Development of Rh-Catalyzed Chemoselective *Z*-Olefin Synthesis and Ir- and Pd-Catalyzed Decarboxylative Enantioselective Benzylation

by

Zhongyu Wei

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

Master of Science

Department of Chemistry
University of Alberta

Abstract

Transition metal-catalyzed bond-forming reactions are powerful strategies in modern organic synthesis, which enable various functional group transformations and cross-coupling processes in a highly chemo-, regio- and enantioselective manner. Selectivity can be achieved through the appropriate choice of metal/ligand system, which facilitates the rapid buildup of molecular complexity. Thus, diverse methodologies based on transition metal catalysis have emerged and offer improved synthetic routes to pharmaceuticals and agrochemicals. This thesis describes the development of two selective transition metal-catalyzed bond-forming processes, which are positioned to help accelerate the discovery of next-generation functional small molecules.

Z-olefins are useful synthetic units, yet difficult to prepare due to the relative thermodynamic instability compared to the *E*-isomer. Chapter 1 describes the chemo- and regioselective synthesis of *Z*-olefins through reduction on activated dienes, where the selectivity is driven by rhodium catalysis via stereospecific chelation. Formic acid serves as a cheap, safe and readily available hydrogen surrogate, showing its unique advantages in contrast with other hydride sources or hydrogen gas.

Chapter 2 describes a highly enantioselective benzylation process using aryl acetic acids as benzylating reagents, catalyzed by cyclometallated iridium-phosphoramidite complex or palladium catalyst with Trost-type chiral ligand. This process shows dramatically improved scope and compatibility with protic and electrophilic functional groups, in contrast with established methods. As a result, this strategy provides novel synthetic routes to generate a class of valuable chiral organic molecules.

Preface

All of the research conducted for this thesis was performed in collaboration with Rylan Lundgren. Chapter 1 has been published as Dada, R.; Wei, Z.; Gui, R.; Lundgren, R. J. "Chemoselective *Z*-olefin synthesis via Rh-catalyzed, formate mediated 1,6-reduction" *Angew. Chem. Int. Ed.* **2018**, 57, 3981–3984. Reaction discovery and optimization, additive screens, mechanistic studies, diene scope and related dienoate synthesis were carried out by Raphael Dada (Table 1-1, Figure 1-12, 1-13). Studies regarding effect of diene geometry on regioselectivity was conducted by Ruohua Gui (Figure 1-14). Reaction optimization on dienyl amides, scope studies varying the ester or amide activating groups, synthesis of corresponding starting materials as well as product derivatizations described in Chapter 1 are my original work.

Chapter 2 has been published as Moon, P. J.; Wei, Z.; Lundgren, R. J. "Direct catalytic enantioselective benzylation from aryl acetic acids" *J. Am. Chem. Soc.* **2018** [DOI: 10.1021/jacs.8b11390]. Reaction discovery and scope studies of most benzyl partners for the iridium process, examination of the kinetic profile, synthesis of related substrates and clinical candidate cores were carried out by Patrick Moon (Figure 2-17, 2-21). Reaction optimization, functional group compatibility screens, crossover experiments, scope studies of allylic partners and remaining benzyl partners, as well as preparation of corresponding starting materials described in Chapter 2 are my original work.

Acknowledgments

I would like to extend my sincere thanks to the past and current members of the Lundgren group, including Alex Gabbey, Anis Fahandej-Sadi, Bryce Thomas, Chris Cooze, Duanyang Kong, Felix Francis, Heather Halperin, Odey Bsharat, Ruohua Gui, Shengkang Yin, Wenyu Qian and Wesley McNutt. A very special thanks is made to Patrick Moon for his selfless guidance both in and out of the lab, for discussing chemistry and answering me inquires, as well as Raphael Dada for his mentorship early in my program.

Acknowledgment is made to Jing Zheng and Angelina Morales-Izquiedrdo for collection of numerous HRMS data, as well as all the other staff in mass spectrometry facility for assistance with running GC-MS and LC-MS. I would like to thank Mark Miskolzie for putting up my questions and help with NMR experiments. I would also like to thank the members of my committee, Dr. Jeffrey Stryker and Dr. Florence Williams, for their guidance on my graduate research and career path.

I would also like to extend my deepest gratitude to Rylan Lundgren for taking me as a graduate student, for his patient guidance and huge support during the course of my graduate studies, for his assistance in my career development. His mentorship made this a memorable experience for which I will always be grateful.

Special thanks are extended to my parents for their endless support throughout my entire life and helping me pull through those difficult periods.

Table of Contents

List of Tables

List of Figures

Abbreviations

°C	degrees Celsius
AAA	asymmetric allylic alkylation
Ar	generic aryl moiety
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
Bpin	pinacol boronic ester
Bu	neo-butyl
COD	1,5-cyclooctadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dioxane	1,4-dioxane
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dppe	ethylenebis(diphenylphosphine)
eq. or equiv.	equivalents
E	generic electrophile

Et	ethyl
HMDS	bis(trimethylsilyl)amine
HRMS	high resolution mass-spectrometry
i-Pr	*iso*-propyl
L	generic ligand
[M]	generic metal complex
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
NEt_3	triethylamine
NMR	nuclear magnetic resonance
Nu	generic nucleophile
OAc	acetate
OBoc	*tert*-butyl carbonate
OTBS	*tert*-butyldimethylsilyl ether
OTf	triflate
p-ABSA	4-acetamidobenzenesulfonyl azide
Ph	phenyl
PMP	*p*-methoxyphenyl
R	generic group
RCM	ring-closing metathesis
r.t.	room temperature
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin-layer chromatography
Tol	tolyl

Chapter 1 – Chemoselective *Z*-Olefin Synthesis via Rh-Catalyzed, Formate Mediated 1,6-Reduction

1.1 Introduction

Z-olefins are useful synthetic units to generate molecular complexity and are found embedded within many complex bioactive natural products (nakadomarin A, epothilone C), drug molecules (latanoprost, paritaprevir), and pheromone insecticides (cyhalothrin) (Figure 1-1). However, highly selective processes to access *Z*-alkenes are less common compared to the *E*-selective processes due to the relative thermodynamic instability of *Z*-olefins.[1]

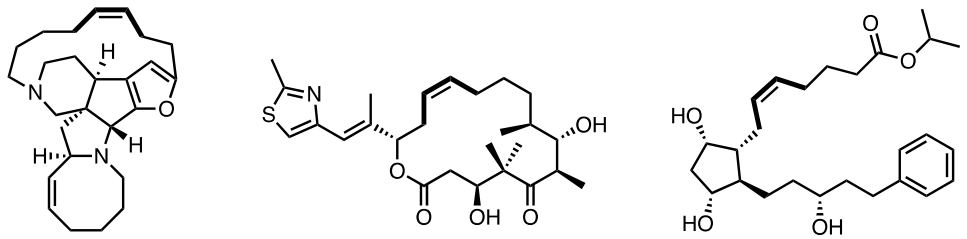


Figure 1-1 Bioactive natural products and drug molecules contain *Z*-alkene units

1.1.1 Overview of Common Methods to Prepare Z-Olefins

The Wittig reaction, discovered in 1954 by Georg Wittig,[2] has proved to be one of the most prominent methods to generate olefins and has been broadly used in natural product synthesis.[3-4] In this transformation, an aldehyde or ketone reacts with a phosphorus ylide (Wittig reagent) to form the alkene product and triphenylphosphine oxide as a side product. In general, control of alkene stereochemistry can be mediated by numerous factors, including solvent, temperature, counter cation and additives. Above all, the nature of ylides plays an essential role in controlling the stereoselectivity. Unstabilized ylides tend to give *Z*-alkene product predominantly whereas electron withdrawing group stabilized ylides usually result in *E*-alkene. This principal has been

elegantly employed in synthesizing an intermediate to access nature product, (+)-discodermolide, where two complex building blocks are coupled together in a high *Z*-selective manner (Figure 1-2a).[5] Another remarkable application has been demonstrated in the synthesis of *Z*-alkenyl iodides, useful precusors for cross coupling reactions, through Stork's ylide (Figure 1-2b).[6]

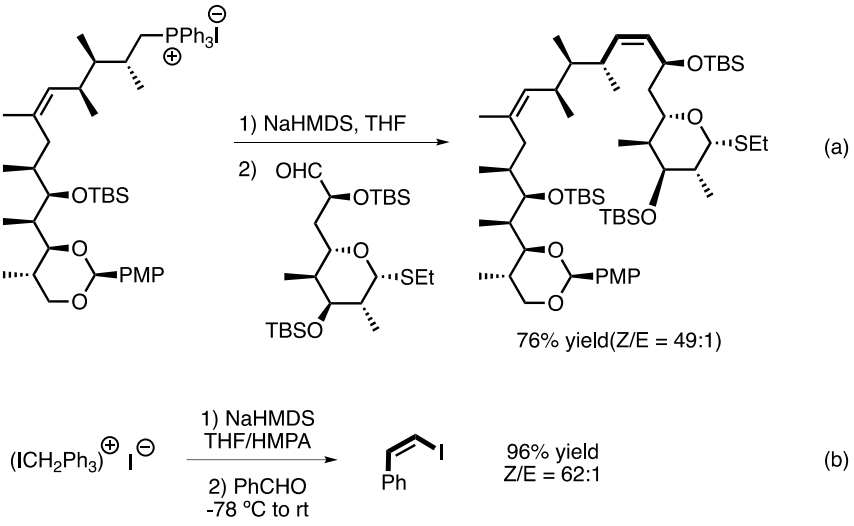


Figure 1-2 *Z*-selective Wittig olefination via unstabilized ylides

Despite the wide utility of Wittig reaction to access *Z*-alkenes, the major drawback is its inherent requirement for the generation of unstabilized ylide precursors. Thus, people have paid great efforts to develop different kinds of ylide variants. An important modification, Horner–Wadsworth–Emmons (HWE) reaction, was developed employing stabilized phosphorus ylides to exclusively access *E*-alkenes.[7] Based on this work, Still and Gennari introduced a second variant to generate *Z*-α,β-unsaturated esters using potassium bis(trifluroethoxyl) phosphonates.[8] This strategy serves as a supplementary process to obtain *Z*-alkenes with electron-withdrawing substituents, in contrast with electron-neutral alkenes generated from *Z*-selective Wittig olefinations.[9] One example was the use to access a key precursor for the total synthesis of spinosyn A (Figure 1-3), an insecticide discovered from bacteria. However, stoichiometric generation of

phosphorous ylide intermediates is inevitable in carbonyl olefination, resulting in limited reaction efficiency and tedious separation of phosphine oxide side product from desired product in some cases. In addition, strong bases are employed to generate reactive carbanions in these transformations, under which conditions protic or electrophilic groups require chemical protection/deprotection steps.[10]

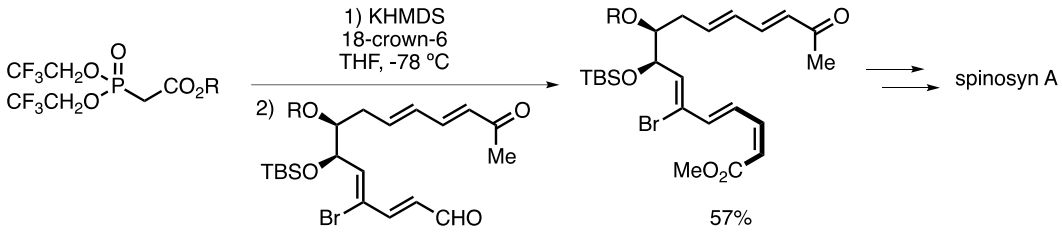


Figure 1-3 Still–Gennari modified HWE reaction to synthesize an intermediate for spinosyn A

Alternatively, metal mediated methods serve as additional popular processes to selectively generate *Z*-olefins. Alkyne semi-reduction through hydrogenation utilizing Lindlar's catalyst is one of the traditional and well-known strategies, which has been extensively applied to access disubstituted *Z*-alkenes since its discovery by Herbert Lindlar in 1966.[11] Lindlar's catalyst is a heterogeneous catalyst, in which palladium (usually 5% by weight) is deposited on $CaCO_3$ and further poisoned by lead oxide or lead acetate and quinoline. The resulting catalyst system is deactivated, so reduction can cease at the alkene stage without further reduction into alkane, in contrast with palladium on activated carbon. The stereoselectivity is controlled by activation of hydrogen gas on the surface of catalyst, followed by *syn*-addition to alkyne units. Lindlar's catalyst is commercially available due to its practical application in organic synthesis. One fantastic example was reported by Ghosh's group in the total synthesis of natural product (–)-Laulimalide, where geometry of the endocyclic olefin was established with high *Z*-selectivity (Figure 1-4).[12]

Although the Lindlar reduction has achieved general utility in organic synthesis, the heterogeneous nature of this catalyst system has come to be its 'Achilles's heel' as its performance may not be consistent with different substrates. Processes employing Lindlar's catalyst often need to be optimized in a case-by-case manner to achieve high alkyne conversion while avoiding over-reduction to alkanes, which is not always trivial to do. Moreover, 5% *E*-isomers would always present in the crude mixture, causing isolation problems. There remains a need to develop homogeneous catalytic system as complements of Lindlar's catalyst.

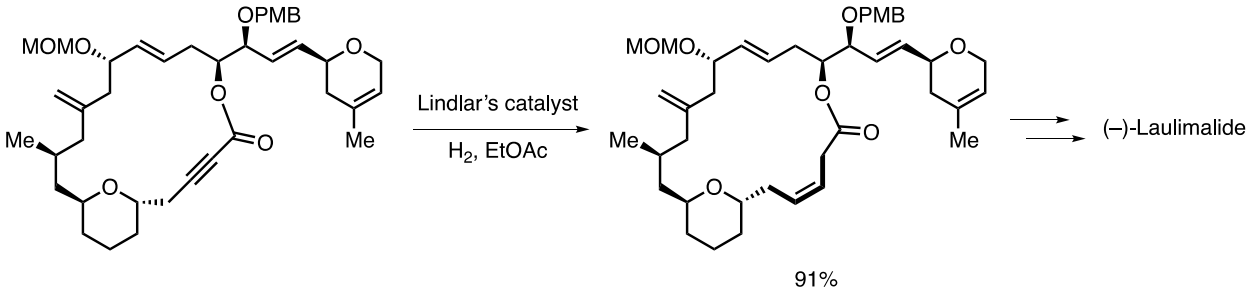


Figure 1-4 Late stage total synthesis of an antitumor employing Lindlar's catalyst

In the last decades, olefin metathesis has emerged as a rapidly growing research area with various transition metal catalysts having been developed, mainly by the groups of Grubbs,[13-15] Hoveyda[16-17] and Shrock[18-19]. However, these processes are typically reversible and thermodynamically-driven and thus liberate olefins that are lower in energy. Therefore, the generation of *E*-alkenes is generally preferred for acyclic systems. For standard catalysts, *Z*-selective olefin metathesis is limited to the formation of small-sized rings through ring-closing metathesis (RCM), resulting from minimization of ring strain in the products. In term of intermolecular olefin metathesis, only moderate *Z*-selectivity (generally 3:1 to 9:1 *Z*:*E*) can be achieved in some specific cases.[20-25] In recent years, progress has been made through the development of tailored Mo-, W- and Ru-complexes, establishing metathesis strategies to access *Z*-alkenes in good to excellent stereoselectivity.[26-28] The Mo-catalyzed process developed by

Hoveyda and co-workers has been applied to stereoselective synthesis of an anti-oxidant plasmalogen phospholipid, C18 (plasm)-16:0 (PC) (Figure 1-5).[26] Despite its remarkable and growing utility, *Z*-selective olefin metathesis remains limited to certain classes of olefins to avoid homocoupling of starting materials and product isomerization. In addition, metathesis reactions on molecules bearing multiple alkene units can suffer from poor chemoselectivity problem, which becomes a major challenge for the late-stage formation of *Z*-olefins. Hence complementary catalytic approaches to access *Z*-olefins in the presence of additional carbon-carbon π-bonds and protic or electrophilic groups remains valuable strategies to develop.

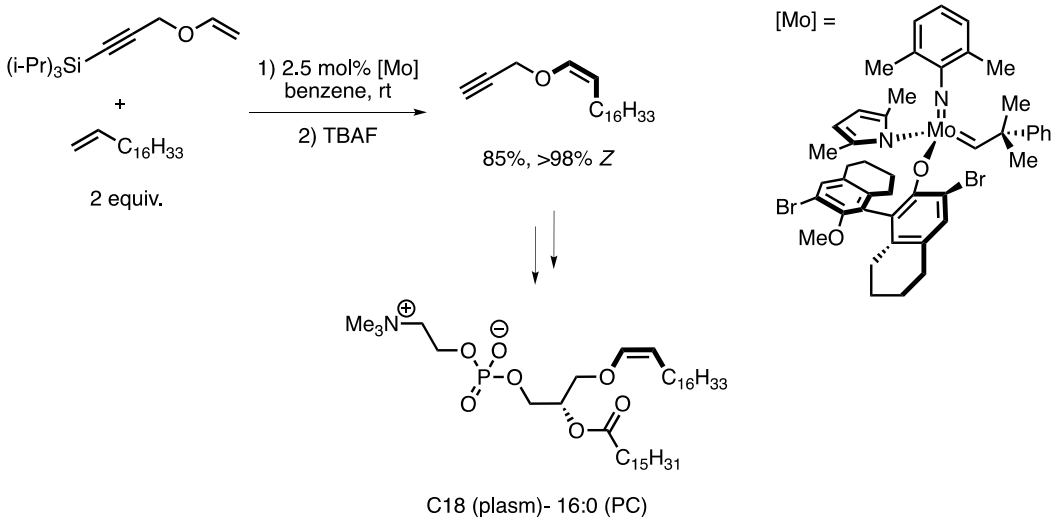


Figure 1-5 Stereoselective generation of the precursor to a plasmalogen phospholipid

1.1.2 Overview of Catalytic Additions to Activated Dienes

Catalyst-controlled conjugate addition of nucleophiles to carbonyl-activated dienes is a pivotal method to generate functionalized olefins and can serve as a potential protocol to access *Z*-olefins. As there are three electrophilic sites existing in these extended Michael acceptors, various regioisomers of addition products (1,2-; 1,4- and 1,6- adducts) can be generated (Figure 1-6).[29] In this type of transformations, 1,2-adducts can be accessed by nucleophilic addition onto the

carbonyl unit, resulting in derivatized diene molecules. 1,4-Addition at β-position leads to an isolated carbon-carbon double bond in the δ,γ-position of the molecule. In contrast with classical Michael acceptors, 1,6-addition can occur at the δ-position of the extended Michael acceptor to form the characteristic β,γ-unsaturated compounds. Diversified 1,6-adducts varying in olefin geometry can be accessed through this process and we questioned if this principal could be utilized to selectively generate *Z*-olefins. However, simultaneously controlling stereo- and regioselectivity of the addition process is essential to achieve a synthetically useful strategy and remains a main challenge in catalytic conjugate addition chemistry.

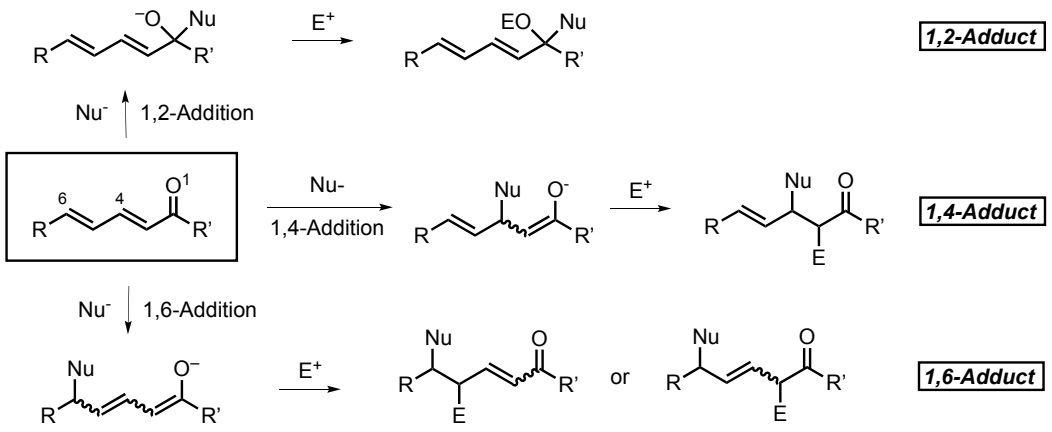


Figure 1-6 Conjugate addition to extended Michael acceptor

Transition metals have been discovered to provide excellent catalyst control in many conjugate addition processes. Successful catalytic systems include copper, iron, nickel, zinc, rhodium, iridium and palladium. Among those transition metal complexes, copper catalysis is commonly employed in the nucleophilic addition of alkyl derived organometallic reagents, whereas rhodium is popular used in addition of aryl or vinyl groups, formed via transmetallation from corresponding boronic acid reagents.[30] Owing to its rapid growth of catalytic 1,6-addition methodologies, diverse processes have been developed and enabled highly regioselective

transformations delivering *β,γ*-unsaturated *E*-alkenes.[31-33] An impressive process involving regio- and enantioselective 1,6-conjugate addition of propargyl groups was reported by Hoveyda and co-workers recently.[31] The utility of this approach has been demonstrated by its application in the synthesis of the anti-HIV agent (–)-equisetin (Figure 1-7).

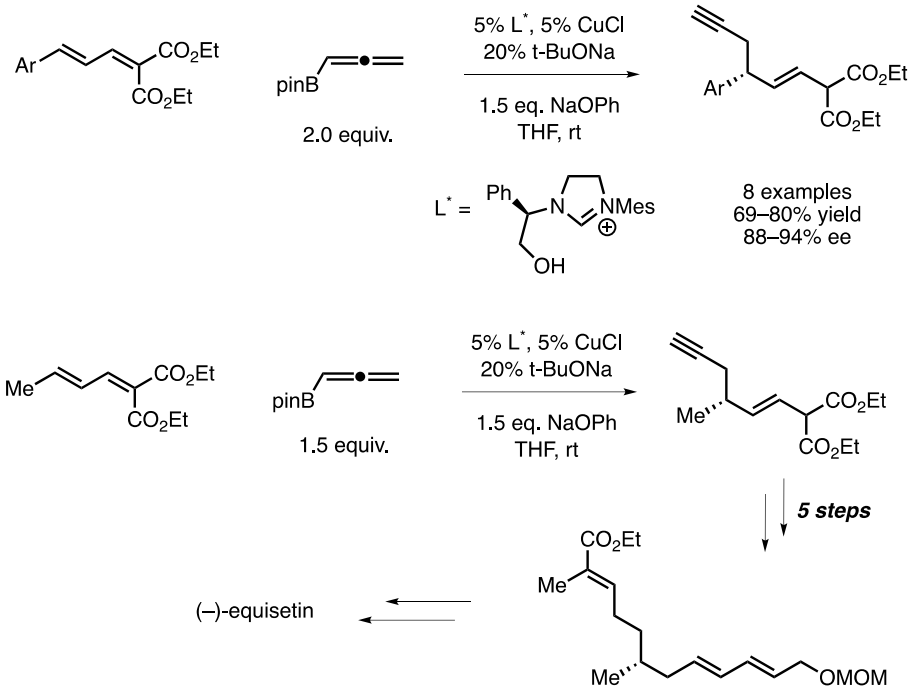


Figure 1-7 Regio- and enantioselective 1,6-conjugate addition and its application

On the other hand, *Z*-selective 1,6-additions to electron-poor dienes remain scarce. Established methods are limited to the addition of aryl Grignard reagents mediated by iron complexes[34-35] or the addition of aryl or alkenyl boronic acids mediated by rhodium or iridium complexes.[36-37] Recently Csaky's group reported a process involving stereodivergent nucleophilic addition to 2,4-dienoate esters catalyzed by Rh.[36] Three types of products including 1,6-addition product, 1,4-addition product and Heck reaction product were formed through different addition patterns (Figure 1-8). Stereoselectivity of this reaction was dependent on the electronics of substituents installed in the dienoate and the nature of organoboronic acid reagents. As a result,

stereoselective generation of a desired product class cannot be achieved by simply adjusting the reaction conditions, limiting its general synthetic utility.

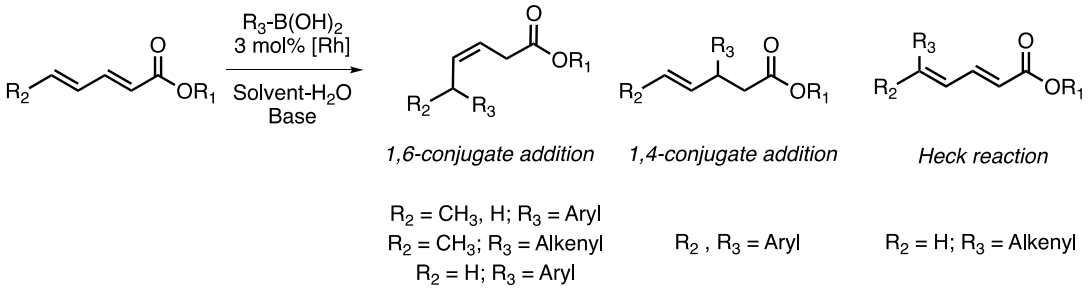


Figure 1-8 Stereodivergent conjugate addition catalyzed by Rh

Significant effort has been dedicated to developing methods for the 1,6-addition of carbon nucleophiles. In contrast, the addition of hydrogen or hydride equivalents to extended Michael acceptors accessing *cis*-olefin products are limited to Cr- and Ru-catalyzed processes. The Cr-catalyzed regio- and stereoselective hydrogenation of dienoate species to generate β,γ-unsaturated *Z*-olefins was first reported by Cais and co-worker in 1968.[38] Under general conditions with (arene)•$Cr(CO)_3$, at 150 ºC and 700 psi pressure of hydrogen gas, methyl sorbate was reduced to *Z*-methyl 3-hexenoate. Although these conditions are very harsh, this strategy has been employed in several cases since it serves as the only process for this type of transformation. Corey's group employed the (arene)•$Cr(CO)_3$ in the preparation of dimethyl (*Z*)-(2-oxohept-4-enyl)phosphine, a key intermediate in the total synthesis of C_{22}-prostanoids (Figure 1-9).[39]

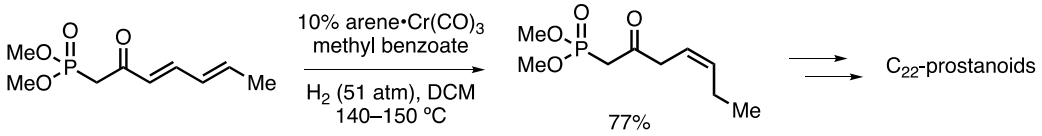


Figure 1-9 Preparation of a *Z*-geometry intermediate in total synthesis of C_{22}-prostanoids

A mechanism for the reduction was proposed after performing reduction on various suitable diene substrates by different research groups (Figure 1-10a).[40] The arene ligand is a 6-

electron donor to stabilized the pre-catalyst. Arene dissociation can lead to an activated $Cr(CO)_3$ complex bearing three vacant coordination sites, which is weakly-bounded with solvent. Electron deficient diene and hydrogen gas then occupy those empty sites to make it saturated again with 18-electron configuration. In the last step, 1,6-conjugate addition of hydrogen yields a reduced *Z*-olefin. The product can be quickly liberated from the "$Cr(CO)_3$" fragment as such a simple olefin species doesn't have affinity with this metal complex, inhibiting isomerization and over-reduction of olefin product (Figure 1.10b). The excellent regio- and stereoselectivity of the Cr-promoted process has been explained by an essential diene-bounded metal complex, in which diene unit behaves as a bidentate ligand in coordination with chromium by adopting *s-cis* conformation. This diene-metal complex in certain coordination geometry has also been extended to explain origin of *Z*-selectivity in other metal-catalyzed 1,6-addition processes.

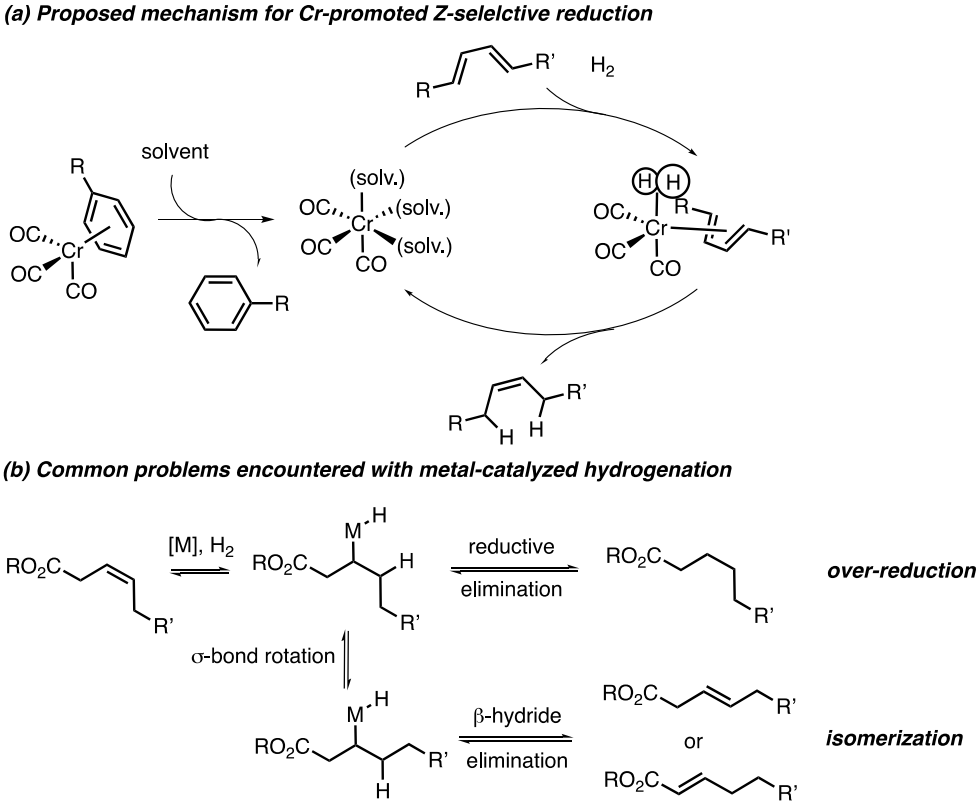


Figure 1-10 Proposed mechanism for Cr-promoted *Z*-olefin synthesis

Kinetic studies indicated the hydrogenation rate is controlled by combinations of arene ligands and solvents. As the activation of pre-catalyst involves dissociation of arene ligand and solvation of chromium, complexes with readily dissociable arene ligands bear higher catalytic reactivity. Solvents such as benzene that would strongly coordinate to $Cr(CO)_3$ tend to suppress the generation of the active catalyst species and reduce reaction rate, whereas weakly-coordinating solvents (THF, DCM, acetone) are prone to facilitate ligands dissociation and accelerate the overall process. In a very specific case, using the dissociable naphthalene ligand and weakly coordinating THF as solvent allows the reaction to proceed at ambient temperature (30 ºC) and atmospheric pressure (H_2, 1 atm).

In an effort to develop complementary metal-catalyzed 1,6-reduction processes avoiding the typical harsh conditions in Cr-catalyzed process, Driessen-Holscher's group and Kotova's successively reported a novel Ru-catalyst to facilitate such transformations.[41-42] Under the presence of catalytic amount of Cp*-Ru(I)-sorbic acid complex with a suitable counter anion (triflate or tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), sorbic acid, sorbic alcohol or sorbate would be selectively reduced to *cis*-hex-3-enoic acid, *cis*-hex-3-en-1-ol or *cis*-hex-3-enoate respectively (Figure 1-11). The hydrogenation process can be conducted under much milder conditions (50 – 60 ºC, 200 – 300 psi H_2) in comparison with the previously reported Cr-catalyzed reaction. Unfortunately, substrate scope is strictly restricted to presented cases. Moreover, the activated ruthenium complex can competitively bind with *cis*-olefin product when the reaction reaches high conversions (80–90%), driving side-reactions such as product isomerization and over-reduction. The formation of these side-products is irreversible and presents additional product isolation challenges. Thus, carefully monitoring the reaction progress is necessary to achieve

optimal result, with a typically short optimal time window to stop the reaction. These drawbacks impose restrictions on the practical utility of this process.

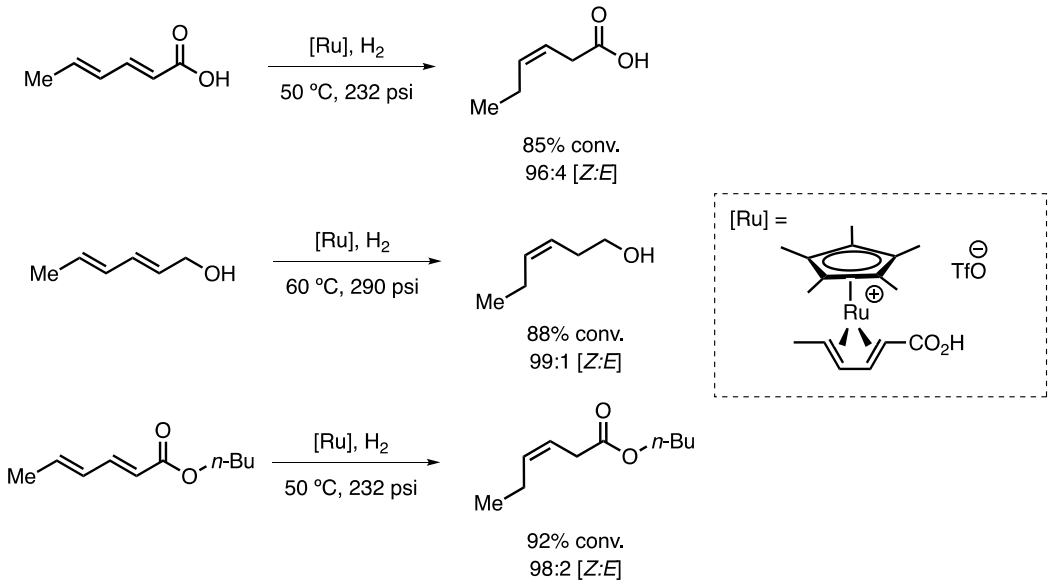
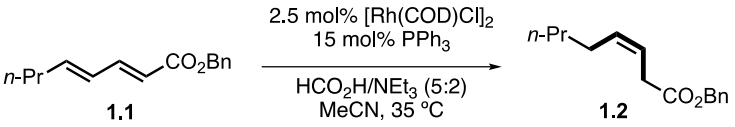


Figure 1-11 Ru-catalyzed *Z*-selective 1,6-reduction process

We are interested in developing a transition metal-catalyzed 1,6-reduction process on activated diene species to access *Z*-olefins with high chemo- and regioselectivity. In 2016, Raphael Dada, a PhD student in our group, discovered a process employing 2.5 mol% $[Rh(COD)Cl]_2$ as catalyst, 15 mol% triphenylphosphine as ligand and formic acid as hydrogen surrogate to convert dienoate **1.1** to the corresponding *cis*-olefin **1.2** in 80% yield, 96:4 *Z/E* selectivity (Table 1-1, entry 1). The reaction can be conducted at 35 ºC, hence much milder than established methods. A series of optimization reactions were carried out before the best condition was set. Employing other Rh/PPh_3 stoichiometries resulted in reduction with moderate to low *E*-selectivity (Table 1-1, entry 2-3). Use of other ligands, including monodentate ligands varying in electronic properties or bidentate ligands, led to either lower yield or *Z/E* selectivity (Table 1-1, entry 4-9). Screening with Wilkinson's catalyst, $RhCl(PPh_3)_3$ resulted in moderate *E*-selectivity, whereas with other metal catalysts such as iridium, copper and palladium complexes did not generate desired product (Table

1-1, entry 10-13). Employing other hydrogen sources did not provide good selectivity either (Table 1-1, entry 14-16). It's worthwhile to point out that reactions could be conducted with 0.5 mol% catalyst loading at 50 ºC to afford product in similar yield and selectivity, a more economic set of conditions for larger-scale synthesis (Table 1-1, entry 17).

Table 1-1 Effect of reaction parameters on dienoate 1,6-reduction



1.1 **1.2**

entry	deviation from above	conv. (%)	yield (%) [*Z*/*E*]
1	**none**	**91**	**80 [96:4]**
2	1:1 $Rh:PPh_3$ instead of 1:3	93	40 [28:72]
3	no PPh_3	93	52 [25:75]
4	$P(OPh)_3$ instead of PPh_3	59	47 [50:50]
5	$(2\text{-MeO-}C_6H_4)_3P$ instead of PPh_3	52	22 [29:71]
6	$(4\text{-F-}C_6H_4)_3P$ instead of PPh_3	69	58 [93:7]
7	dppp instead of PPh_3	59	53 [90:10]
8	dppe instead of PPh_3	7	7 [nd]
9	BINAP instead of PPh_3	76	11 [36:64]
10	$Rh(PPh)_3Cl$ (no PPh_3)	94	41 [31:69]
11	$[Ir(COD)Cl]_2$	24	<2
12	CuI	<2	<2
13	$Pd(OAc)_2$	20	<2
14	H_2 (1 atm) instead of HCO_2H/NEt_3	37	5 [nd]
15	Ph_2SiH_2 instead of HCO_2H/NEt_3	54	7 [57:43]
16	HB(pin) instead of HCO_2H/NEt_3	54	14 [86:14]
17[a]	0.5 mol% $[Rh(COD)Cl]_2$ 3 mol% PPh_3	89	79 [96:4]

0.2 mmol scale, 1.0 equiv. HCO_2H, 0.2 M; [a]at 50 ºC, 48h; yields and conversions determined by calibrated ^1H NMR

Concomitant over-reduction or isomerization that commonly occurs with Ru-catalysis was not observed under standard reaction conditions, suggesting a potential process that selectively drives hydride addition on ester activated diene over simple olefins. A preliminary mechanistic hypothesis involved a chemoselective chelation between reactive rhodium species and properly polarized dienes. Thus, we reasoned that reduction rates on electron-rich dienes, mono-alkene and alkyne units may not be competitive with extended Michael acceptors. To rapidly test this

hypothesis, a functional group compatibility screen was carried out with an array of unsaturated substrates (Figure 1-12). Under standard reaction conditions, terminal and internal alkenes, classical Michael acceptors, electron-rich diene and some alkyne units are well tolerated (>70% yield of **1.2**, <20% of additive consumption). The excellent chemoselectivity depicted an encouraging blueprint for the site-selective reduction of diene units to corresponding *Z*-olefins without interference from other unsaturated functional groups.

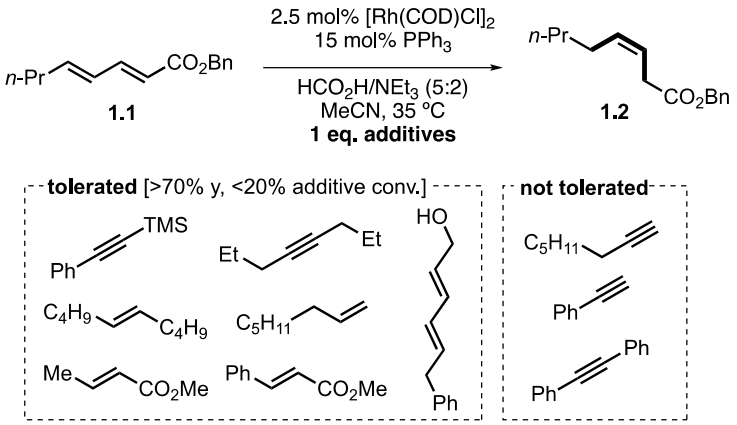


Figure 1-12 Unsaturated functional group tolerance survey

Mechanistic experiments were conducted to help rationalize the high stereoselectivity of this process. Use of D-labelled formic acid at the formyl position under otherwise standard reaction conditions resulted in **d_1-1.2a** with 70% D-incorporation at the remote δ-position, whereas carboxyl labelled formic acid afforded **d_1-1.2b** with exclusive deuterium incorporation at the α-carbonyl position (Figure 1-13a). This indicated a proposed mechanism that Rh–H was generated through extrusion of CO_2 from formate, followed by *Z*-selective 1,6-addition to form a Rh-enolate (**1.4**). Fast protonolysis of **1.4** ensures retention of *Z*-geometry, in which the proton originates from the carboxylic acid in formic acid (Figure 1-13b). Essentially, the chemo- and regioselective generation of complex **1.3**, where diene unit is adopting *s-cis* geometry, controlling the stereoselectivity for this process.

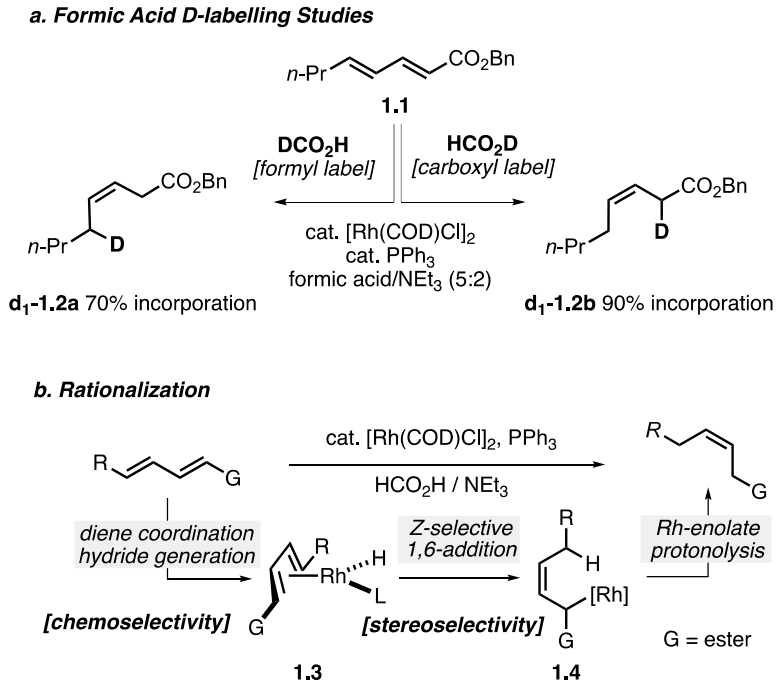


Figure 1-13 Formic acid D-labelling studies and rationalization

To solidify this hypothesis, standard reaction conditions were performed on dienoates with different olefin geometries (Figure 1-14). Both *E,E* and *Z,E*-dienes (**1.1, 1.5**) readily adopting *s-cis* configuration provided products in high regioselectivity (>10:1 β,γ to α,β). A *E,Z*-diene (**1.6**) that would experience significant steric repulsion in *s-cis* geometry (**1.6'**) from interaction between the sp^3-carbon center and α-proton resulted in a much lower selectivity (1.5:1 β,γ to α,β).

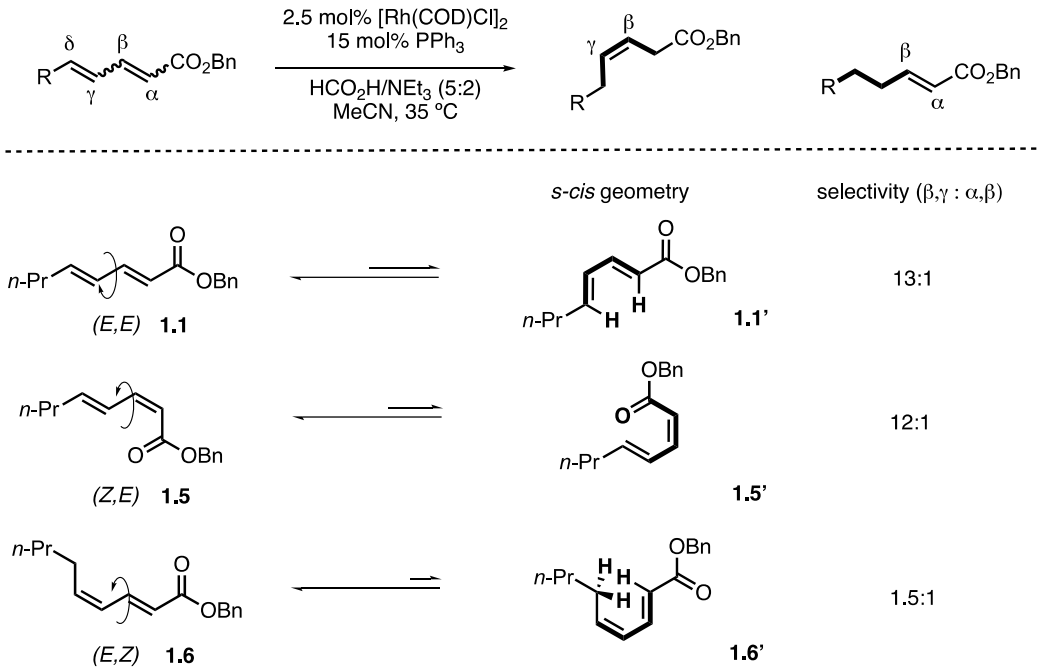
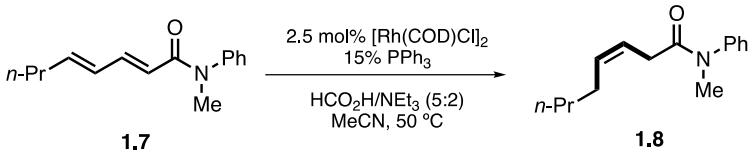


Figure 1-14 Effect of diene geometry on regioselectivity

1.2 Optimization on Dienyl Amide and Dienoates Derivatized from Bioactive Molecules

Amides and nitrogen-containing heterocycles are universally encountered in pharmaceuticals and bioactive molecules. As a result, I made some efforts to extend our 1,6-reduction reaction to dienyl amides. However, the reduction selectivity of *N*-phenyl, *N*-methyl amide activated diene (**1.7**) turned out to be moderate under standard conditions (44% yield, 86:14 *Z/E*, Table 1-2, entry 1). Screening with a variety of ligands revealed that triarylphosphines with electron withdrawing substituents afforded *cis*-products (**1.8**) in highest selectivity (Table 1-2, entry 4-5), whereas bidentate and electron-rich monodentate ligands decreased yield and selectivity (Table 1-2, entry 2-3). Amide is a slightly worse electron withdrawing group in comparison with ester, thus diene activated by amide would be less electron deficient. We proposed that using electron-deficient triarylphosphine ligands would provide a more electrophilic Rh-species, which would match up with amide activated diene bearing higher π-electron density, ensuring their chemoselective chelation.

Table 1-2 Effect of ligand on reduction selectivity with a simple dienyl amide



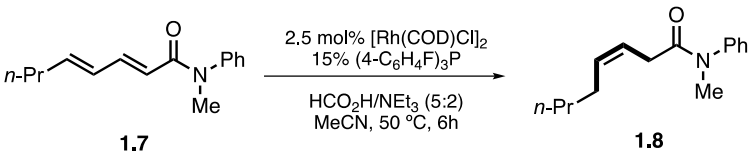
1.7 **1.8**

entry	deviation from above	conv. (%)	yield (%) [Z/E]
1	none	84	44 [86:14]
2	(4-$MeOC_6H_4$)$_3$P instead of PPh_3	100	34 [60:40]
3	R-BINAP instead of PPh_3	<2	<2
4	**(3,5-bis$CF_3C_6H_3$)$_3$P instead of PPh_3**	**93**	**76 [96:4]**
5	**(4-C_6H_4F)$_3$P instead of PPh_3**	**88**	**70 [90:10]**

0.2 mmol scale, 1.0 equiv. HCO_2H, 0.2 M; yields, selectivities, and conversions determined by calibrated ^1H NMR using trimethoxylbenzene as internal standard.

Reaction temperature was shown to play a role in mediating reaction rate and effecting stereoselectivity (Table 1-3). Lowering reaction temperature slows down reduction rates, resulting in low conversion and yield (Table 1-3, entry 2-3). Catalyst loading can be reduced to 3 mol% Rh equivalent by using tris(4-fluorophenyl)phosphine and increasing the temperature to 60 ºC (Table 1-3, entry 4). However, tris[3,5-bis(trifluoromethyl)phenyl]phosphine cannot tolerate such low Rh loading (Table 1-3, entry 5).

Table 1-3 Effect of temperature on reduction selectivity with a simple dienyl amide



1.7 **1.8**

entry	deviation from above	conv. (%)	yield (%) [Z/E]
1	none	84	70 [90:10]
2	r.t., 6 days	76	48 [83:17]
3	35 °C, 31 h	80	51 [91:9]
4	**60 °C, 3% Rh, 12% (4-C_6H_4F)$_3$P, 7 h**	**93**	**63 [95:5]**
5	60 °C, 3% Rh, 12% (3,5-bis$CF_3C_6H_3$)$_3$P, 9 h	61	49 [93:7]

0.2 mmol scale, 1.0 equiv. HCO_2H, 0.2 M; yields, selectivities, and conversions determined by calibrated ^1H NMR using trimethoxylbenzene as internal standard.

The stoichiometry of formic acid plays an essential role in mediating reaction progress. When excess formic acid (>1.0 equiv.) was introduced under otherwise standard conditions,

reduction proceeded faster and achieved its optimal result after 3 hours (97% conv., 71% yield, 89:11 *Z/E*). Though similar yield and selectivity were observed, the *cis*-product (**1.8**) would undergo fast isomerization and over-reduction, providing desired product in reduced *Z/E* ratio and driving significant formation of other side-products (**1.9–1.11**, Figure 1-15). This phenomenon was not encountered with one equivalent formic acid, under which condition reaction would cease at ~90% conversion. As an explanation, it's believed that reactive Rh-species could bond with **1.8** when starting material **1.7** was fully consumed. Under the presence of excess formic acid Rh–H intermediates are generated and hydrorhodation of **1.8** would occur**,** followed by C–C bond rotation and β-hydride elimination, resulting in the other isomers that are thermodynamically more stable (Figure 1-16).

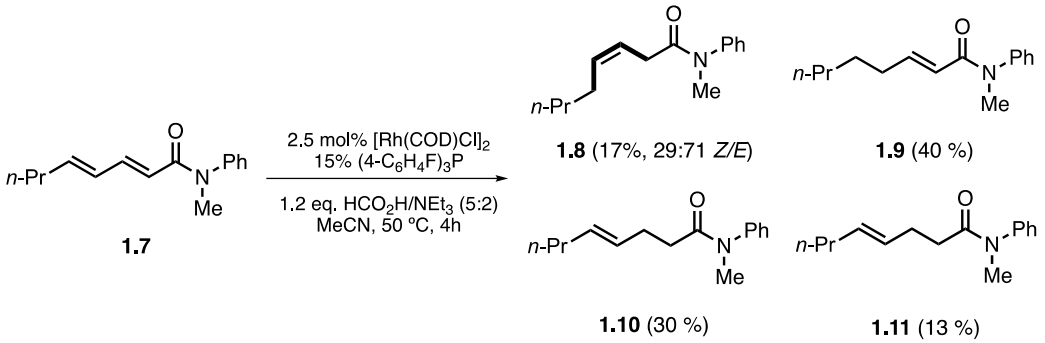


Figure 1-15 Reaction profile with excess formic acid

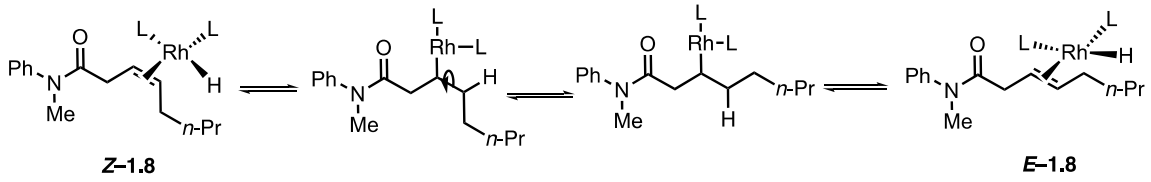
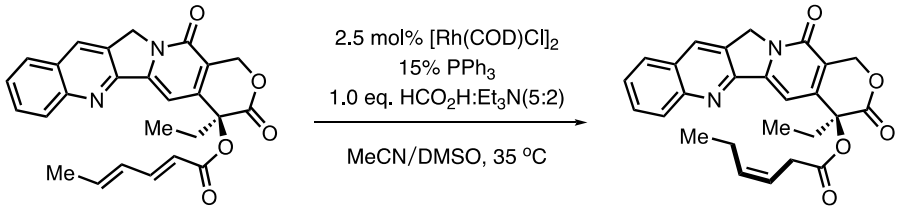


Figure 1-16 Rh-promoted isomerization of *cis*-product with excess formic acid

Heterocycles are valuable functional units in active pharmaceutical ingredients (API), but manipulation on heteroatom-containing bioactive molecules could be challenging due to their unique physical properties (solubility, Lewis-basicity). Moreover, transition metal catalysts bear

the risk of being poisoned by heteroatoms. To demonstrate broad utility and functional group compatibility of our approach, heteroatom-containing dienoates derivatized with commercial drugs were tested, including camptothecin (**1.12**) and stavudine. Since acetonitrile is an essential solvent to promote reduction process, DMSO was utilized as co-solvent to improve their solubility (20% by volume). The 1,6-reduction suffered from low stereoselectivity with standard stoichiometries of Rh-precatalyst, triphenylphosphine and formic acid (Table 1-4, entry 1). After a few modifications of the reaction conditions, yield and selectivity of **1.13** were recovered with higher catalyst and formate loading (Table 1-4, entry 4). Similarly modified conditions were applied to the stavudine derivative.

Table 1-4 Optimization on derivative of camptothecin



1.12 **1.13**

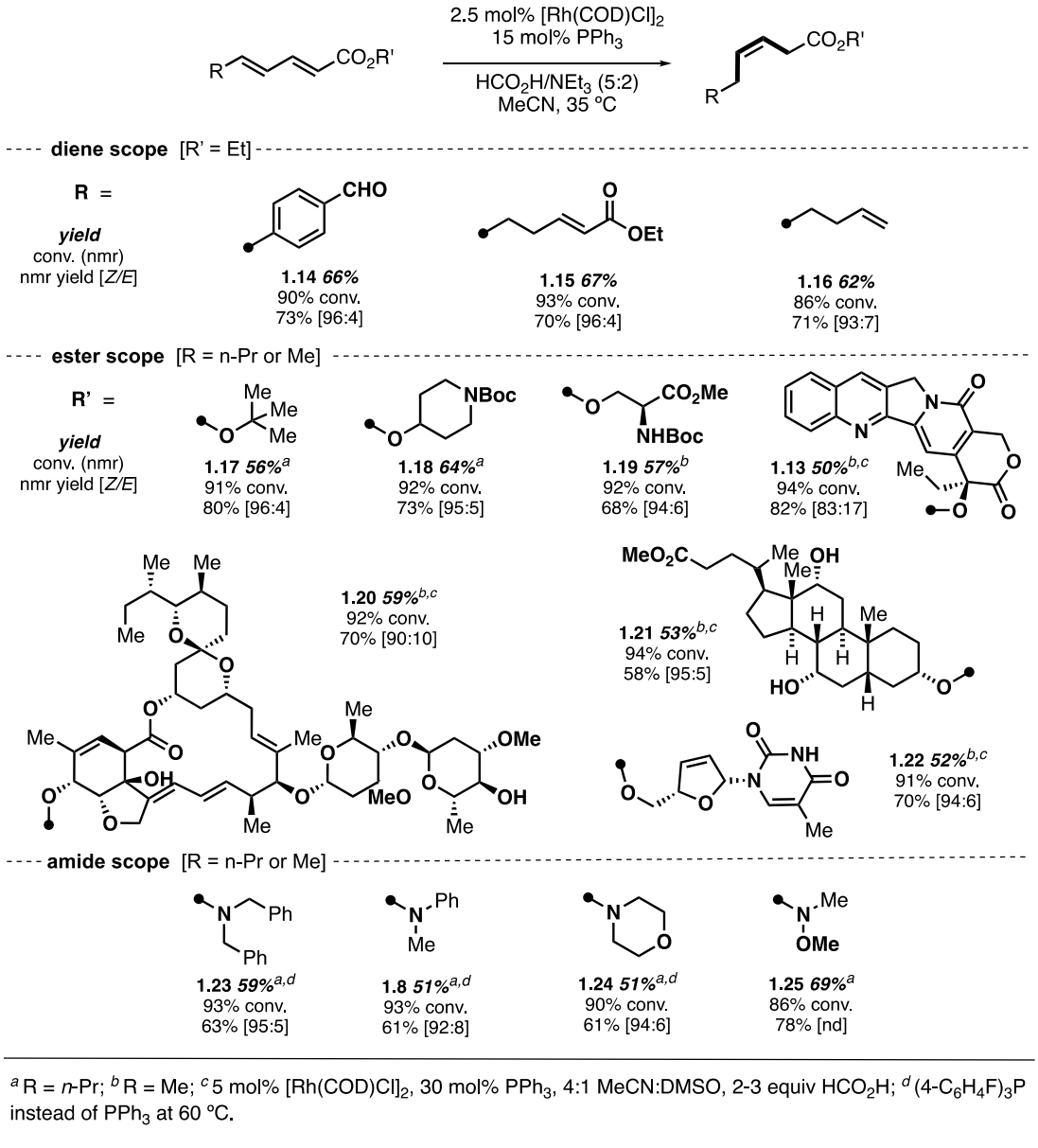
entry	deviation from above	conv. (%)	yield (%) [Z/E]
1	none	79	34 [65:35]
2	60 °C	81	43 [72:28]
3	15 mol% Rh, 45% PPh_3	96	73 [83:17]
4	10 mol% Rh, 30% PPh_3, 2 eq. formate	**94**	**82 [83:17]**

0.2 mmol scale, 1.0 equiv. HCO_2H, 0.2 M; yields, selectivities, and conversions determined by calibrated ^1H NMR using trimethoxylbenzene as internal standard.

1.3 Reaction Scope for Chemo- and Stereoselective *Z*-Olefin Synthesis

The chemo- and stereoselectivity of our approach has been demonstrated with diverse diene substitutions and activating groups (Figure 1-17). Under standard reaction conditions, molecules containing electrophilic aldehyde (**1.14**) or other carbon-carbon unsaturation, such as

α,β-unsaturated ester (**1.15**) and terminal olefin (**1.16**), are selectively reduced with good yields and typically >95:5 *Z/E* selectivity. These types of stereochemically defined polyunsaturated products would be difficult to prepare directly via established semi-reduction or metathesis.



[a] R = *n*-Pr; [b] R = Me; [c] 5 mol% $[Rh(COD)Cl]_2$, 30 mol% PPh_3, 4:1 MeCN:DMSO, 2-3 equiv HCO_2H; [d] $(4\text{-}C_6H_4F)_3P$ instead of PPh_3 at 60 °C.

Figure 1-17 Reaction scope for chemo- and stereoselective *Z*-olefin synthesis

The dienes can be activated by diverse esters, varying from steric bulky *tert*-butyl group (**1.17**); protected amines (**1.18, 1.19**) including an amino acid derivative; complex functional units

including quinoline alkaloid camptothecin (**1.13**), polyketide ivermectin (**1.20**), hydroxylated sterol methyl cholate (**1.21**) and nucleoside analog stavudine (**1.22**). Even though derivatives of bioactive molecules (**1.13, 1.22**) would pose considerable difficulty in established *Z*-olefin forming process, reduction could be performed under slightly modified conditions to obtain moderate yield and selectivity. In addition, a series of dienes activated by amides (**1.8, 1.23, 1.24**), including Weinreb amide (**1.25**) can be smoothly reduced with good selectivity under modified conditions.

1.4 Derivatization of *Z*-Olefins to Other Classes of Molecules

The *β*-carbonyl containing *Z*-olefins are useful synthetic precursors to a wide range of other product classes (Figure 1-18). *Z*-homoallylic alcohol (**1.26**) could be readily prepared in good yield (85%) by $LiAlH_4$ reduction. Oxidation of **1.26** by DMP afforded *Z*-homoallylic aldehyde, which was further converted to skipped *Z,E*-dienes (**1.27**) through HWE olefination. Propargylic *Z*-1,5-enynes (**1.28**) could be synthesized by simple addition of Li-TMS acetylene to the aldehyde precursor. Finally, an α-amino ester (**1.29**) can be accessed through diazotization, followed by Rh-catalyzed amination.

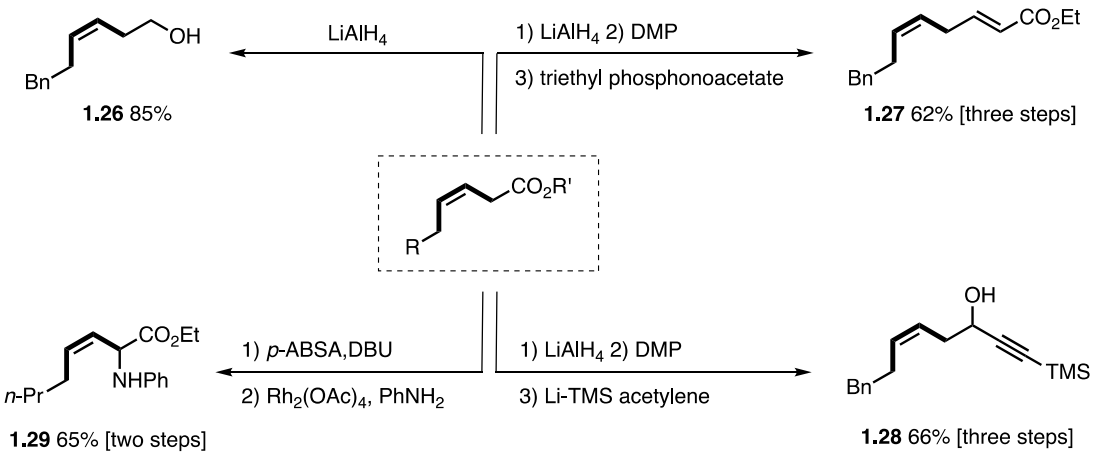


Figure 1-18 Derivatization of *Z*-olefins to other classes of molecules

1.5 Less Successful Substrates for *Z*-Selective 1,6-Addition

Even though broad functional group compatibilities have been demonstrated by scope studies, our approach bears some inherent limitations as well (Figure 1-19). Under standard reaction conditions, reduction on secondary amide (**1.30**) resulted in largely α,β-olefin product. Diene in conjugation with methyl pyrazole unit (**1.31**) provided γ,δ-olefin side-product in a higher ratio, probably driven by thermodynamic force. Dienoate derivatized from ergosterol (**1.32**) has extremely poor solubility in acetonitrile, hence no evidence of reduced product was observed. Another complex dienoate derivatized from lovastatin (**1.33**) can rapidly undergo elimination of the ester unit initiated by triethylamine.

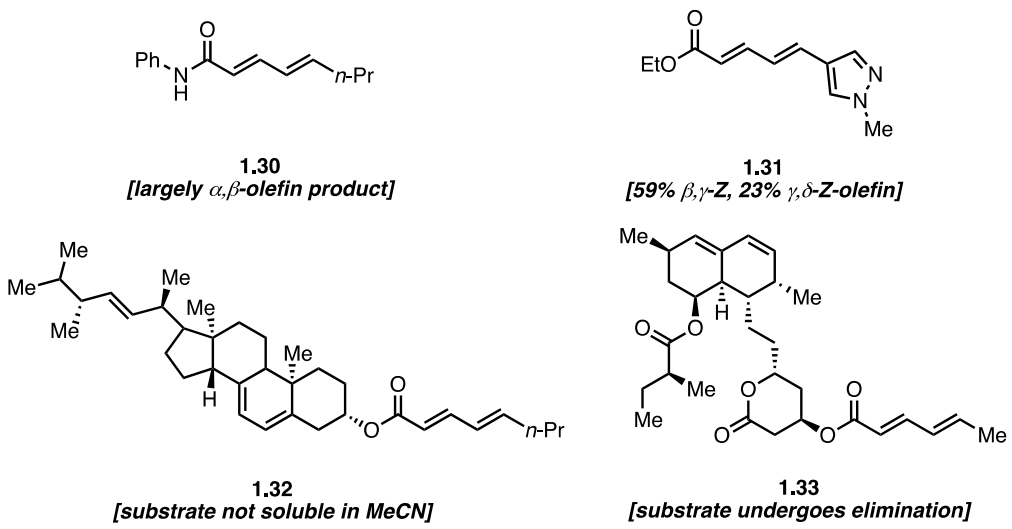


Figure 1-19 Less successful substrates for *Z*-selective 1,6-addition

1.6 Summary

A catalytic approach for chemo- and stereoselective 1,6-addition to ester or amide activated dienes was reported. The process was catalyzed by simple Rh precatalyst and mediated by readily available formic acid, which acts as a safe and practical hydrogen surrogate. Mechanistic studies suggest that excellent selectivities are driven by a key intermediate, a diene-bound Rh-hydride

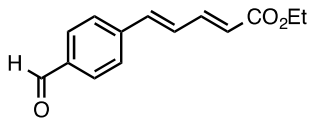
complex, where the diene is adopting an *s-cis* geometry. This approach tolerates multiple protic, electrophilic groups and molecules that contain poly-unsaturated carbon-carbon bonds, overcoming difficulties associated with established catalytic methods such as alkyne semi-reduction and *Z*-selective olefin metathesis. Since these findings, other group members have established that Rh/formic acid mixtures promote *Z*-selective reductive coupling reactions of dienes and aldehydes, demonstrating the generality of our approach.

1.7 Procedures and Characterization

1.7.1 General Procedure for Starting Material Synthesis

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

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

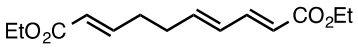


1.34 Triethyl 4-phosphonocrotonate (0.73 ml, 3.3 mmol, 1.1 equiv.) and dry THF (20 ml) were added to a N_2 flushed 100 ml round bottom flask charged with a stir bar. The solution was maintained at 0 ºC and *n*-BuLi (2.5 M in hexane, 1.4 ml, 1.2 equiv.) was add dropwise. The mixture was stirred at room temperature for 45 minutes. Meanwhile terephthalaldehyde (0.40 g, 3.0 mmol, 1 equiv.) was added to another 100 ml round bottom flask charged with a stir bar. The flask was purged with N_2. Anhydrous THF (10 ml) was added. The phosphonate solutions previously made was transferred to terephthalaldehyde solution. The reaction mixture was heated at reflux for 4 h. Upon completion of the reaction, the mixture was quenched with 30 ml NH_4Cl (sat.), transferred to a separation funnel and 100 ml Et_2O was added. The aqueous layer was further extracted with Et_2O (2 × 100 ml) and the organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. Isolated in 16% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.01 (s, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.45 (dd, J = 15.4, 10.5 Hz, 1H), 7.05–6.92 (m, 2H), 6.08 (d, J = 15.5 Hz, 1H), 4.25 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.5, 166.7, 143.6, 141.9, 138.5, 136.3, 130.2, 129.5, 127.6, 123.5, 60.6, 14.4;

HRMS (EI): calcd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943. Found 230.0941.

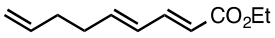


1.35 Prepared according to a literature procedure.[43] Isolated in 21% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a light yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (dd, *J* = 15.4, 10.5 Hz, 1H), 6.96–6.89 (m, 1H), 6.20 (dd, *J* = 15.4, 10.5 Hz, 1H), 6.11–6.06 (m, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 5.81 (d, *J* = 15.5 Hz, 1H), 4.22–4.17 (m, 4H), 2.35–2.34 (m, 4H), 1.29 (t, *J* = 7.5 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 166.5, 147.4, 144.4, 141.9, 129.4, 122.2, 120.2, 60.3(2), 31.3 (2), 14.3(2);

HRMS (EI): calcd for $C_{14}H_{20}O_4$ $[M]^+$: 252.1362. Found 252.1361.

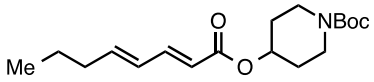


1.36 A 100 ml round bottom flask charged with stir bar was purged with N_2. Triethyl 4-phosphonocrotonate (1.5 g, 6.0 mmol, 1.2 equiv.) and dry THF (50 ml) were added sequentially. The solution was maintained at 0 ºC and *n*-BuLi (2.5 M in hexane, 3.2 ml, 1.6 equiv.) was add dropwise. The mixture was stirred at room temperature for 45 minutes. Then 4-pentenal (0.49 ml, 5.0 mmol, 1 equiv.) was added dropwise. The reaction mixture was heated at reflux for 4 h. Upon competition of the reaction, the mixture was quenched with 50 ml NH_4Cl (sat.), transferred to a separation funnel and 100 ml Et_2O was added. The aqueous layer was further extracted with Et_2O (2 × 100 ml) and the organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. Isolated in 14% yield [(*E,E*)/(*Z,E*) = 13:1] after purification by column chromatography (20:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (dd, *J* = 15.4, 10.5 Hz, 1H), 6.19–6.10 (m, 2H), 5.82–5.77 (m, 2H), 5.06–4.98 (m, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.28–2.19 (m, 4H), 1.29 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 144.9, 143.5, 137.5, 128.8, 119.6, 115.4, 60.2, 32.9, 32.3, 14.4;

HRMS (EI): calcd for $C_{11}H_{16}O_2$ $[M]^+$: 180.1150. Found 180.1149.

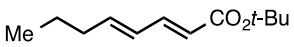


137 Prepared according to the General Procedure A for Wittig Olefination from (tertuButoxymethylene)triphenylphosphorane (5.19 g, 13.79 mmol, 1.00 equiv.) and trans-2-hexenal (1.61 mL, 13.79 mmol, 1.00 equiv.). Isolated in 72 % yield after purification by column chromatography (20:1 Hexane/EtOAc) as a light yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 (dd, *J* = 15.5 Hz, 10.8 Hz, 1H), 6.17–6.06 (m, 2H), 5.71 (d, *J* = 15.3 Hz, 1H), 2.13 (q, *J* = 7.3 Hz, 2H), 1.49–1.43 (m, 11H), 0.91 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.7, 144.0, 143.7, 128.5, 121.2, 80.0, 35.0, 28.2, 22.0, 13.6;

HRMS (EI): calcd for $C_{12}H_{20}O_2$ $[M]^+$ 196.1463. Found 196.1462.

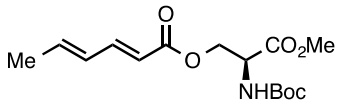


1.38 Prepared according to the General Procedure B for DCC Coupling from octa-2,4-dienoic acid and *t*-butyl-4-hydroxypiperidine-1-carboxylate (0.40 g, 2.0 mmol, 1.0 equiv.). Isolated in 35% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a light yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.19 (dd, *J* = 15.4, 10.5 Hz, 1H), 6.13–6.04 (m, 2H), 5.71 (d, *J* = 15.4 Hz, 1H), 4.92 (m, 1H), 3.65 (m, 2H), 3.20–3.16 (m, 2H), 2.08 (q, *J* = 7.0 Hz, 2H), 1.81–1.79 (m, 2H), 1.56 (m, 2H), 1.42–1.37 (m, 11H), 0.85 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 154.6, 145.2, 144.6, 128.4, 119.1, 79.4, 69.3, 40.7 (br), 34.9, 30.6, 28.3, 21.8, 13.5;

HRMS (ESI): calcd for $C_{18}H_{29}NNaO_4$ $[M+Na]^+$: 346.1989. Found 346.1988.

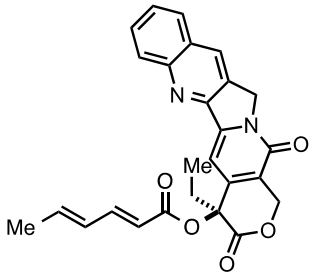


1.39 Prepared according to the General Procedure B for DCC Coupling from sorbic acid and Boc-Ser-OMe (0.44 g, 2.0 mmol, 1.0 equiv.). Isolated in 99% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26–7.21 (m, 1H), 6.21–6.14 (m, 2H), 5.74 (d, *J* = 15.0 Hz, 1H), 5.32–5.30 (m, 1H), 4.61–4.59 (m, 1H), 4.52–4.49 (m, 1H), 4.38 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.76 (s, 3H), 1.86 (d, *J* = 5.0 Hz, 3H), 1.45 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 166.7, 155.2, 146.2, 140.3, 129.7, 117.9, 80.3, 64.2, 53.1, 52.7, 28.3, 18.7;

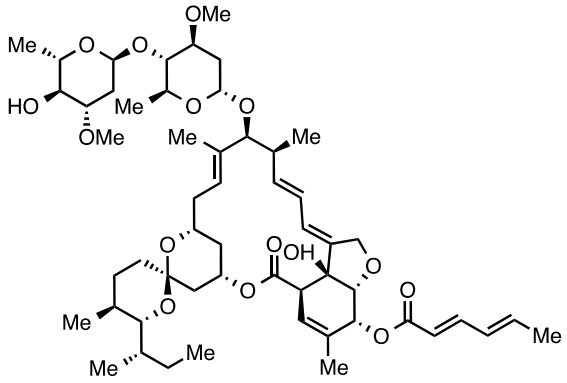
HRMS (ESI): calcd for $C_{15}H_{23}NNaO_6$ $[M+Na]^+$: 336.1418. Found 336.1420.



1.12 Prepared according to the General Procedure B for DCC Coupling from sorbic acid and camptothecin (0.70 g, 2.0 mmol, 1.0 equiv.). Isolated in 64% yield after purification by column chromatography (20:1 DCM/MeOH) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.38 (s, 1H), 8.21 (d, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.84–7.81 (m, 1H), 7.68–7.65 (m, 1H), 7.31 (dd, *J* = 15.5, 10.5 Hz, 1H), 7.24 (s, 1H), 6.27–6.16 (m, 2H), 5.91 (d, *J* = 15.5 Hz, 1H), 5.70 (d, *J* = 17.0 Hz, 1H), 5.43 (d, *J* = 17.0 Hz, 1H), 5.32–5.24 (m, 2H), 2.36–2.32 (m, 1H), 2.22–2.17 (m, 1H), 1.87 (d, *J* = 6.0 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 166.0, 157.5, 152.6, 148.9, 147.7, 146.1(2), 141.4, 131.2, 130.7, 129.7, 129.6, 128.5, 128.3, 128.2, 128.0, 120.5, 117.1, 96.3, 75.6, 67.2, 49.9, 32.0 18.8, 7.7; **HRMS (ESI):** calcd for $C_{26}H_{22}N_2NaO_5$ $[M+Na]^+$: 465.1421. Found 465.1421.

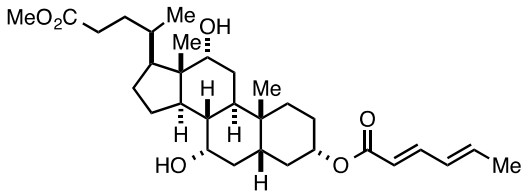


1.40 Ivermectin B_{1a} (2.60 g, 3.0 mmol, 1.0 equiv.) and DMAP (0.18 g, 1.5 mmol, 0.50 equiv.) was added to a 100 ml round bottom flask charged with a stirbar. The flask was purged with N_2 and anhydrous dichloromethane (30 ml, 0.10 M) and triethylamine (0.50 ml, 3.6 mmol, 1.2 equiv.) were added sequentially. Reaction mixture was cooled down to 0 °C and sorbyl chloride (0.44 ml, 3.6 mmol, 1.2 equiv.) was added dropwise. The solution was stirred for 2.5 h and the organic layer was washed with saturated $NaHCO_3$ (2 × 30 ml), dried with Na_2SO_4 and concentrated *in vacuo*. Isolated in 41% yield after purification by column chromatography (1:1 Hexane/EtOAc) as a yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (dd, *J* = 15.4, 10.5 Hz, 1H), 6.23–6.14 (m, 2H), 5.89–5.83 (m, 2H), 5.77–5.67 (m, 2H), 5.63–5.61 (m, 1H), 5.54–5.53 (m, 1H), 5.39 (d, *J* = 4.0 Hz, 1H), 5.37–5.30 (m, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.78 (d, *J* = 3.5 Hz, 1H), 4.67–4.55 (m, 2H), 4.10 (d, *J* = 6.0 Hz, 1H), 4.03 (s, 1H), 3.94 (s, 1H), 3.86–3.74 (m, 2H), 3.70–3.60 (m, 2H), 3.51–3.45 (m, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.38–3.36 (m, 1H), 3.25–3.14 (m, 3H), 2.53–2.49 (m, 2H), 2.35–2.20 (m, 4H), 2.04–1.15 (m, 31H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.86–0.78 (m, 7H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 166.9, 146.1, 140.0, 139.5, 138.0, 135.1, 133.9, 129.8, 124.8, 120.4, 120.1, 118.4, 118.1, 98.6, 97.5, 94.8, 81.8, 80.6, 80.5, 79.4, 78.2, 77.4, 76.8, 76.2, 69.8, 68.9, 68.3, 68.2, 67.3, 56.6, 56.5, 45.8, 41.3, 39.8, 36.9, 35.8, 35.5, 34.6, 34.2(2), 31.3, 28.1, 27.4, 20.3, 19.6, 18.7, 18.5, 17.7, 17.5, 15.2, 14.2, 12.5, 12.1;

HRMS (ESI): calcd for $C_{54}H_{80}NaO_{15}$ $[M+Na]^+$: 991.5389. Found 991.5394.

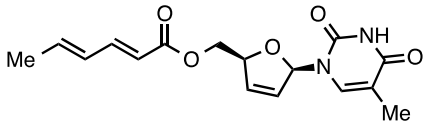


1.41 Prepared according to a literature procedure[44] from methylcholate (0.85 g, 2.0 mmol, 1.0 equiv.) and sorbic acid. Isolated in 46% yield after purification by column chromatography (20:1 DCM/MeOH) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.36–6.29 (m, 1H), 6.15–6.09 (m, 1H), 5.80–5.74 (m, 1H), 5.15 (d, J = 17.0 Hz, 1H), 5.04 (d, J = 10.0 Hz, 1H), 4.62–4.56 (m, 1H), 4.00–3.98 (m, 1H), 3.86–3.84 (m, 1H), 3.66 (s, 3H), 3.07 (dd, J = 7.5, 1.0 Hz, 2H), 2.40–2.18 (m, 4H), 1.98–1.88 (m, 3H), 1.86–1.28 (m, 15H), 1.19–1.01 (m, 2H), 0.98 (d, J = 6.0 Hz, 3H), 0.90 (s, 3H), 0.69 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 171.1, 136.5, 134.1, 126.1, 116.7, 74.7, 72.9, 68.3, 51.6, 47.3, 46.6, 42.1, 41.2, 39.6, 38.5, 35.2, 34.9, 34.7, 34.4, 31.1, 30.9, 28.4, 27.5, 26.8, 26.7, 23.2, 22.6, 17.4, 12.6;

HRMS (ESI): calcd for $C_{31}H_{48}NaO_6$ $[M+Na]^+$: 539.3343. Found 539.3338.

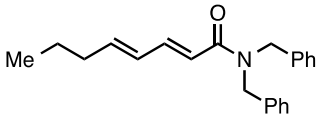


1.42 Prepared according to the General Procedure B for DCC Coupling from sorbic acid and stavudine (0.45 g, 2.0 mmol, 1.0 equiv.). Isolated in 60% yield after purification by column chromatography (20:1 DCM/MeOH) as a white solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96–7.95 (br, 1H), 7.32–7.28 (m, 1H), 7.21–7.20 (m, 1H), 6.99–6.98 (m, 1H), 6.32–6.30 (m, 1H), 6.19–6.17 (m, 2H), 5.89–5.88 (m, 1H), 5.75 (d, *J* = 15.4 Hz, 1H), 5.08–5.07 (m, 1H), 4.50 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.33 (dd, *J* = 9.0, 2.0 Hz, 1H), 1.89 (d, *J* = 1.0 Hz, 3H), 1.87 (d, *J* = 4.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8, 163.3, 150.5, 146.7, 141.1, 135.6, 133.6, 129.5, 127.1, 117.5, 110.1, 89.8, 84.7, 64.3, 18.8, 12.6;

HRMS (ESI): calcd for $C_{16}H_{17}N_2O_5$ $[M–H]^-$: 317.1143. Found 317.1145.

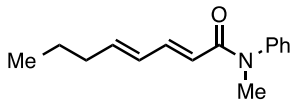


1.43 Prepared according to the General Procedure B for DCC Coupling from octa-2,4-dienoic acid and dibenzylamine (0.99 g, 5 mmol, 1.0 equiv.). Isolated in 84% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a light yellow oil.

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

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

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

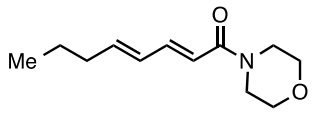


1.7 Prepared according to the General Procedure A for Wittig Olefination from *N*-methyl-*N*-phenyl-2-(triphenylphosphoranylidene)acetamide (8.2 g, 20 mmol, 1.0 equiv.) and *trans*-2-hexenal (2.3 ml, 20 mmol, 1.0 equiv.). Isolated in 55% yield after purification by column chromatography (4:1 Hexane/EtOAc)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

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

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

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

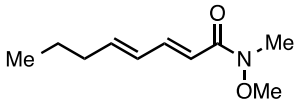


1.44 Prepared according to the General Procedure A for Wittig Olefination from (morpholinocarbomethylene)triphenylphosphorane (3.5 g, 9.1 mmol, 1.0 equiv.) and *trans*-2-hexenal (1.1 ml, 9.1 mmol, 1.0 equiv.). Isolated in 72% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (dd, *J* = 15.4, 10.5 Hz, 1H), 6.20–6.06 (m, 3H), 3.68–3.56 (m, 8H), 2.15–2.11 (m, 2H), 1.47–1.43 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.0, 143.8, 143.3, 128.8, 117.4, 66.9, 46.1 (br), 42.4 (br), 35.0, 22.0, 13.7;

HRMS (EI): calcd for $C_{12}H_{19}NO_2$ $[M]^+$: 209.1416. Found 209.1412.



1.45 Prepared according to the General Procedure A for Wittig Olefination from *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (1.6 g, 4.4 mmol, 1.0 equiv.) and *trans*-2-hexenal (0.50 ml, 4.4 mmol, 1.0 equiv.). Isolated in 56% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (dd, J = 15.0, 10.5 Hz, 1H), 6.38 (d, J = 15.0 Hz, 1H), 6.25–6.20 (m, 1H), 6.14–6.10 (m, 1H), 3.70 (s, 3H), 3.24 (s, 3H), 2.16–2.12 (m, 2H), 1.48–1.44 (m, 2H), 0.92 (t, J = 7.0 Hz, 3H);

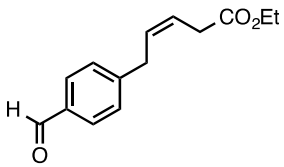
^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 144.0, 143.8, 129.0, 116.9, 61.8, 35.1, 32.5, 22.0, 13.7;

HRMS (EI): calcd for $C_{10}H_{17}NO_2$ $[M]^+$: 183.1259. Found 183.1255.

1.7.2 General Procedure for Formate Mediated Rh-Catalyzed 1,6-Reduction (Esters)

In an atmosphere controlled glovebox, PPh_3 (19.7 mg, 0.075 mmol, 0.15 equiv.) and $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.025 equiv.) were weighed into separate 1 dram vials. To the $[Rh(COD)Cl]_2$ was added MeCN (1.0 mL) and the solution was transferred into the vial containing the PPh_3. MeCN (2 x 0.25 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the PPh_3 to make catalyst mixture. To a 1-dram vial was weighed diene (0.5 mmol, 1 equiv.), followed by addition of catalyst solution. Additional MeCN (2 x 0.25 mL) was used to wash the

remaining catalyst solution into the diene containing vial. Formic acid/triethylamine (5:2, 43.2 mg, 0.5 mmol, 1.0 equiv.), was weighed into a ½ dram vial and then transferred into the vial containing the reaction mixture. The formic acid containing vial was washed into the solution with MeCN (2 x 0.25 mL). A stir-bar was added into the mixture, the vial was capped with a PTFE-line cap, taken out of the glovebox and placed in an aluminum block heated to 35 °C and stirred. The reaction progress was monitored periodically by NMR and quenched once ~90% conversion of the diene was observed. [Note: If 1.00 equivalent of formic acid is employed, the reaction can proceed for prolonged periods without isomerization and over-reduction, the reaction is not time-sensitive. The use of excess formic acid can result in *Z*-olefin isomerization and over-reduction.] The solution was filtered through silica to quench the reaction, concentrated *in vacuo* and purified by silica gel chromatography. Confirmation of *Z*-olefin geometry was established by comparison of ^{1}H NMR shifts, coupling constants to reported compounds and through-space NMR correlation experiments establishing the proximity of protons at C_2 and C_5.

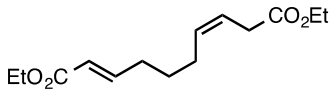


1.14 Prepared according to the General Procedure from the corresponding diene (69.1 mg, 0.30 mmol). Crude diene conversion: 90%, crude product yield: 73% [96:4 *Z:E*]. Isolated in 66% yield as a colorless oil after purification by column chromatography (4:1 Pentane/Et_2O).

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

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

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

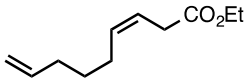


1.15 Prepared according to the General Procedure from the corresponding triene (50.5 mg, 0.20 mmol). Crude triene conversion: 93%, crude product yield: 72% [96:4 *Z:E*]. Isolated in 62% yield as a colorless oil after purification by column chromatography (4:1 Pentane/Et_2O).

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

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

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

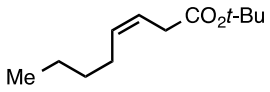


1.16 Prepared according to the General Procedure from the corresponding triene (72.0 mg, 0.40 mmol). Crude triene conversion: 86%, crude product yield: 71% [*Z:E* = 97:3]%. Isolated in 62% yield as a colorless oil after purification by column chromatography (20:1 Hex/EtOAc).

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

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

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

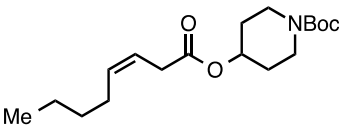


1.17 Prepared according to the General Procedure from the corresponding diene (98.1 mg, 0.50 mmol). Crude diene conversion: 91%, crude product yield: 80% [96:4 *Z:E*]. Isolated in 56% yield as a colorless oil after purification by column chromatography (20:1 Pentane/Et_2O) using Ag/SiO_2.

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

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

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

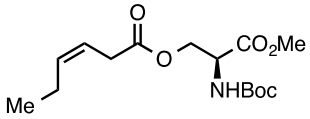


1.18 Prepared according to the General Procedure from the corresponding diene (161.7 mg, 0.50 mmol). Crude diene conversion: 92%, crude product yield: 73% [95:5 *Z:E*]. Isolated as a colorless oil in 64% yield after purification by column chromatography (4:1 Hex/EtOAc) using Ag/SiO_2.

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

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

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

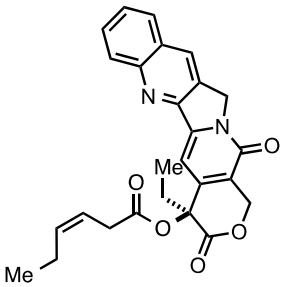


1.19 Prepared according to the General Procedure from the corresponding diene (62.6 mg, 0.20 mmol). Crude diene conversion: 92%, crude product yield: 68% [94:6 *Z:E*]. Isolated as a colorless oil in 57% yield after purification by chromatography (4:1 Hex/EtOAc) using Ag/SiO_2.

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

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

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



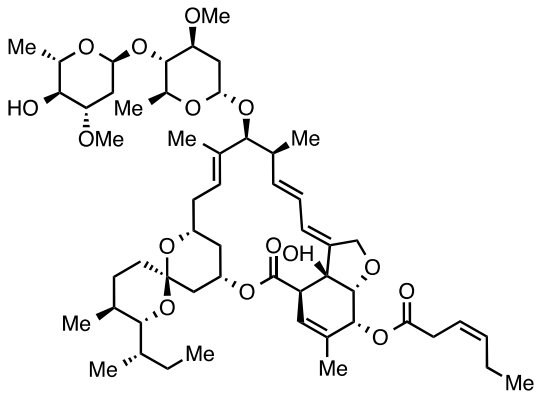
1.13 In an atmosphere controlled glovebox, PPh_3 (7.9 mg, 0.030 mmol, 0.30 equiv.) and $[Rh(COD)Cl]_2$ (2.5 mg, 0.005 mmol, 0.05 equiv.) were weighted into separate 1 dram vial. To the $[Rh(COD)Cl]_2$ was added MeCN (0.20 mL), shaken to dissolve and the solution was transferred

to the vial containing the phosphine. Additional MeCN (0.20 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the phosphine to make the catalyst solution. To a 1-dram vial was added substrate (44.2 mg, 0.10 mmol, 1.0 equiv.), followed by the catalyst solution. Additional MeCN (0.20 mL) was used to wash the remaining catalyst solution into the reaction vial. To another 1-dram vial was added formic acid/triethylamine (5:2; 17.3 mg, 0.20 mmol, 2.0 equiv.) and MeCN (0.10 mL). The solution was then added to the reaction mixture. Additional MeCN (0.10 mL) was used to wash the remaining formic acid into the mixture. DMSO (0.20 mL) was added to the mixture as co-solvent, followed by a teflon coated magnetic stir-bar. The vial was capped with a PTFE-lined cap, taken out of the glovebox, placed in an aluminum block heated to 35 °C and stirred overnight. Upon the completion of the reaction, the mixture was diluted by EtOAc (10 mL), extracted with water (3 × 10 mL), concentrated *in vacuo* and purified by chromatography. Crude diene conversion: 94%, crude product yield: 82% [83:17 *Z:E*]. Isolated in 50% yield as a white solid after purification by column chromatography (20:1 DCM/MeOH) using Ag/SiO_2.

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

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

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

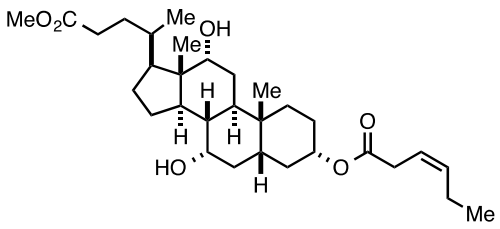


1.20 Prepared according to the General Procedure from the corresponding ivermectin-derived dienyl ester (96.9 mg, 0.10 mmol). Crude diene conversion: 92%, crude product yield: 70% [90:10 *Z:E*]. Isolated in 59% yield after purification by chromatography (1:3 Pentane/Et_2O) as a white solid.

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

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

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

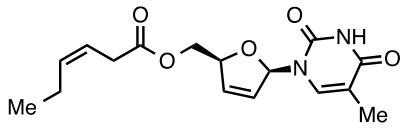


1.21 Prepared according to the General Procedure from corresponding methyl cholate-derived dienyl ester (103.3 mg, 0.20 mmol). Crude diene conversion: 94%, crude product yield: 58% [95:5 *Z:E*]. Isolated in 53% yield after purification by column chromatography (1:2 Pentane/Et_2O) as a white solid.

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

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

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



1.22 In an atmosphere controlled glovebox, PPh_3 (15.7 mg, 0.06 mmol, 0.30 equiv.) and $[Rh(COD)Cl]_2$ (4.90 mg, 0.01 mmol, 0.05 equiv.) were weighted into separate 1 dram vial. To the $[Rh(COD)Cl]_2$ was added MeCN (0.40 mL), shaken to dissolve and the solution was transferred to the vial containing the phosphine. Additional MeCN (0.40 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the phosphine to make the catalyst solution. To a 1-dram vial was added diene (63.6 mg, 0.20 mmol, 1.0 equiv.), followed by the catalyst solution. Additional MeCN

(0.40 mL) was used to wash the remaining catalyst solution into the substrate containing vial. To another 1-dram vial was added formic acid/triethylamine (5:2; 51.9 mg, 0.60 mmol, 3.0 equiv.) and MeCN (0.20 mL). The solution was then added to the reaction mixture. Additional MeCN (0.20 mL) was used to wash the remaining formic acid solution into the mixture. DMSO (0.40 mL) was added to the mixture as co-solvent, followed by a teflon coated magnetic stirbar. The vial was capped with a PTFE-lined cap, taken out of the glovebox, placed in an aluminum block heated to 35 °C and stirred overnight. Upon the completion of the reaction, the mixture was diluted by EtOAc (10 mL), extracted with water (3 × 10 mL), concentrated *in vacuo* and purified by chromatography. Crude diene conversion: 91%, crude product yield: 70% [94:6 *Z:E*]. Isolated in 52% yield after purification by column chromatography (20:1 DCM/MeOH) using Ag/SiO_2 as a white solid.

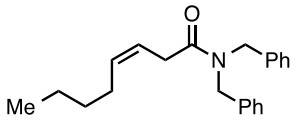
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (br, 1H), 7.21–7.20 (m, 1H), 7.00–6.99 (m, 1H), 6.29–6.27 (m, 1H), 5.92–5.90 (m, 1H), 5.64–5.58 (m, 1H), 5.52–5.46 (m, 1H), 5.07–5.04 (m, 1H), 4.42 (dd, *J* = 10.0, 4.5 Hz, 1H), 4.25 (dd, *J* = 12.0, 3.5 Hz, 1H), 3.11 (d, *J* = 7.0 Hz, 2H), 2.04–2.03 (m, 2H), 1.93 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 3H);

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

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

General Procedure for Formate Mediated Rh-Catalyzed 1,6-Reduction (Amides)

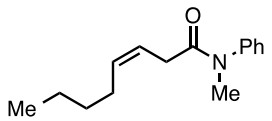
In an atmosphere controlled glovebox, tri(4-fluoro-phenyl)phosphine (19.0 mg, 0.0600 mmol, 0.12 equiv.) and $[Rh(COD)Cl]_2$ (3.8 mg, 0.00750 mmol, 0.015 equiv.) were weighted into separate 1 dram vials. To the $[Rh(COD)Cl]_2$ was added MeCN (0.50 mL), shaken to dissolve and the solution was transferred to the vial containing the phosphine. Additional MeCN (0.50 mL) was used to wash the remaining $[Rh(COD)Cl]_2$ solution into the phosphine to make the $[Rh(COD)Cl]_2$/phosphine solution. To a 1-dram vial was added dienyl amide (0.50 mmol, 1.0 equiv.), followed by the catalyst solution. Additional MeCN (0.50 mL) was used to wash the remaining catalyst solution into the dienyl amide solution. To a separate 1-dram vial was added formic acid/triethylamine (5:2; 41.0 mg, 0.475 mmol, 0.95 equiv.) and MeCN (0.50 mL). The solution was then added to the reaction mixture. Additional MeCN (0.50 mL) was used to wash the remaining formic acid solution into the mixture, followed by a teflon coated magnetic stir-bar. The vial was capped with a PTFE-lined cap, taken out of the glovebox, placed in an aluminum block heated to 60 °C and stirred overnight. Upon the completion of the reaction, the mixture was concentrated *in vacuo* and purified by chromatography.



1.23 Prepared according to the General Procedure (amides) from the corresponding diene (164.8 mg, 0.52 mmol). Crude diene conversion: 93%, crude product yield: 63% [95:5 *Z:E*]. Isolated in 59% yield after purification by chromatography (4:1 Hex/EtOAc) using Ag/SiO_2 as a colorless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.38–7.36 (m, 2H), 7.33–7.30 (m, 3H), 7.28–7.25 (m, 1H), 7.22 (d, J = 7.0 Hz, 2H), 7.16 (d, J = 7.0 Hz, 2H), 5.68–5.63 (m, 1H), 5.60–5.55 (m, 1H), 4.61 (s, 2H), 4.45 (s, 2H), 3.22 (d, J = 6.5 Hz, 2H), 1.98–1.93 (m, 2H), 1.32–1.23 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H);

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

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

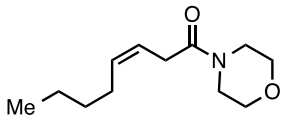


1.8 Prepared according to the General Procedure (amides) from the corresponding diene (114.7 mg, 0.50 mmol). Crude diene conversion: 93%, crude product yield: 61% [92:8 *Z:E*]. Isolated in 51% yield after purification by column chromatography (4:1 Hex/EtOAc) using Ag/SiO_2 as a colorless oil.

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

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

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

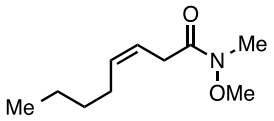


1.24 Prepared according to the General Procedure (amides) from the corresponding diene (104.7 mg, 0.50 mmol). Crude diene conversion: 90%, crude product yield: 61% [94:6 *Z:E*]. Isolated in 51% yield after purification by chromatography (4:1 Hexane/EtOAc) using Ag/SiO_2 as a colorless oil.

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

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

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



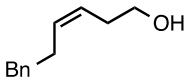
1.25 Prepared according to the General Procedure from the corresponding diene (91.6 mg, 0.50 mmol). Crude diene conversion: 86%, crude product yield: 78%, selectivity not determined due to overlap of ^{1}H NMR signals. Isolated in 69% yield after purification by chromatography (4:1 Hexane/EtOAc) using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

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

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

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

1.7.3 Functionalization of *Z*-Olefin Products



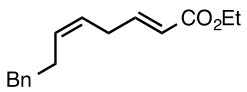
1.26 $LiAlH_4$ (0.18 g, 4.9 mmol, 1.4 equiv.) was added to a 50 mL round bottom flask charged with a stirbar. The flask was purged with 3 times N_2, Et_2O (20 ml, 0.2 M) was added and the reaction

mixture was cooled to 0 °C. *Z*-olefin (1.0 g, 3.6 mmol, 1.0 equiv.) was added dropwise and the mixture was stirred for 2 h at room temperature. Upon completion of the reaction, the solution was re-cooled to 0 °C and diluted with Et_2O. Water (0.18 ml), 2 M NaOH (0.36 ml), additional water (0.54 ml) were added slowly in sequence. The mixture was allowed to warm to room temperature and stirred for 15 min. Na_2SO_4 was then added. The mixture was further stirred for 15 min and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (Ag/SiO_2, 3:1 EtOAc/Hexane). Isolated in 85% yield as a colorless oil.

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

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

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



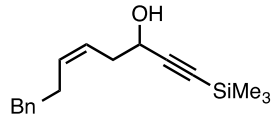
1.27 DMP (0.64 g, 1.5 mmol, 1.0 equiv.) was added to a 50 mL round bottom flask charged with a stirbar. The flask was purged with N_2 and CH_2Cl_2 (15 ml, 0.1 M) followed by **1.35** (0.26 g, 1.5 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at room temperature for 2 h. Upon completion of the reaction, the solution was filtered through a pad of silica, rinsed with Hexane/EtOAc (1:1), concentrated *in vacuo*. Isolated in 82% yield as a colorless oil and used in next step without further purification. NaH (4.8 mg, 0.12 mmol, 1.2 equiv.) was added to a 4-dram vial charged with a stirbar. The flask was purged with N_2, THF (1 ml, 0.1 M) was added and the solution was cooled to 0 °C. Triethyl phosphonoacetate (24 µl, 0.12 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred for 10 min and the aldehyde prepared above (17 mg, 0.10 mmol,

1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Upon completion of the reaction, the mixture was concentrated *in vacuo* and purified by flash chromatography (10:1 Hexane/EtOAc). Isolated in 89% yield as a colorless oil.

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

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

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

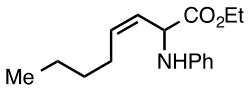


1.28 A 4-dram vial charged with a stirbar was purged with N_2, ethynyltrimethylsilane (15 mg, 0.1 mmol, 1.5 equiv.) and THF (1 ml, 0.1 M) were added and the solution was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 60 µl, 1.5 equiv.) was added dropwise. The mixture was stirred for 1 h and the aldehyde prepared above (17 mg, 0.10 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at -78 C °C for 2 h. Upon completion of the reaction, the mixture was quenched with saturated aqueous solution of NH_4Cl (1 ml) and the aqueous layer was extracted with EtOAc (3 × 1 ml). The organic layers were combined, concentrated *in vacuo* and purified by column chromatography (4:1 Hexane/EtOAc). Isolated in 94% yield as a colorless oil.

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

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

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



1.29 *p*-ABSA (2.0 g, 8.4 mmol, 2.0 equiv.) was added to a 50 mL round bottom flask charged with a stirbar. The flask was purged with N_2, MeCN (20 ml, 0.2 M) and *Z*-olefin (0.72 g, 4.2 mmol, 1.0 equiv.) were added sequentially. The reaction mixture was cooled to 0 °C and DBU (1.3 ml, 8.4 mmol, 2.0 equiv.) was added dropwise. The mixture was stirred at room temperature for 3.5 h. Upon completion of the reaction, the solution was filtered through a pad of silica, rinsed with Pentane/Et_2O (1:1), concentrated *in vacuo*. Isolated in 81% yield as an orange oil and used in next step without further purification. A 4-dram vial charged with a stir bar was purged with N_2, aniline (0.21 ml, 2.3 mmol, 5.0 equiv.), the diazo ester prepared above (90 mg, 0.46 mmol, 1.0 equiv.) and benzene (3 ml) were added sequentially. $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol, 0.022 equiv.) was then added in a solution of benzene (2 ml). The reaction mixture was heated at reflux for 10 min. Upon the completion of the reaction, the mixture was concentrated *in vacuo*. Isolated in 80% yield after purification by chromatography (10:1 Hexane/EtOAc) as a yellow oil (65% over two steps).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dd, *J* = 8.8, 7.4 Hz, 2H), 6.73 (dd, *J* = 14.0, 7.3 Hz, 1H), 6.60 (dd, *J* = 8.7, 1.1 Hz, 2H), 5.74–5.69 (m, 1H), 5.32–5.27 (m, 1H), 4.82 (dd, *J* = 14.7, 6.8 Hz, 1H),

4.37 (d, J = 5.9 Hz, 1H), 4.23–4.17 (m, 2H), 2.32–2.27 (m, 2H), 1.47–1.35 (m, 4H), 1.26 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H);

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

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

Chapter 2 – Catalytic Enantioselective Benzylation Directly from Aryl Acetic Acids

2.1 Introduction

Carboxylic acids are stable and readily available chemical feedstocks, making them ideal starting materials in organic synthesis.[45] Besides direct functionalization of carboxyl units such as esterification and amidation, carboxylic acids can be regarded as masked carbon nucleophiles, and widely employed in C–C or C–X (X = heteroatom) bond forming processes through extrusion of CO_2. The utility of decarboxylation event has already been elegantly demonstrated by nature, as there exists numerous enzymes that would facilitate decarboxylative transformations in chemical synthesis.[46-48] One representative enzyme-promoted decarboxylative condensation reaction is demonstrated by a pivotal step in biosynthesis of polyketides and fatty acids (Figure 2-1).[49] A carbon nucleophile is generated by extrusion of CO_2 from the acyl carrier protein bounded malonyl group, which is further condensed with a acyl moiety attached to the cysteine thiol unit of ketosynthase, providing the extended carbon backbone. This type of reactions could proceed under almost neutral conditions without the use of stoichiometric amount of base to afford reactive carbon nucleophiles, hence has attracted great interests from chemists.

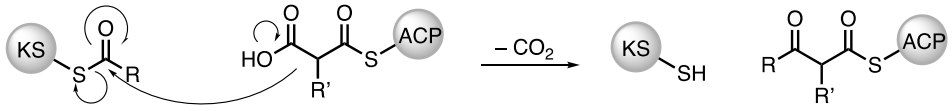


Figure 2-1 Enzymatic decarboxylative condensation in biosynthesis of polyketides and fatty acids (KS = ketosynthase, ACP = acyl carrier protein)

Inspired by these enzyme-facilitated decarboxylative functionalization processes, diverse carbon-carbon bond forming strategies have been developed employing carboxylic acids as stable carbon nucleophile precursors. Organocatalyst-promoted enantioselective decarboxylative carbon-carbon bond forming reactions are one of the attractive subclass methods to develop due

to their biomimetic and environmentally friendly properties,[50] including aldol reactions;[51-53] Mannich reactions;[54-56] and 1,4-conjugate additions.[57-59] An example of enantioselective decarboxylative aldol reaction of β-ketoacids with trifluoromethylketones was introduced by Ma and co-workers in 2012, where stereoselectivity was achieved by employing chiral cinchona alkaloid, $(DHQD)_2AQN$, as the catalyst (Figure 2-2).[52] Nevertheless, the use of complex organocatalyst became a major drawback decreasing overall efficiency.

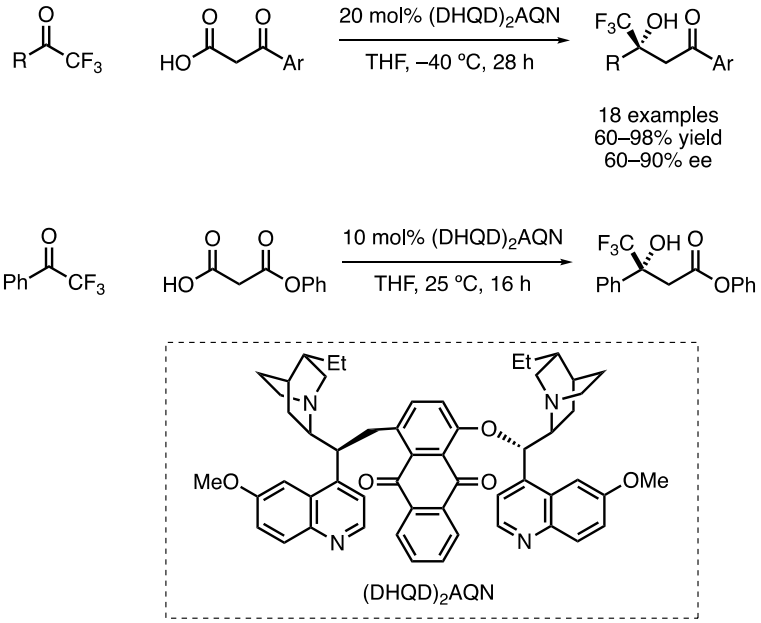


Figure 2-2 Enantioselective decarboxylative aldol reaction of β-ketoacids

Alternatively, transition metal-catalyzed decarboxylative cross-coupling reactions have emerged as a prominent strategy to form carbon-carbon or carbon-heteroatom bonds in the past decades.[60] In comparison with enzyme and organocatalyst-facilitated methods that are restricted to the use of malonic half esters, carboxylic acids or carboxylates that are less prone to decarboxylate, such as aryl carboxylic acids, aryl acetic acids and alkyl acids, have been employed as carbon nucleophile surrogates (Figure 2-3),[61-63] because extrusion of CO_2 could be promoted by

single-electron transfer (SET, representatively via photoredox processes), thermal activation, or by other activation methods under the presence of metal species.[64-66]

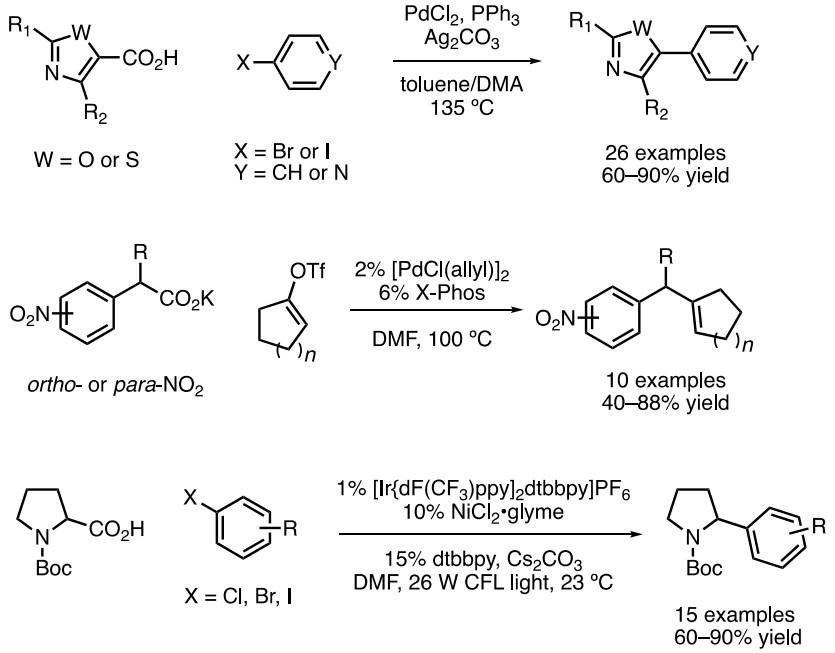


Figure 2-3 Decarboxylative coupling reactions with various nucleophile partners

The development of catalytic enantioselective decarboxylative cross-coupling reactions has attracted great interests from chemists, as those processes could potentially serve as valuable synthetic methods to access enantiopure pharmaceuticals.[45] As extrusion of CO_2 from carboxylic acids usually generates highly reactive intermediates, obtaining mechanistic insights into the key decarboxylation event is essential to ensure effective trapping of nucleophilic species. Unmodified carboxylic acids are typically engaged in ionic decarboxylation process to form a carbanion intermediate, which would be intercepted stereoselectively with electrophile partners mediated by catalysts (Figure 2-4a).[51, 67-68] For example, the Rh-catalyzed enantioselective decarboxylative alkynylation process undergoing such a mechanism pathway was demonstrated by Breit and co-workers (Figure 2-4b).[69] In the proposed catalytic cycle, extrusion of CO_2 occurs from

arylpropiolate in coordination with allyl-Rh(III) complex. Reactive arylacetylide anion will be directly captured by π-allyl fragment through reductive elimination.

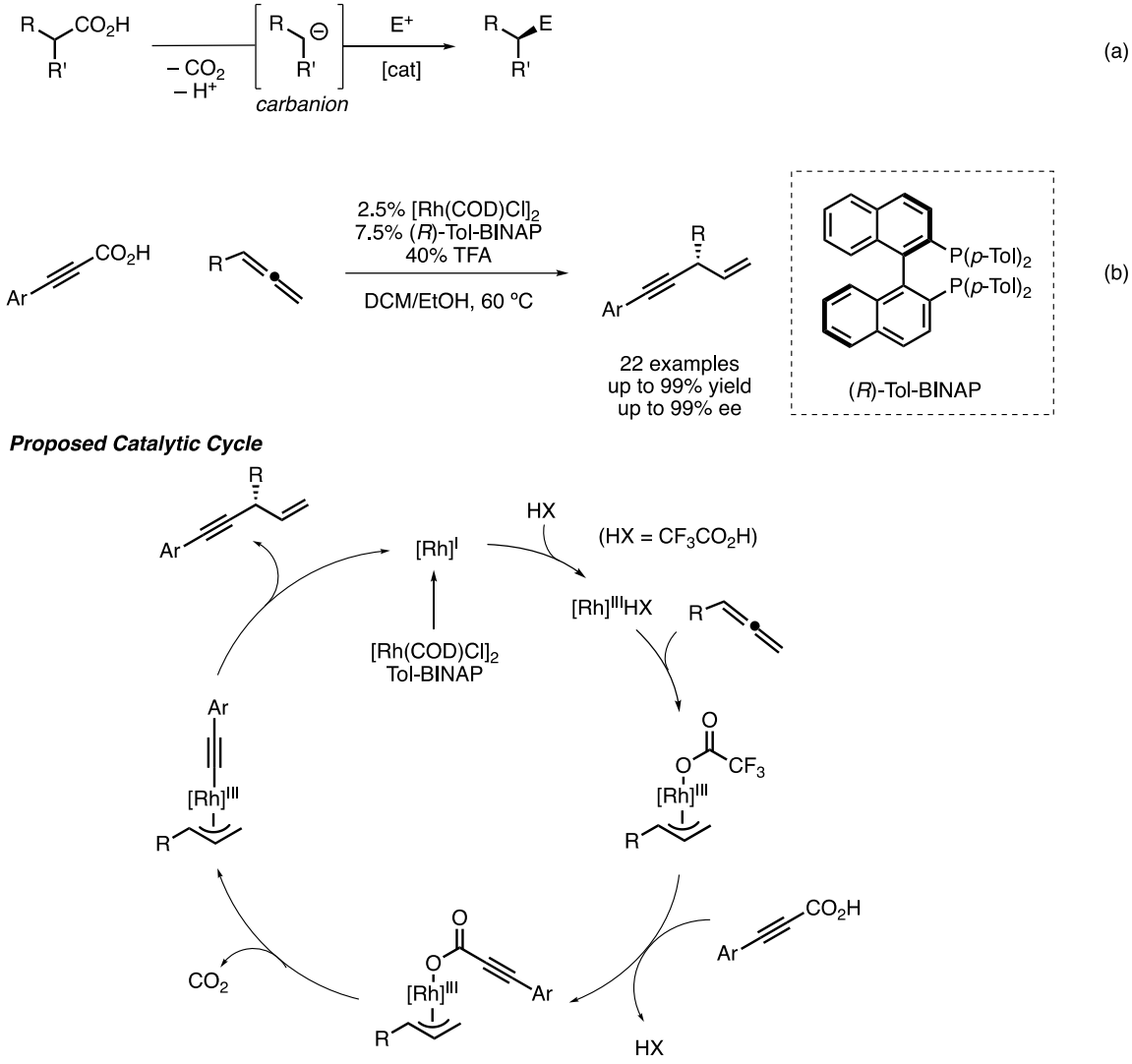


Figure 2-4 Ionic decarboxylation as the primary event for catalytic enantioselective reactions of carboxylic acids

Alternatively, single electron oxidation of carboxylic acids results in the loss of CO_2 by homolysis, generation of a radical species, and enantioselective trapping with a suitable reaction partner mediated by chiral catalysts (Figure 2-5a).[70-71] A representative method that undergoes this pathway is demonstrated by enantioselective decarboxylative arylation of α-amino acids reaction

via a merger of nickel catalysis and photoredox (Figure 2-5b).[72] In this process, a photocatalyst facilitates extrusion of CO_2 from alkyl carboxylic acids, which would be challenging under otherwise conditions. Cross-coupling event between generated radical species and aryl halides is mediated by chiral nickel catalyst, stereoselectively forming a new bond between sp^3 and sp^2 carbons.

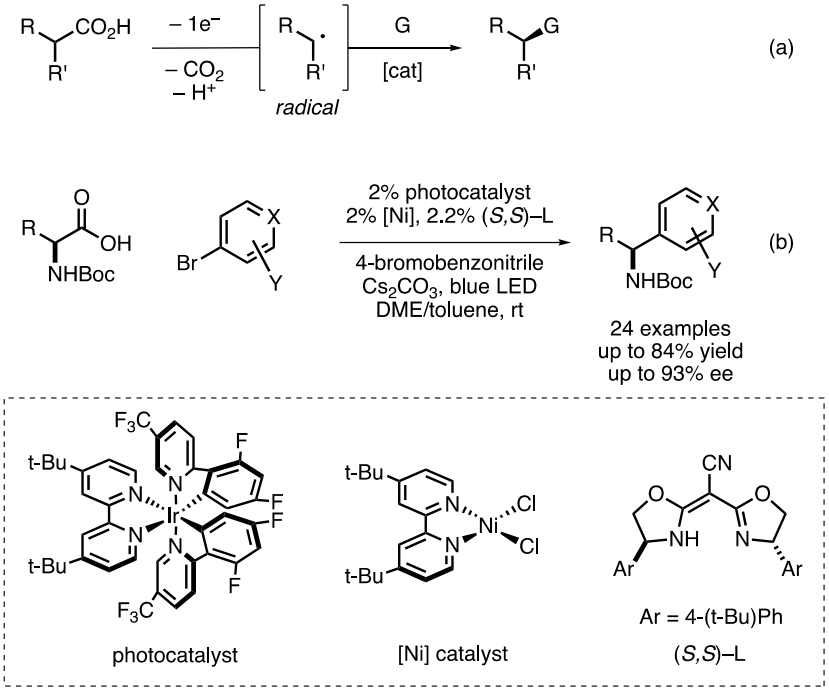


Figure 2-5 Homolysis decarboxylation as the primary event for catalytic enantioselective reactions of carboxylic acids

In both these reaction manifolds mentioned above, carboxylic acids that are recalcitrant to undergo decarboxylation can be covalently modified by organic moieties, resulting in carboxylic acid derivatives that can more easily engage in oxidative insertion[73-77] (typically allylic esters that can be applied in Tsuji-Trost reaction, Figure 2-6a) or homolysis[78-82] (redox-active esters such as N-acyloxyphthalimides, Figure 2-6b) to initiate reactivity. However, these indirect decarboxylative cross-coupling strategies limit overall reaction economy and efficiency.

Moreover, reactive intermediates are generated in both pathways, stereoselective interception of which could be challenging under specific conditions to induce decarboxylation.

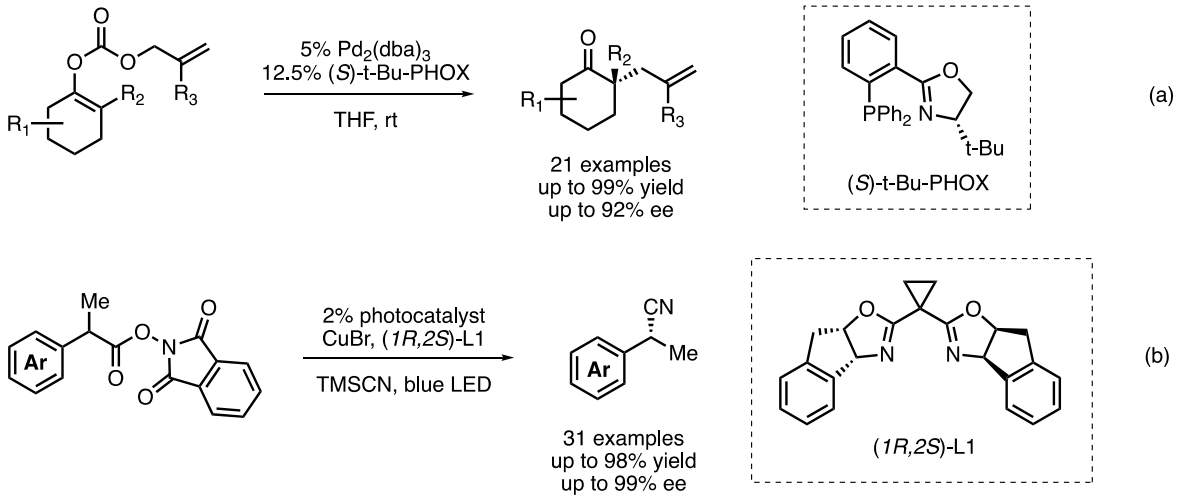


Figure 2-6 Using covalently modified carboxylic acid derivatives to initiate reactivity

A third mechanistic pathway for decarboxylative coupling involves a stereoselective bond-forming process prior to extrusion of CO_2 (Figure 2-7a). As the enantioselectivity-determining step is isolated from decarboxylation event, this framework shows outstanding advantage over the other strategies strictly requiring coordination of reaction rates between formation of reactive intermediates and its effective trapping. Protic and electrophilic groups that are able to quench highly reactive nucleophilic intermediates, as well as π-systems and weak abstractable C–H bonds that could intercept radicals would potentially be tolerated in this process, providing better chemoselectivity and functional group compatibility. An elegant utilization of this principle was demonstrated by a Cu-catalyzed enantioselective thioester aldol reaction developed by Shair and co-workers (Figure 2-7b).[83] Since strongly basic intermediates are not generated, diverse unprotected protic functionalities including alcohols, phenols, enolizable aldehydes, enolizable ketones are well tolerated in the Aldolization. This type of decarboxylative reactivity is limited to addition reactions to polarized π-units, such as aldol, Mannich and conjugate addition reactions.

A major difficulty to overcome when employing this process is to avoid irreversible interference from carboxylic acid itself, as this unit is generally more acidic than carbon nucleophiles and the corresponding carboxylate can potentially behave as a competitive nucleophilic species. This challenge helps to explain why this area of decarboxylative coupling is underdeveloped.

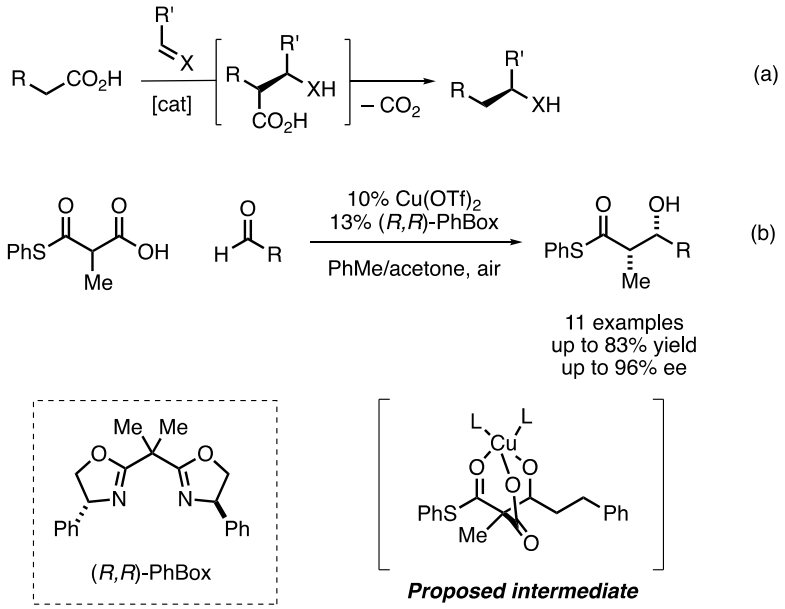


Figure 2-7 Stereoselective bond-forming process prior to decarboxylation

In considering new transformations that would leverage the advantage of pre-decarboxylative coupling of acids in enantioselective catalysis, we questioned whether aryl acetic acids could be employed as benzylating reagents in metal-catalyzed asymmetric cross-coupling reactions. The groups of Tunge[84], Liu[85] and Zhu[61] demonstrated that nitro-activated aryl acetate would undergo thermal induced decarboxylation (100–140 ºC). The nucleophilic species could be intercepted by allyl, aryl and alkenyl electrophiles through palladium catalysis (Figure 2-8a). One main drawback of these protocols is that substrate scope is limited to highly stabilized nitro aryl fragments, restricting their broader applications in organic synthesis. Inspired by their work, Patrick Moon, a PhD student in our group, discovered potassium nitroaryl acetates can

decarboxylate at room temperature in polar aprotic solvents such as DMF, DMA, DMSO. The generated benzyl anion can be captured by aryl or alkenyl boronic esters through Cu-catalyzed oxidative coupling process (Figure 2-8b).[86] Remarkably, the reaction smoothly proceeds under much milder conditions (r.t. to 40 ºC). Encouraged by the success of decreasing the thermal energy required for CO_2 extrusion of nitroaryl acetates, we believed less activated aryl acetates could decarboxylate at slightly higher temperature, hence scope of benzyl partners could be extended from nitro-benzyl units to other benzyl groups that are activated by weaker electron withdrawing substitution. Duanyang Kong, Patrick Moon and Wenyu Qian in our group were able to employ a diversity of modestly electron-deficient aryl acetates in Pd-catalyzed decarboxylative benzylation reactions with aryl bromide electrophile partners (Figure 2-8c).[87] Sulfonyl, sulfonamide, ketone, ester, amide, nitrile and trifluoromethyl groups are suitable activating moieties to enable cross-coupling reactivity of aryl acetates.

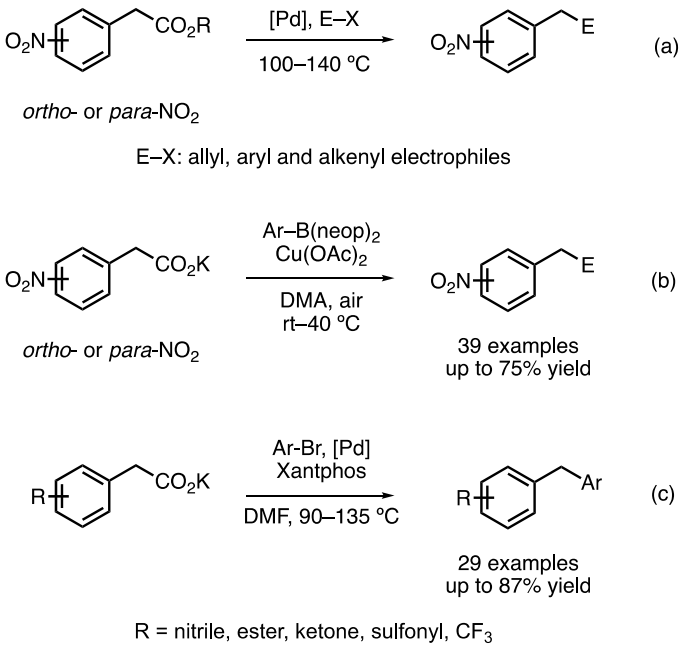


Figure 2-8 Employing aryl acetate as benzyl anion surrogate in metal-catalyzed cross-coupling reactions

Since we have obtained considerable knowledge on the behavior of aryl acetic acids in the context of CO_2 extrusion, we sought to develop asymmetric allylic benzylation reactions directly from aryl acetic acids, owing to the diverse utility of chiral allylated products and the wealth of information of transition metal catalysts that can affect allylation process.[88-89] After preliminary searching for established strategies to access this class of products, we discovered methods were limited to the use of toluene derivatives (p*K*a ≈ 44[90]) as precursors to generate reactive carbon anion. Those processes are well recognized as challenging reactions to develop as asymmetric allylic alkylations (AAAs) are favored with stabilized carbon or heteroatom nucleophiles, with conjugate acids' p*K*a less than 25.[91] Hence, much effort has been extended to stabilize the nucleophilic species, representatively through the addition of activating reagents (Figure 2-9a). Trost and co-workers reported Pd-catalyzed process employing 2-methyl pyridine derivatives or other nitrogen-containing aromatic heterocycle derivatives as carbon nucleophile precursor (Figure 2-9b).[92] The 'hard' nucleophiles are first reacted *in situ* with BF_3•OEt_2 by coordination, resulting in a complex with lower p*K*a value. Deprotonation of this complex with LiHMDS affords a 'soft' carbon anion that is readily intercepted by a Pd-allyl species in high enantioselectivity.

Following Trost's work, You's group reported an Ir-catalyzed strategy using the same nucleophile class and similar activating method to deliver chiral branched product (Figure 2-9c).[93] Despite these reactions successfully involve unstabilized carbon nucleophiles in metal-catalyzed AAA, the nucleophile scope is highly restricted to nitrogen-containing aromatic heterocycles where nitrogen is two bonds away from carbon anion center. The extremely basic condition resulting from the strong base LiHDMS further narrows the reaction scope, as protic and electrophilic groups will not be tolerated.

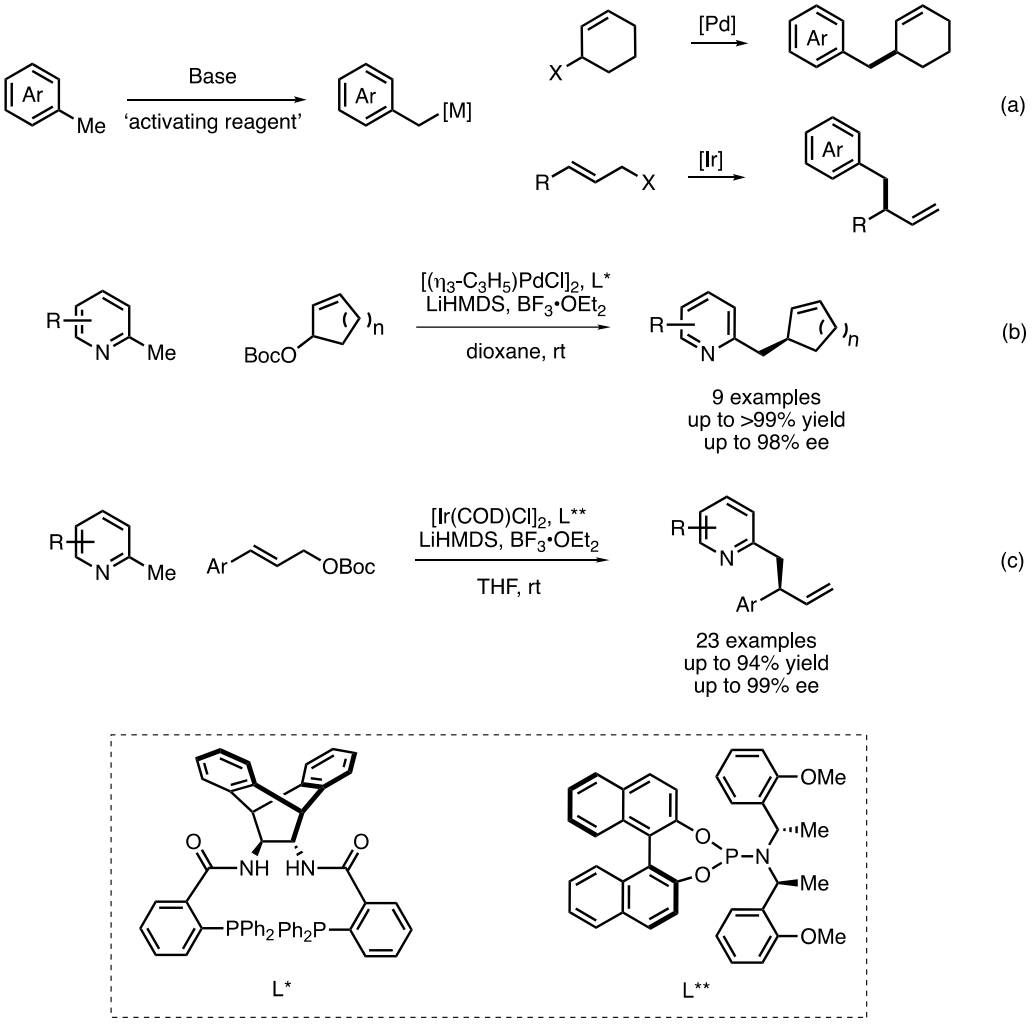


Figure 2-9 Asymmetric allylic benzylation employing 2-methylpyridine derivatives

To broaden the synthetic utility of Pd-catalyzed asymmetric allylic benzylation, a different activation strategy on toluene derivatives was exhibited by Walsh and co-workers (Figure 2-10).[94] By introducing η^6-aryl–$Cr(CO)_3$ complexes, the acidity of the benzylic C–H bonds is significantly decreased. The reactive carbanion would be formed *in situ* through the treatment with LiHMDS, then intercepted by electrophile partner to yield enantioriched product. This process requires stochiometric utilization of activating reagent $Cr(CO)_3$, imposing restriction on overall reaction economy and efficiency. Furthermore, decreased yield and erosion in enantioselectivity occurs during the removal of chromium.

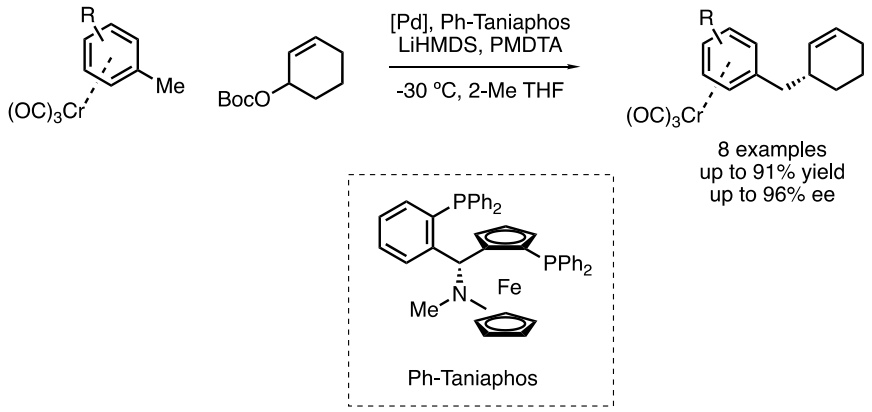


Figure 2-10 Asymmetric allylic benzylation employing toluene derivatives

General strategies for enantioselective allyl benzylation do not exist. We hypothesized aryl acetic acid could potentially be employed as benzyl anion surrogates in AAA reactions.

2.2 Optimization on Ir-Catalyzed Decarboxylative Enantioselective Benzylation

In 2017, Patrick Moon in our group discovered potassium nitrophenyl acetate can undergo stereocontrolled decarboxylative cross-coupling reaction with cinnamyl carbonate partner mediated by cyclometallated Ir-phosphoramidite catalyst,[95-96] delivering the benzylated C(sp^3)–C(sp^3) coupled product (**2.1**) in 58% yield and 95% enantiomer excess (Figure 2-11a). Even though product yield was moderate, the excellent enantioselectivity motivated us to further optimize the reaction conditions. I started to optimize the reaction conditions by repeating Patrick's reaction conditions. By monitoring the reaction progress through NMR experiment, a bis-allylation side-product (**2.2**) was observed in 20% yield, consuming 40% mass balance of allyl fragment. We proposed potassium nitrophenyl acetate was not well dissolved in DMA solvent and despite an excess amount (1.5 equiv.) of carboxylate partner was used, the concentration of allylic electrophile was likely greater in solution than that of the carboxylate nucleophile, resulting in double allylation. By monitoring this reaction by ^{1}H NMR, the formation of an allylic ester intermediate (**2.3**) was observed at the beginning of the reaction, possibly resulting from direct

nucleophilic addition of carboxylate to Ir-allyl species. This key observation led us to consider conducting such reaction from preformed allylic ester (**2.3**) as it would provide better solubility.

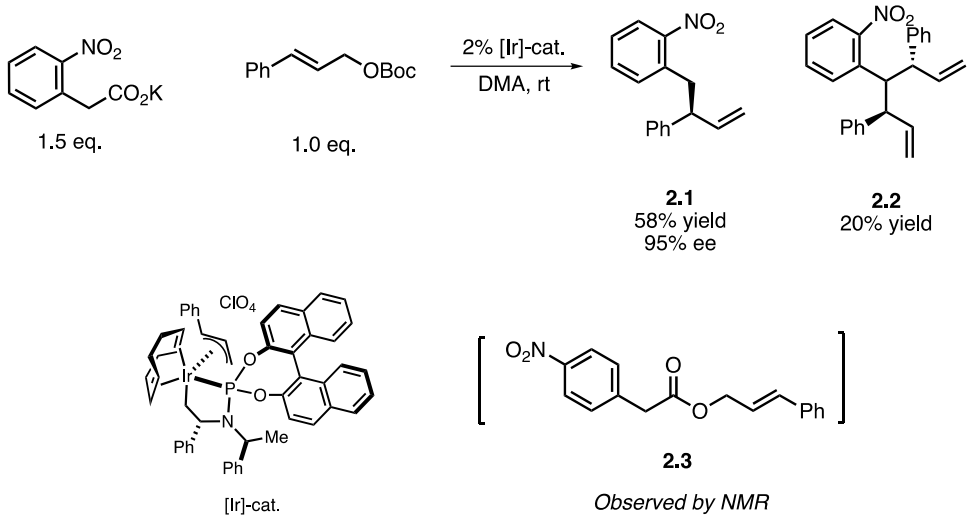
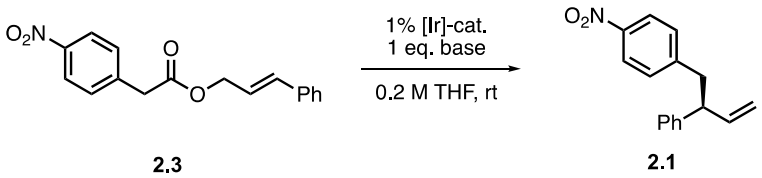


Figure 2-11 Discovery of Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

After screening against a variety of solvents (DMA, THF, DCM etc.) and organic bases, a combination of THF and DBU was discovered to yield **2.1** in 88% yield and 98% ee (Table 2-1, entry 1). DBU is an essential base for this process. Replacement with a similar base, DBN, resulted in slightly lower yield but still excellent enantioselectivity (Table 2-1, entry 2). Employing *t*-BuOK led to full conversion of **2.3**, however, did not afford any product (Table 2-1, entry 3). Under such condition we discovered the allylated carboxylate precursor (will be discussed later in **Section 2.3**) was poorly soluble in THF with potassium counter cation, hence was slow to decarboxylate. Weaker bases such as triethylamine and *N,N*-diisopropylethylamine showed poor reaction efficiency (low conversion of **2.3**) and did not provide any product (Table 2-1, entry 4, 5). Employing more polar solvent DMA resulted in reduced yield and more proto-decarboxylation side-product (4-nitrotoluene) since decarboxylation process was accelerated. The use of less polar

solvent DCM did not deliver any desired product as the carboxylate species would not decarboxylate.

Table 2-1 Effect of bases on Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles



2.3 **2.1**

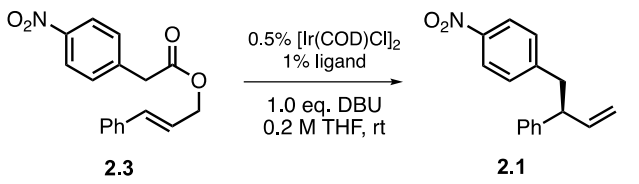
entry	base	conv. (%)	yield (%)	e.e. (%)	4-nitrotoluene(%)
1	**DBU**	**100**	**88**	**98**	**12**
2	DBN	100	76	98	23
3	t-BuOK	100	<3	nd	<3
4	NEt_3	65	<3	nd	<3
5	DIPEA	55	<3	nd	<3

Reactions performed on 0.10 mmol scale. Yields determined by calibrated ^{1}H NMR using durene as internal standard.

To quickly test the effect of chiral phosphoramidite ligands on reaction behavior, a ligand screen was conducted through *in situ* catalyst generation with $[Ir(COD)Cl]_2$ as precatalyst under otherwise standard conditions (Table 2-2). Since the activated catalyst was generated gradually with **L1**, reaction proceeded at a much slower rate and 4-nitrotoluene emerged competitively, hence the yield of **2.1** significantly decreased but the enantioselectivity remained excellent (Table 2-2, entry 1). This result indicated that enantioselectivity was well controlled by chiral phosphoramidite ligand, but product yield was dependent on reaction rates of proto-decarboxylation versus catalyst-mediated trapping. Higher concentration of activated catalyst would ensure sufficient Ir-allyl intermediate in solution that readily intercepted unstable carbanion. Employing other ligand variants (**L3**, **L4** and **L5**) afforded product in reduced yield and enantioselectivity (Table 2-2, entry 3–5). It is worthwhile to point out using an *ortho*-methoxy

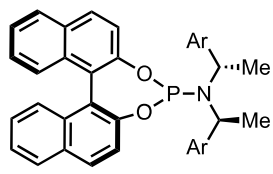
substituted variant **L2** provided desired product in good yield (80%) and increased enantioselectivity (Table 2-2, entry 2), in comparison with standard ligand **L1**. Noticing this excellent result, we believed preformed cyclometallated **[Ir]-2** complex would stand out to be a more efficient catalyst, especially for some challenging substrates that may fail with **L1**. As a result, activated catalysts (**[Ir]-1** and **[Ir]-2**, Figure 2-12) were both synthesized and used on a case-by-case basis.

Table 2-2 Effect of chiral ligands on Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

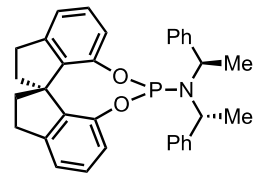


entry	ligand	conv. (%)	yield (%)	e.e. (%)	4-nitrotoluene(%)
1	L1	100	37	96	29
2	**L2**	**100**	**80**	**99**	**14**
3	L3	87	20	26	32
4	L4	27	<3	nd	8
5	L5	25	<3	nd	12

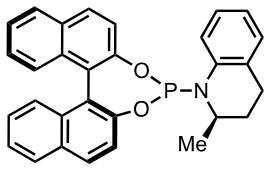
Reactions performed on 0.10 mmol scale. Yields determined by calibrated ^{1}H NMR using durene as internal standard.



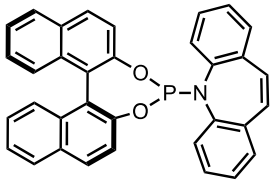
(S_a, S)-L1: Ar = Ph
(S_a, S)-L2: Ar = o-MeOPh



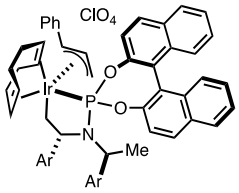
(S_a, R)-L3



(S_a, R)-L4



(S_a)-L5



[Ir]-1 Ar = Ph
[Ir]-2 Ar = 2-(OMe)C_6H_4

Figure 2-12 Activated Ir-catalysts utilized in decarboxylative enantioselective benzylation of allylic electrophiles

Since allylic ester **2.3** can be formed *in situ* as we previously observed, we also sought to diversify synthetic route to access desired product **2.1** by directly employing aryl acetic acid and

allylic carbonate. However, reduced yield and more proto-decarboxylation side-product was observed with **[Ir]-1** catalyst as additional proton source presented in reaction mixture. To facilitate Ir-allyl interception process over proto-decarboxylation, use of the more efficient **[Ir]-2** catalyst resulted in as excellent yield and enantioselectivity (Figure 2-13b). A combination of aryl acetic acid and allylic carbonate or allylic aryl acetate ester can be employed as substrate components. The alcohol activation step (carbonate vs ester) provides additional flexibility in substrate preparation. The preformed ester strategy (Figure 2-13a) bears several advantages in good atom-economy, low catalyst loading and inexpensive ligand cost, whereas the acid/carbonate pathway (Figure 2-13b) is more efficient to prepare enantiopure products with various benzyl partners simultaneously from diverse commercially available aryl acetic acids, without taking additional step to make allylic ester.

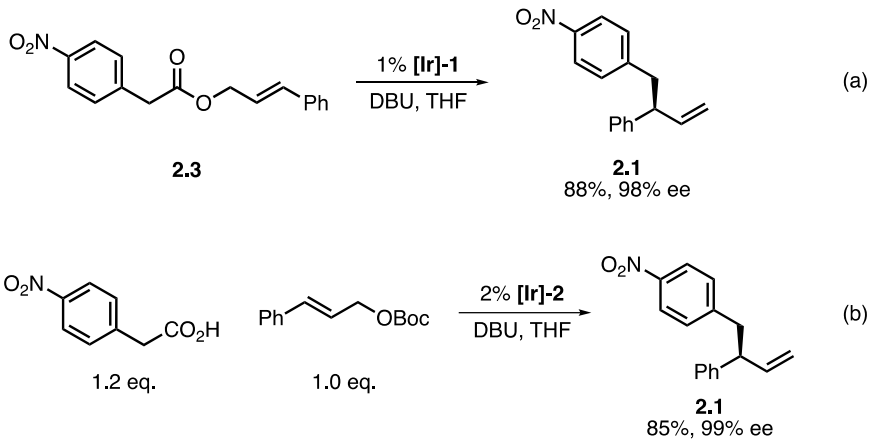


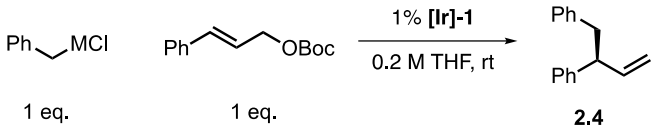
Figure 2-13 Two pathways to conduct Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

2.3 Mechanistic Study on Ir-Catalyzed Decarboxylative Enantioselective Benzylation

To obtain mechanistic insight into key decarboxylation step (decarboxylation prior to or after cross-coupling event), reactions were conducted with preformed benzyl nucleophiles (benzyl-

Grignard and zinc reagents). In both cases, low yield of product (**2.4**) was observed (Table 2-3). Linear allylic product was predominant over desired branched product.

Table 2-3 Employing preformed benzyl nucleophiles in Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles



entry	metal	conv. E^+(%)	yield (%)	l/b
1	Mg	28	40	4
2	Zn	50	16	3

Reactions performed on 0.10 mmol scale. Yields determined by calibrated ^{1}H NMR using durene as internal standard.

Extrusion of CO_2 could occur post cross-coupling event, in which case the enolized aryl acetic esters would behave as actual nucleophiles. There are reports indicating that deprotonated aryl acetic esters are suitable nucleophile partners in Ir-catalyzed asymmetric allylic allylations.[97-98] To confirm that esters similar in structure are suitable nucleophilic precursors under our conditions, reaction was carried out with methyl aryl acetate (**2.5**) that would not undergo decarboxylation. As a result, allylated enolate was observed as a mixture of diastereomers (**2.6**), with high enantioselectivity at allylic position (Figure 2-14). This observation solidifies that decarboxylation can be the terminal event.

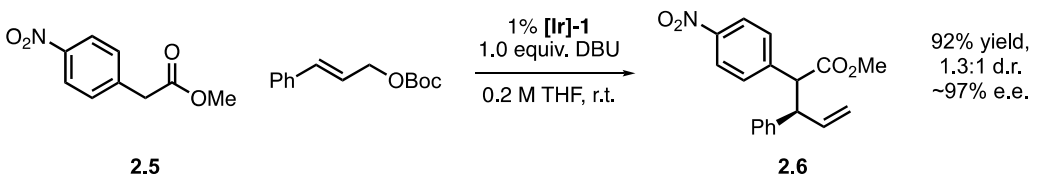


Figure 2-14 Employing methyl aryl acetate in Ir-catalyzed asymmetric allylic allylations

After discovering that decarboxylation was a terminal event in our approach, we noticed that there was possibility that reaction undergoes intramolecular allyl fragment transfer through Ireland-Claisen rearrangement,[76] delivering carboxylate precursor **2.7** without nucleophilic addition process (Figure 2-15). To elucidate the operating mechanism, a crossover experiment was carried out by treating two allylic aryl acetates (**2.8** and **2.9**) with different portions of aryl units and allyl fragments (Figure 2-16). All four possible combinations **2.1, 2.10–2.12** were formed, excluding the possibility of Ireland-Claisen rearrangement mechanism.

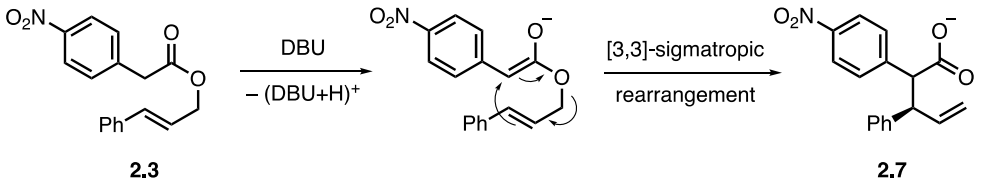


Figure 2-15 Potential Ireland-Claisen rearrangement process in Ir-catalyzed enantioselective decarboxylative allylations

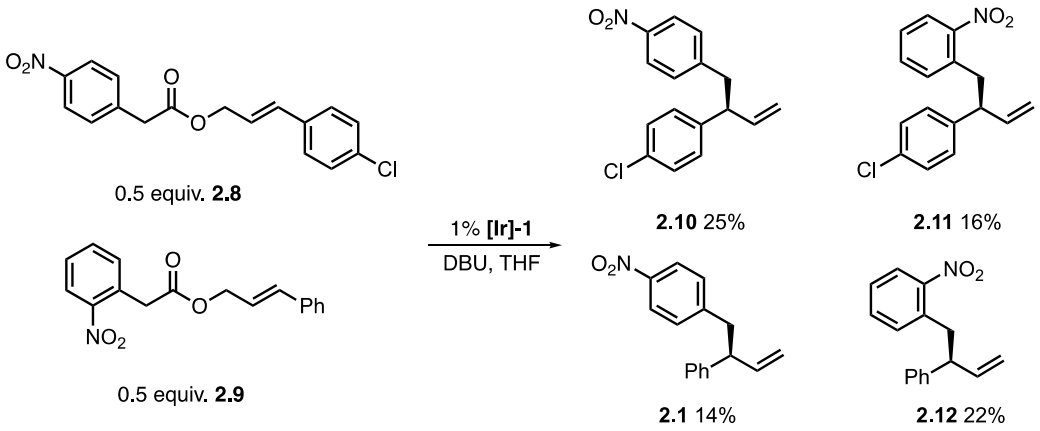


Figure 2-16 Crossover experiment between allylic aryl acetates bearing different aryl and cinnamyl units

The mechanism of this process was further clarified by Patrick Moon through studying the kinetic profile of the reaction with allylic 4-cyanophenyl acetate (**2.13**). By carefully monitoring the reaction progress by ^{1}H NMR, the *C,O*-bis-allylic ester (**2.14**) was observed along with the

decay of starting material **2.13**, which suggested **2.13** was deprotonated first to form the corresponding enolate, then captured by Ir-allyl affording **2.14**.

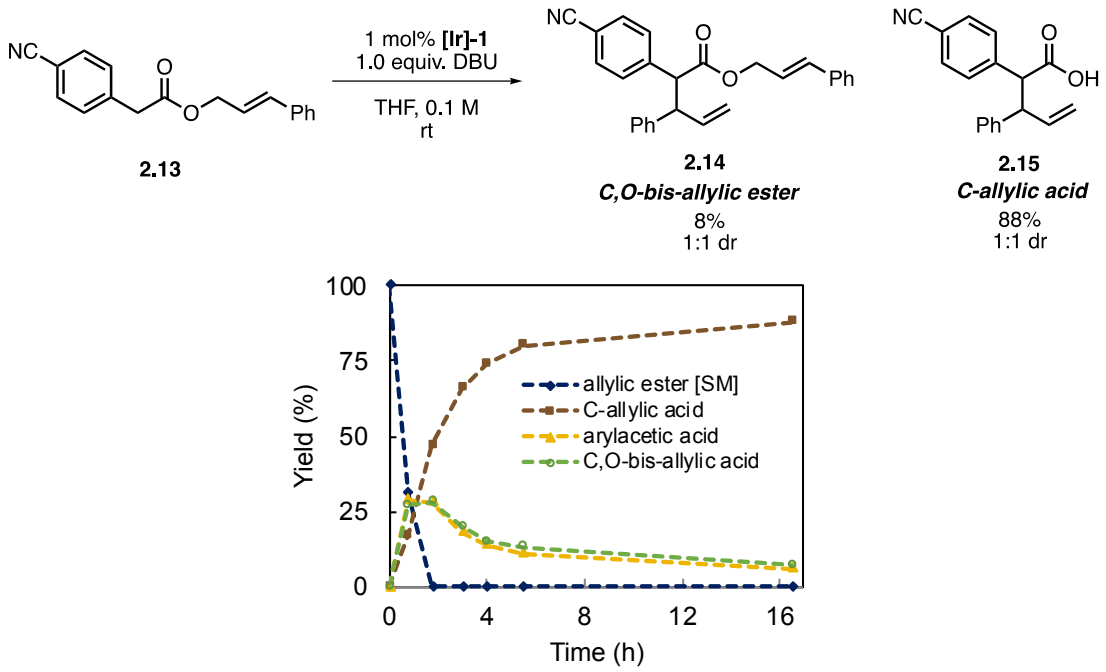


Figure 2-17 Kinetic profile of Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

Based on previously demonstrated mechanistic studies, a mechanistic hypothesis for this process is brought forward (Figure 2-18). Ir-catalyzed reversible *O*-allylation of carboxylate is fast and generates the thermodynamically more stable linear allylic aryl acetate. This species could undergo a second Ir-catalyzed allylic substitution at enolate position to form a *C,O*-bis-allylated ester (**2.14**) as an ultimately inconsequential mixture of diastereomers with high enantioselectivity at the allylic position. Reversible *O*-deallylation via oxidative insertion would deliver a new Ir-allyl fragment for re-entry into the catalytic cycle and liberate the *C*-allylated carboxylic acid (**2.15**). At this stage, decarboxylation event would lead to the chiral benzylated product. This terminal event can occur spontaneously for nitro-activated aryl groups, otherwise extrusion of CO_2

can easily be induced through introducing thermal energy for substrates with moderately activated aryl groups, namely heating the reaction mixture for a short period.

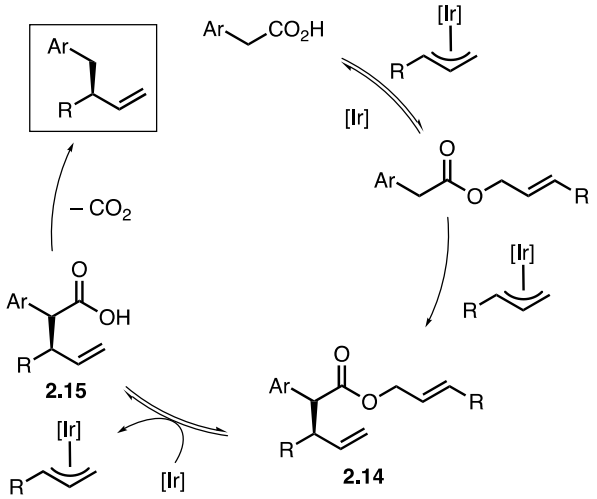


Figure 2-18 Mechanistic hypothesis for Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

2.4 Additive Screen of Ir-Catalyzed Decarboxylative Enantioselective Benzylation

Since the benzylation process involves a stereoselective bond-forming process prior to extrusion of CO_2, the system should have broad functional group compatibility. To quickly test this hypothesis, reactions were conducted under standard conditions with a variety of additives bearing unique functional group units (Figure 2-19). Encouragingly, reactions proceeded with similar yields and enantioselectivities in the presence of protic and electrophilic groups (aldehyde, ketone, free NH-groups, water, phenol, 5% EtOH by volume, alkyl alcohol, conjugate acceptors, alkyl chloride). Weak nucleophiles such as tosylamide can survive. Aryl halides that could undergo oxidative addition and nitrogen-containing heterocycles that can poison Ir-catalyst are compatible under reaction conditions. Furthermore, the enantioselective cross-coupling process occurs chemoselectively at the activated aryl acetic acids over alternative acid classes, such as benzoic

acid, bulky alkyl acid, phenyl acetic acid. Although *O*-allylation still happens with these acids, the metal-allyl species can be recovered since this process is reversible. Finally, several bioactive small organic molecules including caffeine, sugars, amino acids were also confirmed to be compatible.

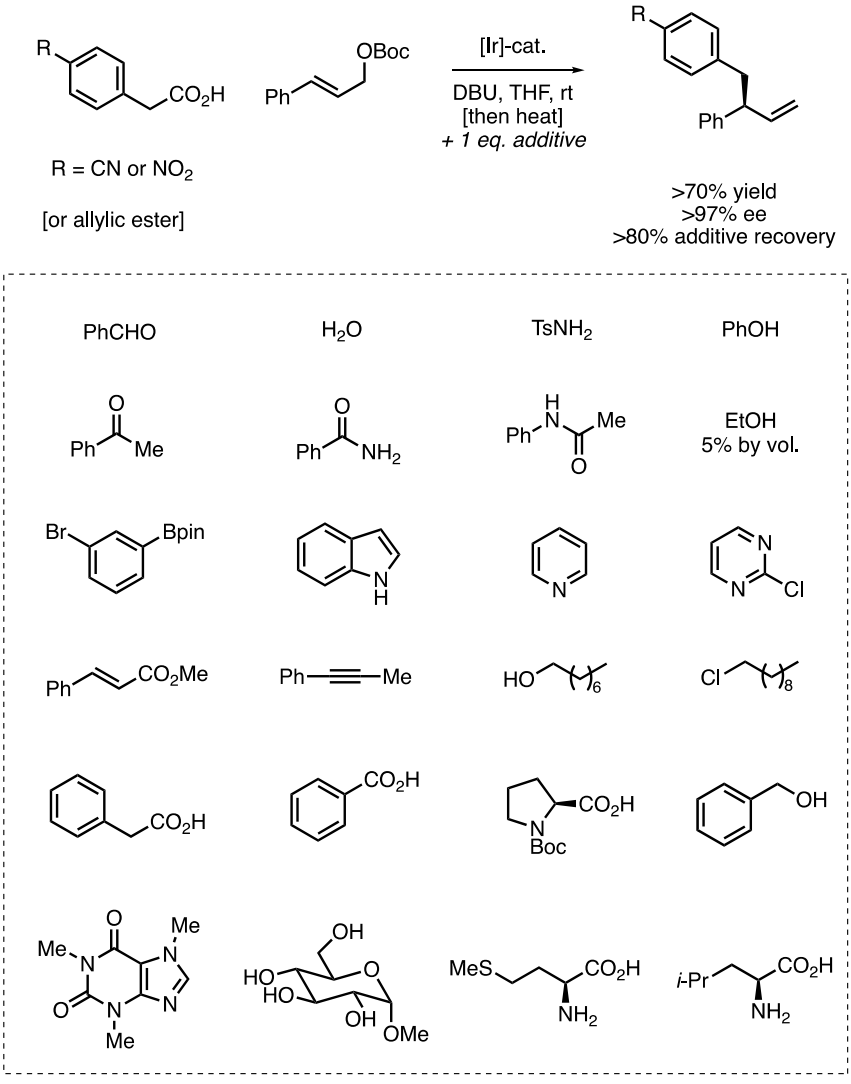


Figure 2-19 Functional group compatibility screen of Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

2.5 Reaction Scope of Ir-Catalyzed Decarboxylative Enantioselective Benzylation

The broad scope of our approach has been demonstrated with diverse activating groups on aryl acetate partners. Under standard reaction conditions, uniformly high enantioselectivities (97–99%) are observed, including strongly activating substituents *para*- and *ortho*-nitro (**2.1**, **2.12**), moderate activating functionalities cyano (**2.16**, **2.23**), sulfonyl (**2.17**), trifluoromethyl (**2.18**), *N*-heterocycles (**2.19–2.21**). Substrates bearing potentially reactive electrophilic or protic groups (**2.22**, **2.24**) are tolerated. It's worthwhile to point out catalyst loading as low as 0.1 mol% could be used in some cases (**2.1**).

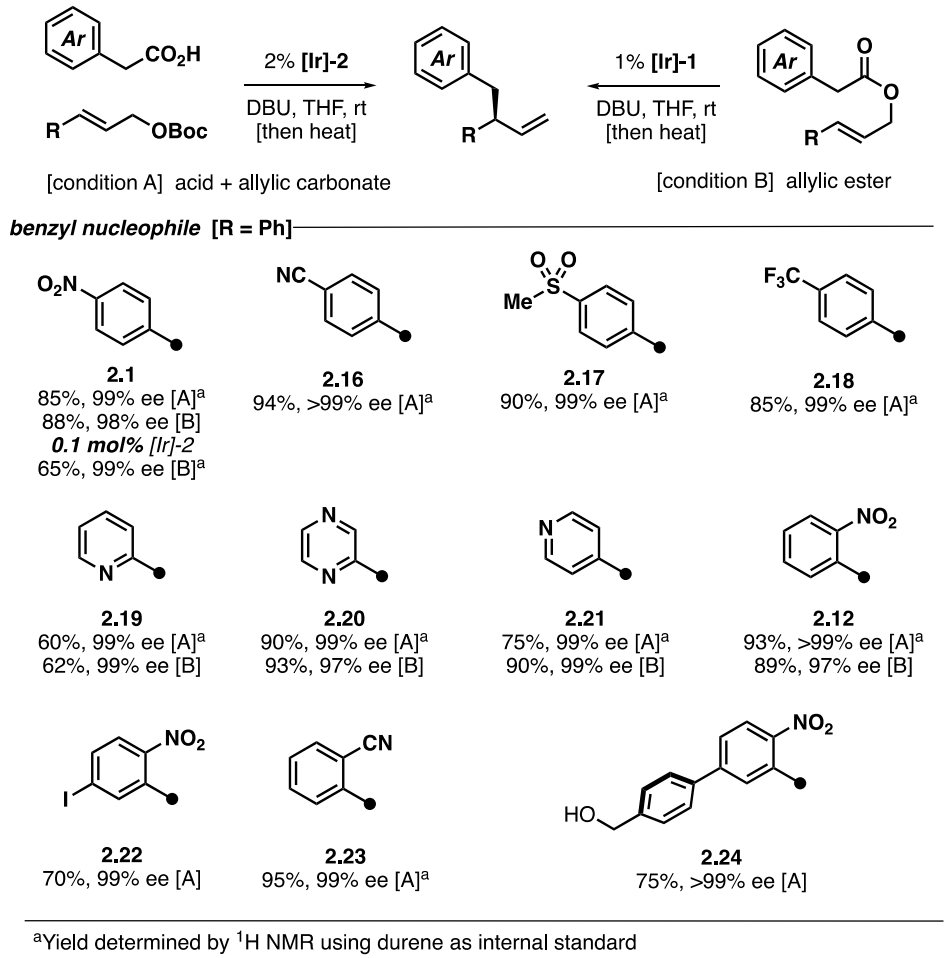
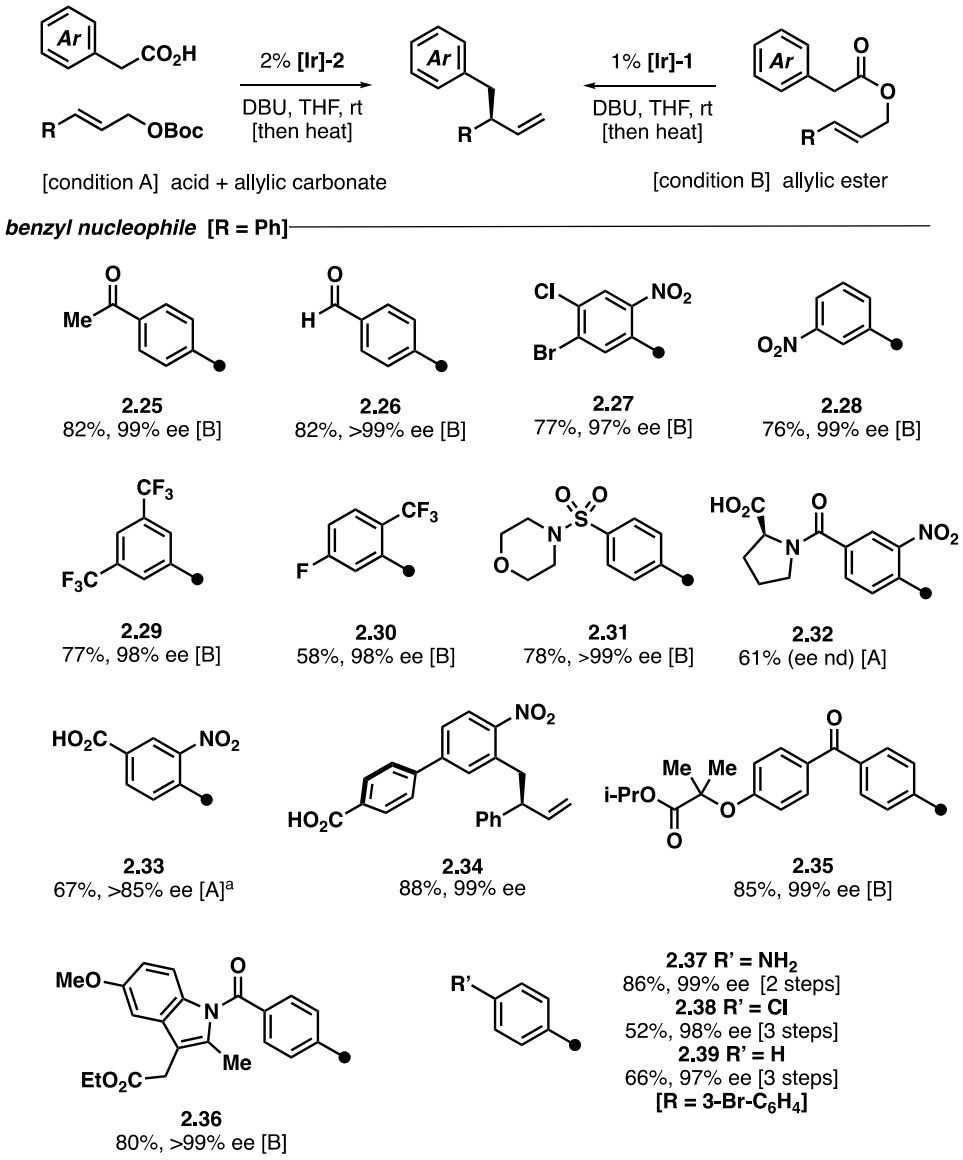


Figure 2-20 Benzyl partner scope of Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

Meanwhile, Patrick Moon finalized exhibiting scope of benzyl partners with comprehensive functional groups units (Figure 2-21). Additional electrophilic groups including ketone (**2.25**), aldehyde (**2.26**) and aryl halide (**2.27**) are tolerated. Weak activating groups such as 3-nitro (**2.28**), CF_3 (**2.29, 2.30**) and sulfonyl amide (**2.31**) are suitable partners in our approach. Substrates containing other carboxylic acids (**2.32–2.34**) are cross-coupled at the benzylic position



[a]Yield determined by ^{1}H NMR using durene as internal standard

Figure 2-21 Additional benzyl partner scope screened by Patrick Moon

without interfering with benzoic or alkyl acid units as they do not present enolizable carbons and *O*-allylation is reversible. Complex functionalities derivatized from fenofibrate (**2.35**) and indomethacin (**2.36**) are not affected, indicating the potential broad utility of our approach in medicinal chemistry. Substrates bearing worse activating groups might be resistant to decarboxylative coupling under standard condition, but can be accessed in reasonable yield by nitro group manipulations (**2.37–2.39**).

The allyl fragment can vary in structure and also host a number of potentially reactive functional groups (Figure 2-22). Electron donating groups (**2.40, 2.42**), electro withdrawing groups (**2.41**), halogens (**2.10, 2.44–2.46**), NH-groups (**2.42**), *N*- and *S*-heterocycles (**2.47, 2.48**) are displayed in the scope table. Alkyl substituted allylic electrophiles are typically considered to be challenging partners in similar processes,[99] but are competent in our approach, including simple methyl (**2.51**–**2.54**), long-chain (**2.49, 2.55**), heteroatom-substituted alkyl (**2.50, 2.56**) and propenyl unit (**2.57**) from regioselective addition of activated sorbic alcohol.

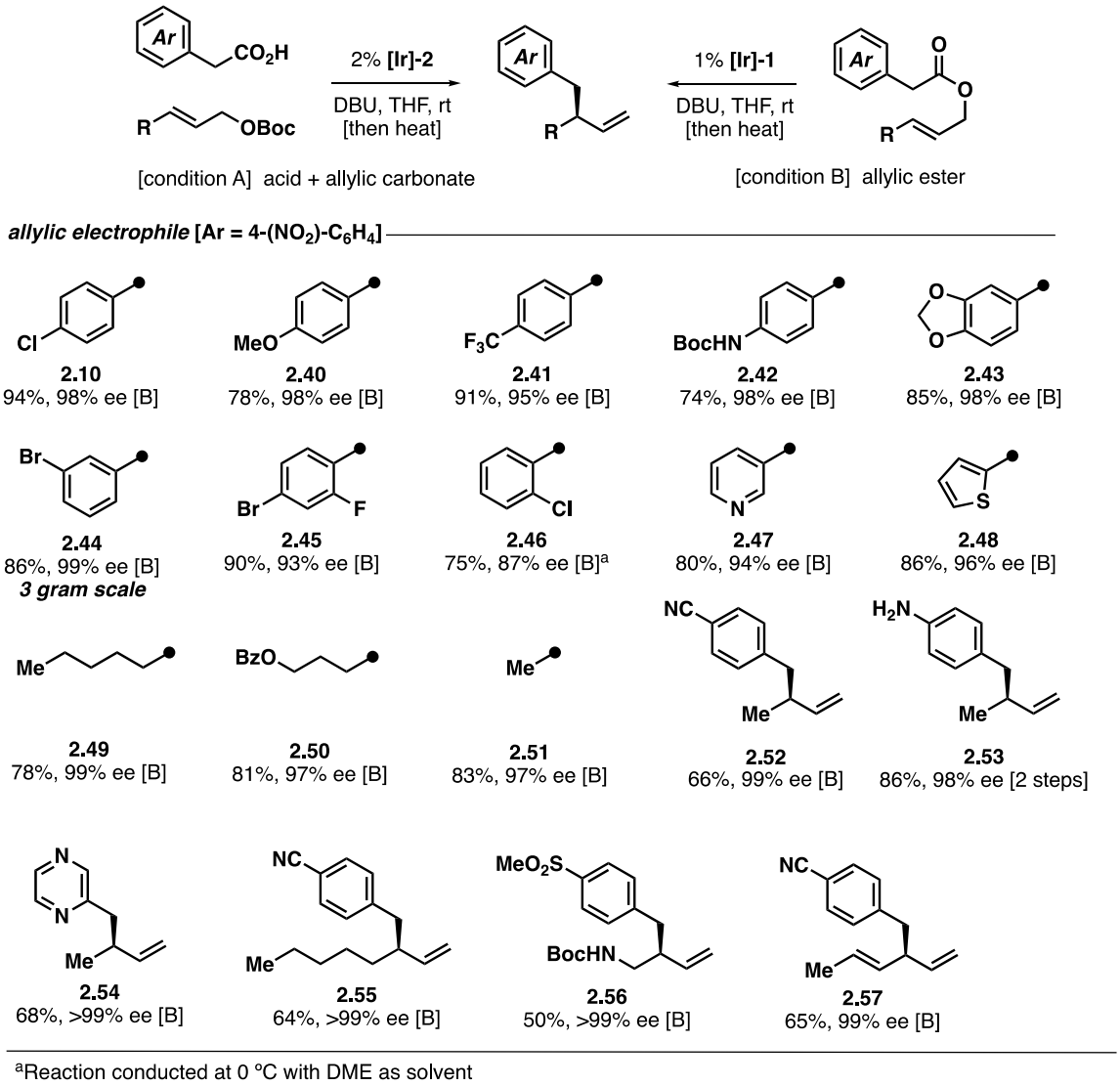


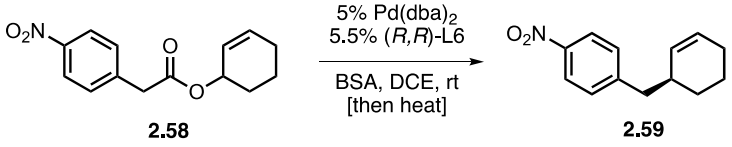
Figure 2-22 Allylic partner scope of Ir-catalyzed decarboxylative enantioselective benzylation of allylic electrophiles

2.6 Optimization on Pd-Catalyzed Decarboxylative Enantioselective Benzylation

After the discovery on Ir-catalyzed process, we hypothesized employing aryl acetic acid as benzyl nucleophile surrogate would be a general strategy in asymmetric allylic alkylation, which could be demonstrated by Pd-catalyzed benzylation of cyclic allylic electrophiles. Optimization reactions were conducted on **2.58** under conditions varying in temperature, solvent, base and Trost-

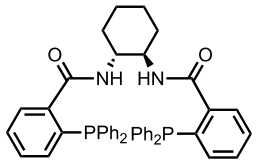
type ligand (Table 2-4).[100] Employing a combination of DACH-phenyl Trost ligand (**L6**), DCE, BSA and 0 ºC provided the optimal enantioselectivity (Table 2-4, entry 2).

Table 2-4 Condition optimization on Pd-catalyzed decarboxylative enantioselective benzylation

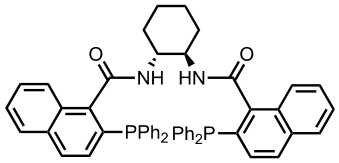


entry	derivation from above	yield (%)	ee(%)
1	none	>95	86
2	0 ºC instead of rt	77[a]	90
3	THF instead of DCE	>95	38
4	toluene instead of DCE	>95	74
5	DBU instead of BSA	15	nd
6	L7 instead of L6	54	87
7	L8 instead of L6	20	40

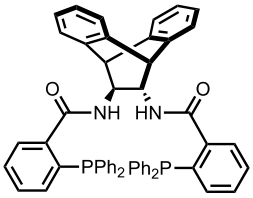
Reaction performed on 0.10 mmol scale at 0.3 M using 1.1 equiv. BSA; yields determined by calibrated ^{1}H NMR using durene as internal standard. [a]Isolated yield.



(*R,R*)-L6



(*R,R*)-L7



(*S,S*)-L8

2.7 Reaction Scope of Pd-Catalyzed Decarboxylative Enantioselective Benzylation

Pd-catalyzed processes can be used to access benzylated cyclic allylic stereocenters with slightly lower selectivity (83–91% ee), but similarly broad scope of aryl acetic acid partner from either allylic carbonate electrophiles or preformed allylic esters (Figure 2-23, **2.59**–**2.64**).

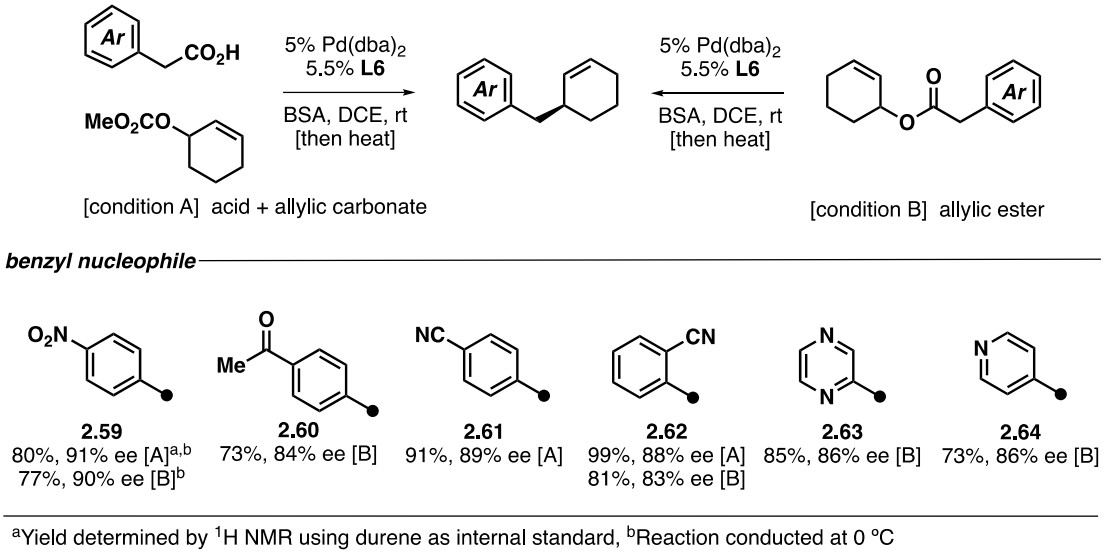


Figure 2-23 Benzyl partner scope of Pd-catalyzed decarboxylative enantioselective benzylation

2.8 Less Successful Substrates for Decarboxylative Enantioselective Benzylation

Our approach exhibited some limitations during the course of scope studies (Figure 2-24). Substrates with trisubstituted allylic units (**2.65, 2.66**) cannot undergo efficient decarboxylative benzylation process, probably resulting from steric repulsion between bulky methyl substituent and iridium catalyst.[101-102] Allylic partners bearing highly electron-deficient aryl groups (**2.67**) led to large amount of styrene side product through fast isomerization of the branched product, as the allylic proton is more acidic. Substrates **2.68** can undergo oxidative addition, yet much slower without activating groups. Substrates **2.69** contains a steric bulky methyl substitution at the reactive benzylic position, therefore, trapping of the corresponding enolate is inefficient. Competitive elimination product was observed with allylic aryl acetate containing alkyl bromide (**2.70**). Cinnamyl unit bearing steric bulky substitution at *ortho*-position (**2.71**) afforded product in slower rate and reduced enantioselectivity. Sterically bulky **2.72** and **2.73** would deliver benzylated cyclohexene in low enantioselectivity. Conducting the reaction with benzyl substituted diene as electrophile partner (**2.74**) yielded a mixture of regioisomers. Furthermore, allylic units with alkyl-

OH functionality (**2.75**) provided vinyl-THF as a major product, through a more favorable intramolecular *O*-allylation process.

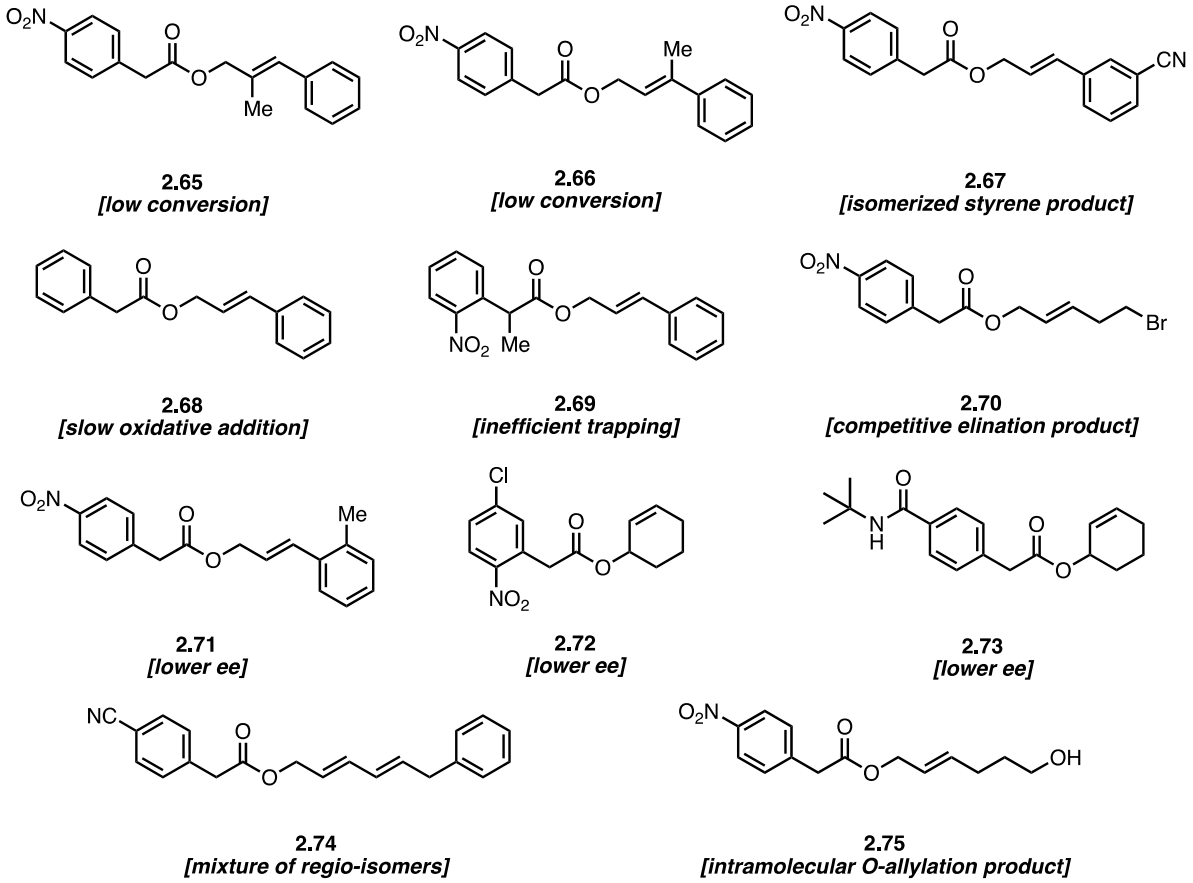


Figure 2-24 Less successful substrates for decarboxylative enantioselective benzylation

2.9 Summary

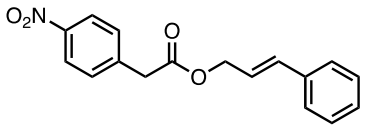
The decarboxylative enantioselective benzylation of allylic electrophiles, directly from aryl acetic acids has been established. This process can either be catalyzed by cyclometallated Ir-phosphoramidite catalyst or Pd-precatalyst with a Trost-type chiral phosphine ligand. Reactions can be performed from either free acids and carbonates or from allylic aryl acetate esters, differentiating the possible synthetic routes. Mechanistic studies revealed the process proceeded through a functionalization then decarboxylation pathway, showing the advantage of broad

functional group compatibility (protic and electrophilic groups), which has not been achieved via established strategies.

2.10 Procedure and Characterization

2.10.1 General Procedure for Starting Material Synthesis

General Procedure: [EDC Coupling] To a flask charged with stir bar and purged with N_2 was added EDCl (1.2 equiv.), DCM (0.2 M), alcohol (1.0 equiv.) and DMAP (0.2 equiv.). The solution was cooled to 0° C and aryl acetic acid (1.2 equiv.) was added in one portion. The mixture was warmed to room temperature and stirred overnight. Upon completion of the reaction, the mixture was washed sequentially with 1 M HCl, water and brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by silica gel chromatography.

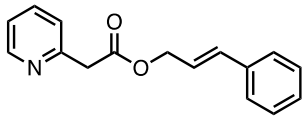


2.3 Prepared according to the General Procedure from the corresponding allylic alcohol (1.34 g, 10.0 mmol, 1.0 equiv.) and aryl acetic acid (2.17 g, 12.0 mmol, 1.2 equiv.). Isolated in 87% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.2 (m, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 (m, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.78 (d, *J* = 6.5 Hz, 2H), 3.78 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 147.3, 141.2, 136.0, 135.0, 130.4, 128.7, 128.3, 126.7, 123.8, 122.5, 66.0, 41.1;

HRMS (ESI): calcd for $C_{17}H_{14}NO_4$ $[M-H]^-$: 296.0928. Found 296.0931.

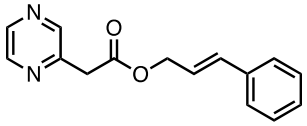


2.76 Prepared according to the General Procedure from the corresponding allylic alcohol (0.34 g, 2.5 mmol, 1.0 equiv.), aryl acetic acid • HCl (0.52 g, 3.0 mmol, 1.2 equiv.) and additional Et_3N (0.42 ml, 3.0 mmol, 1.2 equiv.). Washed twice with water instead of 1 M HCl in work-up. Isolated in 98% yield after purification by silica gel chromatography (20:1 DCM:MeOH) as a brown oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.58 (d, *J* = 4.9 Hz, 1H), 7.66 (dt, *J* = 1.7, 7.7 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.31 (m, 3H), 7.26 (m, 1H), 7.20 (dd, *J* = 5.2, 7.2 Hz, 1H), 6.62 (d, *J* = 16.4 Hz, 1H), 6.28 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.80 (dd, *J* = 1.2, 6.5 Hz, 2H), 3.91 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.5, 154.4, 149.6, 136.7, 136.3, 134.3, 128.6, 128.1, 126.7, 123.9, 123.0, 122.2, 65.6, 44.0;

HRMS (ESI): calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$: 254.1176. Found 254.1174.

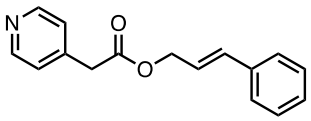


2.77 Prepared according to the General Procedure from the corresponding allylic alcohol (0.27 g, 2.0 mmol, 1.0 equiv.) and aryl acetic acid (0.30 g, 2.2 mmol, 1.1 equiv.). Washed twice with water instead of 1 M HCl in work-up. Isolated in 85% yield after purification by silica gel chromatography (1:1 hexane:EtOAc) as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.62 (d, *J* = 1.3 Hz, 1H), 8.55 (dd, *J* = 1.6, 2.4 Hz, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 7.38 (m, 2H), 7.32 (m, 2H), 7.27 (m, 1H), 6.64 (d, *J* = 16.4 Hz, 1H), 6.27 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.81 (dd, *J* = 1.2, 6.5 Hz, 2H), 3.93 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.5, 150.3, 145.4, 144.3, 143.3, 136.1, 134.8, 128.7, 128.2, 126.7, 122.6, 66.0, 41.3;

HRMS (ESI): calcd for $C_{15}H_{15}N_2O_2$ $[M+H]^+$: 255.1128. Found 255.1128.

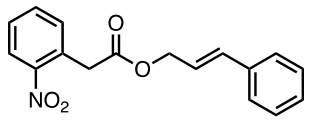


2.78 Prepared according to the General Procedure from the corresponding allylic alcohol (0.34 g, 2.5 mmol, 1.0 equiv.), aryl acetic acid • HCl (0.52 g, 3.0 mmol, 1.2 equiv.) and additional Et_3N (0.42 ml, 3.0 mmol, 1.2 equiv.). Isolated in 79% yield after purification by silica gel chromatography (1:2 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.57 (dd, *J* = 1.6, 4.4 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 (m, 1H), 7.25 (d, *J* = 5.7 Hz, 2H), 6.63 (d, *J* = 16.4 Hz, 1H), 6.26 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.78 (dd, *J* = 1.2, 6.5 Hz, 2H), 3.67 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.9, 150.1, 142.7, 136.1, 134.8, 128.7, 128.3, 126.7, 124.6, 122.6, 65.9, 40.7;

HRMS (ESI): calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$: 254.1176. Found 254.1177.

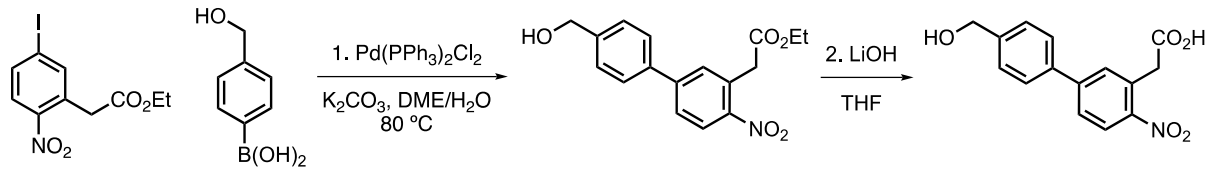


2.9 Prepared according to the General Procedure from the corresponding allylic alcohol (1.34 g, 10.0 mmol, 1.0 equiv.) and aryl acetic acid (2.17 g, 12.0 mmol, 1.2 equiv.). Isolated in 64% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.37 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.25 (m, 1H), 6.63 (d, *J* = 16.4 Hz, 1H), 6.27 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.78 (d, *J* = 6.5 Hz, 2H), 4.08 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.7, 148.8, 136.2, 134.4, 133.5, 133.3, 129.7, 128.6(2), 128.1, 126.6, 125.3, 122.7, 65.8, 39.8;

HRMS (ESI): calcd for $C_{17}H_{14}NO_4$ $[M-H]^-$: 296.0928. Found 296.0929.



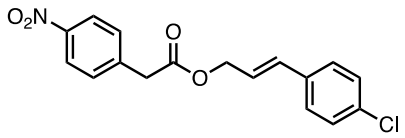
2.79 *Step 1.* To a flask charged with stir bar was added ethyl (5-iodo-2-nitrophenyl)acetate (335.1 mg, 1.0 mmol, 1.0 equiv.), 4-hydroxymethylphenylboronic acid (182.4 mg, 1.2 mmol, 1.2 equiv.), $Pd(PPh_3)_2Cl_2$ (21.0 mg, 0.03 mmol, 0.03 equiv.) and potassium carbonate (345.5 mg, 2.5 mmol, 2.5 equiv.). The flask was flushed with 3 × N_2, followed by the addition of DME (3 mL) and water (0.4 mL). The reaction mixture was heated at 80° C for 2 h. Upon completion of the reaction, the reaction mixture was concentrated *in vacuo*, transferred to EtOAc/brine mixture to extract. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by silica gel chromatography (1:1 hexane:EtOAc). Isolated in 83% yield as a yellow oil.

Step 2. To a flask charged with stir bar was added the bi-aryl intermediate from from *Step 1.* (261.7 mg, 0.83 mmol, 1.0 equiv.), THF (4 mL) and 2 M LiOH solution (2 mL). The mixture was stirred at rt overnight. Upon completion of the reaction, the mixture was acidified with concentrated HCl to pH = 1. The mixture was extracted with EtOAc, dried over Na_2SO_4, concentrated *in vacuo*. Isolated in 90% yield as a pale yellow solid.

^{1}H NMR (CD_3OD, 700 MHz) δ 8.19 (d, *J* = 8.5 Hz, 1H), 7.77 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 7.71 (m, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 4.66 (s, 2H), 4.12 (s, 2H);

^{13}C NMR (CD_3OD, 176 MHz) δ 174.0, 149.0, 147.5, 143.7, 138.7, 133.0, 132.6, 128.6, 128.4, 127.6, 126.8, 64.7, 40.7;

HRMS (ESI): calcd for $C_{14}H_{12}NO_3$ $[M\text{-}H\text{-}CO_2]^-$: 242.0823. Found 242.0820.

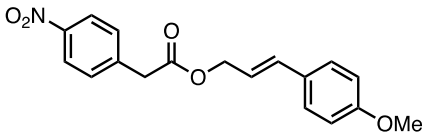


2.8 Prepared according to the General Procedure from the corresponding allylic alcohol (0.52 g, 3.1 mmol, 1.0 equiv.) and aryl acetic acid (0.67 g, 3.7 mmol, 1.2 equiv.). Isolated in 83% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.30 (s, 4H), 6.58 (d, *J* = 16.4 Hz, 1H), 6.23 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.77 (dd, *J* = 1.1, 6.5 Hz, 2H), 3.78 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 147.3, 141.2, 134.5, 134.1, 133.6, 130.4, 128.9, 127.9, 123.9, 123.2, 65.8, 41.0;

HRMS (ESI): calcd for $C_{17}H_{13}ClNO_4$ $[M\text{-}H]^-$: 330.0539. Found 330.0539.

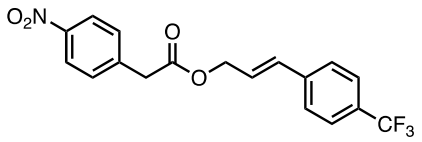


2.80 Prepared according to the General Procedure from the corresponding allylic alcohol (0.43 g, 2.6 mmol, 1.0 equiv.) and aryl acetic acid (0.56 g, 3.1 mmol, 1.2 equiv.). Isolated in 75% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 16.4 Hz, 1H), 6.12 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.75 (dd, *J* = 1.1, 6.5 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 159.8, 141.3, 134.8, 130.4, 130.3, 128.7, 128.0, 123.8, 120.1, 114.1, 66.3, 55.4, 41.1;

HRMS (ESI): calcd for $C_{18}H_{16}NO_5$ $[M-H]^-$: 326.1034. Found 326.1036.



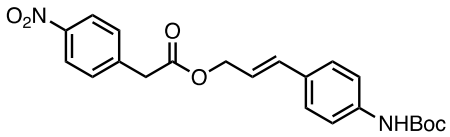
2.81 Prepared according to the General Procedure from the corresponding allylic alcohol (1.01 g, 5.0 mmol, 1.0 equiv.) and aryl acetic acid (1.09 g, 6.0 mmol, 1.2 equiv.). Isolated in 78% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 6.65 (d, *J* = 16.4 Hz, 1H), 6.35 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.80 (d, *J* = 6.5 Hz, 2H), 3.80 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 169.9, 147.4, 141.1, 139.5 (q, *J* = 1.0 Hz), 133.1, 130.4, 130.1 (q, *J* = 32.2 Hz), 126.8, 125.7 (q, *J* = 3.8 Hz), 125.3, 124.1 (q, *J* = 271.6 Hz), 123.9, 65.5, 41.0;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.6 (s);

HRMS (ESI): calcd for $C_{18}H_{13}F_3NO_4$ $[M-H]^-$: 364.0802. Found 364.0802.

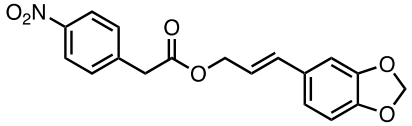


2.82 Prepared according to the General Procedure from the corresponding allylic alcohol (0.28 g, 1.9 mmol, 1.0 equiv.) and aryl acetic acid (0.42 g, 2.3 mmol, 1.2 equiv.). Isolated in 42% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.20 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.29 (m, 4H), 6.57 (d, *J* = 15.4 Hz, 1H), 6.48 (br, 1H), 6.16 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.75 (dd, *J* = 1.0, 6.5 Hz, 2H), 3.77 (s, 2H), 1.52 (s, 9H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 152.6, 147.3, 141.3, 138.5, 134.6, 130.8, 130.4, 127.4, 123.8, 121.0, 118.5, 80.8, 66.2, 41.1, 28.4;

HRMS (ESI): calcd for $C_{22}H_{23}N_2O_6$ $[M-H]^-$: 411.1562. Found 411.1561.

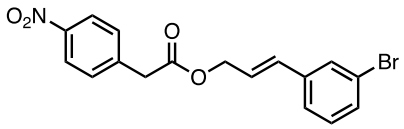


2.83 Prepared according to the General Procedure from the corresponding allylic alcohol (0.89 g, 5.0 mmol, 1.0 equiv.) and aryl acetic acid (1.09 g, 6.0 mmol, 1.2 equiv.). Isolated in 51% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 1.6 Hz, 1H), 6.80 – 6.75 (m, 2H), 6.54 (d, *J* = 15.6 Hz, 1H), 6.08 (dt, *J* = 6.5, 15.8 Hz, 1H), 5.96 (s, 2H), 4.73 (dd, *J* = 1.0, 6.5 Hz, 2H), 3.76 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.0, 148.2, 147.9, 141.3, 134.9, 130.4 (2), 124.4, 123.8, 121.7, 120.6, 108.4, 105.8, 101.3, 66.1, 41.1;

HRMS (ESI): calcd for $C_{18}H_{14}NO_6$ $[M-H]^-$: 340.0827. Found 340.0829.

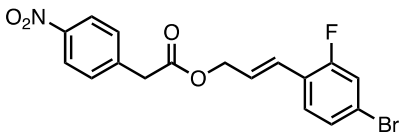


2.84 Prepared according to the General Procedure from the corresponding allylic alcohol (2.56 g, 12.0 mmol, 1.0 equiv.) and aryl acetic acid (2.61 g, 14.4 mmol, 1.2 equiv.). Isolated in 83% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.52 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.27 (m, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.26 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.77 (dd, *J* = 1.3, 6.1 Hz, 2H), 3.78 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.9, 147.3, 141.1, 138.2, 133.2, 131.2, 130.4, 130.2, 129.5, 125.4, 124.2, 123.9, 122.9, 65.6, 41.0;

HRMS (ESI): calcd for $C_{17}H_{13}BrNO_4$ $[M-H]^-$: 374.0033. Found 374.0032.



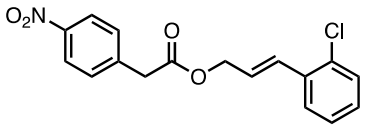
2.85 Prepared according to the General Procedure from the corresponding allylic alcohol (1.15 g, 5.0 mmol, 1.0 equiv.) and aryl acetic acid (1.09 g, 6.0 mmol, 1.2 equiv.). Isolated in 54% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.21 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 2.4, 6.7 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.34 (m, 1H), 6.94 (dd, *J* = 8.8, 10.0 Hz, 1H), 6.67(d, *J* = 15.6 Hz, 1H), 6.34 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.79 (dd, *J* = 1.3, 6.1 Hz, 2H), 3.80 (s, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 169.8, 159.3 (d, *J* = 251.9 Hz), 147.4, 141.1, 132.2 (d, *J* = 9.2 Hz), 130.4, 130.3 (d, *J* = 3.7 Hz), 126.7 (d, *J* = 4.8 Hz), 125.9 (d, *J* = 13.7 Hz), 125.3 (d, *J* = 3.3 Hz), 123.9, 117.7 (d, *J* = 23.8 Hz), 116.9 (d, *J* = 3.0 Hz), 65.5, 41.0;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -119.9 (m);

HRMS (ESI): calcd for $C_{17}H_{12}BrFNO_4$ $[M-H]^-$: 391.9939. Found 391.9936.

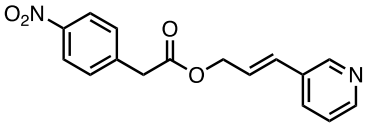


2.86 Prepared according to the General Procedure from the corresponding allylic alcohol (0.51 g, 3.0 mmol, 1.0 equiv.) and aryl acetic acid (0.65 g, 3.6 mmol, 1.2 equiv.). Isolated in 87% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.51 – 7.49 (m, 3H), 7.36 (dd, *J* = 1.8, 7.2 Hz, 1H), 7.22 (m, 2H), 7.01 (d, *J* = 15.6 Hz, 1H), 6.24 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.82 (dd, *J* = 1.3, 6.1 Hz, 2H), 3.80 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.9, 147.3, 141.2, 134.2, 133.3, 130.5, 130.4, 129.9, 129.3, 127.0 (2), 125.4, 123.9, 65.7, 41.0;

HRMS (ESI): calcd for $C_{17}H_{13}ClNO_4$ $[M-H]^-$: 330.0539. Found 330.0539.

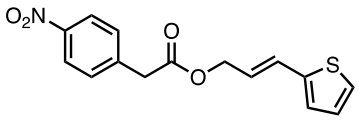


2.87 Prepared according to the General Procedure from the corresponding allylic alcohol (0.34 g, 2.5 mmol, 1.0 equiv.) and aryl acetic acid (0.54 g, 3.0 mmol, 1.2 equiv.). Washed twice with water instead of 1 M HCl in work-up. Isolated in 96% yield after purification by silica gel chromatography (20:1 DCM:MeOH) as a brown solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.60 (d, *J* = 2.2 Hz, 1H), 8.51 (dd, *J* = 1.3, 4.8 Hz, 1H), 8.21 (d, *J* = 8.7 Hz, 2H), 7.68 (dt, *J* = 2.0, 7.9 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.25 (m, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.33 (dt, *J* = 6.5, 15.8 Hz, 1H), 4.80 (dd, *J* = 1.3, 6.1 Hz, 2H), 3.80 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.9, 149.4, 148.5, 147.4, 141.1, 133.1, 131.7, 131.1, 130.4, 125.0, 123.9, 123.6, 65.6, 41.0;

HRMS (ESI): calcd for $C_{16}H_{15}N_2O_4$ $[M+H]^+$: 299.1026. Found 299.1023.

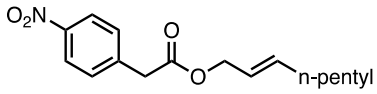


2.88 Prepared according to the General Procedure from the corresponding allylic alcohol (0.70 g, 5.0 mmol, 1.0 equiv.) and aryl acetic acid (1.09 g, 6.0 mmol, 1.2 equiv.). Isolated in 68% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.20 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 4.9 Hz, 1H), 6.98 – 6.97 (m, 2H), 6.75 (d, J = 15.6 Hz, 1H), 6.09 (dt, J = 6.5, 15.8 Hz, 1H), 4.73 (dd, J = 1.3, 6.1 Hz, 2H), 3.77 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 147.3, 141.2, 140.9, 130.4, 128.2, 127.5, 126.8, 125.3, 123.8, 121.9, 65.7, 41.0;

HRMS (ESI): calcd for $C_{15}H_{12}NO_4S$ $[M-H]^-$: 302.0493. Found 302.0491.

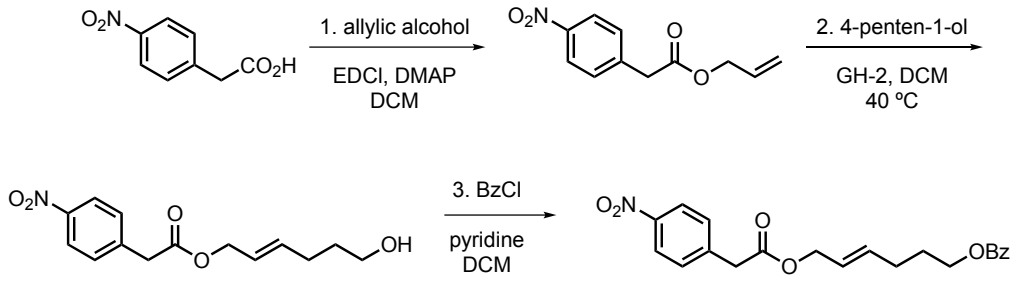


2.89 Prepared according to the General Procedure from the corresponding allylic alcohol (0.26 g, 2.0 mmol, 1.0 equiv.) and aryl acetic acid (0.40 g, 2.2 mmol, 1.1 equiv.). Isolated in 78% yield after purification by silica gel chromatography (10:1 hexane:EtOAc) as a light yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.19 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 5.76 (m, 1H), 5.54 (m, 1H), 4.55 (d, J = 6.6 Hz, 2H), 3.74 (s, 2H), 2.04 (q, J = 7.2 Hz, 2H), 1.39 – 1.23 (m, 6H), 0.88 (t, J = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 147.3, 141.4, 137.6, 130.4, 123.8, 123.2, 66.2, 41.1, 32.2, 31.4, 28.6, 22.5, 14.1;

HRMS (ESI): calcd for $C_{16}H_{20}NO_4$ $[M-H]^-$: 290.1398. Found 290.1397.



2.90 *Step 1.* Prepared according to the General Procedure from allylic alcohol (1.36 ml, 20.0 mmol, 1.0 equiv.) and aryl acetic acid (3.98 g, 22.0 mmol, 1.1 equiv.). Isolated in 96% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a light yellow oil.

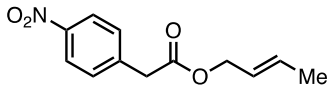
Step 2 In an atmosphere-controlled glovebox, the allyl ester from *Step 2.* (1.33 g, 6.0 mmol, 2.0 equiv.), 4-penten-1-ol (0.26 g, 3.0 mmol, 1.0 equiv.), DCM (15 mL) and 2nd-Generation Hoveyda-Grubbs catalyst (37.6 mg, 0.06 mmol, 0.02 equiv.) were sequentially added to an 8-dram vial charged with a stir bar. The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at 40° C. Upon completion of the reaction, the reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (1:1 hexane:EtOAc). Isolated in 52% yield as a grey solid. *Step 3.* To a flask charged with stir bar and purged with N_2 was added the allylic ester from from *Step 2.* (0.24 g, 0.87 mmol, 1.0 equiv.), DCM (5 mL) and pyridine (0.07 mL, 0.87 mmol, 1.0 equiv.). The solution was cooled to 0° C and benzoyl chloride (0.10 mL, 0.87 mmol, 1.0 equiv.) was added dropwise. The mixture was stirred at 0° C for 1.5 h. Upon completion of the reaction, the mixture was quenched with NH_4Cl (sat.), washed sequentially with 1 M HCl, $NaHCO_3$ (sat.)

and brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by silica gel chromatography (4:1 hexane:EtOAc). Isolated in 90% yield as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.19 (d, *J* = 8.9 Hz, 2H), 8.04 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.42 (m, 4H), 5.83 – 5.78 (m, 1H), 5.63 – 5.59 (m, 1H), 4.56 (d, *J* = 6.6 Hz, 2H), 4.32 (t, *J* = 6.5 Hz, 2H), 3.73 (s, 2H), 2.24 (q, *J* = 7.6 Hz, 2H), 1.88 (m, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 166.6, 147.3, 141.3, 135.6, 134.6, 133.0, 130.4, 129.6, 128.4, 124.4, 123.8, 65.9, 64.2, 41.0, 28.8, 27.9;

HRMS (ESI): calcd for $C_{21}H_{20}NO_6$ $[M\text{-}H]^-$: 382.1296. Found 382.1296.

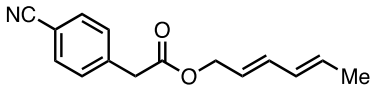


2.91 Prepared according to the General Procedure from the corresponding allylic alcohol (0.43 ml, 5.0 mmol, 1.0 equiv.) and aryl acetic acid (1.09 g, 6.0 mmol, 1.2 equiv.). Isolated in 78% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 5.79 (m, 1H), 5.57 (m, 1H), 4.55 (m, 2H), 3.73 (s, 2H), 1.72 (m, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 147.3, 141.4, 132.2, 130.4, 124.6, 123.8, 66.2, 41.1, 17.8;

HRMS (ESI): calcd for $C_{12}H_{12}NO_4$ $[M\text{-}H]^-$: 234.0772. Found 234.0772.

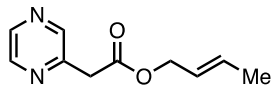


2.92 Prepared according to the General Procedure from the corresponding allylic alcohol (0.29 g, 3.0 mmol, 1.0 equiv.) and aryl acetic acid (0.58 g, 3.6 mmol, 1.2 equiv.). Isolated in 81% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.22 (dd, *J* = 10.3, 15.4 Hz, 1H), 6.04 (m, 1H), 5.75 (m, 1H), 5.59 (m, 1H), 4.60 (d, *J* = 6.6 Hz, 2H), 3.69 (s, 2H), 1.77 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.1, 139.3, 135.5, 132.4, 131.8, 130.3, 130.2, 123.0, 118.7, 111.2, 65.9, 41.3, 18.2;

HRMS (ESI): calcd for $C_{15}H_{15}NNaO_2$ $[M+Na]^+$: 264.0995. Found 264.0993.

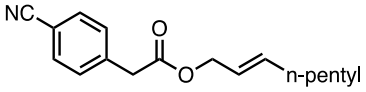


2.93 Prepared according to the General Procedure from the corresponding allylic alcohol (0.17 g, 2.0 mmol, 1.0 equiv.) and aryl acetic acid (0.30 g, 2.2 mmol, 1.1 equiv.). Washed twice with water instead of 1 M HCl in work-up. Isolated in 93% yield after purification by silica gel chromatography (1:1 hexane:EtOAc) as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.60 (d, *J* = 1.3 Hz, 1H), 8.54 (m, 1H), 8.49 (d, *J* = 2.4 Hz, 1H), 5.82 – 5.77 (m, 1H), 5.61 – 5.56 (m, 1H), 4.58 (d, *J* = 6.6 Hz, 2H), 3.89 (s, 2H), 1.72 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.5, 150.4, 145.4, 144.2, 143.2, 132.1, 124.6, 66.1, 41.3, 17.7;

HRMS (ESI): calcd for $C_{10}H_{13}N_2O_2$ $[M+H]^+$: 193.0972. Found 193.0970.

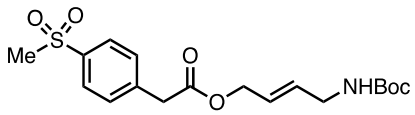


2.94 Prepared according to the General Procedure from the corresponding allylic alcohol (0.46 ml, 3.0 mmol, 1.0 equiv.) and aryl acetic acid (0.53 g, 3.3 mmol, 1.1 equiv.). Isolated in 88% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 5.76 (m, 1H), 5.53 (m, 1H), 4.55 (d, *J* = 6.6 Hz, 2H), 3.67 (s, 2H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.39 – 1.24 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.2, 139.4, 137.5, 132.4, 130.2, 123.2, 118.8, 111.2, 66.2, 41.4, 32.2, 31.4, 28.6, 22.5, 14.1;

HRMS (ESI): calcd for $C_{17}H_{25}N_2O_2$ $[M+NH_4]^+$: 289.1911. Found 289.1910.

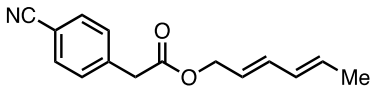


2.95 Prepared according to the General Procedure from the corresponding allylic alcohol (0.29 g, 1.6 mmol, 1.0 equiv.) and aryl acetic acid (0.34 g, 1.6 mmol, 1.0 equiv.). Isolated in 49% yield after purification by silica gel chromatography (1:2 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 5.79 – 5.68 (m, 2H), 4.60 (m, 3H), 3.76 – 3.73 (m, 4H), 3.05 (s, 3H), 1.45 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 155.7, 140.1, 139.5, 132.3, 130.4, 127.7, 124.8, 79.7, 65.1, 44.6, 41.8, 41.0, 28.4;

HRMS (ESI): calcd for $C_{18}H_{25}NNaO_6S$ $[M+Na]^+$: 406.1295. Found 406.1292.

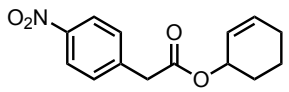


2.96 Prepared according to the General Procedure from the corresponding allylic alcohol (0.29 g, 3.0 mmol, 1.0 equiv.) and aryl acetic acid (0.58 g, 3.6 mmol, 1.2 equiv.). Isolated in 81% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.22 (dd, *J* = 10.3, 15.4 Hz, 1H), 6.04 (m, 1H), 5.75 (m, 1H), 5.59 (m, 1H), 4.60 (d, *J* = 6.6 Hz, 2H), 3.69 (s, 2H), 1.77 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.1, 139.3, 135.5, 132.4, 131.8, 130.3, 130.2, 123.0, 118.7, 111.2, 65.9, 41.3, 18.2;

HRMS (ESI): calcd for $C_{15}H_{15}NNaO_2$ $[M+Na]^+$: 264.0995. Found 264.0993.

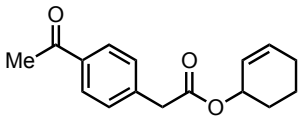


2.58 Prepared according to the General Procedure from 2-cyclohexen-1-ol (196.2 mg, 2.0 mmol, 1.0 equiv.) and the corresponding aryl acetic acid (398.4 mg, 2.2 mmol, 1.1 equiv.). Isolated in 53% yield after purification by silica gel chromatography (10:1 hexane:EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 5.97 (m, 1H), 5.68 (m, 1H), 5.28 (m, 1H), 3.72 (s, 2H), 2.09 (m, 1H), 1.99 (m, 1H), 1.85 (m, 1H), 1.70 (m, 2H), 1.63 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.8, 147.2, 141.6, 133.4, 130.3, 125.1, 123.8, 69.2, 41.4, 28.2, 24.9, 18.7;

HRMS (ESI): calcd for $C_{14}H_{14}NO_4$ $[M-H]^-$: 260.0926. Found 260.0926.

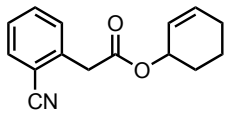


2.97 Prepared according to the General Procedure from 2-cyclohexen-1-ol (163.0 mg, 1.7 mmol, 1.2 equiv.) and the corresponding aryl acetic acid (244.0 mg, 1.4 mmol, 1.0 equiv.). Isolated in 79% yield after purification by silica gel chromatography (19:1 to 4:1 hexane:EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 5.96 (m, 1H), 5.69 (m, 1H), 5.28 (m, 1H), 3.67 (s, 2H), 2.59 (s, 3H), 2.08 (m, 1H), 1.98 (m, 1H), 1.85 (m, 1H), 1.74 – 1.59 (m, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.8, 170.5, 139.7, 136.0, 133.1, 129.6, 128.6, 125.3, 68.9, 41.7, 28.2, 26.7, 24.9, 18.8;

HRMS (ESI): calcd for $C_{16}H_{18}NaNO_3$ $[M+Na]^+$: 281.1148. Found 281.1147.

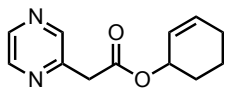


2.98 Prepared according to the General Procedure from 2-cyclohexen-1-ol (196.2 mg, 2.0 mmol, 1.0 equiv.) and the corresponding aryl acetic acid (354.6 mg, 2.2 mmol, 1.1 equiv.). Isolated in 58% yield after purification by silica gel chromatography (4:1 hexane:EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (dd, *J* = 1.1, 7.7 Hz, 1H), 7.56 (dt, *J* = 1.3, 7.7 Hz, 1H), 7.42 (dd, *J* = 0.6, 7.9 Hz, 1H), 7.38 (dd, *J* = 1.1, 7.6 Hz, 1H), 5.96 (m, 1H), 5.72 (m, 1H), 5.31 (m, 1H), 3.87 (d, *J* = 1.9 Hz, 2H), 2.08 (m, 1H), 1.98 (m, 1H), 1.87 (m, 1H), 1.78 – 1.70 (m, 2H), 1.63 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.5, 138.1, 133.2, 132.9, 132.8, 130.6, 127.7, 125.2, 117.6, 113.6, 69.4, 40.0, 28.2, 24.9, 18.8;

HRMS (ESI): calcd for $C_{15}H_{15}NNaO_2$ $[M+Na]^+$: 264.0995. Found 264.0993.



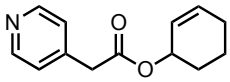
2.99 Prepared according to the General Procedure from 2-cyclohexen-1-ol (123.0 mg, 1.25 mmol, 1.04 equiv.) and the corresponding aryl acetic acid (165.7 mg, 1.20 mmol, 1.0 equiv.). A modified

workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated in 73% yield after purification by silica gel chromatography (1:1 hexane:EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.60 (d, *J* = 1.3 Hz, 1H), 8.53 (m, 1H), 8.48 (d, *J* = 2.6 Hz, 1H), 5.96 (m, 1H), 5.71 (m, 1H), 5.32 (m, 1H), 3.88 (s, 2H), 2.08 (m, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.77 – 1.67 (m, 2H), 1.63 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.4, 150.6, 145.4, 144.2, 143.2, 133.2, 125.2, 69.3, 41.7, 28.2, 24.9, 18.8;

HRMS (EI): calcd for $C_{12}H_{14}N_2O_2$ $[M]^+$: 218.1055. Found 218.1055.



2.100 Prepared according to the General Procedure from 2-cyclohexen-1-ol (226.0 mg, 2.5 mmol, 1.04 equiv.), the corresponding aryl acetic acid • HCl (416.4 mg, 2.4 mmol, 1.0 equiv.) and additional Et_3N (0.34 ml, 2.4 mmol, 1.0 equiv.). A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated in 52% yield after purification by silica gel chromatography (1:2 hexane:EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.56 (d, *J* = 5.7 Hz, 2H), 7.23 (d, *J* = 5.7 Hz, 2H), 5.97 (m, 1H), 5.69 (m, 1H), 5.28 (m, 1H), 3.61 (s, 2H), 2.08 (m, 1H), 1.98 (m, 1H), 1.85 (m, 1H), 1.74 – 1.67 (m, 2H), 1.63 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.7, 150.0, 143.1, 133.3, 125.2, 124.5, 69.1, 41.0, 28.2, 24.9, 18.7;

HRMS (ESI): calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$: 218.1176. Found 218.1176.

2.10.2 General Procedure for Decarboxylative Enantioselective Benzylation

General Procedure A: In an atmosphere controlled glovebox, (*S,S,S*)-[Ir]-2 (2.2 mg, 0.002 mmol, 0.02 equiv.), aryl acetic acid (1.00–1.20 equiv.), cinnamyl carbonate (23.4 mg, 0.10 mmol, 1.00 equiv.) and durene internal standard were sequentially added to a 1-dram vial charged with a stir bar. THF (0.5 mL) was added and the mixture was stirred until homogeneous (approx. 1 minute), followed by the addition of DBU (1.00–1.20 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (14–24 h), the yield was determined by ^{1}H NMR using durene as internal standard. For products that undergo spontaneous decarboxylation at room temperature, the reaction mixture was concentrated *in vacuo* and purified by preparative TLC. For products that do not undergo spontaneous decarboxylation at room temperature, the reaction mixture was diluted with an equal volume of DMF (0.5 mL), then heated (70 to 90° C for 2–5 h to induce decarboxylation. Upon completion of the reaction, the yield was determined by ^{1}H NMR using durene as internal standard. The mixture was diluted with 12 mL EtOAc, washed with 1 mL 1 M HCl and 2 x 2 mL brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by silica gel chromatography.

General Procedure B: In an atmosphere controlled glovebox, (*S,S,S*)-[Ir]-1 or (*S,S,S*)-[Ir]-2 (0.005 mmol, 0.01 equiv.), allylic aryl acetate (0.5 mmol, 1.00 equiv.), and durene internal standard were sequentially added to a 1-dram vial charged with a stir bar. THF (2.5 mL) was added and the mixture was stirred until homogeneous (approximately 1 minute), followed by the addition of DBU (76.1 mg, 0.50 mmol, 1.0 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (2 – 24 h) as determined by ^{1}H NMR using durene as internal standard, the reaction mixture was

concentrated *in vacuo* and purified by silica gel chromatography. For products that do not undergo spontaneous decarboxylation at room temperature, the reaction mixture was transferred to a 4-dram vial and diluted with an equal volume of DMF (2.5 mL). The vial was sealed with a PTFE-lined cap and flushed with N_2 for 5 min. The solution was then heated (70 to 90° C) for 1 to 19 h to induce decarboxylation. Upon completion of the reaction, the mixture was diluted with 60 mL EtOAc, washed with 5 mL 1 M HCl and 2 x 10 mL brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by silica gel chromatography.

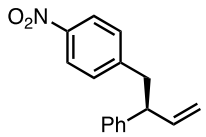
General Procedure C: In an atmosphere controlled glovebox, $Pd(dba)_2$ (2.9 mg, 0.005 mmol, 0.05 equiv.) and (*R,R*)-DACH-phenyl Trost ligand L6 (3.8 mg, 0.0055 mmol, 0.055 equiv.) were sequentially added to a 0.5-dram vial charged with a stir bar. DCE (0.1 mL) was added and the mixture was stirred for 10 minutes. In a separate 0.5-dram vial charged with a stir bar, aryl acetic acid (0.15 mmol, 1.5 equiv.), cyclohex-2-enyl methyl carbonate (15.6 mg, 0.10 mmol, 1.0 equiv.) and durene internal standard were added. The Pd-ligand solution was transferred to the vial with DCE rinses (2 x 0.2 mL). The reaction mixture was stirred for another 10 minutes, followed by the addition of BSA (61.0 mg, 0.30 mmol, 3.0 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (14–48 h) as determined by ^1H NMR using durene as internal standard, the reaction mixture was treated with diethylamine (150 μL) and stirred for 1 h. The mixture was then concentrated *in vacuo*, dissolved in EtOAc and concentrated *in vacuo* again to fully remove DCE. The crude mixture was transferred to a 4-dram vial with DMF rinses (0.5 mL) and DBU (50 μL) was added. The vial was sealed with a PTFE-lined cap and flushed with N_2 for 5 min. The solution was then heated (rt–140° C) for 1 to 2 h to induce decarboxylation. Upon completion of the reaction, the mixture was diluted with 10 mL EtOAc, washed with 1 mL 1 M HCl and 2 x 2 mL brine. The

organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by silica gel chromatography.

General Procedure D: In an atmosphere controlled glovebox, $Pd(dba)_2$ (6.9 mg, 0.012 mmol, 0.05 equiv.) and (*R,R*)-DACH-phenyl Trost ligand L6 (9.1 mg, 0.0132 mmol, 0.055 equiv.) were sequentially added to a 1-dram vial charged with a stir bar. DCE (0.4 mL) was added and the mixture was stirred for 10 minutes. In a separate 1-dram vial charged with a stir bar, 2-cyclohexenyl aryl acetate (0.24 mmol, 1.0 equiv.) and durene internal standard were added. The Pd-ligand solution was transferred to the vial with DCE rinses (2 x 0.2 mL), followed by the addition of BSA (53.7 mg, 0.264 mmol, 1.1 equiv.). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at room temperature. Upon completion of the reaction (22–50 h) as determined by ^1H NMR using durene as internal standard, the reaction mixture was treated with diethylamine (125 μL) and stirred for 1 h. The mixture was then concentrated *in vacuo*, dissolved in EtOAc and concentrated *in vacuo* again to fully remove DCE. The crude mixture was transferred to a 4-dram vial with DMF rinses (1.0 mL) and DBU (50 μL) was added. The vial was sealed with a PTFE-lined cap and flushed with N_2 for 5 min. The solution was then heated (rt–100° C) for 1 to 6 h to induce decarboxylation. Upon completion of the reaction, the mixture was diluted with 30 mL EtOAc, washed with 3 mL 1 M HCl and 2 x 5 mL brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by silica gel chromatography.

General Procedure E: [product derivatization via cross-metathesis for HPLC analysis] To a vial under N_2 containing the appropriate terminal olefin product (0.02 mmol, 1 equiv.) and methyl acrylate (0.2 mmol, 10 equiv.) was added a stock solution of 0.1 M Grubbs-Hoveyda catalyst in CH_2Cl_2 (0.2 mL, 0.002 mmol, 0.10 equiv.). The reaction was stirred at room temperature until full

consumption of the starting material was observed by ^{1}H NMR. The mixture was passed through a plug of silica (washing with 4:1 Hexane/EtOAc), concentrated *in vacuo* to remove excess methyl acrylate and analyzed by HPLC.



2.1 Prepared according to the General Procedure A from 4-nitrophenylacetic acid (21.7 mg, 0.12 mmol, 1.2 equiv.), 24 h. 85% yield, determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (149 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 18 h. Isolated in 88% yield, 98% ee after purification by silica gel chromatography (2:1 hexane:toluene) as a yellow oil.

Prepared according to the General Procedure B with 0.1 mol% catalyst from the corresponding allylic aryl acetate (297 mg, 1.0 mmol, 1.0 equiv.) and **[Ir]-2** (1.1 mg, 0.001 mmol, 0.001 equiv.), 15 h. 65% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

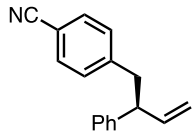
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.0 Hz, 2H), 6.02 (m, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 3.58 (q, *J* = 7.6 Hz, 1H), 3.16 (m, 1H), 3.09 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 148.0, 146.5, 142.5, 140.5, 130.0, 128.7, 127.7, 126.8, 123.4, 115.4, 51.3, 42.1;

HRMS (EI): calcd for $C_{16}H_{15}NO_2$ $[M]^+$: 253.1103. Found 253.1099.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 3.9 min (minor), t_r = 4.4 min (major).

$[\alpha]_D^{25}$ -91.2 (c = 0.76, $CHCl_3$)



2.16 Prepared according to the General Procedure A from 4-cyanophenylacetic acid (16.1 mg, 0.10 mmol, 1.0 equiv.), 14 h. Subsequent decarboxylation was achieved at 70° C, 2h. 94% yield determined by ^{1}H NMR using durene as internal standard, >99% ee.

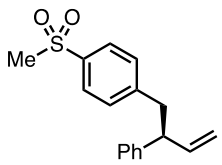
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.50 – 7.47 (m, 2H), 7.29 – 7.26 (m, 2H), 7.20 (m, 1H), 7.14 – 7.09 (m, 4H), 6.01 (m, 1H), 5.06 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.98 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.55 (q, *J* = 8.2 Hz, 1H), 3.11 (m, 1H), 3.04 (m, 1H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 145.8, 142.6, 140.6, 131.9, 130.0, 128.6, 127.7, 126.7, 119.1, 115.3, 109.9, 51.3, 42.3;

HRMS (EI): calcd for $C_{17}H_{15}N$ $[M]^+$: 233.1205. Found 233.1207.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 4.5 min (minor), t_r = 4.8 min (major).

$[\alpha]_D^{25}$ -107.6 (c = 0.89, $CHCl_3$)



2.17 Prepared according to the General Procedure A from 4-(methylsulfonyl)phenyl acetic acid (21.4 mg, 0.10 mmol, 1.0 equiv.), 14 h. Subsequent decarboxylation was achieved at 70° C, 3h. 90% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

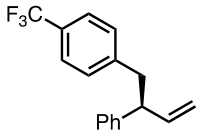
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 – 7.75 (m, 2H), 7.31 – 7.17 (m, 5H), 7.15 – 7.10 (m, 2H), 6.02 (m, 1H), 5.06 (dt, *J* = 1.3, 10.5 Hz, 1H), 4.98 (dt, *J* = 1.3, 17.1 Hz, 1H), 3.58 (q, *J* = 7.4 Hz, 1H), 3.17 – 3.05 (m, 2H), 3.02 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.7, 142.6, 140.6, 138.2, 130.2, 128.6, 127.7, 127.2, 126.7, 115.3, 51.3, 44.6, 42.1;

HRMS (EI): calcd for $C_{17}H_{18}O_2S$ $[M]^+$: 286.1028. Found 286.1026.

Chiral HPLC: ChiralPak IB column (10% IPA in hexane, 1.5 mL/min), t_r = 6.2 min (major), t_r = 6.8 min (minor).

$[\alpha]_D^{25}$ -69.9 (c = 1.12, $CHCl_3$)



2.18 Prepared according to the General Procedure A from 4-(trifluoromethyl)phenyl acetic acid (24.5 mg, 0.12 mmol, 1.2 equiv.), 16 h. Subsequent decarboxylation was achieved at 90° C, 19 h. 85% yield determined by ^{1}H NMR using durene as internal standard, >99% ee.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.46 – 7.44 (m, 2H), 7.29 – 7.25 (m, 2H), 7.19 (m, 1H), 7.15 – 7.12 (m, 4H), 6.01 (m, 1H), 5.04 (dt, *J* = 1.2, 10.3 Hz, 1H), 4.97 (dt, *J* = 1.2, 17.1 Hz, 1H), 3.56 (q, *J* = 8.0 Hz, 1H), 3.11 – 3.02 (m, 2H);

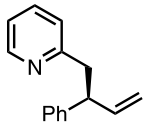
^{13}C NMR ($CDCl_3$, 176 MHz) δ 144.2, 143.0, 140.8, 129.5, 128.6, 128.3 (q, *J* = 34.1 Hz), 127.8, 126.6, 125.0 (q, J = 4.0 Hz), 124.3 (q, *J* = 277 Hz), 115.1, 51.4, 42.0;

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

HRMS (EI): calcd for $C_{17}H_{15}F_3$ $[M]^+$: 276.1126. Found 276.1125.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product **2.28'** according to General Procedure E. Whelk-O1 column (10% IPA in hexane, 1.5 mL/min), t_r = 6.6 min (minor), t_r = 7.4 min (major).

$[\alpha]_D^{25}$ -50.2 (c = 1.39, $CHCl_3$)



2.19 Prepared according to the General Procedure A from 2-pyridylacetic acid • HCl (17.4 mg, 0.10 mmol, 1.0 equiv.) and an additional equivalent DBU (30 μL, 0.20 mmol, 2.0 equiv.), 18 h. Subsequent decarboxylation was achieved at 70° C, 1h. 60% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (25.3 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-2** (2.2 mg, 0.002 mmol, 0.02 equiv.), 20 h. Subsequent decarboxylation was achieved at 70° C, 1h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated in 62%yield, 99% ee after purification by silica gel chromatography (1:1 hexane:EtOAc) as a colorless oil.

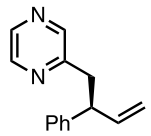
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.53 (m, 1H), 7.48 (dt, *J* = 1.9, 7.6 Hz, 1H), 7.27 – 7.25 (m, 2H), 7.19 – 7.16 (m, 3H), 7.06 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.04 (m, 1H), 5.00 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.97 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.90 (q, *J* = 7.8 Hz, 1H), 3.22 (m, 1H), 3.16 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.6, 149.3, 143.4, 141.1, 136.0, 128.4, 127.8, 126.4, 123.9, 121.1, 114.8, 49.9, 44.4;

HRMS (ESI): calcd for $C_{15}H_{16}N$ $[M+H]^+$: 210.1277. Found 210.1275.

Chiral HPLC: Whelk-O1 column (1% IPA in hexane, 1.5 mL/min), t_r = 10.6 min (major), t_r = 12.1 min (minor).

$[\alpha]_D^{25}$ -54.4 (c = 0.26, $CHCl_3$)



2.20 Prepared according to the General Procedure A from 2-pyrazine acetic acid (13.8 mg, 0.10 mmol, 1.0 equiv.), 22 h. Subsequent decarboxylation was achieved at 70° C, 1h. 90% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (127.2 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (5.3 mg, 0.005 mmol, 0.01 equiv.), 15 h. Subsequent decarboxylation was achieved at 70° C, 2h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated in 93% yield, 97% ee after purification by silica gel chromatography (1:1 hexane:EtOAc) as a yellow oil.

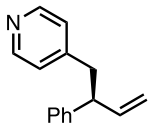
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.49 (dd, *J* = 1.6, 2.4 Hz, 1H), 8.35 (d, *J* = 2.5 Hz, 1H), 8.22 (d, *J* = 1.4 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.20 – 7.16 (m, 3H), 6.04 (m, 1H), 5.04 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.99 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.89 (q, *J* = 7.8 Hz, 1H), 3.25 (m, 1H), 3.18 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.7, 145.3, 144.1, 142.7, 142.3, 140.5, 128.7, 127.7, 126.7, 115.3, 49.6, 41.4;

HRMS (EI): calcd for $C_{14}H_{14}N_2$ $[M]^+$: 210.1157. Found 210.1152.

Chiral HPLC: Chiralpak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 3.2 min (major), t_r = 3.4 min (minor).

$[\alpha]_D^{25}$ -75.4 (c = 0.86, $CHCl_3$).



2.21 Prepared according to the General Procedure A from 4-pyridylacetic acid • HCl (17.4 mg, 0.10 mmol, 1.0 equiv.) and an additional equivalent DBU (30 μL, 0.20 mmol, 2.0 equiv.), 18 h. Subsequent decarboxylation was achieved at 70° C, 1h. 75% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (126.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 17 h. Subsequent decarboxylation was achieved at 70° C, 1h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated in 90% yield, 99% ee after purification by silica gel chromatography (1:1 hexane:EtOAc) as a yellow oil.

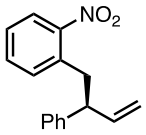
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.42 (m, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 7.13 (m, 2H), 6.97 (d, *J* = 5.9 Hz, 2H), 6.07 (m, 1H), 5.06 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.99 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.57 (q, *J* = 7.8 Hz, 1H), 3.04 (m, 1H), 2.99 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.6, 149.0, 142.7, 140.6, 128.6, 127.7, 126.7, 124.6, 115.3, 50.7, 41.4;

HRMS (EI): calcd for $C_{15}H_{15}N$ $[M]^+$: 209.1205. Found 209.1203.

Chiral HPLC: Chiralpak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 9.5 min (minor), t_r = 10.6 min (major).

$[\alpha]_D^{25}$ -54.9 (c = 0.84, $CHCl_3$)



2.12 Prepared according to the General Procedure A from 2-nitrophenylacetic acid (21.7 mg, 0.12 mmol, 1.2 equiv.), 24 h. 93% yield determined by ^{1}H NMR using durene as internal standard, >99% ee.

Prepared according to the General Procedure B from the corresponding allylic aryl acetate (148.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 17 h. Isolated in 89% yield, 97% ee after purification by silica gel chromatography (2:1 hexane:toluene) as a yellow oil.

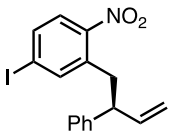
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.88 (dd, *J* = 0.7, 8.4 Hz, 1H), 7.38 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.30 (m, 1H), 7.28 – 7.26 (m, 2H), 7.20 (m, 1H), 7.15 (dd, *J* = 0.7, 8.4 Hz, 2H), 7.06 (dd, *J* = 0.7, 7.7 Hz, 1H), 6.05 (m, 1H), 5.03 (dt, *J* = 1.4, 10.5 Hz, 1H), 4.95 (dt, *J* = 1.2, 16.8 Hz, 1H), 3.64 (q, *J* = 7.7 Hz, 1H), 3.40 (m, 1H), 3.27 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.7, 142.9, 140.3, 135.0, 133.1, 132.4, 128.6, 127.7, 127.2, 126.7, 124.7, 115.5, 50.7, 39.4;

HRMS (EI): calcd for $C_{16}H_{15}NO_2$ $[M]^+$: 253.1103. Found 253.1098.

Chiral HPLC: Whelk-O1 column (1% IPA in hexane, 1.5 mL/min), t_r = 7.5 min (minor), t_r = 8.2 min (major).

$[\alpha]_D^{25}$ -44.4 (c = 0.63, $CHCl_3$)



2.22 Prepared according to General Procedure A from the corresponding arylacetic acid (36.9 mg, 0.12 mmol, 1.2 equiv.), 20 h. Isolated in 70% yield, 99% ee after purification by silica gel chromatography (20:1 pentane/Et_2O) as a yellow oil.

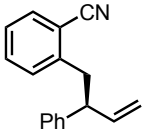
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 1H), 7.59 (m, 1H), 7.41 (d, *J* = 1.7 Hz, 1H), 7.29 (m, 2H), 7.22 (m, 1H), 7.14 – 7.12 (m, 2H), 6.03 (m, 1H), 5.06 (m, 1H), 4.96 (m, 1H), 3.59 (q, *J* = 7.7 Hz, 1H), 3.34 (m, 1H), 3.20 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.2, 142.5, 142.1, 139.8, 136.9, 136.4, 128.7, 127.6, 126.9, 126.0, 115.9, 99.7, 50.6, 39.1;

HRMS (EI): calcd for $C_{16}H_{13}NOI$ $[M\text{-}OH]^+$: 362.0042. Found 362.0037;

Chiral HPLC: Chiralpak IA column (1% IPA in hexane, 1.5 mL/min), t_r = 3.7 min (minor), t_r = 4.9 min (major);

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ 2.8 (c = 1.19, $CHCl_3$)



2.23 Prepared according to the General Procedure A from 2-cyanophenylacetic acid (16.1 mg, 0.10 mmol, 1.0 equiv.), 14 h. Subsequent decarboxylation was achieved at 70° C, 5h. 95% yield determined by ^{1}H NMR using durene as internal standard, 99% ee.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.58 (m, 1H), 7.41 (m, 1H), 7.29 – 7.24 (m, 3H), 7.22 – 7.18 (m, 3H), 7.13 (m, 1H), 6.07 (m, 1H), 5.05 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.97 (dt, *J* = 1.2, 17 Hz, 1H), 6.68 (q, J = 7.8 Hz, 1H), 3.28 (m, 1H), 3.21 (m, 1H);

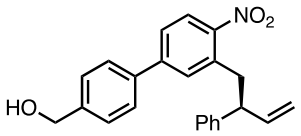
^{13}C NMR ($CDCl_3$, 176 MHz) δ 144.1, 142.6, 140.1, 132.7, 132.3, 130.5, 128.6, 127.7, 126.70, 126.67, 118.3, 115.6, 112.9, 51.2, 40.9;

149.3, 141.2, 134.9, 133.3, 132.6, 132.0, 130.3, 129.9, 127.9, 127.8, 125.2, 122.8, 38.2;

HRMS (EI): calcd for $C_{17}H_{15}N$ $[M]^+$: 233.1205. Found 233.1206.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.3 min (minor), t_r = 6.0 min (major).

$[\alpha]_D^{25}$ -39.0 (c = 1.12, $CHCl_3$)



2.24 Prepared according to the General Procedure A from the corresponding aryl acetic acid (34.5 mg, 0.12 mmol, 1.2 equiv.) and **[Ir]-2** (5.6 mg, 0.005 mmol, 0.05 equiv.), 0.1 M in THF, 18 h. Isolated in 75% yield, >99% ee after purification by silica gel chromatography (2:1 pentane:THF) as a yellow oil (contains 7% protodecarboxylation impurity).

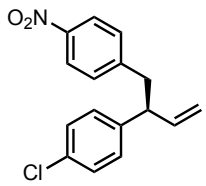
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.45 – 7.36 (m, 4H), 7.31 – 7.17 (m, 5H), 7.13 (d, *J* = 1.9 Hz, 1H), 6.12 (m, 1H), 5.08 (dt, *J* = 1.2, 10.2 Hz, 1H), 5.03 (dt, *J* = 1.2, 17.0 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 2H), 3.71 (q, *J* = 8.2 Hz, 1H), 3.52 (m, 1H), 3.28 (m, 1H), 1.70 (t, *J* = 6.0 Hz, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.3, 144.9, 142.9, 141.4, 140.4, 138.2, 135.7, 131.9, 128.6, 128.0, 127.5 (2), 126.7, 125.6, 125.5, 115.5, 64.9, 50.7, 39.9;

HRMS (EI): calcd for $C_{23}H_{21}NO_3$ $[M]^+$: 359.1521. Found 359.1522.

Chiral HPLC: ChiralPak IC column (5% IPA in hexane, 1.5 mL/min), t_r = 11.9 min (major), t_r = 12.8 min (minor).

$[\alpha]_D^{25}$ 53.6 (c = 0.79, $CHCl_3$)



2.10 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (165.9 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 15 h. Isolated in 94% yield, 98% ee after purification by silica gel chromatography (20:1 hexane:EtOAc) as a yellow solid.

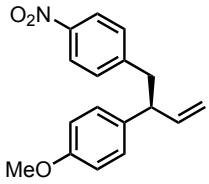
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.07 (m, 2H), 7.24 (m, 2H), 7.12 (m, 2H), 7.04 (m, 2H), 5.98 (m, 1H), 5.09 (dt, *J* = 1.2, 10.3 Hz, 1H), 5.00 (dt, *J* = 1.3, 17.1 Hz, 1H), 3.56 (q, *J* = 7.8 Hz, 1H), 3.15 (m, 1H), 3.04 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.5, 146.6, 140.9, 140.0, 132.5, 130.0, 129.1, 128.8, 123.5, 115.8, 50.6, 41.9;

HRMS (EI): calcd for $C_{16}H_{14}NO_2Cl$ $[M]^+$: 287.0713. Found 287.0718.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 4.4 min (minor), t_r = 5.1 min (major).

$[\alpha]_D^{25}$ -114.7 (c = 0.93, $CHCl_3$)



2.40 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (163.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 15 h. Isolated in 78% yield, 98% ee after purification by silica gel chromatography (20:1 hexane:EtOAc) as a yellow solid.

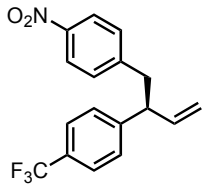
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.06 (d, *J* = 9.3 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.00 (m, 1H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.98 (d, *J* = 17.3 Hz, 1H), 3.78 (s, 3H), 3.53 (q, *J* = 7.5 Hz, 1H), 3.13 (m, 1H), 3.04 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.4, 148.1, 146.5, 140.9, 134.5, 130.0, 128.7, 123.4, 115.0, 114.0, 55.3, 50.5, 42.1;

HRMS (EI): calcd for $C_{17}H_{17}NO_3$ $[M]^+$: 283.1209. Found 283.1211.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.8 min (minor), t_r = 6.8 min (major).

$[\alpha]_D^{25}$ -115.5 (c = 0.69, $CHCl_3$)



2.41 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (182.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (10.6 mg, 0.01 mmol, 0.02 equiv.), 2 h. The reaction mixture was passed through a pad of silica to remove DBU before concentrating *in vacuo*. Isolated in 91% yield, 95% ee after purification by silica gel chromatography (20:1 hexane:EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.08 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.00 (m, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 5.01 (d, *J* = 16.7 Hz, 1H), 3.66 (q, *J* = 7.5 Hz, 1H), 3.19 (m, 1H), 3.09 (m, 1H);

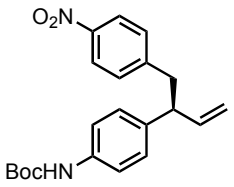
^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.2, 146.7, 146.6, 139.5, 130.0, 129.2 (q, *J* = 31.8 Hz), 128.1, 125.6 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 270.7 Hz), 123.6, 116.3, 51.1, 41.8;

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

HRMS (EI): calcd for $C_{17}H_{14}NO_2F_3$ $[M]^+$: 321.0977. Found 321.0977.

Chiral HPLC: Chiralpak IG column (3% IPA in hexane, 1.5 mL/min), t_r = 2.4 min (minor), t_r = 2.6 min (major).

$[\alpha]_D^{25}$ -76.9 (c = 1.11, $CHCl_3$)



2.42 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (206.2 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 20 h. Isolated in 74% yield, 98% ee after purification by silica gel chromatography (4:1 pentane:Et_2O) as a light yellow solid.

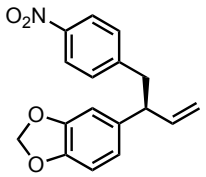
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.26 (m, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.40 (br, 1H), 5.99 (m, 1H), 5.05 (dt, *J* = 1.2, 10.1 Hz, 1H), 4.97 (dt, *J* = 1.2, 17.0 Hz, 1H), 3.53 (q, *J* = 7.8 Hz, 1H), 3.13 (m, 1H), 3.04 (m, 1H), 1.51 (s, 9H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.9, 152.7, 147.9, 146.4, 140.6, 136.9, 130.0, 128.2, 123.3, 118.6, 115.1, 80.6, 50.6, 42.0, 28.4;

HRMS (ESI): calcd for $C_{21}H_{24}N_2NaO_4$ $[M+Na]^+$: 391.1628. Found 391.1622.

Chiral HPLC: Chiralpak IA column (15% IPA in hexane, 1.5 mL/min), t_r = 3.3 min (major), t_r = 3.7 min (minor).

$[\alpha]_D^{25}$ -109.5 (c = 0.60, $CHCl_3$)



2.43 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (170.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 14 h. Isolated in 85% yield, 98% ee after purification by silica gel chromatography (10:1 hexane:EtOAc) as a yellow oil.

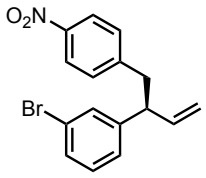
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.07 (m, 2H), 7.18 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.52 (dd, *J* = 1.7, 8.0 Hz, 1H), 5.97 (m, 1H), 5.93 (m, 2H), 5.06 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.99 (dt, *J* = 1.2, 17.1 Hz, 1H), 3.50 (q, *J* = 7.8 Hz, 1H), 3.12 (m, 1H), 3.03 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.9, 147.8, 146.5, 146.3, 140.6, 136.3, 130.0, 123.4, 120.8, 115.2, 108.3, 107.9, 101.0, 50.9, 42.1;

HRMS (EI): calcd for $C_{17}H_{15}NO_4$ $[M]^+$: 297.1001. Found 297.0999.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 8.2 min (minor), t_r = 8.8 min (major).

$[\alpha]_D^{25}$ -139.5 (c = 0.62, $CHCl_3$)



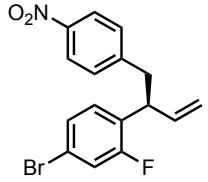
2.44 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (188.1 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 17 h. Isolated in 87% yield after purification by silica gel chromatography (20:1 pentane:Et_2O) as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.30 (s, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.97 (m, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 3.55 (q, *J* = 7.8 Hz, 1H), 3.14 (m, 1H), 3.07 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.4, 146.6, 144.9, 139.6, 130.7, 130.2, 130.0, 129.9, 126.5, 123.5, 122.8, 116.1, 50.9, 41.8;

HRMS (EI): calcd for $C_{16}H_{14}NO_2Br$ $[M]^+$: 331.0208. Found 331.0208.

$[\alpha]_D^{25}$ -97.4 (c = 1.08, $CHCl_3$)



2.45 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (197.1 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 23 h. Isolated in 90% yield, 93% ee after purification by silica gel chromatography (10:1 hexane:EtOAc) as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.10 (m, 2H), 7.31 – 7.29 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 8.3, 9.5 Hz, 1H), 5.98 (m, 1H), 5.13 (dt, *J* = 1.2, 10.2 Hz, 1H), 5.04 (d, *J* = 17.4 Hz, 1H), 3.89 (q, *J* = 7.8 Hz, 1H), 3.15 (m, 1H), 3.07 (m, 1H);

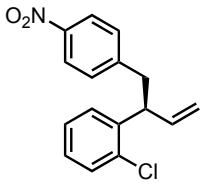
^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.6 (d, *J* = 245.8 Hz), 147.0, 146.7, 138.0, 131.9 (d, *J* = 16.8 Hz), 131.8 (d, *J* = 4.6 Hz), 131.3 (d, *J* = 8.6 Hz), 129.9, 123.6, 117.5 (d, *J* = 24.6 Hz), 116.9, 116.8, 44.3, 40.8 (d, *J* = 1.2 Hz);

^{19}F NMR ($CDCl_3$, 376 MHz) δ -119.9 (m);

HRMS (EI): calcd for $C_{16}H_{13}NO_2FBr$ $[M]^+$: 349.0114. Found 349.0109.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.2 mL/min), t_r = 4.6 min (minor), t_r = 4.8 min (major).

$[\alpha]_D^{25}$ -87.4 (c = 0.80, $CHCl_3$)



2.46 Modified conditions were required to obtain high ee. In an atmosphere-controlled glovebox, **[Ir]-2** (5.6 mg, 0.005 mmol, 0.05 equiv.), the corresponding allylic aryl acetate (33.2 mg, 0.10 mmol, 1.00 equiv.), and durene internal standard were sequentially added to a 1-dram vial charged with a stir bar. DME (0.5 mL) was added and the mixture was stirred until homogeneous (approx. 1 minute). The vial was sealed with a PTFE-lined cap, removed from the glovebox and gently stirred at 0° C for 10 min, followed by the addition of DBU (15.2 mg, 0.10 mmol, 1.0 equiv.). Upon completion of the reaction (40 h) as determined by ^{1}H NMR using durene as internal standard, the reaction mixture was warmed to room temperature to induce decarboxylation (3 h). Then the reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (20:1 pentane:Et_2O). Isolated in 75% yield, 87% ee as a colorless oil.

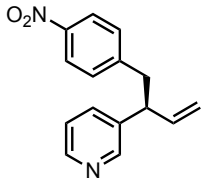
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.08 (d, *J* = 8.9 Hz, 2H), 7.32 (dd, *J* = 0.9, 8.0 Hz, 1H), 7.28 – 7.23 (m, 4H), 7.15 (m, 1H), 6.00 (m, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 5.03 (d, *J* = 17.3 Hz, 1H), 4.23 (q, *J* = 7.7 Hz, 1H), 3.12 (d, *J* = 7.2 Hz, 2H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.5, 146.6, 140.1, 138.7, 133.8, 130.0, 129.9, 128.5, 127.9, 127.1, 123.4, 116.5, 46.5, 41.1;

HRMS (EI): calcd for $C_{16}H_{14}NO_2Cl$ $[M]^+$: 287.0713. Found 287.0710.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 3.5 min (major), t_r = 3.8 min (minor).

$[\alpha]_D^{25}$ -32.1 (c = 1.50, $CHCl_3$)



2.47 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (29.8 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-1** (2.1 mg, 0.002 mmol, 0.02 equiv.), 2 h. The reaction mixture was passed through a pad of silica to remove DBU before concentrating *in vacuo*. Isolated in 80% yield, 94% ee after purification by silica gel chromatography (20:1 DCM:MeOH) as a brown oil.

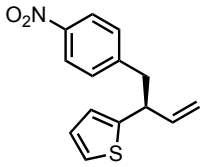
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.46 (dd, *J* = 1.4, 4.8 Hz, 1H), 8.37 (d, *J* = 2.1 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.43 (dt, *J* = 2.0, 7.8 Hz, 1H), 7.21 (dd, *J* = 4.6, 7.9 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.00 (m, 1H), 5.13 (d, *J* = 10.1 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 3.62 (q, *J* = 7.8 Hz, 1H), 3.19 (m, 1H), 3.07 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.5, 148.4, 147.0, 146.7, 139.3, 137.8, 135.1, 130.0, 123.6, 123.5, 116.5, 48.7, 41.7;

HRMS (EI): calcd for $C_{15}H_{14}N_2O_2$ $[M]^+$: 254.1055. Found 254.1055.

Chiral HPLC: Whelk-O1 column (30% IPA in hexane, 1.5 mL/min), t_r = 11.9 min (major), t_r = 13.2 min (minor).

$[\alpha]_D^{25}$ -79.4 (c = 0.54, $CHCl_3$)



2.48 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (151.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 6 h. Isolated in 86% yield, 96% ee after purification by silica gel chromatography (10:1 hexane:EtOAc) as a yellow solid.

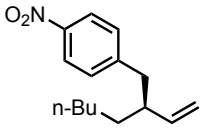
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.10 (m, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.17 (dd, *J* = 1.1, 5.1 Hz, 1H), 6.91 (dd, *J* = 3.5, 5.1 Hz, 1H), 6.73 (m, 1H), 5.96 (m, 1H), 5.08 (dt, *J* = 1.2, 10.2 Hz, 1H), 5.03 (dt, *J* = 1.2, 17 Hz, 1H), 3.88 (q, *J* = 7.8 Hz, 1H), 3.19 (m, 1H), 3.14 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.3, 146.7, 146.1, 139.8, 130.1, 126.8, 124.2, 123.9, 123.5, 116.0, 46.6, 43.0;

HRMS (EI): calcd for $C_{14}H_{13}NO_2S$ $[M]^+$: 259.0667. Found 259.0668.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.5 min (major), t_r = 6.0 min (minor).

$[\alpha]_D^{25}$ -32.7 (c = 0.85, $CHCl_3$)



2.49 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (29.1 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-2** (1.1 mg, 0.001 mmol, 0.01 equiv.), 12 h. Isolated in 78% yield after purification by silica gel chromatography (20:1 pentane:Et_2O) as a colorless oil, 99% ee after derivatization according to General Procedure E.

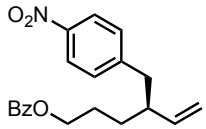
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.12 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 5.54 (m, 1H), 4.94 (dd, *J* = 1.5, 10.3 Hz, 1H), 4.82 (m, 1H), 2.79 (m, 1H), 2.65 (m, 1H), 2.30 (m, 1H), 1.42 – 1.20 (m, 8H), 0.87 (t, *J* = 7.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.8, 146.4, 141.4, 130.1, 123.4, 115.5, 45.7, 41.7, 34.5, 31.9, 26.8, 22.6, 14.1;

HRMS (EI): calcd for $C_{15}H_{21}NO_2$ $[M]^+$: 247.1572. Found 247.1576.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product **2.46'** according to General Procedure E. Chiralpak IA column (5% IPA in hexane, 1.5 mL/min), t_r = 2.7 min (major), t_r = 3.0 min (minor).

$[\alpha]_D^{25}$ -11.3 (c = 0.67, $CHCl_3$)



2.50 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (115.0 mg, 0.30 mmol, 1.0 equiv.) and **[Ir]-2** (3.3 mg, 0.003 mmol, 0.01 equiv.), 15 h. Isolated in 81% yield, 97% ee after purification by silica gel chromatography (10:1 hexane:EtOAc) as a colorless oil (contains 8% linear allylation product).

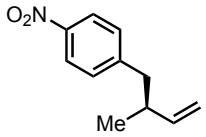
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.09 (m, 2H), 7.97 (dd, *J* = 1.2, 8.3 Hz, 2H), 7.55 (tt, *J* = 1.4, 7.4 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 5.56 (m, 1H), 5.00 (dd, *J* = 1.4, 10.3 Hz, 1H), 4.89 (m, 1H), 4.29 (m, 2H), 2.79 (m, 1H), 2.71 (m, 1H), 2.37 (m, 1H), 1.87 – 1.82 (m, 1H), 1.73 – 1.68 (m, 1H), 1.61 – 1.56 (m, 1H), 1.44 – 1.39 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) □δ 166.6, 148.3, 146.5, 140.7, 133.0, 130.3, 130.0, 129.5, 128.4, 123.5, 116.3, 64.6, 45.3, 41.7, 30.5, 26.4;

HRMS (ESI): calcd for $C_{20}H_{21}NNaO_4$ $[M+Na]^+$: 362.1363. Found 362.1359;

Chiral HPLC: Chiralpak IB column (5% IPA in hexane, 1.5 mL/min), t_r = 3.2 min (minor), t_r = 3.9 min (major);

$[\alpha]_D^{25}$ -23.0 (c = 0.93, $CHCl_3$)



2.51 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (117.6 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 14 h. Isolated in 83% yield after purification by silica gel chromatography (10:1 hexane:EtOAc) as a light yellow oil, 97% ee after derivatization according to General Procedure E.

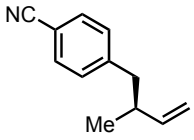
^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.13 (m, 2H), 7.28 (m, 2H), 5.72 (m, 1H), 4.94 – 4.89 (m, 2H), 2.74 (m, 1H), 2.66 (m, 1H), 2.48 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.7, 146.5, 142.7, 130.0, 123.5, 113.8, 43.0, 39.3, 19.6;

HRMS (EI): calcd for $C_{11}H_{13}NO_2$ $[M]^+$: 191.0946. Found 191.0942.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product **2.48'** according to General Procedure E. Chiralpak IG column (5% IPA in hexane, 1.5 mL/min), t_r = 6.4 min (major), t_r = 6.8 min (minor).

$[\alpha]_D^{25}$ 14.4 (c = 0.72, $CHCl_3$)



2.52 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (107.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 22 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated in 66% yield after purification by silica gel

chromatography (10:1 hexane:EtOAc) as a colorless oil, 99% ee after derivatization according to General Procedure E.

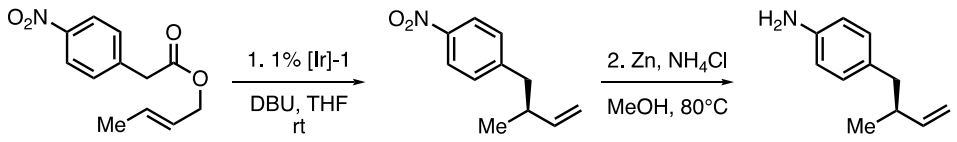
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.56 (m, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.73 (m, 1H), 4.94 – 4.90 (m, 2H), 2.71 (m, 1H), 2.61 (m, 1H), 2.46 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.4, 142.9, 132.0, 130.0, 119.2, 113.7, 109.8, 43.3, 39.2, 19.6;

HRMS (EI): calcd for $C_{12}H_{13}N$ $[M]^+$: 171.1048. Found 171.1044.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product **2.49'**according to General Procedure E. Chiralpak IG column (10% IPA in hexane, 1.5 mL/min), t_r = 4.8 min (major), t_r = 5.1 min (minor).

$[\alpha]_D^{25}$ 18.4 (c = 0.87, $CHCl_3$)



2.51 **2.53**

2.53 *Step 1* Prepared according to the General Procedure B from the corresponding allylic aryl acetate (235.2 mg, 1.00 mmol, 1.0 equiv.) and **[Ir]-1** (10.6 mg, 0.01 mmol, 0.01 equiv.), 14 h. Isolated in 187.3 mg with 10% 4-nitrotoluene side-product after purification by silica gel chromatography (20:1 hexane:EtOAc) as a light yellow oil. *Step 2* To a 1-dram vial charged with a stir bar was added crude **2.48** (81.5 mg, from *Step 1*), zinc powder (202.9 mg, 3.20 mmol, 7.5 equiv.), and NH_4Cl (46.0 mg, 0.86 mmol, 2.0 equiv.) and 3 mL MeOH. The reaction was heated to 80° C for 1 h, then cooled to room temperature. The reaction mixture was passed through a silica plug, washing with EtOAc, the filtrate was concentrated *in vacuo*. Isolated as a light yellow oil, 86% over two steps after purification by silica gel chromatography (4:1 hexane:EtOAc), 98% ee after derivatization according to General Procedure E.

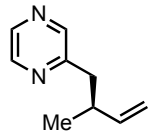
^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.94 (d, *J* = 8.1 Hz, 2H), 6.62 (m, 2H), 5.79 (m, 1H), 4.93 (dt, *J* = 1.3, 17.2 Hz, 1H), 4.90 (m, 1H), 3.54 (br, 2H), 2.58 (m, 1H), 2.43 – 2.35 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.3, 144.2, 130.9, 130.0, 115.1, 112.5, 42.4, 39.5, 19.3;

HRMS (EI): calcd for $C_{11}H_{15}N$ $[M]^+$: 161.1205. Found 161.1207.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product **2.50'**according to General Procedure E. Whelk-O1 column (20% IPA in hexane, 1.5 mL/min), t_r = 11.4 min (minor), t_r = 12.4 min (major).

$[\alpha]_D^{25}$ 20.0 (c = 1.02, $CHCl_3$)



2.54 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (96.1 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 14 h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Subsequent decarboxylation was achieved at 80° C, 2h. Isolated in 68% yield, >99% ee after purification by silica gel chromatography (1:1 hexane:EtOAc) as a light yellow oil.

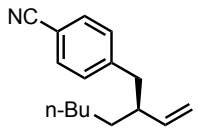
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (dd, *J* = 1.4, 2.2 Hz, 1H), 8.41 (d, *J* = 1.4 Hz, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 5.77 (m, 1H), 4.94 – 4.90 (m, 2H), 2.86 – 2.68 (m, 3H), 1.06 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.4, 145.3, 144.1, 142.8, 142.3, 113.7, 42.5, 38.1, 19.8;

HRMS (EI): calcd for $C_9H_{12}N_2$ $[M]^+$: 148.1001. Found 148.0998.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 5.5 min (major), t_r = 6.2 min (minor).

$[\alpha]_D^{25}$ 14.6 (c = 0.85, $CHCl_3$)



2.55 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (135.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-2** (11.1 mg, 0.01 mmol, 0.02 equiv.), 15 h. Subsequent decarboxylation was achieved at 70° C, 6h. Isolated in 64% yield after purification by silica gel chromatography (20:1 hexane:EtOAc) as a light yellow oil, >99% ee after derivatization according to General Procedure E.

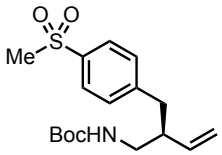
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.53 (m, 1H), 4.93 (dd, *J* = 1.6, 10.4 Hz, 1H), 4.81 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.28 (m, 1H), 1.40 – 1.18 (m, 8H), 0.87 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.6, 141.5, 131.9, 130.1, 119.2, 115.3, 109.7, 45.6, 42.0, 34.4, 31.9, 26.8, 22.6, 14.1;

HRMS (EI): calcd for $C_{16}H_{21}N$ $[M]^+$: 227.1674. Found 227.1674.

Chiral HPLC: Derivatized to the corresponding cross-metathesis product **2.52'** according to General Procedure E. Chiralpak IA column (5% IPA in hexane, 1.0 mL/min), t_r = 4.2 min (major), t_r = 4.5 min (minor).

$[\alpha]_D^{25}$ -8.9 (c = 0.83, $CHCl_3$)



2.56 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (38.3 mg, 0.10 mmol, 1.0 equiv.) and **[Ir]-1** (1.1 mg, 0.001 mmol, 0.01 equiv.), 16 h. Subsequent

decarboxylation was achieved at 70° C, 4h. Isolated in 50% yield (9:1 ratio of amide rotamers), >99% ee after purification by silica gel chromatography (1:1 hexane:EtOAc) as a light yellow oil.

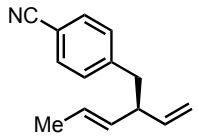
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.58 (m, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 4.98 (d, *J* = 17.0 Hz, 1H), 4.57 (br, 1H), 3.31 (m, 1H), 3.04 (s, 3H), 3.00 (m, 1H), 2.83 (m,1 H), 2.68 (m, 1H), 2.54 (m, 1H), 1.44 (s, 9H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.9, 146.3, 138.5, 138.4, 130.2, 127.5, 117.9, 79.5, 45.8, 44.6, 44.1, 38.7, 28.4;

HRMS (ESI): calcd for $C_{17}H_{25}NNaO_4S$ $[M+Na]^+$: 362.1397. Found 362.1395.

Chiral HPLC: Chiralpak IG column (20% IPA in hexane, 1.5 mL/min), t_r = 8.1 min (minor), t_r = 9.1 min (major).

$[\alpha]_D^{25}$ -10.3 (c = 1.58, $CHCl_3$)



2.57 Prepared according to the General Procedure B from the corresponding allylic aryl acetate (120.7 mg, 0.50 mmol, 1.0 equiv.) and **[Ir]-1** (5.3 mg, 0.005 mmol, 0.01 equiv.), 20 h. Subsequent decarboxylation was achieved at 70° C, 3h. Isolated in 65% yield, 99% ee after purification by silica gel chromatography (20:1 pentane:Et_2O) as a colorless oil.

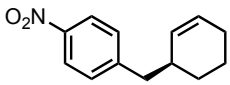
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.72 (m, 1H), 5.41 – 5.30 (m, 2H), 4.98 (d, *J* = 10.2 Hz, 1H), 4.92 (dt, *J* = 1.4, 17.1 Hz, 1H), 2.96 (m, 1H), 2.75 (d, *J* = 7.5 Hz, 2H), 1.63 (d, *J* = 4.7 Hz, 3H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.0, 140.3, 132.2, 131.9, 130.2, 126.3, 119.2, 114.9, 109.8, 48.1, 41.7, 18.0;

HRMS (EI): calcd for $C_{14}H_{15}N$ $[M]^+$: 197.1205. Found 197.1206.

Chiral HPLC: Chiralpak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 3.7 min (major), t_r = 3.9 min (minor).

$[\alpha]_D^{25}$ -25.7 (c = 0.57, $CHCl_3$)



2.59 Prepared according to General Procedure C from 4-nitrophenylacetic acid (27.2 mg, 0.15 mmol, 1.5 equiv.), 48 h. The reaction mixture was stirred under 0° C for 1 h before adding BSA and conducted at 0° C. Subsequent decarboxylation was achieved at rt, 1h. 80% yield, determined by ^{1}H NMR using 1,3,5-trimethoxybezene as internal standard, 91% ee.

Prepared according to General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (62.7 mg, 0.24 mmol, 1.0 equiv.), 50 h. Subsequent decarboxylation was achieved at rt, 1h. Isolated in 77% yield, 90% ee after purification by silica gel chromatography (10:1 pentane/Et_2O) as a yellow oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.73 (m, 1H), 5.51 (m, 1H), 2.74 (m, 1H), 2.66 (m, 1H), 2.42 (m, 1H), 1.99 (m, 2H), 1.71 (m, 2H), 1.52 (m, 1H), 1.26 (m, 1H);

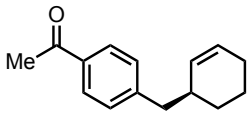
^{13}C NMR ($CDCl_3$, 176 MHz) δ 148.9, 146.5, 130.2, 129.9, 128.4, 123.5, 42.6, 37.0, 28.8, 25.3, 21.2;

HRMS (EI): calcd for $C_{13}H_{15}NO_2$ $[M]^+$: 217.1103. Found 217.1105.

Chiral HPLC: 2.59 was derivatized to the corresponding epoxide **2.59'.** To a solution of **2.59** (10mg, 0.035 mmol) in $CDCl_3$ (1 mL) in a half-dram vial, was added excess mCPBA (20mg, 4.7 equiv.), and the mixture was stirred at rt for 16 h. Crude NMR showed full conversion to the

corresponding epoxides. Whelk-O1 column (10% IPA in hexane, 1.5 mL/min), t_r = 11.0 min (major), t_r = 12.4 min (minor).

$[\alpha]_D^{25}$ -41.7 (c = 0.75, $CHCl_3$)



2.60 Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (62.0 mg, 0.24 mmol, 1.0 equiv.), 48 h. Diethylamine treatment was not applied during work-up. Subsequent decarboxylation was achieved at 100° C, 1h. Isolated in 73% yield, 84% ee after purification by silica gel chromatography (10:1 pentane/Et_2O) as a colorless oil.

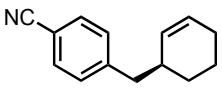
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 5.71 (m, 1H), 5.53 (m, 1H), 2.69 (m, 1H), 2.60 (m, 1H), 2.59 (s, 3H), 2.41 (m, 1H), 1.99 (m, 2H), 1.71 (m, 2H), 1.51 (m, 1H), 1.26 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.9, 146.9, 135.2, 130.8, 129.4, 128.4, 127.9, 42.7, 37.0, 28.9, 26.6, 25.3, 21.2;

HRMS (EI): calcd for $C_{15}H_{18}O$ $[M]^+$: 214.1358. Found 214.1359.

Chiral HPLC: ChiralPak IG column (1% IPA in hexane, 1.5 mL/min), t_r = 8.8 min (major), t_r = 9.8 min (minor).

$[\alpha]_D^{25}$ -35.5 (c = 0.83, $CHCl_3$)



2.61 Prepared according to the General Procedure C from 4-cyanophenylacetic acid (24.2 mg, 0.15 mmol, 1.5 equiv.), 19 h. Subsequent decarboxylation was achieved at 120° C, 2h. Isolated in 91%

yield, 89% ee after purification by silica gel chromatography (10:1 hexane/EtOAc) as a colorless oil.

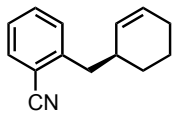
^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.72 (m, 1H), 5.50 (m, 1H), 2.69 (m, 1H), 2.60 (m, 1H), 2.39 (m, 1H), 1.99 (m, 2H), 1.70 (m, 2H), 1.51 (m, 1H), 1.23 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.9, 132.0, 130.3, 129.9, 128.2, 119.1, 109.7, 42.8, 36.9, 28.8, 25.2, 21.1;

HRMS (EI): calcd for $C_{14}H_{15}N$ $[M]^+$: 197.1205. Found 197.1208.

Chiral HPLC: 2.61 was derivatized to the corresponding epoxide **2.61'.** To a solution of **2.61** (10mg, 0.035 mmol) in $CDCl_3$ (1 mL) in a half-dram vial, was added excess mCPBA (20mg, 4.7 equiv.), and the mixture was stirred at rt for 16 h. Crude NMR showed full conversion to the corresponding epoxides. ChiralPak IC column (10% IPA in hexane, 1.5 mL/min), t_r = 6.7 min (major), t_r = 7.9 min (minor).

$[\alpha]_D^{25}$ -49.3 (c = 0.76, $CHCl_3$)



2.62 Prepared according to the General Procedure C from 2-cyanophenylacetic acid (24.2 mg, 0.15 mmol, 1.5 equiv.), 14 h. Subsequent decarboxylation was achieved at 140° C, 1h. Isolated in 99% yield, 88% ee after purification by silica gel chromatography (10:1 hexane/EtOAc) as a light-yellow oil.

Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (57.9 mg, 0.24 mmol, 1.0 equiv.), 21 h. Subsequent decarboxylation was achieved at 140°

C, 1h. Isolated in 81% yield, 83% ee after purification by silica gel chromatography (10:1 hexane/EtOAc) as a light-yellow oil.

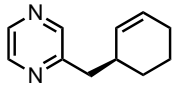
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (dd, *J* = 1.0, 7.5 Hz, 1H), 7.51 (dt, *J* = 1.3, 7.7 Hz, 1H), 7.32 – 7.28 (m, 2H), 5.73 (m, 1H), 5.54 (m, 1H), 2.87 (m, 1H), 2.80 (m, 1H), 2.49 (m, 1H), 2.00 (m, 2H), 1.73 (m, 2H), 1.52 (m, 1H), 1.34 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.0, 132.9, 132.5, 130.4, 130.2, 128.3, 126.5, 118.3, 113.0, 41.0, 36.8, 28.7, 25.3, 21.1;

HRMS (EI): calcd for $C_{14}H_{15}N$ $[M]^+$: 197.1205. Found 197.1208.

Chiral HPLC: 2.62 was derivatized to the corresponding epoxide **2.62'.** To a solution of **2.62** (10mg, 0.035 mmol) in $CDCl_3$ (1 mL) in a half-dram vial, was added excess mCPBA (20mg, 4.7 equiv.), and the mixture was stirred at rt for 16 h. Crude NMR showed full conversion to the corresponding epoxides. ChiralPak IC column (10% IPA in hexane, 1.5 mL/min), t_r = 5.0 min (major), t_r = 5.6 min (minor).

$[\alpha]_D^{25}$ -53.1 (c = 0.74, $CHCl_3$)



2.63 Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (52.4 mg, 0.24 mmol, 1.0 equiv.), 24 h. Subsequent decarboxylation was achieved at 100° C, 1h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated in 85% yield, 86% ee after purification by silica gel chromatography (1:1 pentane/Et_2O) as a light-yellow oil.

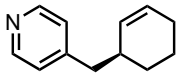
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (m, 1H), 8.44 (s, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 5.73 (m, 1H), 5.54 (m, 1H), 2.83 (m, 1H), 2.75 (m, 1H), 2.64 (m, 1H), 2.00 (m, 2H), 1.72 (m, 2H), 1.53 (m, 1H), 1.32 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.6, 145.3, 144.2, 142.2, 130.4, 128.2, 42.0, 35.7, 28.8, 25.3, 21.1;

HRMS (EI): calcd for $C_{11}H_{14}N_2$ $[M]^+$: 174.1157. Found 174.1157.

Chiral HPLC: ChiralPak IG column (5% IPA in hexane, 1.5 mL/min), t_r = 2.9 min (major), t_r = 3.2 min (minor).

$[\alpha]_D^{25}$ -37.6 (c = 0.74, $CHCl_3$)



2.64 Prepared according to the General Procedure D from the corresponding 2-cyclohexenyl aryl acetate (52.2 mg, 0.24 mmol, 1.0 equiv.), 22 h. Subsequent decarboxylation was achieved at 70° C, 6h. A modified workup was used, washing with saturated NH_4Cl instead of 1 M HCl. Isolated in 73% yield, 86% ee after purification by silica gel chromatography (1:1 hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.49 (m, 2H), 7.10 (m, 2H), 5.72 (m, 1H), 5.51 (m, 1H), 2.62 (m, 1H), 2.54 (m, 1H), 2.41 (m, 1H), 1.99 (m, 2H), 1.71 (m, 2H), 1.51 (m, 1H), 1.26 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.9, 149.6, 130.4, 128.2, 124.7, 42.0, 36.4, 28.8, 25.3, 21.2;

HRMS (EI): calcd for $C_{12}H_{15}N$ $[M]^+$: 173.1205. Found 173.1206.

Chiral HPLC: ChiralPak IG column (2% IPA in hexane, 1.5 mL/min), t_r = 8.7 min (major), t_r = 9.1 min (minor).

$[\alpha]_D^{25}$ -48.6 (c = 0.84, $CHCl_3$)

REFERENCES

1. Siau, W. Y.; Zhang, Y.; Zhao, Y., In *Stereoselective Alkene Synthesis*, Wang, J., Ed. Springer-Verlag Berlin: Berlin, 2012; Vol. 327, pp 33-58.

2. Wittig, G.; Schollkopf, U., *Chem. Ber.-Recl.* **1954,** *87*, 1318-1330.

3. Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A., *Liebigs. Ann./Recueil.* **1997,** *1997*, 1283-1301.

4. Rocha, D. H. A.; Pinto, D. C. G. A.; Silva, A. M. S., *Eur. J. Org. Chem.* **2018,** *2018*, 2443-2457.

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

6. Stork, G.; Zhao, K., *Tetrahedron Lett.* **1989,** *30*, 2173-2174.

7. Wadsworth, W. S., In *Organic Reactions*, 1977; Vol. 25, p 73.

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

9. Ando, K., *J. Org. Chem.* **1999,** *64*, 8406-8408.

10. Gu, Y. H.; Tian, S. K., In *Stereoselective Alkene Synthesis*, Wang, J., Ed. Springer-Verlag Berlin: Berlin, 2012; Vol. 327, pp 197-238.

11. Lindlar, H.; Dubuis, R., *Org. Synth.* **1966,** *46*, 89-91.

12. Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L., *J. Am. Chem. Soc.* **2002,** *124*, 4956-4957.

13. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H., *Angew. Chem. Int. Ed. Engl.* **1995,** *34*, 2039-2041.

14. Schwab, P.; Grubbs, R. H.; Ziller, J. W., *J. Am. Chem. Soc.* **1996,** *118*, 100-110.

15. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H., *Org. Lett.* **1999,** *1*, 953-956.

16. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2000,** *122*, 8168-8179.

17. Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H., *J. Am. Chem. Soc.* **1999,** *121*, 791-799.

18. Schrock, R.; Rocklage, S.; Wengrovius, J.; Rupprecht, G.; Fellmann, J., *J. Mol. Catal.* **1980,** *8*, 73-83.

19. Wengrovius, J. H.; Schrock, R. R.; Churchill, M. R.; Missert, J. R.; Youngs, W. J., *J. Am. Chem. Soc.* **1980,** *102*, 4515-4516.

20. Crowe, W. E.; Goldberg, D. R., *J. Am. Chem. Soc.* **1995,** *117*, 5162-5163.

21. Hansen, E. C.; Lee, D., *Org. Lett.* **2004,** *6*, 2035-2038.

22. Kang, B.; Kim, D.-h.; Do, Y.; Chang, S., *Org. Lett.* **2003,** *5*, 3041-3043.

23. Kang, B.; Lee, J. M.; Kwak, J.; Lee, Y. S.; Chang, S., *J. Org. Chem.* **2004,** *69*, 7661-7664.

24. Randall, M. L.; Tallarico, J. A.; Snapper, M. L., *J. Am. Chem. Soc.* **1995,** *117*, 9610-9611.

25. Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S., *Synlett* **2001,** *3*, 430-432.

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

27. Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H., *Nature* **2011,** *479*, 88-93.

28. Endo, K.; Grubbs, R. H., *J. Am. Chem. Soc.* **2011,** *133*, 8525-8527.

29. Csákÿ, A. G.; Herrán, G. d. l.; Murcia, M. C., *Chem. Soc. Rev.* **2010,** *39*, 4080-4102.

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

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

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

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

34. Fukuhara, K.; Urabe, H., *Tetrahedron Lett.* **2005,** *46*, 603-606.

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

36. de la Herrán, G.; Murcia, C.; Csákÿ, A. G., *Org. Lett.* **2005,** *7*, 5629-5632.

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

38. Cais, M.; Frankel, E. N.; Rejoan, A., *Tetrahedron Lett.* **1968,** *9*, 1919-1923.

39. Corey, E. J.; Ohuchida, S.; Hahl, R., *J. Am. Chem. Soc.* **1984,** *106*, 3875-3876.

40. Sodeoka, M.; Shibasaki, M., *Synthesis* **1993,** *7*, 643-658.

41. Kotova, M.; Vyskočilová, E.; Červený, L. J. C. L., *Catal. Lett.* **2017,** *147*, 1665-1672.

42. Steines, S.; Englert, U.; Drießen-Hölscher, B., *Chem.Commun.* **2000,** *3*, 217-218.

43. Hong, B.-C.; Tseng, H.-C.; Chen, S.-H., *Tetrahedron* **2007,** *63*, 2840-2850.

44. Hu, X.; Zhang, Z.; Zhang, X.; Li, Z.; Zhu, X. X., *Steroids* **2005,** *70*, 531-537.

45. Schwarz, J.; König, B., *Green Chem.* **2018,** *20*, 323-361.

46. Jordan, F.; Patel, H., *ACS Catal.* **2013,** *3*, 1601-1617.

47. Li, T. F.; Huo, L.; Pulley, C.; Liu, A. M., *Bioorganic Chem.* **2012,** *43*, 2-14.

48. Richard, J. P., *Pure Appl. Chem.* **2011,** *83*, 1555-1565.

49. Pfeifer, B. A.; Khosla, C., *Microbiol. Mol. Biol. Rev.* **2001,** *65*, 106-118.

50. Nakamura, S., *Org. Biomol. Chem.* **2014,** *12*, 394-405.

51. Hara, N.; Nakamura, S.; Funahashi, Y.; Shibata, N., *Adv. Synth. Catal.* **2011,** *353*, 2976-2980.

52. Zheng, Y.; Xiong, H.; Nie, J.; Hua, M.; Ma, J., *Chem. Commun.* **2012,** *48*, 4308-4310.

53. Zhong, F.; Yao, W.; Dou, X.; Lu, Y., *Organic Lett.* **2012,** *14*, 4018-4021.

54. Jiang, C. H.; Zhong, F. R.; Lu, Y. X., *Beilstein J. Org. Chem.* **2012,** *8*, 1279-1283.

55. Pan, Y.; Kee, C. W.; Jiang, Z.; Ma, T.; Zhao, Y.; Yang, Y.; Xue, H.; Tan, C., *Chem. Eur. J.* **2011,** *17*, 8363-8370.

56. Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Herrera, R. P.; Sgarzani, V., *Adv. Synth. Catal.* **2007,** *349*, 1037-1040.

57. Bae, H. Y.; Some, S.; Lee, J. H.; Kim, J.; Song, M. J.; Lee, S.; Zhang, Y. J.; Song, C. E., *Adv. Synth. Catal.* **2011,** *353*, 3196-3202.

58. Lubkoll, J.; Wennemers, H., *Angew. Chem. Int. Ed.* **2007,** *46*, 6841-6844.

59. Moon, H. W.; Kim, D. Y., *Tetrahedron Lett.* **2012,** *53*, 6569-6572.

60. Rodríguez, N.; Goossen, L. J., *Chem. Soc. Rev.* **2011,** *40*, 5030-5048.

61. Xu, Z.; Wang, Q.; Zhu, J., *Angew. Chem. Int. Ed.* **2013,** *52*, 3272-3276.

62. Zhang, F.; Greaney, M. F., *Org. Lett.* **2010,** *12*, 4745-4747.

63. Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C., *Science* **2014,** *345*, 437-440.

64. Patra, T.; Maiti, D., *Chemistry* **2017,** *23*, 7382-7401.

65. Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C., *Nat. Rev. Chem.* **2017,** *1*, 1-19.

66. Weaver, J. D.; Recio, A., 3rd; Grenning, A. J.; Tunge, J. A., *Chem. Rev.* **2011,** *111*, 1846-1913.

67. Shibatomi, K.; Kitahara, K.; Sasaki, N.; Kawasaki, Y.; Fujisawa, I.; Iwasa, S., *Nat. Commun.* **2017,** *8*, 15600.

68. Yin, L.; Kanai, M.; Shibasaki, M., *J. Am. Chem. Soc.* **2009,** *131*, 9610-9611.

69. Grugel, C. P.; Breit, B., *Org. Lett.* **2018,** *20*, 1066-1069.

70. Li, J.; Kong, M.; Qiao, B.; Lee, R.; Zhao, X.; Jiang, Z., *Nat. Commun.* **2018,** *9*, 2445-2453.

71. Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z., *J. Am. Chem. Soc.* **2018,** *140*, 6083-6087.

72. Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2016,** *138*, 1832-1835.

73. Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M., *Nat. Chem.* **2011,** *4*, 130-133.

74. Behenna, D. C.; Stoltz, B. M., *J. Am. Chem. Soc.* **2004,** *126*, 15044-15045.

75. He, H.; Zheng, X.; Li, Y.; Dai, L.; You, S., *Org. Lett.* **2007,** *9*, 4339-4341.

76. Singh, O. V.; Han, H., *J. Am. Chem. Soc.* **2007,** *129*, 774-775.

77. Trost, B. M.; Xu, J.; Schmidt, T., *J. Am. Chem. Soc.* **2009,** *131*, 18343-18357.

78. Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S., *J. Am. Chem. Soc.* **2016,** *138*, 2174-2177.

79. Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J., *J. Am. Chem. Soc.* **2016,** *138*, 5016-5019.

80. Okada, K.; Okamoto, K.; Oda, M., *J. Am. Chem. Soc.* **1988,** *110*, 8736-8738.

81. Proctor, R. S. J.; Davis, H. J.; Phipps, R. J., *Science* **2018,** *360*, 419-422.

82. Wang, D.; Zhu, N.; Chen, P.; Lin, Z.; Liu, G., *J. Am. Chem. Soc.* **2017,** *139*, 15632-15635.

83. Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D., *J. Am. Chem. Soc.* **2005,** *127*, 7284-7285.

84. Waetzig, S. R.; Tunge, J. A., *J. Am. Chem. Soc.* **2007,** *129*, 14860-14861.

85. Shang, R.; Huang, Z.; Chu, L.; Fu, Y.; Liu, L., *Org. Lett.* **2011,** *13*, 4240-4243.

86. Moon, P. J.; Fahandej-Sadi, A.; Qian, W.; Lundgren, R. J., *Angew.Chem. Int.Ed.* **2018,** *57*, 4612-4616.

87. Kong, D.; Moon, P. J.; Qian, W.; Lundgren, R. J., *Chem. Commun.* **2018,** *54*, 6835-6838.

88. Hartwig, J. F.; Stanley, L. M., *Acc. Chem. Res.* **2010,** *43*, 1461-1475.

89. Trost, B. M.; Van Vranken, D. L., *Chem. Rev.* **1996,** *96*, 395-422.

90. Bordwell, F. G., *Acc. Chem. Res.* **1988,** *21*, 456-463.

91. Trost, B. M.; Thaisrivongs, D. A., *J. Am. Chem. Soc.* **2008,** *130*, 14092-14093.

92. Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J., *J. Am. Chem. Soc.* **2011,** *133*, 12439-12441.

93. Liu, X.; You, S., *Angew.Chem.Int. Ed.* **2017,** *56*, 4002-4005.

94. Mao, J.; Zhang, J.; Jiang, H.; Bellomo, A.; Zhang, M.; Gao, Z.; Dreher, S. D.; Walsh, P. J., *Angew.Chem.Int. Ed.* **2016,** *55*, 2526-2530.

95. Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F., *J. Am. Chem. Soc.* **2003,** *125*, 14272-14273.

96. Lipowsky, G.; Miller, N.; Helmchen, G., *Angew. Chem. Int. Ed.* **2004,** *43*, 4595-4597.

97. Jiang, X.; Beiger, J. J.; Hartwig, J. F., *J. Am. Chem. Soc.* **2017,** *139*, 87-90.

98. Schwarz, K. J.; Amos, J. L.; Klein, J. C.; Do, D. T.; Snaddon, T. N., *J. Am. Chem. Soc.* **2016,** *138*, 5214-5217.

99. Meza, A. T.; Wurm, T.; Smith, L.; Kim, S. W.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J., *J. Am. Chem. Soc.* **2018,** *140*, 1275-1279.

100. Trost, B. M.; Fandrick, D. R., *Aldrichimica Acta* **2007,** *40*, 59-72.

101. Chen, M.; Hartwig, J. F., *Angew.Chem. Int.Ed.* **2016,** *55*, 11651-11655.

102. Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M., *Angew.Chem. Int.Ed.* **2017,** *56*, 11545-11548.