Part I: Palladium-catalyzed alkylation of alkenes using epoxides. Part II: Palladium-catalyzed asymmetric wacker-type anti-attack of alkenes

Teng, Shenghan

2020

Teng, S. (2020). Part I: Palladium-catalyzed alkylation of alkenes using epoxides. Part II: Palladium-catalyzed asymmetric wacker-type anti-attack of alkenes. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/146048>

<https://doi.org/10.32657/10356/146048>

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

Downloaded on 26 Apr 2023 18:14:53 SGT

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**PART I: PALLADIUM-CATALYZED ALKYLATION OF
ALKENES USING EPOXIDES**

**PART II: PALLADIUM-CATALYZED ASYMMETRIC
WACKER-TYPE ANTI-ATTACK OF ALKENES**

TENG SHENGHAN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2020

**PART I: PALLADIUM-CATALYZED ALKYLATION OF
ALKENES USING EPOXIDES**

**PART II: PALLADIUM-CATALYZED ASYMMETRIC
WACKER-TYPE ANTI-ATTACK OF ALKENES**

TENG SHENGHAN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2020

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

30/07/2020

.....
Date

.....
Teng Shenghan

Supervisor Declaration Statement

I have reviewed the content and presentation style of this thesis and declare it of sufficient grammatical clarity to be examined. To the best of my knowledge, the thesis is free of plagiarism and the research and writing are those of the candidate's except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

. July 30 2020 .
Date

.....
Prof. Robin Chi

Authorship Attribution Statement

This thesis contains material from two papers published in the following peer-reviewed journals in which I am listed as an author.

Chapter 1 is published as Shenghan Teng, Malcolm E. Tessensohn, Richard D. Webster and Jianrong Steve Zhou, Palladium-Catalyzed Intermolecular Heck-Type Reaction of Epoxides. *ACS Catal.* **2018**, 8, 7439-7444.

The contributions of the co-authors are as follows:

- Assoc. Prof. Zhou provided the initial project direction and revised the manuscript drafts.
- I prepared the manuscript drafts and conducted all experiments including substrate synthesis, condition optimization, catalytic reactions and product characterization.
- Dr. Tessensohn conducted the cyclovoltammetric experiments and Assoc. Prof. Webster provided guidance in the interpretation of the data.

Chapter 2 is published as Shenghan Teng, Zhiwei Jiao, Robin Chi Yonggui and Jianrong Steve Zhou, Asymmetric Wacker-Type Oxyallenylation and Azaallenylation of Cyclic Alkenes. *Angew. Chem. Int. Ed.* **2020**, 59, 2246-2250.

The contributions of the co-authors are as follows:

- Assoc. Prof. Zhou conceptualized the project and edited the manuscript drafts.
- I found the optimal condition in this project, collected all characterization data and wrote the first version of the manuscript drafts.
- Dr. Jiao provided the preliminary results of ligand screening and gave guidance in the product derivatization.
- Prof. Chi granted the permission of purchasing chemical reagents and provided room for lab experiments.
- All authors contributed to discussions and manuscript preparation.

28/07/2020

.....
Date

Teng S H.

.....
Teng Shenghan

Abstract

This dissertation describes two types of palladium-catalyzed cross-coupling reactions that achieve alkene functionalization. The first type focuses on epoxides as the alkylating reagent in the Heck-type radical process, which will be discussed in the first chapter. The second type highlights the Wacker-type addition of cycloalkenes in the novel enantioselective three-component couplings. This will be presented in the last two chapters.

In chapter one, we reported palladium-catalyzed alkylation of alkenes using epoxides. The reaction of epoxides and alkenes provides a highly atom economical access to valuable homoallylic alcohols. In previous reports, successful examples were limited to cobalt catalysis in harsh conditions. Hence, we reported the additive $\text{Et}_3\text{N}\cdot\text{HI}$ as the halide ion source to facilitate the ring opening of an epoxide, which tolerated sensitive functional groups in the tandem Heck-type alkylation. In reactions of unsymmetrical epoxides, a new C–C bond is predominantly formed at the less-hindered position, and the stereocenters of the epoxides are fully retained.

In chapter two, we described an asymmetric alkoxyallenylation and azaallenylation of cycloalkenes using propargylic acetates and heteroatom nucleophiles. It is a novel methodology to achieve a three-component Wacker-type addition of mono-olefins via *anti*-attack in an enantioselective fashion. The choice of an electron-deficient furyl-MeOBIPHEP ligand is crucial to the reactivity, diastereocontrol and enantiocontrol of this transformation. Besides alcohols, other nucleophiles such as carboxylic acids, phenols, water and electron-deficient aryl amines are also good coupling partners in this catalytic system. Furthermore, this reaction can also be applied to the concise synthesis of chiral 3-benzylpyrrolidines.

In the last chapter, we developed a palladium-catalyzed asymmetric allenyl (hetero)arylation of cyclic alkenes through a stereospecific Wacker-type *anti*-attack. In this method, asymmetric alkylation of heteroarenes through *anti*-nucleopalladation can be accompanied by the introduction of an allenyl group onto the alkene, thus allowing a maximal increase in molecular complexity. The reaction proceeds smoothly with some electron-rich arenes like tertiary anilines and a broad range of heteroarenes including *N*-H indoles, *N*-protected indoles, pyrroles, furans and thiophenes.

Acknowledgements

First, I would like to express my deepest gratitude to my supervisors, Professor Robin Yonggui Chi (main supervisor) and Associate Professor Jianrong Steve Zhou (co-supervisor). Prof. Chi not only gives me the opportunity and freedom to venture my research in this rigorous academic environment, but also shows concerns in every aspect of my research progress. I would also like to thank him for his continuous support, patience and guidance throughout these years. Prof. Zhou teaches me not only the knowledge of organometallic chemistry, but also the attitude towards research. Honestly, I'm impressed by his enthusiasm in chemistry. I am deeply grateful to him for choosing me as a PhD student and motivating me to do better.

Second, I would like to take this opportunity to thank two members in thesis advisory committee, Prof. Zhao Yanli and Prof. Xu Rong, for their valuable suggestions in my yearly progress report.

Third, I would like to thank all my present and past lab mates for sharing me precious experience and providing the friendly work environment. To name them: Dr. Jiao Zhiwei, Dr. Huang Xiaolei, Dr. Qin Xurong, Dr. Cao Zhongyan, Dr. Zhu Daoyong, Dr. Zhao Xiaohu, Dr. Lei Chuanhu, Wu Chunlin, Xu Haiyan, Guo Siyu, Lei Kaining, Lim Lihui, Cao Jiajia and Minh Hieu Minh. I would like to acknowledge Dr. Huang, Dr. Cao, Dr. Zhu and Ko Weiting (PhD candidate in Assoc. Prof. Roderick W. Bates' group) for proofreading my PhD thesis carefully.

Fourth, I also give my thanks to all the support staff in SPMS, especially Ms. Lee Yean Chin, Ms. Tong Wan Ling, Mr. Clemence Cheong Pak Hoe, Mr. Loh Poh Ming Wilson, Mr. Wang Wee Jian, Dr. Li Yongxin, Ms. Goh Ee Ling and Ms. Zhu Wenwei.

I greatly acknowledge Nanyang Technological University, which provides me financial support in my PhD study.

Last but not least, I would like to thank my family and friends for their love, support and understanding during this long journey.

Table of Contents

Abstract

Acknowledgements

List of Abbreviations

Chapter 1 Palladium-Catalyzed Intermolecular Heck-Type Reactions of Epoxides

.....	1
1.1 Introduction	1
1.1.1 Reactivity of Palladium Complexes towards Alkyl Halides	1
1.1.2 Palladium-Catalyzed Intramolecular Heck-Type Alkylation	4
1.1.3 Palladium-Catalyzed Intermolecular Heck-Type Alkylation	6
1.2 Reaction Design: Epoxides as Alkyl Radical Precursors	10
1.3 Results and Discussion	13
1.3.1 Reaction Optimization	13
1.3.2 Substrate Scope	17
1.3.3 Unsuccessful Examples	22
1.3.4 Mechanistic Studies	23
1.4 Conclusion	27
1.5 Experimental Section	28
1.5.1 General	28
1.5.2 A Typical Procedure for Condition Optimization	29
1.5.3 A Typical Procedure for Product Isolation of Heck-Type Reaction of Cyclic Epoxides	30
1.5.4 A Typical Procedure for Product Isolation of Heck-Type Reaction of Acyclic Epoxides	60

1.5.5 Experiment of Mechanistic Studies	72
1.6 References.....	82
 Chapter 2 Asymmetric Wacker-Type Oxyallenylation and Azaallenylation of Cyclic Alkenes	 87
2.1 Introduction.....	87
2.1.1 Brief Introduction of Wacker-Type Reaction	87
2.1.2 Asymmetric Wacker-Type Reaction via <i>syn</i> -Insertion	88
2.1.3 Asymmetric Wacker-Type Reaction via <i>anti</i> -Attack	93
2.1.4 Asymmetric Wacker-Type Reaction via Catalyzed by Copper	96
2.2 Reaction Design	98
2.3 Results and Discussion	100
2.3.1 Optimization of Reaction Conditions	100
2.3.2 Asymmetric Oxyallenylation and Azaallenylation of Cyclic Alkenes ..	102
2.3.3 Derivatizations of Alkoxyallenylation Adducts.....	107
2.4 Conclusion	110
2.5 Experimental Section.....	110
2.5.1 A Typical Procedure for Condition Optimization	110
2.5.2 Asymmetric Oxyallenylation of 2,3-Dihydrofuran.....	111
2.5.3 Asymmetric Oxyallenylation of <i>N</i> -Boc-2,3-dihydropyrrole.....	147
2.5.4 Asymmetric Azaallenylation of Cycloalkenes.....	164
2.5.5 Product Derivatization	170
2.6 References.....	187
 Chapter 3 Pd-Catalyzed Asymmetric C-Alkylation of (Hetero)arenes through Wacker-Type <i>anti</i>-Addition to Cycloalkenes	 192
3.1 Introduction	192
3.1.1 <i>syn</i> -Migratory Insertion of (Hetero)aryl Metal Complexes to Alkenes....	193

3.1.2 C–C Reductive Elimination of (Hetero)aryl Metal Complexes	196
3.1.3 Wacker-Type Attack of Nucleophilic (Hetero)arenes on Alkenes	198
3.2 Reaction Design	201
3.3 Results and Discussion	204
3.3.1 Optimization of Reaction Conditions	204
3.3.2 Substrate Scope	207
3.3.3 Unsuccessful Examples	211
3.3.4 Derivatization	212
3.3.5 The Proposed Reaction Mechanism	213
3.4 Conclusion	214
3.5 Experimental Section	215
3.5.1 A Typical Procedure for Condition Optimization	215
3.5.2 Asymmetric Allenyl(hetero)arylation of Cycloalkenes	215
3.6 References	250
General Conclusion and Perspective	254

List of Abbreviations

Ac	acetyl
Ar	aryl
BenzoFu	benzofuryl
BINAP	(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
calcd	calculated
cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
conv.	conversion
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
dr	diastereomeric ratio
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplets
EC	ethylene carbonate
ee	enantiomeric excess
EI	electronic ionization
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl

Et ₂ O	diethyl ether
EtOAc	ethyl acetate
Fu	furyl
GC	gas chromatography
Hz	hertz
IMes	1,3-bis(mesityl)imidazole-2-ylidene
<i>i</i> -Pr	<i>iso</i> -propyl
m	multiplet
Me	methyl
MeCN	acetonitrile
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
MS	mass spectrometry
Nap	Naphthyl
<i>n</i> -Bu	<i>n</i> -butyl
<i>n</i> -hex	<i>n</i> -hexyl
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
PC	propylene carbonate
PCy ₃	tricyclohexylphosphine
Ph	phenyl
PhCF ₃	α, α, α -trifluorotoluene
PhMe	toluene
ppm	parts per million
q	quartet
rt	room temperature
<i>t</i> -Bu	<i>tert</i> -butyl
TADDOL	$\alpha, \alpha, \alpha, \alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanols
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine

TMS	trimethylsilyl
Ts	toluenesulfonyl
δ	chemical shift

Chapter 1: Palladium-Catalyzed Intermolecular Heck-Type Reactions of Epoxides

1.1 Introduction

1.1.1 Reactivity of Palladium Complexes towards Alkyl Halides

Pd-catalyzed Heck reaction is one of the fundamental synthetic transformations for catalytic C–C bond formation and won Nobel Chemistry prize in 2010. Conventionally, the oxidative addition (O. A.) of aryl or alkenyl (pseudo)halides to Pd(0) via two-electron transfer initiates the catalytic cycle, followed by alkene insertion and β -H elimination to furnish the arylation or alkenylation product (Scheme 1.1).¹

Scheme 1.1 Mechanism of conventional Heck reaction

Compared to the well-developed Heck-type arylation or alkenylation, Heck-type alkylation has significantly lagged behind. This is primarily due to the higher barrier of the oxidative addition of unactivated alkyl halides to Pd(0).² Alkyl carbon centers lack π^* orbitals to stabilize the transition state of oxidative addition. In addition, the steric nature of alkyl halides also disfavors the nucleophilic attack from Pd(0) species. Moreover, even if the oxidative addition was feasible, the resulting alkylpalladium

species would easily undergo early β -H elimination before alkene insertion.

To address the above issues in the classical two-electron mode, strong σ -donor ligands with bulky groups were employed to lower the activation energy in the key step of Pd-catalyzed alkylation.³ In 2002, Gregory Fu and coworkers first separated and characterized crystallographically the oxidative adduct of primary alkyl bromide and $P(t\text{-Bu})_2\text{Me}$ -ligated Pd(0) complex (Scheme 1.2).^{3a} The large steric hindrance of trialkyl monophosphine impeded β -hydride elimination to occur. This alkyl Pd complex proved competent in the Suzuki-type alkylation. Later, in reactions of deuterium-labelled alkyl tosylates, the main products were formed with inversion of the configuration, which supported the S_N2 mechanism in the oxidative-addition step (Scheme 1.3).^{3b}

Scheme 1.2 The characterization of O. A. adducts in Suzuki reaction of alkyl bromides

Scheme 1.3 Stereochemistry of $\text{Pd}/P(t\text{-Bu})_2\text{Me}$ -catalyzed Suzuki reaction

Early in the 1970s, John Osborn reported that $\text{Pd}(0)$ complexes of phosphines reacted stoichiometrically with secondary and tertiary alkyl halides to produce alkyl

1.1.2 Palladium-Catalyzed Intramolecular Heck-Type Alkylation

In 2007, Fu et al. reported the seminal work of Pd-catalyzed intramolecular Heck-type reaction of primary alkyl bromides and chlorides with pendant olefins (Scheme 1.6).⁸ The use of electron-rich and bulky SIMes favored the oxidative addition and inhibited premature β -hydride elimination. Despite the breakthrough, only primary alkyl halides can participate in the Heck-type cyclization while secondary and tertiary alkyl halides remain unreactive.

Scheme 1.6 Intramolecular Heck reaction of alkyl bromides via S_N2 mechanism

In 2011, Alexanian and coworkers reported Pd-catalyzed carbocyclization of alkyl iodides in an atmosphere of 10 atm CO (Scheme 1.7).⁹ Rather than the expected carbonylative process, Heck-type alkylation took place exclusively. Based on the result of TEMPO-trapping experiment, hybrid organometallic-radical mechanistic hypothesis was proposed.

Scheme 1.7 Intramolecular Heck reaction of alkyl iodides via a radical mechanism

The same group later developed conditions for an intramolecular Heck-type

reaction of unactivated alkyl bromides in the absence of CO (Scheme 1.8).¹⁰ The selection of electron-rich diphosphine dtbpf was the key to increasing the reaction efficiency. The atom transfer radical addition (ATRA) product was observed at the short reaction time and pre-synthesized ATRA intermediate underwent quantitative dehydrohalogenation under the reaction conditions. Both the addition of radical scavengers and the replacement of Pd(0) catalyst with simple radical initiators led to low conversion. These mechanistic studies indicated that the carbocyclization of alkyl bromides proceeded via an ATRA pathway, in which the palladium served as a true catalyst instead of a simple initiator for radical chain reaction.

Scheme 1.8 Intramolecular Heck reaction of alkyl bromides involving the formation of ATRA intermediate

Most of intramolecular Heck reactions of alkyl halides provided 5-*exo*-trig cyclized products due to fast ring closure. Interestingly, Liu et al. developed a palladium-catalyzed 6-*endo*-selective carbocyclization of unactivated alkyl iodides in 2016 (Scheme 1.9).¹¹ The α -aryl group was crucial for the *endo* selectivity by stabilizing the tertiary-benzyl radical intermediate. The result of deuterium erosion also supported a hybrid Pd-radical process.

Scheme 1.9 6-*Endo*-selective palladium-catalyzed carbocyclization of unactivated alkyl iodides

In an earlier report, Gevorgyan and coworkers also reported 7-*endo*-selective Pd-catalyzed Heck-type silylmethylation (Scheme 1.10).¹² The 7-*endo* selectivity for terminal alkenes was probably due to the relatively long Si–C bond and stabilization of the *endo* transition state as proposed by Koreeda et al.¹³ The silicon group can be easily removed via oxidative cleavage.¹⁴

Scheme 1.10 *Endo*-selective palladium-catalyzed intramolecular Heck reaction of iodomethylsilyl ethers

1.1.3 Palladium-Catalyzed Intermolecular Heck-Type Alkylation

Compared to intramolecular Heck-type alkylation, the intermolecular version is more difficult to achieve due to competitive β -H elimination of alkyl halides and the higher entropic cost during radical addition. α -Carbonyl alkyl electrophiles were capable of intermolecular cross-coupling.¹⁵ For unactivated alkyl halides bearing β -hydrogens, cobalt catalysts have been reported for Heck-type reactions,¹⁶ however, in

these cases strongly basic Grignard reagents were needed to produce low-valent metal catalysts in situ, which limited their synthetic applicability.

As a continuation of earlier works, Alexanian and coworkers expanded the Pd catalysis to the intermolecular Heck-type alkylation (Scheme 1.11).¹⁷ The Pd complex PdCl₂(dppf) enabled primary and secondary unactivated alkyl iodides to couple with styrenes and other electron-deficient olefins such as methyl acrylate and acrylonitrile, albeit with low *E/Z* ratio in most cases other than styrenes.

Scheme 1.11 Pd-catalyzed intermolecular Heck reaction of alkyl iodides

Almost at the same time, Zhou et al. independently developed an intermolecular Heck reaction of common alkyl halides with an in-situ formed Pd/dppf catalyst (Scheme 1.12).¹⁸ In addition to alkyl iodides, alkyl bromides and chlorides were suitable coupling partners in the presence of lithium iodide. The authors excluded the ATRA pathway since dehydrohalogenation of 1-iodopropyl benzene proceeded in low conversion when added into a living catalytic reaction.

Scheme 1.12 Pd-catalyzed intermolecular Heck reaction of unactivated alkyl halides

Later, Zhang and coworkers also disclosed Pd-catalyzed Heck-type reaction of fluoroalkyl bromides (Scheme 1.13).¹⁹ Pd(0) species coordinated with Xantphos

reacted to produce fluoroalkyl radical and Pd(I)Br species. A radical clock, α -cyclopropylstyrene delivered ring-rearrangement product instead of normal Heck-type alkylation, which was consistent with the putative hybrid Pd-radical pathway.

Scheme 1.13 Pd-catalyzed intermolecular Heck reaction of fluoroalkyl bromides

Recently, the photoexcited-state reactivity of Pd complex has regained attention.²⁰ Photoexcitation of Pd(0) complex allowed both bond cleavage and formation under mild conditions. For example, irradiation by UV light ($\lambda = 350\text{-}365 \text{ nm}$) activated Pd(0) species in the absence of exogenous photosensitizers, which could react with alkyl halides to generate hybrid Pd/radical intermediate through a Pd(I)/Pd(0) cycle (Scheme 1.14).

Scheme 1.14 The use of excited-state Pd complex in the generation of alkyl radicals under visible-light irradiation

The first example that employed visible light in Pd-catalyzed Heck-type alkylation was developed by Gevorgyan et al. (Scheme 1.15a).^{21a} α -Heteroatom substituted alkyl

halides including silyl, pinacol boronyl and phosphonyl methyl iodides were competent in the cross-coupling with vinyl (hetero)arenes, affording functionalized allylic synthons in high stereoselectivity. The same conditions can be applied to Heck-type alkylation with unactivated tertiary alkyl halides at room temperature (Scheme 1.15b).^{21b}

Scheme 1.15 Visible light-induced Heck reaction of functionalized primary and unactivated tertiary alkyl iodides

Soon after, Fu and Shang et al. also reported photoirradiation Heck-type reaction with 1°, 2° and 3° alkyl bromides and conducted detailed mechanistic investigations (Scheme 1.16a).²² This reaction entirely stopped in the absence of light source, excluding the possibility that irradiation served as an initiator of a radical chain process.²³ Moreover, the result of UV-vis absorption measurement suggested the Pd(0) complex was the only light-absorbing species. Later, other research groups including Rueping, Zhou and Yu also contributed to the photoinduced Pd-catalyzed alkylation reactions.²⁴

In 2020, Fu et al. reported palladium-catalyzed alkylation of enamides and silyl enol ethers under blue light irradiation (Scheme 1.16b).²⁵ This reaction proceeded by inner-sphere electron transfer from Pd⁰ species to alkyl bromides. Theoretical studies

demonstrated the dual phosphine ligand system and spin prohibition contributed to stabilizing the hybrid Pd^I-radical species (Scheme 1.16c).

Scheme 1.16 Visible light-induced alkylation of vinylarenes

1.2 Reaction Design: Epoxides as Alkyl Radical Precursors

Epoxides are versatile electrophiles in organic synthesis due to their ready accessibility from alkenes or carbonyl compounds and a high tendency towards ring opening by various heteroatom nucleophiles or low-valent transition metals.²⁶ As a common family of alkyl electrophiles, epoxides can also serve as the precursors of carbon-centered radicals in the Heck-type reaction. The reaction of epoxides and alkenes provides a highly atom economical access to valuable homoallylic alcohols (Scheme 1.17).²⁷ In spite of this advantage, successful examples of Heck-type alkylation with epoxides are limited to cobalt catalysis under harsh conditions.

Scheme 1.17 Natural products containing β -homoallylic alcohols

For instance, Oshima et al. reported the first example of intermolecular coupling between epoxides and alkenes catalyzed by a cobalt complex ligated with bis(diphenylphosphino) hexane (dppe) (Scheme 1.18).²⁸ Initial epoxide opening by *in situ* formed MgBr_2 led to the formation of β -bromoalkoxy magnesium bromide, which underwent a SET process with $\text{Co}(0)$ species to deliver the alkyl radical. The use of stoichiometric Grignard reagents promoted reduction of cobalt(II) to generate catalytically active low-valent Co species, however, they were not compatible with many polar groups. Moreover, the Heck-type reaction with α -substituted epoxides resulted in a mixture of two regioisomers.

Scheme 1.18 Cobalt-catalyzed reaction of epoxides and styrene

In 2016, Morandi and coworkers reported a cobalt-catalyzed cyclization of epoxides with pendant olefins (Scheme 1.19).²⁹ Oxidative addition of the epoxide and an anionic Co^{I} complex via $\text{S}_{\text{N}}2$ type pathway produced the regioselectively ring-opened β -hydroxyalkylcobalt(III) intermediate, followed by photolysis of the weak $\text{Co}^{\text{III}}-\text{C}$ bond to produce an alkyl radical. Strong base $\text{NaO}t\text{-Bu}$ used in methanolic

solvent facilitated the regeneration of low valent cobalt complex. However, this may bring about the issue of acidic functional group tolerance.

Scheme 1.19 Cobalt-catalyzed intramolecular coupling of epoxides and olefins

Previously, Nugent, RajanBabu and Gansäuer group applied Cp_2TiCl in the cross-coupling reactions of epoxides and some electron-deficient olefins.³⁰ The ring opening of α -substituted epoxides took place at the sterically more hindered site, affording the more favourable secondary alkyl radicals (Scheme 1.20). However, this method only provided the reductive product. Additionally, in the case of terminal epoxides, new C–C bonds formed at the more substituted site led to the loss of stereochemical information from the chiral epoxides.

Scheme 1.20 Titanocene-catalyzed reductive addition of epoxides to electron-deficient olefins

In order to harness β -halohydrin derived from epoxides *in situ* and promote Heck-type alkylation with alkenes,³¹ other additives must be used that are not only effective for the β -halohydrin formation, but also compatible with $\text{Pd}(0)$ catalysis.

In 2014, Weix and coworkers reported nickel-catalyzed reductive arylation of epoxides (Scheme 1.21a).^{32a} A combination of catalytic NaI and stoichiometric Et₃N·HCl facilitated selective epoxide opening at the sterically less hindered carbon and *in-situ* generation of β -iodohydrin, which then reacted with low valent nickel species to deliver an alkyl radical. A similar method was also reported by Yamamoto et al.^{32b}

Inspired by these results, we decided to take advantage of *in-situ* halohydrin formation to achieve palladium-catalyzed intermolecular Heck-type reaction of epoxides (Scheme 1.21b). Triethylamine hydroiodide is easily prepared from Et₃N·HCl and NaI in methanol. The use of Et₃N·HI is superior to other salts for three reasons: 1) A mild and nearly neutral condition can be maintained during Pd catalysis and it is regenerated at the end of each catalytic cycle. 2) Unlike the titanocene-catalyzed system, which causes the formation of reductive products, it will allow formation of alkenes as final products via β -hydrogen elimination. 3) Alkylamine salts of HI enable selective epoxide opening at the sterically less hindered site of terminal epoxides, which may preserve the configuration of stereocenters from enantiopure epoxides.

a) Weix (2014)

b) My reaction design

Scheme 1.21 Coupling reactions of *in-situ* halohydrin formation from epoxides

1.3 Results and Discussion

1.3.1 Reaction Optimization

At the initial attempt, the direct coupling of a β -iodohydrin and styrene led to low yield of the desired product (30%) under the reaction parameters that Zhou et al. previously described for Heck-type alkylation with alkyl halides (Scheme 1.22).¹⁸ Other byproducts included cyclohexanone (45%), cyclohexanol (5%), and a small amount of bicyclic ethers (14%) derived from epoxide ring-expansion with alkenes. In addition, my effort in testing other Pd catalysts did not lead to significant improvement. For example, a catalyst comprised of Pd(PPh₃)₄ and Xantphos together with Et₃N as base furnished 55% yield of two diastereomers in a *trans/cis* ratio of 3:1.

Scheme 1.22 Initial attempts at Pd-catalyzed Heck-type reaction of β -iodohydrins

Later, the stoichiometric ring opening of epoxides with Et₃N·HI was tested (Scheme 1.23). As expected, cyclohexene oxide was fully converted into β -iodohydrin at 80 °C within 2 h in dioxane or trifluorotoluene, while a terminal aliphatic epoxide underwent exclusive ring cleavage at the less substituted carbon. In contrast, the reaction of styrene oxide was less regioselective with a ratio of 3.5:1 along with aldehyde as isomerization byproduct.

Scheme 1.23 Stoichiometric reaction of epoxides and Et₃N·HI

On the basis of these preliminary results, we decided to investigate whether trialkylamine salt of HI could facilitate the model reaction of cyclopentene oxide **1a** and styrene **2a** to undergo Heck-type transformation in a single step (Table 1.1). Fortunately, we identified only 20 mol% of Et₃N·HI was effective to afford the desired product **3a** in 80% yield with a 10:1 *trans/cis* ratio, when Pd(PPh₃)₄ (5 mol%) and Xantphos (7 mol%) were used in trifluorotoluene at 110 °C (entry 1). Other palladium sources including Pd(OAc)₂ and Pd(dba)₂ led to worse results (entries 2-3). We also noticed the performance of palladium catalysts was highly dependent on natural bite angles of chelating bisphosphines. For example, ligands with relatively small bite angles such as dppp and BINAP resulted in <10% yield (entries 6-7), whereas the catalyst of DPEphos or dppf furnished **3a** only in moderate yield (entries 8-9).

Table 1.1 Optimization of conditions for the model reaction

entry	deviation from conditions described above	yield (%) (<i>trans/cis</i>)
1	none	80 (10:1)
2	Pd(OAc) ₂ instead of Pd(PPh ₃) ₄	36 (8:1)
3	Pd(dba) ₂ instead of Pd(PPh ₃) ₄	41 (8:1)
4	no ligand added	30 (8:1)
5	PCy ₃ instead of Xantphos	2
6	dppp instead of Xantphos	0
7	<i>rac</i> -BINAP instead of Xantphos	6
8	DPEphos instead of Xantphos	36 (7:1)
9	dppf instead of Xantphos	42 (8:1)
10	Cy ₂ NMe (1.5 equiv) as base	80 (10:1)
11	K ₃ PO ₄ (1.5 equiv) as base	0
12	Cs ₂ CO ₃ (1.5 equiv) as base	0
13	Et ₃ N (1.5 equiv) as base	60 (10:1)
14	DIPEA (1.5 equiv) as base	57 (10:1)
15	dioxane instead of PhCF ₃	73 (10:1)
16	toluene instead of PhCF ₃	55 (5:1)
17	veratrole instead of PhCF ₃	70 (10:1)

Other solvents including dioxane, veratrole (1,2-dimethoxybenzene) and toluene were inferior to trifluorotoluene (entries 15-17). Furthermore, the model reaction did not need additional bases since the free alkylamine released from Et₃N·HI could function as the base in the later part of the catalytic cycle. Instead, I found that inorganic bases such as K₃PO₄ and Cs₂CO₃ inhibited the productive pathway, and the addition of 1.5 equiv of Et₃N and DIPEA led to lower yields (entries 11-14). Cy₂NMe was the exception that did not have any deleterious effect (entry 10). Reducing the amount of **1a** to 1.5 equiv resulted in a slightly lower yield (75%).

1.3.2 Substrate Scope

Under the optimal conditions with 5 mol% Pd catalyst and Xantphos, most of substituted vinylarenes were coupled with cyclopentene oxide in satisfactory yields and good *trans* selectivity on the cyclic ring (Scheme 1.24). These products contained exclusively (*E*)-geometry in the olefinic part. Both electron-donating and -withdrawing groups were well tolerated on the aryl part. Notably, styrenes with sensitive functionalities, such as an acetyl group, which cannot survive in the presence of Grignard reagents, were compatible with the model reaction parameters. The relative configuration of the major isomer of **3i** was determined to be *trans* by X-ray diffraction analysis.³³ Moreover, 1,1-diphenylethylene exhibited high reactivity to produce **3o** in nearly quantitative yield, whereas in the reaction of α -methylstyrene, Pd/dppf was a better catalyst affording terminal alkene **3p** as the major isomer.

Scheme 1.24 Examples of Heck-type reactions of cyclopentene oxide

Subsequently, we examined other cyclic epoxides in the Heck-type reaction (Scheme 1.25). Cyclohexene oxide also reacted with good efficiency with vinylarenes bearing electron-rich and -deficient substituents, although the *trans/cis* ratio was only approximately 3:1. We also found that cycloheptene oxide was reactive, however, the reaction with cyclooctene oxide led to low conversion. Interestingly, other five-membered cyclic epoxides including 2,5-dihydrofuran oxide and 3,3-disubstituted cyclopentene oxide afforded desired β -homoallylic alcohols **4g** and **4h** in a good *trans* selectivity (>10:1).

Scheme 1.25 Examples of Heck-type reactions of other symmetrical cyclic epoxides

Remarkably, some cyclic epoxides having preexisting stereocenters on the ring framework were able to undergo the late stage functionalization with this protocol (Scheme 1.26). The treatment of (+)-*trans*-limonene oxide **1c** with styrene delivered two diastereomers with a ratio of 3:1. The *cis* configuration of the major isomer was assigned by a strong NOE signal between the hydrogen atoms H² and H⁴. Moreover, β -epoxide **1d** derived from pregnenolone acetate also reacted successfully with styrene, affording the major product **4j** with the styrenyl group at the equatorial position. In both cases, the new C–C bond in two diastereomers was formed selectively at the less substituted carbon of the epoxide.

Scheme 1.26 Examples of Heck-type reactions of unsymmetrical cyclic epoxides

Besides cyclic epoxides, this alkylation protocol can be further extended to α -substituted epoxides. A variety of terminal epoxides in Scheme 1.27 afforded the desired β -homoallylic alcohols in the presence of catalytic $\text{Pd(PPh}_3)_4$ and dppf. In comparison, the Pd catalyst of Xantphos gave **5c** in only 21% yield. As expected, the Heck-type reaction occurred at the less hindered carbon center of epoxides with a ratio of more than 10:1 in most cases. Overall, the catalytic alkylation was carried out smoothly with monoalkyl-, 1,1-dialkyl-, and benzyl-substituted epoxides. Gratifyingly, the reactions of enantioenriched glycidyl ether and its derivatives **1f-h** ($\text{R} = \text{Ph}$, H and TBS) afforded the desired products with high enantio-specificity. This transformation is of practical importance because it allowed a straightforward chiral 1,2-diol synthesis. However, the enantiopure styrene oxide **1i** furnished both regioisomers, along with a significant amount of byproduct **5n''** derived from epoxide isomerization and subsequent self-aldol condensation.³⁴ Notably, **5n** was obtained in only 60% ee. Real-time analysis of the reaction mixture revealed that **1i** underwent partial racemization under the catalytic conditions, probably through the reversible formation of

phenylacetaldehyde.

Scheme 1.27 Examples of Heck-type reactions of α -substituted epoxides

The scope of other types of olefins was also explored (Scheme 1.28). We found that aromatic conjugate dienes exhibited the similar reactivity to vinylarenes, furnishing the corresponding products in satisfactory diastereoselectivities. The alkylation took place selectively at the terminal site of dienes. For reactions of α -phenyl acrylate and α -phenyl acrylamides, new C–C bonds were also formed at the terminal carbon of the alkenes to provide *Z*-isomers exclusively, although the *trans/cis* ratio on the

cyclopentane ring was in the range of 2:1 to 3:1. More notably, coumarins and *N*-methyl-2-quinolinone were also reactive under the catalytic conditions, providing the exclusive C-3 alkylation products as confirmed by X-ray crystallography. Owing to the favorable formation of stabilized benzylic radicals, similar regioselectivity was also observed by Zhang et al. in Pd-catalyzed difluoroacetylation of coumarin.¹⁹

Scheme 1.28 Substrate scope with respect to 1,3-diene and electron-deficient olefins

1.3.3 Unsuccessful Examples

We attempted some hindered cyclic epoxides including α -pinene oxide **1k**, *exo*-2,3-

epoxy norbornane **1l** and *trans*-stilbene oxide **1m**. However, none of them underwent ring-opening to produce β -hydroxyalkyl radicals under the standard reaction conditions (Scheme 1.29a).

For simple electron-withdrawing olefins **2f-i**, the expected Heck-type products were not formed due to phosphine-promoted anionic polymerization (Scheme 1.29b).³⁵ The reaction of β -methylstyrene led to low conversion, presumably owing to the steric factors. Electron-neutral olefins **2j-k** and electron-rich olefins **2l-m** failed to provide Heck-type products, since the addition of nucleophilic alkyl radicals to these olefins were too slow.

Scheme 1.29 Unsuccessful examples of epoxides and alkenes

1.3.4 Mechanistic Studies

To understand the reaction mechanism, I first probed stoichiometric reactions of *in-situ* formed Pd(0) complex of Xantphos with β -iodohydrin **1j** in the absence of styrene. It formed cyclohexanone and cyclohexanol in a ratio of 11:1 (Scheme 1.30a).

A similar conversion of β -bromohydrins to ketone under photolysis was reported previously.³⁶ Another stoichiometric reaction of Pd(0) complex with epoxide **1b** gave similar results in the presence of 1 equiv of Et₃N·HI (Scheme 1.30b).

Additionally, when 1 equiv of TEMPO was added to the model reaction of **1a** and styrene, no Heck-type alkylation product was detected. Instead, a TEMPO adduct **7a** was isolated, which supported the radical-involved mechanism instead of S_N2 pathway (Scheme 1.30c). The configuration of **7a** was determined to be *cis*.³⁷ The major byproduct in this reaction was found to be cyclopentanone. When the Pd source was omitted in the reaction above, none of these products were observed.

Next, we tested α -cyclopropylstyrene **2f** in the alkylation with the epoxide **1a** (Scheme 1.30d). Instead of normal Heck-type product, a dihydronaphthalene derivative **7b** was formed in 37% yield via opening of the cyclopropyl ring (with a ring-opening rate of $6 \times 10^4 \text{ s}^{-1}$)³⁸ and subsequent radical cyclization on the arene ring.

In another radical-clock experiment, epoxide **1k** carrying a pendant homoallyl group provided ring-closure isomer **7c** without the formation of linear products (Scheme 1.30e).

Scheme 1.30 Experiments for mechanistic studies

The reduction potential of β -iodohydrin (-2.2 V vs Fc^+/Fc , shown in Figure 1.1) was found to be similar to that of cyclohexyl iodide. It was determined to be much more negative than half-wave reduction potential of $(\text{Xantphos})\text{PdI}$ (-1.5 V vs Fc^+/Fc , shown in Table 1.2). Consequently, we excluded an outer-sphere single electron transfer between $(\text{L-L})\text{Pd}^0$ and alkyl iodides since it was a rather unfavorable endergonic process (about $+16$ kcal·mol $^{-1}$). Alternatively, an *inner-sphere halogen abstraction* was more likely. Cyclic voltammographic measurements were conducted in collaboration with Dr. Tessensohn and Prof. Richard Webster at NTU.

Figure 1.1 Cyclic voltammograms of 1.0 mM alkyl iodides in PhCN (left) and DCM (right). Half-wave reduction potential of CyI is -2.20 V in DCM and -2.47 V in PhCN and half-wave reduction potential of β -iodohydrin is -2.21 V in DCM.

Table 1.2 Half-wave potentials of Pd complexes. All potentials are reported as volts versus the ferrocene/ ferrocenium couple

Compound	Solvent	$E_{1/2}(\text{II/I})$	$E_{1/2}(\text{II/0})$	$E_{1/2}(\text{I/0})$
Pd(Xantphos) I_2	DCM	-0.95		-1.48
	PhCN		-0.90	
Pd(dppf) I_2	DCM	-1.12		-1.84
	PhCN	-1.07		-1.82
Pd(dppp) I_2	DCM	-1.34		-1.90
	PhCN	-1.33		-1.88

Finally, we proposed a hybrid Pd-radical catalytic cycle intersected with the reversible conversion of $\text{Et}_3\text{N}\cdot\text{HI}$ and Et_3N (Scheme 1.31a). The β -hydroxyalkyl iodide, which was generated *in situ* from the epoxide and $\text{Et}_3\text{N}\cdot\text{HI}$, reacted with $(\text{L-L})\text{Pd}^0(\text{PPh}_3)$ species to afford alkyl radical **A** and a $(\text{L-L})\text{Pd}^{\text{I}}(\text{PPh}_3)$ complex.²⁵ Next, radical **A** added to styrene at the terminal site to provide benzylic radical **B**, which was a fast process.³⁹ The combination of radical **B** with $(\text{L-L})\text{Pd}^{\text{I}}(\text{PPh}_3)$ formed alkylpalladium(II) species **C**, which subsequently underwent β -H elimination to deliver the expected product.

Taking into account the cyclic voltammetry experiments, an alternative pathway involving electron transfer from radical **B** to complexes of Pd^I or Pd^{II} to form benzylic cation **D** was excluded due to high endothermic costs (Scheme 1.31b). The half-wave oxidation potential of a secondary benzylic radical is approximately 0.0 V vs Fc⁺/Fc,⁴⁰ whereas half-wave reduction potentials of (Xantphos)Pd^I and (Xantphos)Pd^{II} in DCM were -1.5 and -1.0 V vs Fc⁺/Fc, respectively (Table 1.2). Furthermore, another pathway of atom transfer radical addition followed by E2 elimination of benzylic halides was also discounted based on previous works in our group.¹⁸

Scheme 1.31 Proposed reaction pathway

1.4 Conclusion

In summary, a Pd-catalyzed intermolecular Heck-type reaction of both cyclic and acyclic epoxides is reported with wide tolerance of acidic hydrogens and sensitive polar

groups. Suitable alkenes include vinylarenes, conjugate dienes, and some electron-deficient olefins. The additive Et₃N·HI can function as the halide ion source to facilitate epoxide ring-opening, and the resulting free alkylamine acts as base to assist in the regeneration of Pd(0) species. In the reaction of an unsymmetrical epoxide, a new C–C bond is predominantly formed at the sterically less hindered positions, and the stereocenters of the epoxide are fully retained. Mechanistic studies provide evidence for *in situ* generation of β -halohydrins, formation of alkyl radicals and radical addition to alkenes as key steps.

1.5 Experimental Section

1.5.1 General

All NMR spectra were acquired on Bruker 500 MHz, 400 MHz or 300 MHz NMR spectrometers. ¹H NMR chemical shifts were recorded relative to SiMe₄ (δ 0.00) or residual protiated solvents (CDCl₃: δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a *J* value in Hz. ¹³C NMR spectra were obtained at 125 MHz on 500 MHz, 100 MHz on 400 MHz or 75 MHz on 300 MHz NMR instruments and chemical shifts were recorded relative to solvent resonance (CDCl₃: δ 77.16). ¹⁹F NMR spectra were recorded at 376 MHz on 400 MHz NMR spectrometers without any external standard. Proof of purity of new compounds was demonstrated with copies of ¹H, ¹³C, and ¹⁹F NMR spectra.

Glassware was dried at 120 °C for at least 3 hours before use. Anhydrous PhCF₃

and 1,4-dioxane (Aldrich) were degassed by argon bubbling and then stored over activated 4 Å molecular sieve beads in the glove box before use. Veratrole (1,2-dimethoxybenzene) was distilled from sodium under argon and stored over activated 4 Å molecular sieve beads in an argon-filled glove box. Other solvents used in the solvent optimization were dried and purified according to the procedure from “Purification of Laboratory Chemicals Book 5th Edition”. All of anhydrous solvents were stored in Schlenk tubes in the glove box. Unless noted otherwise, commercially available chemicals were used as received without purification.

Flash chromatography was performed using Merck 40-63 D 60 Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J&W GC column DB-5MS-UI. The GC internal standard $n\text{-C}_{12}\text{H}_{26}$ was degassed with argon and dried over activated 4 Å molecular sieve beads before use. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer.

High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiralcel columns at 25 °C and a mixture of HPLC-grade hexanes and isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as c .

1.5.2 A Typical Procedure for Condition Optimization

In an argon-filled glove box, Pd(PPh₃)₄ (5.8 mg, 0.005 mmol), Xantphos (4.1 mg, 0.007 mmol) and dry PhCF₃ (0.4 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, cyclopentene oxide (18 μL, 0.2 mmol), NEt₃·HI (4.6 mg, 0.02 mmol), styrene (11.6 μL, 0.1 mmol) and 10 μL of GC standard *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 °C. After 24 h, the reaction mixture was cooled to room temperature and aliquots were passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC to determine the calibrated yield of the product, ratio of *trans* and *cis* isomers and conversion of styrene.

1.5.3 A Typical Procedure for Product Isolation of Heck-Type Reaction of Cyclic Epoxides

In an argon-filled glove box, Pd(PPh₃)₄ (17.4 mg, 0.015 mmol), Xantphos (12.3 mg, 0.021 mmol) and dry PhCF₃ (1.2 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, cyclopentene oxide (54 μL, 0.6 mmol), NEt₃·HI (13.8 mg, 0.06 mmol), styrene (1 equiv, 0.3 mmol) and 20 μL of GC standard *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 °C for 48 h. After cooled down to rt, the reaction mixture was subjected to flash chromatography with ethyl acetate/ hexanes as eluent. The structure of the desired product was confirmed by ¹H NMR spectroscopy of the

purified sample, and ratio of isomers was determined by ^1H NMR spectroscopy of the reaction mixture after the reaction or GC and GCMS. 0.3 mmol of substituted styrene was used for isolation, unless stated otherwise. The reactions can also be conducted with standard Schlenk technique and a vacuum manifold.

(*E*)-trans-2-Styrylcyclopentanol (3a) [82537-31-3]

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as colorless oil. 43 mg, 77% yield. The *trans/cis* ratio was determined to be 10:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38-7.36 (m, 2H), 7.32-7.28 (m, 2H), 7.23-7.19 (m, 1H), 6.47 (d, $J = 15.8$ Hz, 1H), 6.14 (dd, $J = 15.8, 8.3$ Hz, 1H), 3.96 (ψq, $J = 7.0$ Hz, 1H), 2.53-2.45 (m, 1H), 2.09-1.96 (m, 2H), 1.82-1.50 (m, 5H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.4, 132.3, 130.5, 128.5, 127.2, 126.1, 78.7, 52.4, 33.6, 30.1, 21.3.

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{16}\text{O}$ M^+ : 188.1; found: 188.0.

(*E*)-trans-2-(4-Methylstyryl)cyclopentanol (3b)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:12) as

white solid. 50 mg, 82% yield. The *trans/cis* ratio was determined to be 7:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.25 (d, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 6.43 (d, $J = 15.8$ Hz, 1H), 6.07 (dd, $J = 15.8, 8.3$ Hz, 1H), 3.94 (ψq , $J = 7.0$ Hz, 1H), 2.50-2.42 (m, 1H), 2.32 (s, 3H), 2.06-1.94 (m, 2H), 1.82 (s, 1H), 1.81-1.48 (m, 4H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 136.9, 134.6, 131.2, 130.3, 129.2, 126.0, 78.7, 52.4, 33.6, 30.1, 21.3, 21.2.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ M^+ : 202.1; found: 202.1.

(*E*)-trans-2-(4-Methoxystyryl)cyclopentanol (3c)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as white solid. 48 mg, 73% yield. The *trans/cis* ratio was determined to be 8:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.29-7.27 (m, 2H), 6.84-6.82 (m, 2H), 6.40 (d, $J = 15.8$ Hz, 1H), 5.98 (dd, $J = 15.8, 8.3$ Hz, 1H), 3.93 (ψq , $J = 6.9$ Hz, 1H), 3.79 (s, 3H), 2.48-2.40 (m, 1H), 2.07-1.93 (m, 2H), 1.90 (s, 1H), 1.84-1.45 (m, 4H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 158.9, 130.2, 130.1, 129.8, 127.2,

114.0, 78.7, 55.3, 52.4, 33.6, 30.2, 21.2.

GC-MS (EI): Calcd for C₁₄H₁₈O₂ M⁺: 218.1; found: 218.0.

(*E*)-trans-2-(4-Acetoxyphenyl)cyclopentanol (3d)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as white solid. 48 mg, 65% yield. The *trans/cis* ratio was determined to be 9:1 by crude ¹H NMR spectroscopy.

¹H NMR of the major isomer (400 MHz, CDCl₃): δ 7.35 (d, *J* = 6.7 Hz, 2H), 7.02 (d, *J* = 6.7 Hz, 2H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.09 (dd, *J* = 15.8, 8.2 Hz, 1H), 3.94 (ψq, *J* = 7.0 Hz, 1H), 2.51-2.43 (m, 1H), 2.28 (s, 3H), 2.04-1.95 (m, 2H), 1.80-1.51 (m, 5H).

¹³C NMR of the major isomer (100 MHz, CDCl₃): δ 169.6, 149.8, 135.4, 132.7, 129.6, 127.1, 121.7, 78.8, 52.4, 33.8, 30.2, 21.4, 21.2.

GC-MS (EI): Calcd for C₁₅H₁₈O₃ M⁺: 246.1; found: 246.1.

(*E*)-trans-2-(3,4,5-Trimethoxyphenyl)cyclopentanol (3e)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:2) as white solid. 43 mg, 51% yield. The *trans/cis* ratio was determined to be 7:1 by crude ¹H NMR

spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 6.58 (s, 2H), 6.39 (d, $J = 15.7$ Hz, 1H), 6.06 (dd, $J = 15.7, 8.2$ Hz, 1H), 3.97 (ψq , $J = 7.1$ Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 2.52-2.44 (m, 1H), 2.06-1.96 (m, 2H), 1.83 (s, 1H), 1.82-1.62 (m, 3H), 1.56-1.50 (m, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 153.3, 137.5, 133.2, 131.8, 130.3, 103.1, 78.7, 60.9, 56.1, 52.2, 33.7, 30.1, 21.3.

MS (EI): Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_4$ M^+ : 278.2; found: 278.1.

(*E*)-trans-2-(2,5-dimethylstyryl)cyclopentanol (3f)

The product was isolated by flash chromatograph (ethyl acetate/hexanes 1:15) as colorless oil. 44 mg, 68% yield. The *trans/cis* ratio was determined to be 8:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.26 (s, 1H), 7.02 (d, $J = 7.6$ Hz, 1H), 6.95 (d, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 15.6$ Hz, 1H), 6.01 (dd, $J = 15.6, 8.4$ Hz, 1H), 3.97 (ψq , $J = 6.8$ Hz, 1H), 2.55-2.47 (m, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 2.08-1.98 (m, 2H), 1.87-1.52 (m, 5H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 136.3, 135.5, 133.4, 132.1, 130.3, 128.5, 128.0, 126.2, 78.9, 52.8, 33.7, 30.3, 21.4, 21.2, 19.5.

GC-MS (EI): Calcd for C₁₅H₂₀O M⁺: 216.2; found: 216.1.

(*E*)-trans-2-(3,4-Methylenedioxyphenyl)cyclopentanol (3g)

Cy₂NMe (105 μL, 0.45 mmol) was added as a base to increase the yield of product.

The product was isolated by flash chromatograph (ethyl acetate/hexanes 1:6) as colorless oil. 48 mg, 70% yield. The *trans/cis* ratio was determined to be 9:1 by GC.

¹H NMR of the major isomer (400 MHz, CDCl₃): δ 6.88 (d, *J* = 1.6 Hz, 1H), 6.77-6.70 (m, 2H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.93 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.91 (s, 2H), 3.91 (ψq, *J* = 7.0 Hz, 1H), 2.46-2.38 (m, 1H), 2.03-1.91 (m, 2H), 1.83 (s, 1H), 1.76-1.45 (m, 4H).

¹³C NMR of the major isomer (100 MHz, CDCl₃): δ 148.0, 146.8, 131.9, 130.5, 130.0, 120.5, 108.2, 105.5, 101.0, 78.7, 52.3, 33.6, 30.1, 21.2.

GC-MS (EI): Calcd for C₁₄H₁₆O₃ M⁺: 232.1; found: 232.0.

(*E*)-trans-2-(4-Methoxycarbonylstyryl)cyclopentanol (3h)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as colorless oil. 46 mg, 62% yield. The *trans/cis* ratio was determined to be 6:1 by crude

^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.96 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 15.9 Hz, 1H), 6.28 (dd, J = 15.9, 8.2 Hz, 1H), 3.99 (ψ q, J = 7.0 Hz, 1H), 3.90 (s, 3H), 2.56-2.48 (m, 1H), 2.09-1.96 (m, 2H), 1.86 (s, 1H), 1.85-1.50 (m, 4H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 167.0, 141.9, 135.3, 129.9, 129.6, 128.5, 125.9, 78.6, 52.4, 52.0, 33.8, 30.1, 21.4.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3$ M^+ : 246.1; found: 246.0.

(*E*)-*trans*-2-(4-Acetylstyryl)cyclopentanol (3i)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as white solid. 42 mg, 61% yield. The *trans/cis* ratio was determined to be 10:1 by crude ^1H NMR spectroscopy. Single crystals for X-ray diffraction were obtained by slow evaporation from a solution of 1:3 ethyl acetate/hexanes at room temperature. The relative configuration of the major isomer on cyclopentane was determined to be *trans* (CCDC: 1570943).

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.86 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 6.48 (d, J = 15.9 Hz, 1H), 6.30 (dd, J = 15.9, 8.2 Hz, 1H), 3.99 (ψ q, J = 6.9 Hz, 1H), 2.56 (s, 3H), 2.56-2.48 (m, 1H), 2.06-1.96 (m, 3H), 1.85-1.50 (m, 4H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 197.8, 142.3, 135.8, 129.6, 128.9, 126.2, 78.7, 52.5, 34.0, 30.2, 26.6, 21.5.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$ M^+ : 230.1; found: 230.0.

(*E*)-trans-2-(4-Trifluoromethylstyryl)cyclopentanol (3j)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as colorless oil. 60 mg, 78% yield. The *trans/cis* ratio was determined to be 7:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.55 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 6.50 (d, J = 15.8 Hz, 1H), 6.26 (dd, J = 15.8, 8.2 Hz, 1H), 4.00 (ψ q, J = 7.0 Hz, 1H), 2.57-2.49 (m, 1H), 2.08-1.98 (m, 2H), 1.87-1.77 (m, 1H), 1.74 (s, 1H), 1.73-1.61 (m, 2H), 1.57-1.52 (m, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 140.9, 135.1, 129.2, 128.9 (q, J_{CF} = 32.4 Hz), 126.2, 125.5 (q, J_{CF} = 3.8 Hz), 124.3 (q, J_{CF} = 271.7 Hz), 78.6, 52.3, 33.9, 30.0, 21.3.

^{19}F NMR (376.6 MHz, CDCl_3): δ -62.4.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{15}\text{F}_3\text{O}$ M^+ : 256.1; found: 256.0.

(*E*)-trans-2-(4-Cyanostyryl)cyclopentanol (3k)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as white solid. 44 mg, 69% yield. The *trans/cis* ratio was determined to be 6:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.55 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 8.3$ Hz, 2H), 6.46 (d, $J = 15.9$ Hz, 1H), 6.29 (dd, $J = 15.9, 8.1$ Hz, 1H), 3.98 (ψ q, $J = 6.9$ Hz, 1H), 2.56-2.48 (m, 1H), 2.07-1.96 (m, 2H), 1.82-1.78 (m, 2H), 1.73-1.50 (m, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 142.1, 136.8, 132.5, 129.0, 126.6, 119.2, 110.3, 78.7, 52.4, 34.1, 30.1, 21.5.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}$ M^+ : 213.1; found: 213.1.

(*E*)-trans-2-(4-Chlorostyryl)cyclopentanol (3l)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as colorless oil. 37 mg, 56% yield. The *trans/cis* ratio was determined to be 5:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.29-7.22 (m, 4H), 6.40 (d, $J = 15.8$ Hz, 1H), 6.10 (dd, $J = 15.8, 8.2$ Hz, 1H), 3.94 (ψq , $J = 7.0$ Hz, 1H), 2.50-2.42 (m, 1H), 2.07-1.93 (m, 2H), 1.81-1.74 (m, 2H), 1.72-1.56 (m, 2H), 1.52-1.45 (m, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 135.9, 133.0, 132.6, 129.2, 128.6, 127.3, 78.6, 52.3, 33.7, 30.1, 21.3.

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{15}^{35}\text{ClO}$ M^+ : 222.1; found: 222.0.

(*E*)-trans-2-[(β -Naphthyl)vinyl]cyclopentanol (3m)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as white solid. 41 mg, 58% yield. The *trans/cis* ratio was determined to be 6:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.80-7.76 (m, 3H), 7.70 (s, 1H), 7.59 (dd, $J = 8.6, 1.7$ Hz, 1H), 7.48-7.40 (m, 2H), 6.64 (d, $J = 15.8$ Hz, 1H), 6.27 (dd, $J = 15.8, 8.3$ Hz, 1H), 4.01 (ψq , $J = 7.0$ Hz, 1H), 2.59-2.51 (m, 1H), 2.08-2.0 (m, 2H), 1.88-1.58 (m, 5H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 135.0, 133.8, 132.9, 132.8, 130.7, 128.2, 128.0, 127.8, 126.3, 125.8, 125.7, 123.7, 78.9, 52.6, 33.8, 30.3, 21.5.

GC-MS (EI): Calcd for $\text{C}_{17}\text{H}_{18}\text{O}$ M^+ : 238.1; found: 238.0.

(*E*)-trans-2-[(*N*-benzylindol-3-yl)vinyl]cyclopentanol (3n)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as white solid. 40 mg, 42% yield. The *trans/cis* ratio was determined to be 5:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.86 (d, $J = 6.5$ Hz, 1H), 7.32-7.26 (m, 4H), 7.21-7.11 (m, 5H), 6.65 (d, $J = 16.0$ Hz, 1H), 6.08 (dd, $J = 16.0, 8.4$ Hz, 1H), 5.28 (s, 2H), 3.97 (ψ q, $J = 6.9$ Hz, 1H), 2.52-2.44 (m, 1H), 2.08-1.98 (m, 2H), 1.86-1.54 (m, 5H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.4, 137.3, 129.0, 128.9, 127.8, 127.0, 126.8, 126.5, 123.1, 122.4, 120.3, 120.1, 114.4, 110.0, 79.1, 53.4, 50.2, 33.5, 30.5, 21.3.

GC-MS (EI): Calcd for $\text{C}_{22}\text{H}_{23}\text{NO}$ M^+ : 317.2; found: 317.2.

***trans*-2-(2,2-Diphenylvinyl)cyclopentanol (3o)**

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as colorless oil. 72 mg, 90% yield. The *trans/cis* ratio was determined to be 10:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.37-7.33 (m, 2H), 7.30-7.17 (m, 8H), 5.89 (d, $J = 10.1$ Hz, 1H), 3.98 (ψq , $J = 6.6$ Hz, 1H), 2.54-2.46 (m, 1H), 1.99-1.93 (m, 1H), 1.88-1.82 (m, 1H), 1.68-1.62 (m, 2H), 1.54-1.43 (m, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 142.8, 142.5, 140.1, 132.0, 130.0, 128.3, 128.1, 127.2, 127.1, 127.0, 79.8, 48.9, 34.0, 31.4, 21.6.

GC-MS (EI): Calcd for $\text{C}_{19}\text{H}_{20}\text{O}$ M^+ : 264.2; found: 264.0.

***trans*-2-(2-Phenallyl)cyclopentanol (3p)**

Dppf (11.7 mg, 0.021 mmol) was used instead of Xantphos, and dioxane (1.2 mL) instead of PhCF_3 to increase the yield of products. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as colorless oil. 32 mg, 52% yield. Two isomers of terminal and internal alkenes were inseparable by silica and the ratio was determined to be 9:1 by GC.

^1H NMR of the terminal alkene isomer (400 MHz, CDCl_3): δ 7.43-7.40 (m, 2H), 7.35-7.31 (m, 2H), 7.29-7.26 (m, 1H), 5.29 (d, $J = 1.6$ Hz, 1H), 5.10 (d, $J = 1.6$ Hz, 1H), 3.89 (ψq , $J = 6.1$ Hz, 1H), 2.69 (dd, $J = 14.2, 5.4$ Hz, 1H), 2.41 (dd, $J = 14.2, 7.1$ Hz, 1H), 1.95-1.80 (m, 3H), 1.72-1.40 (m, 5H).

^{13}C NMR of the terminal alkene isomer (100 MHz, CDCl_3): δ 148.0, 141.2, 128.5, 127.6, 126.4, 113.5, 79.2, 46.6, 40.0, 34.5, 30.0, 21.7.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ M^+ : 202.1; found: 202.0.

(*E*)-2-Styrylcyclohexanol (4a and 4a') [865606-50-4 for *trans* isomer]

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as white solid. 52 mg, 85% yield. The *trans/cis* ratio was determined to be 3:1 by GC. The two isomers were separated by silica.

^1H NMR of *trans* isomer (400 MHz, CDCl_3): δ 7.37 (d, $J = 7.3$ Hz, 2H), 7.31 (ψt, $J = 7.5$ Hz, 2H), 7.22 (ψt, $J = 7.2$ Hz, 1H), 6.54 (d, $J = 15.9$ Hz, 1H), 6.08 (dd, $J = 15.9$, 8.8 Hz, 1H), 3.35 (ψtd, $J = 9.9$, 4.0 Hz, 1H), 2.09-2.06 (m, 2H), 1.94 (s, 1H), 1.82-1.72 (m, 3H), 1.34-1.27 (m, 4H).

^{13}C NMR of *trans* isomer (100 MHz, CDCl_3): δ 137.2, 132.3, 132.1, 128.7, 127.5, 126.3, 73.4, 50.7, 34.0, 31.6, 25.4, 25.0.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ M^+ : 202.1; found: 202.0.

^1H NMR of *cis* isomer (400 MHz, CDCl_3): δ 7.38 (d, $J = 7.3$ Hz, 2H), 7.31 (ψt, $J = 7.4$ Hz, 2H), 7.24-7.21 (m, 1H), 6.48 (d, $J = 16.2$ Hz, 1H), 6.35 (dd, $J = 16.2$, 7.0 Hz, 1H), 3.96-3.91 (m, 1H), 2.48-2.42 (m, 1H), 1.81-1.60 (m, 6H), 1.48-1.42 (m, 3H).

^{13}C NMR of *cis* isomer (100 MHz, CDCl_3): δ 137.6, 131.6, 131.3, 128.7, 127.4, 126.3, 70.1, 45.1, 32.5, 26.6, 24.4, 21.2.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ M^+ : 202.1; found: 202.1.

(*E*)-2-(4-Methoxystyryl)cyclohexanol (4b and 4b')

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as white solid. 49 mg, 70% yield. The *trans/cis* ratio was determined to be 2.7:1 by GC. The single crystals for X-ray diffraction were obtained by slow evaporation of a solution of 1:5 ethyl acetate/hexanes at rt. The configuration of the major isomer on cyclohexane was determined to be *trans* (CCDC: 1556727). The two isomers were separated by silica.

¹H NMR of *trans* isomer (400 MHz, CDCl₃): δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.46 (d, *J* = 15.9 Hz, 1H), 5.91 (dd, *J* = 15.9, 8.8 Hz, 1H), 3.80 (s, 3H), 3.30 (ψtd, *J* = 9.9, 4.0 Hz, 1H), 2.07-2.00 (m, 2H), 1.94 (s, 1H), 1.81-1.78 (m, 2H), 1.70-1.68 (m, 1H), 1.35-1.22 (m, 4H).

¹³C NMR of *trans* isomer (100 MHz, CDCl₃): δ 159.1, 131.5, 129.9, 129.8, 127.3, 114.0, 73.3, 55.3, 50.6, 33.8, 31.6, 25.3, 24.8.

GC-MS (EI): Calcd for C₁₅H₂₀O₂ M⁺: 232.2, found: 232.1.

¹H NMR of *cis* isomer (400 MHz, CDCl₃): δ 7.31 (d, *J* = 6.9 Hz, 2H), 6.84 (d, *J* = 6.9 Hz, 2H), 6.42 (d, *J* = 16.1 Hz, 1H), 6.22 (dd, *J* = 16.1, 7.1 Hz, 1H), 3.95-3.88 (m, 1H), 3.80 (s, 3H), 2.45-2.40 (m, 1H), 1.78-1.58 (m, 7H), 1.50-1.42 (m, 2H).

^{13}C NMR of *cis* isomer (100 MHz, CDCl_3): δ 159.2, 130.7, 130.4, 129.2, 127.4, 114.1, 70.1, 55.5, 45.0, 32.4, 26.7, 24.4, 21.2.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$ M^+ : 232.2; found: 232.2.

(*E*)-2-(3-Methylstyryl)cyclohexanol (4c and 4c')

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as foam. 52 mg, 80% yield. The *trans/cis* ratio was determined to be 3.2:1 by GC. The two isomers were separated by silica.

^1H NMR of *trans* isomer (400 MHz, CDCl_3): δ 7.22-7.16 (m, 3H), 7.04 (d, $J = 7.1$ Hz, 1H), 6.50 (d, $J = 15.9$ Hz, 1H), 6.06 (dd, $J = 15.9, 8.8$ Hz, 1H), 3.34 (ψtd, $J = 9.8, 4.4$ Hz, 1H), 2.34 (s, 3H), 2.08-2.05 (m, 2H), 1.91 (s, 1H), 1.83-1.79 (m, 2H), 1.72-1.70 (m, 1H), 1.37-1.25 (m, 4H).

^{13}C NMR of *trans* isomer (100 MHz, CDCl_3): δ 138.3, 137.2, 132.2, 132.1, 128.6, 128.3, 127.0, 123.5, 73.4, 50.8, 34.0, 31.6, 25.4, 25.0, 21.5.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{20}\text{O}$ M^+ : 216.2; found: 216.0.

^1H NMR of *cis* isomer (400 MHz, CDCl_3): δ 7.22-7.17 (m, 3H), 7.04 (d, $J = 6.7$ Hz, 1H), 6.45 (d, $J = 16.1$ Hz, 1H), 6.33 (dd, $J = 16.1, 6.9$ Hz, 1H), 3.94-3.90 (m, 1H), 2.47-2.42 (m, 1H), 2.34 (s, 3H), 1.80-1.58 (m, 7H), 1.50-1.36 (m, 2H).

^{13}C NMR of *cis* isomer (100 MHz, CDCl_3): δ 138.2, 137.5, 131.4, 131.3, 128.6, 128.2,

127.0, 123.5, 70.1, 45.1, 32.4, 26.6, 24.4, 21.5, 21.2.

GC-MS (EI): Calcd for $C_{15}H_{20}O$ M^+ : 216.2; found: 216.2.

(*E*)-2-(4-Acetylstyryl)cyclohexanol (4d and 4d')

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as white solid. 46 mg, 63% yield. The *trans/cis* ratio was determined to be 2.7:1 by GC. The two isomers were separated by silica.

^1H NMR of *trans* isomer (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 6.54 (d, J = 15.9 Hz, 1H), 6.26 (dd, J = 15.9, 8.6 Hz, 1H), 3.40-3.36 (m, 1H), 2.57 (s, 3H), 2.13-2.02 (m, 2H), 1.89 (s, 1H), 1.82-1.78 (m, 2H), 1.72-1.68 (m, 1H), 1.36-1.23 (m, 4H).

^{13}C NMR of *trans* isomer (100 MHz, $CDCl_3$): δ 197.7, 142.0, 135.9, 135.8, 130.8, 128.9, 126.3, 73.4, 50.6, 34.4, 31.4, 26.7, 25.2, 24.9.

GC-MS (EI): Calcd for $C_{16}H_{20}O_2$ M^+ : 244.2; found: 244.1.

^1H NMR of *cis* isomer (400 MHz, $CDCl_3$): δ 7.88 (d, J = 6.7 Hz, 2H), 7.43 (d, J = 6.7 Hz, 2H), 6.51-6.49 (m, 2H), 3.97-3.94 (m, 1H), 2.58 (s, 3H), 2.48-2.42 (m, 1H), 1.81-1.58 (m, 6H), 1.54 (s, 1H), 1.49-1.32 (m, 2H).

^{13}C NMR of *cis* isomer (100 MHz, $CDCl_3$): δ 197.7, 142.3, 135.8, 135.2, 130.0, 128.9,

126.3, 70.0, 45.3, 32.6, 26.7, 26.5, 24.4, 20.9.

GC-MS (EI): Calcd for $C_{16}H_{20}O_2$ M^+ : 244.2; found: 244.1.

2-(2,2-Diphenylvinyl)cyclohexanol (4e and 4e')

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as foam.

68 mg, 81% yield. The *trans/cis* ratio was determined to be 2.7:1 by GC. The two isomers were separated by silica.

^1H NMR of *trans* isomer (400 MHz, $CDCl_3$): δ 7.40-7.22 (m, 10H), 5.91 (d, J = 10.2 Hz, 1H), 3.40 (wtd, J = 9.5, 3.5 Hz, 1H), 2.22-2.12 (m, 1H), 2.02-1.95 (m, 1H), 1.71-1.60 (m, 4H), 1.31-1.08 (m, 4H).

^{13}C NMR of *trans* isomer (100 MHz, $CDCl_3$): δ 144.4, 142.4, 139.9, 131.8, 129.9, 128.3, 128.2, 127.2, 127.1, 74.5, 46.8, 33.8, 31.8, 24.9, 24.8.

LC-MS (ESI): Calcd for $C_{20}H_{22}O$ ($M+H$) $^+$: 279.2; found: 279.3.

^1H NMR of *cis* isomer (400 MHz, $CDCl_3$): δ 7.39-7.36 (m, 2H), 7.34-7.32 (m, 1H), 7.24-7.18 (m, 7H), 6.27 (d, J = 10.4 Hz, 1H), 3.84-3.79 (m, 1H), 2.47-2.41 (m, 1H), 1.77-1.62 (m, 4H), 1.50-1.34 (m, 4H), 1.28-1.23 (m, 1H).

^{13}C NMR of *cis* isomer (100 MHz, $CDCl_3$): δ 142.8, 140.5, 130.4, 129.9, 128.4, 128.2, 127.4, 127.2, 127.1, 70.9, 41.9, 32.5, 28.2, 23.9, 21.1.

LC-MS (ESI): Calcd for $C_{20}H_{22}O$ ($M+H$) $^+$: 279.2; found: 279.3.

(major)

(minor)

(*E*)-2-Styrylcycloheptanol (4f and 4f') [865606-51-5 for *trans* isomer]

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as foam. 47 mg, 80% yield. The *trans/cis* ratio was determined to be 4.5:1 by GC. The two isomers cannot be separated by silica.

^1H NMR of a mixture of *trans* and *cis* isomers (400 MHz, CDCl_3): δ 7.39-7.36 (m, 2.4H), 7.33-7.29 (m, 2.4H), 7.25-7.22 (m, 1.2H), 6.51-6.46 (m, 1.2H), 6.34 (dd, $J = 16.0, 8.0$ Hz, 0.2H of *cis* isomer), 6.13 (dd, $J = 15.9, 9.2$ Hz, 1H of *trans* isomer), 3.99-3.96 (m, 0.2H of *cis* isomer), 3.51 (ψtd, $J = 8.6, 3.6$ Hz, 1H of *trans* isomer), 2.62-2.57 (*cis* isomer, m, 0.2H), 2.21 (ψqd, $J = 9.3, 3.1$ Hz, 1H of *trans* isomer), 2.00-1.94 (m, 1.2H), 1.83 (d, $J = 1.7$ Hz, 1.2H), 1.78-1.47 (m, 10.8H).

^{13}C NMR of a mixture of *trans* and *cis* isomers (100 MHz, CDCl_3): δ 137.5 and 137.2, 133.9 and 132.1, 131.2 and 131.3, 128.7, 127.5 and 127.4, 126.4 and 126.3, 75.9 and 73.7, 52.9 and 48.6, 35.1 and 34.9, 30.5 and 28.5, 27.8 and 28.3, 26.1 and 25.9, 22.4 and 22.7.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{20}\text{O}$ M^+ : 216.2; found: 216.0.

Dimethyl (*E*)-*trans*-3-hydroxy-4-styrylcyclopentane-1,1-dicarboxylate (4g)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as colorless oil. 67 mg, 74% yield. The *trans/cis* ratio was determined to be 11:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.36-7.33 (m, 2H), 7.31-7.27 (m, 2H), 7.23-7.19 (m, 1H), 6.49 (d, $J = 15.8$ Hz, 1H), 6.09 (dd, $J = 15.8, 7.6$ Hz, 1H), 4.03 (ψq, $J = 6.9$ Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.71-2.64 (m, 3H), 2.30-2.22 (m, 2H), 2.13-2.06 (m, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 173.1, 172.6, 137.1, 131.8, 129.9, 128.7, 127.5, 126.3, 77.1, 57.0, 53.2, 53.0, 51.4, 41.4, 37.7.

LC-MS (ESI): Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 305.1; found: 305.2.

(*E*)-*trans*-4-Styryltetrahydrofuran-3-ol (4h)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:2) as white solid. 45 mg, 79% yield. The *trans/cis* ratio was determined to be 15:1 by crude ^1H NMR spectroscopy. The two isomers cannot be separated by silica.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.37-7.29 (m, 4H), 7.26-7.23 (m, 1H), 6.53 (d, $J = 15.8$ Hz, 1H), 6.10 (dd, $J = 15.8, 8.7$ Hz, 1H), 4.31-4.27 (m, 1H), 4.19 (dd, $J = 8.8, 7.0$ Hz, 1H), 4.01 (dd, $J = 9.7, 5.2$ Hz, 1H), 3.76 (dd, $J = 9.7, 3.4$ Hz, 1H), 3.72 (dd, $J = 8.8, 5.8$ Hz, 1H), 2.94-2.90 (m, 1H), 1.89 (s, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.0, 132.2, 128.8, 128.1, 127.7,

126.3, 77.9, 74.5, 72.1, 52.5.

GC-MS (EI): Calcd for C₁₂H₁₄O₂ M⁺: 190.1; found: 190.0.

The (+)-*trans*-limonene oxide **1c** [6909-30-4] was prepared by kinetic resolution of two (+)-limonene oxide isomers (from Aldrich) with pyrazole according to a reported process.⁴¹ ¹H NMR of **1c** (400 MHz, CDCl₃): δ 4.66 (s, 2H), 2.99 (ψd, *J* = 4.1 Hz, 1H), 2.05-2.02 (m, 2H), 1.92-1.86 (m, 1H), 1.75-1.72 (m, 2H), 1.71 (s, 3H), 1.40-1.36 (m, 2H), 1.32 (s, 3H). GC-MS (EI): Calcd for C₁₀H₁₆O M⁺: 152.1; found: 152.1.

The products were isolated by flash chromatography (ethyl acetate/hexanes 1:25) as colorless oil. 46 mg, 60% combined yield. The *cis/trans* ratio was determined to be 3:1 by GC. The two isomers were separated by silica. We detected a stronger cross-signal between hydrogens H² and H⁴ in the major isomer and hence assigned it *cis* configuration with respect to the alcohol group.

Major *cis* isomer:

(1*S*,2*S*,4*R*)-1-Methyl-4-(2-propenyl)-(2*E*)-styrylcyclohexanol (4i)

¹H NMR (400 MHz, CDCl₃): δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.31 (ψt, *J* = 7.3 Hz, 2H), 7.26-7.20 (m, 1H), 6.44 (d, *J* = 16.1 Hz, 1H), 6.35 (dd, *J* = 16.1, 8.2 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 2H), 2.22-2.16 (m, 1H), 2.15-1.97 (m, 1H), 1.82 (ψdt, *J* = 13.2, 2.4 Hz, 1H), 1.77 (s, 3H), 1.67-1.59 (m, 4H), 1.54-1.49 (m, 1H), 1.30 (s, 1H), 1.24 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 150.0, 137.7, 131.5, 131.2, 128.6, 127.2, 126.2, 108.8, 70.6, 50.4, 44.9, 40.0, 33.4, 29.6, 26.9, 21.1.

LC-MS (ESI): Calcd for $\text{C}_{18}\text{H}_{24}\text{ONa}$ ($\text{M}+\text{Na}$) $^+$: 279.2; found: 279.2.

$[\alpha]_D^{23} = +17.5^\circ$ ($c = 1.80$, CHCl_3).

Minor *trans* isomer:

(1*R*,2*R*,4*R*)-1-Methyl-4-(2-propenyl)-(2*E*)-styrylcyclohexanol (4i')

^1H NMR (400 MHz, CDCl_3): δ 7.38 (d, $J = 7.1$ Hz, 2H), 7.33 (ψ t, $J = 7.1$ Hz, 2H), 7.24-7.20 (m, 1H), 6.47 (d, $J = 15.7$ Hz, 1H), 6.32 (dd, $J = 15.7, 9.4$ Hz, 1H), 4.75 (s, 2H), 2.49-2.45 (m, 1H), 2.26-2.18 (m, 1H), 2.04 (ψ td, $J = 12.3, 4.3$ Hz, 1H), 1.74 (s, 3H), 1.72-1.59 (m, 5H), 1.40 (s, 1H), 1.19 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.6, 137.7, 131.6, 131.0, 128.7, 127.4, 126.3, 109.2, 71.5, 50.0, 38.8, 35.5, 33.2, 29.0, 26.8, 21.3.

LC-MS (ESI): Calcd for $\text{C}_{18}\text{H}_{24}\text{ONa}$ ($\text{M}+\text{Na}$) $^+$: 279.2; found: 279.2.

$[\alpha]_D^{23} = +6.7^\circ$ ($c = 0.80$, CHCl_3).

(major)

(minor)

A mixture of epoxide isomers ($\alpha:\beta$ 6:94) was prepared from pregnenolone acetate (Aldrich) with KMnO_4 and $\text{CuSO}_4(5\text{H}_2\text{O})$.⁴² **3 β -Acetoxy-5 β ,6 β -epoxypregnan-20-one (1d) [6661-94-5]** ^1H NMR (400 MHz, CDCl_3): δ 4.80-4.74 (m, 1H), 3.08 (ψ d, $J =$

2.1 Hz, 1H), 2.48 (ψt, $J = 8.9$ Hz, 1H), 2.17-2.11 (m, 2H), 2.10 (s, 3H), 2.03 (s, 3H), 2.01-1.95 (m, 2H), 1.85-1.82 (m, 1H), 1.70-1.62 (m, 2H), 1.49-1.18 (m, 10H), 1.07-1.03 (m, 1H), 1.00 (s, 3H), 0.71-0.64 (m, 1H), 0.59 (s, 3H). GC-MS (EI): Calcd for $C_{23}H_{34}O_4$ M^+ : 374.2; found: 374.2.

The reaction runs on 0.2 mmol scale. The two isomers of the Heck product were separated by flash chromatography (ethyl acetate/hexanes 1:4) as white solid. 50 mg, 53% combined yield. The ratio of α - and β -isomers in the crude mixture was determined to be 2.3:1 by ^1H NMR spectroscopy. The configuration of major α -isomers in Ring B was assigned by detection of a strong NOE signal between H(6) and $CH_3(19)$. The chemical shift of $CH_3(19)$ was assigned by comparison with chemical shifts in pregnenolone acetate.⁴³

Major isomer: **(3*S*,5*R*,6*R*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-Acetyl-5-hydroxy-10,13-dimethyl-6-((*E*)-styryl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ylacetate (4j)**

^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 2H), 7.29 (ψt, $J = 7.6$ Hz, 2H), 7.21-7.17 (m, 1H), 6.38-6.36 (m, 2H), 5.24-5.22 (m, 1H), 2.86 (s, 1H), 2.69-2.63 (m, 1H), 2.54 (ψt, $J = 9.2$ Hz, 1H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 2.10-2.04 (m, 2H), 1.78-1.51 (m, 8H), 1.48-1.20 (m, 8H), 1.04 (s, 3H), 0.64 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5, 169.7, 137.9, 131.3, 130.6, 128.6, 127.2, 126.3, 75.8, 71.0, 63.8, 56.9, 44.4, 44.3, 43.3, 41.2, 39.1, 34.5, 33.7, 31.6, 31.5, 26.0, 24.6, 24.4, 23.1, 21.8, 21.7, 17.2, 13.6.

HRMS (ESI): Calcd for $C_{31}H_{43}O_4$ ($M+H$) $^+$: 479.3161; found: 479.3163.

$[\alpha]_D^{23} = +45.1^\circ$ ($c = 0.30$, CHCl_3).

Minor isomer:

(3*S*,5*R*,6*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-Acetyl-5-hydroxy-10,13-dimethyl-6-((*E*)-styryl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (4*j'*)

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.37 (m, 2H), 7.34 (pt, $J = 7.4$ Hz, 2H), 7.25-7.21 (m, 1H), 6.58-6.56 (m, 2H), 5.04-4.95 (m, 1H), 3.70 (s, 1H), 2.58-2.53 (pt, $J = 9.3$ Hz, 1H), 2.26-2.17 (m, 2H), 2.13 (s, 3H), 2.09-2.04 (m, 2H), 2.01 (s, 3H), 1.85-1.82 (m, 2H), 1.66-1.58 (m, 5H), 1.52-1.47 (m, 5H), 1.30 (s, 3H), 1.28-1.20 (m, 4H), 0.66 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 209.6, 170.8, 138.0, 134.5, 130.0, 128.8, 127.5, 126.3, 77.8, 71.0, 63.9, 56.6, 47.6, 46.4, 44.6, 39.3, 37.8, 35.0, 34.6, 32.9, 31.7, 30.6, 29.9, 26.7, 24.5, 23.0, 21.6, 18.1, 13.9.

HRMS (ESI): Calcd for $\text{C}_{31}\text{H}_{43}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 479.3161; found: 479.3159.

$[\alpha]_D^{23} = +19.9^\circ$ ($c = 0.30$, CHCl_3).

(1*E*,3*E*)-trans-2-[4-Phenylbuta-1,3-dien-1-yl]cyclopentanol (6a)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as white solid. 34 mg, 53% yield. The *trans/cis* ratio was determined to be 10:1 by GC.

^1H NMR of the all *trans* isomer (400 MHz, CDCl_3): δ 7.39-7.37 (m, 2H), 7.32-7.29 (m, 2H), 7.23-7.19 (m, 1H), 6.76 (dd, $J = 15.6, 10.4$ Hz, 1H), 6.49 (d, $J = 15.6$ Hz, 1H),

6.30 (dd, $J = 15.2, 10.4$ Hz, 1H), 5.75 (dd, $J = 15.2, 8.3$ Hz, 1H), 3.92 (ψq, $J = 6.9$ Hz, 1H), 2.47-2.39 (m, 1H), 2.06-1.94 (m, 2H), 1.82-1.58 (m, 4H), 1.50-1.45 (m, 1H).

^{13}C NMR of the all *trans* isomer (100 MHz, CDCl_3): δ 137.6, 137.0, 131.2, 131.1, 129.1, 128.7, 127.4, 126.4, 78.9, 52.3, 33.8, 30.2, 21.4.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{18}\text{O}$ M^+ : 214.1; found: 214.1.

(1E,3E)-trans-2-[3-Methyl-4-phenylbuta-1,3-dien-1-yl]cyclopentanol (6b)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as white solid. 41 mg, 60% yield. The isomeric ratio was determined to be 10:1 by GC.

^1H NMR of the all *trans* isomer (400 MHz, CDCl_3): δ 7.36-7.32 (m, 2H), 7.29-7.26 (m, 2H), 7.23-7.19 (m, 1H), 6.47 (s, 1H), 6.34 (d, $J = 15.6$ Hz, 1H), 5.69 (dd, $J = 15.6, 8.3$ Hz, 1H), 3.92 (ψq, $J = 7.1$ Hz, 1H), 2.48-2.40 (m, 1H), 2.05-1.96 (m, 2H), 2.00 (s, 3H), 1.79-1.46 (m, 5H).

^{13}C NMR of the all *trans* isomer (100 MHz, CDCl_3): δ 138.1, 136.1, 135.6, 131.7, 130.3, 129.3, 128.2, 126.5, 79.0, 52.5, 33.8, 30.5, 21.4, 14.1.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{20}\text{O}$ M^+ : 228.2; found: 228.1.

(major)

(minor)

(Z)-Ethyl 3-(2-hydroxycyclopentyl)-2-phenylacrylate (6c and 6c')

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as colorless oil. 36 mg, 46% yield. The *trans/cis* ratio was determined to be 2.6:1 by GC. The two isomers were separated on silica. The Z configuration of both isomers was established by NOE signals between the olefinic hydrogen and ortho hydrogens of phenyl group.

Major isomer:

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.31 (m, 3H), 7.23-7.20 (m, 2H), 6.89 (d, $J = 10.6$ Hz, 1H), 4.20 (ψq, $J = 7.1$ Hz, 2H), 4.10-4.03 (m, 1H), 2.54-2.45 (m, 1H), 2.03-1.96 (m, 1H), 1.89-1.81 (m, 1H), 1.73-1.65 (m, 2H), 1.58-1.47 (m, 2H), 1.39 (s, 1H), 1.25 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.3, 146.6, 135.5, 135.1, 130.0, 128.1, 127.6, 79.4, 61.1, 48.6, 34.5, 31.0, 21.9, 14.4.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ M^+ : 260.1; found: 260.1.

Minor isomer:

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.29 (m, 5H), 6.06 (d, $J = 9.9$ Hz, 1H), 4.34-4.28 (m, 2H), 4.02-3.96 (m, 1H), 3.18 (d, $J = 3.0$ Hz, 1H), 2.98-2.89 (m, 1H), 2.12-2.02 (m, 2H), 1.82-1.63 (m, 3H), 1.52-1.46 (m, 1H), 1.31 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 169.1, 143.1, 137.6, 135.9, 128.5, 127.9, 127.4, 79.4, 61.5, 49.6, 34.5, 31.9, 22.4, 14.3.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ M^+ : 260.1; found: 260.1.

(major)

(minor)

(Z)-N,N-Diethyl-3-(2-hydroxycyclopentyl)-2-phenylacrylamide (6d and 6d')

Cy₂NMe (105 µL, 0.45 mmol) was added as a base to increase the yield of products.

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:2) as oil. 46 mg, 53% yield. The *trans/cis* ratio was determined to be 3:1 by crude ¹H NMR spectroscopy. The two isomers were separated by silica. The Z configuration of both isomers was established by NOE signals between the olefinic hydrogen and ortho hydrogens of phenyl group.

Major isomer:

¹H NMR (400 MHz, CDCl₃): δ 7.35-7.30 (m, 4H), 7.28-7.25 (m, 1H), 5.92 (d, *J* = 10.0 Hz, 1H), 4.34 (br s, OH), 3.89 (ψq, *J* = 6.8 Hz, 1H), 3.69 (dq, *J* = 13.6, 7.1 Hz, 1H), 3.34 (dq, *J* = 13.6, 7.1 Hz, 1H), 3.21 (dq, *J* = 14.5, 7.1 Hz, 1H), 3.08 (dq, *J* = 14.5, 7.1 Hz, 1H), 2.50-2.42 (m, 1H), 2.07-1.95 (m, 2H), 1.80-1.52 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 170.6, 139.4, 136.4, 134.1, 129.0, 128.0, 125.5, 78.1, 49.9, 43.1, 39.4, 34.2, 31.6, 22.3, 14.0, 12.9.

GC-MS (EI): Calcd for C₁₈H₂₅NO₂ M⁺: 287.2; found: 287.2.

Minor isomer (containing a small amount of the major isomer):

¹H NMR (400 MHz, CDCl₃): δ 7.37-7.25 (m, 5H), 6.06 (d, *J* = 9.4 Hz, 1H), 4.26 (ψq, *J* = 5.8 Hz, 1H), 3.59 (dq, *J* = 13.6, 7.1 Hz, 1H), 3.44 (dq, *J* = 13.6, 7.1 Hz, 1H), 3.25-3.11 (m, 2H), 2.70-2.63 (m, 1H), 1.98-1.82 (m, 2H), 1.77-1.58 (m, 5H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.1, 139.4, 136.6, 128.9, 127.9, 125.6, 76.2, 45.9, 42.9, 39.0, 30.5, 22.3, 14.0, 12.9.

GC-MS (EI): Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2$ M^+ : 287.2; found: 287.2.

(Z)-3-(2-Hydroxycyclopentyl)-1-morpholino-2-phenylprop-2-en-1-one (6e and 6e')

Dioxane (1.2 mL) was used instead of PhCF_3 . The product was isolated by flash chromatography (ethyl acetate/hexanes 2:1) as colorless oil. 44 mg, 49% yield. The *trans/cis* ratio on the cyclopentane ring was determined to be 1.9:1 by GC. The *Z* configuration of both isomers was established by NOE signals between the olefinic hydrogen and ortho hydrogens of phenyl group.

Major isomer:

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.28 (m, 5H), 6.00 (d, $J = 10.1$ Hz, 1H), 3.92 (ψq , $J = 7.4$ Hz, 1H), 3.87-3.79 (m, 1H), 3.74-3.66 (m, 3H), 3.41 (ψt , $J = 4.8$ Hz, 2H), 3.34-3.20 (m, 2H), 2.55-2.46 (m, 1H), 2.10-1.96 (m, 2H), 1.85-1.48 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 169.5, 138.1, 136.0, 135.0, 129.1, 128.3, 125.6, 78.3, 67.0, 66.9, 49.9, 47.3, 42.2, 34.2, 31.5, 22.2.

GC-MS (EI): Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3$ M^+ : 301.2; found: 301.2.

Minor isomer:

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.31 (m, 4H), 7.29-7.26 (m, 1H), 6.19 (d, $J = 9.8$ Hz, 1H), 4.27 (ψ q, $J = 4.5$ Hz, 1H), 3.79-3.75 (m, 2H), 3.72-3.69 (m, 2H), 3.47-3.35 (m, 2H), 3.34-3.26 (m, 2H), 2.70-2.60 (m, 2H), 2.00-1.82 (m, 3H), 1.78-1.59 (m, 3H).
 ^{13}C NMR (100 MHz, CDCl_3): δ 169.4, 137.9, 136.0, 131.7, 129.0, 128.2, 125.6, 76.3, 67.0, 47.1, 46.2, 42.0, 34.5, 30.5, 29.9, 22.4.

GC-MS (EI): Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3$ M^+ : 301.2; found: 301.2.

(major)

(minor)

3-(2-Hydroxycyclopentyl)coumarin (6f and 6f')

Cy_2NMe (105 μL , 0.45 mmol, 1.5 equiv) was added to the standard conditions. Without it, the combined yield was only 37%.

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:3) as white solid. 47 mg, 68% yield. The *trans/cis* ratio was determined to be 3.5:1 by GC. The C3 alkylation of coumarin in both isomers was determined by X-ray diffraction of both isomers. The two isomers were separated on silica.

The relative configuration of the major isomer was determined to be *trans* on cyclopentane ring by X-ray diffraction (CCDC: 1816547). Single crystals suitable for X-ray diffraction were obtained by slow evaporation from a solution of 1:2 dichloromethane/ hexanes at room temperature.

^1H NMR of *trans* isomer (400 MHz, CDCl_3): δ 7.53 (s, 1H), 7.50-7.45 (m, 2H), 7.34-7.25 (m, 2H), 4.20-4.16 (m, 1H), 3.39 (s, 1H), 3.03-2.98 (m, 1H), 2.14-1.99 (m, 2H), 1.93-1.74 (m, 4H).

^{13}C NMR of *trans* isomer (100 MHz, CDCl_3): δ 163.2, 152.9, 137.4, 131.1, 131.0, 127.6, 124.7, 119.5, 116.6, 77.9, 50.9, 34.9, 29.6, 23.4.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$ M^+ : 230.1; found: 230.1.

The relative configuration of the minor isomer on cyclopentane ring was determined to be *cis* (CCDC: 1815718). Single crystals suitable for X-ray diffraction were obtained by slow evaporation from a solution of 1:2 ethyl acetate/ hexanes at room temperature.

^1H NMR of *cis* isomer (400 MHz, CDCl_3): δ 7.64 (s, 1H), 7.49-7.46 (m, 2H), 7.32-7.24 (m, 2H), 4.62-4.57 (m, 1H), 3.19-3.12 (m, 1H), 2.16-1.86 (m, 4H), 1.82-1.65 (m, 2H), 1.54-1.51 (m, 1H).

^{13}C NMR of *cis* isomer (100 MHz, CDCl_3): δ 162.4, 153.1, 139.8, 130.9, 128.3, 127.6, 124.5, 119.6, 116.5, 73.8, 46.6, 34.9, 27.0, 22.0.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$ M^+ : 230.1; found: 230.1.

(major)

(minor)

3-(2-Hydroxycyclopentyl)-6-methylcoumarin (6g and 6g')

Cy_2NMe (105 μL , 0.45 mmol) was added as a base to increase the yield of products.

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as white

solid. 59 mg, 80% yield. The *trans/cis* ratio was determined to be 2.8:1 by GC. The two isomers were separated on silica. The relative configuration of the major isomer on cyclopentane ring was determined to be *trans* (CCDC: 1816494). Single crystals suitable for X-ray diffraction were obtained by slow evaporation from a solution of 1:2 ethyl acetate/ hexanes at room temperature.

^1H NMR of *trans* isomer (400 MHz, CDCl_3): δ 7.47 (s, 1H), 7.29-7.26 (m, 1H), 7.24-7.20 (m, 2H), 4.18-4.14 (m, 1H), 3.45 (s, 1H), 3.02-2.96 (m, 1H), 2.39 (s, 3H), 2.13-2.06 (m, 1H), 2.04-1.97 (m, 1H), 1.92-1.85 (m, 1H), 1.83-1.74 (m, 3H).

^{13}C NMR of *trans* isomer (100 MHz, CDCl_3): δ 163.5, 151.0, 137.4, 134.4, 132.1, 130.8, 127.4, 119.2, 116.2, 78.0, 50.9, 34.9, 29.6, 23.4, 20.9.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3$ M^+ : 244.1; found: 244.1.

^1H NMR of *cis* isomer (400 MHz, CDCl_3): δ 7.58 (s, 1H), 7.28-7.25 (m, 2H), 7.21-7.18 (m, 1H), 4.59-4.55 (m, 1H), 3.17-3.11 (m, 1H), 2.39 (s, 3H), 2.15-1.85 (m, 4H), 1.81-1.61 (m, 2H), 1.57 (s, 1H).

^{13}C NMR of *cis* isomer (100 MHz, CDCl_3): δ 162.7, 151.2, 139.8, 134.2, 131.9, 128.1, 127.5, 119.3, 116.2, 73.7, 46.6, 34.8, 27.0, 22.0, 20.9.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3$ M^+ : 244.1; found: 244.1.

(major)

(minor)

3-(2-Hydroxycyclopentyl)-*N*-methyl-2-quinolinone (6h and 6h')

Cy₂NMe (105 μ L, 0.45 mmol) was added as a base to increase the yield of products.

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:3) as light yellow oil. 38 mg, 52% yield. The *trans/cis* ratio was determined to be 2.5:1 by GC.

The two isomers were separated on silica.

¹H NMR of *trans* isomer (400 MHz, CDCl₃): δ 7.57 (s, 1H), 7.55-7.52 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.28-7.24 (m, 1H), 5.01 (s, 1H), 4.04-3.99 (m, 1H), 3.78 (s, 3H), 3.19-3.14 (m, 1H), 2.07-1.80 (m, 5H), 1.70 (br s, OH).

¹³C NMR of *trans* isomer (100 MHz, CDCl₃): δ 164.4, 138.7, 135.1, 133.3, 130.0, 128.6, 122.6, 120.9, 114.2, 78.8, 51.0, 35.0, 30.1, 29.6, 23.8.

GC-MS (EI): Calcd for C₁₅H₁₇NO₂ M⁺: 243.1; found: 243.1.

¹H NMR of *cis* isomer (400 MHz, CDCl₃): δ 7.65 (s, 1H), 7.57-7.52 (m, 2H), 7.36 (d, J = 8.3 Hz, 1H), 7.24-7.22 (m, 1H), 4.59-4.56 (m, 1H), 3.76 (s, 3H), 3.34-3.28 (m, 1H), 2.31 (br s, OH), 2.18-1.95 (m, 3H), 1.89-1.66 (m, 3H).

¹³C NMR of *cis* isomer (100 MHz, CDCl₃): δ 163.4, 139.1, 136.7, 132.3, 130.0, 128.6, 122.4, 120.8, 114.1, 74.6, 47.6, 34.8, 30.1, 27.3, 22.2.

GC-MS (EI): Calcd for C₁₅H₁₇NO₂ M⁺: 243.1; found: 243.1.

1.5.4 A Typical Procedure for Product Isolation of Heck-Type Reaction of Acyclic Epoxides

In an argon-filled glove box, Pd(PPh₃)₄ (17.4 mg, 0.015 mmol), dppf (11.7 mg, 0.021 mmol) and dry dioxane (1.2 mL) were charged into a dry 10 mL of Schlenk tube. After stirring at rt for 10 min, acyclic epoxide (0.6 mmol), NEt₃·HI (13.8 mg, 0.06

mmol), styrene (35 μ L, 0.3 mmol) and 20 μ L of GC standard *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 $^{\circ}$ C for 48 h. After cooled down to rt, the reaction mixture was subjected to flash chromatography with ethyl acetate/ hexanes as eluent. The structure of the desired product was confirmed by ^{1} H NMR spectroscopy of the purified sample, and the *trans/cis* ratio was determined by ^{1} H NMR spectroscopy of the crude reaction mixture or GC and GCMS. 0.3 mmol of styrene was used for all the isolation, unless stated otherwise. The reactions can also be conducted with standard Schlenk technique and a vacuum manifold.

(*E*)-1,5-Diphenylpent-4-en-2-ol (5a)

A racemic epoxide was used. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as light yellow oil. 46 mg, 64% yield. The ratio of regioisomers was determined to be 11:1 by crude ^{1} H NMR spectroscopy.

^{1} H NMR of the major isomer (400 MHz, CDCl_3): δ 7.35-7.25 (m, 6H), 7.23-7.17 (m, 4H), 6.47 (d, J = 15.9 Hz, 1H), 6.24 (ψ dt, J = 15.9, 7.3 Hz, 1H), 3.94 (m, 1H), 2.84 (dd, J = 13.6, 4.9 Hz, 1H), 2.74 (dd, J = 13.6, 8.0 Hz, 1H), 2.46-2.44 (m, 1H), 2.40-2.32 (m, 1H), 1.71 (s, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 138.5, 137.4, 133.3, 129.6, 128.7, 128.6, 127.4, 126.7, 126.3, 126.2, 72.3, 43.6, 40.6.

GC-MS (EI): Calcd for $\text{C}_{17}\text{H}_{18}\text{O}$ M^+ : 238.1; found: 238.0.

(*E*)-6-Phenylhex-5-en-3-ol (5b) [54985-35-2]

Veratrole (1.2 mL) was used instead of dioxane to increase the yield of product.

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as light yellow oil. 40 mg, 76% yield. The ratio of regioisomers was determined to be 9:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38-7.36 (m, 2H), 7.32-7.29 (m, 2H), 7.24-7.22 (m, 1H), 6.49 (d, $J = 15.8$ Hz, 1H), 6.26 (ψ dt, $J = 15.8, 6.9$ Hz, 1H), 3.70-3.64 (m, 1H), 2.50-2.43 (m, 1H), 2.33-2.29 (m, 1H), 1.64 (s, 1H), 1.62-1.51 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.4, 133.2, 128.7, 127.4, 126.6, 126.2, 72.7, 40.8, 29.8, 10.1.

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{16}\text{O}$ M^+ : 176.1; found: 176.1.

(*E*)-1-Phenyloct-1-en-4-ol (5c) [1488206-39-8]

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as light yellow oil. 43 mg, 70% yield. The ratio of regioisomers was determined to be 12:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.39-7.36 (m, 2H), 7.33-7.29 (m, 2H), 7.24-7.20 (m, 1H), 6.49 (d, $J = 15.8$ Hz, 1H), 6.23 (ψ dt, $J = 15.8, 6.9$ Hz, 1H),

3.76-3.70 (m, 1H), 2.46-2.42 (m, 1H), 2.35-2.30 (m, 1H), 1.66 (s, 1H), 1.52-1.34 (m, 6H), 0.93 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.4, 133.2, 128.6, 127.4, 126.5, 126.2, 71.3, 41.3, 36.8, 28.0, 22.8, 14.2.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{20}\text{O}$ M^+ : 204.2; found: 204.0.

(*E*)-1-Phenyldec-1-en-4-ol (5d)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:15) as light yellow oil. 43 mg, 62% yield. The ratio of regioisomers was determined to be 8:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38-7.36 (m, 2H), 7.32-7.28 (m, 2H), 7.23-7.20 (m, 1H), 6.49 (d, $J = 15.8$ Hz, 1H), 6.24 (ψdt, $J = 15.8, 7.2$ Hz, 1H), 3.76-3.70 (m, 1H), 2.48-2.42 (m, 1H), 2.35-2.28 (m, 1H), 1.55-1.50 (m, 4H), 1.36-1.27 (m, 7H), 0.89 (t, $J = 5.7$ Hz, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.5, 133.3, 128.7, 127.4, 126.6, 126.3, 71.4, 41.3, 37.1, 32.0, 29.5, 25.8, 22.8, 14.2.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{24}\text{O}$ M^+ : 232.2; found: 231.9.

(*4E*)-2-Methyl-5-phenylpent-4-en-2-ol (5e)

Cy_2NMe (105 μL , 0.45 mmol) was added as a base to increase the yield of product.

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as colorless oil. 27.5 mg, 52% yield. The ratio of regioisomers in the crude mixture was determined to be 12:1 by GC. The two isomers were separated by silica.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38 (d, $J = 7.8$ Hz, 2H), 7.33-7.29 (m, 2H), 7.24-7.22 (m, 1H), 6.47 (d, $J = 15.8$ Hz, 1H), 6.31 (dt, $J = 15.8, 7.5$ Hz, 1H), 2.39 (d, $J = 7.5$ Hz, 2H), 1.49 (s, 1H), 1.28 (s, 6H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.5, 133.9, 128.7, 127.4, 126.3, 125.9, 71.1, 47.5, 29.4.

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{16}\text{O}$ M^+ : 176.1; found: 176.1.

8-Cinnamyl-1,4-dioxaspiro[4.5]decan-8-ol (5f)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as colorless oil. 49 mg, 60% yield. The ratio of regioisomers was determined to be 20:1 by GC.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38-7.28 (m, 4H), 7.25-7.21 (m, 1H), 6.47 (d, $J = 15.8$ Hz, 1H), 6.29 (dt, $J = 15.8, 7.4$ Hz, 1H), 3.96-3.94 (m, 4H), 2.39 (d, $J = 7.5$ Hz, 2H), 1.96-1.88 (m, 2H), 1.74-1.70 (m, 3H), 1.64-1.58 (m, 3H), 1.39 (br s, OH).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.3, 134.3, 128.7, 127.5, 126.3, 125.0, 108.9, 70.7, 64.4, 64.3, 46.2, 35.0, 30.7.

GC-MS (EI): Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3$ M^+ : 274.2; found: 274.2.

1,5,5-Triphenylpent-4-en-2-ol (5g)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as light yellow oil. 71 mg, 75% yield. The ratio of regioisomers in the crude mixture was determined to be 20:1 by ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.36-7.13 (m, 15H), 6.19 (wt, J = 7.4 Hz, 1H), 3.93-3.87 (m, 1H), 2.78 (dd, J = 13.6, 4.5 Hz, 1H), 2.64 (dd, J = 13.6, 8.3 Hz, 1H), 2.38-2.34 (m, 2H), 1.69 (s, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 144.0, 142.4, 139.8, 138.3, 129.8, 129.3, 128.5, 128.2, 128.0, 127.2, 127.1, 127.0, 126.4, 125.2, 72.7, 43.4, 37.0.

GC-MS (EI): Calcd for $\text{C}_{23}\text{H}_{22}\text{O}$ M^+ : 314.2; found: 314.1.

2-Methyl-5,5-diphenylpent-4-en-2-ol (5h)

Veratrole (1.2 mL) was used instead of dioxane to increase the yield of product.

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as light yellow oil. 48 mg, 64% yield. The ratio of regioisomers was determined to be 12:1 by crude ^1H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38-7.34 (m, 2H), 7.32-7.17 (m, 8H), 6.23 (t, J = 7.6 Hz, 1H), 2.31 (d, J = 7.6 Hz, 2H), 1.38 (s, 1H), 1.22 (s, 6H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 144.1, 142.7, 140.0, 130.0, 128.2,

128.1, 127.2, 127.1, 127.0, 125.0, 71.4, 43.6, 29.4.

GC-MS (EI): Calcd for C₁₈H₂₀O M⁺: 252.2; found: 252.0.

6,6-Diphenylhex-5-en-3-ol (5i)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as light yellow oil. 53 mg, 70% yield. The ratio of regioisomers was determined to be 16:1 by crude ¹H NMR spectroscopy.

¹H NMR of the major isomer (400 MHz, CDCl₃): δ 7.38-7.34 (m, 2H), 7.31-7.29 (m, 1H), 7.25-7.17 (m, 7H), 6.17 (ψt, *J* = 7.5 Hz, 1H), 3.67-3.61 (m, 1H), 2.33-2.25 (m, 2H), 1.61 (s, 1H), 1.54-1.40 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H).

¹³C NMR of the major isomer (100 MHz, CDCl₃): δ 144.0, 142.6, 140.0, 130.0, 128.3, 128.2, 127.3, 127.2, 127.1, 125.6, 73.4, 37.3, 29.8, 10.0.

GC-MS (EI): Calcd for C₁₈H₂₀O M⁺: 252.2; found: 252.0.

1,1-Diphenyldec-1-en-4-ol (5j)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as light yellow oil. 61 mg, 66% yield. The ratio of regioisomers was determined to be 15:1 by crude ¹H NMR spectroscopy.

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38-7.34 (m, 2H), 7.31-7.27 (m, 1H), 7.25-7.17 (m, 7H), 6.16 (ψt, $J = 7.6$ Hz, 1H), 3.72-3.68 (m, 1H), 2.36-2.22 (m, 2H), 1.54 (s, 1H), 1.46-1.25 (m, 10H), 0.87 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 144.0, 142.5, 139.9, 129.9, 128.2, 128.0, 127.2, 127.0, 126.9, 125.5, 71.9, 37.6, 37.0, 31.8, 29.2, 25.5, 22.6, 14.0.

GC-MS (EI): Calcd for $\text{C}_{22}\text{H}_{28}\text{O}$ M^+ : 308.2; found: 307.9.

(2R,4E)-1-Phenoxy-5-phenyl-pent-4-en-2-ol (5k)

A sample of enantiopure epoxide (99.6% ee, TCI) was used. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as white solid. 47 mg, 62% yield in 99.7% ee. The ratio of regioisomers was determined to be 9:1 by crude ^1H NMR spectroscopy.

Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95:5, flow rate = 1.0 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	14.076	246573	50.158
2	19.130	245018	49.842
Total		491591	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	14.157	1939370	99.856
2	19.202	2789	0.144
Total		1942158	100.000

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.37-7.34 (m, 2H), 7.31-7.26 (m, 4H), 7.23-7.19 (m, 1H), 6.98-6.91 (m, 3H), 6.51 (d, $J = 15.8$ Hz, 1H), 6.29 (ψdt, $J =$

15.8, 7.2 Hz, 1H), 4.17-4.11 (m, 1H), 4.01 (dd, $J = 9.4, 3.6$ Hz, 1H), 3.92 (dd, $J = 9.4, 7.0$ Hz, 1H), 2.57-2.52 (m, 2H), 2.39 (d, $J = 3.9$ Hz, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 158.7, 137.3, 133.4, 129.7, 128.7, 127.5, 126.3, 125.4, 121.3, 114.8, 71.6, 69.9, 37.3.

GC-MS (EI): Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_2$ M^+ : 254.1; found: 254.0.

$[\alpha]_D^{23} = -15.3^\circ$ ($c = 1.40$, CHCl_3).

(2R,4E)-5-Phenyl-4-pent-4-ene-1,2-diol (5I)

An epoxide of 99.6% ee (TCI) was used. The product was isolated by flash chromatography (ethyl acetate/ hexanes 1:1) as colorless oil. 26 mg, 48% yield. The ratio of regioisomers in the crude mixture was determined to be 8:1 by GC. The two isomers were separated by silica. The major isomer was in 98.5% ee.

Daicel Chiralcel IC, *n*-hexane/isopropanol 90:10, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 254nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	23.673	5759727	50.740
2	27.371	5591797	49.260
Total		11351524	100.000

1 PDA Multi 1 / 254nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	23.832	41749	0.773
2	27.446	5361406	99.227
Total		5403154	100.000

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.37-7.35 (m, 2H), 7.32-7.29 (m, 2H), 7.24-7.20 (m, 1H), 6.50 (d, $J = 15.8$ Hz, 1H), 6.22 (vdt, $J = 15.8, 7.3$ Hz, 1H),

3.88-3.82 (m, 1H), 3.73 (dd, $J = 11.1, 3.0$ Hz, 1H), 3.54 (dd, $J = 11.1, 7.1$ Hz, 1H), 2.44-2.39 (m, 2H), 2.24 (s, 1H), 2.02 (s, 1H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.2, 133.5, 128.7, 127.6, 126.3, 125.5, 71.7, 66.5, 37.3.

GC-MS (EI): Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$ M^+ : 178.1; found: 178.1.

$[\alpha]_D^{23} = +4.1^\circ$ ($c = 0.98$, CHCl_3).

(2R,4E)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-phenyl-pent-4-en-2-ol (5m)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as colorless oil. 60 mg, 68% yield. The ratio of regioisomers was determined to be 18:1 by crude ^1H NMR spectroscopy. The major isomer was in 99.6% ee.

Daicel Chiralcel IC, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	14.091	3284167	50.825
2	15.483	3177603	49.175
Total		6461770	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	14.142	3035287	99.815
2	15.566	5640	0.185
Total		3040927	100.000

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.37-7.35 (m, 2H), 7.32-7.28 (m, 2H), 7.23-7.19 (m, 1H), 6.47 (d, $J = 15.8$ Hz, 1H), 6.25 (ψ dt, $J = 15.8, 7.2$ Hz, 1H), 3.82-3.75 (m, 1H), 3.67 (dd, $J = 10.0, 3.7$ Hz, 1H), 3.51 (dd, $J = 10.0, 6.8$ Hz, 1H), 2.45 (d, $J = 4.0$ Hz, 1H), 2.42-2.38 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 137.6, 132.6, 128.6, 127.3, 126.2,

71.6, 66.7, 37.0, 26.0, 18.4, -5.1, -5.2.

LC-MS (ESI): Calcd for C₁₇H₂₈O₂Si (M+H)⁺: 293.2; found: 293.2.

[α]_D²³ = -3.4° (*c* = 0.60, CHCl₃).

An epoxide of 99.5% ee (Aldrich) was used. The product was isolated by flash chromatography (ethyl acetate/ hexanes 1:12) as white solid. 28 mg, 42% combined yield of two regioisomers. The ratio of regioisomers in the crude mixture was determined to be 2:1 by GC. Epoxide isomerization to phenylacetaldehyde and subsequent aldol condensation produced two isomers of byproducts (34 mg, 52% yield with *E/Z* ratio of 7:1).

(*E*)-1,4-Diphenylbut-3-en-1-ol (5n) [84107-76-6]

The major isomer was in 60% ee. Daicel Chiralcel OZ, *n*-hexane/isopropanol 95:5, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	16.512	1071710	51.160
2	19.666	1023107	48.840
Total		2094818	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	16.552	380978	80.701
2	19.706	91109	19.299
Total		472087	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.34 (m, 6H), 7.32-7.28 (m, 3H), 7.24-7.22 (m, 1H), 6.51 (d, $J = 15.9$ Hz, 1H), 6.22 (ψdt , $J = 15.9, 7.4$ Hz, 1H), 4.84-4.80 (m, 1H), 2.70-2.66 (m, 2H), 2.06 (d, $J = 3.3$ Hz, OH).

^{13}C NMR (100 MHz, CDCl_3): δ 144.1, 137.4, 133.6, 128.7, 128.6, 127.8, 127.5, 126.3, 126.0, 125.9, 73.9, 43.2.

LC-MS (ESI): Calcd for $\text{C}_{16}\text{H}_{16}\text{ONa}$ ($\text{M}+\text{Na}$) $^+$: 247.1; found: 247.2.

$[\alpha]^{23}_{\text{D}} = -12.3^\circ$ ($c = 0.70$, CHCl_3).

(*E*)-2,4-Diphenylbut-3-en-1-ol (5n')

The minor isomer was in 0% ee. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95:5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.34 (m, 4H), 7.32-7.29 (m, 5H), 7.26-7.20 (m, 1H), 6.54 (d, $J = 16.0$ Hz, 1H), 6.39 (dd, $J = 16.0, 7.8$ Hz, 1H), 3.92 (ψt , $J = 6.0$ Hz, 2H), 3.71 (ψq , $J = 7.3$ Hz, 1H), 1.51 (t, $J = 6.3$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 141.0, 137.1, 132.4, 129.8, 129.0, 128.7, 128.2, 127.7, 127.2, 126.4, 66.6, 52.0.

LC-MS (ESI): Calcd for $\text{C}_{16}\text{H}_{16}\text{ONa}$ ($\text{M}+\text{Na}$) $^+$: 247.1; found: 247.2.

Byproduct: (*E*)-2,4-Diphenylbut-2-enal (5n'') [115872-75-8]

The NMR spectroscopy of this compound was identified by comparison with reported NMR data.

^1H NMR (400 MHz, CDCl_3): δ 9.65 (s, 1H), 7.45-7.35 (m, 3H), 7.33-7.29 (m, 2H), 7.26-7.22 (m, 3H), 7.16-7.14 (m, 2H), 6.86 (t, $J = 7.6$ Hz, 1H), 3.68 (d, $J = 7.6$ Hz, 2H).

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{14}\text{O}$ M^+ : 222.1; found: 222.1.

1.5.5 Experiment of Mechanistic Studies

(a) Ring opening of epoxides with $\text{NEt}_3 \cdot \text{HI}$

A typical procedure: Two 10 mL Schlenk tubes containing a magnetic stir bar were charged with cyclohexene oxide (10.4 μL , 0.1 mmol), $\text{NEt}_3 \cdot \text{HI}$ (28 mg, 0.12 mmol), 10 μL of GC standard *n*-dodecane and dry PhCF_3 (0.3 mL). The experiments were conducted at 25 °C and 80 °C, respectively. At intervals, aliquots of the reaction mixture were taken and passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC analysis for determination of the yield of **1j**. Only the *trans* isomer of **1j** was detected by GC and GCMS.

Table 1.3 Ring opening of cyclohexene oxide in the presence of $\text{NEt}_3 \cdot \text{HI}$

entry	T (°C)	time (min)	yield (%)
1	25	120	0
2	80	40	42
3	80	60	65
4	80	120	100

trans-2-Iodocyclohexanol (**1j**) [10039-14-2]

^1H NMR (400 MHz, CDCl_3): δ 4.07-4.00 (m, 1H), 3.65 (ψtd, $J = 9.9, 4.5$ Hz, 1H), 2.50-2.45 (m, 1H), 2.34 (br s, OH), 2.14-2.00 (m, 2H), 1.86-1.82 (m, 1H), 1.55-1.49 (m, 1H), 1.42-1.23 (m, 3H).

GC-MS (EI): Calcd for C₆H₁₁IO M⁺: 226.0; found: 226.0.

1-Iodo-3-phenoxypiran-2-ol (1k) [82430-40-8]

Dioxane was used instead of PhCF₃, since dioxane was used in the catalytic reaction of terminal epoxides. The iodide was added selectively to the less hindered carbon of the epoxide by GCMS and NMR spectroscopy.

¹H NMR (400 MHz, CDCl₃): δ 7.32-7.28 (m, 2H), 7.01-6.99 (m, 1H), 6.93-6.91 (m, 2H), 4.13-4.04 (m, 2H), 4.02-3.96 (m, 1H), 3.48 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.40 (dd, *J* = 10.3, 5.8 Hz, 1H), 2.52 (br s, OH).

GC-MS (EI): Calcd for C₉H₁₁IO₂ M⁺: 278.0; found: 277.9.

For ring opening of styrene oxide, dioxane was used instead of PhCF₃. After 5 h, 90% conversion of epoxide was detected. The ratio of regioisomers generated from β- and α-attack was determined to be 3.5:1 by crude ¹H NMR spectroscopy. Phenylacetaldehyde was formed by epoxide isomerization in 13% NMR yield.

(b) Heck-type reaction of *trans*-2-iodocyclohexanol

A typical procedure: In an argon-filled glove box, Pd(PPh₃)₄ (29 mg, 0.025 mmol), dppf (19.5 mg, 0.035 mmol) and dry PhCF₃ (2 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, **1j** (226 mg, 1 mmol), styrene (58.5 μL, 0.5 mmol), Cy₂NMe (175 μL, 0.75 mmol) and 20 μL of GC standard *n*-dodecane were added

sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 °C for 24 h. After cooled down to rt, aliquots were taken from the reaction mixture and passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC and GCMS to determine the distribution of products.

***trans*-2-Phenyloctahydrobenzofuran [2159069-08-4] and *cis*-2-**

Phenyloctahydrobenzofuran [2159069-07-3]

The four isomers were inseparable by silica gel and they were isolated by flash chromatography (hexanes) as colorless oil. 14 mg in total, containing 12% yield for the *trans* isomers and 2 mg of *cis* isomers. The *endo/exo* ratio of both *trans* and *cis* isomers was determined to be 1:1 by ¹H NMR spectroscopy. The structural assignment of the four isomers was assisted by comparison with reported NMR data.

¹H NMR of a mixture of four diastereomers (400 MHz, CDCl₃): δ 7.34-7.23 (m, 6H), 5.18 (ψt, *J* = 7.3 Hz, 0.1H), 5.09-5.05 (m, 1H), 4.96 (ψt, *J* = 8.1 Hz, 0.1H), 4.24 (ψq, *J* = 3.4 Hz, 0.1H), 4.02 (ψq, *J* = 4.7 Hz, 0.1H), 3.40 (ψtd, *J* = 9.8, 3.6 Hz, 0.5H), 3.24 (ψtd, *J* = 10.3, 3.8 Hz, 0.5H), 2.49-2.41 (m, 0.7H), 2.28-2.12 (m, 1.6H), 2.08-1.80 (m, 3.6H), 1.75-1.15 (m, 7.3H).

¹³C NMR of a mixture of four diastereomers (100 MHz, CDCl₃): δ 145.1 and 145.0, 128.5 and 128.4, 127.1, 126.0 and 125.6, 84.5 and 84.2, 80.0 and 79.0, 46.9 and 44.2,

41.2 and 40.1, 31.8 and 31.6, 29.2 and 29.1, 26.0 and 25.9, 24.5.

GC-MS (EI): Calcd for $C_{14}H_{18}O$ M^+ : 202.1; found: 202.1.

(c) A stoichiometric reaction of in situ formed palladium(0) complex of Xantphos and **1j**

A typical procedure. In an argon-filled glove box, $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), Xantphos (20 mg, 0.035 mmol) and dry $PhCF_3$ (0.4 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, **1j** (11.3 mg, 0.05 mmol) and 10 μ L of GC standard, *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 °C for 12 h. After cooled down to rt, aliquots were taken from the reaction mixture and passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC and GCMS to determine the distribution of products.

(d) A stoichiometric reaction with **1b in the presence of 1 equiv of $Et_3N \cdot HI$**

A typical procedure. In an argon-filled glove box, $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), Xantphos (20 mg, 0.035 mmol) and dry $PhCF_3$ (0.4 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, **1b** (5.2 μ L, 0.05 mmol), $NEt_3 \cdot HI$ (11.5 mg,

0.05 mmol), and 10 μ L of GC standard, *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 $^{\circ}$ C for 12 h. After cooled down to rt, aliquots were taken from the reaction mixture and passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC and GCMS to determine the yields of products by comparing with authentic samples.

(e) TEMPO-trapping experiment

A typical procedure. In an argon-filled glove box, Pd(PPh₃)₄ (46.2 mg, 0.04 mmol), Xantphos (32.4 mg, 0.056 mmol) and dry PhCF₃ (0.8 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, cyclopentene oxide (71.2 μ L, 0.8 mmol), NEt₃·HI (45.8 mg, 0.2 mmol), styrene (46.8 μ L, 0.4 mmol), TEMPO (62.5 mg, 0.4 mmol) and 20 μ L of GC standard, *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 $^{\circ}$ C for 24 h. After cooled down to rt, no Heck product was detected by GC and GCMS. The TEMPO-trapped byproduct was isolated and its *cis* configuration was assigned by comparison with reported NMR data.

cis-2-[(2,2,6,6-Tetramethylpiperidin-1-yl)oxy]cyclopentanol (**7a**) [1826104-56-6]

The byproduct was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as light yellow oil. 22 mg, 23% yield.

^1H NMR (400 MHz, CDCl_3): δ 4.20 (ψt , $J = 4.1$ Hz, 1H), 4.11 (ψtd , $J = 9.1, 4.2$ Hz, 1H), 2.44 (s, 1H), 2.09-2.01 (m, 1H), 1.81-1.62 (m, 4H), 1.55-1.36 (m, 7H), 1.22-1.08 (m, 12H).

^{13}C NMR (100 MHz, CDCl_3): δ 89.4, 71.6, 59.7, 40.4, 33.8, 30.8, 28.3, 20.7, 20.3, 19.5, 17.3.

HRMS (ESI): Calcd for $\text{C}_{14}\text{H}_{28}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 242.2120; found: 242.2120.

(f) Heck type reaction of α -cyclopropylstyrene

A typical procedure. In an argon-filled glove box, $\text{Pd}(\text{PPh}_3)_4$ (17.4 mg, 0.015 mmol), Xantphos (12.3 mg, 0.021 mmol) and dry PhCF_3 (1.2 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, cyclopentene oxide (54 μL , 0.6 mmol), $\text{NEt}_3\cdot\text{HI}$ (13.8 mg, 0.06 mmol), α -cyclopropylstyrene (43.3 mg, 0.3 mmol) and 20 μL of GC standard, *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 $^\circ\text{C}$ for 48 h. After cooled down to rt, the reaction mixture was subjected to flash chromatography with ethyl acetate/ hexanes as eluent.

trans-2-[(3,4-Dihydro-1-naphthyl)methyl]cyclopentanol (7b)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:12) as colorless oil. 25 mg, 37% yield. The ratio of *trans* and *cis* isomers was determined to

be 8:1 by GC and GCMS. No other isomer was detected by GCMS.

^1H NMR of trans isomer (400 MHz, CDCl_3): δ 7.30-7.14 (m, 4H), 5.90 (t, $J = 4.5$ Hz, 1H), 3.92 (ψq, $J = 5.8$ Hz, 1H), 2.74 (ψt, $J = 8.0$ Hz, 2H), 2.58 (dd, $J = 14.0, 7.0$ Hz, 1H), 2.36 (dd, $J = 14.0, 8.0$ Hz, 1H), 2.28-2.23 (m, 2H), 2.01-1.85 (m, 3H), 1.70-1.54 (m, 3H), 1.45 (s, 1H), 1.29-1.22 (m, 1H).

^{13}C NMR of trans isomer (100 MHz, CDCl_3): δ 136.9, 135.8, 134.7, 127.8, 126.9, 126.5, 126.1, 123.0, 79.4, 46.5, 37.3, 34.3, 30.3, 28.6, 23.3, 21.6.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{20}\text{O}$ M^+ : 228.2; found: 228.2.

(g) Heck-type reaction of 1,2-epoxy- 5-hexene

A typical procedure: In an argon-filled glove box, $\text{Pd}(\text{PPh}_3)_4$ (17.4 mg, 0.015 mmol), dppf (11.7 mg, 0.021 mmol) and dry dioxane (1.2 mL) were charged into a dry 10 mL Schlenk tube. After stirring at rt for 10 min, 1,2-epoxy- 5-hexene (70 μL, 0.6 mmol), $\text{NEt}_3 \cdot \text{HI}$ (13.8 mg, 0.06 mmol), styrene (35 μL, 0.3 mmol) and 20 μL of GC standard *n*-dodecane were added sequentially. The reaction mixture was capped tightly and vigorously stirred in a heating block maintained at 110 °C for 48 h. After cooled down to rt, the reaction mixture was subjected to flash chromatography with ethyl acetate/hexanes as eluent.

3-[(E)-Cinnamyl]cyclopentanol (7c)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as colorless oil. 29 mg, 47% yield. The ratio of diastereomers was determined to be 1.6:1

by crude ^1H NMR spectroscopy.

^1H NMR of a mixture of two diastereomers (400 MHz, CDCl_3): δ 7.36-7.28 (m, 6.4H), 7.22-7.18 (m, 1.6H), 6.42-6.37 (m, 1.6H), 6.23 (major isomer, ψtd , $J = 7.1, 1.7$ Hz, 1H), 6.19 (minor isomer, ψtd , $J = 6.8, 2.0$ Hz, 0.6H), 4.39-4.29 (m, 1.6H), 2.34-2.14 (m, 4.8H), 2.04-1.95 (m, 1.6H), 1.84-1.42 (m, 8H), 1.30-1.24 (m, 1.6H).

^{13}C NMR of a mixture of two diastereomers (100 MHz, CDCl_3): δ 137.9, 130.7, 129.9, 128.6 (and 128.9), 127.0, 126.1 (and 126.2), 73.8, 42.0 (and 42.3), 40.1 (and 39.4), 38.4 (and 37.4), 35.3 (and 35.6), 30.1 (and 30.0).

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ M^+ : 202.1; found: 202.0.

(h) Synthesis of (bisphosphine) PdI_2 complexes

The Pd complexes were prepared according to a reported procedure.⁴⁴ A mixture of PdI_2 (108 mg, 0.3 mmol), bisphosphine (0.3 mmol) and dry toluene (0.3 mL) were added to a dry 10 mL Schlenk tube under argon. The reaction mixture was stirred at 120 °C for 3 h. After cooled down to rt, the crude product was filtered under vacuum in air, and then washed carefully with anhydrous Et_2O . The precipitate was collected and dried under vacuum. These complexes have poor solubility in d_6 -DMSO.

$\text{Pd}(\text{Xantphos})\text{I}_2$

^1H NMR (400 MHz, CD_2Cl_2): δ 7.73-7.71 (m, 8H), 7.47-7.09 (m, 18H), 1.82 (s, 6H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ 154.0, 135.2, 134.9, 132.7, 130.5, 130.3, 128.1, 127.9, 126.2, 124.0, 36.1, 29.0. Broad peaks were recorded due to structural dynamics.

^{31}P NMR (162 MHz, CD_2Cl_2): δ 16.3, 4.0 (due to partial ionization of the complex).

LC-MS (ESI): Calcd for $\text{C}_{39}\text{H}_{32}\text{OP}_2\text{I}_2\text{Pd}$ (M-I) $^+$: 811.0; found: 811.1.

Pd(dppf)I₂

¹H NMR (400 MHz, CD₂Cl₂): δ 7.95-7.90 (m, 8H), 7.55-7.47 (m, 12H), 4.40 (s, 4H), 4.20 (s, 4H).

¹³C NMR (100 MHz, CD₂Cl₂): δ 135.2, 135.2, 135.1, 134.4, 133.9, 131.0, 127.9, 127.9, 127.8, 127.7, 76.2, 76.1, 76.1, 75.8, 75.7, 75.3, 75.2, 73.7, 73.7, 73.6.

³¹P NMR (162 MHz, CD₂Cl₂): δ 24.5.

LC-MS (ESI): Calcd for C₃₄H₂₈FeP₂I₂Pd (M-I)⁺: 786.9; found: 786.4.

Pd(dppp)I₂

¹H NMR (400 MHz, CD₂Cl₂): δ 7.80-7.76 (m, 8H), 7.55-7.48 (m, 12H), 2.45-2.40 (m, 4H), 2.10-1.99 (m, 2H).

¹³C NMR (100 MHz, CD₂Cl₂): δ 133.8, 131.7, 131.3, 128.4, 25.3, 18.2.

³¹P NMR (162 MHz, CD₂Cl₂): δ 0.5.

LC-MS (ESI): Calcd for C₂₇H₂₆P₂I₂Pd (M-I)⁺: 645.0; found: 645.1.

(i) Cyclic voltammetry experiments

The cyclic voltammetry experiments were conducted with a computer-controlled Eco Chemie Autolab PGSTAT302N potentiostat in a three-electrode cell. All electrochemical measurements were carried out under an argon atmosphere and the samples were bubbled with argon before measurement. Cyclic voltammograms of 1.0 mM Pd complexes or alkyl iodides with 0.1 M *n*-Bu₄NPF₆ as the supporting electrolyte were recorded respectively at a scan rate of 100 mV/s with a planar glassy carbon disc (1mm diameter) as working electrode, a platinum wire as counter electrode and an Ag wire (in 0.5 M *n*-Bu₄NPF₆ in CH₃CN) as a pseudo-reference electrode at 298±2 K.

Ferrocene (Fc) was added to the sample solution as an internal reference. The first reduction peak is shown in the solid line and the second one is shown in the dashed line.

Figure 1.2 Cyclic voltammograms of 1.0 mM Pd(Xantphos)I₂ in PhCN (left) and DCM (right)

Figure 1.3 Cyclic voltammograms of 1.0 mM Pd(dppf)I₂ in PhCN (left) and DCM (right)

Figure 1.4 Cyclic voltammograms of 1.0 mM Pd(dppp)I₂ in PhCN (left) and DCM (right)

1.6 References

1. Oestreich, M. *The Mizoroki-Heck Reaction*; John Wiley & Sons: West Sussex, U. K., 2009.
2. (a) Ariaifard, A.; Lin, Z. *Organometallics* **2006**, *25*, 4030. (b) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937.
3. (a) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910. (c) Hadei, N.; Kantchev, E. A. B.; O'Brie, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805.
4. (a) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7145. (b) Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7832.
5. (a) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923. (b) Bloome, K. S.; Alexanian, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 12823. (c) Takeda, Y.; Ikeda, Y.; Kuroda, A.; Tanaka, S.; Minakata, S. *J. Am. Chem. Soc.* **2014**, *136*, 8544.
6. Reviews on the participation of alkyl radicals in Pd-catalyzed reactions: (a) Liu, Q.; Dong, X.; Li, J.; Xiao, J.; Dong, Y.; Liu, H. *ACS Catal.* **2015**, *5*, 6111. (b) Kwiatkowski, M. R.; Alexanian, E. J. *Acc. Chem. Res.* **2019**, *52*, 1134.
7. (a) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563. (b) Sumino, S.; Ui, T.; Hamada, Y.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2015**, *17*, 4952.
8. Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340.
9. Bloome, K. S.; McMahan, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146.
10. Venning, A. R. O.; Kwiatkowski, M. R.; Roque Peña, J. E.; Lainhart, B. C.; Guruparan, A. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2017**, *139*, 11595.

11. Dong, X.; Han, Y.; Yan, F.; Liu, Q.; Wang, P.; Chen, K.; Li, Y.; Zhao, Z.; Dong, Y.; Liu, H. *Org. Lett.* **2016**, *18*, 3774.
12. Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 17926.
13. Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 8175.
14. Fujiwara, T.; Yanai, K.; Shimane, K.; Takamori, M.; Takeda, T. *Eur. J. Org. Chem.* **2001**, 155.
15. Examples: (a) Surapanich, N.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. *Eur. J. Org. Chem.* **2012**, 5943. (b) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* **2013**, *135*, 16372. (c) Zhu, K.; Dunne, J.; Shaver, M. P.; Thomas, S. P. *ACS Catal.* **2017**, *7*, 2353.
16. (a) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514. (b) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068.
17. McMahon, C. M.; Alexanian, E. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 5974.
18. Zou, Y.; Zhou, J. *Chem. Commun.* **2014**, *50*, 3725.
19. Feng, Z.; Min, Q.-Q.; Zhao, H.-Y.; Gu, J.-W.; Zhang, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 1270.
20. Reviews: (a) Parasram, M.; Gevorgyan, V. *Chemical Society Reviews* **2017**, *46*, 6227. (b) Chuentragool, P.; Kurandina, D.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2019**, *58*, 11586.

21. (a) Kurandina, D.; Parasram, M.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2017**, *56*, 14212. (b) Kurandina, D.; Rivas, M.; Radzhabov, M.; Gevorgyan, V. *Org. Lett.* **2018**, *20*, 357. (c) Chuentragool, P.; Yadagiri, D.; Morita, T.; Sarkar, S.; Parasram, M.; Wang, Y.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2019**, *58*, 1794.
22. (a) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 18307. (b) Wang, G.-Z.; Shang, R.; Fu, Y. *Org. Lett.* **2018**, *20*, 888.
23. One of our reviewers suggested “on-off” experiment could only be used to confirm the existence of a chain reaction, not to rule out this mechanism. See reference: Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426.
24. (a) Zhou, W.-J.; Cao, G.-M.; Shen, G.; Zhu, X.-Y.; Gui, Y.-Y.; Ye, J.-H.; Sun, L.; Liao, L.-L.; Li, J.; Yu, D.-G. *Angew. Chem. Int. Ed.* **2017**, *56*, 15683. (b) Jiao, Z.; Lim, L. H.; Hirao, H.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2018**, *57*, 6294. (c) Kancherla, R.; Muralirajan, K.; Maity, B.; Zhu, C.; Krach, P. E.; Cavallo, L.; Rueping, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 3412.
25. Zhao, B.; Shang, R.; Wang, G.-Z.; Wang, S.; Chen, H.; Fu, Y. *ACS Catal.* **2020**, *10*, 1334.
26. Reviews: (a) Crotti, P.; Pineschi, M. *Epoxides in Complex Molecule Synthesis. In Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006. (b) Huang, C.-Y.; Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153.
27. (a) Golakoti, T.; Ogino, J.; Heltzel, C. E.; Le Husebo, T.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1995**, *117*, 12030. (b) Shrestha, S. P.; Amano, Y.; Narukawa, Y.;

- Takeda, T. *J. Nat. Prod.* **2008**, *71*, 98. (c) Cheenpracha, S.; Karalai, C.; Ponglimanont, C.; Kanjana-Opas, A. *J. Nat. Prod.* **2009**, *72*, 1395. (d) Ayers, S.; Graf, T. N.; Adcock, A. F.; Kroll, D. J.; Matthew, S.; Carcache de Blanco, E. J.; Shen, Q.; Swanson, S. M.; Wani, M. C.; Pearce, C. J.; Oberlies, N. H. *J. Nat. Prod.* **2011**, *74*, 1126.
28. Ikeda, Y.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Adv. Synth. Catal.* **2004**, *346*, 1631.
29. Prina Cerai, G.; Morandi, B. *Chem. Commun.* **2016**, *52*, 9769.
30. Reports on titanocene-catalyzed intermolecular reactions of epoxides and electron-deficient olefins: (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986. (b) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 2909. (c) Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem.-Eur. J.* **2003**, *9*, 531. (d) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 2041. (e) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359.
31. Examples: (a) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1992**, *48*, 3805. (b) Fagnou, K.; Lautens, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 26.
32. (a) Zhao, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 48. (b) Banerjee, A.; Yamamoto, H. *Org. Lett.* **2017**, *19*, 4363.
33. CCDC 1570943, 1556727, 1816547 and 1815718 contain the supplementary crystallographic data of compounds **3i**, **4b**, **6f** and **6f'**.

34. Kim, J.-H.; Kulawiec, R. J. *J. Org. Chem.* **1996**, *61*, 7656.
35. Lecomte, P.; Drapier, I.; Dubois, P.; Teyssié, P.; Jérôme, R. *Macromolecules* **1997**, *30*, 7631.
36. Piva, O. *Tetrahedron Lett.* **1992**, *33*, 2459.
37. Gharpure, S. J.; Vishwakarma, D. S.; Nanda, S. K. *Org. Lett.* **2017**, *19*, 6534.
38. Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **2000**, *122*, 2988.
39. Citterio, A.; Arnoldi, A.; Minisci, F. *J. Org. Chem.* **1979**, *44*, 2674.
40. Half-wave oxidation potential of PhC·H(Me) is +0.37 V vs SCE in MeCN: Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 132.
41. Steiner, D.; Ivison, L.; Goralski, C. T.; Appell, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2359.
42. Matovic, N. J.; Stuthe, J. M. U.; Challinor, V. L.; Bernhardt, P. V.; Lehmann, R. P.; Kitching, W.; De Voss, J. J. *Chem.-Eur. J.* **2011**, *17*, 7578.
43. Szendi, Z.; Forgó, P.; Sweet, F. *Steroids* **1995**, *60*, 442.
44. Yu, H.; Zhang, G.; Huang, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 10912.

Chapter 2. Asymmetric Wacker-Type Oxyallenylation and Azaallenylation of Cyclic Alkenes

2.1 Introduction

2.1.1 Brief Introduction of Wacker-Type Reaction

Wacker oxidation is a classical named reaction and has been widely applied in the industrial synthesis of acetaldehyde from ethylene.¹ The addition of oxygen/nitrogen nucleophiles to alkenes based on palladium catalysis, known as Wacker- or aza-Wacker-type reaction, is one of the most versatile methods for olefin functionalization and for construction of a variety of heterocycles.²

Scheme 2.1 Stereochemical pathways of nucleopalladation

The pivotal step in Wacker-type reaction is nucleopalladation, which can proceed via *syn*-insertion or *anti*-attack.³ These two different stereochemical pathways result in two diastereomeric alkyl $Pd(II)$ species (Scheme 2.1). In addition to subsequent β -H elimination, the reactive $Pd(II)$ intermediate can participate in a myriad number of other transformations including alkene insertion, arylation, carbonylation and oxidative cleavage. For domino reactions involving Wacker-type process, one C–C bond and one C–O/N bond can be formed in a single step without isolating the intermediate.

The first enantioselective Wacker-type reaction was reported by Hosokawa in 1978, affording the cyclization product of *ortho*-allyl phenols in 12% ee.⁴ However, there was no more example of novel transformations in the next two decades. One reason is the narrow scope of chiral ligand screening in the oxidative Wacker-type reaction. Phosphine ligands, highly successful in other asymmetric transformations, are often incompatible with oxidants used in such reactions. Another reason is the competition between *syn*- and *anti*-heteropalladation pathways, which makes it difficult to achieve high levels of asymmetric induction.³

2.1.2 Asymmetric Wacker-Type Reaction via *syn*-Insertion

Despite the challenges associated with asymmetric heteropalladation, a number of highly enantioselective Wacker-type reactions and related transformations via *syn*-insertion have been reported in the last two decades. Most of the examples were restricted to intramolecular heteropalladation, owing to the ease of asymmetric induction in *syn*-insertion when the olefin is covalently linked to the heteroatom.

In 1997, Hayashi *et al.* found binaphthyl-derived bisoxazoline (*S,S*)-*i*-Pr-boxax induced much higher levels of enantiocontrol in the intramolecular Wacker reaction.⁵ Deuterium-labeling studies showed that the reaction took place via *syn*-oxypalladation (Scheme 2.2).⁶

Scheme 2.2 Deuterium-labeling methods establishing stereochemistry at the oxypalladation step

In 2003, Stoltz and coworkers developed the first example of enantioselective Pd-catalyzed oxidative cyclization under aerobic conditions.⁷ The precatalyst [(-)-sparteine]Pd(TFA)₂ along with excess (-)-sparteine in non-polar solvent provided the optimal results (Scheme 2.3). Although limited in substrate scope, the reaction used O₂ directly, instead of benzoquinone.

Scheme 2.3 Asymmetric aerobic oxidative phenol cyclization

In 2001, Sasai *et al.* reported desymmetrization of homoallylic alcohols using Pd(TFA)₂/SPRIX (Scheme 2.4).⁸ It is the first asymmetric example using alcohols as nucleophiles in the alkene functionalization. The reaction proceeds via *syn*-oxypalladation, followed by intramolecular alkene insertion to afford the unique bicyclic product.

Scheme 2.4 Asymmetric Pd-catalyzed oxidative cyclization of alcohols

Later in 2005, Tietze *et al.* reported an enantioselective reaction of *ortho*-homoallyl phenol and methyl acrylate. The Pd-alkyl species formed by intramolecular *syn*-insertion was trapped by acrylates. Although it needed 3.5 days for full conversion, this transformation was applied in the total synthesis of vitamin E (Scheme 2.5).⁹

Scheme 2.5 *Syn*-oxypalladation step with subsequent intermolecular alkene insertion

The first enantioselective example of oxidative aza-Wacker reactions was described by Yang *et al.* (Scheme 2.6).^{10a} The catalytic system developed by Stoltz's group can be applied to the aerobic aminovinylation of acrylbenzamide, affording the indoline product in 86% ee. Soon later, the same group found that the use of Quinox led to a higher level of enantioinduction.^{10b} In addition, other transformations associated with oxidative aza-Wacker reactions via *syn*-insertion have been reported by the groups of Zhang and Liu.¹¹

Scheme 2.6 Enantioselective Pd-catalyzed oxidative tandem cyclization via aminopalladation

Asymmetric Wacker-type reactions via *syn*-insertion was reported under non-oxidative conditions in recent years.¹² Chiral phosphine ligands such as phosphoamidites, phosphinooxazolines, MeOBIPHEP(O) and TADDOL/2-arylcylohexanol-derived phosphites have been found effective in this type of reactions.

Wolfe and co-workers employed an alkene equipped with a pendant *N*- or *O*-nucleophile in the cross-coupling with aryl or alkenyl bromide.¹³ The commonly accepted mechanism is shown in Scheme 2.7. After oxidative addition of Pd(0) with aryl bromides, both the alkene and the deprotonated heteroatom are coordinated to arylpalladium species to generate either a Pd alkoxide or a Pd amido complex. This double-point contact between the substrate and the catalyst provides the high degree of preorganization, which induces excellent stereocontrol in the subsequent *syn*-insertion step. The final product was formed by reductive elimination along with the regeneration of Pd(0) catalyst. The outcome of deuterium-labeling studies confirmed the reaction occurred with *syn*-heteropalladation. Furthermore, the same strategy has been utilized by Zhang, Tang and others in similar transformations.¹⁴

Scheme 2.7 Asymmetric Wacker-type reactions in the coupling of aryl halides and alkenes bearing a pendant heteroatom

Different from the mechanism described above, Mazet *et al.* strategically placed a hydroxy group at *ortho* positions of aryl palladium species,¹⁵ which enabled intramolecular *cis*-annulation with cycloalkenes in high diastereo- and enantioselective control (Scheme 2.8). The chiral bisphosphine monoxide was *in situ* generated by oxidation in the presence of Pd(OAc)₂ and a catalytic amount of water. Similarly, *cis*-annulation of 2-bromosulfonamide and 2,3-dihydrofuran were developed by the same group.

Scheme 2.8 Pd-catalyzed asymmetric *cis*-carboetherification of 2,3-dihydrofurans

2.1.3 Asymmetric Wacker-Type Reaction via *anti*-Attack

In intramolecular heteropalladation, *anti*-attack may also take place as the dominant pathway, in the presence of suitable supporting ligands and other reaction parameters including coordinating ability of counterions and solvent polarity.¹⁶

For example, Stahl *et al.* developed an asymmetric aerobic aza-Wacker-type reaction of aliphatic *N*-tosylamines in the combination of Pd(TFA)₂ and pyrox (Scheme 2.9).¹⁷ They found that both the enantiocontrol and reactivity decreased sharply by replacing the counterion by acetate. Moreover, the yields were much lower without the use of pyrox. Implementation of a novel substrate probe 6-*d*-1 demonstrated that the chiral neutral-donor ligand (pyrox) was able to alter the stereochemical pathway from *syn*-insertion to *anti*-attack by switching from acetate to a much weakly coordinating counterion such as triflate.

Scheme 2.9 Reconciling the stereo-outcome of nucleopalladation

In 2017, Yang and coworkers reported the asymmetric intramolecular aza-Wacker-type reaction of alkene-tethered aliphatic acrylamides.¹⁸ Under the conditions similar

to Stahl's, the reaction proceeded with *anti*-aminopalladation, which was supported by deuterium-labeling experiment (Scheme 2.10). The excellent enantiocontrol was attributed to high *anti* specificity of the nucleopalladation.

Scheme 2.10 Asymmetric oxidative aza-Wacker-type reaction via *anti*-attack

Until now, very few examples of asymmetric intermolecular nucleopalladation have been reported. While many intramolecular cases favor *syn*-insertion, in intermolecular examples, external *anti*-attack may become the predominant pathway.¹⁶

Early in 2009, Hosokawa and coworkers disclosed the asymmetric coupling of cinnamyl alcohols and vinyl ethers in modest enantiocontrol (Scheme 2.11).¹⁹ The reaction was triggered by *anti*-oxypalladation, followed by intramolecular alkene insertion and subsequent β -hydride elimination. Both the reactivity and enantioselectivity decreased in the absence of catechol due to the competitive binding of the chiral ligand to copper.

Scheme 2.11 Asymmetric Pd-catalyzed coupling of vinyl ethers and cinnamyl alcohols

Later in 2015, Wolfe and coworkers developed a non-oxidative enantioselective *anti*-carboamination.²⁰ Aryl triflates were used to ensure the formation of a cationic Pd center in order to activate alkenes.^{12,16} Nucleophilic aliphatic amines were found to be suitable coupling partners while amides and sulfonamides failed to deliver any product. As shown in Scheme 2.12, linking an aryl ring with a pendant olefin restricted the conformation of the bound alkene, which facilitated highly enantioface-selective *anti*-attack by external amines.

Scheme 2.12 Asymmetric Pd-catalyzed carboamination of *ortho*-allylaryl triflates and external aliphatic amines

As a special case, Sigman *et al.* developed a series of enantioselective aerobic difunctionalized reactions of *ortho*-vinyl phenols.²¹ The oxypalladation of *ortho*-vinyl phenol substrates can be initiated either by external methanol in solvent amount or by the tethered hydroxy group (Scheme 2.13). In both cases, *anti*-attack pathway is favored since all four coordination sites on the square plane of palladium have been occupied by the bidentate quinox, alkene and the internal phenolic group. Mechanistic studies support a reaction pathway involving *in-situ* formation of an *ortho*-quinone methide intermediate after *anti*-oxypalladation step.

Scheme 2.13 Asymmetric difunctionalization of *ortho*-vinyl phenols with alcohols

2.1.4 Asymmetric Wacker-Type Reaction Catalyzed by Copper

In addition to nucleopalladation via *syn*-insertion and *anti*-attack, other methods can be implemented in the asymmetric Wacker-type reactions. For instance, Chemler *et al.* developed asymmetric examples of oxidative carboamination and carboetherification of alkenes initiated by *syn*-heterocupration.²² The following C–Cu(II) homolysis generated the β -aminoalkyl radical *in situ*, which could undergo intermolecular addition of vinyl arenes (Scheme 2.14) and intramolecular addition of arenes.^{22a,b,e} In all cases, Cu(II)/bisoxazoline formed the active catalyst.

Scheme 2.14 Asymmetric Wacker-type reactions initiated by *syn*-aza- or oxycupration

So far, there has been only one enantioselective example of three-component carboamination of simple monoolefins disclosed by Liu and coworkers (Scheme 2.15).²³ In a catalytic system of Cu(I)/bisoxazoline, it proceeds via amino-radical addition to an alkene and subsequent radical coupling with chiral $\text{L}^*\text{Cu}^{\text{II}}\text{-Ar}$ species, delivering an arylation product after formal reductive elimination of Cu^{III} species. *N*-fluoro-*N*-methyl arylsulfonamide acted as an amino-radical precursor, and other sulfonamides with larger steric hindrance or stronger electrophilicity led to inferior results.

Scheme 2.15 Enantioselective Cu-catalyzed arylamidation of styrenes via radical pathway

2.2 Reaction Design

In previous reports, the electrophiles used in asymmetric non-oxidative Wacker-type reactions are restricted to aryl and alkenyl halides (or pseudohalides). Although other types of electrophiles including amins²⁴ and alkynylbromide²⁵ have been coupling partners in the two-component or three-component carboetherification and carboamination of alkenes, the enantioselective versions still remain unsolved due to the lack of efficient catalytic systems. Furthermore, the discovery of general and fully intermolecular asymmetric Wacker-type domino reactions is in urgent need.

Recently, our group reported an asymmetric annulation of propargylic acetates with cycloolefins (Scheme 2.16-d).²⁶ After oxidative addition of Pd(0) with the propargylic electrophile, the presence of *gem*-dialkyl groups favors the formation of a nucleophilic η^1 -allenyl complex rather than an electrophilic η^3 -propargylic complex. The two methyl groups also increase the nucleophilicity of the η^1 -allenyl complex during alkene insertion.

Alternatively, the cationic Pd(II) center of η^1 -allenyl complex generated from the propargylic electrophile²⁷ may activate the cyclic alkene which can undergo *anti*-attack by amine or alcohol. Subsequent reductive elimination of the resulting alkyl Pd

complex led to the oxyallenylation product (Scheme 2.16-c). The key to achieving this novel transformation is finding a suitable catalytic system in which *anti*-attack nucleopalladation is the predominant pathway rather than the insertion of η^1 -allenyl Pd complex into the alkenes.

To improve the selectivity toward the Wacker-type pathway, several side reactions must be prevented. Firstly, the σ -allenyl complex of palladium should undergo fast *anti*-heteropalladation instead of *syn*-carbopalladation. Secondly, the allenyl complex may exist in equilibrium with a π -propargyl complex, which can undergo β -hydride elimination to give an enyne (Scheme 2.16-b). Thirdly, the π -propargyl complex is electrophilic and it can undergo facile nucleophilic substitution (Scheme 2.16-a).

Scheme 2.16 A plausible pathway of heteroallenylation and side reactions

2.3 Results and Discussion

2.3.1 Optimization of Reaction Conditions

In a study of a model reaction of 3-phenylpropargyl acetate **2a** and 2,3-dihydrofuran, we were surprised to find that the three-component product **3a** with the cosolvent isopropanol was obtained in 68% yield in the presence of Pd(dba)₂ and dppp (**L1**) at 60 °C. We were delighted to find the chiral bisphosphine BDPP (**L3**) favored the formation of the desired product in 46% ee (Scheme 2.17).

Encouraged by the preliminary result, we screened other chiral bisphosphine ligands to develop a highly enantioselective variant. In most cases, β -H elimination to the enyne was the main side reaction, whereas Heck annulation was rarely seen, except with Norphos **L4**. For example, biaryl diphosphines such as BINAP, Segphos and Difluorophos gave **3a** in less than 5% yield. Notably, the electron-deficient Josiphos **L7** and **L8** showed higher Wacker reactivity than electron-rich **L6**. Another Josiphos ligand **L8** bearing 2-furyl groups afforded **3a** in nearly quantitative yield. A former postdoc in our lab, Dr. Zhiwei Jiao conducted initial screening of chiral ligands in the model reaction.

Gratifyingly, a MeO-BIPHEP derivative **L10** containing *P*-2-furyl substituents afforded **3a** in 85% yield with 84% ee at 60 °C with no enyne byproduct. Moreover, 90% ee and 80% yield were observed at 45 °C with 0.1 mol% catalyst loading. In contrast, catalysts formed by other MeOBIPHEP ligands **L11-L14** bearing electron-neutral and electron-donating *P*-aryl groups had almost no activity, and enyne was the main byproduct.

Alternatively, the Pd(II) source Pd(cod)Cl₂ also provided satisfactory results. To test whether the bisphosphine monoxide formed *in situ* by the oxidation of **L10** with Pd(II) in the presence of trace water participated in the catalytic cycle,^{15a} (*R*)-2-furyl MeOBIPHEP(O) was prepared in advance²⁸ and tested under the optimal conditions using Pd(dba)₂ or Pd(cod)Cl₂. However, it only led to **3a** in low yield with less than 10% ee, demonstrating the combination of palladium and **L10** itself formed the active catalyst.

Scheme 2.17 The ligand effect on a model alkoxyallenylation of 2,3-dihydrofuran

As compared to triarylphosphines, 2-furylphosphines are much weaker σ -donors and better π -acceptors to transition metals.²⁹ They form an electronically deficient allenyl palladium center in polar solvents, which can activate the olefin for Wacker attack of nucleophiles. Moreover, the backbone of MeOBIPHEP forms quite a wide bite angle at the Pd center, which may also help to prevent the β -H elimination.³⁰

2.3.2 Asymmetric Oxyallenylation and Azaallenylation of Cyclic Alkenes

The combination of $\text{Pd}(\text{dba})_2$ and **L10** was then applied to reactions of 2,3-dihydrofuran with 0.2 mol% catalyst loading in most cases (Scheme 2.18-b). Both electron-rich and -deficient aryl rings at the 3-position of propargylic acetates were well tolerated. Functional groups including esters, ketones, acetals, aryl bromides, chlorides and fluorides were compatible. Furthermore, the reaction tolerated heteroaryl rings such as quinoline, thiophene and indole. When aromatic rings were replaced by 3-alkenyl group, the reaction could also take place, affording the desired product in good yield and excellent enantioselectivity. Unfortunately, 3-alkyl propargylic acetates only gave the adduct in trace amount.

Other tertiary propargylic acetates bearing 1,1-diethyl and *gem*-cycloalkyl substituents were able to give full conversion when 1-2 mol% of the Pd catalyst was used. However, primary and secondary propargylic acetates did not react at all, which was probably attributed to the dominant existence of electrophilic π -propargylic complex.

(b) Examples from other 3-(hetero)arylpropargylic acetates

(c) Examples from other alcohols

(d) Reaction of a racemic 3-phenyl-propargylic acetate

(e) Kinetic resolution of racemic 2-aryl-2,3-dihydrofuran

Scheme 2.18 Substrate scope of alkoxyallenylation of 2,3-dihydrofuran

Notably, other alcoholic substrates, including benzyl alcohol, methanol, cyclohexanol, *tert*-butyl alcohol and ethylene glycol also reacted smoothly (Scheme 2.18-c). The reaction of racemic propargylic acetate **2b** with 2,3-dihydrofuran and ethylene glycol led to a mixture of two allenyl isomers, both with 88% ee (Scheme 2.18-d). More remarkably, a racemic 2,3-dihydrofuran **1b** bearing a *p*-methoxyphenyl group underwent kinetic resolution, affording the single diastereomer **4h** with 80% ee. The observed enantiofacial selectivity corresponds to an *s* value of 9 (Scheme 2.18-e). Unfortunately, in the reaction of 2,3-dihydropyran, only simple addition of isopropanol to the cyclic olefin was detected.

N-*tert*-butoxycarbonyl-2,3-dihydropyrrole **1c** was another reactive olefin in this transformation (Scheme 2.19), whereby different aryl rings at the 3-position of the propargylic acetates underwent alkoxyallenylation smoothly under the catalytic system of Pd(cod)Cl₂ and **L10**. The model reaction of **1c**, **2a** and isopropanol at a 1.5 mmol scale produced the Wacker adduct in almost the same yield with no erosion of ee value (Scheme 2.23). Both primary and secondary alcohols were coupled in good yields and high levels of enantioselectivity. Notably, the direct addition of alcohols to the alkene was also detected, accounting for the rest of the material balance. Reactions of cyclopentene provided only a trace amount of the desired products, however.

Scheme 2.19 Substrate scope of alkoxyallenylation of *N*-Boc-2,3-dihydropyrrole

We also attempted to replace alcohols with other types of oxygen nucleophiles in acetonitrile (Scheme 2.20-a). When **1a** was treated with acetic acid, the *trans* adduct **6a** was generated exclusively. Notably, adduct **6a** was also detected in small amounts in reaction mixtures of alkoxyallenylation without acetic acid. However, purified **6a** remained unreactive when subjected to the conditions of catalytic alkoxyallenylation, demonstrating it was chemically incompetent as intermediate for this transformation.

For the coupling of phenol, **1a** and **2a** under the typical conditions, **6b** was delivered in low yield owing to the relatively lower nucleophilicity of phenol compared to acetate counterion. To address the issue, we tried to increase the ratio of phenol to KOAc in order to suppress the formation of **6a**. Gratifyingly, when Pd(cod)Cl₂ along with reduced amount of KOAc (20 mol%) was applied to the reaction, the chemoselectivity was raised significantly. It should be noted that this transformation occurred only at the position of phenolic hydroxy group instead of the C-2 site (Scheme 2.20-b).

Scheme 2.20 Wacker-type oxyallenylation of cyclic olefins using other O-nucleophiles

Interestingly, water, while much less nucleophilic than aliphatic alcohols and acetate ion, was able to undergo hydroxyallenylation of 2,3-dihydrofuran, providing **6c** in moderate yield. Similarly, reaction of water with *N*-Boc dihydropyrrole **1c** and **2a** gave exclusively *trans* diastereomer **6d** (Scheme 2.20-c,d). The minor *cis*-lactol **6c** was probably formed through reversible ring opening of the *trans* isomer.

To further assess the generality of these catalytic conditions, we next explored the reactions of amine nucleophiles (Scheme 2.21). When aniline and indoline were used, direct propargylic amination of **2a** was the main side reaction. Moreover, aliphatic amines, such as pyrrolidine and diethyl amine, led to elimination of **2a** to provide the enyne byproduct. Fortunately, fluorinated aryl amines and pyridyl amines with attenuated nucleophilicity reacted smoothly to deliver azaallenylation adducts. The

initially formed *trans* *N,O*-acetals **6e,f** probably underwent reversible ring opening to generate the minor *cis* isomers which was also detected in the reaction mixture. The additive NaOTf accelerated the reactivity of *anti* attack of pyridyl amines to give products **6g,h**, without which no conversion was detected.

Scheme 2.21 Wacker-type aza-allenylation triggered by *anti*-attack of arylamines

2.3.3 Derivatizations of Alkoxyallenylation Adducts

In order to demonstrate the synthetic utility, we subjected **3a** to Friedel-Crafts allylation and heteroarylation with an allylsilane³¹ and furan, affording **7a** and **7d** respectively in a single diastereomer (Scheme 2.22-a). Acetal **3a** was also reduced to **7b** by triethylsilane, and then underwent facile iodocyclization upon treatment with NIS.³² *anti*-Nucleophilic attack of the phenyl ring to the iodonium species afforded 2-iodoindene product **7c**. Acidic hydrolysis of **3a** followed by PCC oxidation furnished γ -butyrolactone **7e**. In all cases above, no erosion of enantiopurity was observed.

Scheme 2.22 Synthetic utility of alkoxyallenylation adducts

Next, we attempted arylation of the oxocarbenium species derived from **3a** under Friedel-Crafts conditions (Scheme 2.22-b). Surprisingly, $\text{Sc}(\text{OTf})_3$ efficiently catalyzed the addition of 1,3,5-trimethoxybenzene to **3a**, giving a highly strained and fused cyclobutane **7f** via an unprecedented sequence of cationic reactions including 1,3-aryl and 1,3-hydride migrations. Similarly, a bromophenylated acetal **3l** was also readily converted into **7h**, whose configuration was established by X-ray crystallography.³³

However, the analogous Friedel-Crafts reaction of **5a** resulted in simple arylation under the same reaction condition (Scheme 2.22-c).

Furthermore, a thermal Diels-Alder cycloaddition of **3s** with *N*-aryl maleimide produced **7j** as a mixture of two isomers with a dr ratio of 1.2:1 (Scheme 2.22-d).

Chiral 3-benzylpyrrolidines are frequently used five-membered heterocyclic amines in drug discovery, however, few efficient stereoselective methods for their synthesis exist to date.³⁴ Finally, we designed a concise asymmetric synthesis of 3-benzylpyrrolidine starting from the adduct **5a** in three steps (Scheme 2.23). After silane reduction, **7k** then underwent a selective ozonolysis to give ketone **7l**.³⁵ Later, palladium-catalyzed reduction with PMHS afforded the desired product **7m** with almost no erosion of ee.³⁶ However, it should be noted that Wolff-Kishner reduction of **7l** using hydrazine and KOH in glycol solvent led to a racemic product without the Boc group.³⁷

Scheme 2.23 Concise synthesis of chiral 3-benzoyl and benzylpyrrolidine

2.4 Conclusion

In summary, we have reported an enantioselective Wacker-type coupling of propargylic acetates and cyclic olefins with external nucleophiles, including alcohols, carboxylic acids, phenols, water and electron-deficient aryl amines. The concise synthesis of chiral 3-benzylpyrrolidines from **5a** along with other simple functional group transformations were accomplished to illustrate the utility of this method. It is the first example to apply propargylic acetates as the carbon electrophiles in the non-oxidative asymmetric Wacker-type reactions. Furthermore, asymmetric *anti*-attack of truly external nucleophiles on simple mono-olefins proceeded without the aid of tethers or directing groups. Notably, the choice of electron-deficient furyl-MeOBIPHEP is crucial to the reactivity and enantiocontrol of the Wacker-type process.

2.5 Experimental Section

2.5.1 A Typical Procedure for Condition Optimization

In an argon-filled glove box, Pd(dba)₂ (2.9 mg, 0.005 mmol), ligand (0.006 mmol) and 0.1 mL of dry MeCN were charged into a dry 10 mL reaction tube. After stirring for about 15 minutes, 0.1 mL of *i*-PrOH, **2a** (20.4 mg, 0.1 mmol), 2,3-dihydrofuran **1a** (10 μ L, 0.12 mmol, 1.2 equiv), KOAc (15 mg, 0.15 mmol, 1.5 equiv) and GC standard *n*-dodecane 10 μ L were added sequentially. The reaction mixture was capped tightly and stirred on a hotplate maintained at 60 °C for 24 hours. After it was cooled down to rt, aliquots were taken from the reaction mixture and passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC to determine the

calibrated GC conversion of **1a** and GC yields of product **3a**. Chiral HPLC analysis was performed on the crude product to determine enantioselectivity.

2.5.2 Asymmetric Oxyallenylation of 2,3-Dihydrofuran

A typical procedure. In an argon-filled glove box, Pd(dba)₂ (2.3 mg, 0.004 mmol), ligand **L10** (2.6 mg, 0.0048 mmol) and 0.4 mL of dry MeCN were charged into a dry 4-mL vial. After stirring for about 15 minutes, 40 μ L resulting yellow stock solution of Pd complex (0.0004 mmol, 0.2 mol%) was added to a dry 10-mL reaction tube via a microsyringe and diluted with 0.16 mL of dry MeCN and 0.2 mL of dry alcohol. Propargylic acetate (0.2 mmol), 2,3-dihydrofuran (20 μ L, 0.24 mmol, 1.2 equiv), KOAc (30 mg, 0.3 mmol, 1.5 equiv) and GC standard *n*-dodecane (20 μ L) were then added sequentially. The reaction was capped tightly and stirred on a hotplate maintained at 45 °C for 36 hours. After it was cooled down to rt, the reaction mixture was subjected to flash chromatography using ethyl acetate/hexanes as eluent. The enantioselectivity (ee) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns. Similar results were obtained when standard Schlenk tubes and vacuum manifolds were used to set up the reaction.

(2*R*,3*R*)-2-Isopropoxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (**3a**)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 48 mg, 88% yield.

$[\alpha]_D^{23} = +70.2^\circ$ ($c = 1.9$, CHCl₃).

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.727	4160565	49.952
2	10.041	4168535	50.048
Total		8329100	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.758	14693637	94.955
2	10.149	780734	5.045
Total		15474371	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.44-7.42 (m, 2H), 7.33-7.29 (m, 2H), 7.19 (t, $J = 7.2$ Hz, 1H), 5.06 (d, $J = 1.5$ Hz, 1H), 4.04-3.99 (m, 1H), 3.97-3.91 (m, 1H), 3.86 (hept, $J = 6.2$ Hz, 1H), 3.25-3.22 (m, 1H), 2.35-2.30 (m, 1H), 1.93-1.86 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 137.8, 128.4, 126.6, 126.5, 106.7, 105.0, 100.8, 69.2, 67.2, 46.1, 30.4, 23.8, 22.0, 20.43, 20.36.

HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{21}\text{O}_3$ $[\text{M}+\text{H}]^+$: 273.1491; found: 273.1488.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-methylphenyl)allenyl]tetrahydrofuran (3b)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 46 mg, 80% yield.

$[\alpha]^{23}_D = +60.9^\circ$ ($c = 1.9$, CHCl_3).

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.31 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 5.05 (d, $J = 1.3$ Hz, 1H), 4.04-3.98 (m, 1H), 3.96-3.90 (m, 1H), 3.85 (hept, $J = 6.2$ Hz, 1H), 3.22-3.19 (m, 1H), 2.33 (s, 3H), 2.36-2.27 (m, 1H), 1.92-1.84 (m, 1H), 1.82 (s, 3H), 1.81 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.8, 136.2, 134.8, 129.2, 126.5, 106.7, 104.8, 100.6, 69.1, 67.2, 46.1, 30.3, 23.8, 22.0, 21.2, 20.5, 20.4.

HRMS (ESI): Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 309.1831; found: 309.1823.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-methoxyphenyl)allenyl]tetrahydrofuran (3c)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:60) as colorless oil. 43 mg, 72% yield.

$[\alpha]_D^{23} = +64.2^\circ$ ($c = 1.2$, CHCl_3).

Ee = 92%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.32 (d, $J = 6.8$ Hz, 2H), 6.85 (d, $J = 6.8$ Hz, 2H), 5.04 (d, $J = 1.5$ Hz, 1H), 4.03-3.97 (m, 1H), 3.95-3.90 (m, 1H), 3.85 (hept, $J = 6.2$ Hz, 1H), 3.80 (s, 3H), 3.20-3.17 (m, 1H), 2.33-2.26 (m, 1H), 1.90-1.84 (m, 1H), 1.81 (s, 3H), 1.80 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.5, 158.5, 130.1, 127.7, 113.9, 106.7, 104.5, 100.6, 69.1, 67.2, 55.4, 46.2, 30.3, 23.8, 22.0, 20.6, 20.5.

HRMS (ESI): Calcd for $\text{C}_{19}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$: 303.1960; found: 303.1968.

**(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(3,5-dimethylphenyl)allenyl]
tetrahydrofuran (3d)**

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 48 mg, 80% yield.

$[\alpha]_D^{23} = +53.6^\circ$ ($c = 1.9$, CHCl_3).

Ee = 93%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 100:0, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.04 (s, 2H), 6.84 (s, 1H), 5.05 (d, $J = 1.4$ Hz, 1H), 4.04-3.98 (m, 1H), 3.96-3.90 (m, 1H), 3.86 (hept, $J = 6.2$ Hz, 1H), 3.23-3.20 (m, 1H), 2.31 (s, 6H), 2.29-2.26 (m, 1H), 1.91-1.85 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 1.14 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.0, 137.8, 137.7, 128.2, 124.5, 106.8, 105.0, 100.5, 69.1, 67.2, 46.2, 30.3, 23.9, 21.9, 21.6, 20.5, 20.4.

HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}]^+$: 301.2168; found: 301.2167.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(3,5-dimethoxyphenyl)allenyl]tetrahydrofuran (3e)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as light yellow oil. 46 mg, 69% yield.

$[\alpha]_D^{20} = +52.7^\circ$ ($c = 1.1$, CHCl_3).

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 6.60 (d, $J = 2.2$ Hz, 2H), 6.33 (t, $J = 2.2$ Hz, 1H), 5.06 (d, $J = 1.4$ Hz, 1H), 4.03-3.97 (m, 1H), 3.95-3.90 (m, 1H), 3.87 (hept, $J = 6.2$ Hz, 1H), 3.79 (s, 6H), 3.20-3.17 (m, 1H), 2.36-2.28 (m, 1H), 1.92-1.84 (m, 1H), 1.82 (s, 6H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 160.9, 140.2, 106.6, 105.0, 100.8, 98.6, 69.1, 67.1, 55.4, 46.2, 30.4, 23.8, 22.0, 20.4, 20.3.

HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{29}\text{O}_4$ $[\text{M}+\text{H}]^+$: 333.2066; found: 333.2075.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(2-methoxyphenyl)allenyl]tetrahydrofuran (3f)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:60) as colorless oil. 35 mg, 58% yield.

$[\alpha]_D^{23} = +76.3^\circ$ ($c = 1.1$, CHCl_3).

Ee = 91%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.20-7.16 (m, 2H), 6.91-6.85 (m, 2H), 4.99 (d, $J = 1.8$ Hz, 1H), 3.97-3.84 (m, 2H), 3.89 (s, 3H), 3.76 (hept, $J = 6.2$ Hz, 1H), 3.28-3.23 (m, 1H), 2.21-2.16 (m, 1H), 1.86-1.80 (m, 1H), 1.77 (s, 3H), 1.75 (s, 3H), 1.15 (d, $J = 6.2$ Hz, 3H), 1.00 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.6, 157.1, 130.7, 128.2, 128.0, 120.6, 111.3, 106.7, 102.5, 97.3, 69.0, 67.2, 55.7, 47.9, 30.3, 23.8, 22.0, 20.7, 20.6.

HRMS (ESI): Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 325.1780; found: 325.1783.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(naphthalen-2-yl)allenyl]tetrahydrofuran (3g)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as light yellow oil. 57 mg, 88% yield.

$[\alpha]_D^{22} = +18.4^\circ$ ($c = 1.5$, CHCl_3).

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

1 I

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	10.688	2596258	50.398
2	20.628	2555270	49.602
Total		5151528	100.000

1 I

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	10.660	5106273	94.373
2	20.484	304456	5.627
Total		5410730	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.85 (s, 1H), 7.81-7.79 (m, 2H), 7.75 (d, $J = 8.6$ Hz, 1H), 7.58 (dd, $J = 8.6, 1.8$ Hz, 1H), 7.48-7.41 (m, 2H), 5.14 (d, $J = 1.3$ Hz, 1H), 4.10-4.04 (m, 1H), 4.02-3.96 (m, 1H), 3.89 (hept, $J = 6.2$ Hz, 1H), 3.41-3.37 (m, 1H), 2.41-2.36 (m, 1H), 1.99-1.96 (m, 1H), 1.89 (s, 3H), 1.88 (s, 3H), 1.26 (d, $J = 6.2$ Hz, 3H), 1.18 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.8, 135.1, 133.8, 132.4, 128.1, 127.8, 127.6, 126.2, 126.0, 125.7, 124.1, 106.9, 105.4, 101.2, 69.2, 67.2, 46.1, 30.3, 23.9, 22.0, 20.5, 20.4.

HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$: 323.2011; found: 323.2005.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(6-methoxynaphthalen-2-yl)allenyl]

tetrahydrofuran (3h)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:60) as colorless oil. 59 mg, 84% yield.

$[\alpha]_D^{23} = +16.5^\circ$ ($c = 2.5$, CHCl_3).

Ee = 88%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.77 (s, 1H), 7.70-7.64 (m, 2H), 7.54 (dd, $J = 8.6, 1.7$ Hz, 1H), 7.14-7.11 (m, 2H), 5.12 (d, $J = 1.2$ Hz, 1H), 4.08-4.02 (m, 1H), 4.00-3.95 (m, 1H), 3.92 (s, 3H), 3.88 (hept, $J = 6.2$ Hz, 1H), 3.38-3.35 (m, 1H), 2.40-2.35 (m, 1H), 1.98-1.92 (m, 1H), 1.87 (s, 3H), 1.86 (s, 3H), 1.24 (d, $J = 6.2$ Hz, 3H), 1.16 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.4, 157.7, 133.5, 132.9, 129.6, 129.2, 126.7, 126.5, 124.0, 118.8, 106.9, 106.0, 105.3, 101.1, 69.2, 67.2, 55.4, 46.1, 30.3, 23.9, 22.0, 20.6, 20.5.

HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{29}\text{O}_3$ $[\text{M}+\text{H}]^+$: 353.2117; found: 353.2113.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-piperonylallenyl]tetrahydrofuran (3i)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:60) as colorless oil. 48 mg, 76% yield.

$[\alpha]_D^{22} = +68.4^\circ$ ($c = 1.7$, CHCl_3).

Ee = 94%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 6.92 (d, $J = 1.7$ Hz, 1H), 6.89 (dd, $J = 8.1, 1.7$ Hz, 1H), 6.75 (d, $J = 8.1$ Hz, 1H), 5.93 (s, 2H), 5.02 (d, $J = 1.5$ Hz, 1H), 4.02-3.96 (m, 1H), 3.94-3.89 (m, 1H), 3.85 (hept, $J = 6.2$ Hz, 1H), 3.14-3.12 (m, 1H), 2.33-2.27 (m, 1H), 1.88-1.82 (m, 1H), 1.81 (s, 3H), 1.80 (s, 3H), 1.20 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.6, 147.9, 146.4, 132.0, 119.5, 108.1, 107.4, 106.7, 104.8, 101.1, 100.9, 69.1, 67.1, 46.4, 30.4, 23.8, 21.9, 20.5, 20.4.

HRMS (ESI): Calcd for $\text{C}_{19}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$: 317.1753; found: 317.1750.

(2R,3R)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-fluorophenyl)allenyl]tetrahydrofuran

(3j)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 45 mg, 78% yield.

$[\alpha]_D^{23} = +64.7^\circ$ ($c = 1.5$, CHCl_3).

Ee = 93%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

1 F

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.093	223515	50.763
2	9.208	216792	49.237
Total		440307	100.000

1 F

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.128	867918	96.531
2	9.229	31191	3.469
Total		899109	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.35 (m, 2H), 7.01-6.97 (m, 2H), 5.01 (d, $J = 1.5$ Hz, 1H), 4.03-3.97 (m, 1H), 3.95-3.91 (m, 1H), 3.84 (hept, $J = 6.2$ Hz, 1H), 3.17-3.15 (m, 1H), 2.36-2.25 (m, 1H), 1.91-1.84 (m, 1H), 1.82 (s, 3H), 1.81 (s, 3H), 1.20 (d, $J = 6.2$ Hz, 3H), 1.11 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.9, 161.8 (d, $J_{\text{CF}} = 245.6$ Hz), 133.7 (d, $J_{\text{CF}} = 3.4$ Hz), 128.1 (d, $J_{\text{CF}} = 7.9$ Hz), 115.2 (d, $J_{\text{CF}} = 21.4$ Hz), 106.6, 104.2, 101.0, 69.2, 67.1, 46.3, 30.3, 23.8, 21.9, 20.5, 20.4.

^{19}F NMR (376.6 MHz, CDCl_3): δ -116.6 to -116.7 (m).

HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{24}\text{FO}_2$ $[\text{M}+\text{H}]^+$: 291.1760; found: 291.1758.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-chlorophenyl)allenyl]tetrahydrofuran

(3k)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 47 mg, 77% yield.

$[\alpha]_D^{22} = +65.7^\circ$ ($c = 1.7$, CHCl_3).

Ee = 93%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	8.310	596708	50.123
2	10.211	593774	49.877
Total		1190483	100.000

Peak#	Ret. Time	Area	Area %
1	8.308	2121138	96.335
2	10.185	80687	3.665
Total		2201825	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.37-7.33 (m, 2H), 7.29-7.26 (m, 2H), 5.01 (d, $J = 1.5$ Hz, 1H), 4.03-3.98 (m, 1H), 3.96-3.91 (m, 1H), 3.85 (hept, $J = 6.2$ Hz, 1H), 3.19-3.15 (m, 1H), 2.36-2.27 (m, 1H), 1.91-1.84 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 136.3, 132.2, 128.5, 127.9, 106.6, 104.3, 101.3, 69.2, 67.1, 46.1, 30.3, 23.8, 21.9, 20.4, 20.3.

HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{23}^{35}\text{ClO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 329.1284; found: 329.1288.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-bromophenyl)allenyl]tetrahydrofuran (3l)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:80) as colorless oil. 57 mg, 81% yield.

$[\alpha]_D^{22} = +45.9^\circ$ ($c = 1.8$, CHCl_3).

Ee = 92%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.43-7.40 (m, 2H), 7.29-7.26 (m, 2H), 5.00 (d, $J = 1.6$ Hz, 1H), 4.02-3.97 (m, 1H), 3.95-3.90 (m, 1H), 3.84 (hept, $J = 6.2$ Hz, 1H), 3.18-3.14

(m, 1H), 2.35-2.27 (m, 1H), 1.90-1.83 (m, 1H), 1.82 (s, 3H), 1.81 (s, 3H), 1.20 (d, $J = 6.2$ Hz, 3H), 1.11 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 136.8, 131.5, 128.2, 120.3, 106.6, 104.4, 101.4, 69.2, 67.1, 46.0, 30.3, 23.8, 21.9, 20.33, 20.27.

HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{24}^{79}\text{BrO}_2$ $[\text{M}+\text{H}]^+$: 351.0960; found: 351.0958.

(2*R*,3*R*)-2-Isopropoxy-3-{3,3-dimethyl-1-[(4-methoxycarbonyl)phenyl]allenyl} tetrahydrofuran (3m)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:40) as colorless oil. 48 mg, 73% yield.

$[\alpha]_{\text{D}}^{23} = +49.9^\circ$ ($c = 2.0$, CHCl_3).

Ee = 94%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 5.02 (d, $J = 1.5$ Hz, 1H), 4.04-3.93 (m, 2H), 3.91 (s, 3H), 3.85 (hept, $J = 6.2$ Hz, 1H), 3.24-

3.21 (m, 1H), 2.38-2.30 (m, 1H), 1.91-1.87 (m, 1H), 1.843 (s, 3H), 1.837 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 202.3, 167.2, 142.8, 129.8, 128.1, 126.4, 106.5, 104.8, 101.5, 69.2, 67.1, 52.1, 46.0, 30.3, 23.8, 21.9, 20.3, 20.2.

HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{27}\text{O}_4$ $[\text{M}+\text{H}]^+$: 331.1909; found: 331.1905.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-benzoylphenyl)allenyl]

tetrahydrofuran (3n)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as colorless oil. 60 mg, 80% yield.

$[\alpha]_D^{22} = +40.1^\circ$ ($c = 1.7$, CHCl_3).

Ee = 94%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.80-7.76 (m, 4H), 7.59-7.45 (m, 5H), 5.05 (d, $J = 1.5$ Hz, 1H), 4.05-3.99 (m, 1H), 3.97-3.92 (m, 1H), 3.86 (hept, $J = 6.2$ Hz, 1H), 3.27-3.23

(m, 1H), 2.39-2.31 (m, 1H), 1.94-1.87 (m, 1H), 1.853 (s, 3H), 1.849 (s, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 202.4, 196.4, 142.4, 138.1, 135.4, 132.3, 130.5, 130.1, 128.4, 126.3, 106.5, 104.9, 101.5, 69.2, 67.1, 46.0, 30.3, 23.8, 21.9, 20.25, 20.18.

HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{29}\text{O}_3$ $[\text{M}+\text{H}]^+$: 377.2117; found: 377.2113.

(2*R*,3*R*)-2-Isopropoxy-3-{3,3-dimethyl-1-[(3-fluoro-4-phenyl)phenyl]allenyl}tetrahydrofuran (3o)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:80) as colorless oil. 59 mg, 80% yield.

$[\alpha]_D^{22} = +49.0^\circ$ ($c = 1.5$, CHCl_3).

Ee = 93%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.57-7.55 (m, 2H), 7.46-7.34 (m, 4H), 7.28-7.22 (m, 2H), 5.07 (d, J = 1.4 Hz, 1H), 4.05-4.00 (m, 1H), 3.98-3.93 (m, 1H), 3.88 (hept, J = 6.2

Hz, 1H), 3.22-3.19 (m, 1H), 2.38-2.30 (m, 1H), 1.95-1.87 (m, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.23 (d, $J = 6.2$ Hz, 3H), 1.16 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.4, 160.0 (d, $J_{\text{CF}} = 247.1$ Hz), 139.4 (d, $J_{\text{CF}} = 7.9$ Hz), 135.9, 130.5 (d, $J_{\text{CF}} = 4.2$ Hz), 129.0 (d, $J_{\text{CF}} = 3.1$ Hz), 128.6, 127.7, 126.9 (d, $J_{\text{CF}} = 13.7$ Hz), 122.3 (d, $J_{\text{CF}} = 3.0$ Hz), 114.1 (d, $J_{\text{CF}} = 24.5$ Hz), 106.6, 104.3, 101.6, 69.3, 67.1, 46.1, 30.3, 23.9, 21.9, 20.4, 20.3.

^{19}F NMR (376.6 MHz, CDCl_3): δ -118.4 to -118.5 (m).

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{27}\text{FO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 389.1893; found: 389.1886.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(quinolin-3-yl)allenyl]tetrahydrofuran (3p)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as colorless oil. 47 mg, 73% yield.

$[\alpha]_{\text{D}}^{23} = +12.8^\circ$ ($c = 1.3$, CHCl_3).

$E_e = 91\%$. Daicel Chiralcel IC, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 8.99 (d, $J = 2.2$ Hz, 1H), 8.09 (d, $J = 2.2$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 7.76 (d, $J = 8.1$ Hz, 1H), 7.67-7.62 (m, 1H), 7.54-7.50 (m, 1H), 5.09 (d, $J = 1.7$ Hz, 1H), 4.08-3.96 (m, 2H), 3.88 (hept, $J = 6.2$ Hz, 1H), 3.33-3.29 (m, 1H), 2.40-2.32 (m, 1H), 2.00-1.92 (m, 1H), 1.883 (s, 3H), 1.876 (s, 3H), 1.24 (d, $J = 6.2$ Hz, 3H), 1.14 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.8, 151.2, 146.7, 130.9, 130.7, 129.3, 128.9, 128.1, 127.8, 126.9, 106.6, 102.9, 102.4, 69.3, 67.1, 45.9, 30.2, 23.9, 21.9, 20.4, 20.3.

HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 324.1964; found: 324.1968.

**(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(thiophen-3-yl)allenyl]tetrahydrofuran
(3q)**

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 41 mg, 74% yield.

$[\alpha]^{22}_{\text{D}} = +65.9^\circ$ ($c = 1.6$, CHCl_3).

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.23 (dd, $J = 5.0, 2.9$ Hz, 1H), 7.14 (dd, $J = 2.9, 1.3$ Hz, 1H), 7.07 (dd, $J = 5.0, 1.3$ Hz, 1H), 5.08 (d, $J = 1.5$ Hz, 1H), 4.02-3.96 (m, 1H), 3.95-3.92 (m, 1H), 3.87 (hept, $J = 6.2$ Hz, 1H), 3.13-3.09 (m, 1H), 2.33-2.24 (m, 1H), 1.93-1.82 (m, 1H), 1.81 (s, 3H), 1.80 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.14 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.6, 139.8, 127.5, 125.2, 119.0, 106.7, 101.4, 100.4, 69.1, 67.1, 47.1, 30.1, 23.9, 22.0, 20.6, 20.5.

HRMS (ESI): Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$: 301.1238; found: 301.1236.

(2R,3R)-2-Isopropoxy-3-[3,3-dimethyl-1-(N-tosylindol-5-yl)allenyl]tetrahydrofuran (3r)

200 μL of the resulting yellow solution of the in situ formed complex (0.002 mmol, 1 mol%) was added to a dry 10-mL reaction tube, diluted with 0.2 mL of *i*-PrOH. The

product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as foam. 73 mg, 78% yield.

$[\alpha]_D^{23} = +42.4^\circ$ ($c = 1.4$, CHCl_3).

Ee = 93%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, $J = 8.8$ Hz, 1H), 7.75 (d, $J = 8.3$ Hz, 2H), 7.55 (d, $J = 1.4$ Hz, 1H), 7.52 (d, $J = 3.6$ Hz, 1H), 7.40 (dd, $J = 8.8, 1.7$ Hz, 1H), 7.20 (d, $J = 8.3$ Hz, 2H), 6.61 (d, $J = 3.6$ Hz, 1H), 5.03 (d, $J = 1.4$ Hz, 1H), 4.03-3.90 (m, 2H), 3.83 (hept, $J = 6.2$ Hz, 1H), 3.26-3.22 (m, 1H), 2.33 (s, 3H), 2.35-2.27 (m, 1H), 1.92-1.84 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.10 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.0, 145.0, 135.5, 133.7, 133.2, 131.2, 130.0, 126.9, 126.7, 124.0, 118.8, 113.4, 109.4, 106.7, 104.9, 100.8, 69.2, 67.1, 46.4, 30.4, 23.8, 21.9, 21.6, 20.5, 20.4.

HRMS (ESI): Calcd for $\text{C}_{27}\text{H}_{32}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 466.2052; found: 466.2043.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(cyclohex-1-en-1-yl)allenyl]tetrahydrofuran (3s)

200 μ L of the resulting yellow solution of the in situ formed complex (0.002 mmol, 1 mol%) was added to a dry 10-mL reaction tube, diluted with 0.2 mL of *i*-PrOH. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 42 mg, 76% yield.

$[\alpha]_D^{22} = +63.3^\circ$ ($c = 1.3$, CHCl_3).

Ee = 94%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 5.78-5.76 (m, 1H), 4.98 (d, $J = 1.2$ Hz, 1H), 3.96-3.91 (m, 1H), 3.88-3.81 (m, 2H), 2.97-2.93 (m, 1H), 2.25-2.17 (m, 1H), 2.14-2.09 (m, 2H), 2.03-1.99 (m, 2H), 1.82-1.74 (m, 1H), 1.71 (s, 6H), 1.65-1.53 (m, 4H), 1.18 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.5, 133.7, 122.7, 107.1, 106.9, 99.7, 68.9, 67.1, 44.9, 30.2, 27.7, 26.1, 23.8, 23.2, 22.6, 21.9, 20.8, 20.7.

HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}]^+$: 277.2168; found: 277.2175.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-cyclobutylene-1-phenylallenyl]tetrahydrofuran (3t)

200 μ L of the resulting yellow solution of the in situ formed complex (0.002 mmol, 1 mol%) was added to a dry 10-mL reaction tube, diluted with 0.2 mL of *i*-PrOH. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:80) as colorless oil. 40 mg, 67% yield.

$[\alpha]_D^{22} = +68.5^\circ$ ($c = 1.7$, CHCl_3).

Ee = 88%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 100:0, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.43-7.41 (m, 2H), 7.32-7.28 (m, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 5.06 (d, $J = 1.4$ Hz, 1H), 4.04-3.98 (m, 1H), 3.96-3.91 (m, 1H), 3.85 (hept, $J = 6.2$ Hz, 1H), 3.26-3.23 (m, 1H), 2.55-2.39 (m, 4H), 2.37-2.28 (m, 1H), 1.94-1.85 (m, 1H), 1.77-1.73 (m, 4H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 196.8, 137.8, 128.4, 126.6, 126.5, 109.3, 107.4, 106.7, 69.1, 67.2, 46.2, 31.2, 30.4, 27.4, 27.3, 23.9, 22.0.

HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$: 299.2011; found: 299.2019.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-cyclopentylene-1-phenylallenyl]tetrahydrofuran (3u)

200 μ L of the resulting yellow solution of the in situ formed complex (0.002 mmol, 1 mol%) was added to a dry 10-mL reaction tube, diluted with 0.2 mL of *i*-PrOH. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:80) as colorless oil. 49 mg, 78% yield.

$[\alpha]_D^{22} = +69.4^\circ$ ($c = 2.0$, CHCl_3).

Ee = 87%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 100:0, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.46-7.43 (m, 2H), 7.33-7.29 (m, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 5.06 (d, $J = 1.4$ Hz, 1H), 4.05-3.93 (m, 2H), 3.86 (hept, $J = 6.2$ Hz, 1H), 3.26-3.22 (m, 1H), 2.38-2.29 (m, 1H), 2.26-2.21 (m, 4H), 1.98-1.89 (m, 1H), 1.75-1.58 (m, 6H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.5, 137.8, 128.4, 126.5, 108.1, 106.7, 104.8, 69.1, 67.2, 46.0, 31.6, 31.5, 30.3, 28.0, 26.3, 23.8, 22.0.

HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}]^+$: 313.2168; found: 313.2174.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-cyclohexylene-1-phenylallenyl]tetrahydrofuran (3v)

200 μ L of the resulting yellow solution of the in situ formed complex (0.002 mmol, 1 mol%) was added to a dry 10-mL reaction tube, diluted with 0.2 mL of *i*-PrOH. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:80) as colorless oil. 50 mg, 77% yield.

$[\alpha]^{22}_{\text{D}} = +50.3^\circ$ ($c = 1.6$, CHCl_3).

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.46-7.43 (m, 2H), 7.33-7.29 (m, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 5.07 (d, $J = 1.1$ Hz, 1H), 4.04-3.93 (m, 2H), 3.86 (hept, $J = 6.2$ Hz, 1H), 3.25-3.22 (m, 1H), 2.40-2.29 (m, 5H), 1.97-1.89 (m, 1H), 1.73-1.59 (m, 8H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.3, 137.8, 128.4, 126.44, 126.38, 110.1, 106.7, 104.8, 69.1, 67.1, 46.0, 32.5, 32.4, 30.3, 29.63, 29.56, 28.9, 28.8, 23.9, 22.0.

HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{31}\text{O}_2$ $[\text{M}+\text{H}]^+$: 327.2324; found: 327.2328.

(2*R*,3*R*)-2-Isopropoxy-3-(3,3-diethyl-1-phenylallenyl)tetrahydrofuran (3w)

Pd(dba)₂ (2.3 mg, 0.004 mmol), ligand **L14** (2.6 mg, 0.0048 mmol), 0.2 mL of dry MeCN and 0.2 mL of dry *i*-PrOH were charged into a dry 10-mL reaction tube directly, stirring for about 15 minutes. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:80) as colorless oil. 28 mg, 47% yield.

$[\alpha]_D^{20} = +48.7^\circ$ ($c = 1.3$, CHCl₃).

Ee = 88%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	7.896	6516136	49.035
2	11.327	6772588	50.965
Total		13288724	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	7.879	376410	94.210
2	11.109	23135	5.790
Total		399545	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.48-7.45 (m, 2H), 7.32-7.28 (m, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 5.08 (d, *J* = 1.4 Hz, 1H), 4.03-3.98 (m, 1H), 3.97-3.91 (m, 1H), 3.86 (hept, *J* = 6.2 Hz, 1H), 3.29-3.25 (m, 1H), 2.36-2.28 (m, 1H), 2.18-2.10 (m, 4H), 1.95-1.87 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 3H), 1.040 (t, *J* = 7.4 Hz, 3H), 1.036 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 199.4, 138.0, 128.4, 126.4, 126.2, 114.1, 109.1, 106.8, 69.1, 67.1, 46.1, 30.3, 26.25, 26.21, 23.9, 22.0, 12.5, 12.4.

HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 323.1987; found: 323.1985.

(2R,3R)-2-Methoxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (4a)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 42 mg, 86% yield.

$[\alpha]_D^{23} = +54.7^\circ$ ($c = 1.7$, CHCl_3).

Ee = 90%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.41-7.38 (m, 2H), 7.33-7.29 (m, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 4.84 (d, $J = 0.9$ Hz, 1H), 4.03-3.93 (m, 2H), 3.35 (s, 3H), 3.27-3.24 (m, 1H), 2.35-2.30 (m, 1H), 1.92-1.89 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 137.6, 128.5, 126.6, 126.5, 109.4, 104.7, 100.8, 67.5, 54.9, 45.9, 30.1, 20.4, 20.3.

HRMS (ESI): Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 267.1361; found: 267.1349.

(2*R*,3*R*)-2-Ethoxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (4b)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 47 mg, 91% yield.

$[\alpha]_D^{22} = +79.2^\circ$ ($c = 1.6$, CHCl_3).

Ee = 92%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99.9:0.1, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	8.893	774491	50.413
2	10.558	761799	49.587
Total		1536290	100.000

Peak#	Ret. Time	Area	Area %
1	9.083	20585182	95.876
2	10.789	885365	4.124
Total		21470546	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.43-7.40 (m, 2H), 7.33-7.29 (m, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 4.96 (d, $J = 1.1$ Hz, 1H), 4.02-3.92 (m, 2H), 3.77-3.69 (m, 1H), 3.49-3.41 (m, 1H), 3.28-3.25 (m, 1H), 2.36-2.32 (m, 1H), 1.92-1.87 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 137.7, 128.5, 126.6, 108.2, 104.8, 100.8, 67.4, 63.0, 45.9, 30.3, 20.4, 20.3, 15.4.

HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 281.1517; found: 281.1524.

(2*R*,3*R*)-2-Benzoyloxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (4c)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 53 mg, 83% yield.

$[\alpha]_D^{22} = +122.3^\circ$ ($c = 1.9$, CHCl_3).

Ee = 90%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.26 (m, 9H), 7.20-7.16 (m, 1H), 5.06 (d, $J = 1.0$ Hz, 1H), 4.74 (d, $J = 11.9$ Hz, 1H), 4.47 (d, $J = 11.9$ Hz, 1H), 4.09-3.97 (m, 2H), 3.37-3.34 (m, 1H), 2.40-2.33 (m, 1H), 1.95-1.90 (m, 1H), 1.81 (s, 3H), 1.79 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 138.5, 137.6, 128.51, 128.48, 128.0, 127.7, 126.5, 107.7, 104.7, 100.9, 69.4, 67.9, 45.9, 30.2, 20.4, 20.3.

HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 343.1674; found: 343.1669.

(2*R*,3*R*)-2-Cyclohexyloxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (4d)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:75) as colorless oil. 53 mg, 85% yield.

$[\alpha]^{22}_D = +77.6^\circ$ ($c = 2.2$, CHCl_3).

Ee = 90%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.44-7.41 (m, 2H), 7.32-7.28 (m, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 5.10 (d, $J = 1.4$ Hz, 1H), 4.04-3.99 (m, 1H), 3.96-3.91 (m, 1H), 3.55-3.48 (m, 1H), 3.26-3.22 (m, 1H), 2.35-2.29 (m, 1H), 1.92-1.85 (m, 2H), 1.824 (s, 3H), 1.821 (s, 3H), 1.78-1.66 (m, 2H), 1.55-1.50 (m, 1H), 1.41-1.18 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 137.8, 128.4, 126.6, 126.5, 106.5, 105.0, 100.8, 75.1, 67.2, 46.0, 34.1, 32.1, 30.4, 25.9, 24.6, 24.4, 20.43, 20.37.

HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}]^+$: 313.2168; found: 313.2166.

(2*R*,3*R*)-2-(*tert*-Butoxy)-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (4e)

200 μL of the resulting yellow solution of the in situ formed complex (0.002 mmol, 1 mol%) was added to a dry 10-mL reaction tube, diluted with 0.2 mL of *t*-BuOH. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:90) as colorless oil. 33 mg, 58% yield.

$[\alpha]_D^{22} = +83.0^\circ$ ($c = 1.2$, CHCl_3).

Ee = 86%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.43-7.40 (m, 2H), 7.32-7.28 (m, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 5.23 (d, $J = 2.0$ Hz, 1H), 4.07-4.01 (m, 1H), 3.92-3.87 (m, 1H), 3.21-3.16 (m, 1H), 2.36-2.28 (m, 1H), 1.91-1.84 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.22 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 137.9, 128.4, 126.7, 126.5, 105.1, 103.6, 100.7, 74.2, 67.0, 46.8, 30.7, 29.1, 20.5, 20.4.

HRMS (ESI): Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 309.1831; found: 309.1833.

(2*R*,3*R*)-2-Hydroxyethoxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (4f)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:2) as colorless oil. 50 mg, 91% yield.

$[\alpha]_D^{22} = +59.3^\circ$ ($c = 1.5$, CHCl_3).

Ee = 90%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.41-7.38 (m, 2H), 7.34-7.30 (m, 2H), 7.20 (t, $J = 7.0$ Hz, 1H), 4.97 (d, $J = 1.6$ Hz, 1H), 4.08-3.95 (m, 2H), 3.74-3.67 (m, 4H), 3.34-3.30 (m, 1H), 2.84 (br s, OH), 2.40-2.31 (m, 1H), 1.98-1.90 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 137.5, 128.5, 126.7, 126.5, 109.3, 104.3, 101.0, 70.8, 67.6, 62.6, 45.8, 30.3, 20.4, 20.3.

HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 297.1467; found: 297.1459.

(2R,3R)-2-Hydroxyethoxy-3-(3-ethyl-3-methyl-1-phenylallenyl)tetrahydrofuran
(4g)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:3) as colorless oil. 48 mg, 83% yield. The ratio of two diastereomers is determined to be 1.2:1 based on crude ^1H NMR.

$[\alpha]_D^{19} = +54.4^\circ$ ($c = 1.0$, CHCl_3).

Ee = 88%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR of two diastereomers (400 MHz, CDCl_3): δ 7.43-7.40 (m, 2H), 7.34-7.30 (m, 2H), 7.22-7.18 (m, 1H), 5.00-4.98 (m, 1H), 4.08-3.95 (m, 2H), 3.74-3.67 (m, 4H), 3.35-3.32 (m, 1H), 2.80 (brs, OH), 2.40-2.31 (m, 1H), 2.15-2.09 (m, 2H), 1.95-1.90 (m, 1H), 1.82-1.81 (m, 3H), 1.07-1.02 (m, 3H).

^{13}C NMR of two diastereomers (100 MHz, CDCl_3): δ 200.2 and 200.1, 137.6, 128.6, 126.7, 126.32 and 126.30, 109.4, 107.5 and 107.4, 106.4 and 106.3, 70.9 and 70.8, 67.65 and 67.63, 62.6, 45.91 and 45.88, 30.4 and 30.3, 27.53 and 27.49, 19.0 and 18.9, 12.4 and 12.3.

HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{25}\text{O}_3$ $[\text{M}+\text{H}]^+$: 289.1804; found: 289.1805.

(2R,3R,5R)-2-Isopropoxy-3-[3,3-dimethyl-1-phenylallenyl]-5-(4-methoxyphenyl) tetrahydrofuran (4h)

A stock solution of in situ formed Pd complex (200 μL , 0.002 mmol, 1 mol%) was added to a dry 10-mL reaction tube and diluted with 0.2 mL of *i*-PrOH. Alkene (105.7 mg, 0.6 mmol, 3 equiv) was added. The product was isolated by flash chromatography

(ethyl acetate/hexanes 1:60) as colorless oil. 59 mg, 78% yield. The relative configuration of benzylic carbon atom was assigned based on a strong NOE signal between hydrogen atoms H_a and H_b.

$[\alpha]_D^{20} = +31.2^\circ$ ($c = 1.1$, CHCl₃).

Ee = 80%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.43 (d, $J = 8.6$ Hz, 2H), 7.37-7.31 (m, 4H), 7.21 (t, $J = 7.2$ Hz, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 5.20 (s, 1H), 5.09 (dd, $J = 9.6, 6.5$ Hz, 1H), 4.00 (hept, $J = 6.1$ Hz, 1H), 3.82 (s, 3H), 3.41 (ψd, $J = 6.9$ Hz, 1H), 2.40-2.25 (m, 2H), 1.92 (s, 3H), 1.88 (s, 3H), 1.28 (d, $J = 6.1$ Hz, 3H), 1.17 (d, $J = 6.1$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 201.0, 159.1, 137.2, 135.5, 128.5, 128.0, 126.6, 126.5, 113.8, 106.0, 103.8, 100.8, 82.0, 68.8, 55.4, 47.0, 38.6, 23.8, 21.6, 20.5, 20.3.

HRMS (ESI): Calcd for C₂₅H₃₁O₃ [M+H]⁺: 379.2273; found: 379.2276.

(2*R*,3*R*)-2-Acetoxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (6a)

AcOH (34 μ L, 3 equiv) and KOAc (60 mg, 3 equiv) were added. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as colorless oil. 50 mg, 92% yield.

$[\alpha]_D^{19} = +77.5^\circ$ ($c = 1.4$, CHCl_3).

Ee = 92%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.36 (m, 2H), 7.33-7.29 (m, 2H), 7.20 (t, $J = 7.2$ Hz, 1H), 6.15 (s, 1H), 4.15-4.10 (m, 1H), 4.04-3.98 (m, 1H), 3.39-3.36 (m, 1H), 2.44-2.35 (m, 1H), 2.08 (s, 3H), 2.01-1.95 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 170.5, 137.0, 128.6, 126.8, 126.4, 103.4, 102.6, 101.3, 69.0, 45.2, 29.6, 21.6, 20.4, 20.2.

HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{21}\text{O}_3$ $[\text{M}+\text{H}]^+$: 273.1491; found: 273.1489.

(2*R*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-phenoxytetrahydrofuran (6b)

Pd(cod)Cl₂ was used instead of Pd(dba)₂ to increase the yield of product. PhOH (226 mg, 12 equiv) and KOAc (4 mg, 20 mol%) were added. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:85) as colorless oil. 40 mg, 65% yield. $[\alpha]_D^{19} = +141.9^\circ$ ($c = 1.0$, CHCl₃).

Ee = 90%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.46-7.44 (m, 2H), 7.35-7.26 (m, 4H), 7.21 (t, $J = 7.3$ Hz, 1H), 7.06-7.03 (m, 2H), 6.99 (t, $J = 7.3$ Hz, 1H), 5.67 (d, $J = 0.9$ Hz, 1H), 4.20-4.14 (m, 1H), 4.09-4.04 (m, 1H), 3.61-3.58 (m, 1H), 2.55-2.50 (m, 1H), 2.06-2.01 (m, 1H), 1.87 (s, 3H), 1.86 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 201.2, 157.3, 137.3, 129.5, 128.6, 126.7, 126.5, 121.8, 116.9, 106.7, 104.1, 101.2, 68.4, 46.1, 29.9, 20.4, 20.3.

HRMS (ESI): Calcd for C₂₁H₂₂O₂Na [M+Na]⁺: 329.1517; found: 329.1524.

(2*R*,3*R*)-2-Hydroxy-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (6c)

40 μL of the resulting yellow solution of the in situ formed complex (0.0004 mmol, 0.2 mol%) was added to a dry 10-mL reaction tube, diluted with 0.26 mL of MeCN and 54 μL (15 equiv) of H_2O . The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as colorless oil. 25 mg, 54% yield. dr 4:1 based on proton NMR spectroscopy (inseparable by GC). The structures of two isomers were also confirmed by the following experiment: a purified sample of **3a** was subjected to acidic hydrolysis by 3.6 equiv of TsOH in acetone/water 2:1 at 50 $^\circ\text{C}$ overnight, which resulted in the same two isomers of hemiacetals after purification.

$[\alpha]_D^{23} = +43.4^\circ$ ($c = 0.75$, CHCl_3).

Ee = 88%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

^1H NMR of two diastereomers (400 MHz, CDCl_3): δ 7.43-7.38 (m, 2H), 7.34-7.30 (m, 2H), 7.22-7.18 (m, 1H), 5.50 (qt, $J = 4.8$ Hz, 0.2H), 5.36 (d, $J = 1.4$ Hz, 0.8H), 4.18-4.11 (m, 1H), 3.98-3.89 (m, 1H), 3.32-3.26 (m, 1H), 2.58 (d, $J = 2.6$ Hz, 0.8 Hz), 2.47-2.35 (m, 1H), 2.17-2.07 (m, 0.2H), 1.96-1.92 (m, 1H), 1.88 (s, 1.2H), 1.82 (s, 4.8H).

^{13}C NMR of two diastereomers (100 MHz, CDCl_3): δ 201.2 and 203.2, 137.5, 128.5 and 128.7, 126.6 and 126.9, 126.5 and 126.3, 104.3, 102.9, 100.9 and 97.1, 67.9 and 66.8, 46.6 and 45.5, 29.8 and 28.2, 20.5 and 20.8, 20.3 and 20.4.

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$: 231.1385; found: 231.1384.

2.5.3 Asymmetric Oxyallenylation of *N*-Boc-2,3-dihydropyrrole

A typical procedure. In an argon-filled glove box, $\text{Pd}(\text{cod})\text{Cl}_2$ (1.1 mg, 0.004 mmol), **L10** (2.6 mg, 0.0048 mmol) and 0.4 mL of dry MeCN were charged into a dry 4-mL vial. After stirring for about 15 minutes, 100 μL yellow stock solution of the Pd complex (0.001 mmol, 1 mol%) was added to a dry 10-mL reaction tube via a microsyringe and diluted with 0.1 mL of alcohol. Propargylic acetate (0.1 mmol), *N*-Boc-2,3-dihydropyrrole (33.8 mg, 0.2 mmol, 2 equiv), KOAc (19.6 mg, 0.2 mmol, 2 equiv) and GC standard *n*-dodecane (10 μL) were added sequentially. The reaction was capped tightly and stirred on a hotplate maintained at 45 $^\circ\text{C}$ for 60 hours. After it was cooled down to rt, the reaction mixture was subjected to flash chromatography using ethyl acetate/hexanes as eluent. The enantioselectivity (ee) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns. The use of $\text{Pd}(\text{dba})_2$ resulted in a slower conversion.

(2*R*,3*R*)-2-Isopropoxy-3-(3,3-dimethyl-1-phenylallenyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine (5a)

The product from 0.1 mmol scale was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as colorless oil. 27 mg, 73% yield and 92% ee. When the reaction was conducted on 1.5 mmol scale at 50 °C, **5a** was obtained in 69% yield and 92% ee (see below).

$[\alpha]_D^{22} = +49.2^\circ$ ($c = 1.4$, CHCl_3).

Ee = 92%. Daicel Chiralcel IC, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.37-7.28 (m, 4H), 7.21-7.18 (m, 1H), 5.26 (s, 0.4H), 5.10 (s, 0.6H), 4.04-3.98 (m, 0.4H), 3.90-3.84 (m, 0.6H), 3.44-3.30 (m, 2H), 3.14 (d, $J = 6.9$ Hz, 1H), 2.47-2.34 (m, 1H), 1.88-1.83 (m, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.46 (s, 9H), 1.20-1.16 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 155.2 and 154.7, 137.1, 128.5, 126.6, 126.4, 103.6, 100.4, 89.8, 79.8 and 79.4, 69.4 and 68.4, 45.6 and 45.2, 45.0 and 44.5, 28.6, 28.1, 27.2, 23.4 and 23.3, 22.6 and 22.3, 20.5 and 20.4.

HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 394.2358; found: 394.2363.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-methylphenyl)allenyl]-*N*-(*tert*-butyl oxycarbonyl)pyrrolidine (5b)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as light yellow oil. 21 mg, 55% yield.

$[\alpha]_D^{19} = +40.5^\circ$ ($c = 1.0$, CHCl_3).

Ee = 91%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.242	71787	49.791
2	10.023	72389	50.209
Total		144176	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.240	1041864	95.291
2	9.977	51485	4.709
Total		1093349	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.25-7.23 (m, 2H), 7.13-7.10 (m, 2H), 5.24 (s, 0.4H), 5.09 (s, 0.6H), 4.06-3.98 (m, 0.4H), 3.89-3.83 (m, 0.6H), 3.43-3.32 (m, 2H), 3.12 (d, $J = 7.0$ Hz, 1H), 2.43-2.35 (m, 1H), 2.33-2.31 (m, 3H), 1.87-1.81 (m, 1H), 1.80-1.76 (m, 6H), 1.46 (s, 9H), 1.17-1.15 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.4, 155.2 and 154.7, 136.4, 134.1, 129.3, 126.3, 103.5, 100.2, 90.1 and 89.9, 79.8 and 79.3, 69.4 and 68.4, 45.7 and 45.2, 45.0 and 44.5, 28.7 and 28.6, 28.1, 27.3, 23.5 and 23.4, 22.6 and 22.4, 21.2, 20.5 and 20.4.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{35}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 408.2515; found: 408.2515.

(2R,3R)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-bromophenyl)allenyl]-N-(tert-butyl oxycarbonyl)pyrrolidine (5c)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as light yellow oil. 30 mg, 67% yield.

$[\alpha]_{\text{D}}^{23} = +32.3^\circ$ ($c = 1.3$, CHCl_3).

Ee = 92%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.43-7.40 (m, 2H), 7.22-7.19 (m, 2H), 5.23 (s, 0.4H), 5.07 (s, 0.6H), 4.03-3.97 (m, 0.4H), 3.89-3.82 (m, 0.6H), 3.43-3.29 (m, 2H), 3.08 (d, $J = 7.0$ Hz, 1H), 2.46-2.33 (m, 1H), 1.84-1.81 (m, 1H), 1.80 (s, 3H), 1.77 (s, 3H), 1.45 (s, 9H), 1.18-1.15 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.8, 155.2 and 154.6, 136.2, 131.6, 127.9, 120.4, 103.0, 101.0, 89.8 and 89.6, 79.9 and 79.5, 69.4 and 68.4, 45.5 and 45.1, 44.9 and 44.4, 28.65 and 28.59, 28.0, 27.2, 23.5 and 23.4, 22.5 and 22.2, 20.4 and 20.3.

HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{32}^{79}\text{BrNO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 472.1463; found: 472.1471.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(4-fluorophenyl)allenyl]-*N*-(*tert*-butyl oxycarbonyl)pyrrolidine (5d)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as light yellow oil. 24 mg, 62% yield.

$[\alpha]_D^{22} = +44.1^\circ$ ($c = 1.0$, CHCl_3).

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (300 MHz, CDCl_3): δ 7.32-7.27 (m, 2H), 7.02-6.96 (m, 2H), 5.24 (s, 0.4H), 5.08 (s, 0.6H), 4.03-3.97 (m, 0.4H), 3.89-3.82 (m, 0.6H), 3.43-3.30 (m, 2H), 3.09 (d, $J = 7.0$ Hz, 1H), 2.46-2.33 (m, 1H), 1.85-1.77 (m, 7H), 1.45 (s, 9H), 1.16-1.13 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.5, 161.8 (d, $J_{\text{CF}} = 245.8$ Hz), 155.3 and 154.7, 133.0 (d, $J_{\text{CF}} = 3.9$ Hz), 127.8 (d, $J_{\text{CF}} = 7.8$ Hz), 115.4 (d, $J_{\text{CF}} = 21.4$ Hz), 102.8, 100.7, 89.9 and 89.7, 79.9 and 79.4, 69.4 and 68.4, 45.8 and 45.4, 45.0 and 44.4, 28.7 and 28.6, 28.0, 27.2, 23.5 and 23.4, 22.5 and 22.2, 20.5 and 20.4.

^{19}F NMR of two rotamers (282.4 MHz, CDCl_3): δ -115.08 to -115.11 (m), -116.3 to -116.5 (m).

HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{32}\text{FNO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 412.2264; found: 412.2272.

(2R,3R)-2-Isopropoxy-3-[3,3-dimethyl-1-(3-methoxyphenyl)allenyl]-N-(tert-butyl)oxycarbonylpyrrolidine (5e)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:15) as light yellow oil. 29 mg, 72% yield.

$[\alpha]_D^{22} = +39.2^\circ$ ($c = 0.9$, CHCl_3).

Ee = 87%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.25-7.20 (m, 1H), 6.96-6.94 (m, 1H), 6.91-6.90 (m, 1H), 6.77-6.73 (m, 1H), 5.25 (s, 0.4H), 5.09 (s, 0.6H), 4.04-3.98 (m, 0.4H), 3.89-3.83 (m, 0.6H), 3.80 (s, 3H), 3.44-3.29 (m, 2H), 3.12 (d, $J = 6.9$ Hz, 1H), 2.46-2.33 (m, 1H), 1.88-1.82 (m, 1H), 1.81-1.77 (m, 6H), 1.46 (s, 9H), 1.20-1.15 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.8, 159.9, 155.2 and 154.7, 138.8, 129.4, 118.9, 112.5, 111.8, 103.6, 100.5, 90.1 and 89.9, 79.8 and 79.4, 69.4 and 68.4, 55.4, 45.7 and 45.2, 45.0 and 44.5, 28.7 and 28.6, 28.1, 27.3, 23.4 and 23.3, 22.6 and 22.4, 20.5 and 20.4.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{35}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 424.2464; found: 424.2464.

(2*R*,3*R*)-2-Isopropoxy-3-(3,3-dimethyl-1-piperonylallenyl)-*N*-(*tert*-butyl oxycarbonyl)pyrrolidine (5f)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as colorless oil. 27 mg, 65% yield.

$[\alpha]_D^{23} = +41.1^\circ$ ($c = 1.1$, CHCl_3).

Ee = 91%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 6.85-6.74 (m, 3H), 5.94 (d, $J = 3.0$ Hz, 2H), 5.23 (s, 0.4H), 5.07 (s, 0.6H), 4.03-3.97 (m, 0.4H), 3.89-3.82 (m, 0.6H), 3.42-3.28 (m, 2H), 3.06 (d, $J = 6.9$ Hz, 1H), 2.44-2.31 (m, 1H), 1.85-1.81 (m, 1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.46 (s, 9H), 1.19-1.15 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.25 and 200.16, 155.2 and 154.7, 148.0, 146.5, 131.3, 119.2, 108.2, 107.3 and 107.2, 103.5, 101.1, 100.5, 90.0 and 89.8,

79.9 and 79.4, 69.4 and 68.4, 45.9 and 45.5, 45.0 and 44.5, 28.7 and 28.6, 28.1, 27.3, 23.5 and 23.3, 22.5 and 22.3, 20.6 and 20.5.

HRMS (ESI): Calcd for C₂₄H₃₃NO₅Na [M+Na]⁺: 438.2256; found: 438.2260.

(2*R*,3*R*)-2-Isopropoxy-3-[3,3-dimethyl-1-(naphthalen-2-yl)allenyl]-*N*-(*tert*-butoxycarbonyl)pyrrolidine (5g)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as light yellow oil. 30 mg, 71% yield.

[α]_D²¹ = +12.1° (*c* = 1.1, CHCl₃).

Ee = 88%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

¹H NMR of two rotamers (400 MHz, CDCl₃): δ 7.80-7.73 (m, 4H), 7.54-7.52 (m, 1H), 7.47-7.42 (m, 2H), 5.35 (s, 0.4H), 5.19 (s, 0.6H), 4.10-4.04 (m, 0.4H), 3.95-3.88 (m,

0.6H), 3.48-3.35 (m, 2H), 3.32 (d, $J = 7.0$ Hz, 1H), 2.55-2.43 (m, 1H), 1.95-1.91 (m, 1H), 1.86 (s, 3H), 1.83 (s, 3H), 1.47-1.45 (m, 9H), 1.25-1.19 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 201.4, 155.3 and 154.7, 134.4, 133.8, 132.4, 128.1, 128.0, 127.7, 126.3, 125.82 and 125.76, 125.7, 123.8 and 123.7, 104.0, 100.8, 90.2 and 89.9, 79.9 and 79.4, 69.5 and 68.4, 45.6 and 45.2, 45.1 and 44.6, 28.6, 28.2, 27.4, 23.5 and 23.4, 22.6 and 22.3, 20.6 and 20.5.

HRMS (ESI): Calcd for $\text{C}_{27}\text{H}_{35}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 444.2515; found: 444.2517.

(2R,3R)-2-Isopropoxy-3-(3,3-cyclopentyl-1-phenylallenyl)-N-(tert-butyloxy carbonyl)pyrrolidine (5h)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as light yellow oil. 29 mg, 70% yield.

$[\alpha]_D^{19} = +46.6^\circ$ ($c = 1.1$, CHCl_3).

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.154	88017	49.609
2	13.957	89405	50.391
Total		177422	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.178	6297347	95.088
2	14.047	325284	4.912
Total		6622632	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.40-7.38 (m, 2H), 7.34-7.28 (m, 2H), 7.21-7.16 (m, 1H), 5.27 (s, 0.4H), 5.10 (s, 0.6H), 4.04-3.99 (m, 0.4H), 3.89-3.83 (m, 0.6H), 3.47-3.41 (m, 2H), 3.17 (d, $J = 7.1$ Hz, 1H), 2.44-2.37 (m, 1H), 2.24-2.16 (m, 4H), 1.89-1.85 (m, 1H), 1.68-1.54 (m, 6H), 1.46 (s, 9H), 1.20-1.14 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 197.3 and 197.2, 155.2 and 154.6, 137.3 and 137.2, 128.5, 126.5, 126.2, 107.7 and 107.5, 103.6 and 103.5, 90.2 and 90.1, 79.8 and 79.3, 69.5 and 68.6, 45.9 and 45.3, 45.1 and 44.6, 31.4, 28.6, 28.0 and 27.3, 27.71 and 27.67, 26.2, 23.4 and 23.3, 22.5 and 22.3.

HRMS (ESI): Calcd for $\text{C}_{26}\text{H}_{37}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 434.2671; found: 434.2678.

(2*R*,3*R*)-2-Ethoxy-3-(3,3-dimethyl-1-phenylallenyl)-*N*-(*tert*-butyloxycarbonyl)

pyrrolidine (5i)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as light yellow oil. 23 mg, 64% yield.

$[\alpha]_{\text{D}}^{22} = +48.1^\circ$ ($c = 1.2$, CHCl_3).

Ee = 91%. Daicel Chiralcel IC, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	12.893	166317	50.763
2	14.345	161318	49.237
Total		327635	100.000

Peak#	Ret. Time	Area	Area %
1	13.328	5540502	95.501
2	14.845	260989	4.499
Total		5801491	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.37-7.28 (m, 4H), 7.22-7.17 (m, 1H), 5.18 (s, 0.4H), 5.04 (s, 0.6H), 3.74-3.49 (m, 2H), 3.45-3.32 (m, 2H), 3.21 (d, $J = 7.0$ Hz, 1H), 2.47-2.34 (m, 1H), 1.89-1.83 (m, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.46 (s, 9H), 1.21 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 155.3 and 154.7, 137.1, 128.6, 126.6, 126.4, 103.6, 100.5, 91.8, 79.8 and 79.5, 64.1 and 63.4, 45.3 and 45.2, 44.7 and 44.6, 28.6, 28.2, 27.4, 20.5 and 20.4, 15.6.

HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 358.2382; found: 358.2383.

(2R,3R)-2-Butoxy-3-(3,3-dimethyl-1-phenylallenyl)-N-(tert-butyloxycarbonyl)pyrrolidine (5j)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:30) as light yellow oil. 30 mg, 78% yield.

$[\alpha]_D^{20} = +36.8^\circ$ ($c = 1.3$, CHCl_3).

Ee = 91%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.296	55202	51.268
2	9.141	52472	48.732
Total		107674	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	8.297	5213579	95.428
2	9.140	249801	4.572
Total		5463380	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.37-7.28 (m, 4H), 7.20-7.18 (m, 1H), 5.16 (s, 0.4H), 5.02 (s, 0.6H), 3.67-3.32 (m, 4H), 3.20 (d, $J = 7.0$ Hz, 1H), 2.46-2.32 (m, 1H), 1.88-1.83 (m, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.59-1.52 (m, 2H), 1.46 (s, 9H), 1.41-1.34 (m, 2H), 0.94-0.90 (m, 3H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 155.3 and 154.7, 137.1, 128.6, 126.6, 126.4, 103.6, 100.4, 92.0 and 91.9, 79.8 and 79.4, 68.4 and 67.9, 45.2, 44.7 and 44.6, 32.2 and 32.1, 28.6, 28.2, 27.4, 20.5 and 20.4, 19.6, 14.0.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{35}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 408.2515; found: 408.2512.

(2*R*,3*R*)-2-Benzyloxy-3-(3,3-dimethyl-1-phenylallenyl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine (5k)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as light yellow oil. 37 mg, 88% yield.

$[\alpha]_D^{23} = +51.4^\circ$ ($c = 1.4$, CHCl_3).

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.42-7.28 (m, 9H), 7.22-7.18 (m, 1H), 5.36 (s, 0.5H), 5.21 (s, 0.5H), 4.78-4.54 (m, 2H), 3.52-3.36 (m, 2H), 3.32-3.27 (m, 1H), 2.53-2.40 (m, 1H), 1.93-1.87 (m, 1H), 1.82-1.80 (m, 6H), 1.47 (s, 9H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 155.4 and 154.7, 139.3 and 138.8, 137.0, 128.4, 127.8, 127.7, 127.4, 126.64 and 126.56, 126.3, 103.5, 100.51 and 100.46, 92.3 and 92.0, 80.1 and 79.6, 70.7 and 70.2, 45.3 and 45.2, 44.9 and 44.7, 28.61 and 28.58, 28.1, 27.3, 20.5 and 20.4.

HRMS (ESI): Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 442.2358; found: 442.2357.

(2*R*,3*R*)-2-Cyclobutoxy-3-(3,3-dimethyl-1-phenylallenyl)-*N*-(*tert*-butyloxy carbonyl)pyrrolidine (5I)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as light yellow oil. 32 mg, 83% yield.

$[\alpha]_D^{23} = +43.0^\circ$ ($c = 1.3$, CHCl_3).

Ee = 91%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.36-7.28 (m, 4H), 7.22-7.16 (m, 1H), 5.17 (s, 0.5H), 5.00 (s, 0.5H), 4.33-4.23 (m, 0.5H), 4.18-4.11 (m, 0.5H), 3.47-3.30 (m, 2H), 3.18 (d, $J = 7.0$ Hz, 1H), 2.48-2.15 (m, 3H), 2.02-1.83 (m, 3H), 1.80 (s, 3H), 1.77 (s, 3H), 1.72-1.62 (m, 1H), 1.53-1.49 (m, 1H), 1.46 (s, 9H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.8, 154.9 and 154.5, 137.2, 128.5, 126.63 and 126.58, 126.4, 103.5, 100.4, 90.1 and 90.0, 79.9 and 79.4, 71.6 and 70.7, 45.2 and 45.0, 44.8 and 44.6, 31.6 and 31.4, 31.2 and 31.1, 28.7 and 28.6, 28.0, 27.2, 20.5 and 20.4, 13.1.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{33}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 406.2358; found: 406.2361.

(2*R*,3*R*)-2-Cyclopentyloxy-3-(3,3-dimethyl-1-phenylallenyl)-*N*-(*tert*-butoxy carbonyl)pyrrolidine (5m)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:25) as colorless oil. 27 mg, 68% yield.

$[\alpha]_D^{20} = +38.7^\circ$ ($c = 1.0$, CHCl_3).

Ee = 91%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

PeakTable			
PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	8.981	31131	50.846
2	10.313	30095	49.154
Total		61226	100.000

PeakTable			
PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	9.155	3579827	95.587
2	10.491	165255	4.413
Total		3745082	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.36-7.28 (m, 4H), 7.21-7.18 (m, 1H), 5.22 (s, 0.4H), 5.06 (s, 0.6H), 4.31-4.26 (m, 0.4H), 4.17-4.12 (m, 0.6H), 3.42-3.30 (m, 2H), 3.15 (d, $J = 7.0$ Hz, 1H), 2.45-2.32 (m, 1H), 1.88-1.83 (m, 1H), 1.81 (s, 3H), 1.78 (s, 3H), 1.76-1.62 (m, 6H), 1.55-1.48 (m, 2H), 1.46 (s, 9H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.8, 155.2 and 154.7, 137.2, 128.5, 126.6, 126.4, 103.7, 100.4, 90.6 and 90.4, 79.8 and 79.3, 79.2 and 78.2, 45.2 and 45.0, 44.9 and 44.6, 33.2 and 33.0, 32.8 and 32.6, 28.7, 28.1, 27.3, 23.9 and 23.7, 23.6 and 23.5, 20.5 and 20.4.

HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{35}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 420.2515; found: 420.2518.

(2R,3R)-2-Hydroxy-3-(3,3-dimethyl-1-phenylallenyl)-N-(*tert*-butyloxy carbonyl)pyrrolidine (6d)

Pd(dba)₂ was used instead of Pd(cod)Cl₂ to increase the ee of product and 27 μ L (15 equiv) of H₂O was added. The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as colorless oil. 21 mg, 64% yield.

$[\alpha]_D^{23} = +28.3^\circ$ ($c = 1.3$, CHCl₃).

Ee = 88%. Daicel Chiralcel IC, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

¹H NMR of two rotamers (400 MHz, CDCl₃): δ 7.39-7.37 (m, 2H), 7.34-7.29 (m, 2H), 7.22-7.17 (m, 1H), 5.38 (s, 0.6H), 5.26 (s, 0.4H), 3.57-3.47 (m, 1.6H), 3.41-3.22 (m, 2H), 2.81 (d, $J = 2.3$ Hz, 0.4H), 2.44-2.36 (m, 1H), 1.88-1.82 (m, 1H), 1.80 (s, 3H), 1.79 (s, 3H), 1.49-1.47 (m, 9H).

¹³C NMR of two rotamers (100 MHz, CDCl₃): δ 200.7 and 200.6, 155.2 and 153.8, 137.0 and 136.8, 128.6 and 128.5, 126.7 and 126.6, 126.44 and 126.39, 103.7 and 103.5,

100.74 and 100.69, 86.43 and 86.37, 80.3 and 80.0, 45.7 and 45.2, 45.1 and 44.9, 28.7 and 28.6, 28.4, 27.3, 20.41 and 20.35.

HRMS (ESI): Calcd for $C_{20}H_{27}NO_3Na$ $[M+Na]^+$: 352.1889; found: 352.1887.

2.5.4 Asymmetric Azaallenylation of Cycloalkenes

A procedure for reactions of arylamines: In an argon-filled glove box, $Pd(cod)Cl_2$ (0.6 mg, 0.002 mmol), **L10** (1.3 mg, 0.0024 mmol) and 0.4 mL of dry MeCN were charged into a dry 10-mL reaction tube. After stirring for about 15 minutes, **2a** (40.8 mg, 0.2 mmol), **1a** (30 μ L, 0.4 mmol, 2 equiv), arylamine (0.8 mmol, 4 equiv), KOAc (10 mg, 0.1 mmol, 50 mol%) and GC standard *n*-dodecane 20 μ L were added sequentially. The reaction was capped tightly and stirred on a hotplate maintained at 45 °C for 36 hours. After it was cooled down to rt, the reaction mixture was subjected to flash chromatography using ethyl acetate/hexanes as eluent. The enantioselectivity (ee) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns. The use of $Pd(dba)_2$ resulted in slower conversion.

(2*S*,3*R*)-2-*N*-(3,5-Difluoroanilyl)-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (6e)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as colorless oil. 50 mg, 73% yield. dr 4:1 based on proton NMR spectroscopy (inseparable by GC).

$[\alpha]_D^{20} = +101.4^\circ$ ($c = 1.0$, CHCl_3).

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

PeakTable
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.194	1170973	7.661
2	10.612	1117007	7.308
3	22.100	6470287	42.332
4	32.504	6526512	42.699
Total		15284778	100.000

PeakTable
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.171	934158	10.923
2	10.575	54789	0.641
3	21.927	409724	4.791
4	32.362	7153638	83.646
Total		8552310	100.000

^1H NMR of the major isomer (400 MHz, CDCl_3): δ 7.38-7.31 (m, 4H), 7.24-7.20 (m, 1H), 6.26-6.18 (m, 3H), 5.16 (dd, $J = 8.3, 5.5$ Hz, 1H), 4.52 (d, $J = 8.3$ Hz, NH), 4.09-4.04 (m, 1H), 4.00-3.95 (m, 1H), 3.09-3.04 (m, 1H), 2.48-2.40 (m, 1H), 2.01-1.92 (m, 1H), 1.84 (s, 3H), 1.73 (s, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 200.7, 164.2 (dd, $J_{\text{CF}} = 244.4, 15.7$ Hz), 148.9 (t, $J_{\text{CF}} = 13.4$ Hz), 137.5, 128.7, 126.9, 126.4, 104.1, 101.4, 97.1 (d, $J_{\text{CF}} = 28.6$ Hz), 94.0 (t, $J_{\text{CF}} = 26.1$ Hz), 89.9, 66.6, 46.1, 32.4, 20.4, 20.3.

^{19}F NMR of the major isomer (376.6 MHz, CDCl_3): δ -110.2.

HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{21}\text{F}_2\text{NONa}$ $[\text{M}+\text{Na}]^+$: 364.1489; found: 364.1492.

(2*S*,3*R*)-2-*N*-[3,5-Bis(trifluoromethyl)anilyl]-3-(3,3-dimethyl-1-phenylallenyl)

tetrahydrofuran (6f)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as colorless oil. 53 mg, 60% yield. dr 3:1 based on proton NMR spectroscopy (inseparable by GC).

$[\alpha]_D^{20} = +77.5^\circ$ ($c = 1.0$, CHCl_3).

Ee = 86%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

PeakTable			
PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	6.999	101110	0.809
2	9.382	98548	0.788
3	11.532	6127229	49.025
4	15.232	6171376	49.378
Total		12498264	100.000

PeakTable			
PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	6.976	2410131	21.854
2	9.377	173206	1.571
3	11.483	585970	5.313
4	15.162	7858906	71.262
Total		11028212	100.000

^1H NMR of the major isomer (300 MHz, CDCl_3): δ 7.38-7.30 (m, 4H), 7.24-7.20 (m, 2H), 7.11 (s, 2H), 5.24 (dd, $J = 8.3, 5.5$ Hz, 1H), 4.70 (d, $J = 8.3$ Hz, NH), 4.12-3.98 (m, 2H), 3.14-3.07 (m, 1H), 2.52-2.41 (m, 1H), 2.04-1.97 (m, 1H), 1.83 (s, 3H), 1.69 (s, 3H).

^{13}C NMR of the major isomer (100 MHz, CDCl_3): δ 200.7, 147.4, 137.4, 132.6 (q, J_{CF} = 32.8 Hz), 128.7, 127.0, 126.4, 123.6 (q, J_{CF} = 272.6 Hz), 113.7-113.6 (m), 112.1-111.9 (m), 104.0, 101.5, 89.8, 66.7, 46.2, 32.4, 20.4, 20.3.

^{19}F NMR of the major isomer (282.4 MHz, CDCl_3): δ -63.1.

HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{22}\text{F}_6\text{NO}$ $[\text{M}+\text{H}]^+$: 442.1606; found: 442.1596.

A procedure for reactions of heteroarylamines: In an argon-filled glove box, $\text{Pd}(\text{dba})_2$ (2.3 mg, 0.004 mmol), **L10** (2.6 mg, 0.0048 mmol) and 0.4 mL of dry MeCN were charged into a dry 10-mL reaction tube. After stirring for about 15 minutes, **2a** (40.8 mg, 0.2 mmol), **1a** (30 μL , 0.4 mmol, 2 equiv), heteroarylamine (0.8 mmol, 4 equiv), NaOTf (51.6 mg, 0.3 mmol, 1.5 equiv) and GC standard *n*-dodecane 20 μL were added sequentially. The reaction was capped tightly and stirred on a hotplate maintained at 50 $^\circ\text{C}$ for 48 hours. After it was cooled down to rt, the reaction mixture was subjected to flash chromatography using ethyl acetate/hexanes as eluent. The enantioselectivity (ee) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-*N*-[4-(trifluoromethyl)-2-pyridylamino] tetrahydrofuran (6g**)**

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as colorless oil. 61 mg, 81% yield.

$[\alpha]_D^{19} = +75.0^\circ$ ($c = 1.1$, CHCl_3).

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 8.26 (d, $J = 5.2$ Hz, 1H), 7.38-7.30 (m, 4H), 7.20 (t, $J = 7.2$ Hz, 1H), 6.85 (d, $J = 5.2$ Hz, 1H), 6.77 (s, 1H), 5.52 (dd, $J = 8.7, 5.3$ Hz, 1H), 5.42 (d, $J = 8.7$ Hz, NH), 4.11-3.99 (m, 2H), 3.17-3.12 (m, 1H), 2.48-2.44 (m, 1H), 2.03-1.98 (m, 1H), 1.82 (s, 3H), 1.66 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.8, 158.3, 149.7, 140.1 (q, $J_{\text{CF}} = 33.2$ Hz), 137.4, 128.7, 126.8, 126.4, 123.1 (q, $J_{\text{CF}} = 273.2$ Hz), 109.9 (q, $J_{\text{CF}} = 3.4$ Hz), 104.0, 103.4 (q, $J_{\text{CF}} = 3.9$ Hz), 101.4, 88.2, 66.8, 46.1, 32.3, 20.4, 20.2.

^{19}F NMR (376.6 MHz, CDCl_3): δ -65.2.

HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 375.1684; found: 375.1681.

(2*S*,3*R*)-3-[3,3-Dimethyl-1-(4-fluorophenyl)allenyl]-*N*-[4-(trifluoromethyl)-2-pyridylamino]tetrahydrofuran (6h)

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as colorless oil. 59 mg, 75% yield.

$[\alpha]_D^{22} = +53.5^\circ$ ($c = 1.0$, CHCl_3).

Ee = 91%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	29.798	319459	50.040
2	40.246	318942	49.960
Total		638400	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	29.775	1511521	95.440
2	40.195	72220	4.560
Total		1583741	100.000

^1H NMR (400 MHz, CDCl_3): δ 8.25 (d, $J = 5.2$ Hz, 1H), 7.32-7.28 (m, 2H), 6.99 (t, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 4.4$ Hz, 1H), 6.76 (s, 1H), 5.66-5.55 (m, NH), 5.50 (dd, $J = 8.5$, 5.2 Hz, 1H), 4.10-3.97 (m, 2H), 3.12-3.07 (m, 1H), 2.47-2.39 (m, 1H), 2.04-1.94 (m, 1H), 1.81 (s, 3H), 1.66 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.7, 161.9 (d, $J_{\text{CF}} = 246.1$ Hz), 158.4, 149.6, 140.1 (q, $J_{\text{CF}} = 33.6$ Hz), 133.4 (d, $J_{\text{CF}} = 3.4$ Hz), 128.0 (d, $J_{\text{CF}} = 7.8$ Hz), 123.1 (q, $J_{\text{CF}} =$

273.0 Hz), 115.5 (d, J_{CF} = 21.5 Hz), 109.9 (q, J_{CF} = 3.1 Hz), 103.5 (q, J_{CF} = 4.1 Hz), 103.4, 101.6, 88.2, 66.7, 46.2, 32.2, 20.4, 20.2.

^{19}F NMR (376.6 MHz, CDCl_3): δ -65.2, -116.01 to -116.04 (m).

HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{21}\text{F}_4\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 393.1590; found: 393.1595.

2.5.5 Product Derivatization

To a solution of **3a** (0.2 mmol, 54.5 mg, 90% ee) and allyl trimethylsilane (95 μL , 0.6 mmol) in dry DCM (2.5 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (30 μL , 0.24 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature, before it was quenched with 1.5 mL of saturated aqueous NaHCO_3 . The aqueous layer was extracted with DCM (2 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexanes 1:60) to afford the title product (45 mg, 88% yield, 90% ee) as colorless oil.

(2*R*,3*R*)-2-Allyl-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (**7a**)

$[\alpha]_{\text{D}}^{22} = +76.6^\circ$ (c = 0.7, CHCl_3).

Ee = 90%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 99.8:0.2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.37-7.29 (m, 4H), 7.19 (t, $J = 7.1$ Hz, 1H), 5.93-5.83 (m, 1H), 5.11-5.03 (m, 2H), 4.00-3.94 (m, 1H), 3.87-3.80 (m, 2H), 2.87 (ψdd, $J = 15.7$, 7.4 Hz, 1H), 2.45-2.25 (m, 3H), 1.86-1.77 (m, 7H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 138.2, 135.5, 128.5, 126.6 (two overlapping signals), 116.8, 105.5, 100.4, 83.5, 67.5, 43.9, 39.2, 34.2, 20.52 and 20.46.

HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{22}\text{ONa}$ $[\text{M}+\text{Na}]^+$: 277.1568; found: 277.1564.

To a solution of **3a** (0.2 mmol, 54.5 mg, 90% ee) and triethylsilane (64 μL , 0.4 mmol) in dry DCM (2 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (30 μL , 0.24 mmol) at 0 $^\circ\text{C}$. The mixture was stirred for 1 h at room temperature, before it was quenched with 1.5 mL of saturated aqueous NaHCO_3 . The aqueous layer was extracted with DCM (2 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexanes 1:40) to afford the title product (30 mg, 70% yield, 90% ee) as colorless oil.

(*R*)-3-(3,3-Dimethyl-1-phenylallenyl)tetrahydrofuran (7b)

$[\alpha]_D^{19} = -13.2^\circ$ ($c = 1.4$, CHCl_3).

Ee = 90%. Daicel Chiralcel IC, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.36 (m, 2H), 7.34-7.30 (m, 2H), 7.19 (t, $J = 7.2$ Hz, 1H), 4.14-4.10 (m, 1H), 3.93-3.83 (m, 2H), 3.64-3.60 (m, 1H), 3.34-3.28 (m, 1H), 2.25-2.18 (m, 1H), 1.94-1.83 (m, 7H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.7, 138.1, 128.5, 126.53, 126.46, 105.7, 100.6, 73.4, 68.2, 39.4, 32.9, 20.51, 20.47.

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 215.1436; found: 215.1437.

To a solution of **7b** (0.2 mmol, 42.8 mg, 90% ee) in dry nitromethane (2 mL) was added *N*-iodosuccinimide (0.24 mmol, 54 mg). The mixture was stirred for 15 min at room temperature, before it was quenched with 2 mL of saturated aqueous sodium thiosulfate. The aqueous layer was extracted with ethyl acetate (2 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The

crude product was purified by flash chromatography (ethyl acetate/hexanes 1:75) to afford the title product (51 mg, 75% yield, 90% ee) as colorless oil.

(*R*)-3-(2-Iodo-1,1-dimethyl-1*H*-inden-3-yl)tetrahydrofuran (7c)

$[\alpha]_D^{20} = -3.2^\circ$ ($c = 1.1$, CHCl_3).

Ee = 90%. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.55-7.53 (m, 1H), 7.40-7.37 (m, 1H), 7.24-7.17 (m, 2H), 4.25 (td, $J = 8.3, 3.2$ Hz, 1H), 4.09 (dd, $J = 8.9, 6.4$ Hz, 1H), 3.96 (t, $J = 8.9$ Hz, 1H), 3.86-3.70 (m, 2H), 2.28-2.13 (m, 2H), 1.21 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 153.8, 144.5, 139.3, 126.4, 125.3, 122.4, 120.3, 118.6, 70.5, 69.4, 52.4, 42.2, 31.1, 25.8, 25.6.

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{17}\text{IONa}$ $[\text{M}+\text{Na}]^+$: 363.0222; found: 363.0214.

To a solution of **3a** (0.2 mmol, 54.5 mg, 90% ee) in furan (2 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (25 μL , 0.2 mmol) at -20°C . The mixture was stirred for 15 min at room temperature,

before it was quenched with 1.5 mL of saturated aqueous NaHCO₃. The aqueous layer was extracted with DCM (2 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexanes 1:50) to afford the title product (30 mg, 54% yield, 90% ee) as colorless oil.

(2*R*,3*R*)-2-(Furan-2-yl)-3-(3,3-dimethyl-1-phenylallenyl)tetrahydrofuran (7d)

$[\alpha]_D^{19} = +117.1^\circ$ ($c = 1.4$, CHCl₃).

Ee = 90%. Daicel Chiralcel IC, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.39 (d, $J = 1.7$ Hz, 1H), 7.34-7.27 (m, 4H), 7.18 (t, $J = 7.2$ Hz, 1H), 6.31-6.30 (m, 1H), 6.25 (d, $J = 3.2$ Hz, 1H), 4.84 (d, $J = 6.8$ Hz, 1H), 4.15-4.12 (m, 1H), 4.01-3.96 (m, 1H), 3.53 (dd, $J = 14.7, 7.0$ Hz, 1H), 2.54-2.48 (m, 1H), 2.00-1.93 (m, 1H), 1.85 (s, 3H), 1.76 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 200.8, 154.4, 142.5, 137.7, 128.5, 126.6, 126.5, 110.2, 107.7, 105.0, 101.0, 79.0, 68.2, 43.9, 33.8, 20.5, 20.4.

HRMS (ESI): Calcd for C₁₉H₂₁O₂ [M+H]⁺: 281.1542; found: 281.1541.

To a solution of **3a** (0.2 mmol, 54.5 mg, 90% ee) in acetone (3.6 mL) and water (1.8 mL) was added *p*-toluenesulfonic acid monohydrate (0.72 mmol, 137 mg). The mixture was stirred at 50 °C overnight. The resulting mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford colorless oil which was directly used in the next step without further purification.

The crude product was dissolved in DCM (3 mL) and pyridinium chlorochromate (0.6 mmol, 129 mg) was added. The resulting mixture was then stirred at room temperature for 24 h. Water was added (5 mL) and the aqueous layer was extracted with ethyl acetate (5 mL $\times$ 3). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexanes 1:5) to afford the title product (28 mg, 62% yield, 91% ee) as colorless oil.

(*R*)-3-(3,3-Dimethyl-1-phenylallenyl)dihydrofuran-2(3*H*)-one (7e)

$[\alpha]_{\text{D}}^{19} = +47.1^\circ$ ($c = 1.1$, CHCl₃).

Ee = 91%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90:10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.31 (m, 4H), 7.24-7.20 (m, 1H), 4.39-4.30 (m, 2H), 3.68 (dd, J = 8.8, 5.8 Hz, 1H), 2.65-2.56 (m, 1H), 2.31-2.23 (m, 1H), 1.84 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.3, 177.3, 136.3, 128.6, 127.0, 126.4, 102.5, 101.7, 67.0, 41.4, 30.1, 20.5, 20.0.

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{17}\text{O}_2$ $[\text{M}+\text{H}]^+$: 229.1229; found: 229.1229.

The crude product was purified by flash chromatography (ethyl acetate/ hexanes 1:5) to afford the title product (36 mg, 60% yield, 91% ee) as white solid. The compound **7g** was crystallized from evaporation of a solution of 0.5 mL of dichloromethane and 2.5 mL of hexanes at room temperature. The crystal was subjected to X-ray diffraction to establish the absolute configuration.

(R)-3-[3,3-Dimethyl-1-(4-bromophenyl)allenyl]dihydrofuran-2(3H)-one (7g)

$[\alpha]_{\text{D}}^{21} = +31.9^\circ$ (c = 1.0, CHCl_3).

Ee = 91%. Daicel Chiralcel OJ-H, n -hexane/isopropanol 90:10, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	24.899	233990	49.979
2	31.770	234185	50.021
Total		468175	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	24.962	794503	95.493
2	31.901	37496	4.507
Total		831999	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.42 (d, $J = 8.5$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 4.37-4.27 (m, 2H), 3.61 (dd, $J = 8.7, 6.2$ Hz, 1H), 2.62-2.53 (m, 1H), 2.27-2.19 (m, 1H), 1.82 (s, 3H), 1.81 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.3, 177.0, 135.4, 131.6, 128.1, 120.8, 103.1, 101.0, 67.0, 41.0, 29.9, 20.4, 19.9.

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{16}^{79}\text{BrO}_2$ $[\text{M}+\text{H}]^+$: 307.0334; found: 307.0329.

To a solution of 1,3,5-trimethoxybenzene (33.6 mg, 0.2 mmol), $\text{Sc}(\text{OTf})_3$ (9.8 mg, 0.02 mmol), powdered CaSO_4 (300 mg, 2.2 mmol) in dry DCM (0.8 mL) was added **3a** (0.1 mmol, 27.2 mg, 90% ee) in DCM (0.2 mL) at 0 °C. The mixture was stirred for 3 h at room temperature, before it was quenched with 1 mL of saturated aqueous NaHCO_3 . The aqueous layer was extracted with DCM (2 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude

product was purified by flash chromatography (ethyl acetate/ hexanes 1:20) to afford the title product (29 mg, 76% yield, 90% ee) as white solid.

The compound **7f** was crystallized from slow evaporation of a solution of 0.5 mL of ethyl acetate and 3 mL of hexanes at room temperature. Single-crystal X-ray diffraction helped to establish the absolute configuration.

(1*R*,5*S*,6*S*)-1-Phenyl-7-(propan-2-ylidene)-6-(2,4,6-trimethoxyphenyl)-2-oxabicyclo[3.2.0]heptane (7f)

$[\alpha]_D^{19} = +3.3^\circ$ ($c = 1.0$, CHCl_3).

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.60-7.58 (m, 2H), 7.37-7.33 (m, 2H), 7.23 (t, $J = 7.3$ Hz, 1H), 6.11 (s, 2H), 4.38 (t, $J = 8.0$ Hz, 1H), 4.22-4.14 (m, 2H), 3.80 (s, 3H), 3.60 (s, 6H), 3.06 (ψ t, $J = 6.5$ Hz, 1H), 2.03-1.86 (m, 2H), 1.56 (d, $J = 2.2$ Hz, 3H), 1.41 (d, $J = 1.5$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 159.6, 159.0, 143.9, 136.4, 129.5, 127.7, 127.4, 126.5, 111.5, 90.8, 90.5, 68.7, 55.4, 50.6, 37.8, 32.3, 20.7, 18.8.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{29}\text{O}_4$ $[\text{M}+\text{H}]^+$: 381.2066; found: 381.2071.

The crude product was purified by flash chromatography (ethyl acetate/ hexanes 1:25) to afford the title product (30 mg, 65% yield, 91% ee) as white solid. The compound **7h** was crystallized from evaporation of a solution of 0.3 mL of dichloromethane and 3 mL of hexanes at room temperature. The crystal was subjected to X-ray diffraction to establish the absolute configuration.

(1*R*,5*S*,6*S*)-1-(4-Bromophenyl)-7-(propan-2-ylidene)-6-(2,4,6-trimethoxyphenyl)-2-oxabicyclo[3.2.0]heptane (7h)

$[\alpha]_D^{20} = +0.5^\circ$ ($c = 1.1$, CHCl_3).

Ee = 91%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	13.445	117613	49.785
2	16.747	118628	50.215
Total		236241	100.000

Peak#	Ret. Time	Area	Area %
1	13.534	511255	95.399
2	16.880	24655	4.601
Total		535909	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.49-7.44 (m, 4H), 6.11 (s, 2H), 4.37 (ψt, $J = 7.6$ Hz, 1H), 4.22-4.13 (m, 2H), 3.80 (s, 3H), 3.62 (s, 6H), 3.03 (ψt, $J = 6.3$ Hz, 1H), 1.98-1.82 (m, 2H), 1.52 (d, $J = 2.3$ Hz, 3H), 1.40 (d, $J = 1.7$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 159.6, 159.0, 143.0, 136.0, 130.7, 129.9, 129.3, 120.4, 111.1, 90.8, 90.0, 68.7, 55.4, 50.6, 37.6, 32.2, 20.6, 18.7.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{28}\text{BrO}_4$ $[\text{M}+\text{H}]^+$: 459.1171; found: 459.1172.

To a solution of 1,3,5-trimethoxybenzene (33.6 mg, 0.2 mmol), Sc(OTf)_3 (9.8 mg, 0.02 mmol), powdered CaSO_4 (300 mg, 2.2 mmol) in dry DCM (0.8 mL) was added **5a** (0.1 mmol, 27.2 mg, 92% ee) in DCM (0.2 mL) at 0 °C. The mixture was stirred for 3 h at room temperature, before it was quenched with 1 mL of saturated aqueous NaHCO_3 . The aqueous layer was extracted with DCM (2 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/ hexanes 1:4) to afford the title product (38 mg, 79% yield, 92% ee) as colorless oil.

***tert*-Butyl (2*S*,3*R*)-3-(3,3-dimethyl-1-phenylallenyl)-2-(2,4,6-trimethoxyphenyl)pyrrolidine-1-carboxylate (7i)**

$[\alpha]_{\text{D}}^{20} = +153.7^\circ$ ($c = 1.0$, CHCl_3).

Ee = 92%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95:5, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.18-7.04 (m, 5H), 6.11-6.04 (m, 2H), 5.23-5.11 (m, 1H), 3.78 (s, 3H), 3.67 (s, 6H), 3.64-3.49 (m, 3H), 2.30-2.23 (m, 1H), 1.86-1.80 (m, 7H), 1.40 (s, 1.4H), 1.13 (s, 7.6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 201.4, 160.0, 159.1, 154.5, 138.6, 128.0, 126.8, 126.0, 112.6, 106.7, 100.2, 90.7, 78.2, 58.1, 55.8, 55.4, 46.6, 45.6, 31.8, 28.8 and 28.3, 20.6, 20.5.

HRMS (ESI): Calcd for $\text{C}_{29}\text{H}_{38}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 480.2750; found: 480.2745.

In an argon-filled glove box, **3s** (82.9 mg, 0.3 mmol, 94% ee), *N*-(4-bromophenyl) maleimide (151 mg, 0.6 mmol) and *o*-xylene (1.5 mL) were charged into a dry 10 mL Schlenk tube. The tube was sealed and the mixture was stirred at 130 °C for 12 h. After cooling to room temperature, the mixture was purified by flash chromatography (ethyl acetate/dichloromethane/hexanes 1:1:10) to afford the title product (132 mg, 83%

combined yield) as white solid. The ratio of two diastereomers in the crude product is determined to be 1.2:1 by ^1H NMR.

The compound **7j** was crystallized from evaporation of a solution of 0.5 mL of DCM and 3.5 mL of hexanes at room temperature. The crystal was subjected to X-ray diffraction to establish the absolute configuration.

Major product:

(3a*S*,9a*R*,9b*S*)-2-(4-Bromophenyl)-5-[(2*R*,3*R*)-2-Isopropoxytetrahydrofuran-3-yl]-4-(propan-2-ylidene)-3a,4,6,7,8,9,9a,9b-octahydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (7j)

$[\alpha]_D^{19} = -199.6^\circ$ ($c = 1.1$, CHCl_3).

$E_e = 94\%$. Daicel Chiralcel OZ-3, *n*-hexane/isopropanol 90:10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.54 (d, $J = 8.7$ Hz, 2H), 7.13 (d, $J = 8.7$ Hz, 2H), 5.06 (d, $J = 2.3$ Hz, 1H), 4.18 (d, $J = 8.5$ Hz, 1H), 3.94 (t, $J = 7.7$ Hz, 1H), 3.83-3.72 (m, 2H), 3.15 (dd, $J = 8.4, 5.4$ Hz, 1H), 2.97 (t, $J = 8.8$ Hz, 1H), 2.55-2.48 (m, 1H), 2.38-2.28 (m, 1H), 2.11-2.00 (m, 3H), 1.93 (s, 3H), 1.88-1.78 (m, 2H), 1.76 (s, 3H), 1.73-1.61 (m, 2H), 1.50-1.30 (m, 2H), 1.16 (d, $J = 6.2$ Hz, 3H), 1.08 (d, $J = 6.2$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 177.4, 176.6, 139.5, 134.2, 132.3, 132.0, 131.2, 128.2, 128.0, 122.2, 108.2, 69.5, 67.0, 50.6, 46.2, 45.4, 39.2, 33.3, 24.2, 24.0, 23.8, 22.9, 21.8, 20.8, 20.7, 20.5.

HRMS (ESI): Calcd for C₂₈H₃₄ ⁷⁹BrNO₄Na [M+Na]⁺: 550.1569; found: 550.1567.

Minor product:

(3a*R*,9a*S*,9b*R*)-2-(4-Bromophenyl)-5-[(2*R*,3*R*)-2-Isopropoxytetrahydrofuran-3-yl]-4-(propan-2-ylidene)-3a,4,6,7,8,9,9a,9b-octahydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (7j')

[α]_D¹⁹ = +169.5° (*c* = 1.5, CHCl₃).

Ee = 94%. Daicel Chiralcel IC, *n*-hexane/isopropanol 90:10, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	15.646	147067	49.671
2	20.432	149016	50.329
Total		296083	100.000

Peak#	Ret. Time	Area	Area %
1	15.672	81954	3.081
2	20.408	2578295	96.919
Total		2660249	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 4.93 (d, *J* = 2.0 Hz, 1H), 4.20 (d, *J* = 8.3 Hz, 1H), 3.96 (t, *J* = 8.3 Hz, 1H), 3.83-3.77 (m, 1H), 3.70-3.62 (m, 1H), 3.14 (dd, *J* = 8.3, 5.6 Hz, 1H), 3.00 (t, *J* = 9.0 Hz, 1H), 2.67-2.62 (m, 1H), 2.35-2.25 (m, 1H), 2.16-1.97 (m, 3H), 1.94 (s, 3H), 1.85-1.74 (m, 4H), 1.72 (s, 3H), 1.47-1.30 (m, 2H), 1.12 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 177.3, 176.3, 140.4, 133.7, 132.3, 132.1, 131.2, 128.0, 127.5, 122.2, 108.8, 69.7, 66.8, 49.3, 46.4, 45.3, 39.4, 32.4, 24.1, 24.0, 23.5, 23.1, 21.8, 20.9, 20.8, 20.5.

HRMS (ESI): Calcd for $\text{C}_{28}\text{H}_{34}^{79}\text{BrNO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 550.1569; found: 550.1573.

(2*R*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-isopropoxy-*N*-(*tert*-butoxycarbonyl)pyrrolidine (5a**)**

In an argon-filled glove box, $\text{Pd}(\text{cod})\text{Cl}_2$ (4.3 mg, 0.015 mmol), **L10** (9.8 mg, 0.018 mmol) and 1.5 mL of dry MeCN were charged into a dry 10-mL Schlenk tube. After stirring for about 15 minutes, 1.5 mL *i*-PrOH, **2a** (303 mg, 1.5 mmol), *N*-Boc-2,3-dihydropyrrole (381 mg, 2.25 mmol, 1.5 equiv) and KOAc (221 mg, 2.25 mmol, 1.5 equiv) were added sequentially. The reaction was capped tightly and stirred on an oil bath maintained at 50 °C for 36 hours. After it was cooled down to rt, the reaction mixture was subjected to flash chromatography (ethyl acetate/hexanes 1:25) to afford **5a** (384 mg, 69% yield, 92% ee) as colorless oil.

(*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine (7k**)**

Under argon to a solution of **5a** (0.6 mmol, 223 mg) and triethylsilane (383 μ L, 2.4 mmol) in dry DCM (6 mL) maintained at 0 °C was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (89 μ L, 0.72 mmol). The mixture was warmed to rt and stirred for 5 min at room temperature, before it was quickly quenched with 5 mL saturated aqueous NaHCO_3 . The aqueous layer was extracted with DCM (5 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexanes 1:15) to afford **7k** (171 mg, 91% yield) as colorless oil.

$[\alpha]^{22}_{\text{D}} = +40.2^\circ$ ($c = 0.8$, CHCl_3).

Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min. $T_{\text{R}} = 17.0$ min (major) and 18.3 min (minor).

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.37-7.28 (m, 4H), 7.21-7.16 (m, 1H), 3.71-3.59 (m, 1H), 3.48-3.18 (m, 4H), 2.19-2.08 (m, 1H), 1.82-1.79 (m, 7H), 1.46 (s, 9H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 154.7, 137.7, 128.5, 126.6, 126.5, 105.4 and 105.2, 100.6, 79.1, 51.6 and 51.1, 45.5 and 45.0, 38.8 and 38.2, 31.8, 30.8, 28.8, 20.5.

HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 336.1939; found: 336.1935.

(S)-3-Benzoyl-N-(tert-butyloxycarbonyl)pyrrolidine (7l)

A solution of **7k** (0.45 mmol, 141 mg) and pyridine (108 μ L, 1.35 mmol) in dry DCM (10 mL) was cooled to -78°C , and then a stream of O_3 (~ 3 L/min) was gently bubbled through via a Pasteur pipette. When the solution turned blue, excess ozone was blown

off with a stream of oxygen and the mixture was allowed to warm up to room temperature. The solvent was removed and the residue was subjected to flash chromatography (ethyl acetate/hexanes 1:5) to afford **7l** (88 mg, 71% yield) as colorless oil.

$[\alpha]^{22}_{\text{D}} = +4.3^{\circ}$ ($c = 0.8$, CHCl_3).

Daicel Chiralcel AD-H, *n*-hexane/isopropanol 90:10, flow rate = 0.5 mL/min. $T_{\text{R}} = 14.3$ min (major) and 18.4 min (minor).

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.96 (d, $J = 7.5$ Hz, 2H), 7.59 (t, $J = 6.7$ Hz, 1H), 7.52-7.45 (m, 2H), 4.05-3.92 (m, 1H), 3.80-3.42 (m, 4H), 2.35-2.17 (m, 2H), 1.46 (s, 9H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 199.3, 154.5, 136.2, 133.6, 128.9, 128.6, 79.6, 48.2, 45.7 and 45.5, 44.9, 29.0, 28.7.

HRMS (ESI): Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 298.1419; found: 298.1414.

(S)-3-Benzyl-N-(tert-butyloxycarbonyl)pyrrolidine (7m)

Under argon, to a stirred suspension of **7l** (0.2 mmol, 55 mg) and Pd/C (10 wt%, 10.6 mg, 0.01 mmol) in MeOH (2 mL) was added *p*-chloroanisole (5 μL , 0.04 mmol) and PMHS (60 mg, 1 mmol of SiH). The reaction mixture was then stirred in a 50 $^{\circ}\text{C}$ oil bath for 1 h. After completion, the solvent was removed and the residue was subjected to flash chromatography (ethyl acetate/hexanes 1:8) to afford **7m** (36 mg, 70% yield, 91% ee) as colorless oil.

$[\alpha]^{22}_{\text{D}} = -22.4^{\circ}$ ($c = 0.8$, CHCl_3).

Ee = 91%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.29-7.26 (m, 2H), 7.23-7.15 (m, 3H), 3.53-3.40 (m, 2H), 3.30-3.20 (m, 1H), 3.04-2.95 (m, 1H), 2.72-2.62 (m, 2H), 2.46-2.35 (m, 1H), 1.96-1.88 (m, 1H), 1.61-1.53 (m, 1H), 1.45 (s, 9H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 154.8, 140.5, 128.8, 128.6, 126.3, 79.2, 51.4 and 51.2, 45.8 and 45.4, 40.9 and 40.2, 39.5, 31.7 and 30.9, 28.7.

HRMS (ESI): Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 284.1626; found: 284.1626.

2.6 References

- (1) (a) Henry, P. M. *Oxidation of Monoolefins. In Palladium Catalyzed Oxidation of Hydrocarbons*; Springer: Dordrecht, Netherlands, 1980. (b) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335.
- (2) (a) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815. (b) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. *Tetrahedron Lett.* **1992**, *33*, 6643. (c) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 164. (d) Zeni, G.; Larock, R. C. **2004**, *104*, 2285.
- (3) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

- (4) (a) Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonoda, A. *J. Chem. Soc., Chem. Commun.* **1978**, 16, 687. (b) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S. *J. Am. Chem. Soc.* **1981**, 103, 2318. (c) Hosokawa, T.; Okuda, C.; Murahashi, S. *J. Org. Chem.* **1985**, 50, 1282.
- (5) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, 119, 5063.
- (6) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, 126, 3036.
- (7) (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, 42, 2892. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, 127, 17778.
- (8) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, 123, 2907.
- (9) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, 44, 257.
- (10) (a) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, 128, 3130. (b) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, 11, 5626.
- (11) (a) Yang, G.; Shen, C.; Zhang, W. *Angew. Chem., Int. Ed.* **2012**, 51, 9141. (b) Zhang, W.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2017**, 56, 5336. (c) Kou, X.; Shao, Q.; Ye, C.; Yang, G.; Zhang, W. *J. Am. Chem. Soc.* **2018**, 140, 7587.
- (12) Garlets, Z. J.; White, D. R.; Wolfe, J. P. *Asian J. Org. Chem.* **2017**, 6, 636.
- (13) (a) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, 132, 12157. (b) Hopkins, B. A.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, 51, 9886. (c) Babij, N. R.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2013**, 52, 9247. (d) Hopkins, B. A.; Wolfe, J. P. *Chem. Sci.* **2014**,

- 5, 4840. (e) Hopkins, B. A.; Garlets, Z. J.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2015**, *54*, 13390. (f) Garlets, Z. J.; Parenti, K. R.; Wolfe, J. P. *Chem.-Eur. J.* **2016**, *22*, 5919.
- (14) (a) Hu, N.; Li, K.; Wang, Z.; Tang, W. *Angew. Chem., Int. Ed.* **2016**, *55*, 5044. (b) Wang, L.; Zhang, K.; Wang, Y.; Li, W.; Chen, M.; Zhang, J. *Angew. Chem., Int. Ed.* **2020**, *59*, 4421.
- (15) (a) Borrajo-Calleja, G. M.; Bizet, V.; Mazet, C. *J. Am. Chem. Soc.* **2016**, *138*, 4014. (b) Bizet, V.; Borrajo-Calleja, G. M.; Besnard, C.; Mazet, C. *ACS Catal.* **2016**, *6*, 7183. (c) Borrajo-Calleja, G. M.; Bizet, V.; Besnard, C.; Mazet, C. *Organometallics* **2017**, *36*, 3553.
- (16) Kočovský, P.; Bäckvall, J.-E. *Chem.-Eur. J.* **2015**, *21*, 36.
- (17) (a) McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* **2011**, *13*, 2830. (b) Weinstein, A. B.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11505.
- (18) Du, W.; Gu, Q.; Li, Y.; Lin, Z.; Yang, D. *Org. Lett.* **2017**, *19*, 316.
- (19) Kawamura, Y.; Kawano, Y.; Matsuda, T.; Ishitobi, Y.; Hosokawa, T. *J. Org. Chem.* **2009**, *74*, 3048.
- (20) White, D. R.; Hutt, J. T.; Wolfe, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 11246.
- (21) (a) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076. (b) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074. (c) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (d) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471.

- (22) (a) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (b) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149. (c) Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020. (d) Bovino, M. T.; Liwosz, T. W.; Kendel, N. E.; Miller, Y.; Tyminska, N.; Zurek, E.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 6383. (e) Karyakarte, S. D.; Um, C.; Berhane, I. A.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2018**, *57*, 12921.
- (23) Wang, D.; Wu, L.; Wang, F.; Wan, X.; Chen, P.; Lin, Z.; Liu, G. *J. Am. Chem. Soc.* **2017**, *139*, 6811.
- (24) Xie, Y.; Hu, J.; Xie, P.; Qian, B.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 18327.
- (25) (a) Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324. (b) Nicolai, S.; Sedigh-Zadeh, R.; Waser, J. *J. Org. Chem.* **2013**, *78*, 3783. (c) Orcel, U.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5250. (d) Orcel, U.; Waser, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 12881. (e) Liu, Z.; Wang, Y.; Wang, Z.; Zeng, T.; Liu, P.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 11261.
- (26) Jiao, Z.; Shi, Q.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 14567.
- (27) (a) Tsuji, J.; Mandai, T. *Angew. Chem. Int. Ed.* **1996**, *34*, 2589. (b) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111. (c) Yoshida, M. *Chem. Pharm. Bull.* **2012**, *60*, 285.
- (28) Synthetic methods of the bisphosphine monooxide: Hu, J.; Lu, Y.; Li, Y.; Zhou, J. *Chem. Commun.* **2013**, *49*, 9425.
- (29) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997.
- (30) Values of bite angles on palladium complexes: (a) Bolm, C.; Kaufmann, D.;

- Gessler, S.; Harms, K. *J. Organomet. Chem.* **1995**, 502, 47. (b) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, 23, 194.
- (31) Sarnpitak, P.; Trongchit, K.; Kostenko, Y.; Sathalalai, S.; Gleeson, M. P.; Ruchirawat, S.; Ploypradith, P. *J. Org. Chem.* **2013**, 78, 8281.
- (32) Grandclaudon, C.; Michelet, V.; Toullec, P. Y. *Org. Lett.* **2016**, 18, 676.
- (33) CCDC 1888827 (**7f**), 1937818 (**7g**), 1937817 (**7h**), and 1880117 (**7j**) contain the supplementary crystallographic data. They can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- (34) (a) Yang, W.; Wang, Y.; Roberge, J. Y.; Ma, Z.; Liu, Y.; Michael Lawrence, R.; Rotella, D. P.; Seethala, R.; Feyen, J. H. M.; Dickson, J. K. *Bioorg. Med. Chem. Lett.* **2005**, 15, 1225. (b) Welin, E. R.; Warkentin, A. A.; Conrad, J. C.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2015**, 54, 9668. (c) Kuang, Y.; Wang, X.; Anthony, D.; Diao, T. *Chem. Commun.* **2018**, 54, 2558.
- (35) Willand-Charnley, R.; Fisher, T. J.; Johnson, B. M.; Dussault, P. H. *Org. Lett.* **2012**, 14, 2242.
- (36) Volkov, A.; Gustafson, K. P. J.; Tai, C.-W.; Verho, O.; Bäckvall, J.-E.; Adolfsson, H. *Angew. Chem. Int. Ed.* **2015**, 54, 5122.
- (37) Xia, Z.-L.; Zheng, C.; Liang, X.-W.; Cai, Y.; You, S.-L. *Angew. Chem. Int. Ed.* **2019**, 58, 1158.

Chapter 3: Pd-Catalyzed Asymmetric C-Alkylation of (Hetero)arenes through Wacker-Type *anti*-Addition to Cycloalkenes

3.1 Introduction

Alkylated arenes and heteroarenes are widely used in medicines and advanced materials. Classical Friedel-Crafts alkylation is arguably the most frequently used reaction to install alkyl groups directly on electron-rich (hetero)arenes. Despite its simplicity, it suffers from several limitations that include harsh reaction conditions, stoichiometric use of strong Lewis acids and the formation of byproducts via primary-to-secondary isomerization of carbocations.¹

Parent heteroarenes and arenes are easily accessible or readily made, but their innate reactivity and chemoselectivity during alkylation can become a problem. In comparison, (hetero)aryl metal reagents need to be prepared beforehand and may not be compatible with sensitive functional groups. In addition, (hetero)aryl halides and pseudohalides need to be prepared from (hetero)arenes or their derivatives such as phenols.²

In catalytic Friedel-Crafts reactions of heteroarenes and arenes, alkylating reagents other than alkyl halides have been extensively studied for stereoselective alkylation, including electronically activated alkenes,³ imines,⁴ aziridines⁵ and diazo compounds.⁶ In comparison, electron-neutral and -rich alkenes are compatible with many reaction conditions in multiple-step synthesis. Site-selective (hetero)arylation on

alkenes can also be achieved under metal-catalyzed conditions.⁷ In the past two decades, significant progress has been made on metal-catalyzed enantioselective hydroarylation and carboarylation of alkenes using arenes and heteroarenes directly. So far, three types of metal-catalyzed reactions have been developed which allow asymmetric addition of (hetero)arenes to alkenes: 1) *syn*-migratory insertion of (hetero)aryl metal complexes to olefins; 2) C–C reductive elimination of (hetero)aryl metal complexes; 3) Wacker-type *anti*-attack of nucleophilic (hetero)arenes.

3.1.1 *syn*-Migratory Insertion of (Hetero)aryl Metal Complexes to Alkenes

In 2003, Stoltz et al. reported aerobic annulations of indoles with pendant olefins using a pyridine-ligated Pd(OAc)₂ catalyst (Scheme 3.1).⁸ The observed stereochemistry of the single diastereomer supported a Heck-type pathway involving direct palladation at the C-2 site of indoles and subsequent *syn*-carbopalladation of the tethered alkene. The resulting alkyl Pd(II) species then underwent β -H elimination to afford the annulation product.

Scheme 3.1 Intramolecular dehydrogenative Heck reaction of alkene-tethered indoles

For the intermolecular and asymmetric example of couplings between heteroarenes and alkenes, Sigman and coworkers disclosed oxidative Heck arylation of

trisubstituted (homo)allylic alcohols with indoles to construct C-3 alkylation products bearing quaternary stereocenters (Scheme 3.2).⁹ Regardless of unfunctionalized indoles and indolyl boronic esters, nearly the same level of asymmetric induction was achieved in the Pd-Pyrox catalytic system, indicating a Heck-type pathway instead of *anti*-Wacker addition. However, reactions of *Z*-methyl allylic alcohols led to lower enantioselectivity in most cases, which needed modification of the ligand.

Scheme 3.2 Enantioselective dehydrogenative Heck reaction of trisubstituted alkenes with indoles

Besides dehydrogenative Heck arylation, hydroheteroarylation and hydroarylation of alkenes may also follow the pathway of β -migratory insertion. In early examples, Ellman et al. reported enantioselective *ortho*-alkylation reactions of aromatic imines and indol-3-yl imines with tethered olefins via directed C–H bond activation (Scheme 3.3).^{10a} A rhodium(I) catalyst ligated by chiral phosphoramidite provided the optimal results. These reactions were initiated by oxidative addition of aromatic C–H bonds to the Rh(I) center, followed by hydrometallation of the alkene and final C–C reductive elimination.¹⁰

Scheme 3.3 Asymmetric cyclization of aromatic imines via directed C–H activation

Later, intermolecular hydro(hetero)arylation of a C–H bond across unactivated terminal alkenes was reported by Hartwig and Hiyama separately. In both cases, a combination of $\text{Ni}(\text{cod})_2$ and sterically hindered NHC ligands was found effective in the C-2 alkylation of heteroarenes. In Hartwig's work, alkylation took place without directing groups and a wide range of heteroarenes including indoles, pyrroles, furans and benzofurans could react (Scheme 3.4a).^{11a} In comparison, the reaction developed by Hiyama and coworkers were applicable to electronically activated indoles (Scheme 3.4b).^{11b}

Scheme 3.4 Nickel-catalyzed intermolecular alkylation of heteroarenes with alkenes

In 2013, Hartwig and coworkers developed iridium-catalyzed enantioselective addition of heteroarenes to bicycloalkenes (Scheme 3.5).¹² The alkylation of heteroarenes occurred exclusively at the C–H bond adjacent to heteroatoms, even for unprotected indoles. Initial mechanistic studies of the catalyst resting state demonstrated oxidative addition of heteroaryl C–H bonds to an Ir(I) species preceded the rate-determining step, which was consistent with the observation in the addition of

arylamides to norbornene.¹³

Similarly, Yamamoto and coworkers applied a cationic iridium/Me-BIPAM catalytic system to the direct intermolecular hydroarylation of bicycloalkenes in high enantioselectivity. The regioselectivity of *ortho*-alkylation was attributed to the formation of iridacycle through chelation-assisted C–H bond cleavage.¹⁴

Scheme 3.5 Iridium-catalyzed asymmetric hydroheteroarylation of bicycloalkenes

3.1.2 C–C Reductive Elimination of (Hetero)aryl Metal Complexes

Besides *syn*-migratory insertion, C–C reductive elimination of (hetero)aryl metal complexes is another strategy to achieve C-alkylation of (hetero)arenes through alkene functionalization. Recently, palladium-catalyzed domino Heck/C–H functionalization reactions provided a powerful method to form C–C and C–X bonds in a single step.¹⁵ In addition to terminal alkynes and aryl boronic acids, the reactive alkylpalladium(II) intermediates derived from *syn*-carbopalladation can also be intercepted by some heteroarenes.

Early in 2009, Fagnou et al. reported a domino arylation reaction of aryl triflates bearing pendant olefins with acidic sulfur-containing heteroarenes (Scheme 3.6).¹⁶ The cleavage of C–H bond on heteroarenes were assisted by in-situ generated potassium pivalate through ligand exchange. The formation of a new C–C bond took place at the reductive elimination step. Similar examples of cascade carbopalladation/(hetero)arene

coupling were also reported by Sharma and Liang.¹⁷

Scheme 3.6 Pd-catalyzed cascade carbopalladation/C–H functionalization sequence

In 2017, Zhu et al. reported the first enantioselective domino carbopalladation/azole coupling (Scheme 3.7).¹⁸ The Pd catalyst of phosphino-oxazoline (PHOX) coupled oxindoles and azoles with high enantioselectivities, which was applied to the synthesis of (+)-Esermethole. As an extension of this work, asymmetric double alkylation of 1,3,4-oxadiazole was achieved under the modified conditions.¹⁹

Scheme 3.7 Pd-catalyzed enantioselective domino Heck/azole coupling with azoles

The same group also reported an asymmetric example of tandem Narasaka-Heck iminopalladation/azole coupling (Scheme 3.8).²⁰ This iminoarylation of alkenes was realized in the presence of a bidentate Synphos. 2-Substituted oxadiazoles with acidic C–H bonds were suitable coupling partners.

Scheme 3.8 Pd-catalyzed enantioselective iminoarylation of alkenes through Narasaka-Heck reaction/alkylation of azoles

3.1.3 Wacker-Type Attack of Nucleophilic (Hetero)arenes on Alkenes

Another possibility for the formal addition of (hetero)arene to the alkene is Wacker-type pathway, wherein the nucleophilic (hetero)arenes undergo an *anti*-attack to the olefins without the formation of (hetero)arylmatal species. Unlike the Heck-type pathway, it does not necessitate a transition-metal-mediated C–H cleavage of heteroarenes. The feasibility of this Friedel-Crafts-type alkylation relies on both nucleophilicity of (hetero)arenes and π -Lewis acid activation of alkenes by transition metal ions.^{7b}

Early in 2004, Widenhoefer et al. disclosed platinum-catalyzed intramolecular C3-alkylation of indoles with alkenes (Scheme 3.9a).²¹ The stereochemical result of deuterated alkenes was consistent with the outer-sphere *anti*-attack of the indole on a Pt-bound olefin. Soon later, they found a platinum complex ligated with a hindered MeO-BIPHEP ligand was effective for asymmetric cyclization of alkenyl indoles

(Scheme 3.9b).²² Particularly, the protic solvent of methanol significantly raised the enantioselectivity in this hydroarylation.

Scheme 3.9 Platinum-catalyzed intramolecular C3-alkylation of indoles with alkenes

The same group later developed palladium-catalyzed oxidative cyclization of indole-tethered alkenes followed by alkoxy carbonylation in the presence of CO (Scheme 3.10).²³ Since CO insertion into an Pd–C bond occurred with retention of configuration in the migrating alkyl center, the stereospecific outcome in the cyclization implicated exclusive *anti*-addition of indole to the Pd-bound alkenes.

Scheme 3.10 Palladium-catalyzed dicarbofunctionalization of indolyl alkenes

Compared to the intramolecular versions, intermolecular addition of heteroarenes to alkenes via a Wacker-type pathway is more attractive due to material convergence. However, the development of the intermolecular variants has lagged behind due to the poor reactivity in the intermolecular *anti*-attack.

Recently, Engle et al. employed a removable bidentate auxiliary in Pd-catalyzed hydroarylation of unactivated alkenes with various carbon nucleophiles including indoles (Scheme 3.11).²⁴ The formation of a palladacycle brought the Pd catalyst to proximity of the alkene and facilitated its π -Lewis acid activation. Consequently, the indole attacked at the terminal carbon of the alkene to give rise to a five-membered metallacycles stabilized by coordination of the 8-aminoquinoline directing group.

Scheme 3.11 Pd-catalyzed hydroarylation of unconjugated carbonyl alkenes with diverse carbon nucleophiles

In addition to this regioselective “homo-Michael” γ -addition, Engle et al. also accomplished a β,γ -vicinal dicarbofunctionalization of 3-butenic acid derivatives (Scheme 3.12).²⁵ Due to the stability and conformational rigidity imparted by the directing group, the resulting palladacycle from Wacker-type attack of indole did not undergo β -H elimination. It was intercepted via oxidative addition of the aryl iodide. A similar example of heteroarylboration was later reported, too.²⁶ Despite the broad utility of directed carbopalladation, the corresponding asymmetric version remains elusive to

date.

Scheme 3.12 Pd-catalyzed β,γ -vicinal dicarbofunctionalization of unconjugated carbonyl alkenes via directed nucleopalladation

3.2 Reaction Design

Saturated heterocycles such as tetrahydrofuran and pyrrolidine bearing α -(hetero)aryl groups are common in bioactive natural products and drug candidates (Scheme 3.13).²⁷ They are also present as core motifs of some FDA-approved pharmaceuticals. For example, nucleoside analogues including Galidesivir and Remdesivir are broad-spectrum antivirals and the latter is currently being tested for the treatment for COVID-19. Veliparib is a potential anti-cancer drug acting on poly ADP ribose polymerase (PARP), thereby preventing repair of DNA damage in cancer cells. Notably, a 2-indolylpyrrolidine was highlighted as a selective Histone deacetylase (HDAC)-10 inhibitor.

Scheme 3.13 Bioactive compounds containing 2-(hetero)aryl pyrrolidine/THF units

Considerable progress has been made in α -C–H bond functionalization of saturated heterocycles.²⁸ For instance, Baran and Yu reported an enantioselective vicinal difunctionalization of heterocycles through directed C–H activation and decarboxylative cross-coupling (Scheme 3.14). Although this transformation is amenable to rapid incorporation of diverse (hetero)aryl rings, multi-step synthesis and the use of directing groups are required. Hence, there is continued interest in developing new, straightforward synthesis of 2-heteroaryl tetrahydrofurans/ pyrrolidines.

Scheme 3.14 Vicinal difunctionalization of heterocycles in multi-step synthesis

Recently, palladium-catalyzed asymmetric three-component carboetherification and carboamination of cyclic alkenes was developed by our group through a Wacker-type pathway using propargylic acetates and hetero-nucleophiles (N or O).²⁹ Inspired by this result, I wondered whether allenyl-heteroarylation of alkenes could be realized in a single step if the alcoholic nucleophiles were replaced by electron-rich heteroarenes (Scheme 3.15). The formation of a valuable C–C bond would be especially interesting, yet more challenging than the introduction of a heteroatom.

Scheme 3.15 Reaction design of (hetero)arylation of alkenes activated by allenyl Pd complexes

Domino Heck cyclization/azole coupling reported by Zhu et al. provided facile access to enantioselective alkene dicarbofunctionalization, however, the substrate scope of heteroarenes was limited to azoles that possessed acidic H atoms.¹⁵ Until now, no example has been reported for enantioselective three-component C-alkylation of heteroarenes through alkene dicarbofunctionalization. In previous examples associated with *syn*-migratory insertion pathway, only dehydrogenative Heck arylation and hydro(hetero)arylation of alkenes were reported. In our reaction design, asymmetric

alkylation of heteroarenes through a Wacker-type pathway can be accompanied by the introduction of an allenyl group onto the alkene, thus allowing a maximal increase in molecular complexity. In addition, more types of heteroarenes and electron-rich arenes would be included.

Key challenges in developing such three-component couplings of alkenes include: (1) achieving desired Wacker-type *anti*-attack of (hetero)arenes on Pd-bound alkenes in preference to Heck-type *syn*-allenylpalladation of bound alkenes;³⁰ (2) achieving the chemoselectivity of heteroarene addition instead of addition of acetate ion, a known competing pathway; (3) preventing direct nucleophilic attack of heteroarenes on the alternative π -propargylic complex. Herein, we describe the discovery and development of a palladium-catalyzed asymmetric C-alkylation of heteroarenes through Wacker-type addition of cycloalkenes.

3.3 Results and Discussion

3.3.1 Optimization of Reaction Conditions

Due to the crucial role of furyl-MeOBIPHEP in the enantioselective three-component Wacker-type reaction reported in our group, we expected the use of this type of ligand would facilitate the pathway of Wacker-type addition (Table 3.1). Hence, in the initial attempt at the reaction between 2,3-dihydrofuran **1a**, 3-phenylpropargylic acetate **2a**, and *N*-Me-indole **3a** in acetonitrile at 45 °C, we found the Pd(0) complex derived from Pd(cod)Cl₂, **L1** and sodium formate afforded the desired product in moderate yield and 81% ee (entry 4). Acetoxyallenylation took place concomitantly as

the side reaction, affording the byproduct **5a**. In comparison, no product was detected when HCO₂Na was omitted (entry 3). Other bases including HCO₂K and Et₃N led to the inferior results (entries 6-7). Notably, the enantio-induction of this transformation is sensitive to the temperature since the ee value was better for the reaction occurring at 25 °C than 45 °C (entry 5).

Table 3.1 Initial condition screening

entry	Pd source	additive	T/°C	yield of 4a (%)	ee of 4a (%)	yield of 5a (%)
1	Pd(dba) ₂	none	45	23	79	10
2	Pd(dba) ₂	HCO ₂ Na	45	40	80	27
3	Pd(cod)Cl ₂	none	45	0	---	0
4	Pd(cod)Cl ₂	HCO ₂ Na	45	54	81	33
5	Pd(cod)Cl ₂	HCO ₂ Na	25	46	88	15
6	Pd(cod)Cl ₂	HCO ₂ K	45	29	81	16
7	Pd(cod)Cl ₂	Et ₃ N	45	0	---	0

To improve both catalytic efficiency and reproducibility of results on small scales, we decided to use a preformed **L1**PdCl₂ complex at 1 mol% loading instead of in-situ prepared complex from **L1** and Pd(cod)Cl₂.³¹ Furthermore, the amount of *N*-

methyldindole was reduced to 3 equivalents while the concentration of **2a** was raised from 0.33 M to 2 M (Table 3.2). The reaction conducted at 30 °C in acetonitrile with the refined procedure furnished **4a** with higher enantiocontrol, albeit in a slightly lower yield (Table 3.2, entry 3 compared to Table 3.1, entry 4). Gratifyingly, the solvent had a pronounced effect on the chemoselectivity of **4a** over **5a**. A polar aprotic solvent, ethylene carbonate (EC) was found optimal for this transformation (entry 1),³² which inhibited the undesired acetoxylation pathway. Lower product yields were observed in other polar solvents such as acetone, DMF and DMSO. In DCM, however, the pathway of heteroarene addition was less favored than acetate addition (entry 6).

Table 3.2 The effect of solvents in the model reaction

1a 2 equiv 2a 3a 3 equiv $\xrightarrow[\text{HCO}_2\text{Na 1.2 equiv}]{\text{L1PdCl}_2 \text{ 1 mol\%}}$ $[\text{2a}] = 2 \text{ M in solvent}$ 30°C, 48 h 4a 5a				
entry	solvent	yield of 4a (%)	ee of 4a (%)	yield of 5a (%)
1	ethylene carbonate	64	87	15
2	acetone	36	87	27
3	MeCN	51	85	34
4	DMSO	2	---	0
5	DMF	7	---	14
6	DCM	28	89	37
7	THF	0	---	0
8	dioxane	0	---	0

3.3.2 Substrate Scope

With the optimal conditions in hand, we investigated the scope of indoles in reactions with 2,3-dihydrofuran and 3-phenylpropargylic acetate (Scheme 3.16a). In all cases including reactions of *N*-H indoles, asymmetric alkylation took place selectively at the C-3 site on indole rings, providing exclusively *trans*-isomers. The absolute configuration of **4a** was confirmed by X-ray crystallography.³³ Electron-rich indoles bearing methyl and methoxy substituents proved to be suitable coupling partners, providing the corresponding products in moderate to good yields and up to 90% ee. Notably, the bulky group adjacent to the reaction site was tolerable in this transformation. **L1** showed poor performance in the cases of *N*-H indole and electron-withdrawing indoles due to the formation of acetoxylation product. Encouragingly, we found MeO-BIPHEP ligand bearing a bulky 2-benzofuryl group (**L2**) had a positive effect on the chemo-selective C-functionalization when less reactive indoles acted as nucleophiles (**4f-4i**).³⁴

We also examined the compatibility of other (hetero)arenes in this transformation (Scheme 3.16b). Both 1,2,5-trimethylpyrrole and 2,5-dimethylpyrrole were reactive in this catalytic system, affording the alkylation product **4j** and **4l** at the C3 site in excellent enantiocontrol. 1-Methylpyrrole underwent the coupling smoothly when **L2** was used, providing both C2 and C3 regioisomers with a ratio of 2.1:1. Remarkably, the asymmetric alkylation was carried out successfully with electron-rich aromatic compounds including tertiary anilines. For **4m**, the new C–C bond was formed exclusively at the *ortho* site of methoxy group, which was determined by NOE signal. Interestingly, an electro-active conductive monomer, 3,4-ethylenedioxythiophene

(EDOT) was capable of Wacker-type addition to the Pd-bound alkenes, although the yield was modest.

(a) Other examples of indoles

(b) Other examples of (hetero)arenes

Scheme 3.16 Substrate scope of allenyl(hetero)arylation of 2,3-dihydrofuran with

substituted indoles and other (hetero)arenes

An evaluation of the generality of propargylic acetates followed (Scheme 3.17). In the coupling with 2,3-dihydrofuran and 1,2-dimethylindole under the optimized conditions, both electron-rich and electron-deficient aryl rings in the 3-position of propargylic acetates were well tolerated. When aryl group was replaced by thiophene ring, the reaction also proceeded efficiently. Furthermore, propargylic acetate bearing a conjugated alkenyl group at the 3-position afforded the desired product **6i** when the catalyst loading was raised to 2 mol%.

Subsequently, we found that the allenyl(hetero)arylation process could be extended to *N*-Boc-2,3-dihydropyrrole, another reactive cycloalkene in this transformation (Scheme 3.18). The reactive 1,2-dimethylindole and 2-methylindole were first tested with **1b** and **2a** using 2 mol% of prepared **L1**PdCl₂ complex under the standard conditions. The dicarbo-functionalization took place smoothly in acetonitrile, affording the corresponding products with up to 96% ee. When *N*-Boc protecting group on the 2,3-dihydropyrrole was switched to Cbz, higher temperature (45 °C) was required for the full conversion of **2a**.

Scheme 3.17 Substrate scope of allenyl(hetero)arylation of 2,3-dihydrofuran with substituted propargylic acetates

Scheme 3.18 Examples of allenyl(hetero)arylation of *N*-protected-2,3-dihydropyrrole with 2-methylindoles

Next, substituted indoles and other heteroarenes were examined with **1b** and **2a** (Scheme 3.19). EC was found to be an optimal solvent to accelerate the reaction rate for relatively less reactive heteroarenes, presumably due to the better solubility of Pd complex. Both unprotected indoles and *N*-alkyl indoles were competent coupling

partners, providing the desired products in high yields (78%~90%) and up to 95% ee. Other heteroarenes including 1,2,5-trimethylpyrrole and 2-methoxyfuran were also suitable nucleophiles in this process. The asymmetric alkylation occurred exclusively at the 2-position on furan ring (**7k**). Notably, 3-methoxy-*N,N*-dimethylaniline also participated in the dicarbofunctionalized process of 2,3-dihydropyrrole, furnishing the three-component product **7j** in 82% yield.

Scheme 3.19 Examples of allenyl(hetero)arylation of *N*-Boc-2,3-dihydropyrrole with indoles and other (hetero)arenes

3.3.3 Unsuccessful Examples

We attempted indoles bearing strong electron-withdrawing substituents **3d-e**, however, the acetoxylation took place predominantly instead of the desired pathway (Scheme 3.20a). *N*-Tosyl indole **3f** and 7-aza-1-methylindole **3g** could not provide the

alkylation products either, due to the attenuated nucleophilicity. Some simple heteroarenes **3h-k** also failed to participate in this three-component reaction.

For some electron-rich aryl compounds **3l-o**, none of them provided the expected alkylation products. For 1-naphthol **3p**, the three-component reaction occurred selectively at the hydroxy group rather than C-2 site (Scheme 3.20b).

Scheme 3.20 Unsuccessful examples of (hetero)arenes

3.3.4 Derivatization

To demonstrate the potential utility of the products, the allenes in the adducts can be readily converted to other functional groups (Scheme 3.21). At 2.5 mol% Pd/C loading, **6a** underwent selective mono-hydrogenation to afford **8a** with 10:1 dr. Notably, when Pd/C loading was raised to 25 mol%, not only the allenyl group was fully hydrogenated, but also the tetrahydrofuran ring was selectively cleaved at the benzylic site to provide **8b**. Additionally, both the allene and heterocyclic ring of indole

underwent ozonolysis to provide diketone **8c**. Both aromatic ketones were subsequently deoxygenated to give **8d** via palladium-catalyzed reduction with polymethylhydrosiloxane (PMHS).

Scheme 3.21 Transformations of heteroarylate adducts

3.3.5 The Proposed Reaction Mechanism

The *trans* relationship of two new substituents on the cycloalkene rings is consistent with Wacker-type mechanism. On the basis of the stereochemical outcome and previous studies,^{25,26} a catalytic cycle of this dicarbofunctionalization process is proposed (Scheme 3.22). Initially, the oxidative addition of propargylic acetate to **L1Pd(0)** complex generates σ -allenyl palladium(II) intermediate, which may exist in equilibrium with π -propargyl Pd complex. Next, cycloalkene coordinates to the cationic Pd species, followed by an *anti*-attack of the indole nucleophiles. Finally, reductive elimination from the Pd(II) center and re-aromatization release the desired three-component products.

Scheme 3.22 Proposed catalytic cycle

3.4 Conclusion

In summary, a palladium-catalyzed asymmetric allenyl(hetero)arylation of cycloalkenes has been achieved through stereo-specific Wacker-type addition. It is the first example of three-component C-alkylation of (hetero)arenes in the enantioselective fashion. Chemo-selectivity of C-functionalization over O-functionalization can be achieved by the modification of ligand structure and careful choice of solvents. The reaction proceeded smoothly with some electron-rich arenes such as tertiary anilines and a broad range of heteroarenes including *N*-H indoles, *N*-protected indoles, pyrroles, furans and thiophenes. The versatility of our method was highlighted by the possibility to introduce allenyl groups onto the alkene.

3.5 Experimental Section

3.5.1 A Typical Procedure for Ligand Screening

A general procedure: Pd(cod)Cl₂ (1.4 mg, 0.005 mmol), ligand (0.006 mmol) and 0.1 mL of dry MeCN were charged into a dry 10 mL reaction tube. After stirring for about 15 minutes in an argon-filled glove box, 2-methyl-4-phenylbut-3-yn-2-yl acetate **2a** (20.2 mg, 0.1 mmol), 2,3-dihydrofuran **1a** (15 μ L, 0.2 mmol), 1,2-dimethylindole **3a** (43.6 mg, 0.3 mmol), HCO₂Na (8.2 mg, 0.12 mmol) and GC standard *n*-dodecane 10 μ L were added sequentially. The reaction mixture was capped tightly and stirred on a hotplate maintained at 45 °C for 36 hours. After it was cooled down to rt, aliquots were taken from the reaction mixture and passed through a short plug of silica gel with EtOAc washings. The filtrate was subjected to GC to determine the calibrated conversion of **1a** and yields of the product **4a** and byproduct **5a**.

3.5.2 Asymmetric Allenyl(hetero)arylation of Cycloalkenes

(A) A general procedure: Pd(cod)Cl₂ (9.4 mg, 0.033 mmol), (*R*)-2-furylMeOBIPHEP (19.5 mg, 0.036 mmol) and 0.9 mL of dry MeCN were charged into a dry 8-mL vial. After stirring for about 2 hours in an argon-filled glove box, the supernatant was removed and the yellow precipitate was washed with Et₂O and dried in vacuo. Then 1.5 mg of pre-synthesized Pd complex (0.002 mmol, 1 mol%) from the stock was added to a dry 10-mL reaction tube. Ethylene carbonate (EC, 100 μ L, *d* = 1.321), **2a** (40.8 mg, 0.2 mmol), **1a** (30 μ L, 0.4 mmol, 2 equiv), substituted indole (0.6 mmol, 3 equiv), HCO₂Na (16.4 mg, 0.24 mmol, 1.2 equiv) and GC standard *n*-dodecane (20 μ L) were then added sequentially. The reaction was capped tightly and stirred on a hotplate at 30 °C for 48 hours.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1-methylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as white solid.

The compound **4a** was crystallized from evaporation of a solution of 0.5 mL of ethyl acetate and 2.5 mL of hexanes at room temperature. The crystal was subjected to X-ray diffraction to establish the absolute configuration.

Ee = 87%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 97:3, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.71 (d, $J = 7.9$ Hz, 1H), 7.31-7.19 (m, 6H), 7.16-7.09 (m, 2H), 6.96 (s, 1H), 5.14 (d, $J = 7.1$ Hz, 1H), 4.23-4.18 (m, 1H), 4.00 (ψ dd, $J = 15.2$, 7.4 Hz, 1H), 3.71 (s, 3H), 3.51 (ψ dd, $J = 15.1$, 6.9 Hz, 1H), 2.58-2.51 (m, 1H), 2.04-1.98 (m, 1H), 1.86 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 138.2, 137.6, 128.4, 126.9, 126.8, 126.6, 126.4, 121.8, 120.1, 119.3, 115.6, 109.4, 105.9, 100.6, 80.3, 67.7, 45.3, 34.6, 32.8, 20.6, 20.5.

HRMS (ESI): Calcd for C₂₄H₂₆NO [M+H]⁺: 344.2014; found: 344.2014.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1,5-dimethylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as light yellow oil.

Ee = 87%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.52 (s, 1H), 7.36-7.34 (m, 2H), 7.30-7.26 (m, 2H), 7.20-7.16 (m, 2H), 7.07 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.95 (s, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 4.27-4.21 (m, 1H), 4.07-4.01 (m, 1H), 3.72 (s, 3H), 3.56-3.50 (m, 1H), 2.64-2.55 (m, 1H), 2.48 (s, 3H), 2.08-2.00 (m, 1H), 1.90 (s, 3H), 1.75 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 201.1, 138.4, 136.1, 128.4, 128.3, 127.1, 126.9, 126.7, 126.4, 123.4, 119.8, 115.1, 109.0, 106.1, 100.4, 80.4, 67.6, 45.4, 34.6, 32.8, 21.6, 20.6, 20.5.

HRMS (ESI): Calcd for C₂₅H₂₈NO₂ [M+H]⁺: 358.2171; found: 358.2169.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(2-methylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:5) as white solid.

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95:5, flow rate = 1.0 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.72 (d, $J = 7.7$ Hz, 2H), 7.24-7.22 (m, 1H), 7.14-7.07 (m, 7H), 5.03 (d, $J = 7.7$ Hz, 1H), 4.29 (ψ dd, $J = 13.8, 7.7$ Hz, 1H), 3.99 (ψ dd, $J = 15.3, 7.5$ Hz, 1H), 3.67 (ψ dd, $J = 15.3, 7.7$ Hz, 1H), 2.66-2.57 (m, 1H), 2.22 (s, 3H), 2.16-2.08 (m, 1H), 1.88 (s, 3H), 1.82 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 138.2, 135.8, 133.1, 128.1, 127.1, 126.6, 126.3, 121.1, 119.5, 119.3, 111.3, 110.4, 106.5, 100.6, 81.1, 67.9, 44.4, 35.3, 20.72, 20.68, 11.8.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{26}\text{NO}$ $[\text{M}+\text{H}]^+$: 344.2014; found: 344.2015.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(2-phenylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as white solid.

Ee = 86%. Daicel Chiralcel IC, *n*-hexane/isopropanol 90:10, flow rate = 0.5 mL/min.

PeakTable			
PDA Ch1 220nm 4nm			
Peak#	Ret. Time	Area	Area %
1	20.669	2003511	50.156
2	33.190	1991046	49.844
Total		3994557	100.000

PeakTable			
PDA Ch1 220nm 4nm			
Peak#	Ret. Time	Area	Area %
1	20.708	4559106	7.055
2	33.044	60065445	92.945
Total		64624551	100.000

¹H NMR (300 MHz, CDCl₃): δ 8.04 (s, 1H), 7.88 (d, *J* = 7.4 Hz, 1H), 7.48-7.46 (m, 2H), 7.41-7.34 (m, 4H), 7.23-7.16 (m, 2H), 7.11-7.02 (m, 5H), 5.15 (d, *J* = 7.9 Hz, 1H), 4.33-4.28 (m, 1H), 4.03-3.98 (m, 1H), 3.86-3.80 (m, 1H), 2.87-2.58 (m, 1H), 2.13-2.04 (m, 1H), 1.68 (s, 3H), 1.32 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 201.1, 138.2, 137.4, 136.5, 132.9, 129.1, 128.7, 128.12, 128.09, 127.6, 126.5, 126.2, 122.4, 120.4, 120.2, 112.2, 111.1, 106.2, 100.8, 81.1, 67.9, 44.0, 35.6, 20.4, 19.8.

HRMS (ESI): Calcd for C₂₉H₂₈NO [M+H]⁺: 406.2171; found: 406.2173.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1-isopropylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:15) as colorless oil.

Ee = 88%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, $J = 7.9$ Hz, 1H), 7.35-7.30 (m, 3H), 7.26-7.07 (m, 6H), 5.14 (d, $J = 7.2$ Hz, 1H), 4.67-4.57 (m, 1H), 4.27-4.21 (m, 1H), 4.04-3.99 (m, 1H), 3.59-3.53 (m, 1H), 2.62-2.53 (m, 1H), 2.06-1.98 (m, 1H), 1.88 (s, 3H), 1.74 (s, 3H), 1.49 (d, $J = 2.8$ Hz, 3H), 1.47 (d, $J = 2.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.0, 138.2, 136.5, 128.3, 126.8, 126.7, 126.4, 121.8, 121.4, 120.2, 119.2, 115.6, 109.6, 106.0, 100.5, 80.7, 67.7, 47.0, 45.1, 34.6, 22.90, 22.88, 20.63, 20.61.

HRMS (ESI): Calcd for $\text{C}_{26}\text{H}_{30}\text{NO}$ $[\text{M}+\text{H}]^+$: 372.2327; found: 372.2330.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1*H*-indol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:1) as foam.

Ee = 85%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95:5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 8.04 (s, NH), 7.74 (d, $J = 7.8$ Hz, 1H), 7.33-7.30 (m, 3H), 7.26-7.06 (m, 6H), 5.16 (d, $J = 7.1$ Hz, 1H), 4.26-4.20 (m, 1H), 4.06-4.00 (m, 1H), 3.56-3.51 (m, 1H), 2.61-2.52 (m, 1H), 2.06-1.98 (m, 1H), 1.87 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.0, 138.2, 136.9, 128.4, 126.6, 126.5, 126.3, 122.2, 120.0, 119.8, 117.1, 111.3, 105.9, 100.7, 80.4, 67.7, 45.1, 34.6, 20.6, 20.5.

HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{24}\text{NO}$ $[\text{M}+\text{H}]^+$: 330.1858; found: 330.1855.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(5-fluoro-1-methylindol-3-yl)tetra

hydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as white solid.

Ee = 86%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.37 (dd, J = 9.8, 2.5 Hz, 1H), 7.31-7.28 (m, 2H), 7.26-7.22 (m, 2H), 7.19-7.13 (m, 2H), 6.99 (s, 1H), 6.96 (td, J = 9.0, 2.5 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 4.24-4.18 (m, 1H), 4.04-3.98 (m, 1H), 3.70 (s, 3H), 3.45 (ψ dd, J = 15.5, 7.5 Hz, 1H), 2.61-2.52 (m, 1H), 2.05-1.97 (m, 1H), 1.87 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.0, 157.8 (d, J_{CF} = 233.9 Hz), 138.1, 134.3, 128.5, 128.4, 127.0, 126.6, 126.5, 115.4 (d, J_{CF} = 4.6 Hz), 110.2 (d, J_{CF} = 19.5 Hz), 110.0 (d, J_{CF} = 2.6 Hz), 105.7, 105.0 (d, J_{CF} = 23.7 Hz), 100.6, 80.1, 67.7, 45.3, 34.7, 33.1, 20.6, 20.5.

^{19}F NMR (376.6 MHz, CDCl_3): δ -125.2.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{25}\text{FNO}$ $[\text{M}+\text{H}]^+$: 362.1920; found: 362.1916.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(5-chloro-1-methylindol-3-yl)

tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as white solid.

Ee = 84%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.69 (s, 1H), 7.30-7.22 (m, 4H), 7.18-7.13 (m, 3H), 6.96 (s, 1H), 5.04 (d, $J = 7.6$ Hz, 1H), 4.24-4.18 (m, 1H), 4.04-3.98 (m, 1H), 3.68 (s, 3H), 3.46-3.40 (m, 1H), 2.61-2.54 (m, 1H), 2.04-1.97 (m, 1H), 1.86 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.0, 138.1, 136.0, 128.4, 128.2, 127.8, 126.6, 126.5, 125.2, 122.1, 119.6, 115.2, 110.4, 105.6, 100.6, 80.0, 67.7, 45.5, 34.6, 33.0, 20.6, 20.5.

HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{25}\text{NO}^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$: 378.1625; found: 378.1622.

The products were isolated by flash chromatography (ethyl acetate/hexanes from 1:25 to 1:10) as colorless oil. 42 mg, 72% yield. The ratio of C2- and C3-alkylation isomer is determined to be 2.1:1 by GC. The two isomers were separated by silica.

Major C2 isomer: **(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1-methylpyrrol-2-yl) tetrahydrofuran**

^1H NMR (400 MHz, CDCl_3): δ 7.36-7.28 (m, 4H), 7.19 (t, $J = 7.1$ Hz, 1H), 6.58 (d, $J = 1.9$ Hz, 1H), 6.14 (dd, $J = 3.5, 1.7$ Hz, 1H), 6.05 (d, $J = 3.5$ Hz, 1H), 4.88 (d, $J = 6.5$ Hz, 1H), 4.07-4.02 (m, 1H), 3.97-3.94 (m, 1H), 3.63 (s, 3H), 3.55-3.51 (m, 1H), 2.56-2.47 (m, 1H), 2.03-1.95 (m, 1H), 1.85 (s, 3H), 1.69 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.0, 137.9, 132.1, 128.5, 126.5, 123.1, 106.9, 106.8, 105.8, 100.8, 78.2, 67.4, 43.8, 34.2, 33.9, 20.6, 20.2.

HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{24}\text{NO}$ $[\text{M}+\text{H}]^+$: 294.1858; found: 294.1863.

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

Minor C3 isomer: **(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1-methylpyrrol-3-yl)**

tetrahydrofuran

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.33 (m, 2H), 7.29-7.26 (m, 2H), 7.16 (t, *J* = 7.1 Hz, 1H), 6.55 (s, 1H), 6.51 (ψt, *J* = 2.4 Hz, 1H), 6.13 (ψt, *J* = 2.1 Hz, 1H), 4.78 (d, *J* = 7.0 Hz, 1H), 4.12-4.07 (m, 1H), 3.95-3.90 (m, 1H), 3.58 (s, 3H), 3.25-3.20 (m, 1H), 2.52-2.43 (m, 1H), 1.96-1.88 (m, 1H), 1.84 (s, 3H), 1.76 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 201.1, 138.4, 128.4, 126.6, 126.4, 125.3, 122.0, 119.7, 106.8, 105.8, 100.4, 80.6, 67.5, 46.6, 36.2, 34.5, 20.6, 20.4.

HRMS (ESI): Calcd for C₂₀H₂₄NO [M+H]⁺: 294.1858; found: 294.2148.

Ee = 92%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-[2,4-bis(diethylamino)phenyl]

tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as light

yellow oil.

Ee = 94%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99.5:0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.29-7.26 (m, 3H), 7.22-7.19 (m, 2H), 7.11 (t, $J = 7.1$ Hz, 1H), 6.49 (dd, $J = 8.6, 2.6$ Hz, 1H), 6.39 (d, $J = 2.6$ Hz, 1H), 5.37 (d, $J = 4.6$ Hz, 1H), 4.18-4.14 (m, 1H), 3.91-3.85 (m, 1H), 3.34-3.26 (m, 5H), 2.90 (q, $J = 7.1$ Hz, 4H), 2.40-2.33 (m, 1H), 1.94-1.86 (m, 1H), 1.85 (s, 3H), 1.83 (s, 3H), 1.13 (t, $J = 7.0$ Hz, 6H), 0.89 (t, $J = 7.0$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 201.7, 150.6, 147.7, 138.4, 128.2, 128.1, 128.0, 126.7, 126.1, 108.9, 107.4, 107.0, 100.2, 81.7, 67.8, 48.2, 46.5, 44.7, 33.6, 20.7, 20.4, 12.8, 12.4.

HRMS (ESI): Calcd for $\text{C}_{29}\text{H}_{41}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 433.3219; found: 433.3223.

(B) A general procedure: $\text{Pd}(\text{cod})\text{Cl}_2$ (9.4 mg, 0.033 mmol), (*R*)-2-furyl MeOBIPHEP (19.5 mg, 0.036 mmol) and 0.9 mL of dry MeCN were charged into a dry 8-mL vial. After stirring for about 2 hours in an argon-filled glove box, the supernatant was

removed and the yellow precipitate was washed with Et₂O and dried in vacuo. Then 2.2 mg of pre-synthesized Pd complex (0.003 mmol, 1 mol%) from the stock was added to a dry 10-mL reaction tube. MeCN (100 μ L), **2** (0.3 mmol), **1a** (45 μ L, 0.6 mmol, 2 equiv), **3a** (130.7 mg, 0.9 mmol, 3 equiv), HCO₂Na (24.5 mg, 0.36 mmol, 1.2 equiv) and GC standard *n*-dodecane (30 μ L) were then added sequentially. The reaction was capped tightly and stirred on a hotplate maintained at 30 °C for 48 h.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1,2-dimethylindol-3-yl)

tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:12) as white solid.

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.819	893799	49.977
2	20.885	894613	50.023
Total		1788412	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.716	14583048	94.790
2	20.772	801572	5.210
Total		15384620	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.15-7.09 (m, 6H), 5.10 (d, *J* = 7.8 Hz, 1H), 4.35-4.30 (m, 1H), 4.02

(ψ dd, $J = 15.6, 7.2$ Hz, 1H), 3.71 (ψ dd, $J = 15.2, 8.0$ Hz, 1H), 3.59 (s, 3H), 2.70-2.61 (m, 1H), 2.26 (s, 3H), 2.18-2.10 (m, 1H), 1.91 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.2, 138.2, 137.4, 134.8, 128.0, 126.7, 126.4, 126.2, 120.8, 119.4, 119.2, 110.8, 108.8, 106.7, 100.5, 81.4, 67.9, 44.6, 35.3, 29.4, 20.73, 20.70, 10.5.

HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{28}\text{NO}$ $[\text{M}+\text{H}]^+$: 358.2171; found: 358.2176.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-*p*-tolylallenyl)-2-(1,2-dimethylindol-3-yl)

tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:12) as white solid.

Ee = 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	39.943	1394244	50.310
2	46.048	1377058	49.690
Total		2771302	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	40.677	12414332	94.819
2	46.872	678360	5.181
Total		13092692	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.77 (d, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 8.2$ Hz, 1H), 7.21-7.17 (m, 1H), 7.14-7.10 (m, 1H), 7.04 (d, $J = 8.1$ Hz, 2H), 6.96 (d, $J = 8.1$ Hz, 2H), 5.11 (d, $J = 7.8$ Hz, 1H), 4.34-4.29 (m, 1H), 4.02 (ψ dd, $J = 15.4, 7.4$ Hz, 1H), 3.68

(ψ dd, $J = 15.4, 7.6$ Hz, 1H), 3.60 (s, 3H), 2.68-2.60 (m, 1H), 2.29 (s, 6H), 2.17-2.09 (m, 1H), 1.91 (s, 3H), 1.85 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.8, 137.4, 135.9, 135.3, 134.8, 128.8, 126.6, 126.3, 120.7, 119.4, 119.2, 110.8, 108.8, 106.4, 100.4, 81.3, 67.9, 44.6, 35.4, 29.4, 21.1, 20.81, 20.77, 10.6.

HRMS (ESI): Calcd for $\text{C}_{26}\text{H}_{30}\text{NO}$ $[\text{M}+\text{H}]^+$: 372.2327; found: 372.2328.

(2*S*,3*R*)-3-[3,3-Dimethyl-1-(4-methoxyphenyl)allenyl]-2-(1,2-dimethylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as white solid.

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	25.392	839744	49.026
2	28.633	873110	50.974
Total		1712853	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	25.352	982405	94.369
2	28.616	58622	5.631
Total		1041027	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, $J = 7.8$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.18-7.14 (m, 1H), 7.10-7.06 (m, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 6.65 (d, $J = 8.8$ Hz, 2H),

5.04 (d, $J = 7.8$ Hz, 1H), 4.30-4.25 (m, 1H), 3.97 (ψ dd, $J = 15.5, 7.3$ Hz, 1H), 3.72 (s, 3H), 3.62 (ψ dd, $J = 15.3, 8.0$ Hz, 1H), 3.57 (s, 3H), 2.64-2.55 (m, 1H), 2.23 (s, 3H), 2.13-2.05 (m, 1H), 1.86 (s, 3H), 1.81 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.5, 158.3, 137.4, 134.8, 130.6, 127.7, 126.3, 120.7, 119.4, 119.2, 113.5, 110.8, 108.8, 106.1, 100.4, 81.4, 67.9, 55.4, 44.7, 35.3, 29.4, 20.90, 20.88, 10.6.

HRMS (ESI): Calcd for $\text{C}_{26}\text{H}_{30}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 388.2277; found: 388.2273.

(2S,3R)-3-(3,3-Dimethyl-1-piperonylallenyl)-2-(1,2-dimethylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as white solid.

Ee = 91%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95:5, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	28.493	4408751	50.111
2	34.209	4389231	49.889
Total		8797981	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	28.170	18091895	95.396
2	33.850	873206	4.604
Total		18965101	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.71 (d, $J = 7.8$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.18-7.14 (m, 1H), 7.10-7.06 (m, 1H), 6.68 (t, $J = 1.0$ Hz, 1H), 6.55 (d, $J = 1.0$ Hz, 2H), 5.86

(q, $J = 1.4$ Hz, 2H), 5.04 (d, $J = 7.7$ Hz, 1H), 4.30-4.24 (m, 1H), 3.96 (ψdd, $J = 15.7$, 7.3 Hz, 1H), 3.61-3.55 (m, 4H), 2.65-2.56 (m, 1H), 2.28 (s, 3H), 2.12-2.02 (m, 1H), 1.87 (s, 3H), 1.80 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.6, 147.6, 146.2, 137.4, 134.8, 132.4, 126.3, 120.8, 119.7, 119.4, 119.2, 110.8, 108.8, 107.8, 107.5, 106.5, 100.9, 100.6, 81.3, 67.8, 44.9, 35.4, 29.4, 20.82, 20.79, 10.6.

HRMS (ESI): Calcd for $\text{C}_{26}\text{H}_{28}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 402.2069; found: 402.2066.

(2S,3R)-3-[3,3-Dimethyl-1-(naphthalen-2-yl)allenyl]-2-(1,2-dimethylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:15) as white solid.

Ee = 89%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 97:3, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.84 (d, $J = 7.8$ Hz, 1H), 7.69 (d, $J = 8.6$ Hz, 1H), 7.58 (d, $J = 8.6$ Hz, 1H), 7.40-7.29 (m, 3H), 7.26-7.13 (m, 4H), 7.11 (s, 1H), 5.02 (d, $J = 8.1$

Hz, 1H), 4.35 (ψdd, $J = 14.5, 7.1$ Hz, 1H), 4.08-4.03 (m, 1H), 3.82 (ψq, $J = 8.0$ Hz, 1H), 3.37 (s, 3H), 2.67-2.58 (m, 1H), 2.25-2.18 (m, 1H), 2.05 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.8, 137.4, 135.1, 134.9, 133.4, 132.1, 128.0, 127.3, 127.2, 126.3, 126.1, 125.8, 125.4, 124.4, 120.9, 119.6, 119.3, 110.8, 108.9, 106.7, 100.9, 82.1, 68.0, 44.5, 34.8, 29.2, 20.81, 20.76, 10.4.

HRMS (ESI): Calcd for $\text{C}_{29}\text{H}_{30}\text{NO}$ $[\text{M}+\text{H}]^+$: 408.2327; found: 408.2333.

(2S,3R)-3-{3,3-Dimethyl-1-[(4-methoxycarbonyl)phenyl]allenyl}-2-(1,2-dimethylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as white solid.

Ee = 92%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

PeakTable			
PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	32.418	4244903	49.503
2	35.072	4330181	50.497
Total		8575084	100.000

PeakTable			
PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	32.046	7606231	95.819
2	34.729	331908	4.181
Total		7938139	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.76-7.74 (m, 3H), 7.26-7.25 (m, 1H), 7.20-7.16 (m, 1H), 7.14-7.09 (m, 3H), 5.02 (d, $J = 8.0$ Hz, 1H), 4.34-4.28 (m, 1H), 4.04-3.98 (m, 1H), 3.87 (s, 3H), 3.72-3.66 (m, 1H), 3.55 (s, 3H), 2.67-2.58 (m, 1H), 2.20 (s, 3H), 2.16-2.08 (m, 1H), 1.91 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 202.3, 167.1, 143.2, 137.4, 134.7, 129.3, 127.7, 126.4, 126.2, 120.9, 119.32, 119.31, 110.4, 108.9, 106.3, 101.2, 81.6, 67.8, 52.0, 44.4, 35.0, 29.4, 20.5, 10.5.

HRMS (ESI): Calcd for $\text{C}_{27}\text{H}_{30}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 416.2226; found: 416.2227.

(2*S*,3*R*)-3-[3,3-Dimethyl-1-(4-fluorophenyl)allenyl]-2-(1,2-dimethylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:12) as white solid.

Ee = 93%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	17.908	1693025	50.268
2	23.572	1674939	49.732
Total		3367964	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.177	22642072	96.425
2	23.500	839407	3.575
Total		23481479	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, $J = 7.7$ Hz, 1H), 7.25 (d, $J = 7.9$ Hz, 1H), 7.19-7.16 (m, 1H), 7.12-7.08 (m, 1H), 7.05-7.01 (m, 2H), 6.80-6.75 (m, 2H), 5.01 (d, $J = 7.9$ Hz, 1H), 4.31-4.27 (m, 1H), 4.02-3.96 (m, 1H), 3.66-3.59 (m, 1H), 3.56 (s, 3H), 2.64-2.55 (m, 1H), 2.21 (s, 3H), 2.15-2.07 (m, 1H), 1.88 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.9, 161.5 (d, $J_{\text{CF}} = 245.1$ Hz), 137.4, 134.8, 134.1 (d, $J_{\text{CF}} = 3.2$ Hz), 128.1 (d, $J_{\text{CF}} = 7.9$ Hz), 126.2, 120.8, 119.4, 119.3, 114.7 (d, $J_{\text{CF}} = 21.4$ Hz), 110.6, 108.8, 105.7, 100.8, 81.5, 67.8, 44.7, 35.1, 29.4, 20.8, 10.5 .

^{19}F NMR (282.4 MHz, CDCl_3): δ -117.01 to -117.05.

HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{27}\text{FNO}$ $[\text{M}+\text{H}]^+$: 376.2077; found: 376.2076.

(2S,3R)-3-[3,3-Dimethyl-1-(thiophen-3-yl)allenyl]-2-(1,2-dimethylindol-3-

yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as white solid.

Ee = 87%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	19.169	7626362	51.718
2	22.659	7119788	48.282
Total		14746150	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	19.243	11833706	93.392
2	22.819	837360	6.608
Total		12671066	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, $J = 7.8$ Hz, 1H), 7.25 (d, $J = 7.0$ Hz, 1H), 7.19-7.15 (m, 1H), 7.11-7.08 (m, 2H), 6.92 (dd, $J = 5.0, 1.2$ Hz, 1H), 6.54 (dd, $J = 2.8, 1.2$ Hz, 1H), 5.03 (d, $J = 7.8$ Hz, 1H), 4.32-4.27 (m, 1H), 4.01-3.95 (m, 1H), 3.58 (s, 3H), 3.60-3.51 (m, 1H), 2.65-2.56 (m, 1H), 2.24 (s, 3H), 2.19-2.12 (m, 1H), 1.86 (s, 3H), 1.83 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.6, 139.8, 137.3, 134.9, 127.5, 126.2, 124.6, 120.8, 119.4, 119.3, 119.1, 110.8, 108.9, 102.7, 100.4, 81.6, 68.0, 45.6, 35.0, 29.5, 20.85, 20.82, 10.5.

HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{26}\text{NOS}$ $[\text{M}+\text{H}]^+$: 364.1735; found: 364.1735.

(2*S*,3*R*)-3-[3,3-Dimethyl-1-(cyclohex-1-en-1-yl)allenyl]-2-(1,2-dimethylindol-3-yl)tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:15) as colorless oil.

Ee = 93%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 96:4, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.69 (d, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 8.1$ Hz, 1H), 7.16-7.12 (m, 1H), 7.08-7.05 (m, 1H), 5.39 (t, $J = 3.8$ Hz, 1H), 5.00 (d, $J = 7.6$ Hz, 1H), 4.24-4.19 (m, 1H), 3.92-3.86 (m, 1H), 3.62 (s, 3H), 3.44-3.38 (m, 1H), 2.59-2.49 (m, 1H), 2.38 (s, 3H), 2.04-1.91 (m, 4H), 1.84-1.74 (m, 7H), 1.58-1.37 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.2, 137.3, 134.7, 133.5, 126.4, 122.7, 120.6, 119.5, 119.1, 111.2, 108.7, 99.8, 81.0, 67.9, 42.9, 35.6, 29.5, 27.7, 26.1, 23.2, 22.6, 21.2, 21.1, 10.7.

HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{32}\text{NO}$ $[\text{M}+\text{H}]^+$: 362.2484; found: 362.2485.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1,2,5-trimethylpyrrol-3-yl)

tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as light yellow oil.

Ee = 92%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 99:1, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	28.041	720613	50.758
2	29.696	699085	49.242
Total		1419698	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	28.079	2166704	95.799
2	29.739	95007	4.201
Total		2261711	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.34-7.31 (m, 2H), 7.28-7.24 (m, 2H), 7.15 (t, $J = 7.1$ Hz, 1H), 5.88 (s, 1H), 4.81 (d, $J = 6.9$ Hz, 1H), 4.12-4.06 (m, 1H), 3.89 (dd, $J = 15.1$, 7.2 Hz, 1H), 3.33 (s, 3H), 3.32-3.28 (m, 1H), 2.54-2.46 (m, 1H), 2.18 (s, 3H), 2.13 (s, 3H), 2.00-1.92 (m, 1H), 1.86 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 138.4, 128.3, 127.6, 126.7, 126.2, 125.9, 118.7, 106.3, 103.4, 100.2, 79.8, 67.4, 45.6, 34.9, 30.1, 20.7, 20.4, 12.6, 10.3.

HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{28}\text{NO}$ $[\text{M}+\text{H}]^+$: 322.2171; found: 322.2174.

(2S,3R)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(2,5-dimethylpyrrol-3-yl)

tetrahydrofuran

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as light yellow oil.

Ee = 91%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 98:2, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	28.569	2110924	49.410
2	38.410	2161330	50.590
Total		4272254	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	28.186	13153654	95.489
2	38.280	621354	4.511
Total		13775008	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.44 (s, 1H), 7.33-7.31 (m, 2H), 7.28-7.22 (m, 2H), 7.15 (t, $J = 7.1$ Hz, 1H), 5.84 (s, 1H), 4.76 (d, $J = 7.0$ Hz, 1H), 4.13-4.07 (m, 1H), 3.93-3.88

(m, 1H), 3.31-3.26 (m, 1H), 2.54-2.47 (m, 1H), 2.19 (s, 3H), 2.13 (s, 3H), 2.00-1.92 (m, 1H), 1.86 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 138.4, 128.2, 126.7, 126.3, 125.8, 124.1, 119.6, 106.2, 104.2, 100.2, 79.3, 67.4, 45.8, 34.8, 20.6, 20.4, 13.1, 11.1.

HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{26}\text{NO}$ $[\text{M}+\text{H}]^+$: 308.2014; found: 308.2010.

(C) A general procedure: $\text{Pd}(\text{cod})\text{Cl}_2$ (9.4 mg, 0.033 mmol), (*R*)-2-furyl MeOBIPHEP (19.5 mg, 0.036 mmol) and 0.9 mL of dry MeCN were charged into a dry 8-mL vial. After stirring for about 2 hours, the supernatant was removed and the yellow precipitate was washed with Et_2O and dried in vacuo. Then 1.5 mg of pre-synthesized Pd complex (0.004 mmol, 2 mol%) from the stock was added to a dry 10-mL reaction tube in an argon-filled glove box. MeCN (0.4 mL), **2a** (40.4 mg, 0.2 mmol), **1b** (52 μL , 0.3 mmol, 1.5 equiv), 2-methyl indole substrate (0.6 mmol, 3 equiv), HCO_2Na (16.4 mg, 0.24 mmol, 1.2 equiv) and GC standard *n*-dodecane (20 μL) were then added sequentially. The reaction was capped tightly and stirred on a hotplate maintained at 30 $^\circ\text{C}$ for 48 h.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(2-methylindol-3-yl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:3) as white solid. Ee = 96%.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	16.755	2006875	49.687
2	24.479	2032181	50.313
Total		4039056	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	16.945	3206718	97.936
2	24.832	67568	2.064
Total		3274286	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.67 (s, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.23-7.07 (m, 7H), 7.02 (t, $J = 7.2$ Hz, 1H), 5.14 (s, 0.3H), 4.93 (s, 0.7H), 3.80-3.55 (m, 2H), 3.45-3.28 (m, 1H), 2.36-2.21 (m, 4H), 1.95-1.86 (m, 7H), 1.42 (s, 3H), 1.08 (s, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 201.0, 154.8, 137.6, 135.5, 130.9, 128.3, 127.0, 126.6, 126.4, 120.8, 119.3, 118.5, 113.7, 110.3, 106.1, 100.8, 78.7, 60.8, 46.9, 46.2, 30.3, 28.4, 20.7, 20.6, 11.9.

HRMS (ESI): Calcd for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 443.2699; found: 443.2699.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(2-methylindol-3-yl)-*N*-(benzyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:3) as colorless oil. Ee = 89%.

PeakTable

Peak#	Ret. Time	Area	Area %
1	21.508	14586307	50.065
2	25.642	14548394	49.935
Total		29134701	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	21.443	89616146	94.442
2	25.655	5273795	5.558
Total		94889941	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.80-7.74 (m, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.34-7.26 (m, 2H), 7.21-7.07 (m, 10H), 6.93-6.91 (m, 1H), 5.17-5.11 (m, 2H), 4.98 (s, 1H), 3.84-3.80 (m, 2H), 3.53-3.48 (m, 1H), 2.42-2.34 (m, 1H), 2.20 (s, 1H), 2.06 (s, 2H), 1.99-1.91 (m, 1H), 1.88-1.79 (m, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 155.4 and 154.8, 137.4 and 137.1, 135.4, 131.4, 128.5, 128.3, 128.2, 127.9, 127.6, 126.9, 126.6, 126.5, 121.1, 119.6, 118.5, 113.1, 110.4, 105.9, 101.0, 66.6, 60.8 and 60.4, 46.7 and 46.5, 30.1 and 29.8, 20.6, 20.5, 11.9.

HRMS (ESI): Calcd for $\text{C}_{32}\text{H}_{33}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 477.2542; found: 477.2549.

(2S,3R)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1,2-dimethylindol-3-yl)-N-(tert-butyloxycarbonyl) pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as light yellow oil. Ee = 91%.

PeakTable

Peak#	Ret. Time	Area	Area %
1	17.542	1374161	49.338
2	22.427	1411039	50.662
Total		2785200	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	17.466	24340130	95.465
2	22.345	1156183	4.535
Total		25496313	100.000

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.47 (d, $J = 7.7$ Hz, 1H), 7.24-7.10 (m, 7H), 7.03 (t, $J = 7.1$ Hz, 1H), 5.14 (s, 0.4 H), 4.94 (s, 0.6H), 3.78-3.65 (m, 2H), 3.57 (s, 3H), 3.40-3.30 (m, 1H), 2.34-2.28 (m, 1H), 2.25-2.14 (m, 3H), 1.92-1.86 (m, 7H), 1.42 (s, 3H), 1.05 (s, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 201.0, 154.8, 137.6, 136.9, 132.7, 128.2, 126.7, 126.4, 120.4, 119.0, 118.7, 113.4, 112.9, 108.6, 106.1, 100.7, 78.7, 61.0 and 60.7, 47.2, 46.3, 30.3, 29.4, 28.8, 28.3, 20.8 and 20.7, 10.4.

HRMS (ESI): Calcd for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 457.2855; found: 457.2859.

(2*S*,3*R*)-3-(3,3-Cyclopentylene-1-phenylallenyl)-2-(1,2-dimethylindol-3-yl)-*N*-(*tert*-butyloxycarbonyl) pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:10) as colorless oil. 68 mg, 68% yield. Ee = 92%.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.47 (d, $J = 7.8$ Hz, 1H), 7.26-7.12 (m, 7H), 7.04 (t, $J = 7.2$ Hz, 1H), 5.15 (s, 0.3H), 4.99 (s, 0.7H), 3.85-3.69 (m, 2H), 3.58 (s, 3H), 3.41-3.32 (m, 1H), 2.40-2.19 (m, 8H), 1.98-1.90 (m, 1H), 1.81-1.62 (m, 6H), 1.43 (s, 3H), 1.02 (s, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 197.3, 154.8 and 154.1, 137.5, 136.8, 132.5, 128.2, 126.5, 126.2, 126.0, 120.4, 119.1, 118.7, 113.7, 108.6, 108.1, 105.9, 78.7, 60.9, 47.3, 46.1, 31.9 and 31.8, 30.2, 29.3, 28.7, 28.2, 27.9, 27.7, 26.3, 10.4.

HRMS (ESI): Calcd for $\text{C}_{33}\text{H}_{41}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 497.3168; found: 497.3166.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1,2,5-trimethylpyrrol-3-yl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as colorless oil. Ee = 93%.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.35-7.33 (m, 2H), 7.30-7.26 (m, 2H), 7.17 (t, $J = 7.1$ Hz, 1H), 5.70 (s, 1H), 4.86 (s, 0.4H), 4.72 (s, 0.6H), 3.60-3.45 (m, 2H), 3.35 (s, 3H), 3.12-3.06 (m, 1H), 2.50-2.41 (m, 1H), 2.19 (s, 3H), 2.16-2.08 (m, 3H), 1.88-1.83 (m, 7H), 1.44 (s, 3H), 1.31 (s, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 155.0 and 154.4, 137.5, 128.3, 126.8, 126.7, 126.4, 123.4 and 123.0, 121.6 and 121.3, 106.5, 103.5, 100.4, 78.4, 60.0, 47.3 and 47.0, 45.5 and 45.1, 30.1, 28.6, 20.6, 20.5, 12.6, 10.4.

HRMS (ESI): Calcd for $\text{C}_{27}\text{H}_{37}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 421.2855; found: 421.2852.

(D) A general procedure: $\text{Pd}(\text{cod})\text{Cl}_2$ (9.4 mg, 0.033 mmol), (*R*)-2-FurylMeOBIPHEP (19.5 mg, 0.036 mmol) and 0.9 mL of dry MeCN were charged into a dry 8-mL vial. After stirring for about 2 hours, the supernatant was removed and the yellow precipitate was washed with Et_2O and dried in vacuo. Then 1.5 mg of pre-synthesized Pd complex (0.002 mmol, 2 mol%) from the stock was added to a dry 10-mL reaction tube in an argon-filled glove box. Ethylene carbonate (EC, 100 μL , $d = 1.321$), **2a** (20.2 mg, 0.1 mmol), **1b** (26 μL , 0.15 mmol, 1.5 equiv), substituted indole (0.3 mmol, 3 equiv), HCO_2Na (16.4 mg, 0.24 mmol, 2.4 equiv) and GC standard *n*-dodecane (10 μL) were

then added sequentially. The reaction was capped tightly and stirred on a hotplate maintained at 30 °C for 48 h.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1-methylindol-3-yl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:4) as light yellow oil. Ee = 92%.

¹H NMR of two rotamers (400 MHz, CDCl₃): δ 7.57 (d, *J* = 7.9 Hz, 0.3H), 7.53 (d, *J* = 7.9 Hz, 0.7H), 7.35-7.17 (m, 7H), 7.10-7.02 (m, 1H), 6.84 (s, 0.7H), 6.80 (s, 0.3H), 5.24 (s, 0.3H), 5.14 (s, 0.7H), 3.75-3.73 (m, 3H), 3.66-3.53 (m, 3H), 2.35-2.20 (m, 1H), 2.10-1.86 (m, 7H), 1.46 (s, 3H), 1.25 (s, 6H).

¹³C NMR of two rotamers (100 MHz, CDCl₃): δ 200.8, 155.1, 137.4, 128.5, 126.7, 126.6, 126.2, 125.9, 125.7, 121.6 and 121.5, 119.3, 118.9, 118.8, 118.3, 109.4, 105.7, 100.6, 78.9, 59.9, 54.6, 45.9, 44.9, 32.84 and 32.79, 28.8 and 28.5, 20.7.

HRMS (ESI): Calcd for C₂₉H₃₅N₂O₂ [M+H]⁺: 443.2699; found: 443.2696.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(1,5-dimethylindol-3-yl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as light yellow oil. Ee = 92%.

¹H NMR of two rotamers (400 MHz, CDCl₃): δ 7.40-7.28 (m, 5H), 7.23-7.19 (m, 2H), 7.06 (t, *J* = 6.0 Hz, 1H), 6.80 (s, 0.7H), 6.76 (s, 0.3H), 5.23 (s, 0.3H), 5.13 (s, 0.7H), 3.72-3.71 (m, 3H), 3.68-3.38 (m, 3H), 2.47-2.45 (m, 3H), 2.30-2.22 (m, 1H), 1.94-1.88 (m, 7H), 1.50 (s, 3H), 1.28 (s, 6H).

¹³C NMR of two rotamers (100 MHz, CDCl₃): δ 200.8, 155.1, 137.4, 136.0, 128.5, 128.1, 127.9, 126.7, 126.6, 126.4, 126.2, 125.9, 123.2 and 123.1, 119.0, 109.0, 105.8, 100.5, 79.1 and 78.9, 59.9, 54.6, 45.7, 44.9, 32.84 and 32.79, 28.5 and 28.3, 21.6, 20.6.

HRMS (ESI): Calcd for C₃₀H₃₇N₂O₂ [M+H]⁺: 457.2855; found: 457.2849.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(indol-3-yl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:3) as colorless oil. Ee = 92%.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 8.23-8.17 (m, 1H), 7.58 (d, $J = 8.0$ Hz, 0.3H), 7.54 (d, $J = 8.0$ Hz, 0.7H), 7.36-7.27 (m, 5H), 7.21-7.07 (m, 3H), 6.95 (s, 0.7H), 6.91 (s, 0.3H), 5.26 (s, 0.3H), 5.15 (s, 0.7H), 3.69-3.57 (m, 2H), 3.41-3.38 (m, 0.8H), 2.30-2.23 (m, 1H), 2.09-2.03 (m, 0.2H), 1.93-1.67 (m, 7H), 1.48 (s, 3H), 1.25 (s, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.7, 155.1, 137.3, 136.8, 128.5, 126.63 and 126.57, 125.7, 121.9, 121.1, 119.5, 119.4, 119.2, 119.1, 111.4, 105.6, 100.7, 79.0, 60.0, 54.8, 45.6, 44.9, 28.5, 20.7.

HRMS (ESI): Calcd for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 429.2542; found: 429.2535.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(2-phenylindol-3-yl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:8) as white solid. Ee = 95%.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 8.02 (s, 1H), 7.61-7.30 (m, 7H), 7.21-7.07 (m, 7H), 5.36 (s, 0.25H), 5.09 (s, 0.75H), 3.80-3.30 (m, 3H), 2.40-2.36 (m, 1H), 1.92-1.85 (m, 1H), 1.76 (s, 3H), 1.65-1.55 (m, 3H), 1.40 (s, 3H), 1.00 (s, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 201.0, 154.9, 137.3, 136.1, 134.4, 133.2, 128.8, 128.7, 128.2, 127.7, 127.0, 126.4, 126.3, 122.1, 120.0, 115.6, 110.9, 105.2, 101.0, 78.9, 77.4, 60.9, 47.5, 46.2, 30.1, 28.4, 20.5, 20.1.

HRMS (ESI): Calcd for $\text{C}_{34}\text{H}_{37}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 505.2855; found: 505.2843.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(4-dimethylamino-2-methoxyphenyl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:6) as colorless oil. Ee = 92%.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.37-7.35 (m, 2H), 7.30-7.26 (m, 2H), 7.16 (t, J = 6.8 Hz, 1H), 6.94-6.92 (m, 1H), 6.29-6.26 (m, 2H), 5.14 (s, 0.3H), 5.02 (s, 0.7H), 3.77-3.74 (m, 3H), 3.68-3.48 (m, 2H), 3.13-3.09 (m, 1H), 2.95-2.93 (m, 6H), 2.21-2.12 (m, 1H), 1.88-1.74 (m, 7H), 1.46 (s, 3H), 1.27 (s, 6H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.9, 157.3, 154.9 and 154.2, 151.2 and 151.0, 137.7, 128.3, 127.1, 126.9, 126.8, 126.3, 121.3, 106.3, 104.7 and 104.5, 100.3, 96.9 and 96.5, 78.6, 61.5 and 61.2, 55.4 and 55.2, 45.8 and 45.3, 41.1 and 41.0, 28.8, 28.5 and 28.3, 27.9, 20.6.

HRMS (ESI): Calcd for $\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 463.2961; found: 463.2966.

(2*S*,3*R*)-3-(3,3-Dimethyl-1-phenylallenyl)-2-(5-methoxyfuran-2-yl)-*N*-(*tert*-butyloxycarbonyl)pyrrolidine

The product was isolated by flash chromatography (ethyl acetate/hexanes 1:20) as white solid. Ee = 93%.

^1H NMR of two rotamers (400 MHz, CDCl_3): δ 7.37-7.28 (m, 4H), 7.18 (t, $J = 7.0$ Hz, 1H), 6.02 (s, 0.3H), 5.95 (s, 0.7H), 5.05 (d, $J = 3.1$ Hz, 0.7H), 5.02 (d, $J = 3.1$ Hz, 0.3H), 4.80 (s, 0.3H), 4.67 (s, 0.7H), 3.83 (s, 2.1H), 3.80 (s, 0.9H), 3.54-3.38 (m, 3H), 2.41-2.34 (m, 0.7H), 2.04-1.95 (m, 1H), 1.87-1.81 (m, 6.3H), 1.44-1.38 (m, 9H).

^{13}C NMR of two rotamers (100 MHz, CDCl_3): δ 200.5, 160.8, 154.5, 145.3, 137.0, 128.5, 126.6, 126.5, 106.8, 105.4, 101.0, 79.7, 79.4 and 79.3, 60.3, 57.8, 54.9, 44.8 and 44.1, 31.9, 28.6, 20.5, 20.4.

HRMS (ESI): Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 432.2151; found: 432.2154.

3.6 References

1. (a) Price, C. C. *Org. React.* **1946**, 3, 1. (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley-Interscience: New York, 1973.
2. Selected examples: (a) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, 104, 2667. (b) Race, N. J.; Yuan, Q.; Sigman, M. S. *Chem.-Eur. J.* **2019**, 25, 512.
3. Representative reports on enantioselective Friedel-Crafts alkylation with activated alkenes: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, 123, 4370. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, 125, 10780. (c) Liu, W.; Rajkumar, S.; Wu, W.; Huang, Z.; Yang, X. *Org. Lett.* **2019**, 21, 3563. (d) Staleva, P.; Hernández, J. G.; Bolm, C. *Chem.-Eur. J.* **2019**, 25, 9202.
4. Representative reports on Friedel-Crafts alkylation with imines: (a) Chen, W.; Wilde, R. G.; Seidel, D. *Org. Lett.* **2014**, 16, 730. (b) Xie, L.-H.; Cheng, J.; Luo, Z.-W.; Lu, G. *Tetrahedron Letters* **2018**, 59, 457.
5. Representative reports on enantioselective Friedel-Crafts alkylation with aziridines: (a) Ge, C.; Liu, R.-R.; Gao, J.-R.; Jia, Y.-X. *Org. Lett.* **2016**, 18, 3122. (b) Lin, T.-Y.; Wu, H.-H.; Feng, J.-J.; Zhang, J. *ACS Catal.* **2017**, 7, 4047.
6. Representative reports on enantioselective Friedel-Crafts alkylation with carbenoids that generate highly reactive zwitterionic intermediates: (a) Cai, Y.; Zhu, S.-F.; Wang, G.-P.; Zhou, Q.-L. *Adv. Synth. Catal.* **2011**, 353, 2939. (b) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, L.; Zhai, C.-W.; Doyle, M. P.; Hu, W.-H. *Nat. Chem.* **2012**, 4, 733. (c) Jia, S.; Xing, D.; Zhang, D.; Hu, W. *Angew. Chem. Int. Ed.* **2014**, 53, 13098.

7. (a) Evano, G.; Theunissen, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 7202. (b) Evano, G.; Theunissen, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 7558.
8. Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578.
9. Zhang, C.; Santiago, C. B.; Crawford, J. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 15668.
10. (a) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192. (b) Wilson, R. M.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2006**, *8*, 1745. (c) Lee, P.-S.; Yoshikai, N. *Org. Lett.* **2015**, *17*, 22. (d) Loup, J.; Zell, D.; Oliveira, J. C. A.; Keil, H.; Stalke, D.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 14197.
11. (a) Schramm, Y.; Takeuchi, M.; Semba, K.; Nakao, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 12215. (b) Nakao, Y.; Kashiwara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 4451.
12. Sevov, C. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2116.
13. Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 11960.
14. Shirai, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 9894.
15. Ping, Y.; Li, Y.; Zhu, J.; Kong, W. *Angew. Chem. Int. Ed.* **2019**, *58*, 1562.
16. René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560.
17. (a) Sharma, U. K.; Sharma, N.; Kumar, Y.; Singh, B. K.; Van der Eycken, E. V. *Chem.-Eur. J.* **2016**, *22*, 481. (b) Wu, X.-X.; Chen, W.-L.; Shen, Y.; Chen, S.; Xu, P.-F.; Liang, Y.-M. *Org. Lett.* **2016**, *18*, 1784.
18. Kong, W.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 16028.
19. Tong, S.; Limouni, A.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed.* **2017**,

56, 14192.

20. Bao, X.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 9577.
21. Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700.
22. Han, X.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801.
23. Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250.
24. Yang, K. S.; Gurak, J. A.; Liu, Z.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138*, 14705.
25. Liu, Z.; Zeng, T.; Yang, K. S.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138*, 15122.
26. Liu, Z.; Ni, H.-Q.; Zeng, T.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 3223.
27. (a) Siegel, D.; Hui, H. C.; Doerffler, E.; Clarke, M. O.; Chun, K.; Zhang, L.; Neville, S.; Carra, E.; Lew, W.; Ross, B.; Wang, Q.; Wolfe, L.; Jordan, R.; Soloveva, V.; Knox, J.; Perry, J.; Perron, M.; Stray, K. M.; Barauskas, O.; Feng, J. Y.; Xu, Y.; Lee, G.; Rheingold, A. L.; Ray, A. S.; Bannister, R.; Strickley, R.; Swaminathan, S.; Lee, W. A.; Bavari, S.; Cihlar, T.; Lo, M. K.; Warren, T. K.; Mackman, R. L. *J. Med. Chem.* **2017**, *60*, 1648. (b) Graldy, M.; Morgen, M.; Sehr, P.; Steimbach, R. R.; Moi, D.; Ridinger, J.; Oehme, I.; Witt, O.; Malz, M.; Nogueira, M. S.; Koch, O.; Gunkel, N.; Miller, A. K. *J. Med. Chem.* **2019**, *62*, 4426.
28. (a) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798. (b) Shang, M.; Feu, K. S.; Vantourout, J. C.; Barton, L. M.; Osswald, H. L.; Kato, N.; Gagaring, K.; McNamara, C. W.; Chen, G.; Hu, L.; Ni, S.; Fernndez-Canelas, P.; Chen, M.; Merchant, R. R.; Qin, T.; Schreiber, S. L.; Melillo, B.; Yu, J.-Q.; Baran, P. S. *Proc. Natl Acad. Sci. USA* **2019**, *116*, 8721. (c) Paul, A.; Seidel, D. *J. Am. Chem. Soc.* **2019**, *141*, 8778. (d) Chen, W.; Paul, A.; Abboud, K. A.; Seidel, D. *Nat. Chem.* **2020**, *12*, 545.

29. Teng, S.; Jiao, Z.; Chi, Y. R.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2020**, *59*, 2246.
30. Jiao, Z.; Shi, Q.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 14567.
31. Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 7092.
32. Shevlin, M. *ACS Med. Chem. Lett.* **2017**, *8*, 601.
33. CCDC 1938506 (**4a**) contains the supplementary crystallographic data.
34. Ma, M.-L.; Peng, Z.-H.; Chen, L.; Guo, Y.; Chen, H.; Li, X.-J. *Chin. J. Chem.* **2006**, *24*, 1391.

General Conclusion and Perspective

Overall, this dissertation describes the development of efficient palladium-catalyzed reactions that achieve alkene functionalization.

Part I (chapter 1) reports on a Heck-type alkylation reaction between epoxides and vinylarenes (Scheme 4.1). Using a Pd(0) catalyst derived from Pd(PPh₃)₄ and Xantphos in combination with a catalytic iodide source, Et₃N·HI, valuable β -homoallylic alcohols were obtained in good yields and regioselectivity. Cyclic epoxides as well as a variety of terminal epoxides were appropriate alkylating agents. Alkenes include substituted styrenes, conjugate dienes and coumarins were readily alkylated. In the reactions of unsymmetrical epoxides, a new C–C bond was formed predominantly at the less hindered site, and the stereochemistry of epoxides was fully retained in the products. Based on the detailed mechanistic studies, we proposed the reaction was initiated from ring-opening of the epoxide by iodide source, followed by a hybrid Pd-radical catalytic cycle. Building upon this work, alkene dicarbofunctionalization involving two consecutive addition steps of alkyl radicals is ongoing in our lab. The application of photoinduced palladium catalysis is another direction in our future work.

Scheme 4.1

In part II (chapters 2 and 3), σ -allenyl palladium species are connected to classical Wacker chemistry to accomplish asymmetric *trans*-difunctionalization of cyclic enol

ethers and enamides. We presented in chapter 2 enantioselective oxyallenylation and aza-allenylation of cyclic olefins via Wacker-type (*anti*-attack) mechanism (Scheme 4.2). In addition to alcohols, other external heteroatom nucleophiles such as acetic acid, phenol, water and electron-deficient anilines also afforded the 2,3-disubstituted tetrahydrofurans and pyrrolidines in high yields with excellent *ees*. The choice of MeO-biphep ligand bearing 2-furyl substituent successfully suppressed undesirable competing reactions. Impressively, a number of product derivatizations have been conducted, illustrating the synthetic utility of this novel three-component reaction.

Scheme 4.2

Chapter 3 focuses on enantioselective (hetero)aryllenylation of cycloalkenes using propargylic acetates and heteroarenes (Scheme 4.3). Although it is the extension of the chemistry described in chapter 2, this coupling reaction directly using heteroarenes such as indoles, pyrroles, activated furans and thiophenes is much more challenging to accomplish. Chemoselectivity of heteroarylation over acetoxylation was achieved by the modification of ligand structure and careful choice of polar solvents. Allenyl groups installed on the products readily underwent post-transformations including hydrogenation and ozonolysis, demonstrating the potential utility of the products. For future development in this area, we will investigate in depth the relationship between weak σ -donor ligands and Wacker-type pathway, which can

provide us more inspiration and guidance in further exploration of other types of alkenes and carbon electrophiles.

Scheme 4.3