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Transition metal-catalyzed C-N and C-C bond formation: N-tert-prenylation and alkene hydroacylation

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Transition metal-catalyzed C-N and C-C bond formation: *N*-*tert*-prenylation and alkene hydroacylation

by

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NOMENCLATURE

Ar	aryl
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BF_4	tetrafluoroborate
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
CAM	ceric ammonium molybdate
cat.	catalytic
CF_3	trifluormethyl
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
CHO	aldehyde
CN	cyano/nitrile
CO	carbon monoxide
COD	1,5-cyclooctadiene
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublet of doublets
DBU	1,2-diazabicycloundec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide

dt	doublet of triplets
DTBM	di-*tert*-butyl-4-methoxy
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hour
Hex	hexanes
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IPA	isopropanol
^{i}Pr	isopropyl
m	multiplet
M	molar
MHz	megahertz
mL	milliliter
mp	melting point
NBS	*N*-bromosuccinimide
^{n}Bu	butyl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance

NO_2	nitro
OAc	acetate
OMe	methoxy
OTf	triflate
PFTE	polytetrafluoroethylene
Ph	phenyl
Phth	phthalate
Ppm	parts per million
PTSA	*para*-toluenesulfonic acid
rac	racemic
s	singlet
sat.	saturated
SM	starting material
t	triplet
^{t}Bu	*tert*-butyl
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
Tol	tolyl
UV	ultraviolet
Xyl	xylyl

ACKNOWLEDGMENTS

I first want to express my immense gratitude to my research advisor Dr. Levi Stanley. My graduate school experience would not have been the same without his guidance and support over these last five years. I am so appreciative of the patience, professionalism and wisdom he brings to the direction of his students and I will always be grateful for the confidence he has instilled in me as a scientist. I also want to express my thanks to my thesis committee members and the excellent Iowa State University professors who I have interacted with over the years: Art Winter, Jason Chen, Keith Woo, George Kraus, Javier Vela, Aaron Sadow, Andreja Bakac, Yan Zhao, and many others. The mentorship you have each provided in both coursework and research has been invaluable.

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I experienced many ups and downs over my graduate school career and my sanity would not have been preserved without the incredible friends I have made here at Iowa State: Dr. Holly Walen, soon-to-be Dr. Keith Fritzsching, Dr. Dana Drochner, James Klimavicz and Aaron Jacobson. I have so many great memories of research discussions over handcrafted drinks, our ever-productive Café B group meetings and that epic trivia win as team "Science and Potpourri". Thank you each for your friendship, your encouragement and for providing the distractions I didn't know I needed. To Holly especially: graduate school was made easier having a remarkable friend like you who understands the pressure and the stress and I cannot thank you enough for always being there to listen.

Lastly, I want to acknowledge the endless support of my family and friends. Words cannot express my appreciation for all of your reassurance and encouragement over the past five years. To Kelsey, Carmen, Sam and Robbie: as my best and oldest friends you're obligated to be supportive voices in my life, but you guys go above and beyond. Thank you for always being there for me, even from afar. To Eric: I am so incredibly lucky to have you in my life. I cannot thank you enough for always cheering me on, even though your understanding of what I do was once summed up as "chemistry and alchemy and potions and stuff". To Mom and Dad: I am so grateful for the sense of independence that you instilled in me from a young age and for the freedom you've always given me to pursue my goals. Thank you both for your unwavering support throughout the crazy ride that became this thesis. And for always being proud of me, no matter what.

ABSTRACT

This thesis presents the development of new catalysts for the palladium-catalyzed *N*-*tert*-prenylation of indoles, the rhodium-catalyzed *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes, studies toward the rhodium-catalyzed intramolecular hydroacylation of 1,2-disubstituted alkenes, and the first examples of the rhodium-catalyzed, enantioselective hydroacylation of 1,1,2-trisubstituted alkenes.

Chapter II discusses the development of three distinct protocols for the synthesis of *N*-*tert*-prenylindoles using indole, (η^6-indole)$Cr(CO)_3$, and indoline nucleophiles. These reactions occur in the presence of the same palladium catalyst prepared *in situ* from readily available precursors and require loadings of the palladium catalyst that are up to ten times less than required for previously reported direct *N*-*tert*-prenylations of indoles. These methods for palladium-catalyzed *N*-*tert*-prenylation generate *N*-*tert*-prenylindoles with a range of electronic character in high yields (up to 94%) with high *tert*-prenyl-to-*n*-prenyl selectivity (up to 12:1).

Chapter III describes the development of a rhodium catalyst for *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes. A catalyst generated from $[Rh(COD)Cl]_2$, (*R*)-DTBM-Segphos and NaBARF promotes the enantioselective hydroacylation reactions and minimizes the formation of byproducts from competitive alkene isomerization and ene/dehydration pathways. These rhodium-catalyzed processes generate the 3,4-dihydronaphthalen-1(2*H*)-one products in moderate-to-high yields (49-91%) with excellent enantioselectivities (96-99% ee).

Chapter IV describes studies toward the intramolecular hydroacylation of 1,2-disubstituted alkenes as well as the first examples of catalytic, enantioselective hydroacylation of 1,1,2-trisubstituted alkenes. The intramolecular hydroacylation of 1,2-disubstituted alkenes is facilitated by a cationic rhodium complex and generates the indanone products in high yields (up to 94%). However, the α-center is prone to epimerization and results in racemic mixtures of the bicyclic products.

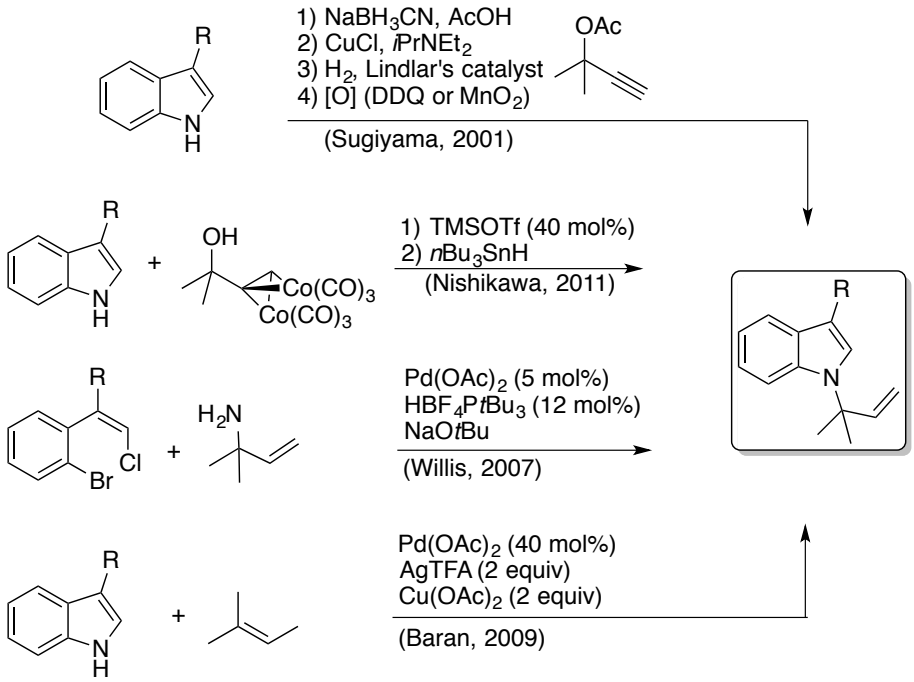
In contrast, the rhodium-catalyzed intramolecular hydroacylation of 1,1,2-trisubstituted alkenes generates highly enantioenriched, polycyclic architectures. The DFT and mechanistic studies presented are consistent with a reaction pathway that includes intramolecular alkene hydroacylation and α-epimerization. This reaction sequence enables the hydroacylation of 2-(cyclohex-1-en-1-yl)benzaldehydes to form hexahydro-9*H*-fluoren-9-ones in moderate to high yields (68-91%) with high enantioselectivities (up to 99% ee) and diastereoselectivities (typically >20:1).

CHAPTER I

INTRODUCTION

Transition-metal catalysis has been well established as an essential component of modern synthetic organic chemistry.[1] This broad research area encompasses chemical transformations such as cross-coupling processes, metathesis reactions, polymerizations, oxidative functionalizations, C-H activation chemistry, allylic substitutions, and hydrofunctionalization reactions, among others.[1] Advances in transition metal-catalyzed processes have contributed to a fundamental understanding of the mechanisms and catalytic principles that govern these reactions and have enabled the development of improved catalysts for many regio- and enantioselective chemical transformations. In this thesis, fundamental principles of transition-metal catalysis will be applied to the development of new catalysts for allylic substitution and hydrofunctionalization reactions including a palladium catalyst for the *N*-*tert*-prenylation of indoles, a rhodium catalyst for the *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes and a rhodium catalyst for the intramolecular hydroacylation of higher order alkenes.

N-*tert*-prenylindoles are a unique class of prenylated indoles that incorporate the *tert*-prenyl moiety through a C-N bond. Compounds with this general architecture and analogues containing oxidized prenyl moieties exhibit an array of medicinal properties distinct from structures that incorporate the linear (*n*-prenyl) isomer.[2-3] However, traditional methods for the synthesis of *N*-*tert*-prenylindoles involve multiple nonstrategic redox steps and the use of heavily prefunctionalized starting materials (Scheme 1).[4-7]

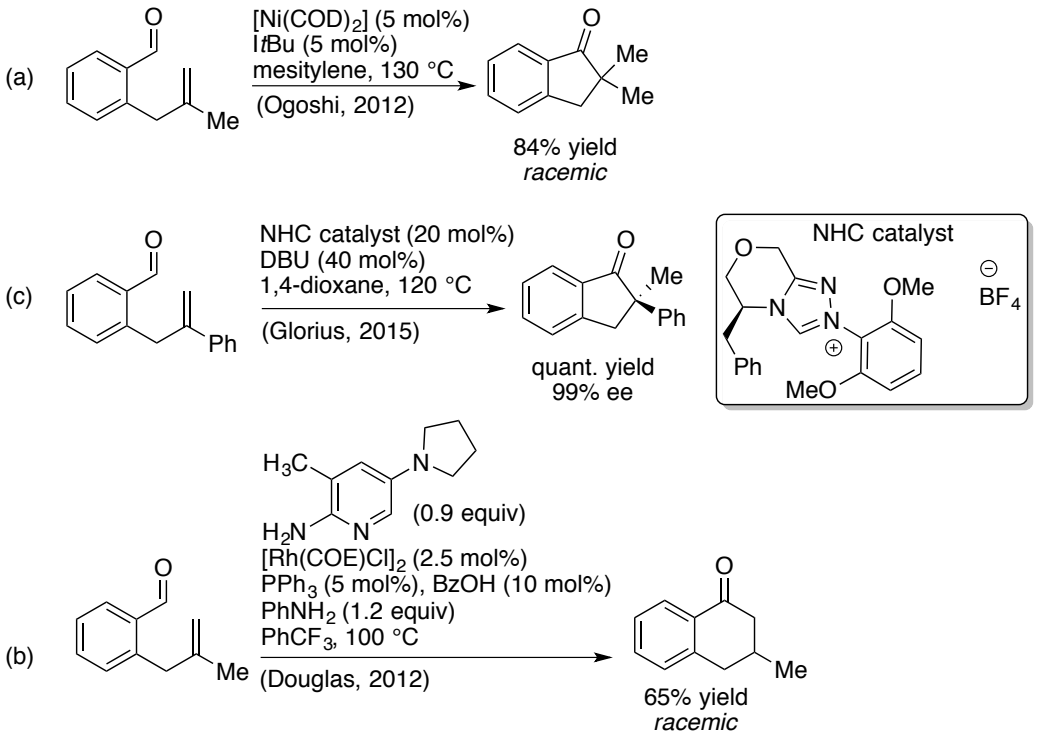


Scheme 1: Methods for the synthesis of *N-tert*-prenylindoles

The only direct method for the synthesis of *N-tert*-prenylindoles was reported by Baran and co-workers and requires high loadings of the palladium catalyst (20-40 mol%) as well as an excess of silver and copper co-oxidants (2.0-2.5 equiv).[6] This thesis presents a method for the direct synthesis of *N-tert*-prenylindoles with a broad range of electronic character via palladium-catalyzed allylic substitution.[8] These reactions require significantly lower catalyst loadings than previously reported direct *N-tert*-prenylations of indoles, and occur without the use of precious metal co-oxidants.

Intramolecular alkene hydroacylation is a valuable strategy to generate a wide variety of carbocyclic and heterocyclic ketones.[9] These reactions can be promoted by transition-metal or *N*-heterocyclic carbene (NHC) catalysts. NHC-catalyzed hydroacylations occur with *exo*-selectivity whereas transition metal-catalyzed hydroacylations can occur with either *exo*- or *endo*-selectivity. *ortho*-Allylbenzaldehydes are one class of substrates that highlights the two potential regiochemical outcomes of intramolecular alkene hydroacylations. *Exo*-

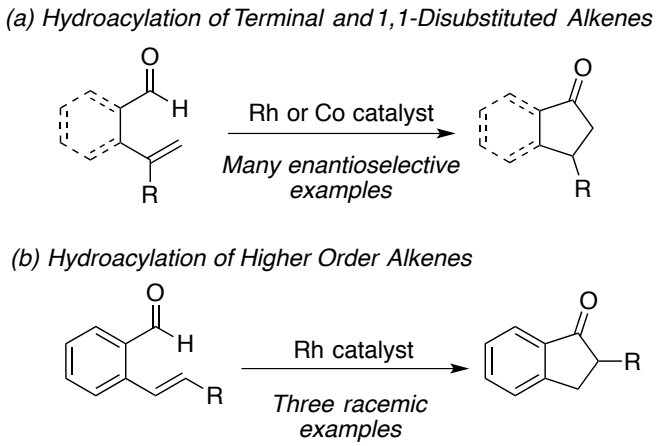
selective hydroacylations of these substrates have been well explored and both racemic and enantioselective variants have been reported.[10-11] However, only one example of *endo*-selective hydroacylation of *ortho*-allylbenzaldehyde substrates has been reported.[12] Douglas and co-workers reported the rhodium-catalyzed hydroacylation of 2-(2-methylallyl)benzaldehyde that requires a chelating additive and results in a racemic product (Scheme 2).



Scheme 2: *ortho*-Allylbenzaldehydes as hydroacylation substrates.

This thesis describes the development of a rhodium catalyst for the *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes.[13] This rhodium-catalyzed process generates the 3,4-dihydronaphthalen-1(2*H*)-one products with high enantioselectivities and mitigates the formation of byproducts resulting from alkene isomerization and ene/dehydration pathways through catalyst design.

Since the initial report of alkene hydroacylation in 1972,[14] terminal and 1,1-disubstituted alkenes have remained the most common substrates used in intramolecular alkene hydroacylations to generate a variety of ketone products (Scheme 3a).



Scheme 3: Hydroacylations of terminal, 1,1-disubstituted and higher order alkenes.

However, intramolecular alkene hydroacylations of higher order alkenes are quite rare.[12, 15-16] Morehead reported a single example of the rhodium-catalyzed hydroacylation of ethyl (*E*)-3-(2-formylphenyl)acrylate that required 5 days to reach 90% conversion (Scheme 3b).[15] Douglas proposed that *exo*-selective hydroacylation of a 1,2-disubstituted alkene occurs following isomerization of 2-homoallylbenzaldehyde in the presence of a rhodium catalyst.[12] This thesis presents studies toward the hydroacylation of 1,2-disubstituted alkenes and discusses efforts made to address challenges in the development of an enantioselective version of this reaction. This thesis also describes the first examples of catalytic, enantioselective hydroacylations of 1,1,2-trisubstituted alkenes. DFT and mechanistic studies are consistent with an alkene hydroacylation/α-epimerization reaction sequence for these catalytic processes. A cationic rhodium complex promotes the hydroacylation of 2-(cyclohex-1-en-1-yl)benzaldehyde to generate hexahydro-9*H*-fluoren-9-ones in high yields and enantioselectivities.

Thesis Organization

This thesis is comprised of five chapters that contain both work that has been published in peer-reviewed journals and research results that are in preparation for publication. Chapter I serves to introduce transition-metal catalysis and catalytic methods development in the context of prenylation and hydroacylation reactions. Chapters II and III are adapted from papers published in *Organic Letters* and have been modified to include data that was not integrated into the published work. Modifications to these chapters also serve to describe the details of this research in greater depth. Chapter IV discusses research results that are currently in preparation for submission to *Angewandte Chemie International Edition*. This chapter also describes results that will not be included in the published manuscript. Chapter V serves as a general summary and conclusion of the presented research and proposes strategies to address the limitations that remain in some of the research projects described.

Chapter II describes the palladium-catalyzed synthesis of *N*-*tert*-prenylindoles and is modified version from a paper published in *Organic Letters* in 2013. The work included in this chapter encompasses the development of three distinct protocols for the synthesis of *N*-*tert*-prenylindoles by palladium-catalyzed allylic substitution using indole, (η^6-indole)$Cr(CO)_3$, and indoline nucleophiles. This catalytic method facilitates the synthesis of *N*-*tert*-prenylindoles with a range of electronic character and substitution. This work was accomplished in collaboration with Ryan Van Zeeland, also of the Stanley group. The author of this thesis is responsible for the synthesis and characterization of all indole, indoline, *N*-*tert*-prenylindole and *N*-*tert*-prenylindolines prepared, as well as the identification of reaction

conditions for this catalytic method. Ryan Van Zeeland is responsible for the synthesis and characterization of all chromium-containing compounds described.

Chapter III describes the rhodium-catalyzed hydroacylation of *ortho*-allylbenzaldehydes and is modified from a paper published in *Organic Letters* in 2015. This chapter discusses the development of a cationic rhodium catalyst that facilitates the *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes to generate 3,4-dihydronaphthalen-1(2*H*)-ones. This work was accomplished in collaboration with Adam C. Schmidt, an undergraduate researcher in the Stanley Lab. Adam assisted in initial evaluation of reaction conditions for the rhodium-catalyzed hydroacylation and synthesis of the parent 2-(2-methylallyl)benzaldehyde substrate. The author of this thesis is responsible for optimization of this catalytic system, as well as the synthesis and characterization of all compounds described.

Chapter IV discusses the development of a rhodium catalyst for the intramolecular hydroacylation of higher order alkenes. The chapter contains modified sections of a paper in preparation for submission to *Angewandte Chemie International Edition,* as well as additional data that will not be included in the submitted manuscript. This chapter discusses efforts toward the development of a rhodium catalyst for the hydroacylation of 1,2-disubstituted alkenes and presents the first examples of the enantioselective hydroacylation of 1,1,2-trisbustituted alkenes. DFT studies to model the catalytic reaction sequence and kinetics experiments are also described. This work was accomplished in collaboration with Prof. Joseph Scanlon as well as undergraduate students Brian P. Schumacher and Eugene A. Schneider of Ripon College. Prof. Scanlon, Brian and Eugene performed the theoretical computational work to identify the catalytic intermediates and potential energy surface for

the reactions described. The author of this thesis is responsible for the experimental mechanistic work, as well as the synthesis and characterization of all compounds described.

Chapter V discusses general conclusions from the work presented and proposes new directions for the continuation of this research in the Stanley lab.

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CHAPTER II

PALLADIUM-CATALYZED SYNTHESIS OF *N-TERT*-PRENYLINDOLES

Adapted from a paper published in *Organic Letters*[1]

Kirsten F. Johnson, Ryan Van Zeeland, Levi M. Stanley

Abstract

Three distinct protocols for the synthesis of *N-tert*-prenylindoles are described using indole, (η^6-indole)$Cr(CO)_3$, and indoline nucleophiles in the presence of the same palladium catalyst prepared *in situ* from readily available precursors. These reactions require loadings of the palladium catalyst that are up to ten times less than required for previously reported direct *N-tert*-prenylations of indoles. These methods for palladium-catalyzed *N-tert*-prenylation generate *N-tert*-prenylindoles with a range of electronic character in high yields (up to 94%) with high *tert*-prenyl-to-*n*-prenyl selectivity (up to 12:1).

Introduction

Prenylated indoles are found in structurally diverse fungal, plant, and bacterial natural products[2-3] and have been the focus of many recent synthetic[4-12] and biosynthetic studies.[13-17] The diversity of these natural products stems from nature's ability to incorporate the prenyl group throughout the indole core as either an *n*-prenyl (prenyl) or *tert*-prenyl (reverse prenyl) moiety. Synthetic chemists have developed a variety of methods to prepare both prenylated and *tert*-prenylated indoles that exhibit promising medicinal properties.[2-17] Despite these efforts, the synthetic methodology necessary to access certain classes of *tert*-prenylated indoles remains underdeveloped.

N-tert-Prenylated indoles (Figure 1) are a unique class of prenylated indoles in which the prenyl group is linked to the indole core through a carbon-nitrogen bond. *N-tert*-

Prenylindoles and analogues containing oxidized prenyl moieties exhibit an array of medicinal properties including activation of insulin receptors, cytotoxicitiy toward cancer cell lines, as well as anti-inflammatory, antimycobacterial, and antifungal activities.[18-22]

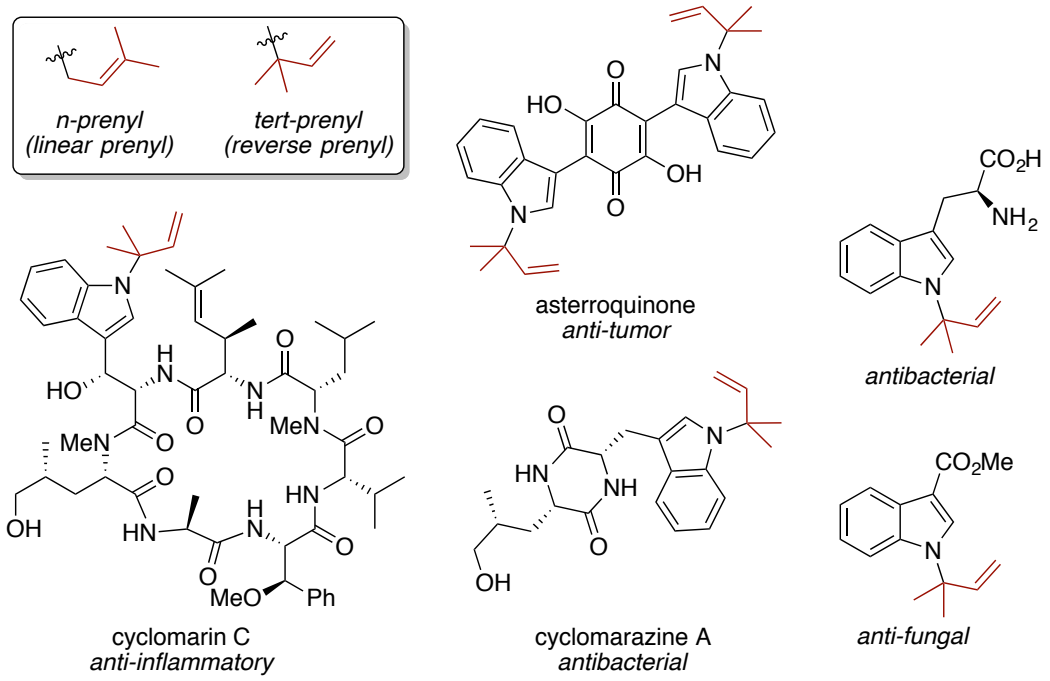
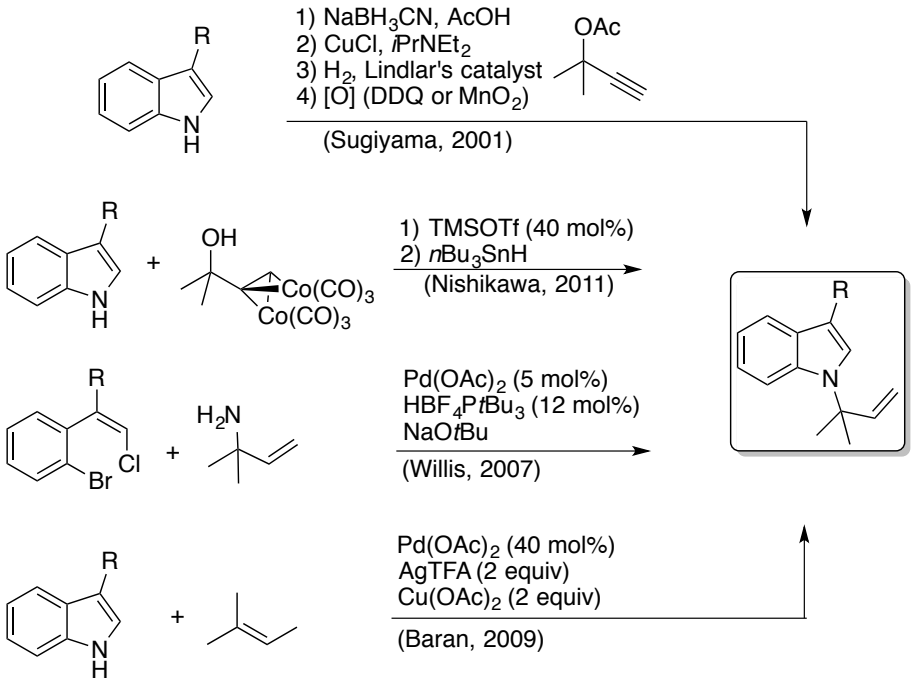


Figure 1: Representative *N-tert*-prenylindole natural products.

Current synthetic routes to *N-tert*-prenylated indoles involve 1) multiple non-strategic redox steps, 2) the use of pre-functionalized starting materials, or 3) high loadings of a precious metal catalyst and metal co-oxidants (Scheme 1). The traditional, four-step synthetic sequence to generate *N-tert*-prenylated indoles was reported by Sugiyama and co-workers in 2001 and includes reduction of the indole to an indoline, Cu(I)-catalyzed propargylic substitution, partial reduction of the alkyne to an alkene, and oxidation of the *N-tert*-prenylindoline to the corresponding indole.[23-26] In 2007, Willis and co-workers reported a tandem Pd-catalyzed synthesis of *N-tert*-prenylindoles from 2-methyl-3-butene-2-amine and 2-bromo-β-chlorostyrenes by a sequence of arylamination and alkenyl amination.[27] In 2011,

Nishikawa and co-workers reported the *N-tert*-prenylation of methyl indole-3-acetate by alkylation with the dicobalthexacarbonyl complex of 2-methyl-3-butyn-2-ol in the presence of TMSOTf, followed by reduction and decomplexation with *n*-Bu_3SnH.[28]

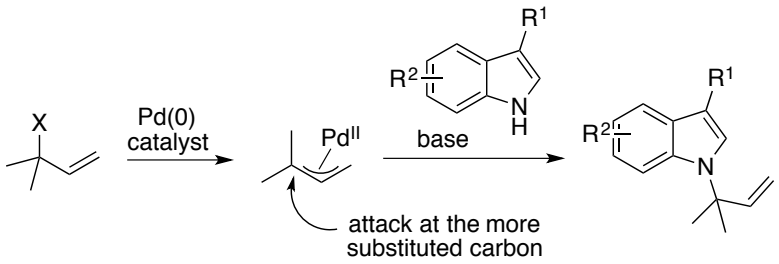


Scheme 1: Strategies for the synthesis of *N-tert*-prenylindoles.

Prior to the studies reported in this thesis, only one direct method for the *N-tert*-prenylation of indoles had been reported. In 2009, Baran and co-workers reported the direct synthesis of *N-tert*-prenylindoles by Pd-mediated C–H functionalization of 2-methyl-2-butene with indoles.[29] The direct C–H functionalization 2-methyl-2-butene enables the synthesis of *N-tert*-prenylindoles from a broad array of readily accessible indoles, but the synthetic utility and practicality of this strategy remains limited because high loadings of the palladium catalyst (20-40 mol %) and a silver co-oxidant (2.0-2.5 equiv) are required.

Results and Discussion

At the outset of this project, we sought to develop a strategy to generate *N*-*tert*-prenylindoles with a range of electronic properties that minimize the number of non-strategic redox steps and employ practical loadings of catalyst precursors. We aimed to identify a method for the synthesis of *N*-*tert*-prenylindoles through a palladium-catalyzed allylic alkylation approach (Scheme 2).[30-31]

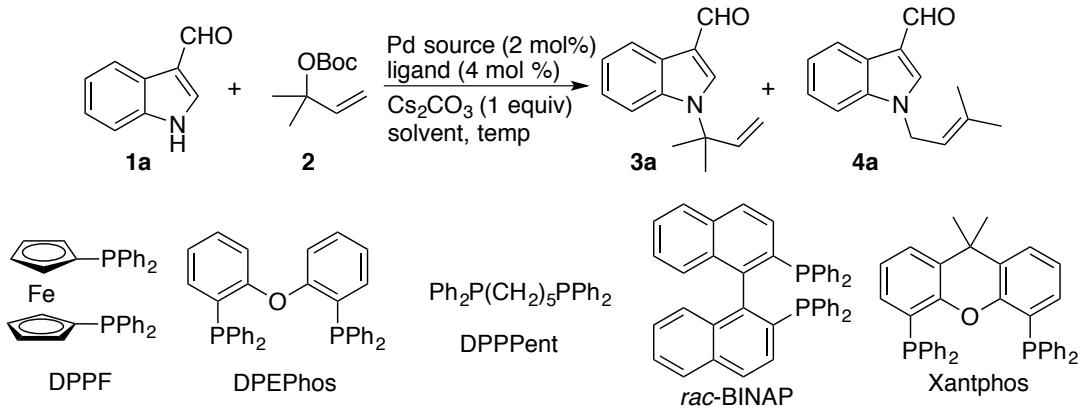


Scheme 2: Proposed scheme for the Pd-catalyzed *N*-*tert*-prenylation of indoles

To establish the viability of our allylic substitution strategy, we conducted reactions of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate with indole-3-carboxaldehyde in the presence of Cs_2CO_3 and catalysts generated from a variety of palladium precursors and bisphosphine ligands (Table 1). We found that palladium complexes of bisphosphine ligands with wide natural bite angles catalyze the *N*-prenylation of indole-3-carboxaldehyde **1a** with high *tert*-prenyl:*n*-prenyl selectivity (9:1 to 13:1) (entries 1-5). We observed traces of the *N*-allylindole product generated from nucleophilic attack of the allylpalladium(II) species from $[Pd(\eta^3\text{-allyl})Cl]_2$. In order to prevent formation of this byproduct we evaluated alternative palladium precursors and found that $[Pd(\eta^3\text{-prenyl})Cl]_2$ was a suitable precatalyst (entries 6 and 7). We then evaluated a range of solvents for the *N*-prenylation of indole-3-carboxaldehyde **1a** and found that CH_2Cl_2 and PhCN generated the *N*-*tert*-prenylindole product with the best combination of yield and selectivity (entries 7-11). Attempts to

completely remove PhCN from the reaction mixture resulted in significant loss of the *N*-prenylindole products so we chose to use CH_2Cl_2 for further evaluation of the reaction conditions. The reaction of **1a** with 2.00 equivalents of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** in the presence of a catalyst generated from $[Pd(\eta^3\text{-prenyl})Cl]_2$ and Xantphos at 0 °C occurred with high *tert*-prenyl:*n*-prenyl selectivity (12:1) and **3a** was isolated in 76% as a single regioisomer (Entry 14).

Table 1: Study of reaction conditions for the *N*-*tert*-prenylation of **1a** with **2**.[a]

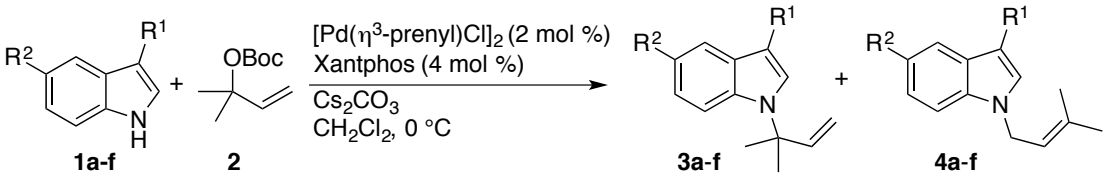


Entry	*Equiv* ***2***	*Ligand*	*Pd source (mol %)*	*Solvent*	*Temp. (° C)*	*Yield*[b] *(%)*	***3a*:*4a***[b]
1	1.00	DPPF	$[Pd(\eta^3\text{-allyl})Cl]_2$ (2)	CH_2Cl_2	rt	59	9:1
2	1.00	DPEPhos	$[Pd(\eta^3\text{-allyl})Cl]_2$ (2)	CH_2Cl_2	rt	53	10:1
3	1.00	DPPPent	$[Pd(\eta^3\text{-allyl})Cl]_2$ (2)	CH_2Cl_2	rt	58	11:1
4	1.00	*rac*-BINAP	$[Pd(\eta^3\text{-allyl})Cl]_2$ (2)	CH_2Cl_2	rt	52	9:1
5	1.00	Xantphos	$[Pd(\eta^3\text{-allyl})Cl]_2$ (2)	CH_2Cl_2	rt	68	13:1
6	1.00	Xantphos	$Pd_2(dba)_3$ (2)	CH_2Cl_2	rt	58	8:1
7	1.00	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	CH_2Cl_2	rt	62	9:1
8	1.00	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	THF	rt	50	9:1
9	1.00	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	MeCN	rt	61	8:1
10	1.00	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	PhCN	rt	69	10:1
11	1.00	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	Dioxane	rt	59	9:1
12	1.50	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	CH_2Cl_2	rt	88	10:1
13	2.00	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	CH_2Cl_2	rt	99	10:1
14	2.00	Xantphos	$[Pd(\eta^3\text{-prenyl})Cl]_2$ (2)	CH_2Cl_2	0	99 (76)[c]	12:1

[a]Reactions run on a 0.500 mmol scale and full experimental procedure is given in the Experimental section of this thesis chapter. [b]Determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield of **3a**.

We then evaluated these conditions for palladium-catalyzed *N-tert*-prenylation in reactions of a series of indoles containing electron-withdrawing groups at either the 3-position or the 5-position with carbonate **2**. The data from these experiments are summarized in Table 2. As shown in entries 1-4, 3-substituted indoles **1a-1d** (R^1 = CHO, C(O)Me, CO_2Me, or CN) reacted with carbonate **2** to form *N-tert*-prenylindoles **3a-3d** in good-to-excellent yield with 10:1 or greater regioselectivity (**3**:**4**). *N-tert*-Prenylindoles **3a** and **3b** were isolated in 76% and 65% yield as single constitutional isomers. In contrast, *N-tert*-prenylindoles **3c** and **3d** were not readily separable from the *N-n*-prenyl isomers **4c** and **4d**. These products were isolated as 12:1 mixtures of the *N-tert*-prenylindole and *N-n*-prenylindole isomers.

Table 2: Scope of Pd-Catalyzed *N-tert*-Prenylation of Indoles.[a]



Entry	***1***	R^1	R^2	***3***	*Yield **3** + **4** (%)*[b]	***3*:*4***[c]
1	**1a**	CHO	H	**3a**	76[d]	12:1
2	**1b**	C(O)Me	H	**3b**	65[d]	10:1
3	**1c**	CO_2Me	H	**3c**	90	12:1
4	**1d**	CN	H	**3d**	94	12:1
5[e]	**1e**	H	CN	**3e**	40	7:1
6[e]	**1f**	H	NO_2	**3f**	62	7:1

[a]Reactions run on a 0.500 mmol scale and full experimental procedure is given in the Experimental section of this thesis chapter. [b]Isolated yield of **3** + **4**. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Isolated yield of **3**. [d]Reactions run at room temperature.

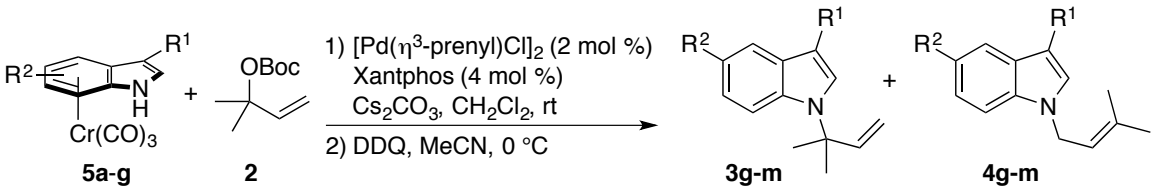
The presence of electron-withdrawing substitution at the 3-position of the indole core is not a strict requirement under our reaction conditions. Reactions of 5-cyanoindole **1e** and 5-nitroindole **1f** with carbonate **2** occurred to form mixtures of *N*-prenylindole products **3e-f** and **4e-f** in 40% and 62% yield with 7:1 *tert*-prenyl:*n*-prenyl selectivity (entries 5 and 6).

However, reactions of indoles lacking electron-withdrawing substitutents and reactions of 2-substituted indoles did not form *N*-prenylindole products.

The disparate reactivity of indoles with and without electron-withdrawing substituents suggested that indolate anions of the electron-deficient indoles were primarily responsible for nucleophilic attack on a prenylpalladium(II) intermediate. Thus, the difference in relative acidity of the indole N–H is likely responsible for the difference in reactivity between more acidic, electron-deficient indoles and less acidic, electron-rich indoles.[32] Since η^6-coordination of metal carbonyl complexes to arenes is known to increase the acidity of benzylic C-H bonds,[33-40] we hypothesized that η^6-coordination of a metal carbonyl complex to the indole core would similarly increase the acidity of the indole N–H bond by reducing the electron density in the indole π-system.

We prepared a series of (η^6-indole)$Cr(CO)_3$ complexes of electron-rich indoles and evaluated their reactivity as nucleophiles in Pd-catalyzed prenylation reactions. Reactions of (η^6-indole)$Cr(CO)_3$ complexes of indoles **5a-g** with carbonate **2** are summarized in Table 3.

Table 3: Scope of Pd-Catalyzed *N-tert*-Prenylation of (η^6-indole)$Cr(CO)_3$ Complexes.[a]



5a-g **2** **3g-m** **4g-m**

Entry	***5***	R^1	R^2	***3***	*Yield **3** + **4** (%)*[b]	***3*:*4***[c]
1	**5a**	H	H	**3g**	86	8:1
2	**5b**	Me	H	**3h**	75	8:1
3	**5c**	CH_2CO_2Me	H	**3i**	78	9:1
4	**5d**	H	4-OMe	**3j**	78	7:1
5	**5e**	H	5-OMe	**3k**	51	8:1
6	**5f**	H	6-OMe	**3l**	72	7:1
7	**5g**	H	7-OMe	**3m**	46	<1:20

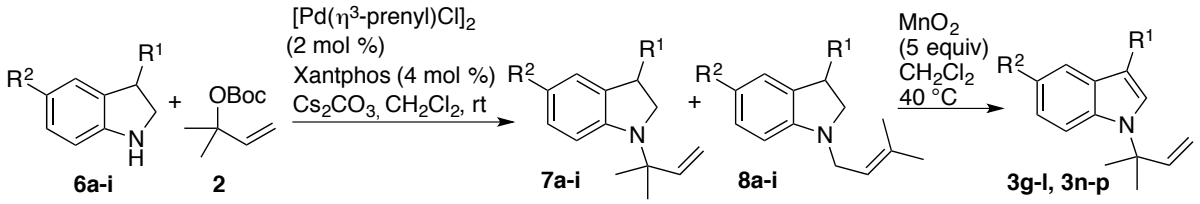
[a]Reactions run on a 0.250 mmol scale and full experimental procedure is given in the Experimental section of this thesis chapter. [b]Isolated yield of **3** + **4**. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

As shown in entries 1-3, (η^6-indole)$Cr(CO)_3$ complexes prepared from indole, 3-methylindole and methyl indole-3-acetate (**5a-c**) reacted with carbonate **2** to form *N*-*tert*-prenylindoles **3g-3i** after oxidative decomplexation with DDQ. These one-pot, two-step transformations gave the *N*-*tert*-prenylindoles **3g-i** and *N*-*n*-prenylindoles **4g-i** in 62-86% yield with 6:1 to 9:1 *tert*-prenyl:*n*-prenyl selectivity. Reactions of (η^6-indole)$Cr(CO)_3$ complexes prepared from 4-MeO-, 5-MeO-, and 6-MeO-indole also occurred in moderate to good yields with high *tert*-prenyl:*n*-prenyl selectivities (entries 4-6). The reactions of (η^6-indole)$Cr(CO)_3$ complexes **5d-f** with **2** and subsequent decomplexation of the $Cr(CO)_3$ unit generated *N*-*tert*-prenylindoles **3j-l** and *N*-*n*-prenylindoles **4j-l** in 51-78% yield and 7:1 to 8:1 *tert*-prenyl:*n*-prenyl selectivity. In contrast, the prenylation of (η^6-7-MeO-indole)$Cr(CO)_3$ **5g** with **2** occurred with >20:1 selectivity favoring the *N*-*n*-prenylindole isomer **4m** (entry 7). We propose that substitution at the 7-position of the indole core increases steric volume near the nucleophilic nitrogen of the indolate species and inhibits attack at the more substituted end of the prenylpalladium(II) intermediate. Nucleophilic attack instead occurs at the less substituted end of the prenylpalladium(II) species resulting in formation of the *N*-*n*-prenylindole isomer **4m**.

The synthesis of *N*-*tert*-prenylindoles from electron-rich indole precursors is enabled by the markedly different electronic properties of the corresponding (η^6-indole)$Cr(CO)_3$ complexes. However, the utility of these complexes is inherently limited by the need for stoichiometric quantities of chromium. Furthermore, the synthesis of (η^6-indole)$Cr(CO)_3$ complexes from indoles containing even weakly deactivating groups is challenging. For example, standard procedures for synthesis of (η^6-indole)$Cr(CO)_3$ complexes generated (η^6-5-bromoindole)$Cr(CO)_3$ in less than 5% yield.

We hypothesized that the increased nucleophilicity of the indoline nitrogen would enable us to synthesize *N-tert*-prenylindoles with a greater range of electronic character after oxidation of the *N-tert*-prenylindoline intermediate. We evaluated this hypothesis by conducting the reaction of a series of indoline derivatives with carbonate **2** (Table 3).[41] Indoline, 3-methylindoline, methyl indoline-3-acetate, and 3-phenylindoline react with carbonate **2** to form **3g-i** and **3n** after oxidation of the intermediate *N-tert*-prenylindolines with MnO_2 (entries 1-4). The reactions occur with 5:1 to 6:1 *tert*-prenyl:*n*-prenyl selectivity, and the *N-tert*-prenylindolines are readily separated from the linear regioisomer. *N-tert*-prenylindoles **3g-i** and **3n** were isolated in 43-80% yield over two steps. Reactions of 4-MeO-, 5-MeO-, and 6-MeO-indolines with **2** occurred with 2:1 to 4:1 selectivity and subsequent oxidation generated *N-tert*-prenylindoles **3j-l** in 26-60% yield (entries 6-8).

Table 4: Scope of Pd-Catalyzed *N-tert*-Prenylation of Indolines.[a]



Entry	***6***	*R^1*	*R^2*	***7*:*8***[b]	*Yield **7** (%)*	***3***	*Yield **3*** (%)[c]	*Yield **3*** (%)[d]
1	**6a**	H	H	6:1	83	**3g**	96	80
2	**6b**	Me	H	5:1	59	**3h**	97	57
3	**6c**	CH_2CO_2Me	H	5:1	56	**3i**	77	43
4	**6d**	Ph	H	5:1	61	**3n**	92	47
5	**6e**	$(CH_2)_2NPhth$	H	4:1	50	**3o**	94	47
6	**6f**	H	4-OMe	4:1	58	**3j**	93	54
7	**6g**	H	5-OMe	2:1	26	**3k**	99	26
8	**6h**	H	6-OMe	5:1	61	**3l**	98	60
9	**6i**	H	5-Br	5.5:1	74	**3p**	87	64

[a]Reactions run on a 0.500 mmol scale and full experimental procedure is given in the Experimental section of this thesis chapter [b]Ratio of *N-tert*-prenylindoline:*N-tert*-prenylindoline determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Isolated yield of **3** for the oxidation of **7** by MnO_2. [d]Isolated yield of **3** over two steps.

The sequence of *N*-prenylation of indolines followed by oxidation to the corresponding indoles allowed us to form *N*-*tert*-prenylindoles that were not accessible via the approaches shown in Tables 2 and 3. Reactions of a protected tryptamine derivative, 3-phenylindole, and 5-bromoindole with carbonate **2** either did not occur in high yields or the corresponding (η^6-indole)$Cr(CO)_3$ complexes were difficult to isolate. However, reactions of 3-phenylindoline **6d**, indoline **6e** (R^1 = $(CH_2)_2$NPhth), and 5-bromoindoline **6i** with **2** occurred with 4:1 to 5.5:1 *tert*-prenyl:*n*-prenyl selectivity (entries 4, 5 and 9). The *N*-prenylindoline isomers were cleanly separable at the indoline oxidation state and oxidation of the isomerically pure *N*-*tert*-prenylindolines by MnO_2 generated *N*-*tert*-prenylindoles **3n**-**p** in 47-64% yield over the two steps.

Conclusions

In summary, we have developed three strategies based on palladium-catalyzed allylic alkylation reactions to generate *N*-*tert*-prenylindoles. In the presence of the same palladium catalyst, good yields and high regioselectivities are observed for three distinct classes of nucleophiles. Direct *N*-*tert*-prenylations of electron-deficient indoles and indolines occur readily, while *N*-*tert*-prenylations of electron-rich indoles are facilitated by complexation with chromium. Straightforward procedures for oxidative decomplexation of the chromium carbonyl fragment from the (η^6-*N*-*tert*-prenylindole)$Cr(CO)_3$ intermediates and oxidation of the *N*-*tert*-prenylindolines provide access to electron-rich *N*-*tert*-prenylindoles in moderate to good yields. Thus, *N*-*tert*-prenylindoles with a broad range of substitution and electronic character can be accessed through these complementary approaches.

Experimental

General synthetic details. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. THF and CH_2Cl_2 were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous *n*-dibutylether, acetonitrile, benzonitrile, and 1,4-dioxane were purchased from Sigma-Aldrich. Flash column chromatography was performed on Fisher brand silica gel 60 (230-400 mesh) using hexanes/ethyl acetate, hexanes/ether, or hexanes/dichloromethane mixtures. Products were visualized on TLC by UV light or by staining with $KMnO_4$.

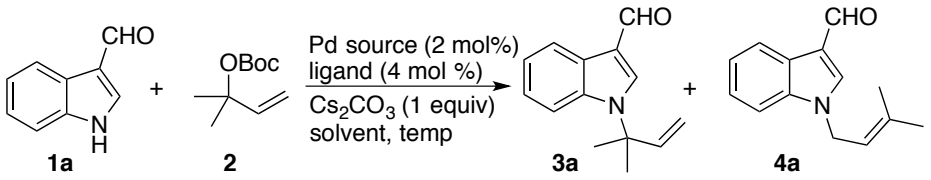
Instrumentation. HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.36 ppm for ^{13}C; C_6D_6 = 7.16 for ^1H and 128.06 for ^{13}C). Coupling constants are reported in hertz.

Materials. Indole-3-carboxaldehyde **1a**, 3-acetylindole **1b**, methyl indole-3-carboxylate **1c**, 3-cyanoindole **1d**, indole, 3-methylindole, 3-indoleacetic acid, and tryptamine were purchased from Sigma-Aldrich and used with out further purification. 5-Cyanoindole **1e** and 5-nitroindole **1f** were purchased from TCI and used without further purification. 4-Methoxyindole, 5-methoxyindole, 6-methoxyindole, and 7-methoxyindole were purchased from AK Scientific and used without further purification. 5-Bromoindole

was purchased from Frontier Scientific and used without further purification. Methyl indole-3-acetate was synthesized according to a literature procedure from 3-indoleacetic acid.[42] 3-Phenylindole was synthesized according to a literature procedure from 2-phenylacetaldehyde and phenylhydrazine.[43] *N*-Phthalimidotryptamine was synthesized according to a literature procedure from tryptamine and phthalic anhydride.[44] *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate was prepared according to a literature procedure from 2-methylbut-3-en-2-ol and Boc_2O.[12]

$[Pd(\eta^3\text{-allyl})Cl]_2$, $Pd_2(dba)_3$, and $PdCl_2$ were purchased from Strem and used without further purification. $[Pd(\eta^3\text{-prenyl})Cl]_2$ was synthesized from $PdCl_2$ and 1-chloro-3-methyl-2-butene according to a literature procedure.[45] DPEPhos (oxydi-2,1-phenylene)bis(diphenylphosphine) and *rac*-BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) were purchased from Strem and used without further purification. DPPPent (1,5-bis(diphenylphosphino)pentane), DPPF (1,1-bis(diphenylphosphino)ferrocene, Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) and Cs_2CO_3 were purchased from Sigma-Aldrich and used without further purification.

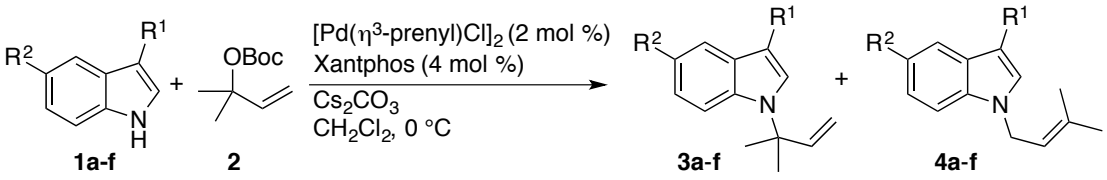
Identification of Reaction Conditions for the *N-tert*-Prenylation of Indoles (Table 1)



In a nitrogen-filled dry-box, indole-3-carboxaldehyde **1a** (72.5 mg, 0.500 mmol, 1.00 equiv), Cs_2CO_3 (162 mg, 0.500 mmol, 1.00 equiv), ligand (0.020 mmol, 0.040 equiv), and the Pd source (0.010 mmol, 0.020 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (0.500-1.00 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from

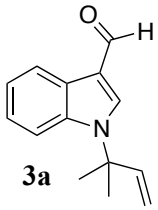
the dry-box. The mixture of **1a**, Cs_2CO_3, and catalyst precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were allowed to stir for 5 minutes at the appropriate temperature. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **1a**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at the reaction temperature (2-20 h) until the consumption of carbonate **2** was observed by TLC analysis. The reaction mixture was filtered through a pad of silica (eluting with Et_2O). The crude reaction mixture was concentrated under reduced pressure. $CDCl_3$ (0.5-0.7 mL) was added to dissolve the crude reaction mixture, and 1,3,5-trimethoxybenzene (28.6 mg, 0.170 mmol) was added as an internal standard. The ratio of *N-tert*-prenylindole **3a**:*N-n*-prenylindole **4a** and the combined yield of *N-tert*-prenylindole **3a** and *N-n*-prenylindole **4a** was then determined by ^1H NMR spectroscopy. For Table 1, entry 14 the crude reaction mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield **3a** (80.6 mg, 0.377 mmol).

***N-tert*-Prenylation of Indoles 1a-f (Table 2)**



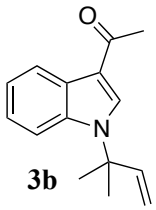
General Procedure A: In a nitrogen-filled dry-box, the appropriate indole **1** (0.500 mmol, 1.00 equiv), Cs_2CO_3 (163 mg, 0.500 mmol, 1.00 equiv), Xantphos (11.6 mg, 0.020 mmol, 0.040 equiv), and $[Pd(\eta^3\text{-prenyl})Cl]_2$ (4.2 mg, 0.010 mmol, 0.020 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (186 mg, 1.00 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture of **1**, Cs_2CO_3, and catalyst

precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were cooled to 0 °C and allowed to stir for 5 minutes. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **1**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at the reaction temperature (4-24 h) until the consumption of carbonate **2** was observed by TLC analysis. The reaction mixture was filtered through a pad of silica (eluting with EtOAc). The crude reaction mixture was concentrated under reduced pressure. $CDCl_3$ (0.5-0.7 mL) was added to dissolve the crude reaction mixture, and the ratio of *N*-*tert*-prenylindole **3**:*N*-*n*-prenylindole **4** was determined by ^{1}H NMR spectroscopy. The crude reaction mixture was purified by flash column silica gel chromatography (hexane:EtOAc or hexane:Et_2O) to yield **3a** and **3b** as single isomers and isomeric mixtures of **3c-f** + **4c-f**.



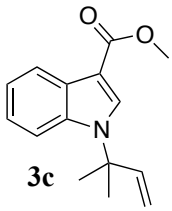
3a

1-(2-Methylbut-3-en-2-yl)-1H-indole-3-carbaldehyde[29] **(3a):** Prepared according to General Procedure A from indole-3-carboxaldehyde **1a** (72.5 mg, 0.500 mmol) (reaction time = 4 h). ^{1}H NMR spectroscopy showed a 12:1 *N*-*tert*-prenylindole **3a**:*N*-*n*-prenylindole **4b** ratio. The mixture was purified by flash column chromatography (1:1 hexane:EtOAc) to yield **3a** (80.6 mg, 0.377 mmol, 76%) as an off-white amorphous solid. R_f 0.16 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.31 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.29 - 7.18 (m, 2H), 6.10 (dd, J = 17.6, 10.8 Hz, 1H), 5.27 (d, J = 10.8 Hz, 1H), 5.19 (d, J = 17.6 Hz, 1H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 142.7, 136.8, 136.6, 126.9, 123.4, 122.8, 122.2, 117.7, 115.1, 114.8, 60.7, 28.1. HRMS (ESI) calcd. for $C_{14}H_{16}NO^+$ $[M+H]^+$ 214.1226, found 214.1226.



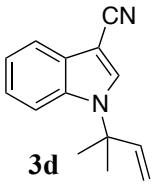
3b

1-(1-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethanone (3b): Prepared according to General Procedure A from 3-acetylindole **1b** (79.6 mg, 0.500 mmol) (reaction time = 24 h). ^{1}H NMR spectroscopy showed a 10:1 *N*-*tert*-prenylindole **3b**:*N*-*n*-prenylindole **4b** ratio. The crude material was purified by flash column chromatography (1:1 hexane:EtOAc) to yield **3b** (73.7 mg, 0.324 mmol, 65%) as a off-white amorphous solid. R_f 0.19 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, *J* = 7.6 Hz, 1H), 7.94 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.20 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.12 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 17.6 Hz, 1H), 2.54 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 143.0, 136.4, 132.7, 127.9, 122.73, 122.68, 122.4, 116.6, 114.9, 114.6, 60.4, 28.2, 28.0. HRMS (ESI) calcd. for $C_{15}H_{18}NO^+$ $[M+H]^+$ 228.1383, found 228.1383.



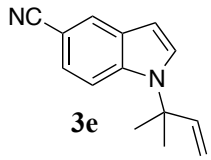
3c

Methyl 1-(2-methylbut-3-en-2-yl)-1*H*-indole-3-carboxylate[29] (3c): Prepared according to General Procedure A from methyl indole-3-carboxylate **1c** (87.6 mg, 0.500 mmol) (reaction time = 22 h). ^{1}H NMR spectroscopy showed a 12:1 *N*-*tert*-prenylindole **3c**:*N*-*n*-prenylindole **4c** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3c** and **4c** (109.1 mg, 0.448 mmol, 90%) as a colorless oil. R_f 0.47 (1:1 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 8.0, 8.4 Hz, 1H), 7.16 (dd, *J* = 8.0. 8.4 Hz, 1H), 6.08 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.15 (d, *J* = 17.6 Hz, 1H), 3.89 (s, 3H), 1.75 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 143.2, 136.1, 132.3, 128.2, 122.2, 121.9, 121.8, 114.7, 114.7, 106.5, 60.4, 51.2, 28.2. HRMS (ESI) calcd. for $C_{15}H_{18}NO_2^+$ $[M+H]^+$ 244.1332, found 244.1333.



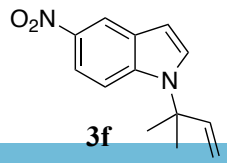
3d

1-(2-Methylbut-3-en-2-yl)-1*H*-indole-3-carbonitrile (3d): Prepared according to General Procedure A from 3-cyanoindole **1d** (71.1 mg, 0.500 mmol) (reaction time = 22 h). ^{1}H NMR spectroscopy showed a 12:1 *N-tert*-prenylindole **3d**:*N-n*-prenylindole **4d** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3d** and **4d** (99.6 mg, 0.474 mmol, 94%) as a colorless oil. R_f 0.41 (80:20 hexane:Et_2O) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.42 - 7.35 (m, 1H), 7.25 - 7.17 (m, 1H), 6.94 - 6.85 (m, 2H), 5.74 (dd, *J* = 17.4, 10.6 Hz, 1H), 4.94 (d, *J* = 10.6 Hz, 1H), 4.83 (d, *J* = 17.4 Hz, 1H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 134.9, 132.8, 129.4, 123.2, 122.1, 120.1, 116.4, 115.1, 110.9, 85.5, 60.9, 28.1. HRMS (ESI) calcd. for $C_{14}H_{15}N_2^+$ $[M+H]^+$ 211.1230, found 211.1229.



3e

1-(2-Methylbut-3-en-2-yl)-1*H*-indole-5-carbonitrile (3e): Prepared according to General Procedure A from 5-cyanoindole **1e** (71.1 mg, 0.500 mmol) (reaction time = 22 h at room temperature). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3e**:*N-n*-prenylindole **4e** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3e** and **4e** (41.6 mg, 0.198 mmol, 40%) as a colorless oil. R_f 0.47 (1:1 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 3.2 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 3.2 Hz, 1H), 6.11 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 17.6 Hz, 1H), 1.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 137.1, 129.9, 127.7, 126.7, 123.7, 121.1, 114.7, 114.5, 102.4, 102.0, 60.0, 28.2. HRMS (ESI) calcd. for $C_{14}H_{15}N_2^+$ $[M+H]^+$ 211.1230, found 211.1230.

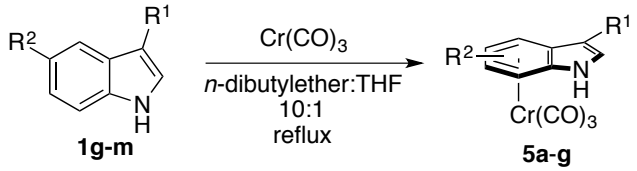


3f

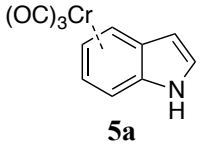
1-(2-Methylbut-3-en-2-yl)-5-nitro-1*H*-indole (3f): Prepared according to General Procedure A from 5-nitroindole **1f** (81.1 mg, 0.500 mmol)

(reaction time = 24 h at room temperature). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3f**:*N-n*-prenylindole **4f** ratio. The mixture was purified by flash column chromatography (1:1 hexane:Et_2O) to yield a mixture of **3f** and **4f** (71.8 mg, 0.312 mmol, 62%) as a light yellow amorphous solid. R_f 0.59 (1:1 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 1.2 1H), 7.98 (d, *J* = 9.2, 1.2 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.44 (d, *J* = 3.2 Hz, 1H), 6.64 (d, *J* = 3.2 Hz, 1H), 6.11 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 1.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 141.4, 138.4, 129.5, 128.7, 118.2, 116.4, 114.6, 113.7, 103.6, 60.2, 28.2. HRMS (ESI) calcd. for $C_{13}H_{15}N_2O_2^+$ $[M+H]^+$ 231.1128, found 231.1128.

Synthesis of (η^6-Indole)Cr(CO)$_3$ Complexes 5a-g

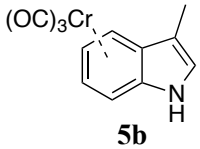


General Procedure B: In a nitrogen-filled dry-box, the appropriate indole **1g-m** (2.00-15.0 mmol), $Cr(CO)_6$ (1.42-1.78 equiv), *n*-dibutylether (40 mL) and THF (4 mL) were added to an oven-dried Schlenk flask (100 mL). The flask was sealed, removed from the dry-box, placed under a positive pressure of nitrogen and equipped with a reflux condenser. Positive pressure of nitrogen gas was maintained throughout the reaction by a nitrogen line equipped to the top of the condenser. The reaction mixture was heated at reflux (oil bath temperature = 145 °C) for 48 h. The resulting yellow/orange solution was allowed to cool to room temperature under nitrogen then filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure (70 °C water bath temp) to remove excess $Cr(CO)_6$ and *n*-dibutylether. The resulting yellow/orange solid was recrystallized from hexane:EtOAc to afford (η^6-indole)Cr(CO)$_3$ complexes **5a-g**.



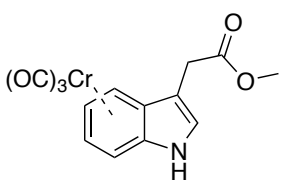
5a

(η^6-Indole)$Cr(CO)_3$[46] (5a): Prepared according to General Procedure B from indole (1.20 g, 10.2 mmol) and $Cr(CO)_6$ (3.20 g, 14.5 mmol, 1.42 equiv). The crude product was purified by recrystallization from hexane:EtOAc to yield **5a** (1.99 g, 7.84 mmol, 73%) as a yellow crystalline solid. Mp = 123-125 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.23 (app s, 1H), 6.41 (app s, 1H), 6.36 (d, *J* = 6.6 Hz, 1H), 6.12 (d, *J* = 6.6 Hz, 1H), 5.40 (t, *J* = 6.6 Hz, 1H), 5.12 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.0, 130.0, 115.5, 104.0, 100.6, 90.5, 88.6, 87.4, 78.4. IR: λ_{max} 1847, 1941, 2848, 2916, 3428. HRMS (ESI) calcd. for $C_{11}H_7CrNO_3^+$ $[M+H]^+$ 253.9904, found 253.9901.



5b

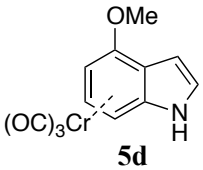
(η^6-3-Methyl-1*H*-indole)$Cr(CO)_3$[47] (5b): Prepared according to General Procedure B from 3-methylindole (1.00 g, 7.62 mmol) and $Cr(CO)_3$ (3.00 g, 13.6 mmol, 1.78 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5b** (1.44 g, 5.39 mmol, 73%) as a yellow crystalline solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 6.96 (s, 1H), 6.27 (d, *J* = 6.0 Hz, 1H), 6.09 (d, *J* = 6.0 Hz, 1H), 5.41 (t, *J* = 6.0 Hz, 1H), 5.11 (t, *J* = 6.0 Hz, 1H), 2.26 (s, 3H). Mp = 121-123 °C (decomposition). ^{1}H NMR (600 MHz, C_6D_6) δ 5.94 (app s, 1H), 5.82 (br s, 1H), 5.58 (d, *J* = 3.4, 1H), 5.24 (d, *J* = 3.4, 1H), 4.73 (app s, 1H), 4.41 (app s, 1H), 1.86 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.4, 128.4, 126.9, 116.5, 113.6, 100.4, 90.8, 87.5, 87.0, 79.0, 9.1. IR: λ_{max} 1848, 1933, 2849, 2917, 3428. HRMS (ESI) calcd. for $C_{12}H_9CrNO_3^+$ $[M+H]^+$ 268.0060, found 268.0061.



5c

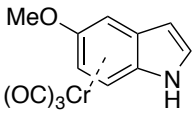
(η^6-Methyl 2-(1*H*-indol-3-yl)acetate)$Cr(CO)_3$ (5c): Prepared according to General Procedure B from methyl indole-3-acetate (0.380 g, 2.01 mmol) and $Cr(CO)_3$ (0.750 g, 3.41 mmol, 1.70 equiv).

The crude product was purified by recrystallization from hexane:EtOAc and to yield **5c** (0.291 g, 0.895 mmol, 45%) as a yellow crystalline solid. Mp = 124-126 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.18 (s, 1H), 6.33 (app s, 1H), 6.08 (app s, 1H), 5.41 (app s, 1H), 5.11 (app s, 1H), 3.77 (s, 3H), 3.68 (s, 2H). ^{13}C NMR (150 MHz, C_6D_6) δ 234.9, 170.6, 128.34, 116.0, 110.1, 99.7, 90.6, 87.5, 87.0, 78.4, 51.7, 30.5. IR: λ_{max} 1721, 1849, 1943, 2848, 2916, 3416. HRMS (ESI) calcd. for $C_{14}H_{11}CrNO_5^+$ $[M+H]^+$ 326.0115, found 326.0122.



5d

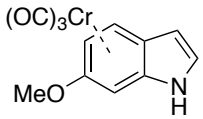
(η^6-4-Methoxy-1*H*-indole)Cr(CO)$_3$ (5d): Prepared according to General Procedure B from 4-methoxyindole (1.00 g, 2.92 mmol) and $Cr(CO)_3$ (1.70 g, 5.10 mmol, 1.75 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5d** (0.256 g, 0.904 mmol, 31%) as a yellow crystalline solid. Mp = 132-134 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.21 (app s, 1H), 6.63 (app s, 1H), 5.74 (app s, 1H), 5.46 (app s, 1H), 4.88 (app s, 1H), 3.97 (s, 3H). ^{1}H NMR (600 MHz, C_6D_6) δ 6.39 (app s, 1H), 6.14 (app s, 1H), 6.02 (br s, 1H), 4.92 (app s, 1H), 4.80 (app s, 1H), 4.08 (app s, 1H), 3.27 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.4, 139.7, 129.2, 118.1, 102.8, 95.4, 90.1, 73.0, 69.6, 55.7. IR: λ_{max} 1815, 1841, 1929, 3437. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0009.



5e

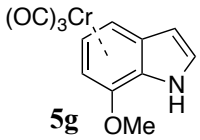
(η^6-5-Methoxy-1*H*-indole)Cr(CO)$_3$ (5e): Prepared according to General Procedure B from 5-methoxyindole (0.650 g, 4.42 mmol) and $Cr(CO)_3$ (1.46 g, 6.63 mmol, 1.50 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5e** (0.591 g, 2.09 mmol, 46%) as a yellow crystalline solid. Mp = 133-135 °C (decomposition). ^{1}HMR (600MHz, $CDCl_3$) δ 6.15 (s, 1H), 6.63 (app s, 1H), 5.74 (app s, 1H), 5.46 (app s, 1H), 4.88 (app s, 1H), 3.11 (s, 3H).

^{1}HMR (600MHz, C_6D_6) 6.15 (app s, 1H), 5.83 (app s, 1H), 5.72 (br s, 1H), 5.41 (app s, 1H), 5.30 (app s, 1H), 4.79 (app s, 1H), 3.11 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.4, 138.7, 131.2, 109.5, 103.4, 102.1, 79.5, 79.2, 71.8, 55.6. IR: λ_{max} 1849, 1933, 2849, 2916, 2961, 3445. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0013.



5f

(η^6-6-Methoxy-1*H*-indole)Cr(CO)$_3$ (5f): Prepared according to General Procedure B from 6-methoxyindole (0.500 g, 3.40 mmol) and $Cr(CO)_3$ (1.12 g, 5.09 mmol, 1.50 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5f** (0.202 g, 0.713 mmol, 21%) as a yellow crystalline solid. Mp = 131-133 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.16 (s, 1H), 6.42 (d, *J* = 6.6 Hz, 1H), 6.31 (s, 1H), 5.95 (s, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 3.78 (s, 3H). ^{1}H NMR (600MHz, C_6D_6) δ 6.18 (s, 1H), 5.90 (br s, 1H), 5.77 (s, 1H), 5.76 (d, *J* = 6.6 Hz, 1H), 5.21 (s, 1H), 4.41 (d, *J* = 6.6 Hz, 1H), 3.17 (s, 1H). ^{13}C NMR (150 MHz, C_6D_6) δ 235.5, 141.2, 129.5, 117.7, 104.3, 95.4, 87.9, 75.6, 65.8, 55.4. IR: λ_{max} 1834, 1877, 1934, 3114, 3146, 3359, 3418. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0013.

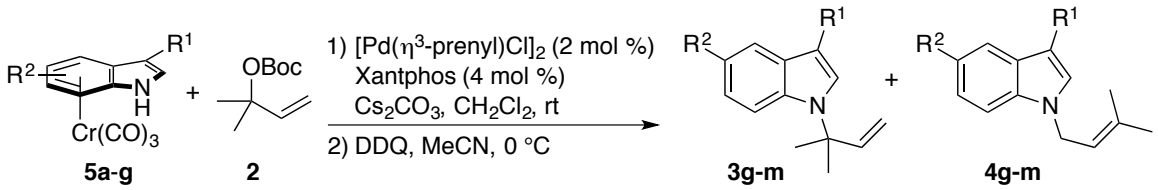


5g

(η^6-7-Methoxy-1*H*-indole)Cr(CO)$_3$ (5g): Prepared according to General Procedure B from 7-methoxyindole (0.500 g, 3.40 mmol) and $Cr(CO)_3$ (1.12 g, 5.09 mmol, 1.50 equiv). The crude product was purified by recrystallization from hexane:EtOAc and to yield **5g** (0.505 g, 1.78 mmol, 53 %) as a yellow crystalline solid. Mp = 116-118 °C (decomposition). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.2 (br s, 1H), 7.32 (app s,1H), 6.49 (app s, 1H), 5.81 (d, *J* = 6.4 Hz, 1H), 5.23 (t, *J* = 6.4, 1H) 5.07 (d, *J* = 6.4, 1H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 235.1, 132.6, 131.3, 108.8, 104.3,

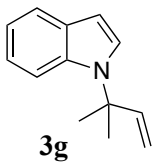
88.6, 82.5, 77.4, 72.2, 56.7. IR: λ_{max} 1825, 1936, 2848, 2916, 3405. HRMS (ESI) calcd. for $C_{12}H_9CrNO_4^+$ $[M+H]^+$ 284.0009, found 284.0011.

***N-tert*-Prenylation of (η^6-Indole)Cr(CO)$_3$ Complexes 5a-g (Table 3)**

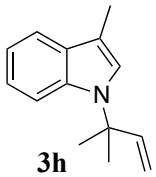


General Procedure C: In a nitrogen-filled dry-box, the appropriate (η^6-indole)Cr(CO)$_3$ complex **5** (0.250 mmol, 1.00 equiv), Cs_2CO_3 (81.2 mg, 0.250 mmol, 1.00 equiv), Xantphos (5.79 mg, 0.010 mmol, 0.020 equiv), and [Pd(η^3-prenyl)Cl]$_2$ (2.11 mg, 0.005 mmol, 0.010 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (93.1 mg, 0.500 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture of **5**, Cs_2CO_3, and catalyst precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were allowed to stir for 5 minutes. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **5**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at room temperature (2-6 h) until the consumption of carbonate **2** was observed by TLC analysis. The solvent was removed under reduced pressure. The residue was taken up in CH_3CN (3 mL), cooled to 0 °C, and DDQ (85.0 mg, 0.750 mmol, 1.50 equiv) was added. The reaction mixture was allowed to stir at 0 °C for 2-6 h. The reaction progress was monitored by TLC analysis. When the reaction was judged to be complete, the solvent was removed under reduced pressure. The resulting residue was taken up in Et_2O, filtered through a short plug of silica

gel (eluting with Et_2O), and concentrated under reduced pressure. $CDCl_3$ (0.5 - 0.7 mL) was added to dissolve the crude reaction mixture and the ratio of *N-tert*-prenylindole **3**:*N-n*-prenylindole **4** was determined by ^1H NMR spectroscopy. The crude reaction mixture was purified by flash column silica gel chromatography (hexane:EtOAc or hexane:Et_2O) to yield isomeric mixtures of **3g-m** + **4g-m**.

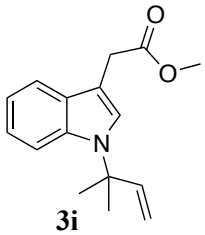

3g

1-(2-Methylbut-3-en-2-yl)-1*H*-indole[25-26] (3g): Prepared according to General Procedure C from (η^6-indole)$Cr(CO)_3$ (63.3 mg, 0.250 mmol) (reaction time = 3 h). ^1H NMR spectroscopy showed an 8:1 *N-tert*-prenylindole **3g**:*N-n*-prenylindole **4g** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3g** and **4g** (39.9 mg, 0.215 mmol, 86%) as a colorless oil. R_f 0.64 (80:20 hexane:EtOAc) ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 - 7.66 (m, 1H), 7.61 - 7.55 (m, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.22 - 7.10 (m, 2H), 6.55 (d, *J* = 2.6 Hz, 1H), 6.21 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 1.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 135.6, 130.3, 125.3, 121.2, 120.9, 119.4, 114.1, 113.8, 100.9, 59.3, 28.2 HRMS (ESI) calcd. for $C_{13}H_{16}N^+$ $[M+H]^+$186.1277, found 186.1279.


3h

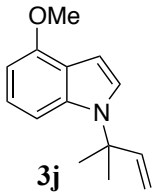
3-Methyl-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3h): Prepared according to General Procedure C from (η^6-3-methyl-1*H*-indole)$Cr(CO)_3$ (70.6 mg, 0.250 mmol) (reaction time = 2 h). ^1H NMR spectroscopy showed an 8:1 *N-tert*-prenylindole **3h**:*N-n*-prenylindole **4h** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3h** and **4h** (37.3 mg, 0.187 mmol, 75%) as a colorless oil. R_f 0.64 (80:20 hexane:EtOAc) ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 - 7.59 (m, 1H), 7.57 - 7.50 (m, 1H), 7.20 - 7.09 (m, 3H), 6.20 (dd, *J* = 18.0, 11.2 Hz, 1H), 5.25 (d, *J* = 11.2 Hz, 1H), 5.21 (d, *J* = 18.0 Hz, 1H), 2.38 (s, 3H), 1.78 (s, 6H). ^{13}C

NMR (100 MHz, $CDCl_3$): δ 144.8, 135.9, 130.4, 123.1, 120.9, 119.2, 118.7, 113.9, 113.6, 109.7, 59.0, 28.2, 10.0. HRMS (ESI) calcd. for $C_{14}H_{18}N^+$ $[M+H]^+$ 200.1434, found 200.1435.



3i

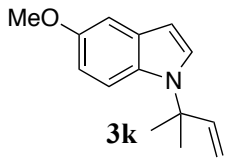
Methyl 2-(1-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)acetate (3i): Prepared according to General Procedure C from (η^6-methyl 2-(1*H*-indol-3-yl)acetate)$Cr(CO)_3$ (85.1 mg, 0.250 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 9:1 *N-tert*-prenylindole **3i**:*N-n*-prenylindole **4i** ratio. The crude material was purified by flash chromatography (70:30 hexane:Et_2O) to yield a mixture of **3i** and **4i** (50.3 mg, 0.195 mmol, 78%) as a colorless oil. R_f 0.51 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (m, 1H), 7.52 (m, 1H), 7.30 (s, 1H), 7.18 - 7.08 (m, 2H), 6.16 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.23 (d, *J* = 11.0, 1H), 5.20 (d, *J* = 17.8 Hz, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 1.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 144.5, 135.8, 129.4, 124.4, 121.2, 119.31, 119.25, 114.1, 113.8, 106.5, 59.3, 52.2, 31.6, 28.2. HRMS (ESI) calcd, for $C_{16}H_{20}NO_2^+$ $[M+H]^+$ 258.1489, found 258.1491.



3j

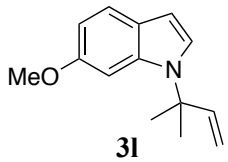
4-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3j): Prepared according to General Procedure C from (η^6-4-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction times = 6 h). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3j**:*N-n*-prenylindole **4j** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3j** and **4j** (41.8 mg, 0.194 mmol, 78%) as a colorless oil. R_f 0.53 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 3.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.07 (app t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.18 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 3.98 (s, 3H), 1.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

153.6, 144.5, 137.0, 123.9, 121.6, 120.9, 113.7, 107.7, 99.2, 98.0, 59.4, 55.6, 28.3. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1381.



3k

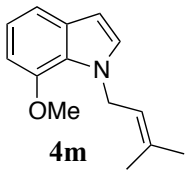
5-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3k): Prepared according to General Procedure C from (η^6-5-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction time = 5 h). ^{1}H NMR spectroscopy showed an 8:1 *N-tert*-prenylindole **3k**:*N-n*-prenylindole **4k** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3k** and **4k** (27.4 mg, 0.127 mmol, 51%) as a colorless oil. R_f 0.35 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.2 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.44 (d, *J* = 2.8 Hz, 1H), 6.16 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.24 (d, *J* = 10.8 Hz, 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 3.87 (s, 3H), 1.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 144.5, 130.9, 130.7, 125.9, 114.7, 113.8, 111.3, 102.6, 100.5, 59.2, 56.0, 28.2. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1385.



3l

6-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3l): Prepared according to General Procedure C from (η^6-6-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction time = 5 h). ^{1}H NMR spectroscopy showed a 7:1 *N-tert*-prenylindole **3l**:*N-n*-prenylindole **4l** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield a mixture of **3l** and **4l** (39.0 mg, 0.181 mmol, 73%) as a colorless oil. R_f 0.54 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 6.80 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 6.18 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 5.22 (d, *J* = 17.6 Hz, 1H), 3.85 (s, 3H), 1.77 (s, 6H). ^{13}C

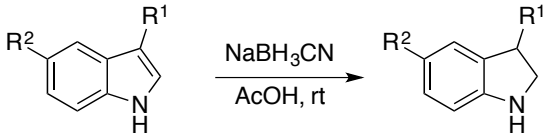
NMR (100 MHz, $CDCl_3$): δ 155.4, 144.5, 136.3, 124.7, 124.3, 121.5, 113.7, 108.9, 100.8, 98.3, 59.2, 56.0, 28.0. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1379.



4m

7-Methoxy-1-(3-methylbut-2-en-1-yl)-1*H*-indole (4m): Prepared according to General Procedure C from (η^6-7-methoxy-1*H*-indole)$Cr(CO)_3$ (74.6 mg, 0.250 mmol) (reaction time = 5 h). ^{1}H NMR spectroscopy showed a <1:20 *N*-*tert*-prenylindole **3m**:*N*-*n*-prenylindole **4m** ratio. The crude material was purified by flash chromatography (95:5 hexane:Et_2O) to yield the linear isomer **4m** (24.5 mg, 0.114 mmol, 46%) as a colorless oil. R_f 0.68 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 2.8 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 2.8 Hz, 1H), 5.43 (t, *J* = 7.0 Hz, 1H), 5.04 (d, *J* = 7.0 Hz, 2H), 3.94 (s, 3H), 1.81 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 135.0, 131.2, 128.5, 126.0, 122.4, 119.9, 114.1, 102.6, 101.7, 55.7, 47.0, 26.0, 18.3. HRMS (ESI) calcd. for $C_{14}H_{18}NO^+$ $[M+H]^+$ 216.1383, found 216.1383.

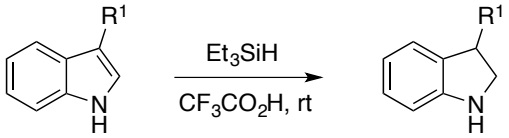
Synthesis of Indolines 6b-i



1h, 1j-n **6b, 6f-i**

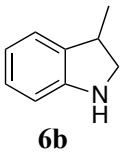
General Procedure D: To a stirred solution of indole **1h**, **1j-m** (2.38 – 6.79 mmol) in acetic acid (4–15 mL) was added $NaBH_3CN$ (5.96-17.0 mmol, 2.50 equiv). The reaction was let stir at room temperature and reaction progress was monitored by TLC analysis. The reaction mixture was diluted with H_2O, basified to pH ~9 using NaOH pellets and extracted using EtOAc (3x). The combined organic layers were washed with H_2O, saturated NaCl

solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane:EtOAc) to yield products **6b** and **6f-i**.



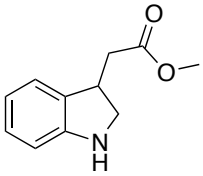
1i, 1n-o **6c-e**

General Procedure E: To a stirred solution of indole **1i**, **1n-o** (1.38 – 2.64 mmol) in trifluoroacetic acid (3–6 mL) at 50 °C was added Et_3SiH (2.76-5.29 mmol, 2.00 equiv) and the reaction was heated for 48 h and reaction progress was monitored by TLC analysis. The reaction mixture was cooled to room temperature, diluted with H_2O, basified to pH ~9 using a saturated solution of $NaHCO_3$ and extracted using $CHCl_3$ (3x). The combined organic layers were washed dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane:EtOAc) to yield products **6c**–**e**.



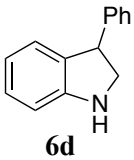
6b

3-Methyl-1*H*-indoline[48] (6b): Prepared according to General Procedure D from 3-methyl-1*H*-indole (0.500 g, 3.81 mmol), $NaBH_3CN$ (0.600 g, 9.53 mmol, 2.50 equiv) and 8 mL acetic acid (reaction time = 4.5 h) and monitored by TLC. The crude product was purified by flash column silica gel chromatography (80:20 hexane:EtOAc) to yield **6b** (0.394 g, 2.96 mmol, 78%) as a brown/red oil. R_f 0.40 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (app d, *J* = 7.6 Hz, 1H), 7.27 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 2H), 6.99 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.81 (app d, *J* = 7.6 Hz, 1H), 3.87 (br s, 1H), 3.82 (t, *J* = 8.8 Hz, 1H), 3.61 - 3.49 (m, 1H), 3.24 (t, *J* = 8.8 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 134.2, 127.1, 123.2,118.4, 109.3, 55.3, 36.5, 18.6. HRMS (ESI) calcd. for $C_9H_{12}N^+$ $[M+H]^+$ 134.0963, found 134.0965.



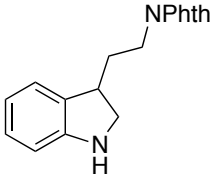
6c

Methyl 2-(indolin-3-yl)acetate[49] (6c): Prepared according to General Procedure E from methyl 2-(1*H*-indol-3-yl)acetate (0.50 g, 2.64 mmol), Et_3SiH (0.59 mL, 5.29 mmol, 2.00 equiv) and 4 mL trifluoroacetic acid (reaction time = 48 h at 50 °C). The crude product was dried on a vacuum line at 40 °C to remove unreacted Et_3SiH and yield **6c** (0.303 g, 1.58 mmol, 60%) as a brown oil. R_f 0.13 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 - 7.02 (m, 2H), 6.72 (ddd, *J* = 7.6, 7.6,1.2 Hz, 1H), 6.65 (app d, *J* = 7.6 Hz, 1H), 3.79 (t, *J* = 8.8 Hz, 2H), 3.74 (s, 1H), 3.72 (s, 3H), 3.27 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.78 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.58 (dd, *J* = 16.0, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 151.5, 131.5, 128.3, 124.2, 119.0, 110.0, 53.7, 52.0, 39.0, 38.8. HRMS (ESI) calcd. for $C_{11}H_{14}NO_2^+$ $[M+H]^+$ 192.1019, found 192.1019.



6d

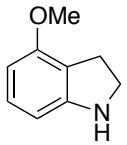
3-Phenyl-1*H*-indoline[50-51] (6d): Prepared according to General Procedure E from 3-phenyl-1*H*-indole (0.500 g, 2.57 mmol), Et_3SiH (0.570 mL, 5.15 mmol, 2.00 equiv) and 6 mL trifluoroacetic acid (reaction time = 48 h). The crude product was dried on a vacuum line at 40 °C to remove unreacted Et_3SiH and yield **6d** (0.356 g, 1.82 mmol, 71%) as a light brown oil. R_f 0.37 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.18 (m, 5H), 7.09 - 7.02 (m, 1H), 6.89 (m, 1H), 6.69 (m, 2H), 4.46 (t, *J* = 9.2 Hz, 1H), 3.90 (t, *J* = 9.2 Hz, 1H), 3.89 (br s, 1H), 3.47 (t, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 143.8, 132.7, 128.9, 128.5, 128.1, 127.0, 125.3, 119.4, 110.1, 57.0, 49.0. HRMS (ESI) calcd. for $C_{14}H_{14}N^+$ $[M+H]^+$ 196.1121, found 196.1119.



6e

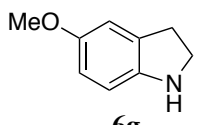
2-(2-(Indolin-3-yl)ethyl)isoindoline-1,3-dione[52] (6e): Prepared according to General Procedure E from 2-(2-(1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (0.400 g, 1.38 mmol), Et_3SiH (0.310 mL,

2.76 mmol, 2.00 equiv) and 3 mL trifluoroacetic acid (reaction time = 48 h). The crude product was purified by flash column chromatography (60:40 hexane:EtOAc) to yield **6e** (0.281 g, 0.96 mmol, 70%) as a tan amorphous solid. R_f 0.31 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 - 7.80 (m, 2H), 7.75 - 7.67 (m, 2H), 7.15 (app d, *J* = 7.6 Hz, 1H), 7.01 (app t, *J* = 7.6 Hz, 1H), 6.70 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 2H), 6.63 (app d, *J* = 7.6 Hz, 1H), 3.84 - 3.74 (m, 3H), 3.33 - 3.25 (m, 2H), 2.27 - 2.16 (m, 1H), 1.99 - 1.88 (m, 1H), 1.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 151.5, 134.3, 132.4, 132.1, 128.0, 124.2, 123.6, 119.1, 110.0, 53.3, 40.0, 36.4, 33.0. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_2^+$ $[M+H]^+$ 293.1285, found 293.1286.



6f

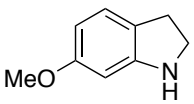
4-Methoxy-1*H*-indoline[53] (6f): Prepared according to General Procedure D from 4-methoxy-1*H*-indole (0.500 g, 3.40 mmol), $NaBH_3CN$ (0.530 g, 8.49 mmol, 2.50 equiv) and 7 mL acetic acid (reaction time = 3 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6f** (0.332 g, 2.22 mmol, 65%) as an opaque oil. R_f 0.28 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.0 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 2H), 3.97 (br s, 1H), 3.83 (s, 3H), 3.57 (t, *J* = 8.4 Hz, 2H), 3.00 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 153.4, 128.9, 116.1, 103.6, 102.0, 55.5, 47.7, 27.1. HRMS (ESI) calcd. for $C_9H_{12}NO^+$ $[M+H]^+$ 150.0913, found 150.0913.



6g

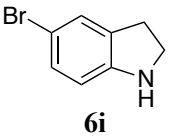
5-Methoxy-1*H*-indoline[54-55] (6g): Prepared according to General Procedure D from 5-methoxy-1*H*-indole (1.00 g, 6.79 mmol), $NaBH_3CN$ (1.07 g, 17.0 mmol, 2.50 equiv) and 14 mL acetic acid (reaction time = 2 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6g** (0.766 g, 5.13 mmol, 76%) as a brown/red oil. R_f 0.16 (80:20 hexane:EtOAc) ^{1}H

NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.65 - 6.55 (m, 2H), 3.75 (s, 3H), 3.52 (t, *J* = 8.4 Hz, 2H), 3.52 (br s, 1H), 3.01 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 145.6, 131.3, 112.3, 111.7, 110.2, 56.1, 48.0, 30.6. HRMS (ESI) calcd. for $C_9H_{12}NO^+$ $[M+H]^+$ 150.0913, found 150.0913.



6h

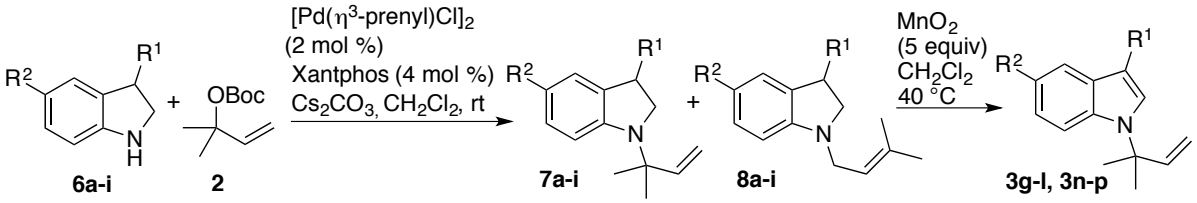
6-Methoxy-1*H*-indoline[56] (6h): Prepared according to General Procedure D from 6-methoxy-1*H*-indole (0.350 g, 2.38 mmol), $NaBH_3CN$ (0.370 g, 5.95 mmol, 2.50 equiv) and 5 mL acetic acid (reaction time = 2 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6h** (0.326 g, 2.19 mmol,, 92%) as a brown/red oil. R_f 0.26 (80:20 hexane:EtOAc) ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.0 Hz, 1H), 6.33 - 6.22 (m, 2H), 3.92 (br s, 1H), 3.77 (s, 3H), 3.55 (t, *J* = 8.2 Hz, 2H), 2.98 (t, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 153.1, 124.7, 121.7, 103.4, 96.4, 55.4, 48.0, 29.1. HRMS (ESI) calcd. for $C_9H_{12}NO^+$ $[M+H]^+$ 150.0913, found 150.0912.



6i

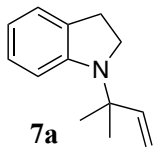
5-Bromo-1*H*-indoline[57] (6i): Prepared according to General Procedure D from 5-bromo-1*H*-indole (0.500 g, 2.55 mmol), $NaBH_3CN$ (0.400 g, 6.38 mmol, 2.50 equiv) and 5 mL acetic acid (reaction time = 2 h). The crude product was purified by flash column chromatography (80:20 hexane:EtOAc) to yield **6i** (0.469 g, 3.14 mmol, 93%) as a brown/red oil. R_f 0.29 (80:20 hexane:EtOAc) ^1H NMR (400 MHz, $CDCl_3$): δ 6.69 (d, *J* = 2.0 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.99 (d, *J* = 8.4 Hz, 1H), 3.16 (br s, 1H), 3.04 (t, *J* = 8.6 Hz, 2H), 2.50 (t, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 132.1, 130.1, 127.8, 110.9, 110.4, 47.8, 30.0. HRMS (ESI) calcd. for $C_8H_9BrN^+$ $[M+H]^+$ 197.9913, observed 197.9914.

***N-tert*-Prenylation of Indolines 6a-i (Table 4)**

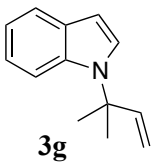


General Procedure F: In a nitrogen-filled dry-box, the appropriate indoline **6** (0.500 mmol, 1.00 equiv), Cs_2CO_3 (163 mg, 0.500 mmol, 1.00 equiv), Xantphos (11.6 mg, 0.020 mmol, 0.040 equiv), and $[Pd(\eta^3\text{-prenyl})Cl]_2$ (4.21 mg, 0.010 mmol, 0.020 equiv.) were added to a 1-dram vial. *tert*-Butyl (2-methylbut-3-en-2-yl) carbonate **2** (186 mg, 1.00 mmol, 2.00 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture of **1**, Cs_2CO_3, and catalyst precursors was suspended in CH_2Cl_2 (1.5 mL). Carbonate **2** was dissolved in CH_2Cl_2 (1 mL). The vials were cooled to 0 °C and allowed to stir for 5 minutes. The solution of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** was then added to the suspension of **1**, Cs_2CO_3, and catalyst precursors. The reaction mixture was allowed to stir at the reaction temperature (1.5-2 h) until the consumption of carbonate **2** was observed by TLC analysis. The reaction mixture was filtered through a pad of silica (eluting with EtOAc) and the crude reaction mixture was concentrated under reduced pressure. $CDCl_3$ (0.5-0.7 mL) was added to dissolve the crude reaction mixture, and the ratio of *N-tert*-prenylindoline **7a-i**:*N-n*-prenylindoline **8a-i** was determined by ^1H NMR spectroscopy. The crude reaction mixture was purified by flash column chromatography (hexane:Et_2O) to yield **7a-d** and **7f-i** as single constitutional isomers and an isomeric mixture of **7e** + **8e**. *N-tert*-prenylindoline **7a-i** (0.125-0.200 mmol, 1.00 equiv) was then added to a scintillation vial, dissolved in 4 mL CH_2Cl_2 and MnO_2 (5.00 equiv) was added. The reaction mixture was heated to 50 °C for 24 - 48 hours in

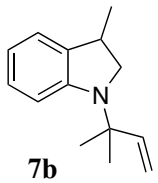
the sealed vial. The reaction mixture was cooled to room temperature, filtered through a pad of celite (eluting with EtOAc) and concentrated under reduced pressure to yield products **3g-l** and **3n-p**.


7a

1-(2-Methylbut-3-en-2-yl)indoline[25-26] (7a): Prepared according to General Procedure F from 1*H*-indoline (59.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 6:1 *N-tert*-prenylindoline **7a**:*N-n*-prenylindoline **8a** ratio. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **7a** (77.5 mg, 0.414 mmol, 83%) as a colorless oil. R_f 0.42 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.18 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 3.47 (t, *J* = 8.4 Hz, 2H), 2.95 (t, *J* = 8.4 Hz, 2H), 1.39 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 147.32, 131.7, 126.7, 124.5, 117.5, 112.4, 111.4, 57.6, 49.3, 28.4, 24.3. HRMS (ESI) calcd. for $C_{13}H_{18}N^+$ $[M+H]^+$ 188.1434, observed 188.1435.

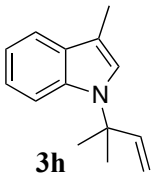

3g

1-(2-Methylbut-3-en-2-yl)-1*H*-indole[25-26] (3g): Prepared according to General Procedure F from **7a** (37.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3g** was isolated as a colorless oil (36.1 mg, 0.195 mmol, 96%). Experimental data matches values for Table 3, entry 1.


7b

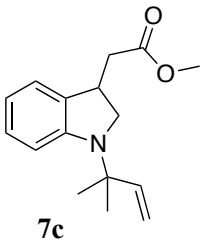
3-Methyl-1-(2-methylbut-3-en-2-yl)-1H-indoline (7b): Prepared according to General Procedure F from **6b** (66.6 mg, 0.500 mmol) (reaction time = 2 h) ^{1}H NMR spectroscopy showed a 5:1 *N-tert*-prenylindoline **7b**:*N-n*-prenylindoline **8b**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **8b** (59.6 mg, 0.296 mmol, 59%) as a colorless oil. R_f 0.65 (80:20

hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (app d, *J* = 7.2 Hz, 1H), 7.01 (app t, *J* = 8.8 Hz, 1H), 6.83 (app d, *J* = 8.0 Hz, 1H), 6.70 (ddd, *J* = 7.2, 7.2, 0.8 Hz, 1H), 6.17 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.27 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.17 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.66 (t, *J* = 8.4 Hz, 1H), 3.33 - 3.19 (m, 1H), 2.99 (t, *J* = 8.4 Hz, 1H), 1.40 (s, 3H), 1.37 – 1.32 (d, *J* = 6.8, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 147.3, 136.6, 126.9, 123.1, 117.5, 112.4, 111.4, 57.4, 34.7, 26.8, 22.0, 18.6. HRMS (ESI) calcd. for $C_{14}H_{20}N^+$ $[M+H]^+$ 202.1590, found 202.1591.



3h

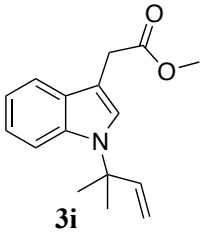
3-Methyl-1-(2-methylbut-3-en-2-yl)-1H-indole (3h): Prepared according to General Procedure F from **7b** (40.3 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3h** was isolated as a colorless oil (38.5 mg, 0.193 mmol, 97%). Experimental data matches values for Table 3, entry 2.



7c

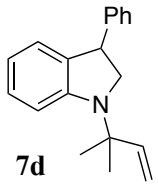
Methyl 2-(1-(2-methylbut-3-en-2-yl)-1*H*-indolin-3-yl)acetate (7c): Prepared according to General Procedure F from **6c** (95.6 mg, 0.500 mmol) (reaction time = 1.5 h). ^{1}H NMR spectroscopy showed a 5:1 *N-tert*-prenylindoline **7c**:*N-n*-prenylindoline **8c**. The crude material was purified by flash chromatography on silica gel (98:2 hexane:Et_2O) to yield **7c** (73.2 mg, 0.282 mmol, 56%) as a colorless oil. R_f 0.51 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 -7.01 (app d, *J* = 7.2 Hz, 1 H), 7.00 - 6.96 (app t, *J* = 8.0, 1H), 6.79 (app d, *J* = 8.0 Hz, 1H), 6.64 (app t, *J* = 7.2 Hz, 1H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.22 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.13 (d, *J* = 10.8, 1.0 Hz, 1H), 3.73 (s, 3H), 3.69 (t, *J* = 8.4 Hz, 1H), 3.63 - 3.52 (m, 1H), 3.15 (dd, *J* = 8.6, 6.0 Hz, 1H), 2.79 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.58 (dd, *J* = 16.4, 8.6 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 150.6, 147.0, 133.4, 127.6,

123.6, 117.5, 112.6, 111.7, 57.4, 55.4, 52.0, 38.9, 36.6, 24.8, 24.1. HRMS (ESI) calcd. for $C_{16}H_{22}NO_2^+$ $[M+H]^+$ 260.1645, found 260.1646.



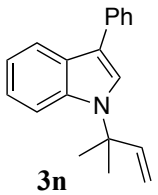
3i

Methyl 2-(1-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)acetate (3i): Prepared according to General Procedure F from **7c** (51.9 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 48 h. Pure isomer **3i** was isolated as a colorless oil (39.6 mg, 0.154 mmol, 77%). Experimental data matches values for Table 3, entry 3.



7d

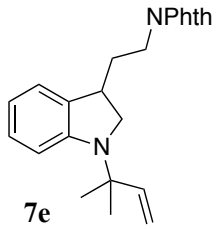
1-(2-Methylbut-3-en-2-yl)-3-phenyl-1*H*-indoline (7d): Prepared according to General Procedure F from **6d** (97.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 5:1 *N*-*tert*-prenylindoline **7d**:*N*-*n*-prenylindoline **7d**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **7d** (80.8 mg, 0.307 mmol, 61%) as a colorless oil. R_f 0.68 (80:20 hexane:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (m, 4H), 7.24 – 7.16 (m, 1H), 6.95 (app t, J = 8.0 Hz, 1H), 6.82 (app d, J = 8.0 Hz, 1H), 6.79 (app d, J = 8.0 Hz, 1H), 6.57 (app t, J = 8.0 Hz, 1H), 6.11 (dd, J = 17.6, 10.4 Hz, 1H), 5.21 (dd, J = 17.6, 0.8 Hz, 1H), 5.10 (dd, J = 10.4, 0.8 Hz, 1H), 4.29 (t, J = 8.8 Hz, 1H), 3.80 (t, J = 8.8 Hz, 1H), 3.30 (t, J = 8.8 Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 147.1, 144.0, 134.6, 128.8, 128.6, 127.3, 127.0, 124.9, 117.9, 112.6, 111.8, 58.7, 57.7, 47.0, 26.6, 22.4. HRMS (ESI) calcd. for $C_{19}H_{22}N^+$ $[M+H]^+$.264.1747, found 264.1745.



3n

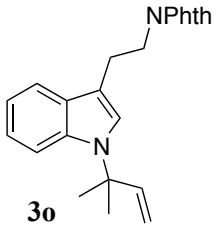
1-(2-Methylbut-3-en-2-yl)-3-phenyl-1*H*-indole (3n): Prepared according to General Procedure F from **7d** (52.7 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3n** was isolated as a colorless oil (48.3 mg, 0.185 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 - 7.72 (m,

1H), 7.47 (m, 2H), 7.42 - 7.35 (m, 1H), 7.28 - 7.20 (m, 3H), 7.14 - 7.04 (m, 1H), 7.00 - 6.92 (m, 2H), 5.99 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.06 (dd, *J* = 10.2, 0.8 Hz, 1H), 5.02 (dd, *J* = 17.0, 0.8 Hz, 1H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 136.4, 136.2, 129.0, 128.0, 127.8, 126.0, 123.4, 121.4, 120.2, 120.0, 116.5, 114.4, 114.0, 59.6, 28.3. HRMS (ESI) calcd. for $C_{19}H_{20}N^+$ $[M+H]^+$ 262.1590, found 262.1591.



7e

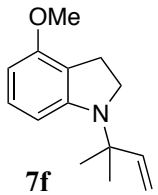
2-(2-(1-(2-Methylbut-3-en-2-yl)indolin-3-yl)ethyl)isoindoline-1,3-dione (7e): Prepared according to General Procedure F from **6e** (146 mg, 0.500 mmol) (reaction time = 3 h). ^{1}H NMR spectroscopy showed a 4:1 *N-tert*-prenylindoline **7e**:*N-n*-prenylindoline **8e**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **7e** (89.5 mg, 0.248 mmol, 50%) as a colorless oil. R_f 0.43 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 - 7.82 (m, 2H), 7.76 - 7.68 (m, 2H), 7.13 - 7.03 (m, 2H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.64 (dt, *J* = 12.9, 7.4 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.20 (dd, 17.6, 0.8 Hz, 1H), 5.12 (dd, *J* = 10.8, 0.8 Hz, 1H), 3.84 – 3.78 (m, 2H), 3.72 - 3.66 (m, 1H), 3.24 - 3.01 (m, 2H), 2.29 - 2.18 (m, 1H), 1.96 - 1.85 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 150.6, 147.1, 134.3, 134.0, 132.5, 127.3, 123.6, 123.5, 117.6, 112.5, 111.6, 57.5, 55.1, 37.6,36.4, 32.9, 25.6, 23.4, HRMS (ESI) calcd, for $C_{23}H_{24}N_2O_2^+$ $[M+H]^+$ 361.1911, found 361.1917.



3o

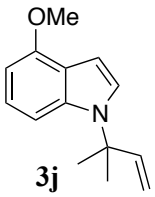
2-(2-(1-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (3o): Prepared according to General Procedure F from **7e** (45.7 mg, 0.125 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3o** was isolated as a yellow/orange oil (42.2 mg, 0.118 mmol, 94%). R_f 0.21 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.83 (m,

2H), 7.77 - 7.68 (m, 3H), 7.51 - 7.47 (m, 1H), 7.20 (s, 1H), 7.14 - 7.08 (m, 2H), 6.13 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 4.01 (dd, *J* = 7.6 Hz, 7.4 Hz, 2H), 3.15 (dd, *J* = 7.6 Hz, 7.4 Hz, 2H), 1.72 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 144.5, 135.9, 134.1, 132.6, 129.5, 123.6, 123.4, 121.1, 119.3, 119.1, 114.0, 113.7, 110.4, 59.2, 38.9, 28.2, 24.8. HRMS (ESI) calcd. for $C_{23}H_{23}N_2O_2^+$ $[M+H]^+$ 359.1754, found 359.1757.



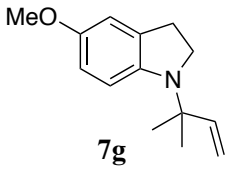
7f

4-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (7f): Prepared according to General Procedure F from **6f** (74.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 4:1 *N*-*tert*-prenylindoline **7f**:*N*-*n*-prenylindoline **8f**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **7f** (63.1 mg, 0.290 mmol, 58%) as a colorless oil. R_f 0.53 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 7.2 Hz, 1H), 6.14 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.23 (d, *J* = 17.6 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 3.82 (s, 3H), 3.47 (t, *J* = 8.4 Hz, 2H), 2.88 (t, *J* = 8.4 Hz, 2H), 1.35 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 152.7, 147.5, 128.0, 112.3, 107.7, 105.5, 100.9, 57.7, 55.5, 49.6, 25.1, 24.5. HRMS (ESI) calcd. for $C_{14}H_{20}NO^+$ $[M+H]^+$ 218.1539, found 218.1545.



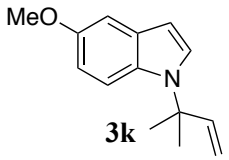
3j

4-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3j): Prepared according to General Procedure F from **7f** (43.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3j** was isolated as a colorless oil (40.2 mg, 0.186 mmol, 93%). Experimental data matches values for Table 3, entry 4.



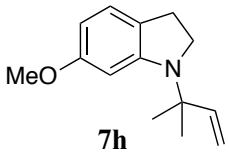
7g

5-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (7g): Prepared according to General Procedure F from **6g** (74.6 mg, 0.500 mmol) (reaction time = 2 h) ^{1}H NMR spectroscopy showed a 2:1 *N-tert*-prenylindoline **7g**:*N-n*-prenylindoline **8g**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **7g** (28.4 mg, 0.131 mmol, 26%) as a colorless oil. R_f 0.32 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, *J* = 8.8 Hz, 1H), 6.71 (s, 1H), 6.52 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.12 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.22 (d, *J* = 17.4 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 3.73 (s, 3H), 3.37 (t, *J* = 8.0 Hz, 2H), 2.88 (t, *J* = 8.0 Hz, 2H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 147.6, 145.2, 133.4, 112.4, 111.8 (2C), 111.2, 57.7, 56.1, 49.7, 28.8, 24.1. HRMS (ESI) calcd. for $C_{14}H_{20}NO^+$ $[M+H]^+$ 218.1539, found 218.1537.



3k

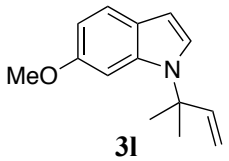
5-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3k): Prepared according to General Procedure F from **7g** (43.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3k** was isolated as a colorless oil (43.4 mg, 0.200 mmol, 99%). Experimental data matches values for Table 3, entry 5.



7h

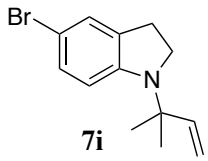
6-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (7h): Prepared according to General Procedure F from **6h** (74.6 mg, 0.500 mmol) (reaction time = 2 h). ^{1}H NMR spectroscopy showed a 5:1 *N-tert*-prenylindoline **7h**:*N-n*-prenylindoline **8h**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **7h** (66.2 mg, 0.305 mmol, 61%) as a colorless oil. R_f 0.54 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 6.24 - 6.07 (m, 2H), 5.25 (d, *J* = 17.6 Hz, 1H), 5.16 (d, *J* = 10.8 Hz, 1H), 3.74

(s, 3H), 3.46 (t, J = 8.0 Hz, 2H), 2.86 (t, J = 8.0 Hz, 2H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 152.2, 147.3, 124.2, 113.7, 112.5, 101.1, 99.3, 55.6, 49.9, 27.9, 27.5, 24.3. HRMS (ESI) calcd. for $C_{14}H_{20}NO^+$ $[M+H]^+$ 218.1539, found 218.1539.



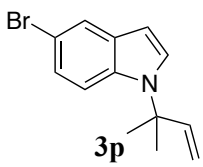
3l

6-Methoxy-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3l): Prepared according to General Procedure F from **7h** (43.5 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3l** was isolated as a colorless oil (42.3 mg, 0.196 mmol, 98%). Experimental data matches values for Table 3, entry 6.



7i

5-Bromo-1-(2-methylbut-3-en-2-yl)-1*H*-indoline (7i): Prepared according to General Procedure F from **6i** (99.0 mg, 0.500 mmol) (reaction time = 1.5 h). ^{1}H NMR spectroscopy showed a 5.5:1 *N-tert*-prenylindoline **7i**:*N-n*-prenylindoline **8i**. The crude material was purified by flash chromatography (98:2 hexane:Et_2O) to yield **7i** (98.0 mg, 0.368 mmol, 74%) as a colorless oil. R_f 0.59 (80:20 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (app s, 1H), 7.03 (dd, J = 8.8, 2.0, Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.08 (dd, J = 17.6, 11.6 Hz, 1H), 5.22 (d, J = 17.6 Hz, 1H), 5.15 (d, J = 11.6 Hz, 1H), 3.44 (t, J = 8.4 Hz, 2H), 2.89 (t, J = 8.4 Hz, 2H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 146.7, 134.1, 129.3, 127.3, 112.8, 112.6, 109.2, 57.6, 49.5, 28.1, 24.3. HRMS (ESI) calcd. for $C_{13}H_{17}BrN^+$ $[M+H]^+$ 266.0539, found 266.0540.



3p

5-Bromo-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3p): Prepared according to General Procedure G from **7i** (53.2 mg, 0.200 mmol) and MnO_2 (87.0 mg, 1.00 mmol, 5.00 equiv) and heated for 24 h. Pure isomer **3p** was isolated as a colorless oil (46.1 mg, 0.175 mmol, 87%). R_f 0.59 (80:20 hexane:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 1.6 Hz, 1H), 7.40 (app d, J = 8.8 Hz, 1H), 7.31 (d, J

= 3.2 Hz, 1H), 7.20 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.43 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.12 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.24 (d, *J* = 11.2 Hz, 1H), 5.15 (d, *J* = 17.6 Hz, 1H), 1.75 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 134.2, 132.0, 126.6, 123.7, 123.6, 115.4, 114.2, 112.9, 100.5, 59.6, 28.2. HRMS (ESI) calcd. for $C_{13}H_{15}BrN^+$ $[M+H]^+$ 264.0382, found 264.0379.

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CHAPTER III

RHODIUM-CATALYZED, ENANTIOSELECTIVE HYDROACYLATION OF *ORTHO*-ALLYLBENZALDEHYDES

Adapted from a paper published in *Organic Letters*[1] and highlighted in *SYNFACTS*

Kirsten F. Johnson, Adam C. Schmidt, Levi M. Stanley

Abstract

The development of a rhodium catalyst for *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes is described. A catalyst generated *in situ* from $[Rh(COD)Cl]_2$, (*R*)-DTBM-Segphos and NaBARF promotes the enantioselective hydroacylation reactions and minimizes the formation of byproducts from competitive alkene isomerization and ene/dehydration pathways. These rhodium-catalyzed processes generate the 3,4-dihydronaphthalen-1(2*H*)-one products in moderate-to-high yields (49-91%) with excellent enantioselectivities (96-99% ee).

Introduction

The development of new catalysts has rendered intramolecular alkene hydroacylation a valuable strategy to generate a wide variety of carbocyclic and heterocyclic ketones.[2-25] These transformations, which involve the formal insertion of an aldehyde C-H bond into an alkene, can be promoted by transition metal or *N*-heterocyclic carbene (NHC) catalysts. The selection of transition metal or NHC catalysts for enantioselective intramolecular hydroacylations is often dictated by the desired regiochemical outcome of the reaction. Intramolecular olefin hydroacylations promoted by NHC-catalysts occur with *exo* selectivity (formal Markovnikov selectivity),[4-11] while transition metal-catalyzed hydroacylations can occur with either *endo* selectivity (formal anti-Markovnikov selectivity)[12-22] or *exo*

selectivity.[23-25] The potential for complementary regioselectivity makes possible the synthesis of two distinct ketone products from the same substrate.

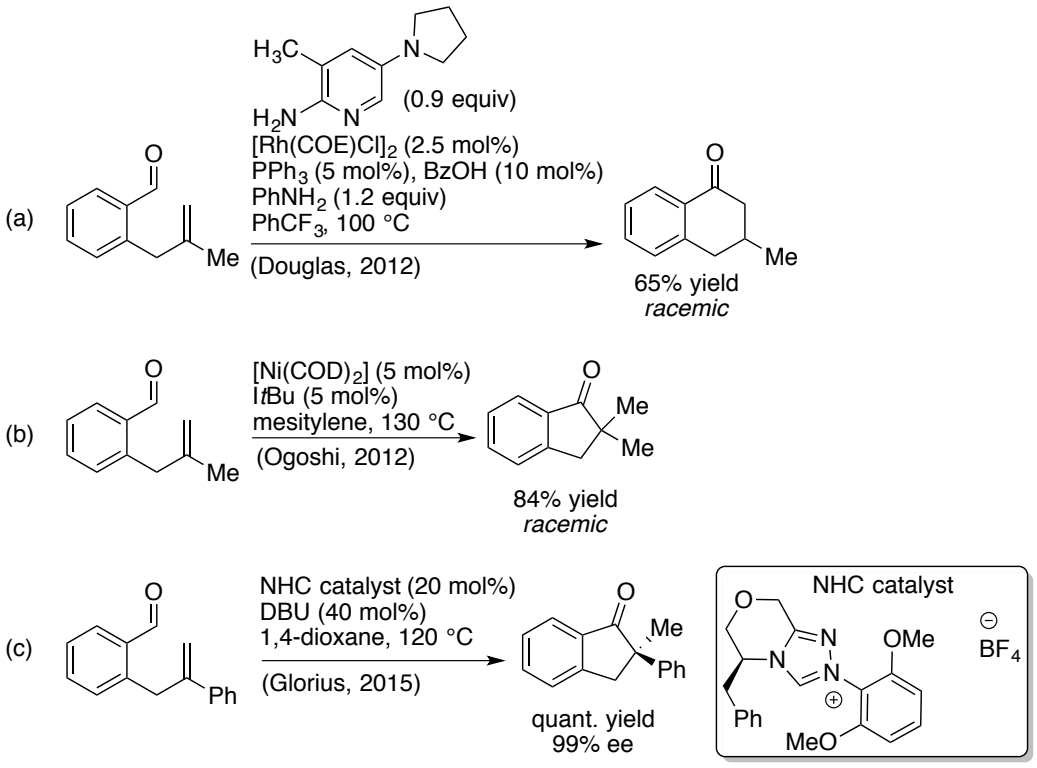


Figure 1: Hydroacylations of *ortho*-allylbenzaldehydes.

ortho-Allylbenzaldehydes are a class of substrates that highlights the two potential regiochemical outcomes of alkene hydroacylation. Douglas and co-workers reported the *endo*-selective hydroacylation of *ortho*-allylbenzaldehydes that occur in the presence of an achiral rhodium catalyst to form racemic 3,4-dihydronaphthalene-1(*2H*)-ones (Figure 1a).[26] The complementary *exo*-selective processes occur in the presence of an achiral nickel catalyst to form racemic 2,3-dihydro-*1H*-inden-1-ones (Figure 1b).[27] In 2015, Glorius and co-workers reported the first catalytic, *exo*- and enantioselective hydroacylations of *ortho*-allylbenzaldehydes to form 2,3-dihydro-*1H*-inden-1-ones containing an all-carbon quaternary stereogenic center (Figure 1c).[28] However, an *endo*- and enantioselective variant of the

hydroacylation of *ortho*-allylbenzaldehydes had not been reported prior to the work described in this thesis chapter.

In 2014, we reported enantioselective hydroacylation of *N*-allyllindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes to generate six-membered ketone products with exclusive *endo* selectivity.[29] These reactions occur in the presence of rhodium complexes containing a chiral bisphosphine ligand and a weakly coordinating counteranion. We envisioned that a related cationic rhodium catalyst would promote the *endo*-selective hydroacylation of *ortho*-allylbenzaldehydes to form 3,4-dihydronaphthalen-1(2*H*)-ones with high enantioselectivities (Figure 2).

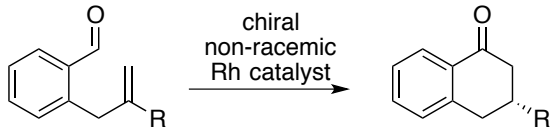


Figure 2: Proposed reaction scheme for *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes.

We envisioned that this reaction could proceed through the accepted mechanism for transition metal-catalyzed olefin hydroacylation reactions, and we expected to encounter the same challenges of catalyst activity described in previous reports (Figure 3).[2, 30-31] The standard hydroacylation mechanism involves oxidative addition to the aldehyde C-H bond to generate an acylmetal(III) hydride intermediate. This species must be sufficiently stabilized to prevent a reaction sequence including decarbonylation and reductive elimination that inactivates the transition metal catalyst.[14-15, 30-31] The productive reaction pathway proceeds with migratory insertion of the olefin into the metal-hydride bond of the acylmetal(III) hydride species. Finally, reductive elimination generates the ketone product and regenerates the active metal catalyst. Previous mechanistic studies on transition metal-catalyzed olefin hydroacylation have found that reductive elimination is the turnover-limiting step in these

processes.[2-3, 30-31] We hypothesized that a cationic rhodium complex could facilitate the hydroacylation of *ortho*-allylbenzaldehydes and proper tuning of the steric and electronic properties of this catalyst could improve catalyst activity by increasing the rate of reductive elimination.

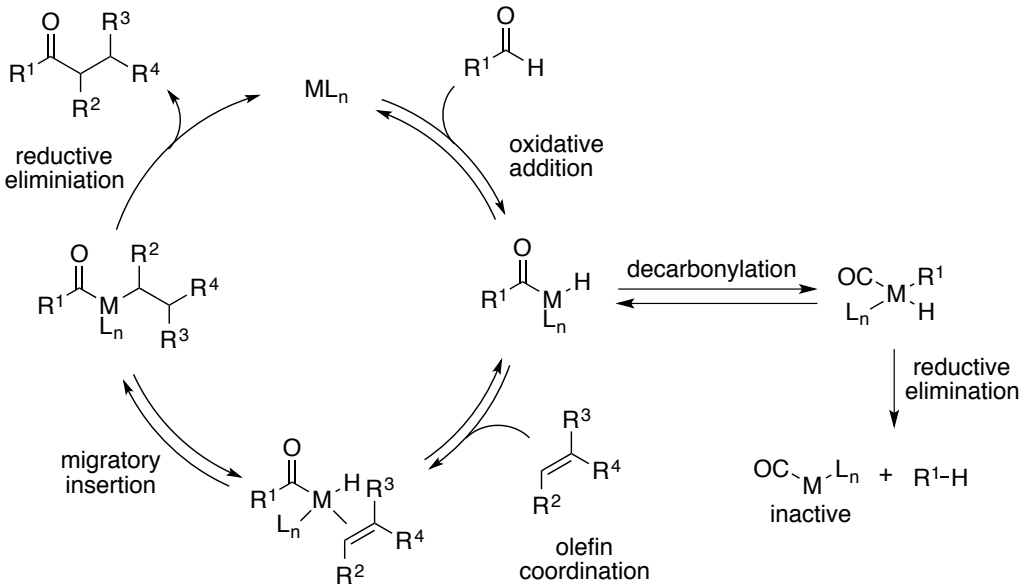
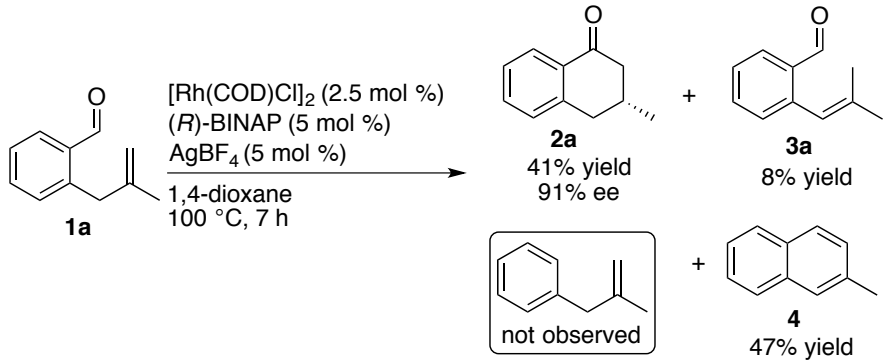


Figure 3: Catalytic cycle for transition metal-catalyzed olefin hydroacylation.

Results and Discussion

To assess the feasibility of *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes, we evaluated the reaction of 2-(2-methylallyl)benzaldehyde **1a** in the presence of a catalyst generated from $[Rh(COD)Cl]_2$, (*R*)-BINAP, and $AgBF_4$ (Scheme 1).



Scheme 1: Rh-catalyzed hydroacylation of 2-(2-methylallyl)benzaldehyde **1a**

This reaction formed the desired hydroacylation product **2a** in 41% yield with 91% ee, but we also observed formation of the alkene isomerization product **3a** in 8% yield and 2-methylnaphthalene **4** in 47% yield. Although transition metal-catalyzed hydroacylation reactions often require high catalyst loadings to overcome competitive decarbonylation,[14-18, 30-31] decarbonylation of **1a** was not observed under these conditions.

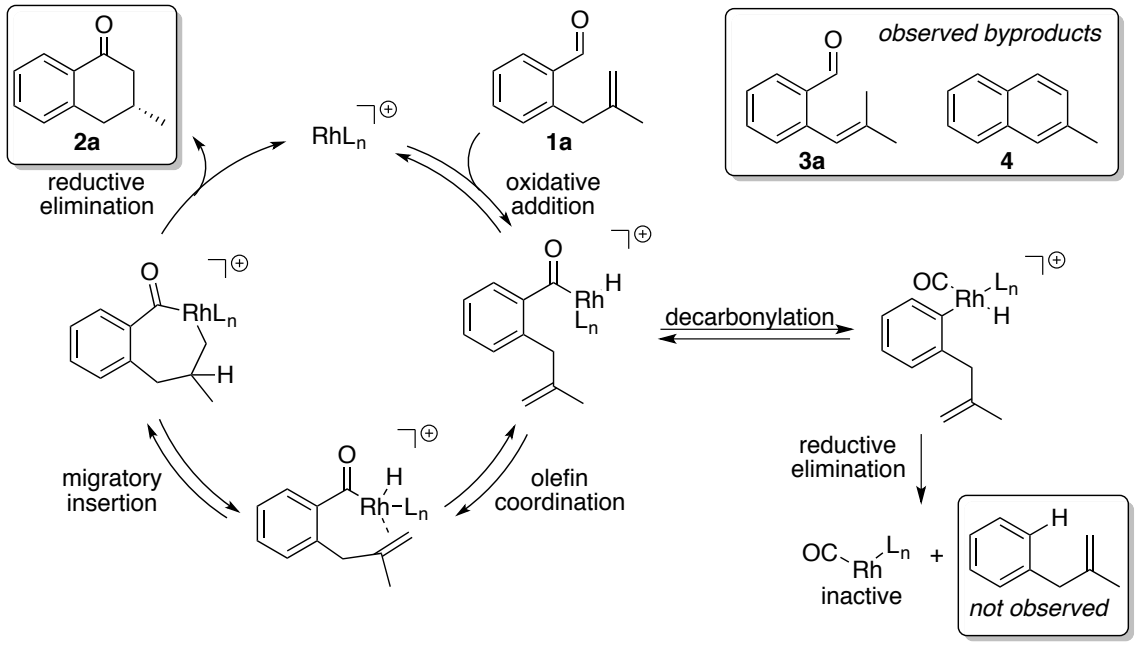
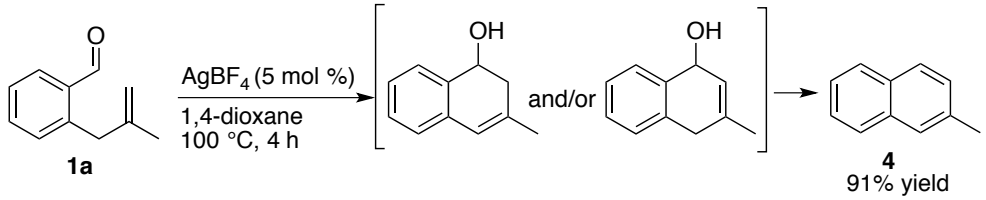


Figure 4: Catalytic cycle for the Rh-catalyzed hydroacylation of *ortho*-allylbenzaldehydes.

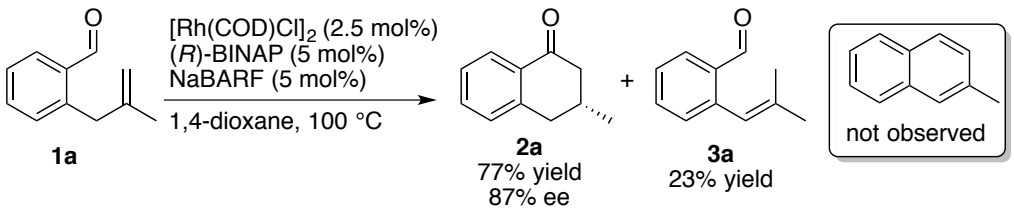
The formation of 2-methylnaphthalene **4** from the reaction of **1a** was unexpected and has not been described in the context of alkene hydroacylation. However, the formation of substituted naphthalene derivatives from *ortho*-allylbenzaldehydes is known to occur by a sequence of Lewis acid-catalyzed intramolecular ene reaction and dehydration.[32] To evaluate whether the silver salt used to generate the active catalyst promotes the formation of **4**, 2-(2-methylallyl)benzaldehyde **1a** was exposed to 5 mol % $AgBF_4$ in the absence of $[Rh(COD)Cl]_2$ and the bisphosphine ligand (Scheme 2). This reaction generated **4** in 91%

yield and demonstrates that $AgBF_4$ is a non-innocent additive under our catalytic reaction conditions.



Scheme 2: Ag(I)-catalyzed ene/dehydration of 2-(2-methylallyl)benzaldehyde

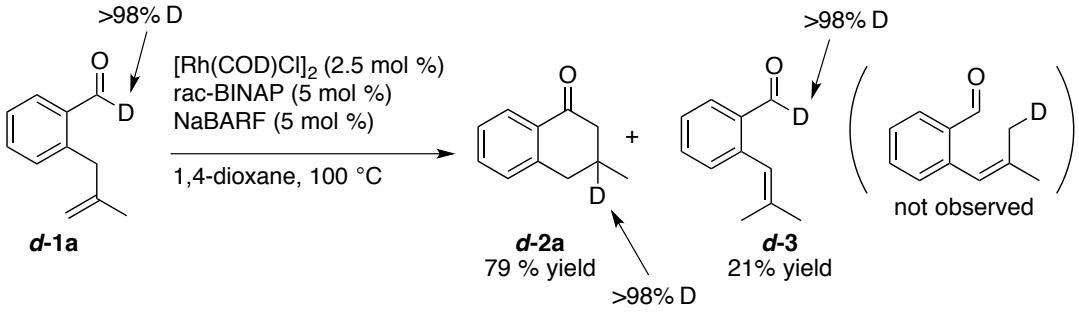
To effect counteranion exchange and enable the *in situ* generation of the active, cationic rhodium complex while mitigating the silver-catalyzed ene/dehydration pathway, we employed sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) in place of $AgBF_4$.[33-35] We hypothesized the absence of Ag(I) would eliminate the formation of **4**. To test this hypothesis, we evaluated the hydroacylation of **1a** in the presence of a catalyst generated from $[Rh(COD)Cl]_2$, (*R*)-BINAP, and NaBARF (Scheme 3). The reaction occurred to form the ketone product **2a** in 77% yield and the alkene isomerization product **3a** in 23% yield. The formation of 2-methylnaphthalene **4** was not observed.



Scheme 3: Hydroacylation of *ortho*-allylbenzaldehyde **1a** using a NaBARF additive

Although this *in situ* generated catalyst eliminates the ene reaction/dehydration pathway to **4**, the enhanced cationic character of this rhodium complex increases the rate of alkene isomerization relative to the rate of alkene hydroacylation.[36-44] The ratio of hydroacylation to isomerization is 5.1:1 when the catalyst contains the tetrafluoroborate counteranion; the ratio decreases to 3.3:1 when the catalyst contains the tetraarylborate

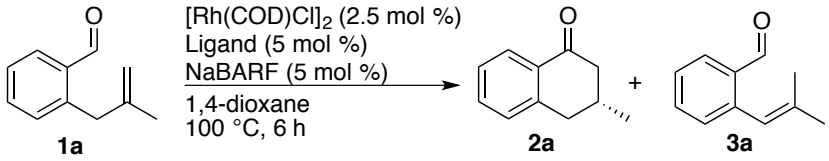
counteranion. We conducted a deuterium isotope incorporation experiment to confirm the mechanism by which this olefin isomerization occurs (Scheme 4). The reaction of ***d*-1a** in the presence of a catalyst generated from $[Rh(COD)Cl]_2$, *rac*-BINAP, and NaBARF formed the hydroacylation product ***d*-2a** with deuterium incorporation exclusively at the β-position, as expected for the hydroacylation product. The olefin isomerization product ***d*-3** was found to contain deuterium exclusively at the aldehyde carbon. Thus, isomerization of **1a** does not occur via endocyclic β-hydride elimination as has been recently reported for the rhodium-catalyzed isomerization of 4-pentenals to 3-pentenals.[45]

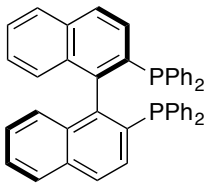


Scheme 4: Rh-catalyzed hydroacylation of ***d*-1a**.

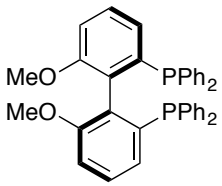
We hypothesized that the steric and electronic properties of the chiral bisphosphine ligand could be leveraged to improve the rate of alkene hydroacylation relative to the rate of alkene isomerization. Rhodium catalysts with less cationic character should attenuate the rates of both alkene isomerization and alkene hydroacylation.[14-15, 36-44] However, bisphosphine ligands with bulky aryl substituents on phosphorous should significantly increase the overall rate of alkene hydroacylation relative to the rate of alkene isomerization by increasing the rate of the turnover-limiting reductive elimination to form the ketone product.[46-50]

Table 1: Identification of catalysts for hydroacylation of 2-(2-methylallyl)benzaldehyde **1a**

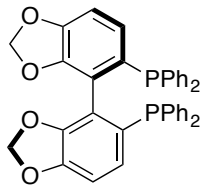




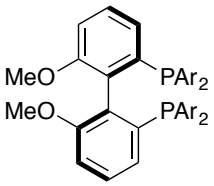
L1: (*R*)-BINAP



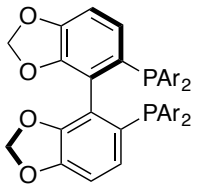
L2: (*R*)-MeO-Biphep



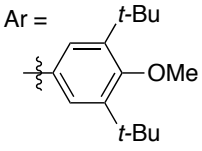
L3: (*R*)-Segphos



L4:
(*R*)-DTBM-MeO-Biphep



L5:
(*R*)-DTBM-Segphos



Entry	*Ligand*	*Yield **2a** (%)*[a,b]	*ee **2a** (%)*[c]	*Yield **3** (%)*[a]	*Ratio **2a:3a***[d]
1	**L1**	77 (56)	87	23	3.3:1
2	**L2**	75 (75)	90	16	4.7:1
3	**L3**	80 (72)	88	16	5.0:1
4	**L4**	80 (80)	99	9	8.9:1
5	**L5**	85 (81)	98	8	10.7:1
6[e]	**L5**	65(63)	99	10	6.5:1
7[f]	**L5**	50(52)	99	5	10.0:1

[a]Yield determined by ^{1}H NMR spectroscopy with dibromomethane as the internal standard. [b]Isolated yield of **2a** is shown in parentheses. [c]Determined by chiral HPLC analysis. [d]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [e]$[Rh(COD)_2]BF_4$ (5 mol %) used in place of $[Rh(COD)Cl]_2$ and NaBARF. [f]$[Rh(COD)_2]$BARF (5 mol %) used in place of $[Rh(COD)Cl]_2$ and NaBARF.

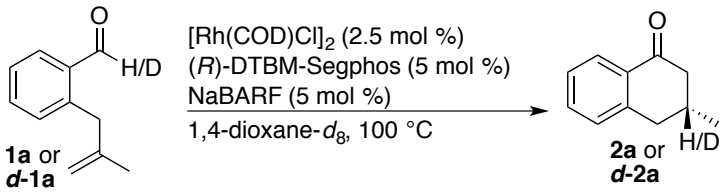
To evaluate the impact of steric and electronic properties of the ligand, we conducted hydroacylations of **1a** with catalysts derived from a series of bisphosphine ligands with axially chiral backbones (Table 1). The rhodium(I) complexes of (*R*)-MeO-Biphep **L2** and (*R*)-Segphos **L3**, which are more electron-rich than the complex derived from (*R*)-BINAP **L1**, catalyze the reaction of **1a** with improved ratios of hydroacylation to isomerization (4.7:1 and 5.0:1) relative to the rhodium(I) complex of **L1** (compare entries 2 and 3 with entry 1).

We then conducted hydroacylations of **1a** in the presence of rhodium catalysts prepared from ligands containing bulky, electron-rich 3,5-di-*tert*-butyl-4-methoxyphenyl substituents on phosphorous. The hydroacylation of **1a** occurs with an 8.9:1 ratio of hydroacylation to isomerization when the reaction is run in the presence of the rhodium(I) complex of (*R*)-DTBM-MeO-Biphep **L4**, and ketone product **2a** is isolated in 80% yield (entry 4). The ratio of hydroacylation to isomerization products can be further improved by conducting the reaction of **1a** with a rhodium(I) complex of the more electron-rich (*R*)-DTBM-Segphos **L5** (entry 5).[51-52] In the presence of this rhodium(I) catalyst, the hydroacylation of **1a** occurs with a 10.7:1 ratio of hydroacylation to isomerization, and ketone **2a** is isolated in 85% yield. The absolute configuration of **2a** was determined to be (*R*) by comparison of optical rotation data with literature values.[53-54]

Additional rhodium(I) precursors were evaluated for the hydroacylation of **1a** using the electron-rich (*R*)-DTBM-Segphos ligand **L5**. A significant decrease in the yield of **2a** and the ratio of hydroacylation to isomerization products is observed when $[Rh(COD)_2]BF_4$ is employed as the catalyst precursor for the hydroacylation of **1a** (63% yield, 6.5:1) (compare entries 5 and 6). Conducting the reaction of **1a** in the presence of a catalyst generated from $[Rh(COD)_2]$BARF results in a 10:1 ratio of hydroacylation to isomerization products. However, the yield of **2a** was comparatively low (compare entries 5 and 7). Thus, we chose to evaluate the scope of hydroacylations of additional *ortho*-allylbenzaldehydes using the reaction conditions from entry 5.

During our efforts to improve catalyst activity through modification of the steric and electronic properties of the bisphosphine ligand we speculated that bulky, electron-rich bisphosphine ligands would facilitate turnover-limiting reductive elimination. We identified

(*R*)-DTBM-Segphos as the optimal bisphosphine ligand of those assessed and conducted a kinetics study using a cationic rhodium catalyst generated with this ligand to determine if reductive elimination is in fact the turnover-limiting step in the rhodium-catalyzed hydroacylation of **1a**.



Scheme 5: Kinetic isotope experiments for **1a** vs. ***d*-1a**

The kinetic isotope effect was determined by measuring the initial rate constants for two independent experiments for the hydroacylation of **1a** and ***d*-1a** (Scheme 5). Figure 5 and Figure 6 show [**1a**] and [***d*-1a**] vs time through the 3rd half-life of the reaction and support first order dependence on **1a** and ***d*-1a** for the overall reaction. The initial rate constants were measured based on the slope of the first-order kinetics plots (Figure 7 and Figure 8): k_H = $(1.826 \pm 0.10) \times 10^{-4}$ sec^{-1} and $k_D = (1.535 \pm 0.06) \times 10^{-4}$ sec^{-1}. The KIE was found to be 1.19 based on the initial rate constants k_H and k_D for the hydroacylation of **1a** and ***d*-1a**. The normal secondary KIE (1.19) suggests that cleavage of the aldehyde C-H bond is not involved in the rate-determining step of this reaction. The aldehyde C-H bond is broken during oxidative addition so we would expect a primary KIE if this step were turnover-limiting, thus, this KIE value is inconsistent with oxidative addition as the turnover-limiting step in the hydroacylation of **1a**. Although these kinetic isotope results do not allow us to conclusively rule out migratory insertion as turnover-limiting, the normal secondary KIE (k_H/k_D = 1.19) is consistent with turnover-limiting reductive elimination since the aldehyde C-H bond is not involved in this elementary reaction. Furthermore, this data is consistent

with reports of rhodium-catalyzed alkene hydroacylations in which reductive elimination was found to be turnover-limiting.[2, 15, 31]

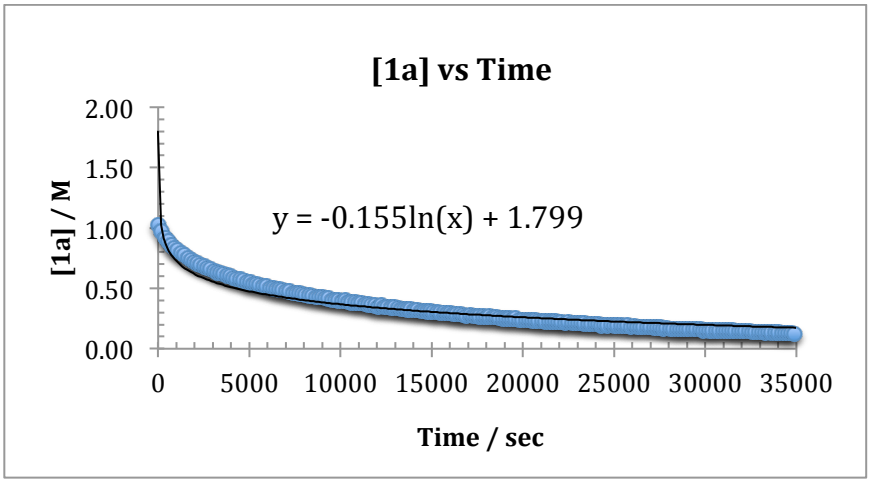


Figure 5: Plot of [**1a**] vs. time through 3rd half-life of the reaction.

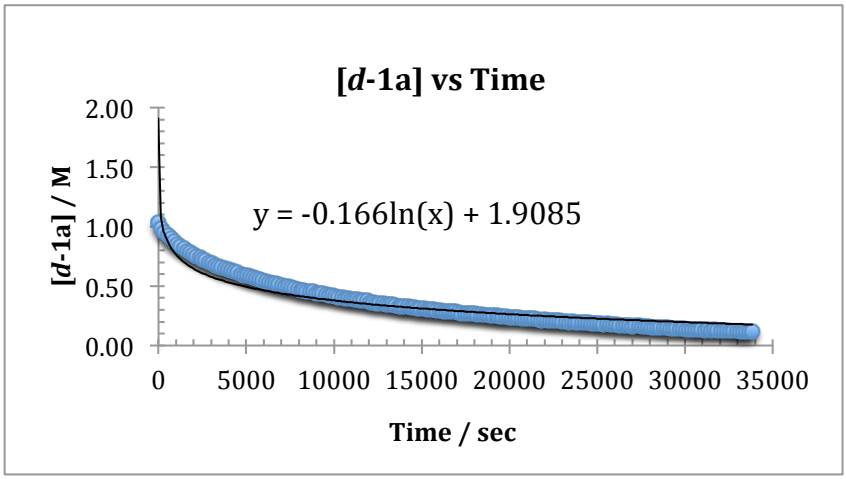


Figure 6: Plot of [***d*-1a**] vs. time through 3rd half-life of the reaction.

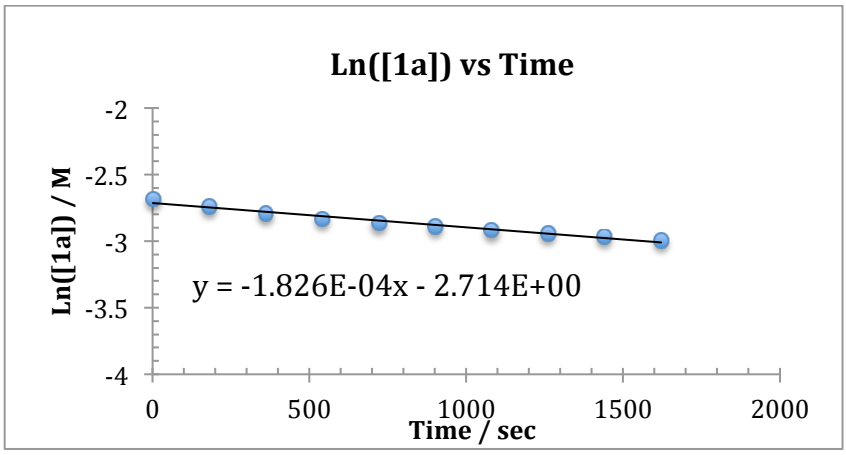


Figure 7: Plot of ln([**1a**]) vs. time for the first 5% of total reaction time.

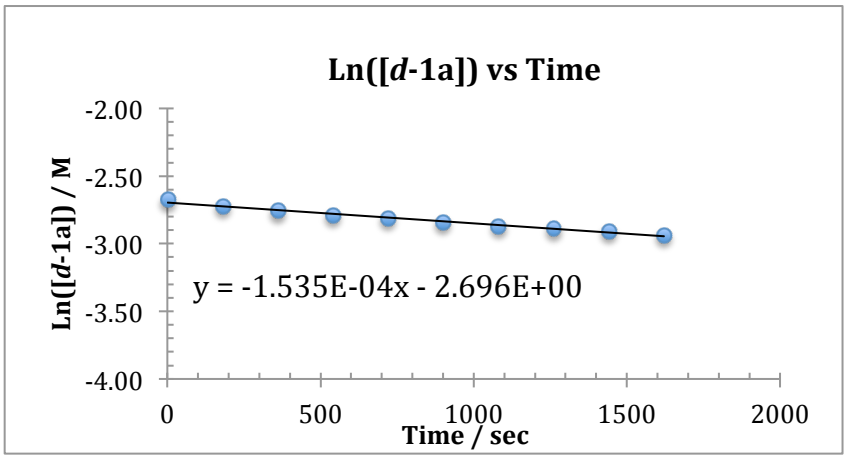
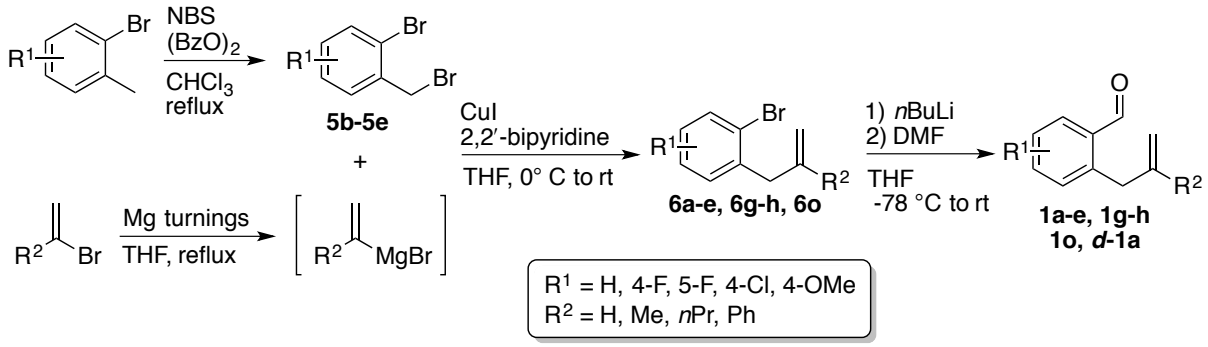


Figure 8: Plot of ln([***d*-1a**]) vs. time for the first 5% of total reaction time.

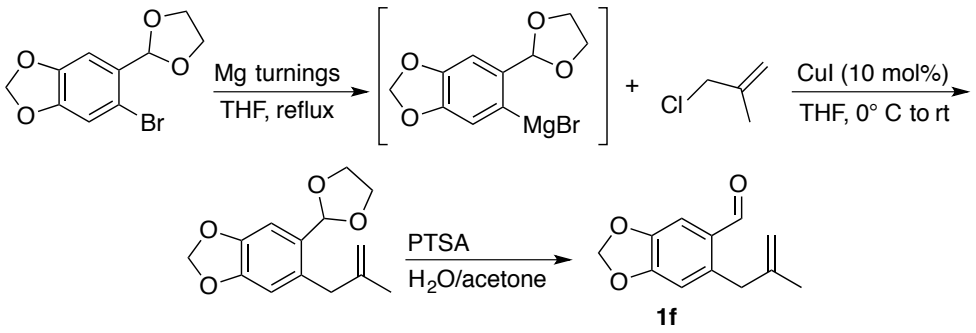
We next sought to evaluate an array of *ortho*-allylbenzaldehydes for the *endo*- and enantioselective rhodium-catalyzed olefin hydroacylation reaction. We synthesized a series of *ortho*-allylbenzaldehydes that contain substitution around the aryl core and on the central carbon of the allyl unit. Three different synthetic procedures were required to access a range of substrates with this general architecture (Scheme 6). In the first approach, 2-bromobenzylbromides were obtained by bromination of the corresponding toluene derivative with *N*-bromosuccinimide (NBS) in chloroform. *ortho*-Allylbromobenzenes **6a-e**, **6g-h** and **6o** were prepared by coupling the Grignard reagent of the appropriate vinylbromide with an a

2-bromobenzylbromide derivative (Scheme 6). *ortho*-Allylbenzaldehydes **1a-e**, **1g-h**, **1o** and ***d*-1a** were obtained by lithium-halogen exchange of the corresponding aryl bromide **6a-e**, **6g-h**, **6o** and quenching with DMF to install the aldehyde moiety. Further synthetic details are described in the Experimental section of this chapter.



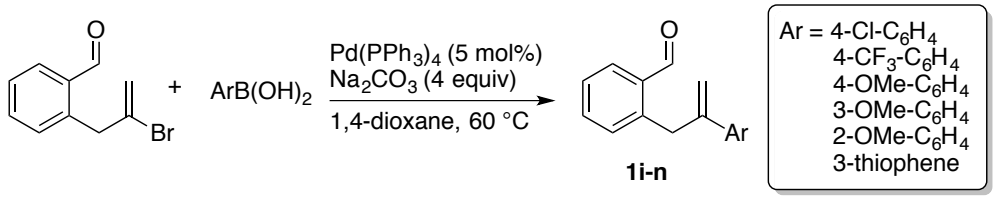
Scheme 6: Synthesis of *ortho*-allylbenzaldehydes **1a-e**, **1g-h**, **1o** and ***d*-1a**.

A modified version of this procedure was used for the synthesis of the piperonal-derived *ortho*-allylbenzaldehyde **1f** (Scheme 7). This substrate was prepared by coupling the Grignard reagent of 5-bromo-6-(1,3-dioxolan-2-yl)benzo[*d*][1,3]dioxole with 3-chloro-2-methylpropene. Deprotection of the acetal in the presence of PTSA generated **1f**.



Scheme 7: Synthesis of **1f**

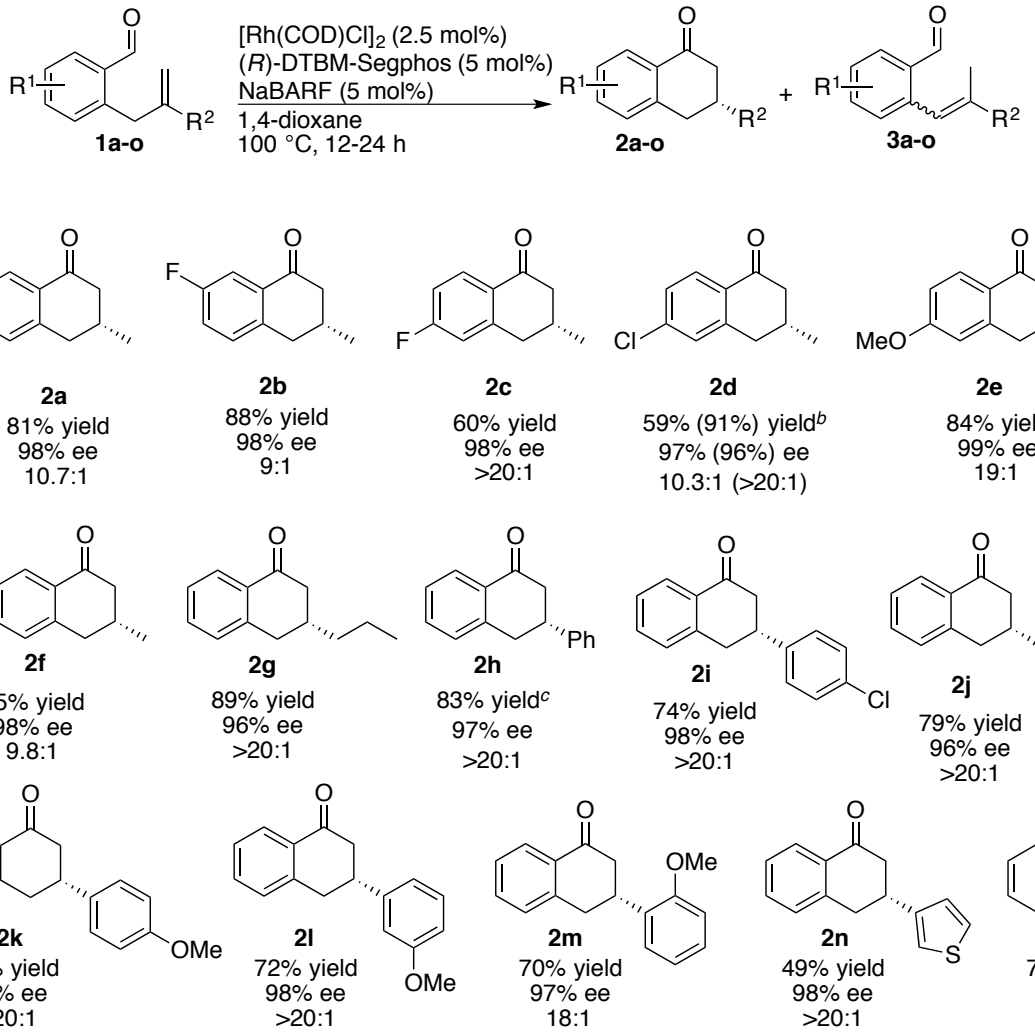
The synthesis of *ortho*-allylbenzaldehydes **1i-n** required an alternative synthetic approach (Scheme 8). 2-(2-Bromoallyl)benzaldehyde was prepared according to a literature procedure, and Suzuki coupling with the appropriate arylboronic acid formed **1i-n** without significant alkene isomerization.[28]



Scheme 8: Synthesis of **1i-n**

With a range of substrates in hand, we evaluated the hydroacylations of a variety of *ortho*-allylbenzaldehydes derivaties (Scheme 9). Hydroacylations of 5-fluoro-2-(2-methallyl)benzaldehyde **1b** and 4-fluoro-2-(2-methallyl)benzaldehyde **1c** form the corresponding 3,4-dihydronaphthalen-1(2*H*)-ones **2b** and **2c** in 88% and 60% yield with 98% ee. The hydroacylation of 4-chloro-2-(2-methylallyl)benzaldehyde **1d** generated **2d** in modest yield in the presence of 5 mol % rhodium catalyst. However, the reaction of **1d** in the presence of 10 mol % catalyst formed **2d** in 91% yield with 96% ee.

The hydroacylations of electron-rich *ortho*-allylbenzaldehydes also occur to form 3,4-dihydronaphthalen-1(2*H*)-ones in high yields with excellent enantioselectivities. The hydroacylations of 4-methoxy-2-(2-methallyl)benzaldehyde **1e** and the piperonal-derived 2-(2-methylallylbenzaldehyde) **1f** provide 3,4-dihydronaphthalen-1(2*H*)-ones **2e** and **2f** in 84% and 85% yields with 99% and 98% ee.



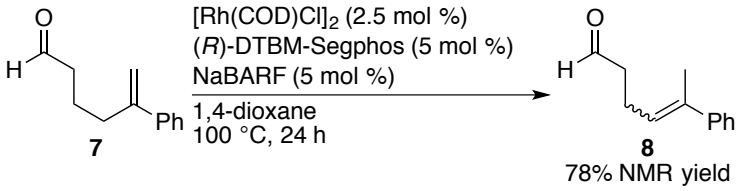
[a]Yields of **2** are isolated yields after column chromatography on silica gel. Enantiomeric excesses were determined by chiral HPLC analysis. Ratios of hydroacylation to alkene isomerization products (**2a-o**:**3a-o**) were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Values in parentheses are for the reaction of **1d** in the presence of 10 mol % rhodium catalyst. [c]Isolated as 96:4 mixture of **2h:3h**.

Scheme 9: Rh-catalyzed hydroacylation of *ortho*-allylbenzaldehydes **1a-1o**.

Alkyl and aryl substituents on the internal carbon of the allyl moiety are also well tolerated. The hydroacylations of *ortho*-allylbenzaldehydes **1g** and **1h** (R^2 = *n*-Pr and Ph) generate **2g** and **2h** in 89% and 87% yield with 96% and 97% ee. Hydroacylations of *ortho*-allylbenzaldehydes **1j-1m** containing substituted aryl groups at the central carbon of the allyl moiety generate the 3-aryl-3,4-dihydronaphthalen-1(2*H*)-one products **2j-2m** in good yields (70-80%) with excellent enantioselectivies (96-98% ee). In addition, the hydroacylation of 2-

(2-(thiopheny-3-yl)allyl)benzaldehyde **1n** forms 3,4-dihydronaphthalen-1(2*H*)-one **2n** in 49% yield with 98% ee. The hydroacylation of 2-allylbenzaldehyde **1o**, which lacks substitution at the central carbon of the allyl moiety, exclusively forms the 3,4-dihydronaphthalen-1(2*H*)-one **2o**; the formation of the 5-membered ketone (2-methyl-2,3-dihydro-1*H*-inden-1-one) is not observed with the current catalyst system.

Although we have developed a practical catalyst for enantioselective hydroacylation of *ortho*-allylbenzaldehydes, the catalyst performs poorly for substrates in which the alkene and aldehyde units are not conformationally constrained. For example, the reaction of 5-phenylhex-5-enal **7** forms alkene isomerization product **8** in 78% yield, and the alkene hydroacylation product is not detected by ^{1}H NMR spectroscopy (Scheme 10).



Scheme 10: Rh-catalyzed hydroacylation isomerization of **7**

Conclusion

In summary, we have developed a rhodium catalyst that promotes the hydroacylation of *ortho*-allylbenzaldehydes to generate 3,4-dihydronaphthalene-1(2*H*)-ones with excellent enantioselectivities. These *endo*-selective processes are complementary to the recently reported *exo*- and enantioselective NHC-catalyzed hydroacylations of the same substrates.[28] Competitive alkene isomerization and ene/dehydration processes are mitigated by a rhodium catalyst containing a bulky, electron-rich bisphosphine ligand and a weakly coordinating counteranion. This catalyst is prepared from readily available precursors and promotes the

desired hydroacylation reactions to form the bicyclic products in good yields and high enantioselectivities.

Experimental

General synthetic details. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried in an oven at 140 °C for at least two hours before use. THF was degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous 1,4-dioxane and DMF were purchased from Aldrich and used as received. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63μm, 60Å) using hexanes, hexanes/ethyl acetate, hexanes/diethyl ether, or pentane/diethyl ether mixtures. Products were visualized on TLC by UV light or by staining with $KMnO_4$, ceric ammonium molybdate (CAM), vanillin or *o*-anisaldehyde.

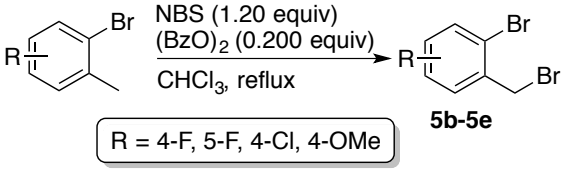
Instrumentation. HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. HPLC analyses were carried out on a Waters Alliance HPLC system with an e2695 separations module and a 2489 dual wavelength detector. Optical rotations were measured on an Atago AP-300 automatic polarimeter using a 0.5 dm cell. The absolute configuration of compound **2a** was assigned as *R* based on comparison of the optical rotation with the literature value,[53-54] and the absolute configuration of compounds **2b-n** were assigned by analogy. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to

residual solvent peaks ($CDCl_3$ = 7.26 ppm for ^1H and 77.16 ppm for ^{13}C) or an external standard (CF_3CO_2H:$CDCl_3$ = -77.56 ppm for ^{19}F). Coupling constants are reported in hertz.

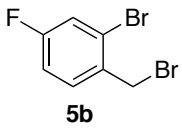
Materials. 2-Bromobenzaldehyde, 2-bromobenzylbromide, 2-bromo-5-fluorotoluene, 2-bromo-5-fluorotoluene, 2-bromo-4-fluorotoluene, 2-bromo-5-chlorotoluene, 4-bromo-3-methylanisole, and 2,2'-bipyridine were purchased from AK Scientific and used without further purification. Ethylene glycol, benzoyl peroxide, α-bromostyrene, δ-valerolactone, 2,3-dibromopropene, pyridium chlorochromate (PCC), methyltriphenylphosphonium bromide, 6-bromopiperonal, 5-oxo-5-phenylvaleric acid, 1,5-cyclooctadiene, ethylmagnesium bromide (3.0 M in diethyl ether), vinylmagnesium bromide (1.0 M in THF), 1-propenylmagnesium bromide (0.5 M in THF), methyllithium (1.6 M in diethyl ether), diisobutylaluminum hydride (1.0 M in hexanes) and copper iodide were purchased from Sigma-Aldrich and used as received. *n*-Butyllithium solution (2.5 M in hexanes) was purchased from Sigma-Aldrich and titrated with recrystallized diphenylacetic acid. 2-Bromopropene was purchased from GFS Chemicals and used without further purification. *N*-bromosuccinimide (NBS) was purchased from Sigma-Aldrich and purified by recrystallization from H_2O before use. 2-Bromopent-1-ene was prepared according to a literature procedure[55] from 2,3-dibromopropene and ethylmagnesium bromide. 5-Bromo-6-(1,3-dioxolan-2-yl)benzo[*d*][1,3]dioxole was prepared according to a literature procedure[56-57] from 6-bromopiperonal and ethylene glycol. 5-Phenylhex-5-enal (**5**) was prepared according to literature procedures from 5-oxo-5-phenylvaleric acid.[58] 2-(2-Bromoallyl)benzaldehyde was prepared according to a literature procedure from 2-bromobenzaldehyde, ethylene glycol and 2,3-dibromopropene.[28] $[Rh(COD)Cl]_2$, $[Rh(COD)_2]BF_4$, *rac*-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene), (*R*)-BINAP ((*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene), (*R*)-MeO-

BIPHEP ((*R*)-2,2′-bis(diphenylphosphino)-1,1′-biphenyl), (*R*)-DTBM-MeO-Biphep ((*R*)-2,2′-bis(di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino)-6,6′-dimethoxy-1,1′-biphenyl), (R)-Segphos ((*R*)-2,2′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole), (*R*)-DTBM-Segphos ((*R*)-2,2′-bis(di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino)-4,4′-bi-1,3-benzodioxole) and silver tetrafluoroborate were purchased from Strem Chemicals and used without further purification. NaBARF (Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was prepared according to a literature procedure.[35] $[Rh(COD)_2]BARF$ was prepared according to a literature procedure from $[Rh(COD)Cl]_2$, 1,5-cyclooctadiene and NaBARF.[59]

General Procedure A: Synthesis of *ortho*-Bromobenzylbromide 5b-e



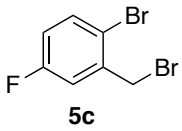
To a solution of the appropriate *ortho*-bromotoluene derivative in $CHCl_3$ was added NBS (1.20 equiv) and $(PhCO_2)_2$ (0.200 equiv). The reaction mixture was heated to reflux under N_2 for 6-24 h. The solution was cooled to room temperature and quenched by the addition of sat. $NaHCO_3$ solution. The organic layer was washed with $NaHCO_3$ (3x) and brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography or recrystallization to yield the appropriate *ortho*-bromobenzylbromide **5b-e**.



5b

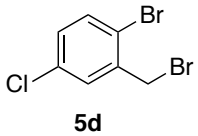
2-Bromo-1-(bromomethyl)-4-fluorobenzene[60-61] (5b): Prepared according to general procedure A from 2-bromo-4-fluorotoluene (5.10 g, 27.0 mmol), NBS (5.77 g, 32.4 mmol) and $Ph(CO_2)_2$ (1.31 g, 5.40 mmol) under reflux for 6 h. The crude product was purified by flash column chromatography (95:5 Hex:EtOAc) to yield **5b** (2.99 g, 11.14 mmol, 46%) as a white amorphous solid. m.p. = 50–

51 °C (lit = 51–52 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.58 (s, 2H), 7.03 (ddd, *J* = 8.4, 8.0, 2.4 Hz, 1H), 7.33 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.44 (dd, *J* = 8.4, 5.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.6, 115.4 (d, *J* = 21.0 Hz), 120.8 (d, *J* = 24.2 Hz), 124.9 (d, *J* = 10.0 Hz), 132.4 (d, *J* = 8.8 Hz), 133.3 (d, *J* = 3.4 Hz), 162.3 (d, *J* = 251.6 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ -111.4 (m, 1F).



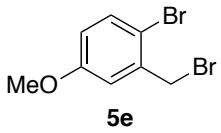
5c

1-Bromo-2-(bromomethyl)-4-fluorobenzene[62] (5c): Prepared according to general procedure A from 2-bromo-5-fluorotoluene (5.10 g, 27.0 mmol), NBS (5.77 g, 32.4 mmol) and $Ph(CO_2)_2$ (1.31 g, 5.40 mmol) under reflux for 24 h. The crude product was purified by flash column chromatography (95:5 Hex:EtOAc) to yield **5c** (2.36 g, 8.91 mmol, 33%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.54 (s, 2H), 6.91 (ddd, *J* = 8.8, 8.8, 3.2 Hz, 1H), 7.20 (dd, *J* = 8.8, 3.2 Hz, 1H), 7.53 (dd, *J* = 8.8, 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.5, 47.3 (d, *J* = 22.0 Hz), 48.1 (d, *J* = 23.0 Hz), 48.5 (d, *J* = 3.2 Hz), 64.5 (d, *J* = 7.8 Hz), 68.8 (d, *J* = 7.6 Hz), 91.8 (d, *J* = 246.8 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ -114.5 (m, 1F).



5d

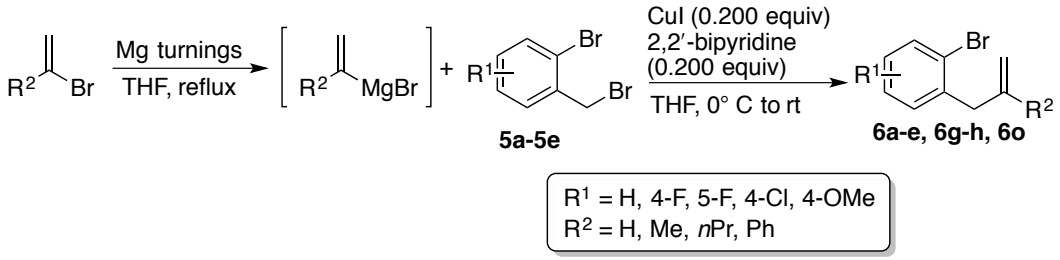
1-Bromo-2-(bromomethyl)-4-chlorobenzene[61] (5d): Prepared according to general procedure A from 2-bromo-5-chlorotoluene (5.55 g, 27.0 mmol), NBS (5.77 g, 32.4 mmol) and $Ph(CO_2)_2$ (1.31 g, 5.40 mmol) under reflux for 18 h. The crude product was purified by flash column chromatography (95:5 Hex:EtOAc) to yield **5d** (2.74 g, 9.65 mmol, 36%) as a pale orange amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.53 (s, 2H), 7.15 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.3, 122.2, 130.1, 131.0, 133.7, 134.3, 138.6.



5e

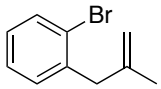
1-Bromo-2-(bromomethyl)-4-methoxybenzene[63] (5e): Prepared according to general procedure A from 4-bromo-3-methylanisole (8.04 g, 40.0 mmol), NBS (8.54 g, 48.0 mmol) and $Ph(CO_2)_2$ (1.94 g, 8.00 mmol) under reflux for 24 h. The crude product was purified by recrystallization from hexanes to yield **S2e** (3.44 g, 12.3 mmol, 31%) as a white crystalline solid. m.p = 92-93 °C (lit = 92-93 °C) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.80 (s, 3H), 4.56 (s, 2H), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.6, 55.7, 114.8, 116.2, 116.7, 134.0, 137.9, 159.3.

General Procedure B: Synthesis of 6a-e, 6g-h, and 6o



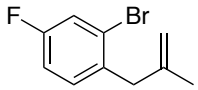
To an oven-dried schlenk flask equipped with a stir bar and under nitrogen atmosphere was added Mg turnings (2.20-3.50 equiv), a few crystals of I_2 and anhydrous THF (4-50 mL). In a separate oven-dried round bottom flask, a solution of the appropriate vinyl bromide (1.67-2.50 equiv) in anhydrous THF (4-10 mL) was prepared. An initial volume of 1 mL of the vinyl bromide solution was added to the Mg suspension and the mixture was heated gently with a heat gun to initiate formation of the Grignard reagent. The remaining vinyl bromide solution was added slowly, keeping the solution of Grignard reagent at reflux. The reaction mixture was refluxed for an additional 2-4 hours and cooled to room temperature. To an oven-dried 100 mL round bottom flask was added the appropriate 2-bromobenzylbromide (1.00 equiv), CuI (0.200 equiv), 2,2′-bipyridine (0.200 equiv) and

dry THF (10 mL), and the mixture was cooled to 0 °C. The solution of Grignard reagent was slowly transferred to this mixture via cannula. The combined reaction mixture was stirred overnight and allowed to warm to room temperature. The reaction was quenched by the addition of sat. NH_4Cl solution and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to yield the appropriate *ortho*-allylbromobenzene derivative **6a-e**, **6g-h**, and **6o**. As noted with each compound, HRMS values for **6b-e** were found after loss of a $-C_3H_5$ unit.



6a

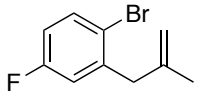
1-Bromo-2-(2-methylallyl)benzene[64] (6a): Prepared according to general procedure B from 2-bromopropene (2.42 g, 20.0 mmol) and 2-bromobenzylbromide (2.99 g, 12.0 mmol). The crude product was purified by flash column chromatography (100% hexanes) to yield **6a** (1.78 g, 8.42 mmol, 70%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (s, 3H), 3.46 (s, 2H), 4.59 (s, 1H), 4.86 (s, 1H), 7.05-7.10 (m, 1H), 7.18-7.29 (m, 2H), 7.55 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6, 44.0, 112.5, 125.3, 127.3, 127.9, 131.0, 132.9, 139.2, 143.5.



6b

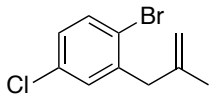
2-Bromo-4-fluoro-1-(2-methylallyl)benzene (6b): Prepared according to general procedure B from 2-bromopropene (1.09 g, 9.00 mmol) and **5b** (1.45 g, 5.40 mmol). The crude product was purified by flash column chromatography (98:2 Hex:EtOAc) to yield **5b** (0.794 g, 3.47 mmol, 64%) as a yellow oil containing 5% 1-fluoro-4-(2-methylallyl)benzaldehyde. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.74 (s, 3H), 3.42 (s, 2H), 4.57 (s, 1H), 4.86 (s, 1H), 6.98 (ddd, J = 8.4, 8.4, 2.8 Hz, 1H), 7.19 (dd, J = 8.4, 6.0 Hz, 1H), 7.30 (dd, J = 8.4, 2.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.5, 43.2, 112.7, 114.5 (d, J = 20.4 Hz), 119.9 (d, J = 24.0 Hz), 124.9 (d, J = 9.2 Hz), 131.6 (d, J

= 8.0 Hz), 135.1 (d, J = 3.4 Hz), 143.4, 161.0 (d, J = 247.4 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ -115.7 (m, 1F). HRMS (ESI) calcd. for $C_{10}H_{10}BrF$ ($M+H^+-C_3H_5$) 186.9558, found 186.9551.



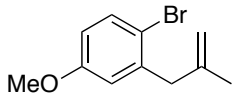
6c

1-Bromo-4-fluoro-2-(2-methylallyl)benzene (6c): Prepared according to general procedure B from 2-bromopropene (1.09 g, 9.00 mmol) and **5c** (1.45 g, 5.40 mmol, 0.600 equiv). The crude product was purified by flash column chromatography (98:2 Hex:EtOAc) to yield **6c** (0.425 g, 1.86 mmol, 34%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (s, 3H), 3.43 (s, 2H), 4.64 (s, 1H), 4.90 (s, 1H), 6.83 (ddd, J = 9.6, 8.8, 3.2 Hz, 1H), 6.97 (dd, J = 9.6, 3.2 Hz, 1H), 7.50 (dd, J = 8.8, 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6, 44.1, 113.2, 115.1 (d, J = 22.4 Hz), 117.6 (d, J = 22.8 Hz), 119.2 (d, J = 3.0 Hz), 133.9 (d, J = 7.8 Hz), 141.4 (d, J = 7.6 Hz), 142.9, 162.1 (d, J = 245.2 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ -116.0 (m, 1F). HRMS (ESI) calcd. for C_7H_5BrF ($M+H^+-C_3H_5$) 186.9558, found 186.9549.



6d

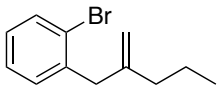
1-Bromo-4-chloro-2-(2-methylallyl)benzene (6d): Prepared according to general procedure B from 2-bromopropene (2.42 g, 20.0 mmol) and **5d** (2.28 g, 8.00 mmol). The crude product was purified by flash column chromatography (100% hexanes) to yield **6d** (1.25 g, 5.10 mmol, 64%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.75 (s, 3H), 3.41 (s, 2H), 4.62 (s, 1H), 4.89 (s, 1H), 7.06 (dd, J = 8.4, 2.8 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9, 43.8, 113.1, 127.4, 127.9, 130.6, 133.3, 133.8, 140.9, 142.7. HRMS (ESI) calcd. for $C_{10}H_{10}BrCl$ ($M+H^+-C_3H_5$) 202.9263, found 202.9260.



6e

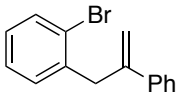
1-Bromo-4-methoxy-2-(2-methylallyl)benzene (6e): Prepared according to general procedure B from 2-bromopropene (2.06 g, 17.0

mmol) and **5e** (2.86 g, 10.2 mmol). The crude product was purified by flash column chromatography (100% hexanes) to yield **6e** (1.55 g, 6.41 mmol, 63%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.78 (s, 3H), 3.43 (s, 2H), 3.78 (s, 3H), 4.65 (s, 1H), 4.89 (s, 1H), 6.66 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.81 (d, *J* = 3.0 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6, 44.2, 55.4, 112.6, 113.6, 115.7, 116.5, 133.3, 140.2, 143.4, 159.0. HRMS (ESI) calcd. for $C_{11}H_{13}BrO$ ($M+H^+-C_3H_5$) 198.9759, found 198.9753.



6g

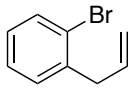
1-Bromo-2-(2-methylenepentyl)benzene (6g): Prepared according to general procedure B from 2-bromopent-1-ene (2.09 g, 14.0 mmol) and 2-bromobenzylbromide (2.10 g, 8.40 mmol). The crude product was purified by flash column chromatography (100% hexanes) to yield **6g** (0.681 g, 2.85 mmol, 34%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, *J* = 7.6, 3H), 1.54 (m, 2H), 2.05 (t, *J* = 7.6 Hz, 2H), 3.47 (s, 2H), 4.58 (s, 1H), 4.88 (s, 1H), 7.03-7.09 (m, 1H), 7.20-7.26 (m, 2H), 7.55 (dd, *J* = 7.2, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 21.0, 38.4, 42.4, 111.6, 125.3, 127.3, 127.8, 131.1, 132.9, 139.4, 147.4. HRMS (ESI) calcd. for $C_{12}H_{15}Br$ ($M+H^+-C_5H_9$) 168.9653, found 168.9645.



6h

1-Bromo-2-(2-phenylallyl)benzene (6h): Prepared according to general procedure B from α-bromostyrene (3.66 g, 20.0 mmol) and 2-bromobenzylbromide (2.99 g, 12.0 mmol). The crude product was purified by flash column chromatography (100% hexanes) to yield **6h** (1.70 g, 6.23 mmol, 52%) as a pale yellow oil which contained 10% of prop-2-ene-1,2-diyldibenzene. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93 (s, 2H), 4.86 (s, 1H), 5.52 (s, 1H), 7.07 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 7.18-7.34 (m, 5H), 7.47 (m, 2H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ

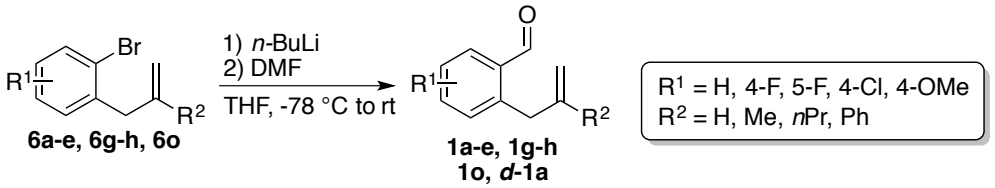
41.5, 114.8, 125.3, 126.1, 127.5, 127.8, 128.0, 128.5, 131.1, 132.9, 139.1, 140.8, 145.6. HRMS (ESI) calcd. for $C_{15}H_{13}Br$ ($M+H^+-C_8H_7$) 168.9653, found 168.9647.



6o

1-Allyl-2-bromobenzene[64-65] **(6o):** Prepared according to a modified version of general procedure B from vinylmagnesium bromide (12.0 mL of a 1.00 M solution, 12.00 mmol) and 2-bromobenzylbromide (1.80 g, 7.20 mmol). The crude product was purified by flash column chromatography (100% hexanes) to yield **6o** (0.880 g, 4.46 mmol, 37%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.52 (d, J = 6.4 Hz, 2H), 5.05-5.14 (m, 2H), 5.98 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H), 7.05 – 7.11 (m, 1H), 7.15-7.32 (m, 2H), 7.55 (dd, J = 8.4, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.3, 116.7, 124.7, 127.6, 128.0, 130.6, 132.9, 135.7, 139.6.

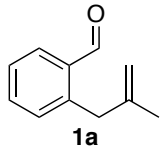
General Procedure C: Synthesis of *ortho*-Allylbenzaldehydes 1a-e, 1g-h, 1o, and *d*-1a



6a-e, 6g-h, 6o → **1a-e, 1g-h 1o, *d*-1a**

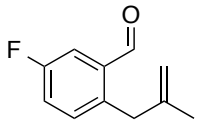
To a solution of the appropriate *ortho*-allylbromobenzene derivative **6a-e, 6g-h**, and **6o** (1.00 equiv) in THF at -78 °C was added *n*-BuLi (1.00-1.10 equiv of 1.10-1.80M solutions in hexanes), dropwise. This solution was kept at -78 °C for 1 hour, warmed to room temperature for 30 minutes, and then cooled back to -78 °C for 10 minutes before DMF (1.50-3.00 equiv) was added dropwise. The solution was allowed to warm to room temperature overnight before it was quenched by the addition of a sat. NH_4Cl solution. The reaction mixture was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified

by flash column chromatography (hexanes:EtOAc) to yield the appropriate *ortho*-allylbenzaldehyde **1a-e**, **1g-h, 1o,** and ***d*-1a**.



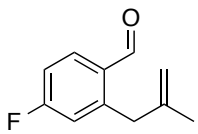
1a

2-(2-Methylallyl)benzaldehyde[64-65] (1a): Prepared according to general procedure C from **6a** (1.27 g, 6.00 mmol), *n*-BuLi (5.08 mL of a 1.30 M solution in hexanes, 1.10 equiv) and DMF (1.34 mL, 3.00 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1a** (0.779 g, 4.86 mmol, 81%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.78 (s, 3H), 3.73 (s, 2H), 4.45 (s, 1H), 4.84 (s, 1H), 7.28 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.40 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.53 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.87 (dd, *J* = 7.6, 1.6 Hz, 1H), 10.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.1, 40.3, 112.6, 127.1, 130.7, 131.8, 134.0, 134.4, 142.2, 145.4, 192.2.



1b

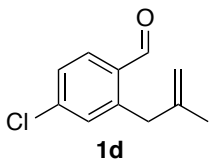
5-Fluoro-2-(2-methylallyl)benzaldehyde (1b): Prepared according to general procedure C from **6b** (0.401 g, 1.75 mmol), *n*-BuLi (1.41 mL of a 1.30 M solution in hexanes, 1.05 equiv) and DMF (0.20 mL, 1.50 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1b** (0.093 g, 0.522 mmol, 30%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.78 (s, 3H), 3.68 (s, 2H), 4.44 (s, 1H), 4.86 (s, 1H), 7.20-7.28 (m, 2H), 7.57 (dd, *J* = 8.8, 1.2 Hz, 1H), 10.2 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9, 39.5, 112.9, 115.8 (d, *J* = 35.7), 121.0 (d, *J* = 21.6 Hz), 133.5 (d, *J* = 7.0 Hz), 135.8 (d, *J* = 6.0 Hz), 137.9 (d, *J* = 3.2 Hz), 145.2, 161.8 (d, *J* = 246.0), 190.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -115.9 (m, 1F). HRMS (ESI) calcd. for $C_{11}H_{11}FO$ ($M+H^+$) 179.0867, found 179.0860.



1c

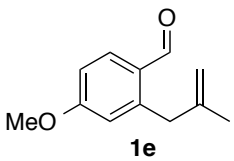
4-Fluoro-2-(2-methylallyl)benzaldehyde (1c): Prepared according to general procedure C from **6c** (0.401 g, 1.75 mmol), *n*-BuLi (1.41 mL of a

1.30 M solution in hexanes, 1.05 equiv) and DMF (0.20 mL, 1.50 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1c** (0.164 g, 0.92 mmol, 53%) as a yellow oil.^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.78 (s, 3H), 3.73 (s, 2H), 4.50 (s, 1H), 4.88 (s, 1H), 6.99 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.07 (ddd, *J* = 9.6, 8.4, 2.8 Hz, 1H), 7.89 (dd, *J* = 8.4, 6.0 Hz, 1H), 10.17 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9, 40.1, 113.2, 114.4 (d, *J* = 22.0 Hz), 118.4 (d, *J* = 22.0 Hz), 131.0 (d, *J* = 2.6 Hz), 133.6 (d, *J* = 10.0 Hz), 144.4, 145.6 (d, *J* = 9.0 Hz), 166.0 (d, *J* = 255.0 Hz), 190.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -104.9 (m, 1F). HRMS (ESI) calcd. for $C_{11}H_{11}FO$ ($M+H^+$) 179.0867, found 179.0863.



1d

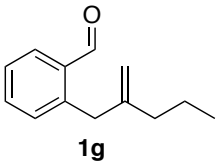
4-Chloro-2-(2-methylallyl)benzaldehyde (1d): Prepared according to general procedure C from **6d** (0.908 g, 3.70 mmol), *n*-BuLi (3.13 mL of a 1.30 M solution in hexanes, 1.10 equiv) and DMF (0.86 mL, 3.00 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1d** (0.219 g, 1.12 mmol, 30%) as a yellow oil.^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.78 (s, 3H), 3.70 (s, 2H), 4.48 (s, 1H), 4.88 (s, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 10.18 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.0, 40.0, 113.3, 127.5, 131.6, 132.0, 132.8, 140.3, 144.0, 144.5, 190.8. HRMS (ESI) calcd. for $C_{11}H_{11}ClO$ ($M+H^+$) 195.0571, found 195.0568.



1e

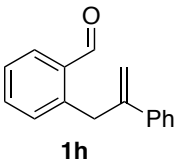
4-Methoxy-2-(2-methylallyl)benzaldehyde (1e): Prepared according to general procedure C from **6e** (1.09 g, 4.50 mmol), *n*-BuLi (3.46 mL of a 1.30 M solution in hexanes, 1.00 equiv) and DMF (0.520 mL, 1.50 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1e** (0.703 g, 3.70 mmol, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70 (s, 3H), 3.64 (s, 2H), 3.79 (s, 3H), 4.44 (s, 1H), 4.77 (s, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.80 (dd,

J = 8.8, 2.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 10.01 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9, 40.4, 55.5, 112.1, 112.5, 116.8, 128.0, 133.5, 144.7, 144.9, 163.6, 190.6. HRMS (ESI) calcd. for $C_{12}H_{14}O_2$ ($M+H^+$) 191.1067, found 191.1065.



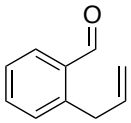
1g

2-(2-Methylenepentyl)benzaldehyde (1g): Prepared according to general procedure C from **6g** (0.957 g, 4.00 mmol), *n*-BuLi (2.33 mL of a 1.80 M solution in hexanes, 1.05 equiv) and DMF (0.93 mL, 3.00 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1g** (0.296 g, 1.57 mmol, 39%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 7.6 Hz, 3H), 1.41 – 1.53 (m, 2H), 2.01 (t, *J* = 7.2 Hz, 2H), 3.68 (s, 2H), 4.36 (s, 1H), 4.80 (s, 1H), 7.22 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.33 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 7.46 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.82 (dd, *J* = 7.6, 1.2 Hz, 1H), 10.18 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 20.9, 38.7, 38.7, 111.7, 126.9, 130.4, 131.8, 133.8, 134.4, 142.2, 149.3, 192.0. HRMS (ESI) calcd. for $C_{13}H_{16}O$ ($M+H^+$) 189.1274, found 189.1271.



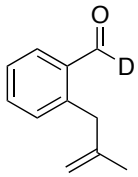
1h

2-(2-Phenylallyl)benzaldehyde[26, 28] (1h): Prepared according to general procedure C from **6h** (1.09 g, 4.00 mmol), *n*-BuLi (2.33 mL of a 1.80 M solution in hexanes, 1.05 equiv) and DMF (0.93 mL, 3.00 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1h** (0.332 g, 1.49 mmol, 37%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.18 (s, 2H), 4.66 (d, *J* = 1.2 Hz, 1H), 5.41 (d, *J* = 1.2 Hz, 1H), 7.16-7.34 (m, 5H), 7.40-7.44 (m, 3H), 7.80 (dd, *J* = 6.4, 1.2 Hz, 1H), 10.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.6, 114.9, 126.0, 127.0, 127.8, 128.4, 131.5, 131.6, 133.9, 134.2, 140.9, 141.7, 147.5, 192.3. HRMS (ESI) calcd. for $C_{16}H_{14}O$ ($M+Na^+$) 245.0937, found 245.0935.



1o

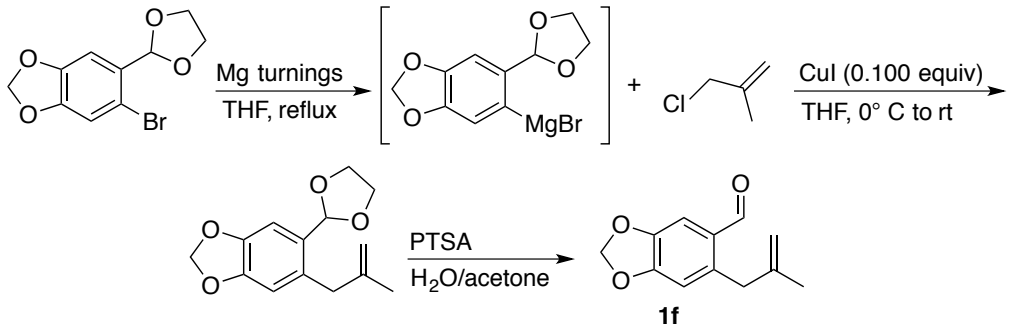
2-Allylbenzaldehyde[64-65] **(1o):** Prepared according to general procedure C from **6o** (0.788 g, 4.00 mmol), *n*-BuLi (4.00 mL of a 1.10 M solution in hexanes, 1.10 equiv) and DMF (0.93 mL, 3.00 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1o** (0.344 g, 2.36 mmol, 59%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.82 (d, *J* = 6.4 Hz, 2H), 4.98 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.09 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.05 (ddt, *J* = 17.2, 10.2, 6.4, 1H), 7.30 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.40 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.55 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.85 (dd, *J* = 7.6, 0.8 Hz 1H), 10.26 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.5, 116.4, 126.9, 131.6, 131.6, 133.8, 133.9, 136.9, 142.2, 192.3.

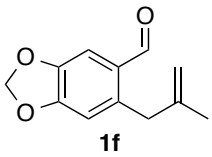


***d*-1a**

***d*$_1$-2-(2-Methylallyl)benzaldehyde (*d*-1a):** Prepared according to a modified version of general procedure C from **6a** (0.866 g, 4.10 mmol), *n*-BuLi (1.87 mL of a 2.30 M solution in hexanes, 1.05 equiv) and DMF-*d*$_7$ (0.957 mL, 3.00 equiv). The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield ***d*-1a** (0.414 g, 2.57 mmol, 63%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.78 (s, 3H), 3.72 (s, 2H), 4.45 (s, 1H), 4.84 (s, 1H), 7.28 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.39 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.6, 0.8 Hz, 1H), 7.87 (dd, 8.0, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.0, 40.3, 112.6, 127.1, 130.6, 131.7, 134.0, 134.3 (t, *J* = 3.0 Hz), 142.2, 145.4, 191.9 (t, *J* = 26.4 Hz). HRMS (ESI) calcd. for $C_{11}H_{11}DO$ ($M+H^+$) 162.1024, found 162.1021.

Synthesis of 6-(2-Methylallyl)benzo[*d*][1,3]dioxole-5-carbaldehyde 1f

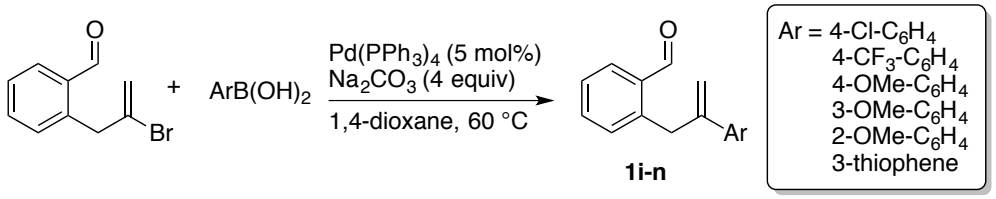




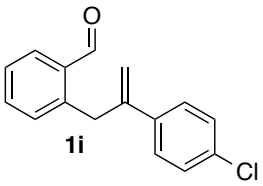
6-(2-Methylallyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (1f): To an oven-dried schlenk flask equipped with a stir bar and under nitrogen atmosphere was added Mg turnings (0.182 g, 7.50 mmol, 1.50 equiv), a few crystals of I_2 and anhydrous THF (20 mL). In a separate oven-dried round bottom flask, a solution of 5-bromo-6-(1,3-dioxolan-2-yl)benzo[*d*][1,3]dioxole (1.37 g, 5.00 mmol, 1.00 equiv) in anhydrous THF (8 mL) was prepared. An initial volume of 1 mL of the solution of 5-bromo-6-(1,3-dioxolan-2-yl)benzo[*d*][1,3]dioxole was added to the Mg suspension via syringe and the mixture was heated gently with a heat gun to initiate the formation of the Grignard reagent. The remaining solution of 5-Bromo-6-(1,3-dioxolan-2-yl)benzo[*d*][1,3]dioxole was added slowly while keeping the solution of the Grignard reagent at reflux. The reaction mixture was refluxed for an additional 2 hours and cooled to room temperature. To an oven-dried 100 mL round bottom flask was added 3-chloro-2-methylprop-1-ene (0.734 mL, 7.50 mmol, 1.50 equiv), CuI (0.143 g, 0.750 mmol, 0.100 equiv) and dry THF (10 mL), and the mixture was cooled to 0 °C. The solution of the Grignard reagent was slowly transferred to this mixture via cannula. The combined reaction mixture was stirred overnight and allowed to warm to room temperature. The reaction was quenched by the addition of sat. NH_4Cl solution and extracted with CH_2Cl_2 (3x). The

combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was refluxed for 2 h following the addition of 20 mL H_2O, 20 mL acetone and PTSA (150 mg). Upon cooling to room temperature, the product was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1f** (0.209 g, 1.02 mmol, 20%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (s, 3H), 3.63 (s, 2H), 4.52 (s, 1H), 4.86 (s, 1H), 6.03 (s, 2H), 6.71 (s, 1H), 7.35 (s, 1H), 10.1 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.8, 40.0, 102.0, 108.0, 111.1, 112.9, 129.1, 139.8, 145.2, 147.2, 152.6, 189.6. HRMS (ESI) calcd. for $C_{12}H_{12}O_3$ ($M+H^+$) 205.0859, found 205.0859.

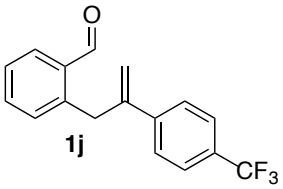
General Procedure D: Synthesis of *ortho*-Allylbenzaldehydes 1i-n



Compounds **1i-n** were prepared according to a procedure reported by Glorius *et al*.[28] To an oven dried Schlenk flask was added $Pd(PPh_3)_4$ (0.050-0.100 mmol, 0.05 equiv), the appropriate arylboronic acid (1.20-3.00 mmol, 1.50 equiv), 1.6-4.0 mL of a 2M solution of aqueous Na_2CO_3, 2-(2-bromoallyl)benzaldehyde (0.800-2.00 mmol, 1.00 equiv) and 4-10 mL of 1,4-dioxane. The flask was evacuated and backfilled with nitrogen three times and stirred for 16 hours at 60 °C. The reaction was quenched with 10 mL of water and extracted with 20 mL EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hex:EtOAc) to yield *ortho*-allylbenzaldehydes **1i-n**.

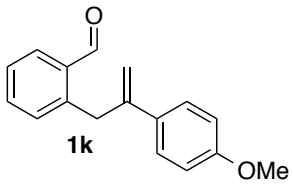


2-(2-(4-Chlorophenyl)allyl)benzaldehyde (1i): Prepared according to general procedure D from $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv), 4-chlorophenylboronic acid (469 mg, 3.00 mmol, 1.50 equiv), 4 mL of a 2M aqueous Na_2CO_3 solution, 2-(2-bromoallyl)benzaldehyde (450 mg, 2.00 mmol, 1.00 equiv) and 10 mL 1,4-dioxane. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1i** (0.378 g, 1.47 mmol, 74%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.23 (s, 2H), 4.75 (s, 1H), 5.44 (s, 1H), 7.27-7.31 (m, 3H), 7.38-7.45 (m, 3H), 7.52 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.6 Hz, 1H), 10.2 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.8, 115.4, 127.3, 127.5, 128.6, 131.6, 132.5, 133.6, 134.0, 134.2, 139.4, 141.4, 146.4, 192.6. HRMS (ESI) calcd. for $C_{16}H_{13}ClO$ ($M+H^+$) 257.0728, found 257.0723.

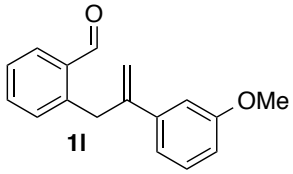


2-(2-(4-(Trifluoromethyl)phenyl)allyl)benzaldehyde[28] (1j): Prepared according to general procedure D from $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv), 4-(trifluoromethyl)phenylboronic acid (570 mg, 3.00 mmol, 1.50 equiv), 4 mL of a 2M aqueous Na_2CO_3 solution, 2-(2-bromoallyl)benzaldehyde (450 mg, 2.00 mmol, 1.00 equiv) and 10 mL 1,4-dioxane. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1j** (0.432 g, 1.49 mmol, 74%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.26 (s, 2H), 4.83 (s, 1H), 5.50 (s, 1H), 7.31 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.40 (ddd, *J* = 7.6, 7.2, 0.8 Hz, 1H), 7.53 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1H), 7.58 (s, 4H), 7.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 10.2 (s, 1H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.8, 116.6, 124.3 (q, *J* = 270.5 Hz), 125.5 (q, *J* = 3.8 Hz), 126.5, 127.4, 129.8 (q, *J* = 32.4 Hz), 131.7, 133.0, 134.0, 134.2, 141.0,

144.6 (q, J = 1.4 Hz), 146.5, 192.7.[19]F NMR ($CDCl_3$, 376 MHz): δ -62.5 (s, 1F). HRMS (ESI) calcd. for $C_{17}H_{13}F_3O$ ($M+H^+$) 291.0991, found 291.0995.

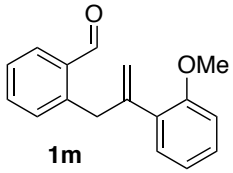


2-(2-(4-Methoxyphenyl)allyl)benzaldehyde[28] (1k): Prepared according to general procedure D from $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv), 4-methoxyphenylboronic acid (456 mg, 3.00 mmol, 1.50 equiv), 4 mL of a 2M aqueous Na_2CO_3 solution, 2-(2-bromoallyl)benzaldehyde (450 mg, 2.00 mmol, 1.00 equiv) and 10 mL 1,4-dioxane. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1k** (0.324 g, 1.28 mmol, 64%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81 (s, 3H), 4.22 (s, 2H), 4.64 (s, 1H), 5.41 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.32 (dd, J = 7.6, 0.8 Hz, 1H), 7.37 – 7.44 (m, 3H), 7.51 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.87 (dd, J = 7.6, 1.6 Hz, 1H), 10.2 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.8, 55.4, 113.6, 113.8, 127.1, 127.2, 131.5, 131.6, 133.3, 134.0, 134.2, 142.0, 146.7, 159.4, 192.5. HRMS (ESI) calcd. for $C_{17}H_{16}O_2$ ($M+H^+$) 253.1223, found 253.1228.



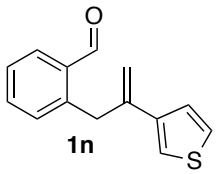
2-(2-(3-Methoxyphenyl)allyl)benzaldehyde (1l): Prepared according to general procedure D from $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv), 3-methoxyphenylboronic acid (456 mg, 3.00 mmol, 1.50 equiv), 4 mL of a 2M aqueous Na_2CO_3 solution, 2-(2-bromoallyl)benzaldehyde (450 mg, 2.00 mmol, 1.00 equiv) and 10 mL 1,4-dioxane. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1l** (0.278 g, 1.10 mmol, 55%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84 (s, 3H), 4.26 (s, 2H), 4.76 (s, 1H), 5.50 (s, 1H), 6.86 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H), 7.03 (dd, J = 2.4, 2.4 Hz, 1H), 7.10 (ddd, J = 8.0, 1.2, 0.8 Hz, 1H), 7.28 (dd, J = 2.4, 1.2 Hz, 1H), 7.35 (dd, J = 7.6, 0.8 Hz, 1H), 7.44 (ddd, J =

8.0, 7.6, 0.8 Hz, 1H), 7.55 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 7.90 (dd, J = 7.6, 1.6 Hz, 1H), 10.3 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.8, 55.4, 112.1, 113.1, 115.3, 118.6, 127.2, 129.5, 131.6, 131.7, 134.0, 134.2, 141.8, 142.5, 147.5, 159.7, 192.5. HRMS (ESI) calcd. for $C_{17}H_{16}O_2$ ($M+H^+$) 253.1223, found 253.1229.



1m

2-(2-(2-Methoxyphenyl)allyl)benzaldehyde (1m): Prepared according to general procedure D from $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv), 2-methoxyphenylboronic acid (456 mg, 3.00 mmol, 1.50 equiv), 4 mL of a 2M aqueous Na_2CO_3 solution, 2-(2-bromoallyl)benzaldehyde (450 mg, 2.00 mmol, 1.00 equiv) and 10 mL 1,4-dioxane. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1m** (0.272 g, 1.08 mmol, 54%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.86 (s, 3H), 4.17 (s, 2H), 4.81 (q, J = 1.6 Hz, 1H), 5.12 (q, J = 1.6 Hz, 1H), 6.84-6.92 (m, 2H), 7.08 (dd, J = 7.6, 2.0 Hz, 1H), 7.23 – 7.32 (m, 2H), 7.34 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.50 (ddd, J = 7.6, 7.2, 1.6 Hz, 1H), 7.80 (dd, J = 7.6, 1.6 Hz, 1H), 10.3 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.5, 55.5, 110.7, 116.6, 120.8, 127.1, 128.96, 129.03, 130.2, 131.6, 132.0, 133.9, 134.5, 142.5, 148.9, 156.5, 192.4. HRMS (ESI) calcd. for $C_{17}H_{16}O_2$ ($M+Na^+$) 275.1043, found 275.1046.

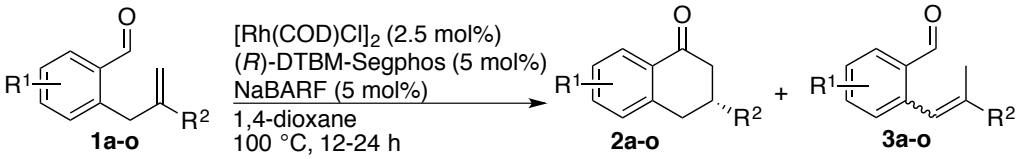


1n

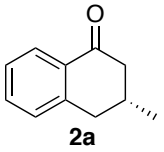
2-(2-(Thiophen-3-yl)allyl)benzaldehyde (1n): Prepared according to a modified version of general procedure D from $Pd(PPh_3)_4$ (46.0 mg, 0.050 mmol, 0.063 equiv), 3-thienylboronic acid (154 mg, 1.20 mmol, 1.50 equiv), 1.6 mL of a 2M aqueous Na_2CO_3 solution, 2-(2-bromoallyl)benzaldehyde (180 mg, 0.800 mmol, 1.00 equiv) and 4 mL 1,4-dioxane. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1n** (94.2 mg, 0.413 mmol, 52%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.19 (s, 2H), 4.63 (s, 1H), 5.51 (s, 1H), 7.22-7.27

(m, 3H), 7.31 (dd, J = 7.6, 0.8 Hz, 1H), 7.40 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.50 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.86 (dd, J = 7.6, 1.6 Hz, 1H), 10.2 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.6, 113.8, 120.9, 125.7, 125.8, 127.2, 131.60, 131.63, 134.0, 134.3, 141.5, 142.0, 142.3, 192.5. HRMS (ESI) calcd. for $C_{14}H_{12}OS$ ($M+H^+$) 229.0682, found 229.0685.

General Procedure E: Hydroacylation of *ortho*-Allylbenzaldehydes 2a-o

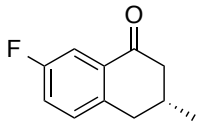


In a nitrogen-filled dry box, the appropriate *ortho*-allylbenzaldehyde **1a-1o** (0.200 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol, 0.050 equiv), NaBARF (8.9 mg, 0.010 mmol, 0.050 equiv), and anhydrous 1,4-dioxane (1 mL) were added to a 1-dram vial. The vial was sealed with a PFTE/silicone-lined septum cap and removed from the dry box. The reaction mixture was heated to 100 °C and allowed to stir at this temperature until the reaction was judged to be complete by TLC analysis. The mixture was cooled to rt, filtered through a pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. $CDCl_3$ (0.7 mL) was added to dissolve the crude mixture along with CH_2Br_2 (7.0 μL, 0.100 mmol) as an internal standard. Conversion and hydroacylation/alkene isomerization ratio were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column silica gel chromatography (hexanes:EtOAc or hexanes:Et_2O) to yield **2a-o**. Enantiomeric excess was determined by chiral HPLC analysis.



(*R*)-3-Methyl-3,4-dihydronaphthalen-1(2*H*)-one[53, 66-67] (2a): Prepared according to general procedure E from **1a** (32.0 mg, 0.200 mmol) (reaction

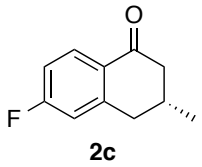
time = 12 h). The crude product (hydroacylation:isomerization = 10.7:1) was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2a** (27.1 mg, 0.169 mmol, 85%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 20.9 min (major); t_R 22.1 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 93:7, 0.3 mL/min] to be 98% ee. Lit:[1,2] $[\alpha]_D^{25}$ = -32.2° (c 6.10, EtOH), found $[\alpha]_D^{25}$= -36.7° (c 0.98, EtOH), $[\alpha]_D^{25}$ = -32.9° (c 0.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.14 (d, *J* = 6.0 Hz, 3H), 2.27-2.34 (m, 2H), 2.65-2.75 (m, 2H), 2.97 (dd, *J* = 16.4, 3.2 Hz, 1H), 7.24 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.30 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.47 (ddd, *J* = 8.0, 7.6, 0.8 Hz, 1H), 8.02 (dd, *J* = 8.0, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 30.6, 38.2, 47.3, 126.7, 127.1, 129.0, 132.3, 133.6, 143.9, 198.7.



2b

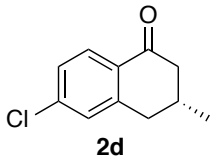
(*R*)-7-Fluoro-3-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2b): Prepared according to general procedure E from **1b** (35.6 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = 9:1) was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2b** (21.3 mg, 0.120 mmol, 60%) as a yellow oil that solidified on standing. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 31.5 min (major); t_R 32.8 min (minor) [Chiracel AS-H+OJ-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 99:1, 0.5 mL/min] to be 98% ee. $[\alpha]_D^{25}$= -32.4° (c 0.68, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (d, *J* = 6.4 Hz, 3H), 2.25-2.39 (m, 2H), 2.64 (dd, *J* = 16.4, 9.2 Hz, 1H), 2.74 (dd, *J* = 13.2, 2.0 Hz, 1H), 2.96 (dd, *J* = 16.4, 3.2 Hz, 1H), 7.18 (ddd, *J* = 9.2, 8.4, 2.8 Hz, 1H), 7.23 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.68 (dd, *J* = 9.2, 2.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 30.7, 37.4, 46.9, 113.0 (d, *J* = 22.0, Hz), 120.9 (d, *J* = 22.0 Hz), 130.7 (d, *J* = 7.0 Hz), 133.9 (d, *J* = 6.0 Hz), 139.6 (d, *J* = 3.0 Hz), 161.7 (d, *J* = 244.6 Hz), 197.6. ^{19}F NMR

($CDCl_3$, 376 MHz): δ -116.2 (m, 1F). HRMS (ESI) calcd. for $C_{11}H_{11}FO$ ($M+H^+$) 179.0867, found 179.0863.



2c

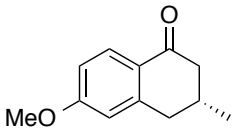
(*R*)-6-Fluoro-3-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2c): Prepared according to general procedure E from **1c** (35.6 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2c** (31.6 mg, 0.177 mmol, 88%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 12.0 min (major); t_R 15.0 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 99:1, 0.5 mL/min] to be 98% ee. $[\alpha]_D^{25}$= -16.4° (c 1.46, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.14 (d, *J* = 6.4 Hz, 3H), 2.23-2.39 (m, 2H), 2.67 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.72 (dd, *J* = 9.6, 1.6 Hz, 1H), 2.95 (dd, *J* = 16.0, 3.6 Hz, 1H), 6.91 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.97 (ddd, *J* = 9.2, 8.8, 2.4, 1H), 8.04 (dd, *J* = 8.8, 6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 30.5, 38.2, 47.0, 114.4 (d, *J* = 22.2), 115.2 (d, *J* = 21.2 Hz), 129.0 (d, *J* = 2.8 Hz), 130.2 (d, *J* = 10.0 Hz), 146.5 (d, *J* = 9.0 Hz), 165.9 (d, *J* = 254.4 Hz), 197.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -105.8 (m, 1F). HRMS (ESI) calcd. for $C_{11}H_{11}FO$ ($M+H^+$) 179.0867, found 179.085.



2d

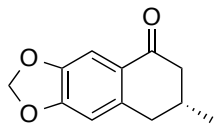
(*R*)-6-Chloro-3-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2d): Prepared according to general procedure E from **1d** (38.9 mg, 0.200 mmol) using 10 mol% catalyst loading (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (90:10 hexanes: EtOAc) to yield **2d** (35.4 mg, 0.182 mmol, 91%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 14.0 min (major); t_R 15.6 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel

Chemical Ind., Ltd.) hexane/^{i}PrOH, 95:5, 0.5 mL/min] to be 97% ee. $[\alpha]_D^{25}$= -68.3° (c 0.82, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.14 (d, *J* = 6.0 Hz, 3H), 2.26-2.39 (m, 2H), 2.67 (dd, *J* = 16.8, 10.4 Hz, 1H), 2.73 (dd, *J* = 13.2, 2.0 Hz, 1H), 2.95 (dd, *J* = 16.8, 3.6 Hz, 1H), 7.25 (d, *J* = 0.8 Hz, 1H), 7.27 (dd, *J* = 8.8, 0.8 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 30.5, 37.9, 47.0, 127.3, 128.81, 128.80, 130.8, 139.8, 145.4, 197.4. HRMS (ESI) calcd. for $C_{11}H_{11}ClO$ ($M+H^+$) 195.0571, found 195.0566.



2e

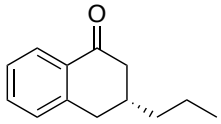
(*R*)-6-Methoxy-3-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2e): Prepared according to general procedure E from **1e** (38.1 mg, 0.200 mmol) (reaction time = 12 h). The crude product (hydroacylation:isomerization = 19:1) was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2e** (32.0 mg, 0.168 mmol, 84%) as a white amorphous solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 23.5 min (major); t_R 25.8 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 99% ee. $[\alpha]_D^{25}$ = -49.4° (c 0.77, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.12 (d, *J* = 6.4 Hz, 3H), 2.19-2.34 (m, 2H), 2.60-2.70 (m, 2H), 2.92 (dd, J = 16.4, 3.6 Hz, 1H), 3.84 (s, 3H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 30.7, 38.6, 47.0, 55.5, 112.8, 113.1, 126.0, 129.5, 145.4, 163.7, 197.4. HRMS (ESI) calcd. for $C_{12}H_{14}O_2$ ($M+H^+$) 191.1067, found 191.1063.



2f

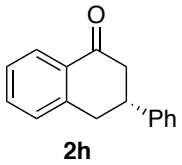
(*R*)-7-Methyl-7,8-dihydronaphtho[2,3-*d*][1,3]dioxol-5(6*H*)-one (2f): Prepared according to general procedure E from **1f** (40.8 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = 9.8:1) was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2f** (35.0

mg, 0.171 mmol, 85%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 26.0 min (major); t_R 28.4 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 99% ee. $[\alpha]_D^{25}$= -61.3° (c 1.24, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.12 (d, *J* = 6.0 Hz, 3H), 2.18-2.35 (m, 2H), 2.59 (dd, *J* = 16.0, 10.4 Hz, 1H), 2.67 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.87 (dd, *J* = 16.0, 3.6, 1H), 6.00 (s, 2H), 6.65 (s, 1H), 7.45 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 30.8, 38.4, 46.8, 101.7, 106.2, 108.1, 127.1, 140.8, 147.0, 152.2, 196.9. HRMS (ESI) calcd. for $C_{12}H_{12}O_3$ ($M+H^+$) 205.0859, found 205.0853.



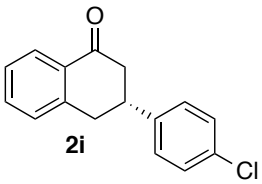
2g

(*R*)-3-Propyl-3,4-dihydronaphthalen-1(2*H*)-one[68] (2g): Prepared according to general procedure E from **1g** (37.7 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (90:10 hexanes:Et_2O) to yield **2g** (33.3 mg, 0.177 mmol, 89%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 11.3 min (major); t_R 12.5 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 95:5, 0.5 mL/min] to be 96% ee. $[\alpha]_D^{25}$ = -28.1° (c 1.21, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88-0.96 (m, 3H), 1.35-1.48 (m, 4H), 2.16-2.25 (m, 1H), 2.31 (dd, *J* = 16.8, 12.0 Hz, 1H), 2.69 (dd, *J* = 16.4, 10.4 Hz, 1H), 2.77 (ddd, *J* = 16.8, 3.2, 1.6 Hz, 1H), 2.96-3.05 (m, 1H), 7.24 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.30 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.46 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 8.01 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 19.8, 35.2, 36.3, 38.1, 45.6, 126.7, 127.1, 129.0, 132.6, 133.6, 144.0, 198.9. HRMS (ESI) calcd. for $C_{13}H_{16}O$ ($M+H^+$) 189.1274, found 189.1270.



2h

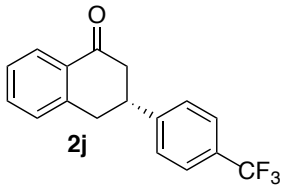
(*R*)-3-Phenyl-3,4-dihydronaphthalen-1(2*H*)-one[26] (2h): Prepared according to general procedure E from **1h** (44.5 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2h** (37.0 mg, 0.166 mmol, 83%) as a pale brown oil which contained 4% of 2-(2-phenylprop-1-en-1-yl)benzaldehyde **3h** (*E*:*Z* = 1:1). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 10.3 min (major); t_R 22.9 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 97% ee. $[\alpha]_D^{25}$ = -5.71° (c 1.40, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.82 (dd, *J* = 16.4, 12.8 Hz, 1H), 2.93-2.99 (ddd, *J* = 16.4, 4.0, 1.6 Hz, 1H), 3.12-3.27 (m, 2H), 3.40-3.49 (m, 1H), 7.40-7.42 (m, 7H), 7.50 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.8, 41.2, 46.1, 126.8, 127.0, 127.1, 127.3, 128.9, 129.0, 132.2, 133.9, 143.4, 143.5, 197.9. HRMS (ESI) calcd. for $C_{16}H_{14}O$ ($M+Na^+$) 245.0937, found 245.0934.



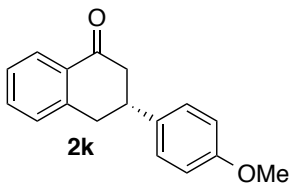
2i

(*R*)-3-(4-Chlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2i): Prepared according to general procedure E from **1i** (51.3 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **2i** (38.0 mg, 0.148 mmol, 74%) as a pale yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 31.9 min (major); t_R 42.9 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 95:5, 0.5 mL/min] to be 98% ee. $[\alpha]_D^{25}$ = -4.21° (c 1.9, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.79 (dd, *J* = 16.4, 12.8 Hz, 1H), 2.93 (ddd, *J* = 16.8, 4.4, 1.2 Hz, 1H), 3.10-3.24 (m, 2H), 3.36-3.49 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.28 (dd, *J* = 7.6, 0.8 Hz,

1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.37 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.52 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 8.07 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.7, 40.6, 46.0, 127.2, 127.4, 128.2, 128.97, 129.04, 132.1, 132.8, 134.0, 142.0, 143.1, 197.5. HRMS (ESI) calcd. for $C_{16}H_{13}ClO$ ($M+H^+$) 257.0728, found 257.0731.

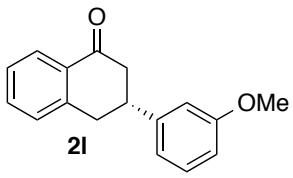


(*R*)-3-(4-(Trifluoromethyl)phenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2j): Prepared according to general procedure E from **1j** (58.1 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2j** (45.6 mg, 0.157 mmol, 79%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 9.75 min (major); t_R 13.5 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 1.0 mL/min] to be 96% ee. $[\alpha]_D^{25}$ = -2.89° (c 2.09, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.85 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.98 (ddd, *J* = 16.8, 4.0, 1.6 Hz, 1H), 3.14-3.29 (m, 2H), 3.46-3.60 (m, 1H), 7.29 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.37 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.53 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 8.09 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.4, 41.0, 45.7, 125.9 (q, *J* = 3.7 Hz), 126.9 (q, *J* = 270.4 Hz), 127.26, 127.30, 127.4, 129.0, 129.4 (q, *J* = 32.4 Hz), 132.1, 134.1, 142.9, 147.4, 197.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -63.46 (s, 1F). HRMS (ESI) calcd. for $C_{17}H_{13}F_3O$ ($M+H^+$) 291.0991, found 291.0995.



(*R*)-3-(4-Methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2k): Prepared according to general procedure E from **1k** (50.5 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (95:5

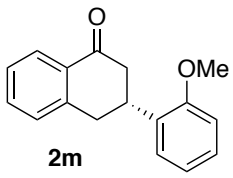
hexanes:EtOAc) to yield **2k** (40.4 mg, 0.160 mmol, 80%) as a pale yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 20.5 min (major); t_R 29.5 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{25}$ = -7.14° (c 1.12, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.80 (dd, *J* = 16.4, 12.8 Hz, 1H), 2.95 (ddd, *J* = 16.4, 4.4, 1.2 Hz, 1H), 3.11-3.23 (m, 2H), 3.36-3.47 (m, 1H), 3.81 (s, 3H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.28 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.35 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.51 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 8.08 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.1, 40.4, 46.3, 55.4, 114.2, 127.0, 127.3, 127.8, 129.0, 132.2, 133.9, 135.7, 143.6, 158.6, 198.1. HRMS (ESI) calcd. for $C_{17}H_{16}O_2$ ($M+H^+$) 253.1223, found 253.1231.



2l

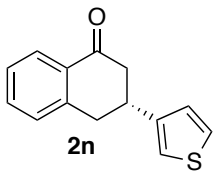
(*R*)-3-(3-Methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2l): Prepared according to general procedure E from **1l** (50.5 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **2l** (36.2 mg, 0.143 mmol, 72%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 13.8 min (major); t_R 16.9 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{25}$ = -10.5° (c 1.72, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.79 (dd, *J* = 16.4, 13.2 Hz, 1H), 2.94 (ddd, *J* = 16.4, 4.0, 1.6 Hz, 1H), 3.09-3.24 (m, 2H), 3.35-3.46 (m, 1H), 3.79 (s, 3H), 6.76-6.84 (m, 2H), 6.87 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.22-7.29 (m, 2H), 7.32 (ddd, *J* = 8.0, 7.6, 0.8 Hz, 1H), 7.48 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 8.05 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.7, 41.2, 46.1, 55.3, 112.0,

113.0, 119.1, 127.1, 127.3, 129.0, 130.0, 132.2, 134.0, 143.5, 145.2, 160.0, 197.9. HRMS (ESI) calcd. for $C_{17}H_{16}O_2$ ($M+H^+$) 253.1223, found 253.1227.



2m

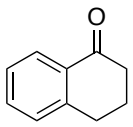
(*R*)-3-(2-Methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2m): Prepared according to general procedure E from **1m** (50.5 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = 18:1) was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **2m** (35.4 mg, 0.140 mmol, 70%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 21.4 min (major); t_R 27.6 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 97% ee. $[\alpha]_D^{25}$ = -6.02° (c 1.66, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.89 (dd, *J* = 16.4, 12.4 Hz, 1H), 2.97 (ddd, *J* = 16.4, 4.0, 1.6 Hz, 1H), 3.17 (ddd, *J* = 16.4, 2.8, 0.8 Hz, 1H), 3.27 (dd, *J* = 12.4, 0.8 Hz, 1H), 3.80-3.93 (m, 4H), 6.94 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.00 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H), 7.24-7.34 (m, 3H), 7.37 (ddd, *J* = 7.6, 7.2, 0.8 Hz, 1H), 7.53 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1H), 8.12 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 35.1, 36.0, 44.8, 55.4, 110.7, 120.8, 126.79, 126.83, 127.3, 128.0, 129.0, 131.6, 132.3, 133.7, 144.3, 157.1, 198.7. HRMS (ESI) calcd. for $C_{17}H_{16}O_2$ ($M+H^+$) 253.1223, found 253.1225.



2n

(*R*)-3-(Thiophen-3-yl)-3,4-dihydronaphthalen-1(2*H*)-one (2n): Prepared according to general procedure E from **1n** (45.7 mg, 0.200 mmol) (reaction time = 24 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **2n** (22.6 mg, 0.099 mmol, 49%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 13.5 min (major); t_R 17.3 min

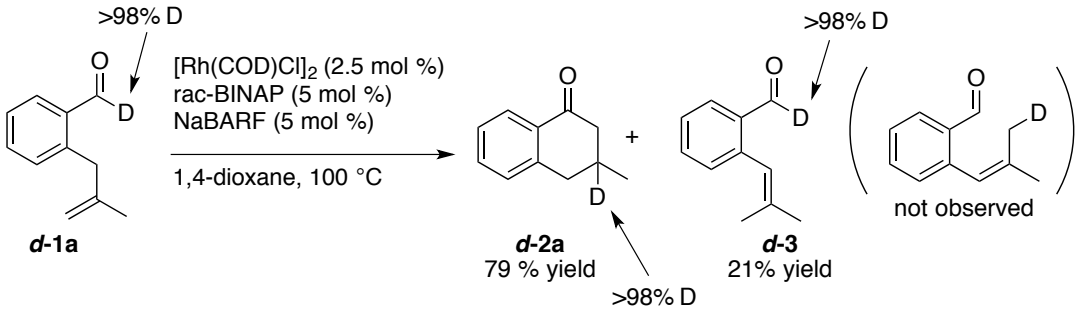
(minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{25}$ = -17.6° (c 1.02, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.80 (dd, *J* = 16.4, 12.4 Hz, 1H), 3.05 (ddd, *J* = 16.4, 3.6, 1.6 Hz, 1H), 3.17 (dd, *J* = 16.4, 10.8 Hz, 1H), 3.28 (ddd, *J* = 16.4, 2.8, 1.6 Hz, 1H), 3.52-3.62 (m, 1H), 7.07 (m, 2H), 7.26-7.40 (m, 3H), 7.51 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 8.07 (dd, *J* = 7.6, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.4, 37.2, 45.8, 120.0, 126.2, 126.4, 127.0, 127.2, 128.9, 132.1, 133.8, 143.1, 144.5, 197.6. HRMS (ESI) calcd. for $C_{14}H_{12}OS$ ($M+H^+$) 229.0682, found 229.0685.

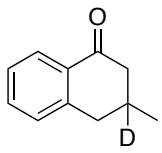


2o

3,4-Dihydronaphthalen-1(2*H*)-one[69] (2o): Prepared according to general procedure E from **1o** (29.2 mg, 0.200 mmol) (reaction time = 10 h). The crude product (hydroacylation:isomerization = >20:1) was purified by flash column chromatography (90:10 hexanes:Et_2O) to yield **2o** (21.2 mg, 0.145 mmol, 73%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.14 (m, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H), 7.25 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.31 (ddd, *J* = 8.0, 7.6, 0.8 Hz, 1H), 7.47 (ddd, *J* = 8.0, 7.6, 1.0 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4, 29.8, 39.3, 126.8, 127.3, 128.9, 132.7, 133.5, 144.6, 198.5.

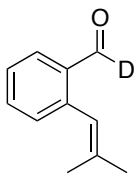
Rh-catalyzed Hydroacylation of *d*-1a





***d*-2a**

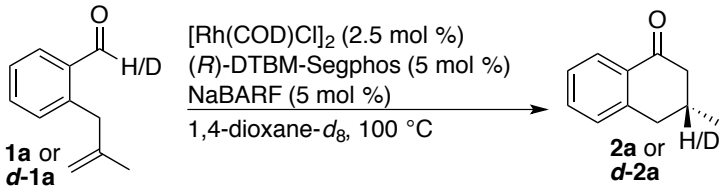
***d*$_1$-3-Methyl-3,4-dihydronaphthalen-1(2*H*)-one-3 (*d*-2a):** Prepared according to a modified version of general procedure E using *rac*-BINAP from ***d*-1a** (32.2 mg, 0.200 mmol) (reaction time = 16 h). The crude product was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield ***d*-2a** (25.2 mg, 0.156 mmol, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.13 (s, 3H), 2.30 (d, J = 16.8 Hz, 1H), 2.68 (d, J = 16.4 Hz, 1H), 2.72 (d, J = 16.8 Hz, 1H), 2.96 (d, J = 16.4, 1H), 7.24 (dd, J = 7.6, 0.8 Hz, 1H), 7.30 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.47 (ddd, J = 7.6, 7.2, 0.8 Hz, 1H), 8.01 (dd, J = 7.2, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 30.2 (t, J = 19.4 Hz), 38.0, 47.2, 126.7, 127.1, 129.0, 132.3, 133.6, 143.9, 198.8. HRMS (ESI) calcd. for $C_{11}H_{11}DO$ ($M+H^+$) 162.1024, found 162.1020.



***d*-3**

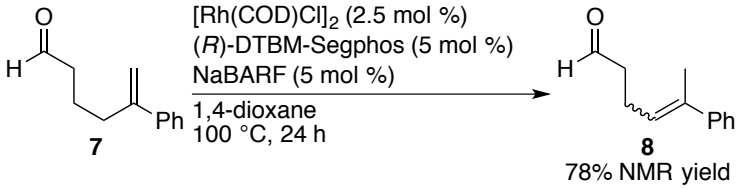
***d*$_1$-2-(2-Methylprop-1-en-1-yl)benzaldehyde (*d*-3):** Prepared according to a modified version of general procedure D using *rac*-BINAP from ***d*-1a** (32.2 mg, 0.200 mmol) (reaction time = 16 h). The crude product was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield ***d*-3** (5.9 mg, 0.037 mmol, 19%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65 (s, 3H), 1.96 (s, 3H), 6.58 (s, 1H), 7.23 (dd, J = 7.6, 0.8 Hz, 1H), 7.36 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.54 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.89 (dd, J = 7.6, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.6, 26.2, 121.3, 126.9, 128.1, 130.9, 133.7, 133.8 (t, J = 3.7 Hz), 139.5, 142.4, 192.6 (t, J = 26.6). HRMS (ESI) calcd. for $C_{11}H_{11}DO$ ($M+H^+$) 162.1024, found 162.1023.

Kinetic Isotope Effect for 1a vs. *d*-1a



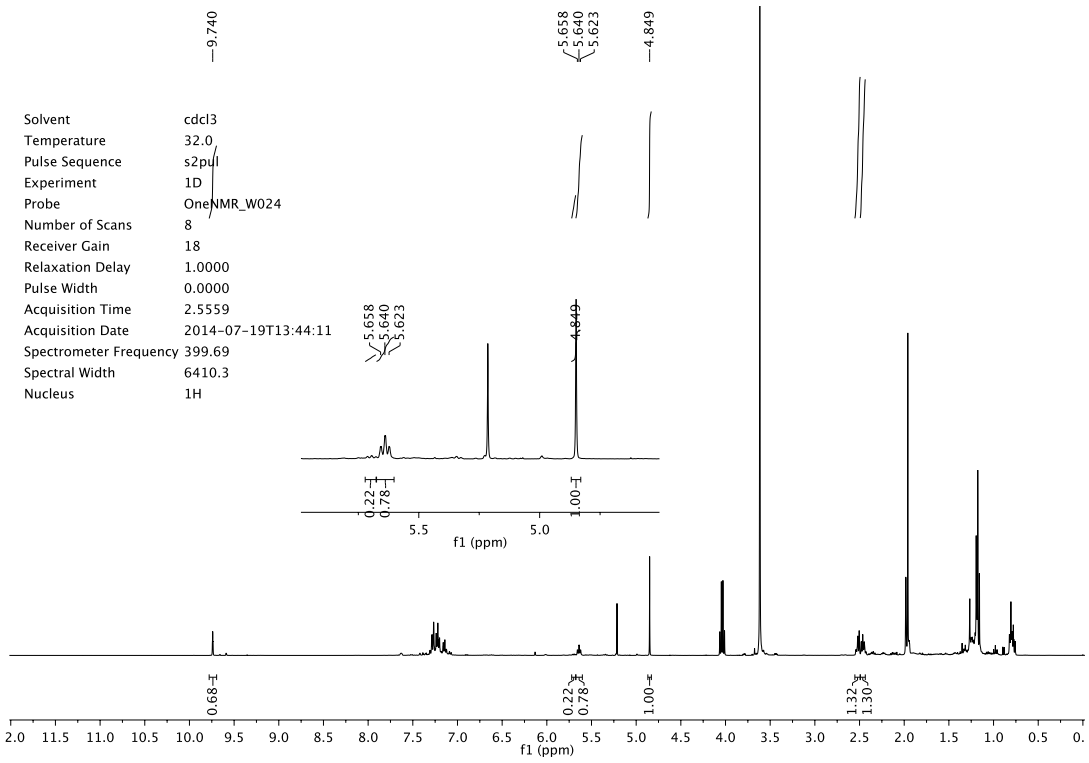
The kinetic isotope effect was determined by measuring the initial rate constants for two independent experiments for the hydroacylation of **1a** and ***d*-1a**. The reactions were monitored by ^{1}H NMR spectroscopy (T = 373K) using 1,3,5-trimethoxybenzene as an internal standard. Reaction mixtures were prepared as follows: In a nitrogen-filled dry box, **1a** or ***d*-1a** (16.0 mg, 0.100 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (1.23 mg, 0.0025 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (5.90 mg, 0.005 mmol, 0.050 equiv), NaBARF (4.43 mg, 0.005 mmol, 0.050 equiv), 1,3,5-trimethoxybenzene (5.61 mg, 0.033 mmol, 0.333 equiv), and anhydrous 1,4-dioxane-d_8 (0.5 mL) were added to a 1-dram vial. The vial was agitated to dissolve all solids and the solution was transferred to a dry J-Young NMR tube, sealed and immediately subjected to ^{1}H NMR analysis (T = 373K). Data points were collected every 3 minutes and the initial rate constants were determined from the first 5% of the reaction data.

Rh-Catalyzed Hydroacylation of 5-Phenylhex-5-enal 7



In a nitrogen-filled dry box, 5-phenylhex-5-enal **7** (0.200 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol, 0.050 equiv), NaBARF (8.9 mg, 0.010 mmol, 0.050 equiv), and anhydrous 1,4-dioxane (1 mL) were added to a 1-dram vial. The vial was sealed with a PFTE/silicone-lined septum cap and removed from the dry box. The reaction mixture was heated to 100 °C and allowed to stir at this temperature until the reaction was judged to be complete by TLC analysis. The mixture was cooled to rt, filtered through a pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. $CDCl_3$ (0.7 mL) was added to dissolve the

crude mixture along with CH_2Br_2 (7.0 μL, 0.100 mmol) as an internal standard. Compound **8** was not isolated. The ^1H NMR spectrum of the crude reaction mixture is shown below, integrated relative to the CH_2Br_2 standard.



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CHAPTER IV

RHODIUM-CATALYZED, ENANTIOSELECTIVE INTRAMOLECULAR HYDROACYLATION OF HIGHER ORDER ALKENES

Modified from a manuscript in preparation for submission to *ACS Catalysis*

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Abstract

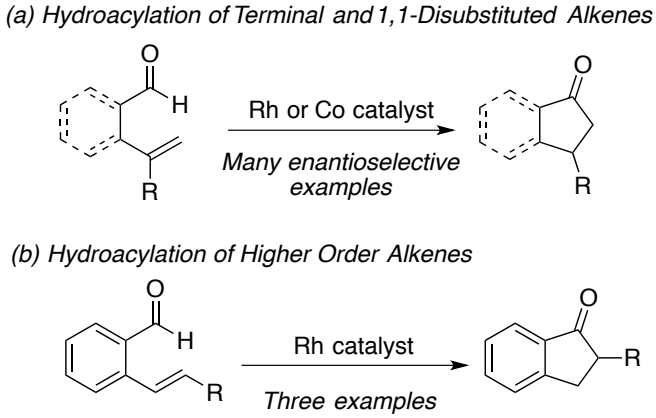
We report studies toward the intramolecular hydroacylation of 1,2-disubstituted alkenes as well as the first examples of catalytic, enantioselective alkene hydroacylation of 1,1,2-trisubstituted alkenes. The intramolecular hydroacylation of 1,2-disubstituted alkenes is facilitated by a cationic rhodium complex and generates the indanone products in high yields (up to 94%). However, the α-center is prone to epimerization and results in racemic mixtures of the bicyclic products. In contrast, the rhodium-catalyzed intramolecular hydroacylation of 1,1,2-trisubstituted alkenes generates highly enantioenriched, polycyclic architectures. DFT and mechanistic studies are consistent with a reaction pathway for these processes that includes intramolecular alkene hydroacylation and α-epimerization. This reaction sequence enables the hydroacylation of 2-(cyclohex-1-en-1-yl)benzaldehydes to form hexahydro-9*H*-fluoren-9-ones in moderate to high yields (68-91%) with high enantioselectivities (up to 99% ee) and diastereoselectivities (typically >20:1).

Introduction

Over forty years of investigation has established transition metal-catalyzed alkene hydroacylation as a powerful method for the formation of carbon-carbon bonds.[1-3]

Intramolecular alkene hydroacylations enable the synthesis of a variety of carbocyclic and heterocyclic ketones from substrates containing terminal and 1,1-disubstituted alkenes.[4-33] However, intramolecular alkene hydroacylation reactions that employ higher order alkenes remain rare.[17, 19, 22, 32-33]

Terminal and 1,1-disubstituted alkenes are excellent substrates for a variety of intramolecular alkene hydroacylation reactions catalyzed by rhodium and cobalt complexes (Scheme 1a). Rhodium-catalyzed hydroacylations of 4-pentenals are established methods to form cyclopentanone derivatives, in many cases with high diastereoselectivity and/or enantioselectivity.[4-15, 18, 20] In addition, rhodium- and cobalt-catalyzed hydroacylations of 1,1-disubstituted 2-vinylbenzaldehydes occur to generate 3-substituted indan-1-ones with high enantioselectivities.[17, 28]



Scheme 1: Intramolecular alkene hydroacylations.

Intramolecular hydroacylation reactions of 1,2-disubstituted alkenes are far less common than hydroacylations of 1,1-disubstituted alkenes (Scheme 1b). In 2005, Morehead reported a single example of the *endo*-selective rhodium-catalyzed hydroacylation of ethyl (*E*)-3-(2-formylphenyl)acrylate (R = CO_2Et) that required 5 days to reach 90% conversion.[17] Douglas observed the formation of a product resulting from hydroacylation of a 1,2-disubstituted alkene upon isomerization of 2-homoallylbenzaldehyde in the presence of a

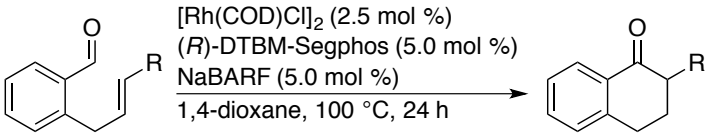
rhodium catalyst.[22] In 2009, Dong and co-workers reported the only enantioselective example of intramolecular hydroacylation of a 1,2-disubstituted alkene.[19] This *exo*-selective reaction forms a seven-membered ring and is facilitated by a chiral, cationic rhodium catalyst, but requires a coordinating sulfur atom to stabilize the key catalytic intermediate.

Several examples of transition metal-catalyzed intermolecular hydroacylation of 1,2-disubstituted alkenes have been reported, but these reactions typically require chelation-assistance strategies and selectivities are often highly substrate dependent.[34-39] To our knowledge there are no examples of transition metal-catalyzed alkene hydroacylation reactions with trisubstituted alkenes as substrates.[40-43]

We report studies toward the development of a rhodium catalyst for the hydroacylation of 1,2-disubstituted alkenes and efforts made to address challenges in the enantioselective hydroacylation of these substrates. We also report the first examples of catalytic, enantioselective hydroacylations of 1,1,2-trisubstituted alkenes. DFT and mechanistic studies are consistent with an intramolecular alkene hydroacylation/α-epimerization sequence for these catalytic processes and a series of hexahydro-9*H*-fluoren-9-ones were synthesized by this method.

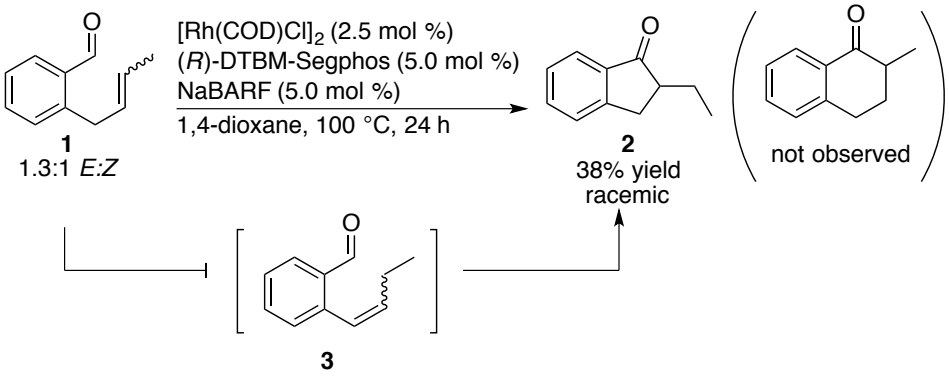
Results and Discussion

Chapter III of this thesis discusses the development of a rhodium catalyst for the *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes.[29] We envisioned that the same cationic, rhodium catalyst could facilitate the *endo*-selective hydroacylation of *ortho*-allylbenzaldehyde derivatives containing substitution at the terminal end of the allyl unit (Scheme 2).



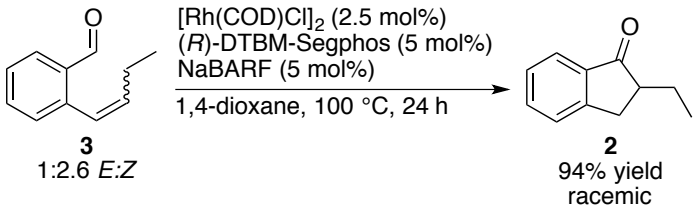
Scheme 2: Proposed reaction scheme for the *endo*-selective hydroacylation of 1,2-disubstituted alkenes.

However, the reaction of a 1.3:1 *E*:*Z* mixture of 2-(but-2-en-1-yl)benzaldehyde **1** forms 2-ethyl-2,3-dihydro-1*H*-inden-1-one **2** in 38% yield as a racemic mixture and formation of the six-membered ring was not observed (Scheme 3).



Scheme 3: Rh-catalyzed hydroacylation of 2-(but-2-en-1-yl)benzaldehyde **1**

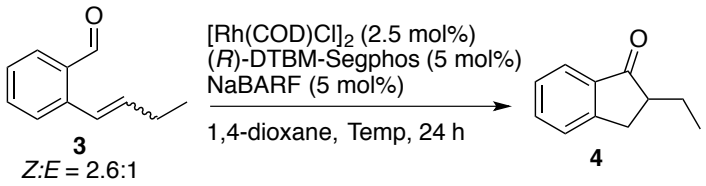
We hypothesized that the formation of **2** results from *endo*-selective hydroacylation of alkene isomerization product **3**. Thus, **3** was independently prepared and isolated as a mixture of isomers (1:2.6 *E*:*Z*). The reaction of 2-(but-1-en-1-yl)benzaldehyde **3** generated **2** in 94% yield as a racemic mixture in the presence of a catalyst generated from $[Rh(COD)Cl]_2$, (*R*)-DTBM-Segphos and NaBARF (Scheme 4). Although it is clear from this result that the cationic rhodium complex enables the hydroacylation of 1,2-disubstituted alkenes, we cannot conclusively rule out *exo*-selective hydroacylation of **1** to form **2** for the reaction shown in Scheme 3.



Scheme 4: Rh-catalyzed hydroacylation of 2-(but-1-en-1-yl)benzaldehyde **3**.

Lower yields of 2-ethyl-2,3-dihydro-1*H*-inden-1-one **2** can be isolated after shorter reaction times (6-12 h) and some degree of enantioenrichment is observed in these cases (30-59% ee). However, compound **2** is isolated as a racemic mixture after reexposure to the hydroacylation reaction conditions. We propose that a racemization event occurs at the α-center following enantioselective, rhodium-catalyzed hydroacylation of the 1,2-disubstituted alkene. In an attempt to prevent this racemization reaction, we evaluated the hydroacylation of **3** at lower reaction temperatures, but found a significant loss of reactivity toward alkene hydroacylation below 100 °C; the reaction of **3** at 60 °C formed 2-ethyl-2,3-dihydro-1*H*-inden-1-one in only 35% yield after 24h. However, ^{1}H NMR analysis of the crude reaction mixture revealed that alkene isomerization occurs in the presence of the cationic rhodium catalyst to form exclusively the *E* isomer after 24 hours. Alkene isomerization is observed for the reaction of **3** at 60 °C and 40 °C, and a room temperature experiment led to an increased ratio of the *E* isomer relative to the *Z* isomer for the starting 2-(but-1-en-1-yl)benzaldehyde **3** (Table 1). Based on this observation we propose that the cationic rhodium complex serves as an alkene isomerization catalyst and one isomer of **3** undergoes the rhodium-catalyzed hydroacylation reaction preferentially.

Table 1: Rh-catalyzed hydroacylation of **3**



3
Z:E = 2.6:1

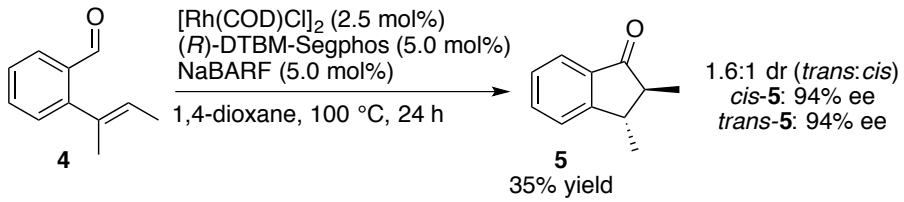
4

Entry	*Temperature (°C)*	*NMR yield* ***2***[a]	*Isomeric ratio* ***3*** *(E:Z)*[a]
1	rt	0	1.1:1
2	40	14	>20:1
3	60	35	>20:1

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture with dibromomethane as an internal standard.

Despite the wide range of potential synthetic applications for the hydroacylation of 1,2-disubstituted alkenes, the racemization process that occurs at the α-center in the presence of the cationic rhodium complex presents a catch-22; the highly cationic rhodium catalyst is critical for the alkene hydroacylation reaction to proceed, but this same complex significantly erodes the enantioselectivity before appreciable yields of the hydroacylation product can be obtained. This dilemma remains an unsolved problem and has prevented practical enantioselective hydroacylations of these substrates at this time.

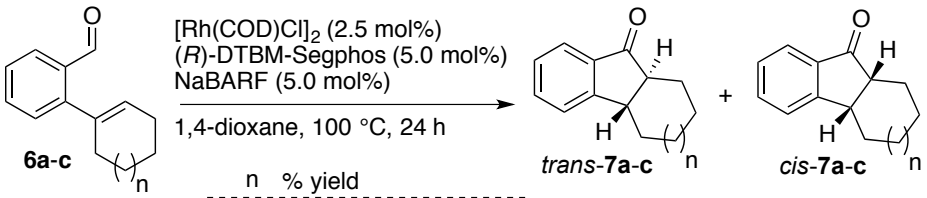
We instead turned our attention to investigation of the rhodium-catalyzed hydroacylation of trisubstituted alkenes. The hydroacylation of a 1,1,2-trisubstituted alkene **4** occurs in the presence of the chiral rhodium catalyst (Scheme 5). However, the hydroacylation of *ortho*-vinylbenzaldehyde **4** generated 2,3-dimethylindanone **5** as a mixture of diastereomers (1.6:1 *trans*:*cis*) with a high level of enantiocontrol at the β-center (94% ee for each diastereomer). The observed enantioselectivities suggest that the β-center is stable to the catalytic conditions, but that the α-center is again prone to the racemization process.



Scheme 5: Rh-catalyzed hydroacylation of (*E*)-2-(but-2-en-2-yl)benzaldehyde **4**.

To assess the viability of 1,1,2-trisubstituted alkenes as substrates for intramolecular hydroacylation, we instead evaluated reactions of *ortho*-vinylbenzaldehyde derivatives containing alkene units fixed within rings of increasing size in the presence of a catalyst generated from $[Rh(COD)Cl]_2$, (*R*)-DTBM-Segphos and NaBARF (Scheme 6).

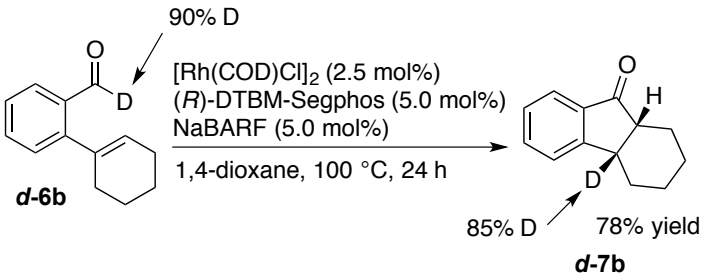
The size of the cycloalkene ring was found to have a significant impact on the reactivity and selectivity of the rhodium-catalyzed hydroacylation reactions. 2-(Cyclopent-1-en-1-yl)benzaldehyde **6a** did not undergo the desired hydroacylation reaction. The hydroacylation of 2-(cyclohex-1-en-1-yl)benzaldehyde **6b** generated **7b** as the *cis* diastereomer in high yield and enantioselectivity (88% yield, 97% ee), and the hydroacylation of 2-(cyclohept-1-en-1-yl)benzaldehyde **6c** formed **7c** as a mixture of diastereomers (1.7:1 *cis*:*trans*) in moderate yield (56%).



Scheme 6: Rhodium-catalyzed hydroacylation of **6a-c**.

The distinct difference in reactivity observed for substrates containing cycloalkenes of varied size, and the unexpected formation of *cis*-**7b** rather than *trans*-**7b,** led us to probe

the mechanism of this transformation. We conducted a kinetic isotope incorporation experiment to confirm where the aldehyde hydrogen resides in **7b** (Scheme 7). The reaction of ***d*-6b** in the presence of the same rhodium catalyst generated ***d*-7b** in 78% yield with deuterium incorporation exclusively at the β-position and only a small loss in the total deuterium content of the material. This result is consistent with the mechanism for alkene hydroacylation described in Chapter III of this thesis.[1]



Scheme 7: Rh-catalyzed hydroacylation of ***d*-6b**.

We conducted DFT studies to model the reaction pathway for hydroacylation of both **6a** and **6b** (Figure 1).[44-51] In these studies, coordination of the substrate to the rhodium(I) catalyst through both the ketone oxygen and cycloalkene unit is highly exothermic (ΔH = -19.5 and -23.2 kcal/mol) and occurs to form **I1**. A conformational change of the substrate around the Rh-center occurs to preorganize the aldehyde C-H bond for oxidative addition and generates **I2.** Oxidative addition of the rhodium(I) catalyst to the aldehyde C-H bond leads to **I3** in which the key acylrhodium(III) hydride is stabilized by the C=C bond of the cycloalkene ring (ΔH = -10.8 and -13.3 kcal/mol). Migratory insertion generates intermediate **I4** in which the acylrhodium(III) unit and the β-hydrogen reside on the same face of the cycloalkane in a *cis* orientation. Reorientation of the substrate occurs to form complex **I5** and this species undergoes reductive elimination to generate the polycyclic ketone product as the *trans* diastereomer.

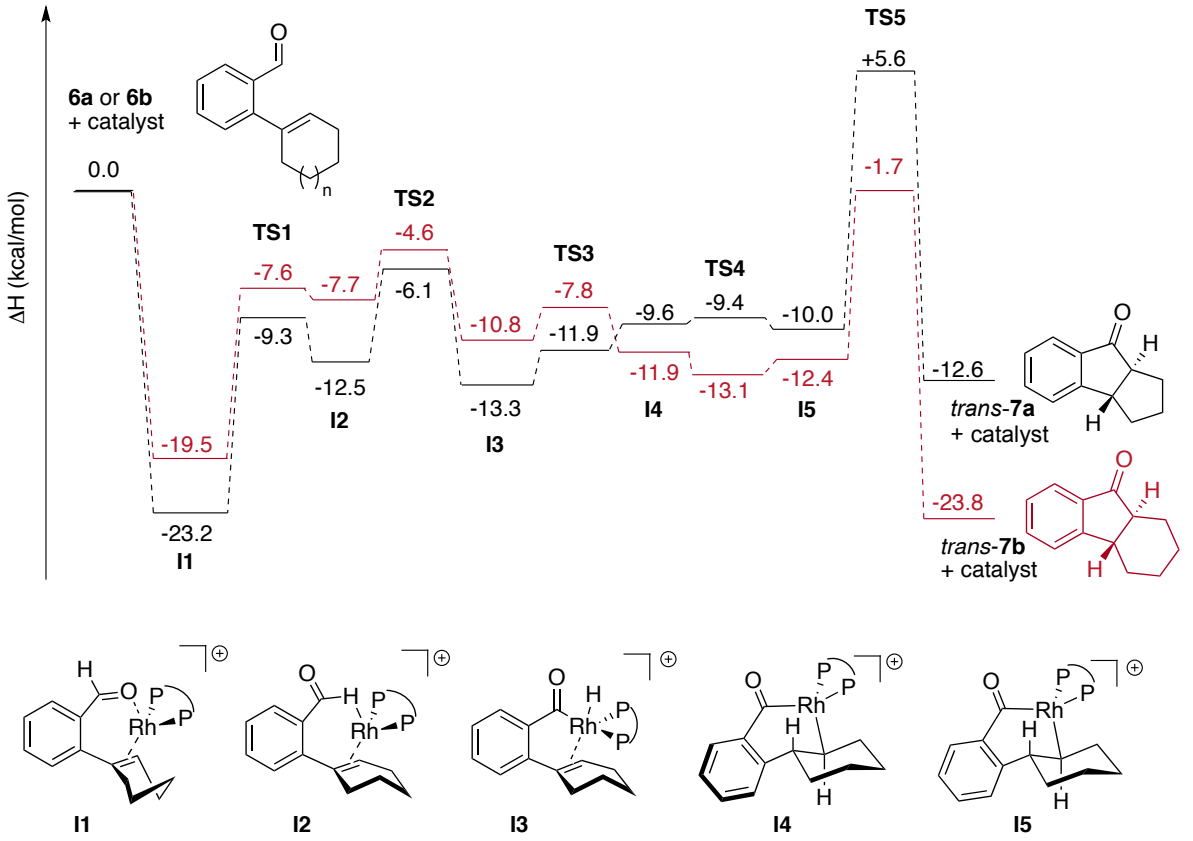


Figure 1. Potential energy surface for the rhodium-catalyzed hydroacylation of **6a** and **6b** and structures of intermediates **I1-5** for the reaction of **6b**. Enthalpies computed as sums of M06-L/6-31G(d) thermal contributions, M05-2X/6-311+G(2d,p)//M06-L/6-31G(d) electronic energies, and a solvation correction with the SMD model (THF) and M05-2X/6-31G(d).

The modeled transition state energies for the alkene hydroacylation reaction sequence are consistent with reductive elimination from **I5** as the turnover-limiting step for this catalytic process and offer support for the marked difference in reactivity between **6a** and **6b**. Consistent with the high transition state energy for turnover-limiting reductive elimination to generate *trans*-**7a** ($\Delta H^{\neq}$ = +15.6 kcal/mol), formation of *trans*-**7a** is not observed in the presence of this rhodium catalyst. However, reductive elimination to generate *trans*-**7b** corresponds to a much lower transition state energy ($\Delta H^{\neq}$ = +10.7 kcal/mol) and *trans*-**7b** is observed as an intermediate in the overall reaction sequence leading to *cis*-**7b**.

Figure 2 shows that two potential pathways exist for the formation of **I2**: 1) coordination of the substrate to generate **I1** and formation of **I2** via reorientation of the substrate to preorganize the aldehyde C-H bond for oxidative addition, or 2) coordination of the substrate to the cationic rhodium complex to generate **I2** directly.

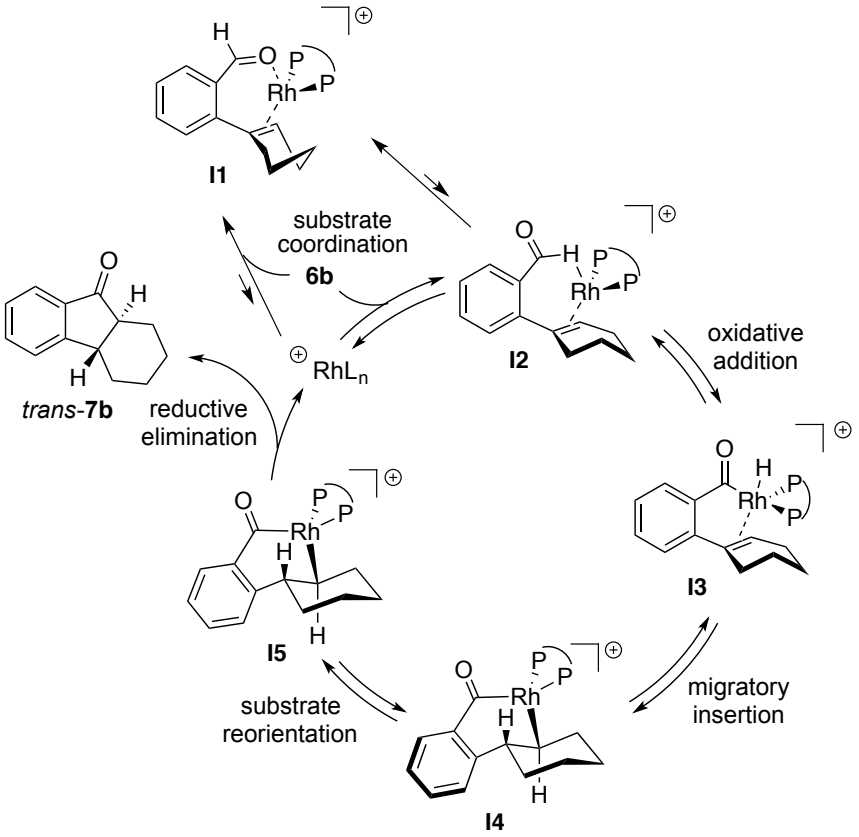
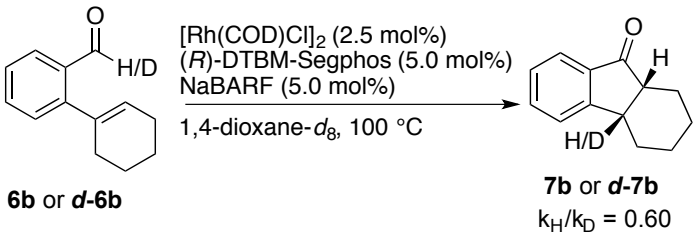


Figure 2: Proposed catalytic cycle for the Rh-catalyzed hydroacylation of **6b**.

Furthermore, comparison of initial rates for independent reactions of **6b** and ***d*-6b** at 100 °C gave a kinetic isotope effect (KIE) of 0.60 (Scheme 8).[52-55] The KIE was calculated based on the initial rates $k_H = (2.002 \pm 0.04) \times 10^{-5}$ sec^{-1} and $k_D = (3.358 \pm 0.09) \times 10^{-5}$ sec^{-1} measured from the slope of the first-order kinetics plots (Figure 3 and Figure 4). We propose that the inverse KIE observed is an equilibrium isotope effect that arises from a preequilibrum to generate **I3** followed by turnover-limiting reductive elimination.[56-62] The

greater strength of the Rh-D bond relative to the Rh-H bond leads to an increased concentration of intermediate **I3** from ***d*-6b** relative to **6b**.[63-64] The larger equilibrium concentration of ***d*-I3** will lead to a higher concentration of ***d*-7b** relative to **7b** and the observed inverse KIE. The combination of inverse KIE and high transition state energy for reductive elimination are consistent with reductive elimination as the turnover-limiting step for this process.



Scheme 8: Kinetic isotope experiments for **6b** vs. ***d*-6b**.

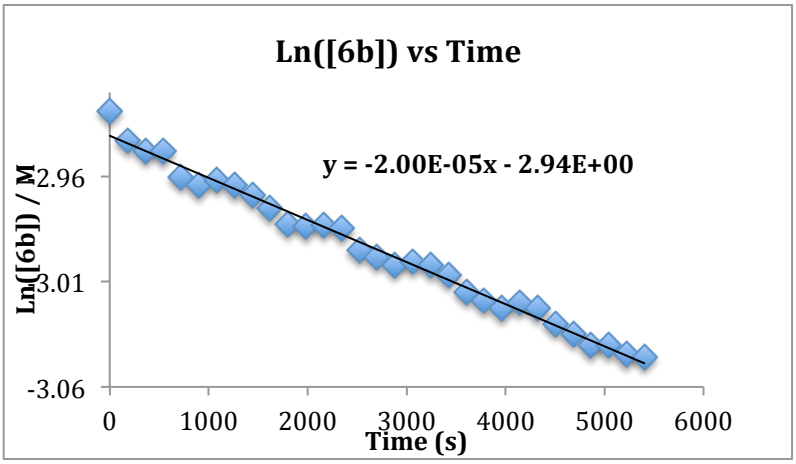


Figure 3: Plot of ln([**6b**]) with time for the first 1.5 h of the total reaction time.

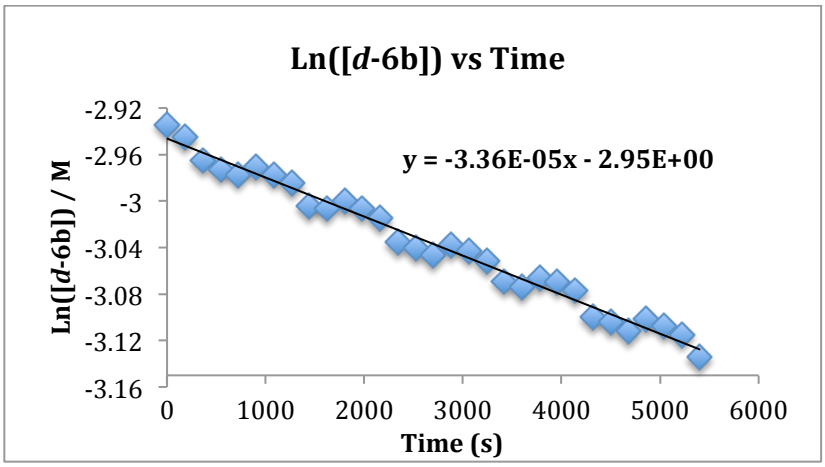
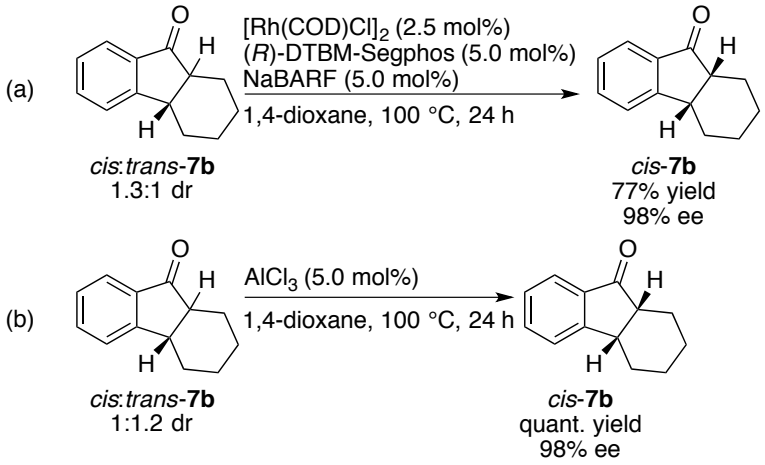


Figure 4: Plot of ln([***d*-6b**]) with time for the first 1.5 h of the total reaction time.

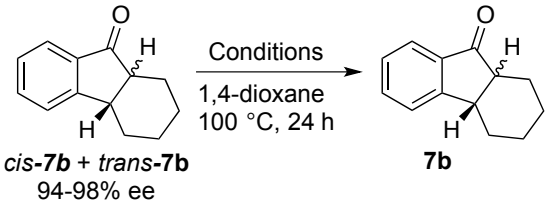
We hypothesized that the rhodium-catalyzed hydroacylation of **6b** generates *trans*-**7b** and this intermediate undergoes epimerization at the α-stereocenter to yield *cis*-**7b**.[65-69] We conducted a series of control experiments to evaluate the proposed α-epimerization pathway leading from *trans*-**7b** to *cis*-**7b**. When a mixture of diastereomers of **7b** (1.3:1 *cis*:*trans*) was re-exposed to the rhodium catalyst, exclusive formation of *cis*-**7b** was observed with high enantioselectivity (Scheme 9a). We hypothesized that the α-epimerization process could occur through Lewis acid-catalyzed activation of the ketone, deprotonation of the α-hydrogen and diastereoselective protonation directed by the fixed β-stereocenter. To evaluate this hypothesis, a mixture of *cis*-**7b** and *trans*-**7b** was exposed to an achiral Lewis acid and quantitative formation of *cis*-**7b** was observed without loss of enantiomeric excess (98% ee) (Scheme 9b).



Scheme 9: Lewis acid-catalyzed α-epimerization of *cis*:*trans*-**7b**.

Table 2 summarizes additional control experiments to ascertain which catalytic components contribute to the α-epimerization reaction. $[Rh(COD)Cl]_2$, (*R*)-DTBM-Segphos and NaBARF each facilitate the α-epimerization reaction, although no single component generates the *cis*-**7b** as a single diastereomer (entries 1-3).

Table 2: α-Epimerization experiments for the reaction of **7b**



Entry	*SM dr* (*trans*:*cis*)	*Conditions*	*Product dr* (*trans*:*cis*)	cis-***7b*** *ee (%)*[a,b]
1	3.0:1.0	$[Rh(COD)Cl]_2$ (2.5 mol%)	1.5:1.0	89(94)
2	3.0:1.0	(*R*)-DTBM-Segphos (5.0 mol%)	1.0:1.3	92(94)
3	1.2:1.0	NaBARF (5.0 mol%)	1.0:2.9	94(98)
4	1.2:1.0	1,4-dioxane only	1.2:1.0	97(98)
5	1.0:1.3	$[Rh(COD)Cl]_2$ (2.5 mol%) (*R*)-DTBM-Segphos (5.0 mol%) NaBARF (5.0 mol%)	<1:20	97(97)
6	1.2:1.0	$AlCl_3$ (5.0 mol%)	<1:20	98(98)

[a]Determined by chiral HPLC analysis. [b]Enantiomeric excess of the starting material is given in parentheses for comparison.

The α-epimerization reaction is not thermally driven; no change in dr was observed when **7b** was heated in 1,4-dioxane at 100 °C for 24 h in the absence of other catalyst

components (entry 4). As shown in Scheme 8a, exposing a mixture of diastereomers of **7b** to the standard hydroacylation reaction conditions led to complete epimerization at the α-center after 24h (entry 5). $AlCl_3$, an achiral Lewis acid unrelated to the rhodium-catalyzed hydroacylation reaction conditions, also promotes the α-epimerization to generate the *cis* diastereomer in quantitative yield and high enantioselectivity (entry 6 and Scheme 9b). These results support the viability of the proposed α-epimerization reaction to generate the *cis*-diastereomer of **7b** following enantioselective rhodium-catalyzed hydroacylation that forms the *trans*-diastereomer of **7b**.

We conducted DFT studies to model this proposed α-epimerization sequence in an effort to understand the marked difference in diastereoselectivity for the hydroacylations of **6b** and **6c**. In these calculated results, coordination of the cationic rhodium species occurs at the ketone oxygen and deprotonation via chloride anion at the α-center generates the corresponding rhodium enolate **I7** (Figure 5). This species is stabilized by the enolate C=C bond, and diastereoselective protonation occurs to produce the *cis* diastereomer. The calculated ground state energy difference between the coordinated forms of the two diastereomers (ΔG = -14.5 kcal/mol), and a low ground state energy for rhodium enolate of **7b** (ΔG = -6.8 kcal/mol) are consistent with exclusive formation of *cis*-**7b** in the overall reaction sequence However, the high ground state energy for the rhodium enolate **7c** (ΔG = +14.7 kcal/mol) disfavors complete epimerization at the α-center and leads to a mixture of diastereomers of the ketone product.

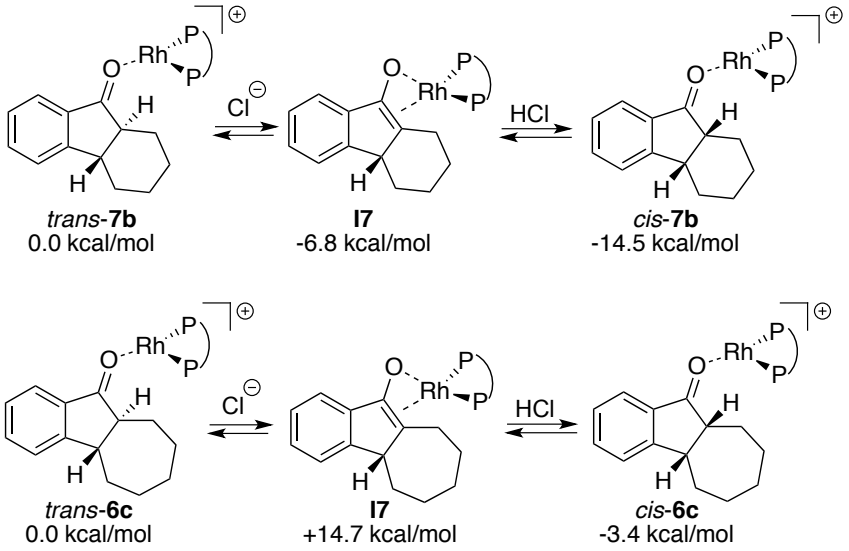
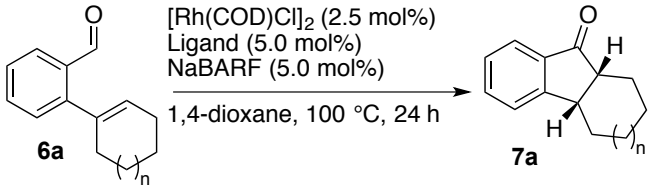
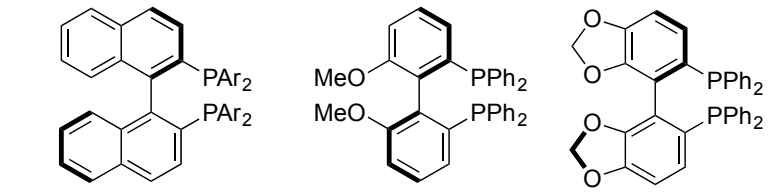


Figure 5. Reaction profile for the rhodium-catalyzed hydroacylation of **6b** and **6c.** Gibbs energies computed as sum of M06-L/6-31G(d) thermal contributions, M05-2X/6-311+G(2d,p)//M06-L/6-31G(d) electronic energies, and a solvation correction with the SMD model (THF) and M05-2X/6-31G(d).

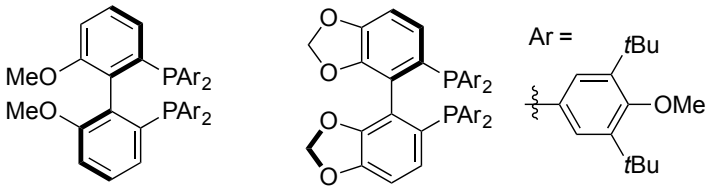
In addition to the theoretical mechanistic investigations, we evaluated a range of ligands for the Rh-catalyzed hydroacylation of **6a** to identify the best conditions for this catalytic process (Table 3). Ligands **L1**-**L4** generated **7b** in low yields (23-28%), but the observed enantioselectivities were high (79-86% ee) (entries 1-4). (*R*)-DTBM-MeO-Biphep **L5**, which contains a bulky aryl unit, generated hexahydro-9*H*-fluoren-9-one **7b** in an improved yield of 49% with high enantioselectivity (98% ee) (entry 5). As shown earlier in this chapter, (*R*)-DTBM-Segphos **L6** generated **7b** in 88% yield with 97% ee (entry 6) and was the most effective bisphosphine ligand evaluated for the rhodium-catalyzed hydroacylation of **6b**.

Table 3: Catalyst identification for the hydroacylation of **6a**[a]





L1: (*R*)-Tol-BINAP (Ar = Tolyl)
L2: (*R*)-Xyl-BINAP (Ar = Xylyl)
L3: (*R*)-MeO-Biphep
L4: (*R*)-Segphos



L5: (*R*)-DTBM-MeO-Biphep
L6: (*R*)-DTBM-Segphos

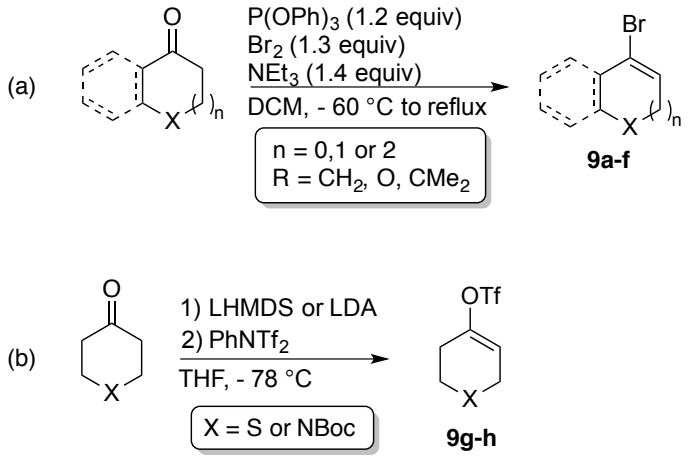
Entry	*Rh precursor*	*Ligand*	*Yield* ***2b***[b,c] *(%)*	*ee (%)*[d]
1	$[Rh(COD)Cl]_2$	**L1**	20(23)	79
2	$[Rh(COD)Cl]_2$	**L2**	32(27)	84
3	$[Rh(COD)Cl]_2$	**L3**	28(27)	87
4	$[Rh(COD)Cl]_2$	**L4**	32(28)	86
5	$[Rh(COD)Cl]_2$	**L5**	48(49)	98
6	$[Rh(COD)Cl]_2$	**L6**	88(88)	96
7[e]	$Rh(COD)_2BF_4$	**L6**	84(79)	46
8[e]	$Rh(COD)_2BARF$	**L6**	79(72)	96

[q]Reactions were conducted on a 0.200 mmol scale and further details are given in the experimental section of this thesis chapter. [b]Yield determined by ^1H NMR spectroscopy with dibromomethane as an internal standard. [c]Isolated yield shown in parentheses. [d]Determined by chiral HPLC analysis. [e]5.0 mol% of Rh precursor used and NaBARF was excluded.

We evaluated alternative rhodium catalyst precursors for the hydroacylation of **6b** (entries 7 and 8). Although $Rh(COD)_2BF_4$ facilitates the desired hydroacylation reaction, the enantioselectivity of the hexahydro-9*H*-fluoren-9-one product was significantly lower in the presence of the BF_4^- counteranion. $Rh(COD)_2BARF$ also promoted the hydroacylation of **6b**

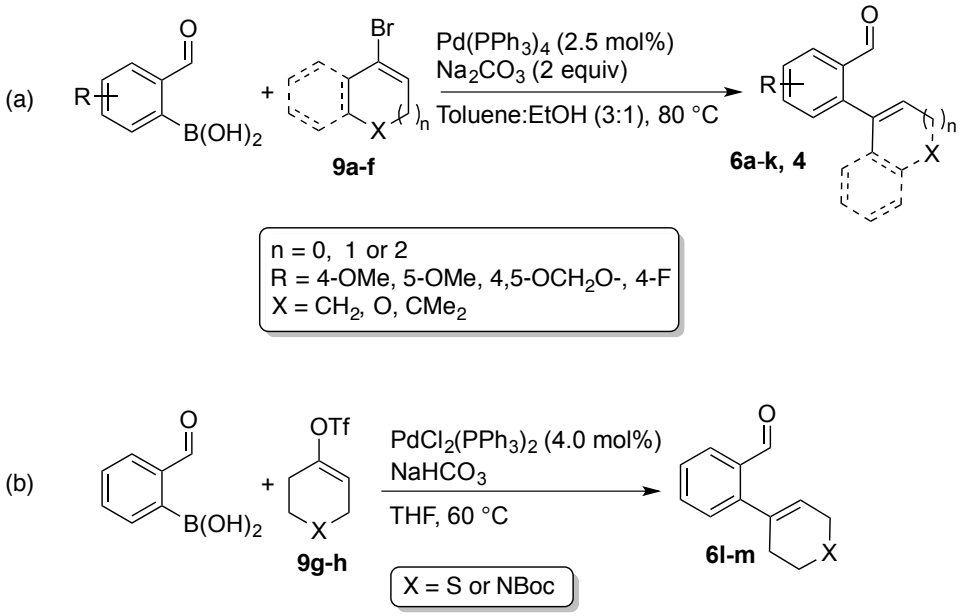
and **7b** was isolated with 96% ee. However, the yield of **7b** was noticeably lower (72% yield) with this catalyst precursor than when each catalyst component was separately weighed out (compare entries 6 and 8).

With suitable catalytic conditions at hand for the hydroacylation of substrates containing a six-membered cycloalkene unit, we synthesized a series of compounds with this general architecture. The following procedures were also used for the synthesis of compounds **1a-c** and the substrates that did not undergo the desired hydroacylation reaction. First a series of 1-bromocycloalkenes were synthesized using an enolizable ketone and a complex generated *in situ* from $P(OPh)_3$ and Br_2 (Scheme 10a). A variety of 1-bromoalkenes were isolated in moderate-to-high yields and spectral data for these compounds (**9a-f**) matches previous reports.[70-72] Vinyl triflates containing S (**9g**) and NBoc (**9h**) units within the cycloalkene were also prepared using known procedures (Scheme 10b).[73-74]



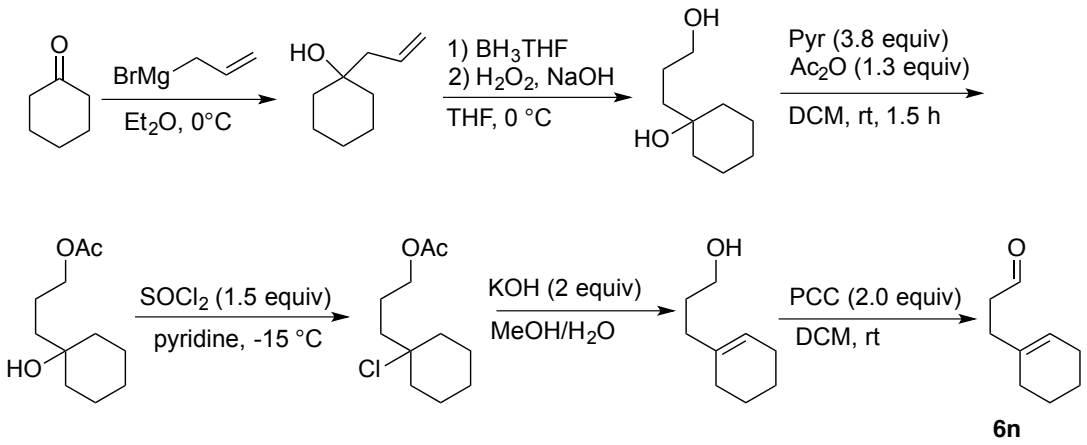
Scheme 10: Synthesis of 1-bromocycloalkenes and vinyl triflates.

Suzuki coupling of the 1-bromocycloalkenes with a variety of 2-formylphenylboronic acid derivatives formed compounds **6a-k** and **4** (Scheme 11a). Modified conditions were used for the Suzuki coupling of the vinyl triflates with 2-formylphenylboronic acid to generate 2-(cyclohex-1-en-yl)benzaldehydes **6l-m** (Scheme 11b). Further discussion of these reaction conditions is included in the Experimental section of this thesis chapter.

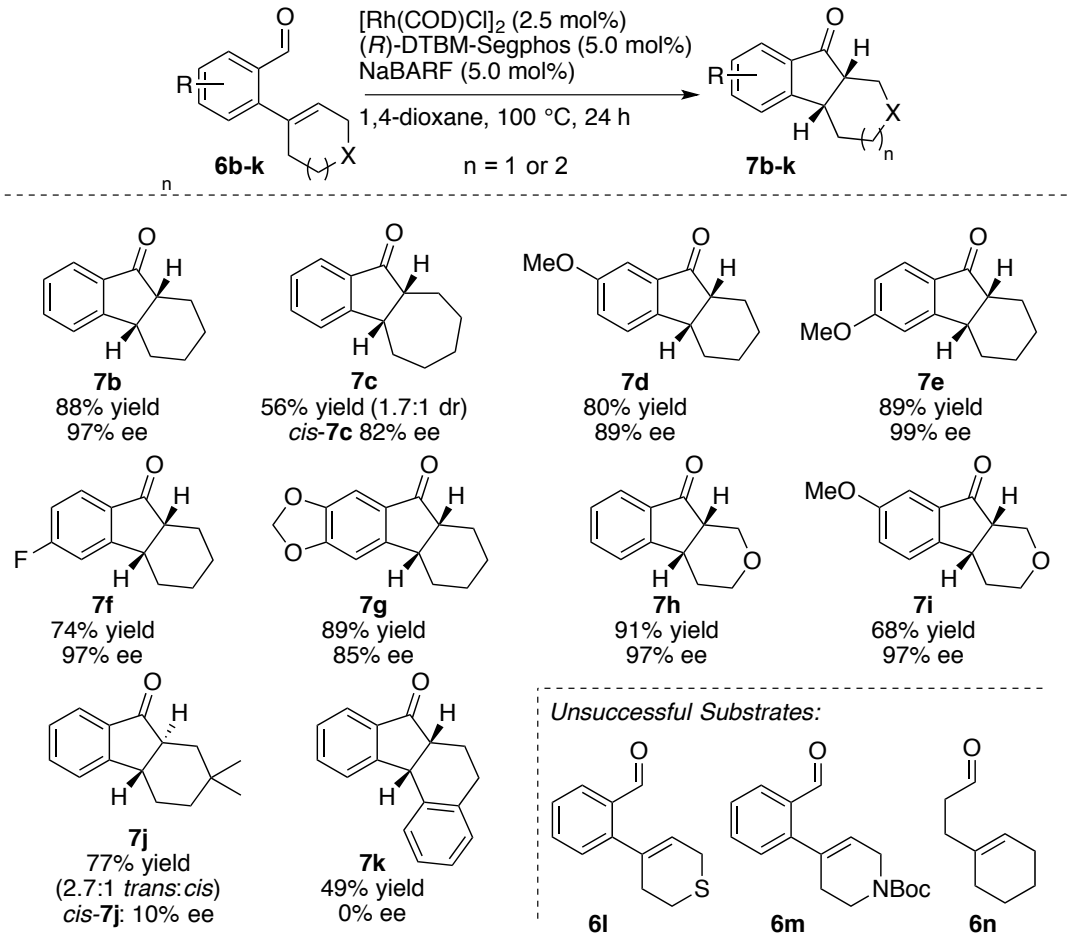


Scheme 11: Synthesis of **6a-m** and **4**.

Cycloalkene **6n** was synthesized by a reported literature procedure according to Scheme 12. Spectral data for all isolated compounds is consistent with previous reports.[75]



Scheme 12: Synthesis of **6n**.



Scheme 13: Rh-catalyzed hydroacylation of **6b-k**

With a variety of substrates in hand, we conducted hydroacylations of compounds **6d-n** (Scheme 13). Electron-rich substrates are well suited to the enantioselective, rhodium-catalyzed hydroacylation reactions. The hydroacylations of **6d** (R = 5-OMe) and **6e** (R = 4-OMe) occur to form the corresponding hexahydro-9*H*-fluoren-9-ones **7d** and **7e** in high yields (80 and 89%) and enantioselectivities (89 and 99% ee). The hydroacylation of **6f** (R = 4-F), which contains a weak electron-withdrawing group, occurs to form **7f** in moderate yield (74%) with excellent enantioselectivity (97% ee). The reaction of **6g** proceeds to form the tetracyclic hexahydro-9*H*-fluoren-9-one **7g** in 89% yield with 85% ee. Single crystal X-ray

structure determination was performed using Cu radiation to determine the relative and absolute configurations of **7g** to be *cis*-(4b*S*,8a*R*) (Figure 6).

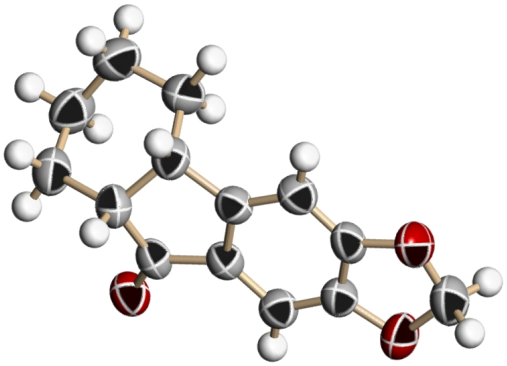
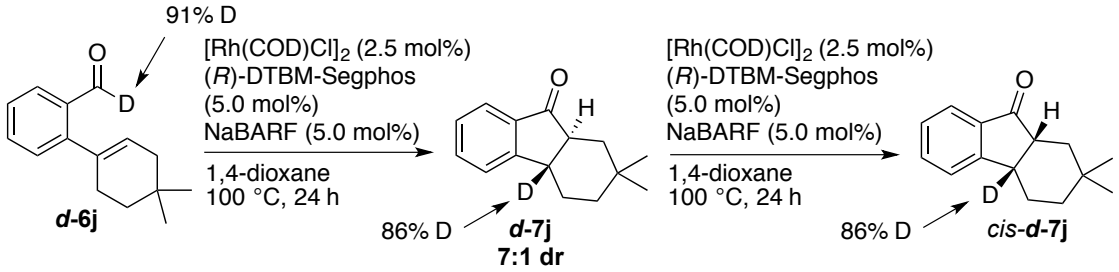


Figure 6: Absolute stereochemistry and structure of (4b*S*,8a*R*)-4b,5,6,7,8,8a-Hexahydro-9*H*-fluoreno[2,3-*d*][1,3]dioxol-9-one (**7g**)

Substrates containing an oxygen atom within the cyclohexene ring were also amenable to the rhodium-catalyzed hydroacylation reaction. The hydroacylation of **6h** and **6i** occurred to form **7h** and **7i** in moderate to high yield (68-91%) with excellent enantioselectivity (97% ee).

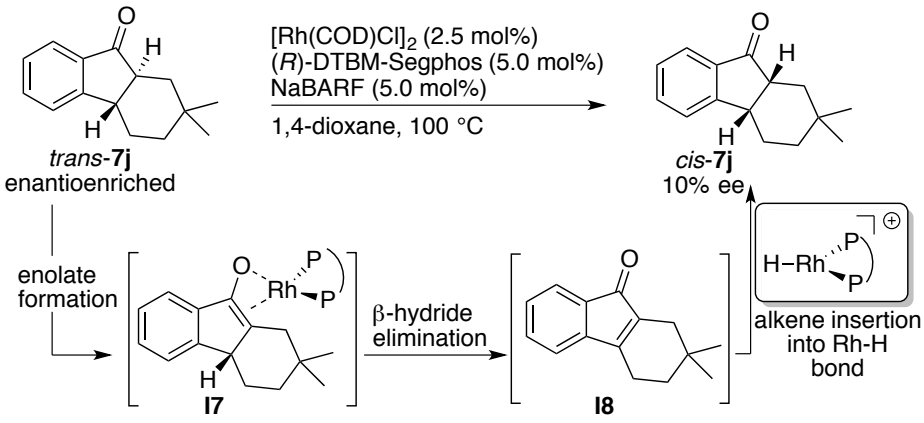
We evaluated the rhodium-catalyzed hydroacylation of substrates with substituted cycloalkene units and found that this substitution can significantly impact the diastereo- and enantioselectivity of the overall hydroacylation/α-epimerization sequence. The hydroacylation of **6j** which contains two methyl groups on the cyclohexene ring led to a mixture of diastereomers of **7j** (2.7:1 *trans*:*cis*) and *cis* diastereomer was found to have only 10% ee. Determination of the enantiomeric excess of the *trans*-diastereomer proved challenging because we were unable to obtain a pure sample of *trans*-**7j**; various conditions for the hydroacylation of **6j** yielded only traces of *trans*-**7j** that were isolated in a mixture with *cis*-**7j**. However, HPLC studies using these mixtures of *cis*- and *trans*-**7j** suggest that the rhodium-catalyzed hydroacylation reaction is enantioselective and that another catalytic

process may occur at a faster rate than the α-epimerization reaction to produce *cis*-**7j** as a racemic product. Formation of racemic *cis*-**7j** by such a background reaction would lead to poor enantioselectivity in the final product. Therefore, we conducted a deuterium isotope experiment to confirm that the rhodium-catalyzed hydroacylation is enantioselective and to probe the lack of enantioselectivity observed for *trans*-**7j**. The hydroacylation of *d*-**6j** generated *trans*-*d*-**7j** with 99% ee and 86% deuterium incorporation at the β-position after 24 hours. Re-exposure of this product to the reaction conditions yielded *cis*-***d***-**7j** with the same level of enantioenrichment (99% ee) and deuterium incorporation (86% D) (Scheme 14).



Scheme 14: Rh-catalyzed hydroacylation of ***d*-6j**

We propose that a potential reaction pathway leading to racemic product includes β-hydride elimination from the rhodium-enolate species **I7** to generate the α,β-unsaturated ketone **I8** (Scheme 15). Insertion of the alkene into the rhodium-hydride bond and reprotonation of the resulting rhodium-enolate leads to racemic *cis*-**7j** and a significant loss of enantioselectivity in the overall formation of *cis*-**7j**. In contrast, the rhodium-enolate of *d*-**7j** does not undergo β-hydride elimination to generate **I8** and a high level of selectivity is preserved in the formation of *cis*-*d*-**7j**.



Scheme 15: Proposed mechanism for the formation of *cis*-**7j** with low enantioselectivity.

Poor enantioselectivity was also observed for the hydroacylation of **6k** in which the cycloalkene moiety contains an aryl backbone. We propose that the planar orientation of the cycloalkene unit in this substrate prevents any facial selectivity for alkene coordination in **I3**. Alternatively, the increased acidity of the bis-benzylic hydrogen atom at the β-center may lead to epimerization of the β-stereogenic center at elevated temperatures on the same time scale as the hydroacylation reaction. Substrates that contain a sulfur (**6l**) or nitrogen atom (**6m**) in the cycloalkene ring, or that lack a rigid aryl backbone for the aldehyde moieties (**6n**), do not undergo the desired hydroacylation reaction.

Conclusions

In summary, we have developed the first examples of catalytic, enantioselective intramolecular hydroacylations of 1,1,2-trisubstituted alkenes. DFT and experimental studies support a reaction sequence in which rhodium-catalyzed alkene hydroacylation forms the *trans*-diastereomer of the ketone product, and Lewis acid-catalyzed α-epimerization is facilitated by the same rhodium complex to subsequently generate the *cis* diastereomer. These highly enantioselective processes offer a snapshot into the mechanistic challenges at play in the hydroacylation of higher order alkenes. Further investigation to improve catalyst

activity and to expand the scope of trisubstituted alkenes that undergo alkene hydroacylation are ongoing in our laboratory.

Experimental

General synthetic details. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried in an oven at 140 °C for at least two hours before use. THF, Et_2O, and DCM were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous 1,4-dioxane and DMF were purchased from Sigma-Aldrich and used as received. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63μm, 60 Å) using hexanes, hexanes/ethyl acetate or hexanes/diethyl ether mixtures. Products were visualized on TLC by UV light or by staining with $KMnO_4$.

Instrumentation. HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. HPLC analyses were carried out on a Waters Alliance HPLC system with an e2695 separations module and a 2489 dual wavelength detector. Optical rotations were measured on an Atago AP-300 automatic polarimeter using a 0.5 dm cell. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemicals shifts are reported in ppm relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for ^1H and 77.16 ppm for ^{13}C) or an external standard (CF_3CO_2H:$CDCl_3$ = -77.56 ppm for ^{19}F). Coupling constants are reported in hertz.

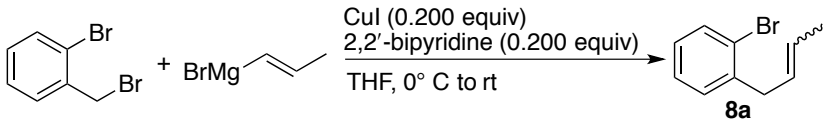
Materials. Triphenylphosphite, bromine, α-tetralone, *p*-toluenesulfonic acid, ethylene glycol, 6-bromopiperonal, lithium bis(trimethylsilyl)amide, diisopropylamine, *m*-anisaldehyde, trimethyl borate, triisopropyl borate, cyclopentanone, cycloheptanone, (*E*)-2-bromo-2-butene, and propyltriphenylphosphium bromide were purchased from Sigma Aldrich and used without further purification. *n*-Butyllithium (2.5M in hexanes) was purchased from Sigma-Aldrich and titrated with recrystallized diphenylacetic acid prior to use. Tetrahydro-4*H*-pyran-4-one and 4,4-dimethylcyclohexanone were purchased from Oakwood Chemicals and used without further purification. Cyclohexanone, triethylamine and *p*-toluenesulfonic acid were purchased from Fisher Scientific and used without further purification. 1-Methylpiperidine-4-one was purchased from TCI Chemicals and used without further purification. 2-Formylphenylboronic acid, *N*-phenyl-bis(trifluoromethanesulfonimide), tetrahydro-4*H*-thiopyran-4-one and *tert*-butyl 4-oxopiperidine-1-carboxylate were purchased from AK Scientific and used without further purification. (2-Formyl-5-methoxyphenyl)boronic acid and (5-fluoro-2-formylphenyl)boronic acid were purchased from Frontier Scientific and used without further purification.

$Pd(PPh_3)_4$, $[Rh(COD)Cl]_2$, $[Rh(COD)_2]BF_4$, *rac*-Tol-BINAP (2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthalene), (*R*)-Tol-BINAP ((*R*)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthalene), (*R*)-Xyl-BINAP ((*R*)-2,2′-bis(di-3,5-dimethylphenylphosphino)-1,1′-binaphthalene), (*R*)-MeO-Biphep ((*R*)-2,2′-bis(diphenylphosphino)-1,1′-biphenyl), (*R*)-Segphos ((*R*)-2,2′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole), (*R*)-DTBM-MeOBiphep ((*R*)-2,2′-bis(di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino)-6,6′-dimethoxy-1,1′-biphenyl), and (*R*)-DTBM-Segphos ((R)-2,2′-bis(di(3,5-di-*t*-butyl-4-

methoxyphenyl)phosphino)-4,4′-bi-1,3-benzodioxole) were purchased from Strem Chemicals and used without further purification.

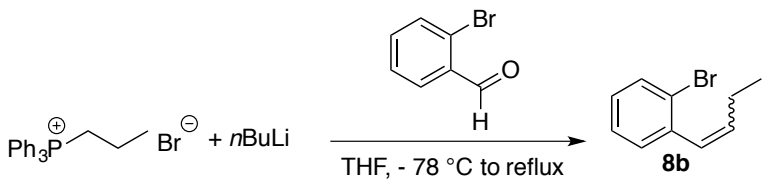
NaBARF (Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was prepared according to a literature procedure.[76] [Rh(COD$_2$]BARF was prepared according to a literature procedure from [Rh(COD)Cl]$_2$ and NaBARF.[77] 1-Bromocyclopent-1-ene, 1-bromocyclohex-1-ene and 1-bromocyclohept-1-ene were prepared according to a literature procedure from cyclopentanone, cyclohexanone or cycloheptanone.[71] 4-Bromo-1,2-dihydronapthalene was prepared according to a literature procedure from α-tetralone.[70] 4-Bromo-3,6-dihydro-2*H*-pyran was prepared according to a literature procedure from tetrahydro-4*H*-pyran-4-one.[72] 3,6-Dihydro-2*H*-thiopyran-4-yl trifluoromethanesulfonate was prepared according to a literature procedure from tetrahydro-4*H*-thiopyran-4-one.[74] *tert*-Butyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate was prepared according to a literature procedure from *tert*-butyl 4-oxopiperidine-1-carboxylate.[73] *tert*-Butyl-4-(2-formylphenyl)-3,6-dihydropyridine-1-(2*H*)-carboxylate was prepared according to a literature procedure.[78] 3-(Cyclohex-1-en-1-yl)propanal was prepared according to a literature procedure starting from cyclohexanone and allylmagnesium bromide.[75] (2-Formyl-4-methoxyphenyl)boronic acid was prepared according to literature procedure from *m*-anisaldehyde.[79] (6-formylbenzo[*d*][1,3]dioxol-5-yl)boronic acid was prepared according to a literature procedure from 6-bromopiperonal.[80]

Preparation of 1-Bromo-2-(but-2-en-1-yl)benzene 8a



To an oven-dried 100 mL round bottom flask was added 2-bromobenzylbromide (1.80 g, 7.20 mmol, 1.00 equiv), CuI (0.200 equiv), 2,2′-bipyridine (0.200 equiv) and dry THF (10 mL) and the mixture was cooled to 0 °C. Then, 1-propenylmagnesium bromide (24.0 mL of a 0.5 M solution, 12.00 mmol) was added dropwise via syringe and the combined reaction mixture was stirred overnight and allowed to warm to room temperature. The reaction was quenched by the addition of sat. NH_4Cl solution and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (100% hexanes) to yield **8** as a mixture of isomers (*E:Z* = 1.6:1.0) (1.38 g, 6.53 mmol, 54%) as a colorless oil. Spectral data is consistent with previous reports.[81]

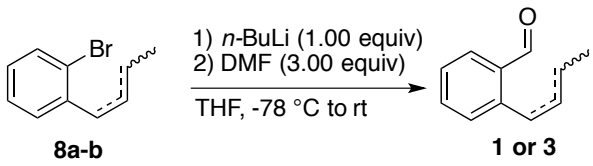
Preparation of 1-Bromo-2-(but-1-en-1-yl)benzene 8b



To a solution of propyltriphenylphosphonium bromide (6.16 g, 16.00 mmol, 2.00 equiv) in anhydrous THF at -78 °C under N_2 was added *n*-BuLi (8.04 mL of a 1.99M solution in hexanes, 2.00 equiv), dropwise. This mixture was allowed to stir at -78 °C for 10 minutes, warmed to room temperature for 30 minutes then cooled to 0 °C and 2-bromobenzaldehyde (0.934 mL, 8.00 mmol, 1.00 equiv) was added via syringe. The combined reaction mixture was let stir at 0 °C for 30 minutes before slowly warming to reflux and allowing to stir overnight (16 h). The reaction mixture was cooled to room temperature quenched by the addition of NH_4Cl (sat. solution). The solution was extracted with Et_2O (3x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column

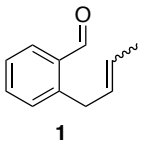
chromatography (100% hexanes) to yield **8b** as a mixture of isomers (*E:Z* = 1.0:2.4) (1.19 g, 5.63 mmol, 70%) as a colorless oil.[82]

Preparation of 1 and 3



8a-b **1 or 3**

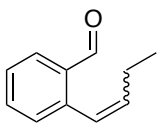
2-(But-2-en-1-yl)benzaldehyde (1): To a solution of **8a** (1.37 g, 6.50 mmol, 1.00 equiv) in



1

THF at -78 °C was added *n*-BuLi (2.83 mL of a 2.30 M solution in hexanes, 1.00 equiv) dropwise. The solution was kept at -78 °C for 1 hour, warmed to room temperature for 30 minutes, and then cooled back to -78 °C for 10 minutes before DMF (1.50 mL, 3.00 equiv) was added. The solution was allowed to warm to room temperature overnight and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **1** (0.797 g, 4.97 mmol, 76%) as a yellow oil (*E:Z* = 1.3:1). Spectral data is consistent with previous reports.[83]

2-(But-1-en-1-yl)benzaldehyde (3): To a solution of **8b** (1.06 g, 5.00 mmol, 1.00 equiv) in

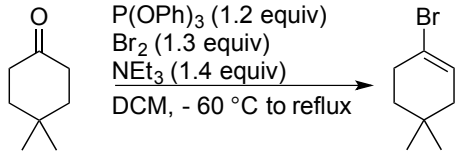


3

THF at -78 °C was added *n*-BuLi (2.51 mL of a 1.99 M solution in hexanes, 1.00 equiv) dropwise. The solution was kept at -78 °C for 2 hours and DMF (1.16 mL, 3.00 equiv) was added. The solution was allowed to warm to room temperature overnight and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (90:10 Hex:EtOAc) to yield **3** (0.502 g, 3.14 mmol, 63%) as a colorless oil (*E:Z* = 1:2.6). Spectral data reported for major (*cis*) regioisomer: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.995 (t, *J* = 7.6 Hz, 3H), 2.04-2.13 (dq, *J* = 7.6,

7.2 Hz, 2H), 5.93 (dt, *J* = 11.2, 7.6 Hz, 1H), 6.78 (d, *J* = 11.2 Hz, 1H), 7.27 (dd, *J* = 8.4 Hz, 1H), 7.39 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.6, 0.8 Hz, 1H), 7.89 (dd, *J* = 7.6, 0.8 Hz, 1H), 10.26 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 14.1, 22.0, 124.8, 127.1, 127.4, 128.7, 130.6, 133.7, 133.8, 137.9, 192.6. **HRMS** (ESI) calcd. for $C_{11}H_{13}O$ ($M+H^+$) 161.0961, found 161.0960.

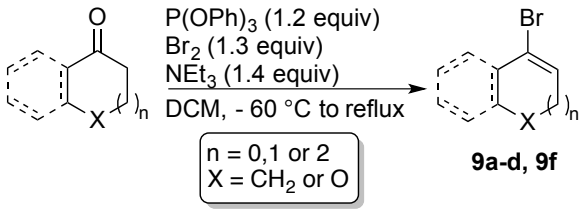
Preparation of 4-bromo-4,4-dimethylcyclohex-1-ene (9e)



9e

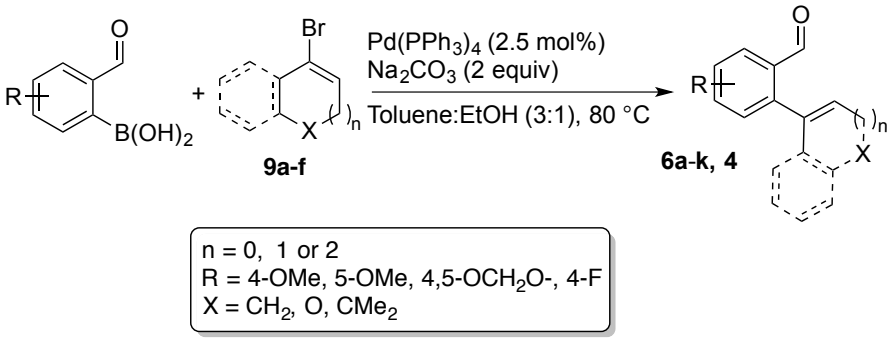
To a solution of triphenylphosphite (5.96 g, 19.2 mmol, 1.2 equiv) in DCM at -60 °C was added Br_2 (1.07 mL, 20.8 mmol, 1.30 equiv) and the mixture was let stir at this temperature for 15 minutes. 4,4-Dimethylcyclohexanone (2.02 g, 16.0 mmol, 1.00 equiv) was added as a solution in CH_2Cl_2 via syringe followed by NEt_3 (3.12 mL, 22.4 mmol, 1.40 equiv) and the evolution of white vapor was observed. The combined reaction mixture was allowed to warm to room temperature and stirred overnight (16 h). The reaction mixture was then heated to reflux for 2h and cooled to room temperature. The mixture was diluted with hexanes (some precipitation was observed) and ~½ of the solvent volume was removed under reduced pressure. The mixture was diluted to the original volume with hexanes, and ~½ of the total solvent volume was once again removed under reduced pressure. The mixture was filtered to remove resulting precipitate (triphenylphosphite oxide and triethylammonium salts) and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (100% hexanes) to yield 1-bromo-4,4-dimethylcyclohex-1-ene **9e** (2.21 g, 11.7 mmol, 73%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.93 (s, 6H), 1.47 (t, *J* = 6.4 Hz, 2H), 1.86 (m, 2H), 2.41 (m, 2H), 5.93 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.0 (2C), 28.2, 33.2, 37.3, 41.3, 121.2, 127.9. **HRMS** (ESI) calcd. for $C_8H_{14}Br$ ($M+H^+$) 189.0273, found 189.0274.



Compounds **9a-d** and **9f** were synthesized by the same synthetic procedure as **9e** from the corresponding ketones and spectral data for those compounds is consistent with previous reports.[70-72]

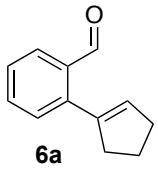
General Procedure A: Synthesis of *ortho*-vinylbenzaldehydes 6a-6k, 4



In a nitrogen-filled dry box, $Pd(PPh_3)_4$ (0.025 equiv) was weighed into dry round bottom flask and anhydrous toluene was added. The flask was sealed with a rubber septum and removed from the dry box. The appropriate bromoalkene (1.00 equiv) was added via syringe, followed by a solution of the appropriate boronic acid (1.10-1.20 equiv) in EtOH, then Na_2CO_3 (2.0 M solution, 2.00 equiv). This mixture was heated to 80 °C, monitored by TLC for consumption of the bromoalkene (16 h) then cooled to room temperature. The reaction mixture was diluted with EtOAc, washed with Na_2CO_3 sat. solution and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was

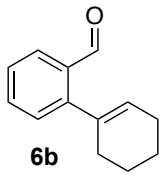
purified by flash column chromatography on silica gel (90:10 hexanes:EtOAc) to yield the corresponding *ortho*-vinylbenzaldehyde **6a-k** or **4**.

2-(Cyclopent-1-en-1-yl)benzaldehyde (6a): Prepared according to general procedure A


6a

from 1-bromocyclopent-1-ene (0.294 g, 2.00 mmol), 2-formylphenylboronic acid (0.360 g, 2.40 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (57.8 mg, 0.050 mmol, 0.025 equiv), Na_2CO_3 (2.0 mL of a 2.0 M solution, 2.00 equiv), toluene (6.0 mL) and EtOH (2.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6a** (0.256 g, 1.48 mmol, 74%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.09 (tt, *J* = 7.6, 7.2 Hz, 2H), 2.60 (tdt, *J* = 7.2, 5.2, 2.4 Hz, 2H), 2.76 (tdt, *J* = 7.6, 5.2, 2.4 Hz, 2H), 5.72-5.75 (m, 1H), 7.33-7.39 (m, 2H), 7.54 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 10.2 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 24.0, 34.1, 37.1, 127.1, 127.7, 128.4, 133.4, 134.3, 135.3, 139.8, 142.6, 192.5. **HRMS** (ESI) calcd. for $C_{12}H_{13}O$ ($M+H^+$) 173.0961, found 173.0962.

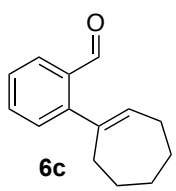
2-(Cyclohex-1-en-1-yl)benzaldehyde (6b): Prepared according to general procedure A from


6b

1-bromocyclohex-1-ene (3.14 g, 19.5 mmol), 2-formylphenylboronic acid (3.51 g, 23.4 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (563 mg, 0.488 mmol, 0.025 equiv), Na_2CO_3 (19.5 mL of a 2.0 M solution, 2.00 equiv), toluene (60.0 mL) and EtOH (19.5 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6b** (1.87 g, 10.1 mmol, 52%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.67-1.75 (m, 2H), 1.77-1.85 (m, 2H), 2.20-2.26 (m, 2H), 2.32-2.38 (m, 2H), 5.61-5.65 (m, 1H), 7.31 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.36 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.25 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.2 Hz, 1H), 10.15 (d, *J* = 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.0, 23.0, 25.8, 31.1, 127.0, 127.6, 128.8, 131.4,

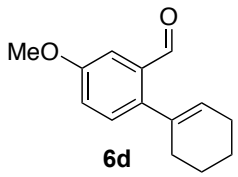
133.5, 133.9, 135.0, 148.9, 192.8. **HRMS** (ESI calcd. for $C_{13}H_{15}O$ ($M+H^+$) 187.1117, found 187.1119.

2-(Cyclohept-1-en-1-yl)benzaldehyde (6c): Prepared according to general procedure A from 1-bromocyclohept-1-ene (1.75 g, 10.0 mmol), 2-formylphenylboronic acid (1.80 g, 12.0 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (289 mg, 0.250 mmol, 0.025 equiv), Na_2CO_3 (10.0 mL of a 2.0 M solution, 2.00 equiv), toluene (30.0 mL) and EtOH (10.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6c** (0.943 g, 4.71 mmol, 47%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.57-1.72 (m, 4H), 1.83-1.91 (m, 2H), 2.31-2.38 (m, 2H), 2.57-2.62 (m, 2H), 5.77 (t, *J* = 6.4 Hz, 1H), 7.28-7.36 (m, 2H), 7.51 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 10.17 (d, *J* = 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 26.9, 27.0, 29.3, 32.6, 35.8, 126.7, 127.7, 128.8, 133.4, 133.5, 136.8, 141.6, 150.3, 192.8. **HRMS** (ESI) calcd. for $C_{14}H_{17}O$ ($M+H^+$) 201.1274, found 201.1276.



6c

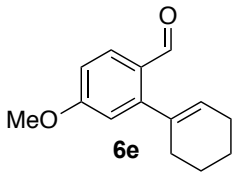
4-Methoxy-2′,3′,4′,5′-tetrahydro-[1,1′-biphenyl]-2-carbaldehyde (6d): Prepared according to general procedure A from 1-bromocyclohex-1-ene (0.306 g, 1.90 mmol), (2-formyl-4-methoxyphenyl)boronic acid (0.410 g, 2.28 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (55.0 mg, 0.048 mmol, 0.025 equiv), Na_2CO_3 (1.9 mL of a 2.0 M solution, 2.00 equiv), toluene (6.0 mL) and EtOH (1.9 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6d** (0.158 g, 0.730 mmol, 38%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.65-1.74 (m, 2H), 1.75-1.84 (m, 2H), 2.17-2.25 (m, 2H), 2.27-2.34 (m, 2H), 3.86 (s, 3H), 5.62-5.68 (m, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 10.0 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.0, 23.0, 25.6, 31.2, 55.6, 113.28, 113.31,



6d

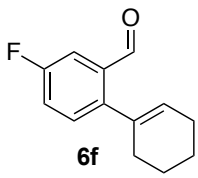
127.4, 130.0, 130.5, 135.1, 151.5, 163.7, 191.3. **HRMS** (ESI) calcd. for $C_{14}H_{17}O_2$ ($M+H^+$) 217.1223, found 217.1218.

5-Methoxy-2′,3′,4′,5′-tetrahydro-[1,1′-biphenyl]-2-carbaldehyde (6e): Prepared according to general procedure A from 1-bromocyclohex-1-ene (0.805 g, 5.00 mmol), (2-formyl-5-methoxyphenyl)boronic acid (0.990 g, 5.50 mmol, 1.10 equiv), $Pd(PPh_3)_4$ (144 mg, 0.125 mmol, 0.025 equiv), Na_2CO_3 (5.0 mL of a 2.0 M solution, 2.00 equiv), toluene (15.0 mL) and EtOH (5.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6e** (0.490 g, 2.26 mmol, 45%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.66-1.75 (m, 2H), 1.76-1.84 (m, 2H), 2.18-2.25 (m, 2H), 2.28-2.36 (m, 2H), 3.87 (s, 3H), 5.64-5.69 (m, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 10.0 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.0, 23.0, 25.7, 31.2, 55.6, 113.29, 113.32, 127.4, 130.1, 130.6, 135.1, 151.6, 163.8, 191.3. **HRMS** (ESI) calcd. for $C_{14}H_{17}O_2$ ($M+H^+$) 217.1223, found 217.1219.



6e

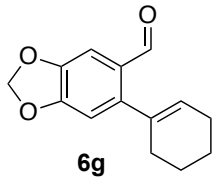
5-Fluoro-2′,3′,4′,5′-tetrahydro-[1,1′-biphenyl]-2-carbaldehyde (6f): Prepared according to general procedure A from 1-bromocyclohex-1-ene (0.805 g, 5.00 mmol), (5-fluoro-2-formylphenyl)boronic acid (0.924 g, 5.50 mmol, 1.10 equiv), $Pd(PPh_3)_4$ (144 mg, 0.250 mmol, 0.025 equiv), Na_2CO_3 (5.0 mL of a 2.0 M solution, 2.00 equiv), toluene (15.0 mL) and EtOH (5.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6f** (0.741 g, 3.62 mmol, 72%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.66-1.75 (m, 2H), 1.76-1.84 (m, 2H), 2.18-2.27 (m, 2H), 2.28-2.36 (m, 2H), 5.67 (m, 1H), 6.97 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.03 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.92 (dd, *J* = 8.4, 6.4 Hz, 1H), 10.1 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100



6f

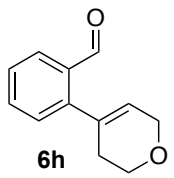
MHz): δ 21.9, 22.9, 25.7, 30.8, 114.6 (d, J = 21.8 Hz), 115.4 (d, J = 21.2 Hz), 130.4 (d, J = 2.6 Hz), 130.6 (d, J = 10.0 Hz), 132.0, 134.1 (d, J = 1.9 Hz), 151.7 (d, J = 9.2 Hz), 165.7 (d, J = 254.2 Hz), 191.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -104.3 (m, 1F). **HRMS** (ESI) calcd. for $C_{13}H_{14}FO$ ($M+H^+$) 205.1023, found 205.1022.

6-(Cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carbaldehyde[84] (6g): Prepared according to general procedure A from 1-bromocyclohex-1-ene (0.483 g, 3.00 mmol), (6-formylbenzo[*d*][1,3]dioxol-5-yl)boronic acid (0.698 g, 3.60 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (87.0 mg, 0.075 mmol, 0.025 equiv), Na_2CO_3 (3.0 mL of a 2.0 M solution, 2.00 equiv), toluene (9.0 mL) and EtOH (3.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6g** (0.437 g, 1.90 mmol, 63%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.62-1.70 (m, 2H), 1.71-1.80 (m, 2H), 2.14-2.21 (m, 2H), 2.22-2.29 (m, 2H), 5.59 (m, 1H), 5.99 (s, 2H), 6.68 (s, 1H), 7.31 (s, 1H), 9.92 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 21.9, 22.9, 25.6, 31.2, 101.9, 106.1, 108.2, 128.7, 131.3, 134.4, 146.7, 147.1, 152.1, 190.7. **HRMS** (ESI) calcd. for $C_{14}H_{15}O_3$ ($M+H^+$) 231.1016, found 231.1018.



6g

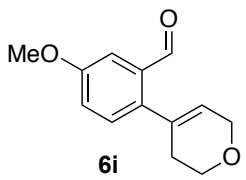
2-(3,6-Dihydro-2*H*-pyran-4-yl)benzaldehyde (6h): Prepared according to general procedure A from 4-bromo-3,6-dihydro-2*H*-pyran (0.815 g, 5.00 mmol), 2-formylphenylboronic acid (0.732 g, 6.00 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (144 mg, 0.125 mmol, 0.025 equiv), Na_2CO_3 (5.0 mL of a 2.0 M solution, 2.00 equiv), toluene (15.0 mL) and EtOH (5.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6h** (0.567 g, 3.01 mmol, 60%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.44-2.51 (m, 2H), 3.92-3.99 (m, 2H), 4.29-4.36 (m, 2H), 5.69 (m, 1H), 7.32 (dd, J = 7.6, 0.8 Hz, 1H), 7.41 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H),



6h

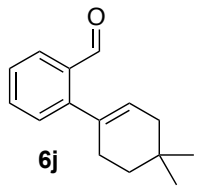
7.56 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.91 (dd, J = 7.6, 1.2 Hz, 1H), 10.2 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 30.7, 64.4, 65.6, 127.7, 128.4, 128.7, 129.0, 133.1, 133.8, 133.9, 146.2, 192.2. **HRMS** (ESI) calcd. for $C_{12}H_{12}O_2Na$ ($M+Na^+$) 211.0730, found 211.0731.

2-(3,6-Dihydro-2*H*-pyran-4-yl)-5-methoxybenzaldehyde (6i): Prepared according to general procedure A from 4-bromo-3,6-dihydro-2*H*-pyran (0.489 g, 3.00 mmol), (2-formyl-4-methoxyphenyl)boronic acid (0.648 g, 3.60 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (87.0 mg, 0.075 mmol, 0.025 equiv), Na_2CO_3 (3.0 mL of a 2.0 M solution, 2.00 equiv), toluene (9.0 mL) and EtOH (3.0 mL). The crude product was purified by flash column chromatography (80:20 hexanes:Et_2O) to yield **6i** (0.396 g, 1.81 mmol, 60%) as a light yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.39-2.47 (m, 2H), 3.82 (s, 3H), 3.93 (t, J = 5.2 Hz, 2H), 4.30 (q, J = 2.4 Hz, 2H), 5.61 (m, 1H), 7.10 (dd, J = 8.4, 2.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 10.1 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 30.8, 55.6, 64.4, 65.6, 110.4, 121.4, 129.0, 129.9, 132.3, 134.8, 139.4, 158.9, 191.9. **HRMS** (ESI) calcd. for $C_{13}H_{15}O_3$ ($M+H^+$) 219.1016, found 219.1016.



6i

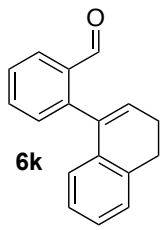
4,4′-Dimethyl-2′,3′,4′,5′-tetrahydro-[1,1′-biphenyl]-2-carbaldehyde (6j): Prepared according to general procedure A from 1-bromocyclohex-1-ene (0.946 g, 5.00 mmol), 2-formylphenylboronic acid (0.900 g, 6.00 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (144 mg, 0.125 mmol, 0.025 equiv), Na_2CO_3 (5.0 mL of a 2.0 M solution, 2.00 equiv), toluene (15.0 mL) and EtOH (5.0 mL). The crude product was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **6j** (0.831 g, 3.88 mmol, 78%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.01 (s, 6H), 1.56 (t, J = 6.4 Hz, 2H), 2.02 (q, J = 2.4 Hz, 2H), 2.34-2.41 (m, 2H), 5.54-5.58 (m, 1H), 7.32 (dd, J = 7.6, 0.8 Hz, 1H), 7.36 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.90 (dd, J =



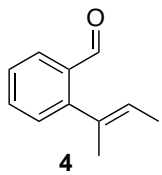
6j

7.6, 1.2 Hz, 1H), 10.1 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 28.36, 28.38 (2C), 28.8, 35.8, 39.8, 127.1, 127.7, 128.9, 130.6, 133.5, 133.7, 134.0, 148.6, 192.7. **HRMS** (ESI) calcd. for $C_{15}H_{18}ONa$ ($M+Na^+$) 237.1250, found 237.1254.

2-(3,4-Dihydronaphthalen-1-yl)benzaldehyde (6k): Prepared according to general procedure A from 4-bromo-1,2-dihydronapthalene (2.09 g, 10.0 mmol), 2-formylphenylboronic acid (1.80 g, 12.0 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (289 mg, 0.250 mmol, 0.025 equiv), Na_2CO_3 (10.0 mL of a 2.0 M solution, 2.00 equiv), toluene (30.0 mL) and EtOH (10.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6k** (2.07 g, 8.83 mmol, 88%) as an light yellow oil that solidified on standing. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.46-2.56 (m, 2H), 2.94 (t, J = 8.0 Hz, 2H), 6.04 (t, J = 4.4 Hz, 1H), 6.66 (dd, J = 7.6, 0.8 Hz, 1H), 7.07 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.16 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.22 (dd, J = 7.6, 0.8 Hz, 1H), 7.35 (dd, J = 7.6, 0.8 Hz, 1H), 7.49 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.62 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 8.01 (dd, J = 7.6, 1.2 Hz, 1H), 9.99 (d, J = 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 23.7, 28.1, 125.6, 126.9, 127.3, 127.7, 127.9, 128.0, 131.1, 131.2, 134.0, 134.7, 135.7, 135.9, 136.1, 144.7, 192.5. **HRMS** (ESI) calcd. for $C_{17}H_{14}ONa$ ($M+Na^+$) 257.0937, found 257.0942.

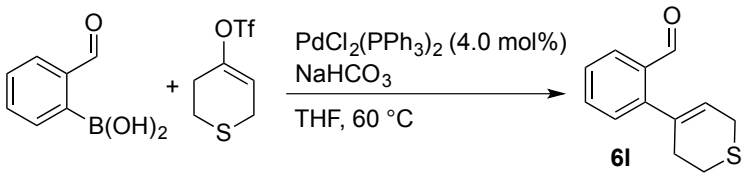


2-(But-2-en-2-yl)benzaldehyde (4): Prepared from (*E*)-2-bromo-2-butene (0.405 g, 3.00 mmol), 2-formylphenylboronic acid (0.540 g, 3.60 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (86.7 mg, 0.075 mmol, 0.025 equiv), Na_2CO_3 (3.0 mL of a 2.0 M solution, 2.00 equiv), toluene (9.0 mL) and EtOH (3.0 mL). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **4** (0.246 g, 1.53 mmol, 51%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.84 (dd, J = 6.8, 0.8 Hz,



3H), 2.05-2.08 (dd, *J* = 1.6, 1.2 Hz, 3H), 5.41 (qq, *J* = 6.8, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.35 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.52 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.2 Hz, 1H), 10.1 (d, *J* = 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 14.5, 18.7, 127.0, 128.9, 129.18, 129.23, 133.0, 133.5, 133.9, 149.9, 192.8. **HRMS** (ESI) calcd. for $C_{11}H_{13}O$ ($M+H^+$) 161.0961, found 161.0962.

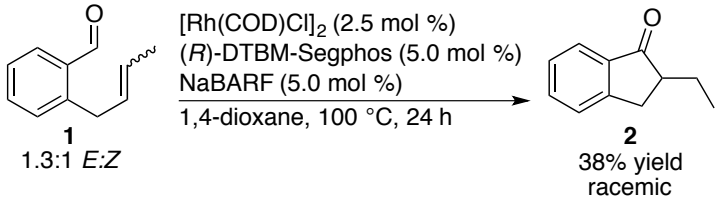
Synthesis of 2-(3,6-Dihydro-2*H*-thiopyran-4-yl)benzaldehyde 6l



In a nitrogen-filled dry box, $PdCl_2(PPh_3)_2$ (84.0 mg, 0.120 mmol, 0.040 equiv), and 2-formylphenylboronic (0.450 g, 3.00 mmol, 1.00 equiv) were weighed into dry round bottom flask. The flask was sealed with a rubber septum and removed from the dry box. Anhydrous THF (30.0 mL) was added via syringe followed by 3,6-dihydro-2*H*-thiopyran-4-yl trifluoromethanesulfonate (0.596 g, 2.40 mmol, 0.800 equiv) and $NaHCO_3$ sat. solution (6.0 mL) . This mixture was heated to 60 °C and monitored by TLC for consumption of 3,6-dihydro-2*H*-thiopyran-4-yl trifluoromethanesulfonate (3 h) then cooled to room temperature. H_2O was added and the reaction mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered then concentrated under reduced pressure. The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **6l** (0.374 g, 1.83 mmol, 61%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.58-2.65 (m, 2H), 2.91 (t, *J* = 5.6 Hz, 2H), 3.35 (dt, *J* = 4.0, 2.4 Hz, 2H), 5.78-5.83 (m, 1H), 7.29 (dd, *J* = 7.6, 0.8 Hz, 1H), (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.56 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.91 (dd, *J* = 7.6, 1.2 Hz, 1H), 10.2 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100

MHz): δ 25.3, 26.0, 31.8, 126.7, 127.7, 128.4, 129.2, 133.77, 133.82, 136.5, 147.9, 192.2. **HRMS** (ESI) calcd. for $C_{12}H_{13}SO$ ($M+H^+$) 205.0682, found 205.0689.

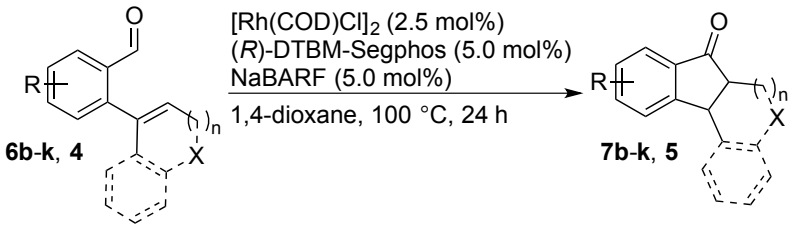
Rh-catalyzed hydroacylation of 1



In a nitrogen-filled dry box, 2-(but-2-en-1-yl)benzaldehyde **1** (0.200 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol, 0.050 equiv), NaBARF (8.9 mg, 0.010 mmol, 0.050 equiv), and anhydrous 1,4-dioxane (1 mL) were added to a 1-dram vial. The vial was sealed with a PFTE/silicone-lined septum cap and removed from the dry box. The reaction mixture was heated to 100 °C and allowed to stir at this temperature until the reaction was judged to be complete by TLC analysis. The mixture was cooled to rt, filtered through a pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. $CDCl_3$ (0.7 mL) was added to dissolve the crude mixture along with CH_2Br_2 (7.0 μL, 0.100 mmol) as an internal standard. The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **2** (12.3 mg, 0.077 mmol, 38%) as a light yellow oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 15.3 min; t_R 19.7 min [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 95:5, 0.5 mL/min] to be 0% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, *J* = 7.2 Hz, 1H), 1.47 – 1.58 (m, 1H), 1.91-2.04 (m, 1H), 2.57 – 2.67 (m, 1H), 2.83 (dd, *J* = 17.2, 4.0 Hz, 1H), 3.32 (dd, *J* = 17.2, 8.0 Hz, 1H), 7.36 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.46 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.58 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.8, 24.6, 32.5, 48.9,

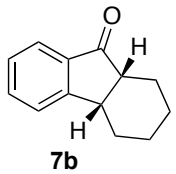
124.0, 126.7, 127.4, 134.8, 137.1, 154.0, 209.2. Spectral data for **2** is consistent with previous reports.[22, 85]

General Procedure B: Hydroacylation of 1,1,2-Trisubstituted Alkenes 6b-k, 4



In a nitrogen-filled dry box, the appropriate *ortho*-vinylbenzaldehyde **6b-k** or **4** (0.200 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol, 0.050 equiv), NaBARF (8.9 mg, 0.010 mmol, 0.050 equiv) and anhydrous 1,4-dioxane (1.0 mL) were added to a 1-dram vial. The vial was sealed with a PFTE/silicone-lined septum cap and removed from the dry box. The reaction mixture was heated to 100 °C and allowed to stir at this temperature until the reaction was judged to be complete by TLC analysis. The mixture was cooled to room temperature, filtered through a pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. $CDCl_3$ (0.7 mL) was added to dissolve the crude mixture along with CH_2Br_2 (7.0 μL, 0.100 mmol) as an internal standard. Conversion was determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude product was purified by flash column chromatography on silica gel (hexanes/Et_2O) to yield **7b-k** or **5**. The enantiomeric excess was determined by chiral HPLC analysis.

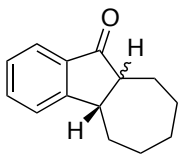
(4a*S*,9a*R*)-1,2,3,4,4a,9a-Hexahydro-9*H*-fluoren-9-one[86-87] (7b): Prepared according to general procedure B from **6b** (37.3 mg, 0.200 mmol). The crude product was purified by flash column chromatography (90:10 hexanes:Et_2O) to yield **7b** (32.7 mg, 0.175 mmol, 88%) as a white solid. The enantiomeric excess was



7b

determined by chiral HPLC analysis (254 nm, 25 °C) t_R 20.3 min (major); t_R 18.6 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 97% ee. $[\alpha]_D^{25}$= -23.5° (c 0.68, $CHCl_3$) **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.15-1.30 (m, 2H), 1.33-1.45 (m, 1H), 1.46-1.63 (m, 2H), 1.70-1.82 (m, 1H), 2.05-2.17 (m, 2H), 2.77 (ddd, *J* = 7.2, 6.8, 5.2 Hz, 1H), 3.39 (ddd, *J* = 8.8, 6.8, 6.4 Hz, 1H), 7.36 (ddd, *J* = 7.2, 7.2, 0.4 Hz, 1H), 7.46 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.57 (ddd, *J* = 7.6, 7.2, 0.8 Hz, 1H), 7.76 (dd, *J* = 7.6, 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.5, 22.8, 23.3, 31.5, 39.0, 48.7, 124.1, 125.0, 127.4, 134.4, 135.8, 158.5, 208.0. **HRMS** (ESI) calcd. for $C_{13}H_{15}O$ ($M+H^+$) 187.1117, found 187.1115.

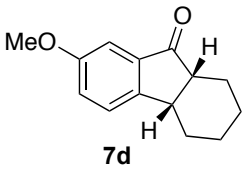
(4b*S*,9a*R*)-5,6,7,8,9,9a-Hexahydrobenzo[*a*]azulen-10(4b*H*)-one[88-89] (7c): Prepared according to general procedure B from **6c** (40.1 mg, 0.200 mmol). The crude product was purified by flash column chromatography (95:5 hexanes:Et_2O) to yield **7c** (23.7 mg, 0.118 mmol, 59%) as a mixture of diastereomers (3.3:1 *cis*:*trans*) a clear oil. The enantiomeric excess was approximated by chiral HPLC analysis (254 nm, 20 °C) t_R 20.3 min (*cis*-major); t_R 27.4 min (*cis*-minor), t_R 20.9 min (*trans*-major); t_R 30.2 min (*trans*-minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, ratio, rate mL/min] to be 82% ee for the *cis* diastereomer and 70% ee for the *trans* diastereomer. **Note**: Chiral HPLC separation conditions for the four diastereomers of **2c** were evaluated on Chiracel AD-H, AS-H, OD-H and OJ-H columns, but baseline separation conditions could not be identified for all four peaks. The enantioselectivities reported were approximated using the tangent line integration method for the *cis*-major and *trans*-major isomer peaks that overlap in the best separation conditions found.[90-92] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.24-1.87 (m, 8H), 2.11-2.22 (m, 2H), 2.85 (ddd, *J* = 10.4, 8.0, 4.4 Hz,



7c

1H), 3.57 (ddd, *J* = 10.2, 8.0, 4.0 Hz, 1H), 7.36 (ddd, *J* = 7.2, 7.2, 0.4 Hz, 1H), 7.49 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.60 (ddd, *J* = 7.2, 7.2, 0.4 Hz, 1H), 7.73 (dd, *J* = 7.6, 0.4 Hz, 1H). Representative *trans*-**2*c*** peaks: 1.24-1.87 (m, 8H), 2.31-2.56 (m, 3H), 3.03-3.10 (m, 1H) **^{13}C NMR** ($CDCl_3$, 100 MHz): δ *cis*-**2c** peaks: 28.2, 28.50, 28.7, 31.4, 32.6, 44.5, 53.1, 123.7, 125.7, 127.5, 134.6, 134.9, 158.7, 209.4. Representative *trans*-**2c** peaks: 25.8, 27.1, 28.46, 29.4, 32.2, 44.6, 55.3, 123.5, 124.6, 127.4, 136.4, 136.5. **HRMS** (ESI) calcd. for $C_{14}H_{17}O$ ($M+H^+$) 201.1274, found 201.1274.

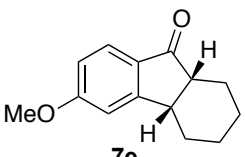
(4a*S*,9a*R*)-7-Methoxy-1,2,3,4,4a,9a-hexahydro-9*H*-fluoren-9-one[93-94] (7d): Prepared



7d

according to general procedure B from **6d** (43.3 mg, 0.200 mmol). The crude product was purified by flash column chromatography (90:10 hexanes:Et_2O) to yield **7d** (34.4 mg, 0.159 mmol, 89%) as an off-white amorphous solid. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 13.1 min (major); t_R 12.3 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 89% ee. $[\alpha]_D^{25}$= -116° (c 0.12, $CHCl_3$) **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.12-1.29 (m, 2H), 1.32-1.43 (m, 1H), 1.44-1.60 (m, 2H), 1.69-1.81 (m, 1H), 2.01-2.13 (m, 2H), 2.77 (ddd, *J* = 6.8, 6.8, 5.2 Hz, 1H), 3.32 (ddd, *J* = 8.8, 6.8, 6.4 Hz, 1H), 3.83 (s, 3H), 7.16 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.4, 22.5, 23.4, 31.4, 38.2, 49.2, 55.7, 105.7, 123.3, 125.8, 137.0, 151.4, 159.4, 208.1. **HRMS** (ESI) calcd. for $C_{14}H_{16}O_2Na$ ($M+Na^+$) 239.1043, found 239.1035.

(4a*S*,9a*R*)-6-Methoxy-1,2,3,4,4a,9a-hexahydro-9*H*-fluoren-9-one[94-95] (7e): Prepared

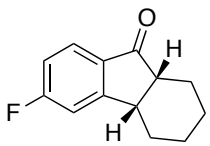


7e

according to general procedure B from **6e** (43.3 mg, 0.200 mmol). The crude product was purified by flash column chromatography (95:5

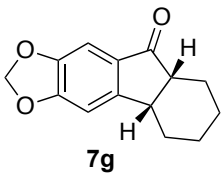
hexanes:Et_2O) to yield **7e** (38.5 mg, 0.178 mmol, 89%) as an off-white amorphous solid. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 45.5 min (major); t_R 37.3 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 99% ee. $[\alpha]_D^{25}$= -25.7° (c 0.70, $CHCl_3$) **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 1.19-1.29 (m, 2H), 1.33-1.43 (m, 1H), 1.45-1.58 (m, 2H), 1.69-1.79 (m, 1H), 1.99-2.11 (m, 2H), 2.73 (ddd, *J* = 7.2, 6.6, 5.4 Hz, 1H), 3.32 (ddd, *J* = 9.0, 6.6, 6.6 Hz, 1H), 3.88 (s, 3H), 6.85-6.90 (m, 2H), 7.68 (d, *J* = 9.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 22.4, 22.6, 23.4, 31.0, 38.8, 48.6, 55.7, 108.8, 114.7, 125.8, 128.9, 161.4, 165.1, 206.4. **HRMS** (ESI) calcd. for $C_{14}H_{17}O_2$ ($M+H^+$) 217.1223, found 217.1222.

(4a*S*,9a*R*)-6-Fluoro-1,2,3,4,4a,9a-hexahydro-9*H*-fluoren-9-one[93] (7f): Prepared according to general procedure B from **6f** (40.9 mg, 0.200 mmol). The crude product was purified by flash column chromatography (95:5 hexanes:Et_2O) to yield **7f** (30.2 mg, 0.148 mmol, 74%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 31.7 min (major); t_R 25.1 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 95:5, 0.5 mL/min] to be 97% ee. $[\alpha]_D^{25}$= -38.0° (c 0.79, $CHCl_3$) **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 1.15-1.27 (m, 2H), 1.34-1.43 (m, 1H), 1.46-1.60 (m, 2H), 1.70-1.79 (m, 1H), 2.03-2.14 (m, 2H), 2.77 (ddd, *J* = 6.6, 6.6, 4.8 Hz, 1H), 3.36 (ddd, *J* = 8.4, 7.2, 6.6 Hz, 1H), 7.04 (ddd, *J* = 9.0, 8.4, 2.4 Hz, 1H), 7.10 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.74 (dd, *J* = 8.4, 6.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 22.4, 22.6, 23.3, 31.2, 38.8, 48.8, 111.9 (d, *J* = 22.0 Hz), 115.5 (d, *J* = 23.4 Hz), 126.4 (d, *J* = 10.2 Hz), 132.1 (d, *J* = 7.8 Hz), 161.4 (d, *J* = 9.2 Hz), 167.1 (d, *J* = 253.8 Hz), 206.0. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -103.5 (m, 1F) **HRMS** (ESI) calcd. for $C_{13}H_{14}FO$ ($M+H^+$) 205.1023, found 205.1020.



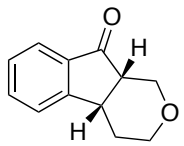
7f

(4b*S*,8a*R*)-4b,5,6,7,8,8a-Hexahydro-9*H*-fluoreno[2,3-*d*][1,3]dioxol-9-one (7g): Prepared according to general procedure B from **6g** (46.1 mg, 0.200 mmol). The crude product was purified by flash column chromatography (90:10 hexanes:Et_2O) to yield **7g** (40.9 mg, 0.178 mmol, 89%) as an off-white solid. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 33.3 min (major); t_R 36.2 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 85% ee. $[\alpha]_D^{25}$= -14.3° (c 0.44, $CHCl_3$) **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.15-1.29 (m, 2H), 1.31-1.42 (m, 1H), 1.43-1.58 (m, 2H), 1.67-1.80 (m, 1H), 1.95-2.1 (m, 2H), 2.74 (ddd, *J* = 6.8, 6.8, 5.6 Hz, 1H), 3.26 (ddd, *J* = 8.8, 6.8, 6.4 Hz, 1H), 6.04 (m, 2H), 6.82 (s, 1H), 7.10 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.1, 22.2, 23.6, 30.9, 38.6, 48.7, 102.2, 102.9, 104.7, 130.3, 148.1, 153.9, 156.1, 206.2. **HRMS** (ESI) calcd. for $C_{14}H_{15}O_3$ ($M+H^+$) 231.1016, found 231.1012.



7g

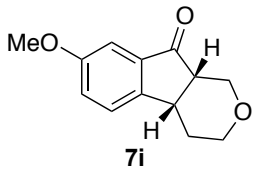
(4a*S*,9a*S*)-3,4,4a,9a-Tetrahydroindeno[2,1-*c*]pyran-9(1*H*)-one (7h): Prepared according to general procedure B from **6h** (37.7 mg, 0.200 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:Et_2O) to yield **7h** (34.2 mg, 0.182 mmol, 91%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 40.4 min (major); t_R 43.0 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 97% ee. $[\alpha]_D^{25}$= -30.8° (c 0.65, $CHCl_3$) **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.47-1.60 (m, 1H), 2.17-2.28 (m, 1H), 2.70-2.76 (m, 1H), 3.50-3.63 (m, 2H), 3.65-3.73 (m, 1H), 3.88 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.31 (dd, *J* = 12.0, 3.6 Hz, 1H), 7.41 (ddd, *J* = 7.6, 7.6, 0.4 Hz, 1H), 7.49 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.61 (ddd, *J* = 7.6, 7.6, 0.4 Hz, 1H), 7.79 (dd, *J* = 7.6, 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 30.9, 35.7, 47.9, 64.4, 65.1, 124.5,



7h

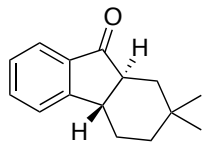
125.1, 127.9, 134.9, 135.8, 157.5, 205.0. **HRMS** (ESI) calcd. for $C_{12}H_{13}O_2$ ($M+H^+$) 189.0910, found 189.0908.

(4a*S*,9a*S*)-7-Methoxy-3,4,4a,9a-tetrahydroindeno[2,1-*c*]pyran-9(1*H*)-one (7i): Prepared according to general procedure B from **6i** (43.7 mg, 0.200 mmol). The crude product was purified by flash column chromatography (80:20 hexanes:Et_2O) to yield **7i** (29.5 mg, 0.135 mmol, 68%) as an orange amorphous solid. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 41.8 min (major); t_R 45.5 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 97% ee. $[\alpha]_D^{25}$= -28.2° (c 0.78, $CHCl_3$) **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.45-1.57 (m, 1H), 2.15-2.25 (m, 1H), 2.71-2.79 (m, 1H), 3.48-3.57 (m, 2H), 3.63-3.71 (m, 1H), 3.84 (s, 3H), 3.87 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.28 (dd, *J* = 120, 3.6 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.23 (d, *J* = 2.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 30.8, 35.0, 48.5, 55.8, 64.5, 65.0, 105.9, 123.9, 125.8, 137.1, 150.4, 159.8, 205.2. **HRMS** (ESI) calcd. for $C_{13}H_{14}O_3Na$ ($M+Na^+$) 241.0835, found 241.0831.



7i

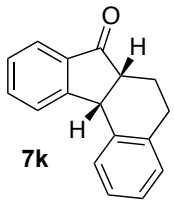
(4a*S*,9a*R*)-2,2-Dimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-fluoren-9-one (7j): Prepared according to general procedure B from **6j** (42.9 mg, 0.200 mmol). The crude product was purified by flash column chromatography (95:5 hexanes:Et_2O) to yield **7j** (33.1 mg, 0.154 mmol, 77%) as mixture of diastereomers (2.7:1 *trans:cis*) a clear oil. Reexposure to the reaction conditions for an additional 24h led to exclusive formation of the *cis* diastereomer. The enantiomeric excess of the *cis* diastereomer was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 24.8 min (major); t_R 19.4 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind.,



7j

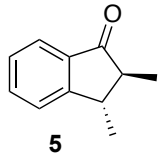
Ltd.) hexane/^{i}PrOH, 95:5, 0.5 mL/min] to be 10% ee. Determination of the enantiomeric excess of the *trans*-diastereomer proved challenging because we were unable to obtain a pure sample of *trans*-**7j**; various conditions for the hydroacylation of **6j** yielded only traces of *trans*-**7j** that were isolated in a mixture with *cis*-**7j**. For this reason, retention times and an ee value for *trans*-**7j** are not reported. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.80 (s, 3H), 1.00 (s, 3H), 1.21-1.33 (m, 2H), 1.49-1.69 (m, 3H), 2.01-2.13 (m, 1H), 2.80 (ddd, *J* = 7.6, 7.6, 7.2 Hz, 1H), 3.35 (ddd, *J* = 7.6, 7.2, 7.2 Hz, 1H), 7.37 (ddd, *J* = 7.6, 7.6, 0.4 Hz, 1H), 7.47 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.59 (ddd, *J* = 7.6, 7.6, 0.4 Hz, 1H), 7.75 (dd, *J* = 7.6, 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 25.7, 29.0, 29.5, 29.7, 36.5, 37.2, 38.0, 46.9, 124.2, 125.0, 127.5, 134.6, 135.6, 157.8, 208.9. **HRMS** (ESI) calcd. for $C_{15}H_{19}O$ ($M+H^+$) 215.1430, found 215.1426.

5,6,6a,11b-Tetrahydro-7*H*-benzo[*c*]fluoren-7-one (7k): Prepared according to general procedure B from **6k** (46.9 mg, 0.200 mmol). The crude product was purified by flash column chromatography (90:10 hexanes:Et_2O) to yield **7k** (23.0 mg, 0.098 mmol, 49%) as an off-white solid. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 21.9 min; t_R 25.0 min [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 0% ee. **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 1.83-1.92 (m, 1H), 2.14-2.23 (m, 1H), 2.49-2.59 (m, 2H), 3.17-3.22 (m, 1H), 4.69 (d, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 7.2, 0.4 Hz, 1H), 7.17 (ddd, *J* = 7.2, 7.2, 0.4 Hz, 1H), 7.30 (ddd, *J* = 7.8, 7.2, 0.4 Hz, 1H), 7.33-7.37 (m, 1H), 7.52-7.59 (m, 3H), 7.76 (dd, *J* = 7.8, 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 26.9, 27.4, 43.2, 47.5, 123.4, 126.5, 126.7, 126.8, 127.8, 128.8, 129.0, 135.3, 136.5, 136.9, 138.7, 157.1, 209.6. **HRMS** (ESI) calcd. for $C_{17}H_{15}O$ ($M+H^+$) 235.1117, found 235.1113.



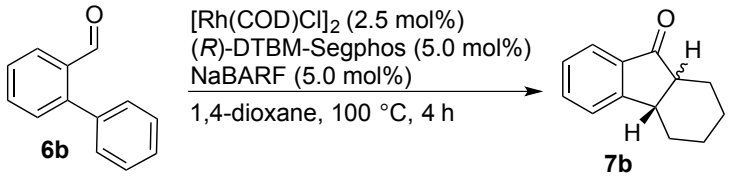
7k

2,3-Dimethyl-2,3-dihydro-1*H*-inden-1-one (5): Prepared according to general procedure B from **4** (32.0 mg, 0.200 mmol). The crude product was purified by flash column chromatography (90:10 hexanes:Et_2O) to yield **5** (11.1 mg, 0.069 mmol, 35%) as a colorless oil (dr = 1.6:1 *trans*:*cis*). **Note**: The mass balance for this reaction is made up of the isomerized starting material **4** (*E*:*Z* = 3.7:1). The enantiomeric excess for **5** was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 14.3 min (*cis*-major); t_R 16.7 min (*cis*-minor) t_R 20.1 min (*trans*-major); t_R 17.6 min (*trans*-minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 95:5, 0.5 mL/min] to be 94% ee for both the *cis* and *trans* diastereomers. Peaks reported for the major (*trans*) diastereomer: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.32 (d, *J* = 7.6 Hz, 3H), 1.45 (d, *J* = 7.2 Hz, 3H), 2.24 (dq, *J* = 7.6, 7.2 Hz, 1H), 2.94 (dq, *J* = 7.6, 7.2 Hz, 1H), 7.36 (m, 1H), 7.49 (m, 1H), 7.60 (m, 1H), 7.74 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 14.3, 19.3, 41.9, 51.6, 123.8, 125.0, 127.6, 134.8, 134.9, 157.9, 208.5. Representative peaks for the minor (*cis*) diastereomer: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.21 (d, *J* = 7.6 Hz, 3H, *cis*), 1.23 (d, *J* = 7.6 Hz, 3H, *cis*), 2.82 (dq, *J* = 7.6, 7.2 Hz, 1H, *cis*), 3.52 (dq, *J* = 7.6, 7.2 Hz, 1H, *cis*). **HRMS** (ESI) calcd. for $C_{11}H_{13}O$ ($M+H^+$) 161.0961, found 161.0960.



5

Preparation of a diastereomeric mixture of 7b

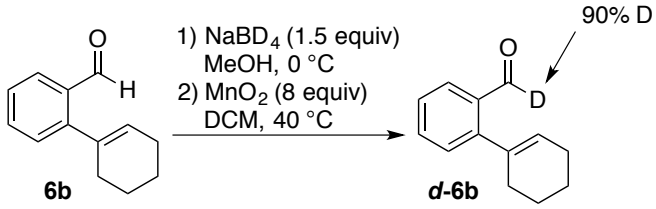


6b 7b

In a nitrogen-filled dry box, **6b** (1.00 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (59.0 mg, 0.050 mmol, 0.050 equiv), NaBARF (44.3 mg, 0.050 mmo, 0.050 equiv) and anhydrous 1,4-dioxane (5.0 mL) were added to a dry scintillation vial. The vial was sealed, removed from the dry box and the

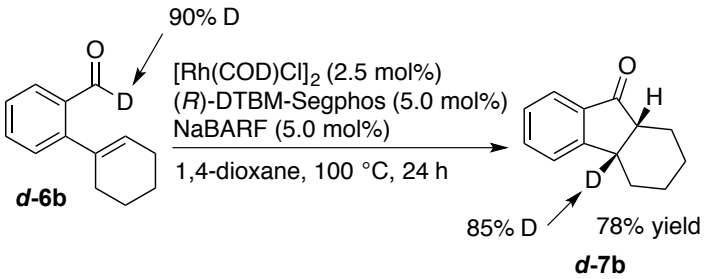
reaction mixture was heated to 100 °C for 4 h. The reaction mixture was cooled to room temperature, filtered through a pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. CH_2Br_2 (35.1 μL, 0.500 mmol) was added as an internal standard and an aliquot of this mixture was dissolved in $CDCl_3$. The diastereomeric ratio (*trans*:*cis*) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture and the crude product was purified by flash column chromatography on silica gel (hexanes/Et_2O) to yield **7b** (58.1 g, 0.312 mmol, 31%) as a 3.0:1.0 (*trans*:*cis*) mixture of diastereomers. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 20 °C) t_R 23.2 min (*cis*-major); t_R 21.4 min (*cis*-minor); t_R 19.9 min (*trans*-major); t_R 26.4 min (*trans*-minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 92% ee for the *cis*-diastereomer and 94% ee for the *trans*-diastereomer. **Note**: Although longer reaction times would lead to a higher yield of **7b**, the reaction was stopped after 4h to generate a mixture of diastereomers favoring the *trans* product. Longer reaction times lead to lower dr's or a diastereomeric mixture favoring the *cis* product. Peaks reported for the major (*trans*) diastereomer: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.33-1.43 (m, 1H), 1.43-1.75 (m, 3H), 1.91-2.02 (m, 2H), 2.21 (ddd, *J* = 11.2, 8.8, 2.8 Hz, 1H), 2.25-2.32 (m, 1H), 2.44-2.53 (m, 1H), 2.69-2.79 (m, 1H), 7.35 (ddd, *J* = 7.6, 7.2, 0.8 Hz, 1H), 7.41 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.55 (ddd, *J* = 7.6, 7.2, 0.8 Hz, 1H), 7.70 (dd, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 24.8, 26.3, 26.5, 29.0, 45.6, 58.4, 123.1, 123.5, 127.4, 133.9, 137.0, 153.9, 205.1. **HRMS** (ESI) calcd. for $C_{13}H_{15}O$ ($M+H^+$) 187.1117, found 187.1116.

Synthesis of *d*-6b



To a solution of **6b** (0.242 g, 1.30 mmol) in MeOH at 0 °C was added $NaBD_4$ (0.082 g, 1.95 mmol, 1.50 equiv) in one portion. This solution was stirred for 30 minutes and monitored by TLC for consumption of **6b**. When the reaction was determined to be complete, it was quenched by the careful addition of 1M HCl. The reaction mixture was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting oil was taken up in CH_2Cl_2 (5 mL) and MnO_2 (0.904 g, 10.4 mmol, 8.00 equiv) was added. This mixture was heated to 40 °C for 16 h. Once the reaction was determined to be complete by TLC analysis, the solution was cooled and filtered through celite. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (90:10 hexanes/Et_2O) to yield ***d*-6b** (0.108 g, 0.581 mmol, 45%) as a colorless oil with 90% incorporation of the deuterium at the aldehyde carbon. **Note**: The large KIE for the oxidation of benzyl alcohol with MnO_2 explains the high deuterium content observed in ***d*-1b** instead of the expected statistical mixture of protio- and deuterio-aldehyde.[96-97] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.67-1.76 (m, 2H), 1.76-1.86 (m, 2H), 2.19-2.28 (m, 2H), 2.31-2.39 (m, 2H), 5.59-5.66 (m, 1H), 7.31 (dd, J = 7.6, 0.8 Hz, 1H), 7.36 (ddd, J = 8.0, 7.6, 0.8 Hz, 1H), 7.53 (ddd, J = 7.6, 1.2 Hz, 1H), 7.90 (dd, J = 8.0, 1.2 Hz, 1H), 10.1 (s, 0.1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.0, 23.0, 25.7, 31.0, 127.0, 127.6, 128.7, 131.4, 133.5, 133.7 (t, J = 3.2 Hz), 134.9, 148.9, 192.4 (t, J = 33.2 Hz). **HRMS** (ESI) calcd. for $C_{13}H_{14}OD$ ($M+H^+$) 188.1180, found 188.1175.

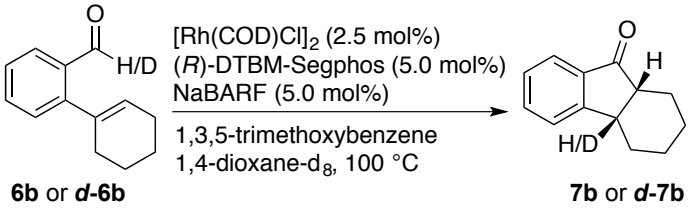
Rhodium-catalyzed Hydroacylation of *d*-6b



In a nitrogen-filled dry box, ***d*-6b** (37.5 mg, 0.200 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol, 0.050 equiv), NaBARF (8.9 mg, 0.010 mmo, 0.050 equiv) and anhydrous 1,4-dioxane (1.0 mL) were added to a 1-dram vial. The vial was sealed with a PFTE/silicone-lined septum cap and removed from the dry box. The reaction mixture was heated to 100 °C and allowed to stir at this temperature until the reaction was judged to be complete by TLC analysis. The mixture was cooled to room temperature, filtered through a pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. $CDCl_3$ (0.7 mL) was added to dissolve the crude mixture along with CH_2Br_2 (7.0 μL, 0.100 mmol) as an internal standard. Conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The crude product was purified by flash column chromatography on silica gel (90:10 hexanes/Et_2O) to yield ***d*-7b** (29.2 g, 0.156 mmol, 78%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 20.3 min (major); t_R 18.6 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 97% ee. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.12-1.29 (m, 2H), 1.33-1.42 (m, 1H), 1.45-1.62 (m, 2H), 1.69-1.81 (m, 1H), 2.04-2.15 (m, 2H), 2.75 (app t, *J* = 6.4 Hz, 1H), 3.38 (ddd, *J* = 6.8, 6.8, 4.4 Hz, 0.15H), 7.35 (dd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.45 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.56 (ddd, *J* = 7.6, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.6, 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz):

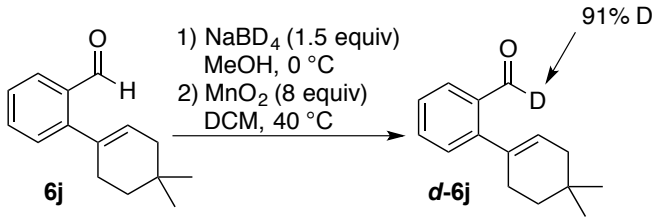
δ 22.5, 22.8, 23.2, 31.4, 38.5 (t, J = 20.6 Hz), 48.6, 124.1, 125.0, 127.4, 134.4, 135.8, 158.4, 208.0. **HRMS** (ESI) calcd. for $C_{13}H_{14}OD$ ($M+H^+$) 188.1180, found 188.1176.

Kinetic isotope effect for the hydroacylation of 6b and *d*-6b



The kinetic isotope effect was determined by measuring the initial rate constants for two independent experiments for the hydroacylation of **6b** and ***d*-6b**. The reactions were monitored by ^{1}H NMR spectroscopy (T = 373K) using 1,3,5-trimethoxybenzene as an internal standard. Reaction mixtures were prepared as follows: In a nitrogen-filled dry box, **6b** or ***d*-6b** (18.6 mg, 0.100 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (1.23 mg, 0.0025 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (5.90 mg, 0.005 mmol, 0.050 equiv), NaBARF (4.43 mg, 0.005 mmol, 0.050 equiv), 1,3,5-trimethoxybenzene (5.61 mg, 0.033 mmol, 0.333 equiv), and anhydrous 1,4-dioxane-d_8 (0.5 mL) were added to a 1-dram vial. The vial was agitated to dissolve all solids and the solution was transferred to a dry J-Young NMR tube, sealed and immediately subjected to ^{1}H NMR analysis (T = 373K). Data points were collected every 3 minutes and the initial rate constants were determined from the first 5% of the reaction data.

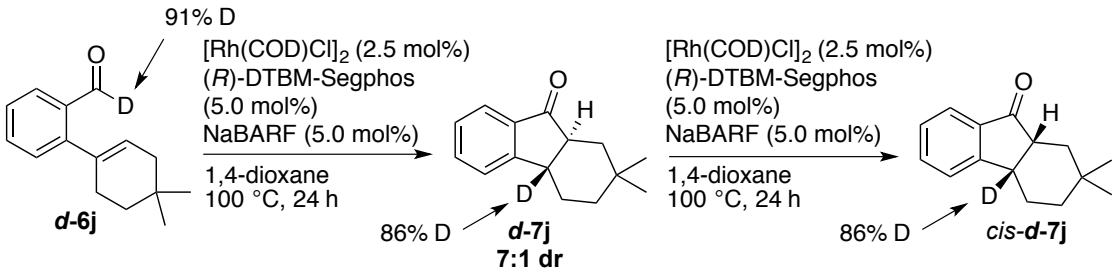
Synthesis of *d*-6j



To a solution of **6j** (0.386 g, 1.80 mmol) in MeOH at 0 °C was added $NaBD_4$ (0.113 g, 2.70 mmol, 1.50 equiv) in one portion. This solution was stirred for 30 minutes and

monitored by TLC for consumption of **6j**. When the reaction was determined to be complete, it was quenched by the careful addition of 1M HCl. The reaction mixture was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting oil was taken up in CH_2Cl_2 (5 mL) and MnO_2 (1.25 g, 14.4 mmol, 8.00 equiv) was added. This mixture was heated to 40 °C for 16 h. Once the reaction was determined to be complete by TLC analysis, the solution was cooled and filtered through celite. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (90:10 hexanes/Et_2O) to yield ***d*-6j** (0.252 g, 1.35 mmol, 75%) as a colorless oil and the deuterium content was determined by ^{1}HNMR analysis. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.01 (s, 6H), 1.56 (t, *J* = 6.4 Hz, 2H), 2.00-2.04 (m, 2H), 2.34-2.42 (m, 2H), 5.54-5.58 (m, 1H), 7.32 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.36 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.53 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.91 (dd, *J* = 7.6, 1.2 Hz, 1H), 10.1 (s, 0.1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 28.19. 28.22 (2C), 28.6, 35.6, 39.6, 126.9, 127.5, 128.7, 130.4, 133.3, 133.5, 133.8 (t, *J* = 3.6 Hz), 148.4, 192.1 (t, *J* = 26.6 Hz). **HRMS** (ESI) calcd. for $C_{15}H_{18}OD$ ($M+H^+$) 216.1493, found 216.1492.

Rhodium-catalyzed Hydroacylation of *d*-6j



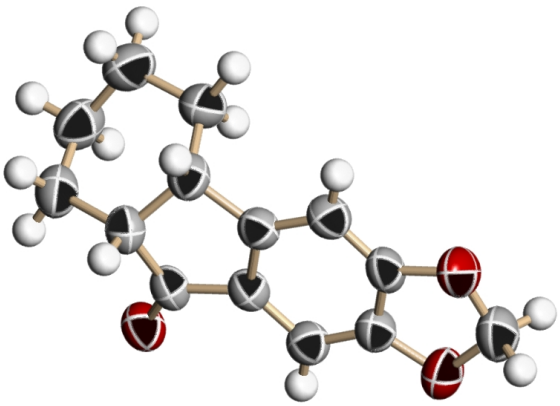
In a nitrogen-filled dry box, ***d*-6j** (43.1 mg, 0.200 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol, 0.050 equiv), NaBARF (8.9 mg, 0.010 mmo, 0.050 equiv) and anhydrous 1,4-dioxane (1.0 mL) were added to a 1-dram vial. The vial was sealed with a PFTE/silicone-lined septum cap and

removed from the dry box. The reaction mixture was heated to 100 °C and allowed to stir at this temperature until the reaction was judged to be complete by TLC analysis. The mixture was cooled to room temperature, filtered through a pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. $CDCl_3$ (0.7 mL) was added to dissolve the crude mixture along with CH_2Br_2 (7.0 μL, 0.100 mmol) as an internal standard. Conversion and deuterium content was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The crude product was purified by flash column chromatography on silica gel (90:10 hexanes/Et_2O) to yield ***d*-7j** as a mixture of diastereomers (7:1 *trans*:*cis*) (40.8 mg, 0.189 mmol, 95%) an off white solid. Peaks reported for the major diastereomer: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.97 (s, 3H), 1.06 (s, 3H), 1.35-1.47 (m, 2H), 1.58-1.69 (m, 2H), 1.92-1.98 (m, 1H), 2.29 (ddd, J = 12.0, 3.6. 2.4 Hz, 1H), 2.43-2.51 (m, 1H), 2.79 (app t, J = 7.6 Hz, 0.14H), 7.35 (ddd, J = 7.6, 7.6, 0.4 Hz, 1H), 7.42 (dd, J = 7.6, 0.4 Hz, 1H), 7.55 (ddd, J = 7.6, 7.6, 0.4 Hz, 1H), 7.70 (dd, J = 7.6, 0.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 25.1, 25.4, 31.9, 33.0, 37.6, 40.0, 45.8 (t, J = 24.2 Hz), 54.4, 123.2, 123.4, 127.4, 133.9, 137.4, 153.4, 205.7. **HRMS** (ESI) calcd. for $C_{15}H_{18}OD$ ($M+H^+$) 216.1493, found 216.1488. The enantiomeric excess for *trans*-**7j** was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 15.8 min (major); t_R 22.4 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 99% ee.

In a nitrogen-filled dry box, ***d*-7j** from above (40.8 mg, 0.189 mmol), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.025 equiv), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol, 0.050 equiv), NaBARF (8.9 mg, 0.010 mmo, 0.050 equiv) and anhydrous 1,4-dioxane (1.0 mL) were added to a 1-dram vial. The reaction mixture was heated to 100 °C and allowed to stir at this temperature for 24 h. The mixture was cooled to room temperature, filtered through a

pad of silica gel (eluting with EtOAc), and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexanes/Et_2O) to yield ***d*-7j** as a mixture of diastereomers (10:1 *cis*:*trans*) (27.6 mg, 0.128 mmol, 64%) as an off white solid. The enantiomeric excess for *cis*-**7j** was determined by chiral HPLC analysis (254 nm, 25 °C) t_R 20.4 min (major); t_R 16.7 min (minor) [Chiracel AS-H (0.46cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/^{i}PrOH, 90:10, 0.5 mL/min] to be 99% ee. Peaks reported for the major diastereomer: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.79 (s, 3H), 1.00 (s, 3H), 1.22-1.36 (m, 2H), 1.44-1.69 (m, 3H), 2.06 (ddd, *J* = 14.0, 6.4, 4.4 Hz, 1H), 2.79 (app t, *J* =7.6 Hz, 1H), 3.35 (app q, *J* = 7.2 Hz, 0.14H), 7.37 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.47 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.58 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.75 (dd, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 25.6, 29.0, 29.5, 29.7, 36.5, 37.2, 37.6 (t, *J* = 20.8 Hz), 46.8, 124.2, 125.0, 127.5, 134.6, 135.6, 157.7, 209.0. **HRMS** (ESI) calcd. for $C_{15}H_{18}OD$ ($M+H^+$) 216.1493, found 216.1489.

Absolute stereochemistry and structure of (4b*S*,8a*R*)-4b,5,6,7,8,8a-Hexahydro-9*H*-fluoreno[2,3-*d*][1,3]dioxol-9-one (7g)



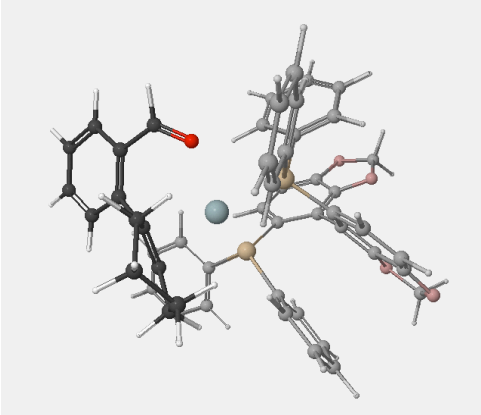
Single crystal X-ray structure determination of **7g** was performed using Cu radiation to determine the absolute configuration of the molecule. The systematic absences in the diffraction data were consistent for the stated space group. The positions of almost all non-

hydrogen atoms were found by direct methods. The remaining atoms were located on an alternating series of least-squares cycles on difference Fourier maps. All non-hydrogen atoms were refined in full-matrix anisotropic approximation. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. Flack,[98-100] Hooft[101] and Parsons[102] parameters were calculated with PLATON software.[103] Flack, Hooft and Parsons parameters -0.02(14), -0.02(14), and -0.03(12) in combination with the enantiomeric purity of **7g** are consistent with our assignment of the absolute stereochemistry as *cis*-(4b*S*,8a*R*). Supplementary X-ray diffraction data and structure refinement for **7g** is contained in CCDC 1484241. These data can be accessed free of charge from the Cambridge Crystallographic Data Center at www.ccdc.cam.ac.uk/data_request/cif.

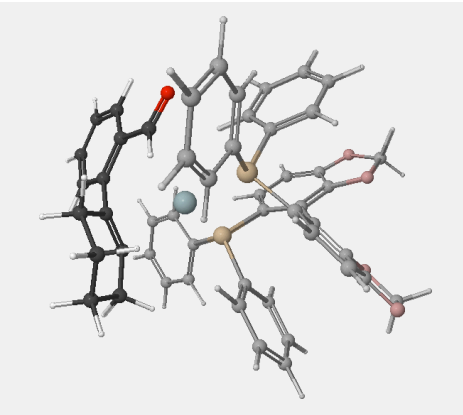
Computed structures of I1-I5 for hydroacylation reaction with 1b.

Reactant is bolded for clarity and black spheres represent carbon, red for oxygen, white for hydrogen, orange for phosphorus, and blue for rhodium.

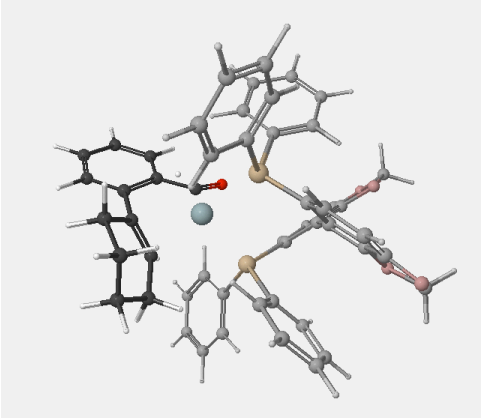
Computed structure of I1:



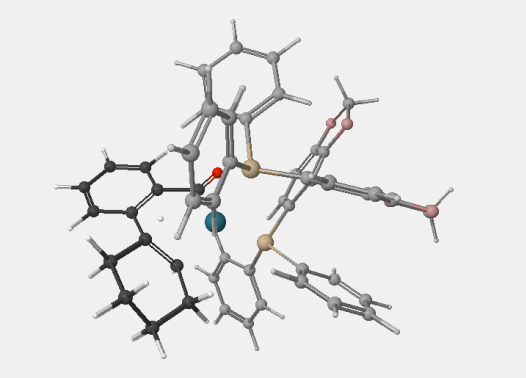
Computed structure of I2:



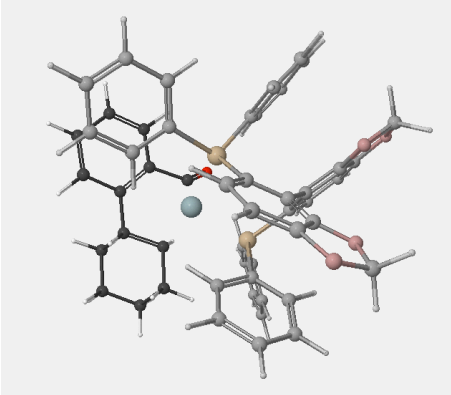
Computed structure of I3:



Computed structure of I4:



Computed structure of I5:



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CHAPTER V

CONCLUSION

This thesis describes the development of new transition metal-catalyzed *N-tert*-prenylation and alkene hydroacylation reactions. The synthesis of a variety of carbocyclic and heterocyclic architectures is enabled by new catalytic methods developed for these allylic substitution and hydrofunctionalization processes. Experimental and computational mechanistic work contributes to the fundamental understanding of the catalytic principles that control these reactions.

The palladium-catalyzed *N-tert*-prenylation studies provide three distinct protocols for the synthesis of the *N-tert*-prenylindoles. Indoles containing strong electron-withdrawing groups readily undergo the allylic substitution reaction and high branched-to-linear ratios are observed in the *N-tert*-prenylindole products. (η^6-Indole)$Cr(CO)_3$ complexes facilitate the formation of *N-tert*-prenylindoles containing electron-neutral or electron-donating substituents and a variety of new *N-tert*-prenylindoles are obtained by this method. Indoline nucleophiles also undergo the palladium-catalyzed prenylation reaction and oxidation of the *N-tert*-prenylindoline products with MnO_2 forms *N-tert*-prenylindoles. The high branched-to-linear ratios observed in these reactions are attributed to the use of a wide bite angle bisphosphine ligand that facilitates nucleophilic attack at the more substituted end of the palladiumprenyl(II) intermediate.

The rhodium-catalyzed *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes utilized fundamental principles of catalyst design to identify a catalyst that minimizes formation of two distinct byproducts. The use of a counteranion derived from

NaBARF eliminates an ene/dehydration pathway that leads to the formation of 2-methylnaphthalene. An electron-rich bisphosphine ligand containing bulky aryl substitutents facilitated turnover-limiting reductive elimination to generate the ketone product with high ratios of hydroacylation to alkene isomerization. This rhodium-catalyzed reaction facilitates the synthesis of wide range of 3,4-dihydronaphthalen-1(2*H*)-one proudcts with high enantioselectivities (up to 99% ee).

This thesis presents studies toward the identification of a catalyst for the intramolecular hydroacylation of 1,2-disubstituted alkenes. Although the rhodium-catalyzed hydroacylation of 1,2-disubstituted alkenes discussed in Chapter IV results in high yields of the indanone product, racemization of the α-center has prevented the development of an enantioselective variant of this reaction at this time. However, this work demonstrates the value of cationic rhodium catalysts for the hydroacylation of higher order alkenes and identifies the challenges to address in reactions of this type. Future studies in this area will require the identification of a catalyst for the hydroacylation of 1,2-disubstituted alkenes that does not promote a Lewis acid-catalyzed racemization process.

The first hydroacylations of 1,1,2-trisubstituted alkenes are presented along with experimental and computational mechanistic studies to elucidate the mechanism by which these reactions occur. These studies are consistent with an alkene hydroacylation/α-epimerization pathway for the rhodium-catalyzed processes. This reaction sequence enables the hydroacylation of a series of 2-(cyclohex-1-en-1-yl)benzaldehydes to form hexahydro-9*H*-fluoren-9-ones with moderate to high yields (68-91%) and up to 99% ee.

Overall, the new synthetic methods presented in this thesis occur with low catalyst loadings to generate a wide variety of products with high levels of regio-, diastereo- and/or

enantiocontrol. Computational studies and mechanistic experiments contribute to a deeper understanding of the mechanisms of these transformations and the application of catalyst design principles improves catalyst activity and minimizes byproduct formation. These new catalytic methods represent significant advancements for prenylation and alkene hydroacylation reactions and highlight the power of transition-metal catalysis in modern synthetic organic chemistry.