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Diastereoselective Transformations and Intramolecular Cyclizations of Enantiomerically Pure Planar Chiral N-Oxazolidinoyl Diene Iron(0) Tricarbonyl Complexes

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"Diastereoselective Transformations and Intramolecular Cyclizations of Enantiomerically Pure Planar Chiral *N*-Oxazolidinoyl Diene Iron(0) Tricarbonyl Complexes"

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Acknowledgements

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List of Common Abbreviations

Boc = tert-Butyloxycarbonyl

DMAP = 4-Dimethylaminopyridine

d.r. = diastereoselective ratio

e.e. = enantiomeric excess

Ns = 2-nitrobenzenesulfonyl, "nosyl"

TBAF = tetrabutylammonium flouride

TBS (TBDMS) = tert-Butyldimethylsilyl ether

TBDPS = tert-Butyldiphenylsilyl ether

TEOC = trimethylsilylethoxycarbonyl

TLC = thin layer chromatography

TMS = trimethylsilane

Abstract

Organoiron complexes have established their utility in organic synthesis as stereodirecting groups as well as diene protecting groups. Since its first discovery in 1930, the diene tricarbonyl iron(0) complex underwent an impressive development that allows us to use its rich chemistry to accomplish complex molecule synthesis and to explore various synthetic methods that would broaden the scope of this field. The Paley laboratory utilizes the planar chirality of *N*-oxazolidinoyl diene tricarbonyl iron complexes to expand the boundaries of diastereoselective synthesis of novel compounds. The findings reported here reflect our attempts not only to reiterate the successful chemistry previously done on the *p*-tolyl sulfoxide diene tricarbonyl iron(0) complexes on the recently investigated *N*-oxazolidinoyl diene iron(0) complexes, but also to further explore possible transformations of the complexes.

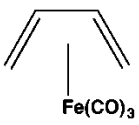
The synthetic goals of this thesis work included various diastereoselective reactions: 1,4 conjugate additions to the alkylidene malonate analog of the title compound, allylation of cyclic oxocarbenium ion on the periphery of the diene, intramolecular ring formation via Rh(II)-catalyzed C-H insertion and the Pictet-Spengler condensation. The first three reactions are shown to be diastereoselective, and an elaborate precursor to the Pictet-Spengler reaction is being pursued.

Introduction

Numerous organometallic compounds are found in modern day synthetic chemistry, playing an integral role as catalysts and substrates in the successful syntheses of complex molecules. Zeise's salt $[PtCl_3(C_2H_4)]^-$, discovered in 1827, was the first known transition-metal organometallic compound.[1] Numerous discoveries of metal carbonyls and metal aryl complexes followed, marking the start of the gradually expanding field of organometallics. The discovery of ferrocene in 1951 by Kealy and Pauson, as well as Miller, Tebboth and Tremaine, is commonly credited as the turning point which established organometallic chemistry as a major discipline.[2,3] There is a rich chemistry of organoiron compounds that expands beyond the so-called "sandwich" cyclopentadienyl iron complexes, including iron carbonyl complexes of a wide range of hapticity, such as η^2-olefin, η^3-allyl, η^4-dienes as well as η^6-aryl ligands. The discussion below will focus on the η^4 diene π complexes of tricarbonyl iron(0).

Introduction to diene iron tricarbonyl complexes and potential applications

While Reihlen *et al.* was the first group to report the synthesis of a butadiene tricarbonyl iron complex **1** in 1930,[4] it wasn't until the discovery of ferrocene in 1951 that the diene tricarbonyl iron chemistry was more thoroughly investigated. Pauson, one of the chemists who introduced ferrocene to the world, continued to study organoiron chemistry and reported in 1958 that such complexation between diene and iron carbonyl fragment protected against catalytic reduction and cycloadditions of the butadiene.[5] Their proposed structure of the complex, which predicted an η^4 hapticity of the diene ligand, was

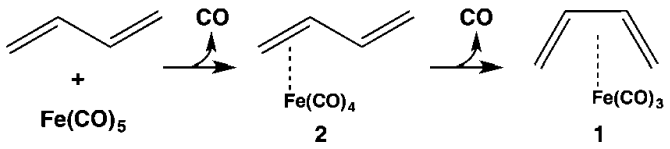


1

confirmed by X-ray crystallography in Mills and Robinson's work five years later.[6] Diene iron complexes have also been found to serve purposes other than pure synthetic applications. Iron carbonyl complexes of butadiene, isoprene and 2,3-dimethylbutadiene were patented as antiknock agents for motor fuel in 1942.[7] The η^4 diene tricarbonyl iron complex was recently used in reversible decoration of multi-walled carbon nano tubes.[8] Nevertheless, the diene iron chemistry is predominantly found in the world of synthetic organic chemistry.

R. B. King contributed to *The Organic Chemistry of Iron Vol. 1*, a compilation of methods used to complex tricarbonyl iron(0) to acyclic dienes.[9] (Diene)-$Fe(CO)_3$ complexes were synthesized originally, and frequently to this day, via a complexation between 1,3 dienes and pentacarbonyliron(0) at ~130 °C. But this method comes with many complications related to the instability of the complex and potential dimerization of the diene at such high temperature. The diene tricarbonyl iron complexes can also be prepared through ultraviolet irradiation; the drawback of this method is the possibility of producing $(diene)_2Fe(CO)$ complex as a side product. A few possible alternative methods include complexation with dodecacarbonyltriiron(0) or enneacarbonyldiiron(0), both of which include potential side reactions, as well as the addition of trimethylamine *N*-oxide as an oxidizing agent in complexation with pentacarbonyliron(0). Additional concerns for diene complexation with pentacarbonyliron(0) involve the tendency of 1,4- and 1,5-dienes to rearrange to a 1,3 diene, and for *cis*-1,3-pentadienes to its *trans* isomer. It was also observed that 4-methyl-1,3-pentadiene rearranges to form the *trans*-2-methylpenta-1,3-diene tricarbonyl iron(0) upon complexation with pentacarbonyliron. In order to

avoid this hydride rearrangement, *cis*-1,3-pentadiene can be treated with nonacarbonyldiiron(0) in boiling ether; lower reaction temperature is attributed to the success of the improved reaction.



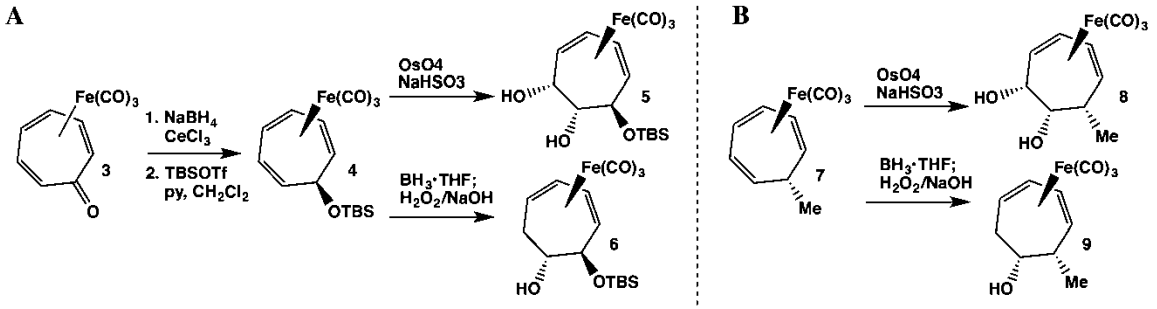
Scheme 1. The complexation of process of butadiene and iron pentacarbonyl (ref 10).

The complexation using pentacarbonyliron(0) is understood to be a two step process in which the tetracarbonylalkeneiron(0) complex **2** is formed first (Scheme 1).[10] Complexation with nonacarbonyldiiron(0), rather than pentacarbonyliron(0), should follow the same process with the release of $Fe(CO)_5$. The loss of the second carbonyl from this η^2 complex allows the association of the second alkene ligand; the resulting complex is stable enough to perform various reactions on the system. Accordingly, tricarbonyl iron(0) has been used extensively as a protecting group for 1,3-dienes.

$Fe(CO)_3$ as a diene protecting group and stereochemistry directing group

The complexation is known to prevent various reactions of alkenes and dienes including, but not limited to, hydroboration, hydration, hydrogenation, osmylation and Diels-Alder reactions.[11] The ability to simply and selectively protect and deprotect dienes allows the implementation of diene iron(0) complexes in a wide range of synthetic applications. Pearson and Srinivasan have found that η^4-cycloheptatriene complexes of iron(0) tricarbonyl (**3** & **7**) undergo hydroboration and osmylation of the remaining unprotected alkene with perfect stereoselectivity as

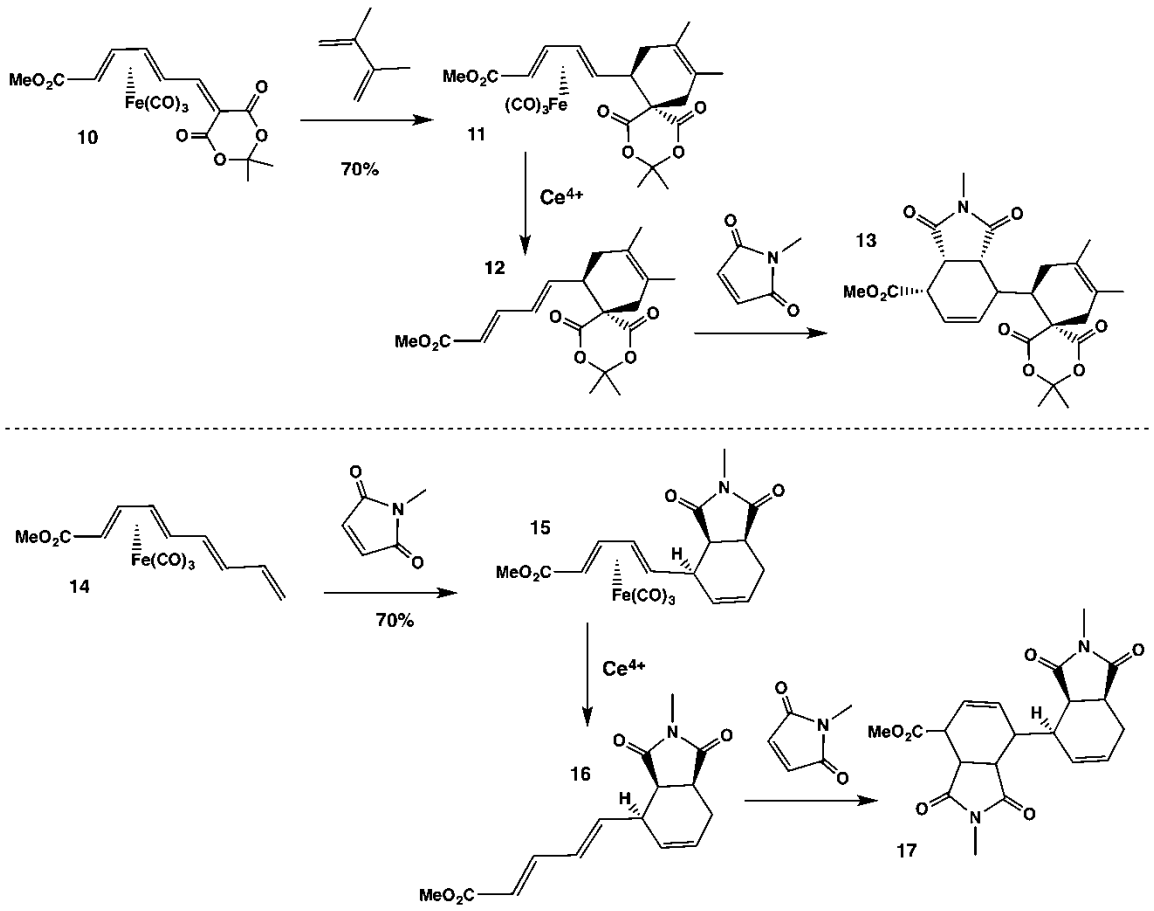
well as regioselectivity (Scheme 2).[12] It was observed that the directing effect of $Fe(CO)_3$ overcame the steric hindrance of the methyl substituent in single diastereomer **7** to yield both **8** and **9** as single isomers as well (Scheme 2B). The regioselectivity in the hydroboration product **9** is thought to be established by the stabilization of a partial carbocation adjacent to the diene tricarbonyl iron complex (see pp. 17).



Scheme 2. Hydroboration and osmylation of cycloheptatriene iron(0) complexes by Pearson and Srinivasan (ref 12).

The first attempt of a Diels-Alder reaction using substrates containing $Fe(CO)_3$ protected diene was reported by Grée *et al.* in 1990 (Scheme 3).[13] Linear polyenes could be selectively protected by the tricarbonyl iron(0) moiety to prepare both dienophile **10** and diene **14**, each of which reacted with respective partners to give single chiral cycloadducts **11** and **15**. Following the first Diels-Alder reaction, the iron decomplexation of **11** yielded diene **12** which underwent another completely diastereoselective Diels-Alder reaction to give **13**. The same procedure was repeated on **15**, but the second Diels-Alder gave a 7:3 mixture of diastereomers (**17**). Overall, the steric hindrance of the iron fragment directs the approach of the reaction partner and establishes the *anti* relationship between $Fe(CO)_3$ and the newly appended carbocycle as shown in products **11** and **15**. Additionally, the selective protection of

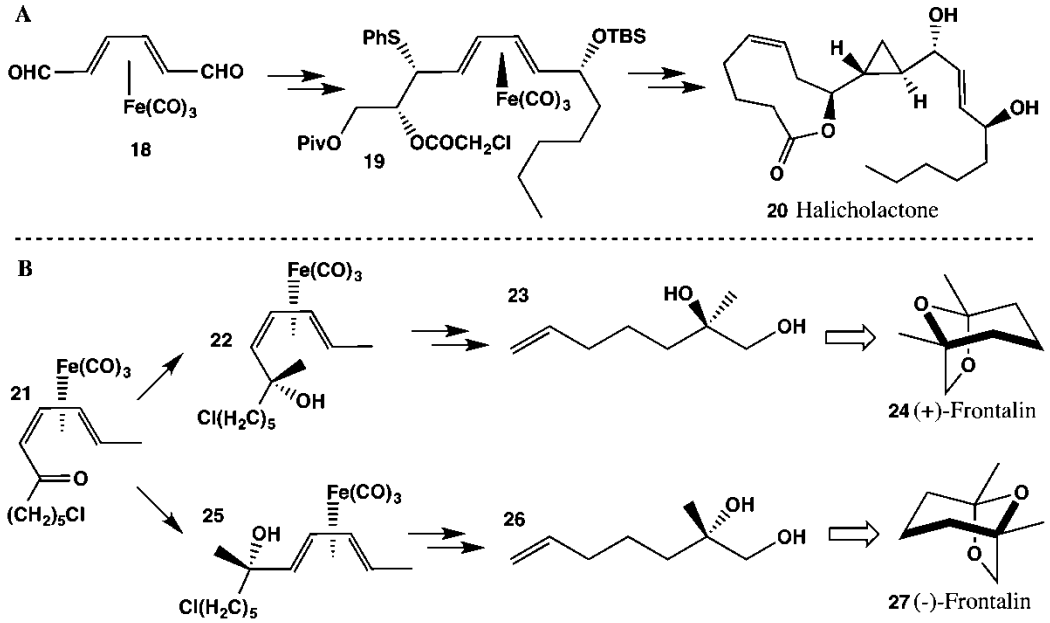
the polyene by $Fe(CO)_3$ allows the preparation of precursors for tandem Diels-Alder reactions with polycyclic products in mind.



Scheme 3. Tandem Diels-Alder reactions on selectively $Fe(CO)_3$-complexed linear polyenes by Grée *et al.* (ref 13).

Furthermore, the planar chirality of diene-$Fe(CO)_3$ has been used in the asymmetric synthesis of natural products, such as Halicholactone (**20**) as well as (+)- and (-)-Frontalin (**24** and **27**), to establish stereocenters adjacent to the scaffold.[14,15] Scheme 4A shows the synthesis of Halicholactone from achiral di-aldehyde **18**, installing three new stereocenters with the aid of $Fe(CO)_3$. The asymmetric synthesis of Frontalin from a dienal iron(0) complex **21** is demonstrated in Scheme 4B. As such,

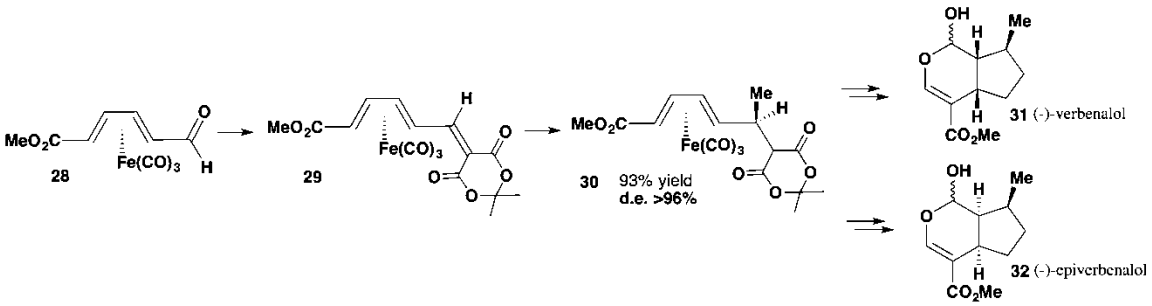
various reactions were attempted to utilize the tricarbonyl iron(0) moiety in influencing the stereochemical outcome.



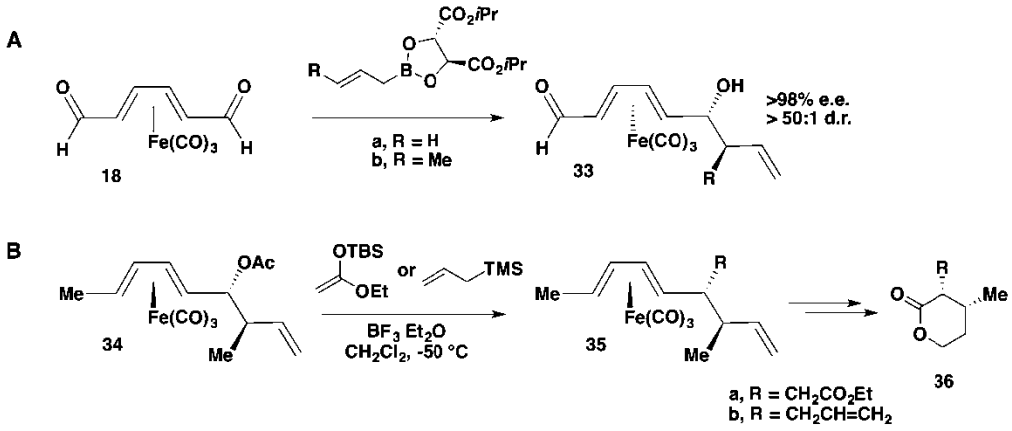
Scheme 4. Examples of (diene)-$Fe(CO)_3$ complexes in natural product synthesis (ref 14, 15).

The nucleophilic addition to an electrophilic position on the periphery of the η^4-diene tricarbonyl iron(0) complex is a highly diastereoselective reaction; the $Fe(CO)_3$ moiety guides the nucleophile to attack from the opposite face of the plane of the diene, establishing an *anti* stereochemical relationship between the new substituent and the metal. Scheme 5 shows Laabassi and Grée's usage of stereospecific Grignard addition on alkylidene malonate diene complex **29,** in the total synthesis of (-)-Verbenalol **31** and (-)-Epiverbenalol **32.**[16] Following this report, Roush and Wada reported an extensive study of 1,4 nucleophilic addition to the alkylidene malonate diene iron compounds, confirming the diastereoselective nature of the addition of the following nucleophiles: vinylmagnesium bromide, trimethylsilyl allylmagnesium bromide, triisopropylsilyl alkynylmagnesium bromide, 3-

triisopropylsilyl-2-propyn-1-yl lithium, phenyl lithium, allylstannane as well as a silyl enol ether.[17] Additionally, Roush and Wada reported a highly diastereoselective (>96% e.e.) allylboration of di-aldehyde **18**, transforming a meso compound into an enantiomerically pure product **33** (Scheme 6A).[18] BF_3•Et_2O-promoted substitution reactions to dienol iron(0) complexes, such as **34**, have been shown to proceed with retention of stereochemistry: a couple of examples with silyl enol ether and allylsilane additions that lead to chiral lactones **36** are shown in Scheme 6B. Using a specific nucleophile customized for the synthetic goal could introduce a stereocenter in asymmetric synthesis through a relatively simple step.

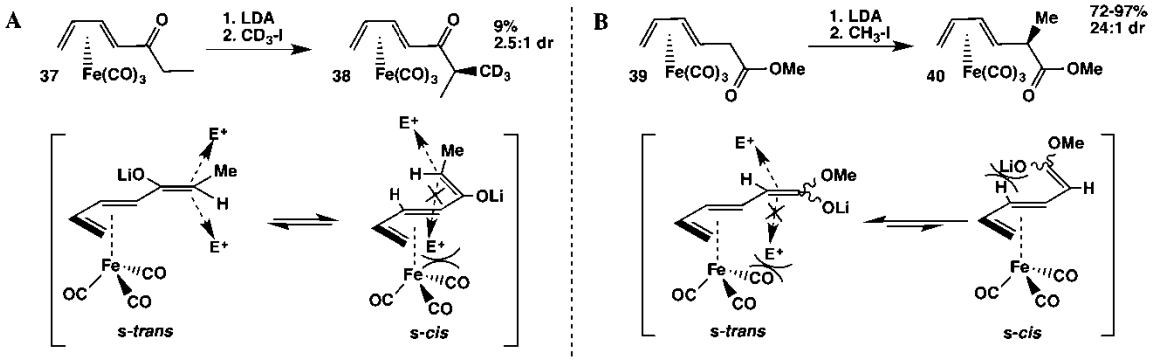


Scheme 5. Alkylidene malonate derivative of diene iron complex
in Laabassi and Grée's synthesis of (-)-verbenalol and (-)-epiverbenalol (ref 16).



Scheme 6. Highly diastereoselective addition reactions
to (dienal)- and (dienol)-iron complexes by Roush and Wada (ref 18).

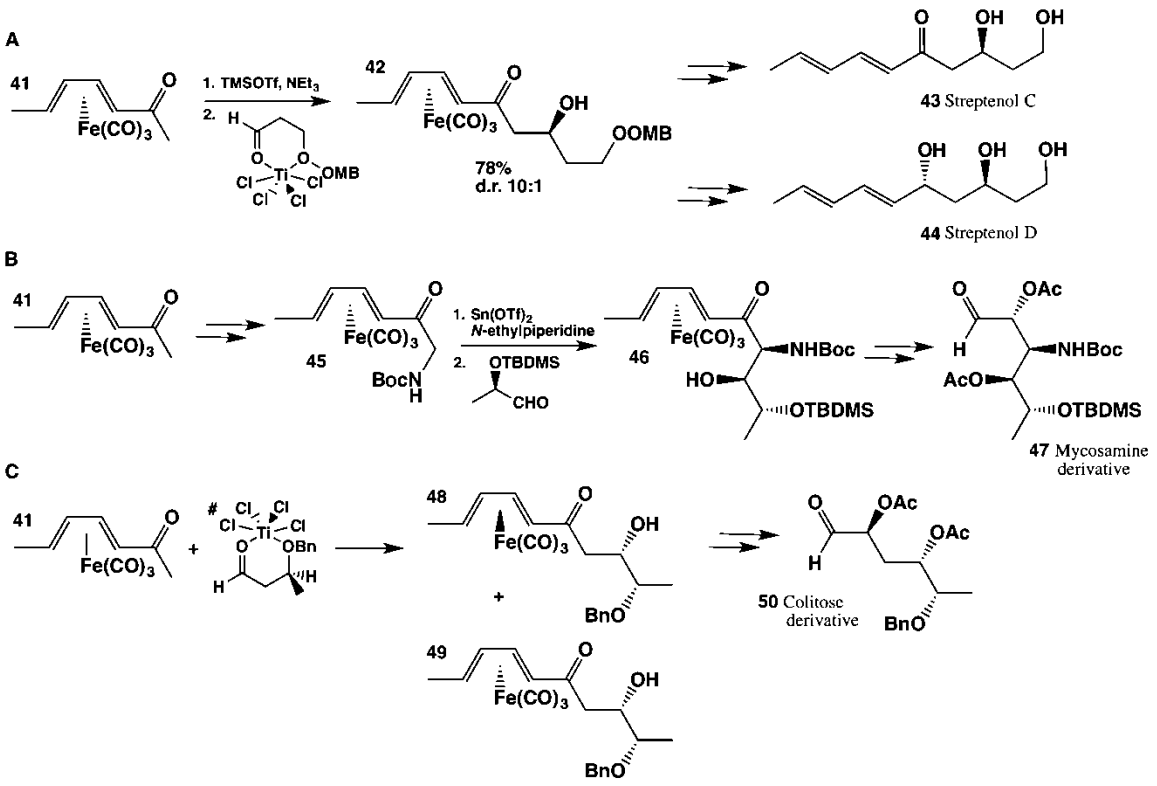
Enolate alkylation and aldol reactions were also found to be compatible and diastereoselective with the $Fe(CO)_3$ diene complex. Donaldson *et al.* reported the diastereoselectivity of alkylation of tricarbonyl(4,6-heptadienone)iron **37** to be no better than 2.5:1.[19] However, the alkylation of tricarbonyl(4,6-hexadienoate)iron **39** gave an excellent diastereoselectivity ratio of >20:1 as well as an improved yield. The diastereoselectivity of the reaction is kinetically controlled by the relative stability of *trans* and *cis* conformers of the enolates, shown in Scheme 7. The ester enolate of **39** has a clear preference for the *s-trans* conformer due to the steric hindrance found in the s-*cis* conformer, and the stereoselectivity is increased as the alkylation favors the *anti* approach to the tricarbonyl iron(0) moiety. However, the dienone iron carbonyl **37** equilibrates between two s-*trans*/*cis* conformations that are similar in stability; the alkylation of s-*cis* conformer does not have a selective facial preference as $Fe(CO)_3$ avoids steric interactions in this conformation. Therefore, the enolate alkylation with η^4-diene tricarbonyl iron(0) complexes proceeds with better diastereoselectivity when the addition is α to the diene, rather than β.



Scheme 7. Enolate alkylation of enantiomerically pure α- and β-carbonyl diene iron complexes by Donaldson *et al.* (ref 19).

Franck-Neumann *et al.* used crossed aldol condensation of tricarbonyl iron(0) dienones with lactaldehydes in the synthesis of natural products including Streptenol C (**43**) and D (**44**), Mycosamine (**47**) and Colitose (**50**) (Scheme 8).[20–22] The use of $Fe(CO)_3$-complexed substrates in aldol reaction was found to give diastereoselective results in some cases where a normal substrate would not do so; however, the selectivity of the Lewis acid-promoted aldol reactions of tricarbonyl iron dienone differed for each case. The aldol reaction of enantiomerically pure (dienone)-$Fe(CO)_3$ **41** in the synthesis of Streptenols C and D (**43**/**44**) shown in Scheme 8A had a diastereomer ratio of 10:1 with major product yield of 79%.[20] The *anti* stereochemistry of the alcohol in the major product relative to the iron tricarbonyl moiety shows that the presence of the metal component directs the stereochemical outcome of the reaction. This is also shown to be true of the ketone reduction later in the sequence; the hydride adds *anti* to $Fe(CO)_3$—*syn* to the alcohol—leading to the final *anti* stereochemistry of the 1,3-diol **44**. In Scheme 8B, divalent tin enolate aldol reaction on α-aminodienone tricarbonyl iron complex **45**, derived from enantiomerically pure dienone complex **41**, led to a major diastereomer **46** with 86% yield.[21] The final steps in the sequence included deprotection of the iron(0) tricarbonyl diene followed by ozonolysis to give the protected acyclic Mycosamine **47**. The synthesis of 3,6-dideoxyhexose sugars took an interesting approach in which the diastereoselective aldol addition on racemic mixture of **41** acted concurrently as resolution of the racemic mixture of dienone tricarbonyl iron (Scheme 8C).[22] The stereochemical outcome of this aldol reaction did not depend on the $Fe(CO)_3$ moiety as it yielded two diastereomers **48** and **49** that only differed in the configuration of

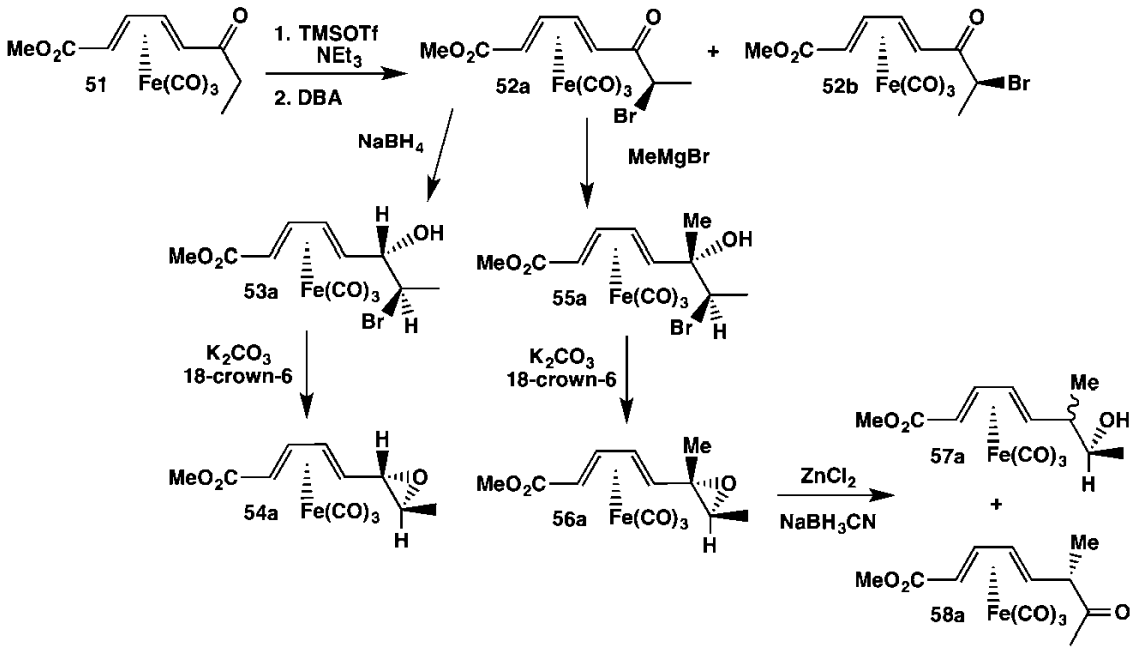
the iron fragment; however, the stereochemical outcome of the following ketone reduction does depend on the metal fragment.



Scheme 8. Aldol reactions of 2-ketohepta-3,5-diene iron complex by Franck-Neumann *et al.* (ref 20-22).

Franck-Neumann *et al.* also used dienone-$Fe(CO)_3$ to prepare α-alkyl β-hydroxy diene iron tricarbonyl complexes via trisubstituted epoxide (Scheme 9).[23] Bromo-dienone **52** was prepared via bromination of the silyl enol ether formed from dienone **51**; this reaction gave a 1:1 diastereomeric mixture but interconversion and chromatographic separation between the diastereomers was easily accomplished to obtain a single isomer. The ketone reduction and Grignard addition of each diastereomer of bromodienone **52** were both completely diastereoselective due to the steric hindrance of iron fragment; the sequence of isomer **52a** is shown in Scheme 9. The resulting halodienols **53a** and **55a** were successfully transformed into their

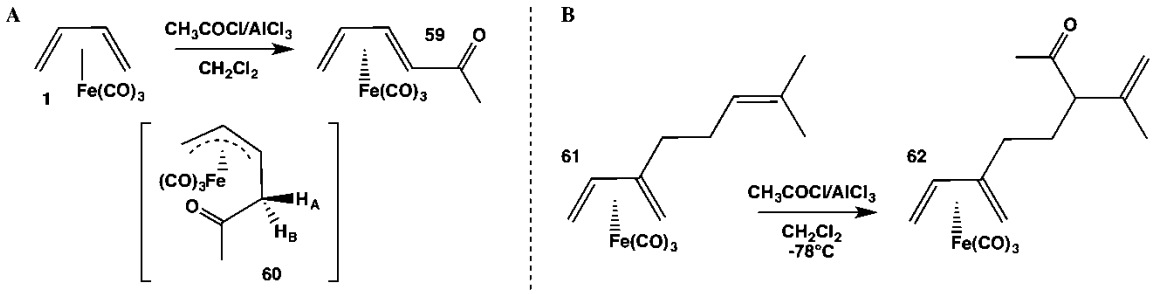
respective epoxide analogs, **54a** and **56a.** The researchers were able to confirm that epoxide **56a** was regioselectively reduced to the β-hydroxy dienones. However, the reaction produced not only a mixture of two diastereomeric β-hydroxy dienes **57a**, but also the β-ketone analog **58**, leading the group to conclude that the chemistry requires more investigation. Numerous antifungal antibiotics include α-alkyl β-hydroxy conjugated polyenic carbon chains that the sequence aimed to obtain and the aforementioned chemistry would make possible a concise and efficient synthesis of such structures.



Scheme 9. Formation of trisubstituted epoxides on the periphery of a $Fe(CO)_3$ complexed diene by Franck-Neumann *et al.* (ref 23).

The dienones described in the starting material of the previously mentioned sequences were synthesized via Friedel Crafts acylation. Although the $Fe(CO)_3$ moiety serves as a protecting group against reactions that would compromise the olefin system, Friedel-Crafts acylation is possible with 1,3-butadiene tricarbonyl iron complexes, as shown in Scheme 10. The reaction was shown to proceed via a π-allyl

complex in 1969, when an allyl cation intermediate **60** was isolated.[24] Furthermore, the X-ray structure obtained in 1974 confirmed this intermediate.[25] It was also observed that in the case of Friedel Crafts acylation on $Fe(CO)_3$-complexed diene substrate containing an uncomplexed olefin, such as **61**, the reaction occurs selectively on the latter at -78 °C.[26] Protection of the diene with tricarbonyl iron would also prevent the polymerization that unprotected butadiene would undergo in Friedel-Crafts conditions.[27]

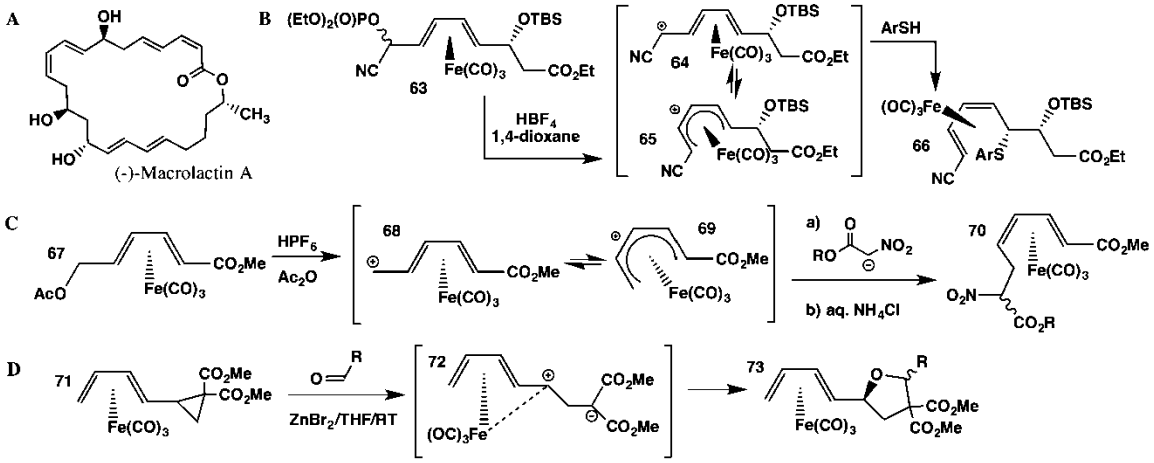


Scheme 10. Examples of Friedel Crafts acylation on diene tricarbonyl iron complexes (ref 26, 27).

Stabilization of electropositive carbon adjacent to the diene iron complex

Another useful attribute of the tricarbonyl iron diene complex is its ability to stabilize a positive charge on a proximal carbon, which was briefly mentioned in the previous discussion of the excellent regioselectivity in the hydroboration-oxidation of η^4-cycloheptatriene tricarbonyl iron complexes **4** and **7**. The formation of a carbocation adjacent to the 1,3-diene tricarbonyl iron is stabilized by the neighboring group participation (also known as anchimeric assistance) of the $Fe(CO)_3$ complex on the η^4 dienyl cation, that is often seen as analogous to η^5 coordination. Takemoto *et al.* synthesized a 15-carbon segment of macrolactin A (Scheme 11A), a complex, 24-membered macrolide with potential antibacterial, antiviral and antitumor activities,

using 1,2 migration of a diene tricarbonyl iron complex as a key step (Scheme 11B).[28] The intermediate formed in the key reaction is a dienyl iron cation **64**, in resonance with the η^5 complex intermediate **65**, that becomes η^4-(E,Z) diene iron complex **66** upon addition of a nucleophile to the electrophilic carbon, which causes the resulting diene to contain different carbons than starting (E,E)-diene **63**. Such chemistry was also used in Li and Donaldson's synthesis of a 18-carbon segment of macrolactin A (Scheme 11C).[29] The nucleophilic addition to the iron carbonyl ligated dienyl cation **68** has a similar η^5-coordinated intermediate **69**. A 1,3-dipolar cycloaddition of vinyl cyclopropane **71** reported by Christie *et al.* produced a dienyltetrahydrofuran **73** via intermediate **72**, which like the previous examples is stabilized by the η^5-coordination with the iron metal (Scheme 11D).[30] The tricarbonyl iron fragment acted as a stereodirecting group, which determined the major product stereochemistry of the tetrahydrofuranyl C-O bond as opposite to the metal.

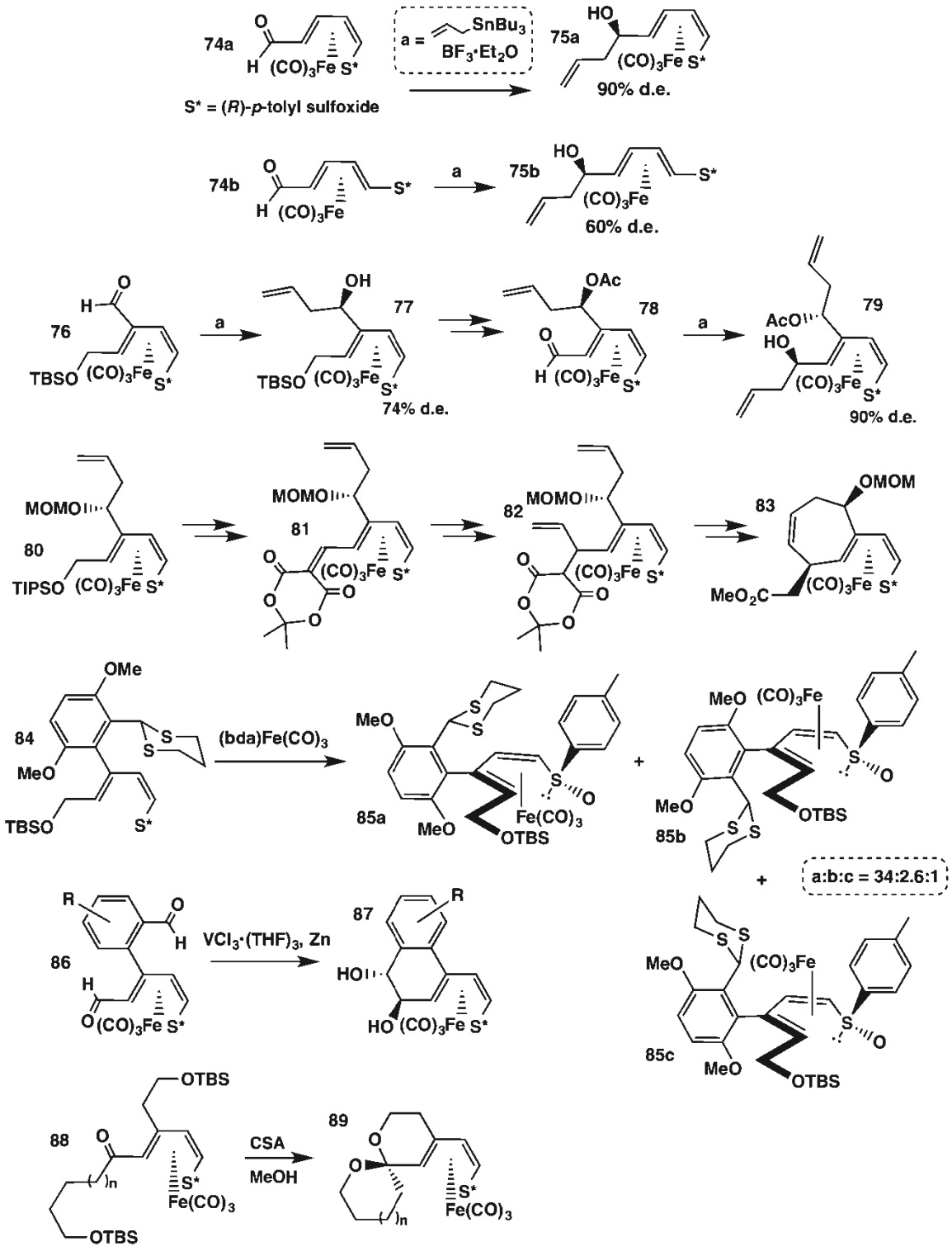


Scheme 11. Stabilization of dienyl iron cation complexes via neighboring group participation seen in synthesis of Macrolactin A (ref 28-30).

η^4 Diene tricarbonyl iron complexes have much potential as a stereodirecting and diene-protecting scaffold in the context of natural and novel product syntheses

and only a fraction of the possible reactions has been summarized here. Continuing reports of various reactions of the title compound that would expand the range of compatible reactions and possible synthetic goals are necessary in the field of organoiron chemistry.

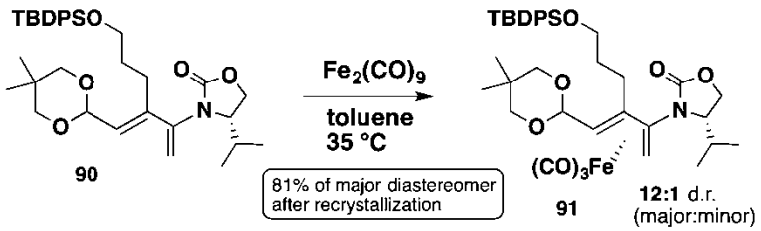
The Paley laboratory studies the diastereoselective transformation of diene-$Fe(CO)_3$ compounds using a chiral auxiliary to aid the stereoselectivity. The stereoselective preparation of *p*-tolyl sulfoxide diene was first reported in 1993 and again in 1995.[31,32] Successful diastereoselective iron tricarbonyl complexation and transformation of these complexes followed, including allylation of dienal complexes, ring closing metathesis, formation of atropisomers, pinacol coupling and spiroketalization; all were reported with high selectivity.[33–39] These transformations are summarized in Scheme 12 and represent the context for the research presented in this thesis. In recent years the use of the sulfoxide as a stereodirecting element has been replaced with an N-atom bound oxazolidinone, and our attempts to define the scope of reactions of these new complexes is where the work described here begins.



Scheme 12. Syntheses of novel sulfinyl diene tricarbonyl iron(0) complexes by Paley *et al.* (ref 33-39).

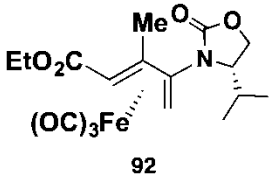
Results and Discussion

The Paley laboratory currently synthesizes and studies transformations of *N*-oxazolidinoyl diene $Fe(CO)_3$ complexes; an example of a diastereoselective complexation is shown in Scheme 13.



Scheme 13. Example of iron tricarbonyl complexation of *N*-oxazolidinoyl diene.

The transition from the sulfinyl auxiliary to the *N*-oxazolidinoyl auxiliary sought to improve chemical yields and diastereoselectivities of the diene tricarbonyl iron complexes as well as their transformations. Recent work in the laboratory has established that the complexation of *N*-oxazolidinoyl diene with $Fe_2(CO)_9$ is a diastereoselective process with a diastereoselectivity up to 15:1. C-N bond rotates so that the isopropyl group on the oxazolidinone can avoid the group on C2 of the 1,3-diene; the iron fragment then adds *anti* to it. The structure of the major diastereomer complex **92** has been confirmed through X-ray crystallography (Paley *et al.*, unpublished work).



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One goal of the laboratory is to use the planar chirality of these complexes to install new stereocenters along the periphery of the iron(0) tricarbonyl diene unit. Several analogs of complex **90** were synthesized on a large laboratory scale (ca. 10 mmol) to explore the compatibility of a variety of diastereoselective transformations that can introduce additional stereocenters and cyclize the molecule. The synthesis of

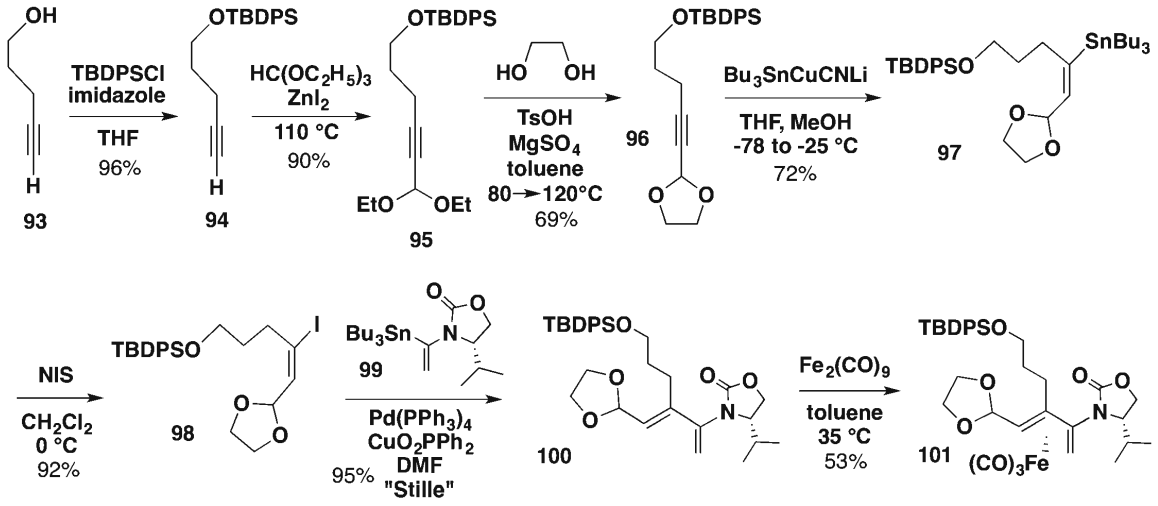
starting materials in each project was unique as it adapted to the needs of the pursued reactions and have been described in their respective sections.

Diastereoselective nucleophilic conjugate additions to alkylidene malonates

The Paley lab has previously established the use of the planar chirality of sulfinyl diene iron(0) tricarbonyl complexes for diastereoselective transformations. Conjugate additions to alkylidene malonate derivatives of the title compound have been used in formation of a precursor to ring closing metathesis of the sulfinyl diene iron complexes (Scheme 12, **80-83**).[36] This reaction was utilized as a method to elaborate the periphery of the sulfinyl diene iron complex with multiple stereocenters to yield an enantiomerically pure carbocycle. The current investigation aims to prove the same use of planar chirality in the *N*-oxazolidinoyl analogs; thus, conjugate additions to alkylidene malonate derivatives of the *N*-oxazolidinoyl diene iron tricarbonyl complexes were explored. The same conjugate addition of various nucleophiles to the alkylidene malonates had been reported by Roush and Wada in 1994 to be diastereoselective with the η^4 diene iron tricarbonyl complexes without any auxiliary.[17] The approach of the nucleophile was *anti* to the iron tricarbonyl substituent of the electrophilic substrate; the same stereochemical outcome was found with the sulfinyl diene iron analog and was expected of the *N*-oxazolidinone substituted substrate.

Commercially available 4-pentyn-1-ol (**93**) was used to begin the synthesis of the propanol diene iron tricarbonyl complex **101**. Once alcohol **93** was protected using TBDPSCl, it was treated with triethylorthoformate and ZnI_2, the resulting acetal

95 was converted into acetal **96** using ethylene glycol. Compound **96** was converted into vinyl stannane **97** via a regioselective stannylcupration: the cuprate reagent was prepared *in situ* at -78 °C. The stannane **97** was converted into a vinyl iodide **98** that undergoes Stille coupling with an *N*-oxazolidinoyl vinyl stannane **99** to create the σ bond in the creation of the 1,3-butadiene. All Stille couplings mentioned here on used a modification of the method reported by Fürstner *et al.* for its improved reaction yield and easily-removable byproduct.[40] Diene **100** is then complexed with $Fe_2(CO)_9$ to give title compound **101**, a highly functionalized derivative of *N*-oxazolidinoyl diene iron(0) tricarbonyl complex.



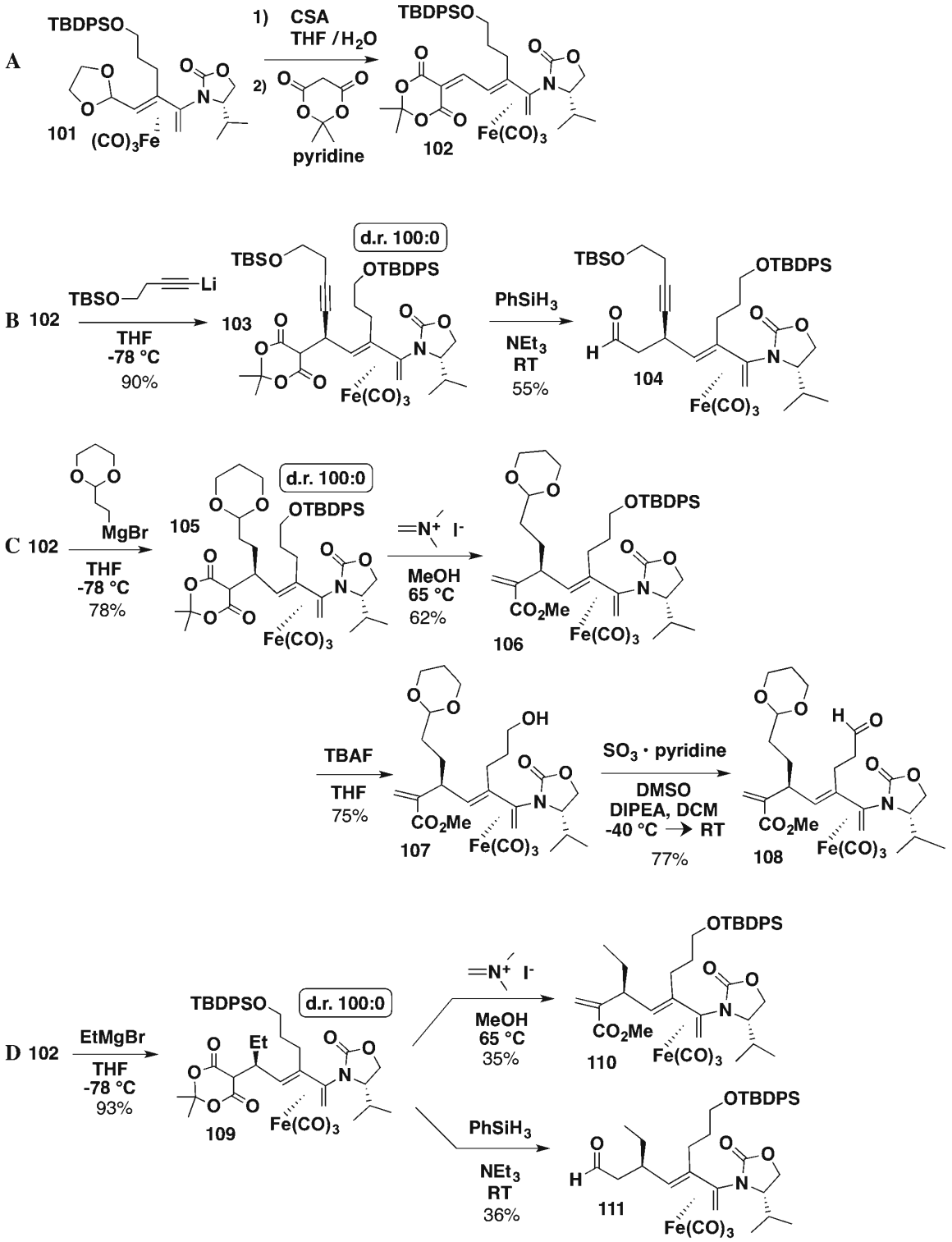
Scheme 14. Synthesis of the precursor for an alkylidene malonate diene iron complex.

Alkylidene malonate **102** was prepared from complex **101** in two steps. The acetal was deprotected via an acidic hydrolysis with camphorsulfonic acid (CSA). Knoevenagel condensation with Meldrum's acid then transformed the deprotected aldehyde into an alkylidene malonate. The purification of the alkylidene malonate **102** proved to be a difficult process that involved multiple column chromatographies to remove excess reagents that were not well-behaved on silica gel. A recrystallization

was attempted but it was unsuccessful. The purified product **102** was divided into aliquots for addition of various nucleophiles.

The successful conjugate additions proved to be perfectly diastereoselective (d.r. 100:0), as shown in Scheme 15. Ethyl Grignard and lithium acetylide addition proceeded with 93 % and 90% yield respectively and 1,3-dioxane-ethyl Grignard reagent gave a 78% yield. However, the additions of allyl stannane, methyl Grignard, phenyl Grignard and phenyl lithium did not produce a recoverable product.

Further modifications of the conjugate addition products were pursued to examine the possibilities of changing the malonate into another functional group that can lead to variations on the addition products. In one instance, malonate **103** was reduced using phenylsilane and triethylamine to yield aldehyde **104**. Malonate **105** was decarboxylated and methyleneated with Eschenmoser's salt to afford an α, β unsaturated ester **106**. It was then converted to alcohol **107** and subsequently oxidized, resulting in aldehyde **108**. Both the phenylsilane reduction and the Eschenmoser's salt decarboxylation-methyleneation was performed on malonate **109** to yield **110** and **111** respectively.



Scheme 15. Conjugate additions to alkylidene malonate diene iron complex and further modifications.

This project demonstrated that the conjugate additions to the alkylidene malonate derivative of the *N*-oxazolidinoyl diene iron(0) tricarbonyl complexes are successful and diastereoselective, as it has been shown with the sulfinyl diene iron(0) tricarbonyl complexes as well as Roush and Wada's 1,4-disubstituted diene iron(0) tricarbonyl complexes. We also saw that the resulting compounds with an added stereocenter can be manipulated to become an aldehyde, the electrophilic reactivity of which brings forth many synthetic possibilities. This chemistry has allowed the variation of side chains on the periphery of the diene iron(0) complex to accomplish ring closing metathesis (Paley *et al.*, unpublished work).

Diastereoselective allylation of an endocyclic oxocarbenium ion

Diastereoselective intramolecular cyclization via an endocyclic oxocarbenium ion has been accomplished previously in the Paley laboratory in the context of spiroketal synthesis; the mechanism is shown in Figure 1. This step demonstrated that the intermediate stabilization by neighboring interaction from metal orbitals helped to form the spiroketal stereocenter.[39] Similarly, an intramolecular cyclization of the *N*-oxazolidionyl analog was attempted using the intramolecular formation of a hemiacetal from diene iron complex **119** functionalized with both aldehyde and alcohol. A subsequent diastereoselective allylation was also planned. Previous examples in the introduction section demonstrated the stabilization of electropositive carbon adjacent to the diene iron complex.[28–30] We anticipated that the empty p orbital on the oxocarbenium ion would be stabilized by the d orbitals of the iron metal in a similar manner.

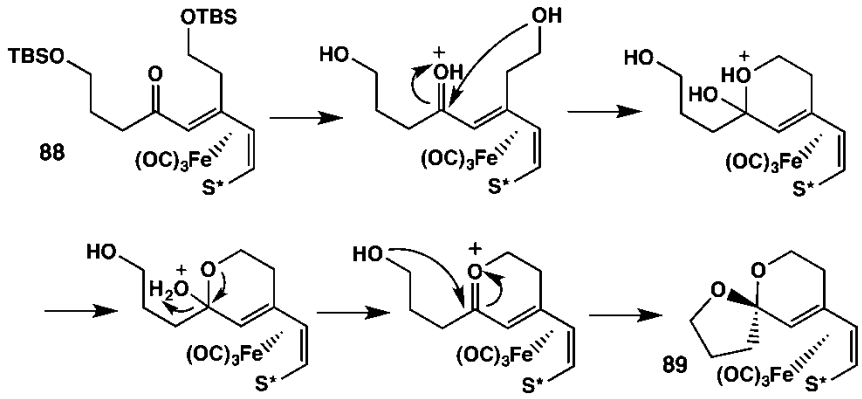
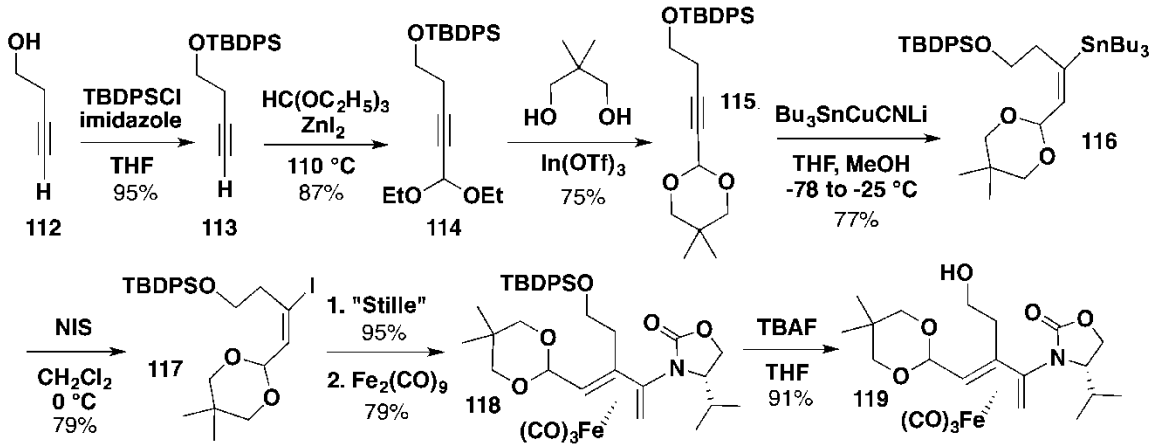


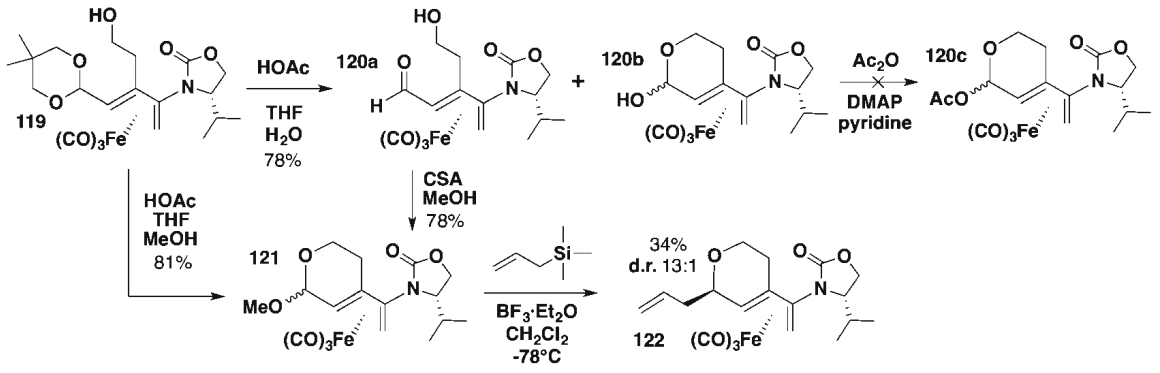
Figure 1. Mechanism of diene iron complex spiroketalization via cyclic oxocarbenium ion.

The sequence introduced above was pursued in ordered to introduce both a ring and a new stereocenter to the periphery of the diene by a diastereoselective allylsilane addition to an oxocarbenium ion adjacent to the iron(0) tricarbonyl diene unit. The synthesis of the starting complex **118** began with the protection of 3-propen-1-ol and the subsequent oxidation of the terminal alkyne, and continued through comparable steps previously described in the synthesis of pentenyl complex **101** used in the alkylidene malonate conjugate addition (Scheme 16).



Scheme 16. Synthesis of starting material for cyclic hemi-acetal and acetal formation.

Following the deprotection of the TBDPS-protected alcohol **118**, the conversion of acetal **119** into an aldehyde gave a mixture of aldehyde **120a** and cyclic hemiacetal **120b** (Scheme 17). We attempted to push the equilibrium towards the cyclized acetal **120c** by treating the mixture of **120a** and **120b** with Ac_2O and pyridine. Unfortunately, we could not accomplish this; only the uncyclized acetylated alcohol was obtained. The same reaction with the addition of DMAP as a catalyst did not improve the results. A more successful route was achieved in the synthesis of the cyclic acetal **121** from **119** by replacing H_2O in the reaction with MeOH. The mixture of **120** could also be converted into **121** with CSA and MeOH. Acetal **121** existed in a single cyclized form and allylation on the material was attempted. While the desired addition of allyl trimethylsilane was highly diastereoselective (d.r.= 13:1, determined by ^1H NMR spectrum of product mixture), the yield of **122** was less than desirable at 34% and could not be optimized despite multiple attempts at changing the reaction temperature as well as the equivalence of nucleophile added. This sequence aimed to utilize the neighboring stabilization of electropositive carbon adjacent to a metal complex in an intramolecular cyclization, which led to a substrate ideal for a diastereoselective reaction. While the alcohol addition to aldehyde was successful in obtaining a cyclic acetal, the subsequent nucleophilic addition had a low yield and was concluded to be unsuitable for further investigation at this time. It is possible that a more thorough screening of Lewis acids and/or nucleophiles could accomplish the desired goal of generating a new stereocenter with a high degree of diastereocontrol.



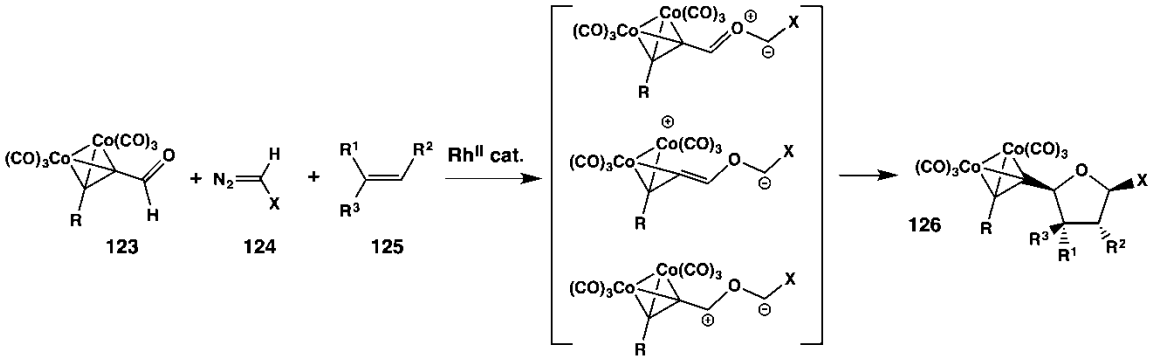
Scheme 17. Formation and allylation of cyclic acetal diene tricarbonyl iron(0) complex.

Diazo-transfer and intramolecular Rh(II)-catalyzed C-H insertion

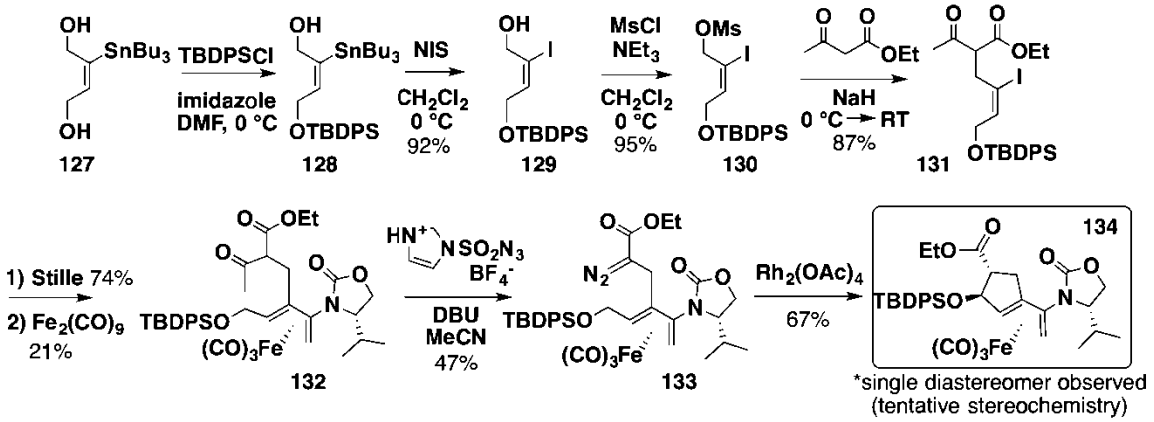
Rh(II)- catalyzed C-H insertion was another method investigated to achieve an intramolecular cyclization at the periphery of the iron(0) diene complex, utilizing the range of possible side chains that can be installed. This type of C-H insertion has provided an important and diastereoselective approach to carbocycle formation in the syntheses of molecules containing cyclopentanes, ranging from natural products (+)-α-cuparenone and ginkgolide to antiobiotic pentalenolactone and cardiovascular and circulatory disease therapeutic (+)-isocarbacyclin.[41–44] Enantioselective versions of this reaction have been accomplished with chiral rhodium catalysts; many groups have reported the use of chiral dirhodium(II) carboxylates and carboxamides in formation of a 3-substituted pentane via intramolecular C-H insertion with 10-46% ee.[45–48] Ikegami *et al.* discovered that the α-diazo β-keto ester substrate can be tuned to optimize the enantioselectivity of dirhodium(II) tetrakis[*N*-phthaloyl-(S)-phenylalaninate] catalyzed C-H insertion reaction up to 76% ee.[49]

In this project we attempted to use the $Fe(CO)_3$ fragment as a stereochemical directing unit that would make the C-H insertion diastereoselective. Rh(II)-catalyzed C-H insertion was reported to be compatible with a metal complex for the first time

when Jamison *et al.* assembled di- and tetra-hydrofuran **126** from a cobalt cluster **123** with a diazo compound **124** and a substituted alkene **125**, via a carbonyl ylide (Scheme 18).[50] The researchers found that the presence of the dicobalt hexacarbonyl cluster improved the reactivity, selectivity and scope of the cycloadditions studied, presumably due to the stabilization of oxonium ion and ylide resonance forms next to the metal fragment. Therefore, the same reactivity was expected of our diene iron(0) tricarbonyl complex, and the following sequence was pursued to discover its compatibility with the Rh(II) catalyzed C-H insertion.



Scheme 18. Jamison *et al.*'s Rh(II)-catalyzed C-H insertion in the presence of a metal complex.



Scheme 19. Rh(II)-catalyzed intramolecular C-H insertion on diene iron(0) complex.

Vinyl stannane **127** was synthesized according to procedures reported by Pour *et al.*.[51] Multiple steps were followed to install an α-diazo ester functional group

on stannane **127** in order to generate a carbene for the C-H insertion. After the conversion of the vinyl stannane **128** to vinyl iodide **129**, β-keto ester was installed on the vinyl iodide in two steps: the conversion of the alcohol to the methanesulfonyl (Ms) leaving group then a subsequent alkylation using the stabilized enolate from a β-keto ester. The nucleophilic substitution of the enolate yielded a modified vinyl ioidide **131**, which was coupled to the *N*-oxazolidinoyl vinyl stannane **99** via Stille reaction with good yield. However, the subsequent complexation with diiron nonacarbonyl gave a comparably low yield, possibly due to decomposition of the diene prior to, or during, the reaction. The iron-complexed β-keto ester **132** was converted to an α-diazo ester **133** via Regitz diazo transfer reaction[52]; imidazole 1-sulfonyl azide tetrafluoroborate was used as the diazo-transferring agent. We propose the following mechanism for this diazo transfer (Figure 2).

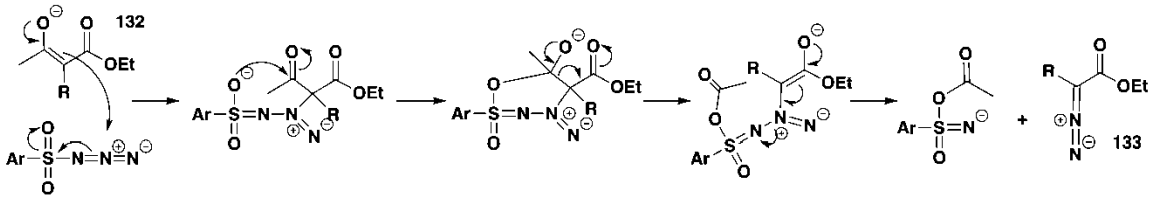


Figure 2. Proposed mechanism of diazo transfer reaction yielding an α-diazo ester.

Treatment of diazo compound **133** with rhodium (II) acetate catalyst gave cyclized product **134** as a single diastereomer. The mechanism for the formation of the rhodium carbene and the subsequent C-H insertion is illustrated in Figure 3. This transformation created two new stereocenters in a single step, significantly expanding the synthetic options available from the title compounds. Our tentative stereochemical assignment of **134** is shown; we propose the transition state shown in Figure 3 which predicts *trans* relative stereochemistry. In addition to the COSY and

NOESY spectra of the compound, the coupling constants (J-values) observed in the ^{1}H NMR spectrum were studied. The protons on the two newly created stereocenters were identified using COSY spectrum as the peaks at 4.88 and 3.20 ppm. We were unable to determine the *trans/cis* relationship of the two protons, as the J value we obtained was around 6 Hz. However, the NOESY spectrum shows coupling between the two peaks which suggest a potential *cis* assignment of the stereocenters. Overall, the results were inconclusive and the stereochemical assignment will need to be further investigated. Optimizing the iron complexation of ketoester dienes and exploring different approaches to this intramolecular cyclization remain a future work for the laboratory.

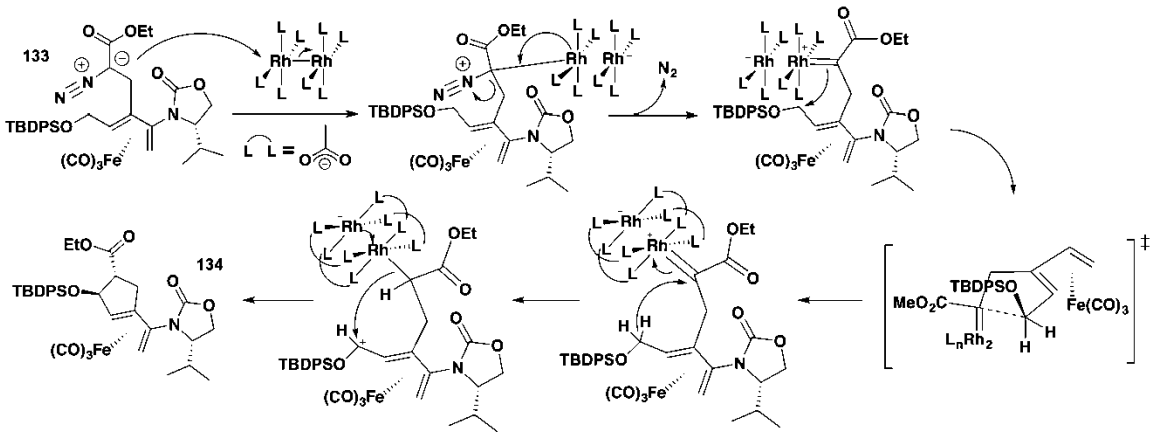


Figure 3. Proposed mechanism of the Rh(II)-catalyzed C-H insertion of diene iron(0) complex.

Enantiomerically pure planar chiral precursor for a Pictet-Spengler reaction

An inspiration for intramolecular cyclization that has never been explored with the diene iron complex, or any planar chiral substrate, came from Tokuda *et. al.*'s total synthesis of Kopsiyunnanine K, in which an intramolecular diastereoselective Pictet-Spengler reaction was utilized as the last key step that introduced two rings.[53] The Pictet-Spengler reaction, a condensation of tryptamines or aryl ethyl amines with

carbonyls was discovered in 1911 by Amé Pictet and Theodor Spengler and has since become an important tool in the synthesis of indole and isoquinoline alkaloids as well as β-carbolines.[54,55] The original reaction of Pictet and Spengler demonstrated the ring-closure of β-phenethylamine with acetone to form tetrahydroisoquinoline.[55] The reaction (Figure 4) begins with the imine formation from a primary amine and a carbonyl and proceeds via electrophilic addition to the iminium ion to the indole. Previous work have shown that electrophilic addition to tri-substituted indole proceeds either through an intermediate that forms via attack of the C(2) or the C(3) position of **135**; in the latter case, the 2,3 di-substituted indole product **139** is formed following the rearrangement into the C(2) position (Figure 4).[56] The reaction pathway through the spiro intermediate has also been found of the Pictet Spengler reaction, in which the attack at C(3) position results in a spiroindolenine **138** that will rearrange to the β-carboline carbonium ion intermediate **137** (Route B, Figure 4).[57] While this intermediate was thought to potentially influence the diastereoselectivity of the product, it was argued that the rate-determining step was the formation of the spiro intermediate and that the cis/trans stereochemistry of the iminium ion substituent in the associated transition state directs the stereochemical outcome of the product.[57] Deprotonation at the C(2) position of **137** restores the aromaticity and yields the final substituted tetrahydro β-carboline, or tryptoline, product **139**.

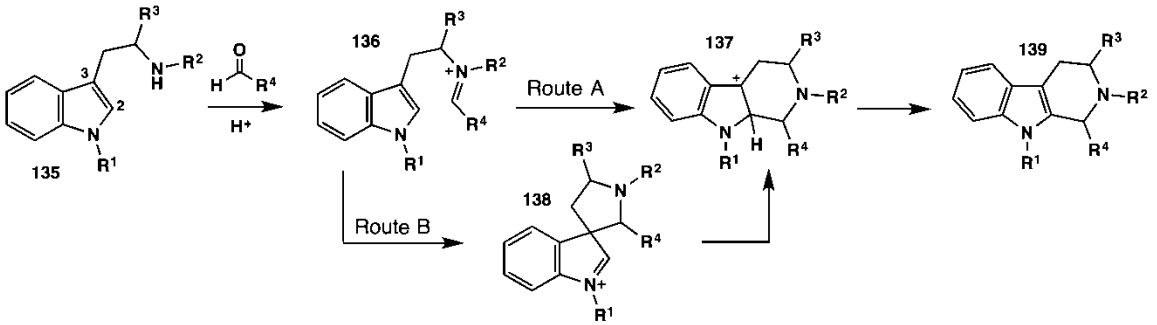


Figure 4. General reaction mechanism of Pictet Spengler condensation.

Catalytic asymmetric Pictet-Spengler reactions using chiral catalysts, such as derivatives of phosphoric acid and thiourea, have been introduced as an enantioselective method.[58,59] While diastereoselective Pictet-Spengler reactions have been reported, the planar chirality of the substrate has not been previously used to direct the stereochemical outcome of the Pictet-Spengler reaction; in the scope of our projected Pictet-Spengler condensation, the planar chirality of the complex would influence the nucleophilic attack of the indole in the condensation. This novel attempt to accomplish the intramolecular diastereoselective Pictet-Spengler reaction, if the preparation of the precursor were to be successful, would contribute to the list of compatible methods for functionalization of the diene iron complexes.

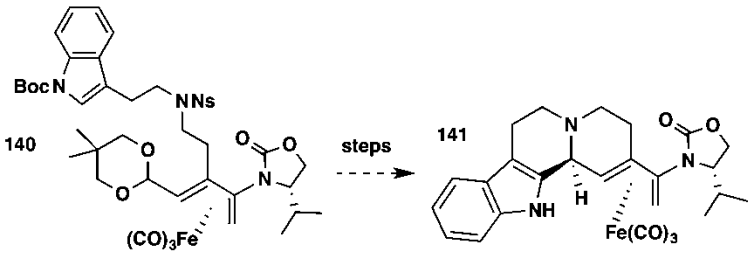
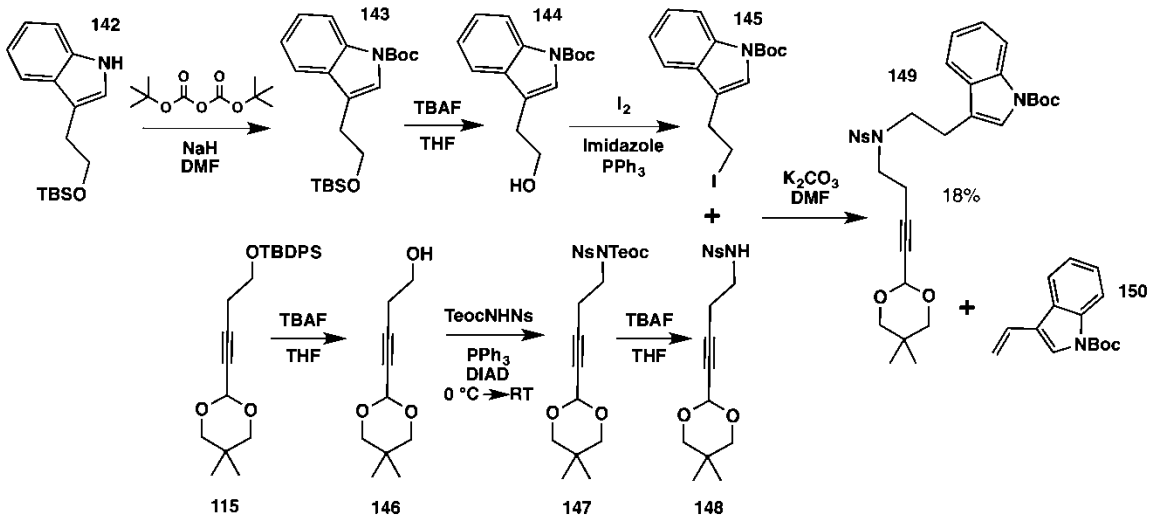


Figure 5. Precursor and target molecule of Pictet Spengler reaction on diene iron(0) complex.

In order to test if this is possible, synthetic routes to complex **140**, which would be the key precursor to the intramolecular Pictet-Spengler reaction, were pursued (Figure 5). Initially, synthesis of alkyne **149** was pursued with hopes to

convert the alkyne into the vinyl iodide analog. This vinyl iodide would participate in the routine Stille coupling that yields the title compound. The resulting diene iron complex would be equipped with all the necessary components that could be deprotected to initiate the condensation in two steps. The tryptophan ethyl trimethylsilyl ether was converted into Boc-protected tryptophan ethyl iodide **145** in three steps.[60] It was then coupled with amine **148**, synthesized from acetal **115** in 4 steps (Scheme 20). However, rather than the intended S_N2 substitution/alkylation, a base-induced elimination of the tryptophan iodide **145** occurred, resulting in a low product yield (18%) due to side product **150**. In order to prevent the unwanted side reaction as well as potential regioselectivity issues in the stannylcupration to be followed, a different sequence was pursued to assemble the desired precursor **140**.



Scheme 20. First attempt of iron(0) complexed Pictet Spengler precursor synthesis.

The key reaction used in the following attempts to synthesize precursor **140** was the Mitsunobu reaction. It was introduced in 1967 by Oyo Mitsunobu who provided many adaptable examples of a substitution reaction between a primary or secondary alcohol and a nucleophile that can be of versatile form, facilitated through

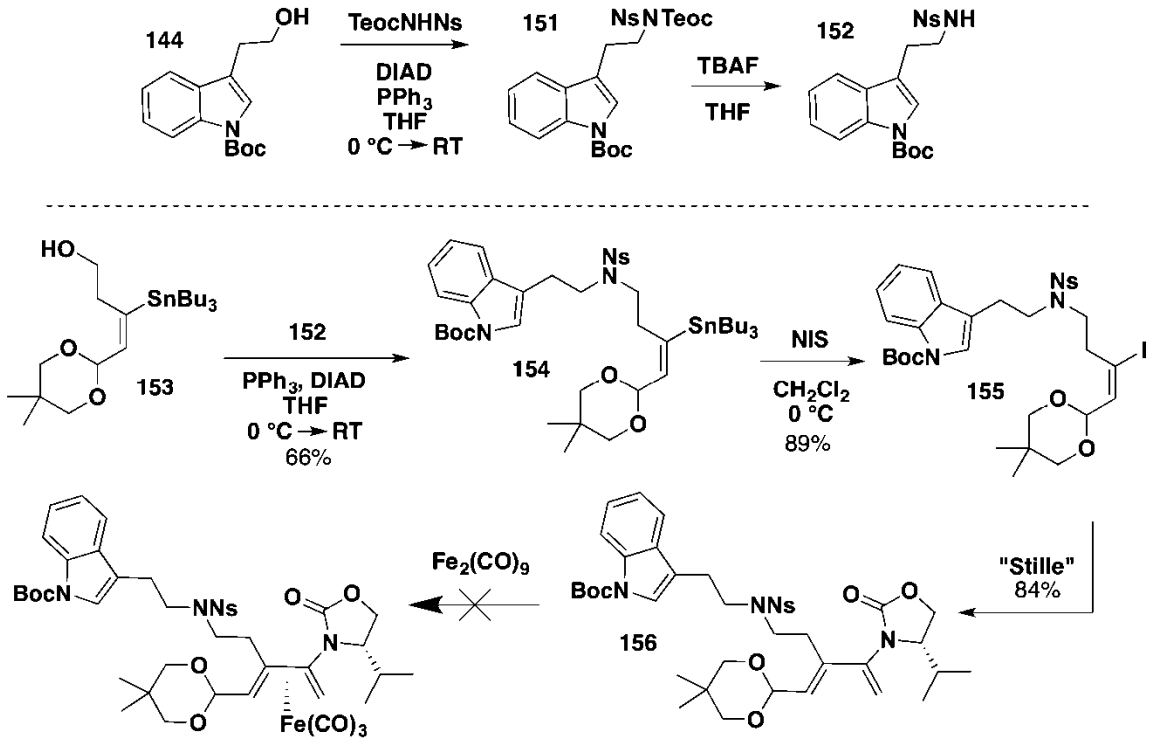
a reduction-oxidation combination of trialkyl or triarylphosphine and dialkyl azodicarboxylate.[61–63] It serves an integral role in natural product synthesis due to its stereospecificity and versatility: a vast range of nucleophiles have been used, generally compounds that contain O-H, N-H or S-H bonds with $pK_a \leq 15$.[64] The Mitsunobu reaction has proven to be a routine transformation in organic synthesis due to its ability to form C-O, C-N, C-S, and C-C bonds producing a variety of compounds including esters, amines, azides, ethers, nitriles, thiocyanides, thioesters and thioethers. Furthermore, the stereocontrol with complete inversion of stereochemistry using a secondary alcohol substrate widens the scope of reaction application. In the context of our project, a primary alcohol and a secondary amine are coupled to form a tertiary amine.

We discovered that the Mitsunobu reaction on diene iron(0) complexes are very difficult to push to 100% conversion and also to purify the product. The reaction stoichiometry was optimized to use 2 molar equivalences or more of PPh_3 and DIAD to increase the conversion rate of the reaction. It was also noted that the byproduct of the reaction had a very similar R_f value as the starting amine and multiple column chromatographies were required to isolate the coupled product.

In the following sequences, the "nosyl" (Ns) amine protecting group, nitrobenzylsulfonamides, was used. Fukuyama and Kan reported in 2004 the successful alkylation of the mono-substituted nitrobenzylsulfonamide in mild conditions and the subsequent deprotection with a soft nucleophile.[65] Since then, the Ns group has been regarded as an efficient protecting and activating group for amines, stable under both acidic and basic conditions. The compatibility of the Ns

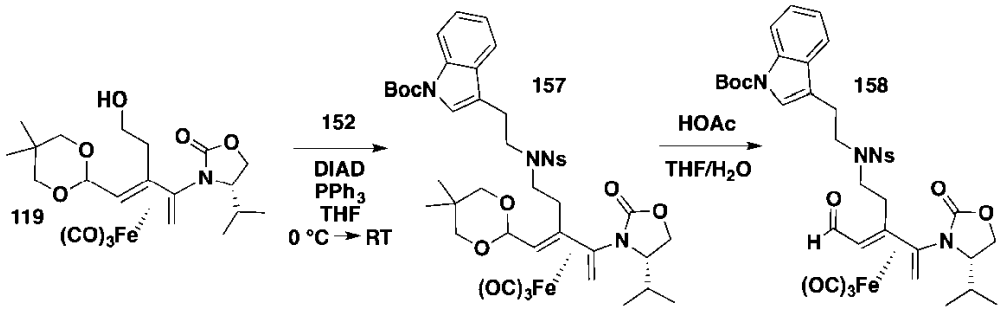
group with the Mitsunobu reaction has already been confirmed in the original paper; therefore, the Ns group was determined suitable for our synthetic purpose of coupling a protected primary amine with an alcohol to yield a secondary amine with a protecting group that can be readily removed for the Pictet-Spengler reaction.

The next approach examined the Mitsunobu coupling of the Boc-protected tryptophan ethyl nosylamine **152**, synthesized from **144** in two steps, one of which was also via Mitsunobu coupling from **144** to **151**, to the vinyl stannane **153** (Scheme 21). While the purification of the product was difficult as expected, the reaction yield was reasonable at 66%. The routine steps were taken to convert the vinyl stannane **154** into a vinyl iodide **155** to participate in Stille coupling with *N*-oxazolidinoyl vinyl stannane to yield diene **156**. Unfortunately a major problem was encountered in this sequence: the attempt to form iron(0) diene complex failed, as instead the nitro group on the nosylamine was reduced. This unexpected reduction made it impossible to remove what was the nosyl protecting group in order to prepare the secondary amine needed for the Pictet-Spengler reaction. It was thus concluded that the complexation must precede the Mitsunobu reaction.



Scheme 21. Second attempt of iron(0) complexed Pictet-Spengler precursor synthesis.

The best approach examined so far was Mitsunobu coupling of Boc-protected tryptophan ethyl nosyl amine **152** with alcohol **119** (Scheme 22). This reaction as well as earlier Mitsunobu couplings were initially carried out with the DIAD reagent. The TLC plate showed multiple compounds in the crude mixture: a non-polar elimination product from the iron(0) dieneol **119** was observed, and the R_f values of the reactant tryptamine **152**, Mitsunobu product **157** and the Mitsunobu byproduct were all very similar. Tryptamine **152** and product **157** were especially difficult to separate, even after repeated chromatography; therefore, the following attempts pursued a complete conversion of the product by using slight excess of the reactant, diene iron complex **119**, and stirring for more than 24 hours.



Scheme 22. Third attempt of iron(0) complexed Pictet-Spengler precursor synthesis.

When the product yield and purification did not improve over multiple attempts of Mitsunobu reaction, the coupling of amine **152** and diene iron complex **119** was repeated using di-*p*-chlorobenzyl azodicarboxylate (DCAD) instead of DIAD. DCAD is an alternative azodicarboxylate reagent that simplifies the reaction by generating byproducts that can be separated readily; the reduced byproduct is of different polarity than those of DIAD facilitated reactions and the hydrazine byproduct precipitates in CH_2Cl_2.[66] Moreover, DCAD is a stable solid at standard conditions that results in comparable yield and reaction rate as the ethyl and isopropyl derivatives. Despite our expectations, the repeated reaction with DCAD gave a complicated product mixture similar to the previous attempt that gave **157.**

The impure mixture of Mitsunobu product **157** was carried on to the acetal hydrolysis to yield aldehyde **158**. At this stage in the sequence, the two remaining steps before the desired Pictet-Spengler condensation were the removal of protecting groups on the amine and the indole. Unfortunately, the aromatic nucleophilic substitution with thiol was not successful in removing the nosyl protecting group; decomplexed material was obtained. Therefore, aldehyde **158** was the final isolated and characterized compound in the sequence.

While this project did not reach the desired Pictet-Spengler cyclization step, it led to the most heavily-functionalized *N*-oxazolidinoyl iron(0) tricarbonyl diene complexes to be synthesized in the Paley laboratory. We gained insight and strategies to avoid complications in synthesizing the Pictet-Spengler precursor on the diene iron(0) scaffold. We have learned that the iron complexation of the diene reduces the nosyl protecting group and therefore the Mitsunobu coupling must be done before the complexation to yield a protected secondary amine. Future members of the laboratory will pursue different sequences to optimize Mitsunobu reaction of diene iron complexes and further explore the compatibility of this chemistry.

Concluding Remarks

Various approaches were taken to emulate the successful chemistry previously reported on sulfinyl diene iron complexes in the context of the new complexes bearing the oxazolidinone chiral auxiliary. In the process, we have found that 1,4 conjugate additions to the alkylidene malonate analogs of the title compound are completely diastereoselective, even though some nucleophiles worked better than others. Also, the diastereoselective allylation of an *in-situ* generated endocyclic oxocarbenium ion on the periphery of the diene was accomplished, though at low yields. Furthermore, other endeavors were undertaken to expand the scope of diastereoselective transformations of diene iron complexes. The Rh(II)-catalyzed C-H insertion was surprisingly successful and realized a diastereoselective intramolecular cyclization to produce a five-membered ring fused on to the diene iron(0) complex. While this opened a new avenue of synthetic pathways towards diene iron(0) complexes containing cyclopentanes, further investigation of the

reaction must be pursued in order to assign absolute stereochemistry of the cyclized products. Synthesizing the Pictet-Spengler reaction precursor on a diene-$Fe(CO)_3$ scaffold proved to be a difficult task but resulted in one of the most elaborate *N*-oxazolidinoyl diene-$Fe(CO)_3$ complexes to be made in the laboratory. Future work in the Paley laboratory will build upon the findings reported here to accomplish the Pictet-Spengler condensation on the periphery of a diene iron complex and to optimize various other transformations accomplished so far.

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Experimental Methods

General Experimental Methods

All air- and moisture-sensitive reactions were carried out in flame-dried glassware under an argon atmosphere on a Schlenk manifold. Anhydrous THF, CH_2Cl_2 and toluene were purchased from J.T. Baker and stored in Innovative Technology solvent still. When dispensed, the solvents were dried through an alumina/copper(II) oxide column. Air-and moisture-sensitive reagents, as well as anhydrous DMSO and DMF solvents, were stored and dispensed in inert N_2 atmophere of a glovebox. Liquid amine bases were distilled and stored in airtight schlenk tubes under Ar. Liquid reagents were transferred into reaction flasks via cannula or gas-tight syringes.

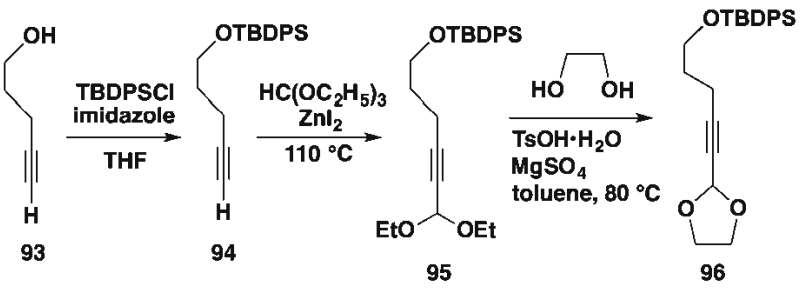
Reaction progress as well as chromatography separation was monitored via TLC on Analtech Uniplate™ 250 micron pre-coated glass slides; the plates were visualized under UV light and sometimes with vanillin or permanganate dip. All crude products were purified via flash chromatography in nitrogen-flushed silica gel (mean diameter 60 Å) purchased from Acros Organics. The eluent used in chromatography is individually mentioned in the procedures; samples that were insoluble in the appropriate eluent were loaded on to the column using toluene or chloroform.

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectroscopy was carried out with Bruker Ascend 400 MHz NMR. All NMR samples were prepared in deuterated chloroform and the spectra were analyzed relative to the TMS peak at 0.00 ppm. Fourier-transform infared (FT-IR) spectra were recorded using a Thermo Scientific Nicolet iS5 spectrometer. Oil samples were prepared on NaCL plates and recorded with an iD1 Transmission attachment, while solid samples were recorded neat on an iD5 ATR attachment. Optical rotation measurements were taken on a JASCO P-2000 polarimeter; the samples were prepared in chloroform.

Experimental Procedures and Spectral Data

Diastereoselective nucleophilic conjugate additions to the alkylidene malonate

Acetal 96



4-pentyn-1-ol (0.5583 mL, 6 mmol, 1 eq) was dissolved THF (20 mL). Imidazole (1.0212 g, 15 mmol, 2.5 eq) and DPSCl (1.8427 mL, 7.2 mmol, 1.2 eq) were added slowly. The reaction was stirred at room temperature for 20.5 hours and quenched with NH_4Cl. The reaction mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 40:1 Hex/EtOAc). Alkyne **94** was obtained with 96% yield.

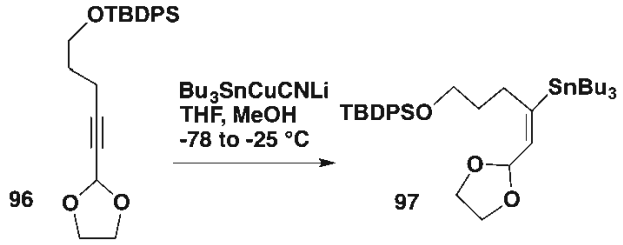
Alkyne **94** (1.86 g, 5.767 mmol, 1 eq) was dissolved in triethylorthoformate (50 mL). ZnI_2 (1.84 g, 5.767 mmol, 1 eq) was added at once. The reaction was placed in a 110 °C oil bath and stirred for 8.5 hours. The reaction mixture was cooled to room temperature and purified via distillation. Acetal **95** was obtained with 90% yield.

Acetal **95** (2.20 g, 5.18 mmol, 1 eq) was dissolved in toluene (36 mL) and ethylene glycol (1.44 mL, 25.9 mmol, 5 eq) was added. The reaction was placed in a 80 °C oil bath. $TsOH{\bullet}H_2O$ (0.197 g, 1.036 mmol, 0.2 eq) and $MgSO_4$ (5.87 g) were added together. The reaction temperature was raised to 120 °C and the reaction was stirred for 2.5 hours under reflux. The reaction was removed from the bath and NEt_3 (1 mL) was added. The reaction

mixture was stirred for 15 minutes, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 19:1 Hex/EtOAc). Acetal **96** was obtained with 69% yield.

^{1}H NMR (400 MHz) $\boldsymbol{\delta}$ 1.04 (t, J = 3 Hz, 9H), 1.77 (m, 2H), 2.39 (m, 2H), 3.72 (t, J = 5/6 Hz, 2H), 3.90 (m, 2H), 4.02 (m, 2H), 5.60 (s, 1H), 7.40 (m, 6H), 7.67 (m, 4H); ^{13}C NMR (100 MHz) δ 15.21, 19.22, 26.82, 31.15, 62.30, 64.42, 86.36, 93.16, 127.64, 129.59, 133.76, 135.55; IR 613.9, 687.7, 702.7, 742.3, 801.0, 822.9, 962.7, 1110.8, 1254.9, 1360.9, 1389.5, 1428.0, 1472.1, 1588.9, 1714.2, 1775.0, 1811.6, 2237.0, 2739.4, 2857.5, 2931.2, 3048.7, 3070.6, 3502.3 cm^{-1}

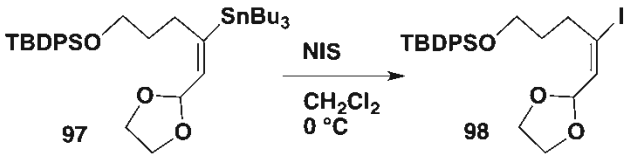
Stannane 97



Bis-tributyltin (3.97 mL, 7.8566 mmol, 2.2 eq) was dissolved in THF (45 mL) under Ar. The reaction was cooled to -78 °C before the addition of 1.6 M BuLi in hexane (4.687 mL, 7.4995 mmol, 2.1 eq). The reaction was stirred at -40 °C for 30 minutes. The reaction was re-cooled to -78 °C before the addition of CuCN (0.6397 g, 7.1424 mmol, 2 eq). The reaction was then stirred for 40 minutes at -40 °C and methanol (0.217 mL, 5.3568 mmol, 1.5 eq) was added. Solution of alkyne **96** (1.4092 g, 3.5712 mmol, 1 eq) in 30 mL THF was added via cannula. The reaction was re-cooled to -78 °C and stirred for 3 hours. The reaction was warmed to -25 °C and quenched with 9:1 solution of saturated NH_4Cl/NH_4OH. The reaction mixture was diluted and transferred with EtOAc to a separatory funnel. The aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, hexane with 3% NEt_3). Stannane **92** was obtained with 72% yield.

^{1}H NMR (400 MHz) δ 0.89 (m, 15H), 1.05 (s, 9H), 1.29 (m, 6H), 1.48 (m, 6H), 1.60 (m, 2H), 2.51 (m, 2H), 3.66 (t, J = 6 Hz, 2H), 3.83 (m, 2H), 4.01 (m, 2H), 5.57 (m, 2H), 7.39 (m, 6H), 7.69 (m, 4H); ^{13}C NMR (100 MHz) δ 9.67, 13.67, 19.22, 26.83, 27.39, 29.05, 30.41, 33.40, 63.30, 64.85, 98.09, 127.60, 129.53, 135.57, 154.66; IR 700.8, 737.0, 822.6, 956.8, 1110.5, 1377.9, 1427.3, 1462.4, 1589.1, 2855.6, 2927.3, 2955.1 cm^{-1}

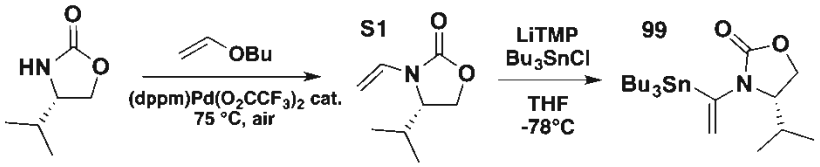
Iodide 98



Stannane **97** (1.78 g, 2.596 mmol, 1 eq) was dissolved in CH_2Cl_2 (26 mL) under Ar and cooled to 0 °C. N-iodosuccinimide (0.642 g, 2.856 mmol, 1.1 eq) was added at once. The reaction was stirred for 2 hours at 0 °C. The reaction was quenched with 1:1 mixture of saturated $NaHCO_3$ and saturated $NaSO_4$. The mixture was diluted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified via column chromatography (40:1 Hex/EtOAc with 0.5% NEt_3). Iodide **98** was obtained with 92% yield.

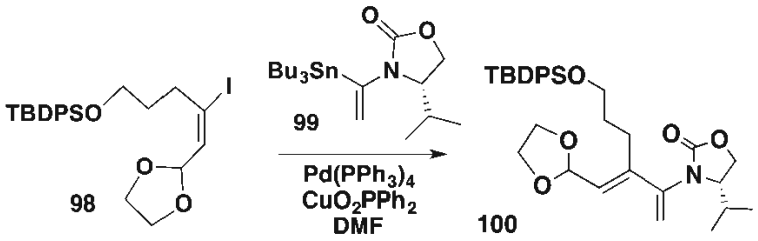
^{1}H NMR (400 MHz) δ 1.05 (t, J = 2 Hz, 9H), 1.76 (m, 2H), 2.70 (t, J =6/7 Hz, 2H), 3.68 (m, 2H), 3.80 (m, 2H), 3.95 (m, 2H), 5.55 (d, J = 6.8 Hz, 1H), 6.24 (m, 1H), 7.40 (m, 6H), 7.66 (m, 4H); ^{13}C NMR (100 MHz) δ 19.22, 26.84, 32.29, 36.40, 61.97, 64.87, 99.20, 111.83, 127.65, 129.62, 133.79, 135.56, 138.04; IR 700.7, 742.4, 822.2, 956.7, 997.8, 1110.2, 1191.6, 1390.0, 1427.6, 1471.2, 1588.9, 1636.3, 1995.6, 2929.7, 3070.0 cm^{-1}

Oxazolidinone vinyl stannane 99



Catalyst **(dpp)Pd(O_2CCF_3)$_2$** and **S1** were synthesized using procedures published by Stahl et al. (*Org. Lett.*, **6**, 11, 1845-1848, 2004). Oxazolidinone vinyl stannane **99** was synthesized using procedures published by Hegedus et al. (*JACS,* **116**, 18, 8126-8132, 1994).

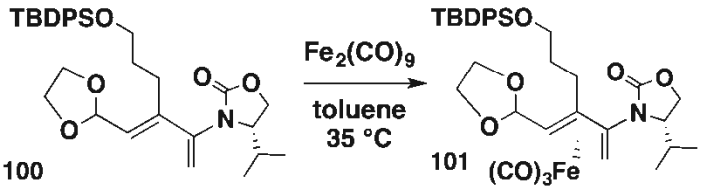
Diene 100



The following reaction was carried out in the glovebox in N_2 atmosphere. Stannyl vinyl oxazolidinone **99** (1.061 g, 2.388 mmol, 1 eq) was dissolved in portions of DMF (12 mL) and transferred to a flask containing vinyl iodide **98** (1.25 g, 2.388 mmol, 1 eq). The solution was stirred while $Pd(PPh_3)_4$ (0.275 g, 0.2388 mmol, 0.1 eq) and CuO_2PPh_2 (0.771 mg, 2.7462 mmol, 1.15 eq) was added together. The reaction was stirred overnight at room temperature. The reaction mixture was filtered through silica gel in a glass frit. The filtered product was redissolved in Et_2O and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 2:1). Diene **100** was obtained as thick pale yellow oil with 95.4% yield.

^{1}H NMR (400 MHz) δ 0.86 (m, 6H), 1.05 (m, 9H), 1.62 (m, 1H), 1.75 (m, 1H), 1.90 (m, 1H), 2.28 (m, 1H), 2.64 (m, 1H), 3.67 (m, 2H), 3.84 (m, 3H), 4.01 (m, 2H), 4.15 (m, 1H), 4.27 (t, J = 8.8 Hz, 1H), 5.32 (s, 1H), 5.47 (s, 1H), 5.61 (q, J = 7.0, 18 Hz, 2H), 7.39 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (100 MHz) δ 14.44, 17.79, 19.23, 25.10, 26.86, 29.08, 31.99, 60.09, 62.68, 62.97, 65.00, 99.67, 113.75, 126.58, 127.65, 129.60, 129.62, 133.77, 133.83, 135.55, 135.56, 141.24, 142.02, 156.46; IR 612.8, 700.5, 822.8, 1217.6, 1325.7, 1408.6, 1470.6, 1567.1, 1589.1, 1612.2, 1754.8, 1892.7, 1962.3, 2067.1, 2296.3, 2738.9, 2771.2, 2957.6, 3048.1, 3070.5, 3117.1, 3503.5 cm^{-1}

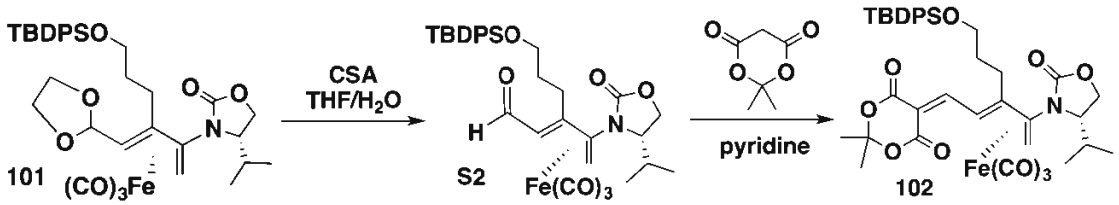
Diene Iron Complex 101



Diene **100** (1.254 g, 2.2787 mmol, 1 eq) was dissolved in toluene (23 mL) and cannulated into a flask containing nonacarbonyldiiron (2.9014 g, 7.9756 mmol, 3.5 eq). The reaction was placed in a 35 °C oil bath and stirred overnight. The reaction mixture was filtered through silica gel in a glass frit. The crude product was purified via column chromatography (12:1 → 6:1 Hex/EtOAc with 0.5% NEt_3). Complex **101** was obtained as a light yellow foam with 53% yield.

IR 555.7, 586.2, 598.4, 615.4, 664.7, 685.4, 702.7, 748.2, 771.5, 801.6, 823.4, 955.0, 1027.3, 1056.9, 1077.0, 1106.6, 1156.1, 1207.6, 1323.1, 1359.7, 1393.3, 1426.2, 1460.3, 1588.2, 1755.3, 1970.8, 2053.0, 2855.9, 2961.8 cm^{-1}; $[\alpha]^{23}$ = +126.2 (c = 0.48 g/mL)

Alkylidene malonate 102



Complex **101** (0.8256 g, 1.2077 mmol, 1 eq) was dissolved in 5:1 mixture of THF/H_2O (13 mL) open to air. Camphorsulfonic acid (56.07 mg, 0.2415 mmol, 0.2 eq) was added. The reaction was sitrred overnight at room temperature. The reaction solution was diluted with EtOAc and washed with $NaHCO_3$ and brine successively. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 4:1 Hex/EtOAc). Aldehyde **S2** was obtained with 87%.

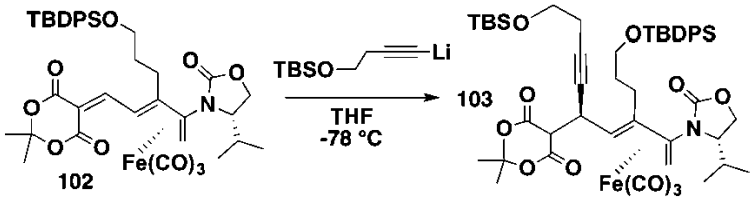
^{1}H NMR (400 MHz) δ 0.700 (d, J=6.8, 1H), 0.770 (s, 1H), 0.898 (d, 6H), 1.059 (s, 9H), 1.803 (m, 2H), 2.151 (s, 1H), 2.326 (m, 1H), 2.743 (m, 2H), 3.724 (m, 2H), 3.892 (m, 1H), 4.046 (m, 2H), 7.405 (m, 6H), 7.643 (m, 4H), 9.347 (d, 1H, aldehyde); ^{13}C NMR (100 MHz) δ 13.7, 18.0, 19.2, 25.3, 26.9, 29.0, 35.0, 38.2, 53.6, 61.5, 63.2, 64.1, 103.9, 105.3, 127.8, 129.8, 133.5, 135.5, 156.1, 195.2; IR 566.1, 596.7, 613.7, 701.0, 739.6, 795.2, 822.7, 973.8, 1030.5, 1057.0, 1105.7, 1152.5, 1203.0, 1326.9, 1392.2, 1427.6, 1462.1, 1676.1, 1753.9, 1984.1, 2061.6, 2857.7, 2930.1 cm^{-1}; $[\alpha]^{23}$ = +213.4 (c = 1.25g/mL).

Aldehyde **S2** (0.6814 g, 1.0507 mmol, 1 eq) was dissolved in pyridine (10 mL) under argon. After Meldrum's Acid (0.1817 g, 1.2608 mmol, 1.2 eq) was added, the reaction flask was stirred at room temperature for 18 hours. The reaction mixture was diluted in EtOAc, washed with 1M HCl. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude

product was purified via column chromatography (silica gel, 4:1 Hex/EtOAc with 0.5% formic acid). Alkylidene malonate **102** was obtained with 51% yield.

^{1}H NMR (400 MHz) δ 0.90 (d, J=6.8, 6J), 1.06 (s, 9H), 1.40 (d, J=4.0 HZ, 1H), 1.71 (d, J=17.6, 6H), 2.35 (m, 2H), 2.55 (m, 1H), 2.69 (d, J=12 Hz, 1H), 2.79 (m, 1H), 3.73 (m, 2H), 3.90 (m, 1H), 4.02 (m, 2H), 7.42 (m, 6H), 7.63 (t, J= 1.6, 7.2 Hz, 4H), 7.91 (d, J=12.4, 1H); ^{13}C NMR (100 MHz) $\boldsymbol{\delta}$ 13.7, 18.0, 19.2, 25.1, 26.9, 27.5, 29.0, 34.7, 38.9, 50.9, 61.6, 63.2, 64.1, 104.5, 104.9, 107.2, 108.9, 127.8, 129.9, 133.4, 135.5, 155.9, 161.5, 162.7, 162.8; IR 555.8, 574.8, 591.3, 604.3, 620.0, 689.1, 700.5, 724.5, 745.7, 766.9, 798.9, 826.8, 889.1, 905.8, 929.1, 954.6, 971.0, 999.3, 1017.3, 1032.8, 1055.1, 1083.2, 1107.3, 1148.6, 1179.2, 1199.0, 1222.9, 1252.5, 1280.0, 1305.7, 1347.8, 1393.0, 1426.5, 1458.4, 1483.5, 1576.8, 1720.7, 1743.5, 1987.2, 2000.4, 2059.2, 2857.3, 2059.4 cm^{-1}; $[\alpha]^{23}$ = +771.3 (c = 0.49 g/mL).

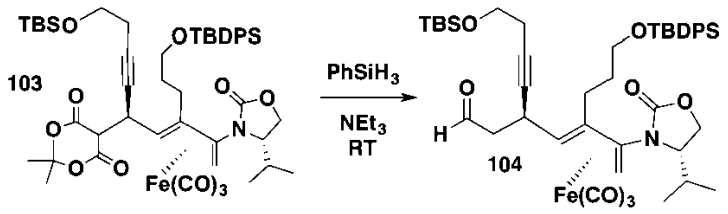
Malonate 103



The acetylide (0.0535 mL, 0.2592 mmol, 2.5 eq) was dissolved in THF and cooled to -78 °C. BuLi (0.1295 mL, 0.2073 mmol, 2 eq) was added dropwise and the mixture was stirred for 45 minutes. the alkylidene malonate **102** (0.0810 g, 0.1037 mmol) was transferred to the alkyne solution via cannula and stirred for 3 hours. The reaction mixture was quenched with saturated NH_4Cl and warmed to room temperature. It was diluted with EtOAc, washed with H_2O. Aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified via column chromatography (silica gel, 2.5:1 Hex/EtOAc). The acetylide addition product was obtain with 90% yield.

^{1}H NMR (400 MHz) δ -0.02 (m, 6 H), 0.45 (d, J=3.6 Hz, 1H), 0.83 (m, 9H), 0.88 (d, J=6.8 Hz, 3H), 0.93 (d, J=7.2 Hz, 3H), 1.07 (s, 9H), 1.46 (d, J=10.4 Hz), 1.57 (s, 1H), 1.82 (m, 4H), 1.85 (s, 1H), 2.31 (m, 5H), 2.80 (m, 1H), 3.43 (dq, J=2.4, 10 Hz, 1H), 3.55 (t, J=7.2 Hz, 2H), 3.73 (m, 1H), 3.78 (d, J=2.8), 3.820 (m, 1H), 3.89 (m, 1H), 4.01 (m, 2H), 7.43 (m, 6H), 7.67 (m, 4H); ^{13}C NMR (100 MHz) δ 13.54, 17.99, 19.16, 23.06, 24.50, 28.42, 29.17, 32.86, 33.27, 38.19, 53.50, 58.66, 61.22, 61.53, 63.94, 64.52, 78.53, 81.30, 101.41, 105.25, 127.77, 129.73, 133.58, 133.71, 155.64, 163.15, 163.58; IR 574.8, 594.5, 610.3, 629.9, 663.5, 685.9, 704.8, 746.1, 780.3, 836.5, 894.1, 941.3, 975.2, 1007.4, 1028.3, 1055.2, 1096.1, 1160.1, 1202.6, 1222.8, 1251.0, 1271.0, 1294.5, 1329.9, 1361.6, 1393.6, 1428.4, 1471.4, 1486.6, 1750.6, 1791.0, 1957.5, 1967.3, 1989.3, 2050.0, 2362.1, 2857.4, 2931.0 cm^{-1}; $[\alpha]^{23}$ = +52.07 (c = 0.52 g/mL)

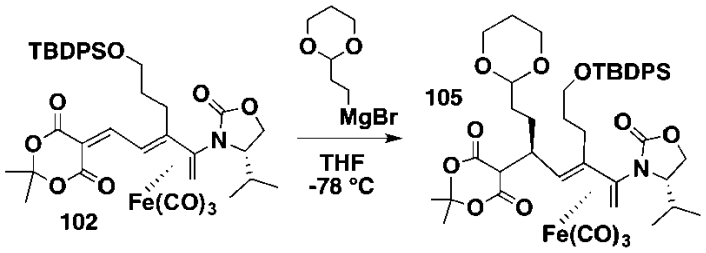
Aldehyde 104



A solution of 0.5 M $PhSiH_3$ and 0.33 M NEt_3 in THF was made beforehand. 0.4 mL (0.1880 mmol, 3 eq of phenylsilane and 0.1253 mmol, 2 eq of triethylamine) of this solution was added to the malonate **103** (0.0599 g, 0.0626 mmol, 1 eq) in the reaction flask. The reaction was stirred for 2 hours at room temperature. 0.05 mL H_2O was added and the reaction was stirred for 15 minutes. The reaction mixture was dissolved in Et_2O, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 6:1 Hex/EtOAc). Aldehyde **104** was obtained with 55 % yield.

^{1}H NMR (400 MHz) δ 0.2 (s), 0.45 (d), 0.85 (s), 0.88 (d, J=6.8), 0.93 (d, J=7.2), 1.07 (s), 1.25 (s), 1.77 (d?, J=3.6), 2.32 (big m), 2.76 (big m), 3.59 (t, J=7.2), 3.71 (septet), 3.81 (quintet), 3.89 (quintet), 4.05 (sextet), 7.4~ (m), 6.68 (m), 9.79 (s); ^{13}C NMR (100 MHz) δ 5.30, 18.86, 23.28, 23.54, 24.47, 28.39, 30.28, 31.16, 32.13, 33.56, 34.49, 38.45, 42.70, 56.05, 65.45, 66.54, 66.96, 69.28, 69.80, 86.43, 87.04, 106.79, 108.94, 133.01, 133.06, 135.02, 138.87, 139.03, 140.85, 140.91, 161.02, 205.59; IR 574.7, 596.4, 609.3, 701.7, 740.9, 776.5, 835.3, 915.2, 973.6, 1007.3, 1028.6, 1056.5, 1104.4, 1202.4, 1250.8, 1331.5, 1391.9, 1427.9, 1462.6, 1726.1, 1755.1, 1965.8, 2049.8, 2359.2, 2855.9, 2929.1 cm^{-1}

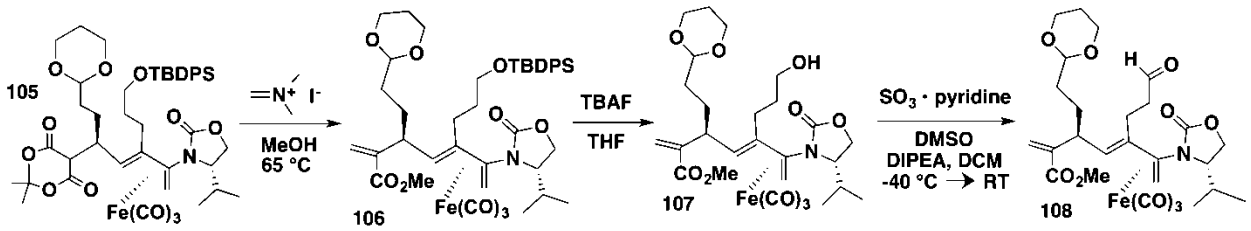
Malonate 105



Alkylidene malonate **102** (0.0150 g, 0.1941 mmol) was dissolved in 7.5 mL of THF under Ar. Grignard reagent (0.7765 mL, 0.3882 mmol, 2 eq) was added to the solution, which was stirred for 3 hours under argon at -78 °C. The reaction mixture was quenched with saturated NH_4Cl and warmed to room temperature. It was then diluted with EtOAc and washed with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 2:1 to 1:2 Hex/EtoAc). 1,3-dioxane addition product was obtained with 78% yield.

^{1}H NMR (400 MHz) δ 0.34 (d, J=3.2 Hz, 1H), 0.91 (dd, J=7.0, 19.4 Hz, 6H), 1.08 (s, 9H), 1.24 (m, 3H), 1.47 (m, 3H), 1.57 (m, 2H), 1.77 (s, 4H), 1.83 (s, 4H), 2.23 (m, 1H), 2.35 (m, 1H), 2.81 (dd, J=8.6, 13 Hz, 2H), 3.58 (q, J=10 Hz, 2H), 3.75 (m, 2H), 3.86 (d, J=1.6 Hz) + 3.92 (m) = 4H, 4.04 (m, 2H), 4.37 (t, J=4.8 Hz, 1H), 7.42 (m, 6H), 7.68 (m, 4H); ^{13}C NMR (100 MHz) δ 13.59, 17.94, 19.16, 23.89, 25.65, 26.66, 26.83, 27.67, 28.12, 29.20, 32.78, 33.11, 38.03, 38.94, 61.20, 63.92, 64.47, 66.67, 101.23, 104.96, 127.73, 127.77, 129.72, 133.55, 133.77, 135.58, 135.61, 155.55, 164.18, 164.64; IR 583.9, 614.3, 638.2, 666.7, 687.6, 704.0, 755.7, 823.6, 882.9, 974.4, 998.6, 1029.2, 1059.8, 1110.9, 1146.0, 1205.7, 1297.7, 1393.6, 1428.2, 1485.7, 1462.3, 1749.7, 1782.0, 1969.7, 2050.5, 2857.7, 2931.4, 2962.1, 3011.7, 3071.5 cm^{-1}; $[\alpha]^{23}$ = +66.7 (c = 0.155 g/mL)

Aldehyde 108



Malonate **105** (0.1334 g, .1502 mmol) was dissolved in 5 mL of methanol under argon. Eschenmoser's salt (0.0810 g, 0.4378 mmol, 3 eq) was added to the solution and stirred overnight. Methanol was removed via rotary evaporation, and the concentrated reaction mixture was diluted in EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 4:1 Hex/EtOAc). The product was obtained with 62 % yield.

^{1}H NMR (400 MHz) δ 0.19 (d, J = 2.4 Hz, 1H), 0.90 (dd, J = 6.8, 18 Hz, 6H), 1.08 (s, 9H), 1.13 (m, 1H), 1.45 (m, 2H), 1.62 (d, J = 3.2 Hz, 3H), 1.90 (m, 3H), 2.01 (m, 1H), 2.17 (t, J = 10 Hz, 1H), 2.35 (m, 1H), 2.51 (s, 1H), 2.75 (td, J = 4, 12.8 Hz, 1H), 3.57 (m, 2H), 3.75 (m, 5H), 3.88 (m, 3H), 4.05 (m, 2H), 4.37 (t, J = 5.2 Hz, 1H), 5.58 (s, 1H), 6.26 (s, 1H), 7.41 (m, 6H), 7.69 (d, J = 7.2 Hz, 4H); ^{13}C NMR (100 MHz) δ 13.61, 17.99, 19.16, 14.06, 25.71, 26.83, 29.17, 32.95, 33.58, 36.63, 51.73, 60.41, 61.20, 64.10, 64.49, 66.68, 101.45, 127.71, 127.76, 129.68, 129.72, 133.61, 133.81, 135.58, 135.63, 166.55; IR 667.0, 687.8, 703.5, 755.6, 822.2, 876.2, 961.1, 997.5, 1028.9, 1058.0, 1110.7, 1146.2, 1204.0, 1242.0, 1323.6, 1392.9, 1428.2, 1461.9, 1485.3, 1621.1, 1719.1, 1757.1, 1974.0, 2048.6, 2359.9, 2857.1, 2960.7 cm^{-1}

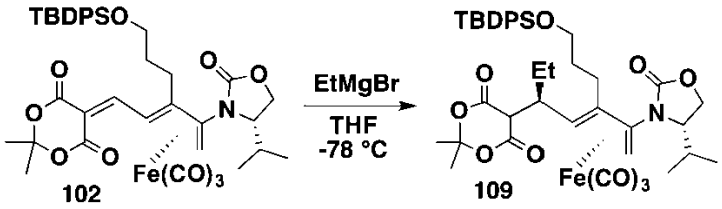
Protected-alcohol **106** (0.0755 g, 0.0909 mmol, 1 eq) was dissolved in 1 mL THF in a schlenk flask, to which TBAF (0.1000 mL, 0.0999 mmol, 1.1 eq) was added dropwise. Reaction mixture was stirred for 22 hours. Reaction mixture was diluted in EtOAc, washed

with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Product was purified via column chromatography (silica gel, 1:2 Hex/EtOAc).

^1H NMR (400 MHz) δ 0.25 (s), 0.93 (s), 0.94 (s), 1.26 (t, J=7.2), 1.3~ (m), 1.52 (m), 1.61 (d, J=3.2), 1.738 (s), 1.9~ (m), 2.38 (m), 2.48 (t?), 2.592 (d), 2.69 (m), 3.65 (m), 3.70 (s), 3.71 (s), 3.85 (septet), 4.0~4.1 (two multiplets), 4.07 (dd, J=4i, 11), 4.17 (dd, J= 3.6, 9.2), 4.33 (t, J=8.8/9.2), 4.51 (t, J=4.8), 5.61 (s), 6.27 (s); ^{13}C NMR (100 MHz) δ 13.62, 13.97, 14.20, 17.98, 20.61, 21.07, 23.39, 25.70, 27.69, 29.11, 29.94, 33.25, 33.86, 36.77, 51.75, 53.03, 60.41, 61.46, 62.10, 64.66, 66.89, 66.94, 101.56, 126.97, 166.55, 214.97; IR 817.9, 1056.8, 1145.2, 1244.0, 1409.7, 1620.7, 1724, 1753.8, 1995.1, 1974, 2045.4, 2856, 2023, 2959.6, 3457.2; $[\alpha]^{23}$ = +141.58 (c = 1.015 g/mL).

Alcohol **107** (38.0 mg, 0.0641 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.8 mL). DMSO (0.16 mL) and DIPEA (0.0447 mL, 0.2564 mmol, 4 eq) was added. The reaction was cooled to -40 °C and SO_3•pyridine (28.9 mg, 0.1924 mmol, 3 eq) was added. The reaction was warmed to 0 °C while stirring (2.5 hours). The reaction was quenched with saturated $NaHCO_3$ and diluted with EtOAc. The organic layer was separated and washed with H_2O and with brine. It was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 1:1.5 Hex/EtOAc). Aldehyde **108** was obtained with 77% yield. NMR spectra show that the **108** was obtained as a mixture with impurities.

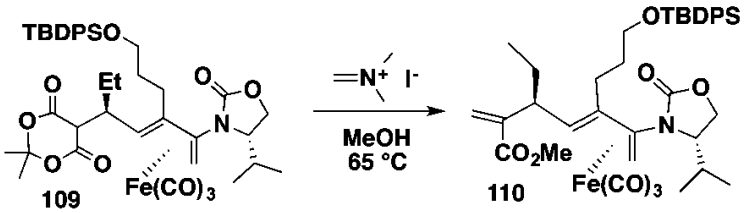
Malonate 109



Malonate **102** (0.2009 g, 0.2603 mmol) was dissolved in 10 mL of THF. 3M solution of ethylmagnesium bromide (.1735 mL, 0.5206 mmol, 2 eq) was added to the starting material solution after it was cooled to -78 °C. The reaction was stirred at -78 °C for 3 hours then quenched with NH_4Cl, diluted with EtOAc and washed with H_2O. The aqueous layer was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 2.5:1 Hex/EtOAc). The ethyl Grignard addition product was obtained with 93% yield.

^{1}H NMR (400 MHz) δ 0.38 (d, J=2.8 Hz, 1H), 0.77 (t, J= 7.4 Hz, 3H), 0.77 (dd, J=6.8, 16.8 Hz, 6H), 1.07 (s, 9H), 1.27 (m, 2H), 1.58 (m, 2H), 1.80 (s, 3H), 1.84 (s, 3H), 2.33 (m, 2H), 2.78 (m, 2H), 3.75 (t, J=6.2 Hz, 2H), 3.82 (d, J=1.6 Hz, 1H), 3.92 (m, 1H), 4.09 (d, J=6.0 Hz, 2H), 7.42 (m, 6H), 7.67 (d, J=6.8 Hz, 4H); ^{13}C NMR (100 MHz) δ 12.61, 13.61, 17.93, 19.17, 23.89, 26.60, 26.76, 26.85, 28.11, 29.25, 33.30, 37.98, 41.03, 53.05, 61.29, 63.90, 64.44, 65.58, 101.10, 104.97, 127.75, 127.77, 129.76, 133.46, 133.60, 135.54, 135.56, 155.55, 164.33, 165.03, 207.36; IR 560.5, 594.9, 612.1, 638.2, 701.6, 739.5, 795.9, 823.7, 896.8, 975.2, 998.0, 1028.1, 1057.0, 1106.6, 1144.3, 1203.4, 1290.7, 1393.1, 1428.0, 1462.6, 1746.8, 1782.7, 1963.6, 2045.7, 2341.7, 2359.2, 2960.0; $[\alpha]^{23}$ = +78.9 (c = 0.59 g/mL)

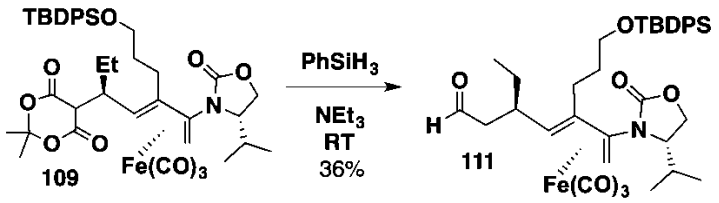
Complex 110



Malonate **109** (74.0 mg, .0924 mmol) was dissolved in 3 mL of methanol under argon. Eschenmoser's salt (36.6 mg, 0.1848 mmol, 2 eq) was added to the solution and the reaction was stirred overnight under reflux at 65 °C. Methanol was removed via rotary evaporation, and the concentrated reaction mixture was diluted in EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 4:1 Hex/EtOAc). The product was obtained with 35 % yield.

^{1}H NMR (400 MHz) δ 0.22 (d, J = 2.8 Hz, 1H), 0.72 (t, J = 7.2 Hz, 3H), 0.89 (dd, J = 6.8, 16 Hz, 7H), 1.07 (s, 9H), 1.52 (m, 1H), 1.63 (d, J = 3.6 Hz, 1H), 1.81 (m, 2H), 1.94 (m, 1H), 2.30 (m, 3H), 2.69 (td, J= 4.8, 12 Hz, 1H), 3.75 (m, 5H), 3.88 (m, 1H), 4.07 (d, J= 6.0 Hz, 2H), 5.56 (d, J = 0.8 Hz, 1H), 6.26 (s, 1H), 7.41 (m, 6H), 7.67 (dd, 4H); ^{13}C NMR (100 MHz) δ 12.74, 13.62, 17.97, 19.19, 24.29, 26.85, 29.16, 33.54, 36.56, 51.70, 61.28, 64.06, 64.47, 126.64, 127.72, 127.76, 129.71, 133.49, 133.70, 135.56, 135.58, 141.99, 166.64, 208.32; IR 596.7, 612.1, 641.7, 661.8, 700.5, 721.0, 737.9, 769.5, 793.8, 823.3, 949.9, 974.3, 997.6, 1012.6, 1027.9, 1054.2, 1087.2, 1104.1, 1138.3, 1165.4, 1202.2, 1236.3, 1312.9, 1392.2, 1426.3, 1463.7, 1727.6, 1740.1, 1967.0, 1982.7, 2043.6, 2360.8, 2958.9 cm^{-1}

Aldehyde 111

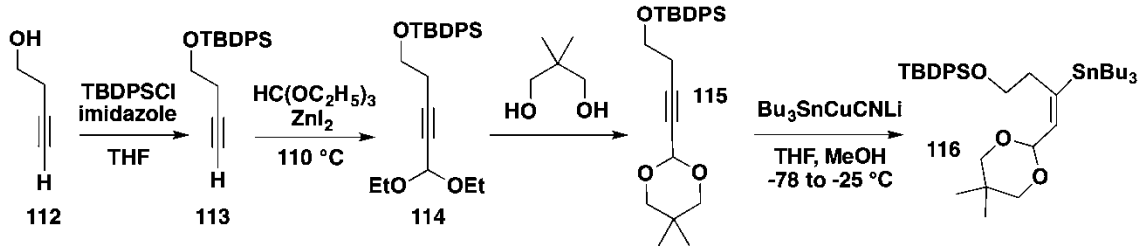


A solution of 0.5 M $PhSiH_3$ and 0.33 M NEt_3 in THF was made beforehand. 0.8 mL (0.4256 mmol, 3 eq of phenylsilane and 0.2837 mmol, 2 eq of triethylamine) of this solution was added to the malonate **109** (0.1136 g, 0.1419 mmol, 1 eq) in the reaction flask. The reaction was stirred for 2 hours at room temperature. 0.14 mL H_2O was added and the reaction was stirred for 15 minutes. The reaction mixture was dissolved in EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 6:1 Hex/EtOAc). Aldehyde **111** was obtained as a wine red foam with 36 % yield.

^{1}H NMR (400 MHz) δ 0.18 (d, J = 3.2 Hz, 1H), 0.58 (d, J = 10 Hz, 1H), 0.81 (m, 3H), 0.89 (m, 7H), 1.06 (s, 9H), 1.52 (m, 2H), 1.73 (d, J = 3.6 Hz, 1H), 1.86 (m, 2H), 2.12 (m, 1H), 2.25 (m, 1H), 2.35 (m, 1H), 2.60 (m 1H), 2.74 (m, 2H), 3.72 (t, 2H), 3.87 (m, 1H), 4.10 (m, 2H) 7.39 (m, 6H), 7.66 (m, 4H), 9.79 (s, 1H); ^{13}C NMR (100 MHz) δ 0.02, 10.28, 13.63, 114.16, 14.22, 17.97, 19.20, 24.28, 26.86, 28.44, 29.26, 29.73, 33.37, 36.49, 37.15, 49.63, 61.32, 63.95, 64.48, 101.18, 104.05, 127.74, 127.79, 127.89, 129.76, 129.80, 133.47, 133.66, 134.03, 134.09, 134.18, 135.57, 135.59, 155.75, 201.40, 207.97; IR 569.0, 594.9, 633.6, 668.2, 701.0, 740.2, 822.8, 974.5, 1028.1, 1057.3, 1105.3, 1202.5, 1392.2, 1427.7, 1462.3, 1723.8, 1751.9, 1962.6, 2045.1, 2341.7, 2360.7, 2929.1 cm^{-1}

Diastereoselective allylation of cyclized oxocarbenium ion

Stannane 116



3-butyn-1-ol (0.4541 mL, 6 mmol, 1 eq) was dissolved in THF (20 mL). Imidazole (1.0212 g, 15 mmol, 2.5 eq) and TBDPSCl (1.8427 mL, 7.2 mmol, 1.2 eq) were added. The reaction was stirred at room temperature overnight. The reaction was quenched with saturated with NH_4Cl and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 40:1 Hex/EtOAc). Protected alcohol **113** was obtained with 95% yield and confirmed with ^1H NMR.

^1H NMR (400 MHz) δ 1.05 (s, 9H), 1.95 (t, J = 2.8 Hz, 1H), 2.45 (td, J = 2.8, 6.8 Hz, 2H), 3.78 (m, 2H), 7.39 (m, 6H), 7.68 (m, 6H)

Alkyne **113** (1.75 g, 5.673 mmol, 1 eq) was dissolved in triethylorthoformate (50 mL) under Ar. ZnI_2 (1.8107 g, 5.673 mmol, 1 eq) was added all at once. The reaction was put into a 110 °C oil bath and stirred for 8.5 hours. The reaction mixture was separated via distillation and the crude product was purified via column chromatography (40:1 Hex/EtOAc with 1% Net_3). Acetal **114** was obtained with 87% yield.

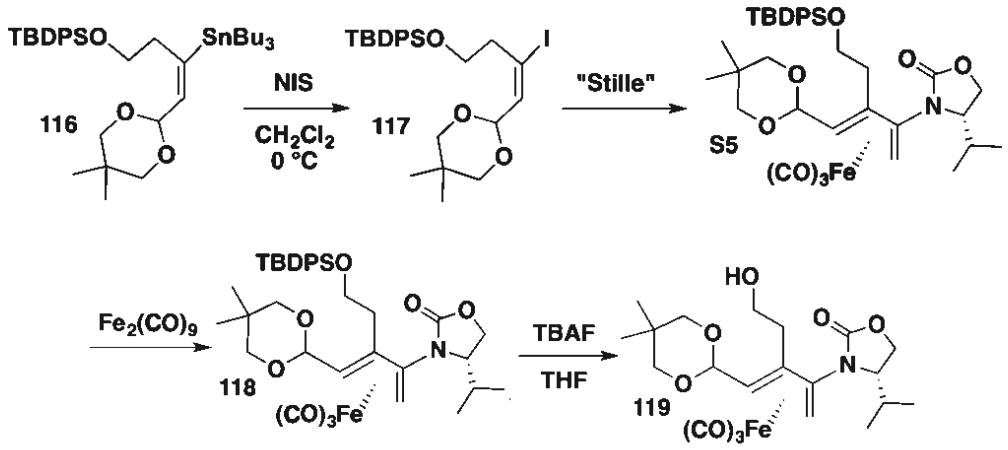
Acetal **114** (2.03 g, 4.944 mmol, 1 eq) was dissolved in CH_2Cl_2 under Ar. Diol (2.574 g, 24.718 mmol, 5 eq) and indium(III) triflate (0.111 g, 0.1977 mmol, 0.4 % mol) were added. The reaction was stirred overnight. The reaction mixture was purified via column

chromatography (basic aluminium oxide, 19:1 Hex/EtOAc, loaded neatly). Acetal **115** was obtained with 75% yield and confirmed with ^{1}H NMR.

^{1}H NMR (400 MHz) δ 0.85 (s, 3H), 0.88 (m, 1H), 1.04 (s, 9H), 1.07 (s, 3H), 1.26 (m, 1H), 2.53 (m, 2H), 3.43 (d, J = 11 Hz, 2H), 3.73 (d, J = 11 Hz, 2H), 3.78 (t, J = 7 Hz, 2H), 5.23 (s, 1H), 7.39 (m, 6H), 7.63 (m, 4H)

$(Bu_3Sn)_2$ (4.105 mL, 8.124 mmol, 2.2 eq) was dissolved in THF (22 mL) under Ar. The solution was cooled to -78 °C and 1.6 M BuLi (4.8468 mL, 7.7548 mmol, 2.1 eq) was added. The reaction was warmed to -40 °C and stirred for 30 minutes. The reaction mixture was re-cooled to -78 °C and CuCN (0.6973 g, 7.3855 mmol, 2 eq) was added. The reaction was stirred at -40 °C for 40 minutes. The reaction was re-cooled to -78 °C and methanol (0.2244 mL, 5.539 mmol, 1.5 eq) was added. Alkyne **115** (1.5607 g, 3.6927 mmol, 1 eq) was dissolved in THF (10 mL) and cooled to -78 °C before being added to the reaction mixture via cannula. The reaction was stirred for 3 hours at -78 °C. The reaction was warmed to -25 °C before being quenched with 9:1 mixture of saturated NH_4Cl and NH_4OH. The mixture was diluted, separated and back extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, hexane with 3% NEt_3). Stannane **116** was obtained with 77% yield and confirmed with ^{1}H NMR.

Alcohol 119



Stannane **116** (2.00 g, 2.802 mmol, 1 eq) was dissolved in CH_2Cl_2 (28 mL) under argon. The solution was cooled to 0 °C and NIS (0.6935 g, 3.0826 mmol, 1.1 eq) was added. The reaction was stirred for 2 hours at 0 °C and quenched with saturated $NaHCO_3$ and saturated Na_2SO_3. The mixture was diluted with EtOAc and the separated organic layer was washed with brine, drived over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 40:1 Hex/EtOAc with 0.5% NEt_3). Iodide **S5** was obtained with 79% yield and confirmed with ^1H NMR.

The following reaction was carried out in the glovebox in N_2 atmosphere. Stannyl vinyl oxazolidinone **99** (0.9843 g, 2.2156 mmol, 1 eq) was dissolved in portions of DMF (11 mL) and transferred to a flask containing vinyl iodide **S5** (1.22 g, 2.2156 mmol, 1 eq). The solution was stirred while $Pd(PPh_3)_4$ (0.2560 g, 0.2216 mmol, 0.1 eq) and CuO_2PPh_2 (0.7154 mg, 2.5479 mmol, 1.15 eq) was added together. The reaction was stirred overnight at room temperature. The reaction mixture was filtered through silica gel in a glass frit. The filtered product was redissolved in Et_2O and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via

column chromatography (silica gel, 4:1). Diene **117** was obtained as yellow oil with 95.4% yield.

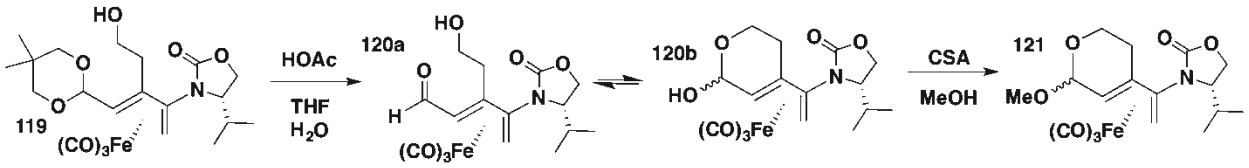
Diene **S5** (1.155 g, 1.9971 mmol, 1 eq) was dissolved in toluene (20 mL) under argon and this solution was cannulated into a flask containing $Fe_2(CO)_9$ (2.5428 g, 6.9898 mmol, 3.5 eq). The reaction was put in a 35 °C oil bath and stirred overnight. The reaction mixture was filtered through silica gel in a glass frit with EtOAc with 0.5% NEt_3. The crude product was purified via column chromatography (7:1 Hex/EtOAc). Complex **118** was obtained with 79% yield.

TBDPS-protected alcohol **118** (400.9 mg, 0.5586 mmol, 1 eq) was dissolved in THF (5 mL). A 1.0 M solution of TBAF in THF (0.6144 mL, 0.6144 mmol, 1.1 eq) was added dropwise. The reaction was stirred for 24 hours at room temperature. The reaction solution was diluted with EtOAc and washed with saturated $NaHCO_3$ and brine. The separated organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 2:1 → 1:1 → 1:1.5 Hex/EtOAc). Alcohol **119** was obtained with 91% yield.

^{1}H NMR (400 MHz) δ 0.39 (d, J = 3.5 Hz, 1H), 0.53 (d, J = 6.9 Hz, 1H), 0.73 (s, 3H), 0.92 (m, 6H), 1.18 (s, 3H), 1.75 (d, J = 3.5 Hz, 1H), 2.38 (m, 1H), 2.47 (m, 1H), 2.98 (m, 1H), 3.15 (m, 1H), 3.47 (q, J = 10 Hz, 25 Hz, 2H), 3.65 (dt, J = 2.7, 13 Hz, 2H), 3.78 (m, 1H), 4.02 (m, 1H), 4.06 (m, 1H), 4.15 (dd, J = 3.7, 9 Hz, 1H), 4.26 (t, J = 9 Hz, 1H), 4.38 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 13.59, 17.94, 21.74, 23.01, 29.07, 29.88, 31.34, 37.49, 56.02, 61.53, 62.15, 64.48, 100.00, 101.80, 102.38, 156.19; IR 561.2, 590.5, 605.9, 630.3, 663.4, 667.8, 701.9, 729.6, 754.6, 773.0, 787.0, 863.6, 906.8, 921.1, 934.1, 977.0, 994.2, 1016.8, 1035.9, 1056.4, 1075.8, 1101.8, 1121.7, 1152.6, 1165.5, 1219.4, 1230.4, 1307.7, 1330.0, 1360.9,

1368.4, 1390.5, 1426.2, 1449.7, 1464.3, 1486.1, 1726.7, 1947.6, 1971.9, 2047.2, 2825.0, 2872.5, 2957.5, 3474.9 cm^{-1}; $[\alpha]^{22}$ = +179.2885 (c = 0.52 g/mL).

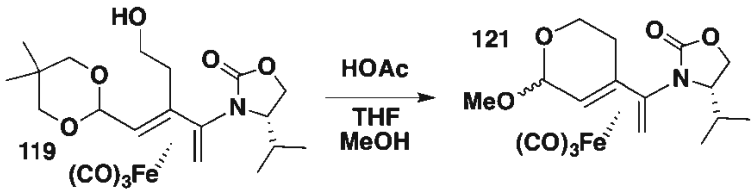
Acetal 121



Acetal **119** (78.2 mg, 0.1632 mmol, 1 eq) was dissolved in 8:5:2 solution of HOAc (2.3 mL), THF (1.5 mL) and H_2O (0.6 mL). The acetal was dissolved in THF first, then H_2O and HOAc were added in order. The reaction was stirred overnight, diluted with EtOAc and washed with 3M NaOH, H_2O and brine. The separated organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was filtered via column chromatography (silica gel, 1:1.5 Hex/EtOAc). The expected aldehyde product **120a** was obtained in a mixture with cyclic hemi-acetal **120b** (78% combined yield).

The product mixture was dissolved in MeOH (1 mL) and camphorsulfonic acid (5.9 mg, 0.0254 mmol, 0.2 eq) was added dropwise. The reaction was stirred overnight at room temperature. The reaction mixture was diluted in EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 2:1 Hex/EtOAc). **121** was obtained as a mixture of diastereomers (78% combined yield).

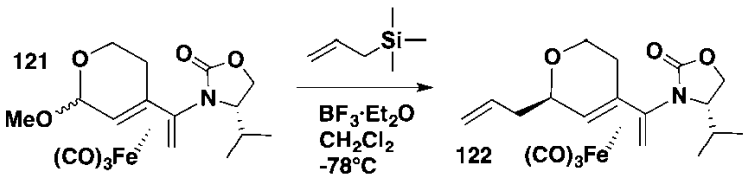
*Acetal **121** was also synthesized directly from **119**.



Acetal **119** (200.2 mg, 0.4177 mmol, 1 eq) was dissolved in 8:5:2 solution of HOAc (5.87 mL), THF (3.67 mL) and MeOH (1.47 mL). The acetal was dissolved in THF first, then MeOH and HOAc were added in order. The reaction was stirred overnight, diluted with EtOAc and washed with 3M NaOH, H_2O and brine. The separated organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was filtered via column chromatography (silica gel, 2:1 Hex/EtOAc). **121** was obtained as a mixture of diastereomers (81% combined yield).

^{1}H NMR (400 MHz) δ 0.02 + 0.09 (d, J = ~3 Hz, 1H), 0.73 (d, 1H), 0.93 (m, 6H), 1.62 + 1.70 (d, J = ~3 Hz, 1H), 2.36 + 2.58 (m, 2H), 2.91 + 3.08 (m, 1H), 3.39 + 3.49 (3H), 3.60 + 3.75 (m, 1H), 3.89 + 3.94 (m, 2H), 4.18 (m, 1H), 4.31 (t, J = 9 Hz, 1H), 4.80 + 4.89 (d, 1H); ^{13}C NMR (100 MHz) δ 13.63, 13.76, 17.99, 24.74, 25.27, 28.76, 28.85, 33.15, 35.26, 53.17, 54.81, 55.16, 56.31, 57.02, 59.87, 61.72, 62.05, 63.11, 63.77, 98.28, 99.32, 99.64, 100.11; IR 555.2, 559.2, 563.6, 566.2, 568.4, 577.2, 603.6, 620.1, 667.7, 676.0, 943.7, 975.4, 1039.9, 1056.8, 1078.1, 1133.3, 1151.9, 1207.3, 1393.8, 1409.2, 1738.9, 1746.4, 1756.2, 1968.5, 2046.3, 2050.5, 2961.1; $[\alpha]^{23}$ = +264.3883 (c = 0.455 g/mL)

Dihydropyran 122

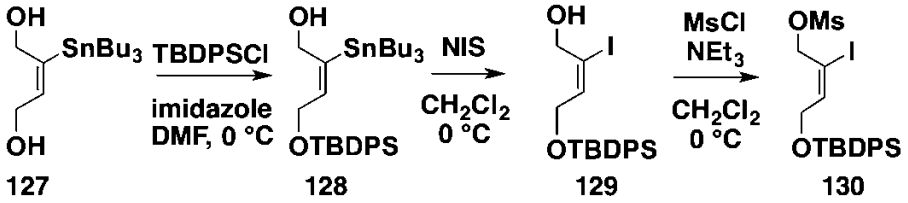


Acetal **121** (36.6 mg, 0.0896 mmol, 1 eq) was dissolved in CH_2Cl_2 (1 mL) under Ar. Trimethyl allylsilane (0.0427 mL, 0.2690 mmol, 3 eq) was added and the reaction solution was cooled to -78 °C. BF_3•Et_2O (0.0332 mL, 0.2690 mmol, 3 eq) was added dropwise. The reaction was stirred at -78 °C for 3 hours and quenched with saturated $NaHCO_3$. The mixture was diluted with EtOAc and the separated aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 2.5:1 Hex/EtOAc). *The reaction had previously been stirred overnight as it warmed to room temperature but the starting material was fully recovered. It was found that the reaction proceeds when stirred at -78 °C for 2-3 hours. The same reaction repeated with 5 eq of trimethyl allylsilane did not improve the yield (35% → 30%). The product of both attempts was confirmed with proton NMR but not fully characterized.

^{1}H NMR (400 MHz) δ 0.07 (d, J = 3.6 Hz, 1H), 0.70 (m, 1H), 0.95 (m, 6H), 1.58 (s, 1H), 1.71 (d, J = 3.6 Hz, 1H), 2.34 (m, 2H), 2.46 (m, 1H), 2.79 (m, 2H), 3.70 (m, 2H), 3.97 (m, 1H), 4.05 (m, 1H), 4.18 (m, 1H), 4.32 (t, J = 9 Hz, 1H), 5.13 (m, J = 14 Hz, 2H), 5.84 (m, 1H)

Diazo-transfer and intramolecular Rh(II)-catalyzed C-H insertion

Mesylate 130



Diol vinyl stannane **127** was prepared using the procedure found in Pour et al. (*Org. Lett.,* 2015, **17**, 520-523).

127 (1.83 g, 4.85 mmol, 1 eq) was dissolved in DMF (35 mL). The solution was cooled to 0 °C under Ar. Imidazole (330 mg, 4.85 mmol, 1 eq) and TBDPSCl (1.24 mL, 4.85 mmol, 1 eq) was added. The solution was stirred for 6 hours at 0 °C and ice (1.5 g) was added. The reaction solution was diluted in Et_2O and washed with saturated NH_4Cl and brine. The separated organic layer was dried in $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (30:1 Hex/EtOAc with 1% NEt_3). Stannane **128** was isolated and carried onto the next reaction.

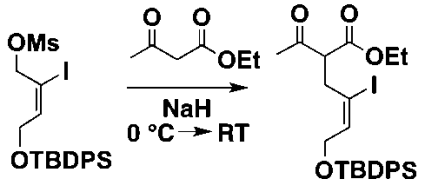
Alcohol **128** (826 mg, 1.3419 mmol, 1 eq) was dissolved in CH_2Cl_2 (13 mL) and cooled to 0 °C. NIS (362.3 mg, 1.6102 mmol, 1.2 eq) was added all at once. The reaction was stirred at 0 °C for 2 hours. The reaction was quenched with a mixture of saturated $NaHCO_3$ and Na_2SO_3 and diliuted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (9:1 Hex/EtOAc with 1% NEt_3). Iodide **129** was obtained with 92% yield and confirmed with ^1H NMR.

^1H NMR (400 MHz) δ 0.75 (s, 3H), 1.20 (s, 3H), 2.54 (t, J = 7 Hz, 1H), 3.49 (m, 2H), 3.64 (m, 2H), 4.32 (d, J = 6.5 Hz, 1H), 5.17 (d, J = 4.8 Hz, 1H), 6.39 (m, 1H)

Alcohol **129** (535.1 mg, 1.1827 mmol, 1 eq) was dissolved in CH_2Cl_2 (12 mL) under Ar. The reaction was cooled to 0 °C then NEt_3 (0.4121mL, 2.9568 mmol, 2.5 eq) and MsCl (0.1831 mL, 2.3654 mmol, 2 eq) were added. The reaction was stirred for 4 hours at 0 °C. The reaction mixture was quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 9:1 Hex/EtOAc). Mesylate **130** was obtained with 95% yield. The product could not be characterized beyond 1H and 13C NMR spectroscopy as we observed discoloration (clear oil to reddish orange) of the product and suspected rapid decomposition. The product was quickly carried on to the next reaction.

^{1}H NMR (400 MHz) δ 1.05 (s, 9H), 1.56 (s, 1H), 3.01 (s, 3 H), 4.24 (d, J = 6.3 Hz, 2H), 4.71 (d, J= 0.5 Hz, 2H), 6.66 (m, 1H), 7.42 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (100 MHz) δ 19.12, 26.70, 38.79, 61.85, 71.12, 92.34, 127.91, 130.02, 132.69, 135.54, 147.15

Keto ester 131

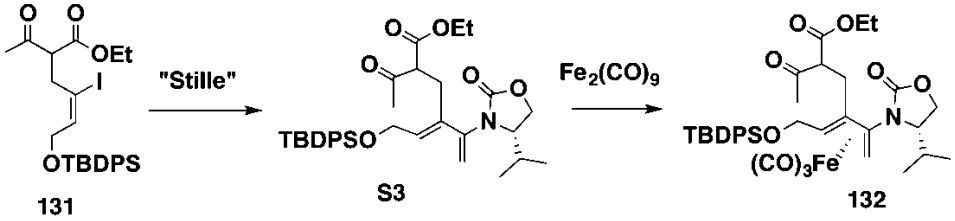


130 131

A solution of NaH, 60% mineral oil, (67.09 mg, 1.6775 mmol, 1.5 eq) in 5 mL of THF was cooled to 0°C. Ethyl acetoacetate (0.2854 mL, 2.2367 mmol, 2 eq) was added dropwise and the reaction was stirred for 45 minutes at room temperature. The reaction was recooled to 0 °C and a solution of mesylate iodide **130** (593.4 mg, 1.1183 mmol, 1 eq) in THF (3 mL) was cannulated into the flask. A 3 mL THF rinse was also cannulated. The reaction was stirred over 3 days and quenched with NH_4Cl. The reaction mixture was diluted with EtOAc and the separated aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (12:1 Hex/EtOAc). Keto ester **131** was obtained with 98% yield.

^{1}H NMR (400 MHz) δ 1.04 (t, J = 3.0 Hz, 9H), 1.20 (t, J = 7.1 Hz, 3H), 2.22 (d, J = 0.16 Hz, 3H), 2.65 (d, J = 7.2 Hz, 2H), 3.82 (t, J = 7.2 Hz, 1H), 4.10 (m, 2H), 4.21 (m, 2H), 6.41 (m, 1H), 7.39 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (100 MHz) δ 14.01, 19.15, 26.75, 30.07, 37.10, 58.62, 61.60, 61.70, 99.53, 127.75, 129.76, 129.79, 133.23, 133.25, 135.57, 143.71, 168.17, 201.33; IR 613.5, 702.8, 740.2, 784.3, 823.1, 856.9, 998.3, 1028.3, 1111.7, 1149.3, 1177.5, 1223.9, 1250.3, 1301.3, 1359.9, 1390.6, 1427.8, 1445.1, 1472.2, 1636.6, 1719.4, 1743.3, 2857.3, 2893.6, 2931.2, 2959.0, 3048.7, 3070.8 cm^{-1}

Iron(0) complex 132

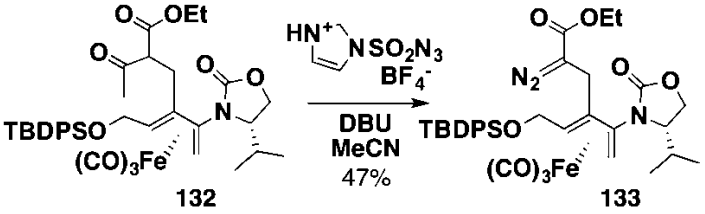


This reaction was carried out under N_2 atmosphere in the glovebox. Vinyl iodide **131** (549.1 mg, 0.9742 mmol, 1 eq) was transferred to the flask containing vinyl stannane **99** (434.7 mg, 0.9785 mmol, 1 eq) with DMF (5 mL). $Pd(PPh_3)_4$ (112.57 mg, 0.09742 mmol, 0.1 eq) and CuO_2PPh_2 (314.5 mg, 1.1203 mmol, 1.15 eq) was added together. The solution was stirred overnight. The reaction mixture was filtered through silica in a glass frit and rinsed with EtOAc. The filtrate was concentrated *in vacuo* and dissolved in Et_2O. The solution was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified via column chromatography (silica gel, 3:1 Hex/EtOAc). Diene **S3** obtained with 73% yield. Due to concerns about decomposition of the product, considering the easily decomposing nature of Stilled-coupled dienes and the previous compounds, the product was carried on to the next reaction without characterization.

$Fe_2(CO)_9$ (0.9136 g, 2.5115 mmol, 3.5 eq) was dissolved in toluene (4 mL) under Ar and cannulated into a flask containing diene **S3** (0.4244 g, 0.7176 mmol, 1 eq). The flask containing $Fe_2(CO)_9$ was rinsed with 1.5 mL of toluene twice and the rinse was cannulated as well. The reaction was heated to 35 °C and stirred overnight (20 hour). The reaction mixture was filtered through silica gel in a glass frit with EtOAc with 2% NEt_3. The crude product was purified via column chromatography (silica gel, 1:1 Hex/EtOAc with 1% NEt_3, repeated with 4:1 Hex/EtOAc). Complex **132** was obtained with 21% yield.

^{1}H NMR (400 MHz) δ 0.15 (m, 1H), 0.33 (s, 1H), 0.90 (m, 3H), 0.95 (t, J=6.6 Hz, 3 H), 1.07 (s, 9H), 1.25 (m, 3H), 1.54 (s, 2H), 1.78 (t, J=4 Hz, 1H), 2.18 (s, 1H), 2.28 (s, 1H), 2.74 (m, 1H), 3.13 (m, 1H), 3.78 (m, 1H), dd, J=4, 11 Hz, 1H), 4.15 (m, 4H), 4.60 (m, 1H), 7.39 (m, 6H), 7.64 (m, 4H); ^{13}C NMR (100 MHz) δ 13.60, 14.03, 14.14, 18.10, 18.15, 19.06, 19.10, 26.50, 26.84, 26.86, 28.65, 29.68, 29.78, 30.86, 59.44, 60.42, 61.40, 61.78, 62.01, 62.12, 62.84, 64.19, 127.86, 129.92, 129.96, 133.16, 135.44, 135.46, 135.62, 168.75, 169.86, 201.35; IR 603.0, 667.7, 755.9, 823.1, 1032.4, 1055.8, 1112.7, 1154.0, 1215.3, 1370.3, 1392.8, 1409.5, 1427.9, 1463.4, 1484.1, 1644.0, 1716.1, 1747.7, 1978.8, 2054.5, 2341.3, 2359.7, 2858.5, 2931.9, 2962.9, 3016.0, 3072.6, 3439.1 cm^{-1}; $[\alpha]^{22}$ = +176.47 (c = 0.375 g/mL)

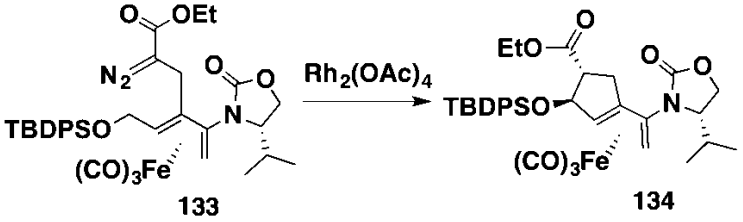
Diazo ester 133



β-keto ester **132** (90.2 mg, 0.1234 mmol, 1 eq) was dissolved in MeCN (1 mL) and the solution was cooled to 0 °C. Imidazole-1-sulfonyl azide tetraflouroborate (48.31 mg, 0.1851 mmol, 1.5 eq) and DBU (54.4 μL, 0.3703 mmol, 3 eq) was added successively. The reaction was stirred for 1 hour at 0 °C then overnight (18.5 hour) at room temperature. The reaction mixture was diluted in EtOAc and washed with H_2O then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 4:1 Hex/EtOAc). Compound **133** was obtained with 47% yield.

^{1}H NMR (400 MHz) δ 0.20 (d, J=3.2 Hz, 1H), 0.50 (t, J=6.8 Hz, 1H), 0.92 (q, J=7.2 Hz, 6H), 1.06 (s, 9H), 1.24 (t, J=7.0 Hz, 3H), 1.78 (d, J=3.6 Hz, 1H), 2.36 (sextet, J=3.6 Hz, 1H), 3.13 (d, J=16 Hz, 1H), 3.62 (d, J=16 Hz, 1H), 3.75 (m, 2H), 4.05 (s, 1H), 4.15 (m, 3H), 4.35 (s, 1H), 7.39 (m, 6H), 7.64 (m, 4H); ^{13}C NMR (100 MHz) δ 13.61, 14.45, 18.04, 19.04, 26.77, 29.17, 36.97, 57.37, 61.08, 61.79, 63.31, 64.01, 98.57, 102.19, 127.76, 129.77, 129.82, 133.17, 133.19, 135.53, 135.60, 156.40, 166.69; IR 702.6, 736.6, 823.5, 909.9, 1058.1, 1112.4, 1154.8, 1208.8, 1314.3, 1371.3, 1392.7, 1427.6, 1462.9, 1687.6, 1754.1, 1995.3, 2054.2, 2088.6, 2857.7, 2962.2, 3071.7 cm^{-1}; $[\alpha]^{22}$ = +152.137 (c = 0.535 g/mL)

Cyclopentene 134



133 134

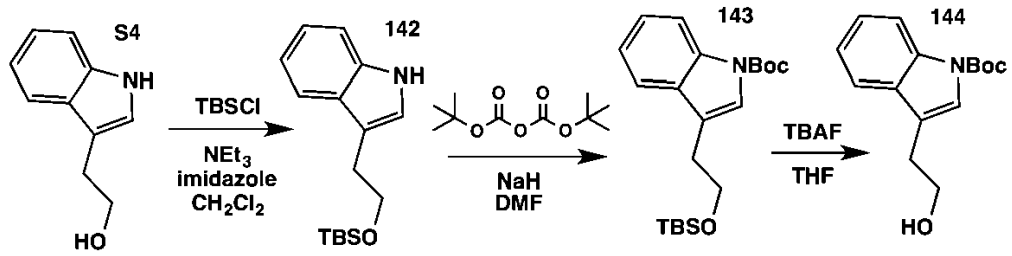
Diazo compound **133** (19.2 mg, 0.0268 mmol) was dissolved in CH_2Cl_2 (0.5 mL) under Ar. Rhodium(II) acetate catalyst (0.2369 mg, 0.0005 mmol, 0.2 eq.) was added and the mixture was stirred for 4 hours. The crude product was purified via column chromatography (silica gel, 4:1 Hex/EtOAc).

^{1}H NMR (400 MHz) δ -0.84 (d, J=3.4, 1H), 0.64 (s, 1H), 0.91 (d, J=7.2, 3H), 1.00 (s, 9H), 1.02 (d, J=7.2, 3H), 1.26 (m, 1H), 1.33 (t, J=7.2, 3H), 1.88 (d, J=3.1, 1H), 2.35 (m, 1H), 2.79 (dd, J=7.8, 15, 1H), 3.20 (m, 1H), 3.41 (dd, J=9.4, 15, 1H), 4.15 (m, 3H), 4.33 (m, 2H), 4.88 (d, J = 6.0 Hz, 1H), 7.39 (m, 6H), 7.63 (dd, 4H); ^{13}C NMR (100 MHz) δ 14.07, 14.14, 17.85, 19.25, 28.86, 29.70, 30.21, 31.59, 33.00, 49.53, 60.44, 61.06, 61.96, 62.89, 77.88, 100.88, 108.84, 127.61, 127.86, 129.73, 129.96, 133.02, 134.68, 135.64, 135.66, 155.42, 170.80, 209.51; IR 702.6, 1057.8, 1111.3, 1160.5, 1197.0, 1240.5, 1346.7, 1393.1, 1427.9, 1463.1, 1755.1, 1988.6, 2051.7, 2931.3 cm^{-1}; $[\alpha]^{22}$ = +67.7213 (c = 0.61 g/mL)

Enantiomerically pure precursor to the Pictet-Spengler condensation

Scheme 20:

Alcohol 144



Hydroxy indole **S4** (2.00 g, 12.4 mmol, 1 eq) was dissolved in CH_2Cl_2 (20 mL) under argon. Net_3 (1.73 mL, 12.4 mmol, 1 eq), imidazole (0.422 g, 6.2 mmol, 0.5 eq) and TBSCl (2.06 g, 13.6 mmol, 1.1 eq) was added in respective order. The reaction was stirred overnight at room temperature and quenched with saturated NH_4Cl. The reaction mixture was diluted with EtOAc and the separated aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 9:1 Hex/EtOAc).

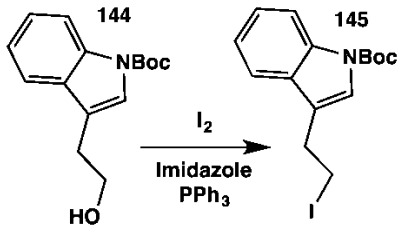
The obtained product **142** was dissolved in DMF in N_2 atmosphere inside the glovebox. The reaction flask was put under Ar outside the glovebox and cooled to 0 °C. NaH, 60% in mineral oil, (0.5455 g, 13.64 mmol, 1.1 eq) was added to the reaction, which was stirred for 30 minutes. Boc_2O (3.134 mL, 13.64 mmol, 1.1 eq) was added and the reaction was stirred at room temperature for 2 hours. The reaction was quenched with H_2O and extracted with Et_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was carried on to the next reaction.

Crude **143** was dissolved in THF (75 mL) open to air. TBAF (13.64 mL, 13.64 mmol, 1.1 eq) was added dropwise. The reaction solution was stirred overnight and concentrated

in vacuo down to 25 mL. The solution was diluted in EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified via column chromatography (silica gel, 3:1 Hex/EtOAc). Alcohol **144** was obtained with 85% yield and confirmed with ^1H NMR.

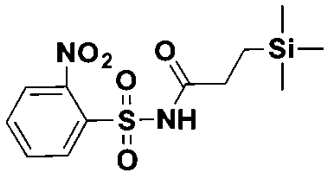
^1H NMR (400 MHz) δ 1.51 (m, 1H), 1.67 (s, 9H), 2.97 (m, 2H), 3.93 (m, 2H), 7.25 (m, 1H), 7.33 (m, 1H), 7.47 (s, 1H), 7.53 (m, 1H)

Iodide 145



Alcohol **144** (511.5 mg, 1.9574 mmol, 1 eq) was dissolved in MeCN (2 mL) and Et_2O (2 mL) under Ar. Imidazole (0.1732 g, 2.5446 mmol, 1.3 eq) and PPh_3 (0.6161 g, 2.3488 mmol, 1.2 eq) were added together. Solid I_2 (0.6458 g, 2.5446 mmol, 1.3 eq) were added slowly. The reaction was stirred slowly at room temperature for 30 minutes, then quenched with saturated Na_2SO_3 dropwise and diluted in EtOAc. The separated aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product could not be purified via column chromatography as it was not soluble in eluent. Recrystallization of the product was attempted in 4 mL of toluene at 55 °C but excess PPh_3 came out of solution instead. Crystallized PPh_3 was removed and the process was repeated once more in 5 mL of 1:1 Hex/toluene solution at 90 °C to remove more PPh_3. The impure product mixture (crude NMR included) was carried onto the next reaction.

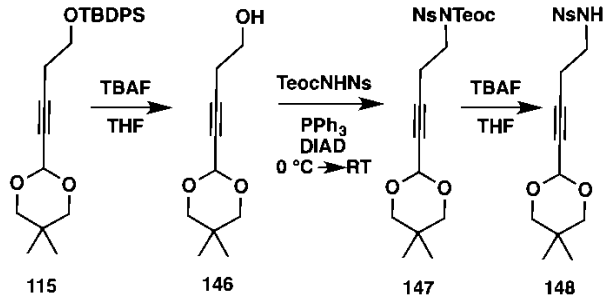
Teoc- protected nosylamine S5



NaH, 60% dispersion in mineral oil, (100 mg, 2.5 mmol, 1 eq) was dissolved in THF (12.5 mL) under Ar and cooled to 0 °C. 2-Nitrobenzenesulfonamide (505.5 mg, 2.5 mmol, 1 eq) was added in portions. The reaction was stirred at room temperature for 1 hr and 10 min. The solution was cooled to 0 °C again and 4-nitrophenyl trimethylsilyl ethyl carbonate (708.4 mg, 2.5 mmol, 1 eq) was added. The solution was stirred at room temperature for 24 hours; a color change from yellow to orange was observed. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The solution was washed with 3M NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 3:1 Hex/EtOAc with 1% formic acid).

^{1}H NMR (400 MHz) δ 0.01 (m, 9H), 1.01 (m, 2H), 4.21 (m, 2H), 7.82 (m, 4H), 8.39 (m, 1H); ^{13}C NMR (100 MHz) δ -1.61, 17.38, 66.32, 125.13, 131.60, 132.60, 133.47, 134.91, 150.15

Nosylamine 148



An impure mixture of protected-alcohol **115** (179,0 mg, 0.4235 mmol, 1 eq) was dissolved in THF (4.2 mL). A 1.0 M solution of TBAF in THF (0.445 mL, 0.445 mmol, 1.05 eq) was added and the reaction was stirred at room temperature for 3.5 hours. The reaction solution was diluted with EtOAc and washed with saturated $NaHCO_3$. The separated organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 3:1 → 1:1 Hex/EtOAc). An impure mixture of alcohol **146** was obtained and used for the next reaction.

146 (assume 0.4117 mmol, 1 eq) was dissolved in THF (2 mL). PPh_3 (119 mg, 0.4529 mmol, 1.1 eq) and TeocNHNs **S5** (157 mg, 0.4529 mmol, 1.1 eq) were added together. The solution was cooled to 0 °C before DIAD (0.088 mL, 0.4529 mmol, 1.1 eq) was added. Bath was removed after 5 minutes and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and purified via column chromatography (silica gel, 5:1 Hex/EtOAc). Tertiary amine **147** was obtained with 73% yield.

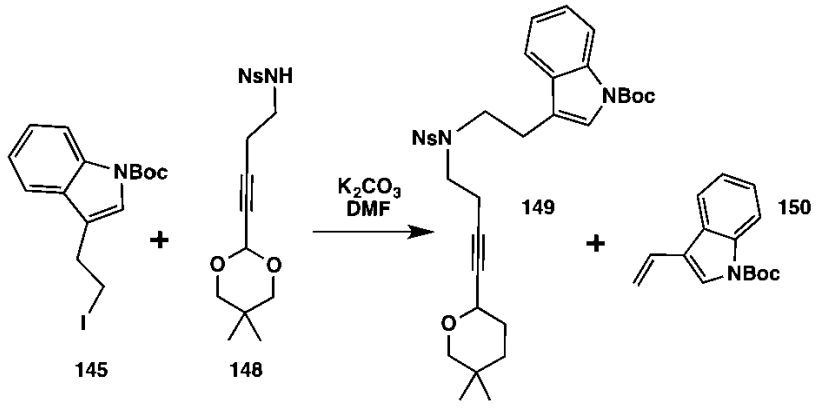
^{1}H NMR (400 MHz) δ 0.01 (s, 9H), 0.89 (s, 3H), 0.99 (m, 2H), 1.09 (s, 3H), 2.74 (m, 2H), 3.45 (d, J=11.4 Hz, 2H), 4.03 (m, 2H), 4.21 (m, 2H), 5.32 (s, 1H), 7.77 (m, 3H), 8.40 (m, 1H); ^{13}C NMR (100 MHz) δ -1.65, 17.52, 20.26, 22.23, 22.66, 30.39, 45.79, 66.77, 75.46, 77.45, 82.12, 90.50, 124.45, 131.73, 132.73, 134.55, 134.59, 147.92, 151.81; IR 657.5, 698.2, 742.0,

853.4, 926.8, 984.5, 1017.1, 1093.2, 1172.5, 1217.2, 1390.5, 1441.2, 1544.2, 1591.5, 1731.7, 2253.8, 2869.5, 2957.1, 3102.6 cm^{-1}

Tertiary amine **147** (154.4 mg, 0.3012 mmol, 1 eq) was dissolved in THF (3 mL). TBAF, 1.0M in THF, (0.33 mL, 0.3313 mmol, 1.1 eq) was added dropwise open to air. The reaction was stirred overnight and concentrated *in vacuo*. The solution was diluted in EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified via column chromatography (silica gel, 1.5:1 Hex/EtOAc). Nosylamine **148** was obtained with 87.6% yield.

^1H NMR (400 MHz) δ 0.84 (s, 3H), 1.10 (s, 3H), 2.52 (sextet, J=1.6 Hz, 2H), 3.30 (dd, J=6.7, 13 Hz, 2H), 3.68 (dd, J=1.16, 10.44 Hz, 2H), 5.18 (t, J=1.4 Hz, 1H), 5.75 (t, J= 6.1 Hz, 1H), 7.75 (m, 2H), 7.90 (m, 1H), 8.13 (m, 1H); ^{13}C NMR (100 MHz) δ 20.05, 22.06, 22.67, 30.32, 42.17, 75.94, 77.89, 81.66, 90.54, 125.73, 130.88, 132.98, 133.67, 133.87, 147.98; IR 668.2 730.0 783.7 916.2, 959.6, 984.0, 1013.9, 1090.2, 1128.1, 1166.4, 1309.9, 1360.6, 1470.2, 1537.9, 1593.7, 2255.3, 2341.3, 2359.9, 2869.4, 2958.2, 3097.2, 3344.4 cm^{-1}

Alkyne 149

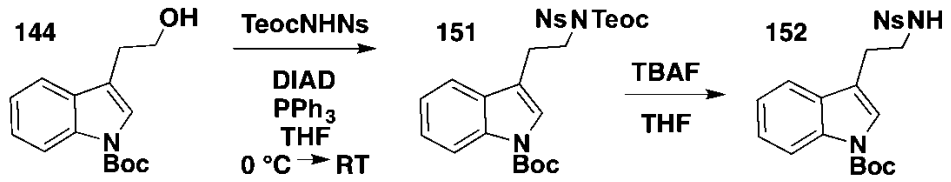


Alkyne **148** (97.2 mg, 0.3005 mmol, 1 eq) was dissolved in DMF (3 mL) under argon. Iodide **145** (111.5 mg, 0.3005 mmol, 1 eq) and potassium carbonate (124.6 mg, 0.9016 mmol, 3 eq) were added. The reaction was stirred at room temperature for 36 hours. The reaction mixture was diluted with Et_2O and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 2.5:1 → 1.5:1 Hex/EtOAc). We obtained 18% yield of product **149**. 70% of starting material (alkyne **148**) was recovered.

^1H NMR (400 MHz) δ 0.85 (s, 3H), 1.10 (s, 3H), 1.66 (s, 9H), 2.63 (t, J = 8 Hz, 2H), 2.97 (t, J = 8 Hz, 2H), 3.43 (d, J = 11 Hz, 2H), 3.67 (m, 6H), 5.23 (s, 1H), 7.20 (m, 1H), 7.29 (m, 1H), 7.31 (m, 1H), 7.36 (1H), 7.45 (m, 1H), 7.54 (m, 2H), 7.72 (d, 1H), 8.05 (d, 1H); ^{13}C NMR (100 MHz) δ 19.25, 22.11, 22.67, 24.03, 28.18, 29.70, 30.35, 45,71, 47.38, 75.84, 77.52, 82.53, 83.62, 90.63, 115.35, 116.12, 118.58, 122.61, 123.66, 124.07, 124,41, 129.82, 130.59, 131.48, 133.19, 133.32, 135.37, 147.50, 149.40

Scheme 21:

Nosylamine 152



Alcohol **144** (96.9 mg, 0.371 mmol, 1 eq) was was dissolved in THF (1.9 mL). PPh_3 (97.3 mg, 0.371 mmol, 1 eq) and TeocNHNs **S5** (117 mg, 0.371 mmol, 1 eq) were added together. The solution was cooled to 0 °C before DIAD (0.072 mL, 0.371 mmol, 1 eq) was added. Bath was removed after 5 minutes and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and purified via column chromatography (silica gel, 5:1 Hex/EtOAc). Tertiary amine **151** was obtained with 89% yield.

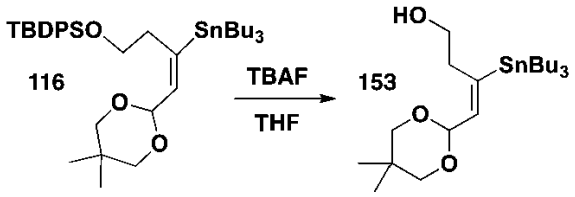
^{1}H NMR (400 MHz) δ 0.84 (m, 2H), 1.68 (s, 9H), 3.17 (m, 2H), 4.12 (m, 4H), 7.24 (m, 1H), 7.33 (m, 1H), 7.50 (s, 1H), 7.67 (m, 1H), 7.76 (m, 3H), 8.15 (d, J = 6 Hz, 1H), 8.39 (d, J = 2Hz, 1H); ^{13}C NMR (100 MHz) δ -1.93, -1.67, -1.42, 17.25, 26.42, 28.21, 47.52, 66.59, 83.53, 115.29, 116.61, 119.03, 122.55, 123.78, 124.43, 130.32, 131.70, 132.90, 134.43, 134.50, 135.53; IR 745.8, 836.3, 1093.4, 1159.0, 1251.1, 1308.3, 1359.9, 1453.5, 1542.5, 17.27.6, 2954.8 cm^{-1}

Tertiary amine **151** (193.8 mg, 0.3286 mmol, 1 eq) was dissolved in THF (3.3 mL). TBAF, 1.0M in THF, (0.36 mL, 0.3615 mmol, 1.1 eq) was added dropwise open to air. The reaction was stirred overnight and concentrated *in vacuo*. The solution was diluted in EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified via column

chromatography (silica gel, 2.5:1 Hex/EtOAc). Nosylamine **152** was obtained with 98% yield.

^{1}H NMR (400 MHz) δ 1.66 (s, 9H), 2.93 (m, 2H), 3.51 (q, J = 6.7 Hz, 2H), 5.39 (t, J = 5.6 Hz, 1H), 7.14 (m, 1H), 7.25 (m, 1H), 7.31 (m, 2H), 7.52 (m, 1H), 7.59 (m, 1H), 7.70 (m, 1H), 7.92 (m, 1H), 8.05 (m, 1H); ^{13}C NMR (100 MHz) δ 25.52, 28.17, 43.30, 83.80, 115.43, 115.90, 118.49, 122.52, 123.93, 124.51, 125.23, 129.52, 130.51, 132.55, 133.26, 133.57, 135.55, 147.41, 149.33; IR 559.9, 595.9, 656.6, 728.3, 748.4, 759.9, 819.3, 831.7, 855.3, 931.4, 943.3, 1022.9, 1045.8, 1092.9, 1123.4, 1162.5, 1226.2, 1255.8, 1273.5, 1298.0, 1350.2, 1364.4, 1384.4, 1422.0, 1456.1, 1594.7, 1723.3, 2359.5, 2949.3, 2986.3, 3094.5, 3325.5 cm^{-1}

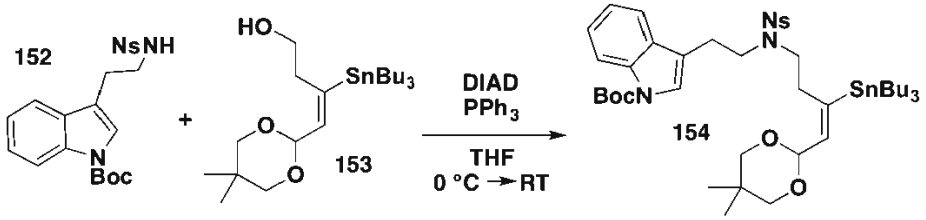
Alcohol 153



Stannane **116** (406.4 mg, 0.5694 mmol, 1 eq) was dissolved in THF (5.7 mL). TBAF, 1.0M in THF, (0.63 mL, 0.6264 mmol, 1.1 eq) was added dropwise open to air. The reaction was stirred overnight and concentrated *in vacuo*. The solution was diluted in EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 7:1 Hex/EtOAc with 0.5% Net_3). Alcohol **153** was obtained with 84% yield.

^{1}H NMR (400 MHz) δ 0.74 (s, 3 H), 0.91 (m, 14H), 1.31 (m, 9H), 1.48 (m, 6H), 2.50 (t, J = 5.4 Hz, 1H), 2.63 (t, J = 5.4 Hz, 2H), 3.52 (d, J = 10.6 Hz, 2H), 3.62 (m, 4H), 5.15 (d, J = 5.5 Hz, 1H), 5.83 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 8.01, 8.09, 9.67, 11.33, 13.65, 21.92, 23.01, 27.10, 27.39, 27.68, 28.91, 29.00, 29.10, 30.01, 37.31, 60.90, 97.13, 139.39, 149.28; IR 874.4, 931.1, 965.7, 984.7, 1021.3, 1042.3, 1073.4, 1105.2, 1142.4, 1215.6, 1231.6, 1308.7, 1338.5, 1378.0, 1417.5, 1464.3, 2851.2, 2870.4, 2925.8, 2955.3, 3424.4 cm^{-1}

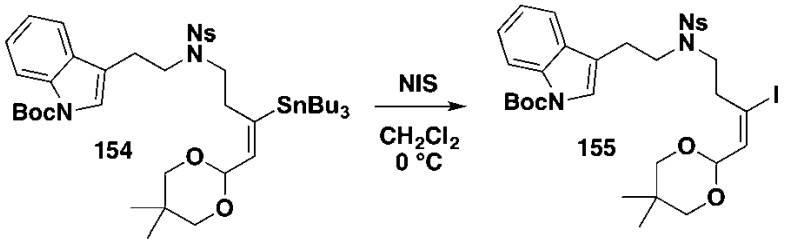
Stannane 154



Alcohol **153** (81.9 mg, 0.1724 mmol, 1 eq) was dissolved in THF (2 mL) under Ar. Sulfonamide **152** (76.8 mg, 0.1724 mmol, 1 eq) and PPh_3 (90.43 mg, 0.3448 mmol, 2 eq) were added together. The reaction was cooled to 0 °C and DIAD (66.8 μL, 0.3448 mmol, 2 eq) was added dropwise. The reaction was stirred at room temperature for 24 hours and checked by TLC. When the reaction didn't seem to have gone to completion, the reaction was cooled to 0 °C and 2 eq of both PPh_3 (90.43 mg, 0.3448 mmol) and DIAD (66.8 μL, 0.3448 mmol) were added. The reaction was stirred for another 24 hours and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 6:1 Hex/EtOAc with 0.5% NEt_3). Nosylamine **154** was obtained with 66% yield.

^1H NMR (400 MHz) δ 0.69 (s, 3H), 0.88 (m, 9H), 0.96 (m, 5H), 1.21 (s, 3H), 1.31 (m, 6H), 1.49 (m, 5H), 1.56 (s, 3H), 1.65 (s, 9H), 2.73 (t, J = 8.4 Hz, 1 H), 2.96 (t, J = 7.4, 2 H), 3.40 (m, 2H), 3.51 (d, J = 10.8 Hz, 2H), 3.62 (m, 4H), 5.20 (d, J = 5.6 Hz, 1H), 0.78 (d, J = 5.6 Hz, 1H), 7.22 (m, 1H), 7.29 (m, 3H), 7.46 (d, J = 8.0 Hz, 1H), 7.52 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 9.61, 11.20, 13.67, 21.51, 23.05, 24.17, 27.12, 27.40, 27.69, 28.17, 28.96, 29.00, 29.05, 29.15, 29.70, 34.18, 47.34, 47.44, 83.59, 97.30, 115.37, 116.29, 118.57, 122.56, 123.54, 123.95, 124.41, 129.82, 130.27, 131.22, 133.05, 133.51, 139.88, 146.90, 147.53; IR 760.4, 852.2, 965.2, 985.9, 1019.8, 1093.5, 1158.9, 1257.4, 1308.5, 1377.5, 1455.2, 1544.8, 1732.6, 2852.0, 2927.3, 2955.7 cm^{-1}

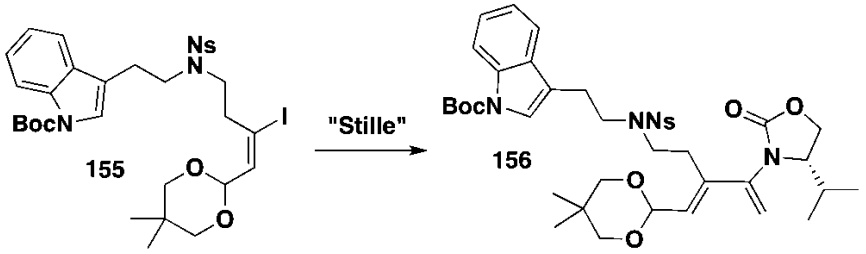
Vinyl iodide 155



Vinyl stannane **154** (106.0 mg, 0.1174 mmol, 1 eq) was dissolved CH_2Cl_2 (1 mL) under Ar and cooled to 0 °C. NIS (31.69 mg, 0.1409 mmol, 1.2 eq) was added at once and reaction was stirred for 2 hours at 0 °C. The reaction was quenched with a mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$, and diluted with EtOAc. The separated organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 4:1 Hex/EtOAc with 0.5% NEt_3). Vinyl iodide **155** was obtained with 89% yield.

^{1}H NMR (400 MHz) δ 0.71 (s, 3H), 1.18 (s, 3H), 1.66 (s, 9H), 2.93 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 3.49 (d, J = 10.4 Hz, 2H), 3.62 (m, 5H), 5.10 (d, J = 5.6 Hz, 1H), 6.38 (d, J = 5.6 Hz, 1H), 7.22 (m, 1H), 7.27 (m, 1H), 7.38 (m, 2H), 7.47 (dd, J = 7 Hz, 1H), 7.55 (m, 2H), 7.80 (d, 1H), 8.15 (d, 1H); ^{13}C NMR (100 MHz) δ 21.80, 22.95, 24.08, 28.19, 29.70, 30.03, 40.95, 46.67, 48.02, 83.66, 98.01, 104.12, 115.38, 116.23, 118.62, 122.60, 123.71, 123.99, 124.44, 129.87, 130.48, 131.40, 133.08, 133.31, 140.94, 147.62; IR 750.8, 852.0, 985.5, 1017.7, 1093.5, 1159.0, 1257.3, 1308.9, 1371.1, 1454.0, 1544.1, 1641.1, 1731.3, 2927.1 cm^{-1}

Diene 156

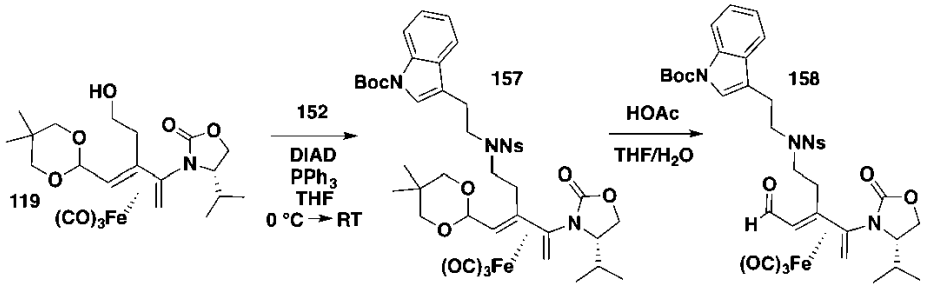


This reaction was performed under N_2 atmosphere in the glovebox. Vinyl iodide **155** (105.6 mg, 0.1395 mmol, 1 eq) was transferred to the flask containing vinyl stannane **99** (61.97 mg, 0.1395 mmol, 1 eq) with DMF (0.7 mL). $Pd(PPh_3)_4$ (16.12 mg, 0.01395 mmol, 0.1 eq) and CuO_2PPh_2 (45.07 mg, 0.1605 mmol, 1.15 eq) was added together. The solution was stirred overnight. The reaction mixture was filtered through silica in a glass frit and rinsed with EtOAc. The filtrate was concentrated *in vacuo* and dissolved in Et_2O. The solution was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified via column chromatography (silica gel, 1:1 Hex/EtOAc). Diene **156** was obtained with 84% yield.

^1H NMR (400 MHz) δ 0.70 (s, 1H), 0.89 (m, 6H), 1.20 (s, 3H), 1.66 (s, 9H), 0.93 (m, 1H), 2.52 (m, 1H), 2.80 (m, 1H), 2.95 (m, 1H), 3.50 (m, 4H), 3.63 (m, 4H), 3.81 (m, 1H), 4.14 (m, 1H), 4.33 (t, J = 8.9 Hz, 1H), 5.19 (d, J = 5.7 Hz, 1H), 5.31 (s, 1H), 5.52 (s, 1H), 5.81 (d, J = 5.6 Hz, 1H), 7.2 (m, 1H), 7.29 (m, 1H), 7.36 (d, J = 7.4 Hz, 2H), 7.52 (m, 3H), 7.75 (d, J = 7.8 Hz, 1H), 8.15 (d, 1H); ^{13}C NMR (100 MHz) δ 14.65, 17.80, 21.87, 23.03, 24.23, 28.19, 29.12, 29.60, 29.70, 30.04, 46.96, 47.96, 60.28, 63.00, 83.58, 98.30, 114.58, 115.34, 116.31, 118.64, 122.58, 123.78, 123.91, 124.39, 129.88, 129.92, 130.34, 131.49, 133.08, 133.19, 135.40, 137.10, 141.14, 147.63, 149.42, 156.672; IR 753.0, 852.2, 966.9, 986.5, 1096.0, 1158.6, 1218.0, 1257.6, 1371.2, 1453.7, 1544.3, 1611.4, 1734.9, 2959.7 cm^{-1}; $[\alpha]^{23}$ = -66.3150 (c = 0.455 g/mL)

Scheme 22:

Aldehyde 158



Alcohol **119** (50.2 mg, 0.1047 mmol) was dissolved in THF (1 mL) under Ar. Nosylamine **152** (46.5 mg, 0.1044 mmol, 1 eq) and PPh_3 (27.35 mg, 0.1043 mmol, 1 eq) were added together and the reaction mixture was cooled to 0 °C. DIAD (20.2 μL, 0.1043 mmol, 1 eq) was added and the reaction was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo* and purified via column chromatography (silica gel, 3:1 Hex/EtOAc). The product could not be completely separated from the starting material and byproduct.

Nosylamine **157** was also synthesized using a different reagent. Alcohol **119** (30.0 mg, 0.0626 mmol, 1 eq) and nosylamine **152** (27.9 mg, 0.0626 mmol, 1 eq) were dissolved in CH_2Cl_2 (0.5 mL) under Ar. PPh_3 (37.5 mg, 0.1371 mmol, 2.1 eq) was added while stirring. Solution of DCAD (47.6 mg, 0.1296 mmol, 2 eq) in 0.5 mL of CH_2Cl_2 was added via cannula. The reaction was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and the crude product was purified via column chromatography (silica gel, 3:1 Hex/EtOAc). The product contained inseparable impurities similar to the first attempt and combined product mixtures were carried on to the next reaction as a mixture.

Impure mixture of acetal **157** was dissolved in 8:5:2 mixture of acetic acid, THF and water (2.2 mL). The solution was stirred overnight at room temperature. The reaction

mixture was diluted with EtOAc and washed with 3M NaOH. The organic layer was washed with water and again with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 3:1 Hex/EtOAc).

^{1}H NMR (400 MHz) δ 0.69 (d, J = 3.6 Hz, 1H), 0.86 (d, J=3.6 Hz, 1H), 0.93 (m, 3H), 0.99 (m, 3H), 1.65 (s, 9H), 2.18 (d, J = 3.8 Hz, 1H), 2.40 (m, 1H), 2.91 (m, 3 H), 3.58 (m, 3H), 3.71 (m, 1H), 3.81 (m, 1H), 4.17 (m, 1H), 4.28 (m, 1H), 4.52 (t, J = 8.9 Hz, 1H), 7.21 (m, 3H), 7.45 (m, 3H), 7.60 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 9.57 (d, J = 3.6 Hz, 1H)