PALLADIUM-CATALYZED DIFUNCTIONALIZATION REACTIONS OF 1,3-DIENES AND TERMINAL ALKENES VIA π-ALLYL STABILIZED INTERMEDIATES

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Palladium-catalyzed alkene difunctionalization reactions represent a powerful methodology for the construction of diverse carbon–carbon and carbon–heteroatom bonds. The success of these transformations requires the effective stabilization of alkyl–Pd intermediates generated following migratory insertion of an alkene. Stabilization of Pd-intermediates helps to prevent side reactions, thus enabling the formation of desired difunctionalization products in high selectivity. Chapter 1 examines distinctive methods used for the interception of alkyl–Pd intermediates and the strategies associated with minimizing byproduct formation.

The Sigman laboratory has been interested in alkene difunctionalization reactions that take advantage of the unique reactivity of π-allyl/benzyl stabilized intermediates in order to generate significant molecular complexity from simple starting materials. Chapter 2 details the development of the Pd-catalyzed 1,4-difunctionalization of the commodity chemical 1,3-butadiene, which affords difficult to access skipped polyene products. This transformation regioselectively functionalizes the two terminal alkenes of 1,3-butadiene by means of a $\sigma \rightarrow \pi \rightarrow \sigma$ isomerization of cationic Pd-intermediates. The utility of the 1,4-difunctionalization of 1,3-butadiene is highlighted by the synthesis of a highly functionalized skipped triene-containing fragment of ripostatin A.

Chapter 3 describes an advancement of the 1,4-difunctionalization reaction, namely using isoprene as the 1,3-diene substrate to generate skipped diene-containing

terpenoid products. This method presents an added challenge resulting from the use of a 1,3-diene with two inequivalent alkenes that can contribute to complex isomeric product mixtures as the result of unselective alkene insertion. Through the use of pyridine-oxazoline-type ligands, good site selectivity of alkene insertion has been achieved. Mechanistic studies that combine design of experiments with systematic multiparameter ligand modulation ultimately suggest that the electronic asymmetry and steric properties of the ligand are critical to the observed enhancement in site selectivity of alkene insertion.

The development of a 1,3-difunctionalization of terminal alkenes using 1,1-disubstituted vinyl triflates and boronic acids is discussed in Chapter 4. This transformation is realized using a novel difunctionalization strategy, and generates a new $C(sp^2)$–$C(sp^2)$ double bond as well as a $C(sp^3)$–$C(sp^2)$ bond. Dependent on the boronic acid coupling partner, the reaction affords skipped diene or allylic arene products stereo- and regioselectively.

Dedicated to my family

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LIST OF ABBREVIATIONS

Å	angstrom
$A^{1,2}$	1,2-allylic
$A^{1,3}$	1,3-allylic
Ac	acetyl
AcOH	acetic acid
app.	apparent
AQ	8-aminoquinoline
Ar	aryl
bipy	bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	benzoquinone
BT	benzothiazol-2-yl
i-Bu	*iso*-butyl
n-Bu	normal butyl
t-Bu	*tert*-butyl
t-BuOH	*tert*-butanol
Bz	benzoyl
c	cyclo

°C	degrees Celsius
C–C	carbon–carbon
C–H	carbon–hydrogen
Cbz	carboxybenzyloxy
CH_2Cl_2	dichloromethane
CH_3Cl	chloroform
cm	centimeter
conc.	concentration
Cy	cyclohexyl
d	doublet
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
dt	doublet of triplet
ddd	doublet of doublet of doublet
dm	decimeter
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio

DTBP	2,6-di-*tert*-butyl-4-methylpyridine
EDG	electron donating group
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
FTIR	Fourier transform infrared spectroscopy
g	gram
GC	gas chromatography
h	hour
H	hydrogen
H_a	allylic hydrogen
H_s	styrenyl hydrogen
Het	heteroaromatic
HPLC	high-performance liquid chromatography
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	hertz

J	coupling constant
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	liter
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LRGC-MS	low resolution gas chromatography mass spectroscopy
M	molar
m	multiplet
m	*meta*
Me	methyl
meas.	measured
MeCN	acetonitrile
MeOH	methanol
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
μL	microliter
mL	milliliter
mmol	millimole
mp	melting point
MS	molecular sieves or mass spectroscopy

MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonace
NOESY1D	nuclear Overhauser effect spectroscopy – 1-dimensional
Nu	nucleophile
o	*ortho*
OAc	acetate
OMs	mesylate
ONf	nonaflate
OTf	triflate
OTs	tosylate
p	*para*
Pd–C	palladium–carbon
Pd–H	palladium–hydrogen
Ph	phenyl
PhMe	toluene
Phth	phthalimide
pin	pinacol
PMA	phosphomolybdic acid stain
ppm	parts per million
i-Pr	*iso*-propyl
pred.	predicted
i-Pr_2NEt	*N*,*N*-diisopropylethylamine
psi	pound-force per square inch

PT	1-phenyl-tetrazol-5-yl
PTFE	polytetrafluoroethylene
PYR	pyridine-2-yl
pyrox	pyridine-oxazoline
q	quartet
quinox	quinoline-oxazoline
quint	quintet
R	ideal gas constant (1.987×10^{-3} $kcalK^{-1}mol^{-1}$)
R_f	retention factor
RNA	ribonucleic acid
rt	room temperature
s	second or singlet
SAR	structure-activity relationship
sext	sextet
t	triplet
T	temperature
TBDPS	*tert*-butyldiphenylsilyl
TBT	1-*tert*-butyl-tetrazol-5-yl
TFA	trifluoroacetice acid
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TLC	thin layer chromatography

TMS	trimethylsilyl
TOF	time-of-flight
Ts	tosyl
wt %	weight percent

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CHAPTER 1

PALLADIUM-CATALYZED DIFUNCTIONALIZATION REACTIONS: MECHANISTIC INSIGHTS AND STRATEGIES FOR THE INTERCEPTION OF HECK INTERMEDIATES

Introduction

The discovery of Pd-catalyzed coupling reactions facilitated an evolution in synthetic organic chemistry and currently serves as an indispensible methodology for the synthesis of organic molecules. Research efforts over the last five decades have resulted in a multitude of developments enabling this chemistry to produce diverse carbon–carbon or carbon–heteroatom bonds within a wide range of molecular scaffolds.[1-3] The importance of Pd-catalyzed coupling reactions was further highlighted by the 2010 Nobel Prize in Chemistry being awarded for the development of the Heck[4] and Suzuki/Negishi cross-coupling reactions (Figure 1.1A).[5] In a Heck reaction, an alkene undergoes functionalization through migratory insertion into a Pd-nucleophile bond **1**, leading to the formation of Pd-alkyl intermediate **2**. Subsequent β-hydride elimination from **2** results in the formation of product **3**.[6]

As research into Pd-catalyzed coupling reactions has progressed, so too has interest into developing Pd-catalyzed difunctionalization reactions that intercept Heck

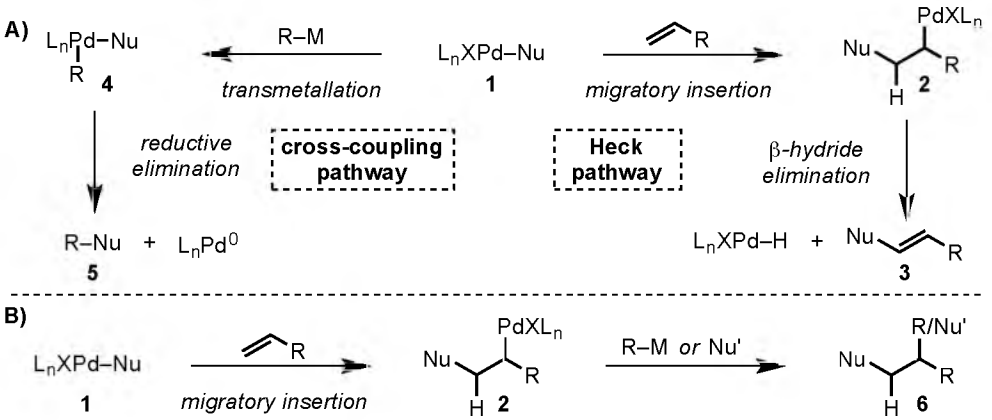


Figure 1.1 Proposed general mechanism for Pd-catalyzed coupling reactions. **A)** Mechanistic rationale for cross-coupling (left) and Heck reactions (right). **B)** Mechanistic rationale for difunctionalization reaction resulting from the interception of Heck insertion intermediates.

insertion intermediates (such as **2**) through a secondary nucleophilic attack or cross-coupling (Figure 1.1B).[7,8] Difunctionalization reactions of this type have the appeal of being able to rapidly increase molecular complexity from simple starting materials. In addition, this methodology has the potential to generate large molecular libraries of functionalized compounds in a modular fashion. Challenges that impede the development of alkene difunctionalization reactions stem from the inability to control reaction selectivity, *e.g.*, the formation of undesired cross-coupling or Heck byproducts.[9] This chapter focuses on the exploration of different strategies and the associated mechanisms used to intercept Heck insertion intermediates in Pd-catalyzed difunctionalization reactions.

Substrate-Controlled Reactions with Norbornene

Several of the first successful Pd-catalyzed difunctionalization reactions were carried out using norbornene as the reaction partner. This alkene-containing molecule

was shown to react in a highly selective manner. In 1989, Mitiga and coworkers reported the Pd-catalyzed arylvinylation reaction of norbornene that produced 2,3-disubstituted norbornanes (**8**, Figure 1.2).[10] The success of norbornene as a difunctionalization substrate is attributed to its rigid bicyclic structure. β-Hydride elimination from alkyl-Pd intermediates requires palladium to adopt a *syn*-coplanar geometry with a β-hydrogen. Following *syn*-carbopalladation alkyl-Pd intermediate **9** is unable to undergo the requisite bond rotation to access a *syn*-coplanar geometry with a β-hydrogen. This in turn prevents β-hydride elimination and the formation of Heck byproducts. Therefore, intermediate **9** is able to undergo a transmetallation and reductive elimination sequence to generate the arylvinylation product (**8**). Subsequent reports have shown the utilization of norbonenes and norbornadiene in difunctionalization reactions for the synthesis of prostaglandin H and leukotriene analogues.[11,12]

Substrate-Controlled Reactions with Alkynes

Alkynes are an important class of coupling partners used in cross-coupling and cascade Heck reactions. This comes as the result of their propensity to undergo facile nucleopalladation, which leads to a diverse array of products that can be formed.[13,14] Accordingly, alkynes are also valuable substrates for difunctionalization reactions. The inability of Pd-alkenyl intermediates, resulting from migratory insertion of an alkyne, to undergo β-hydride elimination makes them particularly interesting reaction substrates. Lim has developed an intramolecular cyclization-coupling reaction that takes advantage of relative stability of Pd-alkenyl intermediates formed following oxidative addition of vinyl bromide **10** and migratory insertion into a pendant alkyne (Figure 1.3 A).[15] The

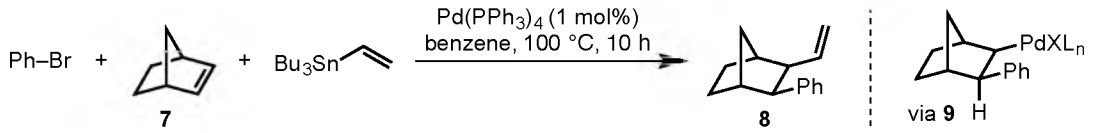


Figure 1.2 Pd-catalyzed 2,3-arylvinylation reaction of norbornene.

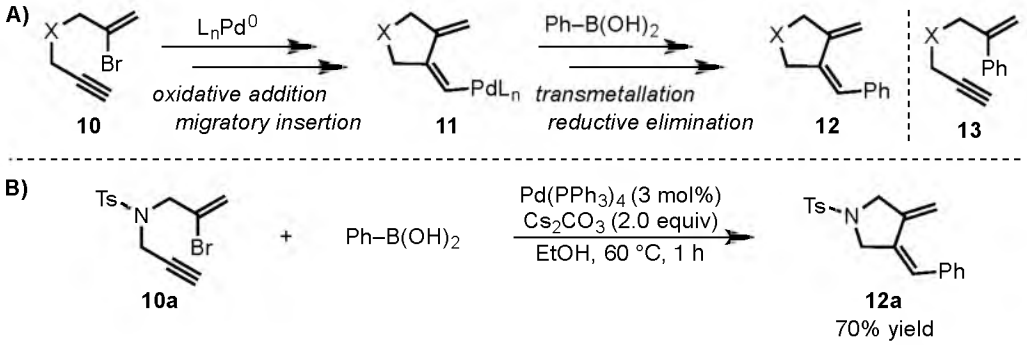


Figure 1.3 Pd-catalyzed intramolecular enyne difunctionalization with phenylboronic acid. **A)** Proposed trapping of an alkenyl-Pd intermediate. **B)** Carbocyclization-coupling of 2-bromo-1,6-enyne.

trapped Pd-intermediate **11**, then completes the difunctionalization through transmetallation with phenylboronic acid and reductive elimination to give **12**. A Suzuki cross-coupling byproduct could be formed if transmetallation with phenylboronic acid occurred prior to carbocyclization with the pendant alkyne (**13**, Figure 1.3 A). Fortunately, while evaluating Pd-sources for the reaction, the authors observed faster reaction times and reduced formation of byproducts when tetrakis(triphenylphosphine)palladium was used as the catalyst. Figure 1.3B demonstrates the synthetic appeal of this transformation with the formation of *N*-tosyl-protected pyrrolidine **12a** in a useful yield.

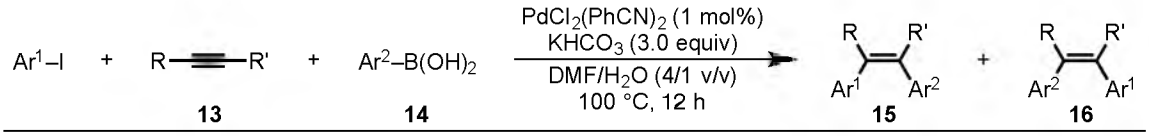
Larock and coworkers have been involved in alkyne difunctionalization reactions since 2003 when they reported an intermolecular diarylation reaction that generates tetrasubstituted alkenes.[16-18] While reaction optimization studies helped to control the

formation of cross-coupling byproducts in this reaction, the authors confronted regioselectivity challenges when evaluating internal alkyne substrates. Initial scope evaluation focused on the reaction of aryl iodides, with symmetric alkyne diphenylacetylene, and phenylboronic acid (entry 1–4, Table 1.1). Tetrasubstituted alkene products were efficiently formed in good to excellent yields when iodobenzene (entry 1), 4-iodophenol (entry 3) or 4-chlorobenzene (entry 4) were employed as reaction substrates. The sterically encumbered 2-tolyl iodide (entry 2) gave a decreased yield for the desired product, likely due to proximal bulk inhibiting carbopalladation. Investigation into electronic or steric influences of arylboronic acids on the reaction proved to only meagerly affect yields (entries 5–7). Researchers were pleased to see that while 2-tolyl iodide resulted in diminished yields, 2-tolyl boronic acid gave the desired olefin product in good yield (entry 5).

As the result of a highly selective *syn*-carbopalladation of the alkyne substrate, tetrasubstituted alkene products were observed as single regio- and stereoisomers. More complex product mixtures of two regioisomers were obtained when unsymmetical alkynes were evaluated in the reaction (entry 8–10, Table 1.1). An interesting steric and electronic trend was identified that affected the regioselectivity of carbopalladation. Specifically, a more electron-deficient alkyne provided 15:1 selectivity for product **15** over regioisomer **16** (entry 8). Alkynes with electron-rich character also favored **15**, although only with 2:1 regioselectivity and decreased yield (entry 10).

The mechanistic rationalization for the selectivity trends of unsymmetrical alkyne substrates can be partially attributed to the steric environment of the Pd-alkyne coordination precursors **17** and **18** that form prior to *syn*-carbopalladation (Figure 1.4 A).

Table 1.1 Evaluation of scope for the Pd-catalyzed intermolecular diarylation reaction of substituted alkynes. THP = tetrahydropyranyl ether.



entry	Ar^1	R	R'	Ar^2	yield (%)	**15**:**16**
1	Ph	Ph	Ph	Ph	92	–
2	2-MeC_6H_4	Ph	Ph	Ph	48	–
3	4-HOC_6H_4	Ph	Ph	Ph	73	–
4	4-ClC_6H_4	Ph	Ph	Ph	65	–
5	Ph	Ph	Ph	2-MeC_6H_4	79	–
6	Ph	Ph	Ph	4-$THPC_6H_4$	86	–
7	Ph	Ph	Ph	4-AcC_6H_4	76	–
8	Ph	Me	4-$NO_2C_6H_4$	4-MeC_6H_4	93	15:1
9	Ph	Me	Ph	4-MeC_6H_4	81	6:1
10	Ph	Me	4-$MeOC_6H_4$	4-MeC_6H_4	45	2:1

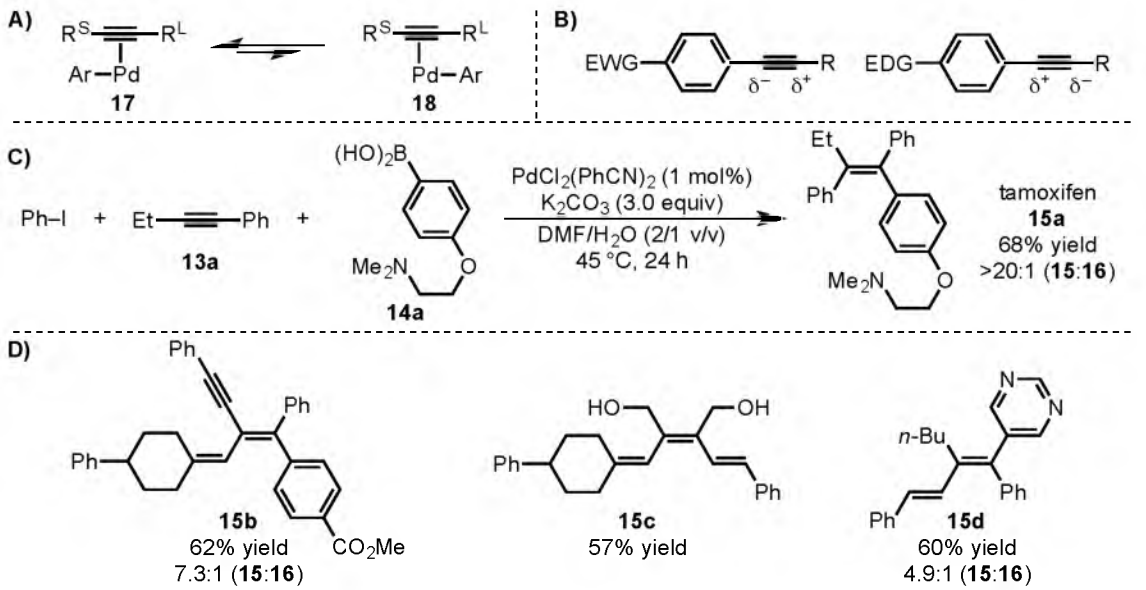


Figure 1.4 Pd-catalyzed intermolecular diarylation reaction of substituted alkynes. **A)** Rationalization of regioselectivity based on steric influence of unsymmetrical alkyne. **B)** Rationalization of regioselectivity based on electronic influence of arylacetylene. **C)** Synthesis of Tamoxifen via diarylation of 1-phenyl-butyne. **D)** Representative scope of challenging coupling partners.

Migratory insertion of the less hindered position of the alkyne (denoted by R^s) would be favored for the relatively large aryl group on palladium. This reasoning also helps to explain the decreased reactivity of bulky aryl iodides, such as 2-tolyl iodide (entry 2, Table 1.1). As entries 8–10 demonstrated, the electronic character of the alkyne also plays a critical role in the regioselectivity resulting from carbopalladation. Palladium favors carbopalladation toward the more electronically stabilizing position on the arylacetylene, denoted by δ^- in Figure 1.4B. The electronic character between the two carbons of the alkyne changes when comparing electron-deficient 1-(4-nitrophenyl)-propyne (entry 8) and electron-rich 1-(4-methoxyphenyl)-propyne (entry 10). This results in significantly different regioselectivity of insertion (15:1 to 2:1, respectively). Conflicting steric and electronic effects help to explain why the selectivity for 1-(4-methoxyphenyl)-propyne favors product **15** rather than the misinsertion product **16** (entry 10). While electronic effects should favor the formation of **16**, this would require alkyne precoordination and migratory insertion from the more sterically encumbered face of 1-(4-methoxyphenyl)-propyne (see Figure 1.4A). Therefore, this result suggests that steric influences outweigh electronic effects by directing coordination and insertion to the less hindered position of the alkyne leading to the formation of **15** as the major regioisomer, albeit with decreased selectivity.

Larock and coworkers were able to demonstrate the synthetic utility of the transformation by synthesizing tamoxifen, a pharmaceutical used for the treatment of breast cancer.[19] Although multiple syntheses of tamoxifen and its derivatives have been previously reported,[20,21] they have failed to generate high regio- and stereoselectivity. Furthermore, they often lack synthetic efficiency by requiring difficult to access starting

materials for multistep reaction sequences. After a brief reoptimization of reaction conditions, Larock and coworkers were able to synthesize tamoxifen in a single step in 68% yield and >20:1 regioselectivity from iodobenzene, 1-phenyl-butyne (**13a**), and a functionalized arylboronic acid (**14a**, Figure 1.4 C).[18] This highly regioselective transformation was used to also synthesize analogs of tamoxifen in good yields.

Recently, Larock's group advanced the diarylation reaction of alkynes to more synthetically intriguing substrates (Figure 1.4 D).[22] 1,4-Diphenylbutadiyne could be utilized as a reaction substrate leading to the formation of alkyne containing product **15b** in good yield and regioselectivity. A 1,3,5-triene (**15c**) could be formed with the extension of the difunctionalization to vinyl iodide and styrenylboronic acid coupling partners. Alkyne starting material substituted with an electron-deficient pyrimidine group was also an effective reaction substrate for the formation of **15d** in good yield and moderate regioselectivity.

Oxidative Interception of Heck Intermediates

The development of difunctionalization reactions of alkene coupling partners without pedant stabilizing groups remains a difficult challenge due to rapid β-hydride elimination of alkyl-Pd intermediates. In 2005, Sorenson and coworkers reported a novel aminoacetoxylation of alkenes that avoided β-hydride elimination of alkyl-Pd intermediates by taking advantage of the Pd^{II}/Pd^{IV} redox couple accessed with hypervalent iodine reagents (Figure 1.5A).[23] Oxidation of the metal center in alkyl-Pd intermediates using iodine(III) reagents leads to preferential reductive elimination due to the highly electrophilic character of Pd^{IV}. The primary obstruction to realizing this

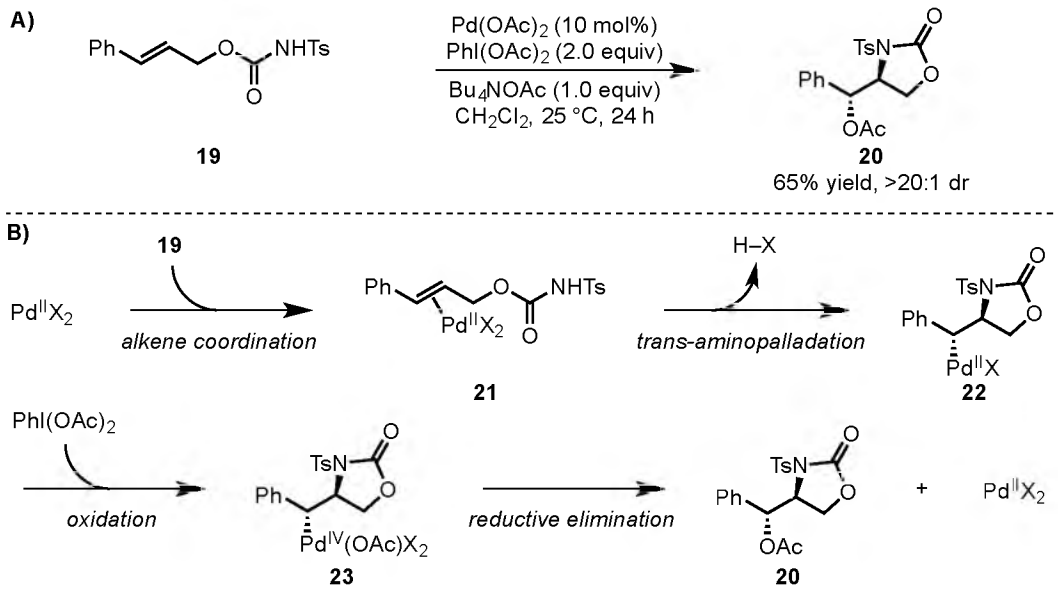


Figure 1.5 Pd-catalyzed intramolecular aminoacetoxylation of alkenes with pendant carbamate groups. **A)** Representative transformation. **B)** Proposed reaction mechanism.

transformation was identifying optimal electron-deficient *N*-protecting groups that would not poison the palladium catalyst. *N*-Tosyl-protected carbamate **19** was found to be optimal for the aminoacetoxylation reaction and resulted in a good yield of 4-acetoxyphenyl *N*-tosyl 2-oxazolidinone **20** in high diastereoselectivity.

Based on experimental observations, Sorensen and coworkers proposed that the mechanism of this transformation initiates with the coordination of alkene **19** to palladium to form **21** (Figure 1.5B). The high diastereoselectivity of the reaction is suggested to result from a *trans*-aminopalladation generating alkyl-Pd intermediate **22**, which can be oxidized by $PhI(OAc)_2$ to the Pd^{IV} species **23**. Efficient oxidation to Pd^{IV} is crucial to prevent formation of β-hydride elimination derived byproducts. The enhanced electrophilic character of **23** facilitates the kinetically preferred reductive elimination of acetate to give product **20** and regenerate the Pd^{II} catalyst.

The Sanford research group has been interested in exploring the function of $Pd^{II/IV}$

catalysis in new organic reactions since their first report in 2004.[24] The first difunctionalization reaction developed by Sanford and coworkers was reported in 2007 and fixated on the interception of enyne cascade cyclizations (Figure 1.6A).[25] Based on previous reports,[26,27] they hypothesized that enyne **24** would undergo acetoxypalladation followed by cyclization, which would yield an alkyl-Pd intermediate. The expected product **26** would then be formed after oxidative interception of the alkyl-Pd species and subsequent reductive elimination. Intriguingly, the major product was bicyclic β-ketolactone **25a**, with the expected product **26** and Heck product **27** being formed in trace amounts (Figure 1.6B). Scope evaluation demonstrated the ability of this method for the stereospecific construction of multiple heterocyclic functionalities including a lactone (**25b**), tetrahydrofuran (**25c**), pyrrolidine (**25d**), and lactam (**25e**). While yields for some enyne substrates were modest, the reaction represents an elegant tool for the stereospecific synthesis of cyclopropane containing molecules.

In an effort to probe the mechanism of this Pd-catalyzed enyne cyclization, substrates with stereochemically defined alkene geometry were evaluated under standard reaction conditions (Figure 1.7A,B). Starting from *E*–**24b** or *Z*–**24b** led to the formation of **25f** and **25g**, respectively, with complete inversion of the stereochemical information from the initial alkene geometry. A putative mechanism consistent with this result is presented below. Further studies provided support for a $Pd^{II/IV}$ mechanism (as opposed to $Pd^{0/II}$) by demonstrating that mild oxidants, such as air or benzoquinone, did not provide the desired cyclization product. In addition to $PhI(OAc)_2$, other strong oxidants such as Oxone and $K_2S_2O_8$ were also shown to successfully facilitate the transformation.

Based on these experimental observations, Sanford and coworkers propose the

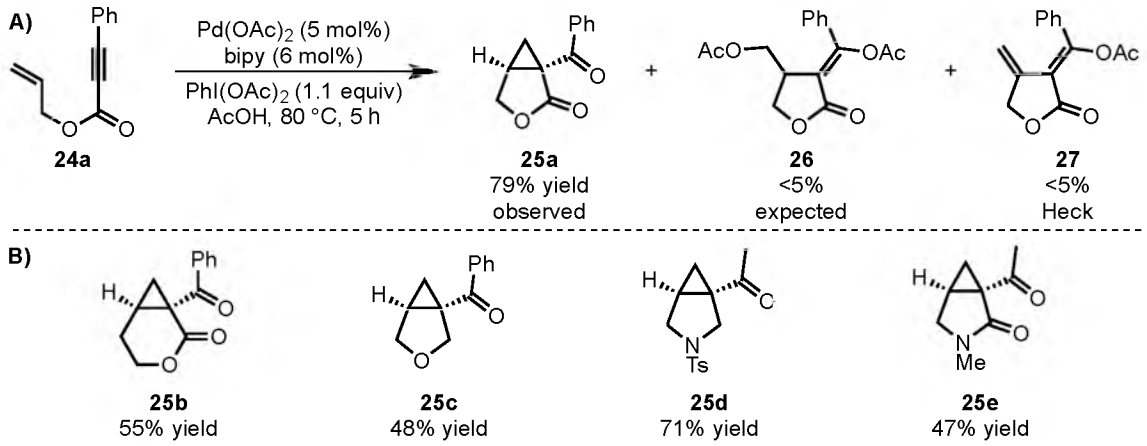


Figure 1.6 Pd-catalyzed difunctionalization of enyne by oxidative interception. **A)** General transformation. **B)** Representative reaction scope.

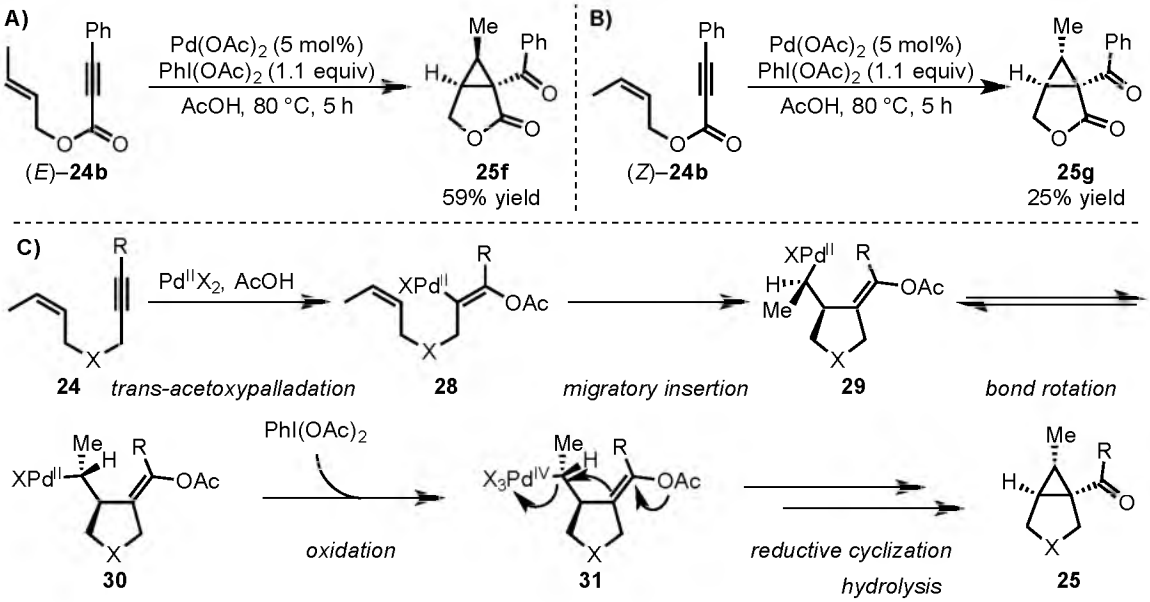


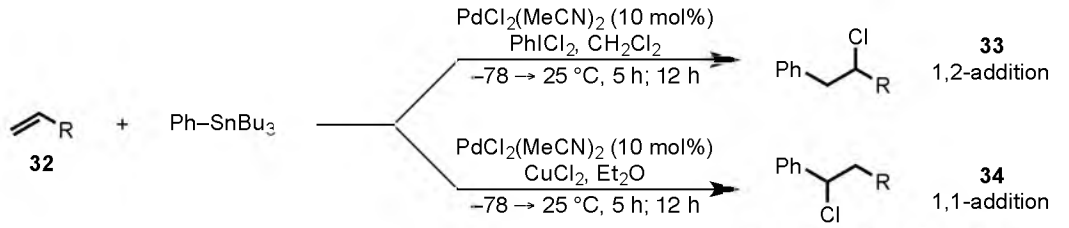
Figure 1.7 Mechanistic experiments and putative reaction mechanism for the oxidative interception of enynes. **A)** Difunctionalization of stereochemically pure enyne starting material (*E*)-**24b**. **B)** Difunctionalization of stereochemically pure enyne starting material (*Z*)-**24b**. **C)** Proposed reaction mechanism.

mechanism of the enyne cyclization is initiated with a *trans*-acetoxypalladation of **24** (Figure 1.7C). The resulting alkenyl-Pd intermediate **28** then inserts into the pendant alkene, which after σ-bond rotation yields alkyl-Pd intermediate **30**. β-hydride elimination is suppressed through oxidation of Pd^{II} to the highly electrophilic Pd^{IV} intermediate **31**. Based on experiments probing the stereochemical outcome of the transformation (Figure 1.7A,B), the authors propose a S_N2-type reductive cyclization of intermediate **31** to account for the observed inversion of the initial alkene stereochemistry. Hydrolysis of the resulting cyclized intermediate would result in the formation of **25**. Despite low to moderate product yields, this methodology is complementary to existing $Pd^{0/II}$ cyclization methodologies, which generate related products with retention of alkene stereochemistry.

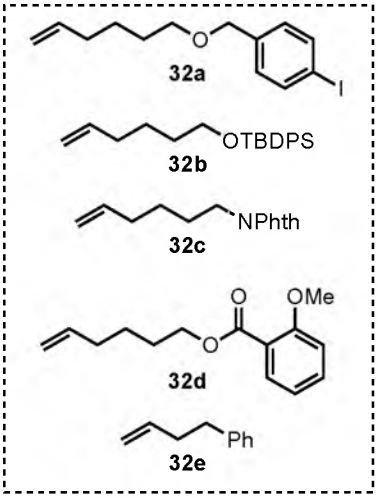
After their first reported $Pd^{II/IV}$ catalyzed difunctionalization reaction, the Sanford research group has remained interested in the development of other powerful strategies for the interception of Heck intermediates in cascade reactions. In some of his pioneering work, Heck reported a Pd-catalyzed 1,2-arylchlorination of methylvinylketone.[28] While the reaction proceeded in 80% yield, the requirement for aryl mercury reagents and the formation of side products from β-hydride elimination limited the synthetic utility of the reaction. In 2008, Sanford and coworkers reported the use of high oxidation state Pd-catalysis to achieve a 1,2- or 1,1-arylchlorination of terminal alkene substrates (Table 1.2).[29] Challenges encountered by Heck associated with β–hydride elimination could be overcome by oxidatively intercepting the problematic alkyl-Pd^{II} intermediate, thereby facilitating secondary functionalization.

Interestingly, it was observed that a more reactive oxidant, such as $PhICl_2$, led to

Table 1.2 Evaluation of scope for the Pd-catalyzed arylchlorination of terminal alkenes.



entry	alkene	oxidant/solvent	yield (%)	**33**:**34**
1	**32a**	$PhICl_2/CH_2Cl_2$	72	8:1
2	**32a**	$CuCl_2/Et_2O$	53	1:>20
3	**32b**	$PhICl_2/CH_2Cl_2$	92	11:1
4	**32b**	$CuCl_2/Et_2O$	66	1:>20
5	**32c**	$PhICl_2/CH_2Cl_2$	85	6:1
6	**32c**	$CuCl_2/Et_2O$	71	1:>20
7	**32d**	$PhICl_2/CH_2Cl_2$	86	8:1
8	**32d**	$CuCl_2/Et_2O$	41	1:>20
9	**32e**	$PhICl_2/CH_2Cl_2$	80	14:1
10	**32e**	$CuCl_2/Et_2O$	82	1:>20



the formation of the 1,2-arylchlorination product **33**, but when a less electrophilic oxidant, such as $CuCl_2$, was employed 1,1-arylchlorination product **34** was formed. Simply by adjusting the oxidant and reaction solvent the methodology can be used to selectively access two distinct and synthetically useful products. Evaluation of the reaction scope demonstrated the ability to generate 1,2- or 1,1-arylchlorination products in good yields with good to excellent regioselectivity (Table 1.2). Terminal alkene substrates containing aromatic halide, benzylic ether (entry 1-2), silyl ether (entry 3-4), amide (entry 5-6), and ester (entry 7-8) functional groups were well tolerated under $PhICl_2$ or $CuCl_2$ oxidative conditions. Recent efforts have revealed the successful extension of this methodology enabling the use of $CuBr_2$ leading to 1,2- and 1,1-arylbromination products.[30]

In an effort to explain the influence of different oxidants on regioselectivity, Sanford and coworkers carried out extensive mechanistic studies.[30] From their observations, they propose that the alkyl-Pd^{II} intermediate formed after migratory insertion is rapidly oxidized by $PhICl_2$ to Pd^{IV}, thus preventing β–hydride elimination and promoting 1,2-regioisomer formation. Alternatively, when $CuCl_2$ is used, the relative rate of β-hydride elimination/reinsertion is greater than that of oxidation. This pathway leads to the formation of a π-benzyl stabilized intermediate (discussed in more detail below). Oxidative functionalization of the resulting π-benzyl stabilized palladium species, then leads to 1,1-arylchlorination product formation.

A deuterium labeling study of 1-octene-(1,1-d_2) provides support for a β-hydride elimination/reinsertion reaction pathway in the formation of 1,1-arylchlorination products (Figure 1.8). Under standard reaction conditions for 1,1-arylchlorination, the authors observed the predicted 1,2-deuterium migration and formation of **34f**. The deuterium migration is the result of β-deuteride elimination followed by reinsertion of Pd-deuteride into the coordinated alkene (**35**) prior to oxidative functionalization. In addition to synthetic appeal, the development and mechanistic investigation of 1,2- and 1,1-arylhaloginations by the Sanford group represents a classic example of tuning relative rates of simple organometallic transformations to control reaction selectivity.

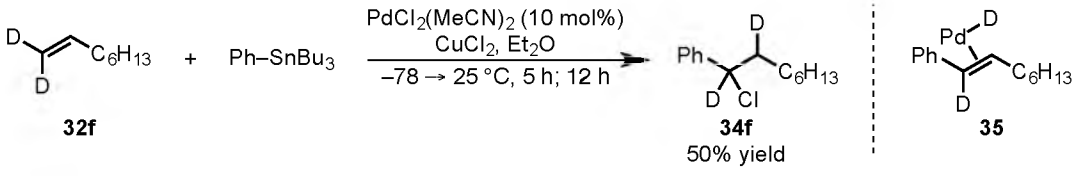


Figure 1.8 Deuterium labeling study of 1-octene-(1,1-d_2).

Reactions of Carbene Precursor Substrates

Traditionally, Pd-carbenes have been used in Heck reactions under both reductive and oxidative reaction conditions.[31-33] Van Vranken and coworkers were the first to report the interception of aryl-Pd intermediates from a Stille cross-coupling sequence with trimethylsilyldiazomethane (**36**, Figure 1.9A).[34] The resulting intermediates underwent secondary functionalization with phenyl tributylstannane leading to the formation of diarylation products (**37a**, **37b**). Since this initial report, interest in difunctionalization reactions of Pd-carbene precursors has gained significant momentum.

The continued advancement of research in this field is appropriately exemplified by Van Vranken's 2009 report describing the Pd-catalyzed vinylamination of ethyl diazoacetate (**40**) to generate α,β-unsaturated γ-amino esters (**41**, Figure 1.9B).[35] The authors observed after reaction optimization experiments that synthetically useful yields of α,β-unsaturated γ-amino esters could be achieved by slow addition of **40** to the reaction mixture and stopping the reaction immediately after complete consumption of

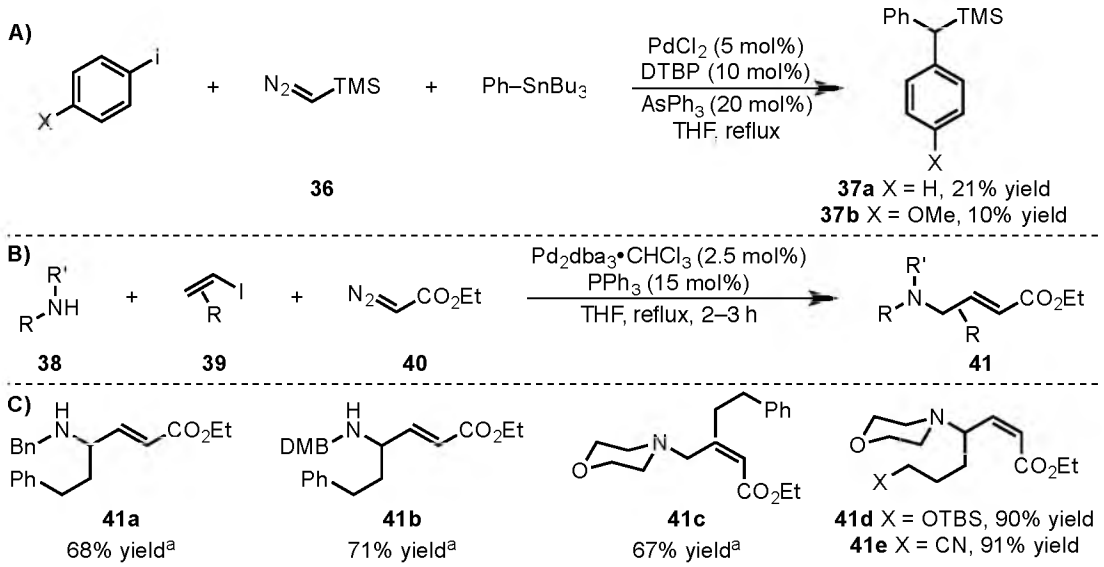


Figure 1.9 Pd-catalyzed difunctionalization of carbene precursor substrates. **A)** Representative diarylation of trimethylsilyldiazomethane. **B)** General vinylamination of ethyl diazoacetate. **C)** Representative reaction scope. [a]5 mol% Pd_2dba_3•$CHCl_3$ was used.

the vinyl iodide (**39**) was detected. Carefully monitoring the reaction reduced the formation of unwanted [3+2] cycloaddition adducts that resulted from reaction between excess α-diazoester starting material (**40**) and the α,β-unsaturated ester containing products (**41**). Evaluation of the reaction scope revealed benzyl amine (**41a**), 2,4-dimethoxybenzylamine (**41b**) and morpholine (**41c**) were effective reaction nucleophiles. Furthermore, the γ-amino ester **41c** was formed with high stereoselectivity for the *cis*-isomer from 1,1-disubstituted iodoalkene starting material. Other iodoalkene substrates containing silyl-protected ethers (**41d**) and cyano (**41e**) functional groups were effective substrates for carbene difunctionalization.

The mechanism of the transformation is proposed to initiate with oxidative addition of **39** to generate Pd–alkenyl intermediate **42** (Figure 1.10). Subsequent Pd-carbene formation through the decomposition of ethyl diazoacetate and reductive insertion into the Pd-carbene gives σ-allyl intermediate **44**. The allylic palladium intermediate can isomerize to the π-allyl intermediate **45** (discussed in detail below), from which nucleophilic attack on the carbon distal to the ester completes the catalytic cycle. Continued research efforts into difunctionalization reactions of carbene precursors

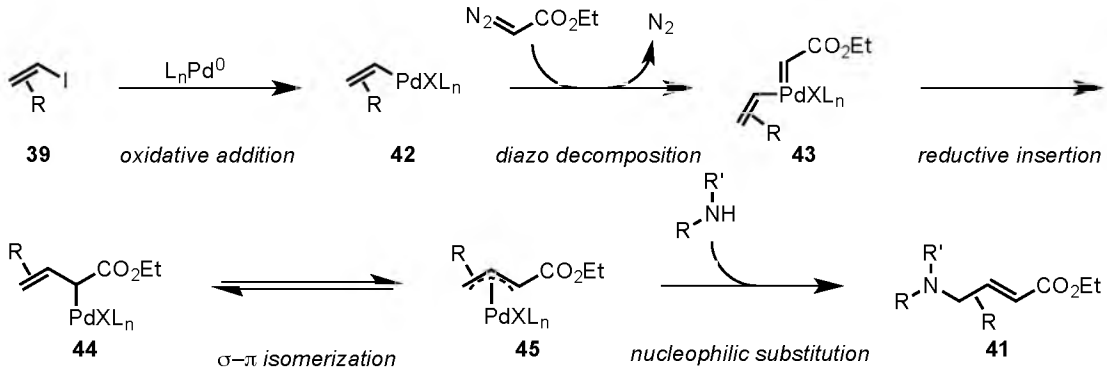


Figure 1.10 Proposed mechanism for the Pd-catalyzed vinylamination of ethyl diazoacetate.

relies on competent reductive insertion into Pd-carbenes and efficient secondary functionalization of resulting carbopalladium intermediates.

Chelation–Assisted Interception of Heck Intermediates

Pendant chelating functional groups have been used in Heck reactions to stabilize intermediates and generate regio- and stereoselectivity. New difunctionalization methodologies have been developed based on this precedent that implement chelating auxiliaries as a means to prevent β-hydride elimination and facilitate secondary functionalization. This strategy has also led to new reactions that generate difficult to access regioisomers with high selectivity. An important consideration to maximize synthetic utility of this type of transformation is the easy installation/detachment of chelating groups, such that a restrictive substrate scope can be circumvented.

One of the first reports of a chelate-assisted difunctionalization was by Larhed and coworkers, wherein they reported a Pd-catalyzed diarylation of chelating vinyl ether substrates (**46a**, Figure 1.11A).[36,37] Interestingly, researchers were able to override the formation of mono-α-arylation and mono-β-arylation Heck products with the use of dimethylamino auxiliaries. Initial screening efforts demonstrated, when bidentate phosphine ligands were used, exclusive formation of mono-α-arylation products were formed. Alternatively, under "ligandless" reaction conditions, the diarylation product (**47**) could be formed in moderate to good yields with high selectivity over mono-β-arylation Heck product (**48**). The importance of a coordinating dimethamino group was illustrated by a screen of other potential coordinating functional groups substituted on the vinyl ether substrate (Figure 1.11B). A diethylamino-chelating group gave greatly

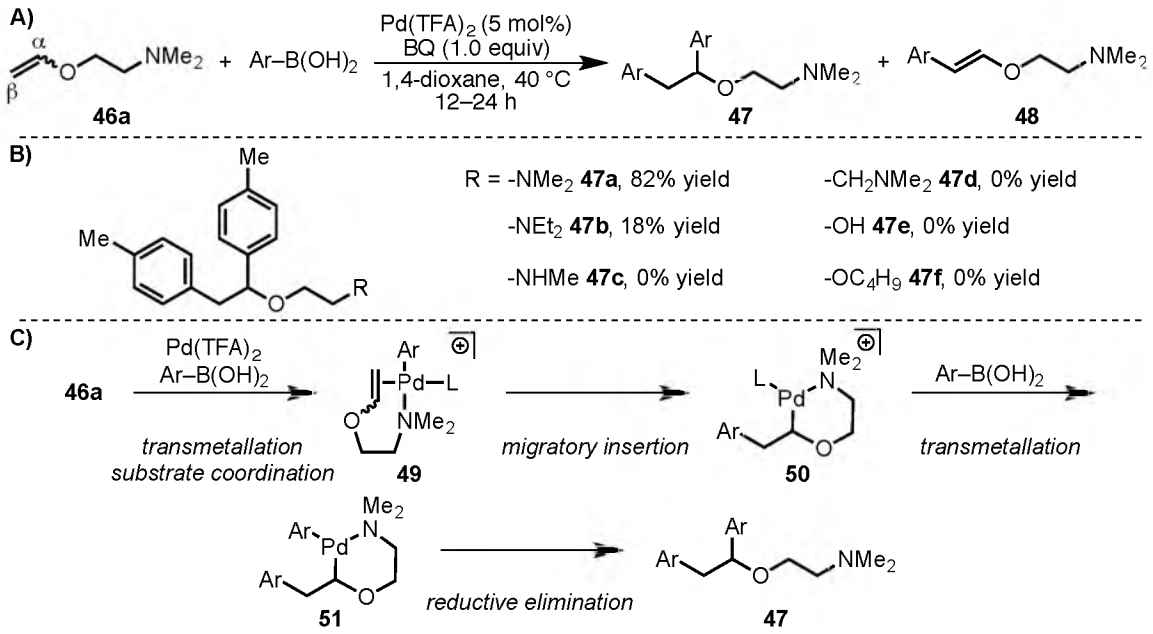


Figure 1.11 Pd-catalyzed diarylation of chelating vinyl ethers with arylboronic acids. **A)** General transformation. **B)** Evaluation of chelating groups. **C)** Proposed reaction mechanism.

reduced yield for the desired product (**47b**) and mostly unreacted starting material. The methylamino auxiliary failed to produce difunctionalized product potentially due to poisoning of the Pd–catalyst by its stronger coordinating ability relative to dialkylamino groups. Extension of the dimethylamino chelating group, alcohol or ether based functional groups were also poor substrates for promoting diarylation.

The putative catalytic cycle for the diarylation of chelating vinyl ethers initiates with transmetallation of an arylboronic acid to palladium and coordination of **46** to give cationic Pd-complex **49** (Figure 1.11C). Chelation-controlled regioselective migratory insertion results in the formation of palladacycle **50**. The authors propose that β-hydride elimination of **50** is slowed by coordination of the amine and BQ to the Pd-center.[38] From intermediate **50**, transmetallation with a second equivalent of arylboronic acid and reductive elimination results in formation of the diarylation product **47**. A clear

limitation of this methodology is the restricted synthetic utility as the result of forming diarylation products with repeated aryl groups.

In 2014, Toste and coworkers reported an innovative method for an asymmetric arylfluorination reaction of styrene derivatives (Figure 1.12A).[39] A critical component of the transformation was the use of an amide-based directing group that could be a ligand for palladium. Initial studies revealed that positioning the directing group in the *ortho*-position of the styrene starting material **52** was optimal to facilitate the formation of fluorinated product **53**. Of the substituted amides evaluated, 8-aminoquinoline (AQ) was the most efficient directing group for the transformation. The authors suggest the directing group binds palladium and both assists migratory insertion and stabilizes the resulting alkyl-Pd species from undergoing β-hydride elimination. In addition to the use of a directing group, the transformation also required the *N*,*N*-bipyridine ligands to occupy coordination sites on palladium and prevent byproduct formation. C–F bond formation is facilitated by generating the highly electrophilic Pd^{IV} complex **54** from the

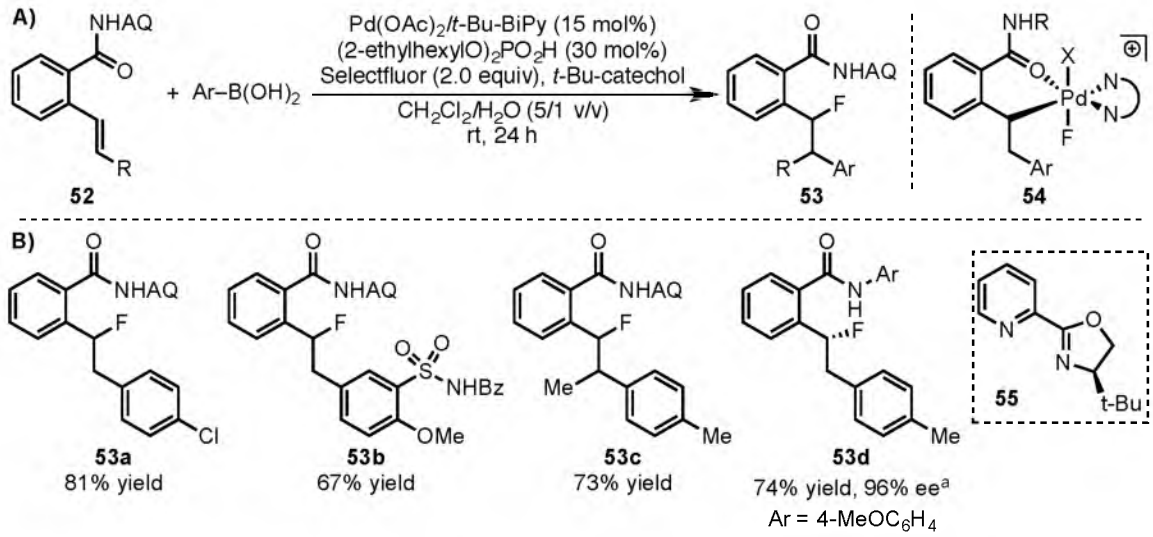


Figure 1.12 Pd-catalyzed arylfluorination of functionalized styrenes with arylboronic acids. **A)** General transformation. **B)** Representative reaction scope. [a]**55** (15 mol%) was used in place of *t*-Bu-BiPy .

oxidation of the corresponding alkyl-Pd^{II} intermediate with Selectfluor.

Investigation into the generality of the reaction revealed tolerance of electron-withdrawing (**53a**) or electron-donating (**53b**–**53d**) functional groups on the arylboronic acid. Product **53c** was formed in good yield and appealingly as a single diastereomer from the (*E*)-internal alkene starting material. Impressively, by adjusting the substrate directing group to 4-methoxyanilide and implementing pyridyl *t*-Bu-oxazoline (**55**) as a chiral ligand, a good yield and 96% enantioselectivity was observed for **53d**. The successful extension of this methodology to an enantioselective variant serves as an appealing complement to existing technologies for the synthesis of asymmetric $C(sp^3)$–F bonds.[40,41]

π–Allyl/Benzyl Stabilized Heck Intermediates

Conjugated dienes, styrenes and allenes have all been utilized as reaction substrates for Pd-catalyzed difunctionalization reactions. In addition to their synthetic appeal, alkenyl/aryl functional groups have been crucial for the development of this reaction class owing to their ability to form π-allyl or π-benzyl stabilizing interactions with adjacent alkyl-Pd intermediates. Bäckvall has reported the development of some of the earliest Pd-catalyzed difunctionalization reactions that exploit stabilizing π-allyl intermediates.[42,43] In 1985, Bäckvall and coworkers reported the 1,4-regioselective acetoxychlorination of cyclic and acyclic 1,3-dienes.[44] A representative example with 1,3-butadiene is shown in Figure 1.13, where product (*E*)–**56** was formed in good yield and regioselectivity. Following initial acetoxypalladation, π-allyl intermediate **58** is proposed to aid in slowing β-hydride elimination. External nucleophilic attack by

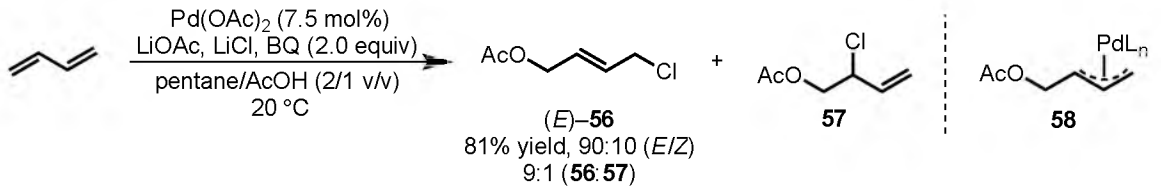


Figure 1.13 Pd-catalyzed acetoxychlorination of 1,3-butadiene.

chloride leads to the formation of either 1,4-addition product **56** or 1,2-addition product **57**.

While π-allyl intermediates have been demonstrated as powerful tools to access alkene difunctionalization manifolds, their use also comes with challenges pertaining to sometimes-complex mixtures of stereo- and regioisomers.[45,46] Two coordination sites are occupied on palladium by η^3 π-allyl groups (**60**), thereby encouraging conformational rigidity that stabilizes the complex and suppresses β-hydride elimination reaction pathways (Figure 1.14).[47] Intermediate **60** can rearrange to the σ-allyl (η^1) complexes **59** or **62**, which frees one coordination site on palladium and allows the respective σ-allyl to undergo functionalization. Reaction at C-2 or C-4 of **60** leads the formation of 1,2-addition product (**61**) or 1,4-addition product (**63**), respectively. Predicting the distribution of regioisomers **61** and **63** in reactions involving π-allyl intermediates is not trivial and often involves fluctuating influences of steric and electronic effects.

E- or *Z*-alkene stereoisomers of 1,4-addition products also form as the result of π-allyl rearragement processes.[47] Following a migratory insertion of a 1,3-diene into a Pd–R bond, σ-allyl intermediate **66** or **67** would be formed (Figure 1.15). Reaction intermediate **66** can isomerize through a σ–π–σ rearrangement to the precursor to a (*Z*)-1,4-addition product (**64**). Alternatively, **66** could undergo carbon–carbon σ–bond

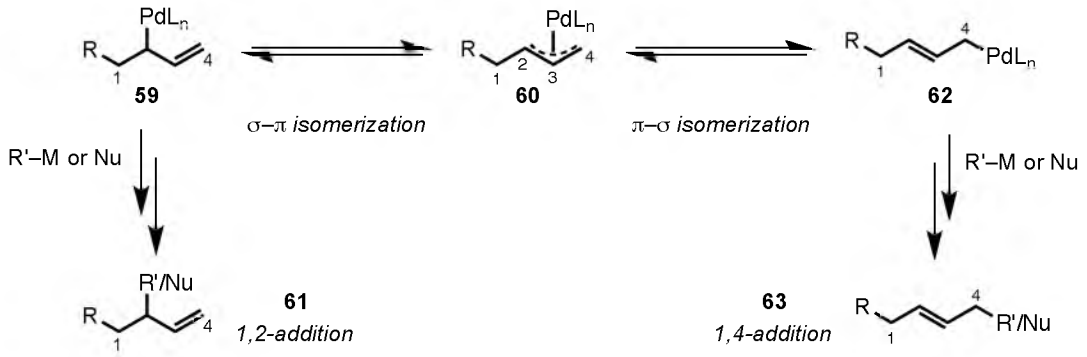


Figure 1.14 Mechanistic rationalization for regioisomers resulting from π-allyl stabilized intermediates.

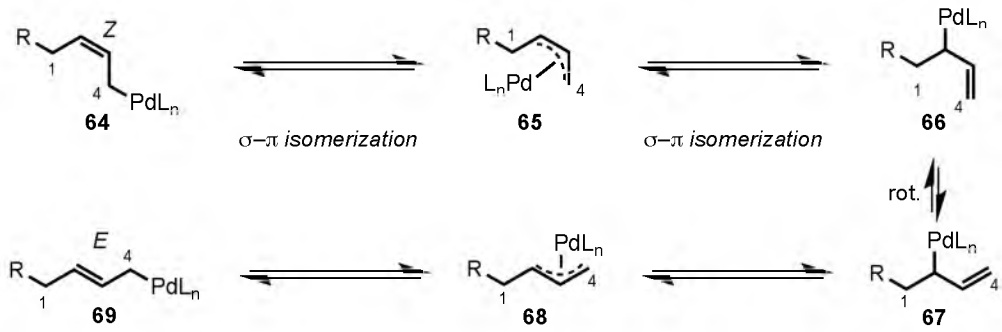


Figure 1.15 Mechanistic rationalization for stereoisomers resulting from π-allyl stabilized intermediates.

rotation to form **67**, which after σ–π–σ rearrangement would form the precursor to a (*E*)-1,4-addition product (**69**). In most examples, this isomerization process provides the more theromodynamically stable *E*-alkene stereoisomer as the major product.

Grigg and coworkers reported in 2002 the synthesis of fused isoxazolidines via a Pd-catalyzed difunctionalization that was immediately followed by a 1,3-dipolar cycloaddition between nitrone and alkene functional groups.[48] Figure 1.16A exemplifies the high molecular complexity and good product yield that this difunctionalization/cycloaddition cascade reaction creates. Interestingly, the transformation avoids the formation of challenging isomeric mixtures by implementing

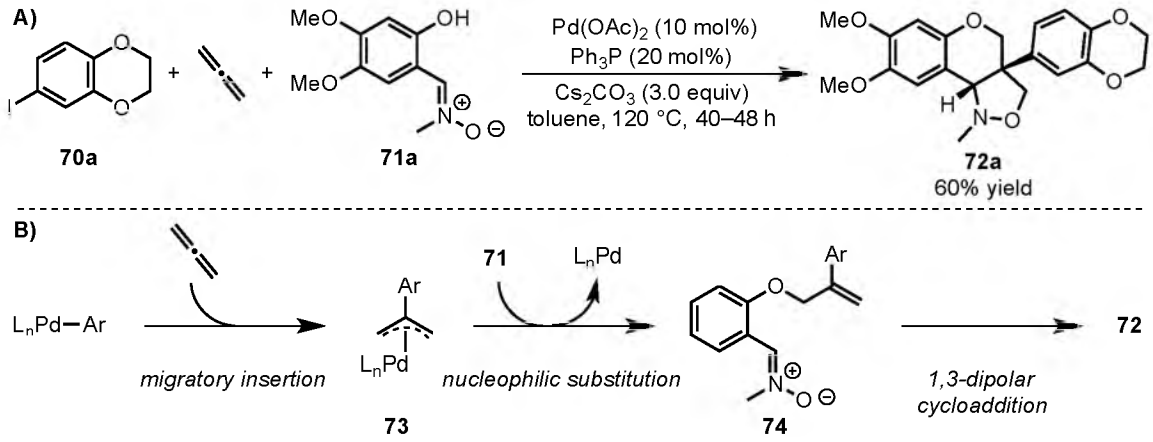


Figure 1.16 Pd-catalyzed difunctionalization of allene and 1,3-dipolar cycloaddition cascade. **A)** Representative transformation. **B)** Proposed reaction mechanism.

allene as the substrate. While regio- and stereoisomers are common for difunctionalization reactions involving π-allyl stabilized intermediates, these complex mixtures are avoided by a highly selective migratory insertion into C-2 of allene to form the symmetric π-allyl intermediate **73** (Figure 1.16B). Phenol **71** completes the catalytic cycle with a nucleophilic substitution of either terminus of the symmetric Pd–complex **73**. The product isoxazolidine (**72**) is produced after a 1,3-dipolar cycloaddition between the 1,1-disubstituted alkene and nitrone functional groups. Overall, this reaction attractively forms two new carbon–carbon bonds as well as two carbon–oxygen bonds.

The Sigman research group has been interested in intercepting σ-alkyl palladium intermediates of Heck reactions for the development of difunctionalization reactions. In an early report, it was shown that styrenes (**76**) serve as good substrates for oxidative diarylation reactions (Figure 1.17A).[49] After an initial Heck insertion, σ-alkyl intermediates are stabilized by a π-benzyl interaction that slows β-hydride elimination enabling secondary functionalization. By tuning the cationic character of the Pd-catalyst, good selectivity for diarylation products was observed over Heck and cross-coupling

products.[50-52] The putative explanation for this observation is that by increasing the electrophilicity of the catalyst, stronger alkene coordination and π-benzyl interactions that are critical for the formation of product are favored.

Intriguingly, selectivity between 1,2-diarylation and 1,1-diarylation regioisomers was directly influenced by the electronic nature of the parent styrene (Figure 1.17A). While an electron-rich substrate (Ar = 4-MeC_6H_4) produced good selectivity for 1,2-diarylation, an electron-deficient styrene (Ar = 4-$CF_3C_6H_4$) gave diminished regioselectivity. The influence of electronic character on product selectivity can be explained by the stabilization of σ-alkyl intermediates by π-benzyl interactions (Figure 1.17B). Electron-deficient styrenes destabilize the cationic π-benzyl intermediate **78**. This in turn causes the relative rate of β-hydride elimination to complete with

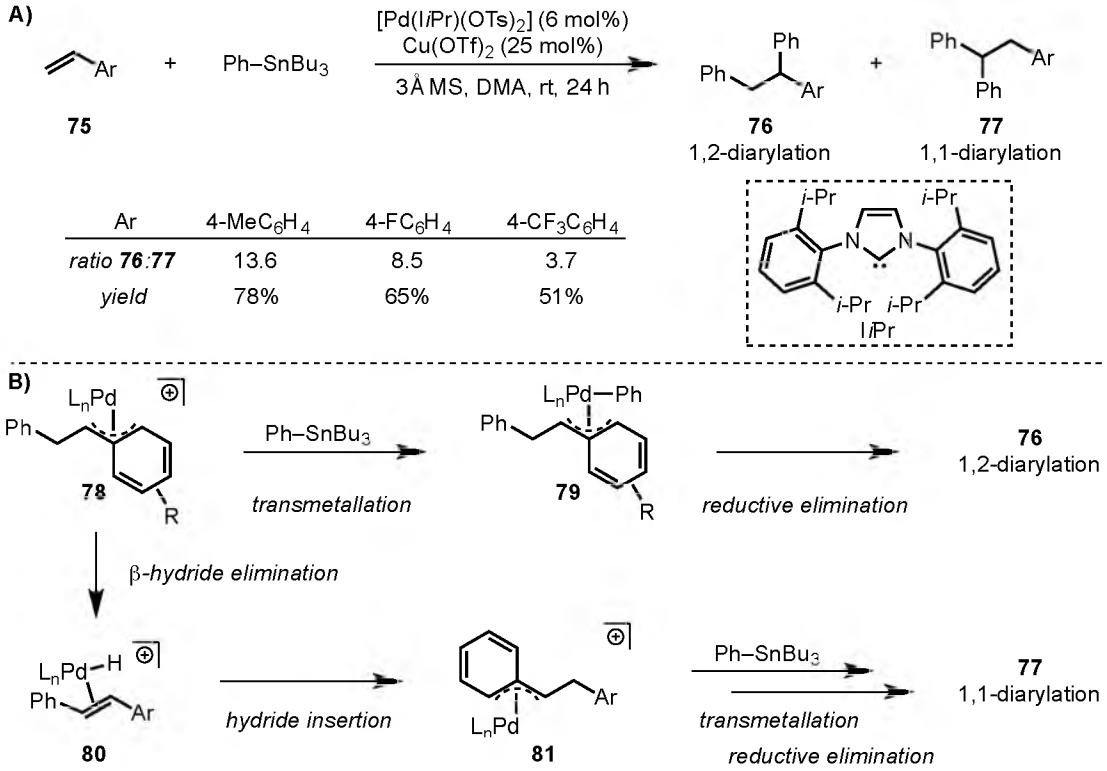


Figure 1.17 Pd-catalyzed diarylation of styrenes with phenyl tributylstannane. **A)** General transformation. **B)** Mechanistic rationalization for the formation of regioisomers.

transmetallation. Therefore, through the process of β-hydride elimination and reinsertion the more electron-rich and stabilizing π-benzyl intermediate **81** can form. A transmetallation and reductive elimination sequence from either **78** or **81** yields the 1,2-diarylation (**76**) and 1,1-diarylation products (**77**), respectively.

Based on these discoveries, the Sigman research group aimed to further develop selective 1,1-difunctionalization reactions of terminal olefin substrates. In 2012, the Sigman group expanded on their efforts with the report of the 1,1-vinylarylation of the commodity chemical ethylene (Figure 1.18A).[53] Analogous to the previously described diarylation technology, the success of the 1,1-vinylarylation is attributed the formation of a stabilized π-allyl reaction intermediate accessed through a β-hydride elimination and reinsertion pathway. Concerns relating to the formation of Suzuki cross-coupling products were addressed with the help of vinyl triflate reagents (**82**), which impart cationic character on palladium intermediates as the result of the noncoordinating character of triflate counter ion. Evaluation of the reaction scope demonstrated that cyclic triflates could be effectively coupled with electron-rich or electron-deficient arylboronic acids in good product yield and selectivity (**83a-83c**, Figure 1.18B).

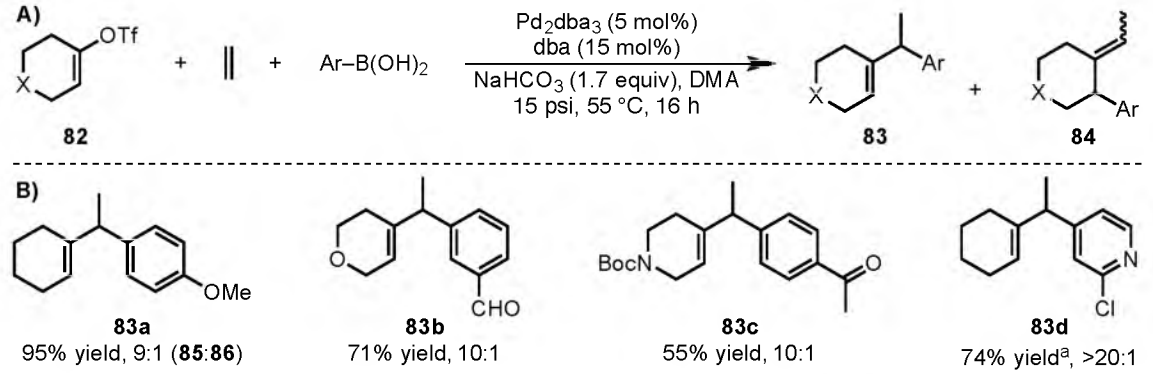


Figure 1.18 Pd-catalyzed vinylarylation of ethylene with vinyl triflates and arylboronic acids. **A)** General transformation. **B)** Representative reaction scope. [a]boronic pinacol ester reagent used in place of boronic acid at 75 °C for 36 hours.

Previous difunctionalization reactions developed by Sigman and coworkers have not tolerated heteroaromatic-coupling partners due to their increased Lewis basicity poisoning the Pd–catalyst.[49,54] Remarkably, for the difunctionalization of ethylene, only a minor reoptimization of conditions was required to attain good yields and regioselectivity with heteroaromatic boronic pinacol ester coupling partners (**83d**).

Continued efforts by the Sigman research group to develop an asymmetric difunctionalization reaction were realized in 2014, when they reported the use of chiral diene ligands for the enantioselective 1,2-diarylation of substituted 1,3-dienes (Figure 1.19).[55] Aryl diazonium tetrafluoroborate reagents were used in this chemistry as a requisite to generate cationic palladium intermediates in addition to their high reactivity toward Pd^0. In a similar fashion to styrenes (discussed above), reaction of 1,3-diene starting materials (**85**) leads to the formation of π-allyl stabilized Pd-intermediates that resist β-hydride elimination. This feature enables secondary functionalization and the formation of a chiral center in the 1,2-diarylation product **86**. The identification of ligands tolerated in the reaction was difficult, as many of the privileged ligand classes, such as phosphines, N-heterocyclic carbenes or diamines, promoted Suzuki cross-coupling pathways. As previously stated, the cationic character of palladium is critical to observe selective migratory insertion of Pd–R intermediates, and strongly donating ligands fail to preserve the electrophilicity required for an effective difunctionalization

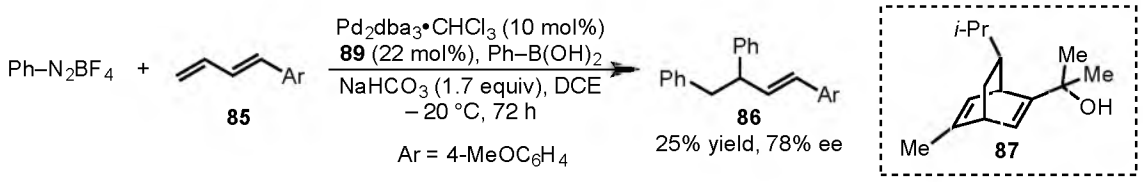


Figure 1.19 Pd-catalyzed enantioselective diarylation of substituted 1,3-dienes using a chiral bicycle[2.2.2]octadienyl ligand.

catalyst. Ligand screens revealed that (*R*)-(–)-α-phellandrene-derived chiral diene **87** could promote asymmetric induction under mild conditions for the formation of diarylation product (**86**), albeit in low yield. This result serves as a promising lead for the potential development of other enantioselective difunctionalizations that do not tolerate the strongly Lewis basic ligands that are traditionally utilized in Pd-catalyzed cross-coupling reactions.

Conclusion

This chapter has focused on various methods to rapidly assemble complex molecules by combining Heck and cross-coupling technologies in difunctionalization reactions. The stabilization of Heck insertion intermediates for secondary functionalization with a nucleophile or organometallic reagent has been accomplished with three primary strategies. These approaches to access difunctionalization reactions include: i) use of reaction substrates that are unable to undergo β-hydride elimination, ii) stimulating reductive elimination pathways by forming high oxidation state palladium intermediates, and iii) slowing β-hydride elimination with the use of pendant stabilizing groups. This chapter has also demonstrated one of the foremost challenges of Pd-catalyzed difunctionalization reactions is the ability to control side reaction pathways to enable formation of desired products in high selectivity.

While methodologies based on the formation of π-allyl/benzyl stabilized intermediates have been instrumental to the development of the research field, questions still remain to be answered. In particular, the ability to selectively access specific regioisomers of difunctionalization reactions that rely on π-allyl stabilized intermediates.

Reactions of this type offer great potential for the ability to rapidly assemble important molecular scaffolds. The following chapters will describe the development of the Pd-catalyzed 1,4-vinylarylation and vinylvinylation reaction of simple 1,3-diene substrates. These reactions are facilitated through the formation of a highly electrophilic palladium catalyst and π-allyl stabilized intermediates. Furthermore, the final chapter details the extension of this chemistry to terminal alkene substrates, wherein 1,3-vinylarylation and vinylvinylation products are formed when a distict class of 1,1-substituted vinyl nonaflates are employed. As will be demonstrated, these 1,4- or 1,3-difunctionalization reactions enable access to unique skipped polyene or allylic arene molecular scaffolds that are difficult to generate using traditional synthetic methods.

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CHAPTER 2

THE DEVELOPMENT OF A PALLADIUM-CATALYZED 1,4-DIFUNCTIONALIZATION OF 1,3-BUTADIENE TO PRODUCE SKIPPED POLYENES

Introduction

Pd-catalyzed difunctionalization reactions of alkenes are powerful synthetic tools for the rapid assembly of carbon–carbon and carbon–heteroatom bonds. This technology has great appeal to create complex synthetic building blocks from simple chemical feedstock starting materials. One of the primary challenges of developing difunctionalization reactions is controlling mechanistic pathways. In particular, after a Heck insertion of an alkene, the stabilization of alkyl-Pd intermediates is essential to preventing undesired β-hydride elimination.[1-3] By employing 1,3-dienes as difunctionalization substrates a Heck insertion of alkene would generate an alkyl-Pd species, which can isomerize to the π-allyl stabilized Pd-intermediate.[4-7] The σ-π-σ rearrangement of π-allyl Pd-intermediates results in the formation of 1,2- or 1,4-addition products. Thus, the selective formation of either 1,2- or 1,4-difunctionalization products represents a significant challenge for modern reaction development. In this chapter, the development of a highly regio- and stereoselective Pd-catalyzed 1,4-difunctionalization reaction of the commodity chemical 1,3-butadiene will be discussed. This methodology

generates skipped diene and triene containing products, which are common scaffolds within a variety of bioactive natural products. Representative strategies for the synthesis of skipped dienes and trienes will also be briefly discussed.

Background

Skipped dienes (1,4-dienes) and higher homologues (skipped polyenes) are abundant structural motifs, composed of alkenes separated by methylene units. From polyunsaturated fatty acids to structurally complex natural products, skipped polyenes are found in a variety of molecules with potent biological properties that include antibiotic, antifungal, and anticancer (Figure 2.1).[8] These structures are most commonly composed of stereochemically defined di- and trisubstituted alkenes. In addition, some skipped polyene containing molecules, such as halichlorine[9,10] or phorbasin C,[11] also have C(sp^3) stereocenters that separate alkenes. The propensity for skipped polyenes to isomerize into a conjugated system is a challenge that often predicates late-stage installation of these groups in natural product total synthesis.[12,13] Although skipped polyenes are frequently present in the structures of bioactive molecules, synthetic methods for their stereoselective synthesis remain limited due to functional group tolerance, selectivity, and reaction efficiency.

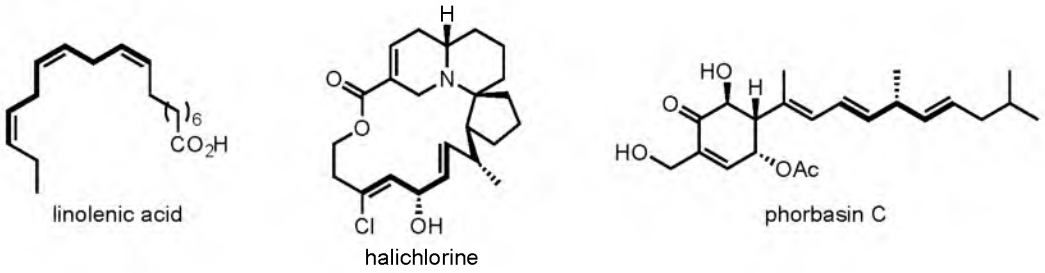


Figure 2.1 Representative skipped polyene containing fatty acid and natural product molecules.

Pd-catalyzed allylic cross-coupling reactions represent a common strategy used for the synthesis of skipped polyenes (Figure 2.2).[14-18] This method is generally accomplished by coupling a vinyl electrophile (**1**) with an allylic organometallic reagent (**2**) in an inter- or intramolecular fashion. One challenge of allylic cross-coupling reactions is the formation of regioisomers due to unselective reductive elimination at either C-1 or C-3 of the π-allyl Pd-intermediate **5**. Unsubstituted organometallic reagents (R' = H) have been used to circumvent complex isomeric mixtures.[19,20] In this case, π-allyl intermediate **5** would be symmetric. Therefore reductive elimination exclusively affords skipped diene product **3**.

In 2012, Prusov and coworkers reported the first total synthesis of bacterial RNA-polymerase inhibitor ripostatin A, wherein they utilized allylic cross-coupling reactions to form the skipped triene structure (Figure 2.3).[21] Due to the sensitive nature of skipped polyenes, the authors proposed late-stage installation of the allylic fragments from functionalized synthetic intermediate **6**. A double Stille cross-coupling reaction of the two vinyl iodides with allyltributylstannane resulted in the regiospecific incorporation of two allylic groups into product **7**. A symmetric π-allyl intermediate (**5**) is accessed after transmetallation with allyltributylstannane, thus resulting in a single product isomer after reductive elimination. Using Grubbs 2nd-generation catalyst, the terminal alkene fragments of **7** were joined through ring-closing metathesis to yield the skipped triene containing macrolactone **8** as a single geometric isomer. While this two-step reaction sequence generates the desired skipped polyene scaffold in good yield and with the correct alkene geometry, 34 mol% of palladium was required to facilitate the double Stille reaction. Other examples from the literature that use allylic cross-coupling

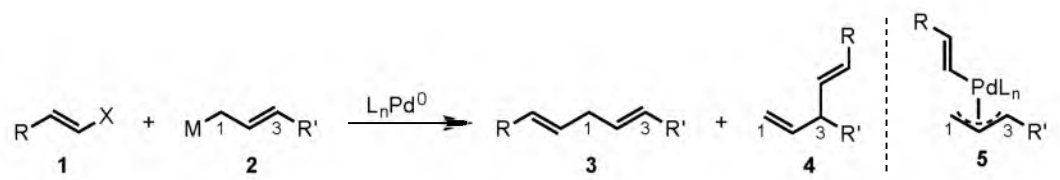


Figure 2.2 General Pd-catalyzed allylic cross-coupling using a vinyl electrophile with an allylic organometallic reagent.

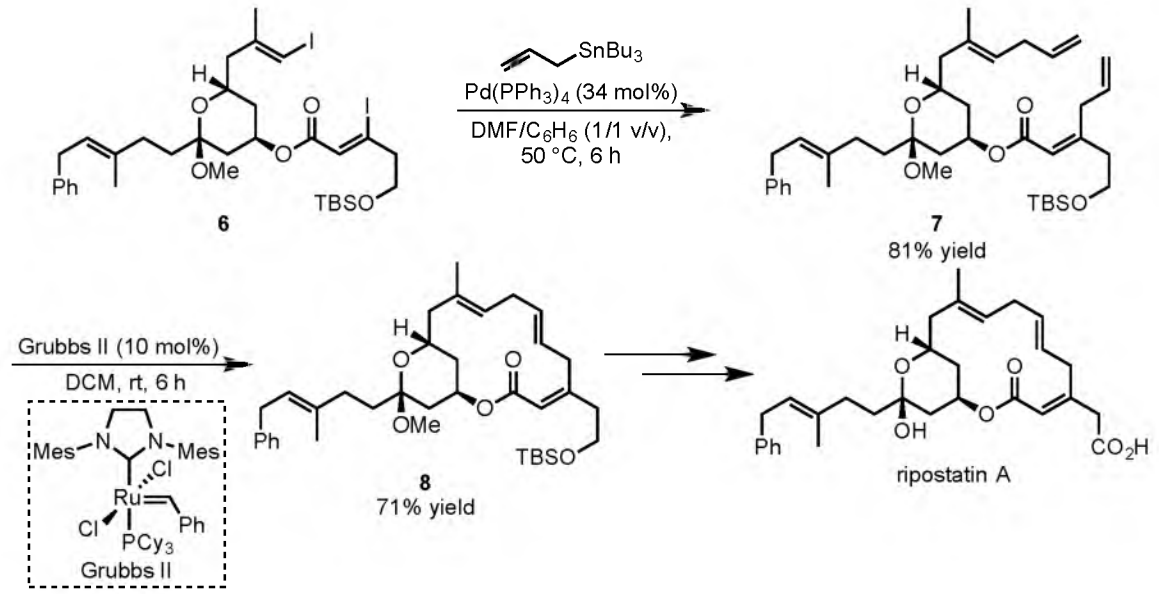


Figure 2.3 The Pd-catalyzed allylic cross-coupling and ring-closing metathesis reactions used in the total synthesis of ripostatin A.

reactions to generate skipped polyenes are also limited by high catalyst loadings, elevated temperatures and low product yields.[14,16,17]

In 1986, Takai and coworkers reported the formation of skipped diene-containing products (**10**) through the stereoselective olefination of aldehydes (**9**, Figure 2.4A).[22] This is a particularly powerful transformation due to the high selectivity observed for the *trans* geometry of **10**, and the generation of the alkenyl iodide synthetic handle. The olefination has also been tolerant of adjacent chiral centers; thus, this is an appealing method to synthesize skipped dienes that include C(sp^3) stereocenters. Since the reaction

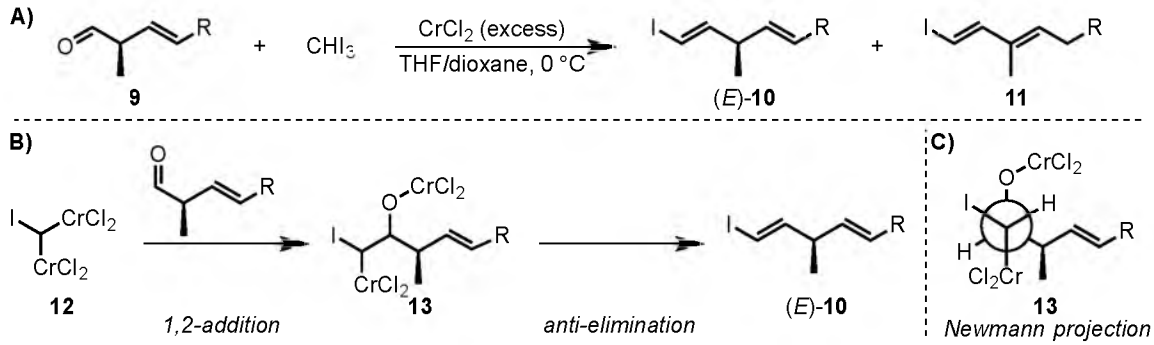


Figure 2.4 Takai and coworkers stereoselective olefination of aldehydes. **A)** General transformation. **B)** Proposed reaction mechanism. **C)** Rationale for stereochemical outcome.

was first reported, the chromium mediated one-carbon homologation has been used in the total syntheses of (+)-ambuticin,[23] (+)-phorbasin,[24] and Iejimalide.[13] These total syntheses detail the formation of skipped diene-containing products in moderate to good yields with >20:1 selectivity for the (*E*)-stereoisomers. Interestingly, Micalizio[24] and Fürstner[13] observed small amounts of a 1,3-diene byproduct (**11**), whose formation was attributed to the sensitive nature of the skipped diene motif.

The proposed mechanism of Takai's olefination initiates with the formation an organochromium dianion **12** from a single-electron oxidation of Cr^{II} with iodoform (Figure 2.4 B). The organochromium species **12** then undergoes a 1,2-addition to the aldehyde starting material to afford **13**. The stereoselective formation of (*E*)-**10** is attributed to an *anti*-elimination of **13**, which can be illustrated with a Newmann projection (Figure 2.4C). The chromium groups orient in an *anti*-conformation to minimize steric interactions, thereby resulting in selective elimination. While this technology is an attractive complement to other olefination reactions for the stereoselective synthesis of skipped dienes, the use of excess amounts of toxic chromium salts clearly restricts this chemistry.

As these examples from the literature have shown the synthesis of functionalized skipped polyenes in a mild and highly selective manner with step-economy remains a significant challenge. A modular Pd-catalyzed alkene difunctionalization reaction would be an appealing, high utility method for the synthesis of these important frameworks. As described in Chapter 1, an interest of the Sigman research group has been developing powerful difunctionalization reactions that intercept palladium intermediates of Heck reactions. In 2011, Sigman and coworkers made a significant advance in the exploration of alkene difunctionalization reactions with their report of the Pd-catalyzed 1,2-vinylarylation of substituted 1,3-dienes (Figure 2.5A).[25] Most notably, while previously reported 1,2-diarylation reactions[26,27] were restricted to the installation of repeated aryl units across an olefin, this work enables the addition of two unique coupling partners to a 1,3-diene. Under relatively mild Pd-catalysis conditions, the 1,2-difunctionalization of **15a** with *N*-Boc-protected piperdinyl vinyl triflate **14a** and *ortho*-tolyl boronic acid (**16a**) affords product **17a** in high yield and selectivity over potential byproducts. Selective formation of alkene difunctionalization products over Suzuki cross-coupling or Heck byproducts is attributed to the formation of cationic Pd-intermediates.[28-30]

The proposed mechanism initiates with oxidative addition of vinyl triflate **14** with the starting Pd^0 catalyst. Due to the poor coordinating ability of the triflate counter ion this affords the cationic Pd-intermediate **18** (Figure 2.5B). Preferential coordination of diene **15** to the highly electrophilic Pd-complex promotes migratory insertion rather than Suzuki cross-coupling pathways. From σ-allyl **19**, isomerization of the cationic intermediate to the π-allyl stabilized species (**20**) inhibits β-hydride elimination and formation of Heck byproducts.[4,31-33] Transmetallation of arylboronic acid and reductive

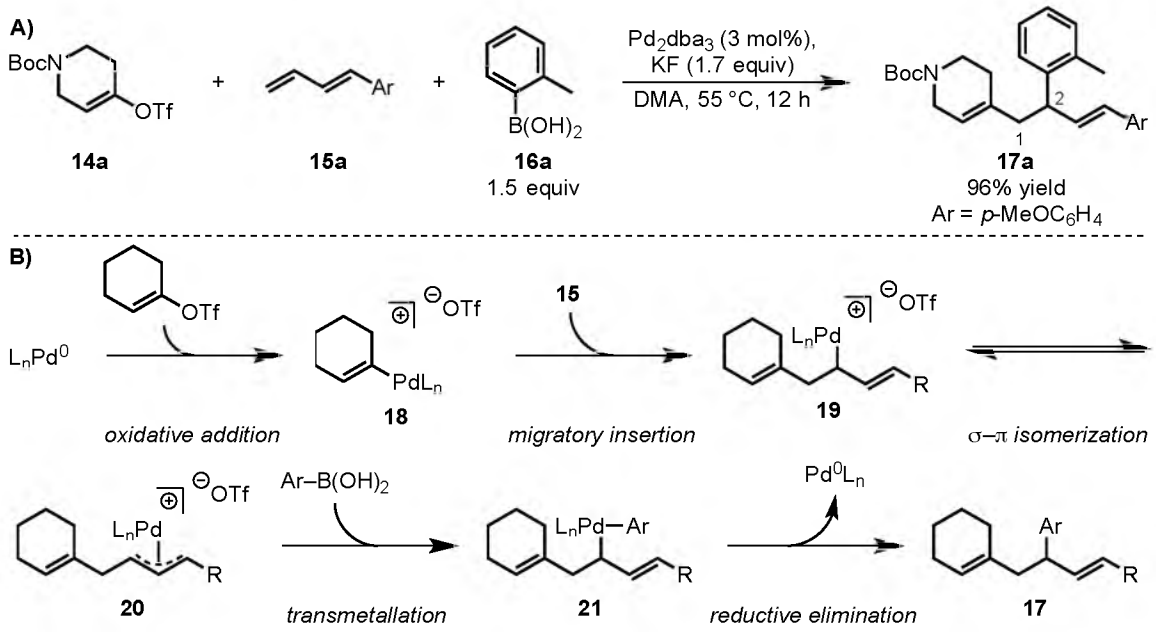


Figure 2.5 Pd-catalyzed 1,2-difunctionalization of substituted 1,3-dienes with vinyl triflates and arylboronic acids. **A)** General transformation. **B)** Proposed mechanism.

elimination results in the formation 1,2-difunctionalization product **17**. Recent studies have suggested the use of DMA as the solvent helps to stabilize cationic palladium intermediates.[30,34] The Pd-catalyzed intermolecular 1,2- vinylarylation of 1,3-dienes affords the formation of $C(sp^2)$–$C(sp^3)$ bonds from distinct coupling-partners in a selective and functional group tolerant manner.

After this first reported 1,2-difunctionalization of substituted 1,3-dienes, the Sigman group has remained interested in developing other alkene difunctionalization reactions that take advantage of the unique reactivity of π-allyl stabilized intermediates. We envisioned an advancement of this methodology that accessed diverse skipped polyene scaffolds by means of a selective 1,4-difunctionalization of feedstock chemical 1,3-butadiene. The σ-π-σ rearrangement of π-allyl Pd-intermediates to the least sterically

hindered C-4 position is proposed to direct carbon–carbon bond formation to the termini of 1,3-butadiene.

Hypothesis and Reaction Optimization

The four-carbon chemical feedstock 1,3-butadiene is produced on over a 10 million ton scale annually and has been used in an array of synthetic transformations.[35-37] A Pd-catalyzed 1,4-difunctionalization of 1,3-butadiene with vinyl triflates (**22**) and boronic acid reagents (**23**) would generate skipped polyene-containing products (**24**) with greatly increased molecular complexity (Figure 2.6A). We proposed the use of vinyl triflate reagents for the generation of cationic Pd-intermediates in a comparable tactic to the previously described 1,2-vinylarylation of substituted 1,3-dienes.[25] Accordingly, the putative mechanism initiates with the oxidative addition of a vinyl triflate with Pd^0, affording the cationic Pd-intermediate **26** (Figure 2.6B). The highly electrophilic palladium species then undergoes selective butadiene coordination in a *cisoid*-type binding mode (**27**),[4,5] which promotes migratory insertion, rather than Suzuki cross-coupling pathways. Following the formation of σ-allyl **28**, σ-π isomerization results in the formation of cationic π-allyl stabilized intermediate **29**. As discussed in Chapter 1, the formation of π-allyl interactions has been shown to stabilize alkyl-Pd species through the suppression of β-hydride elimination, thereby facilitating secondary functionalization. Upon transmetallation of a boronic acid reagent, reductive elimination produces 1,4- (**24**) or 1,2-addition (**25**) regioisomers.

The potential formation of 1,2- and 1,4-addition regioisomers as the result of the uncontrolled reactivity of π-allyl stabilized intermediates was an anticipated challenge of

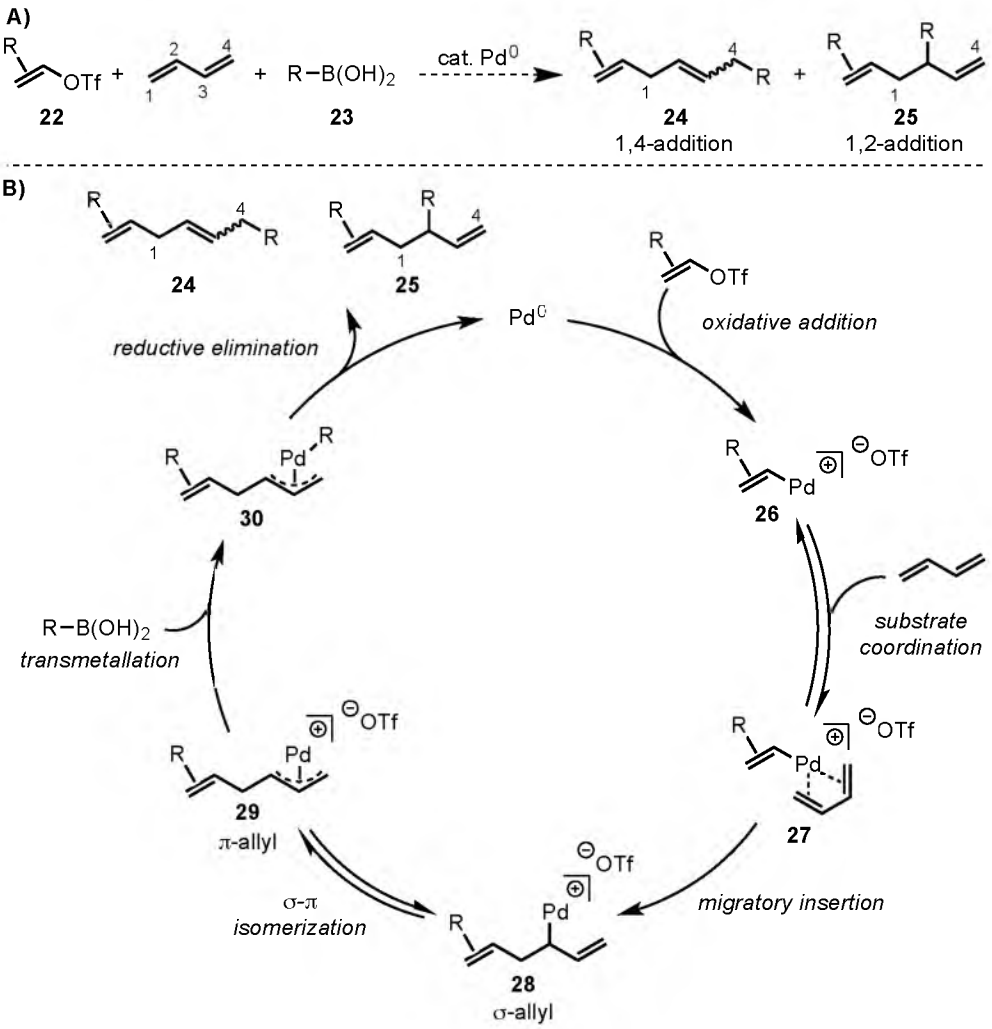


Figure 2.6 Proposed Pd-catalyzed 1,4-difunctionalization of 1,3-butadiene with vinyl triflates and boronic acid reagents. **A)** Representative transformation. **B)** Proposed mechanism.

the 1,4-difunctionalization of butadiene. Following a Heck insertion of 1,3-butadiene into a Pd–R intermediate, σ-allyl **31** (analogous to **28**) would be produced (Figure 2.7). Transmetallation and reductive elimination from **31** would yield the formation of 1,2-addition product (**25**). Alternatively, σ-π isomerization of **31** would afford the π-allyl stabilized species **32**. π-σ Isomerization to the least sterically hindered C-4 position would form **33**, the precursor to the formation of 1,4-addition product **24**.

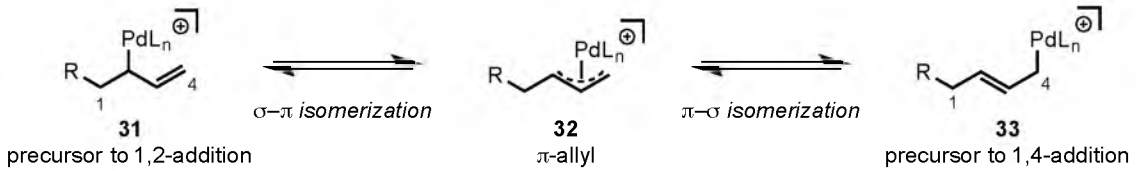


Figure 2.7 Mechanistic rationale for palladium σ-π-σ isomerization.

A report from Bäckvall and coworkers exemplifies the potential for transformations involving π-allyl intermediates to generate complex mixtures of regioisomers.[38] A 4.2:1 mixture of regioisomers in the dialkoxylation of a simple geminal dimethyl substituted 1,3-diene (**34**) was observed (Figure 2.8A). This reaction favored the formation of 1,2-addition product **35** over the 1,4-addition isomer **36**, presumably as the result of steric interactions inhibiting π-allyl isomerization. To avoid complex mixtures of regioisomers, we reasoned that a selective 1,4-difunctinalization of butadiene would require facile σ → π → σ isomerization to readily access the C-4 position of π-allyl intermediates.

We recently described the Pd-catalyzed hydroarylation of substituted 1,3-dienes (**37**) with arylboronic esters, a study that helped to elucidate a trend between product regioselectivity and steric influences on π-allyl intermediates (Figure 2.8B).[39] The formation of 1,2- and 1,4-addition hydroarylation products, **38** and **39** respectively, result from the reductive elimination of π-allyl stabilized intermediates, comparable to those discussed above. An investigation into the influence of substituent effects on the regioselectivity of the reaction revealed an interesting free-energy relationship between the Charton steric parameters and the logarithm of the ratio of 1,2- and 1,4-addition regioisomers (Figure 2.8C).[40-42] Specifically, as the steric component of the diene was decreased, an increase in the formation of the 1,4-addition product **39** was observed

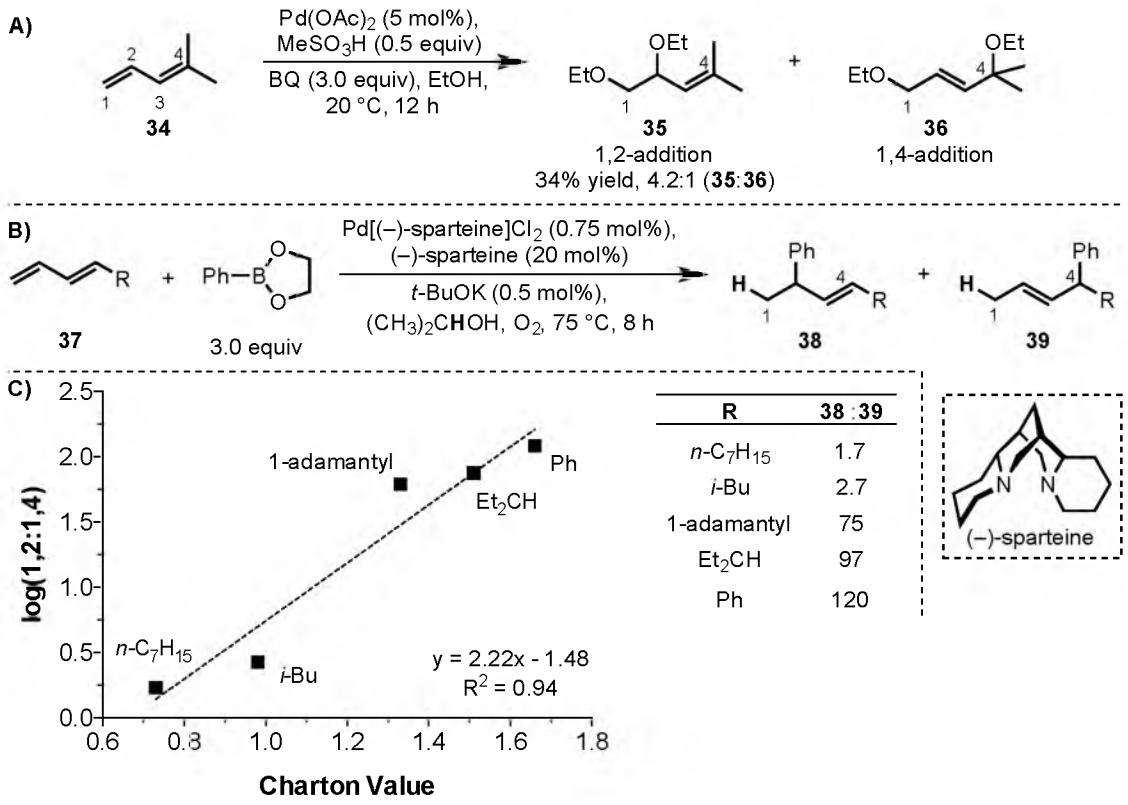


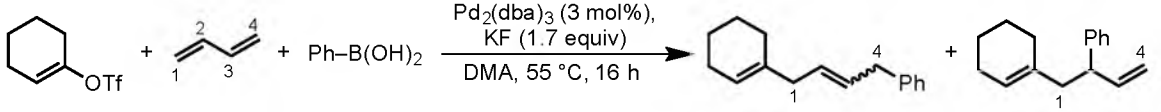
Figure 2.8 Representative examples illustrating reactivity trends of π-allyl stabilized palladium intermediates. **A)** Pd-catalyzed dialkoxylation of a geminal dimethyl substituted 1,3-diene. **B)** Pd-catalyzed hydroarylation of 1,3-dienes with arylboronic esters. **C)** Free-energy relationship between the logarithm of the regioselectivity and Charton steric parameters.

(R = *n*-C_7H_{15}, 1.7:1 for **38**:**39**). Conversely, larger diene substituents gave almost exclusively the 1,2-addition product **38** (R = Ph, 120:1 for **38**:**39**). This observation suggests that the steric environment directly influences the distribution of regioisomers resulting from π-allyl stabilized intermediates. An extrapolation of this relationship predicts that for 1,3-butadiene (R = H), the 1,4-addition product would be favored with >20:1 regioselectivity. While this free energy relationship was identified for a transformation utilizing a Pd–H rather than Pd–vinyl species to initiate alkene functionalization, we were optimistic that under different reaction conditions a similar

trend could be established.

Encouraged by the relationship between steric interactions on π-allyl stabilized intermediates and regioselectivity, we hypothesized that the previously reported 1,2-vinylarylation of substituted 1,3-dienes could be rendered selective for the development of a 1,4-difunctionalization of 1,3-butadiene. Beginning with the optimal conditions for our previously reported difunctionalization,[25] we chose cyclic vinyl triflate **22a**, 1,3-butadiene and phenylboronic acid **23a** for initial reaction screening (Table 2.1).[43] These conditions resulted in an 81% yield of vinylarylation products as an inseparable mixture with 2.4:1 selectivity between 1,4- (**24a**) and 1,2-addition (**25a**) products (entry 1). While 1,3-butadiene was initially introduced in gaseous form, this prevented stoichiometric control of the reagent. Consequently, we transitioned to using a single equivalent of butadiene from a commercially available standard solution (15 wt % in *n*-hexane). As shown in entry 2, this change resulted in decreased product yields (from 81% to 50%, respectively), but a sharp increase in regioselectivity. We proposed the

Table 2.1 Reaction optimization for the Pd-catalyzed 1,4-vinylarylation of 1,3-butadiene. [a]Isolated yield. Yields represent a mixture of 1,4- and 1,2-addition products. [b]Determined by ^{1}H NMR analysis. [c]A 15 wt% solution of 1,3-butadiene in *n*-hexane was used. [d]The nonaflate (NfO) analog of **22a** was used.



22a x equiv | y equiv | **23a** 1.5 equiv | **24a** 1,4-addition | **25a** 1,2-addition

entry	conc. (M)	*x*	*y*	yield (%)[a]	**24a**:**25a**[b]	*E*:*Z*[b]
1	0.05	1.0	*balloon*	81	2.4	88:12
2	0.05	1.0	1.0[c]	50	12.6	91:9
3	0.2	1.0	1.0[c]	79	15.0	91:9
4	0.05	1.5	1.0[c]	71	16.7	90:10
5	0.2	1.5	1.0[c]	84	>20	92:8
6[d]	0.2	1.5	1.0[c]	73	14.3	92:8

basis for this improvement was the result of inhibiting the σ-π-σ isomerization process when a significant excess butadiene was present. If butadiene were in large excess, the diene could occupy coordination-sites on palladium required for facile σ-π-σ isomerization, and therefore lead to an increased formation of the 1,2-addition product **25a**.

Further improvement to regioselectivity and yield was observed by increasing the concentration of the reaction in DMA from 0.05 M to 0.2 M (entry 3). Noting that the undesired product **25a** contained a potentially reactive terminal alkene, we sought to identify conditions to induce additional reactivity of **25a**. This would formally increase the regioselectivity and ease of purification for the 1,4-addition product **24a**. By adding a slight excess of **22a** (entry 4), we observed the regioselectivity increase from 12.6:1 to 16.7:1, likely coming as the result of consuming some of the undesired product **25a**. The optimal reaction conditions were realized with the combination of changes to concentration and stoichiometry, which produced vinylarylation product **24a** with >20:1 regioselectivity and a 92:8 ratio for the *E*-stereoisomer (entry 5). In addition to vinyl triflate **22a**, we also showed a more economical vinyl nonaflate was tolerated within the reaction, providing comparable results (entry 6).[44,45]

Evaluation of Scope

Using the optimal reaction conditions, we began exploring the scope of the 1,4-vinylarylation of 1,3-butadiene (Figure 2.9). We initially focused on evaluating substituted arylboronic acids as well as heterocyclic vinyl triflates/nonaflates. Moderate to good yields were observed for both electron-deficient and electron-rich arylboronic

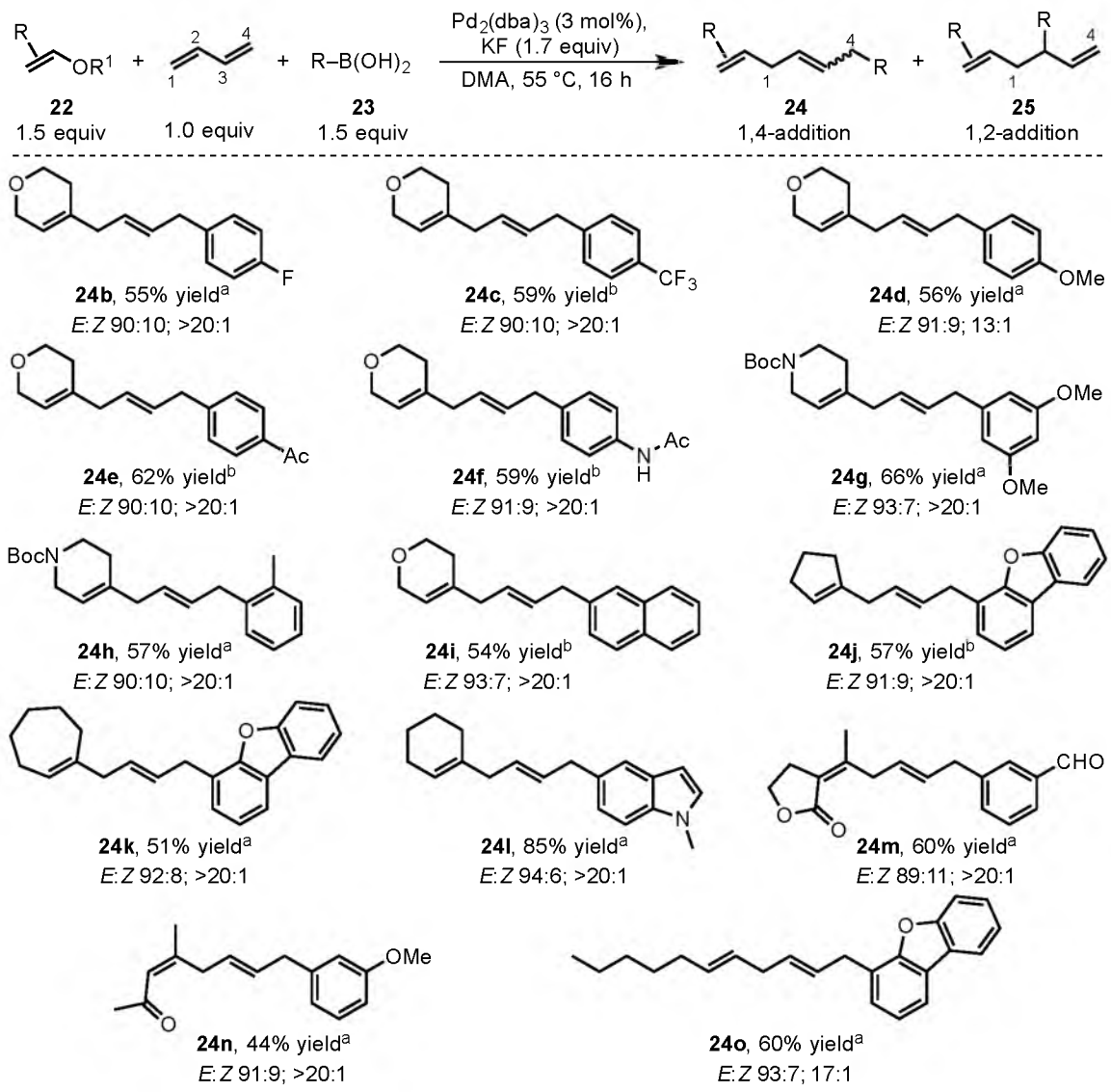


Figure 2.9 Scope of the Pd-catalyzed 1,4-difunctionaliztion of 1,3-butadiene with vinyl triflates and arylboronic acids. Ratios of regio- and stereoisomers were determined by ^{1}H NMR analysis. Yields represent mixtures of stereo- and regioisomers. ^{a}R^1 = Tf. ^{b}R^1 = Nf.

acids (**24b**–**g**). Interestingly, the use of electron-deficient aryl groups resulted in >20:1 regioselectivity, an electron-rich aryl group (**24d**) provided a reduced 13:1 regioselectivity. We were pleased to observe the steric influence of *ortho*-tolylboronic acid (**24h**) was tolerated and afforded good yield and selectivity. Larger arenes, including naphthalene (**24i**) and heteroaromatics (**24j**–**l**), were used as effective coupling partners that resulted in good product regioselectivity. Other heteroaromatic coupling partners containing Lewis basic groups favored the formation of Suzuki and Heck byproducts, presumably as the result of their influence on the electrophilicity of the palladium catalyst. In an effort to access skipped dienes with increased diversity, we evaluated acyclic vinyl triflates derived from β-dicarbonyls. Products **24m** and **24n** were formed from the acyclic vinyl triflate reagents in good selectivity and, most notably, without isomerization of the skipped diene into conjugation with the α,β-unsaturated carbonyl groups. Skipped diene **24o** was formed in good yield, and without loss of stereochemical information from the acyclic vinyl triflate reagent. The evaluation of the reaction scope also demonstrated the formation of the *E*-alkene geometry was favored in all examples, with respect to the internal alkene that results from 1,3-butadiene in the desired product **24**.

In an effort to advance the 1,4-difunctionalization of 1,3-butadiene further, we sought to pursue a vinylvinylation that would generate skipped triene-containing products (Figure 2.10). In this regard, a styrenylboronic acid was evaluated with cyclic and acyclic vinyl triflates resulting in the formation of **24p** and **24q** in moderate to good yields. Skipped triene-containing product **24r** was formed in a useful yield with retention of stereochemistry in the vinylboronic acid fragment. A complex vinylboronic pinacol

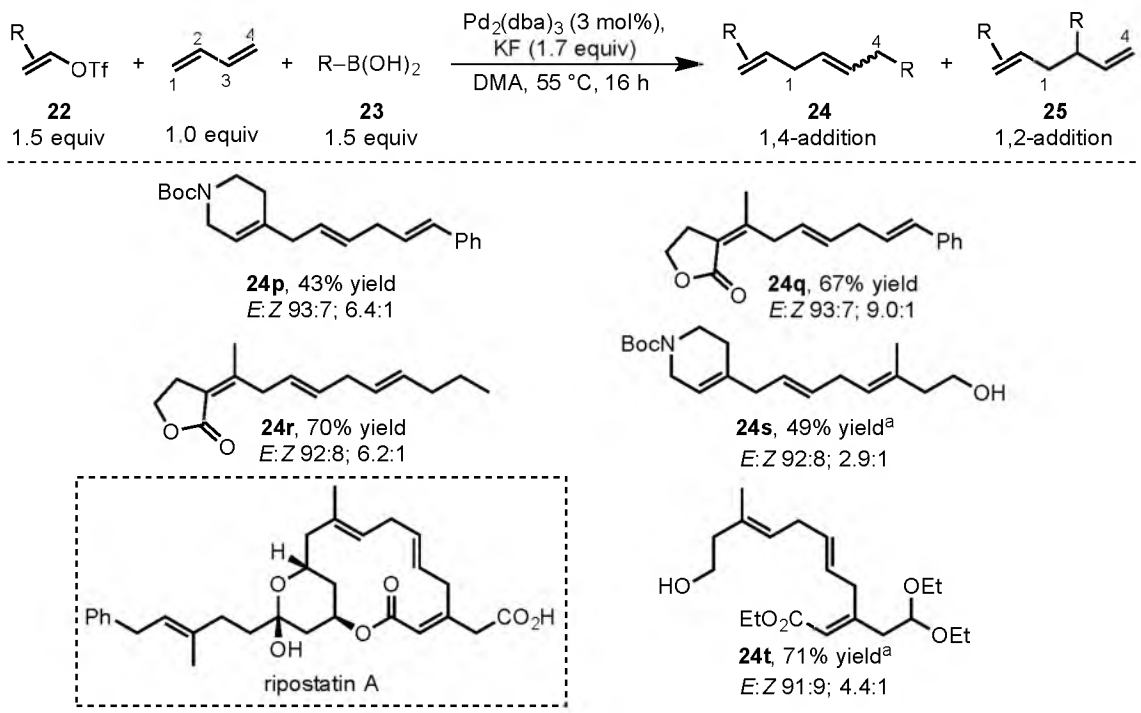


Figure 2.10 Scope of the Pd-catalyzed 1,4-difunctionaliztion of 1,3-butadiene with vinyl triflates and vinylboronic acids. Ratios of regio- and stereoisomers were determined by ^{1}H NMR analysis. Yields are for mixtures of stereo- and regioisomers. [a]The pinacol boronic ester and 6 mol% $Pd_2(dba)_3$ were used.

ester coupling partner containing a trisubstituted olefin as well as a primary alcohol required increased loading of $Pd_2(dba)_3$ to achieve moderate product yield of **24s**. While vinylvinylation products were formed with decreased regioselectivity as compared to those of vinylarylation, the alkene geometry resulting from 1,3-butadiene again favored the desired *E*-stereoisomer. We propose the diminished selectivity between 1,4- and 1,2-addition products results from the decreased steric environment around the π-allyl stabilized palladium intermediate **30**; this then enables reductive elimination at the C-2 position with increased frequency. Enriched mixtures of **24** could be obtained simply by resubmitting the regioisomers to the reaction conditions, wherein the terminal alkene of **25** is selectively consumed.

Encouraged by the successful development of the 1,4-vinylarylation and 1,4-vinylvinylation of 1,3-butadiene, we explored the synthetic utility of the transformation in the context of the skipped triene scaffold of ripostatin (discussed above). Excitingly, the difunctionalization of 1,3-butadiene with highly functionalized coupling partners afforded **24t** in a 71% yield and a moderate 4.4:1 selectivity favoring the desired 1,4-addition product. The formation of **24t** with the correct stereochemistry and functional groups for further modification nicely exemplifies the synthetic potential of this transformation to afford complex molecular scaffolds from a simple feedstock 1,3-diene.

Conclusion

In summary, we have developed a Pd-catalyzed 1,4-difunctionalization of the commodity chemical 1,3-butadiene, which affords efficient access to skipped polyene-containing products. This transformation selectively forms $C(sp^2)$–$C(sp^3)$ bonds at the termini of butadiene using vinyl triflate and aryl or vinylboronic acid coupling partners. High stereochemical control was observed for the formation of the internal alkene from 1,3-butadiene in the *trans* configuration. In addition, the alkene stereochemical information from either coupling partner was preserved through the reaction. Vinylarylation reactions proceeded with exceptional selectivity for the desired 1,4-additions products, and moderate to good regioselectivity was observed when the transformation was evaluated using vinylboronic acid coupling partners. The synthetic power of this methodology was highlighted with the synthesis of the highly functionalized skipped triene core of ripostatin A in only three linear steps from simple chemical building blocks. While a detailed explanation for the variance in

regioselectivity for the reaction remains underdeveloped, we postulate that the steric environment around palladium π-allyl intermediates has a significant influence on the reaction outcome.

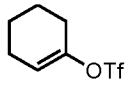
Experimental

General considerations

Anhydrous dimethylacetamide (DMA) was purchased from Aldrich and stored over activated 3 Å molecular sieves (3 Å MS). $Pd_2(dba)_3$ was synthesized according to a previously reported procedure.[46] 1,3-butadiene was used as supplied by Aldrich (15 wt% in *n*-hexane). Unless otherwise noted all reagents and solvents were purchased from Aldrich, Acros, Frontier Scientific, or TCI and used without further purification. ^{1}H-NMR spectra were obtained at 300, 400, or 500 MHz. Chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm. The abbreviations s, d, t, q, quint, sext, dd, ddd, dt, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, quintet, sextet, doublet of doublets, doublet of doublets of doublets, doublet of triplets and multiplet, respectively. ^{13}C NMR spectra were obtained at 75, 100, or 126MHz and referenced to the centerline of the $CDCl_3$ triplet at 77.23 ppm. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). GC separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 50:1 split. IR spectra were recorded using a Thermo Nicolet FTIR. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. LR GCMS data were obtained on an Agilent Technologies 5975C VL MSD instrument.

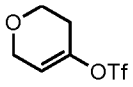
Preparation of vinyl triflate substrates

cyclohex-1-en-1-yl trifluoromethanesulfonate (**22a**):



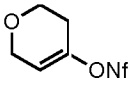
A previously reported procedure was used for the synthesis of **22a** from cyclohexanone.[47]

3,6-dihydro-pyran-4-yl trifluoromethanesulfonate (**22b**):



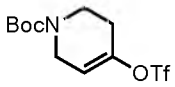
A previously reported procedure was used for the synthesis of **22b** from tetrahydropyran-4-one.[47]

3,6-dihydro-pyran-4-yl nonafluorobutane-1-sulfonate (**22c**):



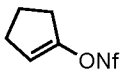
A previously reported procedure was used for the synthesis of **22c** from tetrahydropyran-4-one.[48]

tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1-carboxylate (**22d**):



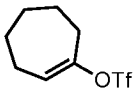
A previously reported procedure was used for the synthesis of **22d** from *tert*-butyl-4-oxopiperidine-1-carboxylate.[49]

cyclopent-1-en-1-yl nonafluorobutane-1-sulfonate (**22e**):



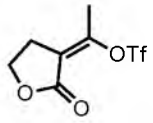
A previously reported procedure was used for the synthesis of **22e** from cyclopentanone.[48]

cyclohept-1-en-1-yl trifluoromethanesulfonate (**22f**):



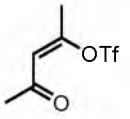
A previously reported procedure was used for the synthesis of **22f** from cycloheptanone.[50]

(*Z*)-1-(2-oxodihydrofuran-3-ylidene)ethyl trifluoromethanesulfonate (**22g**):



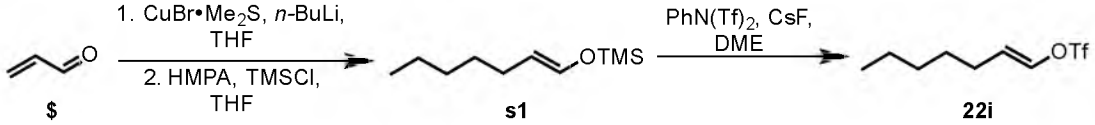
A previously reported procedure was used for the synthesis of **22g** from 3-acetyldihydrofuran-2-one.[51]

(*Z*)-4-oxopent-2-en-2-yl trifluoromethanesulfonate (**22h**):

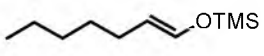


A previously reported procedure was used for the synthesis of **22h** from pentane-2,4-dione.[52]

Preparation of vinyl triflate **22i**



(*E*)-(hept-1-en-1-yloxy)trimethylsilane (**s1**):



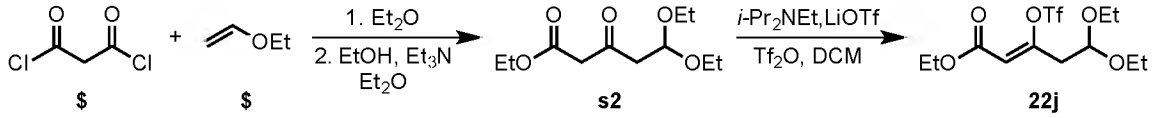
A previously reported procedure was used for the synthesis of **s1**.[53] To a stirred suspension of 2.47 g (12 mmol) of CuBr•Me_2S in 40 mL of THF at –70 °C was added dropwise 9.6 mL of *n*-butyllithium in hexane (2.5 M). The mixture was stirred at –40 °C for 30 min, and then cooled to –70 °C. Then 7.0 mL (40.0 mmol) of hexamethylphosphoramide was added, and following several minutes of stirring a mixture of 1.3 mL (20.0 mmol) of acrolein and 5.0 mL (40.0 mmol) of chlorotrimethylsilane in 12 mL of THF was added dropwise. After 2.5 h of stirring at –70 °C, 5.6 mL (40.0 mmol) of triethylamine and pH 7 phosphate buffer (12 mL) was added. The mixture was diluted with hexanes (20 mL) and filtered through Celite. The filtrate was washed with H_2O (10 x 5 mL) and the aqueous layer was extracted one time with hexanes (10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by distillation to give product in 57% yield (2.135 g, 11.45 mmol) in an *E*/*Z* ratio of 95:5. Analytical data matched the literature.[53]

(*E*)-hept-1-en-1-yl trifluoromethanesulfonate (**22i**):

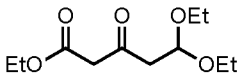
A previously reported procedure was used for the synthesis of **22i**.[54] To a dried round bottom flask 5.72 g (16.0 mmol) of *N*-Phenyl-bis(trifluoromethanesulfonimide) and 3.65 g (24.0 mmol) of vacuum dried (300 °C, 16 h) cesium fluoride was added. A rubber septum was added and the vessel was flushed with N_2. Then 1.49 g (8.00 mmol) of **s1** in 23 mL of DME was added and the rubber septum was replaced with a teflon wrapped plastic cap. The exterior was wrapped with teflon tape and parafilm. After 5 h of stirring the pressure inside the flask was carefully released and the reaction mixture

was portioned between Et_2O (10 mL) and pH 7 phosphate buffer (10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organics were dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography eluting with 2.5% ethyl acetate in hexanes to give product in 56% yield (477 mg, 2.05 mmol) in an *E*/*Z* ratio of 97:3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (d, *J*=11.7 Hz, 1H), 5.77 (dt, *J*=12, 4.2 Hz, 1H), 2.04 (q, *J*=7.5 Hz, 2H), 1.47-1.22 (m, 6H), 0.89 (t, *J*=6.9 Hz, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.0, 123.1, 118.8 (q, ^1J=319 Hz), 31.2, 28.5, 26.7, 22.5, 14.1; FTIR (thin film): 1666, 1421, 1202, 1052, 970, 851, 764 cm^{-1}; LRGC-MS *m*/*z* calculated for $C_8H_{13}F_3O_3$: 246.05, found 246.00.

Preparation of vinyl triflate **22j**



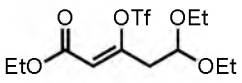
Ethyl-5,5-diethoxy-3-oxopentanoate (**s2**):



A previously reported procedure was used for the synthesis of **s2**.[55] To a mixture of 1.8 mL (18.5 mmol) of ethyl vinyl ether in 1.1 mL of diethyl ether was added a solution of 0.36 mL (3.70 mmol) of malonyl chloride in 1.1 mL of diethyl ether dropwise at 0 °C. This mixture was stirred for 1 h at 0 °C after which time 1.9 mL of absolute ethanol and 1.0 mL (7.40 mmol) of triethylamine in 1.1 mL of diethyl ether was added (caution: exothermic reaction) and stirred for 30 min. At completion, 50 mL of saturated solution of ammonium chloride was added and the mixture was allowed to warm to room

temperature. Organics were washed with H_2O (2 x 30 mL) and brine (30 mL), then dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography eluting with 25% ethyl acetate in hexanes to give product in 56% yield (477 mg, 2.05 mmol). Analytical data matched the literature.[55]

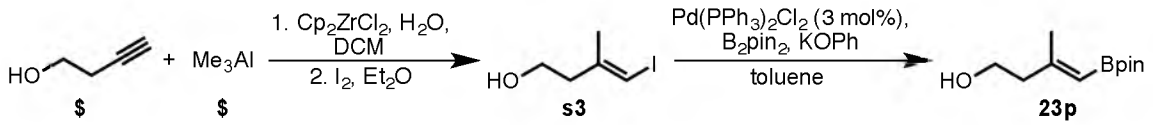
(*Z*)-ethyl 5,5-diethoxy-3-(((trifluoromethyl)sulfonyl)oxy)pent-2-enoate (**22j**):



A previously reported procedure was used in the synthesis of **22j**.[47] To a solution of 430 mg (1.85 mmol) of **s2** and 577 mg (3.70 mmol) of lithium trifluoromethylsulfonate in 57 mL dichlormethane was added 0.35 mL (2.03 mmol) of diisopropyl ethyl amine at 0 °C. After 20 min of stirring at 0 °C, 0.34 mL (2.03 mmol) of trifluoromethanesulfonic anhydride was added and stirred at 0 °C for 25 min at which time TLC analysis showed no remaining starting material. At completion, the mixture was allowed to warm to room temperature followed by addition of 55 mL of saturated solution of ammonium chloride. The aqueous phase was extracted with dichlormethane (2 x 18 mL). The combined organic layers were dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography eluting with 25% ethyl acetate in hexanes with 1% triethyl amine to give product in 65% yield (440 mg, 1.2 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (s, 1H), 4.71 (t, *J*=5.7 Hz, 1H), 4.25 (q, *J*=7.2 Hz, 2H), 3.66 (m, 2H), 3.52 (m, 2H), 2.67 (d, *J*=5.7 Hz, 2H), 1.30 (t, *J*=7.2 Hz, 3H), 1.21 (t, *J*=7.2 Hz, 6H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5, 154.2, 118.5 (q, ^1J=319 Hz), 114.5, 99.3, 62.5, 61.4, 39.7, 15.2, 14.2; FTIR (thin film):

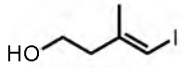
2980, 2359, 1732, 1427, 1140, 926, 668 cm^{-1}; HRMS *m/z* calculated for $C_{12}H_{19}F_3O_7SNa$ $[M+Na]^+$: 387.0701, found 387.0704.

Preparation of vinylboronic acid **23p**



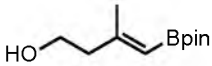
$ $ **s3** **23p**

(*E*)-4-iodo-3-methylbut-3-en-1-ol (**s3**):



A previously reported procedure was used for the synthesis of **s3** from but-3-yn-1-ol.[56]

(*E*)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-ol (**23p**):



To a mixture of 51 mg (0.072 mmol) of $Pd(PPh_3)_2Cl_2$, 1.22 g (4.80 mmol) of bis(pinacolato)diboron, and 952 mg (7.20 mmol) of potassium phenoxide was added a solution of 510 mg (2.40 mmol) of **s3** in 9.0 mL of toluene. The mixture was stirred at 50 °C for 6 h. The reaction mixture was cooled to room temperature, and diluted with 10 mL of diethyl ether. The organic layer was washed with 15 mL of H_2O, 15 mL of brine, dried using magnesium sulfate, and concentrated *in vacuo*. The resulting crude mixture was purified by silica gel flash chromatography eluting with 15% acetone in hexanes to give product in 72% yield (364 mg, 1.72 mmol), R_f = 0.25 (1:5 acetone:hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 5.18 (s, 1H), 3.74 (q, *J*=6.0 Hz, 2H), 2.37 (t, *J*=6.4 Hz, 2H), 2.01 (s, 3H), 1.26 (s, 12H); (The stereochemistry was confirmed by NOESY1D NMR

spectroscopy); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, (vinylic carbon adjacent to boron did not resolve), 83.0, 60.5, 45.2, 25.0, 21.3; FTIR (thin film): 3420, 2359, 1637, 1139, 969, 850 cm^{-1}; HRMS *m/z* calculated for $C_{11}H_{21}O_3BNa$ $[M+Na]^+$: 235.1481, found 235.1479.

General procedure for optimization

In a nitrogen atmosphere glove box, to an oven dried 10 mL Schlenk tube were added 20 mg (0.34 mmol, 1.7 equiv) of KF, 37 mg (0.30 mmol, 1.5 equiv) of **23a**, 6 mg (0.006 mmol, 0.03 equiv) of $Pd_2(dba)_3$, and a solution of 46 mg (0.20 mmol, 1.0 equiv) of **22a** in 4.0 mL of DMA containing an internal standard (tetradecane). The Schlenk tube was transferred from the glove box and 0.14 mL (0.20 mmol, 1.0 equiv) of 1,3-butadiene was added as a 15 wt% solution of *n*-hexane (concentration determined by ^1H NMR - 1.41 M). The vessel was heated at 55 °C in a constant temperature oil bath with stirring for 16 h. After 16 h, a ~200 μL aliquot of the reaction mixture was removed via syringe and filtered through a silica plug, eluting with ethyl acetate. The mixture was analyzed by GC. Conversion of **22a** was calculated using a response factor (^1H NMR was used to measure the response factor to account for varying detector response). Isomeric product ratios were determined using ^1H NMR with a d_1 relaxation time of 5 s for the crude mixtures. Products were purified by silica gel flash chromatography.

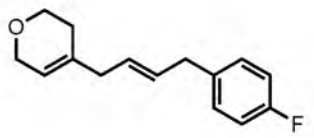
General procedure for the 1,4-difunctionalization of 1,3-butadiene

In a nitrogen atmosphere glove box, to an oven dried 10 mL Schlenk tube were added 49 mg (0.85 mmol, 1.7 equiv) of KF, 91 mg (0.75 mmol, 1.5 equiv) of **23a**, 14 mg

(0.015 mmol, 0.03 equiv) of $Pd_2(dba)_3$, and a solution of 173 mg (0.75 mmol, 1.5 equiv) of **22a** in 2.5 mL of DMA. The Schlenk tube was transferred from the glove box and 0.36 mL (0.50 mmol, 1.0 equiv) of 1,3-butadiene was added as a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.41 M). The vessel was heated at 55 °C in an oil bath with stirring for 16 h. After completion, the mixture was cooled to ambient temperature and diluted with diethyl ether. The organics were washed with H_2O (3 x 10 mL) and brine (1 x 10 mL), then dried over sodium sulfate and concentrated *in vacuo*. Isomeric product ratios were determined using ^{1}H NMR with a d_1 relaxation time of 5 s for the crude mixtures. Crude products were purified by silica gel flash chromatography as noted below. Yields represent a mixture of stereo- and regioisomers.

Product purification and characterization data

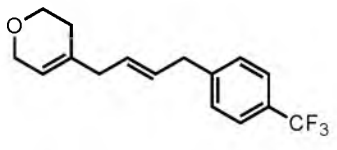
(*E*)-4-(4-(4-fluorophenyl)but-2-en-1-yl)-3,6-dihydro-pyran (**24b**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 105 mg (0.75 mmol) of (4-fluorophenyl)boronic acid (**23b**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 174 mg (0.75 mmol) of 3,6-dihydro-pyran-4-yl trifluoromethanesulfonate (**22b**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24b** and **25b** as a colorless oil (61 mg, 52%, 16.1:1 regioselectivity, *E*/*Z* = 90:10; 67 mg, 58%, >20:1 regioselectivity, *E*/*Z* = 90:10), R_f = 0.42 (3:1 hexanes:EtOAc). **(*E*)-24b**: ^{1}H NMR (300

MHz, $CDCl_3$): δ 7.12 (m, 2H), 6.97 (m, 2H), 5.60 (app. dt, *J*=15.3, 6.6 Hz, 1H), 5.52-5.41 (m, 2H), 4.12 (m, 2H), 3.78 (t, *J*=5.7 Hz, 2H), 3.34 (d, *J*=6.6 Hz, 2H), 2.72 (d, *J*=6.6 Hz, 2H), 2.04 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5 (d, ^1J=244 Hz), 136.4, 134.7, 131.1, 129.9 (d, ^3J=8 Hz), 128.9, 120.5, 115.2 (d, ^2J=21 Hz), 65.7, 64.5, 40.3, 38.3, 28.7. The following signals can be assigned to **(*Z*)-24b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (d, *J*=7.2 Hz, 2H), 2.83 (d, *J*=7.2 Hz, 2H); FTIR (thin film): 2893, 1507, 1218, 1125, 970, 821, 668 cm^{-1}; HRMS *m/z* calculated for $C_{15}H_{18}FO$ $[M+H]^+$: 233.1342, found 233.1345.

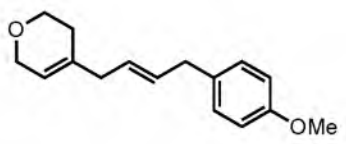
(*E*)-4-(4-(4-(trifluoromethyl)phenyl)but-2-en-1-yl)-3,6-dihydro-pyran (**24c**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 142 mg (0.75 mmol) of (4-(trifluoromethyl)phenyl)boronic acid (**23c**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 287 mg (0.75 mmol) of 3,6-dihydro-pyran-4-yl perfluorobutane-1-sulfonate (**22c**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24c** and **25c** as a yellow oil (75 mg, 54%, >20:1 regioselectivity, *E*/*Z* = 90:10; 90 mg, 64%, >20:1 regioselectivity, *E*/*Z* = 90:10), R_f = 0.43 (3:1 hexanes:EtOAc). **(*E*)-24c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J*=7.9 Hz, 2H), 7.29 (d, *J*=8.5 Hz, 2H), 5.61 (app. dt, *J*=15.3, 6.6 Hz, 1H), 5.51 (app. dt, *J*=15.3, 6.6 Hz, 1H), 5.44 (m, 1H), 4.12 (m, 2H), 3.78 (t, *J*=5.4 Hz, 2H), 3.41 (d, *J*=6.0 Hz, 2H), 2.72 (d, *J*=6.3 Hz, 2H), 2.03 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.9, 134.6, 130.1, 129.7, 128.9, 128.6 (q, ^2J=32 Hz), 125.4 (q,

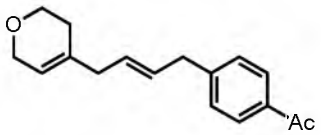
^{3}J=4 Hz), 124.5 (q, ^{1}J=272 Hz), 120.7, 65.7, 64.5, 40.3, 38.9, 28.7. The following signals can be assigned to **(*Z*)-24c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (d, J=6.4 Hz, 2H), 2.84 (d, J=7.2 Hz, 2H); FTIR (thin film): 2923, 2829, 1321, 1160, 1118, 1065, 970, 848, 668 cm^{-1}; HRMS *m/z* calculated for $C_{16}H_{18}F_3O$ $[M+H]^+$: 283.1310, found 283.1307.

(*E*)-4-(4-(4-methoxyphenyl)but-2-en-1-yl)-3,6-dihydro-pyran (**24d**):



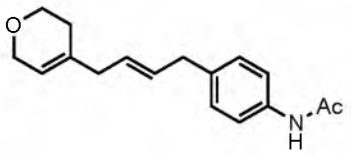
The general procedure was followed using 49 mg (0.85 mmol) of KF, 114 mg (0.75 mmol) of (4-methoxyphenyl)boronic acid (**23d**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 174 mg (0.75 mmol) of 3,6-dihydro-pyran-4-yl trifluoromethanesulfonate (**22b**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24d** and **25d** as a colorless oil (67 mg, 55%, 11.1:1 regioselectivity, *E*/*Z* = 91:9; 69 mg, 57%, 15:1 regioselectivity, *E*/*Z* = 91:9), R_f = 0.40 (3:1 hexanes:EtOAc). **(*E*)-24d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, J=8.9 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 5.61 (app. dt, J=15, 6.6 Hz, 1H), 5.50-5.40 (m, 2H), 4.12 (m, 2H), 3.80-3.76 (m, 5H), 3.30 (d, J=6.6 Hz, 2H), 2.70 (d, J=6.9 Hz, 2H), 2.04 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 134.8, 131.7, 129.5, 128.5, 128.3, 120.4, 114.0, 65.7, 64.6, 55.4, 40.4, 38.2, 28.6. The following signals can be assigned to **(*Z*)-24d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.34 (d, J=7.5 Hz, 2H), 2.82 (d, J=7.2 Hz, 2H); FTIR (thin film): 2896, 2832, 1609, 1242, 1125, 1033, 970, 817 cm^{-1}; HRMS *m/z* calculated for $C_{16}H_{21}O_2$ $[M+H]^+$: 245.1542, found 245.1548.

(*E*)-1-(4-(4-(3,6-dihydro-pyran-4-yl)but-2-en-1-yl)phenyl)ethanone (**24e**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 124 mg (0.75 mmol) of (4-acetylphenyl)boronic acid (**23e**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 287 mg (0.75 mmol) of 3,6-dihydro-pyran-4-yl perfluorobutane-1-sulfonate (**22c**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24e** and **25e** as a yellow oil (73 mg, 57%, >20:1 regioselectivity, *E*/*Z* = 90:10; 86 mg, 67%, >20:1 regioselectivity, *E*/*Z* = 90:10), R_f = 0.36 (3:1 hexanes:EtOAc). **(*E*)-24e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=7.9 Hz, 2H), 5.62 (app. dt, *J*=15, 6.6 Hz, 1H), 5.51 (app. dt, *J*=15.3, 6.6 Hz, 1H), 5.44 (m, 1H), 4.12 (m, 2H), 3.78 (t, *J*=5.7 Hz, 2H), 3.42 (d, *J*=6.5 Hz, 2H), 2.72 (d, *J*=6.5 Hz, 2H), 2.59 (s, 3H), 2.04 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.0, 146.6, 135.4, 134.6, 130.1, 129.6, 128.8, 128.7, 120.7, 65.7, 64.5, 40.3, 39.1, 28.7, 26.7; FTIR (thin film): 2921, 2828, 1680, 1357, 1267, 1125, 970, 848, 668 cm^{-1}; HRMS *m*/*z* calculated for $C_{17}H_{20}O_2Na$ $[M+Na]^+$: 279.1361, found 279.1362.

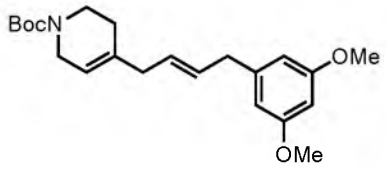
(*E*)-*N*-(4-(4-(3,6-dihydro-pyran-4-yl)but-2-en-1-yl)phenyl)acetamide (**24f**)



The general procedure was followed using 49 mg (0.85 mmol) of KF, 134 mg (0.75 mmol) of (4-acetamidophenyl)boronic acid (**23f**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 287 mg (0.75 mmol) of 3,6-dihydro-pyran-4-yl perfluorobutane-

1-sulfonate (**22c**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (6:4:1:1 EtOAc:DCM:acetone:hexanes) led to the isolation of **24f** and **25f** as a colorless oil (74 mg, 55%, >20:1 regioselectivity, *E*/*Z* = 91:9; 87 mg, 64%, >20:1 regioselectivity, *E*/*Z* = 91:9), R_f = 0.35 (6:4:1:1 EtOAc:DCM:acetone:hexanes). **(*E*)-24f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.24-7.08 (m, 2H), 6.93 (d, *J*=7.7 Hz, 1H), 5.61 (app. dt, *J*=15.3, 6.6 Hz, 1H), 5.54-5.42 (m, 2H) 4.12 (m, 2H), 3.38 (t, *J*=5.7 Hz, 2H), 3.34 (d, *J*=6.3 Hz, 2H), 2.70 (d, *J*=6.6 Hz, 2H), 2.17 (s, 3H), 2.04 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.3, 141.9, 138.1, 134.8, 130.9, 129.1, 128.9, 124.6, 120.5, 120.0, 117.7, 65.7, 64.6, 40.3, 39.0, 28.6, 24.8. The following signals can be assigned to **(*Z*)-24f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (d, *J*=7.2 Hz, 2H), 2.85 (d, *J*=7.3 Hz, 2H); FTIR (thin film): 3303, 2922, 2829, 1664, 1549, 1436, 1317, 1125, 969 cm^{-1}; HRMS *m*/*z* calculated for $C_{17}H_{21}NO_2Na$ $[M+Na]^+$: 294.1470, found 294.1462.

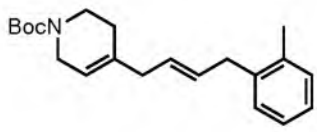
(*E*)-*tert*-butyl 4-(4-(3,5-dimethoxyphenyl)but-2-en-1-yl)-5,6-dihydropyridine-1-carboxylate (**24g**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 136 mg (0.75 mmol) of (3,5-dimethoxyphenyl)boronic acid (**23g**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 249 mg (0.75 mmol) of *tert*-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1-carboxylate (**22d**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane

(concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24g** and **25g** as a yellow oil (121 mg, 65%, >20:1 regioselectivity, *E*/*Z* = 93:7; 125 mg, 67%, >20:1 regioselectivity, *E*/*Z* = 93:7), R_f = 0.38 (3:1 hexanes:EtOAc). **(*E*)-24g**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.34 (d, *J*=2.3 Hz, 2H), 6.30 (t, *J*=2.2 Hz, 1H), 5.59 (app. dt, *J*=15.1, 7 Hz, 1H), 5.48 (app. dt, *J*=15.1, 7 Hz, 1H), 5.38 (s, 1H), 3.85 (m, 2H), 3.77 (s, 6H), 3.47 (t, *J*=6.0 Hz, 2H), 3.28 (d, *J*=6.5 Hz, 2H), 2.70 (d, *J*=7.0 Hz, 2H), 2.03 (m, 2H) 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.9, 155.1, 143.2, 135.7, 130.9, 128.9, 118.7, 106.6, 98.1, 79.5, 55.4, 43.4, 40.4, 39.3, 34.9, 28.6, 28.5. The following signals can be assigned to **(*Z*)-24g**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.31 (d, *J*=7.5 Hz, 2H), 2.80 (d, *J*=7.5 Hz, 2H); FTIR (thin film): 2972, 2836, 1693, 1417, 1238, 1143, 1058, 828 cm^{-1}; HRMS *m*/*z* calculated for $C_{22}H_{31}NO_4Na$ $[M+Na]^+$: 396.2151, found 396.2153.

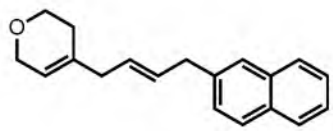
(*E*)-*tert*-butyl 4-(4-(*o*-tolyl)but-2-en-1-yl)-5,6-dihydropyridine-1-carboxylate (**24h**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 102 mg (0.75 mmol) of *o*-tolylboronic acid (**23h**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 249 mg (0.75 mmol) of *tert*-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1-carboxylate (**22d**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24h** and **25h** as a colorless oil (96 mg, 58%, 16.4:1 regioselectivity, *E*/*Z* = 90:10; 92 mg, 56%, >20:1 regioselectivity, *E*/*Z* = 90:10), R_f = 0.50 (3:1 hexanes:EtOAc). **(*E*)-24h**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (m, 4H), 5.59 (app. dt, *J*=15.5, 6.5 Hz, 1H), 5.38 (app. dt, *J*=15, 6.5 Hz, 1H), 5.35 (m, 1H), 3.85 (m, 2H), 3.47 (t, *J*=6.0 Hz, 2H), 3.34 (d, *J*=6.5 Hz, 2H), 2.70 (d, *J*=7.0 Hz, 2H), 2.29 (s, 3H), 2.02 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.1, 138.8, 136.4, 130.5, 130.3, 129.1, 128.5, 126.3, 126.2, 118.6, 79.5, 43.4, 40.5, 36.6, 35.1, 28.6, 28.5, 19.5. The following signals can be assigned to **(*Z*)-24h**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 (d, *J*=7.5 Hz, 2H), 2.80 (d, *J*=7.0 Hz, 2H); FTIR (thin film): 2973, 1693, 1415, 1363, 1237, 1167, 970 cm^{-1}; HRMS *m/z* calculated for $C_{21}H_{29}NO_2Na$ $[M+Na]^+$: 350.2096, found 350.2072.

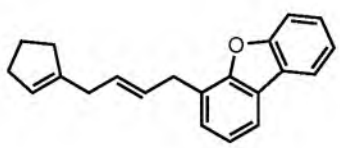
(*E*)-4-(4-(naphthalen-2-yl)but-2-en-1-yl)-3,6-dihydro-pyran (**24i**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 129 mg (0.75 mmol) of naphthalen-2-ylboronic acid (**23i**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 174 mg (0.75 mmol) of 3,6-dihydro-pyran-4-yl trifluoromethanesulfonate (**22b**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24i** and **25i** as a colorless oil (67 mg, 50%, >20:1 regioselectivity, *E*/*Z* = 93:7; 77 mg, 58%, >20:1 regioselectivity, *E*/*Z* = 93:7), R_f = 0.44 (3:1 hexanes:EtOAc). **(*E*)-24i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, *J*=8.0, 6.5 Hz, 3H), 7.62 (s, 1H), 7.44 (quint, *J*=7.5 Hz, 2H), 7.33 (d, *J*=8.5 Hz, 1H) 5.71 (app. dt, *J*=15, 7.5 Hz, 1H), 5.54 (app. dt, *J*=15, 7.0 Hz, 1H), 5.46 (m, 1H), 4.12 (m, 2H), 3.79 (t, *J*=5.5 Hz, 2H), 3.53 (d, *J*=6.5 Hz, 2H), 2.74 (d, *J*=7.0 Hz, 2H), 2.06 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.3, 134.8, 133.8, 132.2, 131.2,

128.9, 128.1, 127.8, 127.6, 127.5, 126.6, 126.0, 125.4, 120.5, 65.7, 64.6, 40.4, 39.3, 28.7. The following signals can be assigned to **(*Z*)-24i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.58 (d, *J*=7.5 Hz, 2H), 2.90 (d, *J*=7.5 Hz, 2H); FTIR (thin film): 2890, 1507, 1425, 1233, 1124, 970, 815, 745 cm^{-1}; HRMS *m/z* calculated for $C_{19}H_{21}O$ $[M+H]^+$: 265.1592, found 265.1584.

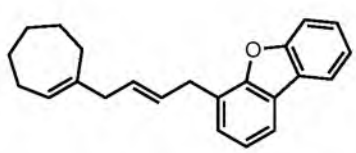
(*E*)-4-(4-(cyclopent-1-en-1-yl)but-2-en-1-yl)dibenzofuran (**24j**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 159 mg (0.75 mmol) of dibenzofuran-4-ylboronic acid (**23j**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 275 mg (0.75 mmol) of cyclopent-1-en-1-yl perfluorobutane-1-sulfonate (**22e**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (99:1 hexanes:EtOAc) led to the isolation of **24j** and **25j** as a colorless oil (75 mg, 52%, >20:1 regioselectivity, *E*/*Z* = 91:9; 88 mg, 62%, >20:1 regioselectivity, *E*/*Z* = 91:9), R_f = 0.53 (19:1 hexanes:EtOAc). **(*E*)-24j**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (dt, *J*=7.7 Hz, 1H), 7.81 (t, *J*=4.5 Hz, 1H), 7.58 (d, *J*=8.5 Hz, 1H), 7.45 (td, *J*=7.8, 1.5 Hz, 1H), 7.33 (td, *J*=7.7, 1.0 Hz, 1H), 7.28 (d, *J*=5.0 Hz, 2H), 5.76 (app. dt, *J*=15, 6.5 Hz, 1H), 5.66 (app. dt, *J*=15, 7 Hz, 1H), 5.36 (m, 1H), 3.72 (d, *J*=6.5 Hz, 2H), 2.80 (d, *J*=6.6 Hz, 2H), 2.30 (m, 2H), 2.23 (t, *J*=6.6 Hz, 2H), 1.85 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.2, 137.0, 130.0, 128.5, 127.3, 127.1, 125.1, 124.7, 124.2, 124.0, 122.9, 122.7, 120.8, 118.5, 111.9, 111.8, 35.3, 34.7, 32.9, 32.6, 23.6. The following signals can be assigned to **(*Z*)-24j**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77 (d, *J*=7.5 Hz, 2H), 3.02 (d,

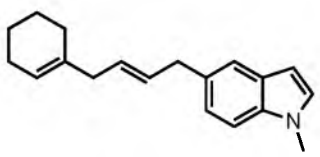
J=7.5 Hz, 2H); FTIR (thin film): 2842, 1450, 1184, 969, 844, 749 cm^{-1};. HRMS *m/z* calculated for $C_{21}H_{21}O$ $[M+H]^+$: 289.1592, found 289.1595.

(*E*)-4-(4-(cyclohept-1-en-1-yl)but-2-en-1-yl)dibenzofuran (**24k**):



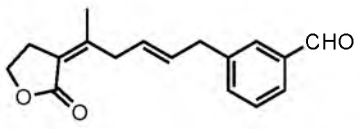
The general procedure was followed using 49 mg (0.85 mmol) of KF, 159 mg (0.75 mmol) of dibenzofuran-4-ylboronic acid (**23j**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 183 mg (0.75 mmol) of cyclohept-1-en-1-yl trifluoromethanesulfonate (**22f**) in 2.5 mL of DMA, and 0.41 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^1H NMR - 1.22 M). Purification by flash chromatography (99:1 hexanes:Et_2O) led to the isolation of **24k** and **25k** as a colorless oil (82 mg, 51%, 20:1 regioselectivity, *E*/*Z* = 92:8; 81 mg, 51%, >20:1 regioselectivity, *E*/*Z* = 92:8), R_f = 0.54 (99:1 hexanes:Et_2O). **(*E*)-24k**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (dt, *J*=8.0 Hz, 1H), 7.81 (t, *J*=4.5 Hz, 1H), 7.59 (d, *J*=8.0 Hz, 1H), 7.46 (td, *J*=7.4, 1.0 Hz, 1H), 7.33 (td, *J*=8.0, 1.0 Hz, 1H), 7.29 (d, *J*=5 Hz, 2H), 5.76 (app. dt, *J*=15.5, 7.0 Hz, 1H), 5.58 (m, 2H), 3.73 (d, *J*=6.5 Hz, 2H), 2.72 (d, *J*=6.5 Hz, 2H), 2.08 (m, 4H), 1.71 (quint, *J*=5.5 Hz, 2H), 1.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 154.7, 143.5, 130.8, 128.6, 127.3, 127.0, 126.7, 125.2, 124.7, 124.0, 122.9, 122.7, 120.8, 118.5, 111.8, 43.4, 32.9, 32.8, 32.7, 28.5, 27.5, 26.8. The following signals can be assigned to **(*Z*)-24k**: ^1H NMR (500 MHz, $CDCl_3$): δ 3.79 (d, *J*=7.0 Hz, 2H), 2.95 (d, *J*=7.5 Hz, 2H); FTIR (thin film): 2916, 2360, 1449, 968, 748 cm^{-1}; HRMS *m/z* calculated for $C_{23}H_{25}O$ $[M+H]^+$: 317.1905, found 317.1914.

(*E*)-5-(4-(cyclohex-1-en-1-yl)but-2-en-1-yl)-1-methyl-indole (**24l**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 131 mg (0.75 mmol) of (1-methyl-indol-5-yl)boronic acid (**23k**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 173 mg (0.75 mmol) of cyclohex-1-en-1-yl trifluoromethanesulfonate (**22a**) in 2.5 mL of DMA, 0.41 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.22 M). Purification by flash chromatography (19:1 hexanes:acetone) led to the isolation of **24l** and **25l** as a colorless oil (114 mg, 86%, >20:1 regioselectivity, *E*/*Z* = 94:6; 112 mg, 84%, >20:1 regioselectivity, *E*/*Z* = 94:6), R_f = 0.42 (19:1 hexanes:acetone). **(*E*)-24l**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.24 (m, 1H), 7.06 (d, *J*=8.6 Hz, 1H), 7.02 (d, *J*=3.0 Hz, 1H), 6.42 (d, *J*=3.0 Hz, 1H), 5.65 (app. dt, *J*=15.3, 7.5 Hz, 1H), 5.48 (m, 2H), 3.77 (s, 3H), 3.44 (d, *J*=6.6 Hz, 2H), 2.65 (d, *J*=6.3 Hz, 2H), 2.03-1.88 (m, 4H), 1.70-1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 135.4, 131.7, 131.4, 128.9, 128.7, 125.4, 122.6, 121.4, 120.1, 109.0, 100.6, 41.3, 39.1, 32.8, 28.4, 25.3, 23.0 22.6. The following signals can be assigned to **(*Z*)-24l**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.51 (d, *J*=7.1 Hz, 2H), 2.83 (d, *J*=7.4 Hz, 2H); FTIR (thin film): 2920, 1512, 1338, 1243, 968, 791 cm^{-1}; HRMS *m*/*z* calculated for $C_{19}H_{24}N$ $[M+H]^+$: 266.1909, found 266.1906.

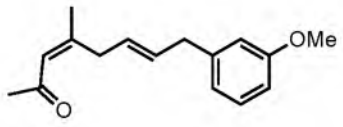
3-((2*E*,5*Z*)-5-(2-oxodihydrofuran-3-ylidene)hex-2-en-1-yl)benzaldehyde (**24m**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 113 mg (0.75 mmol) of (3-formylphenyl)boronic acid (**23l**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a

solution of 195 mg (0.75 mmol) of (*Z*)-1-(2-oxodihydrofuran-3-ylidene)ethyl trifluoromethanesulfonate (**22g**) in 2.5 mL of DMA, and 0.30 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.66 M). Purification by flash chromatography (1:1 hexanes:EtOAc) led to the isolation of **24m** and **25m** as a colorless oil (74 mg, 55%, >20:1 regioselectivity, *E*/*Z* = 89:11; 88 mg, 65%, >20:1 regioselectivity, *E*/*Z* = 89:11), R_f = 0.38 (1:1 hexanes:EtOAc). **(*E*)-24m**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.70 (m, 2H), 7.44 (m, 2H), 5.69 (app. dt, *J*=15, 7.0 Hz, 1H), 5.51 (app. dt, *J*=15.5, 7.0 Hz, 1H), 4.30 (t, *J*=7.5 Hz, 2H), 3.52 (d, *J*=7.0 Hz, 2H), 3.41 (d, *J*=6.5 Hz, 2H), 2.88 (m, 2H), 1.86 (t, *J*=1.5 Hz, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.7, 151.7, 141.9, 136.8, 134.9, 130.6, 129.6, 129.2, 128.9, 128.0, 127.4, 119.1, 64.4, 38.7, 35.9, 27.9, 22.2. The following signals can be assigned to **(*Z*)-24m**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (d, *J*=6.5 Hz, 2H), 3.60 (d, *J*=7.5 Hz, 2H); FTIR (thin film): 2913, 2841, 1736, 1374, 1215, 1035, 969 cm^{-1}; HRMS *m*/*z* calculated for $C_{17}H_{18}O_3Na$ $[M+Na]^+$: 293.1154, found 293.1150.

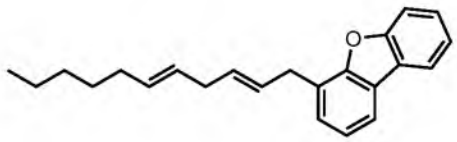
(3*Z*,6*E*)-8-(3-methoxyphenyl)-4-methylocta-3,6-dien-2-one (**24n**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 114 mg (0.75 mmol) of (3-methoxyphenyl)boronic acid (**23m**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 174 mg (0.75 mmol) of (*Z*)-4-oxopent-2-en-2-yl trifluoromethanesulfonate (**22h**) in 2.5 mL of DMA, and 0.41 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR - 1.22 M). Purification by

flash chromatography (9:1 hexanes:acetone) led to the isolation of **24n** and **25n** as a colorless oil (57 mg, 46%, >20:1 regioselectivity, *E*/*Z* = 91:9; 52 mg, 43%, >20:1 regioselectivity, *E*/*Z* = 91:9), R_f = 0.36 (9:1 hexanes:acetone). **(*E*)-24n**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (t, *J*=7.6 Hz, 1H), 6.76 (m, 3H), 6.08 (s, 1H), 5.67 (app. dt, *J*=15.3, 6.9 Hz, 1H), 5.48 (app. dt, *J*=15.0, 6.6 Hz, 1H), 3.90 (s, 3H), 3.35 (d, *J*=6.9 Hz, 2H), 2.83 (d, *J*=7.2 Hz, 2H), 2.18 (s, 3H), 2.12 (s, 3H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 159.7, 157.2, 142.0, 132.4, 129.4, 127.2, 124.0, 120.8, 114.3, 111.3, 55.1, 44.0, 38.9, 31.7, 19.3. The following signals can be assigned to **(*Z*)-24n**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 (d, *J*=6.4 Hz, 2H), 2.97 (d, *J*=7.1 Hz, 2H); FTIR (thin film): 1772, 1684, 1506, 1259, 668, 655 cm^{-1}; HRMS *m*/*z* calculated for $C_{16}H_{20}O_2Na$ $[M+Na]^+$: 267.1361, found 267.1361.

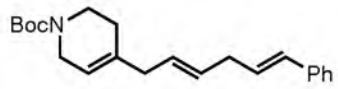
4-((2*E*,5*E*)-undeca-2,5-dien-1-yl)dibenzofuran (**24o**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 159 mg (0.75 mmol) of dibenzofuran-4-ylboronic acid (**23j**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 185 mg (0.75 mmol) of (*E*)-hept-1-en-1-yl trifluoromethanesulfonate (**22i**) in 2.5 mL of DMA, and 0.54 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR – 0.92 M). Purification by flash chromatography (39:1 hexanes:EtOAc) led to the isolation of **24o** and **25o** as a colorless oil (96 mg, 60%, 15.2:1 regioselectivity, *E*/*Z* = 93:7; 94 mg, 59%, 18.1:1 regioselectivity, *E*/*Z* = 93:7), R_f = 0.45 (39:1 hexanes:EtOAc). **(*E*)-24o**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J*=8.0 Hz, 1H), 7.82 (t, *J*=4.4 Hz, 1H), 7.60 (d, *J*=8.2 Hz, 1H), 7.46 (t, *J*=8.0 Hz,

1H), 7.34 (t, *J*=7.6 Hz, 1H), 7.29 (m, 2H), 5.75 (app. dt, *J*=15.8, 7.7 Hz, 1H), 5.63 (app. dt, *J*=15.8, 8.2 Hz, 1H), 5.44 (m, 2H), 3.73 (d, *J*=6.6 Hz, 2H), 2.75 (t, *J*=6.0 Hz, 2H), 1.99 (q, *J*=6.9 Hz, 2H), 1.38-1.23 (m, 6H), 0.88 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 154.8, 131.7, 131.1, 128.3, 127.9, 127.4, 127.1, 125.2, 124.8, 124.1, 123.0, 122.8, 120.9, 118.6, 111.9, 35.8, 32.9, 32.8, 31.7, 29.4, 22.8, 14.3. The following signals can be assigned to **(*Z*)-24o**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.78 (d, *J*=7.8 Hz, 2H), 2.98 (t, *J*=6.8 Hz, 2H); FTIR (thin film): 2922, 1472, 1183, 966, 844, 747 cm^{-1}; HRMS *m/z* calculated for $C_{23}H_{27}O$ $[M+H]^+$: 319.2062, found 319.2070.

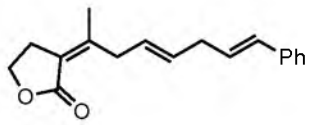
tert-butyl 4-((2*E*,5*E*)-6-phenylhexa-2,5-dien-1-yl)-5,6-dihydropyridine-1-carboxylate (**24p**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 111 mg (0.75 mmol) of (*E*)-styrylboronic acid (**23n**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 249 mg (0.75 mmol) of *tert*-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1-carboxylate (**22d**) in 2.5 mL of DMA, and 0.38 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR – 1.30 M). Purification by flash chromatography (9:1 hexanes:EtOAc) led to the isolation of **24p** and **25p** as a colorless oil (72 mg, 43%, 4.6:1 regioselectivity, *E*/*Z* = 93:7; 73 mg, 43%, 8.3:1 regioselectivity, *E*/*Z* = 93:7), R_f = 0.26 (9:1 hexanes:EtOAc). **(*E*)-24p**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.29 (t, *J*=7.7 Hz, 2H), 7.20 (t, *J*=7.2 Hz, 1H), 6.37 (t, *J*=16 Hz, 1H), 6.21 (app. dt, *J*=16.4, 6.5 Hz, 1H), 5.54 (app. dt, *J*=15.4, 6.5 Hz, 1H), 5.48 (app. dt, *J*=16.3, 6.5 Hz, 1H), 5.38 (s, 1H), 3.86 (m, 2H), 3.48 (m, 2H), 2.93 (t, *J*=6.0 Hz, 2H), 2.71 (d, *J*=6.0 Hz, 2H), 2.05 (m, 2H), 1.47 (m, 9H); ^{13}C NMR (126 MHz,

$CDCl_3$): δ 155.1, 137.8, 132.5, 130.6, 130.1, 129.0, 128.6, 127.1, 126.2, 126.1, 114.9, 79.5, 42.9, 40.5, 36.0, 30.5, 28.6, 28.5. The following signals can be assigned to **(*Z*)-24p**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79 (d, *J*=6.5 Hz, 2H); FTIR (thin film): 2973, 2899, 1675, 1418, 1364, 1171, 668 cm^{-1}; HRMS *m/z* calculated for $C_{22}H_{29}NO_2Na$ $[M+Na]^+$: 362.2096, found 362.2097.

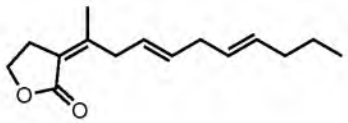
(*Z*)-3-((4*E*,7*E*)-8-phenylocta-4,7-dien-2-ylidene)dihydrofuran-2-one (**24q**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 111 mg (0.75 mmol) of (*E*)-styrylboronic acid (**23n**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 195 mg (0.75 mmol) of (*Z*)-1-(2-oxodihydrofuran-3-ylidene)ethyl trifluoromethanesulfonate (**22g**) in 2.5 mL of DMA, and 0.41 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR – 1.22 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24q** and **25q** as a colorless oil (84 mg, 62%, 10.1:1 regioselectivity, *E*/*Z* = 93:7; 95 mg, 71%, 7.8:1 regioselectivity, *E*/*Z* = 93:7), R_f = 0.29 (3:1 hexanes:EtOAc). **(*E*)-24q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J*=7.2 Hz, 2H), 7.29 (t, *J*=7.6 Hz, 2H), 7.20 (t, *J*=7.2 Hz, 1H), 6.38 (d, *J*=16 Hz, 1H), 6.20 (app. dt, *J*=16, 6.8 Hz, 1H), 5.62 (app. dt, *J*=15.2, 6.4 Hz, 1H), 5.48 (app. dt, *J*=15.2, 6.8 Hz, 1H), 4.30 (t, *J*=8.0 Hz, 2H), 3.51 (d, *J*=6.8 Hz, 2H), 2.89 (m, 4H), 1.87 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 152.0, 137.8, 130.6, 130.5, 128.9, 128.6, 127.7, 127.1, 126.1, 118.9, 64.4, 36.0, 35.9, 27.9, 22.2. The following signals can be assigned to **(*Z*)-24q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (t,

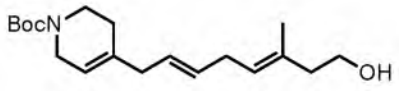
J=7.6 Hz, 2H), 3.64 (d, *J*=7.6 Hz, 2H); FTIR (thin film): 2911, 1493, 1373, 1213, 1035, 966 cm^{-1}; HRMS *m/z* calculated for $C_{18}H_{20}O_2Na$ $[M+Na]^+$: 291.1361, found 291.1361.

(*Z*)-3-((4*E*,7*E*)-undeca-4,7-dien-2-ylidene)dihydrofuran-2-one (**24r**):



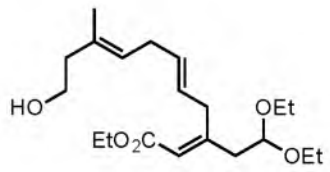
The general procedure was followed using 49 mg (0.85 mmol) of KF, 86 mg (0.75 mmol) of (*E*)-pent-1-en-1-ylboronic acid (**23o**), 14 mg (0.015 mmol) of $Pd_2(dba)_3$, a solution of 195 mg (0.75 mmol) of (*Z*)-1-(2-oxodihydrofuran-3-ylidene)ethyl trifluoromethanesulfonate (**22g**) in 2.5 mL of DMA, and 0.41 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^1H NMR – 1.22 M). Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **24r** and **25r** as a yellow oil (82 mg, 70%, 6.6:1 regioselectivity, *E*/*Z* = 92:8; 83 mg, 70%, 5.8:1 regioselectivity, *E*/*Z* = 92:8), R_f = 0.37 (3:1 hexanes:EtOAc). **(*E*)-24r**: ^1H NMR (500 MHz, $CDCl_3$): δ 5.53 (app. dt, *J*=15, 8.5 Hz, 1H), 5.39 (m, 3H), 4.23 (t, *J*=7.5 Hz, 2H), 3.47 (d, *J*=7.0 Hz, 2H), 2.87 (t, *J*=6.0 Hz, 2H), 2.68 (t, *J*=5.5 Hz, 2H), 1.95 (m, 2H), 1.85 (m, 3H), 1.36 (sext, *J*=6.0 Hz, 2H), 0.88 (t, *J*=6.0 Hz, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 152.4, 131.7, 131.4, 128.4, 126.8, 118.7, 64.4, 36.0, 35.7, 34.8, 28.0, 22.8, 22.2, 13.8. The following signals can be assigned to **(*Z*)-24r**: ^1H NMR (500 MHz, $CDCl_3$): δ 3.58 (d, *J*=7.5 Hz, 2H); FTIR (thin film): 2957, 2359, 1740, 1373, 1036, 967 cm^{-1}; HRMS *m/z* calculated for $C_{15}H_{22}O_2Na$ $[M+Na]^+$: 257.1517, found 257.1519.

tert-butyl 4-((2*E*,5*E*)-8-hydroxy-6-methylocta-2,5-dien-1-yl)-5,6-dihydropyridine-1-carboxylate (**24s**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 159 mg (0.75 mmol) of (*E*)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-ol (**23p**), 28 mg (0.03 mmol) of $Pd_2(dba)_3$, a solution of 249 mg (0.75 mmol) of *tert*-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1-carboxylate (**22d**) in 2.5 mL of DMA, and 0.36 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR – 1.41 M). Purification by flash chromatography (1:1 hexanes:EtOAc) led to the isolation of **24s** and **25s** as a colorless oil (83 mg, 52%, 3.0:1 regioselectivity, *E*/*Z* = 92:8; 75 mg, 46%, 2.8:1 regioselectivity, *E*/*Z* = 92:8), R_f = 0.43 (1:1 hexanes:EtOAc). **(*E*)-24s**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.42 (app. dt, *J*=16.5, 8.5 Hz, 1H), 5.40-5.31 (m, 2H), 5.26 (t, *J*=10 Hz, 1H), 3.85 (m, 2H), 3.68 (t, *J*=8.4 Hz, 2H), 3.47 (t, *J*=8.4 Hz, 2H), 2.75 (t, *J*=7.2 Hz, 2H), 2.67 (m, 2H), 2.27 (t, *J*=8.4 Hz, 2H), 2.01 (m, 2H), 1.64 (s, 3H), 1.46 (s, 9H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.2, 132.4, 130.8, 127.5, 126.4, 125.8, 115.7, 79.6, 60.4, 43.7, 42.9, 40.5, 35.1, 31.4, 28.7, 28.5, 15.9. The following signals can be assigned to **(*Z*)-24s**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.85 (t, *J*=7.8 Hz, 2H); FTIR (thin fillm): 3392, 2359, 1713, 1436, 1218, 1140, 1042, 968, 858 cm^{-1}; HRMS *m*/*z* calculated for $C_{19}H_{31}NO_3Na$ $[M+Na]^+$: 275.1623, found 275.1623.

(2*E*,5*E*,8*E*)-ethyl 3-(2,2-diethoxyethyl)-11-hydroxy-9-methylundeca-2,5,8-trienoate (**24t**):



The general procedure was followed using 49 mg (0.85 mmol) of KF, 159 mg (0.75 mmol) of (*E*)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-ol (**23p**), 28 mg (0.03 mmol) of $Pd_2(dba)_3$, a solution of 268 mg (0.75 mmol) of (*Z*)-ethyl 5,5-diethoxy-3-(((trifluoromethyl)sulfonyl)oxy)pent-2-enoate (**22j**) in 2.5 mL of DMA, and 0.36 mL (0.50 mmol) of 1,3-butadiene in a 15 wt% solution of *n*-hexane (concentration determined by ^{1}H NMR – 1.41 M). Purification by flash chromatography (2:1 hexanes:EtOAc) led to the isolation of **24t** and **25t** as a colorless oil (127 mg, 72%, 2.0:1 regioselectivity, *E*/*Z* = 91:9; 125 mg, 70%, 6.7:1 regioselectivity, *E*/*Z* = 91:9), R_f = 0.27 (2:1 hexanes:EtOAc). **(*E*)-24t**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (s, 1H), 5.50 (app. dt, *J*=15.8, 6.0 Hz, 1H), 5.41 (app. dt, *J*=15.5, 6.3 Hz, 1H), 5.24 (t, *J*=7.2 Hz, 1H), 4.62 (t, *J*=6.0 Hz, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 3.65 (m, 4H), 3.48 (m, 2H), 3.38 (d, *J*=6.3 Hz, 2H), 2.73 (t, *J*=6.3 Hz, 2H), 2.43 (d, *J*=5.7 Hz, 2H), 2.25 (t, *J*=6.3 Hz, 2H), 1.62 (m, 3H), 1.27 (dt, *J*=7.2, 1.2 Hz, 3H), 1.19 (dt, *J*=6.9, 1.0 Hz, 6H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 156.6, 132.4, 131.0, 126.7, 125.6, 118.3, 101.7, 61.9, 60.3, 59.8, 42.8, 42.0, 35.8, 31.4, 15.9, 15.4, 14.4; FTIR (thin film): 3420, 2359, 1698, 1419, 1170, 969, 770 cm^{-1}; HRMS *m*/*z* calculated for $C_{20}H_{34}O_5Na$ $[M+Na]^+$: 377.2304, found 377.2312.

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CHAPTER 3

THE DEVELOPMENT AND MECHANISTIC INVESTIGATION OF A REGIOSELECTIVE PALLADIUM-CATALYZED 1,4-DIFUNCTIONALIZATION OF ISOPRENE

Introduction

Terpenoid scaffolds are ubiquitous in a vast array of important bioactive natural products. Often identified as contiguous five-carbon isoprene units, terpenoids are common in cyclic and acyclic molecules with varying degrees of heteroatom substitution. A larger class of molecular frameworks, skipped polyenes, are often composed of terpenoids groups (Figure 3.1). These scaffolds are made up of methylene interrupted di- or trisubstituted alkenes with stereochemically defined alkene geometry.[1] Natural products containing terpenoid-skipped polyenes exhibit a range of interesting biological properties including potent antimicrobial (actinopyrone A)[2,3] and anticancer activity (lehualide B and intervenoline).[4,5] The importance of the skipped polyene motifs in lehualide B was shown through SAR studies carried out by Micalizio and coworkers.[6] In these studies, they demonstrated a substantial loss of activity against multiple myeloma cancer cell lines if the skipped polyene functionality was removed or significantly altered.

While skipped polyene-containing terpenoids are highly influential in bioactive

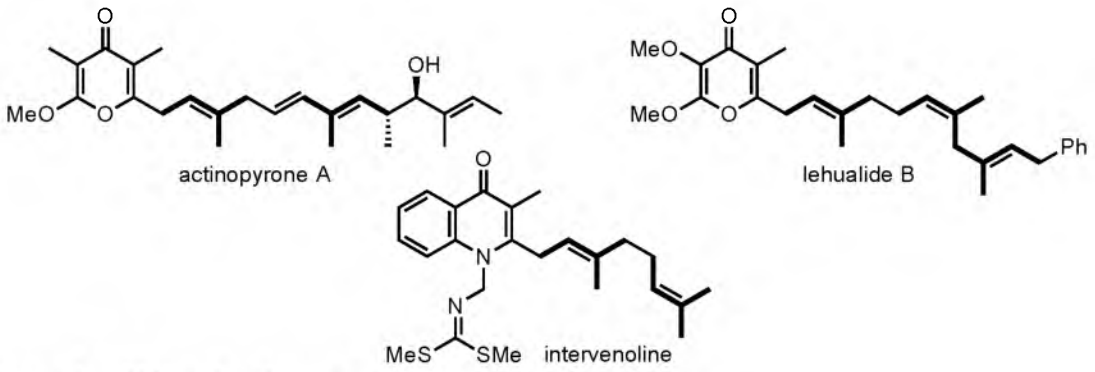


Figure 3.1 Skipped polyene-containing natural products.

molecules, unique substitution and stereochemical definition render the synthesis of these frameworks a formidable challenge to modern synthetic organic chemistry. The synthesis of skipped polyenes from the direct insertion of isoprene between two alkenyl-coupling partners would be a highly attractive method for a modular and rapid construction of these structures. This chapter will discuss the development of a Pd-catalyzed 1,4-difunctionalization of isoprene that employs pyrox ligands to control site selectivity of alkene insertion. In addition, a brief discussion of synthetic methodologies that are frequently used for the synthesis of skipped polyenes will be presented.

Background

The synthesis of skipped polyenes within natural products has been accomplished through multiple strategies. Method selection is largely dependent on product substitution and the required alkene stereochemical outcome. Furthermore, the installation of skipped polyenes can be accomplished in an intra- or intermolecular fashion depending on the specific disconnection. In Chapter 2, Pd-catalyzed allylation and Takai olefination reactions were presented as methods for the synthesis of skipped

polyenes. These chemistries are less frequently used for the formation of skipped polyene-containing terpenoids due to the added challenges resulting from increased alkene complexity. In examples where Pd-catalyzed allylation strategies have been used to construct these scaffolds, high catalyst loadings are often necessary to achieve reasonable product yields.[5,7,8]

A modified Julia olefination has been demonstrated as an attractive method for linking highly functionalized molecular fragments (Figure 3.2A).[9] With the use of a non-nucleophilic base, such as LDA or LiHMDS, a heteroaromatic sulfone derivative (**1**) and an aldehyde (**2**) can be coupled in a stereoselective fashion to generate di- or tri-substituted alkene products (**3**). The evolution of the one-pot Julia olefination has led to the discovery of highly stereoselective transformations as the result of altering the electrophilic heteroaromatic group. While early reports relied on benzothiazol-2-yl (BT) and pyridin-2-yl (PYR) substituted sulfonyl groups, more recent modifications have used

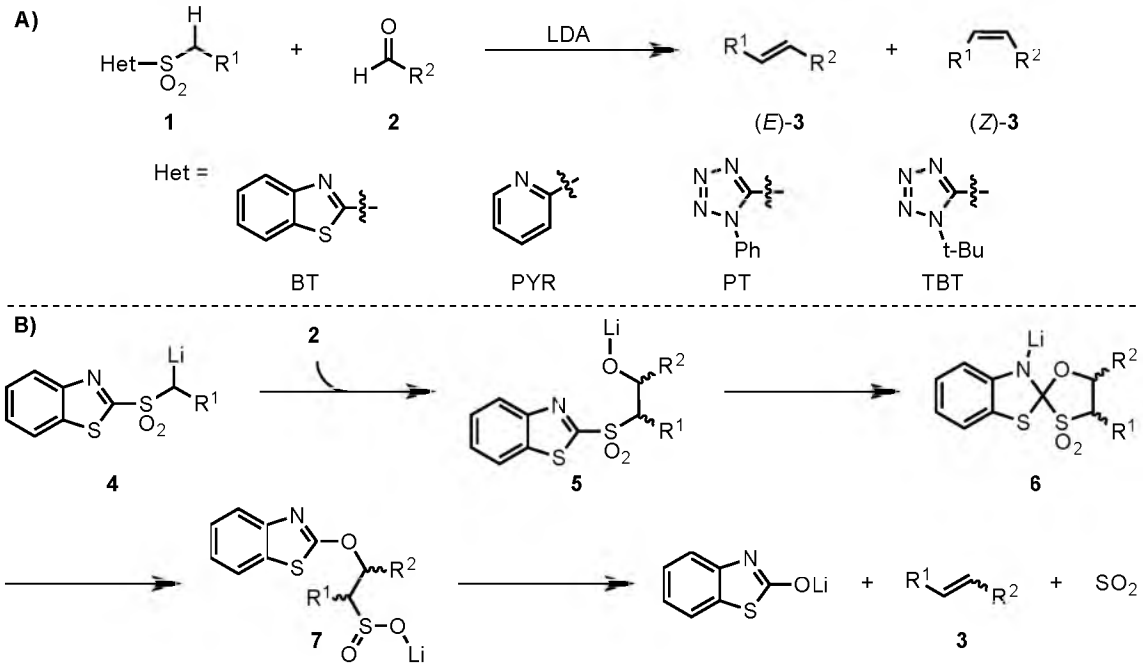


Figure 3.2 The coupling of heteroaromatic sulfones and aldehydes in the modified Julia olefination. **A)** General transformation. **B)** Putative reaction mechanism.

more sterically encumbering 1-phenyl-tetrazol-5-yl (PT) or 1-*tert*-butyl-tetrazol-5-yl (TBT) activating species to yield the *trans* alkene geometry selectively.[10,11]

The proposed mechanism for the modified Julia olefination using a BT-sulfone activator begins with the formation of carbanion **4** (Figure 3.2B). Nucleophilic addition of **4** into aldehyde **2** affords β-alkoxysulfone **5**, which due to the relative instability undergoes a facile Smiles rearrangement. This rearrangement proceeds through the putative spirocyclic intermediate **6** and leads to C–S bond cleavage with the generation of sulfonate salt **7**. Expulsion of sulfur dioxide and the lithium benzothiazolone salt yields the final alkene product **3**. The stereochemical outcome of the reaction is ultimately dependent on the *syn*/*anti* diastereoselection of the addition of carbanion **4** to aldehyde **2**. The selectivity of the transformation with less sterically hindered BT-sulfone derivatives relies heavily on the steric environment of the respective R-groups to help control the nucleophilic addition.

In 1998, Kocienski and coworkers reported a reaction modification with the use of PT-sulfones as an alternative to the BT-variants (known as the Julia-Kocienski olefination).[10] PT-sulfone derivatives were shown to render the Julia olefination more efficient and selective for the formation of *trans* alkenes without the need for sterically biasing R-group substitution. Mechanistic studies have suggested the increased stereoselectivity, relative to BT-sulfones, is the result of a kinetically-controlled diastereoselective *anti*-addition in the formation of β-alkoxysulfone **10** (Figure 3.3).[11] Unfavorable interactions between the sterically encumbering PT-sulfone and R^2-group of the aldehyde preclude the *syn*-addition pathway (**11** to **12**), thereby resulting in the selective production of (*E*)-**3** through the proposed lower energy transition state (**9**).

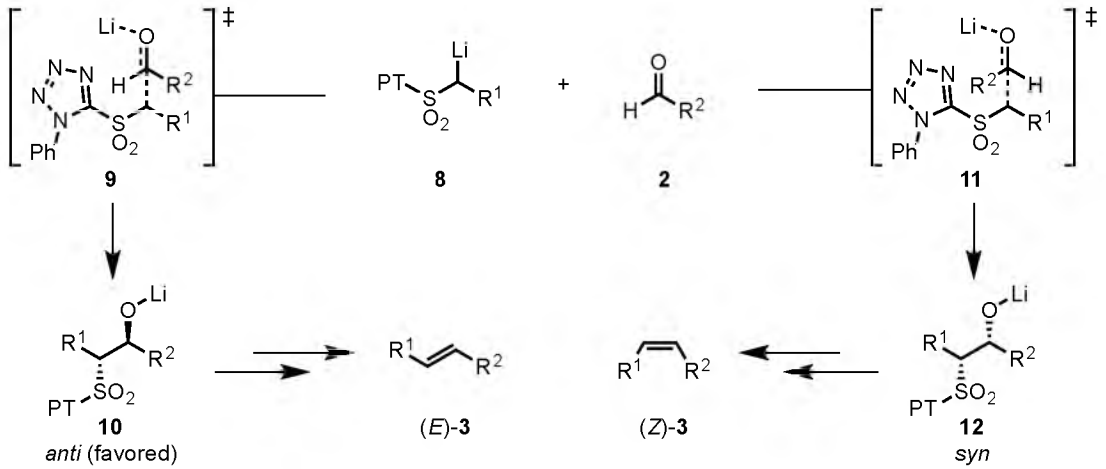


Figure 3.3 Mechanistic rationale for the highly stereoselective Julia-Kocienski olefination using PT-sulfones.

The advancements made to the Julia olefination by Kocienski and coworkers led to multiple examples wherein the methodology has been used for the synthesis of complex skipped polyene-containing molecules.[12-14] In 2006, Boger and coworkers reported the used of this chemistry in the total synthesis of piericidin A.[13] In the olefination of vinyl iodide-containing PT-sulfone **13** and α,β-unstaturated aldehyde **14**, the authors observed good yield and exclusive formation of *trans* alkene geometry in the skipped diene manifold of product **15** (Figure 3.4A). Another example comes from Markó and coworkers, who employed a late stage Julia-Kocienski reaction in the total synthesis of jerangolid D.[14] Here, two highly functionalized molecular fragments (**16** and **17**) were coupled in good stereochemical control and moderate yield (Figure 3.4B). While the Julia olefination has been demonstrated as a highly functional group tolerant and tunable method for alkene synthesis, the primary drawback of the reaction results from needing to prefunctionalize a substrate with heteroaromatic sulfonyl groups. This process requires a two-step reaction sequence starting with the alkylation of a heteroaromatic thiol, often using Mitsunobu conditions, then oxidation of the thiol ether

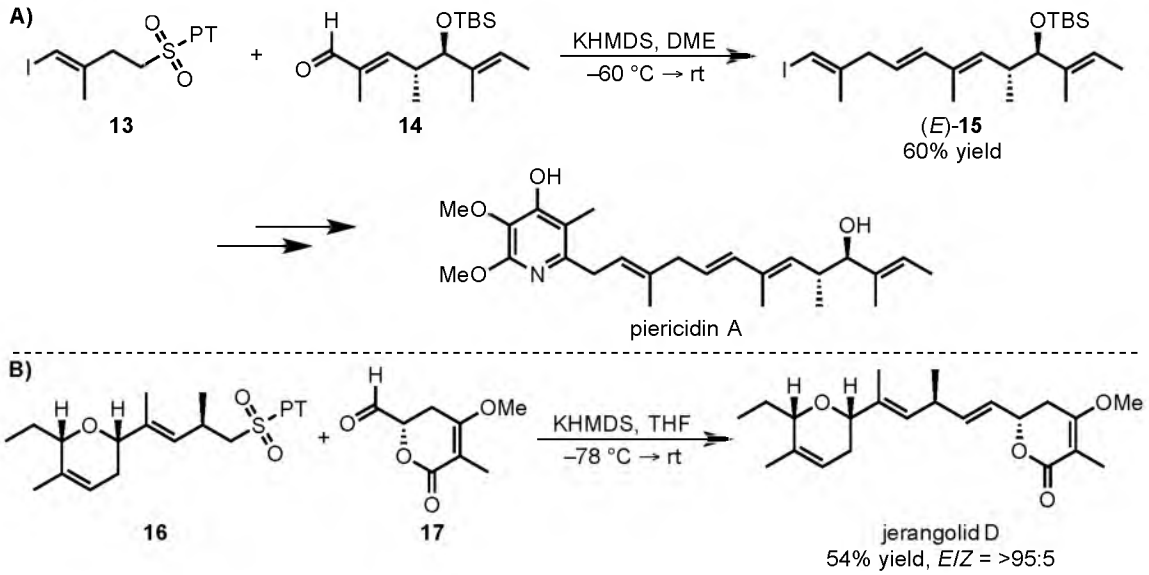


Figure 3.4 Representative examples utilizing the Julia-Kocienski olefination for the synthesis of skipped diene-containing natural products. **A)** Julia-Kocienski olefination reported by Boger in the total synthesis of piericidin A. **B)** Julia-Kocienski olefination reported by Markó used in the total synthesis of jerangolid D.

to yield the sulfone.[11]

In an alternative approach to the synthesis of diverse skipped polyenes scaffolds, the Micalizio group has dedicated a significant portion of their research program to the development of unique titanium-mediated alkylation reactions.[15] In 2007, they reported the use of unactivated allylic alcohols and internal alkynes (**19**) to regioselectively access highly substituted 1,4-dienes (**20**, Figure 3.5A).[16] The reaction is initiated with the pretreatment of allyl alcohols with base to generate lithium alkoxides (**18**) and promote ligand exchange with the *in situ* generated titanium π-complex **21** (Figure 3.5B). Carbometalation, via formal [3,3]-rearrangement of **22**, occurs from the least sterically hindered position of the metallacycle to deliver **23**. Regioselectivity challenges relating to carbometalation from the titanium π-complex **22** were evaded by employing symmetric or sterically biased internal alkyne substrates. After aqueous work-up the

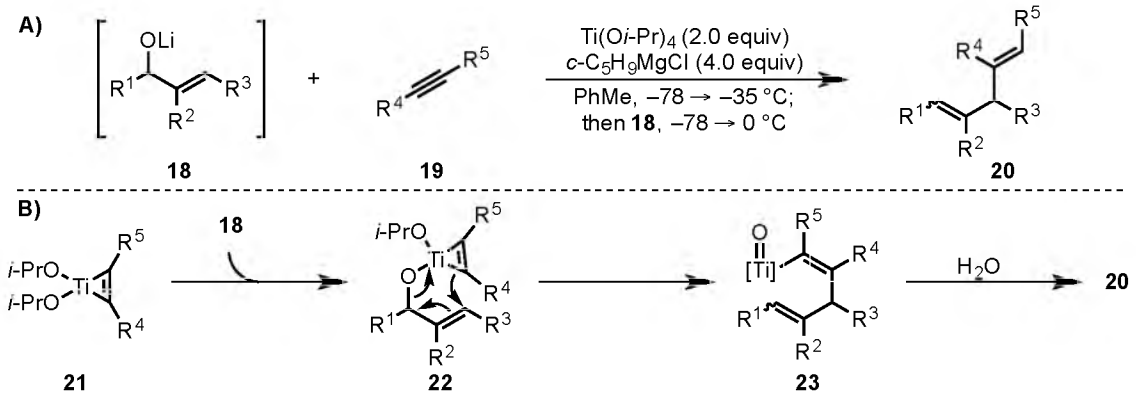


Figure 3.5 Titanium-mediated alkylation of allylic alcohols with internal alkynes. **A)** General transformation. **B)** Putative reaction mechanism.

skipped diene-containing product **20** is formed.

The utility of the titanium-mediated alkylation of allylic alcohols with alkynes was demonstrated in the formation of the skipped diene-containing terpenoid fragment of lehualide B.[6,17] This represents a particularly difficult transformation due to the requirement to form two trisubstituted alkenes in a regio- and stereoselective fashion. To prevent undesired reactivity from the pyrone carbonyl group, the authors pretreated the allylic alcohol starting material with two equivalents of LiHMDS to formally protect the pyrone as the γ-enolate (**24**, Figure 3.6A). Functionalization with 1-(trimethylsilyl)propyne affords **25** in 61% yield with good stereochemical control for the production of the desired alkene geometries. As described above, the use of a sterically biased alkyne directs C–C bond formation to the distal position from the bulky TMS-substituent. Furthermore, the transformation occurs over a single face of the alkyne, thus leading to high *trans* selectivity for the resulting alkene. The second trisubstituted alkene was formed with good 7:1 *Z*:*E* selectivity, which the authors account for with an empirical model based on the minimization of $A^{1,2}$ strain between intermediates **26** and

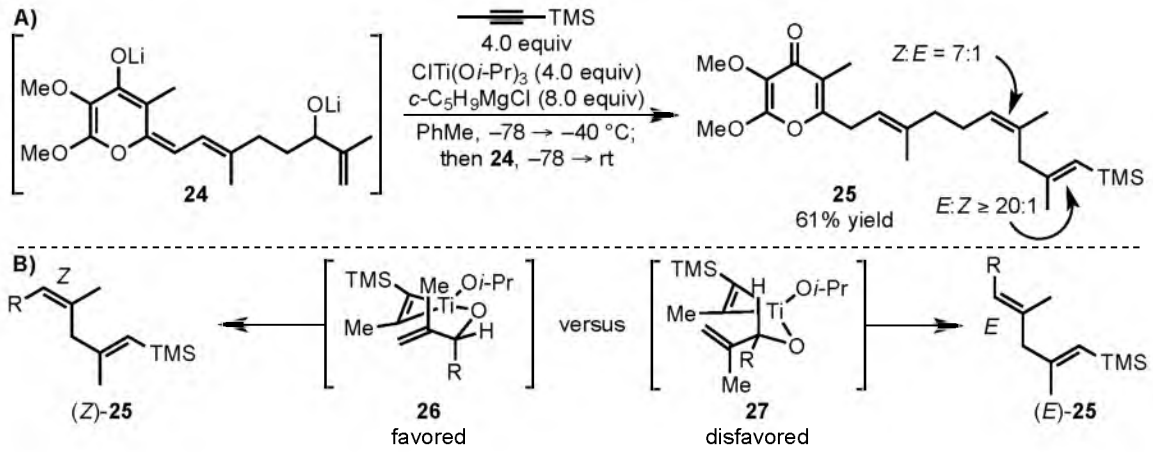


Figure 3.6 The titanium-mediated alkylation reaction used in the total synthesis of lehualide C. **A)** Representative transformation. **B)** Mechanistic rationale for the stereochemical outcome.

27 (Figure 3.6B). Intermediate **26** is favored as the result of the methyl and large R-group orienting away from each other, as opposed to the *trans* alkene precursor **27**, wherein the groups are oriented in close proximity.

Micalizio and coworkers have recently advanced titanium alkoxide-mediated functionalizations to afford skipped triene products from vinylcylcopropane[1] or 1,5-diene-containing alcohol substrates.[18] These transformations are attractive for their ability to regioselectively produce highly substituted skipped polyene-containing products while employing a relatively inexpensive titanium source. Limitations of this work result from the requirement for biasing steric influences on allylic alcohol or alkyne substrates to achieve high stereo- and regioselectivity. In addition, the tolerance for electrophilic functional groups has not been examined in detail and may be problematic as the result of the nucleophilic reaction intermediates.

Modern synthetic methods are limited in their ability to form skipped polyene-containing terpenoids in a modular and highly functional group tolerant approach. As

described in previous chapters, Pd-catalyzed alkene difunctionalization reactions are powerful transformations for the rapid assembly of complex products from relatively simple starting materials.[19-21] A 1,4-difunctionalization reaction of a simple 1,3-diene, such as isoprene, would be an attractive means to generate skipped polyene-containing terpenoids.[22-24] Tsuji and coworkers previously have reported a Pd-catalyzed 1,4-carbosilylation of isoprene that demonstrates the potential to easily generate terpenoid scaffolds from isoprene functionalization (Figure 3.7A).[25] Using benzoyl chloride **28**, isoprene, and hexamethyldisilane **29**, the terpenoid-containing product **30** was formed in good yield and excellent regioselectivity. The proposed mechanism of the transformation begins with the oxidative addition and decarbonylation of benzoyl chloride **28** with the Pd^0 catalyst (Figure 3.7B). A 1,2-migratory insertion of isoprene into the Pd–C bond of **31** forms the σ-allyl Pd-intermediate **32**. The π-allyl stabilized intermediate **33** generated following σ-π isomerization slows the β-hydride elimination process that could lead to the formation of Heck byproducts. Finally, transmetallation of hexamethyldisilane **29** and reductive elimination affords the terpenoid-containing allylic silane product **30**.

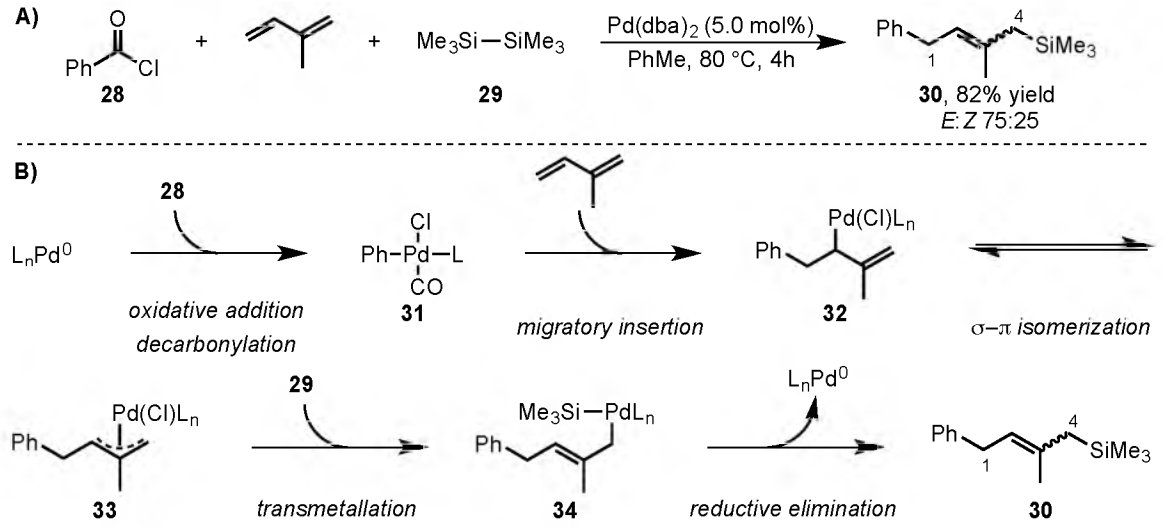


Figure 3.7 Pd-catalyzed 1,4-carbosilylation of isoprene using benzoyl chloride and hexamethyldisilane. **A)** Representative transformation. **B)** Proposed mechanism.

While this work by Tsuji and coworkers does not yield skipped polyenes, it represents a proof-of-concept that isoprene is a compatible substrate for Pd-catalyzed 1,4-difunctionalizations and can be used to rapidly access terpenoid scaffolds.

The synthesis of skipped polyenes that are composed of terpenoid fragments has proven challenging and often requires complex or sterically biased starting materials to afford good regio- and stereoselectivity. The Sigman group and others have reported the development of mild and functional group tolerant Pd-catalyzed alkene difunctionalization reactions.[22,23,26-29] As described in Chapter 2, we have used this methodology to develop a 1,4-difunctionalization of the 1,3-diene chemical feedstock butadiene,[30] which produced skipped polyenes both regio- and stereoselectively. In an effort to develop a new method to directly access skipped polyene-containing terpenoids from simple starting materials, we sought to broaden the scope of the Pd-catalyzed 1,4-difunctionalization with the use of isoprene as the 1,3-diene substrate.

Hypothesis and Reaction Optimization

In an analogous approach to that used in our previous alkene difunctionalization chemistry,[28,30] we proposed the formation of skipped polyene-containing terpenoids product (**37**) from a 1,4-addition to isoprene of a vinyl triflate (**35**) and boronic acid (**36**, Figure 3.8A). The use of vinyl triflates is critical for the generation of cationic Pd-intermediates following oxidative addition at the low-valent metal center. Due to the noncoordinating character of the triflate counter ion, cationic palladium species demonstrate a unique reactivity profile that is well suited for alkene difunctionalization reactions. Pd-intermediates with heightened electrophilicity have been demonstrated to

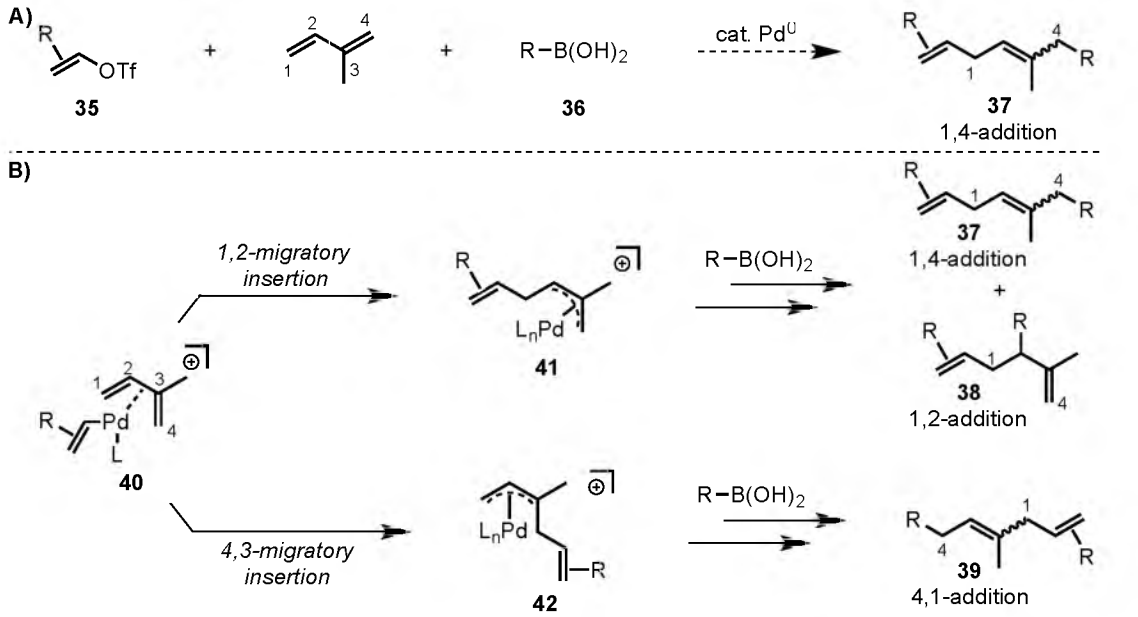


Figure 3.8 Proposed Pd-catalyzed 1,4-difunctionalization of isoprene with vinyl triflates and boronic acid reagents. **A)** Representative transformation. **B)** Mechanistic rationale for site selective migratory insertion and isomer formation.

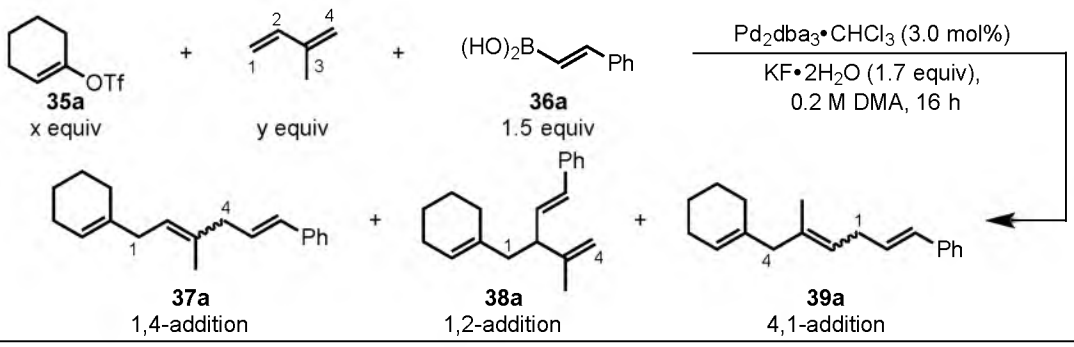
preferentially undergo migratory insertion with alkenes, rather than react directly with organometallic reagents, which would afford cross-coupling products. As discussed in Chapter 1, 1,3-dienes are also important to the success of difunctionalization reactions due to their ability to stabilize alkyl-Pd intermediates through the formation of π-allyl interactions with palladium. Control of the σ-π-σ isomerization of these intermediates can be used to develop selective 1,2- or 1,4-addition difunctionalization reactions.[31,32]

The intention to use isoprene as the 1,3-diene substrate in a 1,4-difunctionalization required that we address the added challenge of a difficult-to-control migratory insertion between two closely related alkenes (Figure 3.8B).[23,25,33] Cationic Pd-intermediate **40** would be formed following the oxidative addition of vinyl triflate and could undergo a 1,2-migratory insertion of isoprene (**40** → **41**) or a 4,3-migratory insertion (**40** → **42**). The desired 1,4-addition product **37** (or the 1,2-addition product **38**)

would be accessed following a transmetallation with boronic acid reagent, and reductive elimination sequence from π-allyl stabilized intermediate **41**. Beyond some noteworthy exceptions,[33,34] simple 1,3-dienes produce the 1,4-addition products as the major isomer in difunctionalization reactions. Alternatively, the 4,1-addition product **39** would be formed from **42** following reaction of the opposite 4,3-migratory insertion pathway. The formal 4,3-addition products (analogous to 1,2-addition) are not often detected, presumably as the result of a high barrier for palladium reductive elimination of a quaternary center. Due to steric influences, we hypothesized that 1,2-migratory insertion would be favored as the result of the less-substituted alkene of isoprene reacting more rapidly than the opposing 4,3-migratory insertion pathway. The tremendous challenge of developing a selective 1,4-difunctionalization of isoprene is understood with the observation that the reaction has the potential to generate five distinct constitutional or stereoisomers as the result of similar energetic pathways.

In our preliminary reaction development, we employed cyclic vinyl triflate **35a**, isoprene, and styrenyl boronic acid **36a** under conditions found to be optimal in our previously reported 1,4-difunctionalization of 1,3-butadiene (entry 1, Table 3.1).[30,35] Product yields are reported as an inseparable mixture of **37a**, **38a**, and **39a**. In addition, the ratios of product isomers were determined by GC analysis. While yields were initially low, we were pleased to observe good selectivity for the desired 1,4-addition product (*E*)-**37a** over other product isomers. At the cost of a modest loss to selectivity, we were able to significantly increase yield for the difunctionalization products from 17% to 61%, by increasing the stoichiometry of isoprene to 7.0 equivalents (entry 3). In conjunction with this change, the stoichiometry of vinyl triflate **35a** was adjusted, making

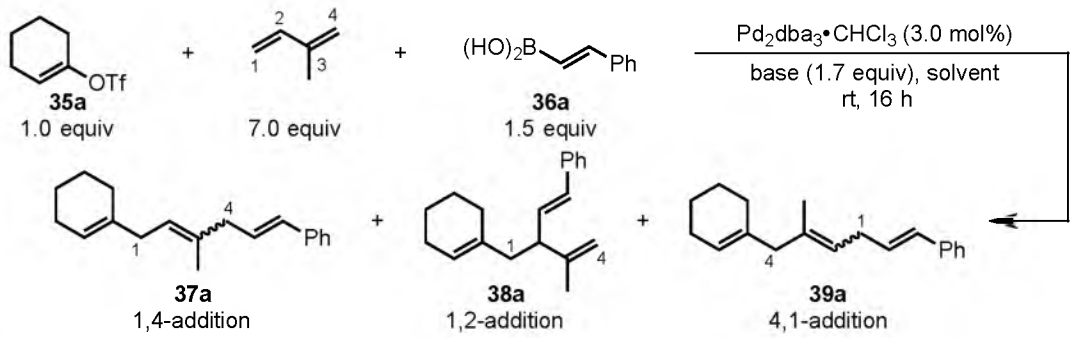
Table 3.1 Reaction optimization for the Pd-catalyzed 1,4-vinylvinylation of isoprene. [a]Measured by GC using an internal standard. Yields represent a mixture of **37a**, **38a**, and **39a**. Ratio of product isomers determined by GC.



entry	temp. (°C)	*x*	*y*	yield (%)[a]	(*E*)–**37a** : (*Z*)–**37a** : **38a** : (*E*)–**39a** : (*Z*)–**39a**
1	55	1.5	1.0	17	10 : 0.64 : 1.9 : 1.0 : 1.1
2	55	1.0	1.0	21	10 : 0.64 : 1.8 : 1.0 : 1.1
3	55	1.0	7.0	61	8.5 : 0.53 : 1.7 : 1.0 : 1.1
4	rt	1.0	7.0	61	8.0 : 0.52 : 1.5 : 1.0 : 1.0

it the limiting reagent of the transformation. Further, experiments revealed that the reaction could be carried out at room temperature without influencing the reaction outcome significantly (entry 4). Interestingly, increased reaction yields were observed by substituting sodium carbonate for potassium fluoride (entry 5, Table 3.2). The role of base in the reaction presumably is to activate the boronic acid for transmetallation; therefore as potassium fluoride has been a suitable base for similar transformations,[28,30] the reasoning behind the improvement in yield with a stronger base is not clear. The optimal reaction procedure was realized with the transition from DMA to DMF (entry 6) and a small adjustment to the reaction concentration (entry 7). Under the optimized conditions, alkene difunctionalization products were formed in 80% yield with good regio- and stereoselectivity for the formation of (*E*)-**37a** (>7:1 (*E*)-**37a** *versus* all other isomers). Over the course of reaction optimization studies, we observed that ligands

Table 3.2 Continued reaction optimization for the Pd-catalyzed 1,4-vinylvinylation of isoprene. [a]Measured by GC using an internal standard. Yields represent a mixture of **37a**, **38a**, and **39a**. Ratio of product isomers determined by GC.



entry	solvent	conc. (M)	base	yield (%)[a]	(*E*)–**37a** :	(*Z*)–**37a** :	**38a** :	(*E*)–**39a** :	(*Z*)–**39a**
4	DMA	0.2	$KF•2H_2O$	61	8.0	0.52	1.5	1.0	1.0
5	DMA	0.2	Na_2CO_3	79	7.6	0.72	1.1	1.0	0.97
6	DMF	0.2	Na_2CO_3	81	7.0	0.80	0.73	1.0	0.93
7	DMF	0.25	Na_2CO_3	80	7.3	0.85	0.64	1.0	0.89

were tolerated in the difunctionalization, although their use resulted in similar product yields with little enhancement of isomeric ratios.

Evaluation of Scope

Using the optimized reaction conditions, we began investigations into the scope of the transformation with the assessment of a range of vinyl triflates. The structures of product isomers were confirmed by preparative separation using a silver impregnated HPLC column and NMR analysis.[36,37] Heterocyclic groups, such as pyranyl (**37b**) and *N*-Boc protected piperdinyl (**37c**), participated in the difunctionalization in moderate to good yields (Figure 3.9). In addition to a simple aliphatic-derived vinyl group (**37d**), the formation of the desired (*E*)-**37** product in these examples occurred with >6:1 selectivity. When boronic acid **36b** was employed low yields were observed (entry 1, Table 3.3).

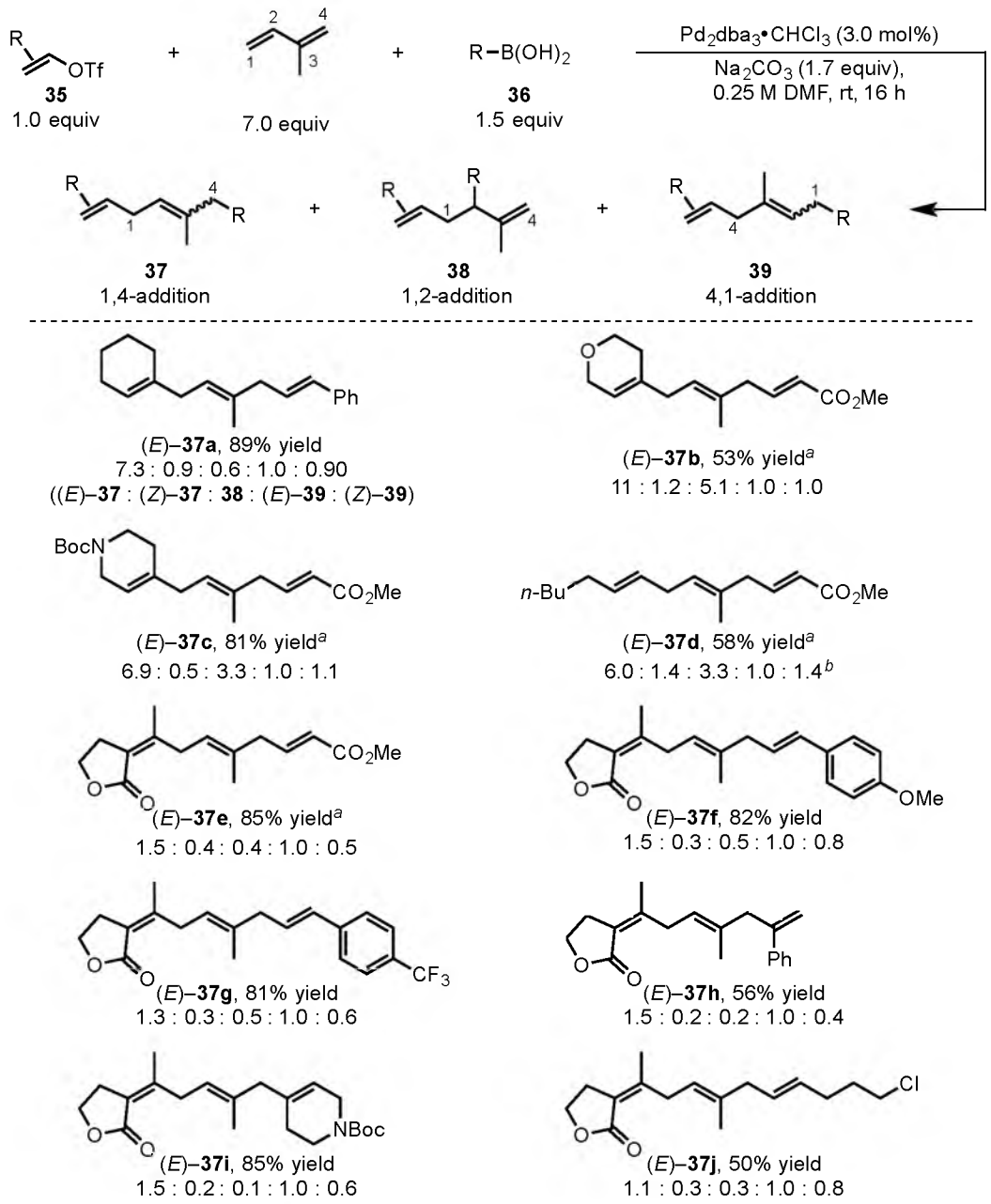
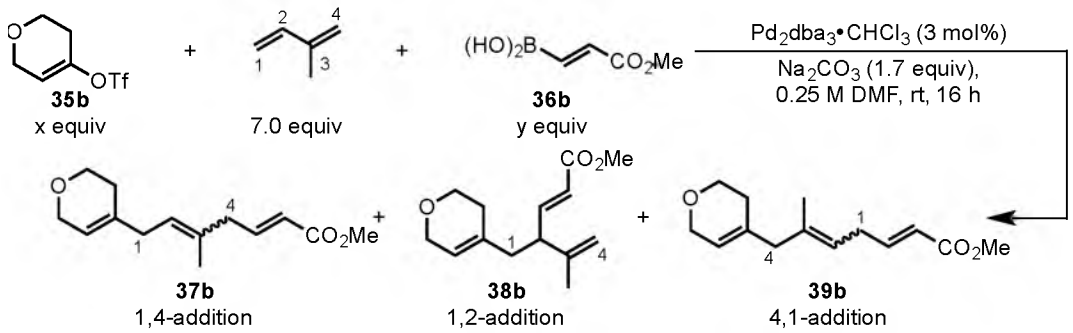


Figure 3.9 Scope of the Pd-catalyzed 1,4-difunctionalization of isoprene with vinyl triflates and vinylboronic acids. Structures of isomers were confirmed by separation using HPLC and ^{1}H NMR analysis. Ratios of regio- and stereoisomers were determined by either ^{1}H NMR or HPLC analysis. Yields represent a mixture of regio- and stereoisomers. [a]Reaction performed with 3.0 equivalents of **35** and 1.0 equivalent of **36**. [b](*Z*)-**37d** and (*Z*)-**39d** were inseparable by HPLC and ^{1}H NMR signals overlapped. Therefore values are reported as a mixture.

We hypothesized this could be the result of catalyst inhibition by means of the boronic acid or through product competitively binding to the palladium center. Fortunately, by simply decreasing the stoichiometry of **36b** (entry 2-3) and increasing the concentration of vinyl triflate **35b** (entry 4-8), we were able to achieve useful yields and selectivity for the skipped triene-containing product (*E*)-**37b**. Therefore, products **37b-37e** were formed using this modified reaction procedure.

Changing the boronic acid from a conjugated ester to styrenyl derivatives (**37f-37h**), *N*-protected heterocycle (**37i**), and a chloride containing aliphatic (**37j**) had little impact on product yields and isomeric ratios. While the vinylogous lactone triflate **35e** was chosen to evaluate the reaction tolerance to different vinylboronic acids, it proved to

Table 3.3 Reaction optimization for the Pd-catalyzed 1,4-vinylvinylation of isoprene using a conjugated ester derived boronic acid. [a]Measured by GC using an internal standard. Yields represent a mixture of **37b**, **38b**, and **39b**. Ratio of product isomers determined by GC.



entry	*x*	*y*	yield (%)[a]	(*E*)–**37b** : (*Z*)–**37b** : **38b** : (*E*)–**39b** : (*Z*)–**39b**
1	1.0	1.5	17	8.8 : 3.4 : 9.0 : 1.0 : 1.1
2	1.0	1.2	28	6.6 : 2.8 : 3.8 : 1.0 : 1.3
3	1.0	1.0	34	6.8 : 2.8 : 3.4 : 1.0 : 1.0
4	1.2	1.0	50	5.5 : 0.74 : 2.1 : 1.0 : 0.95
5	1.5	1.0	57	5.3 : 1.1 : 1.8 : 1.0 : 0.96
6	2.5	1.0	55	6.4 : 1.7 : 1.3 : 1.0 : 1.8
7	3.0	1.0	73	12 : 2.4 : 4.1 : 1.0 : 1.1
8	3.5	1.0	69	12 : 2.7 : 3.7 : 1.0 : 1.5

greatly influence the selectivity as compared to other vinyl triflates. Interestingly, the selectivity between 1,4-addition product (*E*)-**37** and 4,1-addition product (*E*)-**39** dropped to nearly 1:1 in examples when vinyl triflate **35e** was used (*vide infra*).

Additional noteworthy results can be identified from the evaluation of the Pd-catalyzed 1,4-difunctionalization of isoprene. For example, the selectivity between 1,2-(**38**) and 1,4-addition products (**37**) for nonlinear boronic acid coupling partners was greater than that observed for other vinylboronic acids evaluated. Specifically, products (*E*)-**37h** and (*E*)-**37i** were formed with 9.2:1 and 11:1 selectivity over 1,2-addition products, respectively. We proposed this maybe the result of an added steric influence of the nonlinear coupling partners on π-allyl Pd-intermediates (**41**), thus encouraging reductive elimination at the least sterically hindered C-4 position of the intermediate.[38] It is also important to note that product **37h**, derived from 1-phenylvinylboronic acid, was formed in a moderate yield. While 1,1-disubstituted alkenes are known to undergo migratory insertion into Pd–C bonds,[39-41] the product **37h** was not consumed under these reaction conditions.

The altering of coupling partners only marginally influenced the distribution of product stereoisomers for **37** and **39**. In general, (*E*)-**37** was always preferentially formed over (*Z*)-**37**, while (*E*)-**39** and (*Z*)-**39** were invariably formed in nearly equal amounts. The putative interpretation of this observation is that the steric environment of the relevant π-allyl stabilized Pd-intermediate impacts the equilibrium between precursors to *E*- or *Z*-alkene geometry (Figure 3.10). Intermediates **41** and **42** along the 1,4-addition mechanistic pathway can interconvert through a $\pi \rightarrow \sigma \rightarrow \pi$ isomerization process (discussed in detail in Chapter 1).[23,25,30,38] The minimization of $A^{1,3}$ strain would favor

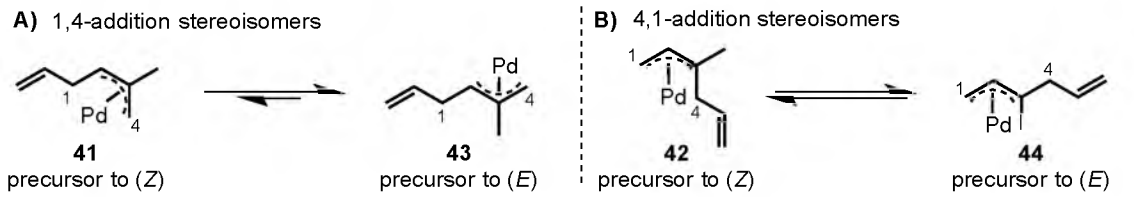


Figure 3.10 Putative π-allyl Pd-intermediates leading to alkene stereoisomers. **A)** Rationale accounting for 1,4-addition stereoisomer formation. **B)** Rationale accounting for 4,1-addition stereoisomer formation.

43, the precursor to (*E*)-**37**. Alternatively, the isomerization of π-allyl intermediates **42** and **44** results in little relief of allylic strain. Therefore stereoisomers (*E*)-**39** and (*Z*)-**39** form in equivalent amounts.

Ligand Evaluation and Site Selectivity Analysis

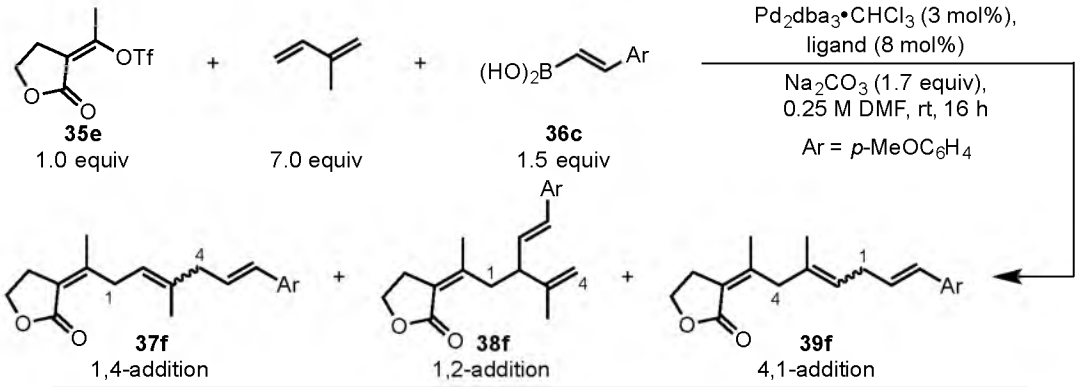
As detailed above, the use of vinylogous lactone triflate **35e** in the Pd-catalyzed 1,4-difunctionalization of isoprene results in an unsatisfactory 1:1 mixture of (*E*)-**37** and (*E*)-**39**. This observation is suggestive of an indiscriminant alkene insertion into the Pd–C bond of intermediate **40**. The selectivity between (*E*)-**37a** and (*E*)-**39a** was 7.3:1. However the selectivity for (*E*)-**37e**, when triflate **35e** was used, was only 1.5:1. If we consider the electronic character of vinyl triflates **35a-35d** to **35e**, the vinyl groups derived from **35a-35d** are comparatively electron-rich (unstabilized). Consequently, we postulated that the electronic character of the vinyl triflates could be influencing the selectivity of alkene migratory insertion from Pd-intermediate **40**. Due to the potential synthetic utility of electron-deficient (stabilized) vinyl triflates, such as **35e**, we sought to resolve this challenge and gain regiocontrol for the formation of (*E*)-**37**.

The electronic character of vinyl coupling partners would be expected to impact the cationic Pd-intermediate **40**. An electronically-stabilized group, such as the

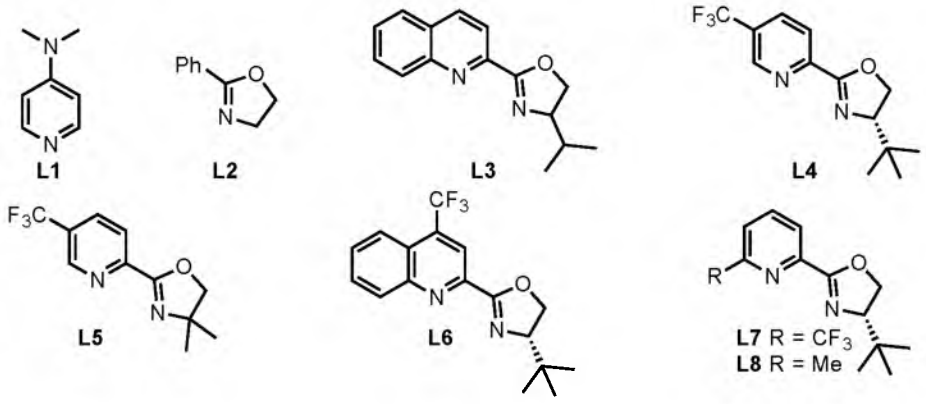
vinylogous lactone of **35e**, would cause the cationic palladium species to be more sensitive to subtle electronic differences between the two alkenes of the bound isoprene molecule. As such, migratory insertion of the more electron-rich disubstituted alkene of isoprene would rationalize the increased formation of 4,1-addition product (*E*)-**39**. Based on this hypothesis, the addition of a ligand to the reaction may outweigh the electronic influences of alkene insertion. As described above, during reaction optimization studies various ligand classes were evaluated and many were tolerated, although generally lower product yields and similar regioselectivity were observed as compared to the "ligandless" conditions found to be optimal.

A selection of ligands were evaluated to assess their ability to override the observed 1:1 selectivity between 1,4- and 4,1-addition products when electronically stabilized vinyl triflates are employed (Table 3.4). Initial investigations with monodentate ligands, 4-dimethylaminopyridine (DMAP) or phenyl oxazoline (**L1** and **L2**) resulted in negligible improvement to the selectivity of (*E*)-**37f**. A bidentate quinoline-oxazoline (quinox) ligand (**L3**) afforded a two-fold increase in selectivity between (*E*)-**37f** and (*E*)-**39f** (2.1:1), although low yield for the difunctionalization products was observed. A structurally similar chiral pyridine-oxazoline (pyrox) ligand (**L4**) significant improved regioselectivity to 7.7:1 ((*E*)-**37f** : (*E*)-**39f**). Interestingly, **L4** has also been successfully used to control facial selection of alkene insertion into Pd–C bonds in Pd-catalyzed redox-relay Heck chemistry developed within our group.[42-44] The evaluation of geminal dimethyl-substituted pyrox (**L5**) emphasized the importance of an open catalyst face, as modest regioselectivity and low yield were observed. Other comparable quinox and pyrox ligands with CF_3-substitution (**L6** and **L7**) were examined

Table 3.4 Ligand evaluation for the Pd-catalyzed 1,4-vinylvinylation of isoprene. [a]Measured by ^{1}H NMR using an internal standard. Yields represent a mixture of **37f**, **38f**, and **39f**. Ratio of product isomers determined by ^{1}H NMR analysis.



ligand	yield (%)[a]	ratio of (*E*)-**37f** : **38f** : (*E*)-**39f**	Suzuki (% yield)
none	82%	1.5 : 0.5 : 1.0	16%
L1	77%	1.3 : 0.4 : 1.0	15%
L2	83%	1.6 : 0.4 : 1.0	19%
L3	25%	2.1 : 1.0 : 1.0	30%
L4	62%	7.7 : 2.4 : 1.0	13%
L5	35%	3.3 : 2.6 : 1.0	36%
L6	67%	1.3 : 0.7 : 1.0	19%
L7	75%	1.3 : 0.8 : 1.0	16%
L8	47%	1.7 : 1.9 : 1.0	35%



and led to poor regioselectivity. While the regioselectivity between 1,4-addition product **37** and 1,2-addition product **38** unfortunately never exceeded 4:1, it is interesting to note that use of 6-Me-substituted pyrox (**L8**) resulted in the selectivity marginally favoring the formation of **38**.

To investigate the mechanistic basis for the observed increase in site-selective alkene insertion in the presence of **L4**, we sought to evaluate a library of easily accessible pyrox ligands. Using the same reaction procedure as found in Table 3.4, we began by evaluating pyrox ligands with different oxazoline substitution. These experiments revealed a distinct relationship between the relative size of the oxazoline substituent and the selectivity of alkene insertion (Figure 3.11). Pyrox ligands with smaller R-substituents resulted in decreased formation of 1,2/1,4-addition products (**37** and **38**) as compared to the undesired 4,1-addition product (*E*)-**39** (*i.e.*, 3.6:1 for R = H, compared to 15:1 for R = *t*-Bu). Furthermore, by calculating the logarithm of product selectivity,

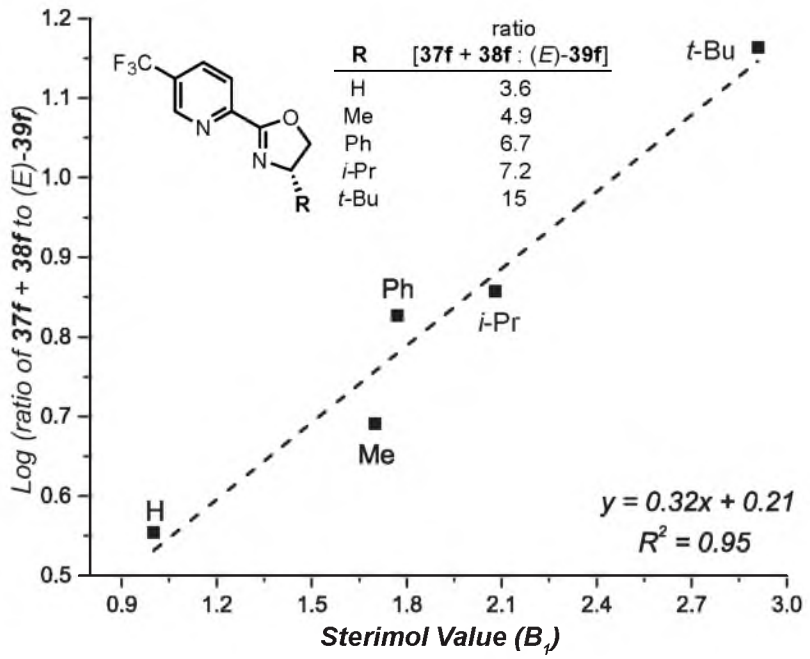


Figure 3.11 Correlation between site selectivity of alkene insertion in the presence of pyrox ligands and Sterimol B_1 values.

which coincides to the presumed relative rate of alkene insertion, a correlation with Sterimol B_1 values for R-substituents was observed. Sterimol B_1 values are descriptors representing the minimum radius of the matching oxazoline R-substituent.[45-47] This trend indicates that the steric environment of the oxazoline group on **L4** is partially accountable for the improved alkene insertion selectivity observed.

After the observation of a distinct trend in the effect of the ligand steric properties, we sought to simultaneously evaluate both electronic effects on the pyridine ring and the influence of steric modification on the oxazoline. From this experiment, we hoped to discern the relative importance of these factors in controlling site selective alkene insertion by comparing the selectivity between 1,2/1,4-addition products and 4,1-addition products. This approach coincides with our recently developed methodology of combining design of experiments with multiparameter ligand modulation to elucidate properties that may be difficult to identify otherwise.[48-51] To help visualize general selectivity trends from the resulting data set, the ratios between **37f**, **38f**, and (*E*)-**39f** were normalized and plotted in a ternary plot (Figure 3.12A). The plot illustrates the observation that ligands with bulky R-substituents and electron-deficient pyridine rings generated the highest selectivity for 1,4-addition product **37f**. Alternatively, the formation of (*E*)-**39f** was favored for pyrox ligands with hydrogen substitution on oxazoline, with little perceivable influence coming from the electronic effects on the pyridine ring.

We next sought to delineate the impact of steric and electronic effects on reaction outcome through the construction of a mathematical model, wherein Sterimol and Hammett values were chosen as respective descriptors. To accelerate the statistical

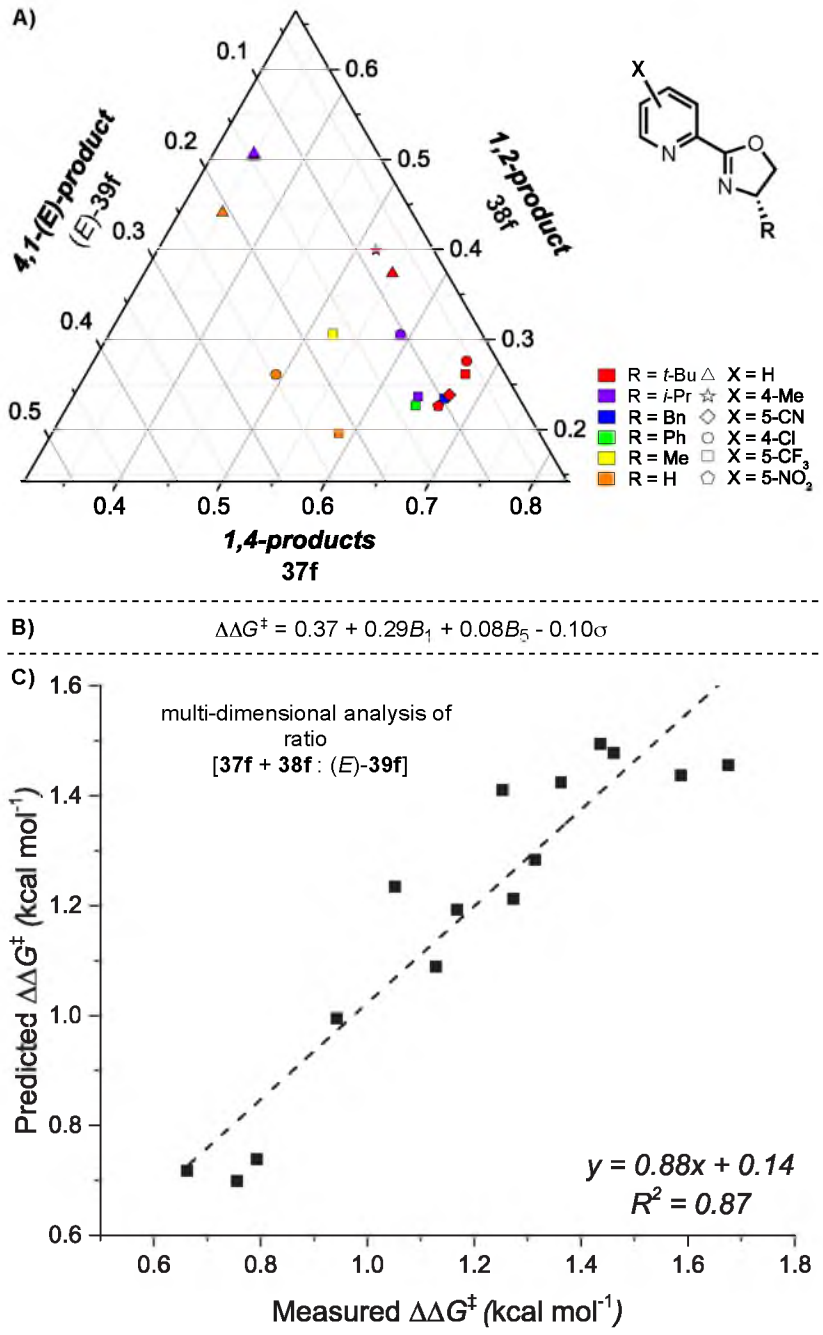


Figure 3.12 Investigation into the mechanistic basis for the proposed site selective alkene insertion in the presence of pyrox ligands. **A)** Ternary plot of the normalized isomeric product distribution resulting from pyrox ligand screen. **B)** Normalized mathematical relationship describing the differential free energy of alkene insertion selectivity. **C)** Predicted *versus* measured $\Delta\Delta G^{\ddagger}$ plot derived from Sterimol B_1 values, and Hammett σ-values for the site selectivity of alkene insertion.

exploration of the relationship between these parameters and $\Delta\Delta G^{\ddagger}$ (experimentally-derived, equal to $-RT\ln$(**37f** + **38f** : (*E*)-**39f**), wherein R is the ideal gas constant and T is temperature), we utilized a standard stepwise linear regression algorithm. The normalized mathematical relationship and a plot of measured *versus* predicted $\Delta\Delta G^{\ddagger}$ values for the equation are shown in Figure 3.12B and C. The relatively high R^2-value and the slope nearly equaling one of the plots validate the strength of the model.

Because the model was constructed using normalized selectivity data, the magnitude of the coefficients can be directly compared to better understand the influence of each parameter. Consistent with the free energy relationship observed in Figure 3.11, the largest coefficient was associated with the Sterimol B_1 parameter suggesting the steric influence of the oxazoline substituent is highly important to site selection. The coefficient for Hammett σ-values, while not large, suggests the electronic properties of the pyridine ring are also important to the reaction outcome. These results are in agreement with previous studies from our laboratory,[42-44,52] which suggest that the electronic asymmetry of pyrox ligands contributes to organization in the catalyst coordination sphere. This effect influences alkene insertion and the resulting isomeric product distribution. Attempts to extrapolate the model for other synthetically accessible ligand derivatives were unsuccessful in predicting a more selective catalyst.

As the result of these investigations into the observed control offered by pyrox ligands over alkene migratory insertion into Pd–C bonds, a mechanistic model is proposed. Collaborative efforts with Olaf Wiest's group provided computed ground and transition state energies for the intermediates of this alkene insertion process. These computations, as well as others on Heck reactions that use **L4**,[53] suggest that following

oxidative addition the coordination sphere of the cationic palladium species is rapidly isomerizing; therefore the structure of the catalyst would be dependent on the relative energy of the alkene insertion transition states. Furthermore, the sterically bulky *tert*-butyl substituent on the oxazoline and the highly electrophilic character of palladium (amplified by the electron-deficient pyridyl group of **L4**) would be expected to promote isoprene association/dissociation. Under these Curtin-Hammett conditions, each of the eight coordination complexes, corresponding to transition states shown in Figure 3.13, leading to 1,2/1,4-addition or 4,1-addition would be in equilibrium. Consistent with computational results, we propose that the transition state of the selectivity-determining step is controlled by the steric influence of the *tert*-butyl substituent on the coordinated alkene, when isoprene is bound *trans* to the pyridine ring (**40‡-A-B**, **E-F**). Therefore, alkene insertion would occur through transition state **40‡-A**, wherein steric interactions are minimized by isoprene pointing away from the *tert*-butyl group. We propose this coordination complex would be favored for isoprene over **40‡-C-D** and **40‡-H-I**, as

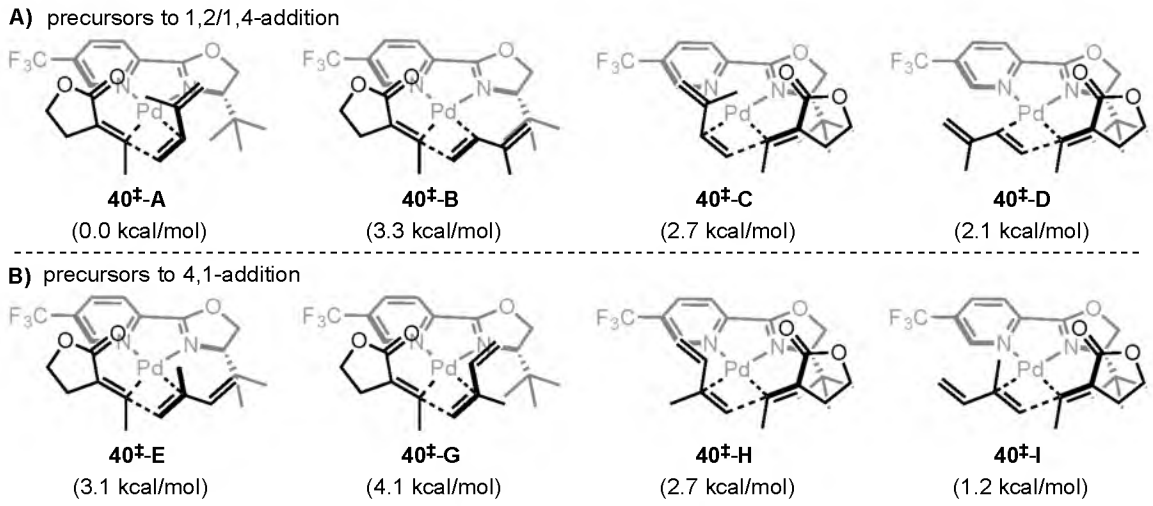


Figure 3.13 Putative mechanistic model accounting for observed alkene insertion site selectivity in the presence of pyrox. **A)** Alkene insertion transition states leading to 1,2/1,4-addition products. **B)** Alkene insertion transition states leading to 4,1-addition product.

isoprene bound to palladium *trans* from the electron deficient pyridyl group is the least susceptible toward a *trans* ligand influencing alkene dissociation. The computed transition state energy differences between **40‡-A** and **40‡-I** are in agreement with the observed selectivity between 1,2/1,4-addition and 4,1-addition products for **L4**.

An additional relationship between the regioselectivity of 1,4- and 1,2-addition products (**37f** and **38f**) was observed in the evaluation of electronic and sterically modified pyrox ligands. These isomers are formed following transmetallation and reductive elimination of π-allyl stabilized Pd-intermediate **41**. We observed a relationship between the product selectivity and the electronic character of the pyridyl substituent of the pyrox ligand (represented by Hammett σ-values, Figure 3.14). This modest electronic effect suggests that as the pyridine ring becomes more electron-deficient an increased amount of the desired 1,4-addition product **37f** is formed. Unfortunately, while greater regioselectivity is observed for pyrox ligands with 5-CN or

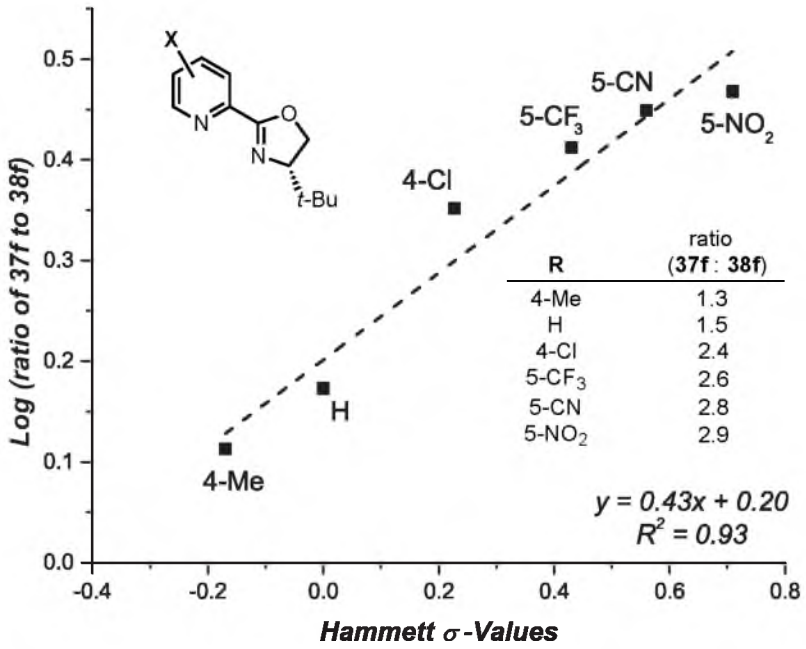


Figure 3.14 Correlation between 1,4- and 1,2-addition regioisomers and Hammett σ-values.

5-NO_2 substitution, the yields of difunctionalization products sharply decrease. The observation of an electronic control on product regioselectivity that results from π-allyl intermediates is intriguing, although the reasoning behind this effect is not clear to us.

Evaluation of Ligand-Controlled Scope

Following the evaluation of a diverse collection of pyrox ligands, **L4** was the most selective and provided skipped polyene-containing terpenoid products in modest yields. After a reoptimization of reaction conditions, improved yields were observed. The newly optimized conditions required an increased reaction temperature and decreased stoichiometry of ligand. To evaluate the tolerance of **L4** to other coupling partners, select examples from Figure 3.9 were evaluated under the new conditions (Figure 3.15). We were pleased to see the selectivity for the 1,4-addition product **37** over 4,1-addition product **39** was enhanced in examples with an electronically stabilized vinyl triflate (**37f-i**). Importantly, (*E*)-**37c** was formed with good regioselectivity with or without added ligand, suggesting that **L4** controls alkene insertion regardless of the electronically character of the vinyl triflate. Yields for the difunctionalized products remained similar in the presence of **L4**, although the formation of considerable amounts 1,2-addition product **38** restricts the production of (*E*)-**37** in higher yields. In examples **37h** and **37i** where we previously had observed increased regioselectivity over **38**, only moderate selectivity is generated using **L4** ((*E*)-**37i** : **38i** 11:1without ligand and 2.7:1 with **L4**). This observation could be explained by the pyrox ligand potentially inhibiting π-allyl isomerization of intermediate **41**, thereby leading to increased formation of 1,2-addition product.

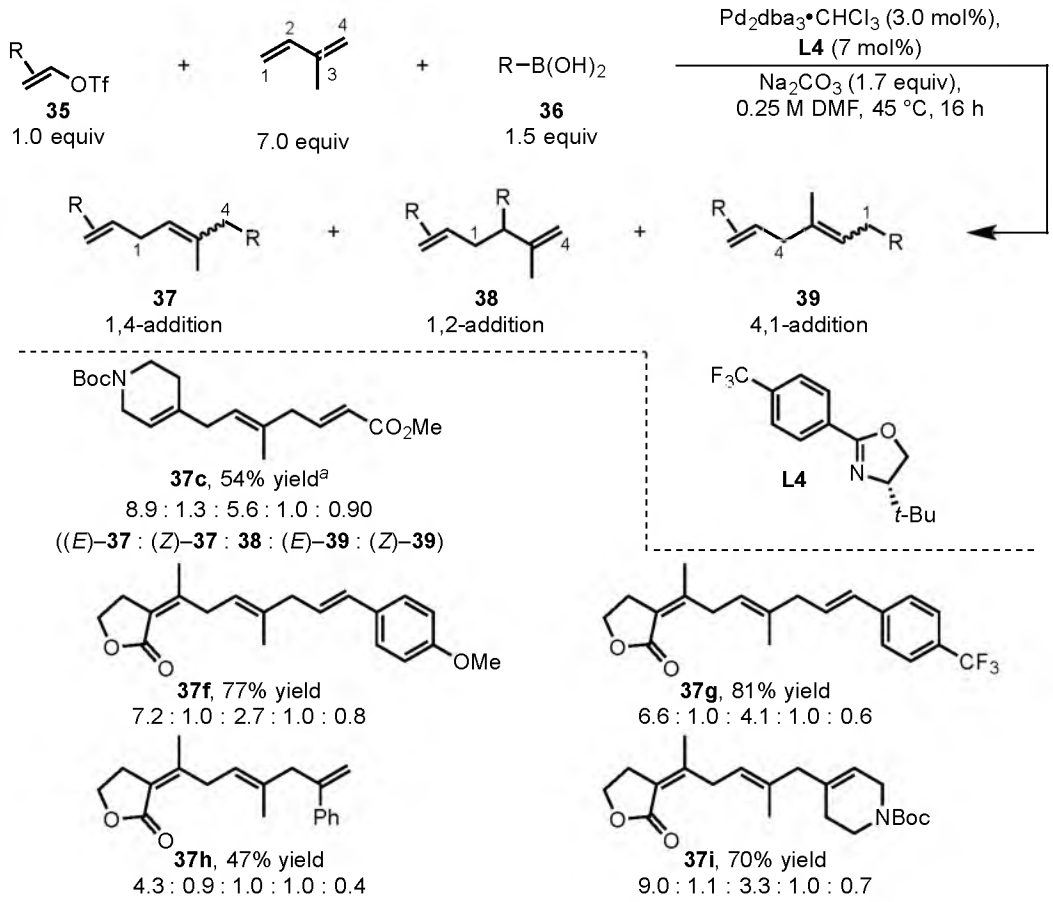


Figure 3.15 Scope of the ligand-controlled 1,4-difunctionalization of isoprene with vinyl triflates and vinylboronic acids. Ratios of regio- and stereoisomers were determined by ^{1}H NMR analysis. Yields represent a mixture of regio- and stereoisomers. [a]Reaction performed with 3.0 equivalents of **35** and 1.0 equivalent of **36**.

Conclusion

While the regio- and stereoselective synthesis of skipped polyene-containing terpenoids remains a significant challenge, we have developed a Pd-catalyzed 1,4-difunctionalization of isoprene that affords these complex scaffolds. Preliminary scope evaluation revealed a major influence of the electronic properties of vinyl triflates on alkene insertion selectivity. In efforts to identify a ligand to increase control over this process, we found the unique electronic asymmetry and steric properties of pyrox ligand **L4** were well suited to control alkene insertion into Pd–C bonds. The examination of a

library of diverse pyrox ligands and collaborative efforts to calculate energies of ground and transition state intermediates led to the development of a mechanistic model to describe the function of **L4** in controlling alkene insertion. The presence of ligand was shown to increase regioselectivity over 4,1-addition products, although understanding and controlling the reactivity of π-allyl stabilized intermediates that result in the formation of 1,4- and 1,2-addition products remain a challenge of this chemistry.

Experimental

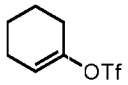
General considerations

Anhydrous dimethylformamide (DMF) was purchased from Sigma Aldrich and stored over activated 3 Å molecular sieves (3 Å MS). $Pd_2(dba)_3 \bullet CHCl_3$ was synthesized according to known procedure.[54] Isoprene was purchased from Alfa Aesar and distilled prior to use. Unless otherwise noted all reagents and solvents were purchased from Sigma Aldrich, Frontier Scientific, Acros, or TCI and used without further purification. ^1H NMR spectra were obtained at 500 MHz or 400 MHz. Chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm. The abbreviations s, d, t, q, quint, sext, sept, dd, ddd, dt, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, quintet, sextet, septet, doublet of doublets, doublet of doublets of doublets, doublet of triplet, and multiplet, respectively. ^{13}C NMR spectra were obtained at 126 MHz and referenced to the centerline of the $CDCl_3$ triplet at 77.23 ppm. Flash chromatography was performed using Silicycle SiliaFlash F60 silica gel (230-400 mesh). Gas Chromatography (GC) separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 50:1 split. Optical rotations

were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length; concentrations are reported in g/100 mL. HPLC separations were performed with an HP series 1100 chromatograph (Agilent ChromSpher 5 Lipids (4.6 x 250 mm)). IR spectra were recorded using a Thermo Nicolet FTIR. Melting points were obtained on an electrothermal melting point apparatus and are uncorrected. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF.

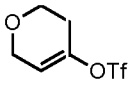
Preparation of vinyl triflate substrates

cyclohex-1-en-1-yl trifluoromethanesulfonate (**35a**):



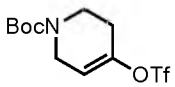
A previously reported procedure was used for the synthesis of **35a** from cyclohexanone.[55]

3,6-dihydro-pyran-4-yl trifluoromethanesulfonate (**35b**):



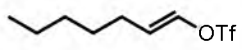
A previously reported procedure was used for the synthesis of **35b** from tetrahydropyran-4-one.[55]

tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1-carboxylate (**35c**):



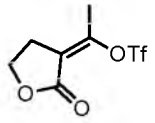
A previously reported procedure was used for the synthesis of **35c** from *tert*-butyl-4-oxopiperidine-1-carboxylate.[56]

(*E*)-hept-1-en-1-yl trifluoromethanesulfonate (**35d**):



A previously reported procedure was used for the synthesis of **35d** from *n*-butyllithium and acrolein.[30,57,58]

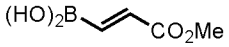
(*Z*)-1-(2-oxodihydrofuran-3-ylidene)ethyl trifluoromethanesulfonate (**35e**):



A previously reported procedure was used for the synthesis of **35e** from 3-acetyldihydrofuran-2-one.[21]

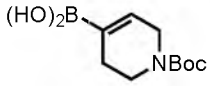
Preparation of vinylboronic acid substrates

(*E*)-(3-methoxy-3-oxoprop-1-en-1-yl)boronic acid (**36b**):



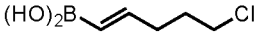
A previously reported procedure was used for the synthesis of **36b** from methyl propiolate.[59]

(1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)boronic acid (**36f**):



A previously reported procedure was used for the synthesis of **36f** from the pinacol boronic ester.[60]

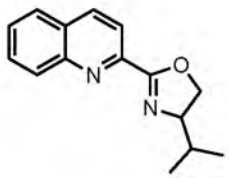
(*E*)-(5-chloropent-1-en-1-yl)boronic acid (**36g**):



A previously reported procedure was used for the synthesis of **36g** from the pinacol boronic ester.[61]

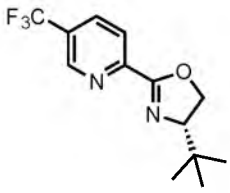
Preparation of quinox and pyrox ligands

4-isopropyl-2-(quinolin-2-yl)-4,5-dihydrooxazole (**L3**):



A previously reported procedure was used for the synthesis of **L3** from 2-amino-3-methylbutan-1-ol and quinoline-2-carboxylic acid.[42]

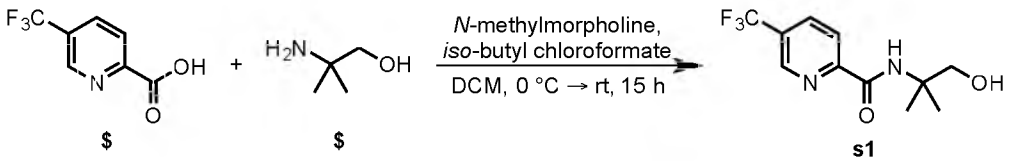
(*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (**L4**):



A previously reported procedure was used for the synthesis of **L4** from (*S*)-tert-leucinol and 5-(trifluoromethyl)pyridine-2-carboxylic acid.[42]

General procedure for the synthesis of quinox and pyrox ligands –

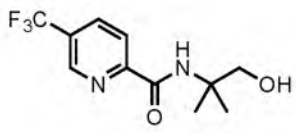
Anderson Coupling[42]



To an oven dried 100 mL round bottom flask was added 191 mg (1.0 mmol, 1.0 equiv) of 5-(trifluoromethyl)picolinic acid. The flask was placed under an N_2 atmosphere. Dichloromethane (20 mL) was added by syringe, followed by 0.13 mL (1.2 mmol, 1.2 equiv) *N*-methylmorpholine. The reaction mixture was cooled to 0 °C, and then 0.16 mL (1.2 mmol, 1.2 equiv) *iso*-butyl chloroformate was added. The mixture was

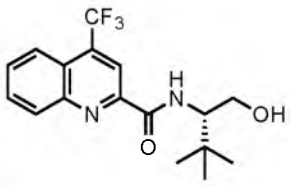
stirred for 20 min, and then 107 mg (1.2 mmol, 1.2 equiv) 2-amino-2-methylpropan-1-ol was added in dichloromethane (15 mL). The mixture was allowed to warm to room temperature and stirred for 15 h. After completion the reaction mixture was transferred to a separatory funnel with dichloromethane (10 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (1 x 15 mL), and the combined organic layers were washed with water (1 x 20 mL), and brine (1 x 20 mL), then dried over sodium sulfate. The dried organic mixture was concentrated *in vacuo* and purified by silica gel flash chromatography.

N-(1-hydroxy-2-methylpropan-2-yl)-5-(trifluoromethyl)picolinamide (**s1**):



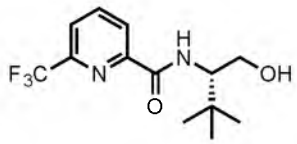
The general procedure was followed using 1.91 g of 5-(trifluoromethyl)picolinic acid (10 mmol) in dichloromethane (200 mL), 1.27 mL *N*-methylmorpholine (11.5 mmol), 1.57 mL *iso*-butyl chloroformate (12 mmol), and 1.15 mL 2-amino-2-methylpropan-1-ol (12 mmol) in dichloromethane (150 mL). Purification by silica gel flash chromatography (2:1 hexanes:ethyl acetate) afforded **s1** as a white solid (2.37 g, 90%).

(*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-(trifluoromethyl)quinoline-2-carboxamide (**s2**):



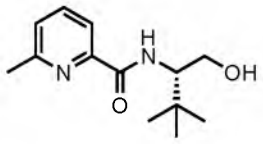
The general procedure was followed using 250 mg of 4-(trifluoromethyl)quinolone-2-carboxylic acid (1.04 mmol) in dichloromethane (20 mL), 0.13 mL *N*-methylmorpholine (1.2 mmol), 0.16 mL *iso*-butyl chloroformate (1.24 mmol), and 145 mg (S)-*tert*-leucinol (1.24 mmol) in dichloromethane (15 mL). Purification by silica gel flash chromatography (2:1 hexanes:ethyl acetate) afforded **s2** as a white solid (290 mg, 82%).

(*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-6-(trifluoromethyl)picolinamide (**s3**):



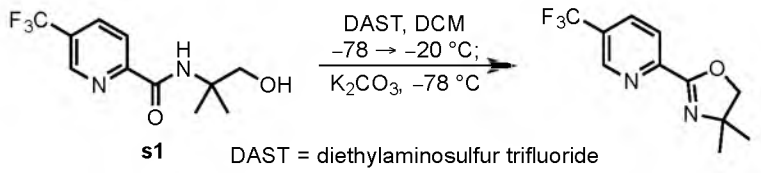
The general procedure was followed using 956 mg of 6-(trifluoromethyl)picolinic acid (5 mmol) in dichloromethane (100 mL), 0.63 mL *N*-methylmorpholine (5.75 mmol), 0.78 mL *iso*-butyl chloroformate (6 mmol), and 703 mg (S)-*tert*-leucinol (6 mmol) in dichloromethane (75 mL). Purification by silica gel flash chromatography (2:1 hexanes:ethyl acetate) afforded **s3** as a white solid (1.34 g, 92%).

(*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-6-methylpicolinamide (**s4**):



The general procedure was followed using 1.91 g of 6-methylpicolinic acid (13.9 mmol) in dichloromethane, 1.76 mL *N*-methylmorpholine (16 mmol), 2.18 mL *iso*-butyl chloroformate (16.7 mmol), and 1.96 g (S)-*tert*-leucinol (16.7 mmol) in dichloromethane. Purification by silica gel flash chromatography afforded **s4** as a white solid (3.0 g, 91%).

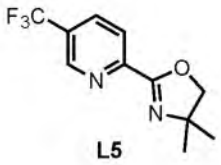
General procedure for the synthesis of quinox and pyrox ligands – oxazoline formation



s1 DAST = diethylaminosulfur trifluoride

To an oven dried 50 mL round bottom flask was added 223 mg (0.85 mmol, 1.0 equiv) of **s1** in dichlormethane (12 mL). The flask was placed under an N_2 atmosphere and cooled to −78 °C. To the mixture was added dropwise 0.16 mL (1.19 mmol, 1.4 equiv) of DAST. The mixture was stirred at −78 °C for 1 h before warming to −20 °C and stirring for an additional 1 h. After completion, the mixture was cooled to −78 °C and 236 mg (1.71 mmol, 2.0 equiv) K_2CO_3 was added in one portion. The mixture was warmed to room temperature, diluted with dichloromethane (5 mL) and washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography.

4,4-dimethyl-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (**L5**):

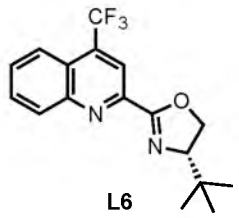


L5

The general procedure was followed using 1.2 g of **s1** (4.58 mmol) in dichloromethane (61 mL), 0.85 mL DAST (6.41 mmol), and 1.26 g K_2CO_3 (9.16 mmol). Purification by silica gel flash chromatography (5:1 hexanes:acetone) led to the isolation of **L5** as a white solid (834 mg, 75%), mp 90 °C, R_f = 0.36 (5:1 hexanes:acetone). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.95 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.02 (dd, J = 8.3, 2.3

Hz, 1H), 4.24 (s, 2H), 1.43 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.4, 150.3, 146.9 (q, J = 3.8), 134.2 (q, J = 3.7), 128.2 (q, J = 33.4), 123.7, 123.3 (q, J = 273), 80.1, 68.6, 28.6; FTIR (thin film): 2974, 1640, 1573, 1324, 1089, 1013, 869, 788 cm^{-1}; HRMS *m/z* calculated for $C_{11}H_{11}F_3N_2ONa$ $[M+Na]^+$: 267.0721, found 267.0721.

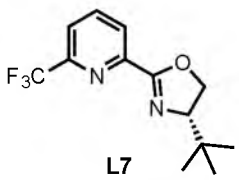
(*S*)-4-(*tert*-butyl)-2-(4-(trifluoromethyl)quinolin-2-yl)-4,5-dihydrooxazole (**L6**):



L6

The general procedure was followed using 290 mg of **s2** (0.85 mmol) in dichloromethane (12 mL), 0.16 mL DAST (1.19 mmol), and 236 mg K_2CO_3 (1.71 mmol). Purification by silica gel flash chromatography (3:1 hexanes:ethyl acetate) led to the isolation of **L6** as a white solid (230 mg, 84%), mp 98 °C, R_f = 0.42 (3:1 hexanes:ethyl acetate). $[\alpha]^{20}_D$ = −94 (c = 0.284, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.54 (s, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 4.56 (dd, J = 9.0, 10.5 Hz, 1H), 4.43 (t, J = 8.5 Hz, 1H), 4.21 (dd, J = 8.5, 10.5 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.2, 148.6, 146.9, 135.2 (q, J = 32.3), 131.5, 130.9, 129.8, 124.2 (q, J = 1.9), 123.7, 123.5 (q, J = 275), 118.5 (q, J = 5.4), 77.0, 70.2, 34.3, 26.2; FTIR (thin film): 2957, 1645, 1325, 1253, 1132, 967, 850, 765 cm^{-1}; HRMS *m/z* calculated for $C_{17}H_{17}F_3N_2ONa$ $[M+Na]^+$: 345.1191, found 345.1195.

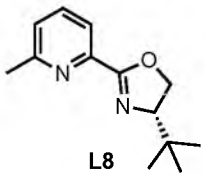
(*S*)-4-(*tert*-butyl)-2-(6-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (**L7**):



L7

The general procedure was followed using 726 mg of **s3** (2.5 mmol) in dichloromethane (33 mL), 0.46 mL DAST (3.5 mmol), and 691 mg K_2CO_3 (5.0 mmol). Purification by silica gel flash chromatography (3:1 hexanes:ethyl acetate) led to the isolation of **L7** as a white solid (509 mg, 75%), mp 122 °C, R_f = 0.29 (3:1 hexanes:ethyl acetate). $[\alpha]^{20}_D$ = −89 (c = 0.334, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.35 (d, *J* = 8.0 Hz, 1H), 7.96 (t, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.50 (dd, *J* = 8.5, 10.3 Hz, 1H), 4.36 (t, *J* = 8.5 Hz, 1H), 4.13 (dd, *J* = 8.5, 10.5 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 161.8, 148.3 (q, *J* = 41), 147.9, 138.2, 127.0, 122.3 (q, *J* = 2.5), 121.4 (q, *J* = 275), 76.6, 70.0, 34.2, 26.1; FTIR (thin film): 2966, 1647, 1363, 1185, 1165, 1077, 955, 836 cm^{-1}; HRMS *m/z* calculated for $C_{13}H_{15}F_3N_2O$ $[M+Na]^+$: 295.1034, found 295.1030.

(*S*)-4-(*tert*-butyl)-2-(6-methylpyridin-2-yl)-4,5-dihydrooxazole (**L8**):



L8

The general procedure was followed using 3.0 g of **s4** (12.7 mmol) in dichloromethane, 2.35 mL DAST (17.8 mmol), and 3.51 g K_2CO_3 (25.4 mmol). Purification by silica gel flash chromatography led to the isolation of **L8** as a white solid (2.1 g, 70%), mp 71 °C, R_f = 0.44 (2:1 hexanes:acetone). $[\alpha]^{20}_D$ = −83 (c = 0.262, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H),

7.24 (d, J = 8.0 Hz, 1H), 4.45 (dd, J = 8.5, 10.5 Hz, 1H), 4.31 (t, J = 8.5 Hz, 1H), 4.10 (dd, J = 8.5, 10.5 Hz, 1H), 2.63 (s, 3H), 0.97 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.9, 158.8, 146.7, 136.9, 125.4, 121.5, 76.6, 69.6, 34.2, 26.2, 24.9; FTIR (thin film): 2951, 1643, 1461, 1360, 1118, 966, 810 cm^{-1}; HRMS *m/z* calculated for $C_{13}H_{18}N_2ONa$ $[M+Na]^+$: 241.1317, found 241.1318.

General procedure for optimization A

To an oven dried 5 mL vial were added 32 mg (0.34 mmol, 1.7 equiv) of $KF•2H_2O$, 44 mg (0.30 mmol, 1.5 equiv) of **36a**, and 6 mg (3.0 mol%) of $Pd_2dba_3•CHCl_3$. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N_2 before being sealed with a septum cap. To the solids were added a solution of 69 mg (0.3 mmol, 1.5 equiv) of **35a** in 1.0 mL of DMA containing an internal standard (2-methoxynaphthalene) and 20 μL (0.2 mmol, 1.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, a ~200 μL aliquot of the reaction mixture was removed via syringe and filtered through a silica plug, eluting with ethyl acetate. The mixture was analyzed by GC. Yields were calculated using a response factor (^{1}H NMR spectroscopy was used to measure the response factor to account for varying detector response).

General procedure A for the 1,4-difunctionalization of isoprene

To an oven dried 10 mL round bottom flask were added 90 mg (0.85 mmol, 1.7 equiv) of Na_2CO_3, 111 mg (0.75 mmol, 1.5 equiv) of **36a**, and 16 mg (3.0 mol%) of $Pd_2dba_3•CHCl_3$. The flask was equipped with a stirbar and a septum, and then was

flushed with N_2. To the solids were added a solution of 115 mg (0.5 mmol, 1.0 equiv) of **35a** in 2.0 mL of DMF and 0.35 mL (3.5 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and filtered through a Celite plug. The organics were washed with H_2O (3 x 10 mL) and brine (1 x 10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography. Yields represent a mixture of stereo- and regioisomers. HPLC methods and NMR analysis were used to isolate and verify the identity of product isomers. ^{1}H NMR spectroscopy was used to determine isomeric ratios of the product mixture.

General procedure for optimization B

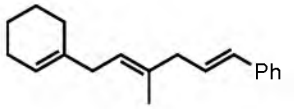
To an oven dried 5 mL vial were added 36 mg (0.34 mmol, 1.7 equiv) of Na_2CO_3, 39 mg (0.3 mmol, 1.5 equiv) of **36b**, and 6 mg (3.0 mol%) of Pd_2dba_3•$CHCl_3$. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N_2 before being sealed with a septum cap. To the solids were added a solution of 46 mg (0.2 mmol, 1.0 equiv) of **35b** in 0.8 mL of DMF and 0.14 mL (1.4 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and the organics were washed with H_2O (3 x 2 mL) and brine (1 x 2 mL), then dried over magnesium sulfate and concentrated *in vacuo*. ^{1}H NMR spectroscopy was used to determine isomeric ratios and yields using an internal standard (2-methoxynaphthalene).

General procedure B for the 1,4-difunctionalization of isoprene

To an oven dried 10 mL round bottom flask were added 90 mg (0.85 mmol, 1.7 equiv) of Na_2CO_3, 65 mg (0.5 mmol, 1.0 equiv) of **36b**, and 16 mg (3.0 mol%) of $Pd_2dba_3 \bullet CHCl_3$. The flask was equipped with a stirbar and a septum, and then was flushed with N_2. To the solids were added a solution of 348 mg (1.5 mmol, 3.0 equiv) of **35b** in 2.0 mL of DMF and 0.35 mL (3.5 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and filtered through a Celite plug. The organics were washed with H_2O (3 x 10 mL) and brine (1 x 10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography as noted below. Yields represent a mixture of stereo- and regioisomers. HPLC methods and NMR analysis were used to isolate and verify the identity of product isomers. ^{1}H NMR spectroscopy was used to determine isomeric ratios of the product mixture.

Product purification and characterization data

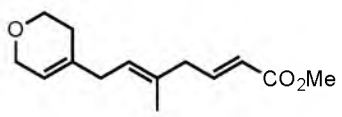
((1*E*,4*E*)-6-(cyclohex-1-en-1-yl)-4-methylhexa-1,4-dien-1-yl)benzene ((*E*)-**37a**):



General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 111 mg of **36a** (0.75 mmol), 16 mg of $Pd_2dba_3 \bullet CHCl_3$ (3 mol%), 115 mg of **35a** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (19:1 hexanes:benzene) led to the isolation of **37a**, **38a**, and **39a** as a colorless oil (112 mg, 89% as a 7.3:0.85:0.64:1.0:0.89 mixture of (*E*)-**37a**:(*Z*)-**37a**:**38a**:(*E*)-**39a**:(*Z*)-**39a** isomers, respectively), isomeric ratios were determined by GC,

R_f = 0.40 (19:1 hexanes:benzene). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 6.20 (app. dt, J = 7.0, 16 Hz, 1H), 5.41 (m, 1H), 5.26 (t, J = 7.5 Hz, 1H), 2.89 (d, J = 7.0 Hz, 2H), 2.65 (d, J = 7.5 Hz, 2H), 1.98 (m, 2H), 1.92 (m, 2H), 1.62 (m, 5H), 1.55 (m, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*Z*)-**37a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.14 (app. dt, J = 7.0, 16 Hz, 1H), 2.93 (d, J = 6.5 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.0, 137.3, 134.8, 131.2, 129.3, 128.7, 127.1, 126.3, 123.9, 121.1, 43.5, 36.9, 28.8, 25.5, 23.2, 22.8, 16.4; FTIR (thin film): 3025, 2923, 2833, 1495, 1447, 962, 919, 888, 739, 691 cm^{-1}; HRMS *m/z* calculated for $C_{19}H_{24}Ag$ $[M+Ag]^+$: 359.0929, found 359.0947.

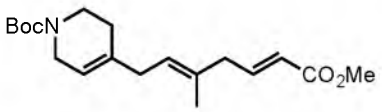
Methyl-(2*E*,5*E*)-7-(3,6-dihydropyran-4-yl)-5-methylhepta-2,5-dienoate ((*E*)-**37b**):



General procedure B was followed using 90 mg of Na_2CO_3 (0.85 mmol), 65 mg of **36b** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 348 mg of **35b** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37b**, **38b**, and **39b** as a colorless oil (63 mg, 53% as a 11:1.2:5.1:1.0:1.0 mixture of (*E*)-**37b**:(*Z*)-**37b**:**38b**:(*E*)-**39b**:(*Z*)-**39b** isomers, respectively), R_f = 0.43 (3:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.95 (app. dt, J = 7.0, 15.5 Hz, 1H), 5.83 (d, J = 15.5 Hz, 1H), 5.41 (m, 1H), 5.24 (t, J = 7.0 Hz, 1H), 4.11 (m, 2H), 3.78, (t, J = 5.5 Hz, 2H), 3.73 (s, 3H), 2.88 (d, J = 7.0 Hz, 2H), 2.70 (d, J = 7.0 Hz, 2H), 2.03 (m, 2H), 1.63 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*Z*)-**37b**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.90 (app. dt, J = 6.8, 16 Hz, 1H),

5.33 (t, J = 7.7 Hz, 1H), 2.91 (d, J = 7.1 Hz, 2H), 2.66 (d, J = 7.8 Hz, 2H), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.2, 147.5, 134.7, 133.7, 124.1, 122.2, 120.1, 65.8, 64.6, 51.7, 42.5, 35.8, 28.9, 16.5; FTIR (thin film): 2951, 1720, 1650, 1434, 1270, 1207, 1165, 1126, 1031, 980, 848 cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{20}O_3Na$ $[M+Na]^+$: 259.1310, found 259.1316.

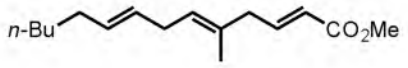
tert-Butyl-4-((2*E*,5*E*)-7-methoxy-3-methyl-7-oxohepta-2,5-dien-1-yl)-3,6-dihydropyridine-1-carboxylate ((*E*)-**37c**):



General procedure B was followed using 90 mg of Na_2CO_3 (0.85 mmol), 65 mg of **36b** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 497 mg of **35c** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (4:1 hexanes:EtOAc) led to the isolation of **37c**, **38c**, and **39c** as a colorless oil (142 mg, 85% as a 6.5:0.42:3.4:1.0:1.1 mixture of (*E*)-**37c**:(*Z*)-**37c**:**38c**:(*E*)-**39c**:(*Z*)-**39c** isomers, respectively; 127 mg, 76% as a 7.3:0.48:3.3:1.0:1.1 mixture of (*E*)-**37c**:(*Z*)-**37c**:**38c**:(*E*)-**39c**:(*Z*)-**39c**, R_f = 0.37 (4:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (app. dt, J = 7.0, 15.5 Hz, 1H), 5.84 (dt, J = 1.5, 16 Hz, 1H), 5.33 (m, 1H), 5.21 (t, J = 7.4 Hz, 1H), 3.85 (m, 2H), 3.73 (s, 3H), 3.48 (m, 2H), 2.88 (d, J = 7.0 Hz, 2H), 2.69 (d, J = 7.0 Hz, 2H), 2.02 (m, 2H), 1.62 (s, 3H), 1.46 (s, 9H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*Z*)-**37c**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.89 (app. dt, J = 6.5, 15.5 Hz, 1H), 5.82 (dt, J = 1.5, 15.5 Hz, 1H), 2.90 (d, J = 7.0 Hz, 2H), 2.66 (d, J = 7.5 Hz, 2H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.2, 155.2, 147.4, 133.7, 128.7, 124.2, 122.2, 118.6, 79.7, 51.7, 43.7, 42.5, 40.0, 35.9, 28.7, 16.5; FTIR (thin film): 2977,

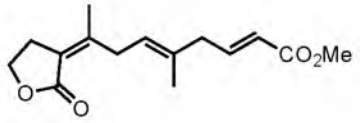
1693, 1415, 1367, 1244, 1209, 1164, 1142, 1062, 871, 769, 611 cm^{-1}; HRMS *m/z* calculated for $C_{19}H_{29}NO_4Na$ $[M+Na]^+$: 358.1994, found 358.2007.

Methyl-(2*E*,5*E*,8*E*)-5-methyltetradeca-2,5,8-trienoate ((*E*)-**37d**):



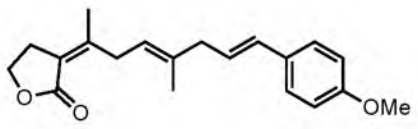
General procedure B was followed using 90 mg of Na_2CO_3 (0.85 mmol), 65 mg of **36b** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 369 mg of **35d** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (19:1 hexanes:EtOAc) led to the isolation of **37d**, **38d**, and **39d** as a colorless oil (77 mg, 62% as a 5.5:1.4:3.0:1.0:1.4 mixture of (*E*)-**37d**:(*Z*)-**37d**:**38d**:(*E*)-**39d**:(*Z*)-**39d** isomers, respectively; 67 mg, 54% as a 6.4:1.4:3.3:1.0:1.4 mixture of (*E*)-**37d**:(*Z*)-**37d**:**38d**:(*E*)-**39d**:(*Z*)-**39d** isomers, respectively), (*Z*)-**37d** and (*Z*)-**39d** isomeric ratios are reported as a inseparable mixture, R_f = 0.27 (19:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.95 (app. dt, *J* = 7.0, 15.5 Hz, 1H), 5.83 (dt, *J* = 1.5, 15.5 Hz, 1H), 5.42 (app. dt, *J* = 6.5, 15.5 Hz, 1H), 5.35 (app. dt, *J* = 6.0, 15.0 Hz, 1H), 5.22 (t, *J* = 7.0 Hz, 1H), 3.73 (s, 3H), 2.89 (d, *J* = 7.0 Hz, 2H), 2.70 (d, *J* = 7.0 Hz, 2H), 1.97 (q, *J* = 7.0 Hz, 2H), 1.62 (s, 3H), 1.30 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*Z*)-**37d**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.90 (d, *J* = 6.6 Hz, 2H), 2.67 (t, *J* = 6.6 Hz, 2H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.3, 147.7, 132.2, 131.2, 128.2, 125.8, 122.0, 51.6, 42.5, 32.7, 31.7, 31.5, 29.4, 22.8, 16.4, 14.3; FTIR (thin film): 2925, 2855, 1725, 1643, 1434, 1268, 1161, 1040, 968, 893, 725 cm^{-1}; HRMS *m/z* calculated for $C_{16}H_{26}O_2Na$ $[M+Na]^+$: 273.1831, found 273.1824.

Methyl-(2*E*,5*E*,8*Z*)-5-methyl-8-(2-oxodihydrofuran-3-ylidene)nona-2,5-dienoate ((*E*)-**37e**):



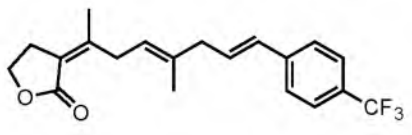
General procedure B was followed using 90 mg of Na_2CO_3 (0.85 mmol), 65 mg of **36b** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 390 mg of **35e** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37e**, **38e**, and **39e** as a colorless oil (110 mg, 83% as a 1.4:0.33:0.30:1.0:0.49 mixture of (*E*)-**37e**:(*Z*)-**37e**:**38e**:(*E*)-**39e**:(*Z*)-**39e** isomers, respectively; 116 mg, 87% as a 1.6:0.39:0.48:1.0:0.52 mixture of (*E*)-**37e**:(*Z*)-**37e**:**38e**:(*E*)-**39e**:(*Z*)-**39e** isomers, respectively), R_f = 0.32 (3:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.93 (app. dt, *J* = 6.8, 15.6 Hz, 1H), 5.82 (dt, *J* = 1.6, 15.6 Hz, 1H), 5.18 (t, *J* = 7.4 Hz, 1H), 4.30 (t, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 3.55 (d, *J* = 7.2 Hz, 2H), 2.88 (m, 4H), 1.84 (s, 3H), 1.71 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.4, 167.2, 152.6, 147.4, 134.2, 123.5, 122.2, 118.8, 64.4, 51.7, 42.5, 31.5, 28.0, 22.3, 16.8; FTIR (thin film): 2914, 1738, 1716, 1653, 1435, 1269, 1214, 1161, 1031, 987, 847, 754 cm^{-1}; HRMS *m/z* calculated for $C_{15}H_{20}O_4Na$ $[M+Na]^+$: 287.1259, found 287.1260.

(*Z*)-3-((4*E*,7*E*)-8-(4-methoxyphenyl)-5-methylocta-4,7-dien-2-ylidene)dihydrofuran-2-one ((*E*)-**37f**):



General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 134 mg of **36c** (0.75 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37f**, **38f**, and **39f** as a colorless oil (126 mg, 81% as a 1.5:0.22:0.44:1.0:0.78 mixture of (*E*)-**37f**:(*Z*)-**37f**:**38f**:(*E*)-**39f**:(*Z*)-**39f** isomers, respectively; 136 mg, 84% as a 1.5:0.26:0.47:1.0:0.74 mixture of (*E*)-**37f**:(*Z*)-**37f**:**38f**:(*E*)-**39f**:(*Z*)-**39f** isomers, respectively), R_f = 0.30 (3:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.33 (d, *J* = 16 Hz, 1H), 6.03 (app. dt, *J* = 7.0, 16 Hz, 1H), 5.20 (t, *J* = 7.4 Hz, 1H), 4.29 (t, *J* = 7.5 Hz, 2H), 3.80 (s, 3H), 3.57 (d, *J* = 7.0 Hz, 2H), 2.87 (m, 4H), 1.85 (t, *J* = 2.0 Hz, 3H), 1.73 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*E*)-**39f**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.28 (t, *J* = 7.0 Hz, 1H), 4.36 (t, *J* = 7.5 Hz, 2H), 1.83 (t, *J* = 1.5 Hz, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.4, 158.9, 152.1, 134.1, 130.8. 129.4, 127.3, 127.1, 124.6, 120.0, 114.1, 64.3, 55.5, 42.0, 31.7, 28.2, 21.8, 16.0; FTIR (thin film): 2911, 1737, 1606, 1509, 1243, 1172, 1029, 965, 837, 750 cm^{-1}; HRMS *m/z* calculated for $C_{20}H_{24}O_3Na$ $[M+Na]^+$: 335.1623, found 335.1633.

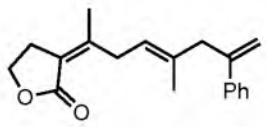
(*Z*)-3-((4*E*,7*E*)-5-methyl-8-(4-(trifluoromethyl)phenyl)octa-4,7-dien-2-ylidene) dihydrofuran-2-one ((*E*)-**37g**):



General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 162 mg of **36d** (0.75 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and

0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37g**, **38g**, and **39g** as a colorless oil (148 mg, 85% as a 1.2:0.24:0.49:1.0:0.55 mixture of (*E*)-**37g**:(*Z*)-**37g**:**38g**:(*E*)-**39g**:(*Z*)-**39g** isomers, respectively; 136 mg, 78% as a 1.3:0.27:0.57:1.0:0.56 mixture of (*E*)-**37g**:(*Z*)-**37g**:**38g**:(*E*)-**39g**:(*Z*)-**39g** isomers, respectively), R_f = 0.31 (3:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 16 Hz, 1H), 6.29 (app. dt, *J* = 7.0, 16 Hz, 1H), 5.21 (t, *J* = 7.5 Hz, 1H), 4.30 (t, *J* = 7.5 Hz, 2H), 3.57 (d, *J* = 7.5 Hz, 2H), 2.88 (m, 4H), 1.85 (t, *J* = 1.5 Hz, 3H), 1.74 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.4, 152.9, 141.3, 135.9, 131.7, 130.2, 129.2, 128.9, 126.4, 125.6 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.5 (q, $J_{C\text{-}F}$ = 272.2 Hz), 122.4, 118.7, 64.4, 43.4, 31.6, 28.0, 22.3, 16.8; FTIR (thin film): 2918, 1739, 1322, 1161, 1109, 1065, 968, 838, 755 cm^{-1}; HRMS *m/z* calculated for $C_{20}H_{21}F_3O_2Na$ $[M+Na]^+$: 373.1391, found 373.1395.

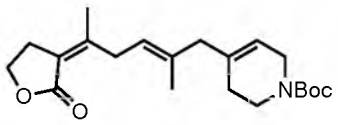
(*Z*)-3-((*E*)-5-methyl-7-phenylocta-4,7-dien-2-ylidene)dihydrofuran-2-one ((*E*)-**37h**):



General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 111 mg of **36e** (0.75 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37h**, **38h**, and **39h** as a colorless oil (81 mg, 57% as a 1.4:0.20:0.22:1.0:0.42 mixture of (*E*)-**37h**:(*Z*)-**37h**:**38h**:(*E*)-**39h**:(*Z*)-**39h** isomers, respectively; 78 mg, 55% as a 1.6:0.20:0.11:1.0:0.42

mixture of (*E*)-**37h**:(*Z*)-**37h**:**38h**:(*E*)-**39h**:(*Z*)-**39h** isomers, respectively), R_f = 0.40 (3:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (m, 2H), 7.27 (m, 3H), 5.37 (s, 1H), 5.17 (m, 1H), 5.07 (s, 1H), 4.27 (t, *J* = 7.6 Hz, 2H), 3.51 (d, *J* = 7.6 Hz, 2H), 3.19 (s, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 1.66 (s, 3H), 1.62 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*E*)-**39h**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.32 (s, 1H), 5.27 (t, *J* = 7.5 Hz, 1H), 4.32 (m, 2H), 3.54 (s, 2H), 3.21 (d, *J* = 7.5 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 1.71 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.4, 153.4, 146.3, 141.4, 135.4, 128.3, 127.4, 126.5, 123.5, 118.3, 114.4, 64.4, 45.9, 31.4, 28.0, 21.9, 16.4; FTIR (thin film): 2912, 1737, 1655, 1443, 1373, 1269, 1187, 1029, 968, 896, 778, 755, 704 cm^{-1}; HRMS *m/z* calculated for $C_{19}H_{22}O_2Na$ $[M+Na]^+$: 305.1526, found 305.1517.

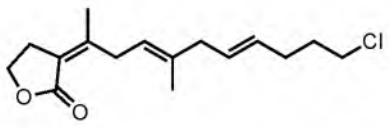
tert-butyl-4-((2*E*,5*Z*)-2-methyl-5-(2-oxodihydrofuran-3-ylidene)hex-2-en-1-yl)-3,6-dihydropyridine-1-carboxylate ((*E*)-**37i**):



General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 170 mg of **36f** (0.75 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37i**, **38i**, and **39i** as a colorless oil (148 mg, 81% as a 1.5:0.09:0.14:1.0:0.60 mixture of (*E*)-**37i**:(*Z*)-**37i**:**38i**:(*E*)-**39i**:(*Z*)-**39i** isomers, respectively; 162 mg, 90% as a 1.5:0.21:0.13:1.0:0.61 mixture of (*E*)-**37i**:(*Z*)-**37i**:**38i**:(*E*)-**39i**:(*Z*)-**39i** isomers, respectively), R_f = 0.32 (3:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.37 (m, 1H), 5.15 (t, *J* = 7.0 Hz, 1H), 4.30 (t, *J* = 7.5 Hz,

2H), 3.86 (m, 2H), 3.55 (d, J = 7.0 Hz, 2H), 3.45 (m, 2H), 2.88 (t, J = 7.8 Hz, 2H), 2.67 (s, 2H), 1.93 (m, 2H), 1.84 (t, J = 2.0 Hz, 3H), 1.61 (s, 3H), 1.46 (s, 9H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*E*)-**39i**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.19 (t, J = 6.5 Hz, 1H), 2.91 (t, J = 8.0 Hz, 2H), 2.70 (d, J = 7.5 Hz, 2H), 1.80 (t, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.5, 155.3, 153.1, 135.2, 130.0, 123.1, 119.6, 118.5, 79.7, 64.4, 48.1, 43.8, 40.0, 31.6, 28.7, 28.0, 22.2, 16.1; FTIR (thin film): 2913, 1742, 1691, 1415, 1364, 1238, 1166, 1036, 966, 864, 755 cm^{-1}; HRMS *m/z* calculated for $C_{21}H_{31}NO_4Na$ $[M+Na]^+$: 384.2151, found 384.2148.

(*Z*)-3-((4*E*,7*E*)-11-chloro-5-methylundeca-4,7-dien-2-ylidene)dihydrofuran-2-one ((*E*)-**37j**):



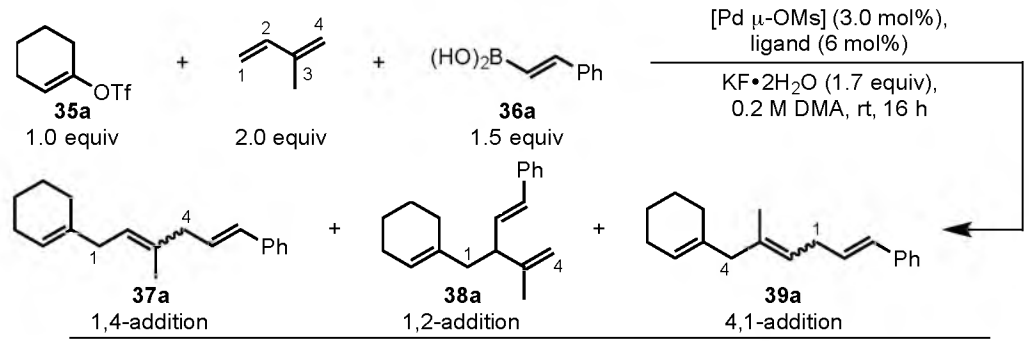
General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 111 mg of **36g** (0.75 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37j**, **38j**, and **39j** as a colorless oil (64 mg, 46% as a 1.1:0.33:0.38:1.0:0.87 mixture of (*E*)-**37j**:(*Z*)-**37j**:**38j**:(*E*)-**39j**:(*Z*)-**39j** isomers, respectively; 76 mg, 54% as a 1.0:0.33:0.30:1.0:0.81 mixture of (*E*)-**37j**:(*Z*)-**37j**:**38j**:(*E*)-**39j**:(*Z*)-**39j** isomers, respectively), R_f = 0.40 (3:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.41 (app. dt, J = 6.5, 16 Hz, 2H), 5.12 (t, J = 7.2 Hz, 1H), 4.29 (t, J = 7.5 Hz, 2H), 3.53 (m, 4H), 2.87 (t, J = 7.0 Hz, 2H), 2.67 (d, J = 6.5 Hz, 2H), 2.16 (q, J = 7.0 Hz, 2H), 1.82 (m, 5H), 1.67 (s, 3H); (The stereochemistry was

confirmed by NOESY1D NMR spectroscopy). The following signals can be assigned to (*E*)-**39j**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.19 (t, *J* = 6.0 Hz, 1H), 2.92 (t, *J* = 7.7 Hz, 2H), 2.71 (d, *J* = 6.8 Hz, 2H), 1.80 (m, 3H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.4, 153.3, 136.8, 130.0, 121.3, 121.1, 118.4, 64.4, 44.6, 43.1, 32.4, 31.5, 29.8, 28.0, 22.2, 16.6; FTIR (thin film): 2913, 1738, 1657, 1441, 1373, 1162, 1035, 967, 753, 646 cm^{-1}; HRMS *m/z* calculated for $C_{16}H_{23}ClO_2Na$ $[M+Na]^+$: 305.1284, found 305.1286.

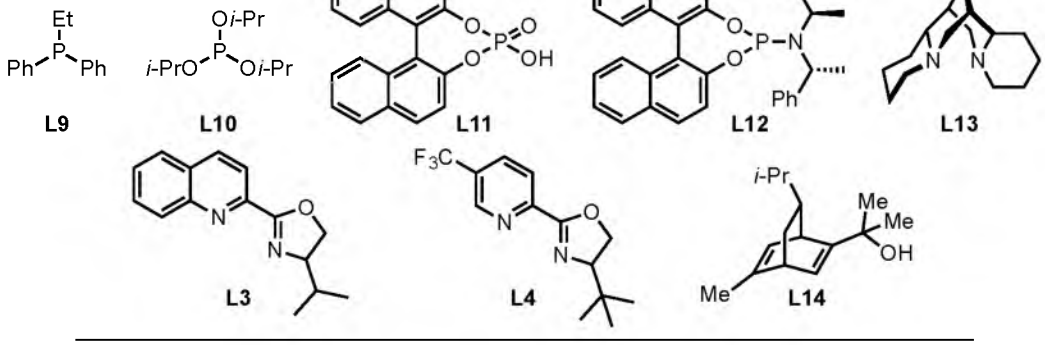
General procedure for preliminary 1,4-difunctionalization ligand screens

To an oven dried 5 mL vial were added 32 mg (0.34 mmol, 1.7 equiv) of $KF•2H_2O$, 44 mg (0.30 mmol, 1.5 equiv) of **36a**, (6 mol%) ligand, and 4 mg (3.0 mol%) of [Pd μ-OMs]. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N_2 before being sealed with a septum cap. To the solids were added a solution of 46 mg (0.2 mmol, 1.0 equiv) of **35a** in 1.0 mL of DMA containing an internal standard (2-methoxynaphthalene) and 40 μL (0.4 mmol, 2.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, a ~200 μL aliquot of the reaction mixture was removed via syringe and filtered through a silica plug, eluting with ethyl acetate. The mixture was analyzed by GC. Yields were calculated using a response factor (^{1}H NMR spectroscopy was used to measure the response factor to account for varying detector response). For a tabular summary of ligand screening results see Table 3.5.

Table 3.5 Summary of preliminary 1,4-difunctionalization ligand screens.



entry	ligand	yield (%)[a]	(*E*)–**37a** :	(*Z*)–**37a** :	**38a** :	(*E*)–**39a**
1	none	37	12	0.75	1.8	1.0
2	**L9**	10	7.6	–	3.4	1.0
3	**L10**	26	9.9	0.65	1.6	1.0
4	**L11**	22	11	1.2	3.2	1.0
5	**L12**	38	11	0.79	2.0	1.0
6	**L13**	30	12	0.79	1.8	1.0
7	**L3**	12	10	1.0	1.3	1.0
8	**L4**	17	13	1.2	1.9	1.0
9	**L14**	22	12	1.0	3.0	1.0



General procedure for 1,4-difunctionalization ligand screens

To an oven dried 5 mL vial were added 36 mg (0.34 mmol, 1.7 equiv) of Na_2CO_3, 52 mg (0.2 mmol, 1.0 equiv) of **35e,** 53 mg (0.3 mmol, 1.5 equiv) of **36c**, 2 mg (8 mol%) **L1,** and 6 mg (3.0 mol%) of Pd_2dba_3•$CHCl_3$. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N_2 before being sealed with a septum cap. To the solids were added 0.8 mL of DMF and 0.14 mL (1.4 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and the organics were washed with H_2O (3 x 2 mL) and brine (1 x 2 mL), then dried over magnesium sulfate and concentrated *in vacuo*. ^{1}H NMR spectroscopy was used to determine isomeric ratios and yields using an internal standard (2-methoxynaphthalene). Alkene insertion selectivity was defined as the ratio of **37f** + **38f** to (*E*)-**39f**. For a tabular summary of selectivity data for pyrox ligand screens and reaction optimization results see Table 3.6 and 3.7, respectively.

Table 3.6 Summary of training set data for pyrox ligand library studies.

entry	R	X	pred. $\Delta\Delta G^{\ddagger}$ (kcal/mol)	meas. $\Delta\Delta G^{\ddagger}$ (kcal/mol)	meas. alkene insertion selectivty
1	H	4-H	0.74	0.79	3.81
2	H	4-Cl	0.72	0.66	3.06
3	H	5-CF_3	0.70	0.76	3.58
4	Me	5-CF_3	0.99	0.94	4.91
5	Ph	5-CF_3	1.09	1.13	6.72
6	Bn	5-CF_3	1.28	1.31	9.19
7	*i*-Pr	4-H	1.23	1.05	5.91
8	*i*-Pr	4-Cl	1.21	1.27	8.59
9	*i*-Pr	5-CF_3	1.19	1.17	7.19
10	*t*-Bu	4-H	1.48	1.46	11.8
11	*t*-Bu	4-Cl	1.46	1.68	17.0
12	*t*-Bu	5-CF_3	1.44	1.59	14.6
13	*t*-Bu	4-Me	1.49	1.44	11.3
14	*t*-Bu	5-CN	1.42	1.36	9.98
15	*t*-Bu	5-NO_2	1.41	1.25	8.29

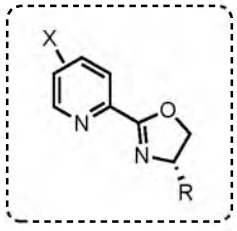


Table 3.7 Summary of reaction optimization studies with pyrox ligand.

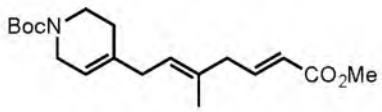
x (mol%)	temp.	yield (%)	(*E*)-**37f** : **38f** : (*E*)-**39f**	Suzuki (%)
8	rt	52	8.0 : 4.0 : 1.0	16
7	rt	59	7.7 : 3.6 : 1.0	15
7	45 °C	66	6.8 : 3.1 : 1.0	11

General procedure C for 1,4-difunctionaliztion of isoprene with ligand

To an oven dried 10 mL round bottom flask were added 90 mg (0.85 mmol, 1.7 equiv) of Na_2CO_3, 130 mg (0.5 mmol, 1.0 equiv) of **35e**, 134 mg (0.75 mmol, 1.5 equiv) of **36c**, 10 mg (7.0 mol%) of **L4**, and 16 mg (3.0 mol%) of $Pd_2dba_3 \bullet CHCl_3$. The flask was equipped with a PTFE-lined stirbar and a septum, and then was flushed with N_2. To the solids were added a solution of in 2.0 mL of DMF and 0.35 mL (3.5 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h at 45 °C. After completion, the mixture was diluted with MTBE and filtered through a Celite plug. The organics were washed with H_2O (3 x 10 mL) and brine (1 x 10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography. Yields represent a mixture of stereo- and regioisomers. HPLC methods and NMR analysis were used to isolate and verify the identity of product isomers. ^{1}H NMR spectroscopy was used to determine isomeric ratios of the product mixture.

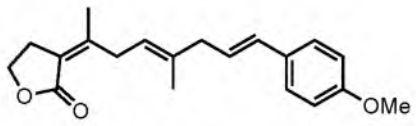
Product purification and characterization data

tert-Butyl-4-((2*E*,5*E*)-7-methoxy-3-methyl-7-oxohepta-2,5-dien-1-yl)-3,6-dihydropyridine-1-carboxylate ((*E*)-**37c**):



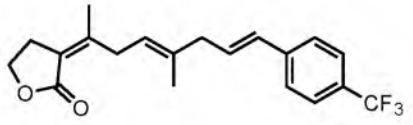
General procedure C was followed using 90 mg of Na_2CO_3 (0.85 mmol), 65 mg of **36b** (0.5 mmol), 10 mg of **L4** (7.0 mol%), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 497 mg of **35c** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (4:1 hexanes:EtOAc) led to the isolation of **37c**, **38c**, and **39c** as a colorless oil (84 mg, 50% as a 9.2:1.3:5.9:1.0:0.79 mixture of (*E*)-**37c**:(*Z*)-**37c**:**38c**:(*E*)-**39c**:(*Z*)-**39c** isomers, respectively; 95 mg, 57% as a 8.6:1.3:5.2:1.0:1.0 mixture of (*E*)-**37c**:(*Z*)-**37c**:**38c**:(*E*)-**39c**:(*Z*)-**39c** isomers, respectively).

(*Z*)-3-((4*E*,7*E*)-8-(4-methoxyphenyl)-5-methylocta-4,7-dien-2-ylidene)dihydrofuran-2-one ((*E*)-**37f**):



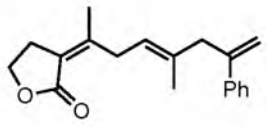
General procedure C was followed using 90 mg of Na_2CO_3 (0.85 mmol), 134 mg of **36c** (0.75 mmol), 10 mg of **L4** (7.0 mol%), 16 mg of Pd_2dba_3•$CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37f**, **38f**, and **39f** as a colorless oil (120 mg, 77% as a 7.2:1.0:2.7:1.0:0.75 mixture of (*E*)-**37f**:(*Z*)-**37f**:**38f**:(*E*)-**39f**:(*Z*)-**39f** isomers, respectively).

(*Z*)-3-((4*E*,7*E*)-5-methyl-8-(4-(trifluoromethyl)phenyl)octa-4,7-dien-2-ylidene)-dihydrofuran-2-one ((*E*)-**37g**):



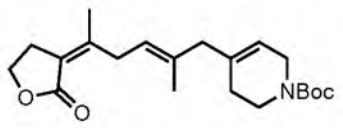
General procedure C was followed using 90 mg of Na_2CO_3 (0.85 mmol), 162 mg of **36d** (0.75 mmol), 10 mg of **L4** (7.0 mol%), 16 mg of $Pd_2dba_3 \bullet CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37g**, **38g**, and **39g** as a colorless oil (142 mg, 81% as a 6.6:0.97:4.1:1.0:0.60 mixture of (*E*)-**37g**:(*Z*)-**37g**:**38g**:(*E*)-**39g**:(*Z*)-**39g** isomers, respectively).

(*Z*)-3-((*E*)-5-methyl-7-phenylocta-4,7-dien-2-ylidene)dihydrofuran-2(3*H*)-one ((*E*)-**37h**):



General procedure C was followed using 90 mg of Na_2CO_3 (0.85 mmol), 111 mg of **36e** (0.75 mmol), 10 mg of **L4** (7.0 mol%), 16 mg of $Pd_2dba_3 \bullet CHCl_3$ (3 mol%), 130 mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37h**, **38h**, and **39h** as a colorless oil (62 mg, 44% as a 4.2:0.92:1.1:1.0:0.43 mixture of (*E*)-**37h**:(*Z*)-**37h**:**38h**:(*E*)-**39h**:(*Z*)-**39h** isomers, respectively; 69 mg, 49% as a 4.3:0.87:0.97:1.0:0.36 mixture of (*E*)-**37h**:(*Z*)-**37h**:**38h**:(*E*)-**39h**:(*Z*)-**39h** isomers, respectively).

tert-butyl-4-((2*E*,5*Z*)-2-methyl-5-(2-oxodihydrofuran-3-ylidene)hex-2-en-1-yl)-3,6-dihydropyridine-1-carboxylate ((*E*)-**37i**):



General procedure C was followed using 90 mg of Na_2CO_3 (0.85 mmol), 170 mg of **36f** (0.75 mmol), 10 mg of **L4** (7.0 mol%), 16 mg of $Pd_2dba_3 \bullet CHCl_3$ (3 mol%), 130

mg of **35e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **37i**, **38i**, and **39i** as a colorless oil (126 mg, 70% as a 9.0:1.1:3.3:1.0:0.67 mixture of (*E*)-**37i**:(*Z*)-**37i**:**38i**:(*E*)-**39i**:(*Z*)-**39i** isomers, respectively).

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CHAPTER 4

THE DEVELOPMENT OF A PALLADIUM-CATALYZED 1,3-DIFUNCTIONALIZATION OF TERMINAL ALKENES FOR THE SYNTHESIS OF ALLYLIC ARENES OR SKIPPED DIENE-CONTAINING PRODUCTS

Introduction

The Sigman group has reported multiple methods for alkene difunctionalization, wherein cationic alkyl–Pd intermediates are intercepted through the formation of stabilizing π-allyl intermediates.[1-5] The stabilization of these intermediates slows β-hydride elimination and allows for secondary functionalization, thereby leading to the generation of significant molecular complexity from simple coupling partners. In this chapter, the development of a Pd-catalyzed 1,3-difunctionalization of terminal alkenes with 1,1-disubstituted vinyl nonaflates and boronic acid coupling partners will be discussed. The use of 1,1-disubstituted vinyl nonaflates facilitates the ability to probe the influence of electronic and steric properties on π-allyl stabilized Pd-intermediates, moreover these reagents are essential to the selectivity of the reaction. This transformation affords skipped diene or allylic arene products that are difficult to selectively access in traditional Heck reactions. Moreover, Pd-catalyzed 1,3-

difunctionalizations offer increased modularity compared to existing allylic cross-coupling technologies.

Background

The Pd-catalyzed intermolecular Heck reaction is a powerful tool for the synthesis of substituted olefins.[6-8] The transformation produces new C–C bonds from the direct functionalization of alkenyl C–H bonds. Unfortunately, the regioselectivity in the Heck reaction is dependent on the influence of substrate on alkene migratory insertion and subsequent β-hydride elimination. Substrates without biasing characteristics (*e.g.*, unactivated terminal alkenes) lead to complex isomeric mixtures as the result of indiscriminate alkene insertion into Pd-complex **1** to generate 1,2-addition intermediate **2** or 2,1-addition intermediate **5** (Figure 4.1A). Furthermore, the ensuing β-hydride elimination from alkyl–Pd intermediate **2** of H_s would afford styrenyl product **3**, whereas β-hydride elimination of H_a would generate the allylic product **4**. A 1,1-disubstituted terminal alkenyl product (**6**) would be formed following the same reactivity of

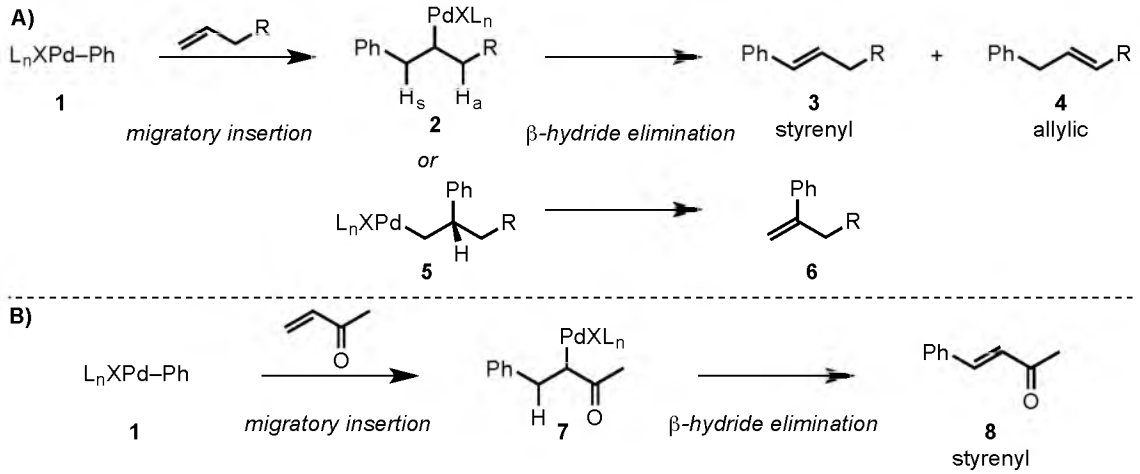


Figure 4.1 Mechanistic rationale for the formation of product isomers in the Pd-catalyzed Heck reaction. **A)** Putative reactivity of a nonbiased alkene substrate. **B)** Reactivity of an electronically biased alkene substrate.

intermediate **5**. Substrate-controlled Heck reactions employ electronically biased alkenes, such as α,β-unsaturated carbonyls[9-12] or styrenes,[10,11,13] to promote selective 1,2-migratory insertion (**7**) and β-hydride elimination to deliver a single styrenyl product (**8**, Figure 4.1B).

Recently, the Sigman group and others have reported highly selective Heck reactions of electronically nonbiased alkenes.[6,14-19] In 2010, Sigman and coworkers reported an oxidative Heck reaction of terminal alkenes (**9**) and aryl boronic esters (**10**) that produced generally high yields and selectivity for (*E*)-styrenyl products (**11**, Figure 4.2).[15] Their studies suggest the electrophilic character of the catalyst is critical to the observed selectivity for styrenyl products over the allylic isomers. The inclusion of coordinating counter ions, such as chloride, resulted in mixtures of styrenyl and allylic products. In 2011, this catalyst-controlled Heck reaction was further extended to employ aryldiazonium salts under traditional Heck conditions.[16] Mechanistic studies designed to interrogate the origin for catalyst-controlled β-hydride elimination in these reactions were carried out with the evaluation of electronically disparate aryl coupling partners. Interestingly, these studies revealed that while these reactions are procedurally similar, β-hydride elimination is controlled by different properties. In the oxidative Heck reaction, β-hydride elimination is controlled by the relative C–H bond strength. Alternatively, studies suggest the relative hydridic character of the β-hydrogens is responsible for

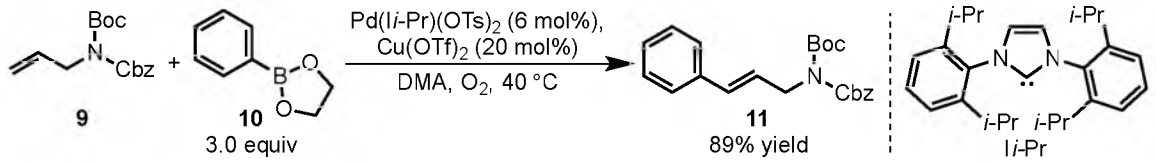


Figure 4.2 Representative example of the Pd-catalyzed oxidative Heck reaction of electronically nonbiased alkenes.

selective β-hydride elimination under traditional Heck conditions.

Methods have been developed to achieve selective styrenyl product formation from nonbiased alkenes, although few techniques have been reported that selectively deliver allylic Heck products.[14,18,19] Such a transformation would be highly valuable for accessing allylic arene scaffolds, which are common motifs in natural product molecules with important broad spectrum biological properties.[20-25] The White group has reported a chelation-controlled oxidative Heck reaction of terminal alkenes (**12**) that regio- and stereoselectivity delivers styrenyl (**14**) or allylic products (**15**, Figure 4.3).[14] They proposed the excellent reaction selectivity for styrenyl product **14a** was due to generating palladium intermediates sensitive to chelation effects with proximal oxygen or nitrogen-containing functional groups. Allylic products were generated in >20:1 selectivity over styrenyl isomers with the use of β,γ-unsaturated ketone or ester substrates. In addition to the unique allylic arene selectivity, the resulting α,β-unsaturated ketone (**15b**) or ester (**15c**) is synthetically appealing for further functionalization. The reasoning for the observed change in regioselectivity when β,γ-unsaturated carbonyl groups are employed is not well understood, but the selectivity may be a reflection of the thermodynamic

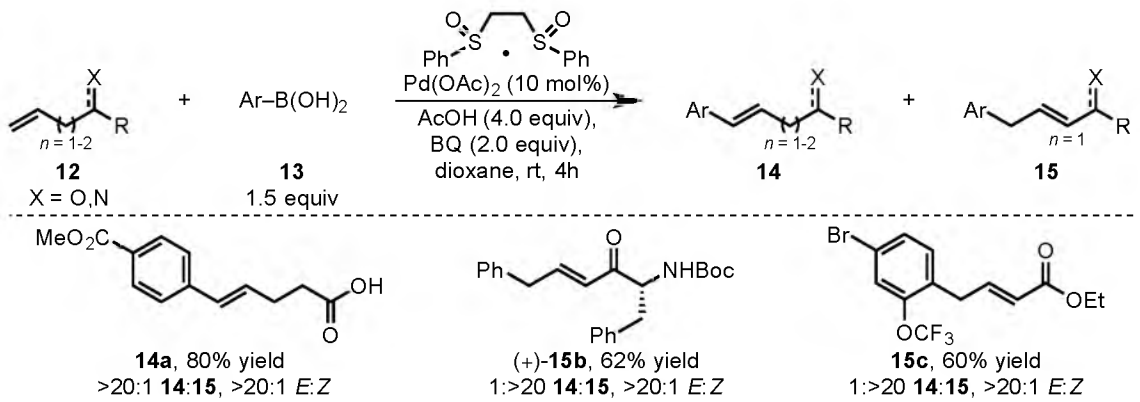


Figure 4.3 Representative examples of the Pd-catalyzed chelate-controlled oxidative Heck reaction.

stability of the allylic products in these examples. The authors rule out the possibility of Pd–H isomerization under the conditions based on the excellent >20:1 *E*:*Z* selectivity for all cases assessed and the observation of no loss of optical purity for substrates with proximal stereogenic centers (not shown).

Attempts to develop Heck reactions that selectively produce allylic arenes remain limited to methods that depend on β,γ-unsaturated carbonyl-containing[14] or cyclic substrates[18,19] to control selectivity. To date, Pd-catalyzed allylic cross-coupling reactions represent the most common approach to forming allylic arene scaffolds.[26-33] Although variations have been reported,[27,29,31] generally these cross-coupling reactions are carried out with aryl halides (**16**) and allylic organometallic reagents (**17**) to afford coupled products **18** and **19** (Figure 4.4A). The putative mechanism of the transformation begins with oxidative addition of an aryl halide by Pd^0 to produce intermediate **20** (Figure 4.4B). Transmetallation of **17** leads to the formation of the π-allyl stabilized Pd-intermediate **21**. Isomeric mixtures of linear product **18** and branched product **19** can be generated by reductive elimination at the α- or γ-carbon of **21**, respectively, by means of σ-π-σ isomerization. Besides the two isomeric coupling products, the linear product **18** can be generated with *E*- or *Z*-alkene geometry.

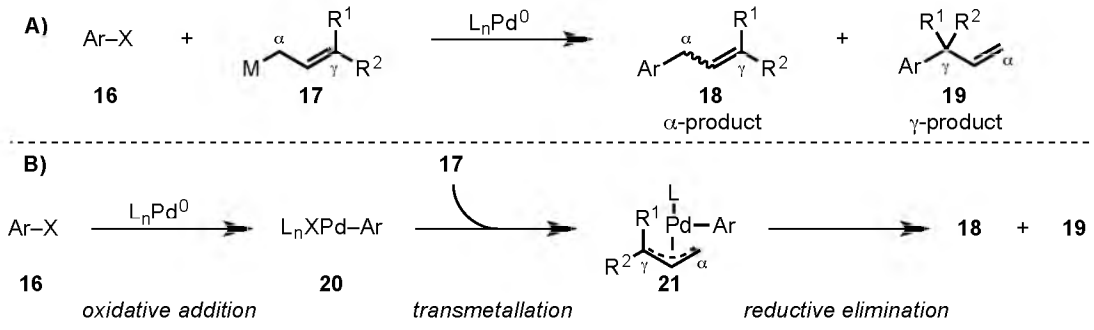


Figure 4.4 Pd-catalyzed cross-coupling of aryl electrophiles with allylic organometallic reagents. **A)** General transformation. **B)** Putative mechanism.

Buchwald and coworkers reported in 2013, a ligand-controlled regiodivergent cross-coupling of (hetero)aryl halides (**16a**) and allylboronates (**17a**, Figure 4.5).[33] In this report, the authors aimed to develop a method to rapidly access either linear (**18**) or branched (**19**) allylic arene products selectively using structurally similar catalysts. Allylic cross-coupling reactions are generally hindered by regioselectivity challenges that result from multiple pathways for reductive elimination of π-allyl Pd-intermediate **21**. To overcome these challenges, Buchwald reasoned that the influence of a ligand could help to control the formation and reactivity of the π-allyl intermediates. Studies examining the impact of bulky biaryl phosphine ligands revealed that *t*-BuXPhos greatly favored the formation of linear product **18**. The authors suggest the sterically demanding ligand inhibits σ-π-σ isomerization to the more hindered γ-position, thus limiting formation of branched product **19**. Furthermore, they observed that a less sterically encumbering biaryl phosphine ligand **L1** effectively reversed the selectivity of the transformation and generated the branched product **19** in high selectivity (Figure 4.6).

A representative summary of the scope of this regiodivergent cross-coupling is illustrated in Figures 4.5 (*t*-BuXPhos) and 4.6 (**L1**). Using similar procedures and either *t*-BuXPhos or **L1** high levels of regioselectivity and good product yields were observed for functionalized linear and branched products **18**/**19**. While the authors were nicely able to demonstrate the selective coupling of multiple heteroaromatic halides, such as a functionalized pyrimidine (**18b**, Figure 4.5) and *N*-Boc protected indole (**19b**, Figure 4.6), they were unable to develop regiodivergent conditions for these substrates. The evaluation of a geranyl derived unsymmetrical 3,3-disubstituted allylboronate resulted in mixtures of *E*/*Z* alkene stereoisomers for the linear product **18c** (Figure 4.5), albeit with

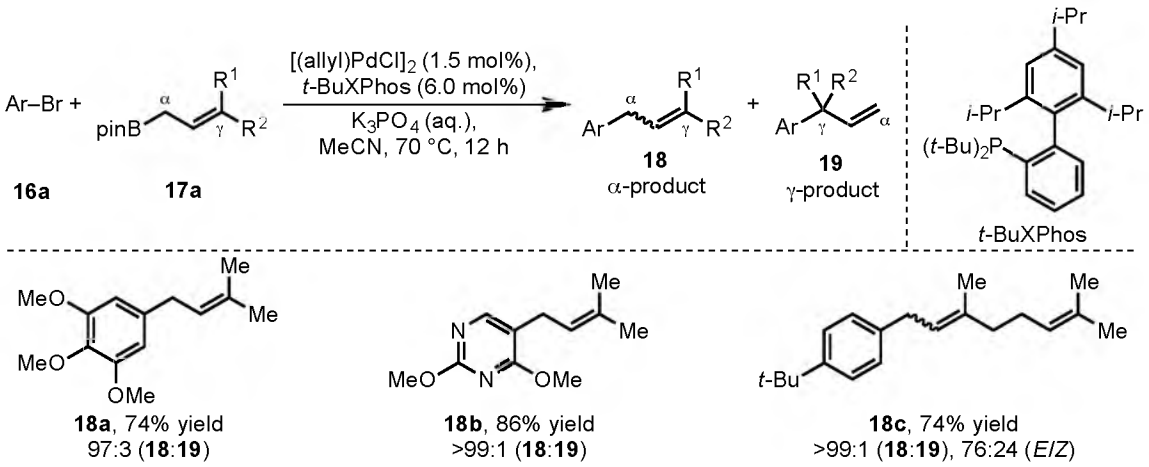


Figure 4.5 Pd-catalyzed α-product selective cross-coupling of aryl bromides and 3,3-disubstituted allylboronates.

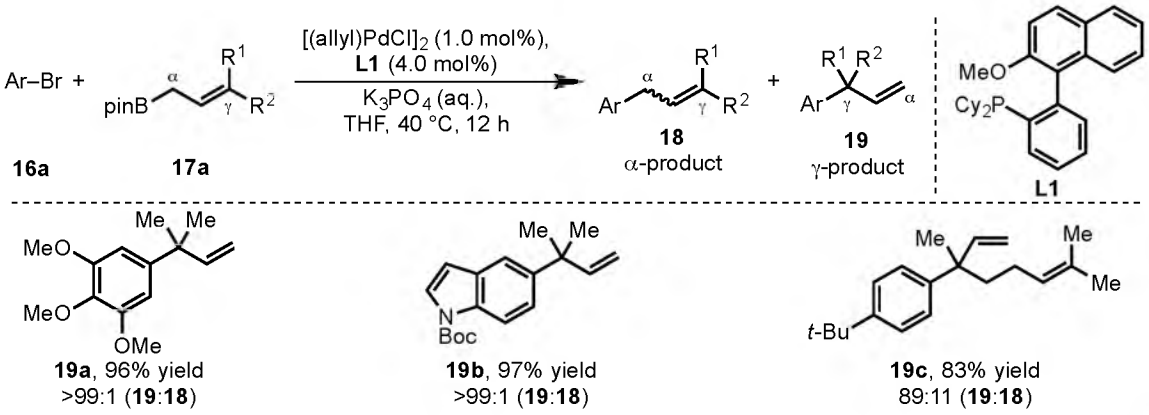


Figure 4.6 Pd-catalyzed γ-product selective cross-coupling of aryl bromides and 3,3-disubstituted allylboronates.

excellent selectivity over the branched product. Under the complementary conditions, the use of **L1** afforded **19c** in good regioselectivity (Figure 4.6). The limitation of Pd-catalyzed allylic cross-coupling reactions remains the formation of complex isomeric mixtures when unsymmetrical allylboronates are used. In addition, the stereo- and regioselective synthesis of functionalized allyl coupling partners can be laborious.[34-37]

A Pd-catalyzed alkene difunctionalization reaction would offer a complementary

approach to allylic cross-coupling reactions for the construction of allylic arene architectures. Such a transformation would avoid the need for sometimes-difficult-to-access allyl coupling partners and if rendered selective would afford a highly modular approach to these scaffolds. The Sigman research group has been interested in alkene difunctionalization reactions as a means to rapidly access value added products from simple starting materials. In 2012, the difunctionalization of commodity chemical ethylene using cyclic vinyl triflates (**22**) and arylboronic acids was reported (Figure 4.7).[2] This transformation generated 1,1-addition products (**23a-d**) with allylic (hetero)arene functionality in good yields and selectivity over 1,3-addition regioisomers (**24**). The authors proposed the presence of an exocyclic alkene thermodynamically disfavors the formation of 1,3-addition product **24**, although the low regioselectivity observed for **23b** is not well understood.

The regioselectivity of the ethylene 1,1-difunctionalization is proposed to result from reductive elimination at either terminus of the π-allyl stabilized Pd-intermediate **25**. This intermediate is formed following ethylene insertion into the Pd–vinyl bond and rearrangement via a β-hydride elimination/hydride reinsertion process. While this

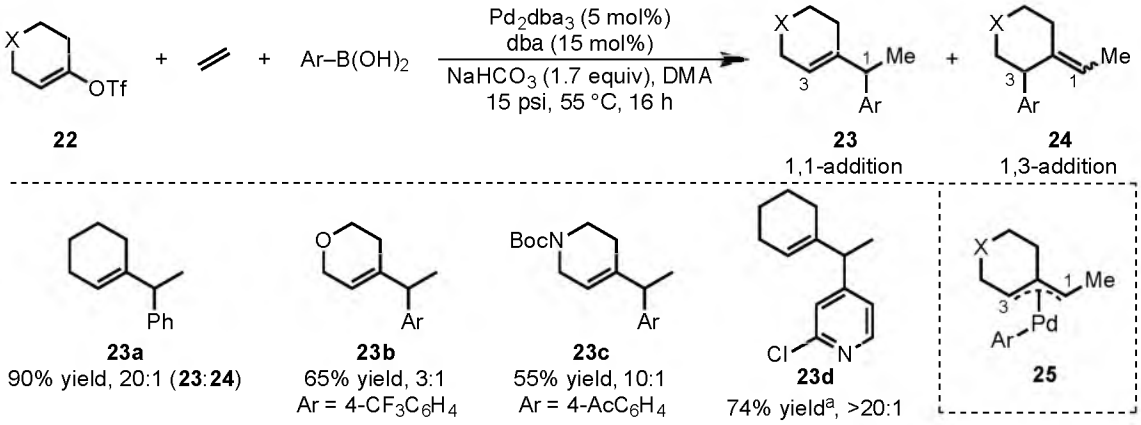


Figure 4.7 Pd-catalyzed 1,1-difunctionalization of ethylene with vinyl triflates and arylboronic acids. [a]boronic pinacol ester reagent used in place of boronic acid at 75 °C for 36 h.

difunctionalization reaction is mechanistically more complex, the π-allyl intermediate **25** is analogous to that formed in allylic cross-couplings (**21**). Furthermore, the stereo- and regioisomers that result from these common intermediates are structurally very similar: branched cross-coupling product **19** is akin to 1,1-addition product **23**, while linear product **18** is related to 1,3-addition product **24**. As the result of common mechanistic intermediates, alkene difunctionalization and allylic cross-coupling reactions are hindered by the same regioselectivity challenges.

While Pd-catalyzed 1,1-difunctionalization of terminal alkenes was demonstrated as a successful approach to branch allylic arene motifs,[1,2] difunctionalization methods to access linear allylic arene scaffolds remain underexplored. Therefore, we envisioned the development of a novel 1,3-difunctionalization of terminal alkenes using 1,1-disubstituted vinyl nonaflates. This approach would offer increased modularity to allylic arenes and represent a unique disconnection strategy for the formation of these molecular architectures.

Hypothesis and Reaction Optimization

A previous report from the Sigman laboratory, detailing the Pd-catalyzed hydroarylation of 1,3-dienes, demonstrated a correlation between the regioselectivity of reductive elimination from π-allyl intermediates and the steric influence of adjacent groups (discussed in Chapter 2).[38] This trend suggested that reductive elimination is favored at the least sterically hindered carbon of the π-allyl intermediate. We hypothesized that a similar trend may exist for π-allyl stabilized Pd-intermediates in the above described 1,1-difunctionalization of ethylene.[2] Accordingly, we proposed the

formation of linear allylic products (**29**) from the 1,3-difunctionalization of terminal alkenes (**26**) with 1,1-disubstituted vinyl nonaflates (**27**) and boronic acids (**28**, Figure 4.8A). By employing 1,1-disubstituted vinyl nonaflates any steric impact on π-allyl intermediate (**31**) at C-3 would be minimized, such that reductive elimination at the least hindered site (**33**) would favor the formation of **29** (Figure 4.8B). The generation of 1,3-difunctionalization products by this method would be particularly attractive for the unique C–C bonds being formed. The desired 1,3-addition product **29** is composed of a new $C(sp^2)$–$C(sp^2)$ double bond as well as a $C(sp^3)$–$C(sp^2)$ bond.

The putative mechanism of this transformation begins with the oxidative addition of 1,1-disubstituted vinyl nonaflate **27** (Figure 4.8C). Due to the noncoordinating properties of the nonaflate anion, oxidative addition is proposed to result in the formation of a cationic Pd-intermediate **34**. The electrophilic character of palladium is important to promote alkene coordination rather than transmetallation, and therefore suppresses the production of unwanted Suzuki cross-coupling products.[1-5,39,40] Alkene migratory insertion of **26** would afford the unstabilized alkyl–Pd intermediate **35**. Rearrangement of palladium via a β-hydride elimination/reinsertion sequence (**35** → **36** → **37**) generates the cationic σ-allyl complex **37**. Experimental evidence for an analogous β-hydride elimination/reinsertion pathway was previously shown in the Pd-catalyzed 1,1-diarylation of terminal alkenes with a deuterium labeling study.[41] The examination of deuterium labeled alkene substrate non-1-ene-1,1-d_2 clearly demonstrated the migration of one deuterium atom from C-1 to C-2 in the resultant product (not shown). From intermediate **37** isomerization to the π-allyl stabilized intermediate **38** suppresses β-hydride elimination and the formation of Heck byproducts (see Chapter 1). Following

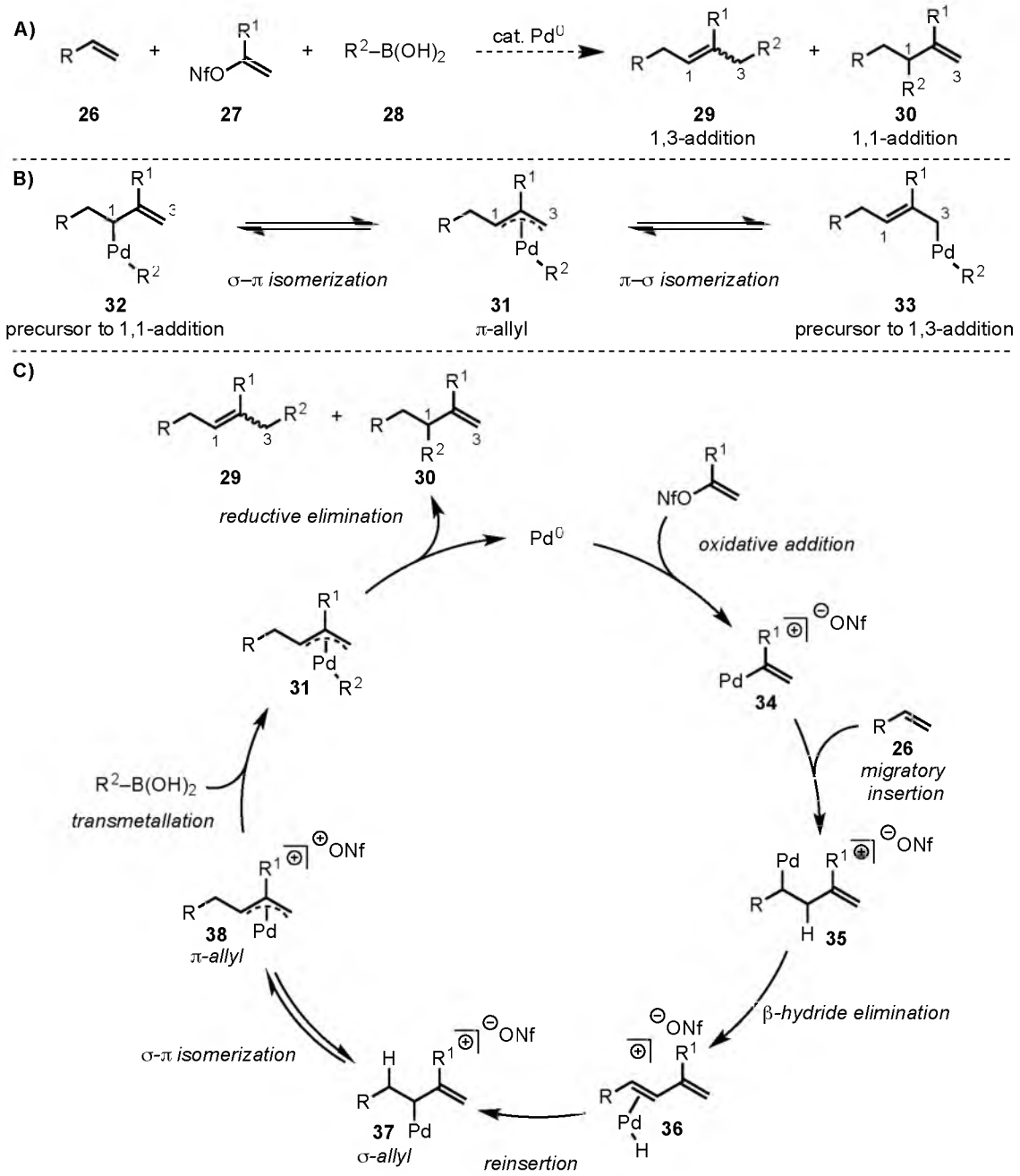


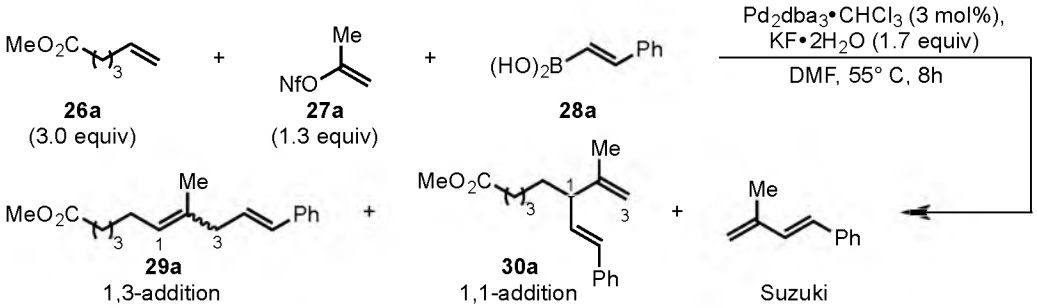
Figure 4.8 Proposed Pd-catalyzed 1,3-difunctionalization of terminal alkenes with 1,1-disubstituted vinyl nonaflates and boronic acids. **A)** Representative transformation. **B)** Rationale accounting for the formation of regioisomers. **C)** Proposed mechanism.

transmetallation with a boronic acid coupling partner, reductive elimination yields 1,3-addition product **29** or 1,1-addition product **30**.

The presence of a terminal alkene in vinyl nonaflate **27** could present challenges as it could participate in Heck-type side reactions. We proposed the electron-deficient character of **27** as compared to **26** would disfavor alkene coordination to palladium, thus limiting the potential for alkene insertion side reactions to occur. Furthermore, Weinreb and coworkers have demonstrated that similar 1,1-disubstituted vinyl halides are compatible oxidants for Pd-catalyzed intramolecular cyclization reactions.[42-45]

In an effort to develop a highly versatile 1,3-difunctionalization, we chose alkene **16a**, vinyl nonaflate **17a**, and styrenyl boronic acid **28a** as reaction coupling partners (Table 4.1). The previous use of vinylboronic acids has been shown to afford less selective difunctionalization reactions, relative to when arylboronic acids are utilized.[3,5] In addition, if rendered selective a 1,3-difunctionalization using vinylboronic acids would be an appealing method for the synthesis of skipped dienes (see Chapters 2 and 3). Initial studies were conducted with vinyl nonaflates because they are more economical starting materials and are easier to prepare/handle than their lighter triflate counterparts.[46] Product yields shown in Table 4.1 represent a mixture of **29a** and **30a**, and along with ratios of product isomers, were determined by GC analysis. Initial investigations revealed the stoichiometry of terminal alkene **26a**, vinyl nonaflate **27a**, and styrenyl boronic acid **28a** was critical to minimizing the formation of the Suzuki cross-coupling product. Using 3.0 equivalents of **26a** helped create a concentration bias, such that alkene migratory insertion of intermediate **34** out completed transmetallation with boronic acid, thus limiting formation of Suzuki product. The optimized stoichiometry of

Table 4.1 Reaction optimization for the Pd-catalyzed 1,3-difunctionalization of terminal alkenes with vinyl nonaflates and boronic acids. [a]Measured by GC using an internal standard. Yields represent mixtures of **29a** and **30a**. Ratio of product isomers determined by GC.



entry	change	yield (%)[a]	**29a**:**30a**[a]	*E*:*Z*[a]	Suzuki (%)[a]
1	none	90	4.9	92:8	8.3
2	Na_2CO_3 (base)	85	4.9	91:9	8.2
3	$NaHCO_3$ (base)	79	4.3	90:10	8.5
4	DMA (solvent)	88	4.3	92:8	11
5	*t*-BuOH (solvent)	48	2.1	84:16	6.6
6	35 °C	82	4.7	93:7	16
7	75 °C	90	4.2	92:8	8.4
8	pinB Ph	37	4.1	88:12	15

26a and **27a** was determined using a design of experiments approach to explore a greater reaction space than sequential studies exploring a single variable (see Experimental).[47,48] Yields from the resultant experiments were then modeled using linear regression analysis. The mathematical model generated from this was then used to predict optimal conditions, which were evaluated and found to afford the optimized stoichiometry of alkene **26a** (3.0 equivalents) and vinyl nonaflate **27a** (1.3 equivalents).

With this stoichiometry further reaction optimization was carried out. We were pleased to observe excellent product yields (90%) and good selectivity (4.9:1) for the desired 1,3-addition product (*E*)-**29a** (entry 1). Altering the base of the transformation established that potassium fluoride or sodium carbonate (entry 2) were each well

tolerated, while use of sodium bicarbonate (entry 3) resulted in decreased yield and selectivity. As observed previously, DMF and DMA (entry 4) can be used interchangeably with little impact to reaction outcome.[1,3,5] The use of *tert*-butanol as the reaction medium (entry 5) had a detrimental effect on the yield and selectivity, possibly alluding to the importance of solvent to stabilize cationic Pd-intermediates as a ligand.[40,49] Adjustments to temperature revealed decreased product yields at 35 °C (entry 6) with increased formation of Suzuki byproduct, while increasing temperature to 75 °C (entry 7) had negligible impact on reaction outcome. Finally, the use of boronic pinacol ester in place of boronic acid **28a** (entry 8) led to diminished yield of **29a**. The evaluation of multiple ligand classes for controlling selectivity between π-allyl derived products **29a** and **30a** failed to out perform the optimized "ligandless" reaction conditions (see Experimental).

Evaluation of Scope

Having optimized the reaction, we next sought to evaluate the scope of the transformation beginning with the assessment of various boronic acid coupling partners (Figure 4.9). Reported yields correspond to an inseparable mixture of 1,3- and 1,1-addition products **29** and **30**. Enriched samples of stereo- and regioisomers were obtained by performing column chromatography using silica gel impregnated with silver nitrate.[50,51] Isomeric product ratios were determined by GC analysis of crude reaction mixtures. The evaluation of styrenyl boronic acids revealed the formation of skipped diene-containing terpenoids (*E*)-**29a** and (*E*)-**29b** in good to excellent regioselectivity. The modest yield of **29b** may be the result of the 1,1-disubstituted olefin of the product

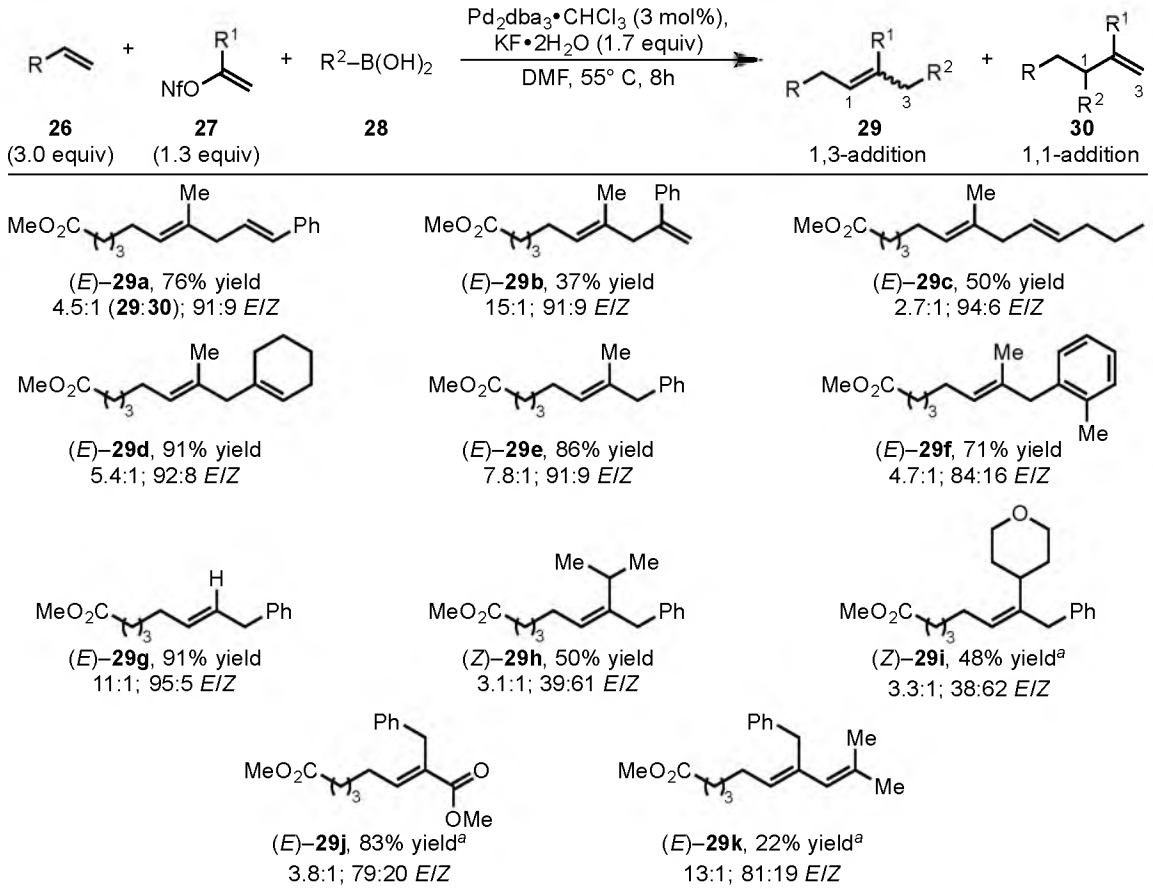


Figure 4.9 Scope of the Pd-catalyzed 1,3-difunctionalization of terminal alkenes with vinyl nonaflates and boronic acids. Structures of isomers were confirmed after separation by column chromatography using silica gel impregnated with silver nitrate and NMR analysis. Ratios of regio- and stereoisomers were determined by GC analysis. Yields represent a mixture of regio- and stereoisomers. [a]Triflate analog of **27** was used in place of nonaflate.

being further consumed in the reaction by migratory insertion processes. Vinylboronic acids with a simple alkyl chain (*E*)-**29c** or cyclohexenyl ring (*E*)-**29d** were tolerated with moderate to good yields. Furthermore, phenylboronic acid (**29e**) and sterically encumbering *ortho*-tolylboronic acid (**29f**) afforded allylic arene scaffolds with good yields and selectivity for the linear 1,3-addition products in complementary fashion to allylic cross-coupling methods. It should be noted that no erosion in alkene geometry was observed when boronic acids (*E*)-**28a** or (*E*)-**28c** were used for the production of **29a**

and **29c**, respectively.

The reasoning for the observed variation in selectivity between 1,3- and 1,1-addition products is not well understood. We have previously proposed that the isomeric distribution of π-allyl derived products is largely controlled by the influence of the steric properties of the boronic acid coupling partner on the π-allyl Pd-intermediate (**31**).[3,5,38] While this rationale is reflected by the respective regioselectivity for products **29b** and **29c**, other bulky coupling partners, such as cyclohexenyl (**29d**) and *ortho*-tolyl (**29f**) boronic acid, afford regioselectivities that are similar to those for coupling partners with less proximal steric bulk (**29a**). Moreover, attempts to develop a mathematical model to correlate the impact of sterics to the regioselectivity of the reaction were unsuccessful.

The evaluation of R^1-substituents for 1,1-disubstituted vinyl nonaflates presented synthetic challenges, as many derivatives were unstable and few examples of these molecules had been reported in the literature.[52-54] Nonetheless, we were interesting in how the electronic and steric properties of these groups would affect the reaction outcome. Transitioning from methyl-substituted vinyl nonaflate **27a** to an unsubstituted derivative provided (*E*)-**29g** in excellent yield and selectivity. Other vinyl nonaflates with *iso*-propyl (**29h**) or tetrahydropyran (**29i**) substitution were tolerated under the reaction conditions and generated moderate product yields. The α,β-unsaturated ester (*E*)-**29j** was accessed in good yield and demonstrates the ability for this methodology to access unique products with synthetic handles for further elaboration. The 1,3-diene vinyl triflate **27f** was relatively unstable and likely decomposed under the reaction conditions. Thus we observed a low yield of product **29k**.

The examination of various vinyl nonaflate R^1-groups uncovered a clear

relationship between the relative size of the vinyl nonaflate substituent and the regioselectivity between π-allyl derived products **29** and **30**. Specifically, improved selectivity was observed for 1,3-addition product **29** with smaller R^1-substituents as compared to derivatives with larger substituents (*i.e.*, 11:1 for R^1 = H (**29g**), versus 3.1:1 for R^1 = *i*-Pr (**29h**)). By calculating the logarithm of regioselectivity, a correlation was observed with Sterimol B_5 values, which are descriptors for the maximum radius of the corresponding substituent (Figure 4.10).[55-57] This trend suggests that the steric properties of vinyl nonaflate R^1-groups directly influence the σ-π-σ isomerization of Pd-intermediates, such that as the R^1-groups become smaller, reductive elimination at the terminal C-3 position of π-allyl (**31**) is increasingly more favorable. While 1,3-diene-containing product **29k** did not coincide with this correlation, it is possible the geminal dimethyl substituted alkene coordinates to palladium, thus disrupting π-allyl isomerization.

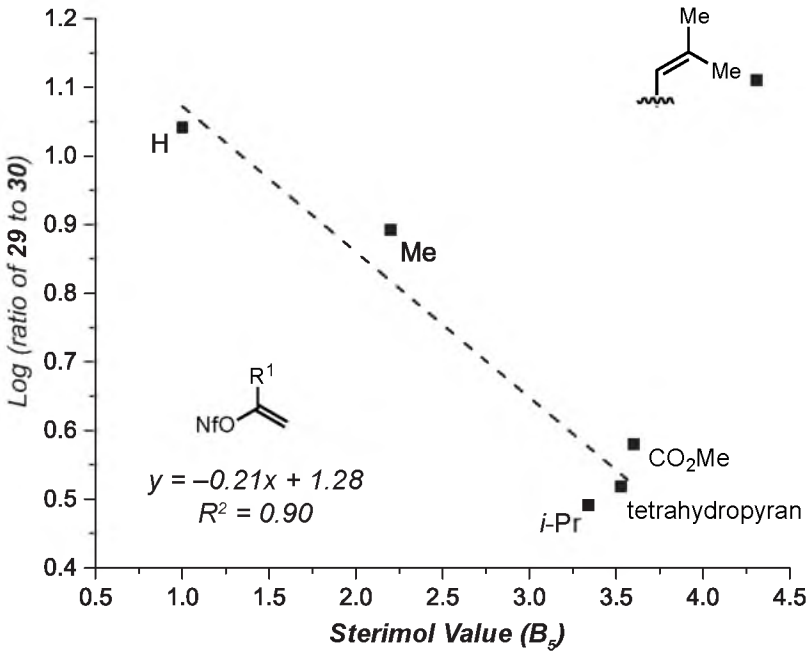


Figure 4.10 Correlation between 1,3- and 1,1-addition regioisomers and Sterimol B_5 values.

Additional noteworthy results relating to the stereoselectivity of the 1,3-difunctionalization can be discerned from the evaluation of vinyl nonaflate R^1-groups. The stereochemical outcome of the reaction is synthetically important, but without careful consideration of the relevant mechanistic intermediates, subtle details can be easily overlooked or over interpreted. While the selectivity for alkene geometry shifts from favoring *trans* in **29e** and **29g** to the *cis* configuration in **29h-i**, this observation solely reflects the change in assigning priority to the alkene substituents. Meanwhile, the formation of (*E*)-**29j-k** does reflect a significant change to the reaction mechanism. These stereoisomers are derived from the σ-π-σ isomerization of π-allyl Pd-intermediates and their formation is largely dependent on the minimization of allylic strain with adjacent groups (Figure 4.11A). By considering the *anti*/*syn* relationship of H^a and R^1 in the critical π-allyl intermediates **38** and **41**, the stereoselectivity of the reaction can be normalized for any R^1-substitutent. In π-allyl intermediate **38**, H^a and R^1 are *anti* to one another, while a *syn* relationship between these groups exists in intermediate **41**. By isomerizing to the σ-allyl **37**, bond rotation effectively results in *anti*/*syn* isomerization of these species.

Analyzing the selectivity between *anti*-**29** and *syn*-**29** for products **29e**,**g-k** reveals a discrete trend with the relative size of the vinyl nonaflate R^1-substitutent. When R^1 = H, the σ-π-σ isomerization sequence favors formation of *anti*-**29** via **37** → **38** → **39**. Alternatively, as R^1 becomes more sterically encumbering an increased formation of *syn*-**29** is observed, presumably due to bond rotation of **37** → **40** stimulated by $A^{1,2}$ strain between R^1 and the adjacent R–methylene group. Consistent with this hypothesis, we observed a correlation between the logarithm of the selectivity between *anti*-**29** and *syn*-

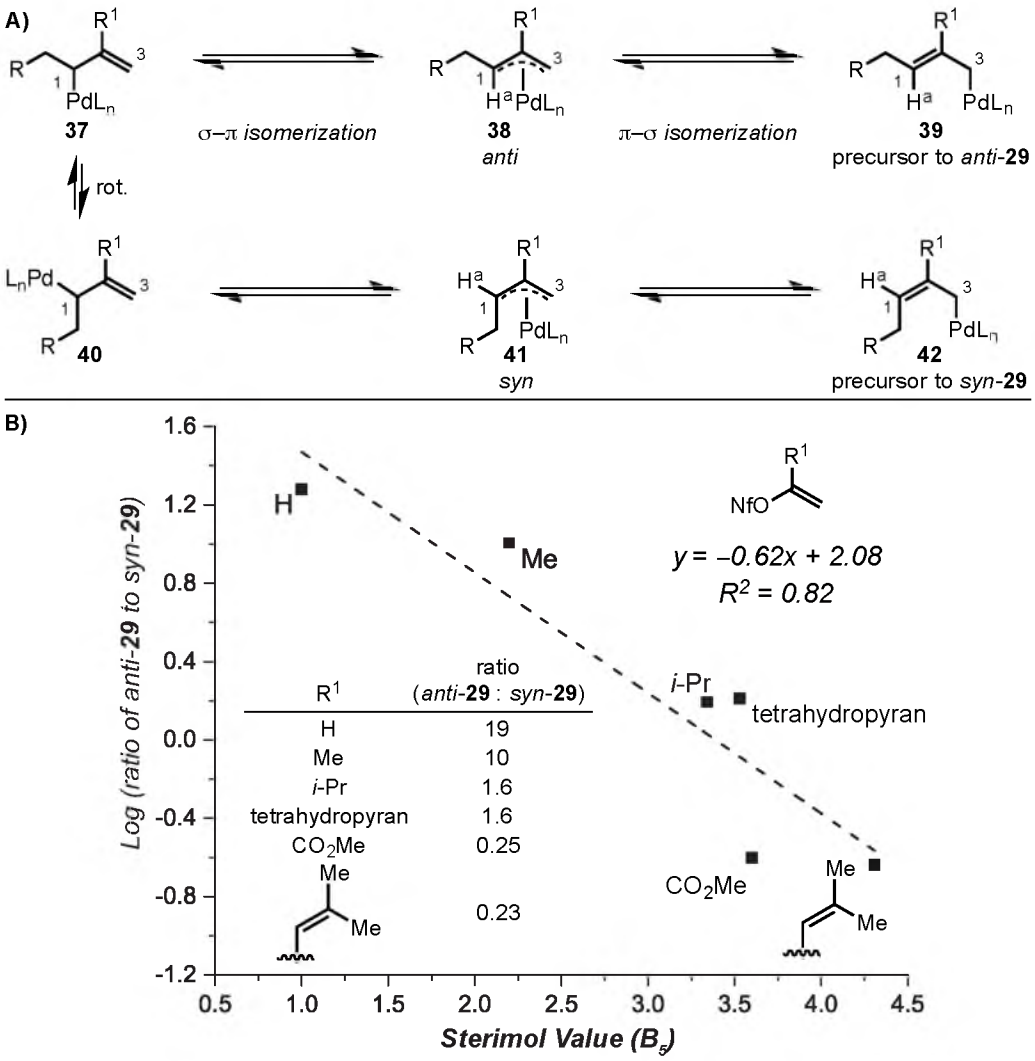


Figure 4.11 Rationalization and correlation for the formation of *anti*/*syn* isomers from π-allyl stabilized Pd-intermediates. **A)** Mechanistic rationale. **B)** Correlation between *anti*/*syn* isomers and Sterimol B_5 values.

29 and Sterimol B_5 values (Figure 4.11B). This trend indicates that the steric environment of vinyl nonaflate R^1-substitutents, in addition to being responsible for regioselectivity, is also accountable for the stereoselectivity of the transformation. Unfortunately, the identification of these correlations is suggestive that a relatively limited group of vinyl nonaflate substituents can be employed for a highly regio- and stereoselective 1,3-difunctionalization.

In collaboration with a postdoctoral fellow in our laboratory, Takashi Shigeta, the functional group tolerance of the 1,3-difunctionalization is under exploration. Initial efforts have focused on examining various arylboronic acids in the formation of allylic arene scaffolds. Generally good yields are observed for electron-rich or electron-deficient arylboronic acid coupling partners, which contain methyl sulfonyl ((*E*)-**29n**) and nitro ((*E*)-**29o**) functional groups (Figure 4.12). Products **29n** and **29o** are also formed in excellent selectivity over 1,1-addition product **30**, while good selectivity was observed for more electron-rich aryl units (7.0:1 for **29m**, compared to 19:1 for **29o**). This may indicate a subtle sensitivity of the regioselectivity of reductive elimination from intermediate **31** to the electronic nature of the coupling partner. Consistent with previous studies from our group,[1,3-5] the evaluation of Lewis basic heteroaromatic coupling partners results in low product yields (<15%), likely due to poisoning the critical electrophilic character of the catalyst.

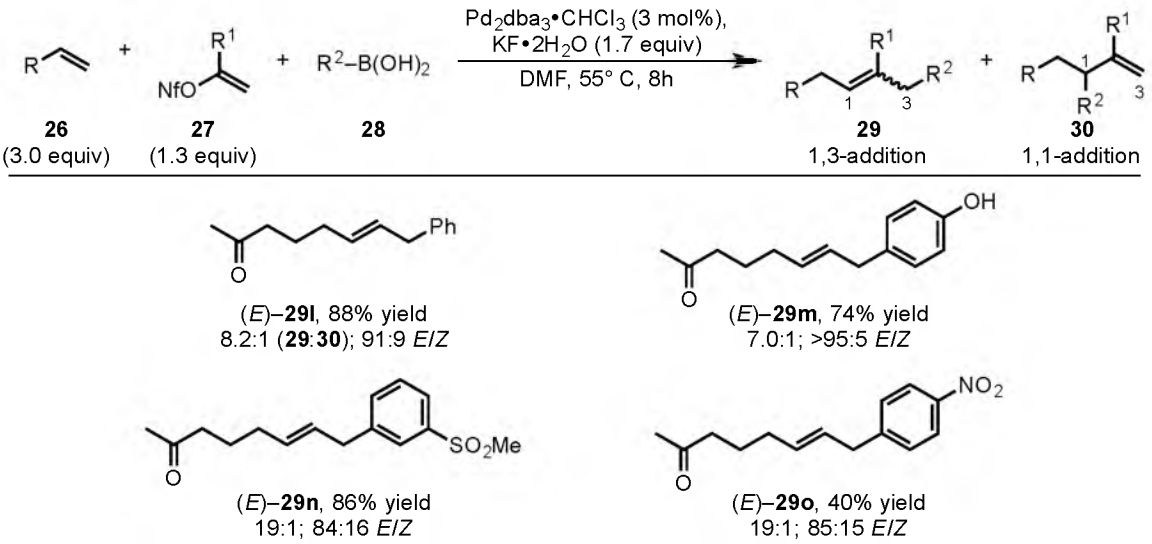


Figure 4.12 Extended scope of the Pd-catalyzed 1,3-difunctionalization of terminal alkenes with vinyl nonaflates and arylboronic acids. Structures of isomers were confirmed after separation by column chromatography using silica gel impregnated with silver nitrate and NMR analysis. Ratios of regio- and stereoisomers were determined by GC analysis. Yields represent a mixture of regio- and stereoisomers.

Future Directions

In collaboration with Takashi Shigeta, the evaluation of terminal alkene substrates and functionalized arylboronic acids for production of allylic arene motifs in the Pd-catalyzed 1,3-difunctionalization is a focus of ongoing studies. We are particularly interested in examining terminal alkenes with diverse distal functional groups, including a primary alcohol (**26c**,**f**), nitrile (**26d**), and methyl acetal (**26e**, Figure 4.13A). Furthermore, perillyl alcohol (**26f**) is a compelling substrate, as it contains two potentially reactive alkenes for migratory insertion as well as a stereocenter adjacent to a 1,1-disubstituted alkene. Experiments to evaluate arylboronic acids that contain halogens (**28j-l**), multiple heteroatoms (**28k-l**), and an *N*-Boc protected amine (**28m**) substituents are also in progress (Figure 4.13B).

Recently, the Sigman group has reported a series of Pd-catalyzed enantioselective redox-relay Heck reactions of 1,2-disubstituted alkenol substrates (**44**, Figure 4.14A).[58-62] Under conditions similar to those used for many of the previously described difunctionalization reactions,[1-3,5] alkene migratory insertion occurs with high facial selectivity with the use of pyridine oxazoline (pyrox) ligand **L2**. Furthermore, repeated β-hydride elimination/hydride reinsertion events (termed "chain-walking") relays

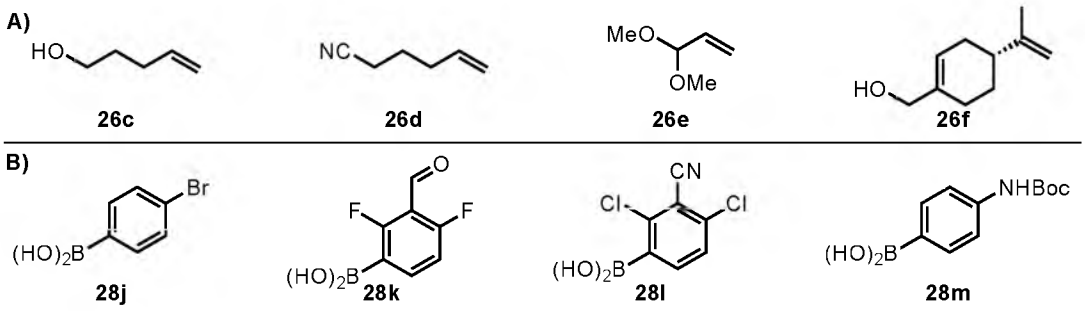


Figure 4.13 Reaction substrates for ongoing scope exploration studies in the Pd-catalyzed 1,3-difunctionalization. **A)** Terminal alkene substrates. **B)** Arylboronic acid substrates.

palladium across the alkyl chain to deliver aldehyde product **45**. A 1,n-difunctionalization reaction of 1,2-disubstituted alkenes, such as **46**, would afford highly functionalized molecules and if rendered enantio- and diastereoselective, would be a powerful transformation for the rapid generation of significant molecular complexity. In preliminary studies, we observed the formation of 1,5-difunctionalization product **47** from 1,2-disubstituted alkene **46** in low yield, although encouragingly, good enantioselectivity was observed in the presence of **L3** (Figure 4.14B). Following initial alkene migratory insertion to afford alkyl–Pd intermediate **48**, a repeated β-hydride elimination/hydride reinsertion sequence leads to the formation of π-benzyl stabilized intermediate **49** (Figure 4.14C). This stabilized species can then undergo secondary functionalization to yield the 1,5-difunctionalization product **47**. The development of this

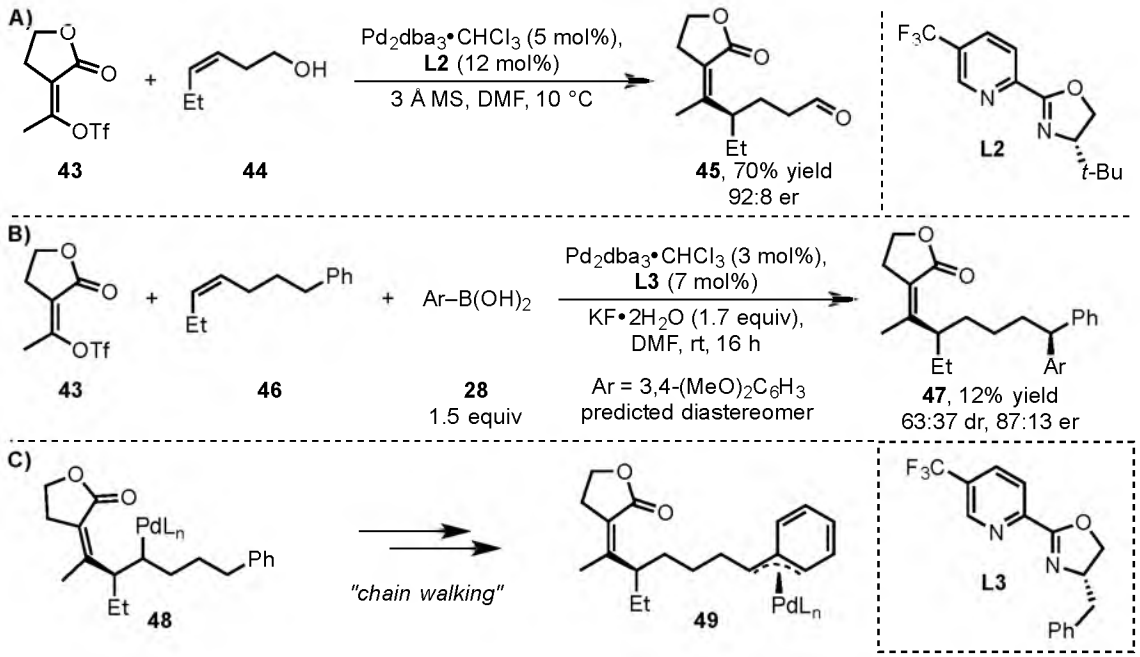


Figure 4.14 Preliminary result for a Pd-catalyzed enantio- and diastereoselective 1,5-difunctionalization of a 1,2-disubstituted alkene. **A)** Pd-catalyzed enantioselective Heck reaction of alkenols using a redox-relay strategy. **B)** Pd-catalyzed 1,5-difunctionalization of 1,2-disubstituted alkene with vinyl triflates and arylboronic acids. **C)** Putative mechanistic intermediates.

transformation will likely require controlling competitive side reactions, including Heck and Suzuki cross-couplings, as well as site- and enantioselective alkene migratory insertion. Current efforts to address these challenges are being undertaken by postdoctoral fellow Nicholas Race in the Sigman laboratory.

Conclusion

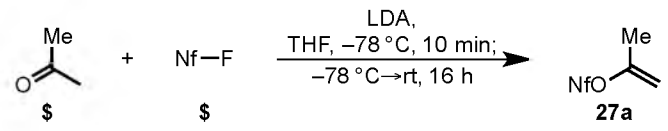
In summary, we have developed a novel Pd-catalyzed difunctionalization strategy for the interception of cationic alkyl–Pd intermediates with π-allyl stabilization. This transformation affords skipped diene or allylic arene products through the 1,3-difunctionalization of terminal alkenes with 1,1-disubstituted vinyl nonaflates and boronic acid coupling partners. The evaluation of various 1,1-disubstituted vinyl nonaflates revealed a significant influence of the steric properties of R^1-substituents on the regio- and stereoselectivity of the reaction. Moreover, correlations between the reaction outcome and Sterimol B_5 values suggest the greatest regio- and stereoselectivity is obtained with less sterically encumbering vinyl nonaflate substituents. This 1,3-difunctionalization is particularly well suited for the modular production of allylic arenes, which are inaccessible using classical Heck methods. Current studies, in collaboration with postdoctoral fellow Takashi Shigeta, are focused on completing investigations into the synthetic utility of the 1,3-difunctionalization.

Experimental

General considerations

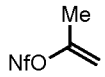
Anhydrous dimethylformamide (DMF) was purchased from Sigma-Aldrich and stored over activated 3 Å molecular sieves (3 Å MS). $Pd_2(dba)_3 \bullet CHCl_3$ was synthesized according to known procedure.[63] Unless otherwise noted all reagents and solvents were purchased from Sigma-Aldrich, Frontier Scientific, Combi-Blocks, Oakwood Chemical, or TCI and used without further purification. ^1H NMR spectra were obtained at 500 MHz or 400 MHz. Chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm. The abbreviations s, d, t, q, quint, sext, dd, ddd, app. dt, dt, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, quintet, sextet, doublet of doublets, doublet of doublets of doublets, apparent doublet of triplet, doublet of triplet, and multiplet, respectively. ^{13}C NMR spectra were obtained at 126 or 100 MHz and referenced to the centerline of the $CDCl_3$ triplet at 77.23 ppm. Flash chromatography was performed using Silicycle SiliaFlash F60 silica gel (230-400 mesh). Silver nitrate impregnated silica gel (10% w/w) for flash chromatography was prepared by dissolving $AgNO_3$ in MeCN, and then mixing with silca gel.[50,51] This was concentrated *in vacuo*, and then further dried in a 150 °C oven for 3 h. Silver impregnated silica gel was stored in the absence of light until use. Gas Chromatography (GC) separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 50:1 split. IR spectra were recorded using a Thermo Nicolet FTIR. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF.

General procedure for the synthesis of vinyl nonaflates



To an oven dried 250 mL round bottom flask under an N_2 atmosphere was added 3.08 mL (22 mmol, 1.1 equiv) freshly distilled diisopropylamine and THF (80 mL). The solution was cooled to –78 °C, and then 8.0 mL (2.5 M in hexanes, 20 mmol, 1.0 equiv) *n*-BuLi was added dropwise. The reaction mixture was stirred for 10 min, and then 1.47 mL (20 mmol, 1.0 equiv) acetone (freshly distilled from $CaSO_4$) was added dropwise. The mixture was stirred for 10 min at –78 °C, then warmed to room temperature. After 30 min the reaction flask was cooled back to –78 °C, and then 4.31 mL (24 mmol, 1.2 equiv) perfluoro-1-butanesulfonyl fluoride was added. The reaction was stirred for 16 h while slowly warming to room temperature. After completion, the reaction was quenched with a saturated solution of $NaHCO_3$ (100 mL) and transferred to a separatory funnel with Et_2O (50 mL). The organic layer was washed with a 1M solution of NaOH (4 x 50 mL), water (2 x 50 mL), and brine (1 x 50 mL), then dried over sodium sulfate. The dried organic mixture was concentrated *in vacuo* and purified by silica gel flash chromatography.

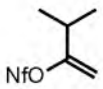
prop-1-en-2-yl nonafluorobutane-1-sulfonate (**27a**):



The general procedure was followed using 3.08 mL (22 mmol) diisopropylamine in THF (80 mL), 8.0 mL (2.5 M in hexanes, 20 mmol) *n*-BuLi, 1.47 mL (20 mmol) acetone (freshly distilled from $CaSO_4$), and 4.31 mL (24 mmol) perfluoro-1-butanesulfonyl fluoride. Purification by silica gel flash chromatography (99:1

pentane:Et_2O, silica gel was neutralized using a 1% solution of NH_4OH) led to the isolation of **27a** as a colorless oil (2.45 g, 36%), R_f = 0.23 (99:1 pentane: Et_2O, visualized by $KMnO_4$ stain). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.09 (d, *J* = 3.2 Hz, 1H), 4.95 (s, 1H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.5, 119.0-106.0 (m, 4C), 105.7, 20.4; FTIR (thin film): 2923, 1653, 1457, 1092, 1016, 795 cm^{-1}; LRGC-MS *m/z* calculated for $C_7H_5F_9O_3S$: 339.98, found 340.00.

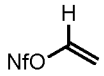
3-methylbut-1-en-2-yl nonafluorobutane-1-sulfonate (**27c**):



The general procedure was followed using 1.54 mL (11 mmol) diisopropylamine in THF (40 mL), 4.0 mL (2.5 M in hexanes, 10 mmol) *n*-BuLi, 1.05 mL (10 mmol) methyl isopropyl ketone (freshly distilled from $CaSO_4$), and 2.16 mL (12 mmol) perfluoro-1-butanesulfonyl fluoride. Purification by silica gel flash chromatography (19:1 hexanes:ethyl acetate, silica gel was neutralized using a 1% solution of NH_4OH) led to the isolation of **27c** as a colorless oil (1.20 g, 50%), R_f = 0.50 (19:1 hexanes:ethyl acetate, visualized by $KMnO_4$ stain). ^1H NMR ($CDCl_3$, 500 MHz): δ 5.09 (d, *J* = 4.0 Hz, 1H), 4.94 (dd, *J* = 3.9, 0.8 Hz, 1H), 2.56 (sept, *J* = 7.0 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.5, 120.0-106.0 (m, 4C), 101.9, 33.3, 20.0; FTIR (thin film): 1418, 1200, 1142, 933, 798, 739 cm^{-1}; LRGC-MS *m/z* calculated for $C_9H_9F_9O_3S$: 368.01, found 368.00.

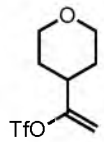
Preparation of vinyl nonaflates/triflates

vinyl nonafluorobutane-1-sulfonate (**27b**):



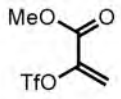
A previously reported procedure was used for the synthesis of **27b** from tetrahydrofuran.[54] Purification by short path distillation led to the isolation of **27b** as a colorless oil (7.24 g, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.77 (dd, J = 13.5, 5.6 Hz, 1H), 5.26 (dd, J = 13.2, 3.6 Hz, 1H), 5.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 142.8, 121.0-104.2 (m, 4C), 104.2; FTIR (thin film): 1646, 1197, 1142, 1085, 960, 895, 755 cm^{-1}; LRGC-MS *m/z* calculated for $C_6H_3F_9O_3S$: 325.97, found 326.00.

1-(tetrahydropyran-4-yl)vinyl trifluoromethanesulfonate (**27d**):



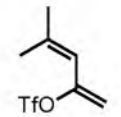
A previously reported procedure was used for the synthesis of **27d** from 4-acetyltetrahydropyran.[53] Purification by silica gel flash chromatography (9:1 hexanes:ethyl acetate, silica gel was neutralized using a 1% solution of NH_4OH) led to the isolation of **27d** as a colorless oil (690 mg, 66%), R_f = 0.21 (9:1 hexanes:ethyl acetate, visualized by $KMnO_4$ stain). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.15 (d, J = 4.0 Hz, 1H), 4.95 (d, J = 4.0 Hz, 1H), 4.03 (dd, J = 11.8, 3.6 Hz, 2H), 3.42 (dt, J = 12.0, 1.6 Hz, 2H), 2.48 (m, 1H), 1.85 (d, J = 12.8 Hz, 2H), 1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.6, 118.6 (q, J = 320), 103.0, 67.4, 39.7, 30.1; FTIR (thin film): 2958, 1414, 1124, 1090, 909, 858, 720 cm^{-1}; HRMS *m/z* calculated for $C_8H_{11}F_3O_4SNa$ $[M+Na]^+$: 283.0228, found 283.0240.

methyl 2-(((trifluoromethyl)sulfonyl)oxy)acrylate (**27e**):



A previously reported procedure was used for the synthesis of **27e** from methyl pyruvate.[52] Purification by silica gel flash chromatography (99:1 pentane:Et_2O, silica gel was neutralized using a 1% solution of NH_4OH) led to the isolation of **27e** as a colorless oil (260 mg, 22%), R_f = 0.13 (99:1 pentane:Et_2O, visualized by $KMnO_4$ stain). ^1H NMR (CD_2Cl_2, 400 MHz): δ 6.34 (d, J = 3.6 Hz, 1H), 5.87 (d, J = 3.6 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 196.2, 160.7, 144.2, 119.1 (q, J = 320), 118.3; FTIR (thin film): 1747, 1646, 1425, 1129, 946, 853, 719 cm^{-1}; HRMS *m/z* calculated for $C_5H_5F_3O_5SNa$ $[M+Na]^+$: 256.9707, found 256.9711.

4-methylpenta-1,3-dien-2-yl trifluoromethanesulfonate (**27f**):



A previously reported procedure was used for the synthesis of **27f** from 4-methyl-3-penten-2-one (freshly distilled from $CaSO_4$).[53] Purification by silica gel flash chromatography (100% hexanes → 99:1 hexanes:ethyl acetate) led to the isolation of **27f** as a colorless oil (203 mg, 7%), R_f = 0.39 (19:1 hexanes:ethyl acetate, visualized by $KMnO_4$). Following isolation by silica gel flash chromatography, the material began to decompose and was used immediately as a substrate.

General procedure for design of experiments optimization

To an oven dried 5 mL vial were added 16 mg (0.17 mmol, 1.7 equiv) of $KF•2H_2O$, 15 mg (0.1 mmol, 1.0 equiv) of (*E*)-(2-phenylvinyl)boronic acid **28a**, and 3.1

mg (3.0 mol%) of $Pd_2dba_3 \bullet CHCl_3$. The vial was equipped with a PTFE-lined stirbar and flushed with N_2 before being sealed with a septum cap. To the solids was added a solution of **27a** (*y* equiv) and methyl 5-hexenoate **26a** (*x* equiv) in 2.0 mL of DMF. The mixture was stirred for 16 h at 55 °C. After completion, a ~200 μL aliquot of the reaction mixture was removed via syringe and filtered through a silica plug, eluting with ethyl acetate. The mixture was analyzed by GC. Yields were calculated using a response factor (^{1}H NMR spectroscopy was used to measure the response factor to account for varying detector response) and 2-methoxynaphthalene as an internal standard. For a tabular summary of design of experiments training set data and a plot of measured *versus* predicted yields see Table 4.2 and Figure 4.15, respectively. Following collection of training set data the following mathematical normalized mathematical model could be generated for stoichiometry optimization studies: yield = $0.64 + 0.85[x] - 0.30[y] - 0.39[x]^2 - 0.33[y]^2$ (Non-normalized: yield = $23.79 + 31.43[x] + 14.72[y] - 5.33[x]^2 - 4.58[y]^2$). For a summary of model extrapolation results see Table 4.3.

Table 4.2 Summary of training set data for design of experiments optimization studies.

entry	*x*	*y*	meas. yield (%)	pred. yield (%)
1	1.0	1.0	60.2	60.0
2	2.0	1.0	74.7	75.5
3	3.0	1.0	80.8	80.2
4	1.0	2.0	61.9	61.0
5	2.0	2.0	79.9	76.4
6	3.0	2.0	76.8	81.2
7	1.0	3.0	51.7	52.8
8	2.0	3.0	65.5	68.2
9	3.0	3.0	76.8	73.0

Figure 4.15 Predicted *versus* measured yield plot for design of experiments optimization studies.

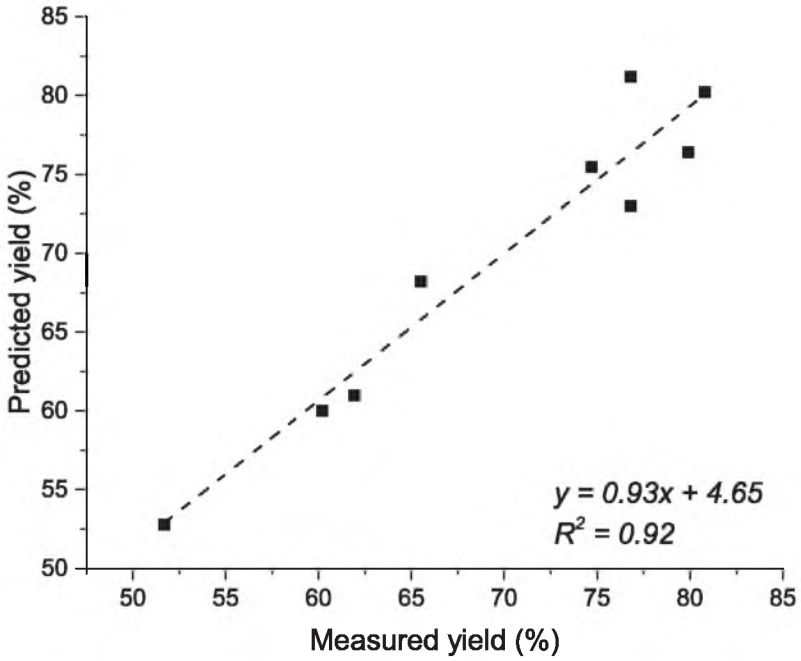


Table 4.3 Summary of extrapolation data set for design of experiments optimization.

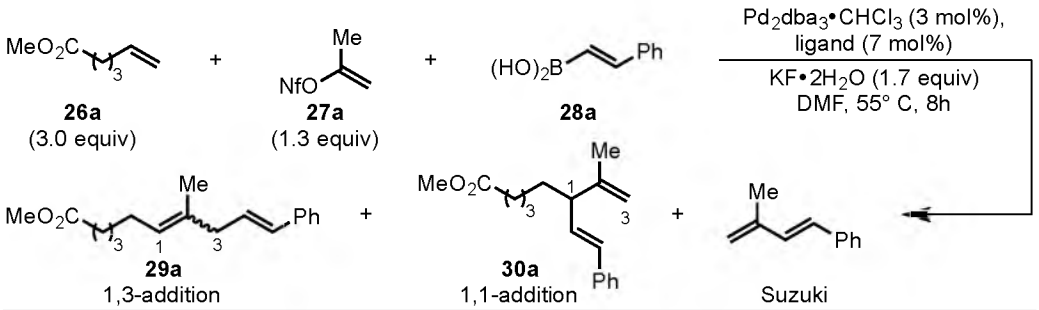
entry	*x*	*y*	meas. yield (%)	pred. yield (%)
1	2.5	1.5	80.1	80.8
2	3.0	1.5	78.5	81.9
3	3.0	1.3	87.5	81.5

General procedure for reaction optimization

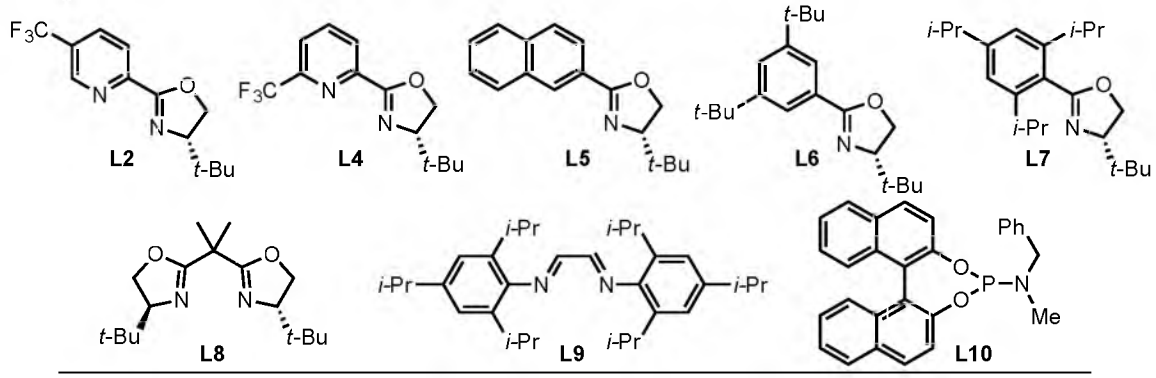
To an oven dried 5 mL vial were added 16 mg (0.17 mmol, 1.7 equiv) of $KF•2H_2O$, 15 mg (0.1 mmol, 1.0 equiv) of (*E*)-(2-phenylvinyl)boronic acid **28a**, and 3.1 mg (3.0 mol%) of $Pd_2dba_3•CHCl_3$. The vial was equipped with a PTFE-lined stirbar and flushed with N_2 before being sealed with a septum cap. To the solids was added a solution of 44 mg (0.13 mmol, 1.3 equiv) of **27a** and 42 μL (0.3 mmol, 3.0 equiv) of methyl 5-hexenoate **26a** in 2.0 mL of DMF. The mixture was stirred for 16 h at 55 °C.

After completion, a ~200 μL aliquot of the reaction mixture was removed via syringe and filtered through a silica plug, eluting with ethyl acetate. The mixture was analyzed by GC. Yields were calculated using a response factor (^{1}H NMR spectroscopy was used to measure the response factor to account for varying detector response) and 2-methoxynaphthalene as an internal standard. For a tabular summary of ligand screening data see Table 4.4.

Table 4.4 Summary of 1,3-difunctionalization ligand screens.



entry	ligand	yield (%)[a]	**29a**:**30a**[a]	*E*:*Z*[a]	Suzuki (%)[a]
1	none	90	4.9	92:8	8.3
2	**L2**	43	2.5	92:8	8.8
3	**L4**	70	4.0	91:9	17
4	**L5**	92	4.9	93:7	7.1
5	**L5**[b]	84	5.0	93:7	14
6	**L6**	73	4.1	92:8	8.4
7	**L6**[b]	62	3.7	91:9	19
8	**L7**	67	3.9	90:10	16
9	**L8**	58	3.3	87:13	13
10	**L9**	35	3.2	92:8	4.9
11	**L10**	78	3.5	93:7	11

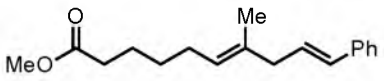


General procedure for the 1,3-difuncationalization of terminal alkenes

To an oven dried 10 mL Schlenk flask were added 80 mg (0.85 mmol, 1.7 equiv) of KF•$2H_2O$, 74 mg (0.5 mmol, 1.0 equiv) of (*E*)-(2-phenylvinyl)boronic acid **28a**, and 16 mg (3.0 mol%) of Pd_2dba_3•$CHCl_3$. The flask was equipped with a PTFE-lined stirbar and glass joints, and then was evacuated with house vacuum and flushed with N_2 three times. To the solids were added 8 mL of DMF and a solution of 221 mg (0.65 mmol, 1.3 equiv) of **27a** and 0.21 mL (1.5 mmol, 3.0 equiv) of methyl 5-hexenoate **26a** in 2.0 mL of DMF. The mixture was stirred for 8 h at 55 °C. After completion, the mixture was diluted with methyl tert-butyl ether and filtered through a Celite plug. The organics were washed with water (3 x 10 mL) and brine (1 x 10 mL), then dried over sodium sulfate and concentrated *in vacuo*. Products were purified by silica gel flash chromatography as noted below. Yields represent a mixture of stereo and regioisomers. Enriched stereo- and regioisomer fractions were isolated using $AgNO_3$ impregnated silica gel flash chromatography. NMR analysis was used to verify the identity of isomers. GC analysis was used to determine isomeric ratios of the crude product mixture.

Product purification and characterization data

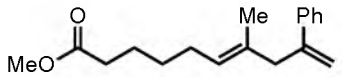
methyl (6*E*,9*E*)-7-methyl-10-phenyldeca-6,9-dienoate ((*E*)-**29a**):



The general procedure was followed using 80 mg of KF•$2H_2O$ (0.85 mmol), 74 mg of (*E*)-(2-phenylvinyl)boronic acid **28a** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 221 mg of **27a** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash

chromatography (19:1 hexanes:ethyl acetate) led to the isolation of **29a** and **30a** as a colorless oil (103 mg, 76% as a 4.1:0.41:1.0 mixture of (*E*)-**29a**:(*Z*)-**29a**:**30a** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.22 (19:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (m, 2H), 7.29 (m, 2H), 7.19 (m, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 6.19 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.21 (t, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 2.86 (d, *J* = 7.2 Hz, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.04 (q, *J* = 7.6 Hz, 2H), 1.63 (m, 5H), 1.38 (pent, *J* = 7.6 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**29a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.13 (m, 1H), 3.65 (s, 3H), 2.91 (d, *J* = 6.4 Hz, 2H) 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.4, 137.9, 134.2, 131.1, 129.2, 128.7, 127.1, 126.2, 125.5, 51.7, 43.4, 34.2, 29.5, 27.9, 24.9, 16.4; FTIR (thin film): 2931, 1736, 1435, 965, 738, 692 cm^{-1}; HRMS *m/z* calculated for $C_{18}H_{24}O_2Na$ $[M+Na]^+$: 295.1674, found 295.1667.

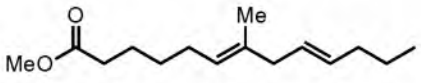
methyl (*E*)-7-methyl-9-phenyldeca-6,9-dienoate ((*E*)-**29b**):



The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 74 mg of (1-phenylvinyl)boronic acid **28b** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 221 mg of **27a** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (99:1 hexanes:Et_2O → 19:1 hexanes:ethyl acetate) led to the isolation of **29b** and **30b** as a colorless oil (51 mg, 37% as a 13.2:1.3:1.0 mixture of (*E*)-**29b**:(*Z*)-**29b**:**30b** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.26 (19:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 500

MHz): δ 7.40 (m, 2H), 7.29 (m, 2H), 7.23 (m, 1H), 5.38 (d, *J* = 1.5 Hz, 1H), 5.20 (t, *J* = 7.3 Hz, 1H), 5.06 (d, *J* = 1.5 Hz, 1H), 3.66 (s, 3H), 3.16 (s, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.99 (q, *J* = 7.5 Hz, 2H), 1.52 (m, 5H), 1.30 (pent, *J* = 7.5 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.4, 146.5, 133.2, 128.3, 127.4, 127.1, 126.4, 114.1, 51.7, 45.9, 34.2, 29.3, 27.8, 24.6, 16.1; FTIR (thin film): 2925, 1739, 1441, 1171, 897, 778, 707 cm^{-1}; HRMS *m/z* calculated for $C_{18}H_{24}O_2Na$ $[M+Na]^+$: 295.1674, found 295.1669.

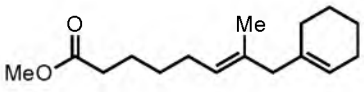
methyl (6*E*,9*E*)-7-methyltrideca-6,9-dienoate ((*E*)-**29c**):



The general procedure was followed using 80 mg of KF•2H_2O (0.85 mmol), 57 mg of (*E*)-1-pentenylboronic acid **28c** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 221 mg of **27a** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (49:1 hexanes:ethyl acetate) led to the isolation of **29c** and **30c** as a colorless oil (52 mg, 50% as a 2.5:0.2:1.0 mixture of (*E*)-**29c**:(*Z*)-**29c**:**30c** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.33 (19:1 hexanes:ethyl acetate, visualized by PMA stain). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.41 (app. dt, *J* = 15.5, 9.0 Hz, 1H), 5.36 (app. dt, *J* = 15.5, 8.9 Hz, 1H), 5.12 (t, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 2.63 (d, *J* = 6.0 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.99 (m, 4H), 1.63 (m, 2H), 1.57 (s, 3H), 1.37 (m, 4H), 0.89 (t, *J* = 7.5 Hz, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**29c**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.28 (m, 2H), 2.68 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.5, 135.0, 131.9, 128.6, 124.6, 51.7, 43.2, 34.9, 34.3, 29.5, 27.8, 24.9,

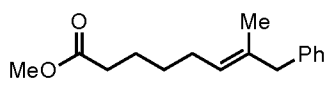
22.9, 16.2, 13.9; FTIR (thin film): 2956, 1741, 1435, 1064, 968, 739 cm^{-1}; HRMS *m/z* calculated for $C_{15}H_{26}O_2Na$ $[M+Na]^+$: 261.1831, found 261.1829.

methyl (*E*)-8-(cyclohex-1-en-1-yl)-7-methyloct-6-enoate ((*E*)-**29d**):



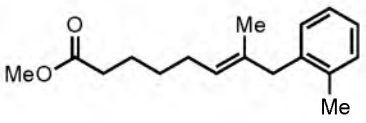
The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 63 mg of 1-cyclohexenylboronic acid **28d** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 221 mg of **27a** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (97:3 hexanes:ethyl acetate) led to the isolation of **29d** and **30d** as a colorless oil (114 mg, 91% as a 4.9:0.44:1.0 mixture of (*E*)-**29d**:(*Z*)-**29d**:**30d** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.26 (19:1 hexanes:ethyl acetate, visualized by PMA stain). ^1H NMR ($CDCl_3$, 500 MHz): δ 5.40 (m, 1H), 5.12 (t, *J* = 7.3 Hz, 1H), 3.66 (s, 3H), 2.57 (s, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.00 (m, 4H), 1.80 (m, 2H), 1.67-1.51 (m, 6H), 1.50 (s, 3H), 1.36 (pent, *J* = 7.5 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**29d**: ^1H NMR ($CDCl_3$, 500 MHz): δ 5.20 (t, *J* = 8.0 Hz, 1H), 2.62 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.5, 136.2, 133.9, 125.8, 122.8, 51.7, 49.0, 34.2, 29.5, 27.9, 27.8, 25.6, 24.8, 23.2, 22.8, 15.7; FTIR (thin film): 2926, 1741, 1436, 1170, 888, 669 cm^{-1}; HRMS *m/z* calculated for $C_{16}H_{26}O_2Na$ $[M+Na]^+$: 273.1831, found 273.1826.

methyl (*E*)-7-methyl-8-phenyloct-6-enoate ((*E*)-**29e**):



The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 61 mg of phenylboronic acid **28e** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 221 mg of **27a** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (19:1 hexanes:ethyl acetate) led to the isolation of **29e** and **30e** as a colorless oil (106 mg, 86% as a 7.1:0.70:1.0 mixture of (*E*)-**29e**:(*Z*)-**29e**:**30e** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.26 (19:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (m, 2H), 7.17 (m, 3H), 5.24 (t, *J* = 7.1 Hz, 1H), 3.67 (s, 3H), 3.28 (s, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.04 (q, *J* = 7.6 Hz, 2H), 1.64 (m, 2H), 1.53 (s, 3H), 1.40 (pent, *J* = 7.6 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**29e**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.30 (t, *J* = 6.8 Hz, 1H), 3.36 (s, 2H), 2.15 (q, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.5, 140.6, 135.0, 129.0, 128.4, 126.4, 126.1, 51.7, 46.5, 34.2, 29.5, 27.8, 24.8, 16.0; FTIR (thin film): 2931, 1737, 1602, 1435, 1170, 733, 699 cm^{-1}; HRMS *m/z* calculated for $C_{16}H_{22}O_2Na$ $[M+Na]^+$: 269.1517, found 269.1516.

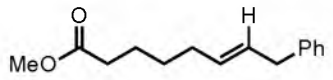
methyl (*E*)-7-methyl-8-(*o*-tolyl)oct-6-enoate ((*E*)-**29f**):



The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 68 mg of *o*-tolylboronic acid **28f** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 221 mg of **27a** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (19:1

hexanes:ethyl acetate) led to the isolation of **29f** and **30f** as a colorless oil (92 mg, 71% as a 3.9:0.75:1.0 mixture of (*E*)-**29f**:(*Z*)-**29f**:**30f** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.26 (19:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (m, 4H), 5.03 (t, *J* = 7.4 Hz, 1H), 3.66 (s, 3H), 3.27 (s, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.66-1.56 (m, 5H), 1.35 (pent, *J* = 7.6 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**29f**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.5, 138.4, 137.1, 133.9, 130.3, 129.9, 126.3, 126.0, 125.9, 51.7, 43.4, 34.2, 29.4, 27.8, 24.8, 19.7, 16.6; FTIR (thin film): 2930, 1603, 1435, 1169, 1051, 888, 738 cm^{-1}; HRMS *m/z* calculated for $C_{17}H_{24}O_2Na$ $[M+Na]^+$: 283.1674, found 283.1670.

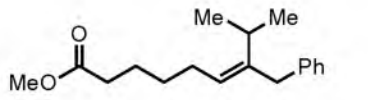
methyl (*E*)-8-phenyloct-6-enoate ((*E*)-**29g**):



The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 61 mg of phenylboronic acid **28e** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 212 mg of **27b** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (97:3 hexanes:ethyl acetate) led to the isolation of **29g** and **30g** as a colorless oil (106 mg, 91% as a 10.6:0.61:1.0 mixture of (*E*)-**29g**:(*Z*)-**29g**:**30g** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.21 (19:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (m, 2H), 7.19 (m, 3H), 5.58 (app. dt, *J* = 15.2, 6.4 Hz, 1H), 5.49 (app. dt, *J* = 15.2, 6.4 Hz, 1H), 3.67 (s, 3H), 3.33 (d, *J* = 6.4 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.64 (pent, *J* = 7.6 Hz,

2H), 1.41 (pent, J = 7.6 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.4, 141.2, 131.5, 129.5, 128.7, 128.6, 126.1, 51.7, 39.3, 34.2, 32.3, 29.1, 24.7; FTIR (thin film): 2926, 1739, 1602, 1435, 1072, 969, 746, 699 cm^{-1}; HRMS *m/z* calculated for $C_{15}H_{20}O_2Na$ $[M+Na]^+$: 255.1361, found 255.1360.

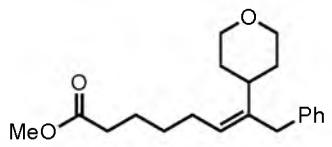
methyl (*Z*)-7-benzyl-8-methylnon-6-enoate ((*Z*)-**29h**):



The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 61 mg of phenylboronic acid **28e** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 239 mg of **27c** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (49:1 hexanes:ethyl acetate) led to the isolation of **29h** and **30h** as a colorless oil (72 mg, 50% as a 1.2:1.9:1.0 mixture of (*E*)-**29h**:(*Z*)-**29h**:**30h** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.24 (19:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (m, 2H), 7.16 (m, 3H), 4.85 (t, J = 6.8 Hz, 1H), 3.66 (s, 3H), 3.27 (s, 2H), 2.85 (sept, J = 7.2 Hz, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.05 (q, J = 7.6 Hz, 2H), 1.62 (pent, J = 7.6 Hz, 2H), 1.34 (pent, J = 7.6 Hz, 2H), 0.96 (d, J = 6.8 Hz, 6H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*E*)-**29h**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.35 (t, J = 7.2 Hz, 1H), 3.42 (s, 2H), 2.14 (m, 2H), 1.40 (m, 2H), 1.07 (d, J = 6.8 Hz, 6H); The following signals can be assigned to **30h**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.94 (d, J = 4.0 Hz, 1H), 4.88 (d, J = 4.0 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.4, 144.4, 141.4, 129.5, 128.3, 126.2, 125.8, 51.7, 38.5, 34.2, 29.8, 29.3,

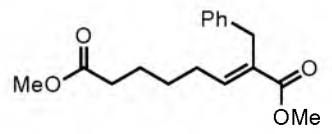
27.3, 24.9, 21.6; FTIR (thin film): 2956, 1737, 1601, 1435, 1361, 1169, 892, 699 cm^{-1}; HRMS *m/z* calculated for $C_{18}H_{26}O_2Na$ $[M+Na]^+$: 297.1831, found 297.1830.

methyl (*Z*)-8-phenyl-7-(tetrahydropyran-4-yl)oct-6-enoate ((*Z*)-**29i**):



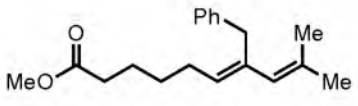
The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 61 mg of phenylboronic acid **28e** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 169 mg of **27d** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (9:1 hexanes:ethyl acetate) led to the isolation of **29i** and **30i** as a colorless oil (76 mg, 48% as a 1.3:2.0:1.0 mixture of (*E*)-**29i**:(*Z*)-**29i**:**30i** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.15 (9:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25 (m, 2H), 7.17 (m, 3H), 5.01 (t, *J* = 7.2 Hz, 1H), 3.94 (dd, *J* = 11.4, 4.4 Hz, 2H), 3.67 (s, 3H), 3.39 (t, *J* = 11.9 Hz, 2H), 3.30 (s, 2H), 2.70 (m, 1H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.10 (q, *J* = 7.6 Hz, 2H), 1.64 (m, 4H), 1.38 (pent, *J* = 7.6 Hz, 2H), 1.30 (m, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.3, 141.7, 140.9, 129.3, 128.4, 128.1, 126.1, 68.6, 51.7, 40.1, 37.8, 34.2, 31.4, 29.8, 27.3, 24.9; FTIR (thin film): 2946, 1736, 1435, 1127, 1013, 736, 699 cm^{-1}; HRMS *m/z* calculated for $C_{20}H_{29}O_3$ $[M+H]^+$: 317.2117, found 317.2114.

dimethyl (*E*)-2-benzyloct-2-enedioate ((*E*)-**29j**):



The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 61 mg of phenylboronic acid **28e** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 152 mg of **27e** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (19:1 hexanes:ethyl acetate) led to the isolation of **29j** and **30j** as a colorless oil (120 mg, 83% as a 3.0:0.78:1.0 mixture of (*E*)-**29j**:(*Z*)-**29j**:**30j** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.40 (3:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25 (m, 2H), 7.17 (m, 3H), 6.92 (t, *J* = 7.5 Hz, 1H), 3.69 (m, 5H), 3.66 (s, 3H), 2.29 (m, 4H), 1.65 (pent, *J* = 7.5 Hz, 2H), 1.49 (pent, *J* = 7.5 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.1, 168.3, 143.8, 139.8, 131.4, 128.6, 128.4, 126.2, 52.0, 51.8, 34.0, 32.6, 28.8, 28.4, 24.9; FTIR (thin film): 2949, 1736, 1601, 1435, 1196, 1062, 736, 698 cm^{-1}; HRMS *m/z* calculated for $C_{17}H_{22}O_4Na$ $[M+Na]^+$: 313.1416, found 313.1414.

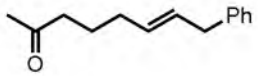
methyl (*E*)-7-benzyl-9-methyldeca-6,8-dienoate ((*E*)-**29k**):



The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 61 mg of phenylboronic acid **28e** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 150 mg of **27f** (0.65 mmol) and 0.21 mL of methyl 5-hexenoate **26a** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (100% hexanes → 97:3 hexanes:ethyl acetate) led to the isolation of **29k** and **30k** as a colorless oil (32 mg, 22% as a 10.4:2.5:1.0 mixture of (*E*)-**29k**:(*Z*)-**29k**:**30k** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.30 (19:1 hexanes:ethyl

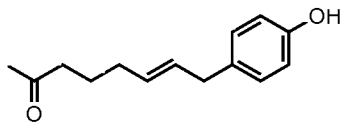
acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (m, 2H), 7.19 (m, 3H), 5.74 (s, 1H), 5.26 (t, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 3.32 (s, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.09 (q, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.70-1.60 (m, 5H), 1.41 (pent, *J* = 7.6 Hz, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.4, 140.5, 134.7, 133.3, 130.9, 129.3, 129.1, 128.4, 126.2, 51.7, 47.3, 34.2, 29.4, 28.0, 24.9, 17.8, 17.2; FTIR (thin film): 2931, 1739, 1653, 1600, 1436, 1171, 1029, 744, 670 cm^{-1}; HRMS *m/z* calculated for $C_{19}H_{26}O_2Na$ $[M+Na]^+$: 309.1855, found 309.1828.

(*E*)-8-phenyloct-6-en-2-one ((*E*)-**29l**):



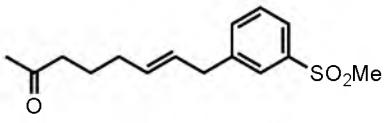
The general procedure was followed using 80 mg of $KF•2H_2O$ (0.85 mmol), 61 mg of phenylboronic acid **28e** (0.5 mmol), 16 mg of $Pd_2dba_3•CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 212 mg of **27b** (0.65 mmol) and 0.18 mL of hex-5-en-2-one **26b** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (95:5 hexanes: ethyl acetate) led to the isolation of **29l** and **30l** as a colorless oil (89 mg, 88% as a 7.5:0.74:1.0 mixture of (*E*)-**29l**:(*Z*)-**29l**:**30l** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.38 (4:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 500 MHz): δ7.30 – 7.27 (m, 2H), 7.22 – 7.14 (m, 3H), 5.66 – 5.54 (app. dt, *J* = 15.2, 7.6 Hz, 1H), 5.51 – 5.40 (app. dt, *J* = 15.2, 7.6 Hz, 1H), 3.33 (d, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.12 (s, 3H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.66 (pent, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 209.0, 140.8, 130.8, 129.9, 128.44, 128.35, 125.9, 43.0, 39.0, 31.8, 29.9, 23.4; FTIR (thin film): 2938, 1715, 1451, 1373 cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{18}ONa$ $[M+Na]^+$: 225.1255, found 225.1254.

(*E*)-8-(4-hydroxyphenyl)oct-6-en-2-one (((*E*)-**29m**):



The general procedure was followed using 80 mg of KF•$2H_2O$ (0.85 mmol), 69 mg of (4-hydroxyphenyl)boronic acid **28g** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 212 mg of **27b** (0.65 mmol) and 0.18 mL of hex-5-en-2-one **26b** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (1:2 hexanes: ethyl acetate) led to the isolation of **29m** and **30m** as a colorless oil (81 mg, 74% as a 6.7:0.28:1.0 mixture of (*E*)-**29m**:(*Z*)-**29m**:**30m** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.35 (1:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.02 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 5.64 – 5.48 (app. dt, *J* = 15.2, 5.4 Hz, 1H), 5.45 – 5.39 (app. dt, *J* = 15.1, 6.7 Hz, 1H), 5.31 (s, 1H), 3.24 (d, *J* = 7.0 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 2.04 (q, *J* = 7.0 Hz, 2H), 1.66 (pent, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 209.8, 153.9, 132.8, 130.4, 129.5, 115.2, 43.0, 38.1, 31.8, 29.9, 23.4; FTIR (thin film): 3369, 2933, 2359, 2338, 1699, 1514 cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{18}O_2Na$ $[M+Na]^+$: 241.1204, found 241.1194.

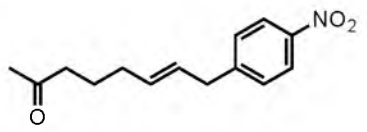
(*E*)-8-(3-(methylsulfonyl)phenyl)oct-6-en-2-one (((*E*)-**29n**):



The general procedure was followed using 80 mg of KF•$2H_2O$ (0.85 mmol), 100 mg of (3-(methylsulfonyl)phenyl)boronic acid **28h** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 212 mg of **27b** (0.65 mmol) and 0.18 mL of

hex-5-en-2-one **26b** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (10:1 hexanes: ethyl acetate) led to the isolation of **29n** and **30n** as a colorless oil (121 mg, 86% as a 16.3:3.0:1.0 mixture of (*E*)-**29n**:(*Z*)-**29n**:**30n** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.36 (4:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 500 MHz): δ7.82 – 7.73 (m, 2H), 7.54 – 7.40 (m, 2H), 5.56 (app. dt, *J* = 15.3, 6.1 Hz, 1H), 5.50 (app. dt, *J* = 15.3, 6.3 Hz, 1H), 3.41 (d, *J* = 6.1 Hz, 2H), 3.05 (s, 3H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 3H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.67 (pent, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 208.2, 142.7, 140.6, 133.9, 132.4, 129.4, 128.3, 127.1, 125.0, 44.5, 42.9, 38.7, 31.8, 30.0, 23.2; FTIR (thin film): 2928, 1171, 1299, 1144 cm^{-1}; HRMS *m/z* calculated for $C_{15}H_{20}O_3SNa$ $[M+Na]^+$: 303.1031, found 303.1030.

(*E*)-8-(4-nitrophenyl)oct-6-en-2-one (((*E*)-**29o**):



The general procedure was followed using 80 mg of KF•2H_2O (0.85 mmol), 83 mg of (4-nitrophenyl)boronic acid **28i** (0.5 mmol), 16 mg of Pd_2dba_3•$CHCl_3$ (3.0 mol%), 8 mL of DMF, and a solution of 212 mg of **27b** (0.65 mmol) and 0.18 mL of hex-5-en-2-one **26b** (1.5 mmol) in 2.0 mL of DMF. Purification by silica gel flash chromatography (19:1 hexanes: ethyl acetate) led to the isolation of **29o** and **30o** as a colorless oil (49 mg, 40% as a 16:2.85:1.0 mixture of (*E*)-**29o**:(*Z*)-**29o**:**30o** isomers, respectively), isomeric ratios were determined by GC, R_f = 0.45 (4:1 hexanes:ethyl acetate, visualized by 254 nm light and PMA stain). ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.14 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 5.56 (app. dt, *J* = 15.2, 6.2 Hz, 1H), 5.51 (app. dt, *J* = 15.3, 6.1 Hz, 1H),

3.42 (d, J = 5.8 Hz, 2H), 2.43 (t, J = 7.4 Hz, 2H), 2.12 (s, 3H), 2.05 (q, J = 6.8 Hz, 2H), 1.67 (pent, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 209.5, 149.4, 147.2, 133.4, 130.0, 128.6, 124.4, 43.7, 39.6, 32.6, 30.7, 24.0; FTIR (thin film): 2935, 1714, 1597, 1517, 1345 cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{17}NO_3Na$ $[M+Na]^+$: 270.1106, found 270.1100.

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