Pd-Catalyzed Oxidative Functionalizations

by

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To Sue, John, and Brian

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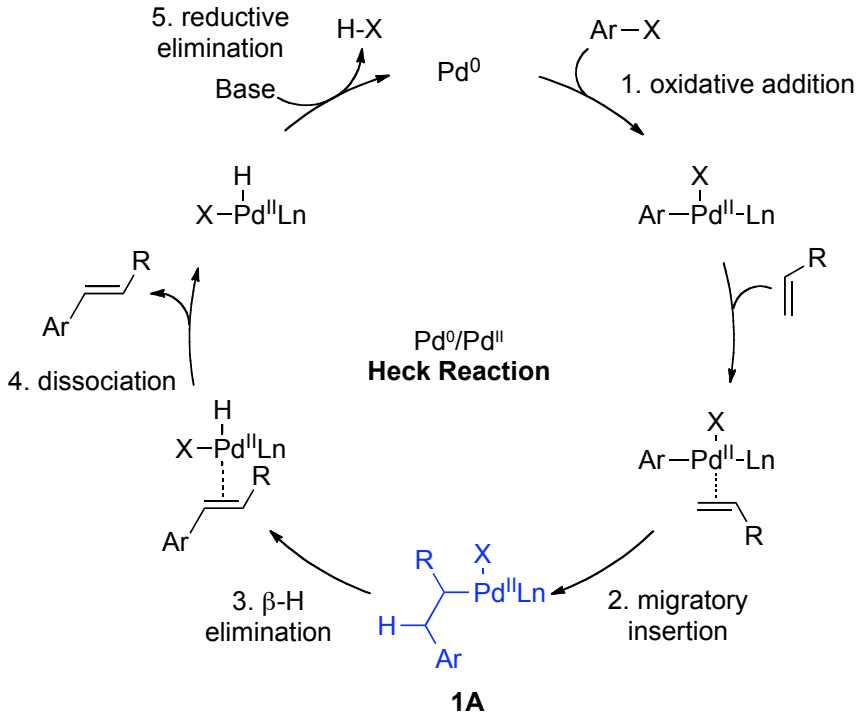
CHAPTER 1

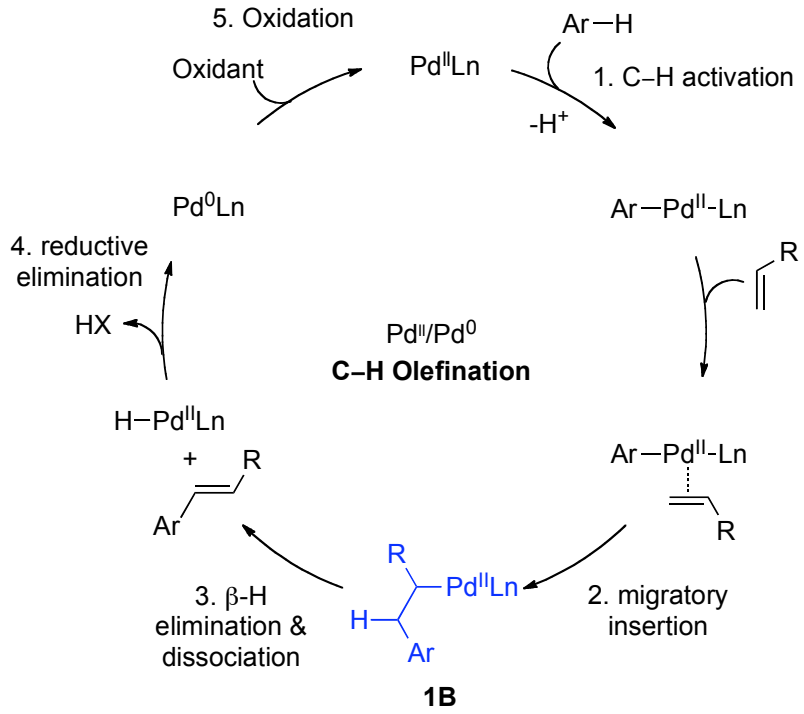
Introduction

Pd-catalyzed transformations have been widely used for the formation of aryl–aryl or aryl–alkenyl bonds in the context of cross coupling reactions, such as the Heck, Suzuki, and Negishi transformations.[1] These reactions are well known to proceed via Pd(0/II) mechanisms. For example, the Heck reaction between an aryl halide and an alkene involves the following steps: 1) oxidative addition of the aryl halide to Pd(0), 2) alkene migratory insertion at the resulting Pd(II) complex to form **1A**, 3) β-hydride elimination to generate an (alkenyl)Pd(II)(hydride) complex, and 4) dissociation of the alkene product (Scheme 1.1).[1a,c] The Pd(0) catalyst is then regenerated via 5) base assisted reductive elimination of HX.



Scheme 1.1. General Mechanism of the Heck Reaction

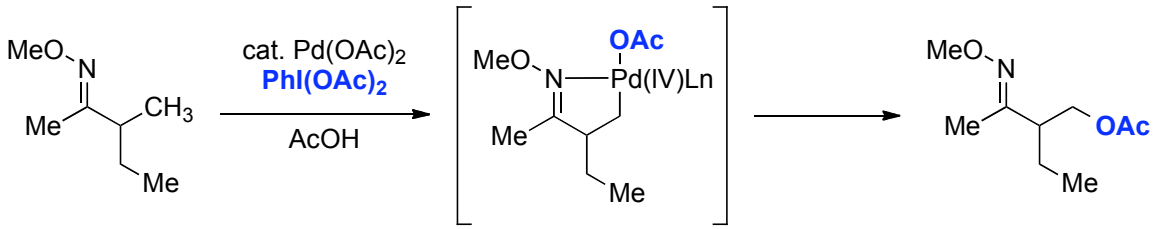
There are also many Pd(II/0)-catalyzed C–C bond-forming reactions where oxidants other than aryl halides are used to generate reactive Pd(II) intermediates. An example of such a transformation is Pd-catalyzed C–H olefination, commonly known as the Fujiwara-Moritani (F-M) reaction, which requires oxidants such as O_2, peroxides, and peroxy esters (Scheme 1.2).[2] The major difference between the F-M reaction and the Heck reaction, which generates similar alkene products, is that the first step in the F-M reaction is C–H activation of arenes at Pd(II). The steps (2-4) following C–H activation to generate the alkene product are analogous to the mechanism of the Heck reaction. Finally, the Pd(0) species generated upon reductive elimination of HX is then oxidized to Pd(II) with an added oxidant.



Scheme 1.2. General Mechanism of the C–H Olefination Reaction

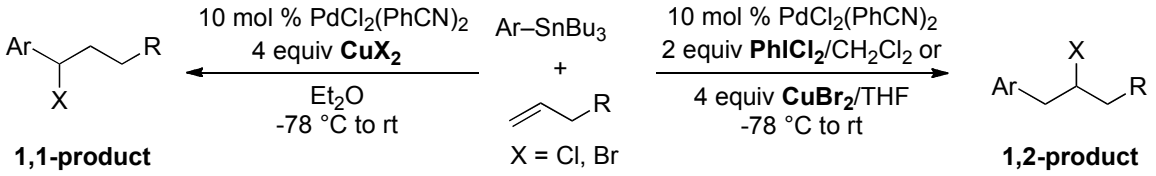
A newer approach to Pd-catalyzed oxidative functionalization reactions involves the use of oxidants that are proposed to oxidize Pd to a higher oxidation state *in situ*. Ligand-directed Pd-catalyzed C–H activation/functionalization is an example of this type of Pd-catalyzed oxidative functionalization.[3] Often, the oxidants utilized in these transformations are also incorporated into the product

via reductive elimination.[4] For instance, as shown in Scheme 1.3, the oxime ether functionality in the substrate directs the C–H activation of a 1° sp^3 C–H bond, while $PhI(OAc)_2$ oxidizes the resulting palladacycle. Carbon–oxygen bond-forming reductive elimination then releases the acetoxylated product.



Scheme 1.3. Oxime Ether-Directed C–H Activation/Acetoxylation

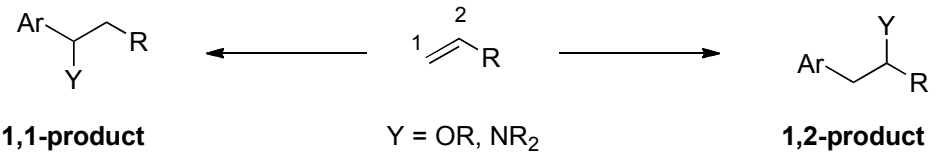
In the first project described in this dissertation, oxidative interception of Pd(II)-alkyl Heck intermediates of general structure **1A** was evaluated. The advantage of intercepting such intermediates would be to introduce further functionalization while retaining the structural complexity inherent to this species. Thus, development of this methodology would allow for the difunctionalization of alkenes in a single step. Previously in our group, this methodology was shown to be feasible for alkene arylhalogenation reactions (Scheme 1.4).[5] This process was shown selective for both 1,1- and 1,2-products based on oxidant or solvent choice.



Scheme 1.4. 1,1- And 1,2-Arylhalogenation[5]

The goal of this project was to expand the olefin difunctionalization methodology to include the formation of aryloxygen and arylamine motifs, which are commonly found in biologically active molecules (Scheme 1.5). Thus, a simple procedure to construct these motifs would be highly desirable. In previous work by our group, hypervalent iodine oxidants, such as $PhICl_2$, were shown to be capable of intercepting Pd(II)-alkyl species (Scheme 1.4). Therefore, we explored hypervalent iodine oxidants in order to carry out the desired

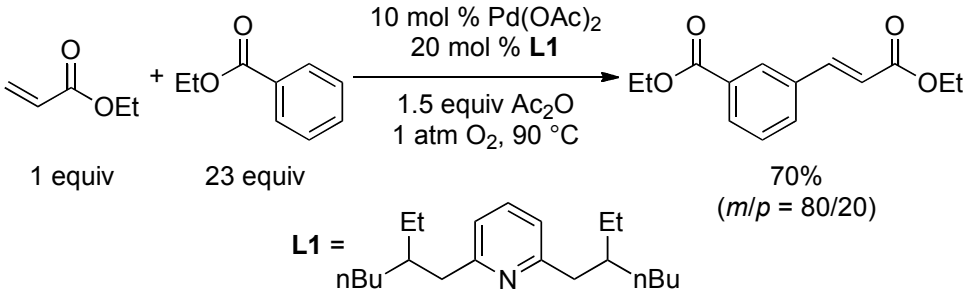
functionalization in conjunction with organostannanes as the source of the aryl group.



Scheme 1.5. Proposed Olefin Difunctionalization

In the second project, we designed new methods that would expand upon currently known C–H olefination reactions. Notably, the Pd(II)-alkyl intermediate formed in the course of this reaction (Scheme 1.2, **1B**) is very similar to intermediates in the Heck reaction (Scheme 1.1, **1A**). For the development of alkene difunctionalization methodology, arylstannane transmetallating reagents were utilized to provide the aryl functionality. However, use of simple unfunctionalized arenes for the aryl source would be more ideal. As such, C–H olefination would provide the basis of a good proof of concept for coupling with new oxidative interception methodology. Before we could fully utilize simple arenes as our aryl source for olefin difunctionalization reactions, some of the challenges associated with the current methods needed to be addressed.

These limitations include the need for electron neutral or electron rich arenes and α,β-unsaturated carbonyl derivatives. In particular, invoking catalyst control to enhance the reactivity of the coupling reaction and improving the site-selectivity of C–H activation of arenes was the project goal. Catalyst control for C–H olefination reaction is not well studied and only one example by Yu demonstrates the use of 2,6-dialkylpyridine as a ligand in conjunction with $Pd(OAc)_2$ catalyst (Scheme 1.6).[6]



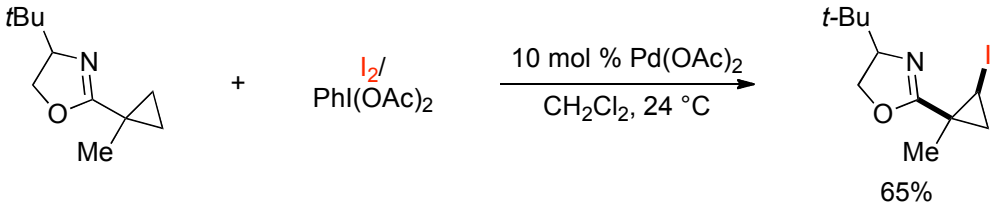
Scheme 1.6. $Pd(OAc)_2$/**L1** Catalyzed C–H olefination with O_2 as Oxidant

Further evidence for the feasibility of catalyst control is shown by a report from our group that studied a different reaction. In this prior study, the use of pyridine as a ligand for Pd-catalyzed C–H activation/acetoxylation was examined. It was reported that an approximately 1:1 ratio of $Pd(OAc)_2$/pyridine accelerated the reaction rate and improved product yields. Since the rate determining step of the C–H acetoxylation reaction is proposed to be the C–H activation step, we hypothesized that the use of pyridine could be beneficial in related C–H activation reactions at Pd(II). The C–H olefination reaction is also proposed to involve rate limiting C–H activation of arenes at Pd(II); therefore, we reasoned that we should be able to develop a general method for catalyst-controlled C–H olefination via a similar approach.

Lastly, the challenges associated with C–H activation/functionalization were evaluated. There are two major obstacles associated with C–H activation/functionalization reactions: (1) to achieve site-selective C–H activation, and (2) to obtain reactivity from relatively inert C–H bonds. The first challenge has been addressed with the use of a ligand directed approach, where a functional group is incorporated in the substrate that will direct the catalyst to react at a specific site on the substrate (Scheme 1.4). These directed C–H activation/functionalization reactions have been successful for functionalizing sp^2 C–H bonds as well as 1° sp^3 C–H bonds, where no sp^2 C–H bonds are present in close proximity. However, a major challenge that still remains is obtaining reactivity of 2° sp^3 C–H bonds. In order to address and understand the reactivity

challenge with 2° sp^3 C–H bonds, a systematic study of cyclopropane substrates bearing directing ligands were studied.

Cyclopropanes are widely used as synthetic intermediates due to their ability to be functionalized upon ring opening or by ring expansion reactions.[7] Lewis acids[8,9] and transition metals (e.g. Pd, Pt, Rh)[10] have previously been used to open cyclopropane rings. However, recently, Yu and coworkers reported C–H activation/iodination of the cyclopropyl C–H bond with $Pd(OAc)_2$ as the catalyst and IOAc as the oxidant with an oxazoline-directed cyclopropane substrate (Scheme 1.7).[11] This selective activation and iodination of the 2° sp^3 C–H bond in the presence of 1° sp^3 C–H bonds was intriguing. The factors that govern Pd catalysts to either assist in ring opening or activation of the 2° C–H bonds of the cyclopropyl group is still unclear. We were interested in developing a general methodology for cyclopropyl C–H activation/functionalization. To this end, an exploratory study on the scope of ligand-directed palladium-catalyzed functionalization of cyclopropanes to gain a better understanding of 2° sp^3 C–H bond activation was initiated.



Scheme 1.7. C–H Activation/Iodination of Cyclopropyl Substrate[11]

In summary, the Pd-catalyzed oxidative transformations described in this dissertation include: (1) olefin difunctionalization via interception of Pd(II)-alkyl Heck intermediates, (2) the use of pyridine ligands as promoters for C–H olefination reactions, and (3) ligand-directed cyclopropane functionalization. These three projects will be discussed individually as separate chapters.

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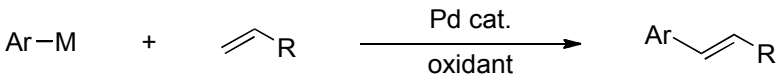
CHAPTER 2

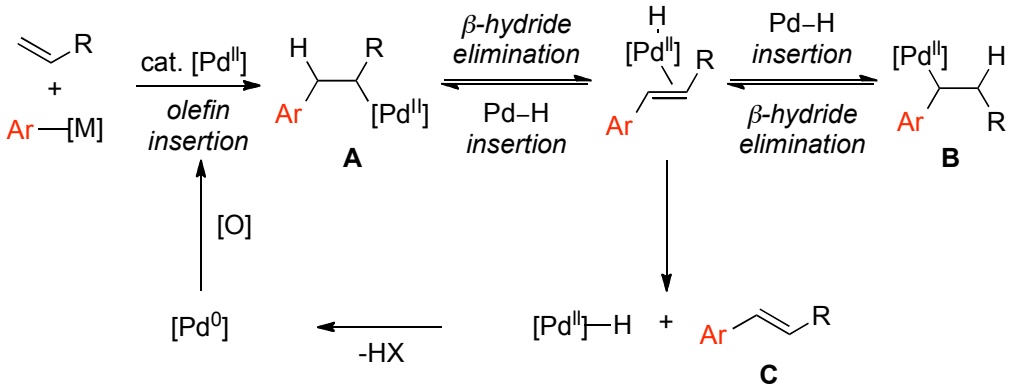
Palladium-Catalyzed Difunctionalization of Terminal Olefins

2.1 Introduction

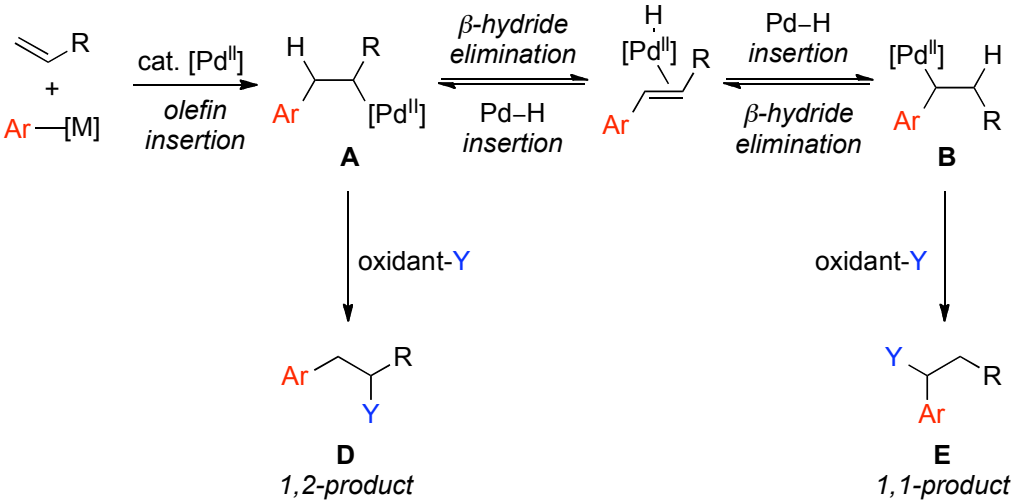
Alkenes serve as very useful building blocks in organic molecule synthesis.[1] The oxidative Heck reaction is a representative example of a transformation that enables the elaboration of alkenes via coupling with an aryl-metal species (Scheme 2.1).[2] The oxidative Heck reaction involves the following steps: 1) transmetallation and migratory insertion of olefin to give intermediate **A** (also in equilibrium with **B**), 2) β-hydride elimination and olefin dissociation to release product **C**, and 3) oxidation of Pd(0) to Pd(II) (Scheme 2.2).[2] While the oxidative Heck reaction is an excellent way of functionalizing alkenes, it is notable that the intermediates **A** and **B** are more complex than the final product **C**, in that they contain two additional bonds and one stereocenter. In an effort to carry the structural complexity of **B** through to the products, we sought to oxidatively intercept Heck intermediate **A** or **B** to generate products such as **D** and **E** (Scheme 2.3). As detailed below, scattered reports by previous Sanford group members[3] as well as other research groups[4,5,6,7] have demonstrated the feasibility of this pathway to achieve olefin difunctionalization.



Scheme 2.1. Oxidative Heck Reaction

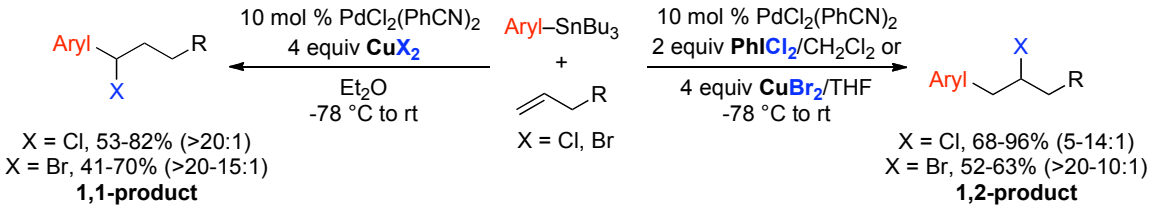


Scheme 2.2. Mechanism of the Oxidative Heck Reaction

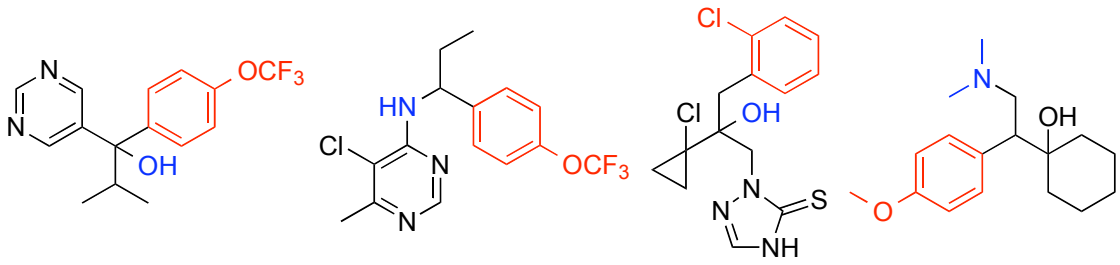


Scheme 2.3. Oxidative Interception of Heck Intermediates

Under this oxidative interception pathway, two new bonds can be constructed in a single step along with up to two new stereocenters. Overall, this methodology provides a convergent way to couple three components (olefin, aryltransmetallating reagent, and oxidant) in a single step.[8] Previously our group developed Pd-catalyzed 1,1- and 1,2-arylhalogenations of unactivated alkenes utilizing arylstannanes and halogen-based oxidants such as $CuCl_2$, $CuBr_2$, and $PhICl_2$ (Scheme 2.4).[3] I was interested in expanding this methodology to include aryloxygenation and arylamination.[9] Both 1,1- and 1,2-arylamino and aryloxygen functionalities can be found in many pharmaceuticals and agrochemicals as shown in Scheme 2.5. Thus, a methodology to construct these motifs could be a valuable tool for the synthetic community.

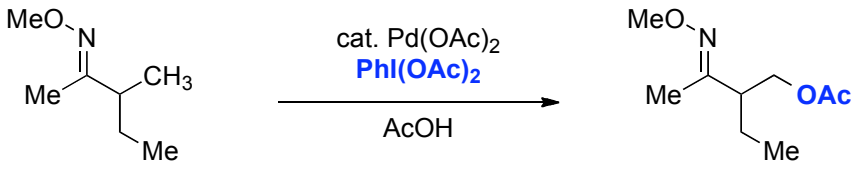


Scheme 2.4. 1,1- and 1,2-Arylhalogenation of Terminal Olefins[3]



Scheme 2.5. Pharmaceuticals and Agrichemicals Containing 1,1- or 1,2-Arylamino or Aryloxygen Motif

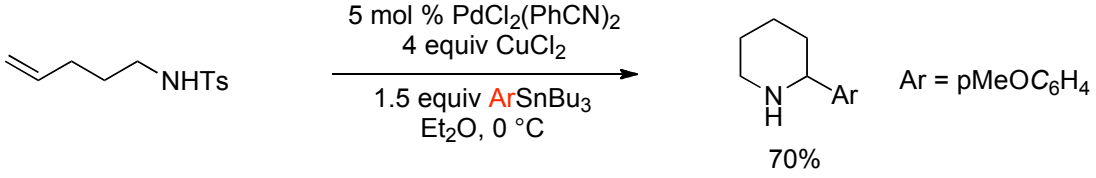
Aryloxygenation. Previously, it has been shown that hypervalent iodine oxidants can intercept Pd(II)-alkyl intermediates in the context of C–H activation/functionalization reactions. When thinking about a strategy for the aryloxygenation, we proposed that hypervalent iodine reagent containing an oxygen ligand could lead to formation of the desired products. In particular, $PhI(OAc)_2$ has been successfully utilized in Pd-catalyzed C–H activation/acetoxylation reactions (Scheme 2.6).[10,11] Therefore, the combination of aryl transmetallating reagents and $PhI(OAc)_2$ was examined for the development of the arylacetoxylation of alkenes.



Scheme 2.6. Pd-Catalyzed Acetoxylation with $PhI(OAc)_2$[10b]

Arylamination. The Pd-catalyzed intramolecular 1,1-arylamination of alkenes was reported by Tamaru and co-workers in 1986.[4b] This single report shows that a very small set of unsaturated amides can undergo $PdCl_2(PhCN)_2$-

catalyzed intramolecular arylamination with $CuCl_2$ as the oxidant and *p*-$MeOC_6H_4SnBu_3$ as the arylating reagent (Scheme 2.7). There are three major limitations to this methodology: 1) the requirement for arylstannanes containing electron donating substituents, 2) the requirement for a tethered amine (such that C–N bond formation is intramolecular), and 3) an extremely limited scope of unsaturated amides. When $PhSnBu_3$ was used instead of *p*-$MeOC_6H_4SnBu_3$, the authors reported the formation of 1,1-arylchlorination product. Furthermore, to the best of our knowledge, there has not been a report on Pd-catalyzed intermolecular 1,1-arylamination via oxidative interception of Pd(II)-alkyl species to date.

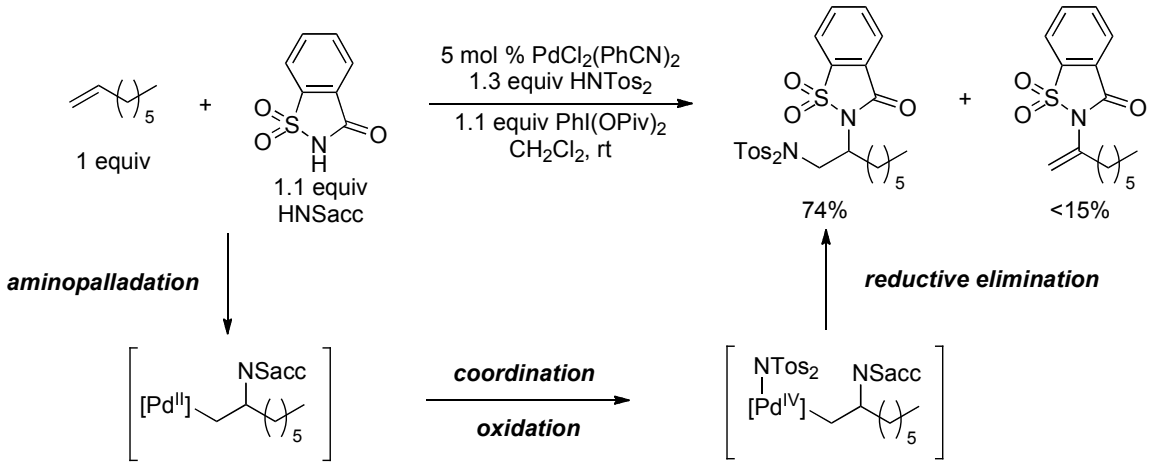


Scheme 2.7. Intramolecular 1,1-Arylamination by Tamaru[4b]

Recently, intra- and intermolecular diamination of alkenes that involves the oxidation of Pd(II)-alkyl intermediates have been developed by Muniz[12] and Michael.[13] For example, intermolecular diamination of 1-octene was shown with saccharin and Ts_2NH utilizing a Pd catalyst and $PhI(OPiv)_2$ oxidant (Scheme 2.8).[12e] The mechanism of this diamination reaction was proposed as follows: 1) aminopalladation of the alkene with saccharin to form the first C–N bond, 2) coordination Ts_2NH and oxidation of Pd by $PhI(OPiv)_2$, and 3) reductive elimination to form the second C–N bond. Surveying the literature, we noticed that the nitrogen source involved in the C–N bond formation from a higher oxidation state Pd species is most frequently a sulfonamide; thus analogous reagents were selected in our initial studies of arylamination.[12,13]

In this chapter, we report the development of Pd-catalyzed 1,1- and 1,2-aryloxygenation of alkenes using arylstannane transmetallating reagents and hypervalent iodine oxidants.[14] Also, this chapter includes the progress we have made in the development of arylamination methodology with the use of

hypervalent iodine oxidants in conjunction with bis-benzene sulfonimide [$HN(PhSO_2)_2$] as a nitrogen source.[15]



Scheme 2.8. Intermolecular Diamination of 1-Octene[12e]

2.2 Results

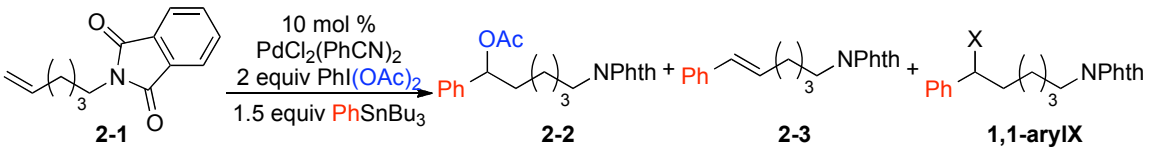
We have developed a selective 1,1-aryloxygenation of various terminal alkenes using a variety of arylstannane reagents and iodobenzene dicarboxylate [$PhI(OCOR)_2$] oxidants. We also developed 1,2-aryloxygenation of activated alkenes such as vinyl ethers. Additionally, we observed that 2,3-dihydrofuran, upon treatment under our standard 1,1-aryloxygenation conditions, provided a 2,5-disubstituted furan as the result of a 1,4-aryloxygenation process. We also explored an alternative three component coupling reaction for aryloxygenation involving replacing the arylstannane reagents with simple arenes. This is a significant advance since it eliminates the requirement for toxic organostannanes. Lastly, we have made considerable progress in the arylamination methodology. We recognized that styrenes can be coupled with aryltin reagents and $HN(PhSO_2)_2$ using iodobenzene dipivalate [$PhI(OPiv)_2$] as the oxidant.

2.2.1 1,1-Aryloxygenation

Hypervalent iodine reagents have been successfully used in Pd-catalyzed oxidative functionalization reactions. In particular, iodobenzene diacetate [$PhI(OAc)_2$] has been shown to oxidatively functionalize Pd(II)-alkyl intermediates

generated in catalytic sp^3 C–H activation, alkene nucleopalladation, and cascade reactions.[16] We hypothesized that $PhI(OAc)_2$ could oxidize Heck intermediates **A** and **B** (Scheme 2.3) in a similar manner leading to olefin aryloxygenation. To this end, in collaboration with Dr. Andrew D. Satterfield, I studied the combination of alkene substrate **2-1**, $PhSnBu_3$, and $PhI(OAc)_2$ in the presence of Pd(II) catalysts. We were pleased to find 10 mol % of $PdCl_2(PhCN)_2$ and 2 equiv of $PhI(OAc)_2$ promoted the formation of 1,1-product **2-2** in 50% yield in Et_2O (Table 2.1, entry 1). The formation of 1,2-product was not observed during the optimization; however, Heck product **2-3** formed in 21% yield under the above conditions.

Table 2.1 Optimization of 1,1-Arylacetoxylation Reaction[a]



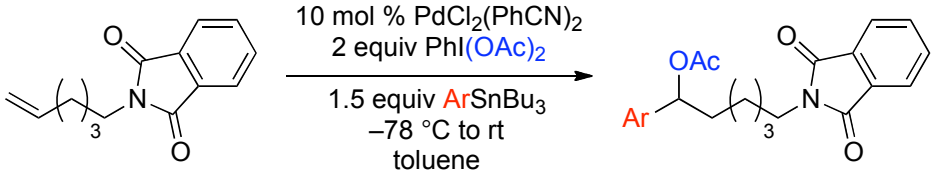
Entry	Solvent	Conditions	**2-2** (%)[b]	**2-3** (%)[b]	1,1-arylX (%)[b]
1	Et_2O	rt	50	21	8(Cl)
2	PhH	rt	21	38	5(Cl)
3	PhMe[c]	rt	22	34	7(Cl)
4	Et_2O	rt, 1 equiv LiBr	59	16	1(Cl), 6(Br)
5	PhH	rt, 1 equiv LiBr	28	35	8(Cl), 6(Br)
6	PhMe	rt, 1 equiv LiBr	35	29	9(Cl), 3(Br)
7	Et_2O	–78 °C to rt	51	13	7(Cl)
8	PhMe	–78 °C to rt	42	29	12(Cl)
9	**PhMe[c]**	**–78 °C to rt**	**61**	**18**	**11(Cl)**
10	PhMe[c]	–78 °C to rt, 1 equiv LiBr	62	12	11(Cl), 4(Br)
11	Et_2O	–78 °C to rt, 1 equiv LiBr	25	7	6(Cl), 17(Br)

[a]In collaboration with Dr. Andrew D. Satterfield. [b]Yields of products determined by ^1H NMR spectroscopic analysis of crude reaction mixture. [c]Degassed toluene used.

We focused on strategies to decrease the formation of **2-3** in order to increase the yield of the desired product **2-2**. The Heck product **2-3** forms when β-hydride elimination takes place at a comparable rate to that of the interception of Pd(II)-alkyl intermediates by $PhI(OAc)_2$. Literature reports have demonstrated the use of LiBr as an additive to suppress β-hydride elimination pathways in other Pd-catalyzed reactions.[17] Therefore, the addition of 1 equiv LiBr was examined in

several solvents (Table 2.1, entries 4-6). Gratifyingly, we observed an increase in the yield of **2-2** to 59% yield in Et_2O at rt along with a concomitant decrease in **2-3** to 16% yield. We also examined the reaction at a lower temperature (entries 7-9) and observed a slight increase (compared to no additive at rt) in **2-2** formation when the reaction was maintained at –78 °C for at least 4 h and allowed to warm up to rt gradually (entries 7-8). Additionally, we found that the use of degassed toluene enhanced the yield of product to 61% (entry 9). However, we did not see a cooperative effect in the reaction with LiBr when cooled to –78 °C (entries 10-11). This may be due to the low solubility of the LiBr additive in toluene at low temperature.

Table 2.2 Scope of Organostannanes[a]



entry	Ar	Product	isolated (crude) yield[b]
1	C_6H_5	**2-2**	66% (66%)[c]
2	2-napthyl	**2-4**	52% (62%)
3	*p*-MeC_6H_4	**2-5**	59% (68%)
4	*p*-$MeOC_6H_4$	**2-6**	75% (78%)
5	*o*-$MeOC_6H_4$	**2-7**	35% (51%)
6	*p*-ClC_6H_4	**2-8**	56% (63%)
7	*p*-BrC_6H_4	**2-9**	50% (57%)
8	*p*-FC_6H_4	**2-10**	49% (56%)

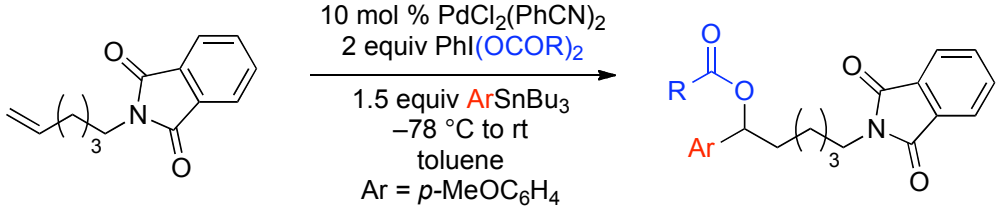
[a]In collaboration with Dr. Andrew D. Satterfield. [b]Crude yields of products determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. In most reactions, the mass balance was the Heck product **2-3** (5-20%) and the 1,1-arylchlorinated product (5-15%). [c]This reaction is scalable and at 1 mmol scale, 68% product was isolated.

With the optimized conditions in hand (Table 2.1, entry 8), we explored the scope of this reaction with respect to arylstannane reagents and iodobenzene dicarboxylate derivatives. First, electronically different organostannanes were examined (Table 2.2). Arylstannane reagents containing both electron donating *para*-substituents (entries 2-4) and electron withdrawing *para*-substituents

(entries 6-8) provided moderate to good yield of products. An arylstannane containing an *ortho*-substituent, on the other hand, reacted poorly (entry 5), which is most likely due to steric effects. The highest product yield was achieved with *p*-$MeOC_6H_4SnBu_3$ (75%, entry 4).

Next, we explored the scope of the iodobenzene dicarboxylates [$PhI(OCOR)_2$]. As shown in Table 2.3, trifluoroacetate, pivalate, and benzoate can also be incorporated using the corresponding hypervalent iodine reagents (entries 1-3). Although the trifluoroacetate product **2-11** was observed in the ^1H NMR spectrum of the crude mixture, the product underwent hydrolysis upon chromatographic purification to yield the free alcohol (**2-11a**). Additionally, benzoates containing both electron donating and withdrawing substituents could be transferred into the product in good yields (entries 4-5).

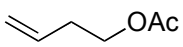
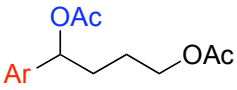
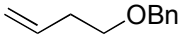
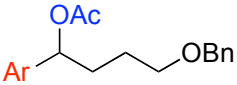
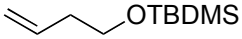
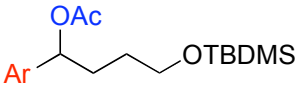
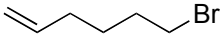
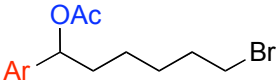
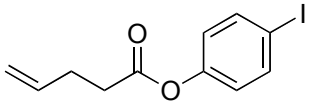
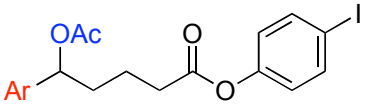
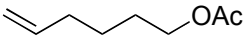
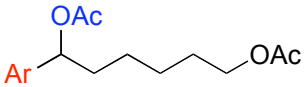
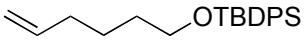
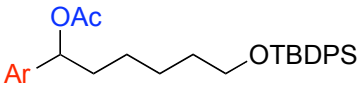
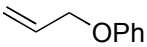
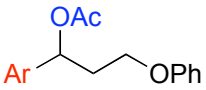
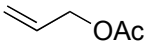
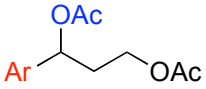
Table 2.3 Scope of Iodobenzene Dicarboxylate[a]



entry	R'	product	isolated (crude) yield[b]
1	CF_3	**2-11**	41% (49%)[c]
2	*t*-Bu	**2-12**	48% (55%)
3	C_6H_5	**2-13**	60% (72%)
4	*p*-$MeOC_6H_4$	**2-14**	53% (52%)
5	*p*-FC_6H_4	**2-15**	68% (73%)

[a]In collaboration with Dr. Andrew D. Satterfield. [b]Crude yields of products determined by ^1H NMR spectroscopic analysis of crude reaction mixture. In most reactions, the mass balance was the Heck product **2-3** (5-20%) and the 1,1-arylchlorinated product (5-15%). [c]Product observed by crude NMR analysis; however, it was hydrolyzed under chromatography conditions and isolated yield is of the hydrolyzed product (**2-11a**).

Table 2.4 Alkene Substrate Scope for 1,1-Arylacetoxylation

entry	substrate	product	isolated (crude) yield[a]
1		 (**2-16**)	62% (64%)
2		 (**2-17**)	61% (62%)
3		 (**2-18**)	47% (54%)
4		 (**2-19**)	53% (61%)
5		 (**2-20**)	64% (67%)
6		 (**2-21**)	67% (72%)
7		 (**2-22**)	62% (62%)
8		 (**2-23**)	64% (71%)
9		 (**2-24**)	58% (69%)

[a]Crude yields of products determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. In most reactions 5-15% of the corresponding Heck product formation was observed along with <5% of the 1,1-arylchlorinated product.

The alkene substrate scope for 1,1-arylacetoxylation was next explored. Terminal olefins containing remote protected alcohol derivatives (Table 2.4, entries 1-3, 6-7), alkyl bromides (entry 4), and aryl iodides (entry 5) all proved to

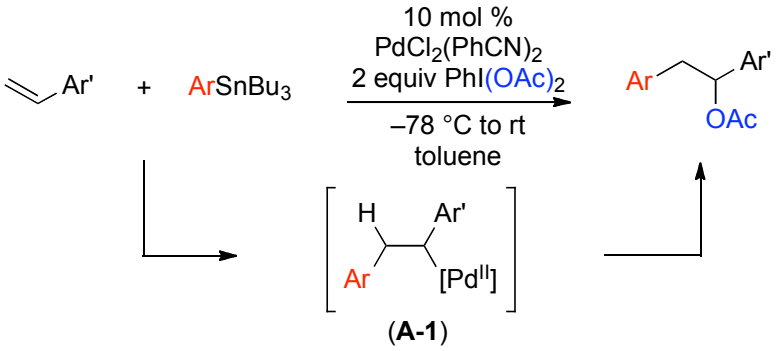
be effective substrates. Additionally, allylic ethers and acetates reacted to give the 1,1-arylacetoxylated products in good to moderate yields (entries 8-9). β-Oxygen elimination is typically a facile process at Pd(II) in the absence of Ag(I) additives;[18,19,20] however, we did not observe such products with allyl acetate or derivatives thereof. All of the substrates shown in Table 2.4 reacted to form products in >20:1 selectivity for the 1,1-arylacetoxylation product (versus 1,2-arylacetoxylation).

The fact that all of the substrates explored thus far selectively formed the 1,1-regioisomer suggests that the oxidative interception of intermediate **A** (Scheme 2.3) with $PhI(OAc)_2$ is much slower than the β-hydride elimination/equilibration to form intermediate **B**. On the basis of these results, we reasoned that Pd(II)-benzyl intermediate **B** is favored in the equilibrium between **A** and **B** and also that **B** is more reactive towards oxidation. The π-benzyl effect on intermediate **B** would account for favoring isomer **B** in the equilibrium. Furthermore, one can suggest that Pd on **B** is more electron rich than Pd on **A** as a result of the delocalized electrons, thus favoring oxidation.[3,21]

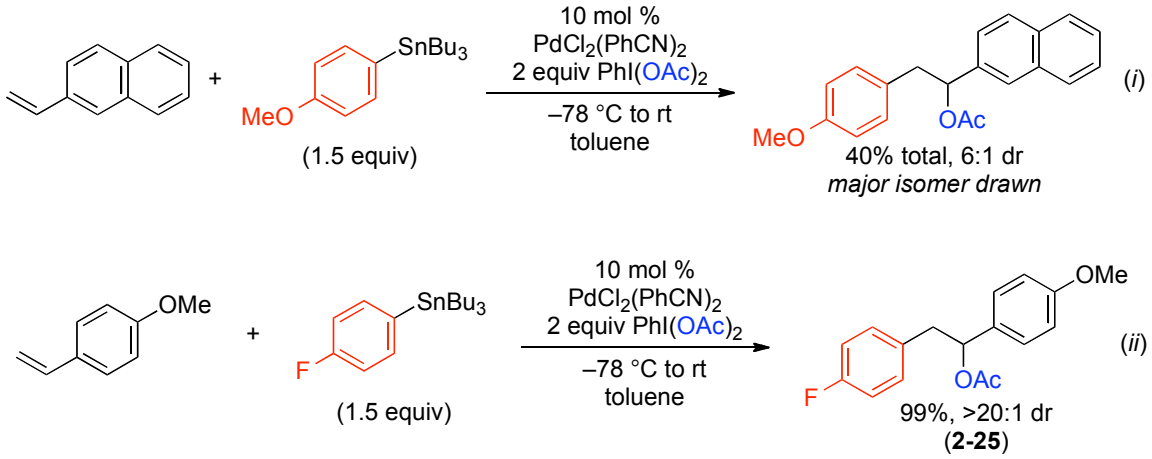
2.2.2 1,2-Aryloxygenation

With the knowledge that π-benzyl Pd(II) intermediates are more reactive towards oxidation, we proposed that 1,2-arylacetoxylation could take place if intermediate **A** (Scheme 2.3) were made to resemble the structure of intermediate **B** (Pd(II)-benzyl complex). One strategy for doing this would be to utilize styrene type substrates, because the initial olefin insertion would lead to a Pd-benzyl intermediate **A-1** (Scheme 2.9). In particular, π-naphtyl Pd(II) complexes are known to be more kinetically reactive than π-benzyl Pd(II) complexes.[3b,6a,22] To this end, we subjected vinylnaphthalene to our optimized conditions and observed a mixture of 1,2- and 1,1-aryacetoxylation products formed in 6:1 ratio (Scheme 2.10, i). In order to gain better selectivity for the 1,2-arylacetoxylation products, we used *p*-methoxystyrene and *p*-fluorophenyl tributyltin. Gratifyingly, with the above combination of substrate and organostannane, we observed the 1,2-product (**2-25**) in >20:1 regioselectivity

(Scheme 2.10, ii). The combination of these reagents were utilized because styrene with electron rich substituent would further favor intermediate **A** and also arylstannane reagent with electron deficient substituent would facilitate the oxidation, thus trapping the favored intermediate **A** much more efficiently.



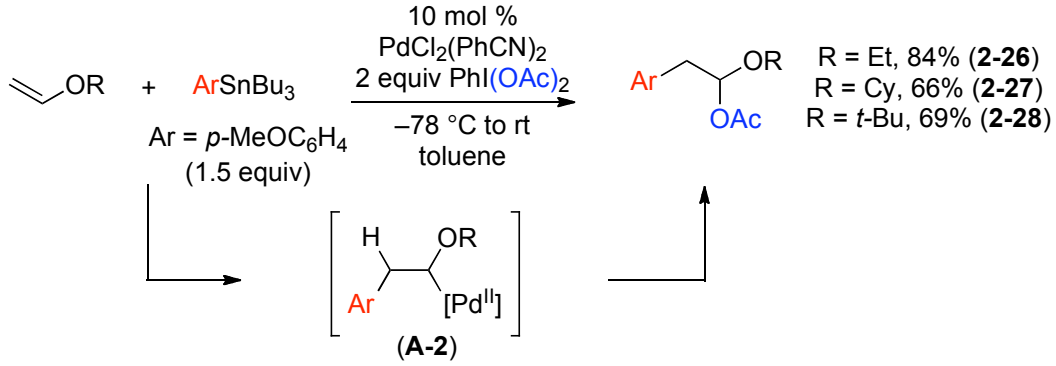
Scheme 2.9. Strategy for 1,2-Arylacetoxylation



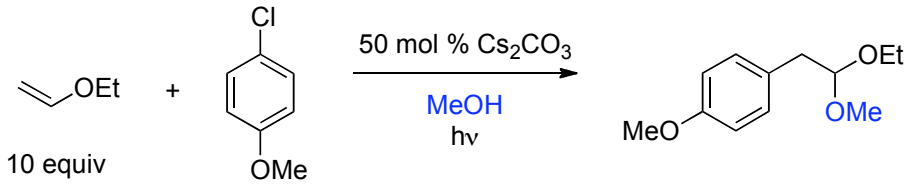
Scheme 2.10. Arylacetoxylation with Vinylnaphthalene and Styrene Derivative

Vinyl ethers were also studied for the 1,2-arylacetoxylation reaction because we hypothesized that the ethereal oxygen would have an electron donating influence on the 2nd carbon making the intermediate **A-2** (Scheme 2.11) more reactive for direct oxidation. As expected, the use of ethyl, cyclohexyl, and *tert*-butyl vinyl ethers under the optimized conditions afforded the 1,2-arylacetoxylated products selectively in good yields. Using our methodology, 1,2-arylacetoxylation can only be achieved with biased alkene substrates. Notably photoinduced pathways have been reported in the literature for 1,2-aryloxygenation of alkenes (Scheme 2.12).[23] In these transformations, irradiation of the aryl halide produces aryl cations, which then react with alkenes to form

oxonium ions. The resulting oxonium ions are then attacked by methanol to yield the 1,2-arylmethoxy product.

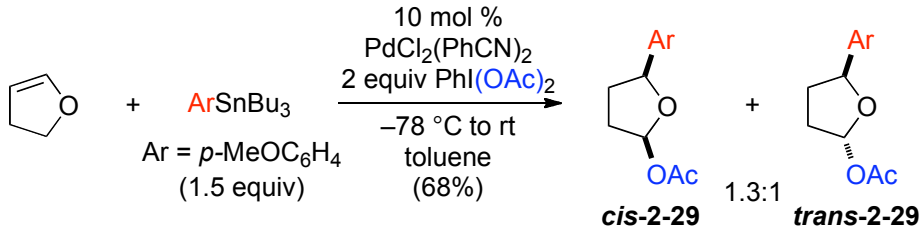


Scheme 2.11. 1,2-Arylacetoxylation of Vinyl Ethers



Scheme 2.12. 1,2-Arylacetoxylation via Photoinduced Pathway[23b]

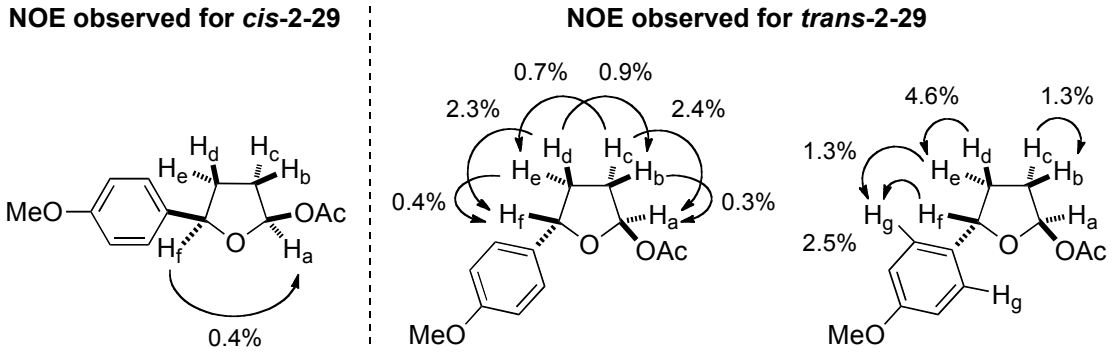
2.2.2 1,4-Aryloxygenation



Scheme 2.13. 1,4-Arylacetoxylation of 2,3-Dihydrofuran

While exploring the alkene substrate scope, we discovered that 2,3-dihydrofuran also reacts under these conditions. However, interestingly this substrate produced 1,4-acetoxylated product **2-29** in 68% yield as a mixture of *cis*/*trans* isomers (Scheme 2.13). As we learned from the vinyl ether substrates, an oxygen atom can make an adjacent Pd(II) species more reactive for oxidation. We propose that after the first olefin insertion, the Pd(II) migrates to the 5-position of the ring through a series of β-H elimination/Pd–H reinsertions. A solvent study revealed that in THF the *cis*-product was more favored (2.5:1, *cis*:*trans*) with the

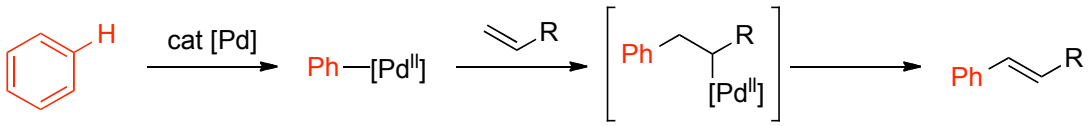
combined yield of 60%. The *cis* and *trans* products were assigned via a series of NOE studies (Scheme 2.14).



Scheme 2.14. NOE Study for the Confirmation of Product Geometry

2.2.4 One-Pot 1,1-Aryloxygenation via C–H Activation

Despite the fact that the three-component coupling methodology we developed for the aryloxygenation of alkenes provides a very simple route to products such as **2-2** to **2-24**, we recognize that one of its key limitations is the requirement for toxic tin reagents. Thus, this methodology would be even more attractive if we could use simple C–H substrates like benzene in place of organostannanes as the aryl group source. In this case, Heck intermediate **A** (Scheme 2.3) could be generated by C–H activation of Ph–H followed by migratory insertion of the alkene. These steps are the first two steps of the Fujiwara-Moritani (F-M) reaction for the olefination with benzene (Scheme 2.15).[2b,7] Therefore, we set out to find conditions that would allow aryloxygenation of an olefin using benzene as the arene source.

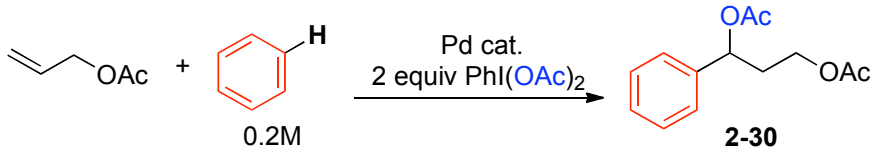


Scheme 2.15. Fujiwara-Moritani Reaction

We chose allyl acetate as the olefin substrate and first examined the reaction with benzene and $PhI(OAc)_2$ in the presence of 10 mol % of $PdCl_2(PhCN)_2$ (the optimal catalyst for arylacetoxylation with organostannanes). As shown in Table 2.5, the use of $PdCl_2(PhCN)_2$ resulted in only 5% yield of 1,1-

arylacetoxylation product at 80 °C (entry 1). Switching the catalyst to $Pd(acac)_2$ afforded an increased yield of the product (38%, entry 2). Also, lowering the temperature to 60 °C and catalyst loading to 5 mol % slightly enhanced the yield of the desired product (entry 3). Finally, examination of substoichiometric amounts of Ag additives led us to identify 0.1 equiv of AgOAc as an additive that improved the yield of **2-30** to 51% (entry 4-5).

Table 2.5 Optimization of Phenylacetoxylation of Allyl Acetate with Benzene



entry	Pd cat.	T (°C)	Additive	yield[a]
1	10 mol % $PdCl_2(PhCN)_2$	80	none	5%
2	10 mol % $Pd(acac)_2$	100	none	38%
3	5 mol % $Pd(acac)_2$	60	none	41%
4	5 mol % $Pd(acac)_2$	60	0.1 equiv Ag_2CO_3	42%
5	5 mol % $Pd(acac)_2$	60	0.1 equiv AgOAc	51%

[a] Product yields are determined by ^1H NMR spectroscopic analysis of crude reaction mixture.

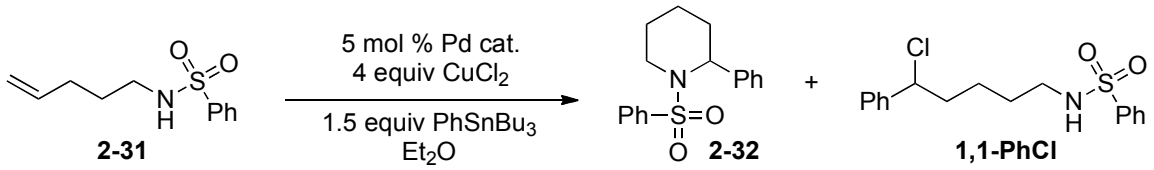
While the C–H activation reaction is still not optimal, this transformation shows that using simple arenes in place of toxic transmetallating reagents is a viable pathway. The use of allyl acetate is particularly interesting because in the F-M reaction, electron rich or neutral α-olefins are typically challenging to functionalize.[24] The challenges associated with F-M reaction will be discussed in greater detail in Chapter 3.

2.2.5 Arylamination

In a similar fashion to the Pd-catalyzed 1,1- and 1,2-aryloxygenation of alkenes developed with hypervalent iodine oxidants and arylstannanes, we were interested in studying the corresponding arylamination reaction to expand our methodology. We first chose to start with Tamaru's system (Scheme 2.7) and address some of the limitations, such as the inability to utilize electron neutral or

electron deficient organostannane reagents.[4b] Secondly, we were interested in achieving intramolecular arylamination using hypervalent iodine oxidants. Lastly, we wanted to show that the intermolecular arylamination of olefins is feasible as proposed.

Table 2.6 Optimization 1,1-Arylamination with **2-31**



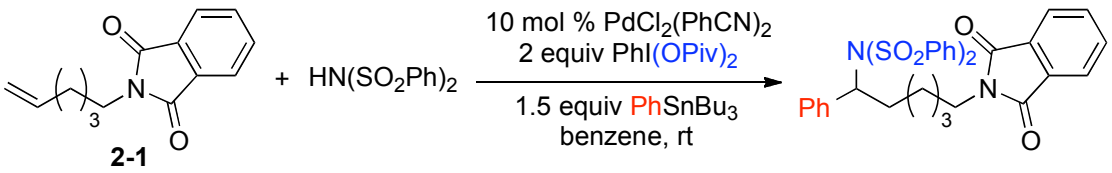
entry	Pd cat.	T (°C)	Additive	2-32[a]	1,1-PhCl[a]
1	$PdCl_2(PhCN)_2$	0 to rt	none	17%	~37%
2	$PdCl_2(PhCN)_2$	0 to rt	2 equiv Ag_2CO_3	5%	42%
3	$Pd(OAc)_2$	0 to rt	2 equiv Ag_2CO_3	21%	20%
4[b]	$Pd(TFA)_2$	0 to rt	2 equiv Ag_2CO_3	25%	<5%
5[b]	$Pd(TFA)_2$	–78 to rt	2 equiv Ag_2CO_3	33%	<5%

[a]Product yields are determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [b]3 equiv $CuCl_2$ used.

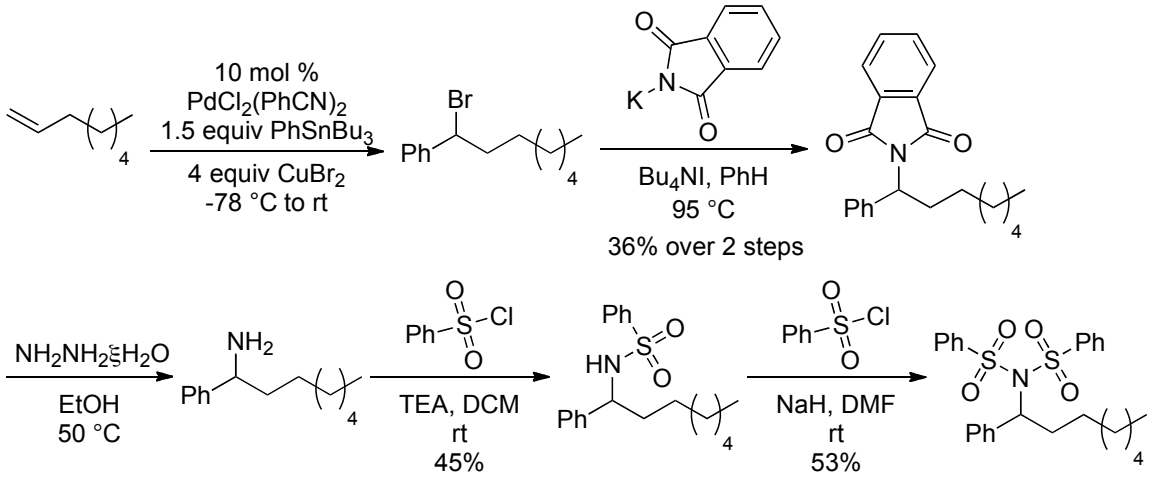
To broaden the scope of Tamaru's reaction, we first examined the intramolecular arylamination of substrate **2-31** with $PhSnBu_3$ and $CuCl_2$.[4b] Under the reported conditions, we observed 17% yield of the desired product **2-32** along with ~37% yield of the corresponding 1,1-arylchlorination product (Table 2.6, entry 1). In order to limit the formation of the halogenated product, we looked into adding Ag salts because the precipitation of AgCl could prevent chlorides from becoming ligands for Pd. Adding 2 equiv of Ag_2CO_3 to the $PdCl_2(PhCN)_2$ conditions resulted in lowered product yields (entry 2). However, with $Pd(OAc)_2$ as the catalyst a slight increase in product yield and a significant decrease in the 1,1-arylchlorination byproduct (to 20% yield) was observed (entry 3). Examination of other Pd catalysts led to identify $Pd(TFA)_2$ as a compatible catalyst as well affording 25% yield of the desired product with 3 equiv of $CuCl_2$ (entry 4). Furthermore, when the reaction was cooled to –78 °C for at least 4 h before it was slowly warmed up to room temperature the yield of **2-32** increased

to 33% (entry 5). Further optimization of this reaction is still ongoing, and we hope to be able to increase the yield of **2-32** even more. Notably, we also looked at achieving arylamination of **2-31** using hypervalent iodine oxidants (instead of $CuCl_2$). However, our attempts so far (using comparable conditions/additives to the reactions shown in Table 2.6) have not yielded quantifiable amounts of **2-32**.

In our attempt to develop intermolecular arylaminations of terminal alkenes, we first used substrate **2-1** and very similar conditions to the ones we developed for the arylacetoxylation transformation. Bis-benzene sulfonimide [$HN(SO_2Ph)_2$] was selected as the amine source, since literature precedent pointed towards the effectiveness of sulfonamides derivatives in related Pd-catalyzed alkene diamination reactions (Scheme 2.8).[12,13] As shown in Scheme 2.16, under the reaction conditions with $PhI(OPiv)_2$ as the oxidant we observed ~5% yield of the desired 1,1-arylamination product in benzene. Although the yield was extremely low for this initial study, we were delighted that the intermolecular arylamination could occur via this approach. The product was determined to be 1,1-arylamination product (versus 1,2-arylamination) by comparison to independently synthesized sample of an analogous product derived from 1-octene (Scheme 2.17). This material was accessed via 1,1-phenylbromination of 1-octene[3] followed by S_N2 substitution of bromide with phthalamide. The phthalyl group was then reduced to the free amine, and the nitrogen was sequentially protected with two benzene sulfonamide groups. A diagnostic proton, alpha to both the phenyl and the nitrogen groups appeared as a doublet of doublets at 5.35 ppm in $CDCl_3$ by ^1H NMR spectroscopic analysis. The 1,1-arylamination product of **3-1** showed a very similar peak at 5.3 ppm in the ^1H NMR spectrum or crude reaction mitxture.



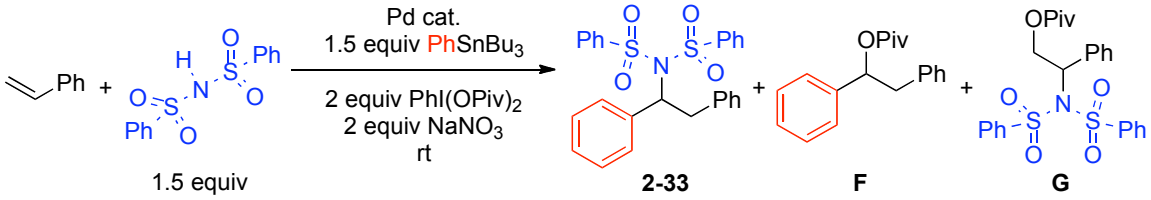
Scheme 2.16. Initial Study for Arylamination of Alkenes



Scheme 2.17. Synthesis of 1,1-Arylamination Product of 1-Octene

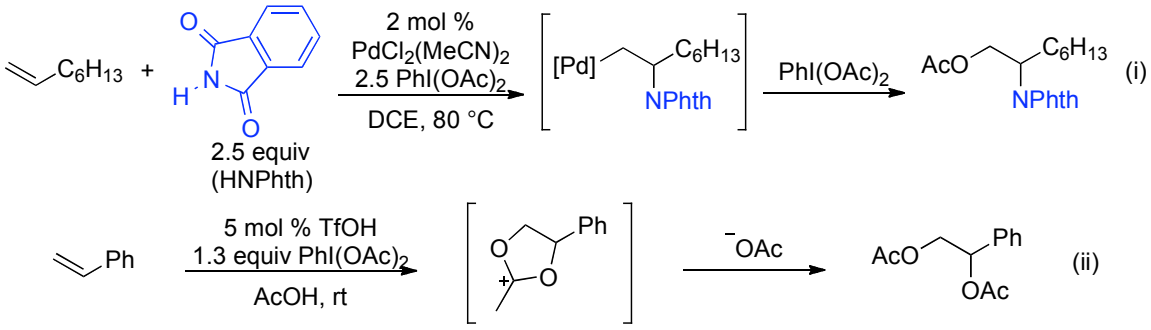
In order to optimize the arylamination reaction, we moved to styrene as the alkene substrate and $PhSnBu_3$ as the arylstannane reagent. The combination of these reagents would afford only one set of arylamination products whether it formed via 1,1- or 1,2-pathways. Furthermore, in the arylacetoxylation reaction discussed above, we showed that styrene makes the initial Pd(II)-alkyl intermediate **A** (Scheme 2.3) more reactive, therefore, we thought styrene would be a good substrate to begin our optimization. After screening various additives in hopes of obtaining a higher yield of our desired product, we discovered that the use of 2 equiv of $NaNO_3$ as a co-oxidant provided 32% yield of arylamination product **2-33** (Table 2.7, entry 1). The major byproducts in this reaction were found to be compounds **F** and **G**. Byproduct **F** is formed via a 1,1-aryloxygenation reaction as discussed earlier in this chapter, where the pivalate group comes from the oxidant $PhI(OPiv)_2$. Based on literature precedent, we can suggest few different routes in which byproduct **G** can be formed.[12c,25,26,27] One possibility is aminopalladation of the styrene followed by oxidation of Pd with $PhI(OPiv)_2$ and reductive elimination to form C–O bond (Scheme 2.18, i).[12c,25] A second possibility is the formation of 5-member cyclic intermediate as a result of a reaction between the alkene and $PhI(OAc)_2$ which is then opened by a nucleophile, in our case the nitrogen group (Scheme 2.18, ii).[26] Notably, **G** also formed in a background reaction in the absence of Pd catalyst.

Table 2.7 Optimization Arylamination with Styrene



entry	Pd cat.	Solvent	2-33[a]	F[a]	G[a]
1	10 mol % $PdCl_2(PhCN)_2$	PhH	32%	16%	nd
2	10 mol % $Pd(OAc)_2$	PhH	35%	18%	18%
3[b]	5 mol % $Pd(OAc)_2$	PhH	42%	19%	15%
4[b,c]	5 mol % $Pd(OAc)_2$	N_2 sparged PhH	45%	15%	11%
5	5 mol % $Pd(OAc)_2$	dry PhMe	49%	25%	7%

[a]Product yields are determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [b] 1.5 equiv of PhI(OPiv)2 used. [b]3 equiv $NaNO_3$ used. nd = not detected



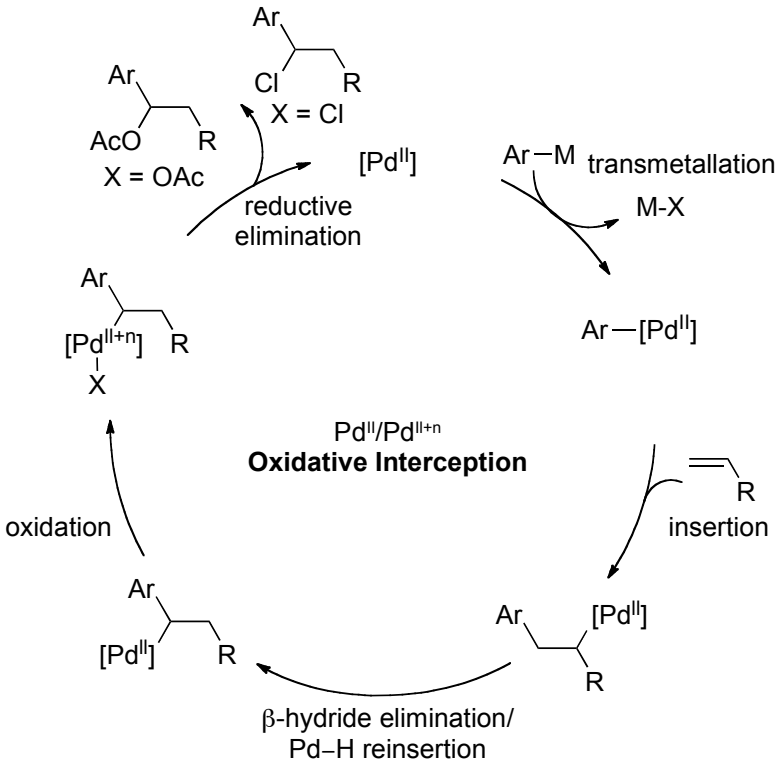
Scheme 2.18. Literature Precedent for Aminooxygenation of Alkene using Hypervalent Iodine Oxidant[25,26]

During the course of the optimization process, we identified $Pd(OAc)_2$ as a better catalyst choice, as it is commercially available and gives cleaner reactions. Lowering the catalyst loading to 5 mol % improved the product yield to 42% (Table 2.6, entry 3). Furthermore, the use of N_2–sparged benzene and dry toluene as solvent resulted in even higher yields of **2-33** at 45% and 49%, respectively (entries 4-5). Extensive oxidant screens were carried out, but so far, $PhI(OPiv)_2$ appears to be optimal despite the formation of byproducts **F** and **G**. While both the intra- and intermolecular arylamination reported in this section will

require further optimization, we were delighted to demonstrate the proof of concept of these transformations.

2.3 Discussion

Pd(II)-alkyl species such as Heck-type intermediates (**A** and **B**, Scheme 2.3) can be intercepted by oxidants for further functionalization. We have utilized this methodology to develop a three component coupling reaction of olefins, arylstannane reagents, and a third component (derived from either the oxidant or an external amine source). When Pd(II)-alkyl intermediates are oxidatively intercepted by hypervalent iodine oxidants, they presumably react to form a higher oxidation state Pd intermediates.[28,29] From these higher oxidation state Pd complexes, reductive elimination allows for the second bond formation (Scheme 2.19, X = OAc). Depending on the oxidant, solvent, and other variables of the reaction conditions the ligands on the higher oxidation state Pd complex will vary. This can result in byproduct formation as other ligands may undergo reductive elimination to form a new bond with the substrate. For example, during the optimization of the 1,1-arylacetoxylation reaction, we observed a fair amount of the 1,1-arylchlorination product (Table 2.1). This byproduct is a result of C–Cl reductive elimination that took place competitively with the desired C–OAc reductive elimination (Scheme 2.19, X = Cl). In the arylacetoxylation case, the Cl ligand was derived from the starting Pd catalyst. These results show that it is important keep in mind what kind of X-type ligands are present in the system in order to tune the conditions to obtain the highest amount of the desired product.



Scheme 2.19 Proposed Mechanism for 1,1-Arylacetoxylation

The selective formation of 1,1-aryloxygenation product can be explained by the Pd(II)-alkyl intermediate equilibrium favoring **B** because **B**, being more electron rich than **A** at the Pd center, is activated towards oxidation (Scheme 2.3). In the past, 1,1- and 1,2- arylhalogenation were selectively achieved by differentiating the reaction conditions through appropriate selection of oxidant or solvent (Scheme 2.4).[3] However, in the aryloxygenation reaction, we were not successful at making intermediate **A** more reactive toward oxidation by tuning reaction conditions. As such, 1,2-arylacetoxylation was only observed when activated alkenes such as styrene derivatives and vinyl ethers were utilized. If 1,2-aryloxygenation could be developed selectively for unactivated terminal alkenes, it would complement the methodology reported in this chapter.

One of the drawbacks of our alkene difunctionalization methodology is the use of toxic organostannane reagents. We were able to address this concern by showing that benzene could be used as the arylating reagent in place of arylstannanes (Table 2.4). Although this was not completely optimized, our

results with allyl acetate under C–H activation conditions give support that this alternative pathway could be optimized for a methodology utilizing less toxic reagents. The main challenge for the development of this methodology moving forward would be controlling the selectivity of C–H activation when substituted arenes are used. Our efforts towards improving the olefination of arenes (Fujiwara-Moritani reaction) will be discussed in Chapter 3.

Lastly, we were able to extend our alkene difunctionalization methodology to arylamination. For the arylamination, instead of using an oxidant that contained the amine moiety for functionalization, we examined the combination of an external amine source and hypervalent iodine oxidants. Using $PhI(OPiv)_2$ as the oxidant and $HN(SO_2Ph)_2$ as the amine source, the arylamination of styrene was demonstrated using $Pd(OAc)_2$ as the catalyst (Table 3.5). Further optimization will be necessary in order to make the arylamination a practical and high yielding method. However, our preliminary results show that it is possible to achieve this transformation.

2.4 Conclusions

In conclusion, this chapter describes the Pd-catalyzed 1,1-aryloxygenation of a variety of α-olefins using arylstannanes and hypervalent iodine oxidants. Also, we have shown 1,2-arylacetoxylation of activated substrates such as styrenes and vinyl ethers. We have demonstrated the 1,1-arylacetoxylation of allyl acetate by replacing $PhSnBu_3$ with benzene through C–H activation pathways. Finally, we have made significant progress on the intermolecular arylamination of styrene with $NaNO_3$ as a co-oxidant.

2.5 Experimental

NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^1H; 125.70 MHz for ^{13}C), a Varian Inova 400 (399.96 MHz for ^1H; 100.57 MHz for ^{13}C; 376.34 MHz for ^{19}F), or a MR400 (400.53 MHz for ^1H: 376.87 MHz for ^{19}F; 100.71 MHz for ^{13}C) spectrometer. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as

an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer.

Alkene Substrates: Unless otherwise noted, alkene substrates were obtained from commercial sources and used as received.

Stannanes: *p*-$ClC_6H_4SnBu_3$,[30] 2-naphthylSnBu_3,[30] and $PdCl_2(PhCN)_2$[31] were prepared using literature procedures. The stannanes *p*-$CH_3C_6H_4SnBu_3$, *p*-$CH_3OC_6H_4SnBu_3$, *o*-$CH_3OC_6H_4SnBu_3$, *p*-$BrC_6H_4SnBu_3$, and *p*-$FC_6H_4SnBu_3$ were prepared via modification of a literature procedure.[30] $PhSnBu_3$ was obtained from Aldrich and used as received.

Aryliodonium salts: $PhI(OAc)_2$ was obtained from AK Scientific and used as received. $PhI(OPiv)_2$, $PhI(O_2CAr)_2$ (Ar = *p*-$MeOC_6H_4$ and *p*-FC_6H_4) were prepared via a literature procedure.[32]

Other reagents, catalysts, and solvents. $Pd(acac)_2$ and AgOAc were obtained from Acros and used as received. Et_2O and benzene were obtained from Fisher and used without further purification. Toluene was purified using an Innovative Technology (IT) solvent purification system composed of activated alumina, copper catalyst, and molecular sieves. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh), and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F254. HPLC was performed on a Varian ProStar 210 HPLC using Waters SunFire Prep Silica 5µm (10 x 150 mm) column.

2.6 Characterization

General Procedure A for Arylacetoxylation Reactions:
$PdCl_2(PhCN)_2$ (10 mol %) and $PhI(OAc)_2$ (2 equiv) were weighed into a 4 mL scintillation vial. The vial was sealed with a rubber septum and purged with N_2. Degassed toluene (1.4 mL) was added via syringe. The resulting mixture was cooled to –78 °C, and the olefin substrate (1.0 equiv, 0.044 mmol) and stannane

(1.5 equiv) were sequentially added using a microsyringe. The vial was quickly sealed with a Teflon-lined cap, and the reaction mixture was stirred overnight as it gradually warmed up to room temperature. The crude reaction mixture was filtered through a pad of Celite, and the Celite was washed with Et_2O (5 mL). The solvent was removed under vacuum, NO_2Ph (0.25 equiv, ^1H NMR resonance at 8.2 ppm) or 1,3-dinitrobenzene (0.25 equiv, ^1H NMR resonance at 9.1 ppm) was added as an internal standard, and the crude mixture was analyzed by ^1H NMR spectroscopy. The products were purified by flash chromatography on silica gel.

General Procedure B for Arylacetoxylation Reactions:
$PdCl_2(PhCN)_2$ (10 mol %) and $PhI(O_2CR)_2$ (2 equiv) were weighed into a 4 mL scintillation vial. The vial was sealed with a rubber septum and purged with N_2. Degassed toluene (0.7 mL) was added via syringe. The resulting mixture was cooled to –78 °C, and the olefin substrate (1.0 equiv, 0.044 mmol) was added via cannula transfer (0.7 mL toluene). $ArSnBu_3$ (1.5 equiv) was the added dropwise by microsyringe. The vial was quickly sealed with a Teflon-lined cap, and the reaction mixture was stirred overnight as it gradually warmed up to room temperature. The crude reaction mixture was filtered through a pad of Celite, and the Celite was washed with Et_2O (5 mL). The solvent was removed under vacuum, NO_2Ph (0.25 equiv) or 1,3-dinitrobenzene (0.25 equiv) was added as an internal standard, and the crude mixture was analyzed by ^1H NMR spectroscopy. The products were then purified by flash chromatography on silica gel.

6-(1,3-Dioxoisoindolin-2-yl)-1-phenylhexyl acetate (**2-2**)

Product **2-2** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (8.4 mg, 0.022 mmol, 10 mol %), $PhI(OAc)_2$ (140 mg, 0.44 mmol, 2 equiv), **2-1**[33] (50 mg, 0.22 mmol, 1 equiv), $PhSnBu_3$ (107 µL, 0.33 mmol, 1.5 equiv), and degassed toluene (6.8 mL). ^1H NMR analysis of the crude reaction mixture showed a 66% yield of **2-2** along with 17% of the Heck product (**2-3**). Compound **2-2** was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% NEt_3 and was isolated as a clear oil (55 mg, 66% yield, 93% purity, R_f = 0.12 in 90% hexanes/10% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (m, 2H), 7.72 (m, 2H), 7.36-7.23 (multiple peaks, 5H), 5.71 (dd, *J* = 7.6, 6.1 Hz, 1H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.07 (s, 3H), 1.91 (m, 1H), 1.78 (m, 1H), 1.66 (m, 2H), 1.43-1.31 (multiple peaks, 3H), 1.27 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 168.4, 140.6, 133.8, 132.1, 128.5, 128.4, 127.8, 126.5, 123.1, 37.9, 36.1, 28.4, 26.6, 25.1, 21.3. IR (neat film): 1772, 1733, 1708 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{22}H_{23}NO_4$, 388.1525; found, 388.1536.

6-(1,3-Dioxoisoindolin-2-yl)-1-(naphthalen-2-yl)hexyl acetate (**2-4**)

Product **2-4** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(OAc)_2$ (112 mg, 0.35 mmol, 2 equiv), **2-1**[33] (40 mg, 0.17 mmol, 1 equiv), 2-napthylSnBu_3 (94 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 62% yield of **2-4** along with 18% of the Heck product. Compound **2-4** was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% NEt_3 and was isolated as a clear oil (38 mg, 52% yield, 96% purity, R_f = 0.15 in 90% hexanes/10% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86-7.80 (multiple peaks, 5H), 7.77 (s, 1H), 7.72 (m, 2H), 7.51-7.43 (multiple peaks, 3H), 5.88 (t, *J* = 7.0 Hz, 1H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.99 (m, 1H), 1.88 (m, 1H), 1.66 (m, 2H), 1.46-1.35 (multiple peaks, 3H), 1.30 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 168.4, 137.9, 133.8, 133.1, 133.0, 132.1, 128.3, 128.0, 127.6, 126.1, 126.0, 125.7, 124.3, 123.1, 76.1, 37.9, 36.0, 28.4, 26.6, 25.1, 21.3. IR (neat film): 1772, 1734, 1709 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{26}H_{25}NO_4$, 438.1681; found, 438.1675.

6-(1,3-Dioxoisoindolin-2-yl)-1-(p-tolyl)hexyl acetate (**2-5**)

Product **2-5** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(OAc)_2$ (112 mg, 0.35 mmol, 2 equiv), **2-5**[33] (40 mg, 0.17 mmol, 1 equiv), *p*-$CH_3C_6H_4SnBu_3$ (89 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 58% yield of **2-5** along with 7% of the Heck product. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (39 mg, 59% yield, 94% purity, R_f = 0.28 in 75% hexanes/25% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.19 (m, 2H), 7.13 (m, 2H), 5.66 (t, *J* = 7.0 Hz, 1H), 3.64 (t, *J* = 10.0 Hz, 2H), 2.32 (s, 3H), 2.04 (s, 3H), 1.87 (m, 1H), 1.74 (m, 1H), 1.65 (m, 2H), 1.39-1.30 (multiple peaks, 3H), 1.26 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 168.4, 137.6, 137.6, 133.8, 132.1, 129.1, 126.5, 123.1, 75.9, 37.9, 36.0, 28.4, 26.6, 25.1, 21.3, 21.1. IR (neat film): 1772, 1734, 1710 $^{-1}$. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{23}H_{25}NO_4$, 402.1681; found, 402.1677.

6-(1,3-Dioxoisoindolin-2-yl)-1-(4-methoxyphenyl)hexyl acetate (**2-6**)

Product **2-6** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (1.7 mg, 0.004 mmol, 10 mol %), $PhI(OAc)_2$ (28 mg, 0.087 mmol, 2 equiv), **2-1**[33] (10 mg, 0.044 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (22 µL, 0.065 mmol, 1.5 equiv), and degassed toluene (1.4 mL). ^{1}H NMR analysis of the crude reaction mixture

showed a 81% yield of **2-6** along with 7% of the Heck product. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (13 mg, 75% yield, R_f = 0.21 in 80% hexanes/20% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.24 (m, 2H), 6.85 (m, 2H), 5.65 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.65 (t, *J* = 7.2 Hz, 2H), 2.03 (s, 3H), 1.88 (m, 1H), 1.74 (m, 1H), 1.64 (m, 2H), 1.39-1.20 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 168.4, 159.2, 133.8, 132.7, 132.1, 127.9, 123.1, 113.8, 75.7, 55.2, 37.9, 35.9, 28.4, 26.6, 25.1, 21.3. IR (neat film): 1772, 1733, 1709 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{23}H_{25}NO_5$, 418.1630; found, 418.1617.

6-(1,3-Dioxoisoindolin-2-yl)-1-(2-methoxyphenyl)hexyl acetate (**2-7**)

Product **2-7** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(OAc)_2$ (112 mg, 0.35 mmol, 2 equiv), **2-1**[33] (40 mg, 0.17 mmol, 1 equiv), *o*-$MeOC_6H_4SnBu_3$ (92 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 51% yield of **2-7** along with 17% of the Heck product. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (24 mg, 35% yield, R_f = 0.20 in 70% hexanes/30% EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.27 (m, 1H), 7.21 (m, 1H), 6.92 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.14 (dd, *J* = 7.1, 5.9 Hz, 1H), 3.82 (s, 3H), 3.65 (t, *J* = 7.3 Hz, 2H), 2.06 (s, 3H), 1.78 (m, 2H), 1.65 (t, *J* = 6.8 Hz, 2H), 1.42-1.29 (multiple peaks, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.2, 168.4, 156.1, 133.8, 132.1, 129.5, 128.4, 126.1, 123.1, 120.5, 110.5, 70.3, 55.4, 38.0, 35.2, 28.5, 26.6, 25.0, 21.3. IR (neat film): 1772, 1735, 1709 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{23}H_{25}NO_5$, 418.1630; found, 418.1625.

1-(4-Chlorophenyl)-6-(1,3-dioxoisoindolin-2-yl)hexyl acetate (**2-8**)

Product **2-8** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(OAc)_2$ (112 mg, 0.35 mmol, 2 equiv), **2-1**[33] (40 mg, 0.17 mmol, 1 equiv), *p*-$ClC_6H_4SnBu_3$ (89 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 63% yield of **2-8** along with 19% of the Heck product. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (39 mg, 56% yield, 90% purity, R_f = 0.56 in 70% hexanes/30% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.70 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.29 (m, 2H), 7.23 (m, 2H), 5.65 (dd, *J* = 7.3, 6.4 Hz, 1H), 3.65 (t, *J* = 7.3 Hz, 2H), 2.04 (s, 3H), 1.88 (m, 1H), 1.76-1.59 (multiple peaks, 3H), 1.41-1.19 (multiple peaks, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.2, 168.4, 139.2, 133.9, 133.6, 132.1, 128.6, 127.9, 123.2, 75.2, 37.8, 36.0, 28.4, 26.5, 25.0, 21.2. IR (neat film): 1773, 1737, 1710 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{22}H_{22}ClNO_4$, 422.1135; found, 422.1134.

1-(4-Bromophenyl)-6-(1,3-dioxoisoindolin-2-yl)hexyl acetate (**2-9**)

Product **2-9** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(OAc)_2$ (112 mg, 0.35 mmol, 2 equiv), **2-1**[33] (40 mg, 0.17 mmol, 1 equiv), *p*-$BrPhSnBu_3$ (89 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 48% yield of **2-9** along with 15% of the Heck product. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (39 mg, 50% yield, 95% purity, R_f = 0.29 in 80% hexanes/20% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (500 MHz): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.44 (m, 2H), 7.18 (m, 2H), 5.63 (t, *J* = 6.8 Hz, 1H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.05 (s, 3H), 1.87 (m, 1H), 1.71 (ddd, *J* = 13.8, 9.7, 5.9 Hz, 1H), 1.64 (m, 2H), 1.41-1.30 (multiple peaks, 3H), 1.25 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.25, 168.41, 139.69, 133.88, 132.10, 131.56, 128.22, 123.17, 121.73, 75.27, 37.80, 35.93, 28.35, 26.51, 24.95, 21.19. IR (neat film): 1771, 1735, 1708 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{22}H_{22}BrNO_4$, 466.0630; found, 466.0638.

6-(1,3-Dioxoisoindolin-2-yl)-1-(4-fluorophenyl)hexyl acetate (**2-10**)

Product **2-10** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(OAc)_2$ (112 mg, 0.35 mmol, 2 equiv), **2-1**[33] (40 mg, 0.17 mmol, 1 equiv), *p*-$FC_6H_4SnBu_3$ (86 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 56% yield of **2-10** along with 22% of the Heck product. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (33 mg, 49% yield, 93% purity, R_f = 0.5 in 70% hexanes/30% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.27 (m, 2H), 7.00 (m, 2H), 5.66 (t, *J* = 5.0 Hz, 1H), 3.64 (t, *J* = 7.3 Hz, 2H), 2.04 (s, 3H), 1.88 (m, 1H), 1.77-1.60 (multiple peaks, 3H), 1.40-1.19 (multiple peaks, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.27, 168.39, 162.26 (d, $^1J_{CF}$ = 246.5 Hz), 136.43 (d, $^4J_{CF}$ = 3.4 Hz), 133.86, 132.09, 128.24 (d, $^3J_{CF}$ = 7.8 Hz), 123.11, 115.27 (d, $^2J_{CF}$ = 21.1

Hz), 75.27, 37.82, 36.02, 28.36, 26.52, 25.02, 21.21. ^{19}F NMR (471 MHz, $CDCl_3$): δ –115.09 to –113.79 (m). IR (neat film): 1773, 1736, 1710 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{22}H_{22}FNO_4$, 406.1431; found, 406.1437.

2-(6-Hydroxy-6-(4-methoxyphenyl)hexyl)isoindoline-1,3-dione (**2-11a**)

Product **2-11a** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(O_2CCF_3)_2$ (150 mg, 0.35 mmol, 2 equiv), **2-1**[33] (40 mg, 0.17 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (90 µL, 0.26 mmol, 1.5 equiv), and toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 43% yield of **2-11** along with 7% of the Heck product. The product was purified by chromatography on silica gel using 80% hexanes/18% EtOAc/2% Et_3N and was isolated as a clear oil (25 mg, 41% yield, 92% purity, R_f = 0.10 in 80% hexanes/20% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (80% hexanes/20% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (m, 2H), 7.70 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.60 (t, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.66 (t, *J* = 6.8 Hz, 2H), 1.84-1.75 (multiple peaks, 2H), 1.72-1.63 (multiple peaks, 3H), 1.49-1.28 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.46, 159.01, 136.88, 133.85, 132.14, 127.10, 123.16, 113.81, 74.04, 55.27, 38.75, 37.89, 28.50, 26.67, 25.37. IR (neat film): 3464, 1708 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{21}H_{23}NO_4$, 376.1525; found, 376.1525.

6-(1,3-Dioxoisoindolin-2-yl)-1-(4-methoxyphenyl)hexyl pivalate (**2-12**)

Product **2-12** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (5.0 mg, 0.013 mmol, 10 mol %), $PhI(OPiv)_2$ (106 mg, 0.26 mmol, 2 equiv), **2-1**[33] (30 mg, 0.13 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (67 µL, 0.20 mmol, 1.5 equiv), and toluene (4.1 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 50% yield of **2-12** along with 10% of the Heck product. The product was purified by chromatography on silica gel using 93% hexanes/5% EtOAc/2% Et_3N and was isolated as a clear oil (31 mg, 48% yield, 92% purity, R_f = 0.13 in 85% hexanes/15% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.61 (t, *J* = 6.8 Hz, 1H), 3.78 (s, 3H), 3.64 (t, *J* = 7.2 Hz, 2H), 1.86 (m, 1H), 1.72 (m, 1H), 1.64 (m, 2H), 1.45-1.29 (multiple peaks, 3H), 1.25 (m, 1H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.63, 168.40, 159.02, 133.83, 133.19, 132.13, 127.53, 123.14, 113.72, 75.29, 55.19, 38.72, 37.89, 36.27, 28.45, 27.09, 26.60, 25.12. IR (neat film): ν 1772, 1707 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{26}H_{30}NO_5$, 460.2094; found, 460.2090.

6-(1,3-Dioxoisoindolin-2-yl)-1-(4-methoxyphenyl)hexyl benzoate (**2-13**)

Product **2-13** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (5.0 mg, 0.013 mmol, 10 mol %), $PhI(O_2CPh)_2$ (117 mg, 0.26 mmol, 2 equiv), **2-1**[33] (30 mg, 0.13 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (67 µL, 0.20 mmol, 1.5 equiv), and toluene (4.1 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 71% yield of **2-13**. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (36 mg, 60% yield, 95% purity, R_f = 0.24 in 80% hexanes/20% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (m, 2H), 7.84 (m, 2H), 7.71 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 7.35 (m, 2H), 6.88 (m, 2H), 5.92 (t, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 3.67 (t, *J* = 7.3 Hz, 2H), 2.06 (br s, 1H), 1.89 (m, 1H), 1.68 (m, 2H), 1.51-1.30 (multiple peaks, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4, 165.8, 159.2, 133.8, 132.8, 132.8, 132.1, 130.6, 129.6, 128.3, 127.9, 123.1, 113.8, 76.3, 55.2, 37.9, 36.2, 28.4, 26.7, 25.2. IR (neat film): 1771, 1708 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{28}H_{27}NO_5$, 480.1781; found, 480.1768.

6-(1,3-Dioxoisoindolin-2-yl)-1-(4-methoxyphenyl)hexyl 4-methoxybenzoate (**2-14**)

Product **2-14** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (5.0 mg, 0.013 mmol, 10 mol %), $PhI(O_2CC_6H_4OMe)_2$ (132 mg, 0.26 mmol, 2 equiv), **2-1**[33] (30 mg, 0.13 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (67 µL, 0.20 mmol, 1.5 equiv), and toluene (4.1 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 53% yield of **2-14**. The product was purified by chromatography on silica gel using 83% hexanes/15% EtOAc/2% Et_3N and was isolated as a clear oil (34 mg, 53% yield, 95% purity, R_f = 0.36 in 70% hexanes/30% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (m, 2H), 7.82 (m, 2H), 7.69 (m, 2H), 7.32 (m, 2H), 6.92-6.81 (multiple peaks, 4H), 5.87 (t, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.65 (t, *J* = 7.1 Hz, 2H), 2.03 (m, 1H), 1.85 (m, 1H), 1.65 (dt, *J* = 14.4, 7.4 Hz, 2H), 1.48-1.27 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 165.6, 163.2, 159.1, 133.8, 133.0, 132.1, 131.6, 127.8, 123.1, 123.0, 113.8, 113.5, 75.9, 55.4, 55.2, 37.9, 36.2, 28.4, 26.7, 25.2. IR (neat film): 1771, 1705 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{29}H_{29}NO_6$, 510.1893; found, 510.1881.

6-(1,3-Dioxoisoindolin-2-yl)-1-(4-methoxyphenyl)hexyl 4-fluorobenzoate (**2-15**)

Product **2-15** was prepared according to general procedure B using $PdCl_2(PhCN)_2$ (5.0 mg, 0.013 mmol, 10 mol %), $PhI(O_2CC_6H_4F)_2$ (126 mg, 0.26

mmol, 2 equiv), **2-1**[33] (30 mg, 0.13 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (67 µL, 0.20 mmol, 1.5 equiv), and toluene (4.1 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 70% yield of **2-15**. The product was purified by chromatography on silica gel using 90% hexanes/8% EtOAc/2% Et_3N and was isolated as a clear oil (45 mg, 68% yield, 93% purity, R_f = 0.28 in 80% hexanes/20% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (85% hexanes/15% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (m, 2H), 7.84 (m, 2H), 7.71 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.34 (m, 2H), 7.10 (m, 2H), 6.88 (m, 2H), 5.90 (t, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 3.66 (t, *J* = 7.3 Hz, 2H), 2.05 (m, 1H), 1.89 (m, 1H), 1.67 (t, *J* = 7.3 Hz, 2H), 1.48-1.30 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.40, 165.69 (d, $^1J_{CF}$ = 253.5 Hz), 164.90, 159.28, 133.84, 132.59, 132.12 (d, $^3J_{CF}$ = 9.4 Hz), 132.11, 127.86, 126.78 (d, $^4J_{CF}$ = 3.1 Hz), 123.15, 115.52 (d, $^2J_{CF}$ = 21.9 Hz), 113.85, 76.52, 55.23, 37.86, 36.07, 28.42, 26.62, 25.19. ^{19}F NMR (377 MHz, $CDCl_3$) δ –106.05 to –105.96 (m, 1F). IR (neat film): 1770, 1736, 1708 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{28}H_{26}FNO_4$, 498.1693; found, 498.1695.

1-(4-Methoxyphenyl)butane-1,4-diyl diacetate (**2-16**)

Product **2-16** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (7.7 mg, 0.020 mmol, 10 mol %), $PhI(OAc)_2$ (129 mg, 0.40 mmol, 2 equiv), but-3-en-1-yl acetate[34] (25 µL, 0.20 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (103 µL, 0.30 mmol, 1.5 equiv), and degassed toluene (6.2 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 68% yield of **2-16** along with 6% of the Heck product. The product was purified by flash column chromatography on silica gel using 96% hexanes/2% EtOAc/2% Et_3N and was isolated as clear oil (35 mg, 62% yield, R_f = 0.13 in 85% hexanes/25% EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.71 (t, *J* = 7.0 Hz, 1H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.96 (m, 1H), 1.82 (m, 1H), 1.66 (m, 1H), 1.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.98, 170.20, 159.45, 131.87, 127.90, 113.95, 72.52, 60.77, 55.26, 35.01, 24.9, 21.21, 20.88. IR (neat film): 1736, 1731 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{15}H_{20}O_5$, 303.1208; found, 303.1210.

4-(Benzyloxy)-1-(4-methoxyphenyl)butyl acetate (**2-17**)

Product **2-17** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (6.7 mg, 0.018 mmol, 10 mol %), $PhI(OAc)_2$ (113 mg, 0.35 mmol, 2 equiv), but-3-en-1-yloxymethylbenzene[35] (30 µL, 018 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (90 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.5 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 65% yield of **2-17**. The product was purified by flash column chromatography on silica gel using 96%

hexanes/2% EtOAc/2% Et_3N and was isolated as clear oil (37 mg, 65% yield, R_f = 0.25 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (multiple peaks, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.71 (t, *J* = 7.2 Hz, 1H), 4.47 (s, 2H), 3.79 (s, 3H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.03 (s, 3H), 1.98 (m, 1H), 1.87 (m, 1H), 1.65 (m, 1H), 1.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.36, 159.24, 138.44, 132.63, 128.34, 127.95, 127.61, 127.52, 113.78, 75.55, 72.90, 69.78, 55.24, 32.80, 25.92, 21.29. IR (neat film): 1733 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{20}H_{24}O_4$, 351.1572; found, 351.1573.

4-((tert-Butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)butyl acetate (**2-18**)

Product **2-18** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (6.7 mg, 0.017 mmol, 10 mol %), $PhI(OAc)_2$ (112 mg, 0.35 mmol, 2 equiv), but-3-en-1yloxy *tert*-butyldimethylsilane[36] (40 µL, 0.17 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (89 µL, 0.26 mmol, 1.5 equiv), and degassed toluene (5.4 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 51% yield of **2-18** along with 3% of the Heck product. The product was purified by flash column chromatography on silica gel using 96.5% hexanes/2% Et_3N/1.5% EtOAc and was isolated as clear oil (29 mg, 47% yield, 94% purity, R_f = 0.41 in 85% hexanes/15% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (97% hexanes/3% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (m, 2H), 6.86 (m, 2H), 5.71 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.60 (dt, *J* = 6.0, 1.2 Hz, 2H), 2.03 (s, 3H), 1.92 (m, 1H), 1.84 (m, 1H), 1.52 (m, 1H), 1.42 (m, 1H), 0.88 (m, 9H), 0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.37, 159.23, 132.75, 127.98, 113.77, 75.59, 62.61, 55.23, 32.39, 28.83, 25.93, 21.30, 18.30, –5.34. IR (neat film): 1735 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{19}H_{32}O_4Si$, 375.1962; found, 375.1963.

6-Bromo-1-(4-methoxyphenyl)hexyl acetate (**2-19**)

Product **2-19** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (6.0 mg, 0.016 mmol, 10 mol %), $PhI(OAc)_2$ (100 mg, 0.39 mmol, 2 equiv), 6-bromohex-1-ene (21 µL, 0.16 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (80 µL, 0.23 mmol, 1.5 equiv), and degassed toluene (4.9 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 61% yield of **2-19**. The product was purified by flash column chromatography on silica gel using 95% hexanes/3% EtOAc/2% Et_3N and was isolated as clear oil (27 mg, 53% yield, 92% purity, R_f = 0.38 in 80% hexanes/20% EtOAc). Samples for HRMS and NMR analysis were obtained after further purification by HPLC (93% hexanes/7% EtOAc, 6 mL/min, Waters SunFire Prep Silica 5 µm).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.68 (t, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.37 (t, *J* = 6.8 Hz, 2H), 2.04 (s, 3H), 1.92

(m, 1H), 1.83 (m, 2H), 1.76 (m, 1H), 1.45 (quin, *J* = 7.6 Hz, 2H), 1.32 (m, 1H), 1.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.43, 159.25, 132.59, 127.94, 113.79, 75.62, 55.23, 35.82, 33.67, 32.54, 27.81, 24.74, 21.32. IR (neat film): 1733 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{15}H_{21}BrO_3$, 351.0566; found, 351.0557.

4-Iodophenyl 5-acetoxy-5-(4-methoxyphenyl)pentanoate (**2-20**)

Product **2-20** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (5.1 mg, 0.013 mmol, 10 mol %), $PhI(OAc)_2$ (85 mg, 0.27 mmol, 2 equiv), 4-iodophenyl pent-4-enoate[37] (40 mg, 0.13 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (68 µL, 0.20 mmol, 1.5 equiv), and degassed toluene (4.1 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 71% yield of **2-20**. The product was purified by flash column chromatography on silica gel using 94% hexanes/4% EtOAc/2% Et_3N and was isolated as clear oil (43 mg, 69% yield, R_f = 0.16 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.73 (t, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.06 (s, 3H), 2.03 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.28, 170.35, 159.39, 150.45, 138.44, 132.19, 127.93, 123.71, 113.91, 89.76, 75.16, 55.26, 35.28, 33.78, 21.29, 20.87. IR (neat film): 1751, 1733 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{20}H_{21}IO_5$,491.0326; found, 491.0319.

1-(4-Methoxyphenyl)hexane-1,6-diyl diacetate (**2-21**)

Product **2-21** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (7.2 mg, 0.019 mmol, 10 mol %), $PhI(OAc)_2$ (121 mg, 0.37 mmol, 2 equiv), hex-5-en-1-yl acetate[34] (30 µL, 0.19 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (96 µL, 0.28 mmol, 1.5 equiv), and degassed toluene (5.8 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 71% yield of **2-21** along with 9% of the Heck product. The product was purified by flash column chromatography on silica gel using 96% hexanes/2% Et_3N/1.5% EtOAc and was isolated as clear oil (39 mg, 68% yield, R_f = 0.16 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.67 (t, *J* = 7.2 Hz, 1H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.80 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.90 (m, 1H), 1.76 (m, 1H), 1.59 (m, 2H), 1.40-1.29 (multiple peaks, 3H), 1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.17, 170.39, 159.23, 132.65, 127.93, 113.77, 75.64, 64.37, 55.22, 35.89, 28.41, 25.64, 25.19, 21.30, 20.96. IR (neat film): 1733 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{17}H_{24}O_5$, 331.1521; found, 331.1514.

6-((tert-butyldiphenylsilyl)oxy)-1-(4-methoxyphenyl)hexyl acetate (**2-22**)

Product **2-22** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (6.0 mg, 0.016 mmol, 10 mol %), $PhI(OAc)_2$ (100 mg, 0.31 mmol,

2 equiv), *tert*-butyl-hex-5-en-1-yloxyldiphenylsilane[38] (54 µL, 0.16 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (80 µL, 0.23 mmol, 1.5 equiv), and degassed toluene (4.9 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 63% yield of **2-22** along with 10% of the Heck product. The product was purified by flash column chromatography on silica gel using 96.5% hexanes/2% Et_3N/1.5% EtOAc and was isolated as clear oil (49 mg, 62% yield, R_f = 0.49 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 6.8 Hz, 4H), 7.44-7.34 (multiple peaks, 6H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.67 (t, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.63 (t, *J* = 6.8 Hz, 2H), 2.04 (s, 3H), 1.89 (m, 1H), 1.75 (m, 1H), 1.54 (m, 2H), 1.38 (m, 2H), 1.30 (m, 1H), 1.20 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 159.18, 135.53, 134.05, 132.82, 129.48, 127.97, 127.56, 113.74, 75.83, 63.75, 55.22, 36.04, 32.35, 26.84, 25.56, 25.35, 21.33, 19.18. IR (neat film): 1732 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{31}H_{40}O_4Si$, 527.2594; found, 527.2577.

1-(4-Methoxyphenyl)-3-phenoxypropyl acetate (**2-23**)

Product **2-23** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (7.0 mg, 0.018 mmol, 10 mol %), $PhI(OAc)_2$ (117 mg, 0.36 mmol, 2 equiv), allyl phenyl ether (25 µL, 0.18 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (94 µL, 0.27 mmol, 1.5 equiv), and degassed toluene (5.7 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 67% yield of **2-23** along with 22% of the Heck product. The product was purified by flash column chromatography on silica gel using 96% hexanes/2% EtOAc/2% Et_3N and was isolated as clear oil (35 mg, 64% yield, R_f = 0.28 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.24 (multiple peaks, 4H), 6.93 (m, 1H), 6.88-6.85 (multiple peaks, 4H), 5.96 (app t, *J* = 8.0 Hz, 1H), 3.98 (m, 1H), 3.88 (m, 1H), 3.79 (s, 3H), 2.42 (m, 1H), 2.20 (m, 1H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.20, 159.36, 158.68, 132.12, 129.40, 127.95, 120.77, 114.50, 113.90, 72.81, 64.00, 55.25, 35.77, 21.26. IR (neat film): 1733 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{18}H_{20}O_4$, 323.1259; found, 323.1256.

1-(4-Methoxyphenyl)propane-1,3-diyl diacetate (**2-24**)

Product **2-24** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (8.9 mg, 0.023 mmol, 10 mol %), $PhI(OAc)_2$ (149 mg, 0.46 mmol, 2 equiv), allyl acetate (25 µL, 0.23 mmol, 1 equiv), *p*-$OMeC_6H_4SnBu_3$ (119 µL, 0.35 mmol, 1.5 equiv), and degassed toluene (7.2 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 58% yield of **2-24** along with 14% of the Heck product. The product was purified by flash column chromatography on silica gel using 96% hexanes/2% EtOAc/2% Et_3N and was isolated as clear oil (30 mg, 58% yield, R_f = 0.21 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.88 (m, 2H), 5.81 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.13 (m, 1H), 4.00 (m, 1H), 3.80 (s, 3H), 2.24 (m, 1H), 2.09 (m, 1H), 2.05 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.98, 170.20, 159.45, 131.87, 127.90, 113.95, 72.52, 60.77, 55.26, 35.01, 21.21, 20.88. IR (neat film): 1733 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{14}H_{18}O_5$, 289.1052; found, 289.1059.

2-(4-Fluorophenyl)-1-(4-methoxyphenyl)ethyl acetate (**2-25**)

Product **2-25** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (8.7 mg, 0.023 mmol, 10 mol %), $PhI(OAc)_2$ (145 mg, 0.45 mmol, 2 equiv), 1-methoxy-4-vinylbenzene (30 µL, 0.23 mmol, 1 equiv), *p*-$FC_6H_4SnBu_3$ (112 µL, 0.34 mmol, 1.5 equiv), and degassed toluene (7.1 mL). ^{1}H NMR analysis of the crude reaction mixture showed a quantitative yield of the product. Compound **2-25** was purified by flash column chromatography on silica gel using 88% hexanes/10% EtOAc/2% Et_3N and was isolated as clear oil (65 mg, 99% yield, R_f = 0.30 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (m, 2H), 7.03 (m, 2H), 6.92 (m, 2H), 6.84 (m, 2H), 5.85 (t, *J* = 7.2 Hz, 1H), 3.16 (dd, *J* = 14, 7.6 Hz, 1H), 3.01 (dd, *J* = 14, 6.4 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.09, 161.65 (d, $^1J_{CF}$ = 244.4 Hz), 159.32, 132.73 (d, $^4J_{CF}$ = 3.1 Hz), 131.78, 130.98 (d, $^3J_{CF}$ = 7.6 Hz), 128.03, 115.01 (d, $^2J_{CF}$ = 21.4 Hz), 113.73, 76.24, 55.22, 41.91, 21.19. ^{19}F NMR (377 MHz, $CDCl_3$) δ –116.62 (m, 1F). IR (neat film): 1735 cm^{-1}. HRMS electron impact (m/z): $[M]^+$ calcd for $C_{17}H_{17}FO_3$, 288.1162; found, 288.1173.

1-Ethoxy-2-(4-methoxyphenyl)ethyl acetate (**2-26**)

Product **2-26** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (7.7 mg, 0.020 mmol, 10 mol %), $PhI(OAc)_2$ (129 mg, 0.40 mmol, 2 equiv), ethyl vinyl ether (19 µL, 0.20 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (79 µL, 0.20 mmol, 1.0 equiv), and degassed toluene (6.3 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 57% yield of **2-26** along with 4% of the Heck product. The product was purified by flash column chromatography on silica gel using 96% hexanes/2% EtOAc/2% Et_3N and was isolated as clear oil (19 mg, 40% yield, product was not stable to silica gel chromatography, R_f = 0.39 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.81 (t, *J* = 5.6 Hz, 1H), 3.79 (s, 3H), 3.71 (m, 1H), 3.49 (m, 1H), 2.91 (dddd, *J* = 14.0, 14.0, 14.0, 6.0, 2H), 2.04 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.76, 158.39, 130.72, 127.66, 113.67, 98.73, 65.24, 55.18, 40.25, 21.16, 14.94. IR (neat film): 1733 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{13}H_{18}O_4$, 261.1103; found, 261.1094.

1-(tert-Butoxy)-2-(4-methoxyphenyl)ethyl acetate (**2-27**)

Product **2-27** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (6.0 mg, 0.016 mmol, 10 mol %), $PhI(OAc)_2$ (100 mg, 0.39 mmol, 2 equiv), *tert*-butyl vinyl ether (20 µL, 0.16 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (80 µL, 0.23 mmol, 1.5 equiv), and degassed toluene (4.9 mL). ^1H NMR analysis of the crude reaction mixture showed a 69% yield of **2-27** along with 4% of the Heck product. The product was purified by flash column chromatography on silica gel using 98% hexanes/2% Et_3N and was isolated as clear oil (25 mg, 60% yield, R_f = 0.17 in 95% hexanes/5% EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.04 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.78 (s, 3H), 2.88 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.81 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.02 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.22, 158.34, 131.01, 127.96, 113.49, 94.65, 75.78, 55.17, 41.46, 27.98, 21.60. IR (neat film): 1726 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{15}H_{22}O_4$, 289.1410; found, 289.1411.

1-(Cyclohexyloxy)-2-(4-methoxyphenyl)ethyl acetate (**2-28**)

Product **2-28** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (6.0 mg, 0.016 mmol, 10 mol %), $PhI(OAc)_2$ (100 mg, 0.39 mmol, 2 equiv), cyclohexyl vinyl ether (22 µL, 0.16 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (80 µL, 0.23 mmol, 1.5 equiv), and degassed toluene (4.9 mL). ^1H NMR analysis of the crude reaction mixture showed a 66% yield of **2-28**. The product was purified by flash column chromatography on silica gel using 98% hexanes/2% Et_3N and was isolated as clear oil (28 mg, 62% yield, R_f = 0.16 in 95% hexanes/5% EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (m, 2H), 6.82 (m, 2H), 5.99 (t, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 3.49 (tt, *J* = 8.8, 4.0 Hz, 1H), 2.90 (m, 2H), 2.03 (s, 3H), 1.77 (m, 1H), 1.67 (m, 2H), 1.56 (m, 1H), 1.45 (m, 1H), 1.34 (m, 1H), 1.29-1.11 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.79, 158.33, 131.80, 127.92, 113.56, 97.50, 77.07, 55.18, 40.74, 33.10, 31.57, 25.48, 23.89, 23.57, 21.37. IR (neat film): 1731 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{17}H_{24}O_4$, 315.1567; found, 315.1565.

5-(4-Methoxyphenyl)tetrahydrofuran-2-yl acetate (**2-29**)

Product **2-29** was prepared according to general procedure A using $PdCl_2(PhCN)_2$ (7.6 mg, 0.020 mmol, 10 mol %), $PhI(OAc)_2$ (128 mg, 0.40 mmol, 2 equiv), 2,3-dihydrofuran (15 µL, 0.20 mmol, 1 equiv), *p*-$MeOC_6H_4SnBu_3$ (102 µL, 0.30 mmol, 1.5 equiv), and degassed toluene (6.2 mL). ^1H NMR analysis of the crude reaction mixture showed a 64% yield of **2-29** as a 1.3 : 1 mixture of the cis : trans isomers. The product was purified by flash column chromatography on silica gel using 93% hexanes/5% EtOAc/2% Et_3N and was isolated as clear oil (27 mg, 58% yield, R_f = 0.23 (cis) and R_f = 0.20 (trans) in 85% hexanes/15% EtOAc).

***cis*-2-29:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.88 (m, 2H), 6.39 (br s, 1H), 5.04 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.81 (s, 3H), 2.32 (m, 1H), 2.18 (m, 2H), 2.09 (s, 3H), 2.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.40, 159.15, 134.03, 127.41, 113.78, 98.87, 83.47, 55.28, 33.56, 32.12, 21.50. IR (neat film): 1735 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{13}H_{16}O_4$, 259.0935; found, 259.0935.

***trans*-2-29:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 2H, $\mathbf{H_g}$), 6.87 (m, 2H), 6.51 (dd, *J* = 5.0, 1.5 Hz, 1H, $\mathbf{H_a}$), 5.20 (t, *J* = 7.0 Hz, 1H, $\mathbf{H_f}$), 3.80 (s, 3H), 2.43 (dddd, *J* = 12.0, 7.0, 7.0, 7.0 Hz, 1H, $\mathbf{H_d}$), 2.31 (dddd, *J* = 16.5, 9.5, 7.0, 5.0 Hz, 1H, $\mathbf{H_c}$), 2.08 (s, 3H), 2.05 (dddd, *J* = 15.5, 7.5, 5.5, 1.5 Hz, 1H, $\mathbf{H_b}$), 1.86 (dddd, *J* = 15.5, 9.5, 6.5, 5.5 Hz, 1H, $\mathbf{H_e}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.49, 159.08, 133.55, 127.00, 113.73, 98.10, 81.02, 55.26, 31.93, 31.90, 21.40. IR (neat film): 1737 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{13}H_{16}O_4$, 259.0935; found, 259.0938.

General Procedure for Phenylacetoxylation Reaction with Benzene:
$Pd(acac)_2$ (5 mol %), $PhI(OAc)_2$ (2.5 equiv), and AgOAc (10 mol %) were weighed into a 4 mL vial. Benzene (0.3 mL) was added and substrate (1 equiv, 0.058 mmol) was introduced via microsyringe. The vial was sealed with a Teflon-lined cap, and the reaction was heated at 60 °C overnight. The resulting mixture was filtered through a pad of Celite, and the Celite was washed with Et_2O (5 mL). The solution was concentrated, and the crude products were then purified by flash chromatography.

1-Phenylpropane-1,3-diyl diacetate (**2-30**)

Product **2-30** was prepared according to the general procedure using $Pd(acac)_2$ (6.0 mg, 0.020 mmol, 5 mol %), $PhI(OAc)_2$ (315 mg, 0.98 mmol, 2.5 equiv), allyl acetate (40 µL, 0.39 mmol, 1 equiv), AgOAc (65 mg, 0.39 mmol, 0.1 equiv), and benzene (2.0 mL). ^{1}H NMR analysis of the crude reaction mixture showed a 62% yield of **2-30** along with 7% of the Heck product. The product was purified by flash column chromatography on silica gel using 96% hexanes/2% EtOAc/2% Et_3N and was isolated as clear oil (51 mg, 49% yield, R_f = 0.23 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (multiple peaks, 5H), 5.86 (dd, *J* = 8.0, 5.6 Hz, 1H), 4.15 (m, 1H), 4.02 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.96, 170.13, 139.86, 128.59, 128.15, 126.37, 72.81, 60.66, 35.21, 21.16, 20.86. IR (neat film): 1738 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{13}H_{16}O_4$, 259.0941; found, 259.0949.

N-(Pent-4-en-1-yl)benzenesulfonamide (**2-31**)

Substrate **2-31** was synthesized using a known procedure[39] from 5-bromopentene (521 mg, 3.5 mmol, 1.1 equiv) and benzenesulfanamide (500 mg,

3.18 mmol, 1.0 equiv) with K_2CO_3 (879 mg, 6.36 mmol, 2.0 equiv) in acetone (3.2 mL). The reaction was stirred at 60 °C for at least 16h. The product was purified by flash column chromatography on silica gel using 80% hexanes/20% EtOAc and was isolated as clear oil (253 mg, 35% yield). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[40]

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[35] Synthesized by reaction of but-3-en-1-ol with NaH and benzyl bromide in THF.

[36] Synthesized by the reaction of but-3-en-1-ol with imidazole and TBDMSCl in DMF.

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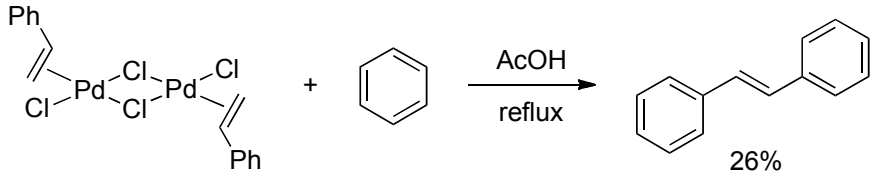
CHAPTER 3

Pyridine Ligands as Promoters in Pd-Catalyzed C–H Olefination Reactions

3.1 Introduction

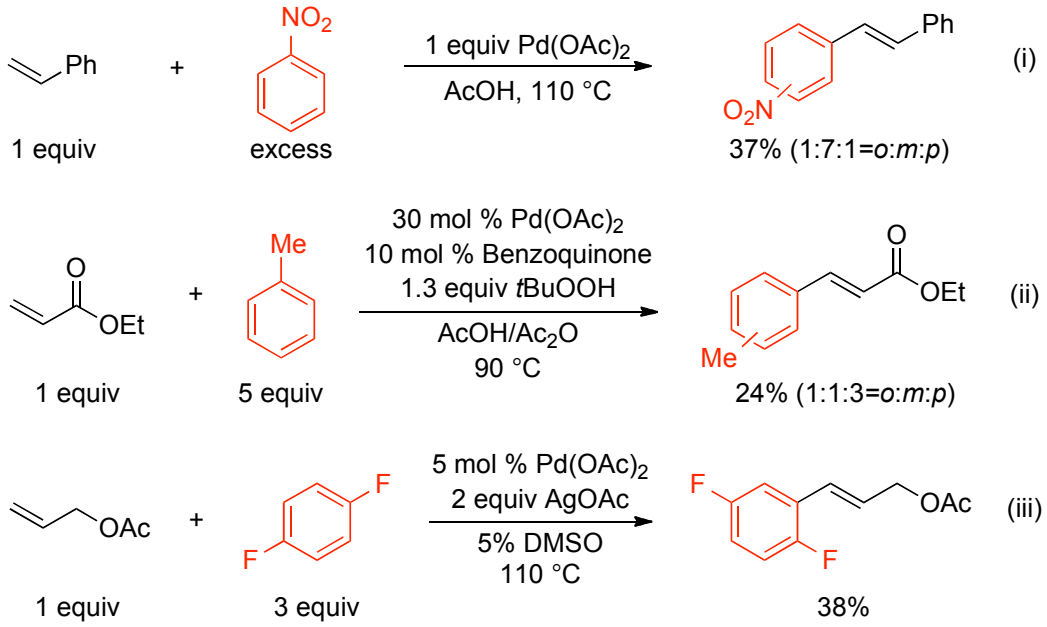
Fujiwara and Moritani discovered the Pd-mediated C–H olefination of benzene in 1967.[1] In this reaction (Scheme 3.1), the chloride bridged dinuclear Pd(II)-styrene complex was refluxed with benzene in acetic acid to afford stilbene.[1] Since this initial report, a variety of Pd-catalyzed transformations for arene C–H olefination have been developed. Most of these methods utilize simple Pd(II) catalysts such as $Pd(OAc)_2$ in the absence of additional L-type ligands. These catalytic reactions require oxidants such as peroxides, peroxyesters, O_2, polyoxometalates, Cu(II) salts, or Ag(I) salts to reoxidize Pd(0) to Pd(II).[2] Currently known methods enable the coupling of various electron neutral and electron rich arenes[2] and good regioselectivity can be obtained using arene substrates that contain directing groups.[2,3,4,5]



Scheme 3.1. First Example of Pd-Mediated C–H Olefination of Benzene[1]

Although there have been significant advances in catalytic C–H olefination reactions, there are still limitations to this methodology.[6,7] One major limitation is the fact that electron deficient arenes that do not contain directing groups generally show sluggish reactivity.[7e,h] For example (Scheme 3.2, i), nitrobenzene in the presence of stoichiometric amount of Pd catalyst afforded only 38% yield of the C–H olefination product with styrene.[7e] Secondly, most substituted arenes react to provide mixtures of regioisomeric products resulting from unselective

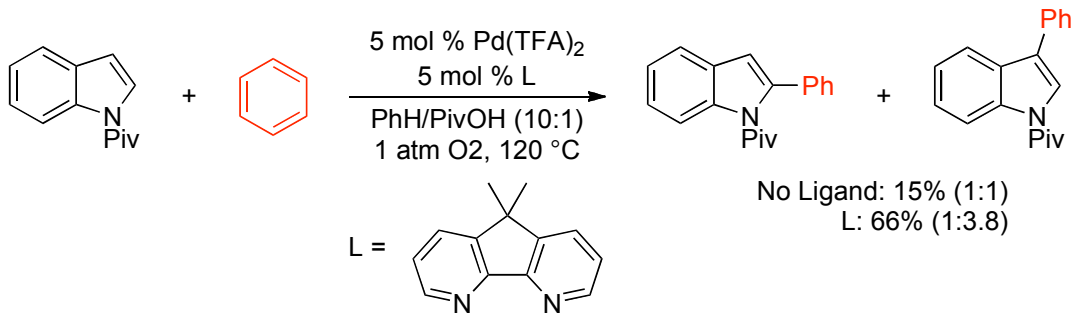
C–H activation.[6,7e] As shown in Scheme 3,2 (ii), reaction with ethyl acrylate and toluene was reported to provide products in a mixture of 1:1:3 (*o*/*m*/*p*) with a low yield of 24%.[6a] In the C–H olefination of heterocycles such as indoles and pyrroles, site selectivity has been successfully achieved through solvent and/or oxidant choice.[8] However, catalyst-controlled site selectivity is still challenging. Third, most Pd-catalyzed C–H olefination reactions require the use of α,β-unsaturated carbonyl derivatives (such as acrylates) as an olefin coupling partner. There are some successful examples of the use of ethylene and styrene as substrates,[7] but other α-olefins generally do not show good reactivity.[7f-h] In the last example of Scheme 3.2, allyl acetate was utilized, but it was reported to only afford 38% yield of the C–H olefination product.[7h]



Scheme 3.2. Current Limitations of C–H Olefination Reactions[6a,7e,h]

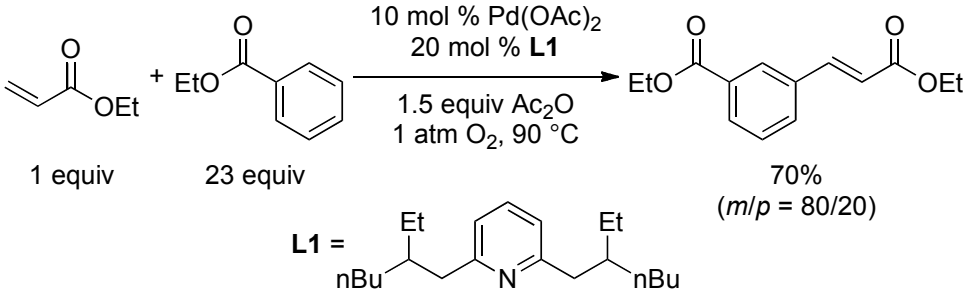
Although catalyst control has been difficult, developing a supporting ligand that could enhance both reactivity and site-selectivity would be an ideal way to address all of the above challenges associated with the C–H olefination reaction.[9] A similar strategy has been shown to be successful for related Pd-catalyzed biaryl coupling reactions.[10] For example, in Scheme 3.3, the site-selective oxidative coupling of indole with benzene was achieved using bidentate nitrogen ligands. This reaction in the absence of ligands proceeded in 15% yield

of products with no selectivity. However, the use of 5 mol % of a bidentate nitrogen ligand significantly improved the reaction yield to 66% and also favored the arylation on the 3-position by 3.8:1.[10b]



Scheme 3.3. Catalyst Control on Oxidative Cross Coupling[10b]

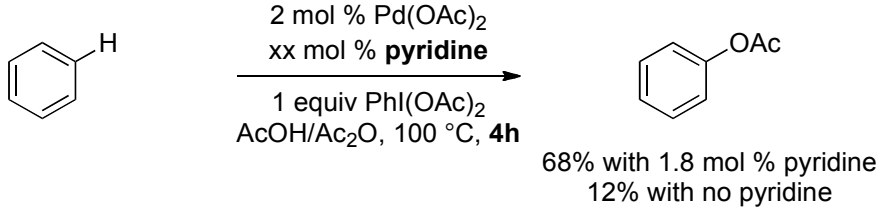
Moreover, in 2009 Yu and co-workers reported that 2,6-dialkylpyridine **L1** is an effective ligand for the coupling of electron deficient arenes with α,β-unsaturated carbonyl derivatives using O_2 as the oxidant (Scheme 3.4).[11] For the coupling of 1,3-bis(trifluoromethyl)benzene with methyl cinnamate, pyridine and 2,6-picoline provided less than 5% of the coupling product, while 52% yield was obtained under analogous condition with **L1**. The combination of 10 mol % of $Pd(OAc)_2$ and 20 mol % of **L1** also afforded good yields with other challenging electron deficient aromatic substrates, such as trifluoromethylbenzene. Additionally, these reactions afforded moderate selectivity (~4:1, *m*:*p*) for olefination at the *meta* site.[11a]



Scheme 3.4. $Pd(OAc)_2$/**L1** Catalyzed C–H Olefination with O_2 as Oxidant

The example in Scheme 3.4 is a great advance in the field. However, there are still areas that need to be improved. First, the catalyst loading is high (10 mol % of $Pd(OAc)_2$ and 20 mol % of **L1**). Second, the site-selectivity for substituted arenes is modest. Finally, the ligand **L1** is not commercially available.

Recently, our group reported that the combination of $Pd(OAc)_2$ and pyridine serves as a highly active catalyst for the C–H acetoxylation of arenes (Scheme 3.5).[12] In this Pd(II/IV)-catalyzed acetoxylation reaction, the use of an approximately 1:1 ratio of $Pd(OAc)_2$/pyridine provided at least a 10-fold increase in reaction rate compared to a ligandless system. It was proposed that the equimolar ratio of $Pd(OAc)_2$/pyridine resulted in the formation of the coordinatively unsaturated catalyst $(pyr)Pd(OAc)_2$, which is highly reactive toward C–H activation.[12] Since the arene C–H activation step of the Pd(II/0)-catalyzed Fujiwara-Moritani (F-M) reaction is expected to occur through a similar intermediate to that of the C–H acetoxylation reaction described above, this report suggested that a much simpler pyridine ligand could also potentially enhance reactivity in Pd-catalyzed C–H olefination reactions. Thus, we hypothesized that the use of an equimolar ratio of $Pd(OAc)_2$ to pyridine would have a accelerative effect on the F-M transformation.[13]



Scheme 3.5. $Pd(OAc)_2$/pyridine Catalyzed Acetoxylation

The ultimate goal for studying the C–H olefination reaction is to apply what we learn from this study to the olefin difunctionalization project discussed in Chapter 2. We are interested in using simple C–H substrates such as benzene to carry out our aryloxygenation and arylamination reactions in order to eliminate the toxic arylstannane requirements.

3.2 Results

We initially focused on the reaction between ethyl cinnamate and benzene to test this hypothesis. We sought an oxidant that would be compatible with $Pd(OAc)_2$/pyridine system so that our hypothesis could be tested. The use of O_2 was examined first (by analogy to the Yu's system); however, due to the

difficulties in controlling the amount of gas added in solution as well as the slow oxidation rate (which leads to catalyst decomposition), yields obtained using O_2 were irreproducible. Upon the examination of other known oxidants for F-M reactions, we found that *tert*-butylperoxy benzoate afforded consistent yields and rates.[8a-b, 9b-c,14]

The yield of the olefination of benzene with ethyl cinnamate was monitored over 24 h at 100 °C in the absence of pyridine, with equimolar $Pd(OAc)_2$/pyridine, and with a 1:2 ratio of $Pd(OAc)_2$/pyridine (Figure 3.1). This time study showed that 5 mol % of $Pd(OAc)_2$ in the absence of pyridine ligand afforded the product **3-1** in modest (~70%) yield after 18 h. The use of a 1:2 ratio of $Pd(OAc)_2$/pyridine, which was the catalyst/ligand ratio Yu had reported with **L1**,[11a] resulted in a substantial decrease in the reaction rate and only provided about 55% yield of **3-1** even after 24 h. Interestingly, when equimolar quantities of $Pd(OAc)_2$/pyridine were employed, we observed a significant enhancement in the reaction rate and 76% yield of **3-1** was observed at only 6 h.

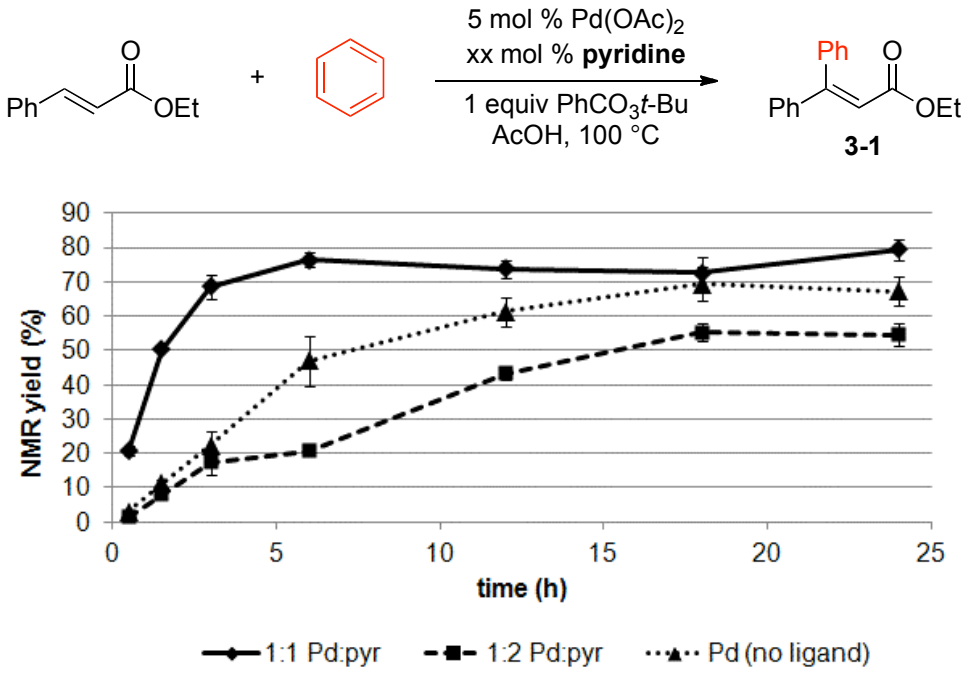


Figure 3.1. Formation of **3-1** over 24 h as a Function of Catalyst and Pyridine [1:1 $Pd(OAc)_2$:pyr (♦), 1:2 $Pd(OAc)_2$:pyr (■), $Pd(OAc)_2$ (▲)]

On the contrary, **L1** (developed for the aerobic oxidation system reported by Yu) did not perform as well as pyridine under our conditions (Figure 3.2). In comparison to the equimolar $Pd(OAc)_2$/pyridine catalyst system, the use of equimolar $Pd(OAc)_2$/**L1** led to a slower rate and lower yields (with the reaction stopping between 55-60% yield of product **3-1**). Furthermore, the slower rate and lower yields were observed regardless of the ratio of $Pd(OAc)_2$/**L1** utilized (Figure 3.2). Overall, we were delighted to find that a very simple pyridine ligand had a significant impact on the C–H olefination reaction as we had hypothesized.

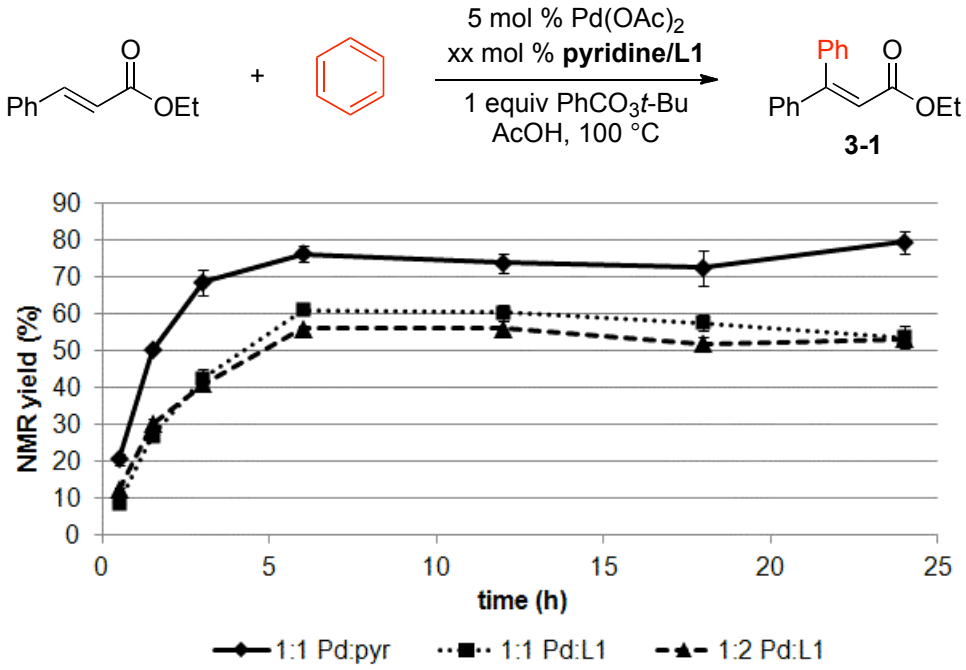


Figure 3.2. Formation of **3-1** over 24 h as a Function of Catalyst and **L1** [1:1 $Pd(OAc)_2$:pyr (♦), 1:1 $Pd(OAc)_2$:**L1** (■), 1:2 $Pd(OAc)_2$:**L1** (▲)]

Next, we examined the performance of various $Pd(OAc)_2$/pyridine ratios in order to optimize the $Pd(OAc)_2$/pyridine catalyst system. The range of $Pd(OAc)_2$/pyridine ratios studied was from 1:0 (no pyridine) to approximately 1:2, which we had already shown was not as effective as 1:1 (Figure 3.1). Taking a closer look at this range for the reaction between benzene and ethyl cinnamate at 3 h, significantly greater yield of **3-1** was observed when 2.5 mol % to 6.2 mol % of pyridine was used with 5 mol % of $Pd(OAc)_2$ (Figure 3.3). These amounts of

pyridine correspond to $Pd(OAc)_2$/pyridine ratios between 1:0.5 and approximately 1:1.

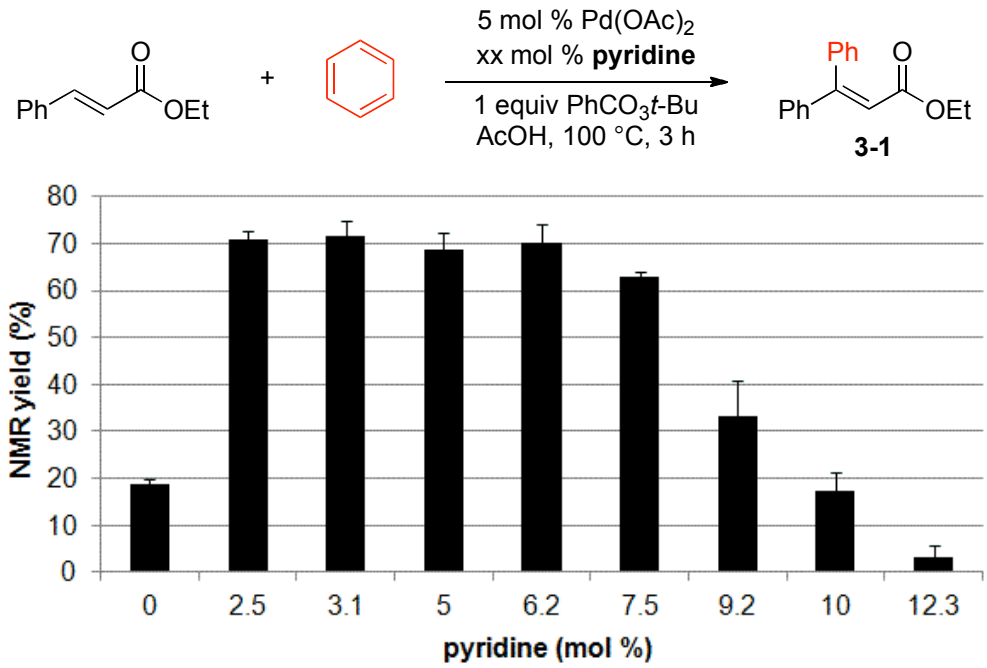
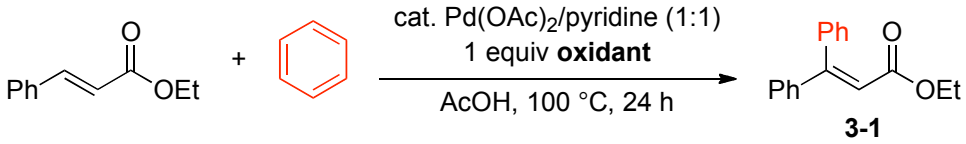


Figure 3.3. Yield of **3-1** after 3 h as a Function of mol % Pyridine

After confirming that an approximately 1:1 ratio of $Pd(OAc)_2$/pyridine is optimal, we did a more thorough oxidant screen with a 1:1 ratio of $Pd(OAc)_2$/pyridine and 1 equiv of oxidant in AcOH (Table 3.1). With $PhCO_3t$-Bu, the catalyst loading could be decreased to 2.5 mol % without a significant drop in the yield. In addition, even with 1 mol % of $Pd(OAc)_2$ we observed 58% yield of **3-1** (Table 3.1, entries 1-3). Overall, $PhCO_3t$-Bu proved to be the most effective oxidant examined, but some other oxidants such as $K_2S_2O_8$ afforded **3-1** in useful yield of 57%.

Table 3.1. Optimization of C–H Olefination Reaction



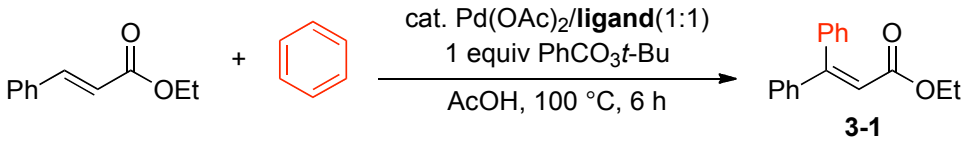
3-1

entry	Pd/pyr (mol %)	Oxidant	% yield[a)]
1	Pd (5)/pyr (5)	$PhCO_3t$-Bu	78
2	Pd (2.5)/pyr (2.5)	$PhCO_3t$-Bu	73
3	Pd (1)/pyr (1)	$PhCO_3t$-Bu	58
4	Pd (5)/pyr (5)	Benzoquinone	8
5	Pd (5)/pyr (5)	AcOOH	9
6	Pd (5)/pyr (5)	O_2[b)]	17
7	Pd (5)/pyr (5)	$(PhCOO)_2$	29
8	Pd (5)/pyr (5)	^{t}BuOOH	41
9	Pd (5)/pyr (5)	Oxone	47
10	Pd (5)/pyr (5)	AgOAc	49
11	Pd (5)/pyr (5)	Ag_2CO_3	54
12	Pd (5)/pyr (5)	$K_2S_2O_8$	57

[a)] NMR average yields based on 1,3-dinitrobenzene standard of at least two reactions.
[b)] 1 atm O_2.

Other pyridine derivatives were also examined as ligands under our optimized conditions. Most commercially available mono- and di-substituted pyridines provided about 70% yield of **3-1** (Table 3.2, entries 1 and 3-7). Acridine, 3-nitropyridine, and 3,5-dichloropyridine (**L2**) afforded slightly higher yields than other commercial pyridine derivatives (entries 8-10). For the substrate scope development, **L2** was utilized because it gave the highest yield of **3-1** (81%). As already shown in Figure 3.2, **L1** was not as effective as pyridine in our system. This is interesting, given that **L1** was shown to be the optimal ligand for C–H olefination under aerobic conditions (Scheme 3.4).11[a] This data suggests that ligand effects in F-M reactions can be dependent on the oxidant used. Also, under our conditions with $PhCO_3t$-Bu, **L1** could be oxidized at the benzylic position, which could be the cause for the difference in the reactivity between the two systems (O_2 versus $PhCO_3t$-Bu)

Table 3.2. Optimization of Ligands for C–H Olefination Reaction



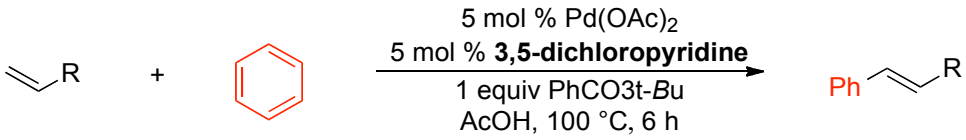
3-1

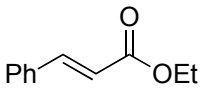
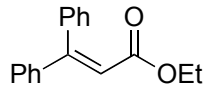
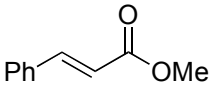
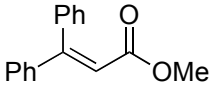
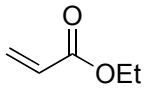
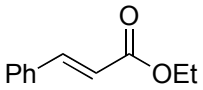
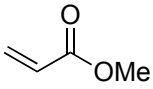
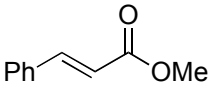
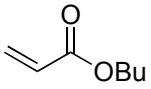
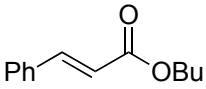
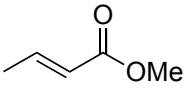
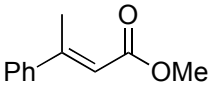
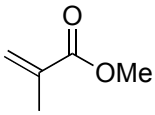
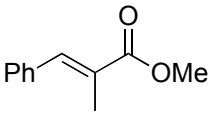
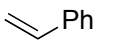
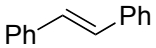
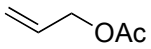
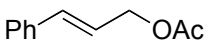
entry	Ligand	% yield[a)]
1	Pyridine	76
2	**L1**	61
3	2-picoline	69
4	2,6-lutidine	69
5	4-methoxypyridine	69
6	3-acetylpyridine	70
7	3-chloropyridine	72
8	3-nitropyridine	78
9	Acridine	80
10	3,5-dichloropyridine (**L2**)	81

[a)] NMR average yields based on 1,3-dinitrobenzene standard of at least two reactions.

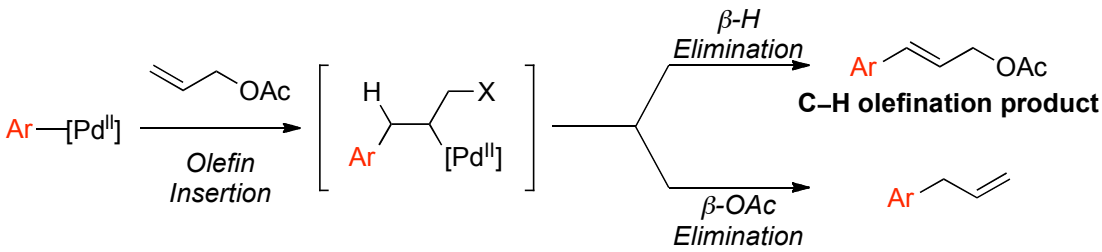
We next explored the substrate scope of this reaction. First, a variety of α,β-unsaturated carbonyl derivatives were tested. As shown in Table 3.3, unsubstituted α,β-unsaturated carbonyl derivatives were very effective in forming the C–H olefinated products (entries 1-5). High yields of the coupled products (85-95%) were obtained when 40 equiv of benzene was used. Furthermore, the amount of benzene could be lowered to 11 equiv while still maintaining good yields of the products (62-76%). Lower yields were observed with α- or β-methyl substituted acrylates (entries 6-7). Furthermore, styrene, allyl acetate, and ethylene all afforded the coupled product in moderate yields (entries 8-10). The use of allyl acetate is particularly remarkable given that α-olefins are challenging substrates for the C–H olefination reactions and also competing β -acetoxy elimination is a well-known process in Heck-type reactions of this substrate (Scheme 3.6).[15,16]

Table 3.3. Alkene Substrate Scope



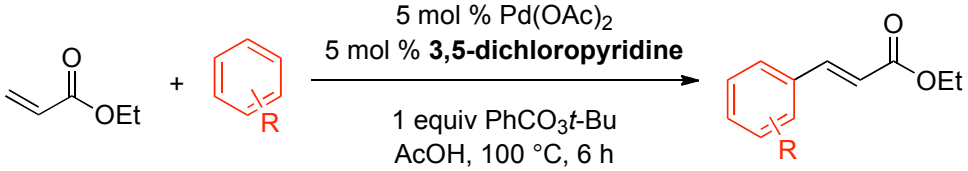
entry	olefin	product		equiv C_6H_6	yield (%)
1			**3-1**	40 11	88[a] 76[a]
2			**3-2**	40 11	95 75[a]
3			**3-3**	40 11	94 62[a]
4			**3-4**	40 11	89 64[a]
5			**3-5**	40 11	85 65[a]
6			**3-6**	40	58[a]
7			**3-7**	40	34[a,c]
8			**3-8**	40	43[a]
9			**3-9**	40	57[a,d]
10			**3-10**	40	26[b,e]

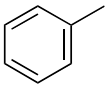
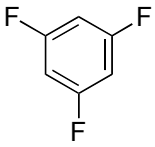
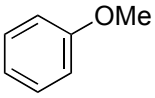
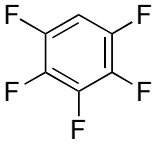
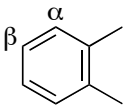
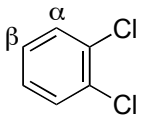
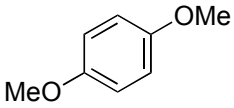
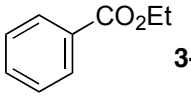
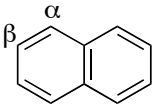
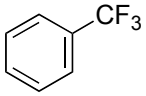
[a]Isolated yield. [b]Yield determined by ^{1}H NMR analysis of crude reaction mixture. [c]Isolated as a mixture with the byproduct phenylated at the α -methyl. [d]Isolated as a mixture with the diphenylated product. [e]Oxidant used as the limiting reagent with an excess of ethylene.



Scheme 3.6. Competing β-Hydride Elimination and β-OAc Elimination

Table 3.4. Arene Substrate Scope



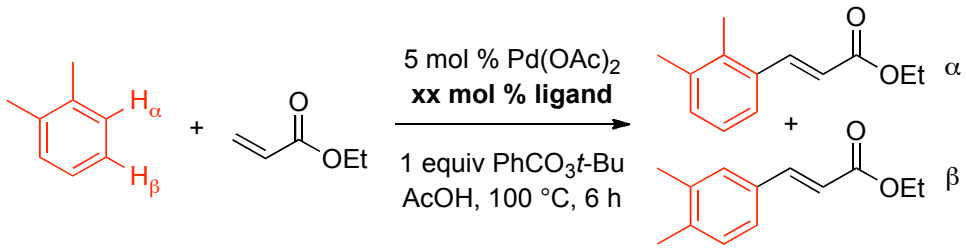
entry	arene	product	isolated yield (%)	entry	arene	product	isolated yield (%)
1[a,b]		**3-11**	73 1/2.5/2.7	6[a]		**3-16**	93
2[a,b]		**3-12**	69 4.1/1/7.4	7[c]		**3-17**	67
3[a,b]		**3-13**	69 1/3.0	8[b,c]		**3-18**	65 1/1.6
4[a]		**3-14**	75	9[b,c]		**3-19**	42 1/5.6/1.5
5[a,b]		**3-15**	79 1.1/1	10[b,c]		**3-20**	32 1/15.8/4.2

[a] [arene] = 1 M. [b] Product ratios determined from isolated mixtures. Ratio reported as *o*/*m*/*p* or α/β. [c] [arene] = 0.28 M.

A study of arene substrate scope showed that both electron rich arenes (Table 3.4, entries 1-5) and electron deficient arenes (entries 6-10) could be coupled with ethyl acrylate. Unfortunately, the C–H activation was not very site-selective, and most substituted arenes provided mixtures of regioisomeric products. Notably, for ethyl benzoate and trifluorotoluene, the major product was the *meta*-substituted isomer and the selectivity (~4:1, *m*:*p*) was similar to reported values by Yu under his aerobic conditions (~4:1, *m*:*p*).[11a] We were encouraged by the reactivity shown with electron deficient arenes under our simple $Pd(OAc)_2$/**L2** catalyst system, as it indicates that catalyst control can be

used to improve the scope and allow reactivity from traditionally difficult substrates under these conditions.[7e,h] The purification of **3-19** and **3-20** were particularly difficult, so the isolated yields reported in Table 3.4 are fairly low. However, ^{1}H NMR analysis of crude reaction mixtures reports **3-19** and **3-20** in 70% and 52% yield, respectively, under the conditions reported in Table 3.4.

Table 3.5. Ligand Effects on Site-Selectivity



entry	ligand (mol %)	% yield[a]	β/α
1	none	61	2.8 ± 0.1
2	**L1** (5)	61	2.6 ± 0.1
3	**L2** (5)	81	2.9 ± 0.1
4	acridine (5)	62	4.2 ± 0.5
5	acridine (15)	63	4.7 ± 0.3

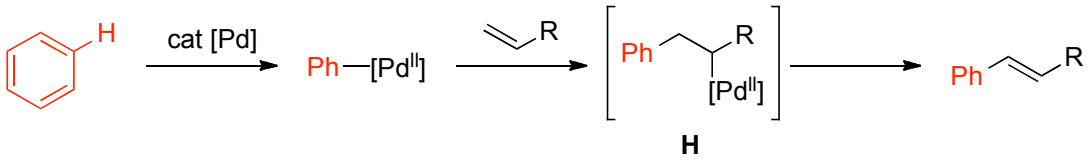
[a]Yield and isomer ratio determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture based on 1,3-dinitrobenzene standard. Reported yields represent averages of three reactions.

As shown above, $Pd(OAc)_2$/**L2** showed enhanced reactivity compared to $Pd(OAc)_2$ alone, and thereby allowed us to expand the scope for both alkenes and arenes. However, the site-selectivity of these C–H olefination reactions was modest at best. We believe that with the appropriate tuning of pyridine derivatives, the site-selectivity can be further improved. Our preliminary studies show that the presence of ligands **L1** or **L2** has minimal effect on site-selectivity compared to ligandless conditions in the reaction of *o*-xylene with ethyl acrylate (Table, 3.5, entries 1-3). However, the addition of 5 mol % of acridine enhanced the site-selectivity from 2.9:1 to 4.2:1 for the β-product. A further increase in selectivity (to 4.7:1) was observed upon raising the loading of acridine from 5 to 15 mol % (entries 4-5). Although this remains a relatively small effect to date, we believe that this data provides promising preliminary precedent that ligands can

be utilized to control the selectivity of C–H activation while retaining catalytic activity for F-M transformations.

3.3 Discussion

We were particularly interested in studying the F-M reaction because the Pd(II)-alkyl intermediate (Scheme 3.7, **H**) in this reaction is similar to the ones we discussed in Chapter 2. In the previous chapter, we developed methodology for oxidative interception of such Pd(II)-alkyl intermediates. Also, we were interested in generating the Pd(II)-alkyl intermediates via C–H activation and migratory insertion (the first two steps of the F-M reaction) that could allow us to replace the toxic organostannane requirements with simple arenes.



Scheme 3.7. Mechanism of the Fujiwara-Moritani Reaction

Initially when we surveyed the F-M reaction, we noticed areas in which this methodology could be improved. First, the reactivity was limited to electron neutral or electron rich arenes and α,β-unsaturated carbonyl derivatives as olefin partners. Secondly, the site-selectivities with substituted arenes were generally low. We sought to address these challenges with the use of simple pyridine-based ligands based on recent precedent from our group that pyridine can accelerate the $Pd(OAc)_2$-catalyzed C–H activation of arenes (Scheme 3.5).[12]

As predicted, the addition of pyridine ligands had a significant effect on the rate and the yield of the C–H olefination reaction with $Pd(OAc)_2$ as catalyst. We found that having 1:1 ratio of $Pd(OAc)_2$/pyridine was optimal for the C–H olefination reaction with $PhCO_3t$-Bu oxidant. This is presumably due to the active species for C–H activation being the coordinatively unsaturated complex $Pd(OAc)_2(Pyr)$.[11,12] An open coordination site on the Pd center is presumably desirable to facilitate binding of the arene prior to the C–H activation event. Excess amounts of pyridine ligand (1:2 Pd/Pyr) were shown to decrease the rate

and the yield of the reaction, and we believe that this is due to the formation of coordinatively saturated $Pd(OAc)_2(Pyr)_2$ complex as the major species in solution.

We have identified commercially available **L2** to be the optimal ligand choice for improved reactivity. Although still preliminary, we have also shown that ligands can influence the site-selectivity of the C–H activation step. A key future direction for this project involves identifying a ligand that will render the C–H activation step more site-selective while maintaining high reactivity in the coupling reaction. Another important long-term goal is to apply such Pd/L catalyst systems to the olefin difunctionalization reactions discussed in Chapter 2.

3.4 Conclusions

In summary, this chapter demonstrated the use of simple and commercial pyridine-based ligands as promoters for the $Pd(OAc)_2$-catalyzed F-M reaction. We have shown that the ratio of $Pd(OAc)_2$/pyridine is very important for accelerating the rate of the reaction. Also, preliminary results show that tuning of this supporting ligand enables modulation of site-selectivity in the C–H olefination of substituted arenes.

3.5 Experimental

NMR spectra were obtained on a Varian vnmrs 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C; 470.56 MHz for ^{19}F) or a Varian MR400 (400.53 MHz for ^{1}H; 100.71 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer.

3.6 Characterizations

Preparation of authentic samples.[17]

Ethyl acrylate (100 µL, 0.92 mmol, 1.0 equiv.), aryl iodide (1.19 mmol, 1.3 equiv.), $Pd(OAc)_2$ (10.3 mg, 0.046 mmol, 0.1 equiv.), and triethylamine (166 µL, 1.19 mmol, 1.3 equiv.) were added to a 20 mL scintillation vial equipped with a magnetic stir bar. MeCN (1.8 mL, 0.5 M) was added. The vial was sealed with a Teflon-lined cap, and the reaction was stirred at 100 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with 30 mL of diethyl ether. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel.

(E)-Ethyl 3-(2,3-dimethylphenyl)acrylate (**α-3-13**)

The title compound was prepared according to the general procedure using ethyl acrylate (100 µL, 0.92 mmol, 1.0 equiv.), 1-iodo-2,3-dimethylbenzene (277 mg, 1.19 mmol, 1.3 equiv.), $Pd(OAc)_2$ (10.3 mg, 0.046 mmol, 0.1 equiv.), triethylamine (166 µL, 1.19 mmol, 1.3 equiv.), and MeCN (1.8 mL, 0.5 M). The product was purified by chromatography on silica gel using 98% hexanes/2% EtOAc and was isolated as a clear oil (100 mg, 53% yield, R_f = 0.17 in 95% hexanes/5% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 15.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.31 (d, *J* = 15.6 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 2.31 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.10, 143.33, 137.33, 136.05, 133.76, 131.46, 125.74, 124.44, 119.70, 60.44, 20.59, 15.42, 14.32. IR (neat film): 1711, 1632 cm^{-1}. HRMS (EI) : *m*/*z* $[M]^+$ calcd for $C_{13}H_{16}O_2$, 204.1150; found, 204.1150.

(E)-Ethyl 3-(3,4-dimethylphenyl)acrylate (**β-3-13**)

The title compound was prepared according to the general procedure using ethyl acrylate (100 µL, 0.92 mmol, 1.0 equiv.), 4-iodo-1,2-dimethylbenzene (277 mg, 1.19 mmol, 1.3 equiv.), $Pd(OAc)_2$ (10.3 mg, 0.046 mmol, 0.1 equiv.), triethylamine (166 µL, 1.19 mmol, 1.3 equiv.), and MeCN (1.8 mL, 0.5 M). The product was purified by chromatography on silica gel using 98% hexanes/2% EtOAc and was isolated as a clear oil (161 mg, 86% yield, R_f = 0.23 in 95% hexanes/5% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 16.0 Hz, 1H), 7.30 (s, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.28 (s, 6H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.25, 144.75, 139.37, 137.08, 132.10, 130.12, 129.25, 125.64, 116.94, 60.34, 19.79, 19.74, 14.32. IR (neat film): 1708, 1635 cm^{-1}. HRMS (EI) : *m*/*z* $[M]^+$ calcd for $C_{13}H_{16}O_2$, 204.1150; found, 204.1147.

(E)-Ethyl 3-(2,3-dichlorophenyl)acrylate (**α-3-18**)

The title compound was prepared according to the general procedure using Ethyl acrylate (100 µL, 0.92 mmol, 1.0 equiv.), 1,2-dichloro-3-iodobenzene (325 mg, 1.19 mmol, 1.3 equiv.), $Pd(OAc)_2$ (10.3 mg, 0.046 mmol, 0.1 equiv.), triethyl amine (166 µL, 1.19 mmol, 1.3 equiv.), and MeCN (1.8 mL, 0.5 M). The product was purified by chromatography on silica gel using 98% hexanes/2% EtOAc and was isolated as a white solid (161 mg, 71% yield, R_f = 0.19 in 95% hexanes/5% EtOAc, mp 70.0-72.0 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 16.5 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 16.5 Hz, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.16, 140.32, 135.11, 133.96, 132.95, 131.43, 127.36, 125.76, 122.20, 60.83, 14.27. IR (thin film with CH_2Cl_2): 1716, 1637 cm^{-1}. HRMS (EI) : *m*/*z* $[M]^+$ calcd for $C_{11}H_{10}Cl_2O_2$, 224.0058; found, 224.0055.

(E)-Ethyl 3-(3,4-dichlorophenyl)acrylate (**β-3-18**)

The title compound was prepared according to the general procedure using Ethyl acrylate (100 µL, 0.92 mmol, 1.0 equiv.), 1,2-dichloro-4-iodobenzene (325 mg, 1.19 mmol, 1.3 equiv.), $Pd(OAc)_2$ (10.3 mg, 0.046 mmol, 0.1 equiv.), triethyl amine (166 µL, 1.19 mmol, 1.3 equiv.), and MeCN (1.8 mL, 0.5 M). The product was purified by chromatography on silica gel using 98% hexanes/2% EtOAc and was isolated as a white solid (219 mg, 97% yield, R_f = 0.17 in 95% hexanes/5% EtOAc, mp 55.5-56.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.35, 141.79, 134.47, 134.10, 133.21, 130.87, 129.58, 126.96, 120.14, 60.77, 14.26. IR (thin film with CH_2Cl_2): 1710, 1640 cm^{-1}. HRMS (EI) : *m*/*z* $[M]^+$ calcd for $C_{11}H_{10}Cl_2O_2$, 224.0058; found, 224.0062.

Typical experimental procedure for small scale including time study.[18] (Table 3.1, entry 1).

Ethyl cinnamate (10.5 mg, 0.0595 mmol, 1.0 equiv.), benzene (50 µL, 11.2 equiv. total including volume from pyridine standard solution), $Pd(OAc)_2$ (60 µL of a 0.0496 M standard solution prepared in acetic acid-d_4, 0.05 equiv.), pyridine (10 µL of a 0.3 M standard solution prepared in benzene, 0.05 equiv.), *tert*-butyl peroxybenzoate (11 µL, 1.0 equiv.), and acetic acid-d_4 (220 µL) were combined in a 4 mL scintillation vial equipped with a magnetic stir bar. The vial was sealed with a Teflon-lined cap. The reaction was stirred at 100 °C for 24 h. The resulting reaction mixture was cooled to room temperature, and 1,3-dinitrobenzene (50 µL of a 0.595 M standard solution prepared in $CDCl_3$, 0.5 equiv., ^{1}H NMR resonance

at 9.1 ppm for 1H) was added. The vial was capped and shaken. An aliquot was removed, and the yield was determined by ^{1}H NMR spectroscopic analysis in $CDCl_3$. For time studies, each time point was repeated at least 3 times (otherwise noted).

Typical experimental procedure for preparative scale.[18] (Table 3.3, entry 1).

Ethyl cinnamate (246 mg, 1.50 mmol, 1.0 equiv.), benzene (1.5 mL, 11.2 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL) were combined in a 20 mL scintillation vial equipped with a magnetic stir bar. The vial was sealed with a Teflon-lined cap. The reaction was stirred at 100 °C for 6 h. The resulting reaction mixture was diluted with ethyl acetate (15 mL) and quenched with a 10% aqueous Na_2SO_3 solution (20 mL). The organic layer was separated and washed with 10% aqueous Na_2SO_3 solution (2 x 20 mL), saturated aqueous $NaHCO_3$ solution (3 x 20 mL), and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel. Some products were further purified by HPLC (6 mL/min, Waters SunFire Prep Silica 5 µm).

Ethyl 3,3-diphenylacrylate (**3-1**)

The title compound was prepared via the standard procedure using ethyl cinnamate (246 mg, 1.50 mmol, 1.0 equiv.), benzene (1.5 mL, 11.2 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (286 mg, 76% yield). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[19]

Methyl 3,3-diphenylacrylate (**3-2**)

The title compound was prepared via the standard procedure using methyl cinnamate (243 mg, 1.50 mmol, 1.0 equiv.), benzene (1.5 mL, 11.2 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (269 mg, 75% yield). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[20]

trans-Ethyl cinnamate (**3-3**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1 equiv.), benzene (1.5 mL, 11.2 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (164 mg, 62% yield). ^{1}H and ^{13}C NMR spectral data of the

isolated material matched the spectral data reported in the literature for this compound.[21]

trans-Methyl cinnamate (**3-4**)

The title compound was prepared via the standard procedure using methyl acrylate (135 µL, 1.50 mmol, 1.0 equiv.), benzene (1.5 mL, 11.2 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (156 mg, 64% yield). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[21]

trans-Butyl cinnamate (**3-5**)

The title compound was prepared via the standard procedure using butyl acrylate (215 µL, 1.50 mmol, 1.0 equiv.), benzene (1.5 mL, 11.2 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (199 mg, 65% yield). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[22]

(E)-Methyl 3-phenylbut-2-enoate (**3-6**)

The title compound was prepared via the standard procedure using (*E*)-methyl but-2-enoate (150 mg, 1.50 mmol, 1.0 equiv.), benzene (5.4 mL, 40.0 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (152 mg, 58% yield). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[23]

(E)-Methyl 2-methyl-3-phenylacrylate (**3-7**)

The title compound was prepared via the standard procedure using methyl methacrylate (160 µL, 1.50 mmol, 1.0 equiv.), benzene (5.4 mL, 40.0 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (116 mg as a 1:0.31 mixture with the byproduct phenylated at the α-methyl position, 58% corrected yield for the desired product). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[24,25]

trans-Stilbene (**3-8**)

The title compound was prepared via the standard procedure using styrene (172 µL, 1.50 mmol, 1.0 equiv.), benzene (5.4 mL, 40 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl

peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a white solid (116 mg, 43% yield). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[21]

trans-Cinnamyl acetate (**3-9**)

The title compound was prepared via the standard procedure using styrene (154 µL, 1.50 mmol, 1.0 equiv.), benzene (5.4 mL, 40 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (151 mg as a mixture of 92:8 with diphenylated product (**3-9B**), 57% corrected yield for the desired product). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[26,27]

Styrene (**3-10**)

The title compound was prepared by bubbling ethylene for approximately 3 minutes into a reaction mixture of benzene (5.4 mL, 40 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.50 mmol, 1.0 equiv.), and acetic acid (7.0 mL) in a 25-50 mL Schlenk tube. The Schlenk tube was then sealed with a Teflon stopcock, and the reaction was stirred at 100 °C for 6 h in an oil bath. The reaction mixture was cooled to room temperature and diluted with 5 mL of chloroform. 1,3-Dinitrobenzene (36.9 mg, 0.2 equiv., ^{1}H NMR resonance at 9.1 ppm) was added and the reaction mixture was mixed thoroughly. An aliquot (approximately 50 µL) was removed, and the yield was determined by ^{1}H NMR spectroscopic analysis in $CDCl_3$ (33%, an average of three reactions).

(E)-Ethyl 3-(o-/m-/p-tolyl)acrylate (**3-11**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), toluene (1.5 mL, 10.9 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (208 mg as a mixture of product isomers, 73% yield, 1:1.2:1.3 *o:m:p*). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[28]

(E)-Ethyl 3-(2-/3-/4-methoxyphenyl)acrylate (**3-12**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), anisole (1.5 mL, 9.2 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (212 mg as a mixture of product isomers, 69% yield, 4.1:1:7.4 *o:m:p*). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[29,30]

(E)-Ethyl 3-(2,3-/3,4-dimethylphenyl)acrylate (**3-13**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), *o*-xylene (1.5 mL, 9.4 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear yellow oil (210 mg as a mixture of product isomers, 69% yield, 1:3 α:β). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data of samples authentically synthesized.

(E)-Ethyl 3-(2,5-dimethoxyphenyl)acrylate (**3-14**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), 1,4-dimethoxybenzene (1.5 mL, 7.6 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (267 mg, 75% yield). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[31]

(E)-Ethyl 3-(naphthalen-1-/2-yl)acrylate (**3-15**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), naphthalene (1.9 g, 10 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (267 mg as a mixture of product isomers, 79% yield, 1.1:1 α:β). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[32]

(E)-Ethyl 3-(2,4,6-trifluorophenyl)acrylate (**3-16**)

The title compound was prepared according to the general procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), 1,3,5,-trifluorobenzene (1.5 mL. 9.7 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was purified by chromatography on silica gel using 98% hexanes/2% EtOAc and was isolated as a clear viscous oil (322 mg, 93% yield, R_f = 0.27 in 95% hexanes/5% EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 16.8 Hz, 1H), 6.72 (t, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 16.8 Hz, 1H), 4.27 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.76, 163.05 (dt, *J* = 254.8, 15.8 Hz), 162.00 (ddd, *J* = 256.8, 14.7, 9.8 Hz), 129.73, 123.81 (td, *J* = 7.8, 1.9 Hz), 109.21 (td, *J* = 15.6, 4.9 Hz), 100.92 (m), 60.75, 14.26. ^{19}F NMR (471 MHz, $CDCl_3$) δ –104.33 (quin, *J* = 8.5 Hz, 1F), –106.79 (t, *J* = 8.5 Hz, 2F). IR (neat film): 1719, 1630, 1183 cm^{-1}.

HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{11}H_9F_3O_2$, 231.0627; found, 231.0627.

(E)-Ethyl 3-(perfluorophenyl)acrylate (**3-17**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.5 mmol, 1.0 equiv.), 1,2-dichlorobenzene (5.4 mL, 33.0 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (268 mg, 67% yield). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[33]

(E)-Ethyl 3-(2,3-/3,4-dichlorophenyl)acrylate (**3-18**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), 1,2-dichlorobenzene (5.4 mL, 32.0 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was purified by chromatography on silica gel using 98% hexanes/2% EtOAc and was isolated as a a clear yellow oil (242 mg as a mixture of product isomers, 66% yield, 1:1.6 α:β). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data of samples authentically synthesized.

(E)-Ethyl 2-/3-/4-(3-ethoxy-3-oxoprop-1-en-1-yl)benzoate (**3-19**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), ethyl benzoate (5.4 mL, 25.1 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (155 mg as a mixture of product isomers, 42% yield, 1:5.6:1.5 *o:m:p*). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[34,35,36]

*(E)-Ethyl 3-(2-/3-/4-(trifluoromethyl)phenyl)*acrylate (**3-20**)

The title compound was prepared via the standard procedure using ethyl acrylate (164 µL, 1.50 mmol, 1.0 equiv.), (trifluoromethyl)benzene (5.4 mL, 29.3 equiv.), $Pd(OAc)_2$ (16.8 mg, 0.05 equiv.), 3,5-dichloropyridine (11.1 mg, 0.05 equiv.), *tert*-butyl peroxybenzoate (285 µL, 1.0 equiv.), and acetic acid (7.0 mL). The product was obtained as a clear oil (155 mg as a mixture of product isomers, 32% yield, 1:15.8:4.2 *o:m:p*). ^1H and ^{13}C NMR spectral data of the isolated material matched the spectral data reported in the literature for this compound.[3738]

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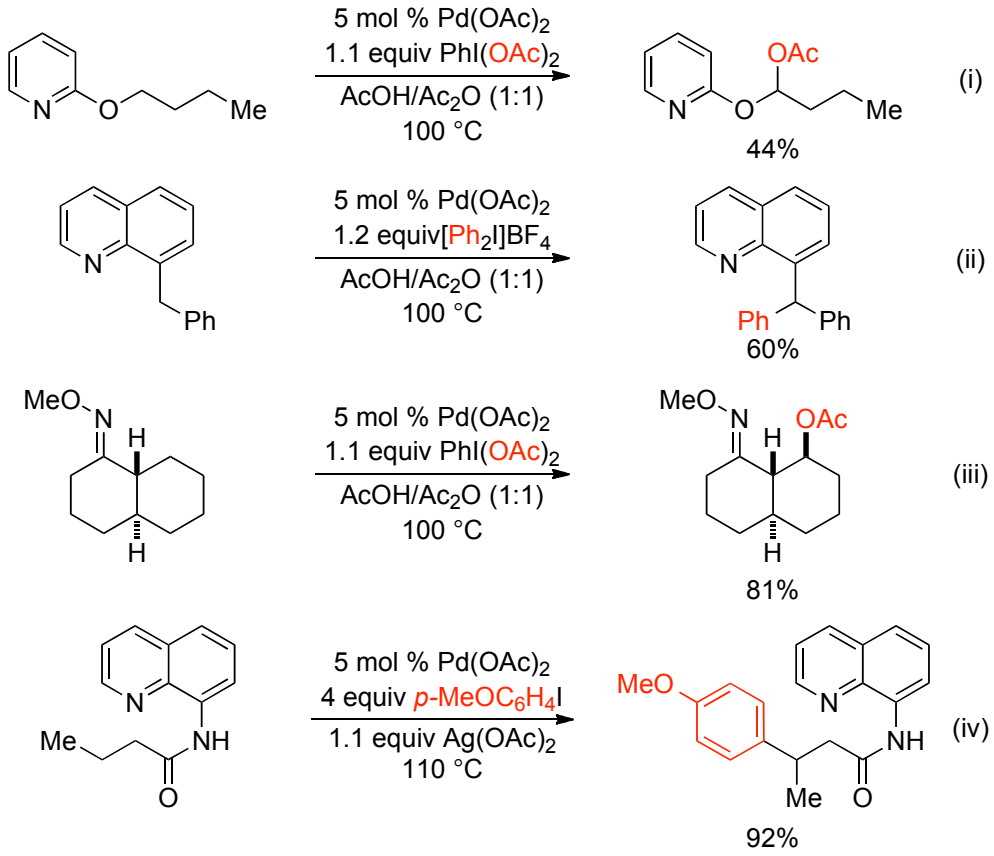
CHAPTER 4

Palladium-Catalyzed Ligand-Directed Oxidative Functionalization of Cyclopropanes

4.1 Introduction

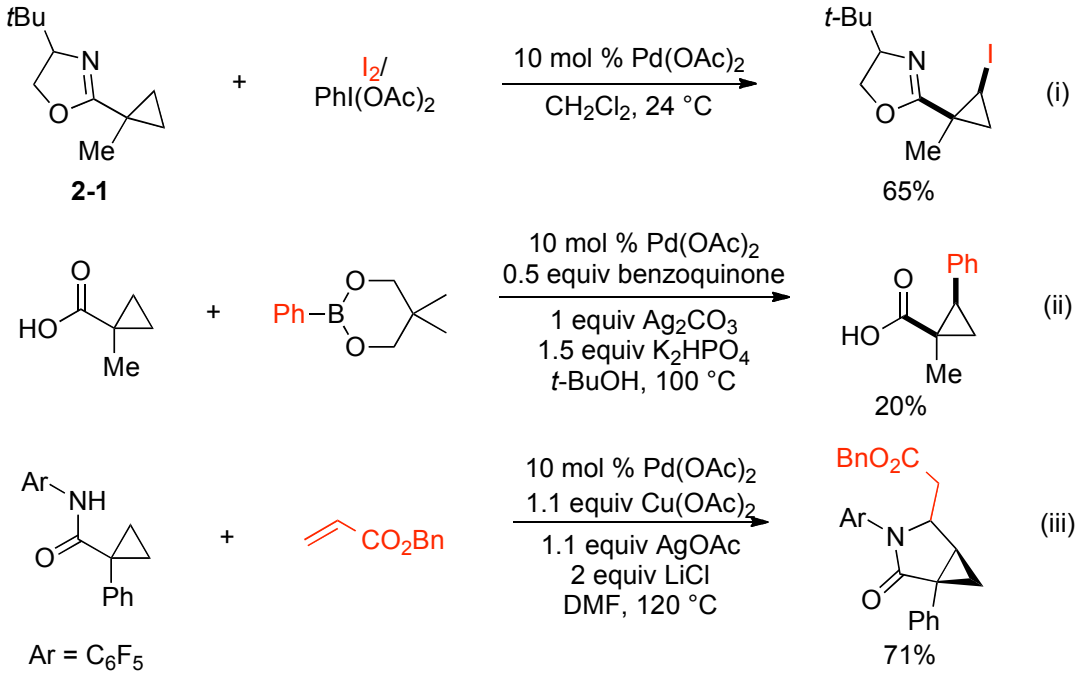
Direct C–H functionalization via transition metal catalysis serves as an atom economical method for the synthesis of a variety of organic molecules.[1] This field has significantly expanded over the past decade, and ligand-directed Pd-catalyzed reactions have emerged as an active sub-field.[2] These transformations involve the conversion of C–H bonds into C–O, C–halogen, C–S, C–N, and C–C bonds.[2] Numerous examples of Pd-catalyzed C–H functionalization methods have been reported for diverse aromatic and olefinic C–H (sp^2) and 1° sp^3 C–H bonds.[2] However, a main challenge remaining in this field is to obtain reactivity from 2° and 3° sp^3 C–H bonds.

There are few reported examples of Pd-catalyzed ligand-directed 2° sp^3 C–H activation/functionalization reactions. Furthermore, the vast majority of these reactions were achieved with electronically and/or sterically biased substrates (Scheme 4.1). For example, the C–H bond that is being functionalized in **A** and **B** is activated by an adjacent heteroatom (oxygen) or aryl group (Scheme 4.1, i and ii).[3,4] The fused bicyclic structure of **C** provides a conformational bias such that only a 2° sp^3 C–H is accessible for functionalization (Scheme 4.1, iii).[3] Finally, both nitrogen atoms in substrate **D** coordinate to Pd, thereby facilitating the cleavage and the functionalization of the unactivated 2° sp^3 C–H bond (Scheme 4.1, iv).[5]



Scheme 4.1. Examples of 2° sp^3 C–H Activation/Functionalization

Sporadic examples of Pd-catalyzed ligand-directed 2° sp^3 C–H functionalization of cyclopropanes have also been reported. These transformations include C–H halogenation,[6] arylation,[7] alkylation,[8] and olefination[9,10] of various substituted cyclopropanes (Scheme 4.2). As shown in Scheme 4.2, Yu and co-workers have reported directed iodination with IOAc (i),[6] arylation using an organoboron reagent (ii),[7] and olefination with an acrylate followed by Michael addition to form a fused ring system (iii).[9] These reports are interesting because cyclopropyl C–H bonds have a pK_a values of approximately 46 and bond dissociation energies of 106 kcal/mol. Given these characteristics, they are not particularly activated for homolytic or heterolytic cleavage.[11] Nonetheless, the examples in Scheme 4.2 show selective functionalization of the cyclopropyl C–H bonds in the presence of other potentially reactive sp^2 and/or 1° sp^3 C–H bonds.



Scheme 4.2. Examples of Ligand-Directed C–H Functionalization of Cyclopropane Derivatives[6,7,9]

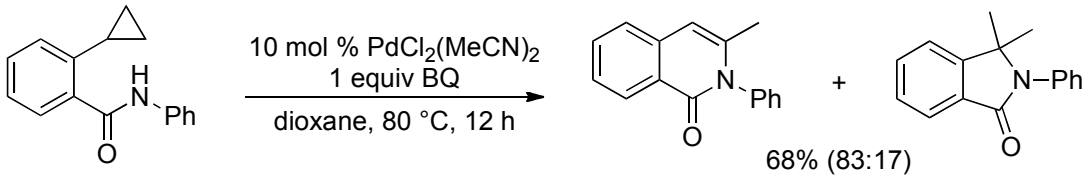
Substituted cyclopropanes are particularly interesting as they are widely used as intermediates in organic synthesis; therefore, Pd-catalyzed C–H functionalization of cyclopropane derivatives, such as the ones shown in Scheme 4.2, is an important advance for the synthetic community.[12] Previous reports of Pd-catalyzed cyclopropyl C–H functionalization represented isolated examples, and no systematic investigation of such transformations had been reported prior to our work.[13]

Detailed studies of the Pd-catalyzed ligand-directed oxidative functionalization of cyclopropane derivatives were carried out in order to gain some insights into the reactivity trends of cyclopropyl C–H bonds. This chapter describes the Pd-catalyzed reactions of cyclopropyl oxazolines, oxime ethers, and pyridines. Their reactivity was explored with three oxidants: IOAc, $PhI(OAc)_2$, and benzoquinone (BQ). The Pd-catalyzed oxidative functionalization reactions were found to be extremely sensitive to small perturbations of the directing group, substituents on the cyclopropyl ring, and the reaction conditions. As detailed below, seemingly minor changes of these variables often resulted in

competing C–C bond activation of the cyclopropane to afford ring-opened products.

4.2 Results

We focused on three different oxidative conditions for this study. The first oxidant investigated was IOAc, which is generated *in situ* from I_2 and $PhI(OAc)_2$. This reagent was successfully utilized for the iodination of cyclopropyl oxazoline **4-1** by Yu and co-workers (Scheme 4.2, i).[6] Second, we examined $PhI(OAc)_2$, as our group[14] and others[15] have developed Pd-catalyzed C–H acetoxylation protocols using this oxidant. Lastly, benzoquinone (BQ) in conjunction with acetic acid (AcOH) (which supplies the external nucleophile for the acetoxylation) was employed. Notably, $PhI(OAc)_2$ is frequently used in Pd(II/IV) transformations, whereas BQ typically mediates Pd(II/0) catalysis. For example, in a relevant report by Yudin, BQ was used as the terminal oxidant for the Pd-catalyzed oxidative C–C activation of arylcyclopropanes (Scheme 4.3).[16]

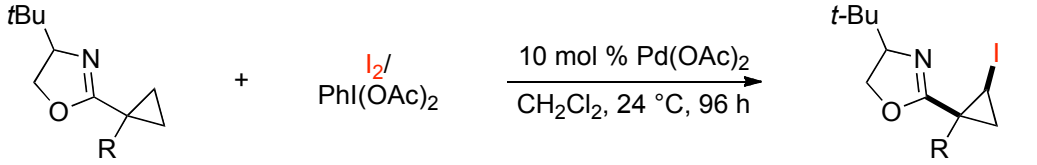


Scheme 4.3. Pd-Catalyzed Oxidative C–C Activation of Arylcyclopropane[16]

4.2.1 Cyclopropyl Oxazoline Substrates

Based on Yu's report on the Pd-catalyzed ligand-directed iodination of cyclopropanes with IOAc, we began our study with cyclopropyl oxazolines **4-1** and **4-2**.[6] Yu's report with substrate **4-1** was particularly intriguing to us because he reported that the functionalization was selective for a cyclopropyl 2° sp^3 C–H bond over a 1° sp^3 C–H site present at the same distance from the directing nitrogen atom (Scheme 4.2, i). In our hands, the reaction of **4-1** with 10 mol % of $Pd(OAc)_2$ and 1 equiv of IOAc in CH_2Cl_2 at room temperature for 96 h (Yu's reported conditions) afforded 34% yield of **4-1a** based on ^1H NMR spectroscopic analysis of the crude reaction mixture (Yu reported 65% yield, Scheme 4.2, i). However, under identical conditions, substrate **4-2** (synthesized via analogous

route to that reported for **4-1**)[6] was found to be completely unreactive towards iodination. In this case, the starting material remained unreacted even after 96 h (Scheme 4.4). Interestingly, the only difference between substrates **4-1** and **4-2** is the methyl group at the α-position; therefore, the drastic change in the reactivity appears to indicate that C–H iodination is extremely sensitive to the steric and/or the electronic environment around the reaction site.

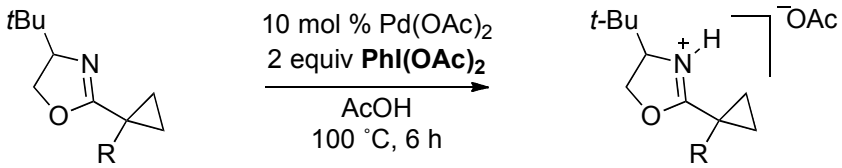


R = Me (**4-1**)
R = H (**4-2**)

R = Me, 34% (**4-1a**)
R = H, not detected

Scheme 4.4. Oxazoline-Directed C–H Iodination

Next, oxazoline substrates **4-1** and **4-2** were subjected to $Pd(OAc)_2/PhI(OAc)_2$. Standard Pd-catalyzed C–H acetoxylation conditions require the use of 10 mol % of $Pd(OAc)_2$ and 2 equiv of $PhI(OAc)_2$ in AcOH at 100 °C.[3,14,15] When **4-1** and **4-2** were subjected to these conditions in AcOH, the oxazolium acetate salts were formed as the major observable products (19% **4-1b** and 26% **4-2b**) and no C–H acetoxylation products were detected by mass spectrometric or ^{1}H NMR spectroscopic analysis (Scheme 4.5). Notably, these oxazolium salts **4-1b** and **4-2b** were also formed (in 59% and 62% yield, respectively) when **4-1** and **4-2** were stirred in AcOH at 100 °C for 6 h in the absence of Pd catalyst and $PhI(OAc)_2$.



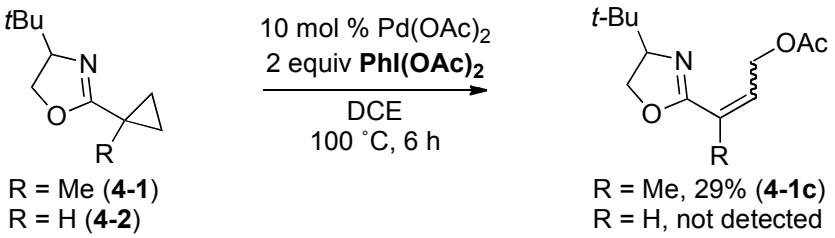
R = Me (**4-1**)
R = H (**4-2**)

R = Me, 19% (**4-1b**)
R = H, 29% (**4-2b**)

Scheme 4.5. Oxazolium Acetate Salt Formation

To eliminate the salt formation, the acetoxylation reaction was studied in dichloroethane (DCE) instead of AcOH. From Yu's reaction, we knew that the

oxazoline substrates were tolerated in CH_2Cl_2, but since we needed to heat the acetoxylation reaction to 100 °C, we chose a similar solvent with higher boiling point. Under the same conditions in DCE, C–C bond activation was observed with substrate **4-1** to afford the ring-opened alkene **4-1c** in 29% yield as a mixture of E/Z isomers (Scheme 4.6). Notably, **4-1c** was also formed at room temperature under otherwise analogous conditions, but in lower (12%) yield. In contrast, substrate **4-2** did not yield any acetoxylation products under these conditions. This is similar to the reactivity pattern observed for the iodination, where substrate **4-1** showed reactivity but **4-2** did not.



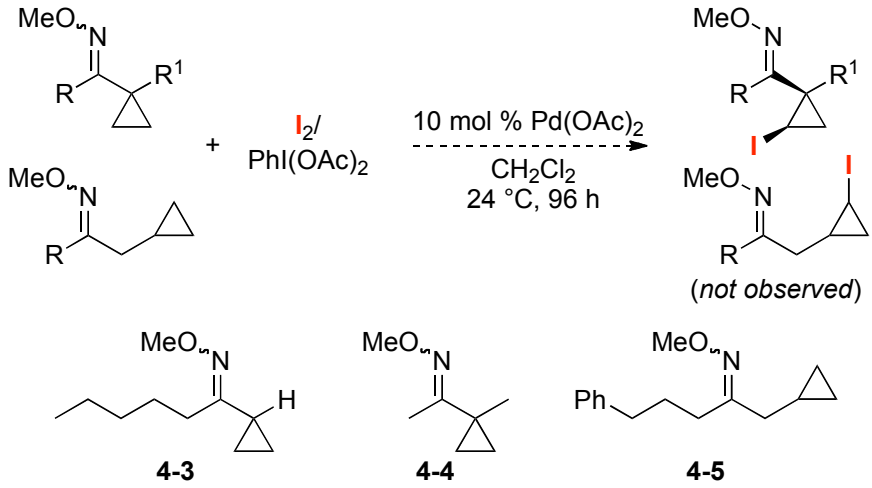
Scheme 4.6. Oxazoline-Directed C–C Activation/Acetoxylation

Finally, the oxazoline substrates were subjected to 10 mol % of $Pd(OAc)_2$ and 2 equiv of BQ in AcOH at 100 °C. Under these conditions the acetate source is the AcOH, so the solvent could not be changed. Again we observed the oxazolium salt formation. Although the salt formation only occurred in low yield (<10% for **4-1b** and 25% for **4-2b**), none of the corresponding C–H acetoxylation products were detected by mass spectrometric or ^{1}H NMR spectroscopic analysis.

4.2.2 Cyclopropyl *O*-Methyloxime Substrates

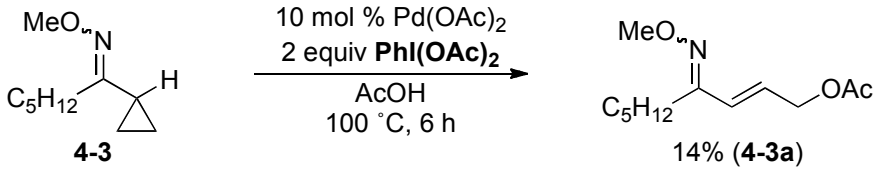
Oxime ethers have been shown to be excellent directing groups for Pd-catalyzed reactions.[3,14c,f] Thus, we next studied substrates **4-3** to **4-5** under the conditions previously examined with the oxazoline derivatives. These substrates were synthesized by oximation of the corresponding ketones. We designed these substrates in order to investigate the role that sterics play in reactivity (**4-3** versus **4-4**) and also to see if the distance between the cyclopropane and the directing ligand is important (**4-3** versus **4-5**). These substrates were first subjected to Yu's

iodination conditions.[6] As shown in Scheme 4.7, none of the expected C–H iodination products were observed. ^{1}H NMR spectroscopic analysis of the crude reactions showed the presence of a significant amount of starting material after 96 h (42% **4-3**, 22% **4-4**, 71% **4-5**). Mixtures of unidentified byproducts were also detected; however, by electrospray mass spectrometry no peak associated with mono-iodinated cyclopropane products was observed in any of the three reactions.



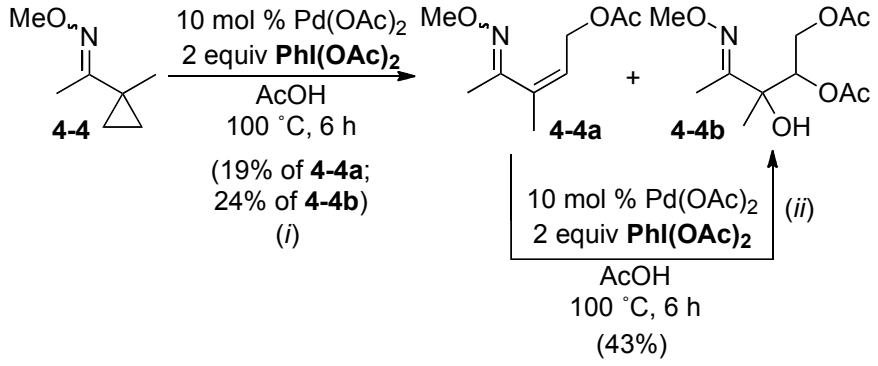
Scheme 4.7. Oxime Ether-Directed C–C Activation/Acetoxylation

Next, we studied the reactivity of the same oxime substrates with $Pd(OAc)_2$/$PhI(OAc)_2$ in AcOH. All three substrates underwent C–C activation to give ring-opened products. For example, **4-3** reacted to afford 14% yield of the α,β-unsaturated allylic acetate **4-3a** (Scheme 4.8). Attempts to optimize this reaction were unsuccessful, and the mass balance was poor. This is most likely due to product decomposition under the reaction conditions. For example, when isolated product **4-3a** was re-subjected to the reaction conditions, only 6% remained after 6 h at 100 °C.

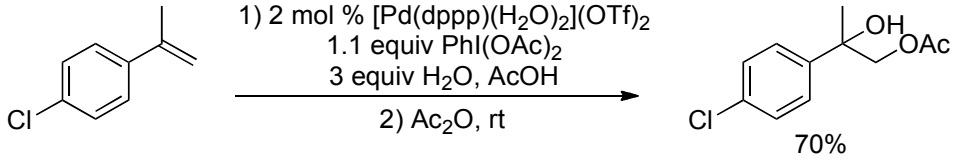


Scheme 4.8. Acetoxylation of **4-3** with $Pd(OAc)_2$/$PhI(OAc)_2$

The ring-opened acetoxylation products were different from substrate to substrate. With **4-4**, monoacetoxylated product **4-4a** and trioxygenated product **4-4b** were formed in 19% and 24% yield, respectively (Scheme 4.9, i). The monoacetoxylated product **4-4a** is the result of similar reactivity seen with **4-3** to form **4-3a**. However, trioxygenated product **4-4b** was not seen previously. We propose that **4-4b** forms via *in situ* dioxygenation of the alkene moiety of **4-4a** through a Pd-catalyzed pathway (Scheme 4.9, ii). This proposal is supported by the observation that when an isolated sample of **4-4a** was subjected to the reaction conditions, 43% yield of **4-4b** was observed after 6 h. This proposal is also consistent with a literature report showing that an analogous Pd-catalyzed dioxygenation reaction of 1,1-disubstituted alkenes placed an OAc group at the least substituted carbon and an OH group at the most substituted carbon of the product (Scheme 4.10).[17]

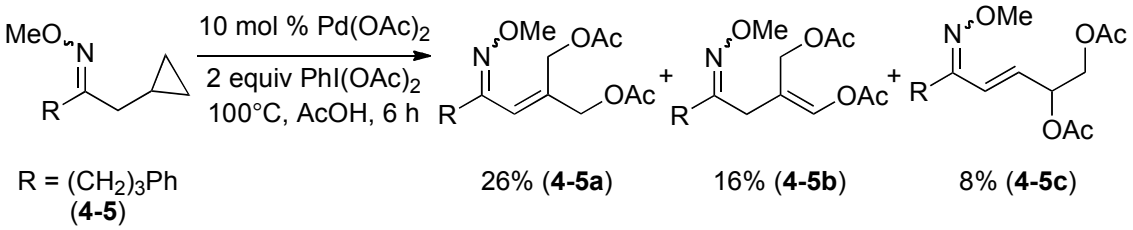


Scheme 4.9. Acetoxylation of **4-4** with $Pd(OAc)_2$/$PhI(OAc)_2$



Scheme 4.10. Pd-Catalyzed Alkene Dioxygenation with $PhI(OAc)_2$[17a]

When substrate **4-5** was subjected to the $Pd(OAc)_2/PhI(OAc)_2$ conditions, three different diacetoxylated ring-opened products were observed (**4-5a**-**c**, Scheme 4.11). Branched products **4-5a** and **4-5b** were formed in 26% and 16% yield, respectively, along with the linear product **4-5c** in 8% yield at 100 °C. While further modifying the reaction conditions, we realized that the ratio of products **4-5a** and **4-5b** was highly dependent on reaction temperature. For example, at 60 °C **4-5a** was the major product (45% yield) and **4-5b** was not observed (Table 4.1, entry 1). In contrast, at 120 °C **4-5a** was formed in only 9% yield along with 10% yield of **4-5b** (Table 4.1, entry 4).



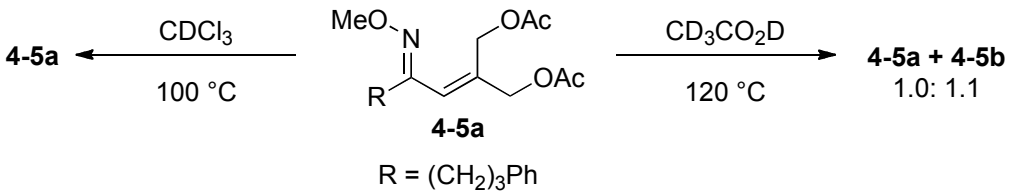
Scheme 4.11. Acetoxylation of **4-5** with $Pd(OAc)_2/PhI(OAc)_2$

Table 4.1. Product Distribution as a Function of Temperature

Entry	T (°C)	**4-5a** (%)	**4-5b** (%)	**4-5c** (%)	**4-5** (%)
1	60	45	nd	7	3
2	80	44	nd	8	6
3	100	26	12	8	3
4	120	9	10	9	3

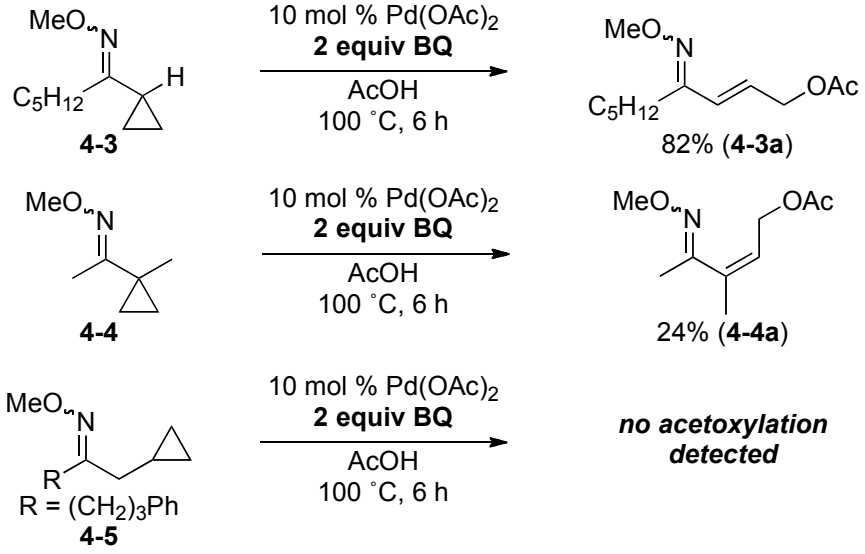
nd = not detected

Although the mass balance was poor at higher temperature, we reasoned that this temperature dependence was due to **4-5a** being the kinetic product with **4-5b** as the thermodynamic product. To test this hypothesis, we heated pure samples of **4-5a** in CD_3CO_2D (at 120 °C) and in $CDCl_3$ (at 100 °C). ^1H NMR spectroscopic analysis after heating showed a 1.0:1.1 ratio of **4-5a** and **4-5b** in CD_3CO_2D. In contrast, no isomerization was observed in $CDCl_3$ (Scheme 4.12). These experiments suggest that **4-5a** isomerizes to **4-5b** via an acid assisted pathway in AcOH.



Scheme 4.12. Isomerization of **4-5a** at 120 °C in CD_3CO_2D

Lastly, the oxime substrates were reacted with BQ/AcOH under the Pd-catalyzed acetoxylation conditions. Substrates **4-3** and **4-4** produced the monoacetoxylated products **4-3a** and **4-4a** in 82% and 24% yield, respectively (Scheme 4.13). Interestingly, **4-4** did not give the triacetoxylated **4-4b**, presumably because its formation requires $PhI(OAc)_2$. On the contrary, substrate **4-5** did not yield any acetoxylated product under Pd-catalyzed BQ/AcOH conditions (Scheme 4.13).

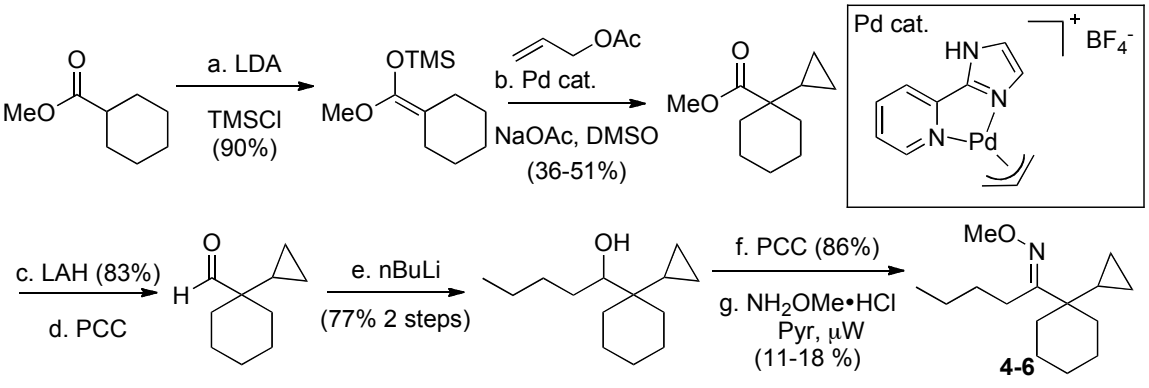


Scheme 4.13. Reaction of Oxime Substrates with $Pd(OAc)_2$ and BQ/AcOH

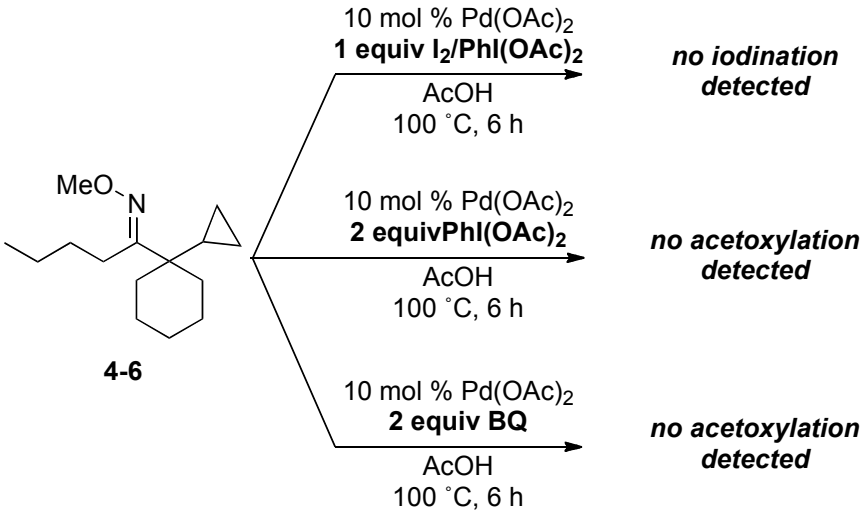
The major difference between substrates **4-3** and **4-4** is the methyl group at the α-position, which most likely provides some steric influence over the acetoxylation reaction. Similar to the analogous oxazoline substrates (**4-1** versus **4-2**), there is a large difference in the reactivity with the oxime substrates bearing an α-methyl group. In the $PhI(OAc)_2$ oxidation system, **4-4** afforded slightly increased amounts of acetoxylated products than **4-3** (Schemes 4.8 and 4.9) but

in the BQ/AcOH system, **4-4** showed significantly higher reactivity than **4-3** (Scheme 4.13).

In the attempts to further understand how sterics may play a role with oxime substrate under these oxidative conditions, we synthesized substrate **4-6**, which contains a cyclohexyl group between the cyclopropyl group and the directing group (Scheme 4.14). Methylcyclohexane carboxylate was deprotonated with LDA and the resulting enolate was trapped with TMSCl. The TMS enolate was then subjected to a cyclopropanation reaction using allyl acetate and a Pd-allyl complex as reported in the literature.[18] The resulting cyclopropyl methyl ester was reduced to the corresponding aldehyde in two steps. The butyl addition to the aldehyde was achieved using *n*BuLi, and the resulting alcohol product was then oxidized to the ketone using PCC. The final oximation step from the ketone was not successful under typical thermal conditions (presumably due to the highly hindered nature of this ketone). However, when oximation was conducted in a microwave reactor, small amounts (11-18% yield) of the desired oxime **4-6** were obtained. Substrate **4-6** can be considered a more sterically crowded analogue of substrate **4-5**, as their distance between the directing ligand and the cyclopropane are the same in both cases. Disappointingly, when **4-6** was subjected to all three oxidation conditions, no iodinated or acetoxylated products were observed (Scheme 4.15). We hypothesized that this lack of reactivity may be due to the significant amount of steric crowding around the reaction site.



Scheme 4.14. Synthesis of Substrate **4-6**
Step b and catalyst synthesis[18]

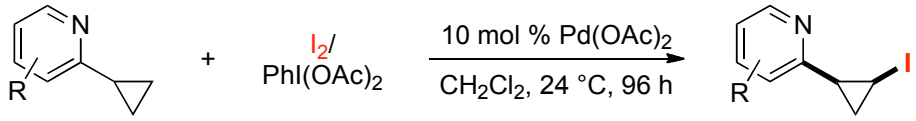


Scheme 4.15. Reaction of **4-6** with $Pd(OAc)_2$ and IOAc, $PhI(OAc)_2$, and BQ/AcOH

4.2.3 Cyclopropyl Pyridine Substrates

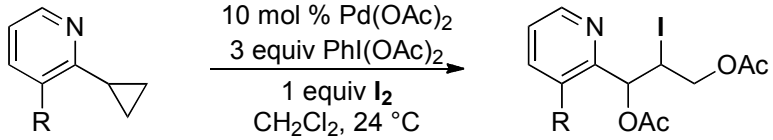
We next turned to one of the most effective directing groups known for Pd-catalyzed C–H functionalization reactions – pyridine derivatives.[3,4,14f] We synthesized a series of 2-cyclopropylpyridines **4-7**-**4-11**, via Suzuki coupling of cyclopropyl boronic acids with the corresponding halogenated pyridines,[19] to study their reactivity under the oxidative conditions. In general, pyridine substrates were found to be very sensitive to substitution patterns, and only 3-substituted 2-cyclopropyl pyridines showed any reactivity. For example, under Yu's iodination conditions, 4-methyl and 6-methyl substituted substrates did not yield any desired product; however, 3-substituted pyridines afforded the *cis* isomer of C–H activation/iodination products (**4-9a**, **4-10a**, and **4-11a**), albeit in low yields (Table 4.2). Attempts to optimize the iodination reaction with IOAc were not successful, and varying reaction time, temperature, and iodine salt additives did not improve the formation of *cis*-iodinated products. Interestingly, however, we discovered that when the amount of $PhI(OAc)_2$ was increased to 3 equiv, the 3-substituted pyridine derivatives formed ring-opened linear monoiodo-diacetoxylated products (**4-9b**, **4-10b**, and **4-11b**) as a single diastereomer (Scheme 4.16).

Table 4.2. C–H iodination of 2-cyclopropylpyridines with $Pd(OAc)_2$/IOAc



Entry	R	Yield (%)
1	4-Me (**4-7**)	nd
2	6-Me (**4-8**)	nd
3	3-Me (**4-9**)	19% (**4-9a**)
4	3-Et (**4-10**)	21% (**4-10a**)
5	3-MeO (**4-11**)	19% (**4-11a**)

nd = not detected

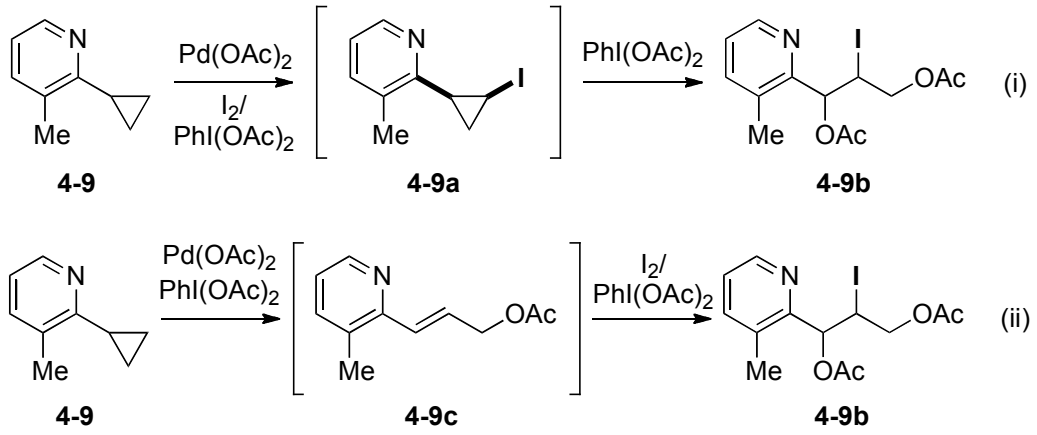


R = Me: 35% (**4-9b**)
R = Et: 26% (**4-10b)**
R = OMe: 65% (**4-11b**)

Scheme 4.16. Iodo-Diacetoxylation of 3-Substituted 2-Cyclopropyl Pyridines

Initially, it seemed reasonable to think that this ring-opened product was a result of overfunctionalization of the *cis*-iodinated product that is formed first (Scheme 4.17, i). To test this idea, an isolated sample of **4-9a** was subjected to the reaction conditions (10 mol % of $Pd(OAc)_2$, 1 equiv of I_2, 3 equiv of $PhI(OAc)_2$, CH_2Cl_2, rt); however, interestingly, product **4-9b** was not observed. Another possible pathway to **4-9b** would involve the *in situ* formation of monoacetoxylated olefin (**4-9c**), which then undergoes iodo-acetoxylation on the alkene site (Scheme 4.17, ii). From our experience with the oxazoline and oxime substrates, the formation of monoacetoxylated olefin (such as **4-1c**, **4-3a**, and **4-4a**) in the presence of excess $PhI(OAc)_2$ seemed reasonable for pyridine substrates as well. To confirm that **4-9c** is forming in situ, **4-9** was subjected to the reaction conditions in the absence of I_2 (10 mol % of $Pd(OAc)_2$ and 1 equiv of $PhI(OAc)_2$ in CH_2Cl_2 at rt). After 48 h, 12% yield of **4-9c** was observed by ^1H

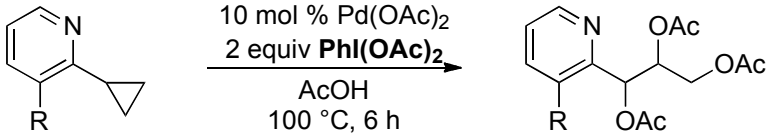
NMR spectroscopic analysis of the crude reaction mixture. Also, in the next set of studies it becomes more evident that **4-9c** is a viable intermediate under the Pd-catalyzed oxidative functionalization conditions.



Scheme 4.17. Potential Pathways for the Formation of **4-9b**

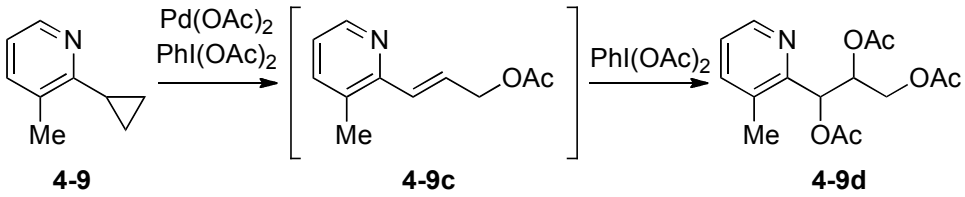
The pyridine substrates were next treated with $Pd(OAc)_2$ and $PhI(OAc)_2$. Similar to the oxazoline and oxime substrates, these conditions also yielded C–C activation/acetoxylation, but in this case, the major product was a linear triacetoxylated species (Table 4.3). Again, only 3-substituted pyridine derivatives successfully reacted to afford the triacetoxylated products in 21-34% yield as mixtures of diastereomers (entries 3-5).

Table 4.3. C–C Activation of 2-Cyclopropylpyridines with $Pd(OAc)_2$/$PhI(OAc)_2$



Entry	R	Yield (%)
1	4-Me (**4-7**)	nd
2	6-Me (**4-8**)	nd
3	3-Me (**4-9**)	29% (**4-9d**)
4	3-Et (**4-10**)	21% (**4-10d**)
5	3-MeO (**4-11**)	34% (**4-11d**)

The structures of triacetoxylated products **4-9d**, **4-10d**, and **4-11d** observed for pyridine substrates are very similar to the trioxygenated product **4-4b** formed with the oxime substrate. In the previous section, we reasoned that **4-4b** formed from the monoacetoxylated olefin product **4-4a**. We believe that a similar intermediate, alkene **4-9c**, is formed that then undergoes Pd-catalyzed diacetoxylation at the alkene site (Scheme 4.18). Monoacetoxylated alkene **4-9c**, isolated from the reaction mentioned previously, was treated under the reaction conditions. Re-subjection of **4-9c** to the standard reaction conditions then afforded 17% of **4-9d** after 6 h at 100 °C (and <10% **4-9c** was recovered under these conditions).



4-9 **4-9c** **4-9d**

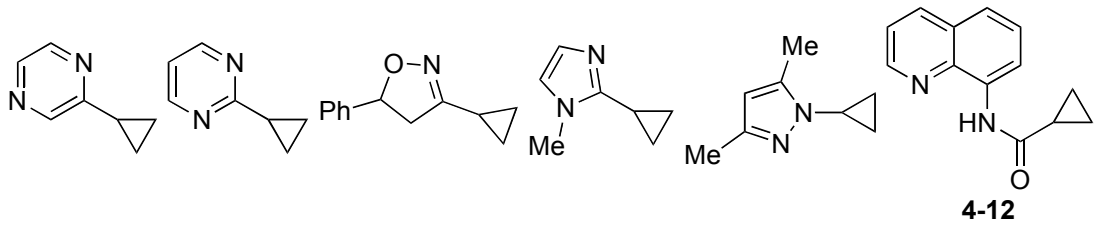
Scheme 4.18. Possible Pathway to Triacetoxylated Product **4-9d**

Lastly, the pyridine substrates were subjected to the Pd-catalyzed BQ/AcOH oxidative conditions. Unfortunately, even the 3-substituted pyridine substrates (**4-9**, **4-10**, and **4-11**) did not provide any acetoxylation products. In all of these cases, significant amounts of starting material were observed after 6 h at 100 °C (65% **4-9**, 55% **4-10**, and 81% **4-11**). The reaction mixtures were analyzed by ^{1}H NMR spectroscopy and electrospray mass spectrometry, but no resonances or peaks associated with the acetoxylation product were detected.

4.2.3 Other Directed Cyclopropane Substrates

A number of other different types of *N*-heterocycle-substituted cyclopropanes were synthesized as shown in Scheme 4.19. Under the three oxidative conditions examined, these substrates were generally not reactive or decomposed to unidentifiable products. Only substrate **4-12** showed any reactivity. Substrate **4-12** was synthesized by the coupling of 8-aminoquinoline and cyclopropane carbonyl chloride. When **4-12** was subjected to Pd-catalyzed

acetoxylation conditions with BQ/AcOH, 34% yield of product **4-12a** was obtained (Scheme 4.20). All of the substrates examined for this project contained a single nitrogen atom that could coordinate to Pd, but with **4-12** both nitrogen atoms are expected to participate in the chelation, forming a more rigid Pd complex. This is exemplified in Scheme 4.1 (iv), where bidentate nitrogen directing group facilitated the C–H activation/arylation of 2° sp^3 C–H bond.[5] This could potentially explain the observed reactivity caused by the rigid Pd complex intermediates.



4-12

Scheme 4.19. Other *N*-Heterocycle Directed Cyclopropanes Synthesized

4-12 34% (**4-12a**)

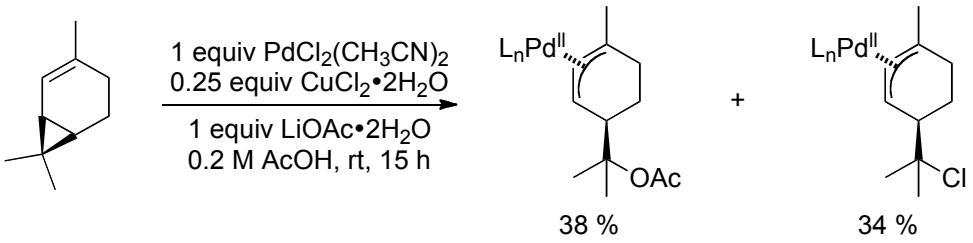
Scheme 4.20. Acetoxylation of **4-12**

4.3 Discussion

Originally we set out to study the reactivity of cyclopropanes under Pd-catalyzed oxidative conditions in order to gain insights into ligand-directed 2º sp^3 C–H activation/functionalization reactions. However, our results show that cyclopropane substrates are not general substrates for these transformations. The reactivity of the cyclopropanes did not follow any clear trends; therefore, products could not be easily predicted. The reactivity of the cyclopropanes was extremely sensitive to directing ligand choice, as well as substitution patterns on the substrate. The only conditions that resulted in C–H functionalization involved Pd-catalyzed iodination using IOAc as the oxidant. Under Pd-catalyzed

acetoxylation conditions with $PhI(OAc)_2$ or BQ/AcOH, C–C activation of the cyclopropanes was observed, which resulted in ring-opened products.

The mechanism of the ring-opening transformations reported in this chapter has not been studied in detail. It is likely that nucleopalladation of the cyclopropane initiates the reaction. Nucleopalladation of 2-carene with $PdCl_2(CH_3CN)_2$ is well precedented as shown in Scheme 4.21.[20] Also, nucleophilic ring opening pathways have recently been proposed by Yudin in the catalytic transformation of cyclopropanes to heterocycles (Scheme 4.3).[16]



Scheme 4.21. Nucleopalladation of Cyclopropane[20]

Recently, after our work was published, Yu and co-workers showed the use of *N*-arylamides as directing groups for cyclopropane C–H activation followed by arylation/vinylation/alkylation using organoboron reagents.[21] In this report, he also demonstrated the use of chiral amino acids to obtain enantioselectivity.

4.4 Conclusions

In conclusion, we carried out a systematic study of the Pd-catalyzed oxidative functionalization of cyclopropane substrates bearing potential directing substituents. In some instances, these substrates underwent C–H oxidation. However, in most cases, C–C activation of the cyclopropane was observed in preference to the C–H oxidation, providing ring-opened products. Overall, cyclopropanes proved to be a difficult substrate class to work with under Pd-catalyzed oxidative conditions, since seemingly minor changes in substrate structure resulted in major changes in their reactivity.

4.5 Experimental

NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), a Varian Inova 400 (399.96 MHz for ^{1}H; 100.57 MHz for ^{13}C), or a MR400 (400.53 MHz for ^{1}H; 100.71 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of doublets of doublets of doublets (dddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), septet (sept), multiplet (m), and broad resonance (br). Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F254. HPLC was performed on a Varian ProStar 210 HPLC using Waters SunFire Prep Silica 5μm (19 x 150 mm) column. IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer.

All reagents mentioned below were obtained from commercial sources and used as received unless noted otherwise. Benzoquinone (BQ) was obtained from Acros and sublimed prior to use. The parent ketone of **4-3** was synthesized from 1-octen-3-ol via Simmons-Smith cyclopropanation followed by oxidation of the alcohol.[22] The parent ketone of **4-5** was synthesized by the addition of allymagnesium bromide to 4-phenylbutanal, Simmons-Smith cyclopropanation, and oxidation of the alcohol.[22,23]

4.6 Characterization

Procedure for synthesis of substrates 4-1 and 4-2

Substrates **4-1** and **4-2** were synthesized according to the reported procedure[6] by converting cyclopropanecarboxylic acid to its acid chloride and coupling with (*S*)-*tert*-leucinol. The coupled product was then cyclized using PPh_3.

4-(tert-butyl)-2-(1-methylcyclopropyl)-4,5-dihydrooxazole (**4-1**)

The three-step synthesis[6] from 1-methylcyclopropanecarboxylic acid (320 mg, 3.2 mmol, 1.0 equiv) afforded substrate **4-1** as a clear oil after purification by chromatography on silica gel using 80% petroleum ether/20% Et_2O (349 mg, 60% yield over 3 steps, R_f = 0.31 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.06 (dd, *J* = 9.6, 8.8 Hz, 1H), 3.99 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.78 (dd, *J* = 9.6, 6.8 Hz, 1H), 1.34 (s, 3H), 1.12 (m, 1H), 1.06 (m, 1H), 0.86 (s, 9H), 0.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.00, 75.68, 68.52, 33.82, 25.64, 20.94, 14.80, 14.58, 14.01. IR (neat film): 3008, 1663 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$ calcd for $C_{11}H_{20}NO$, 182.1539; found, 182.1536.

4-(tert-butyl)-2-cyclopropyl-4,5-dihydrooxazole (**4-2**)

The three-step synthesis[6] from cyclopropanecarboxylic acid (2.0 g, 23.2 mmol, 1.0 equiv) afforded substrate **4-2** as a clear oil after purification by chromatography on silica gel using 80% petroleum ether/20% Et_2O (1.7 g, 43% yield over 3 steps, R_f = 0.24 80% hexanes/20% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.06 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.94 (dd, *J* = 6.8, 6.0 Hz, 1H), 3.75 (dd, *J* = 8.0, 6.0 Hz, 1H), 1.62 (dddd, *J* = 6.8, 6.8, 4.0, 4.0 Hz, 1H), 0.90 (m, 1H), 0.87 (m, 1H), 0.87 (s, 9H), 0.79 (m, 1H), 0.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.01, 75.57, 68.28, 33.60, 25.71, 8.43, 6.75, 6.34. IR (neat film): 3015, 1669 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$ calcd for $C_{10}H_{18}NO$, 168.1383; found, 168.1377.

General procedure for synthesis of oxime substrates 4-3 to 4-5

The oxime substrates were prepared by combining the corresponding ketones (1.0 equiv) and NH_2OMe•HCl (1.35 equiv) in pyridine (2.7 M). The resulting solution was stirred at 80 °C for 15 min and then at rt overnight. The reaction mixture was diluted with Et_2O and washed with H_2O containing a few drops of concentrated AcOH, H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The products were then purified by flash chromatography if necessary.

1-cyclopropylhexan-1-one O-methyl oxime (**4-3**)

1-Cyclopropylhexan-1-one (1.07 g, 7.6 mmol) reacted to form **4-3** as a 2.3:1 mixture of oxime isomers as a clear oil (1.18 g, 91% yield). Purification by column chromatography was not necessary.

IR (neat film, mixture of oxime isomers): 3088, 1621 cm^{-1}. HRMS obtained for mixture of oxime isomers, electron impact (m/z): $[M]^+$ calcd for $C_{10}H_{19}NO$, 169.1467; found, 169.1467.

Major oxime isomer: R_f = 0.53 in 90% hexanes/10% EtOAc.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 2.13 (dd, *J* = 8.0, 7.5 Hz, 2H), 1.53-1.44 (multiple peaks, 3H), 1.36-1.25 (multiple peaks, 4H), 0.94-0.87 (multiple

peaks, 5H), 0.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.99, 61.07, 32.05, 27.35, 25.96, 22.39, 13.98, 13.96, 5.02.

Minor oxime isomer: R_f = 0.28 in 90% hexanes/10% EtOAc.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 2.19 (dddd, *J* = 11.0, 11.0, 5.5, 5.5 Hz, 1H), 1.76 (dd, *J* = 8.0, 8.0 Hz, 2H), 1.48 (m, 2H), 1.36-1.25 (multiple peaks, 4H), 0.82 (m, 2H), 0.71-0.66 (multiple peaks, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.12, 61.26, 31.71, 28.98, 27.30, 22.42, 14.03, 8.64, 5.06.

1-(1-methylcyclopropyl)ethanone O-methyl oxime (**4-4**)

Methyl 1-methylcyclopropyl ketone (1.0 g, 10.2 mmol) reacted to form **4-4** as a single detectable oxime isomer as a clear oil (0.88 g, 68% yield). Purification by column chromatography was not necessary.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H), 1.72 (s, 3H), 1.24 (s, 3H), 0.85 (m, 2H), 0.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.06, 61.13, 21.78, 20.13, 12.51, 11.29. IR (neat film): 3084, 1613 cm^{-1}. HRMS electron impact (m/z): $[M]^+$calcd for $C_7H_{13}NO$, 127.0997; found, 127.0999.

1-cyclopropyl-5-phenylpentan-2-one O-methyl oxime (**4-5**)

Reaction with 1-cyclopropyl-5-phenylpentan-2-one (1.27 g, 6.3 mmol) afforded **4-5** as 1:1 mixture of oxime isomers as a clear oil after purification by chromatography on silica gel using 95% hexanes/5% EtOAc (1.41 g, 97% yield).

IR (neat film, mixture of oxime isomers): 3079 cm^{-1}. HRMS obtained for mixture of oxime isomers, electron impact (m/z): $[M]^+$ calcd for $C_{15}H_{21}NO$, 231.1631; found, 231.1625.

Oxime isomer 1: R_f = 0.52 in 90% hexanes/10% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (m, 2H), 7.20-7.16 (multiple peaks, 3H), 3.81 (s, 3H), 2.65 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.30 (dd, *J* = 8.0, 7.6 Hz, 2H), 2.20 (d, *J* = 6.8 Hz, 2H), 1.86 (m, 2H), 0.84 (m, 1H), 0.45 (m, 2H), 0.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.58, 142.01, 128.43, 128.28, 125.77, 61.04, 35.53, 33.53, 32.27, 28.39, 7.68, 4.70.

Oxime isomer 2: R_f = 0.48 in 90% hexanes/10% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (m, 2H), 7.20-7.17 (multiple peaks, 3H), 3.81 (s, 3H), 2.64 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.41 (dd, *J* = 8.0, 8.0 Hz, 2H), 2.04 (d, *J* = 7.2 Hz, 2H), 1.83 (m, 2H), 0.81 (m, 1H), 0.46 (m, 2H), 0.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.01, 141.90, 128.36, 128.28, 125.82, 61.01, 38.84, 36.03, 27.56, 27.51, 8.55, 4.63.

1-(1-cyclopropylcyclohexyl)pentan-1-one O-methyl oxime (**4-6**)

This substrate was synthesized by the route shown in Scheme 4.14.[18] The oximation was carried out with 1-(1-cyclopropylcyclohexyl)pentan-1-one (100 mg, 0.36 mmol) using microwave at 100 °C for 2.5 h and **4-6** was obtained as a clear oil after purification by chromatography on silica gel using 97% hexanes/3% EtOAc (20 mg, 18% yield, R_f = 0.64 in 95% hexanes/5% EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.81 (s, 3H), 2.23 (m, 2H), 1.80 (d, *J* = 13.0, 2H), 1.58-1.42 (multiple peaks, 6H), 1.35 (sextet, *J* = 7.5 Hz, 2H), 1.34-1.12 (multiple peaks, 2H), 1.08 (quin, *J* = 7.0 Hz, 2H), 0.91 (t, *J* = 7.5, 3H), 0.75 (quin, *J* = 7.0, 1H), 0.32-0.31 (multiple peaks, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ:164.11, 61.13, 42.10, 31.50, 29.70, 28.85, 26.56, 23.75, 22.72, 21.05, 13.83, 1.10. IR (neat film): 1617, 1455, 1051 cm^{-1}. HRMS electrospray (m/z): $[M]^+$calcd for $C_{15}H_{27}NO$, 238.2165; found, 238.2171.

General procedure for synthesis of pyridine substrates 4-7 to 4-9 and 4-11

The pyridine substrates were prepared from the corresponding 2-bromopyridine and cyclopropylboronic acid via a modification of a literature procedure.[19] The reactions were run overnight and then cooled to room temperature. A 3 M aqueous solution of HCl was added, and the aqueous layer was extracted with EtOAc. The EtOAc extracts were discarded, the aqueous layer was basicified with 3 M aqueous NaOH, and the product was extracted with Et_2O. The ether extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The products were then purified by flash chromatography.

2-cyclopropyl-4-methylpyridine (**4-7**)

2-Bromo-4-methylpyridine (1.0 g, 5.8 mmol) reacted to afford substrate **4-7** as a clear oil after purification by chromatography on silica gel using 90% hexanes/10% EtOAc (310 mg, 40% yield, R_f = 0.22 in 90% hexanes/10% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 5.2 Hz, 1H), 6.94 (m, 1H), 6.84 (m, 1H), 2.29 (s, 3H), 1.98 (dddd, *J* = 8.0, 8.0, 5.2, 5.2 Hz, 1H), 0.98-0.96 (multiple peaks, 3H), 0.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.56, 148.97, 146.75, 122.03, 121.46, 20.90, 16.94, 9.49. IR (neat film): 3089 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$ calcd for $C_9H_{12}N$, 134.0964; found, 134.0964.

2-cyclopropyl-6-methylpyridine (**4-8**)

2-Bromo-6-methylpyridine (344 mg, 2.0 mmol) reacted to afford substrate **4-8** as a clear oil after purification by chromatography on silica gel using 90% petroleum ether/10% Et_2O (168 mg, 63% yield, R_f = 0.41 in 90% hexanes/10% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 2.47 (s, 3H), 2.02 (m, 1H), 0.96 (m, 2H), 0.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.18, 157.66, 136.06, 119.79, 117.09, 24.57, 17.25, 9.45. IR (neat film): 3064 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$ calcd for $C_9H_{12}N$, 132.0964; found, 132.0965.

2-cyclopropyl-3-methylpyridine (**4-9**)

2-Bromo-3-methylpyridine (5.0 g, 29.1 mmol) reacted to afford substrate **4-9** as a clear oil after purification by chromatography on silica gel using 90% petroleum ether/10% Et_2O (3.1 g, 80% yield, R_f = 0.28 in 90% hexanes/10% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 4.8 Hz, 1H), 7.36 (m, 1H), 6.93 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.41 (s, 3H), 2.08 (dddd, *J* = 9.6, 9.6, 5.2, 5.2 Hz, 1H), 1.06 (m, 2H), 0.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.45, 146.56, 136.75, 130.98, 120.07, 18.83, 13.54, 8.76. IR (neat film): 3087 cm^{-1}. HRMS electron impact (m/z): $[M-H]^+$ calcd for $C_9H_{10}N$, 132.0813; found, 132.0816.

2-cyclopropyl-3-methoypyridine (**4-11**)

2-Bromo-3-methoxypyridine (1.0 g, 5.3 mmol) afforded substrate **4-11** as a clear oil after purification by chromatography on silica gel using 90% petroleum ether/10% Et_2O (590 mg, 74% yield, R_f = 0.36 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.05 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.93 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.86 (s, 3H), 2.47 (dddd, *J* = 10.0, 10.0, 4.8, 4.8 Hz, 1H), 1.05 (m, 2H), 0.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.68, 152.55, 140.57, 120.28, 116.05, 55.37, 10.24, 9.01. IR (neat film): 3063, 1430 cm^{-1}. HRMS electron impact (m/z): $[M-H]^+$ calcd for $C_9H_{10}NO$, 148.0762; found, 148.0766.

Procedure for synthesis of substrate 4-10

A solution of **4-9** (1.0 g, 7.5 mmol, 1.0 equiv) in THF (1.5 mL) was added to a solution of LDA (1.5 equiv) in THF (23 mL) at –40 °C under N_2. The reaction was stirred for 30 min and then cooled to –78 °C. MeI (5.3 g, 37.5 mmol, 5.0 equiv) was added, and resulting solution was stirred for 2 h at –78 °C. The reaction was quenched with H_2O (15 mL) at –78 °C and then slowly warmed to rt. The product was obtained using the same work-up as that for the synthesis of substrate **4-7**.

2-cyclopropyl-3-ethylpyridine (**4-10**)

Substrate **4-10** was obtained as a clear oil after purification by chromatography on silica gel using 97.5% petroleum ether/2.5% Et_2O (1.1 g, 98% yield, R_f = 0.23 in 95% hexanes/5% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 4.8 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 6.97 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.79 (q, *J* = 7.6 Hz, 2H), 2.13 (dddd, *J* = 9.6, 9.6, 4.8, 4.8 Hz, 1H), 1.27 (t, *J* = 7.6 Hz, 3H), 1.08 (m, 2H), 0.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.90, 146.53, 136.76, 135.17, 120.22, 25.49, 14.55, 13.09, 9.03. IR (neat film): 3051, 1586, 1572 cm^{-1}. HRMS electron impact (m/z): $[M-H]^+$calcd for $C_{10}H_{12}N$, 146.0970; found, 146.0971.

Procedure for synthesis of substrate 4-12

Substrate **4-12** was synthesized using literature procedures[24] by conversion of cyclopropanecarboxylic acid to its acid chloride with oxalyl chloride followed by condensation with 8-aminoquinoline.

N-(quinolin-8-yl)cyclopropanecarboxamide (**4-12**)

2-Step procedure beginning with cyclopropanecarboxylic acid (2 g, 23.1 mmol, 1.1 equiv) and further condensation with 8-methylquinoline (3 g, 21 mmol, 1.0 equiv) yielded substrate 9 as white solid after purification by chromatography on silica gel using 90% hexanes/10% EtOAc (1.3 g, 27% yield, R_f = 0.22 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.30 (bs, 1H), 8.82 (m, 1H), 8.74 (d, J = 7.6 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.55-7.45 (multiple peaks, 3H), 1.82 (sept, J = 4.4 Hz , 1H), 1.16 (m, 2H), 0.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.24, 148.02, 138.20, 136.34, 134.69, 127.92, 127.43, 121.52, 121.14, 116.35, 16.23, 8.11. IR (KBr): 3362, 1684, 1520 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$calcd for $C_{13}H_{13}N_2O$, 213.1028; found, 213.1021.

Procedure for synthesis of oxazolium acetate salts 4-1b and 4-2b

The appropriate substrate (100 mg, 0.5 mmol, 1.0 equiv) was weighed into a scintillation vial containing a stir bar. Acetic acid (4.6 mL, 0.12 M) was added and the vial was sealed with Teflon lined cap. The resulting solution was stirred at 100 °C for 12 h. The reaction mixture was concentrated under vacuum, and the product was recovered as a white solid.

4-(tert-butyl)-2-(1-methylcyclopropyl)-4,5-dihydrooxazol-3-ium acetate salt (**4-1b**)

Substrate **4-1** (100 mg, 0.55 mmol, 1.0 equiv) yielded **4-1b** as a white solid (82 mg, 62% yield, R_f = 0.48 in 50% hexanes/50% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.70 (d, *J* = 9.2 Hz, 1H), 4.28 (m, 1H), 4.11-4.05 (multiple peaks, 2H), 2.03 (s, 3H), 1.31 (s, 3H), 1.18 (dd, *J* = 3.2, 9.6 Hz, 1H), 1.12 (dd, *J* = 3.2, 9.6 Hz, 1H), 0.95 (s, 9H), 0.56 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.79, 171.42, 63.54, 55.85, 33.94, 26.69, 20.91, 19.59, 19.10, 15.82, 15.74. IR (thin film with CH_2Cl_2): 3310, 3002, 1739, 1632 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{13}H_{23}NO$, 264.1570; found, 264.1565. Mp 92.8–93.7 °C

4-(tert-butyl)-2-cyclopropyl-4,5-dihydrooxazol-3-ium acetate salt (**4-2b**)

Substrate **4-2** (100 mg, 0.60 mmol, 1.0 equiv) yielded **4-2b** as a white solid (80 mg, 59% yield, R_f = 0.31 in 50% hexanes/50% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.64 (d, *J* = 9.6 Hz, 1H), 4.22 (dd, *J* = 11.6, 8.8 Hz, 1H), 4.13-4.05 (multiple peaks, 2H), 2.02 (s, 3H), 1.62 (dddd, *J* = 8.0, 8.0, 4.4, 4.4 Hz, 1H), 0.95 (s, 9H), 0.93 (m, 2H), 0.71 (dd, *J* = 8.0, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.54, 171.38, 63.68, 55.80, 33.85, 26.67, 20.89, 14.79,

7.01, 6.97. IR (thin film with CH_2Cl_2): 3301, 3010, 1739, 1645 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{12}H_{21}NO_3$, 250.1414; found, 250.1412. Mp 53.8–54.9 °C.

General iodination procedure

The appropriate pyridine substrate (1.0 equiv), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (1.0 equiv), and I_2 (1.0 equiv) were weighed into a scintillation vial containing a stir bar. Methylene chloride was added to make a 0.2 M solution (in substrate), and the vial was sealed with Teflon lined cap. The reaction was stirred at rt overnight. The reaction mixture was washed with saturated sodium thiosulfate solution. The organic layer was collected, the solvent was removed under vacuum, NO_2Ph (0.25 equiv, ^1H NMR resonance at 8.2 ppm) or 1,3-dinitrobenzene (0.25 equiv, ^1H NMR resonance at 9.1 ppm) was added as an internal standard, and the crude mixture was analyzed by ^1H NMR spectroscopy. The products were then purified by flash chromatography.

2-(cis-2-iodocyclopropyl)-3-methylpyridine (**4-9a**)

^1H NMR spectroscopic analysis of the crude reaction mixture showed that substrate **4-9** (60 mg, 0.45 mmol) reacted to form **4-9a** in 19% yield. Product **4-9a** was purified by chromatography on silica gel using 90% CH_2Cl_2/10% EtOAc and was isolated as a white solid (19 mg, 16% yield, R_f = 0.42 in 90% CH_2Cl_2/10% EtOAc).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.40 (m, 1H), 7.48 (m, 1H), 7.12 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.02 (td, *J* = 7.6, 5.6 Hz, 1H), 2.38 (s, 3H), 2.25 (td, *J* = 8.0, 7.6 Hz, 1H), 1.98 (td, *J* = 6.4, 5.6 Hz, 1H), 1.65 (ddd, *J* = 8.8, 7.6, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.67, 146.11, 137.31, 133.27, 121.94, 21.07, 18.70, 13.54, –7.97. IR (thin film with CH_2Cl_2): 3051 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$calcd for $C_9H_{11}IN$, 259.9936; found, 259.9936.

2-(cis-2-iodocyclopropyl)-3-ethylpyridine (**4-10a**)

^1H NMR spectroscopic analysis of the crude reaction mixture showed that substrate **4-10** (50 mg, 0.34 mmol) reacted to form **4-10a** in 30% yield. Product **4-10a** was purified by chromatography on silica gel using 85% hexanes/15% EtOAc and was isolated as a yellow oil (15 mg, 16% yield, R_f = 0.32 in 85% hexanes/15% EtOAc).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (dd, *J* = 4.8,1.2 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.15 (dd, *J* = 7.6, 5.2 Hz, 1H), 3.02 (td, *J* = 7.6, 5.6 Hz, 1H), 2.76 (q, *J* = 3.6 Hz, 2H), 2.08 (td, *J* = 7.6, 7.6 Hz, 1H), 1.98 (td, *J* = 6.4, 6.4 Hz, 1H), 1.64 (td, *J* = 8.0, 6.4 Hz, 1H), 1.31 (t, *J* = 3.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.94, 145.93, 138.75, 135.32, 122.05, 24.76, 20.29, 13.70, 13.52, –7.04. IR (neat film): 3049 cm^{-1}. HRMS electron impact (m/z): $[M+H]^+$ calcd for $C_{10}H_{13}IN$, 274.0087; found, 274.0085.

2-(cis-2-iodocyclopropyl)-3-methoxypyridine **(4-11a)**

^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that substrate **4-11** (50 mg, 0.34 mmol) reacted to form **4-11a** in 13% yield. Product **4-11a** was purified by chromatography on silica gel using 85% hexanes/15% EtOAc and was isolated as a yellow oil (14 mg, 15% yield, R_f = 0.21 in 85% hexanes/15% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.19-7.13 (multiple peaks, 2H), 3.89 (s, 3H), 3.01 (td, *J* = 8.0, 5.6 Hz, 1H), 2.48 (td, *J* = 8.0, 7.2 Hz, 1H), 1.90 (td, *J* = 7.2, 5.6 Hz, 1H), 1.59 (td, *J* = 8.0, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.97, 148.38, 139.98, 122.34, 116.68, 55.45, 17.93, 13.29, –6.87. IR (neat film): 3058, 1435 cm^{-1}. HRMS electron impact (m/z): $[M+H]^+$ calcd for $C_9H_{11}INO$, 275.9880; found, 275.9881.

General iod-acetoxylation procedure

The appropriate pyridine substrate (1.0 equiv), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (3.0 equiv), and I_2 (1.0 equiv) were weighed into a scintillation vial containing a stir bar. Methylene chloride was added to make a 0.2 M solution (in substrate), and the vial was sealed with Teflon lined cap. The reaction was stirred at rt overnight. The reaction mixture was washed with saturated sodium thiosulfate solution. The organic layer was collected, the solvent was removed under vacuum, NO_2Ph (0.25 equiv, ^{1}H NMR resonance at 8.2 ppm) or 1,3-dinitrobenzene (0.25 equiv, ^{1}H NMR resonance at 9.1 ppm) was added as an internal standard, and the crude mixture was analyzed by ^{1}H NMR spectroscopy. The products were then purified by flash chromatography.

^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that **4-9** (50 mg, 0.38 mmol) reacted to form **4-9b** in 35% yield. The product was purified by chromatography on silica gel using 15% EtOAc/85% hexanes and was isolated as single diastereomer as yellow oil (42 mg, 30% yield, R_f = 0.26 in 30% EtOAc/70% hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43 (d, *J* = 3.5 Hz ,1H), 7.48 (d, *J* = 7.5 Hz ,1H), 7.12 (dd, *J* = 7.5, 4.5 Hz ,1H), 6.18 (d, *J* = 4.5 Hz ,1H), 4.93 (ddd, *J* = 9.5, 5.0, 5.0 Hz ,1H), 4.37 (dd, *J* = 12.5, 5.0 Hz ,1H), 3.96 (dd, *J* = 12.5, 4.5 Hz ,1H), 2.48 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H). ^{13}C NMR NMR (100 MHz, $CDCl_3$) δ: 170.06, 169.96, 153.44, 147.52, 138.83, 132.57, 123.67, 73.45, 66.27, 29.41, 20.98, 20.70, 18.17. IR (thin film): 1738, 1217 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$calcd for $C_{13}H_{17}INO_4$, 378.0202; found, 378.0190.

2-iodo-1-(3-ethylpyridin-2-yl)propane-1,3-diyl diacetate (**4-10b**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that **4-10** (50 mg, 0.34 mmol) reacted to form **4-10b** in 26% yield. The product was purified by chromatography on silica gel using 15% EtOAc/85% hexanes and was isolated as single diastereomer as yellow oil (29 mg, 20% yield, R_f = 0.25 in 30% EtOAc/70% hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.23 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.29 (d, *J* = 9.2 Hz, 1H), 4.96 (td, *J* = 9.2, 4.8 Hz, 1H), 4.33 (dd, *J* = 12.4, 4.8 Hz, 1H), 3.99 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.84 (m, 2H), 2.13 (s, 3H), 2.01 (s, 3H), 1.27 (t, *J* = 7.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.04, 169.87, 152.65, 147.36, 138.12, 136.90, 123.88, 72.67, 66.27, 29.92, 23.90, 21.10, 20.67, 14.54. IR (thin film): 1741 cm^{-1}. HRMS electron impact (m/z): $[M+H]^+$ calcd for $C_{14}H_{18}INO_4$, 392.0353; found, 392.0352.

2-iodo-1-(3-methoxypyridin-2-yl)propane-1,3-diyl diacetate (**4-11b**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that **4-11** (50 mg, 0.34 mmol) reacted to form **4-11b** in 65% yield. The product was purified by chromatography on silica gel using 15% EtOAc/85% hexanes and was isolated as single diastereomer as yellow oil (79 mg, 60% yield, R_f = 0.26 in 50% EtOAc/50% hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.22 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.17 (d, *J* = 6.0 Hz, 1H), 4.80 (td, *J* = 7.2, 6.0 Hz, 1H), 4.37 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.28 (dd, *J* = 12.0, 7.2 Hz, 1H), 3.86 (s, 3H), 2.18 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.09, 169.84, 152.99, 145.22, 141.05, 124.09, 117.89, 69.97, 66.17, 55.60, 28.61, 20.95, 20.64. IR (thin film): 1741 cm^{-1}. HRMS electron impact (m/z): $[M+H]^+$ calcd for $C_{13}H_{17}INO_5$, 394.0146; found, 394.0144.

General acetoxylation procedure with $PhI(OAc)_2$ or benzoquinone

Substrate (1.0 equiv), $Pd(OAc)_2$ (10 mol %), and $PhI(OAc)_2$ (2.0 equiv) or benzoquinone (2.0 equiv) were weighed into a scintillation vial containing a stir bar. Solvent was added to make a 0.12 M solution in substrate, and the vial was sealed with Teflon lined cap. The reaction was stirred at 100 °C for 6-12 h. The reaction mixture was filtered through Celite, and the Celite was washed with Et_2O. The solvent was removed under vacuum, NO_2Ph (0.25-0.5 equiv, ^{1}H NMR resonance at 8.2 ppm) or 1,3-dinitrobenzene (0.25 equiv, ^{1}H NMR resonance at 9.1 ppm) was added as an internal standard, and the crude mixture was analyzed by ^{1}H NMR spectroscopy. The products were then purified by flash chromatography.

3-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)but-2-en-1-yl acetate (**4-1c**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 ºC showed that substrate **4-1** (50 mg, 0.28 mmol) reacted with $PhI(OAc)_2$ in DCE to form **4-1c** in 29% yield as a 2.6:1 mixture of *E:Z* isomers. The products were purified by chromatography on silica gel using 90% CH_2Cl_2/10% EtOAc and were isolated a clear oils (12 mg (*E*)-**4-1c**, 18% yield; 5 mg (*Z*)-**4-1c**), 8% yield).

(*E*)-isomer: R_f = 0.16 in 85% hexanes/15% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.41 (t, *J* = 6.4 Hz, 1H), 4.74 (d, *J* = 6.4 Hz, 2H), 4.20 (dd, *J* = 9.6, 8.8 Hz, 1H), 4.10 (dd, *J* = 8.8, 8.0 Hz, 1H), 3.93 (dd, *J* = 9.6,

8.0 Hz, 1H), 2.08 (s, 3H), 1.99 (br s, 3H), 0.89 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.79, 164.03, 129.95, 128.09, 76.13, 68.47, 60.96, 33.93, 25.79, 20.86, 13.70. IR (neat film): 1741 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$ calcd for $C_{13}H_{22}NO_3$, 240.1594; found, 240.1586.

(*Z*)-isomer: R_f = 0.25 in 85% hexanes/15% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85 (t, *J* = 6.0 Hz, 1H), 5.03 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.96 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.20 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.08 (dd, *J* = 8.4, 8.0 Hz, 1H), 3.93 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.07 (s, 3H), 1.98 (br s, 3H), 0.90 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.87, 163.17, 132.60, 126.33, 75.88, 68.27, 62.91, 33.81, 25.82, 21.08, 20.99. IR (neat film): 1744 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$ calcd for $C_{13}H_{22}NO_3$, 240.1594; found, 240.1586.

(2E)-4-(methoxyimino)non-2-en-1-yl acetate (**4-3a**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 12 h at 100 ºC showed that substrate **4-3** (50 mg, 0.30 mmol) reacted with benzoquinone to afford **4-3a** in 76% yield as a 2.2:1 mixture of oxime isomers. Product **4-3a** was purified by chromatography on silica gel using 95% hexanes/5% EtOAc and was isolated as a 3.0:1.0 mixture of oxime isomers as a clear oil (44 mg, 66% yield).

IR (neat film, mixture of isomers): 1741 cm^{-1}. HRMS obtained for mixture of isomers, electrospray (m/z): $[M+Na]^+$calcd for $NaC_{12}H_{21}NO_3$, 250.1419; found, 250.1417.

Major oxime isomer: R_f = 0.40 in 85% hexanes/15% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.26 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.06 (dt, *J* = 16.0, 6.0 Hz, 1H), 4.68 (dd, *J* = 6.0, 1.6 Hz, 2H), 3.89 (s, 3H), 2.42 (m, 2H), 2.09 (s, 3H), 1.46 (m, 2H), 1.35-1.29 (multiple peaks, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.66, 158.51, 129.93, 127.48, 64.29, 61.81, 31.96, 26.22, 24.64, 22.38, 20.89, 13.94.

Minor oxime isomer: R_f = 0.47 in 85% hexanes/15% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.87 (dt, *J* = 16.4, 1.6 Hz, 1H), 6.15 (dt, *J* = 16.4, 5.6 Hz, 1H), 4.69 (dd, *J* = 5.6, 1.6 Hz, 2H), 3.87 (s, 3H), 2.34 (m, 2H), 2.10 (s, 3H), 1.54 (m, 2H), 1.34-1.29 (multiple peaks, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.61, 154.67, 131.08, 121.41, 64.30, 61.60, 31.63, 30.95, 27.42, 22.38, 20.88, 13.99.

4-(methoxyimino)-3-methylpent-2-en-1-yl acetate (**4-4a**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 12 h at 100 ºC showed that substrate **4-4** (60 mg, 0.47 mmol) reacted with benzoquinone to afford **4-4a** in 35% yield as a 3.4:1 mixture of oxime isomers. Product **4-4a** was purified by chromatography on silica gel using 90% hexanes/10% EtOAc and

was isolated as a 7.0:1.0 mixture of oxime isomers as a clear oil (29 mg, 33% yield).

Major oxime isomer: R_f = 0.42 in 85% hexanes/15% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.90 (t, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 2H), 3.92 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.93, 155.64, 137.14, 124.61, 61.83, 61.37, 20.94, 12.86, 10.55. IR (neat film, major oxime isomer): 1589, 1739 cm^{-1}. HRMS obtained for E isomer, electrospray (m/z): $[M+Na]^+$ calcd for $NaC_9H_{15}NO_3$, 208.0950; found, 208.0947.

Minor oxime isomer: R_f = 0.35 in 85% hexanes/15%/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.56 (t, *J* = 6.4 Hz, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 3.89 (s, 3H), 2.05 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.83, 155.43, 136.22, 124.92, 62.23, 61.74, 21.37, 20.98, 13.44.

3-hydroxy-4-(methoxyimino)-3-methylpentane-1,2-diyl diacetate (**4-4b**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 12 h at 100 ºC showed that substrate **4-4** (100 mg, 0.79 mmol) reacted with $PhI(OAc)_2$ to form **4-4b** in 37% yield as a 1.6:1 mixture of diastereomers. Product **4-4b** was purified by chromatography on silica gel using 80% hexanes/20% EtOAc and was isolated as a 1.7:1.0 mixture of diastereomers as a yellow oil (83 mg, 40% yield).

Major diastereomer: R_f = 0.17 in 80% hexanes/20% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.21 (dd, *J* = 8.0, 2.8 Hz, 1H), 4.51 (dd, *J* = 12.0, 2.8 Hz, 1H), 4.16 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.03 (s, 1H), 3.87 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.75, 170.03, 156.93, 74.64, 74.18, 62.41, 62.08, 23.10, 20.78, 20.74, 10.93. IR (neat film): 3481, 1744 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$calcd for $NaC_{11}H_{19}NO_6$, 284.1105; found, 284.1100.

Minor diastereomer: R_f = 0.12 in 80% hexanes/20% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.27 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.49 (dd, *J* = 12.0, 3.6 Hz, 1H), 4.02 (s, 1H), 4.01 (dd, *J* = 12.0, 8.4 Hz, 1H), 3.86 (s, 3H), 2.14 (s, 3H), 1.98 (s, 3H), 1.90 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.71, 170.65, 156.90, 74.89, 73.80, 62.71, 62.18, 23.32, 20.88, 20.69, 11.13. IR (neat film): 3475, 1744 cm^{-1}. HRMS electrospray (m/z): $[M+Na]^+$calcd for $NaC_{11}H_{19}NO_6$, 284.1105; found, 284.1099.

Acetoxylation of substrate 4-5

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 ºC showed that substrate **4-5** (200 mg, 0.87 mmol) reacted with $PhI(OAc)_2$ to form **4-5a** (26% yield as a 2.3:1.0 mixture of oxime isomers), **4-5b** (16% yield as a 3.0:1.0 mixture of oxime isomers), and **4-5c** (8% yield as a single detectable oxime isomer). The products were purified by chromatography on silica gel using

90% hexanes/10% EtOAc gradient to 80% hexanes/20% EtOAc. The mixture of isomers **4-5a**-**c** was isolated as a yellow oil (145 mg, 48% total yield). Each isomers was separated and isolated using HPLC (93% hexanes/7% EtOAc, 22 mL/min, Waters SunFire Prep Silica 5µm).

2-(2-(methoxyimino)-5-phenylpentylidene)propane-1,3-diyl diacetate (**4-5a**)

Major oxime isomer: R_f = 0.47 in 70% hexanes/30% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (m, 2H), 7.20-7.16 (multiple peaks, 3H), 6.00 (s, 1H), 4.96 (s, 2H), 4.67 (s, 2H), 3.90 (s, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 1.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.52, 170.43, 155.77, 141.64, 135.75, 128.35, 128.30, 126.21, 125.88, 65.22, 62.99, 61.45, 35.66, 28.66, 27.51, 20.85, 20.79. IR (neat film): 1742 cm^{-1}.HRMS, electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{19}H_{25}NO_5$, 370.1630; found, 370.1621.

Minor oxime isomer: R_f = 0.42 in 70% hexanes/30% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (m, 2H), 7.18-7.16 (multiple peaks, 3H), 5.94 (s, 1H), 4.64 (s, 2H), 4.50 (s, 2H), 3.84 (s, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 2.03 (s, 3H), 1.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.46, 170.39, 154.08, 141.69, 135.36, 128.42, 128.33, 125.88, 122.73, 64.51, 62.01, 61.63, 35.35, 33.97, 28.39, 20.84, 20.68.

(Z)-2-(2-(methoxyimino)-5-phenylpentyl)prop-1-ene-1,3-diyl diacetate (**4-5b**)

Major oxime isomer: R_f = 0.47 in 70% hexanes/30% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 2H), 7.20-7.16 (multiple peaks, 3H), 7.08 (s, 1H), 4.65 (s, 2H), 3.81 (s, 3H), 3.06 (s, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.19 (t, *J* = 7.6 Hz, 2H), 2.16 (s, 3H), 2.04 (s, 3H), 1.84 (quin, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.80, 167.30, 156.51, 141.82, 135.25, 128.44, 128.34, 125.85, 115.03, 61.30, 59.80, 35.41, 33.10, 29.69, 28.14, 20.77, 20.65. IR (neat film): 1761, 1740 cm^{-1}. HRMS, electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{19}H_{25}NO_5$, 370.1630; found, 370.1640.

Minor oxime isomer: R_f = 0.41 in 70% hexanes/30% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 2H), 7.20-7.16 (multiple peaks, 3H), 7.11 (s, 1H), 4.70 (s, 2H), 3.81 (s, 3H), 2.89 (s, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.17 (s, 3H), 2.03 (s, 3H), 1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.80, 167.36, 157.57, 135.26, 128.45, 128.33, 126.23, 125.89, 115.78, 61.33, 59.27, 36.38, 35.83, 34.88, 27.27, 20.82, 20.67.

(3E)-5-(methoxyimino)-8-phenyloct-3-ene-1,2-diyl diacetate (**4-5c**)

^{1}H NMR analysis of the crude reaction mixture showed a single oxime isomer of **4-5c**. However, this compound underwent isomerization to a mixture of oxime isomers during chromatographic purification on silica gel.

Major oxime isomer: R_f = 0.43 in 70% hexanes/30% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (m, 2H), 7.21-7.17 (multiple peaks, 3H), 6.27 (dd, *J* = 16.4, 1.6 Hz, 1H), 5.75 (dd, *J* = 16.4, 6.0 Hz, 1H), 5.57 (m, 1H), 4.24 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.08 (dd, *J* = 12.0, 6.8 Hz, 1H), 3.90 (s, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.59, 169.89, 157.81, 141.67, 129.94, 128.40, 128.34, 127.56, 125.94, 71.15, 64.58, 61.92, 35.75, 27.87, 24.10, 21.02, 20.74. IR (neat film): 1744 cm^{-1}. HRMS, electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{19}H_{25}NO_5$, 370.1625; found, 370.1622.

Minor oxime isomer: R_f = 0.45 in 70% hexanes/30% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (m, 2H), 7.21-7.17 (multiple peaks, 3H), 6.89 (dd, *J* = 16.4, 1.6 Hz, 1H), 5.90 (dd, *J* = 16.4, 6.0 Hz, 1H), 5.57 (m, 1H), 4.27 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.10 (dd, *J* = 11.6, 6.8 Hz, 1H), 3.88 (s, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.11 (s, 3H), 2.05 (s, 3H), 1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.57, 169.88, 153.68, 141.82, 130.95, 128.48, 128.35, 125.89, 121.72, 71.33, 64.49, 61.72, 35.42, 30.20, 29.06, 21.01, 20.72.

1-(3-methylpyridin-2-yl)propane-1,2,3-triyl triacetate (**4-9c**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 12 h at 100 ºC showed that substrate **4-9** (20 mg, 0.15 mmol) reacted with $PhI(OAc)_2$ to form **4-9c** in 41% yield as a 2.4:1 mixture of diastereomers. Product **4-9c** was purified by chromatography on silica gel using 50% hexanes/50% EtOAc and was isolated as a 2.6:1.0 mixture of diastereomers as a yellow oil (17 mg, 37% yield). Diastereomers were characterized from individual fractions containing pure material.

IR (neat film, mixture of diastereomers): 1739 cm^{-1}.

Major diastereomer: R_f = 0.30 in 60% EtOAc/40% hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (m, 1H), 7.46 (m, 1H), 7.13 (m, 1H), 6.15 (d, *J* = 6.4 Hz, 1H), 5.52 (td, *J* = 6.4, 2.4 Hz, 1H), 4.60 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.46 (dd, *J* = 12.0, 6.4 Hz, 1H), 2.48 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.63, 170.03, 169.65, 153.25, 147.20, 138.25, 132.40, 123.29, 72.23, 70.24, 62.02, 20.84, 20.74, 20.68, 18.08. HRMS, electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{15}H_{19}NO_6$, 332.1110; found, 332.1106.

Minor diastereomer: R_f = 0.27 in 60% EtOAc/40% hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (m, 1H), 7.48 (m, 1H), 7.16 (m, 1H), 6.25 (d, *J* = 8.0 Hz, 1H), 5.82 (ddd, *J* = 8.0, 4.8, 3.2 Hz, 1H), 4.38 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.74 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.49 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.35, 170.26, 169.98, 152.78, 147.44, 138.70, 132.57, 123.63, 71.85, 70.82, 62.43, 20.82, 20.73, 20.67, 18.11.

1-(3-ethylpyridin-2-yl)propane-1,2,3-triyl triacetate (**4-10c**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 12 h at 100 ºC showed that substrate **4-10** (50 mg, 0.34 mmol) reacted with $PhI(OAc)_2$ to form **4-10c** in 81% yield as a 13:5 mixture of diastereomers. The product was purified by chromatography on silica gel using 50% EtOAc/50% hexanes and was isolated as a 3.2:1.0 mixture of diastereomers as a yellow oil (23 mg, 21% yield, R_f = 0.18 in 50% EtOAc/50% hexanes). Diastereomers were characterized from individual fractions containing pure material.

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (m, 1H), 7.51 (m, 1H), 7.18 (m, 1H), 6.24 (d, *J* = 6.8 Hz, 1H), 5.55 (ddd, *J* = 6.8, 6.0, 2.4 Hz, 1H), 4.61 (dd, *J* = 12.4, 2.4 Hz, 1H), 4.46 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.86 (m, 2H), 2.12 (s, 3H), 2.06 (s, 3H), 1.91 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.65, 170.04, 169.61, 152.55, 147.18, 138.26, 136.62, 123.56, 72.34, 69.64, 62.03, 24.27, 20.92, 20.76, 20.68, 14.68. IR (neat film): 1741 cm^{-1}. HRMS, electron impact (m/z): $[M+H]^+$ calcd for $C_{16}H_{22}NO_6$, 324.1442; found, 324.1443.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (m, 1H), 7.54 (m, 1H), 7.22(m, 1H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.85 (ddd, *J* = 7.6, 4.8, 3.2 Hz, 1H), 4.36 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.79 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.86 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.39, 170.16, 169.99, 151.99, 147.29, 138.22, 136.84, 123.87, 72.06, 70.13, 62.44, 23.99, 20.90, 20.84, 20.71, 14.59.

1-(3-methoxypyridin-2-yl)propane-1,2,3-triyl triacetate (**4-11c**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 12 h at 100 ºC showed that substrate **4-11** (50 mg, 0.34 mmol) reacted with $PhI(OAc)_2$ to form **4-11c** in 28% yield as a 1.3:1.0 mixture of diastereomers. The product was purified by chromatography on silica gel using 60% EtOAc/50% hexanes and was isolated as a 1.4:1.0 mixture of diastereomers as a yellow oil (37 mg, 34% yield). Diastereomers were characterized from individual fractions containing pure material.

IR (neat film, mixture of diastereomers): 1734 cm^{-1}. HRMS obtained for mixture of diastereomers, electrospray (m/z): $[M+Na]^+$ calcd for $NaC_{15}H_{19}NO_7$, 348.1059; found, 348.1051.

Major diastereomer: R_f = 0.16 in 60% EtOAc/40% hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (m, 1H), 7.22 (m, 1H), 7.17 (m, 1H), 6.40 (d, *J* = 5.6 Hz, 1H), 5.74 (ddd, *J* = 6.4, 5.6, 4.0 Hz, 1H), 4.29 (dd, *J* = 12.0, 4.0 Hz,

1H), 4.09 (dd, *J* = 12.0, 6.4 Hz, 1H), 3.88 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.52, 170.05, 170.05, 153.29, 144.06, 141.03, 124.12, 117.83, 70.80, 68.72, 62.47, 55.63, 20.88, 20.72, 20.70.

Minor diastereomer: R_f = 0.22 in 60% EtOAc/40% hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (m, 1H), 7.22 (m, 1H), 7.18 (m, 1H), 6.37 (d, *J* = 4.8 Hz, 1H), 5.62 (m, 1H), 4.47 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.36 (dd, *J* = 12.0, 7.2 Hz, 1H), 3.88 (s, 3H), 2.15 (s, 3H), 2.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.68, 169.95, 169.87, 153.48, 144.15, 140.99, 124.09, 117.83, 71.14, 69.46, 62.23, 55.65, 20.91, 20.84, 20.74.

Procedure for synthesis of 4-9c

Substrate **4-9** (200 mg, 1.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol, 10 mol %), and $PhI(OAc)_2$ (484 mg, 1.5 mmol, 1.0 equiv) were weighed into a scintillation vial containing a stir bar. Methylene chloride (7.5 mL) was added, and the vial was sealed with a Teflon lined cap. The reaction was stirred at rt for 48 h. The solvent was then removed under vacuum.

3-(3-methylpyridin-2-yl)allyl acetate (**4-9c**)

The product **4-9c** was obtained as a yellow oil after purification by flash chromatography on silica gel using 80% petroleum ether/20% Et_2O (5 mg (*E*)- **4-9c**, 14 mg (*Z*)- **4-9c**, 7% total yield).

(*E*)-isomer: R_f = 0.35 in 70% EtOAc/30% hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (d, *J* = 4.8 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.05 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.68 (d, *J* = 11.6 Hz, 1H), 5.97 (ddd, *J* = 11.6, 5.6, 5.6 Hz, 1H), 5.22 (dd, *J* = 5.6, 1.6 Hz, 2H), 2.33 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.98, 154.00, 146.61, 137.57, 131.58, 131.52, 126.98, 121.85, 63.48, 21.07, 18.95. IR (neat film, isomer 1): 1736 cm^{-1}. HRMS electron impact (m/z): $[M+H]^+$ calcd for $C_{11}H_{14}NO_2$, 192.1019; found, 192.1017.

(*Z*)-isomer: R_f = 0.17 in 70% EtOAc/30% hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (m, 1H), 7.43 (m, 1H), 7.07 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.90-6.89 (multiple peaks, 2H), 4.81 (dd, *J* = 2.8, 1.2 Hz, 2H), 2.36 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.71, 152.47, 147.06, 138.19, 130.62, 129.04, 128.81, 122.51, 64.60, 20.95, 18.65. IR (neat film, isomer 1): 1736 cm^{-1}. HRMS electron impact (m/z): $[M+H]^+$ calcd for $C_{11}H_{14}NO_2$, 192.1019; found, 192.1019.

2-methyl-3-oxo-3-(quinolin-8-ylamino)propyl acetate (**4-12a**)

^{1}H NMR spectroscopic analysis of the crude reaction mixture after 12 h at 100 ºC showed that substrate **4-12** (80 mg, 0.38 mmol) reacted to form **4-12a** in 67% yield. The product was purified by chromatography on silica gel using 75%

hexanes/25% EtOAc and isolated as orange oil (59mg, 58% yield, R_f = 0.22 in 70% hexanes/30% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.04 (bs, 1H), 8.81-8.78 (multiple peaks, 2H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.57-7.51 (multiple peaks, 2H), 7.47 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.32 (m, 2H), 3.00 (m, 1H), 2.08 (s, 3H), 1.36 (d, *J* = 7.2 Hz , 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.16, 170.86, 148.15, 138.44, 136.39, 134.40, 127.93, 127.42, 121.65, 121.63, 116.65, 66.11, 41.77, 20.91, 14.31. IR (thin film): 3346, 1743, 1684, 1527 cm^{-1}. HRMS electrospray (m/z): $[M+H]^+$calcd for $C_{15}H_{17}N_2O_3$, 273.1234; found, 273.1238.

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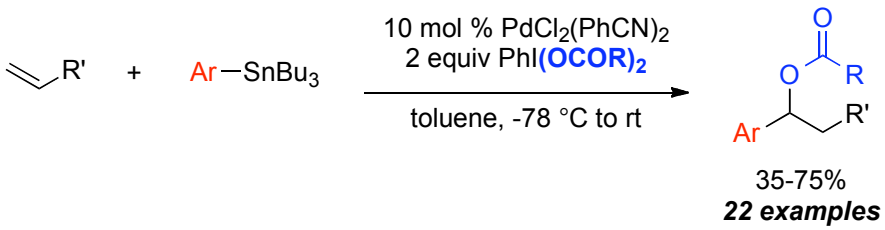
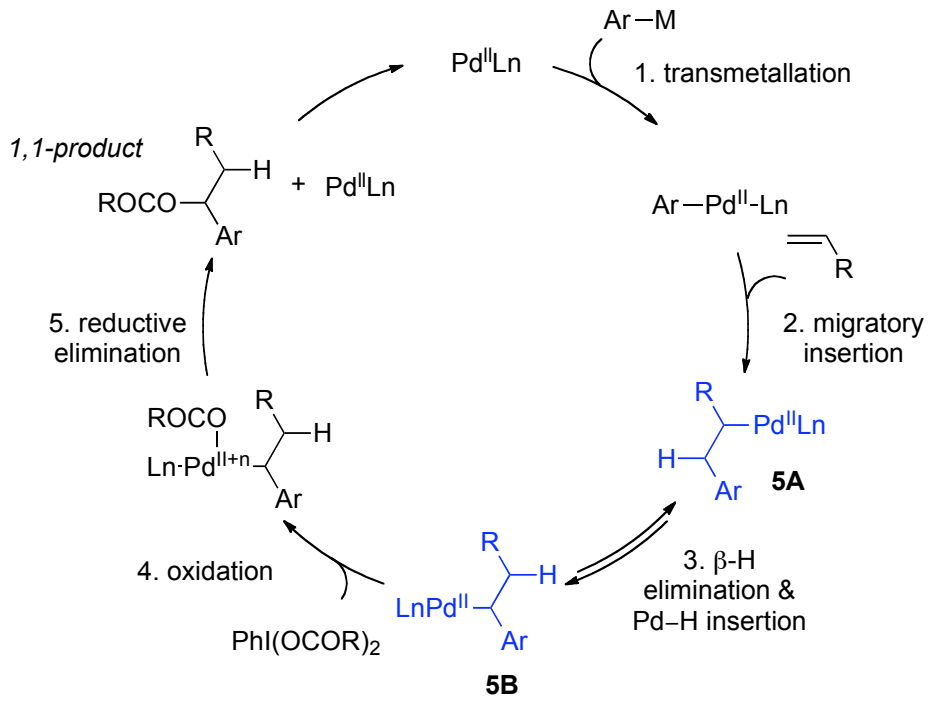
CHAPTER 5
Conclusion

During my graduate career, I have been able to address several difficult challenges associated with Pd-catalyzed oxidative functionalization reactions. Chapter 2 described the development of methodology for alkene aryloxygenation and alkene arylamination via oxidative interception of Pd(II)-alkyl intermediates. Pd-catalyzed selective 1,1-aryloxygenation of unactivated alkenes was achieved using iodobenzene dicarboxylate oxidants and arylstannanes (Scheme 5.1). The versatility of this three component coupling reaction was shown with wide substrate scopes for all three components. The mechanism for this transformation was proposed as follows: 1) transmetallation between Pd catalysts and arylstannanes to generate Pd-aryl complexes, 2) migratory insertion of the alkene into Pd-aryl bond to form a C–C bond, 3) β-hydride elimination and subsequent Pd–H re-insertion (equilibrium between **5A** and **5B**), 4) oxidation of Pd(II)-alkyl complexes with iodobenzene dicarboxylates, and 5) reductive elimination of OCOR group to form a C–O bond (Scheme 5.2).



Scheme 5.1. 1,1-Aryloxygenation of Alkenes

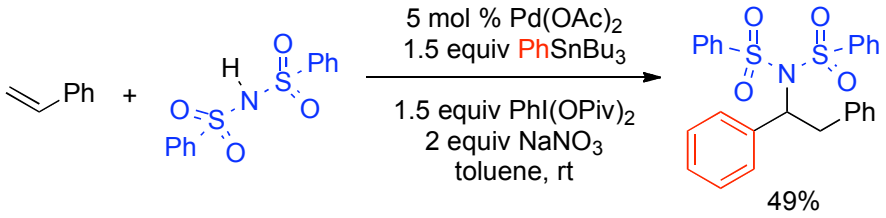


Scheme 5.2. Proposed Mechanism of 1,1-Arylacetoxylatioin

Activated alkenes such as vinyl ethers and styrene derivatives were utilized for the development of the 1,2-arylacetoxylation, which is derived from the functionalization of Pd(II)-alkyl intermediate **5A** instead of **5B** (Scheme 5.2). Understanding the equilibrium between **5A** and **5B** allowed us to develop both 1,1- and 1,2-aryloxygenation of alkenes. We hypothesized **5B** is favored with unactivated alkenes (R ≠ aryl, OR, Scheme 5.2) due to the formation of π-benzyl Pd(II) intermediates, which are more reactive towards oxidation than **5A**. On the other hand, by using activated alkenes (R = aryl, OR), Pd(II) complex **5A** can be made to resemble **5B** thus allowing oxidation to take place and achieve 1,2-aryloxygenation.

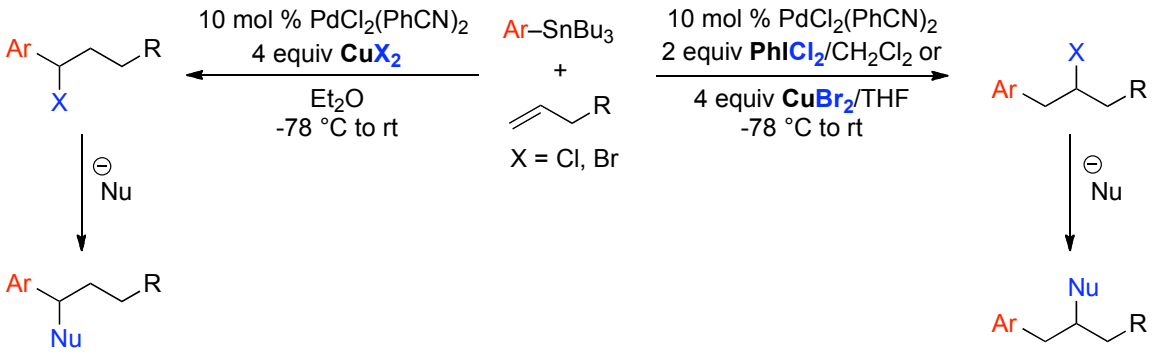
Alkene difunctionalization through oxidative interception of Pd(II)-alkyl intermediates was applied for the development of arylamination. Our preliminary results showed $Pd(OAc)_2$-catalyzed 1,1-arylamination of styrene can be achieved utilizing $PhI(OPiv)_2$, $PhSnBu_3$, $HN(SO_2Ph)_2$, and $NaNO_3$. (Scheme 5.3). This reaction and the intramolecular arylamination reaction requires additional optimization; however, we have shown that arylamination through oxidative

interception of Pd(II)-alkyl intermediate is feasible. Further optimization for the arylamination reaction may be possible by studying various cyclic hypervalent I(III) oxidant so that competing ligand reductive elimination can be avoided. Another area that could be explored is differentiating the electronics on the sulfonamides. For example, adding *para* substituent on the phenyl group to change the basicity of the nitrogen could potentially lead to identifying a better nitrogen source for this transformation.

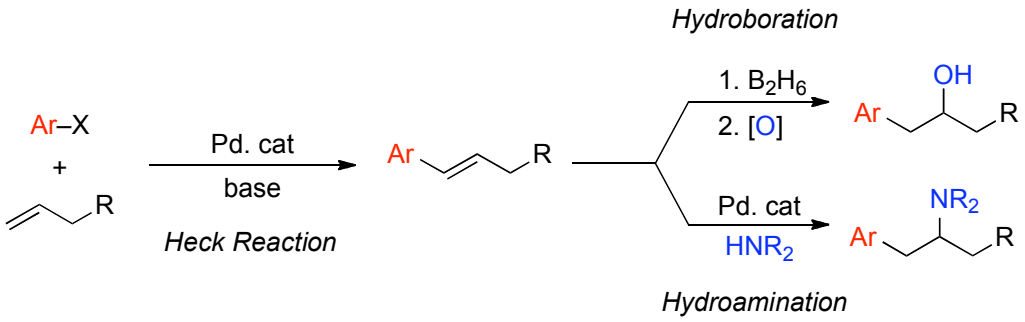


Scheme 5.3. 1,1-Arylamination of Styrene

The significance of this new alkene difunctionalization methodology is that in allows the formation of both C–C and C–O or C–N bonds in a single step. This is an advance considering alternative methods one could think of using to achieve aryloxygen or arylamine motifs. One way to achieve these motifs would involve two steps: arylchlorination of alkenes (methodology developed previously from our group)[1] and displacement of the resulting halogen with a nucleophile (RO^- or R_2N^-) (Scheme 5.4). This approach would be available only if the installed halogen is the only leaving group in the substrate for the S_N2 transformation. A different approach to 1,1-aryloxygenation would to add a aryl Grignard reagent to a carbonyl compound. This would be a single step; however, the low function group tolerance of the Grignard reaction would limit the substrates that could be prepared without further protection group manipulations. 1,2-Arylfunctionalization products can also be accessed via Heck coupling of arylhalides with terminal alkenes then either using hydroboration/oxidation sequence or hydroamination on the resulting alkene (Scheme 5.5). In comparison to these alternative methods, which often require multiple steps or conditions that may have lower functional group tolerance, our methodology provides a straightforward approach to the desired motif.

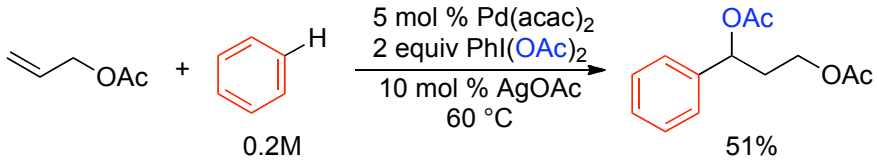


Scheme 5.4. Alternative Synthesis via Arylhalogenation



Scheme 5.5. Alternative Synthesis via Heck Coupling

The requirement for organostannanes in the aryloxygenation methodology developed is a clear limitation. To address this challenge, we sought to replace organostannanes with simple arenes and utilize C–H activation of the arene as the first step to generate Pd-aryl species. In a preliminary studies carried out with allyl acetate and benzene, 1,1-arylacetoxylation was achieved utilizing $Pd(acac)_2$, $PhI(OAc)_2$, and substoichiometric amounts of AgOAc (Scheme 5.6).

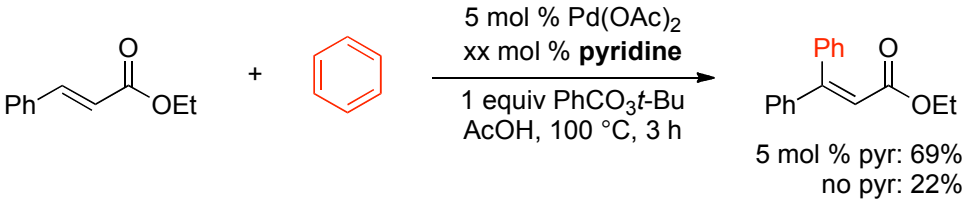


Scheme 5.6. 1,1-Arylacetoxylation of Allyl Acetate by C–H Activation of Benzene

In order to further improve the use of simple arenes for the olefin difunctionalization methodology, we need to understand and be able to control the site-selectivity of the arene C–H activation step. The use of arenes would

change the mechanism such that the first step becomes C–H activation instead of transmetallation. This means that the Pd(II)-alkyl intermediate **5A** would be generated via the steps of the Fujiwara-Moritani (F-M) reaction. Thus, we aimed to address challenges that remain in the field of F-M reactions so that the olefin difunctionalization methodology with arenes instead of organostannanes could ultimately be improved.

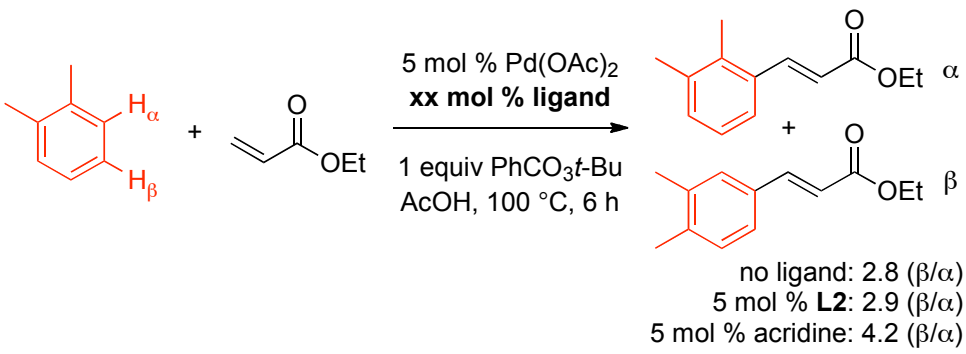
Our approach for addressing key challenges in F-M reactions involved use of catalyst control as described in Chapter 3. We showed that a simple catalyst system with $Pd(OAc)_2$ and pyridine was effective in significantly improving the rates of F-M reactions (Scheme 5.7). Furthermore, we found that 3,5-dichloropyridine (**L2**) was an effective ligand that enabled an expansion of the substrate scope to include some examples of electron deficient arenes and α-olefins. The ligand effect on C–H activation is still not well understood. Pyridine-based ligands may be particular good ligands as their binding abilities allows to effectively break up $Pd(OAc)_2$ trimers, which is the available form of the starting catalyst, to form the catalytically active species. Also, ligands are thought to stabilize Pd(0) species to keep catalyst active for a longer time allowing for oxidation to take place prior to Pd(0) plating out, at which point the catalyst is no longer active.



Scheme 5.7. $Pd(OAc)_2$/Pyridine-Catalyzed C–H Olefination

Preliminary studies indicated that these pyridine-based ligands do affect the site-selectivity of the aryl C–H activation as well. Thus far, the use of acridine have shown the most improvement on site-selectivity for the C–H olefination of *o*-xylene with ethyl acrylate favoring the formation of the less hindered product (Scheme 5.8). We believe that with further studies of ligands the site-selectivity

can be further improved without loss of reactivity. Currently, we do not understand whether the highly conjugated aromatic system or the larger size of acridine was beneficial for obtaining selectivity when compared to pyridine. For future directions, pyridine ligands, resembling acridine in size and electronics, can be studied to identify ligands that will allow improvement of the site-selectivity of the C–H olefination reactions. Also, screening other monodentate ligands such as nitriles may lead to the identification of a more reactive catalyst system.



Scheme 5.8. C–H Olefination of *o*-Xylene with Ethyl Acrylate

In the project described in Chapter 4, I set out to gain a better understanding of Pd-catalyzed ligand-directed C–H activation/functionalization reactions of challenging 2° sp^3 C–H bonds. To this end, various directing ligand tethered cyclopropanes were synthesized and subjected to several Pd-catalyzed oxidative functionalization reactions. We discovered that the reactivity of the cyclopropanes was extremely sensitive to reaction conditions and the ligand structures or substitutions. In most cases, we observed the C–C activation of cyclopropanes (to form ring-opened products) instead of the intended C–H activation.

In summary, I was able to develop alkene aryloxygenation methodology and started developing alkene arylamination transformations through oxidative interception of Pd(II)-intermediates. Additionally, I was able to demonstrate the use of catalyst control to improve the reactivity and the site-selectivity of C–H olefination reactions by utilizing equimolar amounts of $Pd(OAc)_2$ and pyridine

derivatives. Lastly, I carried out a systematic study on Pd-catalyzed ligand-directed functionalization of cyclopropanes, which was shown to be challenging substrate sets for the study of 2° sp^3 C–H activation/functionalization.

References

[1] (a) Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130,* 2150. (b) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132,* 8419.