Part I: Iron (III)-catalyzed reactions of benzylic
analogues with organosilanes & Conia-ene
cyclization. Part II: Palladium (II)-catalyzed C-H
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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**PART I: IRON(III)-CATALYZED REACTIONS OF
BENZYLIC ANALOGS WITH ORGANOSILANES
& CONIA-ENE CYCLIZATION**

**PART II: PALLADIUM(II)-CATALYZED C-H
FUNCTIONALIZATIONS USING MONO-PHOSPHORIC
ACID DIRECTING GROUP**

**CHAN LI YAN
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
2013**

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ACID DIRECTING GROUP

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS	i
TABLE OF CONTENTS	ii
SUMMARY	vi
LIST OF ABBREVIATIONS	ix

Chapter 1 : INTRODUCTION

1.1 Introduction	3
1.2 Iron and Its Properties	4
1.3 Iron in Our Daily Life	4
1.4 Iron Catalysis in Organic Reactions	6
1.5 Application of Iron-Catalyzed Reactions	8

Chapter 2 : FE(III)-CATALYZED REACTIONS OF BENZYLIC DERIVATIVES WITH ORGANOSILANES

2.1 Introduction	15
2.1.1 Introduction	15
2.1.2 Lewis Acid Catalyzed Reduction	17
2.2 Results and Discussion	24
2.2.1 Preliminary Studies	24
2.2.2 Optimizing Reaction Conditions	26
2.2.3 Reactions of Benzylic Acetates with Various Organosilanes	27

2.2.4	Proposed Mechanism	30
2.2.5	Optimizing Reaction Conditions for Reductive Dehydroxylation	31
2.2.6	Reductive Dehydroxylation of Benzylic Alcohols	32
2.2.7	Proposed Mechanism	37
2.3	Conclusion	37

Chapter 3 : Fe(III)-CATALYZED CONIA-ENE CYCLIZATION OF 2-ALKYNIC 1,3-DICARBONYL COMPOUNDS

3.1	Introduction	41
3.2	Results and Discussion	46
3.2.1	Optimizing Reaction Conditions	46
3.2.2	Fe(III)-Catalyzed Conia-ene Cyclization	48
3.2.3	Preliminary Studies on Stannyl Conia-ene Type Cyclization	51
3.2.4	Fe(III)-Catalyzed Stannyl Conia-ene Type Cyclization	53
3.2.5	Proposed Mechanism	55
3.3	Conclusion	55

Chapter 4 : PALLADIUM CATALYSIS IN CROSS COUPLING REACTIONS

4.1	Introduction	59
4.2	Palladium and Its Properties	59
4.3	Palladium Catalysis in Cross Coupling Reactions	60

4.4	Application of Palladium-Catalyzed Cross Coupling Reactions	62
4.5	Importance of Directing Group in C-H Activation Reactions	65
4.6	Organophosphorus Compounds as a Potential Directing Group in C-H Activation Reactions	66
4.7	Organophosphorus Compounds in Organic Reactions	67

Chapter 5 : PD-CATALYZED *ORTHO*-ALKENYLATION OF ARYL HYDROGEN PHOSPHATES USING A NEW MONO-PHOSPHORIC ACID DIRECTING GROUP

5.1	Introduction	73
5.2	Results and Discussion	77
5.2.1	Optimizing Reaction Conditions	77
5.2.2	Pd(II)-Catalyzed <i>ortho</i> -Alkenylation via mono-Phosphoric Acid Directing Group	79
5.2.3	Proposed Mechanism	82
5.3	Conclusion	83

Chapter 6 : PD-CATALYZED *ORTHO*-ARYLATION AND *ORTHO*-ACETOXYLATION WITH VARIOUS IODONIUM SALTS

6.1	Introduction	87
6.2	Results and Discussion	91
6.2.1	Preliminary Studies	91
6.2.2	Optimizing Reaction Conditions	93

6.2.3	Pd(II)-Catalyzed <i>ortho</i> -Arylation of Aryl Hydrogen Phosphates	94
6.2.4	<i>ortho</i> -Acetoxylation of mono-Phosphoric Acids via Pd(II)-Catalysis	96
6.2.5	Proposed Mechanism	98
6.3	Conclusion	99
 Chapter 7 : EXPERIMENTAL SECTION		
7.1	General Information	103
7.2	The Addition of Benzylic Acetates with Various Organosilanes	104
7.3	Reductive Dehydroxylation of Benzylic Alcohols with PMHS	111
7.4	Conia-ene Cyclization of 2-Alkynic 1,3-Dicarbonyl Compounds	118
7.5	Pd-Catalyzed C-H <i>ortho</i> -Alkenylation of Aryl Hydrogen Phosphates	129
7.6	Pd-Catalyzed C-H <i>ortho</i> -Arylation and <i>ortho</i> - Acetoxylation of Aryl Hydrogen Phosphates with Various Iodonium Salts	146
 List of Publications		 169

SUMMARY

Part I

Iron is an attractive catalyst as it is naturally abundant, cheap and easy to handle with low toxicity. With the increasing trend towards green chemistry, it is of our interest to use environmentally friendly iron to catalyze organic reactions.

C-C bond formation was observed during the addition of benzylic acetates with organosilanes in the presence of a catalytic amount of Fe(OTf)_3 in 1,2-dichloroethane. Reactions of various benzylic acetates were carried out with allyltrimethylsilane, azidotrimethylsilane, and cyanotrimethylsilane to afford the corresponding allylated, azido, and cyano products in high yields. 2-Trimethylsilyl substituted benzofuran and indole also worked well to furnish the benzyl and allyl substituted benzofuran and indole.

When the reaction was carried out using an organosilane with reducing properties, such as polymethylhydrosiloxane (PMHS), reductive dehydroxylation of benzylic alcohols could be achieved. In general, secondary benzylic alcohols worked best, while primary alcohols were inert towards the reaction conditions. Tertiary alcohols generated cation intermediates that are too stable, which then increased the formation of byproducts formed

via an elimination pathway. This methodology is selective towards alcohols only, and the carbonyl functionality was kept intact in both intra- and intermolecular fashions.

Conia-ene cyclization is an efficient tool for the formation of cyclic molecules, therefore, we have developed cheap and green Fe(III)-catalysis to perform such important reaction. The reaction followed 5-*exo-dig*, 5-*endo-dig* or 6-*exo-dig* pathways, and worked well for terminal as well as substituted alkynes. Vinylstannanes were synthesized via a stannyl Conia-ene type cyclization, and proven to be useful for further coupling reactions.

Part II

C-H activation reactions via Pd-catalysis are useful synthetic methods, especially for *ortho*-functionalization of arenes. Such reactions are remarkably enhanced with the help of directing groups or ligands to control the selectivity. Therefore, it is essential for the continual discovery of new efficient functional groups for *ortho*-selective C-H activations.

Organophosphates are the main building block in DNA and RNA, thus are important constituents of living organisms. Furthermore, they are very useful functional groups in organic synthesis, and are widely exploited as organic catalysts and cross coupling partners in Pd-catalyzed cross coupling reactions.

Herein, we utilized the mono-phosphoric acid functionality to carry out Pd-catalyzed *ortho*-functionalization reactions, namely alkenylation, arylation and acetoxylation. Alkenylation underwent a Pd(II)/Pd(0) catalytic cycle and required AgOAc as the external oxidant. The reaction has a wide substrate scope and also worked well with electron-deficient partners, such as acrylates, styrenes, vinyl phosphate, vinyl sulfonate, and vinyl ketone.

In contrast, arylation and acetoxylation went through a Pd(II)/Pd(IV) catalytic pathway, with iodonium salts that serving as the coupling partner and oxidant. The reactions yield useful biaryls or catechols derivatives that are common motifs of natural products.

In conclusion, the mono-phosphoric acid group is found to be an efficient directing group in Pd-catalyzed *ortho*-C-H functionalization.

INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	heating
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
acac	acetoacetate
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Cacld	calculated
Cat.	catalytic
cm^{-1}	inverse centimeter
DBATO	bis(di-butylacetoxitin) oxide
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
<i>ee</i>	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hour
Hex	hexane
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared
<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constant
LUMO	lowest unoccupied molecular orbital
M	concentration (mol/dm^{-3})

m	multiplet
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
mmol	millimoles
MS	mass spectrum
<i>n</i> -Bu	<i>n</i> -butyl
nmr	nuclear magnetic resonance
NMP	<i>N</i> -methyl-2-pyrrolidone
Nu	nucleophile
Ph	phenyl
PMHS	polymethylhydrosiloxane
ppm	parts per million
PCy ₃	tricyclohexylphosphine
Py	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
<i>t</i> -Bu	<i>tert</i> -butyl
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
tmeda	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	tetramethylsilane

CHAPTER 1

Introduction

1.1 INTRODUCTION

The use of a catalyst in organic synthesis is ubiquitous. A catalyst accelerates the rate of a reaction by providing an alternative pathway for the reaction to proceed, but still stay unchanged at the end. During the process, the overall Gibbs energy change remains the same (Figure 1.1).¹

Figure 1.1 The role of the catalyst in a reaction

Transition metal catalyzed reactions are synthetically very useful in the area of organic chemistry, thus experiencing an explosive development over the decades. As such, there is an increasing demand for such metals, especially when applied as catalysts in important organic reactions. In general, transition metals have incomplete *d*-orbitals and are able to adopt multiple oxidation states, making them more effective as catalysts. The widely used transition metals include gold, ruthenium, rhodium, palladium, platinum, nickel, copper, *etc.* In this thesis, our works will focus on utilizing iron(III) and palladium(II) (which will be discussed in the later chapters) as

¹ Menaught, A. D.; Wilkinson, A. *IUPAC. Compendium of Chemical Terminology, 2nd ed.* (the "Gold Book"); Blackwell Scientific Publications: Oxford, 1997.

the transition metal catalysts to develop useful methodologies in facilitating different organic reactions.

1.2 IRON AND ITS PROPERTIES

Iron is a transition metal, classified as Group 8 in the periodic table, with the symbol Fe and atomic number 26. Its electron configuration is $[\text{Ar}]3d^64s^2$, which consists of incomplete *d*-orbital shells like most transition metals. Although iron exists in a broad range of oxidation states, +2 and +3 are most common, with the name ferrous and ferric, respectively.

The colour of iron surfaces is silvery-gray, but iron combines readily with oxygen and moisture present in air to give hydrated iron oxides ($\text{Fe}_2\text{O}_3 \cdot n\text{H}_2\text{O}$ and $\text{FeO}(\text{OH}) \cdot \text{Fe}(\text{OH})_3$), generally known as rust. The rust formed on the surface is not considered a protective layer to the underlying iron, in contrast to patina formed on copper surfaces.

Iron has low toxicity and exists naturally in high abundance on Earth, thus contributing to its nominal cost. Most of the naturally occurring iron is combined with oxygen and exists as iron oxide minerals such as hematite (Fe_2O_3) and magnetite (Fe_3O_4). With that, iron is definitely an attractive metal towards industrial application, given its cheap and green properties.²

1.3 IRON IN OUR DAILY LIFE

Hemoglobin is well known to be the vital component in red blood cells that transports oxygen in blood of living organisms. In most vertebrates, the hemoglobin molecule consists of four polypeptide-chains subunits, and each subunit is made up of

² Bolm, C. *Nat. Chem.* **2009**, *1*, 420.

Figure 1.2 Structure of Heme b group

the globular protein with an embedded non-protein heme group. A heme has an iron core center of the heterocyclic porphyrin, which comprises four pyrrolic groups joined together by methine bridges (Figure 1.2).³ In the current society, the disease associates with low iron intake is called anemia. Nevertheless, many iron-rich foods such as red meat, egg yolks, spinach, liver *etc.* can act as good source of supplements and are necessary for good nutrition.

Iron gall ink was the standard writing ink in Europe from the 5th to 19th century, and remained popular still, in the 21st century. Iron gall ink is formed by mixing gallic acid with water and FeSO_4 . Gum arabic from acacia trees was added as the suspension agent to improve the viscosity of the ink. The gallic acid is obtained by breaking the ester links of gallotannic acid with water, which was usually extracted from oak galls, hence its name.⁴

Prussian Blue, with the formula $[\text{Fe}_4[\text{Fe}(\text{CN})_6]_3]$ (Figure 1.3), is the pigment heavily used in industry for paints, inks, laundry dyes, as well as in blueprints. The insoluble blue precipitate is formed by the reaction of colourless $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$ and

³ Kaushansky, K. *Blood* **2000**, 95, 1.

⁴ Wilson, H.; Carr1, C.; Hacke, M. *Chem. Cent. J.* **2012**, 6, 44.

Figure 1.3 Structure of Prussian Blue

$[\text{Fe}(\text{CN})_6]^{4-}$ in water.⁵ Interestingly, Prussian Blue is also used as an antidote for heavy metal poisoning, example from thallium or radioactive caesium, as it is an effective sequestering agent for such metals.

1.4 IRON CATALYSIS IN ORGANIC REACTIONS

In contrast to the other transition metals, iron is considered one of the cheapest and environmentally friendly ones. Most of the useful iron salts and complexes can be easily obtained commercially or by simple synthesis. Furthermore, iron also plays a crucial role in various iron-catalyzed organic reactions as illustrated below.

Scheme 1.1 FeCl_3 -catalyzed Michael reaction

In 1997, Christoffers first introduced the use of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst that served as an efficient and practical alternative to the classic Brønsted bases for Michael reactions. Remarkable results were obtained with a wide substrate scope for the addition of cyclic or acyclic β -dicarbonyls with different acceptors under ambient

⁵ Dunbar, K. R.; Heintz, R. A. *Prog. Inorg. Chem.* **1997**, 45, 283.

temperature (Scheme 1.1).⁶ The hydrate water caused partial hydrolysis and subsequent decarboxylation when using 5 mol% catalytic loading. This phenomenon can be significantly omitted when reducing the loading of catalyst to 1 mol%. The cyclic ketoester substrates worked best, while the remaining substrates gave excellent results as well, but at a slower rate.

Scheme 1.2 Friedel-Crafts benzylation

In 2005, the Beller group described the attractiveness of FeCl_3 ⁷ in Friedel-Crafts benzylation among the different late transition metals tested, which consisted of HAuCl_4 ⁸, IrCl_3 , $\text{MesW}(\text{CO})_3$, RhCl_3 , H_2PdCl_4 and H_2PtCl_6 .⁹ This method is simple to handle and able to tolerate a comprehensive range of functional groups, which even includes thiophene and furan (Scheme 1.2). The products obtained may impact future pharmaceutical and drug discovery as diarylmethanes are crucial core structures in numerous biological active compounds such as papaverine (a vasodilator used to treat

⁶ (a) Christoffers, J. *Chem. Commun.* **1997**, 943. (b) Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141. (c) Review: Christoffers, J. *Synlett* **2001**, 723.

⁷ (a) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem.* **2005**, *117*, 3981; *Angew. Chem., Int. Ed.* **2005**, *44*, 3913.

⁸ Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691.

⁹ (a) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem.* **2005**, *117*, 242; *Angew. Chem., Int. Ed.* **2005**, *44*, 238.

vasospasm or erectile dysfunction in men) and beclobrate (mainly used to treat hyperlipoproteinemia).

Scheme 1.3 Highly diastereoselective synthesis of substituted piperidines and tetrahydropyrans

Cossy and coworkers have developed an eco-friendly and highly diastereoselective method to synthesize *cis*-2,6-disubstituted piperidines and *cis*-2,6-disubstituted tetrahydropyrans (Scheme 1.3). These compounds are valuable building blocks for the synthesis of biologically active targets. The use of FeCl₃ is the key account for the high diastereoselectivities observed in favor of the most stable *cis*-isomers.¹⁰

Scheme 1.4 Direct amination from azide derivatives via iron catalysis

In a recent report, Betley and coworkers group achieved the formation of saturated, complex cyclic amine products by using a self-designed iron-dipyrinato

¹⁰ (a) Guérinot, A.; Serra-Muns, A.; Gnam, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808. (b) Guérinot, A.; Serra-Muns, A.; Gnam, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Tetrahedron* **2011**, *67*, 5024.

catalyst to assist the direct amination of linear aliphatic C–H bonds as shown in Scheme 1.4.¹¹ The method required only simple linear starting substrates that contained an azide functionality, and is applicable for forming complex cyclic amine, which promises significant contributions towards drug discovery and natural product synthesis.

1.5 APPLICATION OF IRON-CATALYZED REACTIONS

Scheme 1.5 Total synthesis of isooincinotine

Kochi and coworkers carried out the pioneer work of iron-catalyzed cross coupling in 1971.¹² The report described the cross coupling of Grignard reagents and organohalides, however, with moderate yields in most cases. The application of NMP as cosolvent, done by Cahiez's group in 1998, greatly enhanced the reaction.¹³ Encouraged by their early reports,¹⁴ Fürstner's group has achieved selective cross-coupling reactions with various functionalized Grignard reagents via $\text{Fe}(\text{acac})_3$ catalysis.¹⁵ In one case, he demonstrated the application of the catalysis in the key

¹¹ Hennessy, E. T.; Betley, T. A. *Science* **2013**, 340, 591.

¹² Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, 93, 1487.

¹³ Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.

¹⁴ Kochi, J. K. *Acc. Chem. Res.* **1974**, 7, 351.

¹⁵ (a) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, 124, 13856. (b) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, 41, 609. (c) Fürstner, A.; Méndez, M. *Angew. Chem. Int. Ed.* **2003**, 42, 5355.

step of the total synthesis of isoconcinotine (Scheme 1.5).¹⁶ The reaction was well-controlled whereby double alkylation of 2,6-dichloropyridine **10** could be avoided.

In terms of industrial application, iron is heavily used in the process of steel manufacturing. In another example, Mittasch found the inexpensive iron-based catalyst that could be used to facilitate the industrial production of ammonia from nitrogen and hydrogen gas in Haber–Bosch process.¹⁷ The Haber process was first discovered by the German chemist, Fritz Haber, in the early 20th century. The finding was very important to the industry, as production of ammonia was difficult back then prior to this discovery. Later Carl Bosch, from the German chemical company BASF, upscaled the benchtop Haber process to industrial level, which brought a breakthrough in chemical engineering. For that, Haber and Bosch were awarded Nobel prizes in 1918 and 1931, respectively.

Scheme 1.6 Hydrogenation of saturated bonds using Fe NP catalyst in H-Cube flow reactor

With the growing emphasis of green chemistry, iron is indisputably one of the best choices. The collaborative work of Uozumi and Moores has demonstrated excellent performance of the polymer-stabilized Fe(0) nanoparticle (Fe NP) as a

¹⁶ Scheiper, B.; Glorius, F.; Leitner, A.; Fürstner, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11960.

¹⁷ Oesper, R. E. *J. Chem. Educ.* **1948**, *25*, 531.

hydrogenation catalyst in place of the current expensive platinum (Scheme 1.6). This report highlighted three important green chemistry conditions: flow hydrogenation with H₂, use of water and ethanol as benign solvents and the use of heterogeneous iron as a catalyst. More importantly, this research opens up a practical approach towards industrial application.¹⁸

Iron has proved its importance and advantages in many aspects. However, studies of iron are still underexplored as compared to the other precious metals such as palladium or rhodium, which already have a strong library of organic transformations. This is probably the reason why iron is generally not the first catalyst of choice since it is always more convenient to follow the known approaches, rather than switching to the unknown. Moreover, the majority of the iron complex catalysts are paramagnetic in nature, which often caused complexity in standard analytic studies (for example, via NMR spectroscopy), thus iron-catalyzed reactions are sometimes difficult to follow.

Abundant, non-toxic and inexpensive, iron is still a very attractive catalyst over other transition metals. Iron chemistry has thus grown over the years, especially in the area of iron-catalyzed organic reactions.¹⁹ Encouraged by the reports, our group is interested to develop methodologies as useful organic synthetic tools. In the following chapters, we will focus on the elaborative usage of iron salts as an effective and efficient catalysts in promoting the reactions of (i) benzylic acetates with organosilanes; (ii) reductive dehydroxylation of benzylic alcohols; and (iii) cyclization reactions.

¹⁸ Hudson, R.; Hamasak, G.; Osako, T.; Yamada, Y. M. A.; Li, C.-J.; Uozumi, Y.; Moores, A. *Green Chem.* **2013**, *15*, 2141.

¹⁹ (a) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (b) Bolm, C.; Legros, J.; Pahl, J. L.; Zani, L. *Chem. Rev.* **2004**, *140*, 6217. (c) Gopalaiah, K. *Chem. Rev.* **2013**, *113*, 3248.

CHAPTER 2

*Fe(III)-Catalyzed Reactions of Benzylic
Derivatives with Organosilanes*

2.1 INTRODUCTION

2.1.1 Introduction

Carbon-carbon bond formation is an important area in organic synthesis, and Lewis acids are a popular choice in catalyzing this reaction.²⁰ The electron-pair theory of acid-base reactions was first introduced by Gilbert N. Lewis in 1923.²¹ In the case of Lewis acid catalysis, the Lewis acid will act as the “electron-pair acceptor”, thus escalating the reactivity of the reactant. In the early days, TiCl_4 , BF_3 , SnCl_4 , and AlCl_3 were the usual Lewis acid employed in organic synthesis. Some famous Lewis acid-catalyzed reactions include the Friedel-Crafts reactions, the aldol reactions and the Diels-Alder reactions.

Scheme 2.1 Pioneering work of Friedel-Crafts alkylation

Scheme 2.1 showed the first example of Friedel-Crafts alkylation done by Charles Friedel and James Mason Crafts in 1887, and is also considered one of the first illustrations of Lewis acid catalysis in organic synthesis.²² To date, tremendous improvements were developed, and Friedel-Crafts alkylations continue to be the choice of approach.²³

²⁰ Yamamoto, H.; Ishihara, K. Eds. *Acid Catalysis in Modern Organic Synthesis*, Vol. 1 and 2, **2008**, Wiley-VCH. Weinheim and references cited therein.

²¹ Lewis, G.N. *Valence and the Structure of Atoms and Molecules*, **1923**, 142.

²² Friedel, C.; Crafts, J. M. *J. Chem. Soc.* **1877**, 32, 725.

²³ Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, 6, 6.

Scheme 2.2 Synthesis of functionalized tetrahydrofurans by Reissig

In the late 1980s, Reissig and coworkers used $\text{BF}_3 \cdot \text{OEt}_2$ to achieve the diastereoselective synthesis of functionalized tetrahydrofuran derivatives from γ -lactols. Since the reactants could be easily prepared, this method proved to be synthetically useful for a variety of tetrahydrofurans (Scheme 2.2).²⁴

Scheme 2.3 FeCl_3 -catalyzed allylation of benzylic alcohols or halides

More recently, Liu proposed an efficient way for allylation of benzylic alcohols or halides with allyltrimethylsilane using FeCl_3 as the catalyst. The approach is cheap and mild, providing a beneficial alternative to the other reported methods (Scheme 2.3).²⁵

Scheme 2.4 Substitution of acetate group with thiosilane

²⁴ Brückner, C.; Lorey, H.; Reissig, H.-U. *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 556.

²⁵ Han, J.; Cui, Z.; Wang, J.; Liu, Z. *Syn. Commun.* **2010**, 40, 2042.

Baba's group has been actively using InX_3 ($\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{OTf}, \text{etc.}$) as the catalyst in various organic reactions with organosilanes.²⁶ In 2012, Baba's group successfully made useful thioethers via substitution reaction of alkyl acetates with thiosilanes in the presence of InI_3 catalysts as displayed in Scheme 2.4.²⁷ The classical method to synthesize thioethers usually needed a strong base and produced an equimolar amount of metal halides as the byproducts. The present method proved to be more efficient as it could overcome the above disadvantages, and has high tolerance to a wide scope of alkyl acetates.

2.1.2 Lewis Acid Catalyzed Reduction

Reduction is one of the basic transformations in organic chemistry, thus chemists have been searching for better and improving methods to perform such a reaction over the years.²⁸ Clemmensen and Wolff-Kishner reductions are two classical methods for reducing carbonyls to the corresponding alkanes (Scheme 2.5).

(i) Clemmensen Reduction:

(ii) Wolff-Kishner Reduction:

Scheme 2.5 Clemmensen and Wolff-Kishner reduction

²⁶ For selected reports: (a) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1414. (b) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516. (c) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 793. (d) Nishimoto, Y.; Moritoh, R.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 577.

²⁷ Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Org. Lett.* **2012**, *14*, 1846.

²⁸ (a) Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (c) Kim, S. *Pure & Appl. Chem.* **1987**, *59*, 567. (d) Yoon, N. M. *Pure & Appl. Chem.* **1996**, *68*, 843. (e) Yamamura, S.; Nishiyama, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, **1991**; Vol. 8, 307-325.

The two methods are complementary to each other depending on the sensitivity of substrates towards strong acid and base. The use of harsh conditions reduces the attractiveness of the methods, as most functional groups will not be compatible.

Hydride transfer agents such as organotin hydrides,²⁹ LiAlH_4 ,³⁰ DIBAL,³¹ *etc.* are some commonly used reagents in performing reductive reactions. However, these compounds are generally toxic and well-known for their hazardous properties.³²

Reduction with the aid of organosilanes is considered a favourable way because the Si-H bond is a mild, air and water stable hydride source.³³ The chemical and physical properties of Si-H are similar to hydrocarbon analogs, rather than the familiar hydride reducing agents mentioned above. In comparison, organosilanes are thus safer and easier to handle.³⁴ As such, this gives a better control over the functional group selectivity when employing organosilane reagents in performing reduction reactions.

Particularly, our group is interested in the reductive dehydroxylation of benzylic alcohols to the corresponding derivatives. The most commonly practiced set of conditions for the reduction of alcohols is triethylsilane and trifluoroacetic acid ($\text{Et}_3\text{SiH/TFA}$) in dichloromethane solution.³⁵

²⁹ (a) Nicolaou, K. C.; Sato, M.; Theodorakis, E. A.; Miller, N. D. *Chem. Commun.* **1995**, 1583. (b) Jang, D. O.; Song, S. H.; Cho, D. H. *Tetrahedron* **1999**, *55*, 3479.

³⁰ (a) Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1960**, *25*, 875. (b) Pettit, G. R.; Ghatak, U. R.; Green, B.; Kasturi, T. R.; Piatak, D. M. *J. Org. Chem.* **1961**, *26*, 1685. (c) Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1961**, *26*, 4553. (d) Pettit, G. R.; Piatak, D. M. *J. Org. Chem.* **1962**, *27*, 2127.

³¹ Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.

³² (a) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 3381. (b) Carpentier, J.-F.; Bette, V. *Current Org. Chem.* **2002**, *6*, 913.

³³ Larson, G. L.; Fry, J. L. *Ionic and Organometallic-Catalyzed Organosilane Reductions*; John Wiley and Sons Ltd: New Jersey, **2010**; 5.

³⁴ (a) Málek, J. *Org. React.* **1985**, *34*, 1. (b) Málek, J. *Org. React.* **1988**, *36*, 249.

³⁵ (a) Carey, F. A.; Tremper, H. S. *J. Am. Chem. Soc.* **1968**, *46*, 3325. (b) Kursanov, D.N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

Scheme 2.6 Dehydroxylation of 2,4,6-tri-*t*-butylbenzyl alcohol

As early as 1972, MacDonald's group investigated the hydride transfer to carbonium ions of 2,4,6-tri-*tert*-butylbenzyl compounds formed under acidic condition. Mechanistic studies were done which strongly suggested the formation of benzylic cation as an intermediate (Scheme 2.6).³⁶

Scheme 2.7 Selective dehydroxylation of benzylic alcohol

The mild and specific reductive dehydroxylation of benzylic alcohols when using $\text{Et}_3\text{SiH/TFA}$ reagent is excellently displayed during the synthesis of (-)-anisomycin from D-galactose done by Baer's group. In this example, reduction of benzylic alcohol was selective in the presence of other functional groups such as benzyl ether, tetrahydrofuran and acetal (Scheme 2.7).³⁷

Figure 2.1 Structure of polymethylhydrosiloxane (PMHS)

³⁶ Barclay, L. R. C.; Sonawane, H. R.; MacDonald, M. C. *Can. J. Chem.* **1972**, *50*, 281.

³⁷ Baer, H. H.; Zamkane, M. *J. Org. Chem.* **1988**, *53*, 4786.

Among the available organosilanes, polymethylhydrosiloxane (PMHS), as shown in Figure 2.1, is of our interest. It is a byproduct of the silicone industry, therefore accounting for its low cost. PMHS is readily available, non-toxic, stable and easy to handle. Although PMHS could be easily obtained after the first preparation in 1946 by Sauer's group,³⁸ it was not fully utilized in organic synthesis.

Figure 2.2 Coordination of metal catalyst and PMHS to give intermediate metal hydride

Reagent grade PMHS is colourless and has an active mass per hydride of 60 g/mol. PMHS is generally inert in the absence of catalysts (Figure 2.2), thus making it an attractive reducing agent. The typical catalysts that are used together with PMHS are tin, titanium and palladium, which facilitate reduction via the intermediate metal hydride. Some illustrations are discussed below.

Scheme 2.8 Reduction of aldehydes and ketones by Lipowitz and Bowman

Most of the initial examples reported with PMHS consisted organotin catalyst as the hydride transfer agent, especially in the reduction of aldehydes and ketone. One early report in 1973 by Lipowitz and Bowman³⁹ reported such reductions using the

³⁸ Sauer, R. O.; Scheiber, W. J.; Brewer, S. D. *J. Am. Chem. Soc.* **1946**, 68, 962.

³⁹ Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, 38, 162.

PMHS-DBATO (bis(di-butylacetoxitin) oxide) as seen in Scheme 2.8. This reaction has many benefits over the usual reduction methods, as it does not require the hydrolysis step and is stable in the presence of air and water.

Scheme 2.9 $\text{Ti}(\text{O}^i\text{Pr})_4$ catalyzed reduction of esters

PMHS reduction is not only limited to aldehydes or ketones. Similarly, Ti-catalyzed hydrosilylation using titanium(V) isopropoxide was also effective for the reductions of esters as done separately by Lawrence and Buchwald.⁴⁰ This procedure is compatible with a large variety of functional groups, such as primary alkyl halides, nitro, olefins, epoxides, cyclopropanes, and alkynes. However, extra precautions were essential during the basic workup as a highly dangerous gas (probably SiH_4) was liberated vigorously during the process, and has high tendency to cause explosion (Scheme 2.9).

Scheme 2.10 Pd-catalyzed reduction of benzyl compounds to alcohols or alkanes

In 2011, Maleczka's group developed a $\text{Pd}(\text{OAc})_2/\text{PMHS}/\text{KF(aq)}$ catalytic system to selectively reduce benzylic C-O bonds to either the alcohol or alkane

⁴⁰ (a) Breeden, S. W.; Lawrence, N. J. *Synlett* **1994**, 833. (b) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1995**, 60, 7884.

derivatives as shown in Scheme 2.10.⁴¹ The actual active catalyst in this system was Pd-PMHS nanoparticles which were formed as palladium dispersed through the siloxane polymer matrix.⁴² In this context, adding 10 mol% chlorobenzene played a crucial role in determining the end-product. They presumed that chlorobenzene will form Ph-Pd(II)-Cl species during the reaction, thus releasing HCl at a controlled rate in the presence of PMHS and water.⁴³ The ketone at the benzylic position first underwent reduction via Pd-catalyzed hydrosilylation to give the respective benzylic alcohol. The presence of chlorobenzene in turn generated HCl that promoted Pd-catalyzed transfer hydrogenolysis of the benzylic alcohol. The author showed a comprehensive list of more than 30 examples to demonstrate the efficiency of this methodology.

In our continual search for cheap and effective catalysis procedures in organic synthesis, we deemed that Fe-PMHS system would be an attractive one, given all the known advantages of these two compounds, especially in the economical aspects.

Scheme 2.11 Fe(OAc)₂/PMHS system developed by Beller

As represented in Scheme 2.11, the conversion of aldehydes to the corresponding primary alcohols via Fe(OAc)₂/PMHS catalytic system was nicely

⁴¹ Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Org. Lett.* **2011**, *13*, 584.

⁴² (a) Tour, J. M.; Cooper, J. P.; Pandalwar, S. L. *J. Org. Chem.* **1990**, *55*, 3452. (b) Tour, J. M.; Pandalwar, S. L.; Cooper, J. P. *Chem. Mater.* **1990**, *2*, 647. (c) Fowley, L. A.; Michos, D.; Luo, X.-L.; Crabtree, R. H. *Tetrahedron Lett.* **1993**, *34*, 3075. (d) Chauhan, B. P. S.; Rathore, J. S.; Bando, T. *J. Am. Chem. Soc.* **2004**, *126*, 8493.

⁴³ (a) Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **2002**, *43*, 8823. (b) Rylander, P. *Catalytic Hydrogenation in Organic Synthesis*; Academic: New York, **1979**; 274.

featured by Beller and coworkers. Addition of a catalytic amount of phosphine ligand is important, and a more basic phosphine, such as PCy_3 , benefited the conversion. This method is compatible with a broad range of functional groups that are also sensitive towards reduction, namely Cl, Br, F, NO_2 , CO_2Me , CN, and *O*-benzyl substituted at the *ortho*-, *meta*-, or *para*- position of benzylic substrates. The system is not restricted to benzylic compounds, but also applicable for less reactive aliphatic aldehydes.⁴⁴

Scheme 2.12 Hydrosilylation of ketones to secondary alcohols

In the same year of 2007, Nishiyama and coworkers established a similar $\text{Fe}(\text{OAc})_2/\text{PMHS}$ catalysis as Beller to perform hydrosilylation of ketones to derive a secondary alcohol (Scheme 2.12). The key component of this reaction is the use of multi-nitrogen-based ligands, like *N,N,N',N'*-tetramethylethylenediamine (tmeda).⁴⁵

Scheme 2.13 Microwave-aided reduction of aldehydes and ketones to alkanes

⁴⁴ Shaikh, N. S.; Junge, K.; Beller, M. *Org. Lett.* **2007**, 9, 5429.

⁴⁵ Nishiyama, H.; Furuta, A. *Chem. Commun.* **2007**, 760.

It is noteworthy that PMHS in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyst reduced aldehydes and ketones to their corresponding hydrocarbons, which was done by Campagne in 2009. However, the reaction required a high temperature (120 °C) and microwave irradiation.⁴⁶ Apart from that, the methodology is easy to handle and is suitable for both aromatic and aliphatic substrates (Scheme 2.13).

With an increasing trend towards green chemistry, it is of our interest to use environmentally friendly iron to catalyze organic reactions as compared to the other conventional Lewis acids.⁴⁷ Furthermore, the direct dehydroxylation of alcohols using PMHS is still rarely explored,⁴⁸ and definitely has potential if this was to be performed together with iron catalyst in terms of economical aspects. Herein, we will discuss a new efficient iron (III)-catalyzed reaction of benzylic acetates with various organosilanes, as well as an efficient FeCl_3 /PMHS reducing agent in dehydroxylating benzylic alcohols selectively, even in the presence of other carbonyl functionality.

2.2 RESULTS AND DISCUSSION

2.2.1 Preliminary Studies

We first began our studies by carrying out allylation with a benzylic alcohol, diphenylmethanol **44** as shown in Table 2.1, entry 1. **44** was first treated with 5 mol% $\text{Fe}(\text{OTf})_3$ (generated *in situ* from 5 mol% FeCl_3 and 15 mol% AgOTf)⁴⁹ in 1,2-dichloroethane at room temperature for 2 h (entry 1). During the process, only 31% of

⁴⁶ Zotto, C. D.; Virieux, D.; Campagne, J-M. *Synlett* **2009**, 2, 276.

⁴⁷ For reviews, see: (a) Plietker, B. Ed. *Iron Catalysis in Organic Chemistry: Reactions and Applications*, **2008**, Wiley-VCH, Weinheim. (b) Han, J.; Cui, Z.; Wang, J.; Liu, Z. *Synth. Commun.* **2010**, 40, 2042.

⁴⁸ (a) Eisch, J. J.; Liu, Z.-R.; Boleslawski, M. P. *J. Org. Chem.* **1992**, 57, 2143. (b) Miyai, T.; Ueba, M.; Baba, A. *Synlett* **1999**, 182. (c) Miyai, T.; Ueba, M.; Baba, A. *Synlett* **1999**, 182. (d) Yasuda, M.; Onishi, Y.; Ueda, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, 66, 7741. (e) Yao, M.-J.; Pippin, A. B.; Kabalka, G. W. *Tetrahedron Lett.* **2010**, 51, 853.

⁴⁹ Note: $\text{Fe}(\text{OTf})_3$ catalyst was not available at the point of experiment, thus the catalyst was generated *in situ* by using 5 mol% FeCl_3 and 15 mol% AgOTf .

Table 2.1 Reacting diphenylmethanol with various organosilanes

entry	TMS-X	temp (°C)	time (h)	isolated yield (%)	
				45	46
1	TMS-CH ₂ CH=CH ₂	rt	2	31	59
2	TMS-CH=CH ₂	rt	2	-	95
3	TMS-C≡CH	rt	2	-	93
4	TMS-N ₃	rt	2	96	-

Conditions: 0.30 mmol of **44**, 0.36 mmol of TMS-X, 5 mol% FeCl₃ and 15 mol% AgOTf in 1,2-dichloroethane at room temperature.

the desired allylated product **45** was observed, along with 59% of byproduct ether **46**. This observation was consistent with previously reported results.⁵⁰ As diphenylmethanol **44** was treated with different organosilanes (entries 1-4), it became clear that the formation of **46** depended very much on the nature of the organosilanes chosen. For example, when vinyltrimethylsilane (entry 2) and ethynyltrimethylsilane (entry 3) were used and treated to the same reaction conditions, only the formation of ether **46** was observed. However, when azidotrimethylsilane was employed instead, the desired azidation product **45** was obtained exclusively (entry 4).

Scheme 2.14 Allylation of **47** with allyltrimethylsilane

⁵⁰ (a) Kim, S.; Chung, K. N.; Yang, S. *J. Org. Chem.* **1987**, *52*, 3917. (b) Sharma, G. V. M.; Kumar, K. R.; Sreenivas, P.; Krishna, P. R.; Chorghade, M. S. *Tetrahedron Asymmetry*, **2002**, *13*, 687. (c) Kim, S. H.; Shin, C.; Pai, A. N.; Koh, H. K.; Chang, M. H.; Chung, B. Y.; Cho, Y. S. *Synthesis* **2004**, *10*, 1581. (d) Terrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063.

As shown in Scheme 2.14, the formation of byproduct **46** could be easily avoided by using a better leaving group X (X = OMe or OAc) in replacement of the hydroxyl group. Both benzhydryl acetate (**47**) and (methoxymethylene)dibenzene (**47i**) gave excellent results but **47i** required a longer reaction time of 5 h.

2.2.2 Optimizing Reaction Conditions

Table 2.2 Optimizing reaction conditions with various catalysts

entry	catalyst	temp (°C)	time (h)	isolated yield (%)
1	Fe(acac) ₃	80	15	0
2	FeF ₃	80	15	0
3	FeCl ₂	rt	15	48 (40) ^a
4	FeBr ₃	rt	3	89
5	FeCl ₃	rt	9	89
6	Fe(OTf) ₃ ^b	rt	0.5	96

Conditions: 0.30 mmol of **48**, 0.36 mmol of allyltrimethylsilane, 5 mol% [Fe] in 1,2-dichloroethane. (a) Recovery yield of starting material. (b) 5 mol% FeCl₃ + 15 mol% AgOTf.

The catalytic efficiency of various iron salts was investigated by employing 1-phenylethyl acetate **48** as the standard substrate in allylation. As seen in Table 2.2, Fe(acac)₃ and FeF₃ showed no catalytic activity in allylation even with prolonged heating for 15 h at 80 °C (entries 1-2). When FeCl₂ was used, the reaction proceeded to some extent and furnished 48% of pent-4-en-2-ylbenzene (**48a**), together with 40% recovery of starting material after 15 h at room temperature. FeBr₃ (entry 4) and FeCl₃ (entry 5) catalysts showed obvious improvement to the reactivity with 89% isolated yield after 3 or 9 h respectively. To our delight, the catalysis of allylation is most efficient and went to completion when the more reactive Fe(OTf)₃ catalyst was used. With these optimized reaction conditions, we move on to explore the substrate scope of various benzylic acetates with organosilanes.

2.2.3 Reactions of Benzylic Acetates with Various Organosilanes

Table 2.3 Reactions of benzylic acetates with various organosilanes

$\text{Ar}-\text{CH}(\text{R})-\text{OAc} + \text{TMS}-\text{Nu} \xrightarrow[\text{ClCH}_2\text{CH}_2\text{Cl}]{\text{Fe}(\text{OTf})_3 (5 \text{ mol}\%)} \text{Ar}-\text{CH}(\text{R})-\text{Nu}$						
entry	acetate	TMS–Nu	temp (°C)	time (h)	product	yield (%) ^a
1		TMSN ₃	rt	1		97
2	47	TMSCN	50	1		88
3	47		rt	6		92
4	47		80	12		0
5	47		rt	1		88
6	47		rt	1		90
7		TMSN ₃	rt	1		86
8	48	TMSCN	80	14		0
9	48		80	3		0
10	48		80	16		69
11			rt	1		67
12	49	TMSN ₃	rt	2		85

Table 2.3 Reactions of benzylic acetates with various organosilanes (continued)

entry	acetate	TMS–Nu	temp (°C)	time (h)	product	yield (%) ^a
13	49	TMSCN	80	2		78
14	49		rt	2		66
15		TMS–CH=CH ₂	80	18		0
16		TMS–CH=CH ₂	80	18		0
17		TMS–CH=CH ₂	80	24		71
18	52	TMSN ₃	rt	2		82
19	52		80	24		59
20	52		80	24		56
21		TMS–CH=CH ₂	rt	2		87
22	53	TMSN ₃	rt	0.5		60 : 37

Conditions: 0.30 mmol of benzylic acetate, 0.36 mmol of TMS–Nu, 5 mol% FeCl₃ and 15 mol% AgOTf in 1,2-dichloroethane. (a) Isolated yield.

Different primary and secondary benzylic acetates (**47**, **48**, **49**, **52**) were treated with the respective organosilanes in the presence of 5 mol% Fe(OTf)₃ in 1,2-dichloroethane as summarized in Table 2.3. **47** reacted excellently with

azidotrimethylsilane and TMS enol ether at room temperature to give high yields of 97% **47b** and 92% **47c** respectively (entries 1 and 3). However, when cyanotrimethylsilane was used instead, the reaction was slower and gentle heating at 50 °C for 1 h was required (entry 2). In the case of vinyltrimethylsilane, the reaction did not occur, even under prolonged heating at 80 °C. (entry 4), although similar conversion was achieved with InCl_3 and BiBr_3 .⁵¹ **47** also worked well with electron-rich 2-trimethylsilyl-substituted benzofuran and indole at room temperature and furnished the respective desired products in 88% and 90% yield (entries 5 and 6).

By replacing one phenyl group with a methyl group, 1-phenylethyl acetate (**48**) becomes less reactive. Substrate **48** still proceeded well with allyltrimethylsilane (Table 2.2) and azidotrimethylsilane (entry 7) to form the desired products in high yields. However, **48** did not react with cyanotrimethylsilane (entry 8) and TMS enol ether (entry 9) even in refluxing 1,2-dichloroethane. Nonetheless, it still reacted slowly with 2-trimethylsilylbenzofuran at reflux (entry 10).

For primary benzylic acetates, the substituent on the phenyl ring affected the reactivity significantly. For example, benzyl acetate **50** did not react readily with allyltrimethylsilane even at prolonged heating conditions (entry 15) and the starting material was recovered unchanged. A similar result was obtained with **51** when an electron-withdrawing chloride group was present at the *para*-position (entry 16). Expectedly, when an electron-donating methoxy group was substituted instead, it promoted stabilizing effects to the carbocation intermediate via resonance, thus **49** was much more reactive when compared to **50** and **51**. As such, 4-methoxybenzyl acetate **49** could proceed smoothly with various organosilanes, which include

⁵¹ Nishimoto, Y.; Kajioka, M.; Saito, T.; Yasuda, M.; Baba, A. *Chem. Commun.* **2008**, 6396.

allyltrimethylsilane, azidotrimethylsilane, cyanotrimethylsilane as well as 2-trimethylsilylindole (entries 11 – 14).

When using another secondary benzylic acetate, (*E*)-1,3-diphenylallyl acetate **52**, the reactivity is somewhat lower and prolonged heating is necessary in most cases, such as allylation (entry 17) and alkenylation (entries 19 and 20).

In our final example, a tertiary benzylic acetate, 1,1-diphenyl- ethyl acetate **53** was used. Allylation under the standard optimized conditions produced the desired product in 87% yield (entry 21) but azidation afforded a 60:37 mixture of the desired azide **53b** and olefin **53c** (entry 22).

Scheme 2.15 Azidation of **54**

To our delight, when alcohol **54** was chosen instead of acetate **53**, isolation of **53b** was increased to 84% together with a trace amount of **53c** (6%) as displayed in Scheme 2.15.

2.2.4 Proposed Mechanism

Scheme 2.16 Proposed reaction mechanism

In the mode of iron catalysis, $\text{Fe}(\text{OTf})_3$ first coordinated to the acetate group of the benzylic acetate substrate, and left in a $\text{S}_{\text{N}}1$ manner, giving a stabilized carbocation. This coincides with our observed results, whereby the reactivity for this reaction ranges from tertiary > secondary > primary benzylic substrates. Nucleophilic attack then occurred, followed by the loss of the TMS group, which furnished the desired product as shown in Scheme 2.16. The TMS group plays an important role as the beta-silicon effect stabilized the carbocation generated during the reaction.

2.2.5 Optimizing Reaction Conditions for Reductive Dehydroxylation

Table 2.4 Optimizing reaction conditions with various iron catalysts

$ \begin{array}{c} \text{OH} \\ \\ \text{Ph}-\text{C}-\text{Ph} \\ \mathbf{44} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\begin{array}{c} [\text{Fe}] (5 \text{ mol}\%) \\ \text{PMHS} \end{array}} \begin{array}{c} \text{Ph}-\text{CH}_2-\text{Ph} \\ \mathbf{55} \end{array} + \begin{array}{c} \text{Ph} \quad \text{Ph} \\ \quad \\ \text{Ph}-\text{C}-\text{O}-\text{C}-\text{Ph} \\ \mathbf{46} \end{array} $				
entry	[Fe]	time (h)	isolated yield (%)	
			55	46
1	$\text{Fe}(\text{acac})_3$	5	-	-
2	FeF_3	5	-	-
3	FeCl_2	5	-	-
4	FeCl_3	1	87	-
5	$\text{Fe}(\text{ClO}_4)_3$	1	-	>99
6	$\text{Fe}(\text{OTf})_3$	0.5	-	35

Conditions: 0.3 mmol diphenylmethanol **44**, 0.05 mL PMHS, 5 mol% [Fe] in 2 mL dichloromethane at room temperature.

The use of various $\text{Fe}(\text{II})$ or $\text{Fe}(\text{III})$ salts in catalyzing reductive dehydroxylation of the standard substrate diphenylmethanol **44**, is exemplified in Table 2.4. The iron salts used actually contributed significantly to the kind of product obtained. As shown, $\text{Fe}(\text{acac})_3$, FeF_3 and FeCl_2 are not effective for this kind of reduction reaction in the presence of PMHS in dichloromethane at ambient temperature (entries 1-3). To our delight, 87% of desired diphenylmethane **55** is formed after treating with 5 mol% of FeCl_3 (entry 4). However, when $\text{Fe}(\text{ClO}_4)_3$ and

$\text{Fe}(\text{OTf})_3$ are employed instead, the exclusive formation of ether **46** side product was observed (entries 5-6). Obviously, FeCl_3 was chosen as the iron catalyst to perform the remaining reductive dehydroxylation on other benzylic alcohols.

Table 2.5 Exploring the solvent effects in reductive dehydroxylation

$ \begin{array}{c} \text{OH} \\ \\ \text{Ph}-\text{C}-\text{Ph} \\ \textbf{44} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{FeCl}_3 (5 \text{ mol\%}), \text{PMHS}} \begin{array}{c} \text{Ph}-\text{CH}_2-\text{Ph} \\ \textbf{55} \end{array} + \begin{array}{c} \text{Ph} \quad \text{Ph} \\ \quad \\ \text{Ph}-\text{C}-\text{O}-\text{C}-\text{Ph} \\ \textbf{46} \end{array} $					
entry	solvent	temp (°C)	time (h)	isolated yield (%) 54	isolated yield (%) 55
1	ClCH_2Cl	rt	1	87	-
2	$\text{ClCH}_2\text{CH}_2\text{Cl}$	rt	1	99	-
3	toluene	60	1	-	37
4	THF	60	7	-	-

Conditions: 0.3 mmol diphenylmethanol **44**, 0.05 mL PMHS, 5 mol% FeCl_3 in 2 mL of solvent at room temperature.

We next moved on to screen various solvents using the same diphenylmethanol **44** as the model substrate (Table 2.5). When the reaction was performed in dichloromethane or 1,2-dichloroethane (entries 1-2), the reaction proceeded smoothly to give the desired product **55** in 87% and 99% yield respectively after 1 h at room temperature. Unexpectedly, 37% of ether **46** was isolated exclusively when using toluene as solvent after heating at 60 °C for 1 h (entry 3). THF is not a good solvent for this kind of reductive dehydroxylation as no reaction was observed even after prolonged heating at 60 °C (entry 4). After obtaining the optimized conditions, we continue to explore the substrate scope for reductive dehydroxylating benzylic alcohols using the FeCl_3 /PMHS catalytic system.

2.2.6 Reductive Dehydroxylation of Benzylic Alcohols

The findings from the reductive dehydroxylation of various benzylic alcohols

Table 2.6 Reductive dehydroxylation of benzylic alcohol **56**

$ \begin{array}{c} \text{OH} \\ \\ \text{Ar}-\text{C}-\text{R} \\ \textbf{56} \\ \text{R= alkyl, aryl} \end{array} \xrightarrow[\text{ClCH}_2\text{CH}_2\text{Cl, rt}]{\text{FeCl}_3 (5 \text{ mol\%}), \text{PMHS}} \begin{array}{c} \text{Ar}-\text{CH}_2-\text{R} \\ \textbf{57} \end{array} $				
entry	substrate	time (h)	product	isolated yield (%)
1	56a	1	57a	92
2	56b	1	57b	96
3	56c	2	57c	75
4	56d	1	57d	91
5	56e	1	57e	84
6	56f	0.5	57f	80
7	56g	1	57g	0
8	56h	1	57h	83
9 ^a	56i	3	57i	72
10	56j	2	57j	65

Table 2.6 Reductive dehydroxylation of benzylic alcohol **56** (continued)

entry	substrate	time (h)	product	isolated yield (%)
11 ^a	56k	2	57k	81
12 ^a	56l	2	57l	0
13	56m	1	57m	92
14	56n	1	57n	76 (1:1)
15	56o	1	57o	84 (1.7:1)

Conditions: 0.3 mmol **56**, 0.05 mL PMHS, 5 mol% FeCl₃ in 2 mL 1,2-dichloroethane at room temperature. (a) Reaction was carried out at 60 °C.

are summarized in Table 2.6. The alcohol substrates were synthesized from aldehydes/ketones by NaBH₄ reduction or Grignard reaction. **56a** and **56b** were reduced effectively by the FeCl₃/PMHS catalytic system in 1,2-dichloroethane at room temperature to furnish the respective hydrocarbons **57a** and **57b** at 92% and 96% yield (entries 1-2). **56c** proceeded smoothly as well to yield the desired **57c** after 2 h, notably that the terminal alkene was not affected under this mild condition. (entry 3). The introduction of electron-donating methoxy group at *meta*- and *para*- position of the aromatic ring could stabilize the cationic intermediate via resonance, thus significantly improved the rate of the dehydroxylation reaction (entry 4).

Dehydroxylation of **56e** and **56f** was also possible, even though the hydroxyl group was not at the benzylic position as seen in entry 6. Apparently, the presence of a double bond also has a stabilizing effect for the cationic intermediate via resonance,

thus producing the desired alkanes **57e** and **57f** in good yields of 84% and 80% respectively (entries 5-6). However, cinnamyl alcohol **56g** could only generate primary cationic intermediate, which is not an attractive candidate for such reaction (entry 7). The reaction ran smoothly for bicyclic compound indenol **56h**, and gave 83% indene **57h** after 1 h (entry 8).

It is noteworthy that both **56i** and **56j** underwent dehydroxylation smoothly under this reaction condition to afford the desired products, without affecting the phenolic alcohol at the *ortho*- or *para*- position (entries 9-10). In contrast, the presence of electron-withdrawing bromide group at the *para*- position hindered the reaction rate as heating at 60 °C was required for the reaction to occur (entry 11). Similarly, no reaction was seen when using primary alcohol **56l** as the substrate (entry 12). An example of selective reductive dehydroxylation was highlighted in entry 13. Reaction took place exclusively at the secondary benzylic position, although **56m** contained both primary and secondary benzylic alcohols. No special protecting group was required to achieve such selectivity.

For tertiary alcohol such as 1,1-diphenylethanol **56n** and 1-phenylcyclohexanol **56o**, the cationic intermediates were much more stable. Therefore, there is a tendency for the hydrogen from the neighbouring methyl group to undergo deprotonation to form the eliminated products **57n'** and **57o'**, along with the desired products **57n** and **57o** (entries 14-15).

Carbonyls compounds, which include aldehydes, ketones and esters, were found to be inert under the standard FeCl₃/PMHS catalytic system as illustrated in Table 2.7. Dehydroxylation of diphenylmethanol **53** was carried out under the standard optimized conditions, with the addition of 1 equiv carbonyl compound **58**.

Table 2.7 Selectively dehydroxlation of **44** in the presence of **58**

$\text{Ph}-\text{CH}(\text{OH})-\text{Ph} + \text{R}^1-\text{C}(=\text{O})-\text{R}^2 \xrightarrow[\text{ClCH}_2\text{CH}_2\text{Cl, rt}]{\text{FeCl}_3 (5 \text{ mol\%}), \text{PMHS}}$			
entry		isolated yield (%)	
		55	58
1	58a	97	>99
2	58b	93	95
3	58c	96	97
4	58d	95	82
5	58e	97	89

Conditions: 0.3 mmol **44**, 0.3mmol carbonyl **58**, 0.05 mL PMHS, 5 mol% FeCl₃ in 2 mL of 1,2-dichloroethane for 1 h at room temperature.

Presence of aldehydes **58a-c**, ketone **58d** or ester **58e** were basically inert and did not participate in the reaction at all (entries 1-5).

Scheme 2.17 Selective dehydroxylation of benzylic alcohol in the presence of intramolecular ketone

The selectivity of this catalytic system was further demonstrated in Scheme 2.17. In Table 2.7, the intermolecular effect of carbonyl compounds towards the reaction was studied. In this case, the substrate **59** contained an intramolecular ketone

functionality. Nonetheless, reductive dehydroxylation occurred nicely only at the hydroxyl group located at the benzylic position to form **60** at 80 °C after 3 h.

2.2.7 Proposed Mechanism

Scheme 2.18 Proposed mechanism

This reductive dehydroxylation of benzylic alcohols is proposed to undergo a similar mechanism as the reaction of benzylic acetates with organosilanes as shown in Scheme 2.16. Phenols form a violet complex with Fe(III), which is intensely colored, thus the ferric chloride test is used to determine the presence of phenols. However, reaction proceeded smoothly even for phenol containing substrates, such as **56i** and **56j**. We then postulate that the reaction may proceed by another mechanism as shown in Scheme 2.18. The excess PMHS is first activated by FeCl₃ to generate an iron hydride-like species, whereby the structure is proposed to be like Figure 2.2. The benzylic alcohol then coordinates to the active catalyst, followed by reductive

elimination to yield the desired alkane. The active catalyst can be regenerated with the presence of excess PMHS in the reaction flask.

2.3 CONCLUSION

Lewis acid catalysis has a long history and we are pleased to develop an efficient methodology for $\text{Fe}(\text{OTf})_3$ -catalyzed reactions of benzylic acetates with various organosilanes. This method performed best with secondary benzylic acetates, with comparable results when using reactive primary benzylic acetate such as 4-methoxybenzyl acetate **49**. Tertiary benzylic acetate was very reactive and could cause complication in some cases, for example in azidation. Substantial examples were shown whereby the reaction conditions could tolerate a broad range of functional groups, namely azido, cyano, 2-benzofuran and 2-indole.

Moreover, we also developed a highly efficient and mild FeCl_3 /PMHS system for the reductive dehydroxylation of benzylic alcohols. This method is deemed useful, as the direct conversion of alcohols to the corresponding alkanes is an important aspect in organic synthesis. The catalytic system consists of inexpensive and environmentally friendly materials, which will be advantageous if brought to industrial scale. The reaction conditions work best for secondary benzylic alcohols but inactive for primary benzylic alcohols. Tertiary alcohols work well to a certain extent too, as there is some competition which furnishes olefins as the side products. The selectivity towards benzylic alcohols is remarkable, even in the presence of bromide, phenols, or carbonyl compounds.

In conclusion, the present methods have a wide scope of interest and are easy to handle, making it a useful and attractive process.

CHAPTER 3

Fe(III)-Catalyzed Conia-ene Cyclization of 2-Alkynic 1,3-Dicarbonyl Compounds

3.1 INTRODUCTION

The Diels-Alder reaction is a highly versatile and well-studied reaction, which is applicable in the synthesis of complex molecules or natural products. The method was named after the discovery by Otto Paul Hermann Diels and Kurt Alder in 1928,⁵² and both of them were credited the 1950 Nobel Prize in Chemistry for their contribution. The Diels-Alder reaction is an organic reaction between a conjugated electron-rich diene and an electron-poor alkene (also known as dienophile) to form a substituted cyclohexene. The driving force of this reaction depended very much on the interaction between the HOMO of diene and LUMO of dienophile.

Figure 3.1 Representations of Diels-Alder and Alder-ene

The Alder-ene reaction, documented in 1943 by Alder, is another organic reaction very similar to the Diels-Alder reaction.⁵³ It is a reaction between an allylic C-H σ -bond (the ene) and an unsaturated compound (the enophile), to form new olefins. In simplicity, a new σ -bond is formed with the migration of the ene double bond and 1,5 hydrogen shift (Figure 3.1).

⁵² Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, 460, 98.

⁵³ Alder, K.; Pascher, F.; Schmitz, A., *Ber.* **1943**, 76B, 27.

Figure 3.2 Illustration of Conia reaction

A modified version of Alder-ene reaction was developed by Conia, and was later commonly known as the Conia reaction.⁵⁴ This modified method is an intramolecular ene reaction of unsaturated ketones where the carbonyl group serves as the ene component via tautomerization and the olefinic moiety serves as the enophile (Figure 3.2).

Baldwin's (dis)favoured ring closures

	3		4		5		6		7	
type	<i>exo</i>	<i>end</i>	<i>exo</i>	<i>end</i>	<i>exo</i>	<i>end</i>	<i>exo</i>	<i>end</i>	<i>exo</i>	<i>end</i>
<i>tet</i>	✓		✓		✓	✗	✓	✗	✓	✗
<i>trig</i>	✓	✗	✓	✗	✓	✗	✓	✓	✓	✓
<i>dig</i>	✗	✓	✗	✓	✓	✓	✓	✓	✓	✓

Figure 3.2 Illustration of Conia reaction

A carbocyclic or heterocyclic subunit is a common motif in natural products,⁵⁵ as such, it is important to form desired cyclized structures in a controlled manner. The Conia-ene reaction is an efficient and powerful way to form cyclized compounds via intramolecular cyclization. Henceforth, the designing of substrate can play an important role to facilitate the ring closure. Baldwin's rules are a set of guidelines proposed by Jack Baldwin in 1976, which could predict the possible favourable mode

⁵⁴ Conia, J. M.; Percec, P. L. *Synthesis* **1975**, 1.

⁵⁵ Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, 39, 44.

of cyclization.⁵⁶ The term *exo* or *endo* is used depending on whether the bond broken during ring closure is inside (*endo*) or outside (*exo*) the ring formed. Whereas for *tet*, *trig* or *dig*, these simply refer to either tetrahedral (sp^3), trigonal (sp^2) or diagonal (sp), respectively. In general, most cyclization reactions follow Baldwin's rules in relation to the basic geometric and orbital overlap considerations.⁵⁷

Scheme 3.1 (i) Toste's Au-catalyzed Conia-ene cyclization (ii) Deuterated labeling experiments

Over the years, several groups have used transition metal catalysts, such as Au(I), In(III), and Cu(I), to promote the Conia-ene reaction. In one report documented in 2004, Toste and coworkers developed the methodology using Au(I) catalyst to carry out the Conia-ene reaction of β -ketoesters with alkynes under neutral conditions at room temperature.⁵⁸ The author proposed two plausible mechanism pathways as seen in Scheme 3.1(i). Mechanism A suggested a nucleophilic attack of the enol on

⁵⁶ Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

⁵⁷ Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513.

⁵⁸ Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526.

an Au-alkyne complex to give the vinyl-Au intermediate, whereas mechanism B showed an Au-enolate attacking the alkyne to give another vinyl-Au intermediate. Deuterium-labeling experiments later showed that the reaction actually followed mechanism A. From the results obtained, **61a** selectively cyclized to give cyclopentane **62a** selectively deuterated (90%) *syn* to the ketoester, whereas **61b** furnished **62b** selectively deuterated (48%) *anti* to the ketoester, as drawn in Scheme 3.1(ii). Moreover, the reaction exhibited remarkable diastereoselectivities, which displayed its potential as a tool to synthesize highly substituted cyclic compounds. Nevertheless, this method could not be applied onto substituted alkynes as severe 1,3-allylic strain during the transition state (via mechanism A) greatly inhibited the reaction.

Scheme 3.2 (i) In(OTf)_3 -catalyzed Conia-ene cyclization of pyrrolidinones (ii) Asymmetric synthesis of (-)-salinosporamide A

In 2008, Hatakeyama and coworkers demonstrated the preparation of pyrrolidinones using a catalytic amount of In(OTf)_3 . The addition of DBU base

greatly enhanced the rate. The reaction proceeded with high selectivity and gave exclusively (*E*)-pyrrolidinone products, without observing any racemization even at high temperature. The malonyl group was considered an essential requirement for the reaction to occur as proposed by Hatakeyama. Synthesis of different ring size heterocycles such as piperidinone, azepanone, pyrrolidine, piperidine, tetrahydroisoquinoline, tetrahydrofuran or tetrahydropyran are also possible with $\text{In}(\text{OTf})_3$.

Furthermore, the methodology was elegantly applied to the asymmetric total synthesis of (-)-salinosporamide A, which contains a highly functionalized pyrrolidinone core structure.⁵⁹ The precursor amide **65** was subjected to $\text{In}(\text{OTf})_3$ catalyst in refluxing toluene, and amide **65** eventually converted completely to cyclic **66** with almost quantitative yield. Further transformations led to the total synthesis of (-)-salinosporamide A.

Scheme 3.3 Cu/Ag-cocatalyzed Conia-ene reaction of linear β -alkynic β -ketoesters

Most groups focused on the development of mild and neural conditions to perform the Conia-ene reactions of α -alkynic β -ketoesters, however, only limited

⁵⁹ Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6244.

reports were available for such cyclizations on β -alkynic β -ketoesters. Li's group managed to discover a Cu(I)/Ag catalytic system for the Conia-ene reactions of the linear β -alkynic β -ketoesters as summarized in Scheme 3.3. The formation of *endo* or *exo* products very much depended on the substitutes on alkynes. When terminal alkynes were used, exclusive *exo* products **68** were obtained in moderate yields. Selective *endo* products **69a** were achieved when using various aryl substituted alkyne, which also included a mixture of the corresponding decarboxylated byproducts **69b**. Li explained that the *endo* products synthesized were most probably due to the steric hindrance of the aryl group substituted on alkyne.⁶⁰

Iron-catalysis is very attractive, as iron salts are naturally abundant, cheap and easy to handle with low toxicity. In addition, the Conia-ene reactions proved to be very effective to form useful cyclic compounds. As such, we are very interested to use iron catalysis to explore the Conia-ene cyclizations.

3.2 RESULTS AND DISCUSSION

3.2.1 Optimizing Reaction Conditions

The ketoester substrates were synthesized via enolate alkylation in the presence of NaH. Methyl 2-acetylhept-6-ynoate (**70**) was used as the standard substrate for the optimizing reaction conditions. As displayed in Table 3.1, ketoester **70** was subjected to 5-*exo-dig* cyclization using several Fe(II) and Fe(III) salts, and most of the iron salts were capable to assist Conia-ene cyclization of the standard substrate. A list of iron catalysts such as FeBr₂, FeCl₂, Fe(acac)₃ and Fe(OTf)₃ furnished the desired cyclized product **71** in moderate yield at 70 °C (entries 1-4). Fe₂O₃, however, was inert to such cyclization reaction (entry 5). FeCl₃ proved to be

⁶⁰ Deng, C.-L.; Song, R.-J.; Guo, S.-M.; Wang, Z.-Q.; Li, J.-H. *Org. Lett.* **2007**, 9, 5111.

Table 3.1 Optimizing reaction conditions for Conia-ene cyclization

Reaction scheme: Ketoester **70** (Me-C(=O)-CH2-CH2-C(=O)OMe with a terminal alkyne) reacts with catalytic iron (cat. Fe) in 1,2-dichloroethane (ClCH₂CH₂Cl) to form methylenecyclopentane **71** and its isomer **72**.

entry	Fe (mol%)	solvent	temp (°C)	time (h)	isolated yield (%)	
					71	72
1	FeBr ₂ (10)	ClCH ₂ CH ₂ Cl	70	5	65	-
2	FeCl ₂ (10)	ClCH ₂ CH ₂ Cl	70	6	72	-
3	Fe(acac) ₃ (10)	ClCH ₂ CH ₂ Cl	70	18	53	-
4	Fe(OTf) ₃ (10)	ClCH ₂ CH ₂ Cl	70	18	-	-
5	Fe ₂ O ₃ (10)	ClCH ₂ CH ₂ Cl	70	24	47	-
6	FeCl ₃ (10)	ClCH ₂ CH ₂ Cl	rt	1.5	76	-
7	FeCl ₃ (5)	ClCH ₂ CH ₂ Cl	rt	1.5	65	-
8	FeCl ₃ (20)	ClCH ₂ CH ₂ Cl	rt	1	54	18
9	FeCl ₃ (20)	toluene	70	5	46	19
10	FeCl ₃ (20)	CH ₃ NO ₂	70	18	30	-
11	FeCl ₃ (20)	CH ₃ CN	70	18	50	-
12	FeCl ₃ (10) + Na ₂ CO ₃ (1 equiv)	ClCH ₂ CH ₂ Cl	rt	2.5	64	-

Conditions: 0.30 mmol of **70** and 5-20 mol% [Fe] in 2 mL of solvent at respective temperature.

the best catalyst among the various iron catalysts tested, and reaction proceeded even at room temperature (entries 6-8 and 12). Varying the catalyst loading affected the results to some extent. As seen in entry 8, ketoester **70** readily cyclized to provide methylenecyclopentane **71** in 72% yield using 20 mol% FeCl₃, which isomerized partially to the thermodynamically more stable **72**. The isomerization was not observed when using a lower catalyst loading of 5 mol% (entry 7) or 10 mol% (entry 6), with which 10 mol% of FeCl₃ in 1,2-dichloroethane gave the best results of 76% yield after 1.5 h. We next moved on to run the reaction in different solvents (entries 9-11). Higher temperature of 70 °C was needed when using other solvents apart from 1,2-dichloroethane. When employing toluene as the solvent, 46% of the desired product was formed, alongside 19% of isomerized **72** (entry 9). Nitromethane (entry 10) and acetonitrile (entry 11) were much less effective even after prolonged heating at 70 °C. Addition of Na₂CO₃ did not improve the reaction at all (entry 12).

3.2.2 Fe(III)-Catalyzed Conia-ene Cyclization

Table 3.2 Conia-ene cyclization of **73**, **75** or **77** using FeCl₃ as catalyst

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p>73a-f (n = 2) 75a-c (n = 1) 77 (n = 3)</p> </div> <div style="text-align: center;"> $\xrightarrow[\text{ClCH}_2\text{CH}_2\text{Cl}]{\text{FeCl}_3 (10 \text{ mol}\%)}$ </div> <div style="text-align: center;"> <p>5-exo-dig</p> <p>74a-f (n = 2)</p> </div> <div style="text-align: center;"> <p>5-endo-dig</p> <p>76a-c (n = 1)</p> </div> <div style="text-align: center;"> <p>6-exo-dig</p> <p>78 (n = 3)</p> </div> </div>				
entry	substrate	time (h)	product	isolated yield (%)
1		29		77
2 ^a		26		73
3		14		70
4 ^b		16		72
5 ^a		23		73
6		58		58 (23) ^c
7 ^b		48		51 (38) ^c

Table 3.2 Conia-ene cyclization of **73**, **75** or **77** using FeCl₃ as catalyst (continued)

entry	substrate	time (h)	product	isolated yield (%)
8	75b	38	76b	71
9	75c	31	76c	75
10 ^b	77	48	78a	48 ^d (41) ^c
			78b	

Conditions: 0.30 mmol of **73**, **75** or **77** and 10 mol% FeCl₃ in 2 mL of 1,2-dichloroethane at room temperature. (a) Reaction was carried out at 70 °C. (b) Reaction was carried out at 80 °C. (c) Recovery yield of starting material. (d) **78a:78b** = 1.0:1.8.

The Conia-ene cyclization using 10 mol% FeCl₃ in 1,2-dichloroethane was performed on to several substrates as highlighted in Table 3.2. Reaction progressed well at room temperature to provide 77% of olefin **74a**, when methyl was replaced with phenyl group at R position, however at a longer time of 29 h (entry 1). The addition of an electron-donating methyl group at the *para* position at the aryl R group (**73b**) reduced the iron catalytic activity, therefore cyclization proceeded slower and required heating at 70 °C (entry 2). The introduction of a bulky *tert*-butyl group at the R¹ position did not hinder the reaction, and also furnish olefin **74c** via 5-*exo-dig* pathway in 70% yield (entry 3). Cyclization also occurred for non-terminal alkynes, such as **73d**. In entry 4, methyl-substituted alkyne afforded stereoselective (*E*)-**74d** in 72% yield. Substrate **73e** possessing a pyrrole moiety could also produce the desired olefin **74e** after 23 h of heating at 70 °C (entry 5). This catalytic system was not restricted to ketoesters, but also applicable to the less reactive diketone, such as **73f** (entry 6).

When one carbon was reduced from the alkynyl chain ($n = 1$), FeCl_3 -catalyzed 5-*endo-dig* cyclization was also efficient (entries 7-9). Terminal alkyne **75a** was not very reactive and 38% of starting material could still be recovered, even after prolonged heating for 48 h at 80 °C (entry 7). Nonetheless, ethyl substituted alkynes **75b** and **75c** were more reactive and cyclization could proceed even at ambient temperature under the standard conditions (entries 8-9). Furthermore, extending one carbon at the alkynyl chain ($n = 3$) did not prevent cyclization either. For example, **77** underwent cyclization slowly to yield **78a** via a 6-*exo-dig* pathway, which isomerized to the more stable **78b** (ratio of **78a**:**78b** = 1.0:1.8) (entry 10).

Scheme 3.4 Formation of trisubstituted furan **80** via FeCl_3 catalysis of **79**

In the case of **79**, as shown in Scheme 3.4, the catalytic system was also useful for synthesizing trisubstituted furan ring **80** in high yield of 76%. The result obtained coincided with the previous report by Zhan in 2008, whereby synthesis of substituted furans was possible via FeCl_3 catalysis in refluxing toluene.⁶¹

Unfortunately, this catalytic system was specific to α -alkynic β -ketoesters compounds only. Shifting the alkyne chain affected the reaction significantly as seen in Table 3.3. For example, when FeCl_3 catalyst was added to β -alkynic β -ketoester **81**, no reaction was observed (entry 1). Similarly, α -alkynic α -ketoesters **83a** and **83b** were inert to the reaction conditions, whereby quantitative amount of starting

⁶¹ Ji, W.-H.; Pan, Y.-M.; Zhao, S.-Y.; Zhan, Z.-P. *Synlett* **2008**, 3046.

Table 3.3 Limitations of Fe(III)-catalysis for Conia-ene cyclization

entry	substrate	time (h)	product	isolated yield (%)
1	81	24	82	0
2	83a	24	84a	0
3	83b	24	84b	0
4	85	24	86	0

Conditions: 0.30 mmol of **81**, **83** or **85** and 10 mol% FeCl₃ in 2 mL of 1,2-dichloroethane at 80 °C.

materials were recovered after 16 h of heating (entries 2-3). Alkene **85** was unreactive too, and the starting material was unchanged after prolonged heating (entry 4).

3.2.3 Preliminary Studies on Stannyl Conia-ene Type Cyclization

The Stille reaction is an important Pd-catalyzed organic synthesis method for coupling organotin compounds with an organic halide or triflate.⁶² Trimethylstannyl or tributylstannyl are common candidates for the organotin compounds in Stille coupling reactions. Although trimethylstannyl compounds were usually more reactive, the toxicity of such chemicals is very high as compared to tributylstannyl compounds. As such, we were interested to synthesize stannyl substituted compounds for ease of further coupling purposes.

⁶² Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508.

Scheme 3.5 Stannyl Conia-ene type cyclization (a) Ac_2O (1.2 equiv) and pyridine (1.5 equiv) in CH_2Cl_2 (b) Bu_3SnOMe (1.05 equiv) under neat conditions (c) $\text{Fe}(\text{OTf})_3$ (5 mol%) in $\text{ClCH}_2\text{CH}_2\text{Cl}$

The initial experiment of stannyl Conia-ene type experiments were carried out using the tin enolate **89** as displayed in Scheme 3.5. To generate tin enolate **88**, ketoester **70** was first converted to acetate **87** by stirring with Ac_2O . Tin-enolate **88** was then generated *in-situ* by treating the isolated acetate **87** with neat Bu_3SnOMe , since tin-enolates were known to be unstable. Subsequently, the mixture was directly subjected to the standard FeCl_3 catalysis, with which (*E*)-**90** was formed selectively at a low yield of 23%. The yield was greatly improved to 94% when $\text{Fe}(\text{OTf})_3$ was used instead, affording (*E*)-**90** exclusively as well.

Scheme 3.6 Cyclization of **89** to give (*E*)-stannyl olefin **90**

Delighted with the stereoselectivity, further experiments were carried out, hoping to gain insights of the mechanism. We then discovered that upon treatment with FeX_3 ($\text{X} = \text{Cl}, \text{OTf}$), the SnBu_3 group was substituted at the alkyne position to

provide intermediate **89** at room temperature, which subsequently underwent cyclization at 80 °C (Scheme 3.6). The isolated intermediate **89** also cyclized nicely to afford (*E*)-stannyl olefin **90** in 91% yield under Fe(OTf)₃ catalysis, performed in a separate experiment.

Scheme 3.7 Further transformation of **90**

To further confirm the isomer of the cyclic structure, (*E*)-stannyl olefin **90** was converted to its iodide derivative **91a** by treating with excess iodine. (*E*)-**90** could also be transformed to its deuterated **91b**.⁶³ **91a** and **91b** synthesized were compared to previously reported compounds,^{58,64} which further confirmed the assigned stereostructure.

3.2.4 Fe(III)-Catalyzed Stannyl Conia-ene Type Cyclization

The stannyl Conia-ene type cyclization using Fe(OTf)₃ catalyst was extended to a list of acetates (**92**, **94** and **96**) as represented in Table 3.4. The reaction was smooth to furnish moderate yield of 63-66% cyclic stannyl-olefin **93** via 5-*endo-dig* cyclization in all three cases (entries 1-3). Likewise, acetate **94** derived from ketoester **79** afforded 71% stannyl substituted furan **95** in 3 h at 80 °C (entry 4). Substrate **96** in entry 5 contained similar length of alkynyl chain as **87** in Scheme 3.5, thus it also

⁶³ For synthesizing deuterated **91b**: Porcel, S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2672.

⁶⁴ (a) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140. (b) Chen, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 5595.

Table 3.4 Stannyl Conia-ene cyclization

entry	substrate	time (h)	product	isolated yield (%)
1	92a	8	93a	63
2	92b	5.5	93b	66
3	92c	7	93c	65
4	94	3	95	71
5	96a	5	97a	68
6	96b	5	97b 97b'	86 ^a

Conditions: 0.30 mmol of **92**, **94** or **96** and 5 mol% Fe(OTf)₃ in 2 mL of 1,2-dichloroethane at 80 °C. (a) **97b**:**97b'** = 1.38:1.0.

underwent similar cyclization selectively to yield 68% bicyclic (*E*)-**97a**. However, after replacing the ester group with a sulfonyl (SO₂Ph) group, side reaction was observed (entry 6). For this substrate, the competition between 5-*exo-dig* and 6-*endo-dig* catalytic pathway was more significant. During 6-*endo-dig* cyclization, elimination of SO₂Ph occurred to yield a more stable naphthalene **97b'** with the ratio of **97b**:**97b'** = 1.38:1.0.

3.2.5 Proposed Mechanism

Scheme 3.8 Proposed reaction mechanism

In our developed Fe(III)-catalysis for Conia-ene cyclization, we proposed a mechanism that is different from that proposed by Toste and coworkers as described in Scheme 3.1.⁵⁸ The cyclization of substituted alkynes was not feasible when employing Toste's method. However, for our catalytic system, we successfully cyclized several alkyl- or stannyl-substituted alkynes substrates, such as **73d**, **75b**, **75c**, **89**, **92**, **94** and **96**. In our proposed mechanism, 2-alkynic 1,3-dicarbonyl compound was first coordinated with Fe(III) salt to form a enol-alkyne Fe complex. It then underwent *5-exo-dig* cyclization to yield stereospecific vinyl-Fe species. Protonation then released the desired product in its exclusive (*E*)-isomer form.

3.3 CONCLUSION

The Conia-ene cyclization is an very efficient tool for the formation of cyclic compounds, which are important core structures in natural products. As such, it is

attractive for us to utilize a cheap and green catalyst, like Fe(III)-salts, to perform such important reactions. In the midst of our research, FeX_3 ($\text{X} = \text{Cl}, \text{OTf}$) was found to be very mild and effective in promoting the Conia-ene cyclizations via *5-exo-dig*, *5-endo-dig*, and *6-exo-dig* pathways (depending on the length of alkyne chain). The catalysis system works well for terminal as well as substituted alkynes. The mechanism proposed is hence different from Toste's group, whereby his Au(I)-catalysis was only valid for terminal alkynes. Synthetically useful vinylstannanes formed has the potential to be further utilized, especially in the application of coupling reactions.

CHAPTER 4

Palladium Catalysis in Cross Coupling Reactions

4.1 INTRODUCTION

Naturally occurring organic molecules usually contain numerous carbon-hydrogen bonds, which are relatively inert. Therefore, the ability to functionalize these inert C-H bonds can offer new and shorter synthetic pathways, which benefits towards the overall synthetic efficiency. Direct C-H functionalization is one powerful synthetic method to perform organic transformations of the latent C-H bonds into useful functionalized C-X bonds. The terms “C-H activation” and “C-H functionalization” are often used interchangeably. In fact, C-H activation is the process whereby a metal complex is inserted into a C-H bond, to form a highly reactive C-[M] bond. C-H functionalization, on the other hand, involves the overall transformation of the inert C-H bond to a functionalized C-X bond, via a reactive C-[M] intermediate (Scheme 4.1).⁶⁵

Scheme 4.1 C-H activation and functionalization

4.2 PALLADIUM AND ITS PROPERTIES

Palladium is a rare and lustrous silvery-white transition metal, with the chemical symbol Pd and atomic number 46. Palladium, together with platinum, rhodium, ruthenium, iridium and osmium, are classified as the platinum group metals, and they share similar chemical properties.

Palladium is used in electronics, dentistry, medicine and also play a key role as a catalytic converter in automobiles. When dispersed on to carbon, palladium is an

⁶⁵ Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, 417, 507.

efficient catalyst that accelerates hydrogenation and converts unsaturated bonds to alkanes in the presence of hydrogen gas. Alkynes can be selectively reduced to *cis*-alkenes using deactivated palladium catalyst, commonly known as Lindlar's catalyst (5% palladium on calcium carbonate; poisoned with lead).⁶⁶

4.3 PALLADIUM CATALYSIS IN CROSS COUPLING

REACTIONS

Among the transition metals, palladium is considered one of the most versatile and efficient catalyst, especially in the area of cross coupling reactions.⁶⁷ The discoveries of Pd-catalyzed cross coupling reactions brought a tremendous breakthrough in the area of organic synthesis. In 2010, Richard F. Heck,⁶⁸ Ei-ichi Negishi⁶⁹ and Akira Suzuki⁷⁰ were then awarded the Nobel Prize in Chemistry to compliment their contributions.

Scheme 4.2 Famous examples of Pd-catalyzed cross-coupling reactions

⁶⁶ Lindlar, H. *Helv. Chim. Acta* **1952**, 35, 446.

⁶⁷ Bolm, C. *J. Org. Chem.* **2012**, 77, 5221.

⁶⁸ Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, 37, 2320.

⁶⁹ (a) Negishi, E.-i.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, 42, 1821. (b) King, A. O.; Okukado, N.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1977**, 683.

⁷⁰ Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.

Scheme 4.2 exemplifies a list of different coupling partners with organohalides (or pseudohalides such as triflates) to synthesize new C-C bonds in the presence of Pd-catalyst. The reaction conditions are usually mild and easy to handle. In a typical cross coupling mechanism, RX (X = Cl, Br, I, OTf, *etc.*) and Pd catalyst first form an organopalladium intermediate R-Pd-X via oxidative addition. Subsequently, R-Pd-X reacts with the nucleophilic coupling partner; followed by the regeneration of Pd catalyst after releasing the desired coupled product.

Useful unsaturated alkenes or alkynes can be easily synthesized using the Heck^{66,71} or Sonogashira⁷² cross coupling methods. In both cases, the presence of a base is necessary for the reaction to proceed. However, the Sonogashira reaction also requires the presence of copper as the cocatalyst for effective cross coupling. It is noteworthy that the Heck reaction furnishes olefins of high *trans* selectivity.

The Negishi,^{69,73} Stille,⁷⁴ Suzuki-Miyaura^{70,75} and Hiyama⁷⁶ coupling reactions are a list of efficient ways to synthesize substituted compounds via C-C bond formation. Variation at the R groups allows for broad substrate scope that include alkyl, aryl, alkenyl, alkynyl, allyl *etc.* The different coupling partners, such as zinc, stannyl, borate or silyl derivatives, correspond to the different named reactions. The Suzuki and Hiyama coupling reactions are comparable, as both required activating agent, usually a base. For the Hiyama reaction, activation of the silane with base or fluoride ions (TASF, TBAF) leading to a pentavalent silicon compound is a first

⁷¹ (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jap.* **1971**, *44*, 581. (b) Belestskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

⁷² (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

⁷³ Phapalea, V. B.; Cárdenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598.

⁷⁴ (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508. (c) Mitchell, T. N. *Synthesis* **1992**, 803.

⁷⁵ (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organometallic Chem.* **1999**, *576*, 147. (c) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270.

⁷⁶ (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Nakao, Y.; Hiyama, T. *Chem. Soc. Rev.* **2011**, *40*, 4893.

necessary step. The Negishi reaction can be either Ni- or Pd-catalyzed and show versatility in the substrate scope. The high toxicity and low polarity of stannanes account for the major drawbacks in the Stille reaction, otherwise this coupling condition undergoes very similar chemistry as the Suzuki-Miyaura reaction.

Scheme 4.3 Tsuji-Trost allylic alkylation

Tsuji-Trost allylic alkylation is a Pd-catalysed substitution reaction involving a substrate that contains a leaving group in an allylic position (Scheme 4.3). This work was first pioneered by Jiro Tsuji in 1965 and, later, adapted by Barry Trost in 1973 with the introduction of phosphine ligands.⁷⁷ The introduction of phosphine ligands led to improved reactivity and numerous asymmetric allylic alkylation strategies, which is useful especially in natural product synthesis.

4.4 APPLICATION OF PALLADIUM-CATALYZED CROSS COUPLING REACTIONS

Carbon-carbon bond forming reactions via cross coupling have a large impact in organic synthetic application. Although other transition metals such as copper or iron are more cost effective and less toxic, Pd-catalyzed cross coupling reactions are generally mild and have high tolerance to a wide range of functional groups, thus are

⁷⁷ (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 6, 4387. (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, 95, 292.

attractive methods for natural product synthesis or industrial applications. Some representative examples are highlighted below.

Scheme 4.4 Total synthesis of (-)-morphine by Overman in 1993

Morphine is a potent opiate analgesic drug that acts directly on the central nervous system to relieve severe pain. The first synthesis of morphine⁷⁸ was carried out by Gates and Tschudi in 1952, after Sertürner's isolation from opium. With the robust growth in cross coupling chemistry, Overman's group⁷⁹ successfully synthesized morphine and its analogs via elegant use of Heck coupling in the key step as seen in Scheme 4.4. An intramolecular Heck reaction was performed to form the crucial quaternary morphinan skeleton. This method is versatile as it allows the formation of morphinan enantiomers that does not involve the resolution of an intermediate.

(+)-Dynemicin A was classified under the enediyne family, which was believed to have antitumor properties. One of the steps in the preparation of

⁷⁸ Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, 78, 1380.

⁷⁹ Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, 115, 11028.

⁸⁰ Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.

Scheme 4.6 Synthesis of pumiliotoxin A via Negishi coupling reaction

Another cross coupling example was displayed in the total synthesis of pumiliotoxin A, which was extracted as one of the major toxins found in the skin of neotropical poison-dart frogs. As seen in Scheme 4.6, homoallyl iodide **103** first underwent halogen-metal exchange with *tert*-butyllithium at $-100\text{ }^{\circ}\text{C}$, followed by transmetalation with ZnCl_2 . Kibayashi's group then successfully carried out the Negishi coupling reaction onto the homoallylzinc reagent and **105** with a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$, which yielded 60% of **106** without affecting the stereocenters and (*Z*)-geometry. Subsequent routine deprotection of the protecting groups afforded pumiliotoxin A nicely. Such application of Pd(0)-catalyzed Negishi cross coupling onto *N*-heterocyclic homoallylzinc complex was novel and was considered by Kibayashi as the first example to be performed in natural product synthesis.⁸¹

⁸¹ Hirashima, S.; Aoyagi, S. Kibayashi, C. *J. Am. Chem. Soc.* **1999**, *121*, 9873.

4.5 IMPORTANCE OF DIRECTING GROUP IN C-H

ACTIVATION REACTIONS

Scheme 4.7 Directing group assisted C-H activation

One of the major challenges encountered in C-H functionalization reactions is to achieve high selectivity. Introduction of a coordinating ligand to the substrate is the most commonly employed strategy to address this issue. These ligands, known as directing groups (DG), bind to the metal center and selectively guide the catalyst to a proximal C-H bond, thus achieving selective C-H activation as shown in Scheme 4.7.

Figure 4.1 Recently established directing groups in 2006 - 2013⁸²

⁸² (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (c) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (d) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211. (e) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (f) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137. (g) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem.* **2011**, *123*, 1416. (h) Huang, C.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 12406. (i) Dai, H. X.; Stepan, A. F.; Plummer, M.

The most widely used directing groups in Pd(II)-catalyzed C-H activation reactions utilize carboxylic derivatives, along with *N*-heterocycles. The directing groups can then be converted to another functional group, retained as its form, or removed. A few listed recent examples are illustrated in Figure 4.1. Given the exploding growth in directing groups, our group set out to investigate the potential directing ability of phosphorus-containing compounds, as their usage in this area were not explored.

4.6 ORGANOPHOSPHORUS COMPOUNDS AS A POTENTIAL DIRECTING GROUP IN C-H ACTIVATION REACTIONS

Figure 4.2 Structural versatility of aryl phosphorous compounds

Phosphorus-containing directing group has structural versatility, as seen in Figure 4.2, therefore, organophosphoric acid derivatives possess potential advantage over carboxylic acid derivatives. The expanded valency of phosphate allows for a host of variation. This is deemed to be an important criteria as the substituents present will greatly affect the coordination of P=O or C=O to the metal center, hence affecting its directing ability.

Furthermore, organophosphorus compounds are important constituents of living organisms, and can be found in, for instance, DNA and RNA, phospholipid

S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222. (j) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (k) Wang, C.; Chen, H.; Wang, Z.; Chen, J.; Huang, Y. *Angew. Chem.* **2012**, *124*, 7354. (l) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2013**, *15*, 67.

bilayer in cell membranes, phosphoinositols that function as organelle membrane recognition, ATP that transports chemical energy within cells for metabolism, apatite in bones, teeth, *etc.*

4.7 ORGANOPHOSPHORUS COMPOUNDS IN ORGANIC REACTIONS

(i) Wittig Olefination:

(ii) Horner-Wadsworth-Emmons Reaction:

Scheme 4.8 Wittig olefination and Horner-Wadsworth-Emmons reaction

Organophosphorus compounds have vital roles in organic synthesis. The Wittig reaction, developed by Georg Wittig in 1954, required a phosphonium ylide together with an aldehyde or ketone to form olefin, for which he was later awarded the Nobel Prize in 1979. In the later years, the Wittig reaction was further modified by using phosphonate-stabilized carbanions instead of phosphonium ylides, which produced predominantly (*E*)-alkenes. The reaction was named the Horner-Wadsworth-Emmons reaction (HWE reaction) to give credit to Leopold Horner, William S. Wadsworth and William D. Emmons⁸³ for establishing the reaction. For

⁸³ (a) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (c) Wadsworth, W. *Org. React.* **1977**, *25*, 73.

the HWE reaction, the presence of an electron-withdrawing group (EWG) at the α -position of the phosphonate is essential for the final elimination to take place. In the absence of an electron-withdrawing group, the final product will be α -hydroxyphosphonate **107** instead (Scheme 4.8).

In addition, organophosphorus compounds are also good coupling partners in Pd-catalyzed cross coupling reactions, which are clearly illustrated in the two recent examples carried out by Steel's group in 2008 (Scheme 4.9) and Trost's group in 2012 (Scheme 4.10).

Scheme 4.9 Enol phosphinates lactams as the Suzuki and Stille coupling partners

In this report, Steel's group showed that lactam derived enol phosphinates are excellent coupling partners for both classic Suzuki and Stille coupling reactions (Scheme 4.9). This analogous phosphinate group is believed to be an attractive alternative to triflate group as coupling agents in the cross coupling reactions, since triflates intermediates are often unstable and difficult to handle. Although the conditions were well developed for Suzuki and Stille coupling reactions, attempts for Heck and Sonogashira coupling were unsuccessful.⁸⁴

⁸⁴ Guo, J.; Harling, J. D.; Steel, P. G.; Woods, T. M. *Org. Biomol. Chem.* **2008**, 6, 4053.

Scheme 4.10 Pd-catalyzed coupling reaction using phosphate **111** as the coupling partner

The coupling reaction was first carried out using *p*-methoxybenzyl methyl carbonate as the electrophile instead of **111** (Scheme 4.10). However, the reaction was very slow and gave a low isolated yield of only 25% after heating in toluene at 75 °C. By changing the carbamate leaving group to a more labile diethyl phosphate, the reaction improved tremendously to give the desired product in 90% yield with 96% *ee*, even at ambient temperature. It is noteworthy that this methodology was able to furnish tetrasubstituted azlactone that could be readily converted to quaternary amino acids with high enantiomeric excess, such as α -methyl-D-dopa, after hydrolysis.⁸⁵

Cross-coupling reactions are one of the most effective and practical ways for forming new C-C bonds. Therefore, our group aims to develop methods using organophosphorus compounds as the directing group in Pd-catalyzed C-H functionalization reactions. Among the possible structural variation in organophosphorus compounds, we will focus on the efficiency of phosphate functionality, as a directing group. In the following chapters, we will discuss on the mono-phosphoric acid as a directing group in Pd-catalyzed (i) *ortho*-alkenylation; (ii) *ortho*-arylation; and (iii) *ortho*-acetoxylation of aryl hydrogen phosphates derivatives.

⁸⁵ Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2012**, 134, 5778.

CHAPTER 5

*Pd-Catalyzed ortho-Alkenylation of Aryl
Hydrogen Phosphates Using a New
mono-Phosphoric Acid Directing Group*

5.1 INTRODUCTION

Over the decades, chemists have tried to activate and functionalize inert C-H bonds that can be utilized in further applications. The arylation of olefins, (termed as the Heck reaction) is a pivotal example in constructing new C-C bonds in modern organic chemistry.⁸⁶

Scheme 5.1 Initial discovery of stoichiometric Pd-catalyzed cross coupling of olefins and arenes

In one of the pioneering examples, Fujiwara and Moritani⁸⁷ coupled alkenes and arenes via stoichiometric Pd(II) catalysis during the late 1960s, representing a breakthrough in C-H activation. This was the first example to substitute aromatic compounds to the double bond of styrene, via an olefin-Pd(II) complex, to form stilbene derivatives (Scheme 5.1). The reaction proceeded well only in the presence of acetic acid. When replacing acetic acid with another carboxylic acid, such as monochloroacetic acid, only 18% product was obtained. No reaction was observed when using dry HCl or in the absence of acetic acid.

Although the above reaction in Scheme 5.1 was novel and impactful, chemists were concerned on the substantial amount of palladium consumed. Palladium catalysts, though effective and versatile, are very expensive. The reaction condition

⁸⁶ For recent reviews on Pd-catalyzed C-H activations, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 46, 677. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, 110, 1147. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, 40, 5068. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, 111, 1215. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, 40, 4740. (f) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, 45, 788.

⁸⁷ Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 8, 1119.

Scheme 5.2 Cross coupling of olefins and arenes using catalytic amount of Pd(II)

were quickly improved to be more synthetically practical by using only a catalytic amount of the Pd(II) catalyst. Fujiwara's group discovered that oxidants, such as $Cu(OAc)_2$ or $AgOAc$ together with oxygen (or air), could readily reoxidized the catalyst, hence significantly reducing the amount of catalyst used in the reaction. $Pd(OAc)_2$ was also a more reactive catalyst than $PdCl_2$ as discussed in the report (Scheme 5.2).⁸⁸

The study of aryl C-H bond activation by palladium or other transition metals continues to grow exponentially through the years. In recent approaches, directing groups have played a significant role to control the selectivity in C-H activation, and many research groups have come out with impressive designs of such directing groups to carry out alkenylation in a controlled manner.

Scheme 5.3 Amide directing group for mild Pd-catalyzed C-H activation

⁸⁸ Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166.

One of the early works in applying directing groups to mild Pd-catalyzed C-H activation was researched by the de Vries and van Leeuwen groups.⁸⁹ In this report, they coupled various anilines with *n*-butyl acrylate via Pd(OAc)₂ catalyst. The reaction used cheap oxidant (benzoquinone) and proceeded under ambient temperature, hence enhancing the attractiveness of this reaction condition. The amide functionality was demonstrated as a good directing group as highly *ortho*-selective products were obtained (Scheme 5.3).

Scheme 5.4 Silanol-directed *ortho*-alkenylation by Gevorgyan

Silicon-tethered directing groups are attractive as they can be easily installed and removed under mild conditions, apart from being cheap and environmentally friendly. Gevorgyan envisioned the potential of such directing groups, and thus engaged in a silanol group-directed Pd-catalyzed C-H *ortho*-olefination of phenols. The substrate scope is diverse and an application was accomplished on to a more

⁸⁹ Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.

complex estrone, whereby alkenylation, followed by desilylation which occurred smoothly in high yield of 89%. This example shows the versatility of the method, as it demonstrated applicability to complex phenols even at the late-stage of natural product synthesis (Scheme 5.4).^{82h}

Scheme 5.5 Amide directing group for mild Pd-catalyzed C-H activation

Recently, Yu and coworkers have impressive findings in the area of C-H activation. Yu's research focused on utilizing weakly coordinating directing group for controlling site-selectivity, which also involved detailed mechanistic studies. In one recent report of Yu's, his group demonstrated the synthesis of *ortho*- or *meta*- useful olefinated phenols derivatives by altering the directing group.⁹⁰ The presence of the bulky α,α -dimethyl groups significantly enhanced the mono-selectivity of the reaction. The *ortho*-directing ability of COOK is excellent with the formation of mono-selectivity products in high yield. The results were consistent with his previous COOX (X = H, K, Na, *etc.*) directing C-H functionalization reactions.^{82e,82f,87f,91} In

⁹⁰ Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567.

⁹¹ (a) Giri, R.; Mangel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Mei, T.-S.; Giri, R.; Mangel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215. (c) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (d) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (e) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097.

2012, Yu designed a new template, which he called it a weak “end-on” interaction that would direct the activation of distant *meta*-C-H bonds, instead of the usual proximal *ortho*-C-H bonds.⁹² Building on this, Yu hence applied his “end-on” coordinating nitrile directing group to furnish *meta*-C-H olefinated phenol derivatives in this report.

As discussed earlier in the previous chapter, phosphorus-containing molecules are important components of living organisms and also have been widely employed in useful organic reactions. To the best of our knowledge, phosphoric acids have not been used in the transition-metal-catalyzed C-H activation reactions previously. Our interest in phosphate and phosphoric acid derivatives as directing groups together with their synthetic and biological importance led us to study the Pd-catalyzed *ortho*-alkenylation and provide seminal results in this area.

5.2 RESULTS AND DISCUSSION

5.2.1 Optimizing Reaction Conditions

To study the effectiveness of the phosphoric acid-based directing groups in the C-H activation, we first began our studies with dimethyl *o*-tolyl phosphate (**128a**) as seen in Table 5.1. Substrate **128a** was easily synthesized from *o*-cresol and diethyl chlorophosphate in the presence of pyridine. Reaction of **128a** with ethyl acrylate (2 equiv) using Pd(OAc)₂ (10 mol%) and Na₂S₂O₈ oxidant (3 equiv) in 1,2-dichloroethane at 110 °C for 15 h did not occur and the starting **128a** was recovered (entry 1). Varying the oxidizing agent or changing the solvent did not affect the reaction (entries 2-5). To strengthen the directing ability of the phosphoryl group towards the palladium intermediate, methyl *o*-tolyl phenylphosphoramidate (**128b**)

⁹² Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, 486, 518.

Table 5.1 Optimization of reaction conditions using **128**

Me
 $\text{O}-\text{P}(=\text{O})(\text{OMe})\text{X}$
 128

+ $\text{CH}_2=\text{CHCO}_2\text{Et}$

$\xrightarrow[\text{oxidant}]{\text{cat. Pd(OAc)}_2}$

Me
 $\text{O}-\text{P}(=\text{O})(\text{OMe})\text{X}$
 129

a (X = OMe), b (X = NHPh), c (X = OH)

entry	substrate	oxidant	solvent	yield (%) ^a
1	128a	Na ₂ S ₂ O ₈	ClCH ₂ CH ₂ Cl	0
2	128a	CuO	ClCH ₂ CH ₂ Cl	0
3	128a	Ag ₂ CO ₃	ClCH ₂ CH ₂ Cl	0
4	128a	AgOAc	ClCH ₂ CH ₂ Cl	0
5	128a	AgOAc	dioxane	0
6	128b	BQ	ClCH ₂ CH ₂ Cl	0
7	128b	Cu(OAc) ₂	ClCH ₂ CH ₂ Cl	<5
8	128b	Ag ₂ O	dioxane	0
9	128b	Ag ₂ CO ₃	dioxane	<5
10	128b	AgOAc	dioxane	0
11	128c	Na ₂ S ₂ O ₈	dioxane	0
12	128c	BQ	dioxane	0
13	128c	CuO	dioxane	0
14	128c	Cu(OAc) ₂	dioxane	61
15	128c	Ag ₂ CO ₃	dioxane	44
16	128c	Ag ₂ O	dioxane	54
17	128c	AgOAc	dioxane	100 (80) ^b
18	128c	AgOAc	^t BuOH	26
19	128c	AgOAc	ClCH ₂ CH ₂ Cl	46 (30) ^c
20	128c	AgOAc	toluene	0

Conditions: 0.15 mmol of **128**, 2 equiv of ethyl acrylate, 10 mol% of Pd(OAc)₂, 3 equiv of oxidant in 1 mL of solvent at 110 °C for 15 h. (a) NMR yield. (b) Isolated yield after methylation with TMSCHN₂. (c) Yield of 2-Chloroethyl methyl *o*-tolyl phosphate **129c-ii**.

was chosen, but our attempts for *ortho*-alkenylation via C-H activation under various conditions were totally unsuccessful (entries 6-10). Inspired by recent reports on the hydroxyl-directed C-H activations, such as Yu's carboxylic groups and Gevorgyan's removable silanol groups, we next turned our attention to methyl *o*-tolyl hydrogen phosphate (**128c**). When **128c** was treated with ethyl acrylate (2 equiv) and Cu(OAc)₂ (3 equiv) in the presence of 10 mol% Pd(OAc)₂ in 1,4-dioxane at 110 °C for 15 h, 61% of the desired alkenylated product **129c** was observed (entry 14), suggesting that

the mono-phosphoric acid functionality is crucial in aiding weak coordination of Pd catalyst with the substrate. To search for the optimum condition, various oxidants were then screened. The reaction was relatively sensitive to the choice of oxidants used, with which $\text{Na}_2\text{S}_2\text{O}_8$, BQ, and CuO were totally ineffective (entries 11-13). The oxidants, Ag_2CO_3 and Ag_2O gave moderate conversion of the starting mono-phosphoric acid **128c** (entries 15 and 16). To our delight, AgOAc turned out to be the most effective oxidant that resulted in the complete consumption of **128c** to yield the alkenylated product cleanly (entry 17). Among the solvents tested, 1,4-dioxane gave the best result (entries 18-20). Furthermore, the addition of a base (Li_2CO_3 and Na_2CO_3) and an amino acid ligand such as Boc-Val-OH (20 mol%) did not influence the reaction. Therefore, the remaining reactions were carried out with ethyl acrylate (2 equiv) and AgOAc (3 equiv) using $\text{Pd}(\text{OAc})_2$ (10 mol%) in 1,4-dioxane at 110 °C for 15 h.

5.2.2 Pd(II)-Catalyzed *ortho*-Alkenylation via mono-Phosphoric Acid

Directing Group

As summarized in Table 5.2, various substrates were applied to the standard condition to determine the scope and limitations of the present method. For the facile purification, the crude alkenyl mono-phosphoric acids were methylated using TMS-diazomethane to afford the corresponding methyl esters **131a-o**. Substrates **130a-i** containing electron-donating alkyl or alkoxy groups at the *ortho*- or *meta*-position promoted alkenylation considerably (**131a-i**). Naphthyl derivatives **130j-k** worked well too. However, biaryl derivative **130l** was less reactive and the alkenylated product **131l** was isolated in 66% yield along with the starting material (17%). As expected, *meta*-substituted substrates underwent alkenylations regio-selectively at the

Table 5.2 Substrate scope for *ortho*-selective alkenylation via mono-phosphoric acid directing group

Conditions: (i) 0.15 mmol of **130**, 2 equiv of ethyl acrylate, 10 mol% of $\text{Pd}(\text{OAc})_2$, 3 equiv of AgOAc in 1 mL of 1,4-dioxane at 110 °C for 15 h. (ii) 5 equiv of TMSCHN_2 in 0.5 mL of MeOH at rt for 30 min. (a) Isolated yield is based on the yield over 2 steps. (b) Recovery yield of methylated starting material **130**. (c) 1.2 equiv of ethyl acrylate was used instead. (d) Yield of dialkenylated product.

sterically less hindered position. When unsubstituted **130m** was subjected to the standard condition in the presence of 1.2 equiv of ethyl acrylate, the desired alkenylated product was isolated in 55% yield together with the dialkenylated product

(16%) and the starting material (14%). Although fluoride-substituent **130n** is completely compatible in this mild reaction condition, the reaction was significantly slowed down and gave the alkenylated product **131n** in less than 50% yield. Interestingly, when an electron-withdrawing ester group was located at the *ortho*-position, the reaction proceeded smoothly but hydrolysis of the product occurred, yielding the respective phenol **131o** almost quantitatively. Apparently, dephosphorylation occurred upon acidic workup.⁹³

Scheme 5.6 Alkenylation of mono-phosphoric acid **130c** with various alkenes

The usefulness of this methodology is not limited to only ethyl acrylate. As demonstrated in Scheme 5.6, the scope of the alkenylation is broad and various

⁹³ (a) Yamada, T.; Takemura, K.; Yoshida, J.-i.; Yamago, S. *Angew. Chem., Int. Ed.* **2006**, 45, 7575. (b) Holzwarth, R.; Bartsch, R.; Cherkaoui, Z.; Solladié, G. *Eur. J. Org. Chem.* **2005**, 3536.

electron-deficient alkenes and styrene derivatives can be successfully employed in the *ortho*-alkenylation. Vinyl sulfone and vinyl phosphate reacted with mono-phosphoric acid **130c** to furnish the corresponding alkenyl phosphate **132b** and **132c** in 77% and 78% yield, respectively. Similarly, phenyl vinyl ketone (**132h**) also worked well. Styrene and its derivatives (**132d-g**) were also efficient acceptors toward the palladium intermediate. However, the present method did not work well with allylbenzene and ethyl vinyl ether.

5.2.3 Proposed Mechanism

Scheme 5.7 Proposed mechanism

Scheme 5.7 highlights the proposed reaction mechanism for this Pd-catalyzed olefination. $\text{Pd}(\text{OAc})_2$ first coordinates to the substrate containing phosphoric directing group via C-H activation. The electron deficient coupling partner then also coordinates to the $\text{Pd}(\text{II})$ intermediate, followed by 1,2-migratory insertion

subsequently. β -Hydride elimination and reductive elimination generates the desired product and Pd(0), which can be readily reoxidized by the AgOAc oxidant present in the solution. Finally, the regenerated Pd(II) then continues the catalytic cycle till all substrate converts to the product.

5.3 CONCLUSION

We have demonstrated the effectiveness of mono-phosphoric acid-directing group in the Pd(II)-catalyzed *ortho*-alkenylation of aryl hydrogen phosphates for the first time. The ability to synthesize functionalized phosphorus analogs (in this case, olefinated phosphates) via a single C-H activation step, proved to be beneficial towards organic synthesis. The reaction provides various alkenylated products in high yields and its scope is broad, as this methodology is valid for acrylates, styrenes, vinyl ketone, vinyl phosphate and vinyl sulfone. Moreover, the reaction proceeded in a highly *ortho*-selective manner, and only furnished *ortho*-alkenylated products, even in substrate like **131l** whereby more than one attack site were available. Double *ortho*-olefination occurred, however, in unsubstituted arene such as **131m**. This phenomenon can be avoided when introducing a substituent at the *ortho*- or *meta*-position of the phenyl ring. Furthermore, a wide range of functional groups, including alkyl, alkoxy, aryl, halogen, and ester, are compatible towards the reaction conditions. In conclusion, this phosphoric acid proved to be a good directing group in facilitating *ortho*-alkenylation via Pd(II)-catalyzed C-H activation.

CHAPTER 6

Pd-Catalyzed ortho-Arylation and ortho-Acetoxylation with Various Iodonium Salts

6.1 INTRODUCTION

C-H functionalization catalyzed by transition metals is an attractive method in organic synthesis. As such, this has emerged as a powerful tool for introducing useful functionality via a coordinating directing group. Our recent report exhibits the potential of the organophosphate moiety as a directing group, which is highly *ortho*-selective in C-H activated alkenylation.

Scheme 6.1 Pd(II)-catalyzed *ortho*-alkenylation of aryl hydrogen phosphates **130**

As discussed earlier in Chapter 5, we have discovered the first usage of monophosphoric acid as a directing group in Pd(II)-catalyzed *ortho*-alkenylation reactions (Scheme 6.1). The results obtained were encouraging, as the reaction provides various alkenylated products in high yields and its scope is broad. Delighted with the findings, we continue to explore the potential of P=O chelation with Pd(II) via weak coordination for C-H functionalization.

The Pd(II)/Pd(0) mechanistic pathway for C-H activation reactions was extensively studied due to its versatility, and these reactions usually required the presence of an oxidant to regenerate the catalyst.⁹⁴ Recently, there is a growing interest towards the use of hypervalent iodine compounds in various organic

⁹⁴ Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, 48, 5094.

reactions, as they are mild and highly selective, environmentally friendly, and easily available.⁹⁵

Scheme 6.2 Illustration of different catalytic manifold in Pd-catalyzed C-H functionalization

Extensive mechanistic studies of C-O bond formation via Pd(II)/Pd(IV) catalytic cycle were done by Sanford and coworkers⁹⁶ and have proven beneficial in Pd-catalyzed *ortho*-acetoxylation. An alternative Pd(II)/Pd(III) redox catalysis with I(III) oxidants as demonstrated by Ritter and coworkers offered another insight to the mechanism.⁹⁷ An additional oxidant that is usually needed in Pd(II)/Pd(0) catalytic cycle, is thus omitted in this case, as the arylodonium salt can serve as both the coupling agent, as well as the oxidant (Scheme 6.2).

The first key development of C-H arylation with prefunctionalized arylating reagents was carried out in 2005. In this example, Sanford employed Ph₂IBF₄ to synthesize mono-phenylated derivatives (Scheme 6.3). The method is practical as the reaction was carried out under mild and ambient temperature. At the same time, the

⁹⁵ Yusubov, M. S.; Maskae, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, (i), 370.

⁹⁶ (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (b) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (d) Racowski, J. A.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974. (e) Racowski, J. A.; Nicholas, D. B.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18022.

⁹⁷ (a) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302. (b) Powers, D. C.; Lee, E.; Ariafard, A.; Sanford, M. S.; Yates, B. F.; Canty, A. J.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 12002.

Scheme 6.3 Sanford's C-H arylation with Ar_2IBF_4

reaction was completely compatible with diverse heterocycles, including pyridines, quinolines, pyrrolidinones, and oxazolidinones; as well as a wide range of functionalities, such as ethers, amides, enolizable ketones, aldehydes, aryl halides, and benzylic hydrogens. The aryl substituents could be modified by using $[\text{Mes-I-Ar}]\text{BF}_4$ instead of Ph_2IBF_4 . The large mesityl group was considered as a “dummy ligand”, while the smaller aryl group was transferred with high selectivity.⁹⁸

Scheme 6.4 Daugulis's C-H arylation with Ph_2IPF_6

In the same year, a similar Pd(II)/Pd(IV) C-H arylation using iodonium salts was carried out by Daugulis.⁹⁹ As seen in Scheme 6.4, Daugulis and coworkers utilized Ph_2IPF_6 to perform Pd-catalyzed arylation onto amide scaffolds. The substrate scope was limited by the commercial availability of the arylating reagents. However, this was overcome by using a combination of aryl iodides and AgOAc , in replacement of Ar_2IPF_6 .

⁹⁸ Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

⁹⁹ Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046.

Scheme 6.5 Ester directed C-H arylation at the *ortho* position

Since the early 1980s, extensive work was done using nitrogen-containing directing groups, however, Pd(II) insertion into C-H bonds facilitated by oxygen-only directing groups is still limited. The Fu and Liu groups successfully synthesized crystalline *O*-phenylcarbamate palladacycle and provided the desired biaryl products upon treating with the respective Ar_2IOTf salts.¹⁰⁰ The plausible mechanism for this reaction followed the Pd(II)/Pd(V) catalytic cycle, whereby Ar_2IOTf act as the arylating agent and oxidizing agent. Substituted phenol derivatives synthesized are valuable as they are common organic intermediates in reactions (Scheme 6.5).

In this chapter, we would like to further explore the directing ability of organophosphates in Pd(II)-catalyzed C-H functionalization reactions with various arylodonium salts, namely the Ar_2IOTf and $\text{PhI}(\text{OAc})_2$. When using a variation of Ar_2IOTf , a series of useful biaryl compounds could be synthesized. Similarly, acetoxylated products could be generated by using $\text{PhI}(\text{OAc})_2$. In this case, the products obtained will be useful intermediates to synthesize catechol derivatives that are widely known to be the crucial moieties in natural products. Herein, we report the versatility of such directing groups in *ortho*-arylation and *ortho*-acetoxylation of aryl phosphoric monoacids.

¹⁰⁰ Xiao, B.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, 132, 468.

6.2 RESULTS AND DISCUSSION

6.2.1 Preliminary Studies

Table 6.1 Optimizing reaction conditions with **139a** and **139b**

139a

139b

entry	substrate	base	temp (°C)	solvent	conv (%) ^a
1	139a	-	90	ClCH ₂ CH ₂ Cl	72 (52) ^b
2	139a	Li ₂ CO ₃	90	ClCH ₂ CH ₂ Cl	0
3	139a	Cs ₂ CO ₃	90	ClCH ₂ CH ₂ Cl	0
4	139a	K ₃ PO ₄	90	ClCH ₂ CH ₂ Cl	0
5	139a	Na ₂ CO ₃	90	ClCH ₂ CH ₂ Cl	88 (55) ^b
6	139a	Na ₂ CO ₃	90	ClCH ₂ CH ₂ Cl	0 ^c
7	139a	Na ₂ CO ₃	90	dioxane	16
8	139a	Na ₂ CO ₃	90	PhCF ₃	0
9	139a	Na ₂ CO ₃	90	DMF	0
10	139a	Na ₂ CO ₃	90	xylene	0
11	139b	-	110	DCE	59 (57) ^b
12	139b	Na ₂ CO ₃	110	DCE	61 (60) ^b
13	139b	Na ₂ CO ₃	110	dioxane	14
14	139b	Na ₂ CO ₃	110	toluene	16
15	139b	Na ₂ CO ₃	110	^t BuOH	0

Conditions: 0.15 mmol of **139**, 2 equiv of Ph₂IOTf, 10 mol% of Pd(TFA)₂, 1.5 equiv of base in 1 mL of solvent for 15 h. (a) Conversion of starting material **139**, based on crude NMR. (b) Isolated yield. (c) 20 mol% of DMSO was added.

The preliminary studies of *ortho*-arylation were performed with diethyl *o*-tolyl phosphate (**139a**) as the substrate can be easily synthesized from *o*-cresol and diethylchlorophosphate. The results obtained were summarized in Table 6.1. **139a** was first treated with Ph₂IOTf (2 equiv) and catalyst Pd(TFA)₂ (10 mol%) in 1,2-dichloroethane at 90 °C for 15 h. To our delight, 72% of the starting material **139a** was reacted, however, a low 52% isolated yield of the desired arylated product **140a**

was obtained (entry 1). The reaction was relatively messy and some unidentified byproducts were noticed under this condition. No reaction took place when adding bases, such as Li_2CO_3 , Cs_2CO_3 or K_3PO_4 , to the reaction flask (entries 2-4). Na_2CO_3 , on the other hand, facilitated the reaction to a certain extent, and increased the conversion of **139a** to 88% (entry 5). Nonetheless, low isolation of phenylated **140a** still persisted. The introduction of 20 mol% DMSO to stabilize the Pd catalyst only worsened the reaction (entry 6). No improvements were observed when varying the solvent (1,4-dioxane, trifluorotoluene, DMF, or xylene) (entries 7-10). We postulated that a cyclic phosphate **139b** could be thermally more stable towards the high temperature used in the reaction. Expectedly, **139b** proved to be more stable towards the reaction condition with almost quantitative isolation for each experiments (entries 11-15). Though thermally more stable, **139b** was less reactive than **139a**, and low conversion of the starting substrate was observed even at 110 °C. Apart from $\text{Pd}(\text{TFA})_2$, $\text{Pd}(\text{OTf})_2$, PdCl_2 and other Pd catalysts did not provide satisfactory results.

Table 6.2 Initial studies of *ortho*-arylation using organophosphates **141**

Conditions: 0.15 mmol of **141**, 2 equiv of Ph_2IOTf , 10 mol% of $\text{Pd}(\text{TFA})_2$, in 1 mL of 1,2-dichloroethane at 80 °C for 15 h. (a) Reaction carried out in 90 °C with 1.5 equiv of Na_2CO_3 . (b) Recovery yield of starting material **141**.

In order to justify that the chelation of P=O bond with Pd(II)-catalyst existed, thus promoting *ortho*-arylation, a few examples of *ortho*- or *meta*- alkyl substituted phosphates were examined (Table 6.2). The reactions for all substrates were generally slow and a substantial amount of starting materials were recovered in almost all cases (**141a-141f**).

Scheme 6.6 Moon's *ortho*-arylation of diethyl phosphates

In the midst of this research, Moon and coworkers reported a similar discovery of *ortho*-arylation of aryl diethyl phosphates (Scheme 6.6).¹⁰¹ Their reaction conditions were highly comparable to ours, which further supported the presence of the chelation of P=O bond with Pd(II)-catalyst. In both cases, the results were below expectation, as such there is a need to search for a better alternative.

6.2.2 Optimizing Reaction Conditions

A mono-phosphoric acid is a better directing group than a phosphate triester when performing *ortho*-alkenylation as discussed in Chapter 5. Therefore, we next turned our attention to methyl *o*-tolyl hydrogen phosphate (**139c**) as the model substrate. Surprisingly, the reactivity was significantly increased when employing **139c**, as reaction can proceed even at room temperature (Table 6.3, entries 2, 3). The addition of Na₂CO₃ was redundant as it complicated the reaction (entry 1). The more reactive Pd(TFA)₂ proved to be a better catalyst (entries 2, 3). **139c** performed best at

¹⁰¹ Jeon, W. H.; Lee, T. S.; Kim, E. J.; Moon, B.; Kang J. *Tetrahedron* **2013**, 69, 5152.

Table 6.3 Optimizing reaction conditions

entry	base	temp (°C)	solvent	conv (%) ^a
1	Na ₂ CO ₃	rt	ClCH ₂ CH ₂ Cl	messy
2	-	rt	ClCH ₂ CH ₂ Cl	27 ^b
3	-	rt	ClCH ₂ CH ₂ Cl	54
4	-	80	ClCH ₂ CH ₂ Cl	95 (85) ^c
5	-	80	DME	50
6	-	80	dioxane	messy
7	-	110	ClCH ₂ CH ₂ Cl	messy

Conditions: 0.15 mmol of **139c**, 2 equiv of Ph₂IOTf, 10 mol% of Pd(TFA)₂, 1.5 equiv of base in 1 mL of solvent for 15 h. (a) Conversion of starting material **139c**, based on crude NMR. (b) 10 mol % of Pd(OAc)₂ was used instead. (c) Isolated yield after methylation with TMSCHN₂.

80 °C in 1,2-dichloroethane (entries 4-6), which furnished 95% phenylated **140c** and 85% isolated yield after methylation with TMS-diazomethane (entry 4). However, decomposition occurred when the reaction was carried out at 110 °C (entry 7).

6.2.3 Pd(II)-Catalyzed *ortho*-Arylation of Aryl Hydrogen Phosphates

The standard optimized condition was applied to a list of substrates as shown in Table 6.4. For facile purification, the crude arylated mono-phosphoric acids were first methylated using TMS-diazomethane to give the respective methyl phosphate esters **146a-146l**. Arylation occurred selectively at the sterically less-hindered site for substrates bearing substituents at the *ortho*- or *meta*- position. The reaction proceeded smoothly with alkyl substituents (**146a-146f**), however, for electron-donating methoxy-substituted substrates such as **146g** and **146h**, low isolated yield was obtained as they were too reactive. Electron-withdrawing halogens present in **146e**, **146j** and **146k** slowed down the reaction to a certain extent. For unsubstituted **146l**, double *ortho*-arylation could not be avoided.

Table 6.4 Substrate scope for *ortho*-selective arylation via mono-phosphoric acid directing group^a

Conditions: (i) 0.15 mmol of **145**, 2 equiv of Ph₂IOTf, 10 mol% of Pd(TFA)₂, in 1 mL of 1,2-dichloroethane at 80 °C for 15 h. (ii) 5 equiv of TMSCHN₂ in 0.5 mL of MeOH at rt for 30 min. (a) Isolated yield is based on the yield over 2 steps. (b) Recovery yield of methylated starting material **145**. (c) Reaction carried out at 110 °C. (d) 1.2 equiv of ethyl acrylate was used instead. (e) Yield of diarylated product.

Scheme 6.7 Arylation of mono-phosphoric acid **145c** with various aryl iodonium salts

A variety of functionalized biaryl analogs could be synthesized by using a diverse range of iodonium salts, as shown in Scheme 6.7. A list of [Mes-I-Ar]OTf iodonium salts was reacted with **145c** to afford **147a-147f** in high yield (70-98%). In this case, the transfer of bulky mesityl group was not observed. Functional groups, such as ester, fluoride and amide, are tolerant towards the reaction conditions. The reaction worked best with *meta*- or *para*- substituted aryl iodonium salts.

6.2.4 *ortho*-Acetoxylation of mono-Phosphoric Acids via Pd(II)-Catalysis

Table 6.5 Optimizing reaction conditions of *ortho*-acetoxylation for **139**

<p>139c: X = OH 139d: X = OMe</p> <p>148a: X = OH 148b: X = OMe</p>				
entry	substrate	temp (°C)	solvent	conv (%) ^a
1	139c	110	ClCH ₂ CH ₂ Cl	decomposed
2	139c	80	ClCH ₂ CH ₂ Cl	81
3	139c	60	ClCH ₂ CH ₂ Cl	0
4	139c	80	DME	83
5	139c	80	dioxane	90
6 ^c	139c	80	dioxane	100 (67) ^b
7 ^{c,d}	139c	80	dioxane	0
8	139d	110	dioxane	0
9	139d	110	ClCH ₂ CH ₂ Cl	0
10	139d	110	DME	0

Conditions: (i) 0.15 mmol of **139**, 2 equiv of PhI(OAc)₂, 10 mol% of Pd(OAc)₂, in 1 mL of solvent for 15 h. (a) Conversion of starting material **139**, based on crude NMR. (b) Isolated yield after methylation with TMSCHN₃. (c) 3 equiv of PhI(OAc)₂ was used. (d) Blank test, without Pd catalyst.

Acetoxyated products could be generated by using PhI(OAc)₂ instead of aryl iodonium salts. In this case, the products obtained will be useful intermediates to synthesize catechol derivatives that are widely known to be the crucial moieties in natural products. Methyl *o*-tolyl hydrogen phosphate (**139c**) was first subjected to

$\text{PhI}(\text{OAc})_2$ in the presence of $\text{Pd}(\text{OAc})_2$ catalyst as shown in Table 6.5, but decomposition happened at a high temperature of 110 °C (entry 1). Apparently, phosphoric acid is sensitive towards thermal conditions as it shows very different reactivity at 60, 80 and 110 °C (entries 1-3). To our delight, the reaction works well in 1,2-dichloroethane, dimethoxyethane and 1,4-dioxane at 80 °C, giving high conversion to the desired acetoxyated **148a** (entries 2, 4 and 5). Increasing the amount of $\text{PhI}(\text{OAc})_2$ to 3 equiv further improved the conversion to **148a** (entry 6), which gave 67% isolated yield of **148b** after methylation with TMS-diazomethane.

Table 6.6 Substrate scope for *ortho*-acetoxylation via mono-phosphoric acid directing group^a

Conditions: (i) 0.15 mmol of **149**, 3 equiv of $\text{PhI}(\text{OAc})_2$, 10 mol% of $\text{Pd}(\text{OAc})_2$, in 1 mL of 1,4-dioxane at 80 °C for 15 h. (ii) 5 equiv of TMSCHN_2 in 0.5 mL of MeOH at rt for 30 min. (a) Isolated yield is based on the yield over 2 steps. (b) Yield of dephosphorylated product **150i-i**. (c) Yield of diacetoxyated product **150j-i**. (d) Recovery yield of methylated starting material **149**. (e) 5 equiv of $\text{PhI}(\text{OAc})_2$ was used.

The isolated yield was lower than expected because the acetoxy phosphate **148b** is relatively unstable, and needed to be kept at -20 °C for storage after isolation. **148b** decomposed and turned black after being left at ambient temperature for three days. As expected, palladium catalyst is essential for the reaction to take place (entry 7), and dimethyl *o*-tolyl phosphate **139d** is inert to this reaction condition (entries 8-10).

We then moved on to carry out *ortho*-acetoxylation of a variety of aryl phosphoric monoacids after obtaining the optimized conditions (Table 6.5). Similarly, alkyl, alkoxy and halogenated substitutions at *ortho*- or *meta*- position are tolerant to the reaction conditions (**150a-150h**). Biaryl phosphoric acid also proceeds well (**150d**). Surprisingly, when an even more electron-withdrawing ester group is present at the *ortho*- position (**149i**), partial dephosphorylation to yield the corresponding phenol was noticed (**150i:150i'**=53:24). Diacetoxyated byproduct **150j'** was observed with unsubstituted **149j**, which was similar to the results obtained when performing *ortho*-arylation. When using an excess amount of PhI(OAc)₂ (5 equiv), diacetoxyated **150j'** was formed exclusively in 67% yield.

6.2.5 Proposed Mechanism

For the reaction of aryl hydrogen phosphates with various aryl iodonium salts in the presence of Pd(II)-catalyst, we proposed that the reaction underwent a Pd(II)/Pd(IV) catalytic cycle. An illustration describing the *ortho*-arylation using diphenyliodonium triflate was shown in Scheme 6.8. The presence of phosphoric directing group will first assist the Pd-catalyst to the proximal C-H bond at the *ortho*-position. Oxidative addition of the iodonium salt to the palladacycle will give a Pd(IV) complex, and subsequent reductive elimination will release the desired

phenylated product, along with PhI and Pd(II). The Pd(II) will continue the catalytic cycle until reaction goes to completion.

Scheme 6.8 Plausible Pd(II)/Pd(IV) mechanism for *ortho*-arylation

6.3 CONCLUSION

We have shown concrete examples that organophosphates are excellent directing group for the Pd-catalyzed arylation and acetoxylation of aryl hydrogen phosphates, in the presence of different iodonium salts. This methodology could provide easy access to various biaryl compounds, along with catechol derivatives, that are useful for drug discovery and natural product synthesis. It is noteworthy that products obtained were highly *ortho*-selective, and the reaction conditions could tolerate a wide range of functional groups. The reaction followed the proposed Pd(II)/Pd(IV) mechanistic cycle, whereby the iodonium salt could function as both the coupling partner and the oxidant. In conclusion, mono-phosphoric acid is an effective directing group for facilitating C-H functionalization reactions, such as *ortho*-arylation and acetoxylation.

CHAPTER 7

Experimental Section

7.1 GENERAL INFORMATION

All chemical reagents were purchased and used without further purification. Systematic nomenclature for the compounds follows the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw software. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). After elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

^1H and ^{13}C NMR spectra were measured at 298 K on a Bruker Avance III 400 Fourier Transform NMR spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of TMS. The signals observed are described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets). The number of protons (n) for a given resonance is indicated as $n\text{H}$. Coupling constants are reported as J value in Hz. ^{13}C NMR are reported as δ (ppm) in downfield from TMS and relative to the signal of chloroform- d (δ 77.00, triplet).

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions. High Resolution Mass (HRMS) spectra were obtained using Q-Tof Premier LC HR mass spectrometer. Melting points are uncorrected and were recorded on a Buchi B-54 melting point apparatus.

7.2 THE ADDITION OF BENZYLIC ACETATES WITH VARIOUS ORGANOSILANES

General Procedure for the Reaction of Benzylic Acetates with Organosilanes:

Anhydrous FeCl_3 (2.4 mg, 0.015 mmol) and AgOTf (11.5 mg, 0.045 mmol) were carefully weighed inside a glove box and stirred in 1,2-dichloroethane (2 mL) for 5 min. The nucleophile (0.36 mmol) and benzylic acetate (0.3 mmol) were then added to the prepared catalyst solution and stirred at either room temperature or heated to the specified temperature. The residual crude product was concentrated *in vacuo* and purified by flash chromatography using a mixture of *n*-hexane and ethyl acetate as eluent to afford the desired product.

but-3-ene-1,1-diyl dibenzene (47a).¹⁰² 60.0 mg, 96% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.29-7.23 (m, 8H), 7.19-7.15 (m, 2H), 5.75-5.68 (m, 1H), 5.05-4.93 (m, 2H), 4.01 (t, $J = 7.8$, 7.8 Hz, 1H), 2.84-2.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 144.5, 136.8, 128.4, 127.9, 126.2, 116.3, 51.2, 39.9.

(azidomethylene)dibenzene (47b).¹⁰³ 60.9 mg, 97% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.38-7.29 (m, 10H), 5.71 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 139.6, 128.8, 128.1, 127.4, 68.6.

¹⁰² Niwa, T.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2009**, 65, 1971.

¹⁰³ Maddani, M. R.; Moorthy, S. K.; Prabhu, K. R. *Tetrahedron* **2010**, 66, 329.

2,2-diphenylacetonitrile (47c).¹⁰⁰ 51.0 mg, 88% yield; yellow solid; ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.30 (m, 10H), 5.14 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 135.8, 129.2, 128.2, 127.7, 119.7, 42.6.

methyl 2,2-dimethyl-3,3-diphenylpropanoate (47d).¹⁰⁴ 74.1 mg, 92% yield; white solid; ¹H NMR (400 MHz, CDCl₃): δ 7.30-7.28 (m, 4H), 7.27-7.20 (m, 4H), 7.20-7.14 (m, 2H), 4.41 (s, 1H), 3.49 (s, 3H), 1.28 (d, J = 2.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 178.0, 141.5, 129.7, 127.9, 126.3, 59.0, 51.7, 46.4, 24.4.

2-benzhydrylbenzofuran (47f).¹⁰⁵ 75.1 mg, 88% yield; white solid; ¹H NMR (400 MHz, CDCl₃): δ 7.46 (d, J = 7.7 Hz, 1H), 7.44-7.38 (m, 1H), 7.36-7.15 (m, 12H), 6.27 (s, 1H), 5.58 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 159.9, 155.1, 141.0, 128.9, 128.5, 128.4, 127.0, 123.7, 122.6, 120.6, 111.1, 105.6, 51.3.

2-benzhydryl-1-methyl-1H-indole (47g). 80.3 mg, 90% yield; yellow solid; ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.17 (m, 13H), 6.97 (t, J = 7.6 Hz, 1H), 6.40 (s,

¹⁰⁴ Devineau, A.; Pousse, G.; Taillier, C.; Blanchet, J.; Rouden, J.; Dalla, V. *Adv. Synth. Catal.* **2010**, 352, 2881.

¹⁰⁵ Bras, J. L.; Muzart, J. *Tetrahedron* **2007**, 63, 7942.

1H), 5.66 (s, 1H), 3.68 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 144.1, 137.4, 129.0, 128.7, 128.2, 127.3, 126.1, 121.6, 120.0, 118.8, 118.2, 109.1, 48.8, 32.6; HRMS (ESI, $\text{C}_{22}\text{H}_{20}\text{N}$ (M+H) $^{+}$): calcd: 298.1596; found: 298.1603.

pent-4-en-2-ylbenzene (48a).¹⁰⁶ 42.1 mg, 96% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.39-7.29 (m, 2H), 7.24-7.20 (m, 3H), 5.83-5.68 (m, 1H), 5.05-4.97 (m, 2H), 2.85-2.80 (m, 1H), 2.44-2.39 (m, 1H), 2.35-2.30 (m, 1H), 1.29 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.0, 137.2, 128.3, 127.0, 126.0, 115.9, 42.7, 39.7, 21.5.

(1-azidoethyl)benzene (48b).¹⁰⁷ 38.0 mg, 86% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.40-7.31 (m, 5H), 4.61 (q, J = 6.8 Hz, 1H), 1.53 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 140.8, 128.7, 128.1, 126.4, 61.1, 21.6.

2-(1-phenylethyl)benzofuran (48e).¹⁰⁸ 46.0 mg, 69% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.51-7.47 (m, 1H), 7.40-7.14 (m, 8H), 6.43 (s, 1H), 4.25 (q, J = 7.2 Hz, 1H), 1.70 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.1, 154.8, 143.3, 128.5, 128.4, 127.5, 126.7, 123.4, 122.4, 120.4, 111.0, 102.1, 39.6, 20.3,

¹⁰⁶ Kim, S. H.; Shin, C.; Pae, A. N.; Koh, H. Y.; Chang, M. H.; Chung, B. Y.; Cho, Y. S. *Synthesis* **2004**, 1581.

¹⁰⁷ Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.

¹⁰⁸ Nakao, Y.; Kashiwara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, 49, 4451.

1-(but-3-en-1-yl)-4-methoxybenzene (49a).¹⁰⁹ 32.6 mg, 67% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.09 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 5.88-5.81 (m, 1H), 5.05-4.93 (m, 2H), 3.78 (s, 3H), 2.65 (t, J = 7.8 Hz, 2H), 2.36-2.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 157.7, 138.2, 133.9, 129.3, 114.8, 113.7, 55.2, 35.8, 34.4.

1-(azidomethyl)-4-methoxybenzene (49b).¹¹⁰ 41.6 mg, 85% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.24 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 4.26 (s, 2H), 3.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 159.6, 129.8, 127.4, 114.2, 55.3, 54.4.

2-(4-methoxyphenyl)acetonitrile (49c).¹¹¹ 34.4 mg, 78% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.24 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.69 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 159.3, 129.1, 121.7, 118.7, 114.5, 55.3, 22.8.

¹⁰⁹ Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9294.

¹¹⁰ Kitamura, Y.; Taniguchi, K.; Maegawa, T.; Monguchi, Y.; Sajiki, H.; Kitade, Y. *Heterocycles* **2009**, *77*, 521.

¹¹¹ Mirjafari, A.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Khosropour, A. R. *Tetrahedron Lett.* **2010**, *51*, 3274.

2-(4-methoxybenzyl)-1-methyl-1H-indole (49d). 49.8 mg, 66% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.51 (d, $J = 7.6$ Hz, 1H), 7.29-7.18 (m, 4H), 7.06 (t, $J = 7.4$ Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 2H), 6.72 (s, 1H), 4.04 (s, 2H), 3.77 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.7, 137.1, 133.5, 129.5, 127.8, 127.0, 121.5, 119.2, 118.7, 114.7, 113.7, 109.1, 55.2, 32.6, 30.6, 29.2; HRMS (ESI, $\text{C}_{17}\text{H}_{18}\text{NO}$ ($\text{M}+\text{H}$)): calcd: 252.1388; found: 252.1393.

(E)-hexa-1,5-diene-1,3-diyl dibenzene (52a).¹¹² 49.9 mg, 71% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.17 (m, 10H), 6.38-6.36 (m, 2H), 5.80-5.73 (m, 1H), 5.07-4.97 (m, 2H), 3.52 (dt, $J = 6.0, 6.0$ Hz, 1H), 2.59 (dd, $J = 6.6, 6.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 143.8, 137.4, 136.5, 133.4, 129.7, 128.5, 128.4, 127.7, 127.1, 126.3, 126.1, 116.3, 48.9, 40.2.

(E)-(3-azidoprop-1-ene-1,3-diyl) dibenzene (52b).¹¹³ 57.9 mg, 82% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.41-7.22 (m, 10H), 6.71 (d, $J = 15.6$ Hz, 1H), 6.29 (dd, $J = 15.6, 7.2$ Hz, 1H), 5.20 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 138.5, 135.9, 132.9, 128.8, 128.6, 128.2, 127.1, 127.0, 126.8, 126.7, 67.2.

¹¹² Mirjafari, A.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Khosropour, A. R. *Tetrahedron Lett.* **2010**, 51, 3274.

¹¹³ Uozumi, Y.; Suzuka, T.; Kawade, R.; Takenaka, H. *Synlett* **2006**, 2109.

(*E*)-2-(1,3-diphenylallyl)benzofuran (52c).¹¹⁴ 54.9 mg, 59% yield; white solid; ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.18 (m, 14H), 6.69-6.65 (m, 1H), 6.51-6.47 (m, 2H), 5.04 (d, J = 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 159.2, 155.0, 140.4, 136.9, 132.2, 129.0, 128.7, 128.5, 128.4, 127.6, 127.1, 126.4, 123.6, 122.6, 120.6, 111.1, 104.0, 48.7.

2-(4-methoxybenzyl)-1-methyl-1*H*-indole (52d). 54.3 mg, 56% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.51 (d, J = 7.6 Hz, 1H), 7.29-7.18 (m, 4H), 7.06 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 6.72 (s, 1H), 4.04 (s, 2H), 3.77 (s, 3H), 3.71 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 157.7, 137.1, 133.5, 129.5, 127.8, 127.0, 121.5, 119.2, 118.7, 114.7, 113.7, 109.1, 55.2, 32.6, 30.6, 29.2; HRMS (ESI, C₁₇H₁₈NO (M+H)⁺): calcd: 252.1388; found: 252.1393.

pent-4-ene-2,2-diylidibenzene (53a).¹¹⁵ 58.0 mg, 87% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.15 (m, 10H), 5.65-5.46 (m, 1H), 5.14-5.02 (m, 2H), 2.97

¹¹⁴ Bras, J. L.; Muzart, J. *Tetrahedron* **2007**, 63, 7942.

¹¹⁵ De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, 46, 8345.

(d, $J = 6.9$ Hz, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.2, 135.1, 127.9, 127.6, 125.6, 117.5, 46.3, 45.8, 27.5.

(1-azidoethane-1,1-diyl)dibenzene (53b).¹¹⁶ 40.2 mg, 60% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.24 (m, 10H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 144.4, 128.5, 127.7, 126.8, 69.6, 27.6.

ethene-1,1-diyl dibenzene (53c).¹¹⁷ 20.0 mg, 37% yield; white solid; ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.32 (m, 10H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 150.0, 141.5, 128.3, 128.1, 127.7, 114.3.

¹¹⁶ Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237.

¹¹⁷ Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Shi, Z.-J.; Wang, B.-Q.; Zhao, K.-Q. *Org. Lett.* **2010**, *12*, 884.

7.3 REDUCTIVE DEHYDROXYLATION OF BENZYLIC ALCOHOLS WITH PMHS

General Procedure for the Reductive Dehydroxylation of Benzylic Alcohols:

Anhydrous FeCl_3 (2.4 mg, 0.015 mmol) was carefully weighed and stirred in 1,2-dichloroethane (2 mL). The benzylic alcohol (0.3 mmol) was then added to the prepared catalyst solution, followed by PMHS (0.05 mL, 0.9 mmol) and stirred at either room temperature or heated to the respective temperature. The residual crude product was concentrated *in vacuo* and purified by flash chromatography to afford the desired product.

diphenylmethane (55).¹¹⁸ 50.0 mg, 99% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.27 (m, 4H), 7.21-7.18 (m, 6H), 3.98 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 141.1, 128.9, 128.4, 126.0, 41.9.

benzhydryl ether (46).¹¹⁹ 104.6 mg, 99% yield; white solid; ^1H NMR (400 MHz, CDCl_3): δ 7.38-7.25 (m, 20H), 5.40 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 142.4, 128.6, 127.6, 127.5, 80.2.

¹¹⁸ Srimani, D.; Sarkar, A. *Tetrahedron Lett.* **2008**, 49, 6304.

¹¹⁹ Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Eur. J. Org. Chem.* **2009**, 3, 430.

2-ethylnaphthalene (57a).¹²⁰ 43.1 mg, 92% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.75 (m, 3H), 7.61 (s, 1H), 7.45-7.33 (m, 3H), 2.80 (q, J = 7.6 Hz, 2H), 1.32 (dt, J = 7.6, 1.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 141.7, 133.7, 131.9, 127.8, 127.6, 127.4, 127.1, 125.8, 125.5, 125.0, 29.0, 15.5.

4-ethylbiphenyl (57b).¹²¹ 52.5 mg, 96% yield; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.62-7.27 (m, 9H), 2.70 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 143.4, 141.2, 138.6, 128.7, 128.3, 127.0, 127.0, 126.9, 28.4, 15.7.

2-(3-buten-1-yl)naphthalene (57c).¹²² 41.0 mg, 75% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.81-7.76 (m, 3H), 7.63 (s, 1H), 7.47-7.39 (m, 2H), 7.34 (dd, J = 8.4, 1.6 Hz, 1H), 5.90 (tdd, J = 16.8, 10.1, 6.6 Hz, 1H), 5.11-4.96 (m, 2H), 2.88 (t, J = 7.8 Hz, 2H), 2.46 (td, J = 8.0, 6.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 139.4, 138.1, 133.7, 132.1, 127.8, 127.6, 127.5, 127.4, 126.5, 125.9, 125.1, 115.0, 35.6, 35.4.

¹²⁰ Sloan, M. E.; Staubitz, A.; Lee, K.; Manners, I. *Eur. J. Org. Chem.* **2011**, 4, 672.

¹²¹ Guan, B. T.; Xiang, S. K.; Wang, B. Q.; Sun, Z. P.; Wang, Y.; Zhao, K. Q.; Shi, Z. J. *J. Am. Chem. Soc.* **2008**, 130, 3268.

¹²² Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, 132, 10674.

4-heptyl-1,2-dimethoxybenzene (57d). 64.5 mg, 91% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.26-6.70 (m, 3H), 3.87 (s, 1H), 3.85 (s, 1H), 2.54 (t, $J=7.8\text{Hz}$, 2H), 1.60-0.86 (m, 13H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.7, 147.0, 135.6, 120.1, 111.8, 111.2, 55.9, 55.8, 35.6, 31.8, 31.7, 29.3, 29.2, 22.7, 14.1; FTIR (NaCl, neat): ν 2926, 2855, 1607, 1589, 1516, 1464, 1261, 1236, 1155, 1140, 1032, 802 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{25}\text{O}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 237.1855; found: 237.1850.

(E)-1,3-diphenyl-1-propene (57e).¹²³ 49.0 mg, 84% yield; yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 7.36-7.18 (m, 10H), 6.45 (d, $J = 16.0\text{ Hz}$, 1H), 6.35 (td, $J = 15.6, 6.8\text{ Hz}$, 1H), 3.55 (d, $J = 6.4\text{ Hz}$, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 140.14, 137.45, 131.1, 129.2, 128.6, 128.5, 127.1, 126.2, 126.1, 39.4.

(E)-1-phenyl-1-pentene (57f).¹²⁴ 35.1 mg, 80% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.40-7.01 (m, 5H), 6.38 (d, $J = 15.6\text{ Hz}$, 1H), 6.23 (td, $J = 15.6, 6.8\text{ Hz}$, 1H), 2.22-2.16 (m, 2H), 1.53-1.47 (m, 2H), 0.95 (t, $J = 7.2\text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 131.0, 129.9, 128.5, 126.8, 125.9, 35.1, 22.6, 13.7.

¹²³ Rao, M. L. N.; Banerjee, D.; Giri, S. *J. Organomet. Chem.* **2010**, 695, 1518.

¹²⁴ Jackowski, O.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, 49, 3346.

methyl indane (57h).¹²⁵ 32.9 mg, 83% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.21-1.11 (m, 4H), 3.20-3.15 (m, 1H), 2.93-2.78 (m, 2H), 2.34-2.26 (m, 1H), 1.64-1.55 (m, 1H), 1.28 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 148.7, 143.6, 126.1, 126.1, 124.3, 123.1, 39.4, 34.7, 31.4, 19.8.

2-ethylphenol (57i).¹²⁶ 26.4 mg, 72% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.14 (d, J = 7.2 Hz, 1H), 7.08 (dt, J = 7.6, 1.6 Hz, 1H), 6.88 (dt, J = 7.6, 1.2 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 2.64 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H) ¹³C NMR (100 MHz, CDCl₃): δ 129.28, 126.98, 120.88, 115.08, 22.89, 13.95.

4-heptylphenol (57j).¹²⁷ 37.5 mg, 65% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.05-7.03 (m, 2H), 6.76-6.74 (m, 2H), 2.52 (t, J = 7.6 Hz, 2H), 1.32-1.24 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 153.4, 135.2, 129.4, 115.1, 35.1, 31.8, 31.7, 29.2, 29.2, 22.7, 14.1.

¹²⁵ Cesati, R. R.; Armas, J.; Hoveyda, A. H. *Org. Lett.* **2002**, 4, 395.

¹²⁶ Yang, D.; Fu, H. *Chem. Eur. J.* **2010**, 16, 2366.

¹²⁷ Shindo, T.; Fukuyama, Y.; Sugai, T. *Synthesis* **2004**, 5, 692.

1-bromo-4-heptylbenzene (57k).¹²⁸ 62.0 mg, 81% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H), 1.63-1.53 (m, 2H), 1.36-1.19 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 141.8, 131.2, 130.1, 119.2, 35.3, 31.8, 31.3, 29.1, 29.1, 22.6, 14.1; HRMS (ESI, C₁₃H₂₀Br (M+1)): calcd.: 255.0748; found: 255.0757.

3-benzylbenzyl alcohol (57m).¹²⁹ 54.7 mg, 92% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.14 (m, 9H), 4.62 (s, 2H), 3.96 (s, 2H), 1.81 (s, br, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 141.0, 140.6, 138.6, 129.1, 128.8, 128.4, 127.2, 126.1, 65.1, 41.6.

1-methyl-diphenyl-methane (57n').¹³⁰ 20.8 mg, 38% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.28-7.16 (m, 10H), 4.15 (q, J = 7.2 Hz, 1H), 1.64 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 146.4, 128.4, 127.6, 126.0, 44.8, 21.9.

¹²⁸ Januszko, A.; Glab, K. L.; Kaszynski, P.; Patel, K.; Lewis, R. A.; Mehl, G. H.; Wand, M. D. *J. Mater. Chem.* **2006**, *16*, 3183.

¹²⁹ Lee, W. Y.; Sim, W.; Kim, H. J.; Yoon, S. H. *J. Chem. Soc. Perkin Trans. I* **1993**, *6*, 719.

¹³⁰ Duan, H.; Meng, L.; Bao, D.; Zhang, H.; Li, Y.; Lei, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 6387.

1-phenylcyclohex-1-ene (57o).¹³¹ 25.2 mg, 53% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.35 (m, 2H), 7.31-7.27 (m, 2H), 7.23-7.21 (m, 1H), 6.17-6.08 (m, 1H), 2.44-2.37 (m, 2H), 2.23-2.18 (m, 2H), 1.91-1.82 (m, 2H), 1.69-1.62 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 142.7, 136.6, 128.2, 126.5, 124.9, 124.7, 27.4, 25.9, 23.0, 22.1.

phenylcyclohexane (57o').¹³² 14.9 mg, 31% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.16 (m, 5H), 2.54-2.44 (m, 1H), 1.83-1.72 (m, 5H), 1.50-1.23 (m, 5H); ¹³C NMR (101 MHz, CDCl₃) δ 148.1, 128.2, 126.8, 125.7, 44.6, 34.4, 26.9, 26.2.

3-(3,4-dimethoxyphenyl)-1-(p-tolyl)propan-1-one (60).¹³³ 70.0 mg, 82% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.86 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 6.79-6.77 (m, 3H), 3.86 (s, 6H), 3.25 (t, J = 8.4, 8.2 Hz, 2H), 3.02 (t, J = 4.0, 4.0 Hz, 2H), 2.40 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 199.08, 148.84, 147.33,

¹³¹ Xu, L.; Li, B. J.; Wu, Z. H.; Lu, X. Y.; Guan, B. T.; Wang, B. Q.; Zhao, K. Q.; Shi, Z. J. *Org. Lett.* **2010**, *12*, 884.

¹³² Czaplik, W. M.; Mayer, M.; Wangelin, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 607.

¹³³ Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988.

143.81, 134.39, 133.97, 133.97, 129.24, 128.13, 120.12, 111.80, 111.29, 55.89, 55.79,
40.54, 29.87, 21.59.

7.4 CONIA-ENE CYCLIZATION OF 2-ALKYNIC 1,3-DICARBONYL COMPOUNDS

General Procedure for the Conia-ene Cyclization: Anhydrous FeCl_3 (4.9 mg, 0.03 mmol) was carefully weighed and stirred in 1,2-dichloroethane (2 mL). 1,3-dicarbonyls (0.3 mmol) was then added and stirred at either room temperature or heated to the respective temperature. The residual crude product was concentrated *in vacuo* and purified by flash chromatography to afford the desired cyclized product.

methyl 1-acetyl-2-methylenecyclopentanecarboxylate (71).^{58,134} 41.5 mg, 76% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 5.30 (t, $J = 2.1$ Hz, 1H), 5.23 (t, $J = 2.3$ Hz, 1H), 3.75 (s, 3H), 2.48 – 2.38 (m, 3H), 2.25 – 2.16 (m, 4H), 1.76 – 1.62 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 203.6, 171.7, 148.7, 112.2, 70.42, 52.7, 35.0, 33.9, 26.6, 24.1.

methyl 1-acetyl-2-methylcyclopent-2-enecarboxylate (72). 10.4 mg, 19% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 5.71 (d, $J = 1.2$ Hz, 1H), 3.76 (s, 3H), 2.69 – 2.61 (m, 1H), 2.61 – 2.32 (m, 2H), 2.29 – 2.19 (m, 1H), 2.18 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 205.1, 172.2, 137.4, 132.2, 74.7, 52.3, 32.8, 30.4, 26.6, 14.8; FTIR (NaCl, neat): ν 1703, 1647 cm^{-1} ; HRMS (ESI, $\text{C}_{10}\text{H}_{15}\text{O}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 183.1021; found: 183.1028.

¹³⁴ Deng, C. L.; Zou, T.; Wang, Z. Q.; Song, R. J.; Li, J. H. *J. Org. Chem.* **2009**, 74, 412.

ethyl 1-benzoyl-2-methylenecyclopentanecarboxylate (74a).^{58,135} 60.0 mg, 77% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, J = 7.4, 2H), 7.53 (t, J = 7.4, 1H), 7.42 (t, J = 7.4, 2H), 5.36 (t, J = 2.0, 1H), 5.22 (t, J = 2.1, 1H), 4.13 (m, 2H), 2.86 (dt, J = 13.2, 7.0, 1H), 2.52 (m, 2H), 2.19 (dt, J = 13.2, 7.0, 1H), 1.86 (m, 1H), 1.71 (m, 1H), 1.06 (t, J = 7.2, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.4, 171.8, 149.5, 135.4, 132.7, 128.8, 128.4, 111.8, 67.5, 61.6, 36.8, 34.4, 24.4, 13.7.

methyl 1-(4-methylbenzoyl)-2-methylenecyclopentanecarboxylate (74b).¹³⁶ 57.0 mg, 73% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 8.24, 2H), 7.22 (d, J = 8.14, 2H), 5.35 (t, J = 1.95, 1H), 5.18 (t, J = 2.16, 1H), 3.66 (s, 3H), 2.83 (td, J = 13.3, 6.77, 1H), 2.51 (m, 2H), 2.40 (s, 3H), 2.18 (td, J = 13.3, 6.90, 1H), 1.85 (m, 1H), 1.70 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 195.1, 172.9, 149.8, 143.9, 133.0, 129.6, 129.4, 112.3, 67.8, 53.1, 37.3, 34.7, 24.7, 22.0.

tert-butyl 1-acetyl-2-methylenecyclopentanecarboxylate (74c).¹³³ 47.1 mg, 70% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 5.18 (t, J = 2.0, 1H), 5.13 (t, J = 2.19, 1H), 2.29 (m, 3H), 2.11 (s, 3H), 2.01 (m, 1H), 1.58 (m, 2H), 1.36 (s, 9H); ¹³C NMR

¹³⁵ Gao, Q.; Zheng, B. F.; Li, J. H.; Yang, D. *Org. Lett.* **2005**, 7, 2185.

¹³⁶ Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2008**, 47, 6244.

(100 MHz, CDCl₃) δ 203.6, 170.1, 148.9, 111.6, 81.9, 71.1, 35.0, 34.1, 27.8, 26.8, 23.9.

(E)-ethyl 1-acetyl-2-ethylidenecyclopentanecarboxylate (74d). 45.4 mg, 72% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 5.70 – 5.61 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.46 – 2.26 (m, 3H), 2.22 – 2.12 (m, 4H), 1.84 – 1.45 (m, 5H), 1.26 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.5, 171.6, 140.2, 122.2, 70.6, 61.3, 35.0, 29.5, 26.8, 23.7, 15.3, 14.0; FTIR (NaCl, neat): ν 1699, 1630 cm⁻¹; HRMS (ESI, C₁₂H₁₉O₃ (M+H)⁺): calcd.: 211.1334; found: 211.1348.

ethyl 2-methylene-1-(1H-pyrrole-2-carbonyl) cyclopentanecarboxylate (74e). 54.1 mg, 73% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 6.99 (m, 1H), 6.75 (m, 1H), 6.25 (m, 1H), 5.36 (t, J = 2.0, 1H), 5.29 (t, J = 2.2, 1H), 4.17 (m, 2H), 2.76 (dt, J = 13.2, 6.6, 1H), 2.50 (m, 2H), 2.25 (m, 1H), 1.76 (m, 2H), 1.15 (t, J = 7.1, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 186.7, 172.2, 148.9, 129.9, 124.4, 116.5, 112.8, 111.2, 67.4, 61.9, 38.1, 34.7, 24.7, 14.3; FTIR (NaCl, neat): ν 3292, 1733, 1641 cm⁻¹; HRMS (ESI, C₁₄H₁₇NO₃ (M+H)⁺): calcd.: 247.1208; found: 247.1206.

(2-methylenecyclopentane-1,1-diyl)bis(phenylmethanone) (74f). 50.5 mg, 58% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.81 (app d, $J = 8.0$, 4H), 7.44 (tt, $J = 7.43$, 2H), 7.34 (app t, $J = 7.45$, 4H), 5.39 (t, $J = 1.91$, 1H), 4.96 (t, $J = 2.0$, 1H), 2.65 (m, 4H), 1.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.5, 150.8, 136.4, 133.1, 129.9, 128.8, 113.7, 74.0, 38.0, 35.2, 24.0; FTIR (NaCl, neat): ν 1687, 1681 cm^{-1} ; HRMS (ESI, $\text{C}_{20}\text{H}_{18}\text{O}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 290.1307; found: 290.1305.

methyl 1-acetylcyclopent-2-enecarboxylate (76a).¹³⁷ 25.7 mg, 51% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 6.08 – 6.00 (m, 1H), 5.92 – 5.82 (m, 1H), 3.74 (s, 3H), 2.55 – 2.33 (m, 4H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 203.9, 172.3, 136.4, 128.6, 73.5, 52.6, 31.9, 30.1, 26.4.

methyl 1-acetyl-2-ethylcyclopent-2-enecarboxylate (76b).¹³⁸ 41.8 mg, 71% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 5.74 (m, 1H), 3.75 (s, 3H), 2.62 (m, 1H), 2.41 (m, 2H), 2.22 (m, 1H), 2.17 (s, 3H), 2.13 (m, 2H), 1.10 (t, $J = 7.36$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 205.4, 172.5, 143.9, 129.4, 74.9, 52.3, 32.9, 30.5, 26.7, 21.7, 12.4.

¹³⁷ McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, 38, 7691.

¹³⁸ Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2004**, 43, 5350.

ethyl 1-benzoyl-2-ethylcyclopent-2-enecarboxylate (76c). 61.3 mg, 75% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (app d, $J = 7.07$, 2H), 7.52 (tt, $J = 6.8$, 1.9, 1H), 7.42 (app t, $J = 6.8$, 1.8, 2H), 5.78 (t, $J = 2.05$, 1H), 4.10 (q, $J = 7.12$, 2H), 3.09 (m, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 2.29 (m, 2H), 2.01 (m, 1H), 1.14 (t, $J = 7.38$, 3H), 1.03 (t, $J = 7.19$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.3, 172.5, 144.4, 135.7, 132.6, 128.8, 128.6, 128.4, 72.4, 34.0, 30.9, 21.7, 13.8, 12.5; FTIR (NaCl, neat): ν 1733, 1684 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{20}\text{O}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 272.1412; found: 272.1414.

ethyl 1-acetyl-2-methylene cyclohexanecarboxylate (78a); ethyl 1-acetyl-2-methylcyclohex-2-enecarboxylate (78b). 30.3 mg, 48% combined yield, ratio of **78a**:**78b** = 1.0:1.8; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 5.77 (br s, 1.80H), 5.05 (s, 1H), 4.65 (s, 1H), 4.33 – 4.16 (m, 5.6H), 2.41 – 2.29 (m, 2.8H), 2.25 (s, 3H), 2.19 (s, 5.4H), 2.11 – 2.01 (m, 5.8H), 1.98 – 1.88 (m, 1.8H), 1.76 (dd, $J = 3.4$, 1.9 Hz, 5.4H), 1.62 – 1.52 (m, 8.4H), 1.33 – 1.25 (m, 8.4H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.4 (**78b**), 205.4 (**78a**), 171.9 (**78a** & **78b**), 146.2 (**78a** & **78b**), 129.7 (**78a** & **78b**), 128.2 (**78b**), 112.0 (**78b** & **78b**), 65.4 (**78b** & **78b**), 61.4 (**78b**), 61.2 (**78b**), 34.6 (**78b**), 32.3 (**78b**), 29.9 (**78b**), 27.6 (**78b**), 27.3 (**78b**), 26.7 (**78b**), 25.1 (**78b**), 22.5 (**78b**), 21.7 (**78b**), 18.6 (**78b**), 14.1 (**78b**), 14.0 (**78b**); FTIR (NaCl, neat): ν 1699, 1641 cm^{-1} ; HRMS (ESI, $\text{C}_{12}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 211.1334; found: 211.1355.

methyl 2,5-dimethylfuran-3-carboxylate (80).¹³⁹ 46.2 mg, 76% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 6.20 (s, 1H), 3.80 (s, 3H), 2.52 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.7, 157.7, 149.9, 113.7, 106.1, 51.1, 13.6, 13.2.

methyl 2-(1-acetoxyethylidene)hept-6-ynoate (87). 91.9 mg, 82% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 3.76 (s, 3H), 2.35 (t, $J = 7.8$ Hz, 2H), 2.27 (s, 3H), 2.21 (s, 3H), 2.20 – 2.13 (m, 2H), 1.95 (t, $J = 2.4$ Hz, 1H), 1.81 – 1.51 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.2, 167.9, 157.3, 121.4, 84.3, 68.4, 51.7, 27.3, 26.2, 20.9, 19.4, 18.1; FTIR (NaCl, neat): ν 21156, 1759, 1717, 1647 cm^{-1} ; HRMS (ESI, $\text{C}_{12}\text{H}_{17}\text{O}_4$ ($\text{M}+\text{H}$) $^+$): calcd.: 225.1127; found: 225.1114.

methyl 2-acetyl-7-(tributylstannyl)hept-6-ynoate (89). 97.6 mg, 69% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 3.74 (s, 3H), 3.47 (t, $J = 7.4$ Hz, 1H), 2.28 (dd, $J = 9.5, 4.5$ Hz, 2H), 2.24 (s, 3H), 1.98 (dd, $J = 15.4, 7.8$ Hz, 2H), 1.64 – 1.43 (m, 8H), 1.42 – 1.23 (m, 6H), 1.05 – 0.81 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.9, 170.1, 110.3, 82.5, 59.2, 52.3, 28.8, 28.7, 27.2, 26.9, 19.8, 13.6, 10.9; FTIR (NaCl,

¹³⁹ Peng, W.; Hirabaru, T.; Inokuchi, T.; Kawafuchi, H. *Eur. J. Org. Chem.* **2011**, 28, 5469.

neat): ν 2999, 2955, 2930, 2879, 2118, 1715, 1647, 1435, 1246, 1057, 646 cm^{-1} ;
 HRMS (ESI, $\text{C}_{22}\text{H}_{41}\text{O}_3\text{Sn}$ ($\text{M}+\text{H}$) $^+$): calcd.: 473.2078; found: 473.2120.

(*E*)-methyl 1-acetyl-2-((tributylstannyl)methylene) cyclopentanecarboxylate (90).

132.9 mg, 94% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 6.12 (dt, $^2J_{\text{Sn-H}} = 57.6$, $J = 2.0$ Hz, 1H), 3.72 (s, 3H), 2.51 – 2.32 (m, 3H), 2.26 (dd, $J = 13.2$, 6.6 Hz, 1H), 2.21 (s, 3H), 1.82 – 1.68 (m, 2H), 1.58 – 1.39 (m, 6H), 1.38 – 1.24 (m, 6H), 1.06 – 0.75 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3) δ 204.3, 171.8, 156.6, 126.3, 72.7, 52.4, 35.8, 34.9, 29.1, 27.2, 26.6, 24.3, 13.7, 9.9; FTIR (NaCl, neat): ν 2957, 2926, 2872, 2853, 1710, 1638, 1458, 1233, 1072, 667 cm^{-1} ; HRMS (ESI, $\text{C}_{22}\text{H}_{41}\text{O}_3\text{Sn}$ ($\text{M}+\text{H}$) $^+$): calcd.: 473.2078; found: 473.2083.

(*E*)-methyl 1-acetyl-2-(iodomethylene)cyclopentane carboxylate (91a). 87.8 mg, 95% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 6.51 (t, $J = 2.6$ Hz, 1H), 3.77 (s, 3H), 2.62 – 2.50 (m, 1H), 2.50 – 2.39 (m, 2H), 2.32 (dt, $J = 13.1$, 6.6 Hz, 1H), 2.19 (s, 3H), 1.88 – 1.70 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.9, 170.2, 150.3, 78.2, 71.9, 53.0, 38.1, 36.3, 26.6, 22.9; FTIR (NaCl, neat): ν 1705, 1636 cm^{-1} ; HRMS (ESI, $\text{C}_{10}\text{H}_{14}\text{O}_3\text{I}$ ($\text{M}+\text{H}$) $^+$): calcd.: 308.9988; found: 308.9993.

(*E*)-methyl 1-acetyl-2-(deuteriomethylene) cyclopentanecarboxylate (91b).⁵⁸ 47.8 mg, 87% yield, 84% deuterium incorporation; yellow oil; 84% deuterium incorporation. ¹H NMR (400 MHz, CDCl₃) δ 5.30 (t, J = 2.1 Hz, 0.16H), 5.21 (t, J = 2.3 Hz, 1H), 3.75 (s, 3H), 2.53 – 2.35 (m, 3H), 2.25 – 2.13 (m, 4H), 1.83 – 1.65 (m, 2H).

methyl 1-acetyl-2-methyl-3-(tributylstannyl)cyclopent-2-enecarboxylate (93a). 88.9 mg, 63% yield; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 3.74 (s, 3H), 2.53 (m, 3H), 2.23 (m, 1H), 2.15 (s, 3H), 1.85 (s, 3H), 1.48 (m, 6H), 1.32 (m, 6H), 0.95 (m, 15H); ¹³C NMR (100 MHz, CDCl₃) δ 205.9, 172.8, 146.5, 144.4, 77.2, 52.5, 38.7, 34.5, 29.6, 28.2, 27.7, 27.3, 26.9, 17.9, 17.2, 14.1, 14.0, 10.0; FTIR (NaCl, neat): ν 2955, 2925, 2871, 2851, 1741, 1717, 1462, 1249, 1072, 691 cm⁻¹; HRMS (FAB, C₂₂H₄₀O₃NaSn (M⁺+Na)): calcd.: 495.1987; found: 495.1901.

ethyl 1-benzoyl-2-ethyl-3-(tributylstannyl)cyclopent-2-enecarboxylate (93b). 111.2 mg, 66% yield; colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (app d, J = 7.08, 2H), 7.50 (tt, J = 7.44, J = 1.0, 1H), 7.41 (app t, J = 6.85, 2H), 4.10 (m, 2H), 3.03 (m, 1H), 2.61 (m, 1H), 2.42 (m, 1H), 2.29 (m, 3H), 1.52 (m, 6H), 1.33 (m, 6H),

0.97 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.8, 151.4, 145.3, 136.4, 132.7, 129.0, 128.7, 74.1, 61.7, 38.9, 35.8, 29.6, 27.8, 24.7, 15.9, 14.1, 10.1; FTIR (NaCl, neat): ν 2956, 2927, 2871, 2853, 1734, 1684, 1447, 1254, 693 cm^{-1} ; HRMS (ESI, $\text{C}_{29}\text{H}_{46}\text{O}_3\text{Sn}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 562.2471; found: 562.2469.

ethyl 2-ethyl-1-isobutyryl-3-(tributylstannyl)cyclopent-2-enecarboxylate (93c).

103.0 mg, 65% yield; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 4.20 (m, 2H), 2.84 (m, 1H), 2.61 (m, 1H), 2.50 (m, 1H), 2.35 (m, 1H), 2.21 (m, 3H), 1.49 (m, 6H), 1.31 (m, 9H), 1.11 (d, $J = 6.75$, 3H), 1.09 (d, $J = 6.8$, 3H), 0.92 (m, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ 212.7, 172.8, 151.6, 145.3, 76.7, 38.4, 38.1, 34.7, 29.7, 29.6, 29.5, 27.8, 27.7, 24.8, 21.0, 20.8, 15.9, 14.4, 14.1, 10.1; FTIR (NaCl, neat): ν 2957, 2927, 2871, 2853, 1740, 1712, 1462, 1238, 1070, 690 cm^{-1} ; HRMS (ESI, $\text{C}_{22}\text{H}_{39}\text{O}_3\text{Sn}$ ($\text{M}-\text{Bu}$)): calcd.: 471.1921; found: 471.1922.

methyl 2-methyl-5-((tributylstannyl)methyl)furan-3-carboxylate (95).

94.4 mg, 71% yield; colorless oil; ^1H NMR (400 MHz, CDCl_3): δ 5.94 (t, $^4J_{\text{Sn-H}} = 12.0$ Hz, 1H), 3.79 (s, 3H), 2.49 (s, 3H), 2.13 (t, $^2J_{\text{Sn-H}} = 49.6$ Hz, 2H), 1.50-1.42 (m, 6H), 1.32-1.23 (m, 6H), 0.96-0.79 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.0, 156.2, 155.4, 113.7, 102.3, 102.2, 51.0, 29.0, 28.9, 28.8, 27.4, 27.2, 27.0, 13.6, 9.8, 8.4; FTIR (NaCl, neat): ν 2955, 2924, 2853, 1721, 1616, 1578, 1441, 1285, 1082, 735 cm^{-1} ; HRMS (ESI, $\text{C}_{20}\text{H}_{37}\text{O}_3\text{Sn}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 445.1768; found: 445.1779.

(E)-methyl 3-oxo-4-((tributylstannyl)methylene)octahydropentalene-3a-carboxylate (97a). 98.6 mg, 65% yield; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 6.29 (t, $J = 29.0$, 1H), 3.70 (s, 3H), 3.22 (m, 1H), 2.41 (m, 4H), 2.08 (m, 2H), 1.61 (m, 2H), 1.47 (m, 6H), 1.29 (m, 6H), 0.90 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3) δ 210.1, 170.2, 153.6, 126.6, 71.6, 52.6, 48.5, 37.9, 33.9, 29.4, 29.1, 27.2, 24.5, 13.7, 9.9; FTIR (NaCl, neat): ν 2954, 2927, 2870, 2853, 1737, 1705, 1452, 1246, 1066, 665 cm^{-1} ; HRMS (ESI, $\text{C}_{19}\text{H}_{31}\text{O}_3\text{Sn}$ (M-Bu)): calcd for $\text{C}_{19}\text{H}_{31}\text{O}_3\text{Sn}$ (M-Bu): 427.1295; found: 427.1297.

(E)-1-(2-(phenylsulfonyl)-1-((tributylstannyl)methylene)-2,3-dihydro-1H-inden-2-yl)ethanon-e (97b). 90.2mg, 50% yield; white solid; mp = 41-45 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.92 – 7.84 (m, 2H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.43 – 7.28 (m, 3H), 7.24 – 7.15 (m, 3H), 6.30 (d, $^2J_{\text{Sn-H}} = 31.6$ Hz, 1H), 3.91 (d, $J = 18.2$ Hz, 1H), 3.68 (d, $J = 18.2$ Hz, 1H), 2.29 (s, 3H), 1.55 – 1.42 (m, 6H), 1.36 – 1.22 (m, 6H), 1.14 – 0.94 (m, 6H), 0.87 (t, $J = 7.3$ Hz, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.6, 150.1, 142.7, 140.1, 136.1, 133.6, 132.4, 131.4, 129.3, 127.9, 127.1, 125.0, 121.5, 86.9, 36.9, 29.1, 29.0, 28.9, 27.4, 27.2, 13.6, 10.8; FTIR (NaCl, neat): ν 2957, 2928, 2870, 2853, 1715, 1636, 1447, 1240, 1082, 687 cm^{-1} ; HRMS (ESI, $\text{C}_{30}\text{H}_{43}\text{O}_3\text{SSn}$ (M+H) $^{+}$): calcd.: 603.1955; found: 603.1943.

1-(3-(Tributylstannyl)naphthalen-2-yl)ethanone (97b'). 49.6mg, 36% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.40 (s, 1H), 8.17 (dd, $^2J_{\text{Sn-H}} = 48.0$, $J = 1.7$ Hz, 1H), 7.97 (d, $J = 7.8$ Hz, 1H), 7.80 (d, $J = 8.3$ Hz, 1H), 7.61 (dd, $J = 11.0$, 4.1 Hz, 1H), 7.54 (dd, $J = 8.6$, 5.1 Hz, 1H), 2.73 (s, 3H), 1.59 – 1.51 (m, 9H), 1.33 (dt, $J = 14.7$, 7.4 Hz, 6H), 1.27 – 1.19 (m, 6H), 0.87 (t, $J = 7.3$ Hz, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.6, 144.2, 141.2, 133.4, 132.7, 130.8, 130.6, 130.0, 128.2, 126.2, 29.1, 27.3, 26.7, 13.6, 10.5; FTIR (NaCl, neat): ν 2957, 2928, 2870, 2855, 1638, 1449, 1271, 1072, 746 cm^{-1} ; HRMS (ESI, $\text{C}_{24}\text{H}_{37}\text{OSn}$ ($\text{M}+\text{H}$) $^+$): calcd.: 461.1866; found: 461.1880.

7.5 Pd-CATALYZED C-H *ORTHO*-ALKENYLATION OF ARYL HYDROGEN PHOSPHATES

General Procedure for the Pd-Catalyzed C-H *ortho*-Alkenylation: Pd(OAc)₂ (3.37 mg, 0.02 mmol) and AgOAc (75.1 mg, 0.45 mmol) was carefully weighed to a vial equipped with a magnetic stirrer bar and a tightly-screwed cap. Mono-phosphoric acid (0.15 mmol) in 1,4-dioxane (1 mL) was then added, followed by acrylates, alkenes or styrene derivatives (0.3 mmol). The reaction mixture was stirred at 110 °C for 15 h, and cooled to room temperature. The mixture was diluted with EtOAc (1 mL), quenched with 1N HCl (1 mL), and stirred at room temperature for 5 min. The aqueous layer was further extracted with EtOAc (3 mL X 3), and the combined organic layer was concentrated *in vacuo*. No further purification was needed.

TMS-diazomethane (0.4 mL, 0.75 mmol, 2.0M in hexane) was added to the crude product in MeOH (0.5 mL), and stirred at ambient temperature for 30 min. The residual crude product was concentrated *in vacuo* and purified by flash chromatography (CH₂Cl₂/acetone = 20:1) to afford the desired alkenylated product.

(*E*)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)-3-methylphenyl)acrylate (129c-i).

37.7mg, 80% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.90 (d, *J* = 11.6 Hz, 6H), 2.41 (s, 3H),

1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 147.8 (d, $J_{\text{CP}} = 9.0$ Hz), 139.0, 133.4 (d, $J_{\text{CP}} = 1.0$ Hz), 131.4 (d, $J_{\text{CP}} = 4.0$ Hz), 127.3 (d, $J_{\text{CP}} = 4.0$ Hz), 125.6, 124.8, 119.7, 60.4, 55.1 (d, $J_{\text{CP}} = 6.0$ Hz), 17.0, 14.2; ^{31}P NMR (162 MHz, CDCl_3) δ -4.0; FTIR (NaCl, neat): ν 1722, 1643, 1462 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{20}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 315.0998; found: 315.0993.

(E)-ethyl 3-(2-(((2-chloroethoxy)(methoxy)phosphoryl)oxy)-3-methylphenyl)acrylate (129c-ii). (16.3mg, 30% yield); yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, $J = 16.0$ Hz, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 7.16 (t, $J = 7.6$ Hz, 1H), 6.44 (d, $J = 16.0$ Hz, 1H), 4.45 – 4.35 (m, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.96 (d, $J = 11.5$ Hz, 3H), 3.73 (td, $J = 5.8, 0.7$ Hz, 2H), 2.44 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 147.7 (d, $J_{\text{CP}} = 8.0$ Hz), 138.9, 133.5 (d, $J_{\text{CP}} = 2.0$ Hz), 131.4 (d, $J_{\text{CP}} = 3.0$ Hz), 127.4 (d, $J_{\text{CP}} = 4.0$ Hz), 125.7 (d, $J_{\text{CP}} = 2.0$ Hz), 124.9 (d, $J_{\text{CP}} = 1.0$ Hz), 119.9, 67.8 (d, $J_{\text{CP}} = 5.0$ Hz), 60.5, 55.4 (d, $J_{\text{CP}} = 6.0$ Hz), 42.3 (d, $J_{\text{CP}} = 8.0$ Hz), 17.0, 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -5.4; FTIR (NaCl, neat): ν 1713, 1638, 1464 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{21}\text{ClO}_6\text{P}$ (M+H) $^{+}$): calcd.: 363.0764; found: 363.0785.

(E)-ethyl 3-(3-(*tert*-butyl)-2-((dimethoxyphosphoryl)oxy)phenyl)acrylate (131a).

50.2mg, 94% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 15.9$ Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 2H), 7.16 – 7.14 (m, 1H), 6.37 (d, $J = 15.8$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.87 (d, $J = 11.2$ Hz, 6H), 1.45 (s, 9H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 148.7 (d, $J_{\text{CP}} = 9.0$ Hz), 142.2 (d, $J_{\text{CP}} = 5.0$ Hz), 140.4, 130.0, 128.7, 125.8 (d, $J_{\text{CP}} = 1.0$ Hz), 125.3, 119.7, 60.4, 54.9 (d, $J_{\text{CP}} = 6.0$ Hz), 35.1, 30.6, 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -4.3; FTIR (NaCl, neat): ν 1713, 1636, 1423 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{26}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 357.1467; found: 357.1467.

(E)-ethyl 3-(3-benzyl-2-((dimethoxyphosphoryl)oxy)phenyl)acrylate (131b).

50.9mg, 87% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, $J = 16.0$ Hz, 1H), 7.53 – 7.46 (m, 1H), 7.34 – 7.24 (m, 2H), 7.24 – 7.17 (m, 3H), 7.15 – 7.00 (m, 2H), 6.42 (d, $J = 16.0$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 4.18 (s, 2H), 3.85 (d, $J = 11.4$ Hz, 6H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 147.4 (d, $J_{\text{CP}} = 8.0$ Hz), 139.5, 139.0, 134.4 (d, $J_{\text{CP}} = 3.0$ Hz), 133.1, 129.1, 128.4, 127.6 (d, $J_{\text{CP}} = 3.0$ Hz), 126.2, 125.8, 125.4, 119.8, 60.5, 55.2 (d, $J_{\text{CP}} = 6.0$ Hz), 36.0, 14.3; ^{31}P NMR

(162 MHz, CDCl_3) δ -3.9; FTIR (NaCl, neat): ν 1712, 1634, 1454 cm^{-1} ; HRMS (ESI, $\text{C}_{20}\text{H}_{24}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 391.1311; found: 391.1312.

(E)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)-3,4-dimethylphenyl)acrylate (131c).

48.3mg, 98% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, J = 16.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.38 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.89 (d, J = 11.3 Hz, 6H), 2.29 (d, J = 7.4 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 147.7 (d, J_{CP} = 9.0 Hz), 141.5, 139.2, 129.9 (d, J_{CP} = 4.0 Hz), 127.2 (d, J_{CP} = 2.0 Hz), 124.9 (d, J_{CP} = 3.0 Hz), 123.8, 118.5, 60.3, 55.1 (d, J_{CP} = 6.0 Hz), 20.4, 14.2, 13.2; ^{31}P NMR (162 MHz, CDCl_3) δ -3.8; FTIR (NaCl, neat): ν 1713, 1634, 1454 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{22}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 329.1154; found: 329.1155.

(E)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)-4-methylphenyl)acrylate (131d).

38.2mg, 81% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.95 (d, J = 16.1 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 16.1 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.90 (d, J = 11.4 Hz, 6H), 2.37 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 149.0 (d, J_{CP} = 7.0 Hz), 142.5, 137.9, 127.5, 126.3, 123.2 (d, J_{CP} = 7.0 Hz), 120.9 (d, J_{CP} = 2.0 Hz), 119.1, 60.4, 55.1

(d, $J_{CP} = 6.0$ Hz), 21.4, 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -4.5; FTIR (NaCl, neat): ν 1713, 1614, 1447 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{20}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 315.0998; found: 315.1000.

(E)-ethyl 3-(5-chloro-2-((dimethoxyphosphoryl)oxy)-3-methylphenyl)acrylate (131e). 39.8mg, 76% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, $J = 16.0$ Hz, 1H), 7.42 (d, $J = 2.4$ Hz, 1H), 7.22 (d, $J = 1.9$ Hz, 1H), 6.40 (d, $J = 16.0$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.89 (d, $J = 11.6$ Hz, 6H), 2.38 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 146.3 (d, $J_{CP} = 8.0$ Hz), 137.7, 133.3 (d, $J_{CP} = 3.0$ Hz), 132.8, 130.9 (d, $J_{CP} = 2.0$ Hz), 128.9, 124.5, 120.9, 60.6, 55.2 (d, $J_{CP} = 6.0$ Hz), 17.0, 14.2; ^{31}P NMR (162 MHz, CDCl_3) δ -3.9; FTIR (NaCl, neat): ν 1713, 1639, 1468 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{19}\text{ClO}_6\text{P}$ (M+H) $^{+}$): calcd.: 349.0608; found: 349.0605.

(E)-ethyl 3-(3-(adamantan-1-yl)-2-((dimethoxyphosphoryl)oxy)-5-methylphenyl)acrylate (131f). 64.6mg, 96% yield; yellow solid; m.p. 102 – 109 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 15.8$ Hz, 1H), 7.23 (s, 1H), 7.20 (s, 1H), 6.35 (d, $J = 15.8$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.88 (d, $J = 11.6$ Hz, 6H), 2.31 (s, 3H), 2.11 (s,

9H), 1.84 – 1.72 (m, 6H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 147.0 (d, $J_{\text{CP}} = 9.0$ Hz), 141.8 (d, $J_{\text{CP}} = 5.0$ Hz), 140.7, 134.6, 130.9, 128.3, 125.9, 119.5, 60.3, 54.9 (d, $J_{\text{CP}} = 6.0$ Hz), 40.9, 37.3, 36.6, 29.0, 21.0, 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -4.0; FTIR (NaCl, neat): ν 1711, 1634, 1447 cm^{-1} ; HRMS (ESI, $\text{C}_{24}\text{H}_{34}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 449.2093; found: 449.2090.

(E)-ethyl 3-(4-(tert-butyl)-2-((dimethoxyphosphoryl)oxy)phenyl)acrylate (131g).

45.4mg, 85% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, $J = 16.1$ Hz, 1H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.40 (s, 1H), 7.22 (d, $J = 8.0$ Hz, 1H), 6.43 (d, $J = 16.1$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.89 (d, $J = 11.6$ Hz, 6H), 1.34 – 1.30 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 155.7, 149.0 (d, $J_{\text{CP}} = 6.0$ Hz), 137.9, 127.3, 123.2 (d, $J_{\text{CP}} = 7.0$ Hz), 122.6, 119.2, 117.6 (d, $J_{\text{CP}} = 2.0$ Hz), 60.4, 55.0 (d, $J = 6.0$ Hz), 35.0, 30.9, 14.2; ^{31}P NMR (162 MHz, CDCl_3) δ -4.4; FTIR (NaCl, neat): ν 1713, 1634, 1614, 1505 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{26}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 357.1467; found: 357.1468.

(E)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)-4-methoxyphenyl)acrylate (131h).

38.6mg, 78% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, $J = 16.1$ Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 6.97 (dd, $J = 2.4, 1.0$ Hz, 1H), 6.76 (dd, $J = 8.8, 2.5$ Hz,

1H), 6.35 (d, $J = 16.0$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.90 (d, $J = 11.2$ Hz, 6H), 3.84 (s, 3H), 1.34 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.1, 162.1, 150.2 (d, $J_{\text{CP}} = 7.0$ Hz), 137.7, 128.6, 118.5 (d, $J_{\text{CP}} = 7.0$ Hz), 117.4, 111.8, 106.0 (d, $J_{\text{CP}} = 2.0$ Hz), 60.3, 55.6, 55.1 (d, $J_{\text{CP}} = 7.0$ Hz), 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -4.6; FTIR (NaCl, neat): ν 1713, 1614, 1505 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{20}\text{O}_7\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 331.0947; found: 331.0945.

(*E*)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)-4,5-dimethoxyphenyl)acrylate (131i).

43.2mg, 80% yield; brown solid; m.p. 62 – 64 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, $J = 16.0$ Hz, 1H), 7.03 (s, 1H), 6.97 (s, 1H), 6.34 (d, $J = 16.0$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (d, $J = 6.0$ Hz, 6H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 151.6, 146.5, 143.7 (d, $J_{\text{CP}} = 7.0$ Hz), 137.6, 117.6 (d, $J_{\text{CP}} = 6.0$ Hz), 117.3, 108.3, 104.4, 60.4, 56.2, 56.1, 55.1 (d, $J_{\text{CP}} = 7.0$ Hz), 14.2; ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; FTIR (NaCl, neat): ν 1707, 1634, 1609, 1514, 1445 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{22}\text{O}_8\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 361.1052; found: 361.1034.

(*E*)-ethyl 3-(1-((dimethoxyphosphoryl)oxy)naphthalen-2-yl)acrylate (131j).

43.6mg, 83% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.33 – 8.24 (m, 2H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.73 – 7.63 (m, 2H), 7.63 – 7.51 (m, 2H), 6.54 (d, $J = 16.1$

Hz, 1H), 4.29 (q, $J = 7.1$ Hz, 2H), 3.92 (d, $J = 11.4$ Hz, 6H), 1.36 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 145.7 (d, $J_{\text{CP}} = 9.0$ Hz), 138.4, 135.5, 127.7 (d, $J_{\text{CP}} = 2.0$ Hz), 127.2, 127.2, 126.0, 123.2, 122.8 (d, $J_{\text{CP}} = 4.0$ Hz), 122.7 (d, $J_{\text{CP}} = 2.0$ Hz), 119.8, 60.5, 55.3 (d, $J_{\text{CP}} = 6.0$ Hz), 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.5; FTIR (NaCl, neat): ν 1712, 1634, 1470 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{20}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 351.0998; found: 351.0990.

(E)-ethyl 3-(1-(((dimethoxyphosphoryl)oxy)-5,6,7,8-tetrahydronaphthalen-2-yl)acrylate (131k). 42.5mg, 80% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.05 (d, $J = 16.0$ Hz, 1H), 7.36 (d, $J = 8.1$ Hz, 1H), 6.94 (d, $J = 8.1$ Hz, 1H), 6.37 (d, $J = 16.0$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 3.89 (d, $J = 11.4$ Hz, 6H), 2.81 (dd, $J = 26.7$, 5.8 Hz, 4H), 1.87 – 1.69 (m, 4H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 147.7 (d, $J_{\text{CP}} = 8.0$ Hz), 142.2, 139.1, 130.7 (d, $J_{\text{CP}} = 3.0$ Hz), 126.7, 124.3 (d, $J_{\text{CP}} = 4.0$ Hz), 123.6, 118.4, 60.3, 55.1 (d, $J_{\text{CP}} = 6.0$ Hz), 29.7, 23.8, 22.3, 22.2, 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; FTIR (NaCl, neat): ν 1713, 1639, 1566, 1418 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{24}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 355.1311; found: 355.1298.

(E)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)-[1,1'-biphenyl]-3-yl)acrylate (131l).

37.3mg, 66% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 16.0$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.53 – 7.47 (m, 2H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.40 – 7.32 (m, 2H), 7.31 – 7.23 (m, 1H), 6.47 (d, $J = 16.0$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.44 (d, $J = 11.5$ Hz, 6H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 146.3 (d, $J_{\text{CP}} = 8.0$ Hz), 138.9, 137.4, 135.9 (d, $J_{\text{CP}} = 4.0$ Hz), 133.2, 129.6, 128.3 (d, $J_{\text{CP}} = 3.0$ Hz), 128.2, 127.6, 126.5, 125.8, 120.3, 60.5, 54.5 (d, $J_{\text{CP}} = 6.0$ Hz), 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -4.2; FTIR (NaCl, neat): ν 1712, 1634, 1427 cm^{-1} ; HRMS (ESI, $\text{C}_{19}\text{H}_{22}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 377.1154; found: 377.1154.

[1,1'-biphenyl]-2-yl dimethyl phosphate (131l-i). 7.1mg, 17% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.47 (m, 2H), 7.47 – 7.40 (m, 3H), 7.40 – 7.29 (m, 3H), 7.29 – 7.20 (m, 1H), 3.58 (d, $J = 11.4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.5, 137.3, 133.6, 131.2, 129.5, 128.8 (d, $J_{\text{CP}} = 1.0$ Hz), 128.1, 127.4, 125.4, 120.4 (d, $J_{\text{CP}} = 2.0$ Hz), 54.7 (d, $J_{\text{CP}} = 6.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.6; FTIR (NaCl, neat): ν 1732, 1645, 1479, 1435 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{16}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 279.0786; found: 279.0783.

(*E*)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)phenyl)acrylate (131m). 24.8mg, 55% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, $J = 16.1$ Hz, 1H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.45 – 7.32 (m, 2H), 7.21 (t, $J = 7.4$ Hz, 1H), 6.47 (d, $J = 16.0$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.90 (d, $J = 11.4$ Hz, 6H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 149.2 (d, $J_{\text{CP}} = 7.0$ Hz), 137.9, 131.4, 127.8, 126.2 (d, $J_{\text{CP}} = 7.0$ Hz), 125.4, 120.5 (d, $J_{\text{CP}} = 2.0$ Hz), 120.3, 60.6, 55.1 (d, $J_{\text{CP}} = 7.0$ Hz), 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -4.4; FTIR (NaCl, neat): ν 1713, 1634, 1487, 1454 cm^{-1} ; HRMS (ESI, $\text{C}_{13}\text{H}_{18}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 301.0841; found: 301.0837.

dimethyl phenyl phosphate (131m-i). 4.2mg, 14% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.32 (m, 2H), 7.24 – 7.15 (m, 3H), 3.87 (d, $J = 11.3$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.6 (d, $J_{\text{CP}} = 7.0$ Hz), 129.8, 125.1, 119.8 (d, $J_{\text{CP}} = 5.0$ Hz), 54.9 (d, $J_{\text{CP}} = 6.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; FTIR (NaCl, neat): ν 1639, 1593, 1489 cm^{-1} ; HRMS (ESI, $\text{C}_8\text{H}_{12}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 203.0473; found: 203.0469.

(2E,2'E)-diethyl 3,3'-(2-((dimethoxyphosphoryl)oxy)-1,3-phenylene)diacrylate

(131m-ii). 9.6mg, 16% yield; yellow solid; m.p. 107 – 111 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, $J = 15.4$ Hz, 2H), 7.65 (d, $J = 7.8$ Hz, 2H), 7.28 – 7.20 (m, 1H), 6.44 (d, $J = 11.5$ Hz, 2H), 4.27 (q, $J = 7.1$ Hz, 4H), 3.93 (d, $J = 11.4$ Hz, 6H), 1.34 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 147.6 (d, $J = 8.0$ Hz), 138.1, 128.9, 128.6 (d, $J = 4.0$ Hz), 126.0, 120.9, 60.6, 55.4 (d, $J = 6.0$ Hz), 14.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.7; FTIR (NaCl, neat): ν 1711, 1636, 1435 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{24}\text{O}_8\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 399.1209; found: 399.1200.

(E)-ethyl 3-(2-((dimethoxyphosphoryl)oxy)-3-fluorophenyl)acrylate (131n).

23.4mg, 49% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 16.1$ Hz, 1H), 7.47 – 7.34 (m, 1H), 7.25 – 7.09 (m, 2H), 6.47 (d, $J = 16.1$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.96 (d, $J = 11.5$ Hz, 6H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 154.4 (d, $J_{\text{CF}} = 252.6$ Hz), 137.3 (dd, $J_{\text{CF}}, J_{\text{CP}} = 13.3, 7.7$ Hz), 137.0 (d, $J_{\text{CP}} = 3.0$ Hz), 129.6 (d, $J_{\text{CP}} = 3.0$ Hz), 126.0 (d, $J_{\text{CP}} = 7.0$ Hz), 122.4, 121.5, 118.1 (d, $J_{\text{CF}} = 19.0$ Hz), 60.7, 55.3 (d, $J_{\text{CP}} = 6.0$ Hz), 14.2; ^{31}P NMR (162 MHz, CDCl_3) δ -3.8; ^{19}F NMR (376 MHz, CDCl_3) δ -128.27; FTIR (NaCl, neat): ν 1713, 1643, 1479 cm^{-1} ; HRMS (ESI, $\text{C}_{13}\text{H}_{17}\text{FO}_6\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 319.0747; found: 319.0747.

2-fluorophenyl dimethyl phosphate (131n-i). 11.9mg, 36% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.36 (t, $J = 7.9$ Hz, 1H), 7.30 – 7.01 (m, 3H), 3.91 (d, $J = 11.4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.5 (dd, $J_{\text{CF}}, J_{\text{CP}} = 252.9, 4.2$ Hz), 138.3, 126.1 (d, $J_{\text{CP}} = 7.0$ Hz), 124.6 (d, $J_{\text{CP}} = 4.0$ Hz), 122.4, 122.3, 117.0 (d, $J_{\text{CF}} = 18.0$ Hz), 55.2 (d, $J_{\text{CP}} = 6.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; ^{19}F NMR (376 MHz, CDCl_3) δ -131.33; FTIR (NaCl, neat): ν 1715, 1639, 1611, 1504 cm^{-1} ; HRMS (ESI, $\text{C}_8\text{H}_{11}\text{FO}_4\text{P}$ (M+H) $^+$): calcd.: 221.0379; found: 221.0387.

(E)-methyl 3-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-hydroxy-5-methylbenzoate (131o). 37.3mg, 94% yield; white solid; m.p. 97 – 100 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 11.30 (s, 1H), 7.93 (d, $J = 16.2$ Hz, 1H), 7.68 (d, $J = 1.6$ Hz, 1H), 7.49 (d, $J = 1.8$ Hz, 1H), 6.62 (d, $J = 16.2$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.96 (s, 3H), 2.29 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.6, 167.3, 158.6, 138.8, 135.7, 131.7, 128.1, 123.1, 119.8, 112.6, 60.4, 52.4, 20.3, 14.3; FTIR (NaCl, neat): ν 3426, 1672, 1441 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{17}\text{O}_5$ (M+H) $^+$): calcd.: 265.1076; found: 265.1074.

(E)-benzyl 3-(2-((dimethoxyphosphoryl)oxy)-3,4-dimethylphenyl)acrylate (132a).

53.3mg, 91% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, $J = 16.0$ Hz, 3H), 7.49 – 7.29 (m, 6H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.42 (d, $J = 16.0$ Hz, 1H), 5.24 (s, 2H), 3.80 (d, $J = 11.4$ Hz, 6H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 147.7 (d, $J_{\text{CP}} = 8.0$ Hz), 141.7, 139.8, 136.0, 129.9 (d, $J_{\text{CP}} = 3.0$ Hz), 128.5, 128.2, 128.2, 127.2 (d, $J_{\text{CP}} = 1.0$ Hz), 124.8 (d, $J_{\text{CP}} = 3.0$ Hz), 123.9, 118.1, 66.2, 55.0 (d, $J_{\text{CP}} = 6.0$ Hz), 20.5, 13.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.9; FTIR (NaCl, neat): ν 1713, 1634, 1607, 1454 cm^{-1} ; HRMS (ESI, $\text{C}_{20}\text{H}_{24}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 391.1311; found: 391.1297.

(E)-2,3-dimethyl-6-(2-(phenylsulfonyl)vinyl)phenyl dimethyl phosphate (132b).

45.8mg, 77% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, $J = 15.4$ Hz, 1H), 8.00 – 7.93 (m, 2H), 7.64 – 7.58 (m, 1H), 7.58 – 7.51 (m, 2H), 7.29 – 7.22 (m, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 15.4$ Hz, 1H), 3.89 (d, $J = 11.4$ Hz, 6H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.9 (d, $J_{\text{CP}} = 8.0$ Hz), 142.8, 140.9, 137.8, 133.2, 130.4 (d, $J_{\text{CP}} = 3.0$ Hz), 129.2, 127.6, 127.3, 124.5, 123.0, 122.9, 55.2 (d, $J_{\text{CP}} = 6.0$ Hz), 20.5, 13.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.7; FTIR

(NaCl, neat): ν 1614, 1447, 1410, 1306 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{22}\text{O}_6\text{PS}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 397.0875; found: 397.0871.

(E)-6-(2-(diethoxyphosphoryl)vinyl)-2,3-dimethylphenyl dimethyl phosphate

(132c). 45.9mg, 78% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.81 (dd, J = 22.7, 17.7 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.20 (t, J = 18.1 Hz, 1H), 4.14 (dq, J = 14.0, 7.1 Hz, 4H), 3.89 (dd, J = 11.3, 1.3 Hz, 6H), 2.30 (s, 3H), 2.28 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.3 (d, J_{CP} = 8.0 Hz), 143.1 (d, J_{CP} = 8.0 Hz), 143.1, 141.4, 129.8, 127.1, 125.4 (d, J_{CP} = 21.0 Hz), 123.7, 114.3 (d, J_{CP} = 191.9 Hz), 61.8 (d, J_{CP} = 5.0 Hz), 55.1 (d, J_{CP} = 6.0 Hz), 20.4, 16.3 (d, J_{CP} = 6.0 Hz), 13.2; ^{31}P NMR (162 MHz, CDCl_3) δ 19.4, -3.7; FTIR (NaCl, neat): ν 1614, 1568, 1454, 1410 cm^{-1} ; HRMS (ESI, $\text{C}_{16}\text{H}_{27}\text{O}_7\text{P}_2$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 393.1232; found: 393.1222.

(E)-2,3-dimethyl-6-styrylphenyl dimethyl phosphate (132d). 40.4mg, 81% yield;

yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.46 (m, 3H), 7.43 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.29 – 7.22 (m, 1H), 7.08 – 6.97 (m, 2H), 3.83 (d, J = 11.3 Hz, 6H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.9 (d, J_{CP} = 8.0 Hz), 138.3, 137.6, 129.4 (d, J_{CP} = 4.0 Hz), 129.2, 128.7, 127.6, 127.5, 127.1,

126.5, 123.3, 122.9 (d, $J_{CP} = 1.0$ Hz), 55.0 (d, $J_{CP} = 6.0$ Hz), 20.3, 13.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.4; FTIR (NaCl, neat): ν 1636, 1452, 1277 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{22}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 333.1256; found: 333.1253.

(*E*)-2,3-dimethyl-6-(2-(perfluorophenyl)vinyl)phenyl dimethyl phosphate (132e).

46.2g, 73% yield; yellow solid; m.p. 122 – 124 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, $J = 16.8$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 16.8$ Hz, 1H), 3.86 (d, $J = 11.3$ Hz, 6H), 2.31 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.0 (d, $J_{CP} = 9.0$ Hz), 144.8 (d, $J_{CF} = 247.0$ Hz), 140.0 (d, $J_{CP} = 1.0$ Hz), 139.6 (d, $J_{CF} = 254.0$ Hz), 137.7 (d, $J_{CF} = 251.6$ Hz), 131.8 (t, $J_{CF} = 7.9$ Hz), 129.7 (d, $J_{CP} = 4.0$ Hz), 127.2 (d, $J_{CP} = 2.0$ Hz), 126.9 (d, $J_{CP} = 3.0$ Hz), 122.9, 113.0, 112.6 (td, $J_{CF, CP} = 13.7, 4.1$ Hz), 54.9 (d, $J_{CP} = 6.0$ Hz), 20.3, 13.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.6; ^{19}F NMR (376 MHz, CDCl_3) δ -142.94 (dd, $J_{FF} = 21.5, 7.7$ Hz), -156.72 (t, $J_{FF} = 20.7$ Hz), -163.04 (td, $J_{FF} = 21.3, 7.5$ Hz); FTIR (NaCl, neat): ν 1520, 1454, 1277 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{17}\text{F}_5\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 423.0785; found: 423.0798.

(E)-6-(4-chlorostyryl)-2,3-dimethylphenyl dimethyl phosphate (132f). 39.6mg, 72% yield; yellow solid; m.p. 90 – 95 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.43 (m, 3H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.35 – 7.28 (m, 2H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.96 (d, $J = 16.3$ Hz, 1H), 3.83 (d, $J = 11.3$ Hz, 6H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.9, 138.6, 136.2, 133.1, 129.4 (d, $J_{\text{CP}} = 4.0$ Hz), 128.8, 127.8, 127.6, 127.3, 127.1, 124.1, 122.9, 55.0 (d, $J_{\text{CP}} = 6.0$ Hz), 20.3, 13.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.4; FTIR (NaCl, neat): ν 1493, 1454, 1265 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{21}\text{ClO}_4\text{P}$ (M+H) $^+$): calcd.: 367.0866; found: 367.0865.

(E)-2,3-dimethyl-6-(2-(naphthalen-2-yl)vinyl)phenyl dimethyl phosphate (132g). 36.7mg, 64% yield; orange solid; m.p. 48 – 53 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.88 – 7.74 (m, 5H), 7.63 (d, $J = 16.3$ Hz, 1H), 7.53 – 7.40 (m, 3H), 7.19 (d, $J = 16.3$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 3.84 (d, $J = 11.3$ Hz, 6H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.9 (d, $J_{\text{CP}} = 9.0$ Hz), 138.3, 135.1, 133.7, 133.0, 129.4 (d, $J_{\text{CP}} = 4.0$ Hz), 129.3, 128.3, 128.0, 127.7, 127.1, 126.7, 126.3, 125.8, 123.8, 123.4, 122.9, 55.0 (d, $J_{\text{CP}} = 6.0$ Hz), 20.3, 13.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.3; FTIR (NaCl, neat): ν 1454, 1265, 1186 cm^{-1} ; HRMS (ESI, $\text{C}_{22}\text{H}_{24}\text{O}_4\text{P}$ (M+H) $^+$): calcd.: 383.1412; found: 383.1409.

(*E*)-2,3-dimethyl-6-(3-oxo-3-phenylprop-1-en-1-yl)phenyl dimethyl phosphate (132h). 36.2mg, 67% yield; orange solid; m.p. 121 – 127 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, $J = 15.8$ Hz, 1H), 8.07 – 7.94 (m, 2H), 7.63 – 7.54 (m, 1H), 7.55 – 7.42 (m, 4H), 7.06 (d, $J = 7.9$ Hz, 1H), 3.86 (d, $J = 11.4$ Hz, 6H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.7, 148.3, 141.9, 139.8, 138.2, 132.6, 130.1, 128.6, 128.5, 127.2, 125.4, 124.1, 122.7, 55.1 (d, $J_{\text{CP}} = 6.0$ Hz), 20.6, 13.3; ^{31}P NMR (162 MHz, CDCl_3) δ -3.8; FTIR (NaCl, neat): ν 1663, 1603, 1449, 1265 cm^{-1} ; HRMS (ESI, $\text{C}_{19}\text{H}_{22}\text{O}_5\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 361.1205; found: 361.1198.

7.6 Pd-CATALYZED C-H *ORTHO*-ARYLATION AND *ORTHO*-ACETOXYLATION OF ARYL HYDROGEN PHOSPHATES WITH VARIOUS IODONIUM SALTS

General Procedure for the Pd-Catalyzed C-H *ortho*-Arylation: Pd(OAc)₂ (3.4 mg, 0.015 mmol) and Ph₂IOTf¹⁴⁰ (129.0 mg, 0.3 mmol) or [MesIAr]OTf¹⁴¹ (0.3 mmol) was carefully weighed to a vial equipped with a magnetic stirrer bar and a tightly-screwed cap. Mono-phosphoric acid (0.15 mmol) in 1,2-dichloroethane (1 mL) was then added and stirred at 80 °C for 15 h, and cooled to room temperature. The crude mixture was filtered through a cotton plug to remove the solid residues, and concentrated *in vacuo*. The crude mixture was diluted with EtOAc (1 mL), and washed with aqueous Na₂S₂O₃ (1 mL). The aqueous layer was further extracted with EtOAc (3 mL X 3), and the combined organic layer was concentrated *in vacuo*. No further purification was needed.

TMS-diazomethane (0.4 mL, 0.75 mmol, 2.0M in hexane) was added to the crude product in MeOH (0.5 mL), and stirred at ambient temperature for 30 min. The residual crude product was concentrated *in vacuo* and purified by flash chromatography (CH₂Cl₂/acetone = 20:1) to afford the desired arylated product.

¹⁴⁰ Kitamura, T.; Matsuyuki, J.-i.; Taniguchi, H.; *Synthesis* **1994**, 147.

¹⁴¹ Phipps, R. J.; Gaunt, M. J. *Science* **2009**, 323, 1593.

diethyl (3-methyl-[1,1'-biphenyl]-2-yl) phosphate (140a). 26.4 mg, 55% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.52 – 7.46 (m, 2H), 7.43 – 7.37 (m, 2H), 7.35 – 7.29 (m, 1H), 7.21 – 7.09 (m, 3H), 3.91 – 3.73 (m, 2H), 3.72 – 3.56 (m, 2H), 2.46 (s, 3H), 1.11 (td, $J = 7.1, 1.1$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.4 (d, $J_{\text{CP}}=9.0$ Hz), 138.5, 134.8 (d, $J_{\text{CP}}=4.0$ Hz), 131.2 (d, $J_{\text{CP}}=3.0$ Hz), 130.7 (d, $J_{\text{CP}}=1.0$ Hz), 129.6, 129.0 (d, $J_{\text{CP}}=1.0$ Hz), 128.0, 127.1, 125.3, 63.8 (d, $J_{\text{CP}}=6.0$ Hz), 17.4, 15.9 (d, $J_{\text{CP}}=8.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -6.7; FTIR (NaCl, neat): ν 2984, 1636, 1468, 1422, 1273 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{22}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 321.1258; found: 321.1247.

5,5-dimethyl-2-((3-methyl-[1,1'-biphenyl]-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (140b). 29.9 mg, 60% yield; white solid; m.p. 107 – 109 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.37 (m, 4H), 7.37 – 7.30 (m, 1H), 7.24 – 7.18 (m, 1H), 7.17 – 7.09 (m, 2H), 3.73 – 3.53 (m, 4H), 2.46 (s, 3H), 1.15 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.8 (d, $J_{\text{CP}}=8.0$ Hz), 138.4, 134.7 (d, $J_{\text{CP}}=3.0$ Hz), 131.1 (d, $J_{\text{CP}}=3.0$ Hz), 130.9 (d, $J_{\text{CP}}=2.0$ Hz), 129.7, 128.8 (d, $J_{\text{CP}}=1.0$ Hz), 128.0, 127.3, 125.2, 77.5 (d, $J_{\text{CP}}=7.0$ Hz), 31.7 (d, $J_{\text{CP}}=6.0$ Hz), 21.6, 20.1, 17.4; ^{31}P NMR (162 MHz, CDCl_3) δ -14.2; FTIR (NaCl, neat): ν 2967, 1638, 1470, 1422, 1292 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{22}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 333.1256; found: 333.1258.

diethyl (4-methyl-[1,1'-biphenyl]-2-yl) phosphate (142a). 26.4 mg, 80% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.51 – 7.46 (m, $J = 3.1, 1.7$ Hz, 2H), 7.43 – 7.35 (m, 2H), 7.35 – 7.29 (m, 1H), 7.29 – 7.22 (m, $J = 12.0, 3.5$ Hz, 2H), 7.04 (d, $J = 7.8$ Hz, 1H), 4.03 – 3.82 (m, 4H), 2.39 (s, 3H), 1.19 (td, $J = 7.1, 1.0$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.4 (d, $J_{\text{CP}} = 7.0$ Hz), 139.0, 137.6, 130.8, 130.6 (d, $J_{\text{CP}} = 7.0$ Hz), 129.5, 128.0, 127.1, 126.0, 121.0 (d, $J_{\text{CP}} = 3.0$ Hz), 64.3 (d, $J_{\text{CP}} = 7.0$ Hz), 21.1, 15.9 (d, $J_{\text{CP}} = 7.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -6.9; FTIR (NaCl, neat): ν 2984, 1620, 1485, 1404, 1269 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{22}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 321.1256; found: 321.1223.

diethyl (4-methoxy-[1,1'-biphenyl]-2-yl) phosphate (142b). 21.7 mg, 43% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.47 (dd, $J = 5.2, 3.3$ Hz, 2H), 7.39 (dd, $J = 10.2, 4.8$ Hz, 2H), 7.36 – 7.24 (m, 2H), 7.05 (s, $J = 2.4, 1.1$ Hz, 1H), 6.80 (dd, $J = 8.5, 2.4$ Hz, 1H), 4.04 – 3.86 (m, 4H), 3.84 (s, 3H), 1.20 (td, $J = 7.1, 0.9$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.7, 148.2 (d, $J_{\text{CP}} = 7.0$ Hz), 137.4, 131.5, 129.5, 128.0, 126.9, 126.0 (d, $J_{\text{CP}} = 7.0$ Hz), 111.1, 106.3 (d, $J_{\text{CP}} = 2.0$ Hz), 64.4 (d, $J_{\text{CP}} = 6.0$ Hz), 55.5, 15.9 (d, $J_{\text{CP}} = 7.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -7.0; FTIR (NaCl, neat): ν 2984, 1616, 1485, 1443, 1277 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{22}\text{O}_5\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 337.1205; found: 337.1197.

5,5-dimethyl-2-((4-methyl-[1,1'-biphenyl]-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (142c). 32.4 mg, 65% yield; white solid; m.p. 143 – 147 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.49 (m, 3H), 7.48 – 7.39 (m, 2H), 7.38 – 7.31 (m, 1H), 7.25 (d, $J = 7.5$ Hz, 1H), 7.06 (d, $J = 7.8$ Hz, 1H), 3.53 (dt, $J = 23.0, 10.6$ Hz, 4H), 2.39 (s, 3H), 1.16 (s, 3H), 0.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.7 (d, $J_{\text{CP}} = 6.0$ Hz), 139.6, 137.4, 130.6, 129.7, 129.7, 128.2, 127.4, 126.1, 120.8 (d, $J_{\text{CP}} = 2.0$ Hz), 77.6 (d, $J_{\text{CP}} = 7.0$ Hz), 31.5 (d, $J_{\text{CP}} = 6.0$ Hz), 21.7, 21.1, 19.6; ^{31}P NMR (162 MHz, CDCl_3) δ -14.0; FTIR (NaCl, neat): ν 2978, 1643, 1485, 1265 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{22}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 333.1256; found: 333.1254.

2-((3-(tert-butyl)-[1,1'-biphenyl]-2-yl)oxy)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (142d). 35.4 mg, 63% yield; white solid; m.p. 182 – 186 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46 – 7.28 (m, 6H), 7.19 – 7.07 (m, 2H), 3.96 (d, $J = 10.6$ Hz, 2H), 3.58 (dd, $J = 22.6, 11.1$ Hz, 2H), 1.49 (s, 9H), 1.12 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.6 (d, $J_{\text{CP}} = 9.0$ Hz), 141.6 (d, $J_{\text{CP}} = 5.0$ Hz), 139.2, 136.5 (d, $J_{\text{CP}} = 3.0$ Hz), 130.0, 129.8 (d, $J_{\text{CP}} = 2.0$ Hz), 127.8, 127.3, 127.2, 124.9 (d, $J_{\text{CP}} = 1.0$ Hz), 77.9 (d, $J_{\text{CP}} = 7.0$ Hz), 35.0, 31.7 (d, $J_{\text{CP}} = 6.0$ Hz), 30.7, 21.6, 20.2; ^{31}P NMR (162 MHz, CDCl_3) δ -14.2; FTIR (NaCl, neat): ν 2967, 1636, 1420, 1302 cm^{-1} ; HRMS (ESI, $\text{C}_{21}\text{H}_{28}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 375.1725; found: 375.1727.

2-((3,4-dimethyl-[1,1'-biphenyl]-2-yl)oxy)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (142e). 39.0 mg, 75% yield; white solid; m.p. 106 – 110 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46 – 7.36 (m, 4H), 7.35 – 7.29 (m, 1H), 7.06 – 7.00 (m, 2H), 3.66 – 3.53 (m, 4H), 2.33 (s, 3H), 2.32 (s, 3H), 1.14 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.5, 138.7, 138.1, 132.3 (d, $J_{\text{CP}}=4.0$ Hz), 129.8, 129.7 (d, $J_{\text{CP}}=3.0$ Hz), 128.0, 127.7 (d, $J_{\text{CP}}=2.0$ Hz), 127.1, 126.8 (d, $J_{\text{CP}}=2.0$ Hz), 77.5 (d, $J_{\text{CP}}=7.0$ Hz), 31.7 (d, $J_{\text{CP}}=5.0$ Hz), 21.6, 21.0, 20.2, 20.1, 13.7; ^{31}P NMR (162 MHz, CDCl_3) δ -14.0; FTIR (NaCl, neat): ν 2970, 1614, 1402, 1304 cm^{-1} ; HRMS (ESI, $\text{C}_{19}\text{H}_{24}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 347.1412; found: 347.1410.

2-((3-chloro-[1,1'-biphenyl]-2-yl)oxy)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (142f). 15.3 mg, 29% yield; yellow solid; m.p. 124 – 126 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.34 (m, 6H), 7.24 – 7.14 (m, 2H), 3.94 (d, $J = 10.2$ Hz, 2H), 3.72 (dd, $J = 22.7, 11.2$ Hz, 2H), 1.19 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.8, 137.2, 136.9 (d, $J_{\text{CP}}=4.0$ Hz), 129.7 (d, $J_{\text{CP}}=1.0$ Hz), 129.6, 129.5, 128.1, 127.8, 126.0, 77.9 (d, $J_{\text{CP}}=7.0$ Hz), 31.8 (d, $J_{\text{CP}}=6.0$ Hz), 21.8, 20.1; ^{31}P NMR (162 MHz, CDCl_3) δ -14.7; FTIR (NaCl, neat): ν 2971, 1628, 1456, 1431, 1306 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{19}\text{ClO}_4\text{P}$ (M+H) $^{+}$): calcd.: 353.0710; found: 353.0710.

dimethyl (3-methyl-[1,1'-biphenyl]-2-yl) phosphate (140c-i). 37.3 mg, 85% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.51 – 7.45 (m, 2H), 7.45 – 7.37 (m, 2H), 7.36 – 7.29 (m, 1H), 7.22 – 7.09 (m, 3H), 3.39 (d, $J = 11.4$ Hz, 6H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.3 (d, $J_{\text{CP}} = 8.0$ Hz), 138.3, 134.7 (d, $J_{\text{CP}} = 4.0$ Hz), 131.0 (d, $J_{\text{CP}} = 3.0$ Hz), 130.7 (d, $J_{\text{CP}} = 2.0$ Hz), 129.5, 128.9 (d, $J_{\text{CP}} = 2.0$ Hz), 128.0, 127.2, 125.3 (d, $J_{\text{CP}} = 2.0$ Hz), 54.2 (d, $J_{\text{CP}} = 6.0$ Hz), 17.2; ^{31}P NMR (162 MHz, CDCl_3) δ -4.3; FTIR (NaCl, neat): ν 2957, 1636, 1468, 1422, 1277 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{18}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 293.0943; found: 293.0942.

3-(tert-butyl)-[1,1'-biphenyl]-2-yl dimethyl phosphate (146a). 41.6 mg, 83% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.37 (m, 5H), 7.37 – 7.30 (m, 1H), 7.20 – 7.06 (m, 2H), 3.40 (d, $J = 11.5$ Hz, 6H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.0, 142.1, 139.2, 136.2, 130.2, 130.0, 127.9, 127.4, 127.2, 124.9, 54.2 (d, $J_{\text{CP}} = 6.0$ Hz), 35.3, 30.9; ^{31}P NMR (162 MHz, CDCl_3) δ -4.8; FTIR (NaCl, neat): ν 2956, 1636, 1418, 1275 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{24}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 335.1412; found: 335.1424.

3-benzyl-[1,1'-biphenyl]-2-yl dimethyl phosphate (146b). 42.0 mg, 76% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.48 (m, 2H), 7.46 – 7.38 (m, 2H), 7.38 – 7.29 (m, 3H), 7.29 – 7.23 (m, 2H), 7.24 – 7.16 (m, 2H), 7.14 (t, $J = 7.9$ Hz, 1H), 7.04 (dd, $J = 7.6$ Hz, 1H), 4.22 (s, 2H), 3.36 (d, $J = 11.4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.9 (d, $J_{\text{CP}} = 7.0$ Hz), 140.1, 138.4, 135.0 (d, $J_{\text{CP}} = 3.0$ Hz), 134.1 (d, $J_{\text{CP}} = 3.0$ Hz), 130.4, 129.7, 129.5 (d, $J_{\text{CP}} = 1.0$ Hz), 129.2, 128.4, 128.1, 127.3, 126.1, 125.6, 54.4 (d, $J_{\text{CP}} = 6.0$ Hz), 36.1; ^{31}P NMR (162 MHz, CDCl_3) δ -4.2; FTIR (NaCl, neat): ν 3026, 1636, 1495, 1454, 1279 cm^{-1} ; HRMS (ESI, $\text{C}_{21}\text{H}_{22}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 369.1256; found: 369.1251.

3,4-dimethyl-[1,1'-biphenyl]-2-yl dimethyl phosphate (146c). 42.3 mg, 92% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 7.2$ Hz, 2H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.31 (t, $J = 7.3$ Hz, 1H), 7.09 – 7.02 (m, 2H), 3.38 (d, $J = 11.4$ Hz, 6H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.1 (d, $J_{\text{CP}} = 8.0$ Hz), 138.6, 138.0 (d, $J_{\text{CP}} = 2.0$ Hz), 132.3 (d, $J_{\text{CP}} = 4.0$ Hz), 129.6, 128.0, 128.0 (d, $J_{\text{CP}} = 2.0$ Hz), 127.0, 126.9 (d, $J_{\text{CP}} = 1.0$ Hz), 115.3, 54.3 (d, $J_{\text{CP}} = 6.0$ Hz), 20.2, 13.5; ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; FTIR (NaCl, neat): ν 2957, 1636, 1477, 1402, 1279 cm^{-1} ; HRMS (ESI, $\text{C}_{16}\text{H}_{20}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 307.1099; found: 307.1102.

dimethyl (4-methyl-[1,1'-biphenyl]-2-yl) phosphate (146d). 35.5 mg, 81% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.45 (m, 2H), 7.43 – 7.36 (m, 2H), 7.36 – 7.28 (m, 1H), 7.28 – 7.21 (m, 2H), 7.06 (d, $J = 7.8$ Hz, 1H), 3.58 (d, $J = 11.4$ Hz, 6H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.2 (d, $J_{\text{CP}} = 7.0$ Hz), 139.1, 137.4, 130.9, 130.6 (d, $J_{\text{CP}} = 7.0$ Hz), 129.5, 128.1, 127.2, 126.2, 120.9 (d, $J_{\text{CP}} = 2.0$ Hz), 54.6 (d, $J_{\text{CP}} = 7.0$ Hz), 21.1; ^{31}P NMR (162 MHz, CDCl_3) δ -4.6; FTIR (NaCl, neat): ν 2957, 1620, 1485, 1404, 1281 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{18}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 293.0943; found: 293.0949.

5-chloro-3-methyl-[1,1'-biphenyl]-2-yl dimethyl phosphate (146e). 28.4 mg, 58% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.39 (m, 4H), 7.39 – 7.32 (m, 1H), 7.22 – 7.13 (m, 2H), 3.39 (d, $J = 11.4$ Hz, 6H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.9 (d, $J_{\text{CP}} = 8.0$ Hz), 137.1, 136.3 (d, $J_{\text{CP}} = 3.0$ Hz), 133.0 (d, $J_{\text{CP}} = 3.0$ Hz), 130.4 (d, $J_{\text{CP}} = 2.0$ Hz), 130.3 (d, $J_{\text{CP}} = 2.0$ Hz), 129.5, 128.7 (d, $J_{\text{CP}} = 1.0$ Hz), 128.2, 127.8, 54.4 (d, $J_{\text{CP}} = 6.0$ Hz), 17.2; ^{31}P NMR (162 MHz, CDCl_3) δ -4.3; FTIR (NaCl, neat): ν 2957, 1634, 1470, 1422, 1281 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{17}\text{ClO}_4\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 327.0553; found: 327.0549.

4-chloro-2-methylphenyl dimethyl phosphate (146e-i). 10.5 mg, 28% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.07; ^{13}C NMR (100 MHz, CDCl_3) δ 147.6 (d, J_{CP} = 7.0 Hz), 131.1, 130.1, 129.5, 127.0 (d, J_{CP} = 1.0 Hz), 120.9 (d, J_{CP} = 2.0 Hz), 55.0 (d, J_{CP} = 6.0 Hz), 16.2; ^{31}P NMR (162 MHz, CDCl_3) δ -3.9; FTIR (NaCl, neat): ν 1655, 1485, 1449 cm^{-1} ; HRMS (ESI, $\text{C}_9\text{H}_{13}\text{ClO}_4\text{P}$ (M+H) $^+$): calcd.: 251.0240; found: 251.0243.

4-(tert-butyl)-[1,1'-biphenyl]-2-yl dimethyl phosphate (146f). 40.1 mg, 80% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.47 (m, 2H), 7.47 – 7.36 (m, 3H), 7.36 – 7.24 (m, 3H), 3.58 (d, J = 11.4 Hz, 6H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.5, 147.3, 137.4, 130.6, 130.5 (d, J_{CP} = 6.0 Hz), 129.5, 128.1, 127.2, 122.4, 117.7, 54.6 (d, J_{CP} = 6.0 Hz), 34.7, 31.2; ^{31}P NMR (162 MHz, CDCl_3) δ -4.6; FTIR (NaCl, neat): ν 2961, 1636, 1485, 1281 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{24}\text{O}_4\text{P}$ (M+H) $^+$): calcd.: 335.1412; found: 335.1424.

4-methoxy-[1,1'-biphenyl]-2-yl dimethyl phosphate (146g). 23.1 mg, 50% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.44 (m, 2H), 7.44 – 7.36 (m, 2H), 7.34 – 7.25 (m, 2H), 7.01 (s, J = 2.5, 1.2 Hz, 1H), 6.84 – 6.79 (m, 1H), 3.84 (s, 3H), 3.58 (d, J = 11.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.8, 148.1 (d, J_{CP} = 7.0

Hz), 137.2, 131.5, 129.5, 128.1, 127.0, 126.0 (d, J_{CP} = 7.0 Hz), 111.2, 106.5 (d, J_{CP} = 2.0 Hz), 55.6, 54.6 (d, J_{CP} = 6.0 Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.7; FTIR (NaCl, neat): ν 2957, 1616, 1516, 1485, 1281 cm^{-1} ; HRMS (ESI, $\text{C}_{15}\text{H}_{18}\text{O}_5\text{P}$ (M+H) $^{+}$): calcd.: 309.0892; found: 309.0894.

4,5-dimethoxy-[1,1'-biphenyl]-2-yl dimethyl phosphate (146h). 22.8 mg, 45% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.52 – 7.45 (m, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.29 (m, 1H), 7.02 (s, J = 1.0 Hz, 1H), 6.85 (s, J = 0.6 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.56 (d, J = 11.3 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.8, 146.4, 140.8 (d, J_{CP} = 8.0 Hz), 137.4, 129.5, 128.1, 127.2, 125.2 (d, J_{CP} = 6.0 Hz), 113.2, 104.9, 56.3, 56.2, 54.6 (d, J_{CP} = 7.0 Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.2; FTIR (NaCl, neat): ν 2957, 1614, 1520, 1493, 1265 cm^{-1} ; HRMS (ESI, $\text{C}_{16}\text{H}_{20}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 339.0998; found: 339.1008.

dimethyl (2-phenyl-5,6,7,8-tetrahydronaphthalen-1-yl) phosphate (146i). 44.9 mg, 90% yield; yellow solid; m.p. 66 – 68 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.44 (m, 2H), 7.43 – 7.36 (m, 2H), 7.34 – 7.28 (m, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 3.38 (d, J = 11.4 Hz, 6H), 2.85 (dt, J = 11.6, 5.6 Hz, 4H), 1.89 – 1.74 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.9 (d, J_{CP} = 8.0 Hz), 138.7 (d, J_{CP} = 1.0 Hz), 138.5, 131.6 (d, J_{CP} = 3.0 Hz), 130.4 (d, J_{CP} = 3.0 Hz), 129.6, 128.0, 127.9 (d, J_{CP} = 2.0 Hz), 127.0, 126.4 (d, J_{CP} = 2.0 Hz), 54.2 (d, J_{CP} = 6.0 Hz), 29.4, 24.1, 22.6,

22.4; ^{31}P NMR (162 MHz, CDCl_3) δ -4.3; FTIR (NaCl, neat): ν 2932, 1636, 1476, 1412, 1271 cm^{-1} ; HRMS (ESI, $\text{C}_{18}\text{H}_{22}\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 333.1256; found: 333.1258.

4-bromo-[1,1'-biphenyl]-2-yl dimethyl phosphate (146j). 30.0 mg, 56% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.60 (s, 1H), 7.50 – 7.33 (m, 6H), 7.24 (dd, J = 8.2, 1.1 Hz, 1H), 3.60 (d, J = 11.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.9 (d, J_{CP} = 7.0 Hz), 136.4, 132.7 (d, J_{CP} = 7.0 Hz), 132.2, 129.3, 128.6, 128.3, 127.8, 123.8 (d, J_{CP} = 2.0 Hz), 121.4 (d, J_{CP} = 1.0 Hz), 54.8 (d, J_{CP} = 6.0 Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.8; FTIR (NaCl, neat): ν 2957, 1634, 1470, 1393, 1288 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{13}\text{BrO}_2\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 358.9837; found: 358.9882.

3-bromophenyl dimethyl phosphate (146j-i). 9.3 mg, 22% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.39 (s, J = 0.9 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.25 – 7.16 (m, 2H), 3.87 (d, J = 11.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.1 (d, J_{CP} = 6.0 Hz), 130.8, 128.4, 123.4 (d, J_{CP} = 5.0 Hz), 122.7, 118.7 (d, J_{CP} = 5.0 Hz), 55.1 (d, J_{CP} = 6.0 Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.4; FTIR (NaCl, neat): ν 1636, 1584, 1472 cm^{-1} ; HRMS (ESI, $\text{C}_8\text{H}_9\text{BrO}_2\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 280.9578; found: 280.9575.

3-chloro-[1,1'-biphenyl]-2-yl dimethyl phosphate (146k). 29.5 mg, 63% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.32 (m, 6H), 7.32 – 7.06 (m, 2H), 3.46 (d, $J = 11.6$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.3 (d, $J_{\text{CP}} = 8.0$ Hz), 137.2, 136.8 (d, $J_{\text{CP}} = 3.0$ Hz), 129.8 (d, $J_{\text{CP}} = 1.0$ Hz), 129.8 (d, $J_{\text{CP}} = 2.0$ Hz), 129.6, 128.3, 127.8, 127.4 (d, $J_{\text{CP}} = 4.0$ Hz), 126.0 (d, $J_{\text{CP}} = 2.0$ Hz), 54.6 (d, $J_{\text{CP}} = 7.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.8; FTIR (NaCl, neat): ν 2959, 1634, 1454, 1429, 1285 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{15}\text{ClO}_4\text{P}$ (M+H) $^{+}$): calcd.: 313.0397; found: 313.0398.

2-chlorophenyl dimethyl phosphate (146k-i). 7.1 mg, 20% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (ddt, $J = 7.9, 2.7, 1.3$ Hz, 2H), 7.32 – 7.20 (m, 1H), 7.18 – 7.07 (m, 1H), 3.92 (d, $J = 11.4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.6 (d, $J_{\text{CP}} = 6.0$ Hz), 130.6, 128.0, 125.9, 125.4 (d, $J_{\text{CP}} = 8.0$ Hz), 121.3 (d, $J_{\text{CP}} = 2.0$ Hz), 55.2 (d, $J_{\text{CP}} = 6.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.6; FTIR (NaCl, neat): ν 1636, 1585, 1481 cm^{-1} ; HRMS (ESI, $\text{C}_8\text{H}_9\text{ClO}_4\text{P}$ (M+H) $^{+}$): calcd.: 237.0084; found: 237.0097.

[1,1'-biphenyl]-2-yl dimethyl phosphate (146l). 15.4 mg, 37% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.48 (m, 2H), 7.47 – 7.30 (m, 6H), 7.28 – 7.22 (m,

1H), 3.58 (d, $J = 11.3$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.6 (d, $J_{\text{CP}} = 7.0$ Hz), 137.4, 133.6 (d, $J_{\text{CP}} = 7.0$ Hz), 131.2, 129.5, 128.8, 128.1, 127.5, 125.4, 120.5 (d, $J_{\text{CP}} = 3.0$ Hz), 54.6 (d, $J_{\text{CP}} = 6.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.6; FTIR (NaCl, neat): ν 2957, 1636, 1479, 1435, 1281 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{16}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 279.0786; found: 279.0789.

[1,1':3',1''-terphenyl]-2'-yl dimethyl phosphate (146l-i). 18.6 mg, 35% yield; yellow solid; m.p. 96 – 99 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.61 – 7.55 (m, 4H), 7.48 – 7.41 (m, 4H), 7.38 – 7.30 (m, 5H), 2.96 (d, $J = 11.5$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.8 (d, $J_{\text{CP}} = 8.0$ Hz), 138.3, 135.8 (d, $J_{\text{CP}} = 3.0$ Hz), 130.7 (d, $J_{\text{CP}} = 2.0$ Hz), 129.9, 128.2, 127.4, 125.7 (d, $J_{\text{CP}} = 2.0$ Hz), 53.8 (d, $J_{\text{CP}} = 5.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -4.5; FTIR (NaCl, neat): ν 3055, 1593, 1456, 1418, 1277 cm^{-1} ; HRMS (ESI, $\text{C}_{20}\text{H}_{20}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 355.1099; found: 355.1099.

dimethyl (3,4,4'-trimethyl-[1,1'-biphenyl]-2-yl) phosphate (147a). 42.3 mg, 88% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.37 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.08 – 7.01 (m, 2H), 3.40 (d, $J = 11.4$ Hz, 6H), 2.37 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.1 (d, $J_{\text{CP}} = 8.0$ Hz), 137.8 (d, $J_{\text{CP}} = 2.0$ Hz), 136.6, 135.7, 132.2 (d, $J_{\text{CP}} = 3.0$ Hz), 129.6 (d, $J_{\text{CP}} = 3.0$ Hz), 129.4, 128.7,

128.0 (d, $J_{CP} = 1.0$ Hz), 126.9 (d, $J_{CP} = 2.0$ Hz), 54.3 (d, $J_{CP} = 6.0$ Hz), 21.1, 20.2, 13.5; ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; FTIR (NaCl, neat): ν 2955, 1611, 1454, 1395, 1281 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{22}\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 321.1256; found: 321.1268.

ethyl 2'-((dimethoxyphosphoryl)oxy)-3',4'-dimethyl-[1,1'-biphenyl]-4-carboxylate (147b). 39.7 mg, 70% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.16 – 8.04 (m, 2H), 7.56 (d, $J = 8.3$ Hz, 2H), 7.08 (s, 2H), 4.39 (q, $J = 7.1$ Hz, 2H), 3.43 (d, $J = 11.4$ Hz, 6H), 2.33 (s, 6H), 1.41 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 145.9 (d, $J_{CP} = 9.0$ Hz), 143.4, 139.0, 131.4 (d, $J_{CP} = 3.0$ Hz), 130.0 (d, $J_{CP} = 4.0$ Hz), 129.6, 129.5, 129.4, 129.3, 129.0, 127.8, 127.1 (d, $J_{CP} = 2.0$ Hz), 61.0, 54.5 (d, $J_{CP} = 6.0$ Hz), 20.3, 14.3, 13.5; ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; FTIR (NaCl, neat): ν 2957, 1715, 1614, 1447, 1277 cm^{-1} ; HRMS (ESI, $\text{C}_{19}\text{H}_{24}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 379.1311; found: 379.1312.

3,4-dimethyl-4'-nitro-[1,1'-biphenyl]-2-yl dimethyl phosphate (147c). 43.2 mg, 82% yield; brown solid; m.p. 114 – 116 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.32 – 8.23 (m, 2H), 7.73 – 7.60 (m, 2H), 7.16 – 7.03 (m, 2H), 3.54 – 3.47 (m, 6H), 2.35 (s,

6H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.7, 145.7 (d, $J_{\text{CP}} = 8.0$ Hz), 145.6, 139.8, 130.3, 130.2 (d, $J_{\text{CP}} = 3.0$ Hz), 130.2 (d, $J_{\text{CP}} = 3.0$ Hz), 127.6 (d, $J_{\text{CP}} = 2.0$ Hz), 127.3 (d, $J_{\text{CP}} = 2.0$ Hz), 123.2, 54.5 (d, $J_{\text{CP}} = 6.0$ Hz), 20.3, 13.4; ^{31}P NMR (162 MHz, CDCl_3) δ -3.9; FTIR (NaCl, neat): ν 2955, 1599, 1516, 1447, 1346, 1288 cm^{-1} ; HRMS (ESI, $\text{C}_{16}\text{H}_{19}\text{NO}_6\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 352.0950; found: 352.0959.

4'-fluoro-3,4-dimethyl-[1,1'-biphenyl]-2-yl dimethyl phosphate (147d). 46.7 mg, 96% yield; yellow solid; m.p. 122 – 124 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.40 (m, 2H), 7.15 – 7.00 (m, 4H), 3.45 (d, $J = 11.4$ Hz, 6H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.3, 160.8, 146.1 (d, $J_{\text{CP}} = 8.0$ Hz), 138.2, 134.6 (d, $J_{\text{CP}} = 4.0$ Hz), 131.2 (d, $J_{\text{CP}} = 8.0$ Hz), 130.50 (dd, $J_{\text{CF}}, J_{\text{CP}} = 156.9, 3.4$ Hz), 127.9, 126.9 (d, $J_{\text{CP}} = 2.0$ Hz), 114.8 (d, $J_{\text{CF}} = 21.0$ Hz), 54.3 (d, $J_{\text{CP}} = 6.0$ Hz), 20.2, 13.5; ^{31}P NMR (162 MHz, CDCl_3) δ -4.0; ^{19}F NMR (376 MHz, CDCl_3) δ -115.53; FTIR (NaCl, neat): ν 2957, 1601, 1514, 1481, 1454, 1281 cm^{-1} ; HRMS (ESI, $\text{C}_{16}\text{H}_{19}\text{FO}_4\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 325.1005; found: 325.1010.

3,4-dimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl dimethyl phosphate (147e). 55.0 mg, 98% yield; yellow solid; m.p. 122 – 124 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ

7.75 (s, 1H), 7.67 (d, $J = 7.5$ Hz, 1H), 7.62 – 7.57 (m, 1H), 7.57 – 7.50 (m, 1H), 7.07 (s, 2H), 3.44 (d, $J = 11.4$ Hz, 6H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.9 (d, $J_{\text{CP}} = 8.0$ Hz), 139.5, 139.0 (d, $J_{\text{CP}} = 2.0$ Hz), 132.9, 130.9 (d, $J_{\text{CP}} = 3.0$ Hz), 130.5, 130.1, 130.0 (d, $J_{\text{CP}} = 3.0$ Hz), 128.6, 127.7 (d, $J_{\text{CP}} = 2.0$ Hz), 127.1 (d, $J_{\text{CP}} = 2.0$ Hz), 125.01 (dq, $J_{\text{CF}} = 274.0, 3.7$ Hz), 124.16 (d, $J_{\text{CF}} = 272.2$ Hz), 54.3 (d, $J_{\text{CP}} = 6.0$ Hz), 30.8, 20.2, 13.4; ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; ^{19}F NMR (376 MHz, CDCl_3) δ -62.57; FTIR (NaCl, neat): ν 2957, 1614, 1454, 1337, 1279 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{19}\text{F}_3\text{O}_4\text{P}$ (M+H) $^{+}$): calcd.: 375.0973; found: 375.0976.

ethyl 2'-((dimethoxyphosphoryl)oxy)-3',4'-dimethyl-[1,1'-biphenyl]-3-carboxylate (147f). 44.8 mg, 79% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 8.01 (d, $J = 7.9$ Hz, 1H), 7.69 (d, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 1H), 7.08 (s, 2H), 4.38 (q, $J = 7.2$ Hz, 2H), 3.43 (d, $J = 11.4$ Hz, 6H), 2.34 (s, 3H), 2.33 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 146.0 (d, $J_{\text{CP}} = 8.0$ Hz), 138.9, 138.6, 134.1, 131.3 (d, $J_{\text{CP}} = 3.0$ Hz), 130.6, 130.3, 129.8, 128.2, 128.1, 127.9, 127.0, 61.0, 54.4 (d, $J_{\text{CP}} = 6.0$ Hz), 20.2, 14.3, 13.5; ^{31}P NMR (162 MHz, CDCl_3) δ -4.2; FTIR (NaCl, neat): ν 2957, 1715, 1614, 1447, 1277 cm^{-1} ; HRMS (ESI, $\text{C}_{19}\text{H}_{24}\text{O}_6\text{P}$ (M+H) $^{+}$): calcd.: 379.1311; found: 379.1318.

General Procedure for the Pd-Catalyzed C-H *ortho*-Acetoxylation: Pd(OAc)₂ (3.4 mg, 0.015 mmol) and PhI(OAc)₂ (144.9 mg, 0.45 mmol) was carefully weighed to a vial equipped with a magnetic stirrer bar and a tightly-screwed cap. Mono-phosphoric acid (0.15 mmol) in 1,4-dioxane (1 mL) was then added and stirred at 80 °C for 15 h, and cooled to room temperature. The crude mixture was filtered through celite and concentrated *in vacuo*. No further purification was needed.

TMS-diazomethane (0.4 mL, 0.75 mmol, 2.0M in hexane) was added to the crude product in MeOH (0.5 mL), and stirred at ambient temperature for 30 min. The residual crude product was concentrated *in vacuo* and purified by flash chromatography (CH₂Cl₂/acetone = 20:1) to afford the desired acetoxylation product.

2-((dimethoxyphosphoryl)oxy)-3-methylphenyl acetate (148b). 27.6 mg, 67% yield; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.13 – 7.05 (m, 2H), 7.01 – 6.95 (m, 1H), 3.86 (d, *J* = 11.4 Hz, 6H), 2.38 (s, 3H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.8, 142.0 (d, *J* = 3.0 Hz), 141.0 (d, *J* = 8.0 Hz), 132.0 (d, *J* = 4.0 Hz), 128.6 (d, *J* = 1.0 Hz), 125.4, 121.4 (d, *J* = 2.0 Hz), 55.0 (d, *J* = 6.0 Hz), 20.8, 16.6; ³¹P NMR (162 MHz, CDCl₃) δ -3.9; FTIR (NaCl, neat): ν 1732, 1651, 1485, 1371, 1265 cm⁻¹; HRMS (ESI, C₁₁H₁₆O₆P (M+H)⁺): calcd.: 275.0685; found: 275.0677.

3-(*tert*-butyl)-2-((dimethoxyphosphoryl)oxy)phenyl acetate (150a). 32.7 mg, 69% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.27 – 7.22 (m, 1H), 7.10 (t, $J = 8.0$ Hz, 1H), 7.02 (dd, $J = 8.0, 1.5$ Hz, 1H), 3.86 (d, $J = 11.5$ Hz, 6H), 2.38 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.1, 142.3 (d, $J = 6.0$ Hz), 142.2 (d, $J = 8.0$ Hz), 141.6, 124.7, 124.6, 121.9, 54.9 (d, $J = 6.0$ Hz), 35.1, 30.1, 21.0; ^{31}P NMR (162 MHz, CDCl_3) δ -5.1; FTIR (NaCl, neat): ν 1769, 1643, 1469, 1368, 1269 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{22}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 317.1154; found: 317.1147.

3-benzyl-2-((dimethoxyphosphoryl)oxy)phenyl acetate (150b). 33.1 mg, 63% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 7.13 – 6.99 (m, 2H), 6.93 (d, $J = 7.6$ Hz, 1H), 4.12 (s, 2H), 3.80 (d, $J = 11.4$ Hz, 6H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.7, 141.9 (d, $J = 3.0$ Hz), 140.6, 139.2, 134.7 (d, $J = 5.0$ Hz), 129.0, 128.5, 128.2, 126.3, 125.5, 122.0 (d, $J = 1.0$ Hz), 55.1 (d, $J = 7.0$ Hz), 35.7, 20.8; ^{31}P NMR (162 MHz, CDCl_3) δ -4.1; FTIR (NaCl, neat): ν 1769, 1601, 1470, 1371, 1267 cm^{-1} ; HRMS (ESI, $\text{C}_{17}\text{H}_{20}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 351.0998; found: 351.0996.

2-((dimethoxyphosphoryl)oxy)-3,4-dimethylphenyl acetate (150c). 31.1 mg, 72% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 6.99 (d, $J = 8.3$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 3.85 (d, $J = 11.4$ Hz, 6H), 2.33 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.0, 140.6 (d, $J = 8.0$ Hz), 139.8 (d, $J = 3.0$ Hz), 136.0, 130.3 (d, $J = 4.0$ Hz), 130.3, 126.6, 120.3, 55.0 (d, $J = 6.0$ Hz), 20.8, 19.9, 13.1; ^{31}P NMR (162 MHz, CDCl_3) δ -3.8; FTIR (NaCl, neat): ν 1769, 1614, 1487, 1371, 1273 cm^{-1} ; HRMS (ESI, $\text{C}_{12}\text{H}_{18}\text{O}_6\text{P}$ (M+H) $^+$): calcd.: 289.0841; found: 289.0842.

2-((dimethoxyphosphoryl)oxy)-[1,1'-biphenyl]-3-yl acetate (150d). 25.2 mg, 50% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.46 (m, 2H), 7.43 (t, $J = 7.4$ Hz, 2H), 7.38 – 7.33 (m, 1H), 7.29 – 7.21 (m, 3H), 7.19 – 7.15 (m, 1H), 3.42 (d, $J = 11.5$ Hz, 6H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.8, 142.3, 139.7, 136.9, 136.2 (d, $J = 4.0$ Hz), 129.6, 128.4, 128.2, 127.7, 125.6, 123.1, 54.5 (d, $J = 6.0$ Hz), 20.8; ^{31}P NMR (162 MHz, CDCl_3) δ -4.5; FTIR (NaCl, neat): ν 1769, 1599, 1470, 1371, 1254 cm^{-1} ; HRMS (ESI, $\text{C}_{16}\text{H}_{18}\text{O}_6\text{P}$ (M+H) $^+$): calcd.: 337.0841; found: 337.0840.

2-((dimethoxyphosphoryl)oxy)-4-methylphenyl acetate (150e). 25.5 mg, 62% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.21 (s, 1H), 7.03 – 6.95 (m, 2H), 3.85 (d, $J = 11.4$ Hz, 6H), 2.34 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.7, 141.8, 138.9 (d, $J = 7.0$ Hz), 137.2, 126.2, 123.3, 121.6 (d, $J = 3.0$ Hz), 55.0 (d, $J = 6.0$ Hz), 21.0, 20.6; ^{31}P NMR (162 MHz, CDCl_3) δ -4.4; FTIR (NaCl, neat): ν 1769, 1595, 1510, 1371, 1279 cm^{-1} ; HRMS (ESI, $\text{C}_{11}\text{H}_{16}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 275.0685; found: 275.0680.

4-(tert-butyl)-2-((dimethoxyphosphoryl)oxy)phenyl acetate (150f). 31.3 mg, 66% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 1H), 7.19 (dd, $J = 8.5$, 2.2 Hz, 1H), 7.05 (dd, $J = 8.5$, 1.0 Hz, 1H), 3.85 (d, $J = 11.4$ Hz, 6H), 2.32 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.8, 150.5, 141.6 (d, $J = 7.0$ Hz), 138.7, 123.0, 122.6, 118.5 (d, $J = 2.0$ Hz), 55.0 (d, $J = 6.0$ Hz), 34.7, 31.2, 20.6; ^{31}P NMR (162 MHz, CDCl_3) δ -4.4; FTIR (NaCl, neat): ν 1769, 1591, 1504, 1368, 1269 cm^{-1} ; HRMS (ESI, $\text{C}_{14}\text{H}_{22}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 317.1154; found: 317.1158.

2-((dimethoxyphosphoryl)oxy)-4-methoxyphenyl acetate (150g). 27.9 mg, 64% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.03 (d, $J = 8.9$ Hz, 1H), 6.97 (d, $J = 2.8$ Hz, 1H), 6.71 (dd, $J = 8.9$, 2.8 Hz, 1H), 3.85 (d, $J = 11.4$ Hz, 6H), 3.79 (s, 3H),

2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 157.9, 142.6 (d, $J = 7.0$ Hz), 134.8, 123.9, 110.8, 107.2 (d, $J = 3.0$ Hz), 55.8, 55.0 (d, $J = 6.0$ Hz), 20.5; ^{31}P NMR (162 MHz, CDCl_3) δ -4.5; FTIR (NaCl, neat): ν 1769, 1620, 1514, 1371, 1285 cm^{-1} ; HRMS (ESI, $\text{C}_{11}\text{H}_{16}\text{O}_7\text{P}$ (M+H) $^{+}$): calcd.: 291.0634; found: 291.0634.

3-chloro-2-((dimethoxyphosphoryl)oxy)phenyl acetate (150h). 30.1 mg, 68% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, $J = 7.8$ Hz, 1H), 7.18 – 7.07 (m, 2H), 3.92 (d, $J = 11.5$ Hz, 6H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 143.1 (d, $J = 3.0$ Hz), 139.6 (d, $J = 7.0$ Hz), 127.8, 127.5 (d, $J = 5.0$ Hz), 125.7 (d, $J = 1.0$ Hz), 122.7, 55.4 (d, $J = 6.0$ Hz), 20.7; ^{31}P NMR (162 MHz, CDCl_3) δ -4.7; FTIR (NaCl, neat): ν 1779, 1587, 1470, 1371, 1265 cm^{-1} ; HRMS (ESI, $\text{C}_{10}\text{H}_{13}\text{ClO}_6\text{P}$ (M+H) $^{+}$): calcd.: 295.0138; found: 295.0159.

methyl 3-acetoxy-2-((dimethoxyphosphoryl)oxy)-5-methylbenzoate (150i). 25.3 mg, 53% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 1.9$ Hz, 1H), 7.13 (d, $J = 2.0$ Hz, 1H), 3.89 (d, $J = 12.1$ Hz, 6H), 3.85 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 165.1, 142.4 (d, $J = 3.0$ Hz), 139.2 (d, $J = 7.0$ Hz), 135.6 (d, $J = 2.0$ Hz), 129.1, 128.3 (d, $J = 2.0$ Hz), 125.0 (d, $J = 3.0$ Hz), 55.2 (d, $J = 6.0$ Hz), 52.3, 20.7; ^{31}P NMR (162 MHz, CDCl_3) δ -4.2; FTIR (NaCl, neat): ν

1778, 1732, 1614, 1485, 1371, 1323 cm^{-1} ; HRMS (ESI, $\text{C}_{13}\text{H}_{18}\text{O}_8\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 333.0739; found: 333.0734.

methyl 3-acetoxy-2-hydroxy-5-methylbenzoate (150i-i). 8.1 mg, 24% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 10.70 (s, 1H), 7.54 (d, $J = 1.3$ Hz, 1H), 7.07 (d, $J = 2.0$ Hz, 1H), 3.94 (s, 3H), 2.34 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 168.9, 151.3, 138.8, 129.5, 128.2, 127.2, 113.4, 52.4, 20.6, 20.4; FTIR (NaCl, neat): ν 3165, 1771, 1682, 1620, 1479, 1443, 1346 cm^{-1} ; HRMS (ESI, $\text{C}_{11}\text{H}_{13}\text{O}_5$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 225.0763; found: 225.0772.

2-((dimethoxyphosphoryl)oxy)phenyl acetate (150j). 22.2 mg, 57% yield; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, $J = 7.5$ Hz, 1H), 7.25 – 7.11 (m, 3H), 3.85 (d, $J = 11.4$ Hz, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.4, 142.3 (d, $J = 6.0$ Hz), 141.3, 126.9, 125.6, 123.8, 121.1 (d, $J = 3.0$ Hz), 55.0 (d, $J = 6.0$ Hz), 20.6; ^{31}P NMR (162 MHz, CDCl_3) δ -4.4; FTIR (NaCl, neat): ν 1769, 1599, 1495, 1371, 1285 cm^{-1} ; HRMS (ESI, $\text{C}_{10}\text{H}_{14}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^{+}$): calcd.: 261.0528; found: 261.0542.

2-((dimethoxyphosphoryl)oxy)-1,3-phenylene diacetate (150j-i). 32.0 mg, 67% yield; yellow solid; m.p. 73 – 75 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.24 – 7.16 (m, 1H), 7.07 (d, $J = 8.3$ Hz, 2H), 3.85 (d, $J = 11.5$ Hz, 6H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.2, 143.0 (d, $J = 4.0$ Hz), 134.9 (d, $J = 7.0$ Hz), 125.0, 121.2, 55.2 (d, $J = 7.0$ Hz), 20.6; ^{31}P NMR (162 MHz, CDCl_3) δ -4.4; FTIR (NaCl, neat): ν 1769, 1605, 1472, 1368, 1271 cm^{-1} ; HRMS (ESI, $\text{C}_{12}\text{H}_{16}\text{O}_8\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 319.0583; found: 319.0559.

LIST OF PUBLICATIONS

1. Chan, L. Y.; Kim, S.; Chung, W. T.; Long, C.; Kim, S. Fe(OTf)₃-Catalyzed Reaction of Benzylic Acetates with Organosilicon Compounds. *Synlett* **2011**, 415.
2. Chan, L. Y.; Lim, J. S. K.; Kim, S. Iron-Catalyzed Reductive Dehydroxylation of Benzylic Alcohols Using Polymethylhydrosiloxane (PMHS). *Synlett* **2011**, 2862.
3. Chan, L. Y.; Kim, S.; Park, Y.; Lee, P. H. Iron(III)-Catalyzed Conia-ene Cyclization of 2-Alkynic 1,3-Dicarbonyl Compounds. *J. Org. Chem.* **2012**, 77, 5239.
4. Chan, L. Y.; Kim, S.; Ryu, T.; Lee, P. H. Palladium-Catalyzed *ortho*-Alkenylation of Aryl Hydrogen Phosphates Using A New mono-Phosphoric Acid Directing Group. *Chem. Commun.* **2013**, 49, 4682.
5. Chan, L. Y.; Cheong, L.; Kim, S. Pd(II)-Catalyzed *ortho*-Arylation of Aryl Phosphates and Aryl Hydrogen Phosphates with Diaryliodonium Triflates. *Org. Lett.* **2013**, 15, 2186.
6. Chan, L. Y.; Meng, X.; Kim, S. *ortho*-Acetoxylation of Phosphonic and Phosphoric Monoacids via Pd(II) Catalysis. *J. Org. Chem.* **2013**, 78, 8826.

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