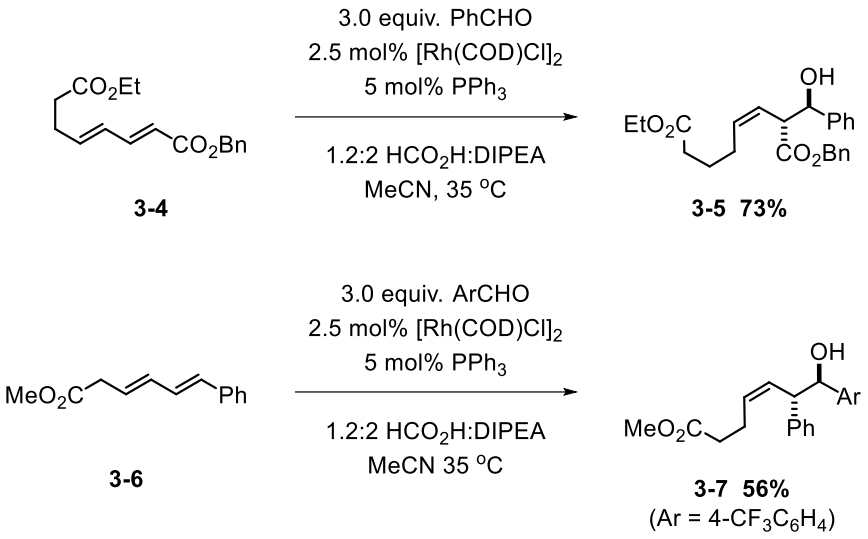
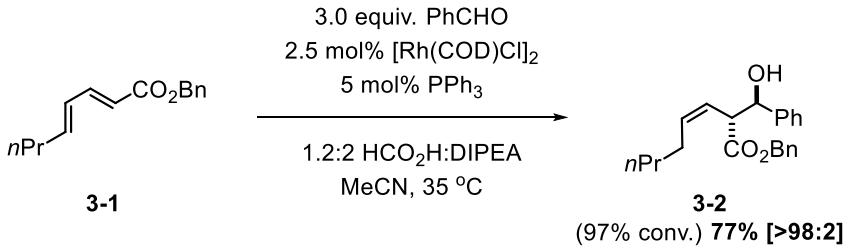
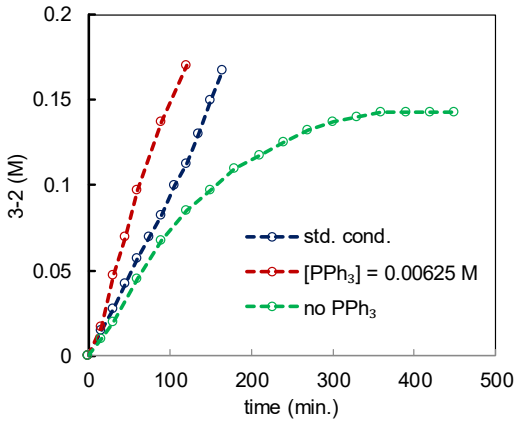


Fig. 3-6 Isomerization test - Direct coupling. <5% chain-walking in both cases.



a. PPh_3 enhances catalyst lifetime



b. COD and PPh_3 essential at low [Rh]

Entry	0.5 mol% [Rh] 50 °C	% yield
1	10% COD + 1% PPh_3	75
2	10% COD + no PPh_3	41
3	no COD + 1% PPh_3	26
4	no COD, no PPh_3	25

Fig. 3-7 Effects of catalysts components.

The role of the catalyst components was elucidated by mechanistic studies (**Fig. 3-7**). The role of PPh_3 was elucidated by using different catalytic amounts of PPh_3 in the reaction. In the absence of PPh_3 (green trace), the reaction proceeds with an initial generation of *Z*-homoallylic alcohol **3-2** which eventually stops as a result of the precipitation of Rh in solution. Use of 2.5 mol% PPh_3 (red trace) under standard reductive coupling condition increased the rate of the reaction. The observation is believed to be due to the faster generation of the active catalyst in the presence of a lower amount of PPh_3. Use of 5 mol% PPh_3 (blue trace) under standard reductive coupling condition slows the rate of reaction, but its presence prevents precipitation of Rh from solution, an event that leads to an erosion in selectivity. The role of PPh_3 is to prevent the irreversible decomposition of off-cycle Rh-species under the reductive conditions. The impact of PPh_3 and COD are more dramatic at reduced catalyst loadings, where both reaction rate and selectivity are reduced without the co-additives (**Fig. 3-7b** entries 2 to 4). Reaction progress kinetic analysis using variable time normalization as developed by Burés were used to determine the rate orders in each reactants as described in Chapter 2.[103] Overall, the process exhibits pseudo zero-order kinetics and is not positive order in any of the substrate components (**Fig. 3-8)**; essentially zero order in aldehyde and formic acid/DIPEA, and partial negative order in diene. The reaction is positive order in Rh and COD, while is negative order in PPh_3. We rationalize these observations by proposing that diene substrate, COD, and PPh_3 ligate Rh in various species that undergo ligand exchange processes. Most of the Rh species exist as off-cycle intermediates and the active species that enters the catalytic cycle is likely a solvated $Rh(COD)^+$. The generation of $Rh(COD)^+$ by ligand dissociation is rate determining and subsequent reaction with formate generates a Rh–H to

initiate the reductive coupling of substrates. It is unlikely that the protonation step is the rate determining step as the use of excess formic acid in the reaction had no effect on the rate of the reaction. COD is essential for reactivity, $[Rh(COE)_2Cl]_2$ or $[Rh(ethylene)_2Cl]_2$ are inactive until COD is added.

The validity of ancillary diene ligated Rh intermediates being involved in the catalytic cycle was confirmed by the observation of modest enantio-induction by use of structurally related chiral diene ligands in place of COD (**Fig. 3-9b)**. Use of different dienoates including benzyl, ethyl and bulky *tert*-butyl dienoate esters (**Fig. 3-9b** entries 1 to 6) and arylidene (**Fig. 3-9b** entries 7 and 8) in the presence of chiral diene B showed enantio-induction in the range of 9 to 30% *ee*. Deuterium labelling experiments using $[D_1]$ formic acid (DCO_2H) gave results consistent with a *syn*-alkene insertion of diene substrate followed by aldehyde trapping of the allylrhodium that occurs via a chair-like transition state (**Fig. 3-10**).[82, 85] No D-label was found at any other position; however, some D was incorporated into COD (**Fig. 3-9a)**, suggesting that while the diene substrate does not undergo reversible Rh–hydride insertion/β-hydride elimination, the ancillary diene ligand can, further demonstrating the importance of the COD ligand framework for catalysis.

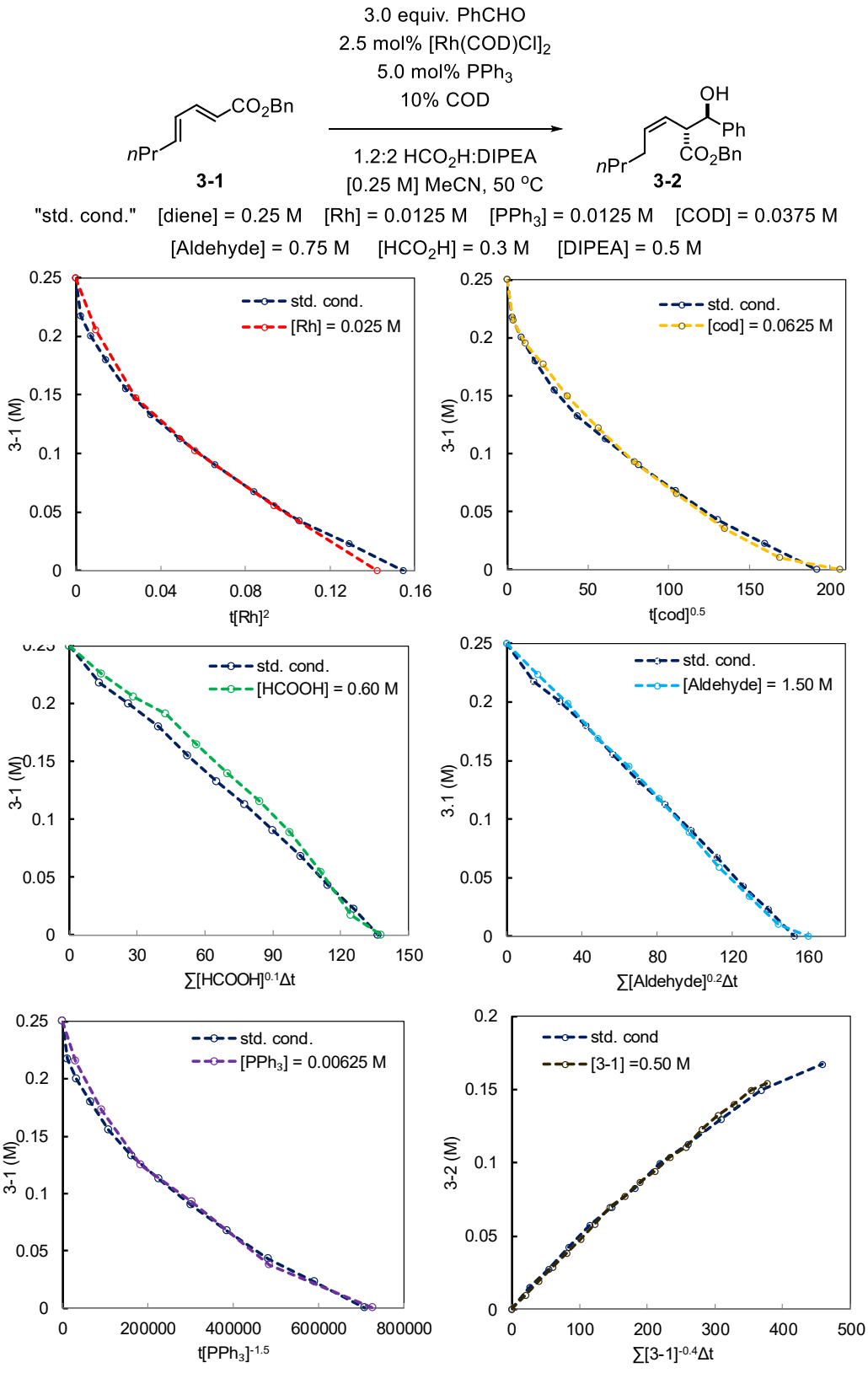
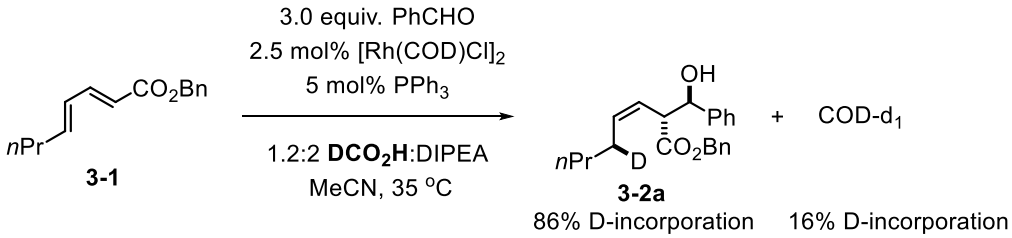
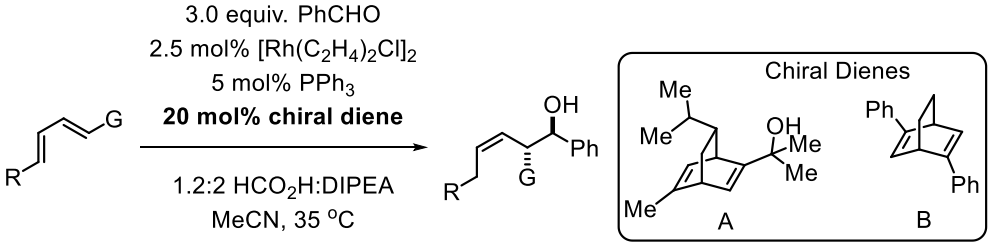


Fig. 3-8 Reaction progress kinetic analysis/variable time normalization plots.

a. Deuterium labelling studies



b. Effect of chiral diene ligands



Entry	G	R	chiral diene	% yield	%*ee*[a]
1	-CO_2Bn	-C_3H_7	A	9	-[b]
2	-CO_2Bn	-C_3H_7	B	21	30[b]
3	-$CO_2{}^tBu$	-CH_3	A	18	-[c]
4	-$CO_2{}^tBu$	-CH_3	B	55	18[c]
5	-CO_2Et	-C_3H_7	A	12	-[b]
6	-CO_2Et	-C_3H_7	B	44	9[b]
7	-4-$CH_3COC_6H_4$	-CH3	A	31	-[d]
8	-4-$CH_3COC_6H_4$	-CH3	B	33	27[d]

Yields determined by caliberated ^1H NMR spectroscopy using dibenzyl ether as internal standard. a) *ee* determined with chiral HPLC using b) ChiralPak IC column (5% IPA in hexane). c) Regis Whelk 0-1 column (10% IPA in hexane). d) ChiralPak IB column (5% IPA in hexane).

Fig. 3-9 Evidence of COD as part of the active catalyst species.

Fig. 3-10 provides a complete potential catalytic cycle. These individual steps likely mirror those in reductive coupling reactions employing Et_3B described earlier (**Fig. 3-3**)[84], with the notable exception that catalyst generation is the rate-determining step and

the Rh–allyl species is trapped faster than undesirable isomerization events. Upon product release from the catalyst, Rh is likely re-trapped by PPh_3.

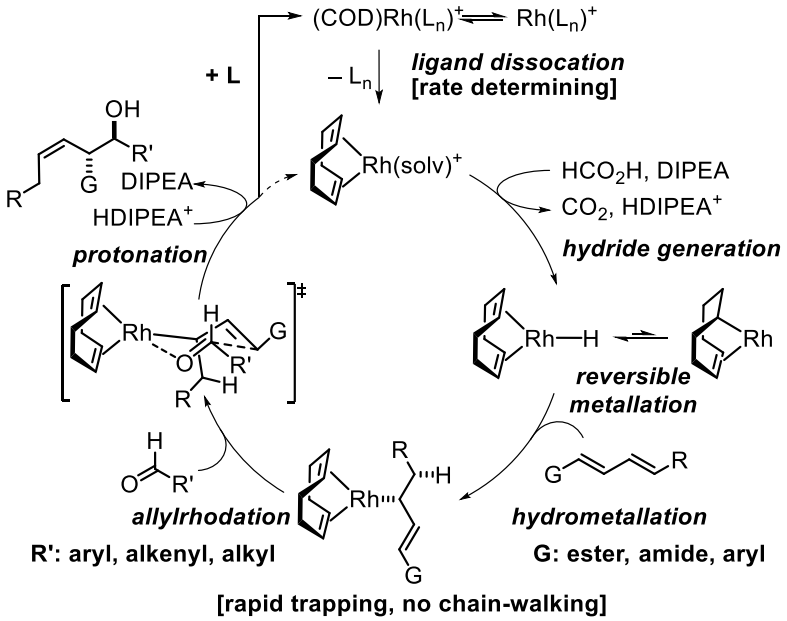
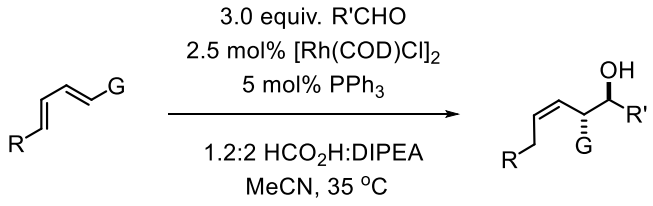
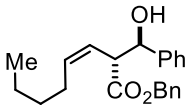


Fig. 3-10 Complete catalytic cycle for the formic acid mediated reductive coupling of electron deficient dienes and aldehydes.

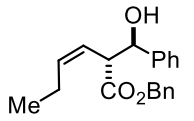
The mechanistic features of the reductive coupling allow for the use of a broad range of diene and aldehyde partners with functional groups that would be incompatible with more aggressively reducing conditions (**Table 3-2**). Alkyl substituted dienoates, including those with bulky groups (**3-10**, **3-11**), isolated alkene units (**3-12**, **3-17**), halogen (**3-13**), nitrile (**3-14**), carbamates and imides (**3-15**, **3-18**), ester (**3-5**), and (hetero)aryl substitution (**3-20**) undergo reaction to give products with good to moderate yields and uniformly high *syn*- and *Z*-selectivity.



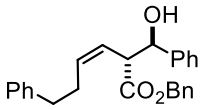
Dienoate Scope



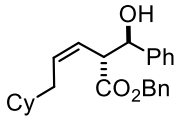
3-2 71% [>98:2]



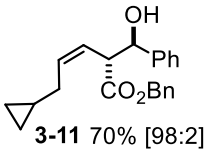
3-8 69% [>98:2]



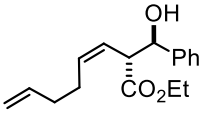
3-9 51% [91:9]



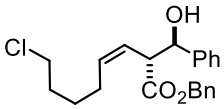
3-10 65% [82:18]



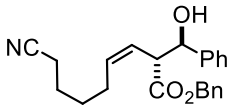
3-11 70% [98:2]



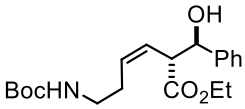
3-12 60% [>98:2]



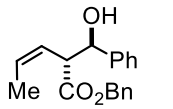
3-13 64% [>98:2]



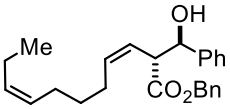
3-14 60% [>98:2]



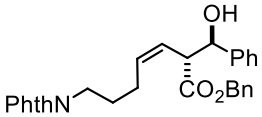
3-15 67% [>98:2]



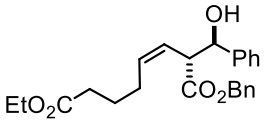
3-16 56% [>98:2]



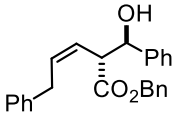
3-17 68% [>98:2]



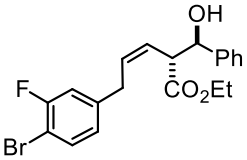
3-18 71% [>98:2]



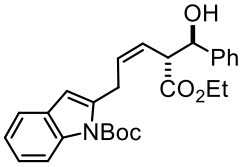
3-5 73% [>98:2]



3-19 69% [>98:2]



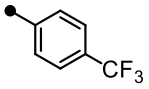
3-20 63% [>98:2]



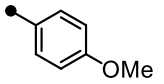
3-21 71% [>98:2]

Aryl Aldehyde Scope [R = *n*Pr] [G = CO_2Bn]

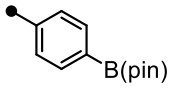
R' =



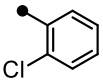
3-22 81% [>98:2]



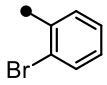
3-23 51% [>98:2]



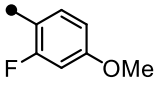
3-24 75% [>98:2]



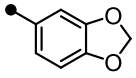
3-25 69% [>98:2]



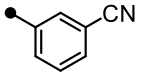
3-26 60% [>98:2]



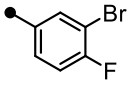
3-27 72% [>98:2]



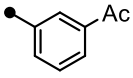
3-28 57% [>98:2]



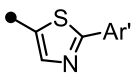
3-29 75% [>98:2]



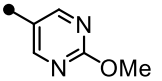
3-30 75% [>98:2]



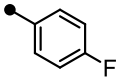
3-31 79% [>98:2]



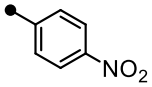
3-32 44% [>98:2]



3-33 45% [>98:2]



3-34 74% [>98:2]



3-35 74% [>98:2]

Yields are of isolated material under standard conditions. *syn dr* value of isolated material is >95:5. Boc = tert-butoxycarbonyl. Ar' = 4-$CF_3C_6H_4$.

Table 3-2 Dienoate and aryl aldehyde scope studies.

The aryl aldehyde partner can take on a range of electronic properties (**3-22**, **3-23**) with more electron-poor 4-nitrobenzaldehyde reacting selectively in competition studies against electron-rich 4-anisaldehyde (**Fig. 3-11)**. Other functionalities tolerated on the aryl aldehyde partners include boronic ester (**3-24**), aryl halide (**3-25**, **3-26**, **3-27**, **3-30**), or reducible functional groups (nitrile **3-29**, ketone **3-31**, or nitro **3-35**), as well as heterocyclic groups (**3-32**, **3-33**). The reaction accommodates a range of ester groups, including *i*Pr (**3-36**), *t*Bu (**3-37**), and more complex alkene (**3-38**, **3-39**), carbamates (**3-40**, **3-41**), alkyl chloride (**3-42**) or polyfunctionalized groups (**3-43**). Aryl dienes are reductively coupled to aldehydes with similar efficiency and selectivity, including those with alcohol (**3-45**), ester (**3-7**), nitrile (**3-47**), and ketone groups (**3-48**). Weinreb (**3-49**) and morpholine (**3-61**) dienyl amides are viable substrates, as are alkyl (**3-51**, **3-52**) or α,β-unsaturated aldehydes (**3-53**).

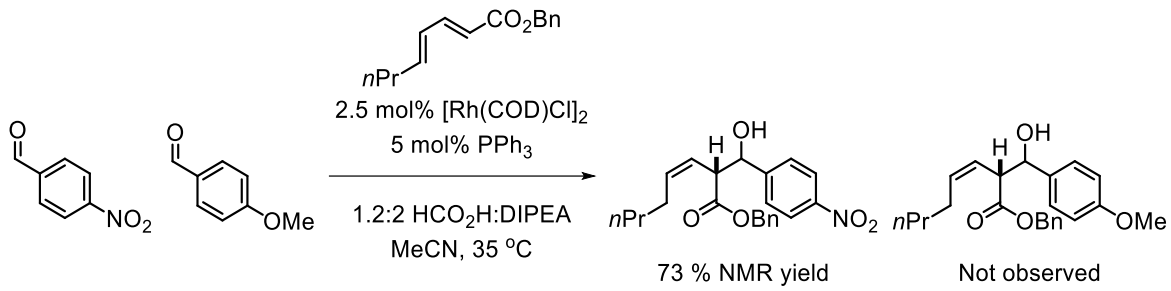
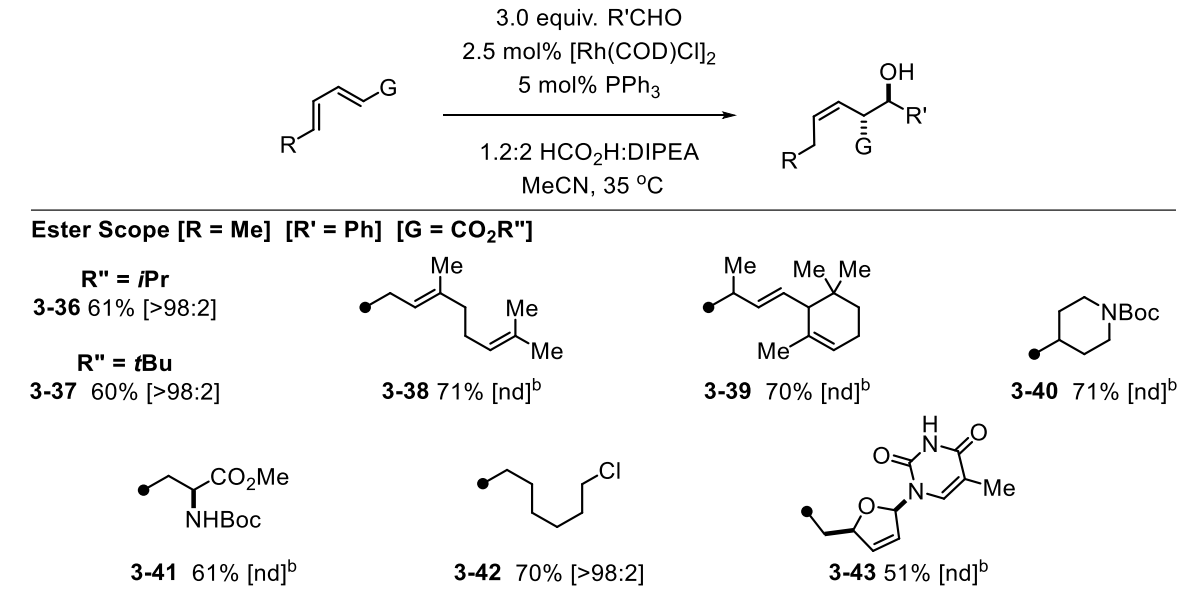


Fig. 3-11 Aldehyde electrophilicity competition study.



Yields are of isolated material under standard conditions. *Syn dr* value of isolated material is >95:5. b) [n.d.] = dr value of the crude reaction mixture could not be determined. Boc = *tert*-butoxycarbonyl. Ar = 4-$CF_3C_6H_4$.

Table 3-3 Ester, aryl diene and other scope studies.

The value of the reaction to generate complex bio-active molecules was demonstrated by the diastereoselective preparation of diarylmethane **3-57**, a key intermediate in the synthesis of a glucagon receptor antagonist (**Fig. 3-12a**). The carbon–carbon bond framework was readily obtained by reductive coupling of diene **3-54** with 4-

chlorobenzaldehyde under reduced catalyst loading using 1 mol% $[Rh(COD)Cl]_2$. Pd-catalyzed alkene hydrogenation and base mediated ester hydrolysis gave **3-55** in 69% overall yield over three steps. Friedel–Crafts alkylation of the alcohol with substituted indole **3-56** delivers the target molecule **3-57** in 76% yield, which can be converted to the drug-candidate via an established protocol.[139, 140]

The stereochemically defined *Z*-homoallylic alcohols generated by formic acid mediated reductive coupling are useful building blocks for more complex fragments (**Fig. 3-12b**). 2,5-dihydrofuran (**3-58**) and tetrasubstituted tetrahydrofuran (**3-59**) were prepared by oxyselenenylation-deselenenylation reaction[141] and iodine-mediated cyclization[138] from **3-2**. Vanadium-catalyzed epoxidation[142] and rhodium-catalyzed aziridination[143] of **3-2** provided access to epoxide and aziridine stereotetrads (**3-60**, **3-61**). Tertiary alcohol (**3-62**) was obtained in a two-step process by oxidation of the alcohol using Dess-Martin periodinane followed by carbonyl methylation using trimethylaluminium ($AlMe_3$).[144]

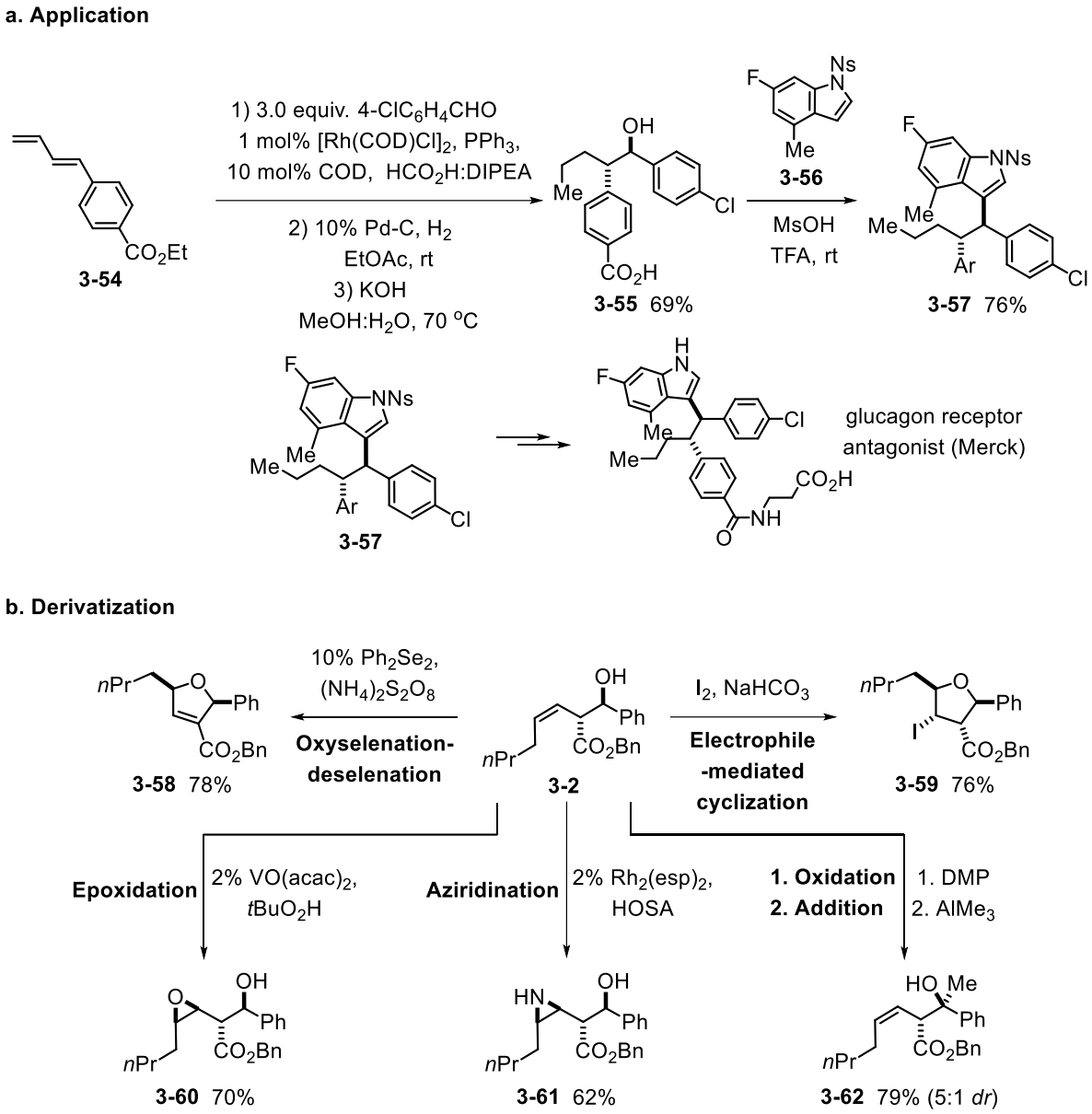


Fig. 3-12 Application to synthesis of glucagon receptor antagonist intermediate and product derivatization.

The extent of diene activation and electrophilicity of the aldehyde directly impact the reductive coupling process **(Fig. 3-13**). Highly reactive aldehydes (**3-64, 3-67**, **3-69**, **3-71**, **3-72**) undergo reduction prior to reductive coupling with the diene. Diene reduction was also observed in the presence of less reactive aldehydes (**3-65**, **3-66**, **3-68**, **3-70**).

Hence, a suitable diene activation to generate a metal allyl nucleophile is desirable for a productive reductive coupling with an aldehyde.

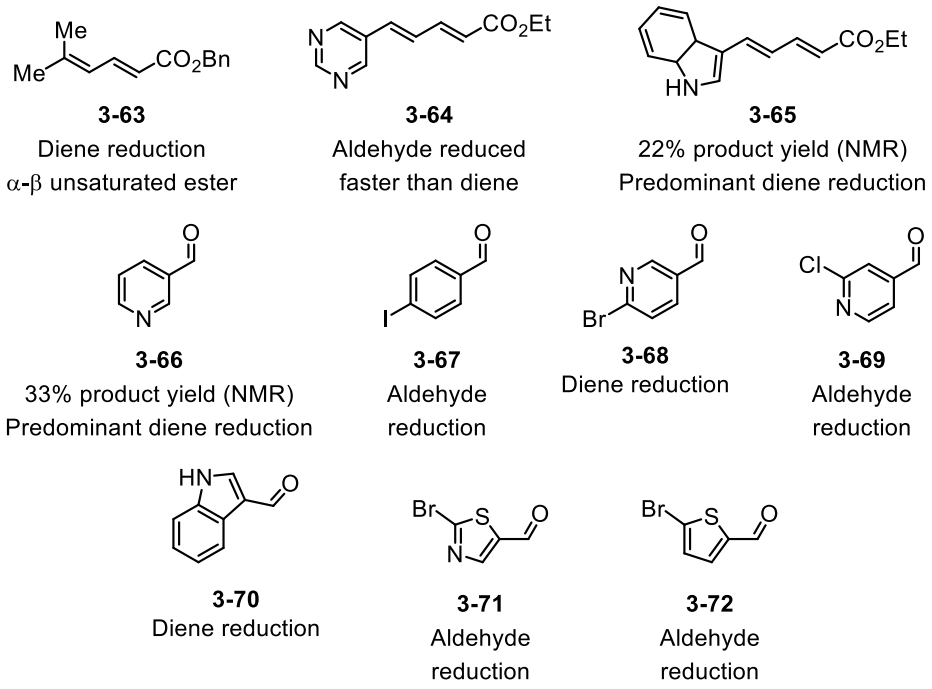


Fig. 3-13 Less successful substrates.

3.3 Summary and Conclusions

The Rh-catalyzed, formic acid mediated reductive coupling of dienes and aldehydes provides a direct route to stereochemically defined *Z*-homoallylic alcohols. The mildly reducing conditions allow for tolerance towards functional groups that would interfere with organometallic reagents or highly polarized hydride donors. A complete absence of chain-walking isomerization is facilitated by comparatively slow liberation of the active catalyst species followed by rapid Rh–H insertion and trapping. The general concept should be amendable to related chemoselective olefin hydrofunctionalization processes.

3.4 Procedures and Characterization

General Considerations

Unless noted, all reactions were conducted under inert atmosphere employing standard Schlenk technique or by use of a N_2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed as described by Still and co-workers[104] (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. IR data were obtained using thermo Nicolet 8700 FTIR spectrometer and continuum FTIR microscope. The absorption maxima are given as wavenumber (cm^{-1}). Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied.

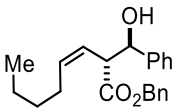
General Procedure A: In an atmosphere controlled glovebox, $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.025 equiv.) and PPh_3 (6.6 mg, 0.025 mmol, 0.050 equiv.) were weighed into separate one dram vials. To the vial containing $[Rh(COD)Cl]_2$ was added MeCN (1 mL) and the solution was transferred into the 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, placed in an aluminum block heated to 35 °C and stirred. The reaction progress was monitored periodically via ^{1}H NMR spectroscopy. 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 **3-2**. 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 a separate one dram vial was weighed diene (0.50 mmol, 1.0 equiv.) followed by aldehyde (1.50 mmol, 3.0 equiv.), 1,5-cyclooctadiene (5.4 mg, 0.050 mmol, 0.10 equiv.) and finally internal standard (dibenzyl ether). Into this mixture was 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 spectroscopy.

General Procedure C [additional COD]: In an inert 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 spectroscopy. Once the reaction reached >95% conversion, the solution was diluted with toluene to quench, concentrated and purified by silica gel chromatography.



3-2 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 eight 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).

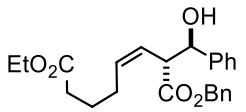
Prepared according to General Procedure C under air (no glovebox used) from the corresponding diene (115.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.50 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 77%, *dr*: >98:2.

^{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.



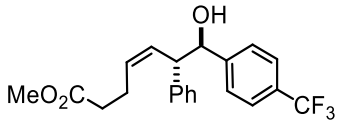
3-5 Prepared according to the General Procedure C from the corresponding diene (144.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 80%, *dr*: >98:2. Isolated in 73% yield as a yellow oil after purification by column chromatography (17:5 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.



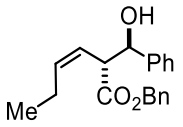
3-7 Prepared according to a modified General Procedure A (additional 0.5 equiv. HCO_2H added upon consumption of first 1.2 equiv.) from the corresponding diene (40 mg, 0.2 mmol) and 4-(trifluoromethyl)benzaldehyde (104 mg, 0.6 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 59%, *dr*: >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.



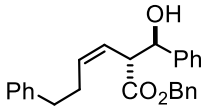
3-8 Prepared according to the General Procedure A from the corresponding diene (101.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 74%, *dr*: >98:2. Isolated in 69% yield as a yellow oil after purification by column chromatography (10:1 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.



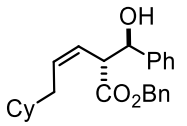
3-9 Prepared according to the General Procedure A from the corresponding diene (139 mg, 0.5 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 53%, *dr*: >98:2. Isolated in 52% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{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.



3-10 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).

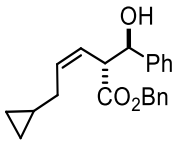
^{1}H NMR ($CDCl_3$, 400 MHz) ***syn* diastereomer:** δ 7.37 – 7.22 (m, 8H), 7.20 – 7.15 (m, 2H), 5.76 – 5.60 (m, 2H), 5.07 – 5.01 (m, 3H), 3.70 (dd, *J* = 9.7, 5.9 Hz, 1H), 2.88 (d, *J* = 2.4 Hz, 1H), 1.90 – 1.71 (m, 2H), 1.65 – 1.43 (m, 5H), 1.18 – 1.01 (m, 4H), 0.83 – 0.67 (m, 2H); ***anti* diastereomer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



3-11 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).

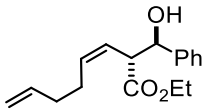
Prepared according to General Procedure B from the corresponding diene (114.2 mg, 0.50 mmol, 1 equiv.) and benzaldehyde (159.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 81%, *dr*: 98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 – 7.27 (m, 7H), 7.26 – 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, *J* = 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 – -0.02 (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.



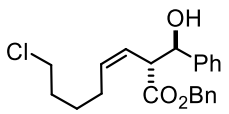
3-12 Prepared according to the General Procedure A from the corresponding diene (16 mg, 0.09 mmol) and benzaldehyde (27 μL, 0.26 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 65%, *dr*: >98:2. Isolated in 60% yield as a yellow oil after purification by column chromatography (4:1 Pentane/Et_2O).

^{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.



3-13 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

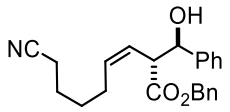
conversion: >99%, crude yield: 65%, *dr*: >98:2. Isolated in 64% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{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.



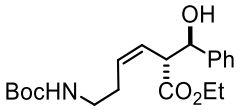
3-14 Prepared according to the General Procedure from the corresponding diene (115 mg, 0.45 mmol) and benzaldehyde (137 μL, 1.4 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >96%, crude yield: 62%, *dr*: >98:2. Isolated in 60% yield as a yellow oil after purification by column chromatography (2:1 Hexane/EtOAc).

^{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.



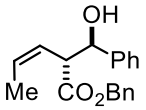
3-15 Prepared according to the General Procedure from the corresponding diene (134 mg, 0.5 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 68%, *dr*: >98:2. Isolated in 67% yield as a yellow oil after purification by column chromatography (4:1 Hexane/EtOAc).

^{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.



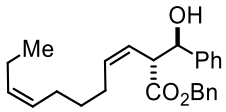
3-16 Prepared according to General Procedure C from the corresponding diene (128.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.) ^{1}H NMR diene conversion: >99%, crude yield: 57%, *dr*: >98:2. Isolated in 56% yield as a yellow-brown oil after purification by column chromatography (17:3 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.



3-17 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).

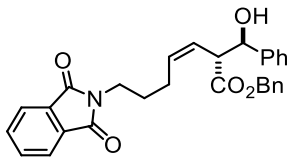
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.28 (m, 7H), 7.27 – 7.23 (m, 1H), 7.19 – 7.16 (m, 2H), 5.73 – 5.67 (m, 1H), 5.65 – 5.59 (m, 1H), 5.37 – 5.31 (m, 1H), 5.25 – 5.20 (m,

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;

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



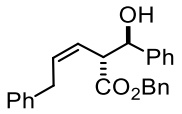
3-18 Prepared according to the General Procedure A from the corresponding diene (187.8 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 76%, *dr*: >98:2. Isolated in 71% yield as a brown solid after purification by column chromatography (2:1 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.



3-19 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.

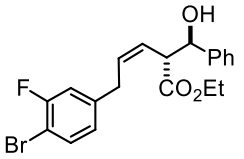
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.39 – 7.28 (m, 8H), 7.23 – 7.13 (m, 5H), 6.96 – 6.92 (m, 2H), 5.86 – 5.81 (m, 1H), 5.80 – 5.76 (m, 1H), 5.16 (d, *J* = 5.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 3.85 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.27 (dd, *J* = 16.1, 7.7 Hz, 1H), 2.17 (dd,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



3-20 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).

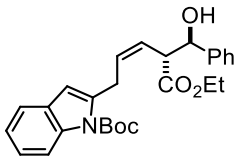
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.28 (m, 5H), 7.14 (dd, *J* = 6.5, 2.0 Hz, 1H), 6.9 (t, *J* = 8.4 Hz, 1H), 6.79 – 6.76 (m, 1H), 5.81 – 5.77 (m, 1H), 5.74 – 5.69 (m, 1H), 5.17 (dd, *J* = 4.6, 2.4 Hz, 1H), 4.15 – 4.10 (m, 2H), 3.69 (dd, *J* = 9.9, 4.6 Hz, 1H), 3.18 (dd, *J* = 15.7, 7.3 Hz, 1H),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



3-21 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).

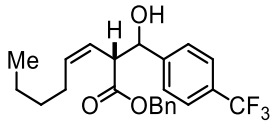
Prepared according to General Procedure B from the corresponding diene (170.7 mg, 0.50 mmol) and benzaldehyde (159.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 90%, *dr*: >98:2.

^{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**.**



3-22 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);

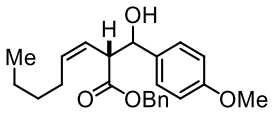
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 144.8, 137.3, 135.3, 129.9 (q, *J* = 32.3 Hz), 128.6, 128.5, 128.2, 126.8, 125.1 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.9 Hz), 121.2, 73.6, 66.9, 51.8, 31.3, 27.4, 22.2, 13.8;

^{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.



3-23 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).

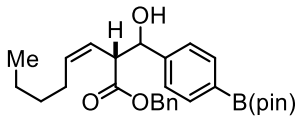
Prepared according to General Procedure B from the corresponding diene (115.2 mg, 0.50 mmol) and 4-methoxybenzaldehyde (204.2 mg, 1.5 mmol, 3 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 65%, *dr*: >98:2.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 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, 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**.**



3-24 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).

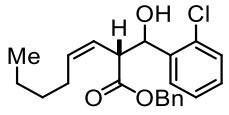
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.33 – 7.29 (m, 5H), 7.17 – 7.15 (m, 2H), 5.69 – 5.64 (m, 1H), 5.61 – 5.56 (m, 1H), 5.08 – 5.00 (m, 3H), 3.69 (dd, *J* =

9.7, 5.4 Hz, 1H), 2.92 (d, *J* = 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 Hz, 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.



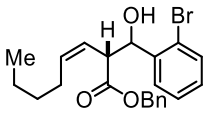
3-25 Prepared according to the General Procedure A from the corresponding diene (92 mg, 0.40 mmol) and 2-chlorobenzaldehyde (168.7 mg, 1.2 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 70%, *dr*: >98:2. Isolated in 69% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.53 (dd, *J* = 7.5, 1.7 Hz, 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, *J* = 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.



3-26 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.

3-27 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.

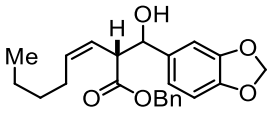
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.36 – 7.29 (m, 4H), 7.26 – 7.23 (m, 2H), 6.65 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.54 (dd, *J* = 12.4, 2.4 Hz, 1H), 5.67 – 5.62 (m, 1H), 5.61 – 5.55 (m, 1H), 5.34 – 5.31 (m, 1H), 5.13 – 5.07 (m, 2H), 3.80 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.77 (s, 3H), 3.11 (d, *J* = 3.1 Hz, 1H),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

^{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**.**



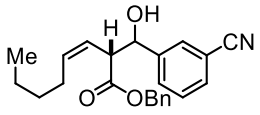
3-28 Prepared according to the General Procedure A from the corresponding diene (115.3 mg, 0.50 mmol) and piperonal (225.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 59%, *dr*: >98:2. Isolated in 57% yield as a yellow oil after purification by column chromatography (17:3 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* = 10.5, 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.



3-29 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.

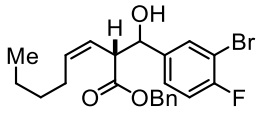
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 (t, *J* = 1.7 Hz, 1H), 7.27 (dt, *J* = 7.9, 1.7 Hz, 2H), 7.13 – 7.05 (m, 4H), 6.99 – 6.96 (m, 2H), 5.46 – 5.41 (m, 1H), 5.32 – 5.27 (m, 1H), 4.86

– 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.



3-30 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.

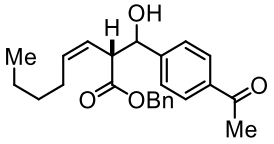
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.55 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.36 – 7.30 (m, 3H), 7.23 – 7.19 (m, 3H), 7.00 (t, *J* = 8.4 Hz, 1H), 5.74 – 5.69 (m, 1H), 5.56 (app tt, *J* = 10.5, 1.4 Hz, 1H), 5.12 – 4.02 (m, 2H), 5.00 (dd, *J* = 5.5, 2.4 Hz, 1H), 3.62 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.04 (d, *J* = 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.



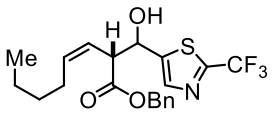
3-31 Prepared according to the General Procedure A from the corresponding diene (115 mg, 0.50 mmol) and 3-acetylbenzaldehyde (222 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 84%, *dr*: >98:2. Isolated in 79% yield as a yellow oil after purification by column chromatography (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.



3-32 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);

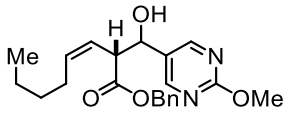
^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 166.3, 141.2, 140.2, 138.1, 135.1, 131.6 (q, *J* = 32.6 Hz), 128.6, 128.4, 128.2, 126.6, 126.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.0 Hz) 120.9, 68.9, 67.1, 51.9, 31.3, 27.6, 22.3, 13.9;

^{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.



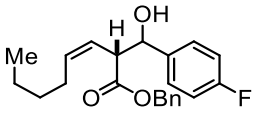
3-33 Prepared according to the General Procedure A from the corresponding diene (115 mg, 0.5 mmol) and 2-methoxypyrimidine-5-carbaldehyde (207 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 49%, *dr*: >98:2. Isolated in 45% yield as a colorless oil after purification by column 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.



3-34 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).

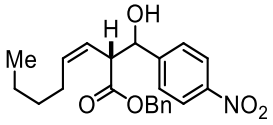
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35 – 7.27 (m, 5H), 7.20 – 7.17 (m, 2H), 6.96 (t, *J* = 8.6 Hz, 2H), 5.71 (td, *J* = 10.7, 7.5 Hz, 1H), 5.57 (tt, *J* = 10.7, 1.6 Hz, 1H), 5.08 – 5.00 (m, 3H), 3.65 (ddd, *J* = 10.0, 5.9, 0.8 Hz, 1H), 2.92 (d, *J* = 2.3 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.89 – 1.83 (m, 1H),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



3-35 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).

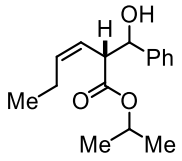
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.31 (m, 3H), 7.23 – 7.21 (m, 2H), 5.72 – 5.67 (m, 1H), 5.58 – 5.53 (m, 1H), 5.16 (dd, *J* = 5.1, 2.3 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 2H), 3.66 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.25

(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.



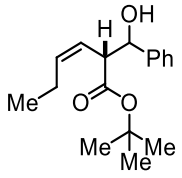
3-36 Prepared according to the General Procedure A from the corresponding diene (77.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 71%, *dr*: >98:2. Isolated in 61% yield as a yellow oil after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 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 (sept, 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.



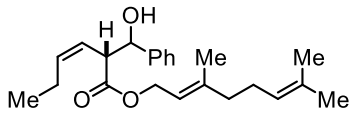
3-37 Prepared according to the General Procedure A from the corresponding diene (84.2 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 62%, *dr*: >98:2. Isolated in 60% yield as a yellow oil after purification by column chromatography (10:1 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.



3-38 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).

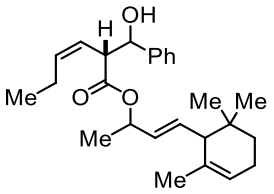
Prepared according to General Procedure B from the corresponding diene (124.2 mg, 0.50 mmol, 1.0 equiv.) and benzaldehyde (159 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 77%, *dr*: >98:2.

^{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 (br s, 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 $C_{23}H_{23}O_3Na$ $[M+Na]^+$ 379.2000. Found 379.2000;

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



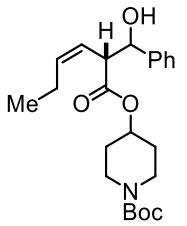
3-39 Prepared according to the General Procedure A from the corresponding diene (144.2 mg, 0.50 mmol, 1 equiv.) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 97%, crude yield: 76%. Isolated as a 1:1:1:1 mixture of diastereomers in 70% yield as a thick yellow oil after purification 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.



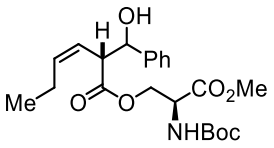
3-40 Prepared according to the General Procedure A from the corresponding diene (156.7 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 93%, crude yield: 76%, *dr*: >98:2. Isolated in 71% yield as a yellow oil after purification by column chromatography (3:1 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 (ddd, *J* = 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 $C_{23}H_{33}NO_5Na$ $[M+Na]^+$ 426.2251. Found 426.2250;

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



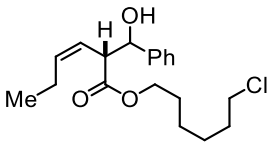
3-41 Prepared according to the General Procedure A from the corresponding diene (156.7 mg, 0.50 mmol) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 96%, crude yield: 65%. Isolated as a 1:1 mixture of diastereomers in 61% yield as a yellow oil after purification by column 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.



3-42 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).

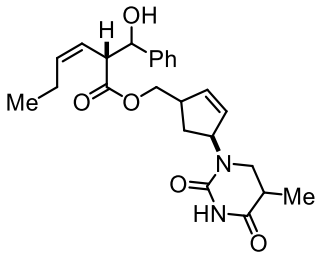
Prepared according to General Procedure B from the corresponding diene (115.4 mg, 0.50 mmol) and benzaldehyde (159.2 mg, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 80%, *dr*: >98:2.

^{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, 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.



3-43 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).

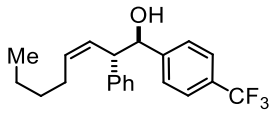
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.17 (s, 2H), 7.35 – 7.30 (m, 8H), 7.29 – 7.26 (m, 2H), 7.04 – 7.03 (m, 1H), 6.99 -6.98 (m, 1H), 6.92 – 6.91 (m, 1H), 6.88 – 6.87 (m, 1H), 6.08 (dt, *J* = 6.0, 1.6 Hz , 1H), 5.88 (dt, *J* = 6.0, 1.6 Hz, 1H), 5.86 – 5.84 (m, 1H), 5.77 – 5.66 (m, 3H), 5.58 – 5.53 (m, 2H), 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 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.



3-44 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 colorless oil after purification by column chromatography (4:1 Hexane/EtOAc).

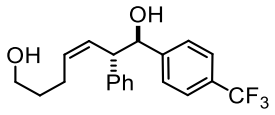
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.16 (m, 5H), 7.09 (d, *J* = 7.2 Hz, 2H), 5.86 – 5.82 (m, 1H), 5.71 – 5.66 (m, 1H), 4.88 (d, *J* = 7.2 Hz, 1H), 3.83 (dd, *J* = 10.1, 7.2 Hz, 1H), 2.31 (bs, 1H), 2.02 – 1.98 (m, 2H), 1.24 – 1.18 (m, 4H), 0.82 (t, *J* = 6.9 Hz, 3H);

^{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): calcd 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.



3-45 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);

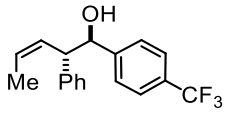
^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.1, 140.8, 133.2, 129.4 (q, *J* = 31.4 Hz), 128.8, 128.6, 128.2, 126.9, 126.8, 124.8 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 270.2 Hz) 77.6, 61.8, 52.3, 31.7, 23.8;

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

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

MP: 73 – 75 ºC;

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



3-46 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 colorless oil after purification by column chromatography (4:1 Hexane/EtOAc).

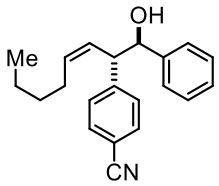
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.16 (m, 5H), 7.09 (d, *J* = 8.3 Hz, 2H), 5.90 – 5.86 (m, 1H), 5.82 – 5.76 (m, 1H), 4.88 (d, *J* = 7.3 Hz, 1H), 3.86 (dd, *J* = 9.7, 7.3 Hz, 1H), 2.31 (d, *J* = 2.0 Hz, 1H), 1.60 (d, *J* = 6.7 Hz, 3H);

^{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): calcd 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.



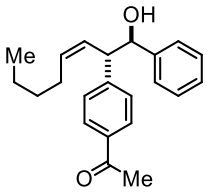
3-47 Prepared according to General Procedure C from the corresponding diene (98.7 mg, 0.5 mmol, 1.0 equiv.) and benzaldehyde (153 μL, 1.5 mmol, 3.0 equiv.). ^{1}H NMR diene conversion: 95%, crude yield: 81%, *dr* >98:2. Isolated in a 77% yield as a yellow oil after purification by column chromatography (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.



3-48 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).

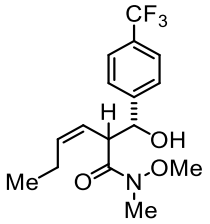
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.24 – 7.13 (m, 7H), 5.87 – 5.80 (m, 1H), 5.70 (tdd, *J* = 10.8, 7.2, 0.7 Hz, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 3.94 (dd, *J* = 9.9, 7.2 Hz, 1H), 2.54 (s, 3H), 2.26 (s, 1H), 2.12 – 1.98 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H);

^{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.



3-49 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 colorless oil after purification by column chromatography (3:2 Hexane/EtOAc).

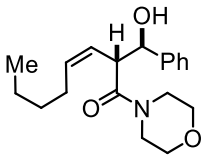
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 5.61 – 5.47 (m, 2H), 5.18 (d, *J* = 2.8 Hz, 1H), 4.46 (s, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 3.58 (s, 3H), 3.19 (s, 3H) 1.78 – 1.64 (m, 1H), 1.51 – 1.40 (m, 1H), 0.56 (t, *J* = 7.6, 3H);

^{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): calcd 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;



3-50 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).

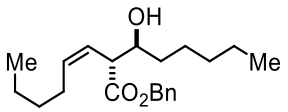
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 – 7.28 (m, 4H), 7.24 – 7.22 (m, 1H), 5.95 -5.52 (m, 2H), 5.15 (d, *J* = 3.6 Hz, 1H), 4.42 (s, 1H), 3.68 (dt, *J* = 13.3, 4.4 Hz, 1H), 3.62 – 3.59 (m, 3H), 3.53 – 3.46 (m, 2H), 3.38 – 3.35 (m, 1H), 3.31 – 3.28 (m, 1H), 3.24 – 3.22 (m, 1H), 1.63 – 1.60 (m, 1H), 1.39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



3-51 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).

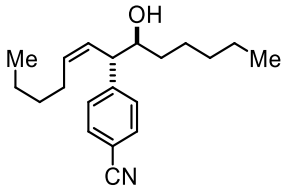
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.30 (m, 5H), 5.75 – 5.70 (m, 1H), 5.57 – 5.52 (m, 1H), 5.14 (s, 2H), 3.93 – 3.89 (m, 1H), 3.44 (ddd, *J* = 10.1, 4.5, 0.7 Hz, 1H), 2.60 (d, *J*

= 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): calcd 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.



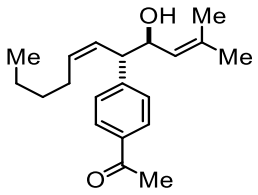
3-52 Prepared according to a modified General Procedure A (extra 0.5 equiv. HCO_2H after consumption of initial 1.2 equiv.) from the corresponding diene (40 mg, 0.2 mmol) and trans-2-hexenal (148 μL, 1.2 mmol, 6.0 equiv.). ^{1}H NMR diene conversion: 92%, crude yield: 55%, *dr*: >98:2. Isolated in 53% yield as a colorless 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): calcd 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.



3-53 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).

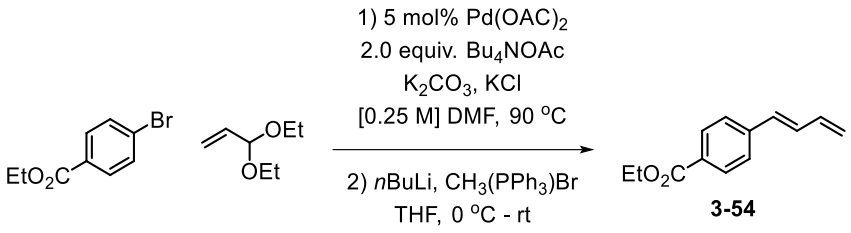
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.78 – 5.65 (m, 2H), 5.11 (d, *J* = 8.7 Hz, 1H), 5.51 (t, *J* = 7.6 Hz, 1H), 3.73 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.58 (s, 3H), 2.21 – 1.98 (m, 2H), 1.62 (s, 3H), 1.48 (s, 3H), 0.94 (t, *J* = 7.6 Hz, 3H)

^{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.

3.5 Synthesis of Glucagon Receptor Antagonist Intermediate



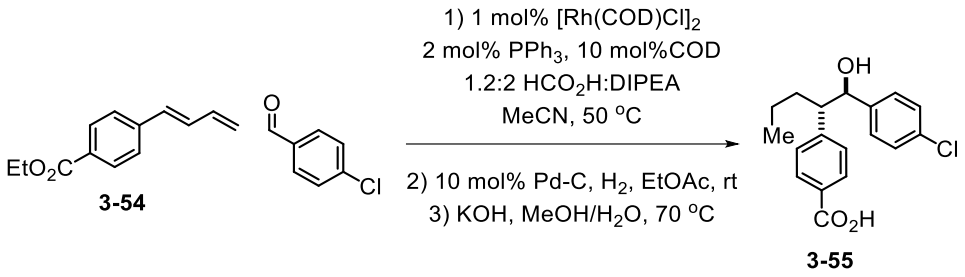
3-54 Step 1. Prepared according to literature procedure.[145] Isolated in 74% yield as an off white solid (10:1 Hexane/EtOAc). The spectral data matched those reported in the literature.[146]

Step 2. Prepared according to literature procedure[147] from ethyl 4-bromobenzoate (2.0 g, 9.8 mmol, 1.0 equiv.). Isolated in 71% yield as yellow oil (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500MHz) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 6.88 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.52 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.40 (d, *J* = 16.8 Hz, 1H), 5.25 (d, *J* = 10.2 Hz, 1H), 4.37 (q, *J* = 14.3, 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ166.3, 141.5, 136.8, 131.9, 131.7, 129.9, 129.3, 126.2, 119.2, 60.9, 14.3;

HRMS (EI): calcd for $C_{13}H_{14}O_2Na$ $[M]^+$ 202.0993. Found 202.0994.

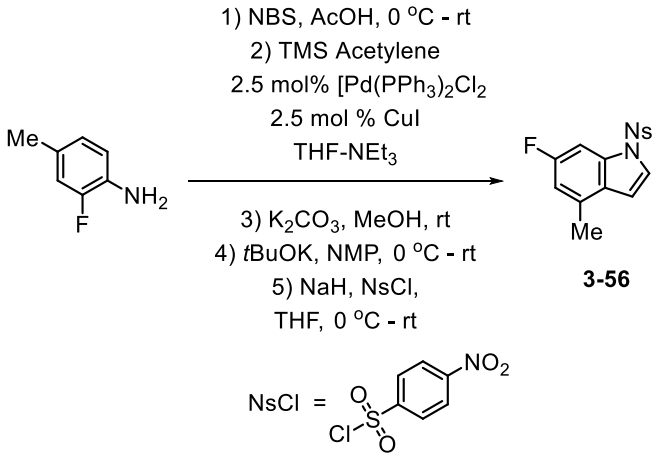


3-54 **3-55**

3-55 Step 1. Prepared according to general procedure C from the corresponding diene (540 mg, 2.7 mmol) and 4-(chloro)-benzaldehyde (1.41 g, 8.1 mmol, 3.0 equiv.). Isolated in 79% yield as yellow oil (4:1 Hexane/EtOAc).

Step 2. Prepared according to literature procedure[148] from the corresponding *Z*-homoallylic alcohol (600 mg, 1.7 mmol, 1.0 equiv.) Isolated as pure in 94% yield as a yellow oil.

Step 3. Prepared according to literature procedure[149] from the corresponding hydrogenated alcohol (320 mg, 0.9 mmol, 1.0 equiv.). Isolated as pure in 97% yield as a yellow oil. The spectral data matched those reported in the literature.[150]



3-56

3-56 Step 1. To a 100 mL round bottom flask was added 2-fluoro-4-methyl-aniline (2.50 g, 20.0 mmol, 1.0 equiv.) followed by acetic acid (20 mL). The resulting solution

was then cooled to 0 °C and *N*-bromosuccinimide (4.00 g, 22.5 mmol, 1.13 equiv.) was added in 4 portions. The reaction mixture was warmed to room temperature and stirred for one hour. The reaction mixture was then added to water (85 mL) and extracted with ethyl acetate (3 x 50 mL). the combined organic layers were washed with water (2 x 85 mL) followed by excess 10% sodium carbonate solution (80 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated. Isolated in a 63% yield as a dark red oil (20:1 Pentane/Et_2O). The spectral data matched those reported in the literature.[151]

Step 2. Prepared according to literature procedure.[150] Isolated in an 85% yield as an orange oil (40:1 Pentane/Et_2O).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.90 (br s, 1H), 6.78 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.09 (br s, 2H), 2.19 (s, 3H), 0.26 (s, 9H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 151.0 (d, *J* = 238.5 Hz), 134.9 (d, *J* = 14.3 Hz), 127.9 (d, *J* = 2.7 Hz) 127.1 (d, *J* = 7.7 Hz), 116.9 (d, *J* = 18.7 Hz), 108.5, 108.4, 82.9, 79.6, 20.3;

^{19}F NMR ($CDCl_3$, 376 MHz) δ –124.9 (s);

HRMS (EI): calcd for $C_{12}H_{16}NFSi$ $[M]^+$ 221.1036. Found 221.1032.

Step 3. To a 100 mL round bottom flask was added 2-fluoro-4-methyl-6-((trimethylsilyl)ethynyl) aniline (1.33 g, 6.0 mmol, 1.0 equiv.) followed by methanol (49 mL). Potassium carbonate (1.66 g, 12.0 mmol, 2.0 equiv.) was added on one portion. Reaction mixture was stirred for 30 minutes. Methanol was then removed *in vacuo* and dissolved in EtOAc, washed with water (2 x 60 mL) and brine (1 x 50 mL). The organic layer was then dried over Na_2SO_4 and concentrated. Isolated in a 78% yield as a red-orange oil (20:1 Pentane/Et_2O).

^{1}H NMR ($CDCl_3$, 700MHz) δ 6.93 (br s, 1H), 6.81 (dd, *J* = 11.6, 1.6 Hz, 1H), 4.12 (br s, 2H), 3.39 (s, 1H), 2.21 (s, 3H);

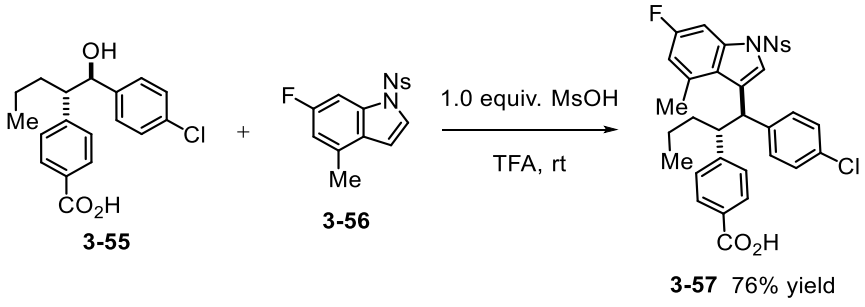
^{13}C NMR ($CDCl_3$, 175 MHz) δ 150.9 (d, *J* = 238.5 Hz), 134.8 (d, *J* = 14.3 Hz), 127.8 (d, *J* = 2.8 Hz), 127.0 (d *J* = 7.7 Hz), 116.8 (d, *J* = 18.3 Hz), 108.4, 82.3, 79.6, 20.2;

^{19}F NMR ($CDCl_3$, 176 MHz) δ 134.8 (d, *J* = 11.9 Hz);

HRMS (EI): calcd for C_9H_8NF $[M]^+$ 149.0641. Found 149.0639.

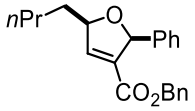
Step 4. To a 150 mL round bottom flask was added 2-ethynyl-6-fluoro-4-methylaniline (1.10 g, 7.37 mmol, 1.0 equiv.) as a solution in NMP (12.9 mL). The solution was then cooled to 0 °C and KO*t*Bu (1.65 g, 14.7 mmol, 2.0 equiv.) was added as a solution in NMP (51.5 mL). The reaction mixture was warmed to room temperature and stirred for 4 hours. The reaction mixture was then added to H_2O (125 mL) and extracted with EtOAc (4 x 50 mL). The combined organic layers are then washed with water (3 x 50 mL) followed by brine (50 mL) dried over Na_2SO_4, filtered and concentrated. Isolated in 81% yield as a slightly yellow solid (20:1 Hexane/Et_2O). The spectral data matched those reported in the literature.[151]

Step 5. Prepared according to literature procedure.[152] Isolated in 53% yield as an off white solid (17:5 Hexane/EtOAc). The spectral data matched those reported in the literature.[151]



3.57 Prepared according to literature procedure [150] from **3.55** (50 mg, 0.16 mmol, 1.05 equiv.) and **3.56** (50 mg, 0.15 mmol, 1.0 equiv.). Isolated in 75% yield as an off white solid (1:1 Hexane/EtOAc). The spectral data matched those reported in the literature.[150]

3.6 Product Derivatization



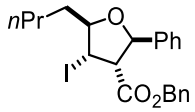
3-58 Prepared according to literature procedure[141] from **3-2** (169 mg, 0.5 mmol, 1.0 equiv.). Isolated in 78% as a light yellow oil (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700MHz) δ 7.35 – 7.26 (m, 8H), 7.08 – 7.07 (m, 2H), 6.98 (t, *J* = 1.8 Hz, 1H) 5.88 (dd, *J* = 4.6, 2.2 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 4.98 – 4.95 (m, 2H), 1.81 – 1.70 (m, 2H), 1.49 – 1.33 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR ($CDCl_3$, 175 MHz) δ 162.4, 142.8, 140.7, 135.5, 135.2, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 86.6, 85.8, 66.2, 35.7, 27.9, 22.6, 13.9;

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

IR: ν (cm^{-1}) 3092, 3064, 3032, 2955, 2930, 2859, 1954, 1721, 1645, 1495, 1455, 1336, 1257.



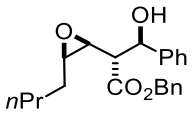
3-59 Prepared according to literature procedure[138] from **3-2** (68 mg, 0.2 mmol, 1.0 equiv.). Isolated in 76% as a colorless oil (4:1 Hexane/EtOAc) (Decomposes over time).

^{1}H NMR ($CDCl_3$, 700MHz) δ 7.41 – 7.27 (m, 10H), 5.24 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 4.90 (d, *J* = 7.1 Hz, 1H), 4.78 (dd, *J* = 4.4, 3.5 Hz, 1H), 3.62 (dd, *J* = 7.1, 3.5 Hz, 1H), 3.16 – 3.14 (m, 1H), 1.84 – 1.72 (m, 1H), 1.68 – 1.63 (m, 1H), 1.44 – 1.38 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 171.8, 139.7, 135.3, 128.6, 128.5 (2), 128.3, 128.2, 126.6, 83.6, 81.8, 67.2, 64.7, 37.0, 31.8, 28.1, 22.6, 14.0;

HRMS (ESI): calcd for $C_{22}H_{25}IO_3Na$ $[M+Na]^+$ 487.0741. Found 487.0747;

IR: ν (cm^{-1}) 3092, 3064, 3033, 2955, 2931, 2860, 1953, 1732, 1604, 1496, 1455, 1378, 1211, 1171.



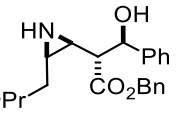
3-60 Prepared according to literature procedure[142] from **3-2** (203 mg, 0.6 mmol, 1.0 equiv.). Isolated in 70% as a colorless oil (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700MHz) δ 7.36 – 7.28 (m, 8H), 7.08 – 7.07 (m, 2H), 5.20 (d, *J* = 7.4 Hz, 1H), 4.93 (d, *J* = 12.3 Hz, 2H), 3.41 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.27 (br s, 1H), 2.97 – 2.95 (m, 1H), 2.72 (dd, *J* = 9.2, 7.4 Hz, 1H), 1.53 – 1.50 (m, 2H), 1.44 – 1.41 (m, 1H), 1.35 – 1.30 (m, 3H), 0.86 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 170.3, 140.4, 135.0, 128.5, 128.4 (2), 128.3, 128.2, 126.5, 75.5, 66.7, 56.2, 56.1, 52.6, 28.5, 27.7, 22.4, 13.9;

HRMS (ESI): calcd for $C_{22}H_{26}O_4$ $[M+Na]^+$ 377.1723. Found 377.1723;

IR: ν (cm^{-1}) 3481,3064, 3032, 2957, 2929, 2872, 1953, 1730, 1607, 1496, 1455, 1308, 1154.



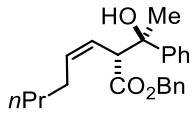
3-61 Prepared according to literature procedure[143] from **3-2** (169 mg, 0.5 mmol, 1.0 equiv.). Isolated in 62% as a light yellow oil (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700MHz) δ 7.34 – 7.32 (m, 2H), 7.28 – 7.23 (m, 6H), 6.95 – 6.94 (m, 2H 5.10 (d, *J* = 8.9 Hz, 1H), 4.83 (d, *J* = 12.2 Hz, 1H), 4.74 (d, *J* = 12.2 Hz, 1H), 2.72 (dd, *J* = 9.2, 6.5 Hz, 1H), 2.48 (t, *J* = 9.2 Hz, 1H), 2.10 – 2.07 (m, 1H), 1.46 – 1.39 (m, 3H), 1.35 – 1.30 (m, 3H), 0.86 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 171.5, 141.0, 135.1, 128.4, 128.3, 128.2, 128.1, 126.8, 76.9, 66.5, 51.7, 35.7, 33.7, 29.6, 28.4, 22.5, 14.0;

HRMS (ESI): calcd for $C_{22}H_{27}NO_3Na$ $[M+H]^+$ 354.2064. Found 354.2066;

IR: ν (cm^{-1}) 3308, 3089, 3063, 3032, 2956, 2929, 2871, 2859, 1958, 1730, 1604, 1496, 1455, 1309, 1153.



3-62 Prepared according to literature procedure[144] from **3-2** (54 mg, 0.2 mmol, 1.0 equiv.). Isolated as an inseparable mixture of diastereomers (*dr*: 5:1) in 79% as a colorless oil (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 400MHz) δ 7.45 – 7.43 (m, 2H), 7.42 – 7.24 (m, 6H), 6.99 – 6.9 (m, 2H), 5.80 – 5.78 (m, 2H), 4.93 (d, *J* = 12.3 Hz, 1H), 4.86 (d, *J* = 12.3 Hz, 1H), 4.34 (s, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 2.19 – 2.15 (m, 2H), 1.43 (s, 3H), 1.39 – 1.37 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 174.6, 147.1, 136.1, 135.3, 128.4, 128.2, 128.1, 127.8, 126.9, 124.7, 122.6, 75.4, 66.4, 53.0, 31.5, 27.8, 27.6, 22.3, 13.9;

HRMS (ESI): calcd for $C_{23}H_{28}O_3Na$ $[M+Na]^+$ 375.1931. Found 375.1931;

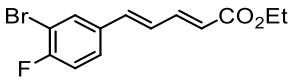
IR: ν (cm^{-1}) 3089, 3062, 3028, 2957, 2929, 2871, 2858, 1950, 1712, 1601, 1495, 1455, 1378, 1167.

3.7 Preparation of Substrates: The synthetic routes towards the preparation of the substrates were not optimized. Unless otherwise noted, diene substrates were prepared according to a literature procedure[137] and all compounds matched the reported spectral data.

General Procedure D [Horner-Wadsworth-Emmons Olefination] To a flask charged with a stir bar and purged with N_2 was added diisopropylamine (1.2 equiv.) followed by THF (0.24 M). The reaction mixture was cooled to –78 °C and a 2.5 M solution of *n*BuLi in hexanes (1.1 equiv.) was added and the mixture stirred for 1 minute at –78 °C. The corresponding diethyl phosphonate (1.0 equiv.) was added and the reaction mixture

was allowed to stir at −78 °C for 15 minutes. The corresponding aldehyde (1.2 equiv.) was then added as a solution in THF (0.6 M) and allowed to stir at −78 °C for 15 minutes and then at 0 °C until reaction was completed by ^{1}H NMR. The reaction mixture was diluted with 1M aqueous NH_4Cl and EtOAc. Organic layer was washed with water and brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was then purified via column chromatography.

General Procedure E [DCC Coupling] To a flask charged with a stir bar and purged with N_2 was added carboxylic acid (1.0 equiv.), DCM (0.40 M), alcohol (1.0 equiv.) and DMAP (0.05 equiv.). The solution was cooled to 0 °C and DCC (1.0 equiv.) was added portion-wise over 5 minutes. The mixture was warmed to room temperature and stirred overnight. The mixture was filtered through silica using DCM as eluent, concentrated *in vacuo* and purified by column chromatography.



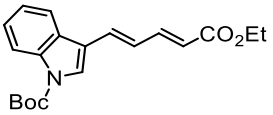
3-73 Prepared according to General Procedure D from triethyl 4-phosponocrotonate (1.2 g, 4.8 mmol, 1.0 equiv.) and 3-bromo-4-fluorobenzaldehyde (1.2 g, 5.7 mmol, 1.2 equiv.). Isolated in 45% yield as a white powder after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.10 (t, *J* = 8.2 Hz, 1H), 6.79 – 6.77 (m, 2H), 6.00 (d, *J* = 15.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8, 143.7, 137.3, 133.8, 131.9, 127.7, 127.6, 127.3 (d, *J* = 2.7 Hz), 122.3, 116.9, 116.7, 60.5, 14.4;

^{19}F NMR ($CDCl_3$, 468 MHz) δ –109.4 (m);

HRMS (EI): calcd for $C_{13}H_{12}BrFO_2$ $[M+H]^+$ 299.9984. Found 299.9981.

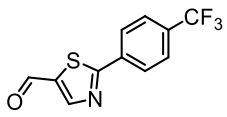


3-74 Prepared according to General Procedure D from triethyl 4-phosponocrotonate (750.7 mg, 3.0 mmol, 1.0 equiv.) and *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (880 mg, 3.6 mmol, 1.2 equiv.). Isolated in 49% yield as a white powder after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (d, *J* = 11.2 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.47 (dd, *J* = 15.2, 10.5 Hz, 1H), 7.37 (td, *J* = 7.8, 1.3 Hz, 1H), 7.32 (td, *J* = 7.8, 1.3 Hz, 1H), 7.06 – 6.93 (m, 2H), 5.98 (d, *J* = 15.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.69 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 149.3, 145.3, 136.2, 131.9, 128.2, 126.1, 125.1, 123.4, 120.2, 120.0, 118.2, 115.6, 84.4, 60.3, 28.2, 14.4;

HRMS (ESI): calcd for $C_{20}H_{24}NO_4$ $[M+H]^+$ 342.1700. Found 342.1694.



3-75 To a flask charged with stir bar was added 2-bromo-5-formylthiazole (500 mg, 2.6 mmol, 1.0 equiv.), 4-(trifluoromethyl)phenylboronic acid (742 mg, 3.9 mmol, 1.5

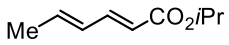
equiv.), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol, 0.05 equiv.) and 2 M Na_2CO_3 (6.5 mL, 13 mmol) in toluene/MeOH (3.5/2.0 mL), purged with N_2 and stirred at 80 °C overnight. Cooled to room temperature added EtOAc and H_2O and extracted (3×) with EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Isolated in 74% yield after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.08 (s, 1H), 8.46 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.7 Hz, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.9, 173.3, 152.1, 139.8, 135.7, 133.4, 133.1, 127.5, 126.3 (q, *J* = 7.5 Hz);

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

HRMS (EI): calcd for $C_{11}H_6OF_3NS$ $[M]^+$ 257.0122. Found 257.0121.

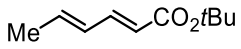


3-76 Prepared according to General Procedure E from sorbic acid (1.13 g, 10.0 mmol, 1.0 equiv.) and 2-propanol (601 mg, 10.0 mmol, 1.0 equiv.). Isolated in 65% yield as a clear colorless oil after purification by column chromatography (20:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.22 (dd, *J* = 15.4, 10.6 Hz, 1H), 6.21 – 6.09 (m, 2H), 5.74 (d, *J* = 15.4 Hz, 1H), 5.07 (sept, *J* = 6.3 Hz, 1H), 1.84 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 6H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 166.9, 144.7, 139.0, 129.9, 119.7, 67.4, 22.0, 18.7;

HRMS (ESI): calcd for $C_9H_{15}O_2$ $[M+H]^+$ 155.1067. Found 155.1068.

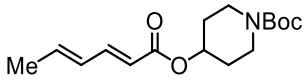


3-77 Prepared according to a literature procedure.[153] Isolated in 54% yield as a clear colorless oil after purification by column chromatography (20:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.15 (dd, *J* = 15.3, 10.7 Hz, 1H), 6.19 – 6.13 (m, 1H), 6.12 – 6.06 (m, 1H), 5.70 (dd, *J* = 15.3, 0.6 Hz, 1H), 1.84 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 9H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 166.7, 143.9, 138.5, 129.8, 121.0, 80.1, 28.2, 18.6;

HRMS (EI) calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150. Found 168.1150.

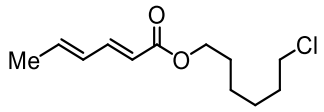


3-78 Prepared according to General Procedure E from sorbic acid (1.13 g, 10.0 mmol, 1.0 equiv.) and *tert*-butyl 4-hydroxypiperidine-1-carboxylate (2.02 g, 10.0 mmol, 1.0 equiv.). Isolated in 64% yield as a yellow solid after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.23 (dd, *J* = 15.3, 10.3 Hz, 1H), 6.21 – 6.10 (m, 2H), 5.75 (d, *J* = 15.3 Hz, 1H), 5.00 – 4.95 (m, 1H), 3.70 (s, 2H), 3.27 – 3.20 (m, 2H), 1.84 (d, *J* = 6.2 Hz, 3H), 1.65 – 1.58 (m, 2H), 1.45 (s, 9H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 166.5, 154.7, 145.1, 139.5, 129.7, 119.0, 79.6, 69.4, 41.0, 30.6, 28.4, 18.6;

HRMS (ESI): calcd for $C_{16}H_{25}NO_4Na$ $[M+Na]^+$ 318.1676. Found 318.1677.

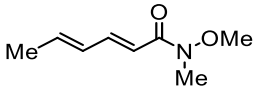


3-79 Prepared according to General Procedure E from sorbic acid (1.13 g, 10.0 mmol, 1.0 equiv.) and 6-chlorohexan-1-ol (1.37 g, 10 mmol, 1.0 equiv.). Isolated in 96% yield as a white solid after purification by column chromatography (10:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.23 (dd, *J* = 15.5, 10.6 Hz, 1H), 6.21 – 6.09 (m, 2H), 5.76 (d, *J* = 15.5 Hz, 1H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.52 (t, *J* = 6.7 Hz, 2H), 1.84 (d, *J* = 6.4 Hz, 3H), 1.80 – 1.75 (m, 2H), 1.70 – 1.64 (m, 2H), 1.50 – 1.44 (m, 2H), 1.42 – 1.36 (m, 2H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 167.3, 145.0, 139.3, 129.8, 118.9, 64.1, 44.9, 32.5, 28.6, 26.6, 25.3, 18.6;

HRMS (ESI): calcd for $C_{12}H_{19}ClO_2Na$ $[M+Na]^+$ 253.0966. Found 253.0968.



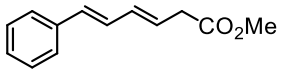
3-80 A 100 mL round bottom flask charged with a stir bar and sorbic acid (2.25 g, 20 mmol, 1.0 equiv.) was purged with N_2. DCM (46 mL) was added followed by portion wise addition of 1,1'-carbonyldiimidazole (3.89 g, 24 mmol, 1.2 equiv.) over 5 minutes. The reaction mixture was stirred for 1 h at room temperature. N_2 was bubbled through the solution for 10 minutes. *N,O*-dimethyl hydroxylamine HCl (2.54 g, 26 mmol, 1.3 equiv.) was added in one portion and allowed to stir at room temperature overnight. The reaction mixture was added to saturated NH_4Cl (40 mL). The aqueous phase was then extracted with DCM (3×), combined organic layers were washed with brine, dried over sodium

sulfate, concentrated *in vacuo*. Residue was purified by column chromatography (3:2 Hexane/EtOAc). Isolated in 40% yield as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.29 (dd, *J* = 15.1, 10.9 Hz, 1H), 6.36 (d, *J* = 15.1 Hz, 1H), 6.27 – 6.21 (m, 1H), 6.16 – 6.09 (m, 1H), 3.69 (s, 3H), 3.24 (s, 3H), 1.84 (dd, *J* = 6.9, 1.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 167.5, 143.8, 138.5, 130.3, 116.7, 61.7, 32.5, 18.6;

HRMS (ESI): calcd for $C_8H_{13}NO_2Na$ $[M+Na]^+$ 156.1019. Found 156.1020.

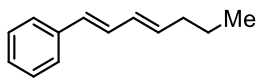


3-81 Prepared according to a literature procedure.[154] Isolated in 24% yield as a brick red solid after purification by column chromatography (4:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.77 (dd, *J* = 15.4, 10.8 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.30 (dd, *J* = 15.8, 10.8 Hz, 1H), 5.89 (dt, *J* = 15.4, 7.5 Hz, 1H), 3.71 (s, 3H), 3.20 (d, *J* = 7.5 Hz, 2H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 167.5, 137.2, 134.0, 132.2, 128.6, 128.3, 127.5, 126.3, 125.5, 51.9, 38.0;

HRMS (EI) calcd for $C_{13}H_{14}O_2$ $[M]^+$ 202.0993. Found 202.0989.

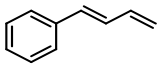


3-82 Prepared according to a literature procedure.[155] Isolated in 80% yield as a colorless oil after purification by column chromatography (20:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.76 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.44 (d, *J* = 15.6 Hz, 1H), 6.21 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.83 (dt, *J* = 14.5, 7.2 Hz, 1H), 2.13 (q, *J* = 7.2 Hz, 2H), 1.46 (sext, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 137.7, 135.8, 130.6, 129.9, 129.5, 128.5, 127.0, 126.1, 34.9, 22.5, 13.7;

HRMS (EI) calcd for $C_{13}H_{16}$ $[M]^+$ 172.1252. Found 172.1256.

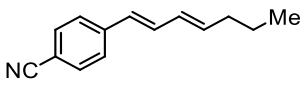


3-83 Prepared according to a literature procedure.[156] Isolated in 67% yield as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.41 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 (m, 1H), 6.80 (dd, *J* = 15.9, 10.8 Hz, 1H), 6.59 – 6.48 (m, 2H), 5.34 (d, *J* = 16.8 Hz, 1H), 5.34 (d, *J* = 10.1 Hz, 1H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 137.2, 137.1, 132.8, 129.6, 128.6, 127.6, 126.4, 117.6;

HRMS (EI) calcd for $C_{10}H_{10}$ $[M]^+$ 130.0782. Found 130.0782.



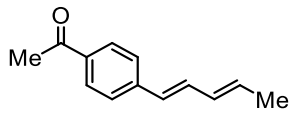
3-84 In an atmosphere controlled glovebox, potassium phosphate tribasic (2.04 g, 9.6 mmol, 2 equiv.), bis(triphenylphosphine)palladium (II) dichloride (168.5 mg, 0.24 mmol, 0.05 equiv.) were added to an eight dram vial followed by THF (6.5 mL). (*E*)-4-(2-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzonitrile (1.28 g, 5.0 mmol, 1.05 equiv.) was added in THF (3 mL) followed by (*E*)-1-iodopent-1-ene (941 mg, 4.8 mmol, 1 equiv.). The reaction mixture was then removed from the glovebox and water (432.3 μL, 24 mmol, 5 equiv.) was added. The mixture was heated at 60 ºC for 1 h at which point the reaction was complete by ^{1}H NMR. Reaction was diluted with EtOAc, washed with 1M KOH, followed by brine. Organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (19:1 Hexane/EtOAc). Isolated in a 44% yield as an orange oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.85 (dd, *J* = 15.6, 10.6 Hz, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 6.22 (dd, *J* = 15.2, 10.6 Hz, 1H), 5.95 (td, *J* = 15.2, 7.1 Hz, 1H), 2.15 (qd, *J* = 7.1, 1.6 Hz, 2H), 1.50 – 1.44 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 142.3, 138.9, 133.1, 132.3, 130.1, 127.9, 126.4, 119.1, 109.9, 35.0, 22.3, 13.7;

HRMS (EI) calcd for $C_{14}H_{15}N$ $[M]^+$ 197.1205. Found 197.1205.

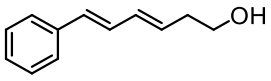


3-85 Prepared according to a literature procedure[157] from 1-(4-(pent-1-yn-1-yl) phenyl)ethenone (2.42 g, 13.0 mmol, 1.0 equiv.). Isolated in 84% yield as an off white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.86 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 6.28 – 6.21 (m, 1H), 5.96 – 5.90 (m, 1H), 2.58 (s, 3H), 1.85 (dd, *J* = 6.9, 1.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 197.5, 135.5, 132.6, 132.2, 131.6, 128.8, 128.7, 126.3, 126.1, 26.6, 18.5;

HRMS (EI) calcd for $C_{13}H_{14}O$ $[M]^+$ 186.1045. Found 186.1045.

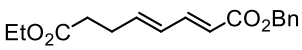


3-86 Prepared according to a literature procedure[158] from methyl (*E, E*)-6-phenylhexa-3,5-dienoate (100 mg, 0.7 mmol, 1 equiv.) and $LiAlH_4$ (39 mg, 1.05 mmol, 1.5 equiv.). Isolated in 54% yield as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.39 – 7.19 (m, 5H), 6.76 (dd, *J* = 15.5, 10.7 Hz, 1H), 6.49 (d, *J* = 15.5 Hz, 1H), 6.32 (dd, *J* = 14.6, 10.7 Hz, 1H), 5.83 – 5.77 (m, 1H), 3.72 (t, *J* = 6.3, 2H), 2.43 (q, *J* = 12.7, 6.2 Hz, 2H), 1.42 (bs, 1H);

^{13}C NMR ($CDCl_3$, 175 MHz) δ 137.4, 133.4, 131.2, 130.7, 128.8, 128.6, 127.3, 126.2, 62.0, 36.2;

HRMS (EI) calcd for $C_{12}H_{14}O$ $[M]^+$ 174.1044. Found 174.1045.



3-87 In an atmosphere controlled glovebox, Cs_2CO_3 (1.76 g, 5.4 mmol, 3 equiv.) palladium acetate (20.2 mg, 0.09 mmol, 0.05 equiv.) SPhos (73.9 mg, 0.18 mmol, 0.10 equiv.) were added to an eight dram vial followed by THF (10 mL). (*E*)-ethyl-5-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enoate (441 mg, 1.8 mmol, 1.0 equiv.) was added in THF (4 mL) followed by benzyl (*E*)-3-bromoprop-2-enoate (650.9 mg, 2.7 mmol, 1.5 equiv.) in THF (10 mL). The reaction mixture was then removed from the glovebox and water (97.3 mg, 5.4 mmol, 3 equiv.) was added. The mixture was heated at 50 ºC for 17 h at which point the reaction was complete by ^{1}H NMR. Reaction was diluted with EtOAc, washed with water followed by brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (17:5 Hexane/EtOAc). Isolated in a 65% yield as a yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.24 (m, 7H), 6.25–6.18 (m, 1H), 6.15–6.07 (m, 1H), 6.86 (d, *J* = 15.4 Hz, 1H), 5.19 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.53–2.40 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 166.9, 145.0, 141.9, 136.2, 129.3, 128.6, 128.2, 128.2, 119.9, 66.2, 60.6, 33.3, 28.2, 14.3;

HRMS (ESI): calcd for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254. Found 311.1254.

CHAPTER 4 - Rh-Catalyzed *Z*-Selective Reductive Coupling of Electron Deficient Dienes and Imines

4.1 Introduction

Functionalized amines are important building blocks in the syntheses of nitrogen containing molecules.[159] Homoallylic amines especially are useful motifs in alkaloid and N-heterocycle syntheses.[160, 161] Nucleophilic allylmetal (boron, magnesium, lithium, zinc, silicon and tin) additions to imines and iminium ions serve as a common pathway to access homoallylic amines (**Fig. 4-1**).[162-167] Imine allylation serves as a useful tool to prepare enantioenriched homoallylic amines by use of chiral auxillaries or chiral catalysts.[168-170]

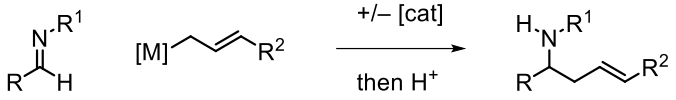


Fig. 4-1 Generic depiction of imine allylation to generate homoallylic amines.

In some cases, imine allylation can be complicated by poor functional group compatibility of basic metallic or main-group allyl reagents. In addition, there are limitations to the type of allyl groups that can be added due to the challenges involved in the preparation of the allyl metal reagents. Potential 1,3-metallotropic shift in allylic metal precursors can lead to different constitutional and geometrical isomers posing a major drawback in the preparation of allymetal reagents.[171-173] Catalytic reductive coupling between allyl transition metal nucleophiles generated from alkenes, and imines can be used to address these complications. Highlights of using alkenes as pronucleophiles in the transition metal catalyzed addition to carbonyls was presented in Chapter 3.

Despite many established examples of alkene reductive couplings to imines, the addition of diene-derived nucleophiles to imines to generate homoallylic amines are rare. Ru, Cu, Rh, and Ni-catalyzed processes have been reported to generate thermodynamically more stable *E*-homoallylic amines (**Fig. 4-2**).[78, 80, 171, 174, 175] Ru-catalyzed reductive coupling of α-imino esters[174] and amino alcohols[175] with diene pronucleophiles to generate α-branched allylic α-amino acid derivatives (**Fig. 4-2a**) and α-branched allylic pyrrolidines (**Fig. 4-2b**) respectively proceeds with the Ru–H addition to the diene to generate an allylruthenium to which the imine derivative adds. The α-branched allylic pyrrolidines synthesis is a redox triggered transformation involving the intermediate generation of 3,4-dihydro-2H-pyrrole from the amino alcohol.[175] Enantioselective formation of an allylcopper intermediate precedes imine addition to generate homoallylic amines in the Cu-catalyzed enantioselective reductive coupling of dienes and imines (**Fig. 4-2c**).[171] The generality of the processes remain low. In some cases, homoallylation products are observed to generate 4,5-unsaturated amines, for example in the case of Ni-catalyzed Et_2Zn-mediated reductive coupling (**Fig. 4-3**).[176]

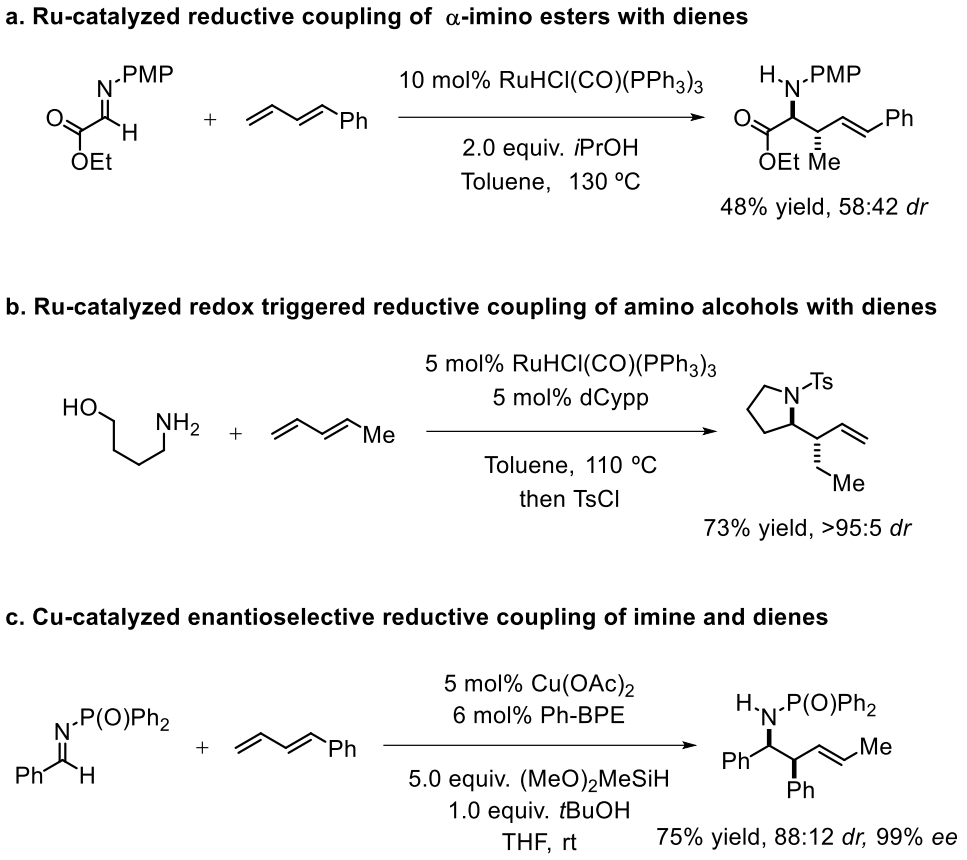


Fig. 4-2. Representative examples of metal-catalyzed reductive coupling of imines and dienes.

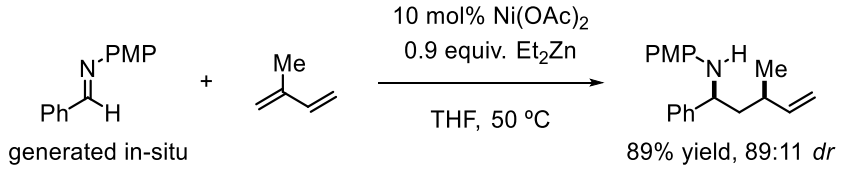


Fig. 4-3. Ni-catalyzed reductive coupling of imines and dienes to generate 4,5-unsaturated amines.

Formal stereoselective reductive coupling of dienes and imines to generate *Z*-homoallylic amines is limited to the Rh-catalyzed nucleophilic allylation of cyclic imines

using allylrhodium species derived from δ-potassium trifluoroboryl β,γ-unsaturated esters by chain walking (**Fig. 4-4**).[84] In the first step, Cu catalyzes the regioselective hydroboration of a dienoate substrate using $B_2(pin)_2$.[127] Treatment of the product with KHF_2 generates the allylic trifluoroborate intermediate which is used in a Rh-catalyzed allylation using cyclic aryl sulfamic acid-derived imines in the second step

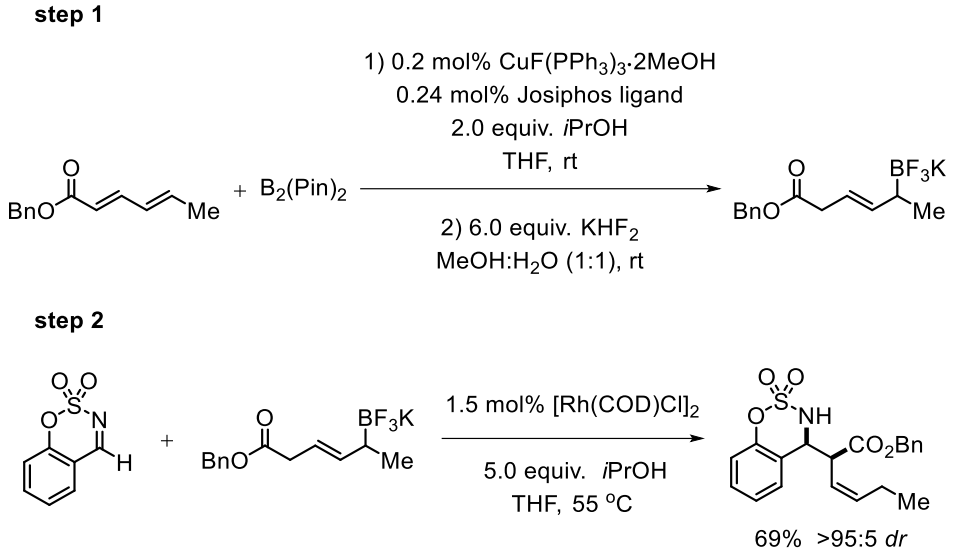


Fig. 4-4 Rh-catalyzed *Z*-selective reductive coupling of allyl boronate and cyclic iminosulfamidate.

The proposed mechanism of the Rh-catalyzed *Z*-selective reductive coupling of allyl boronates and cyclic iminosulfamidates is provided in **Fig. 4-5**. Transmetallation of Rh to allyl boronate generates an allylrhodium intermediate that can undergo allylic isomerization and β-hydride elimination to form a Rh–hydrido diene species. Reinsertion of the Rh–H into the diene can give new allylrhodium intermediates. These steps enable the chain-walking allyl isomerization to give, presumably, the more stable Rh-enolate and

vinylogous Rh-enolates. Addition of the Rh-vinylogous enolate to the cyclic iminesulfamidate through a chair-like transition state generates the major product.

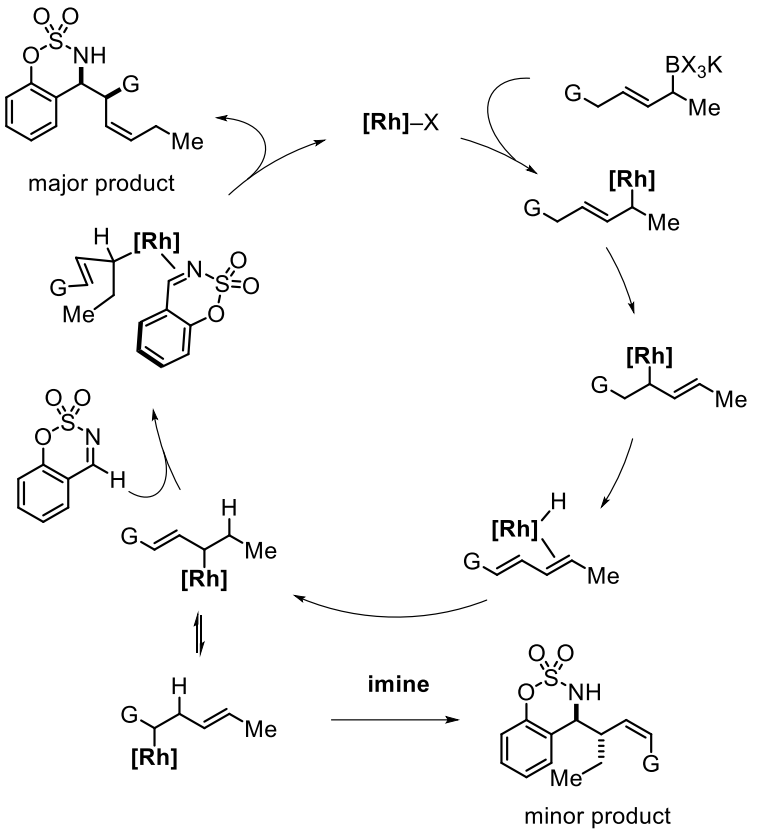


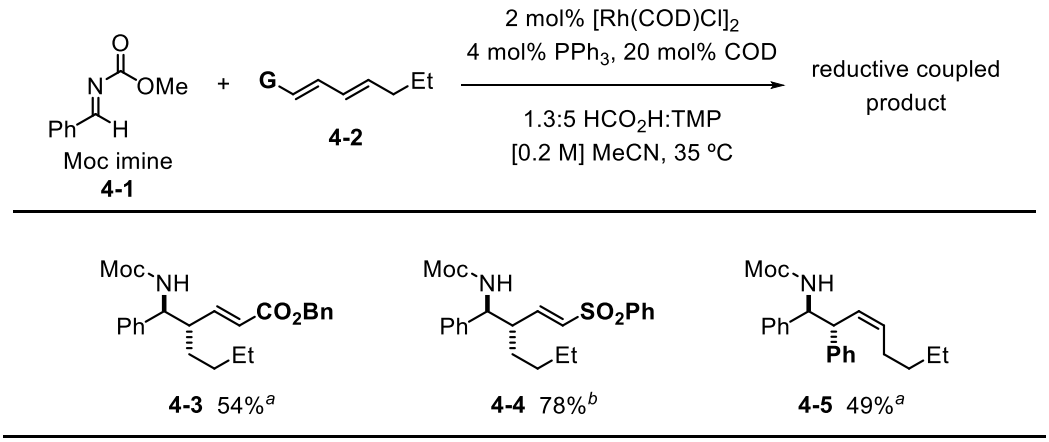
Fig. 4-5 Proposed mechanism of Rh-catalyzed *Z*-selective reductive coupling of allyl boronate and cyclic iminosulfamidates.

To the best of our knowledge, the above example represents the only *Z*-selective reductive coupling reaction of diene-derived nucleophiles and imines. The synthesis of *Z*-homoallylic amines can currently be conducted on specific substrates, typically by stereo-retentive reactions of *Z*-allylic electrophiles, or by Wittig reactions of protected amines.[177-179]

4.2 Development of Direct Formic Acid Mediated *Z*-Selective Reductive Coupling of Electron Deficient Dienes and Imines

With the *Z*-selective reductive coupling of electron-poor dienes and aldehydes mediated by formic acid to generate homoallylic alcohols[180] developed as presented in Chapter 3, it was envisaged that the same strategy could be used to prepare *Z*-homoallylic amines. We hoped the process would provide a more general solution to the catalytic synthesis of this class of compounds. With the objective, a series of electron-poor dienes (dienoates, sulfonyl dienes, and aryl dienes) were reacted with various imines derived from benzaldehyde (*N*-Ts, *N*-benzyl, *N*-Boc, *N*-Moc) imines under Rh-catalyzed reductive conditions similar to the ones used for aldehyde trapping. In most cases reductive coupling products were not obtained, but rather a mixture of diene reduction and imine reduction dominated. The observation suggests, in line with existing literature, that imine trapping by an allyl nucleophile is considerably more challenging than aldehyde trapping.

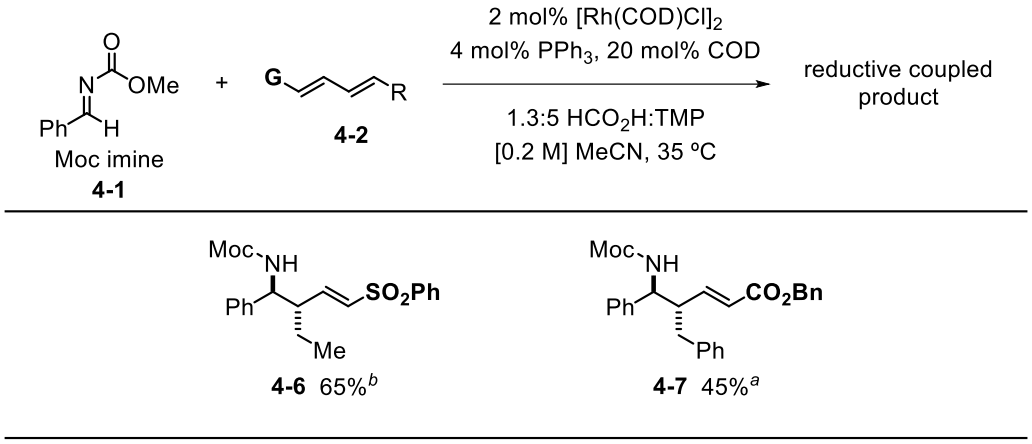
Ultimately, it was found that *N*-methoxycarbonyl phenyl imine (**4-1**) was the most successful electrophile under the conditions screened. The regiochemistry of addition and stereochemistry of the alkene unit in the product was dependent on the nature of the electron-withdrawing group on the diene. Using 2 mol% $[Rh(COD)Cl]_2$, 4 mol% PPh_3, and 20 mol% COD with a 1.3:5 mixture of formic acid and tetramethylpiperidine (TMP), ester and sulfonyl dienes underwent imine trapping at the γ-position and generated *E*-α,β-unsaturated ester, (**4-3)** or sulfonyl, (**4-4)** products (formal 5,6-addition). Imine trapping at the α-position to generate *Z*-β,γ-unsaturated phenyl product (**4-5**) was observed for the phenyl activated diene (**Table 4-1**).



Yields determined by caliberated ^{1}H NMR spectroscopy using dibenzyl ether as internal standard. Stereochemistry of the alkene and diastereoselectivity at the stereocenters are presently not yet ascertained a) 0.2 mmol scale b) 0.5 mmol scale.

Table 4-1 Reductive coupling of *N*-methoxycarbonyl phenyl imine with dienes having different electron-withdrawing groups.

The generality of γ-trapping of imines by sulfonyl dienes and dienoates was confirmed with two other examples **4-6** and **4-7** (**Table 4-2**). A hypothesis for the observed regiochemistry of the reductive coupling product of the sulfonyl diene and dienoates as shown in **Fig. 4-6** using dienoate as an example may involve the imine (**4-1)** addition to the Rh-dienolate (**4-9c)** obtained from the hydrorhodation of the dienoate (**4-8**) and π-allyl isomerization processes. The resulting imine trapping at the γ-position rather than at the α-position reduces the steric clash of the carbamate on the imine with the ester or phenyl sulfonyl group to generate homoallylic amine (**4-3)** (**Fig. 4-6)**. The formation of γ-addition products is what is observed when vinylketene silyl acetal nucleophiles attack imines.[169, 170]



Yields determined by caliberated ^{1}H NMR spectroscopy using dibenzyl ether as internal standard. Stereochemistry of the alkene and diastereoselectivity at the stereocenters are presently not yet ascertained a) 0.2 mmol scale b) 0.5 mmol scale.

Table 4-2 Reductive coupling of *N*-methoxycarbonyl phenyl imine with other dienoate and sulfonyl diene.

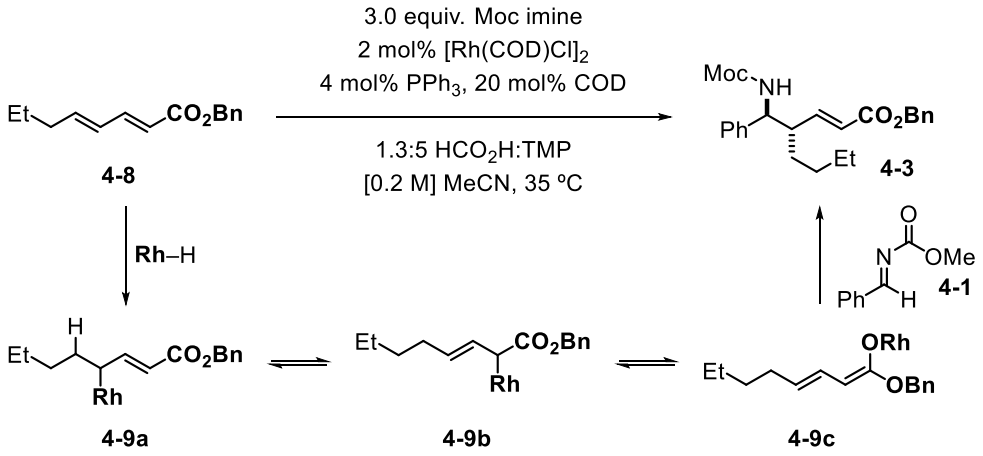
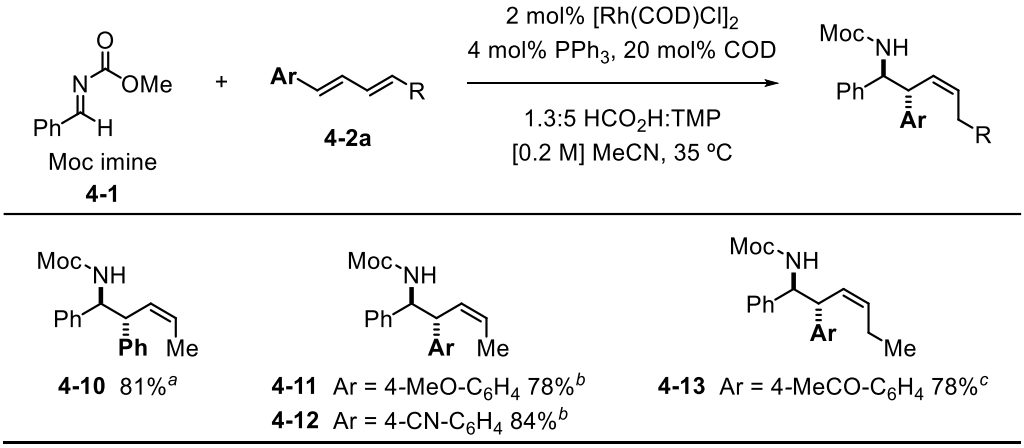


Fig. 4-6 Reductive coupling of *N*-methoxycarbonyl phenyl imine and dienoate to form γ-substituted α,β-unsaturated product.

1-Phenyl-1,3-butadiene can be reductively coupled to *N*-methoxycarbonyl phenyl imine (**4-1)** to generate *Z*-homoallylic amine, **4-10** as a single isomer in good yield (>98:2 *Z*/*E*, 81% yield) (**Table 4-3)**. A range of electronic properties involving electron donating, 4-methoxy group (**4-11)** and electron withdrawing, 4-cyano group (**4-12)** can be tolerated on the phenyl substituent of the diene partner. The reactivity of an alkyl substituted diene can be improved through activation of the phenyl ring with an electron withdrawing group such as a 4-acetyl group (**4-13**) compared to propyl-substituted phenyl diene (**4-5)** with a lower yield (**Table 4-3**).



All yields determined by caliberated ^{1}H NMR spectroscopy using dibenzyl ether as internal standard. >98:2 Z:E selectivity a) 0.5 mmol scale, isolated yield b) 0.5 mmol scale. c) 0.2 mmol scale

Table 4-3 Preliminary scope table for the reductive coupling of *N*-methoxycarbonyl phenyl imine with aryl dienes.

4.3 Summary and Conclusion

Rh-catalyzed formate mediated reductive coupling of electron-poor dienes and imines generate different classes of products depending on the nature of diene. Under

suitable conditions, dienyl esters and sulfonyls undergo imine trapping at the γ-position. Aryl 1,3-butadienes presently show the highest prospect to selectively generate the *Z*-homoallylic amine product with the highest stereo- and regioselectivity. The tolerance to a range of electronic properties shows the possibility of a broad scope. These studies help set the stage for a more comprehensive understanding of how Rh-catalyzed formate-mediated reductive coupling reactions can be used to prepare homoallyic amines. Use of different classes of diene activating groups can tune the selectivity in the preparation of a homoallylic amine via the reductive coupling process. Experiments to probe reaction mechanism by use of preformed intermediates such as allylrhodium species and rhodium dienolate, reaction progress kinetic analysis and expansion of the reaction scope will be the focus of researchers joining the group in the future.

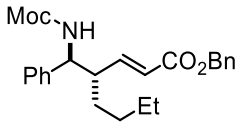
4.4 Procedures and Characterization

General Considerations

Unless noted, all reactions were conducted under inert atmosphere employing standard Schlenk technique or by use of an N_2-filled glovebox. All glassware was oven-dried prior to use. Flash chromatography was performed as described by Still and co-workers[104] (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 500 MHz, spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal ($CDCl_3$: δ H = 7.26 ppm, δ C = 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.

General Procedure A: In an atmosphere controlled glovebox, $[Rh(COD)Cl]_2$ (5.0 mg, 0.01 mmol, 0.02 equiv.) and PPh_3 (5.2 mg, 0.02 mmol, 0.04 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 (0.5 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 imine (1.75 mmol, 3.5 equiv.) (Note: Imine addition to have at least 3.0 equiv. in reaction mixture is

necessary), 1,5-cyclooctadiene (10.8 mg, 0.1 mmol, 0.20 equiv.) and finally internal standard (dibenzyl ether). To this mixture was transferred the catalyst solution using MeCN (0.5 mL) to rinse the remaining solution into the reaction mixture. Tetramethylpiperidine (353 mg, 2.5 mmol, 5.0 equiv.) was added directly by weight. Formic acid (30 mg, 0.65 mmol, 1.3 equiv.) was weighed into a half dram vial and washed into the reaction mixture with MeCN (0.5 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 heated to 35 °C. The reaction progress was monitored periodically via ^{1}H NMR spectroscopy. Once the reaction reached >98% conversion, the solution was diluted with toluene to quench, concentrated and purified by silica gel chromatography.

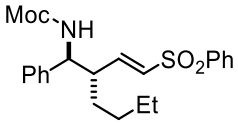


4-3 Prepared according to the General Procedure A from the corresponding dienoate **4-8** (135 mg, 0.5 mmol) and *N*-methoxycarbonyl phenyl imine (285.6 mg, 1.75 mmol, 3.5 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 54%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.34 (m, 6H), 7.28 – 7.19 (m, 4H), 5.89 (d, *J* = 11.7, 1H), 5.77 – 5.71 (m, 2H), 5.18 (s, 2H), 4.73 – 4.71 (m, 1H), 3.84 – 3.81 (m, 1H), 3.62 (s, 3H), 1.61 – 1.58 (m, 1H), 1.28 – 1.19 (m, 5H), 0.81 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.5, 140.7, 139.8, 139.4, 133.5, 132.1, 129.3, 128.4, 127.6, 127.5, 127.2, 58.8, 52.2, 42.2, 31.3, 29.1, 22.6, 14.1;

HRMS (**ESI**): calcd for $C_{24}H_{29}NO_4Na$ $[M+Na]^+$ 418.1989. Found 418.1984.

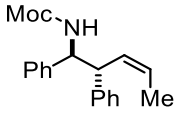


4-4 Prepared according to the General Procedure A from the corresponding phenyl sulfonyl diene (118 mg, 0.5 mmol) and *N*-methoxycarbonyl phenyl imine (285.6 mg, 1.75 mmol, 3.5 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 78%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.82 (m, 2H), 7.63 – 7.60 (m, 1H), 7.54 – 7.51 (m, 2H), 7.32 – 7.29 (m, 2H), 7.26 – 7.23 (m, 3H), 6.33 (d, *J* = 11.2 Hz, 1H), 5.79 – 5.73 (m, 2H), 4.78 (dd, *J* = 7.7, 5.7 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.65 (s, 3H), 1.63 – 1.59 (m, 1H), 1.28 – 1.03 (m, 5H), 0.79 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.4, 146.7, 141.1, 139.4, 133.5, 132.1, 129.3, 128.4, 127.6, 127.5, 127.2, 58.8, 52.2, 42.2, 31.3, 29.1, 22.6, 13.8;

HRMS (**ESI**): calcd for $C_{22}H_{27}NO_4SNa$ $[M+Na]^+$ 424.1553. Found 424.1554.



4-10 Prepared according to the General Procedure A from the corresponding aryl diene (65.0 mg, 0.5 mmol) and *N*-methoxycarbonyl phenyl imine (285.6 mg, 1.75 mmol, 3.5 equiv.). ^{1}H NMR diene conversion: >99%, crude yield: 84%, Isolated in 81% yield as a colorless oil after purification by column chromatography (2:1 Hexane/EtOAc).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 – 7.22 (m, 6H), 7.11 – 7.10 (m, 4H), 5.68 – 5.64 (m, 1H), 5.59 – 5.53 (m, 1H), 5.08 (bs, 1H), 4.99 (bs, 1H), 4.06 – 4.02 (m, 1H), 3.58 (s, 3H), 1.49 (dd, *J* = 6.8, 1.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.2, 140.5, 129.3, 129.1, 128.5, 128.4, 128.3, 128.0, 127.2, 126.8, 126.6, 59.5, 52.1, 48.8, 13.0;

HRMS (**ESI**): calcd for $C_{19}H_{21}NO_2Na$ $[M+Na]^+$ 318.1465. Found 318.1459.

Chapter 5 - Conclusions and Future Works

5.1 Conclusions

The thesis described the synthesis of *Z*-olefins from electron deficient dienes using Rh-catalyzed, formic acid mediated reductive processes. Reduction of electron deficient dienes via 1,6-hydride addition and ability to trap intermediate allylrhodium species generated from diene hydrorhodation with aldehyde or imine electrophiles in a reductive coupling process proceeded successfully to give *Z*-functionalized products. The mild reaction condition, tolerance to unsaturated and other reducible functionalities and high stereoselectivity obtained in these transformations make it a complimentary protocol to already existing access to *Z*-alkenes.

The addition of hydride equivalents to electron deficient dienes to generate *Z*-alkenes depends among other factors on the electron deficient diene having the correct geometry. The ability of the electron deficient diene to adopt an *s-cis* conformation appears to enable selective coordination to Rh which help dictates regio-, stereo- and chemoselectivity (Chapter 2). Controlled equivalent hydride addition can be used to prevent product decomposition leading to unproductive isomerization and over-reduction by maintaining a $(Rh–diene)^+$ complex presence in solution, providing an advantage over previously established *Z*-selective hydrogenations.

Z-Selective reductive coupling of electron deficient dienes with aldehydes to generate *Z*-homoallylic alcohols can also be mediated by formic acid (Chapter 3), an improvement from the previously available method that used pyrophoric Et_3B as terminal reductant.[85] The fast electrophilic aldehyde trapping of the catalytically generated allylrhodium intermediate prevents protonation and allylrhodium chain walking thereby

enhancing chemo- and regio-selectivity. The ancillary diene ligand serves as part of the active catalyst and can induce modest enantioselectivity when a chiral version is used. The drive for *Z*-selectivity through the proposed six-membered transition state as shown in the mechanism (Chapter 3 **Fig. 3-10**), depend on the alkyl substituent occupying a pseudoaxial position. This is to avoid a steric clash with the cylooctadiene ligand. This agrees with the model proposed by Lam and co-workers to explain the *Z*-selectivity observed in the rhodium catalyzed nucleophilic allylation of cyclic imines.[167]

Catalytically generated allylrhodium species with suitable nucleophilicity can be trapped by *N*-methoxycarbonyl phenyl imine to access *Z*-homoallylic amines (Chapter 4). However, the electronic and stearic properties of the diene activating group may have other roles to play in the stereo- and regioselectivity of the reaction.

5.2 Future Works

The thesis describes the foundation for the synthesis of *Z*-alkenes from electron deficient dienes mediated by formic acid. The amenability of the transformations to other diene functionalizations and enantioselective processes would be an interesting exploit.

The *Z*-selective reductive coupling of electron deficient dienes and imines described in Chapter 4 is the report of an optimized reaction condition to synthesize *Z*-homoallylic amines. Other necessary understanding and applications of the process are yet to be fully uncovered. Thought to be similar to the reductive coupling of electron deficient dienes and aldehydes described in Chapter 3, the different regio- and stereoselectivity observed in the imine trapping with ester and sulfonyl activated dienes requires further kinetic and mechanistic experiments for efficient understanding of the new process. In addition, the

enantio-induction observed in the reductive coupling of electron deficient dienes and aldehydes in the presence of a chiral diene ligand (Chapter 3) can be explored in the presence of other chiral dienes or catalysts to access asymmetric reductive coupling of electron deficient dienes with aldehydes and imines.

Z-Selective 1,6-conjugate addition product via Rh-catalyzed addition of arylboronic acids to electron deficient dienes has been reported by Csákÿ and co-workers[54] (**Fig. 5-1a**). Other methods of *Z*-selective 1,6-conjugate addition to electron deficient dienes include Ir-catalyzed addition of arylboronic acids[57] and Fe-catalyzed addition of aryl Grignard reagents.[181, 182] With the reductive coupling method described in Chapter 3 (**Fig. 5-1b**), a one-pot, *Z*-selective three-component coupling of electron deficient dienes, arylboronic acids and aldehydes can be achieved (**Fig. 5-1c**). Urabe and co-workers described the methylation of the intermediate dienolate by methyl iodide in the Fe-catalyzed 1,6-addition of aryl Grignard reagents to electron deficient dienes to form *Z*-selective three-component coupling product.[181, 182] Hence, diversion of the Rh-catalyzed 1,6-conjugate addition pathway via aldehyde trapping of the allyrhodium generated after rhodium aryl addition over the γ,δ-unsaturation can afford the three-component coupling product. Although challenging, due to the regio- and stereoselectivity issues resulting in several isomers that may arise, this method is currently been optimized by another researcher in the group. Preliminary studies show the enantioselectivity of the process can be tuned in the presence of chiral diene ligands and catalysts.

Finally, rhodium belong to the expensive platinum group metals (PGM). Its recovery after the reduction reactions would therefore be necessary to ensure a cost effective process. Hence, rhodium wastes generated in each of the reduction screens are

collected to be combined and recycled later. Recovery of rhodium-containing catalyst has been reported using polyamine ion exchangers.[183]

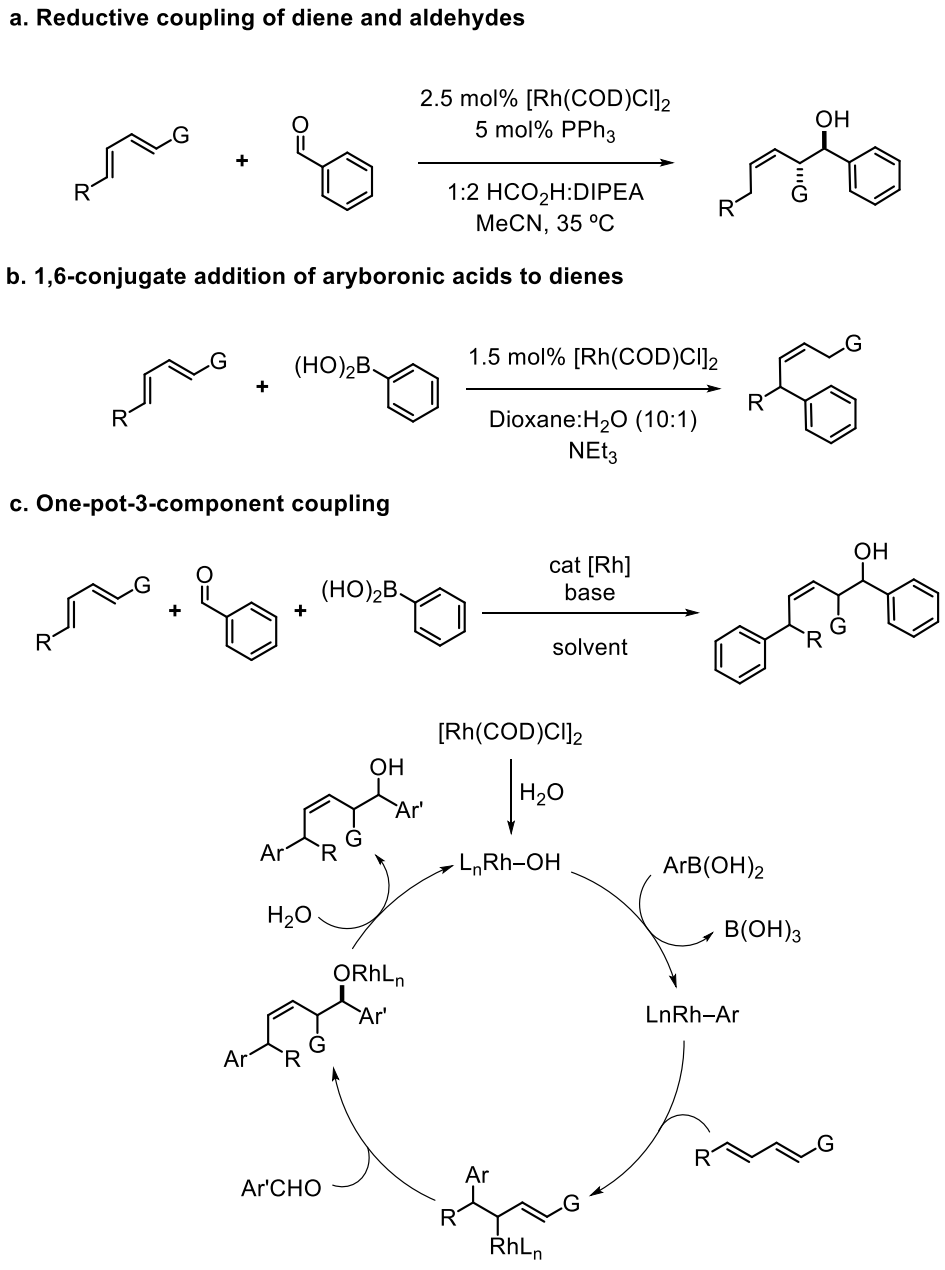


Fig. 5-1 Basis for the 3-component coupling of electron deficient diene, aldehyde and arylboronic acids.

References

1. Denmark, S. E., *Organic Reactions Volume 99*; John Wiley & Sons, Inc., Hoboken, NJ, **2019**.
2. Takacs, J. M.; Jiang, X. T. *Curr. Org. Chem.* **2003,** *7*, 369-396.
3. Sheldon, R. A.; Kochi, J. K. *Metal-catalyzed oxidations of organic compounds;* Academic Press: New York, **1981**.
4. Li, G. G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996,** *35*, 451-454.
5. DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997,** *119*, 9907-9908.
6. Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956,** *78*, 5694-5695.
7. Noyori, R. *Angew. Chem. Int. Ed.* **2002,** *41*, 2008-2022.
8. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive asymmetric catalysis*; Springer: London, **2003**.
9. Knowles, W. S. *Angew. Chem. Int. Ed.* **2002,** *41*, 1999-2007.
10. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990,** *112*, 2801-2803.
11. Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem. Int. Ed.* **1966,** *5*, 385-415.
12. Clayden, J.; Greeves, N.; Warren, S. G. *Organic chemistry*; Oxford University Press: Oxford, **2012**.
13. Siau, W. Y.; Zhang, Y.; Zhao, Y. *Top. Curr. Chem.* **2012,** 327, 33-58.
14. Takeda, T. *Modern carbonyl olefination;* Wiley-VCH: Weinheim, **2006**.
15. Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954,** *87*, 1318-1330.
16. Wittig, G.; Geissler, G. *Liebigs Ann.* **1953,** *580*, 44-57.

17. Vedejs, E.; Cabaj, J.; Peterson, M. J. *J. Org. Chem.* **1993,** *58*, 6509-6512.

18. Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000,** *122*, 8654-8664.

19. Wadsworth, W.; Emmons, W. D. *J. Am. Chem. Soc.* **1961,** *83*, 1733.

20. Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958,** *91*, 61-63.

21. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983,** *24*, 4405-4408.

22. Ando, K. *J. Org. Chem.* **1997,** *62*, 1934-1939.

23. Ando, K. *Tetrahedron Lett.* **1995,** *36*, 4105-4108.

24. Peterson, D. J. *J. Org. Chem.* **1968,** *33*, 780-784.

25. Izod, K.; McFarlane, W.; Tyson, B. V. *Eur. J. Org. Chem.* **2004,** *2004*, 1043-1048.

26. de Vries, J. G.; Elsevier, C. J. *The handbook of homogeneous hydrogenation*; Wiley-VCH: Weinheim, **2007**.

27. van Laren, M. W.; Elsevier, C. J. *Angew. Chem. Int. Ed.* **1999,** *38*, 3715-3717.

28. Monfredini, A.; Santacroce, V.; Marchio, L.; Maggi, R.; Bigi, F.; Maestri, G.; Malacria, M. *Acs. Sustain. Chem. Eng.* **2017,** *5*, 8205-8212.

29. Lindlar, H. *Helv. Chim. Acta.* **1952,** *35*, 446-456.

30. Bates, R. *Organic synthesis using transition metals*; Wiley: Chichester, West Sussex, **2012**.

31. Meijere, A. d.; Diederich, F. *Metal-catalyzed cross-coupling reactions*; Wiley-VCH: Weinheim, 2004.

32. Nakajima, K.; Guo, X. F.; Nishibayashi, Y. *Chem. Asian J.* **2018,** *13*, 3653-3657.

33. Chen, J. H.; Guo, J.; Lu, Z. *Chin. J. Chem.* **2018,** *36*, 1075-1109.

34. Uehling, M. R.; Rucker, R. P.; Lalic, G. *J. Am. Chem. Soc.* **2014,** *136*, 8799-8803.

35. Brown, H. C.; Hamaoka, T.; Ravindra, N. *J. Am. Chem. Soc.* **1973,** *95*, 6456-6457.

36. Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000,** *122*, 4990-4991.

37. Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004,** *126*, 10313-10318.

38. Herbert, M. B.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2015,** *54*, 5018-5024.

39. Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009,** *109*, 3708-3742.

40. Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003,** *42*, 4592-4633.

41. Townsend, E. M.; Hoveyda, A. H.; Schrock, R. R. *Abstr. Pap. Am. Chem. S.* **2013,** *245*.

42. Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011,** *471*, 461-466.

43. Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009,** *131*, 16630-16631.

44. Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009,** *131*, 3844-3845.

45. Cannon, J. S.; Zou, L. F.; Liu, P.; Lan, Y.; O'Leary, D. J.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014,** *136*, 6733-6743.

46. Zheng, K.; Liu, X. H.; Feng, X. M. *Chem. Rev.* **2018,** *118*, 7586-7656.

47. Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012,** *44*, 3109-3128.

48. Chauhan, P.; Kaya, U.; Enders, D. *Adv. Synth. Catal.* **2017,** *359*, 888-912.

49. Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010,** *39*, 2093-2105.

50. Bernardi, L.; Lopez-Cantarero, J.; Niess, B.; Jlrgensen, K. A. *J. Am. Chem. Soc.* **2007,** *129*, 5772-5778.

51. Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013,** *49*, 4869-4883.

52. Heravi, M. M.; Dehghani, M.; Zadsirjan, V. *Tetrahedron Asymmetry* **2016,** *27*, 513-588.

53. Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012,** *134*, 19370-19373.

54. de la Herran, G.; Murcia, C.; Csaky, A. G. *Org. Lett.* **2005,** *7*, 5629-5632.

55. Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982,** *47*, 119-126.

56. Csaky, A. G.; de la Herran, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010,** *39*, 4080-4102.

57. Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2006,** *45*, 5164-5166.

58. Sawano, T.; Ashouri, A.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2012,** *134*, 18936-18939.

59. Nishimura, T.; Noishiki, A.; Hayashi, T. *Chem. Commun.* **2012,** *48*, 973-975.

60. Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010,** *132*, 7872-7873.

61. Magrez, M.; Wencel-Delord, J.; Alexakis, A.; Crevisy, C.; Mauduit, M. *Org. Lett.* **2012,** *14*, 3576-3579.

62. Lopez, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007,** *40*, 179-188.

63. Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem.Int. Ed.* **2008,** *47*, 9122-9124.

64. Fillion, E.; Wilsily, A.; Liao, E. T. *Tetrahedron Asymmetry* **2006,** *17*, 2957-2959.

65. Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem. Int. Ed.* **2005,** *44*, 4224-4227.

66. Hayashi, Y.; Okamura, D.; Umemiya, S.; Uchimaru, T. *Chemcatchem* **2012,** *4*, 959-962.

67. Lee, K. S.; Wu, H.; Haeffner, F.; Hoveyda, A. H. *Organometallics* **2012,** *31*, 7823-7826.

68. Lee, K. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010,** *132*, 2898-2900.

69. Okada, S.; Arayama, K.; Murayama, R.; Ishizuka, T.; Hara, K.; Hirone, N.; Hata, T.; Urabe, H. *Angew. Chem. Int. Ed.* **2008,** *47*, 6860-6864.

70. Cais, M.; Frankel, E. N.; Rejoan, A. *Tetrahedron Lett* .**1968**, 1919-1923.

71. Steines, S.; Englert, U.; Driessen-Holscher, B. *Chem. Commun.* **2000**, 217-218.

72. Holmes, M.; Schwartz, L. A.; Krische, M. J. *Chem. Rev.* **2018,** *118*, 6026-6052.

73. Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016,** *354, aah5133*.

74. Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem. Int. Ed.* **2009,** *48*, 34-46.

75. Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008,** *130*, 14120-14122.

76. Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009,** *131*, 2066-2067.

77. Park, B. Y.; Nguyen, K. D.; Chaulagain, M. R.; Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2014,** *136*, 11902-11905.

78. Oda, S.; Franke, J.; Krische, M. J. *Chem. Sci.* **2016,** *7*, 136-141.

79. Leung, J. C.; Patman, R. L.; Sam, B.; Krische, M. J. *Chem. Eur. J.* **2011,** *17*, 12437-12443.

80. Komanduri, V.; Grant, C. D.; Krische, M. J. *J. Am. Chem. Soc.* **2008,** *130*, 12592-12593.

81. Kim, S. W.; Zhang, W. D.; Krische, M. J. *Acc. Chem. Res.* **2017,** *50*, 2371-2380.

82. Kimura, M.; Nojiri, D.; Fukushima, M.; Oi, S.; Sonoda, Y.; Inoue, Y. *Org. Lett.* **2009,** *11*, 3794-3797.

83. Sato, Y.; Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. *Org. Lett.* **2007,** *9*, 5597-5599.

84. Martinez, J. I.; Smith, J. J.; Hepburn, H. B.; Lam, H. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 1108-1112.

85. Groves, A.; Martinez, J. I.; Smith, J. J.; Lam, H. W. *Chem. Eur. J.* **2018,** *24*, 13432-13436.

86. Yu, Z. Y.; Ely, R. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2014,** *53*, 9632-9636.

87. Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2004,** *10*, 2529-2547.

88. Prevost, S.; Thai, K.; Schutzenmeister, N.; Coulthard, G.; Erb, W.; Aggarwal, V. K. *Org. Lett.* **2015,** *17*, 504-507.

89. Horvath, A.; Depre, D.; Vermeulen, W. A. A.; Wuyts, S. L.; Harutyunyan, S. R.; Binot, G.; Cuypers, J.; Couck, W.; Van den Heuvel, D. *J. Org. Chem.* **2019,** *84*, 4932-4939.

90. Clark, J. S.; Xu, C. *Angew. Chem. Int. Ed.* **2016,** *55*, 4332-4335.

91. Borhan, B.; Souto, M. L.; Um, J. M.; Zhou, B. S.; Nakanishi, K. *Chem. Eur. J.* **1999,** *5*, 1172-1175.

92. Marinescu, S. C.; Schrock, R. R.; Muller, P.; Takase, M. K.; Hoveyda, A. H. *Organometallics* **2011,** *30*, 1780-1782.

93. Schmid, T. E.; Drissi-Amraoui, S.; Crevisy, C.; Basle, O.; Mauduit, M. *J. Org. Chem.* **2015,** *11*, 2418-2434.

94. Tissot, M.; Alexakis, A. *Chem. Eur. J.* **2013,** *19*, 11352-11363.

95. Wang, Z.; Kang, T. F.; Yao, Q.; Ji, J.; Liu, X. H.; Lin, L. L.; Feng, X. M., *Chem. Eur. J.* **2015,** *21*, 7709-7712.

96. Meng, F. K.; Li, X. B.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. *Nature* **2016,** *537*, 387-393.

97. Uraguchi, D.; Yoshioka, K.; Ooi, T. *Nat. Commun.* **2017,** *8*, 14793.

98. Sodeoka, M.; Shibasaki, M. *Synthesis* **1993**, *1993,* 643-658.

99. Kotova, M.; Vyskocilova, E.; Cerveny, L. *Catal. Lett.* **2017,** *147*, 1665-1672.

100. Marcum, J. S.; Roberts, C. C.; Manan, R. S.; Cervarich, T. N.; Meek, S. J. *J. Am. Chem. Soc.* **2017,** *139*, 15580-15583.

101. Collins, K. D.; Glorius, F. *Nat. Chem.* **2013,** *5*, 597-601.

102. Blackmond, D. G. *Angew. Chem. Int. Edit.* **2005,** *44*, 4302-4320.

103. Bures, J. *Angew. Chem. Int. Ed.* **2016,** *55*, 16084-16087.

104. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43*, 2923-2925.

105. Knochel, P. *Handbook of Functionalized Organometallics;* Wiley-VCH: Weinheim, **2008**.

106. Montgomery, J. *Angew. Chem. Int. Ed.* **2004,** *43*, 3890-3908.

107. Sato, K.; Isoda, M.; Tokura, Y.; Omura, K.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron Lett.* **2013,** *54*, 5913-5915.

108. Isoda, M.; Sato, K.; Tokura, Y.; Tarui, A.; Omote, M.; Ando, A. *Chem. Pharm. Bull.* **2014,** *62*, 956-961.

109. Nuhant, P.; Allais, C.; Roush, W. R. *Angew. Chem. Int. Ed.* **2013,** *52*, 8703-8707.

110. Yang, Y.; Zhu, S. F.; Duan, H. F.; Zhou, C. Y.; Wang, L. X.; Zhou, Q. L. *J. Am. Chem. Soc.* **2007,** *129*, 2248-2249.

111. Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007,** *279*, 77-104.

112. Jang, H. Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002,** *124*, 15156-15157.

113. Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016,** *353*, 144-150.

114. Chen, T. Y.; Tsutsumi, R.; Montgomery, T. P.; Volchkov, I.; Krische, M. J. *J. Am. Chem. Soc.* **2015,** *137*, 1798-1801.

115. Haydl, A. M.; Breit, B.; Liang, T.; Krische, M. J. *Angew. Chem. Int. Ed.* **2017,** *56*, 11312-11325.

116. Xiao, H. D.; Wang, G.; Krische, M. J. *Angew. Chem. Int. Ed.* **2016,** *55*, 16119-16122.

117. Takeda, M.; Mitsui, A.; Nagao, K.; Ohmiya, H. *J. Am. Chem. Soc.* **2019,** *141*, 3664-3669.

118. Liu, R. Y.; Zhou, Y.; Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2019,** *141*, 2251-2256.

119. Swyka, R. A.; Zhang, W.; Richardson, J.; Ruble, J. C.; Krische, M. J. *J. Am. Chem. Soc.* **2019,** *141*, 1828-1832.

120. Köpfer, A.; Sam, B.; Breit, B.; Krische, M. J. *Chem. Sci.* **2013,** *4*, 1876-1880.

121. Li, C.; Liu, R. Y.; Jesikiewicz, L. T.; Yang, Y.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2019,** *141*, 5062-5070.

122. Li, J.; Preinfalk, A.; Maulide, N. *Angew. Chem. Int. Ed.* **2019,** *58,* 5887-5890.

123. Cao, K.; Tan, S. M.; Lee, R.; Yang, S.; Jia, H.; Zhao, X.; Qiao, B.; Jiang, Z. *J. Am. Chem. Soc.* **2019**.

124. Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* **2004,** *6*, 1131-1133.

125. Liang, T.; Zhang, W. D.; Krische, M. J. *J. Am. Chem. Soc.* **2015,** *137*, 16024-16027.

126. Hepburn, H. B.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014,** *53*, 11605-11610.

127. Luo, Y. F.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014,** *53*, 4186-4190.

128. Prieto, O.; Lam, H. W. *Org. Biomol. Chem.* **2008,** *6*, 55-57.

129. Pritzius, A. B.; Breit, B. *Angew. Chem. Int. Ed.* **2015,** *54*, 15818-15822.

130. Tao, Z. L.; Adili, A.; Shen, H. C.; Han, Z. Y.; Gong, L. Z. *Angew. Chem. Int. Ed.* **2016,** *55*, 4322-4326.

131. Jing, S. M.; Balasanthiran, V.; Pagar, V.; Gallucci, J. C.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2017,** *139*, 18034-18043.

132. Gui, Y. Y.; Hu, N.; Chen, X. W.; Liao, L. L.; Ju, T.; Ye, J. H.; Zhang, Z.; Li, J.; Yu, D. G., *J. Am. Chem. Soc.* **2017,** *139*, 17011-17014.

133. Wang, C.; Teo, W. J.; Ge, S. *Nat. Commun.* **2017,** *8*, 2258.

134. Luo, Y.; Wales, S. M.; Korkis, S. E.; Roy, I. D.; Lewis, W.; Lam, H. W. *Chem. Eur. J.* **2018,** *24*, 8315-8319.

135. Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2012,** *51*, 2776-2779.

136. Schmidt, V. A.; Kennedy, C. R.; Bezdek, M. J.; Chirik, P. J. *J. Am. Chem. Soc.* **2018,** *140*, 3443-3453.

137. Dada, R.; Wei, Z.; Gui, R.; Lundgren, R. J. *Angew. Chem. Int. Edit.* **2018,** *57*, 3981-3984.

138. Galatsis, P.; Millan, S. D.; Nechala, P.; Ferguson, G. *J. Org. Chem.* **1994,** *59*, 6643-6651.

139. Chung, J. Y. L.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Ball, R. G.; Tsou, N. N. *Org. Lett.* **2008,** *10*, 3037-3040.

140. Chung, J. Y. L.; Steinhuebel, D.; Krska, S. W.; Hartner, F. W.; Cai, C.; Rosen, J.; Mancheno, D. E.; Pei, T.; DiMichele, L.; Ball, R. G.; Chen, C. Y.; Tan, L.; Alorati, A. D.; Brewer, S. E.; Scott, J. P. *Org. Process Res. Dev.* **2012,** *16*, 1832-1845.

141. Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* **1999,** *1999*, 797-803.

142. Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981,** *103*, 7690-7692.

143. Ma, Z. W.; Zhou, Z.; Kurti, L. *Angew. Chem. Int. Ed.* **2017,** *56*, 9886-9890.

144. Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1992,** *33*, 4353-4356.

145. Bohn, M. A.; Schmidt, A.; Hilt, G.; Dindaroglu, M.; Schmalz, H. G. *Angew. Chem. Int. Ed.* **2011,** *50*, 9689-9693.

146. Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003,** *5*, 777-780.

147. Yasukawa, N.; Yokoyama, H.; Masuda, M.; Monguchi, Y.; Sajiki, H.; Sawama, Y., *Green Chem.* **2018,** *20*, 1213-1217.

148. Snajdrova, R.; Braun, I.; Bach, T.; Mereiter, K.; Mihovilovic, M. D. *J. Org. Chem.* **2007,** *72*, 9597-9603.

149. Soni, R.; Hall, T. H.; Morris, D. J.; Clarkson, G. J.; Owen, M. R.; Wills, M. *Tetrahedron Lett.* **2015,** *56*, 6397-6401.

150. Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009,** *74*, 7052-7058.

151. Chung, J. Y. L.; Steinhuebel, D.; Krska, S. W.; Hartner, F. W.; Cai, C. X.; Rosen, J.; Mancheno, D. E.; Pei, T.; DiMichele, L.; Ball, R. G.; Chen, C. Y.; Tan, L. S.; Alorati, A. D.; Brewer, S. E.; Scott, J. P. *Org. Process Res. Dev.* **2012,** *16*, 1832-1845.

152. Garcia-Rubia, A.; Urones, B.; Arrayas, R. G.; Carretero, J. C. *Chem. Eur. J.* **2010,** *16*, 9676-9685.

153. den Hartog, T.; Huang, Y.; Fananas-Mastral, M.; Meuwese, A.; Rudolph, A.; Perez, M.; Minnaard, A. J.; Feringa, B. L. *Acs. Catal.* **2015,** *5*, 560-574.

154. Nongkhlaw, R. L.; Nongrum, R.; Myrboh, B. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1300-1303.

155. Della Sala, G.; Cutignano, A.; Fontana, A.; Spinella, A.; Calabrese, G.; Coll, A. D.; d'Ippolito, G.; Della Monica, C.; Cimino, G. *Tetrahedron* **2007,** *63*, 7256-7263.

156. Yasukawa, N.; Yokoyama, H.; Masuda, M.; Monguchi, Y.; Sajiki, H.; Sawama, Y., *Abstr. Pap. Am. Chem. Soc.* **2018,** *256*.

157. Yasui, H.; Yorimitsu, H.; Oshima, K. *Synlett* **2006**, 1783-1785.

158. Wu, P. L.; Chung, T. H.; Chou, Y. *J. Org. Chem.* **2001,** *66*, 6585-6594.

159. Lawrence, S. A. *Amines*; Cambridge University Press: Cambridge, **2006**.

160. Ovaa, H.; Stragies, R.; van der Marel, G. A.; van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501-1502.

161. Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005,** *46*, 43-46.

162. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993,** *93*, 2207-2293.

163. Ramadhar, T. R.; Batey, R. A. *Synthesis* **2011**, 1321-1346.

164. Puentes, C. O.; Kouznetsov, V. *J. Heterocyclic Chem.* **2002,** *39*, 595-614.

165. Merino, P.; Delso, I.; Mannucci, V.; Tejero, T. *Tetrahedron Lett.* **2006,** *47*, 3311-3314.

166. Kobayashi, S.; Sugiura, M.; Ogawa, C. *Adv. Synth. Catal.* **2004,** *346*, 1023-1034.

167. Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815-2829.

168. Li, H.; Korotkov, A.; Chapman, C. W.; Eastman, A.; Wu, J. *Angew. Chem. Int. Ed.* **2016,** *55*, 3509-3513.

169. Abels, F.; Lindemann, C.; Schneider, C. *Chem. Eur. J.* **2014,** *20*, 1964-1979.

170. Lindemann, C.; Schneider, C. *Synthesis* **2016,** *48*, 828-844.

171. Li, M. F.; Wang, J. P.; Meng, F. K. *Org. Lett.* **2018,** *20*, 7288-7292.

172. Hall, D. G.; Lachance, H. *Allylboration of carbonyl compounds*;. Wiley: Hoboken, NJ, 2012.

173. Diner, C.; Szabo, K. J. *J. Am. Chem. Soc.* **2017,** *139*, 2-14.

174. Zhu, S. J.; Lu, X. X.; Luo, Y. T.; Zhang, W.; Jiang, H. F.; Yan, M.; Zeng, W. *Org. Lett.* **2013,** *15*, 1440-1443.

175. Chen, T. Y.; Tsutsumi, R.; Montgomery, T. P.; Volchkov, I.; Krische, M. J. *J. Am. Chem. Soc.* **2015,** *137*, 1798-1801.

176. Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004,** *126*, 14360-14361.

177. Balasubramanian, T.; Hassner, A. *Tetrahedron Asymmetry* **1998,** *9*, 2201-2205.

178. Gerpe, A.; Bollini, M.; Gonzalez, M.; Cerecetto, H. *Synth. Commun.* **2009,** *39*, 29-47.

179. Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D. X.; Umemura, S.; Micalizio, G. C. *J. Org. Chem.* **2010,** *75*, 8048-8059.

180. Cooze, C.; Dada, R.; Lundgren, R. J. *Angew. Chem. Int. Ed.* **2019,** *58*, 12246-12251.

181. Sugano, G.; Kawada, K.; Shigeta, M.; Hata, T.; Urabe, H. *Tetrahedron Lett.* **2019,** *60*, 885-890.

182. Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005,** *46*, 603-606.

183. Kramer, J.; Erkelens, J. A.; Garcia, A. R. A.; Driessen, W. L.; Reedijk, J. *New J. Chem.* **2002,** *26*, 822-826.