NANYANG TECHNOLOGICAL UNIVERSITY

PART I. TUNGSTEN-CATALYZED CYCLIZATION OF ALKYNE DERIVATIVES
PART II. PALLADIUM-CATALYZED C−H BOND FUNCTIONALIZATION OF BENZYLIC PHOSPHONIC MONOESTERS

MENG XIANGJIAN

SCHOOL OF PHYSICAL AND MATHMATICAL SCIENCE

2013

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School of Physical and Mathematical Sciences

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

2013

DEDICATION

I would like to dedicate this thesis to my father Wu Xinping, mother Meng Xiaolan, brother Wu Tao, sister Wu Zhanzhan, my uncles and aunts for their care and support.

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ABSTRACT

The work of this thesis has been directed towards the development of tungsten-catalyzed chemistry in the transformation of alkyne derivatives, and palladium-catalyzed functionalization of benzylic phosphonic monoesters via C−H activations. This thesis is divided into two parts:

- Part I is aimed at exploring novel approaches for the synthesis of heterocycles via cylization of alkyne derivatives employing tungsten catalysis. Chapter 1 gives an introduction to tungsten catalysis and its application in the formation of heterocycles via cyclization of alkyne derivatives. Chapter 2 describes the tungsten-catalyzed cyclization of *N*-propargylic amides to afford the corresponding oxazolines or oxazines via 5-*exo*-dig or 6-*endo*-dig mode. Chapter 3 details the tungsten-catalyzed cyclization of *α*-alkynyl-*β*-keto acids, keto esters, and diketones to afford methylenelactones, furans, and methylenecyclopentanes via 5-*exo*-dig cyclization under photo conditions. Also, the present approach could be further applied to 5-*endo*-dig cyclization. In addition, pyrroles, pyridines and isoquinolines were also efficiently synthesized via cyclization of alkyne derivatives tethered to nitrogen nucleophiles under thermal conditions in the presence of tungsten catalysis.
- Part II is aimed at exploring phosphoryl-related directing groups-assisted C−H activation reactions employing palladium catalysis. Chapter 4 gives an introduction of palladium-catalyzed directing-group-assisted olefination and arylation of aryl C−H bonds in recent decades and a brief discussion of related mechanisms. In Chapter 5, the new monophosphonic acid directing group was successfully utilized in the Pd(II)-catalyzed *ortho*-olefination and acetoxylation of benzylic phosphonic monoesters. The synthetic utility of *ortho*-olefination was

exemplified by the application of the newly formed olefinated products in Horner-Wadsworth-Emmons reactions. In Chapter 6, the new mono-phosphonic acid-directing group was successfully utilized in the Pd(II)-catalyzed *ortho*-arylation of benzylic phosphonic monoesters with potassium aryltrifluoroborates. A wide range of benzylic phosphonic monoesters underwent clean *ortho*-arylation in high yields and excellent functional group tolerance was also observed. The newly formed arylated products were also successfully applied in Horner-Wadsworth-Emmons reactions. The success of the work in Chapter 4 and 5 offers further development of other phosphoryl-related directing groups in the transition-metal-catalyzed C−H activations.

PUBLICATIONS

1. "Palladium(II)-Catalyzed *ortho*-Arylation of Benzylic Phosphonic Monoesters Using Potassium Aryltrifluoroborates" **Meng, X.**; Kim, S. *J. Org. Chem.* **2013**, *78*, 11247.

2. "*ortho*-Acetoxylation of Phosphonic and Phosphoric Monoacids via Pd(II) Catalysis" Chan, L. Y.; **Meng, X.**; Kim, S. *J. Org. Chem.* **2013**, *78*, 8826.

3. "Palladium(II)-Catalyzed *ortho*-Olefination of Benzylic Phosphonic Monoesters" **Meng, X.**; Kim, S. *Org. Lett.* **2013**, *15*, 1910.

4. "$W(CO)_5$(L)-Catalyzed Cyclization of α-Alkynyl-β-dicarbonyl Derivatives: Synthesis of Methylenelactones, Furans, and Methylenecyclopentanes" **Meng, X.**; Kim, S. *Synlett* **2012**, *13*, 1960.

5. "Tungsten and Molybdenum Catalyst-Mediated Cyclization of *N*-propargyl Amides" **Meng, X.**; Kim, S. *Org. Biomol. Chem*. **2011**, *9*, 4429.

6. "Radical Alkylations of Alkyl Halides and Unactivated C−H Bonds Using Vinyl Triflates" Lee, J. Y.; Lim, K.-C.; **Meng, X.**; Kim, S. *Synlett* **2010**, *11*, 1647.

ABBREVIATIONS

Ac	acetate
AIBN	2,2'-azo *bis*isobutyronitrile
Am	amyl (*n*-pentyl)
Boc	*tert*-butyloxycarbonyl
BQ	benzoquinone
Bu	butyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Equiv	equivalent
ESI	electrospray ionization
GC	gas chromatography
HRMS	high-resolution mass spectrometry

HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
IBX	*o*-iodoxybenzoic acid
IPA	isopropyl alcohol
^{i}Pr	isopropyl
KIE	kinetic isotope effect
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Mes	mesityl
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine oxide
OAc	acetocy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
p-TsOH	*p*-toluenesulfonic acid
SET	single electron transfer
TBAB	tetra-*n*-butylammonium bromide
TLC	thin layer chromatography
TMS	trimethylsilyl

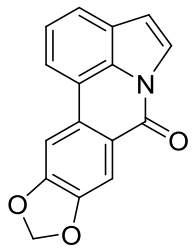
α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1. Group *VI* Metal Carbonyl Complexes-Catalyzed Functionalization of Alkyne Derivatives

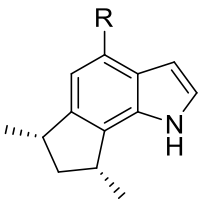
1.1 Introduction

Transition metal catalysts have revolutionized the synthetic methodologies employed to generate new C−C and C−X bonds over the past half century. This is because they have allowed synthetic chemists to design catalytic processes that highly increase the overall efficiency and selectivity.[1] In particular, intramolecular nucleophilic addition onto C−X multiple bonds activated by a catalytic amount of transition metals has been established as an effective cyclization strategy for the construction of ring scaffolds,[2] which are the core frameworks in various biologically active natural products such as Happadine **1**,[3] (-)-Herbindoles A, B, and C **2**,[4] (+)-Acanthodoral **3**[5] etc (Figure 1.1).

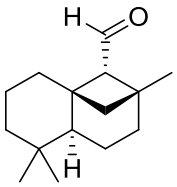
Figure 1.1 Natural Products Synthesized via Transition-Metal Mediated Cyclization Reactions



Happadine **1**



(-)-Herbindoles A, B, and C **2**

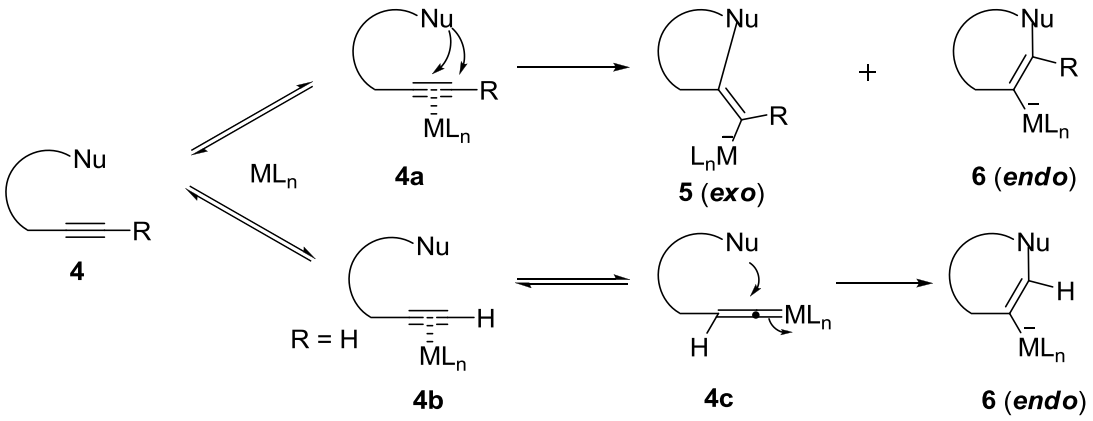


(+)-Acanthodoral **3**

Functionalization of alkyne derivatives is one of the most important and useful transformations due to its widespread applications in synthetic organic chemistry and materials science.[6] In recent decades, electrophilic activation of alkynes through π-complex or its corresponding vinylidene complex formation has been extensively investigated for efficient construction of useful molecules using a large variety of transition-metal complexes, including Au(I),[7] Au(III),[8] Pt(II),[9] Ru(II)[10] etc.

The intramolecular addition of heteronucleophiles onto metal-activated alkynes is a powerful strategy for the synthesis of a novel cyclic carbon skeleton. These approaches have been successfully applied in the synthesis of a vast majority of heteroaromatic compounds such as indoles,[11] benzofurans,[12] pyrroles[13] etc. The proposed mechanism for this process involves the fast and reversible formation of alkyne-π-complex **4a**, **4b** or the corresponding isomerized vinylidene complex **4c** as outlined in Scheme 1.1.[14] The site-formed metal-alkyne complexes are reactive enough to react with nucleophiles. Subsequent nucleophilic addition onto the activated alkyne moiety generates vinyl transition-metal *exo*-species **5** or *endo*-species **6**, which may then undergo various further transformations leading to the desired heterocycles.

Scheme 1.1 General Strategies for Transition-metal Catalyzed Cyclization of Alkyne Derivatives

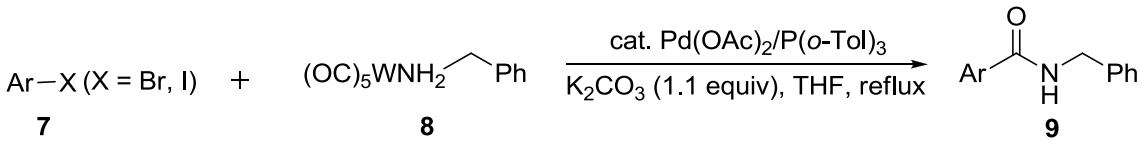


As we all know, Group *VI* metal carbonyl complexes such as $M(CO)_5(L)$ (M = Cr, Mo, W; L = THF, Et_3N etc) exhibit the unique characteristics of catalytic activation of alkynes toward nucleophilic addition.[15] The equilibrium exists between their alkyne-π-complexes and/or their vinylidene complexes especially for the process of activating terminal alkynes. The central carbon of such vinylidene complex shows highly electrophilic character which arise from the electron-withdrawing nature of $W(CO)_5$. This guarantes the subsequently nucleophilic addition to occur at the α position of the alkyne, thus

achieving the *endo* mode cyclization.[16] Based on such unique ability, Group *VI* metal carbonyl complexes have been employed in conversion of various alkynes to bioactive heterocyclic compounds and natural products.[17]

Besides the wide application in functionalization of alkyne derivatives, Group *VI* metal carbonyl complexes were also used in other useful organic reactions. For example, Yamane's group found that amine-substituted $W(CO)_5$ could be employed as nucleophilic acylation reagents to participate in palladium-mediated carbamoylation of aryl halides (Scheme 1.2).[18] $Mo(CO)_6$ was found to be an effective and selective reducing reagent for isoxazoles, azides and nitro compounds etc.[19] Meanwhile, $Mo(CO)_6$ also acts as a catalyst and takes part in the oxidizing process for the preparation of *E* or *Z* enediones via the oxidation of 2,5-dialkylfurans in the presence of cumyl hydroperoxide oxidizing reagent.[20]

Scheme 1.2 $Pd(OAc)_2$-Catalyzed Carbamoylation of Aryl Halides with Tungsten Carbonyl Amine Complex.



The current chapter will mainly focus on the Tungsten and Molybdenum carbonyl complexes-catalyzed transformations of alkyne derivatives to construct carbocyclic and heterocyclic compounds. A brief discussion of some mechanisms and application in total synthesis of natural products will be included.

1.2 Group *VI* Metal Carbonyl Complexes-Catalyzed Cyclization of Alkyne Derivatives

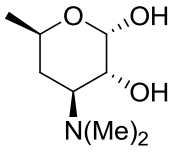
The high coordination number of group *VI* metal hexacarbonyl, the readily available π-allyl and π-alkyne complexes, and numerous evidences from reported literatures

regarding their susceptibility towards nucleophilic attack have attracted much attention from chemistry community.[21] During the last several decades, tungsten or molybdenum hexacarbonyl-mediated organic reactions have been widely studied. In particular, $W(CO)_5(L)$- or $Mo(CO)_5(L)$-catalyzed cyclization of alkyne derivatives has received much attention during the past two decades.[22]

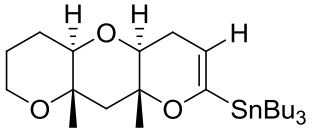
The group *VI* metal hexacarbonyls require activation before acting the role of catalyst. Generally, it can be activated under thermal treatment or by UV irradiation in activating solvent, which involves the dissociation of C=O forming unsaturated coordinating bonds.[23] Usually, thermal activation proceeds under high temperature,[24] thus using UV irradiation in activating solvent such as THF, toluene, DMSO etc has attracted much attention. Based on reported literatures, group *VI* metal hexacarbonyls can be activated under photo conditions to form the active species such as $M(CO)_5L$ (L = Et_3N, THF, toluene etc), which can activate alkynyl moiety to generate π-alkyne complex or vinylidene complex.[25]

Many important contributions in tungsten or molybdenum hexacarbonyl-mediated cyclization of alkynes are from Iwasawa's and McDonald's group.[26, 27] Iwasawa's group has investigated the formation of novel cyclic and bicyclic compounds quite intensively

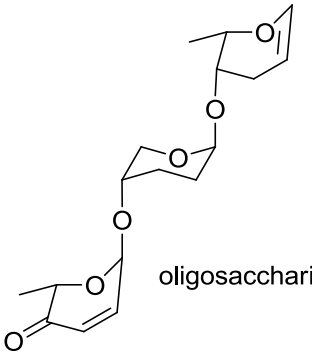
Figure 1.2 Bioactive Substrates Prepared through Tungsten-Catalyzed *endo*-Cycloisomerizations of Alkynyl Alcohols



D-desosamine **10**



trans-syn-trans polypyrans **11**



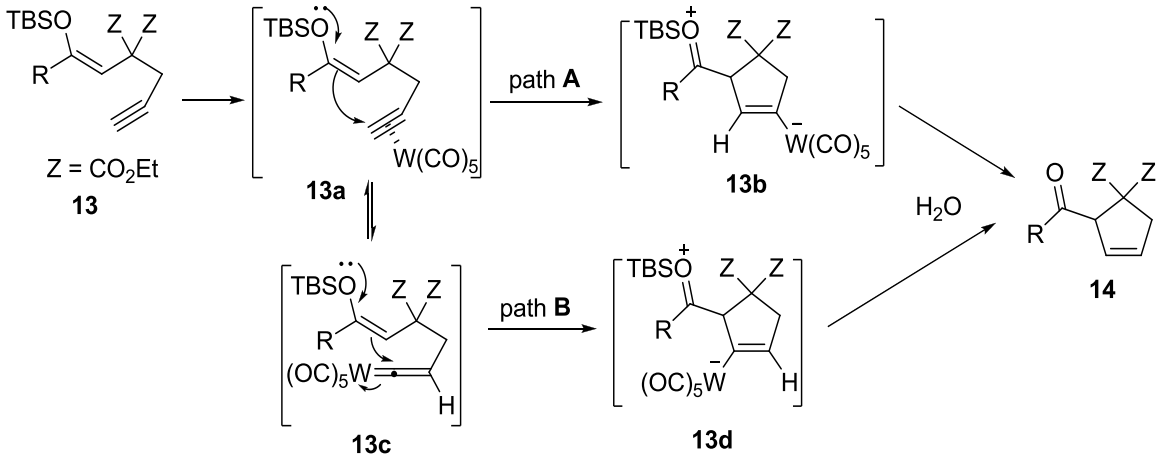
oligosaccharide **12**

using $W(CO)_5(THF)$ as the catalyst. The concept of Iwasawa's group involved the intramolecular nucleophilic attack of enolates (or their equivalents) onto alkynes, which was activated by tungsten under photo irradiation, to afford the corresponding *exo* and *endo* cyclized products. McDonald and co-workers have studied *endo*-cycloisomerizations of alkynyl alcohols and other alkynes tethered with nucleophiles as well as their synthetic applications in preparation of drugs and bioactive substrates such as D-desosamine **10**,[28] polypyrans **11**[29] and oligosaccharide **12** (Figure 1.2).[30]

1.2.1 Cyclization of Alkyne Derivatives Using Enol Ethers as Nucleophilic Group

Using suitable nucleophiles to attack the activated alkyne complex, Iwasawa group achieved several useful intramolecular *endo*-mode cyclization processes. They first explored the possibility of tungsten-promoted *endo*-cyclization of ω-acetylenic silyl enol ether **13**, in which silyl enol ether took on the role of a nucleophile (Scheme 1.3).[31] The reaction conditions were mild and the corresponding cyclized products were isolated in good yield without observing any isomerized byproducts. One of the notable features of such reaction was the *endo* mode of cyclization dominated by all substrates. They proposed two possible mechanistic pathways as shown in Scheme 1.3 and assumed the

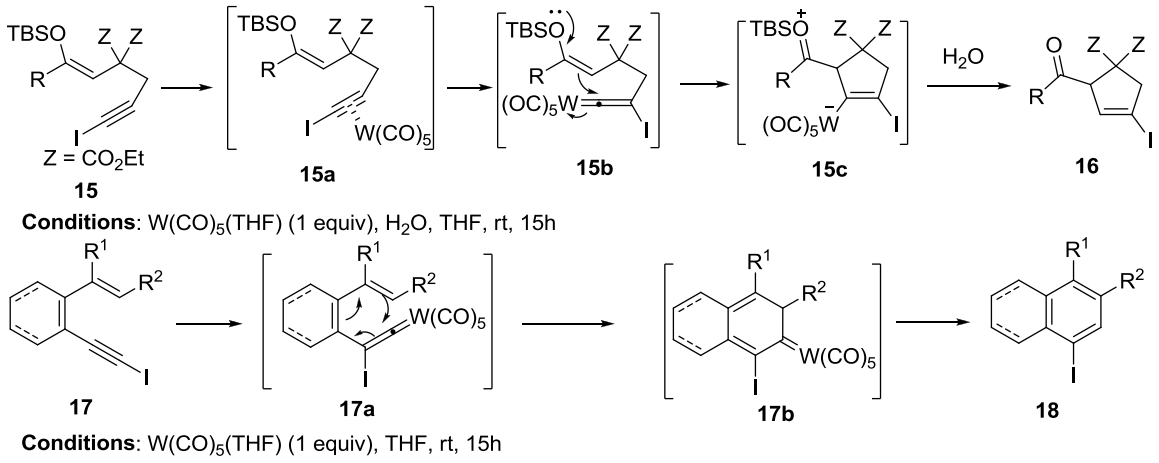
Scheme 1.3 Tungsten-Catalyzed Cyclization of ω-Acetylenic Silyl Enol Ethers



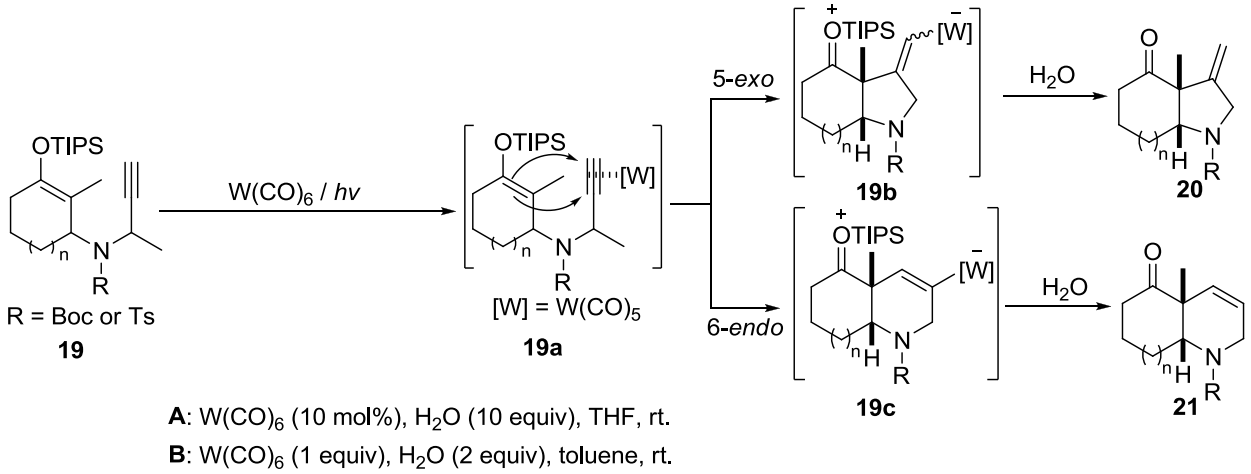
reaction to go through the key intermediate as either a η^2-alkyne complex **13a** or vinylidene complex **13c**.

In $W(CO)_5$(THF)-catalyzed cyclization of iodinealkynes **15**, the *endo*-cyclization proceeded through the iodinated vinylidene complex and succeeded to install a substituent onto the newly formed olefin bonds to give **16** (Scheme 1.4.[32]Similarly, *o*-(iodoethynyl)-styrene (**17**) was also smoothly converted to the desired products **18** under such conditions. This method was a valuable development due to the potential of iodine-retained cyclized products in further coupling reactions.

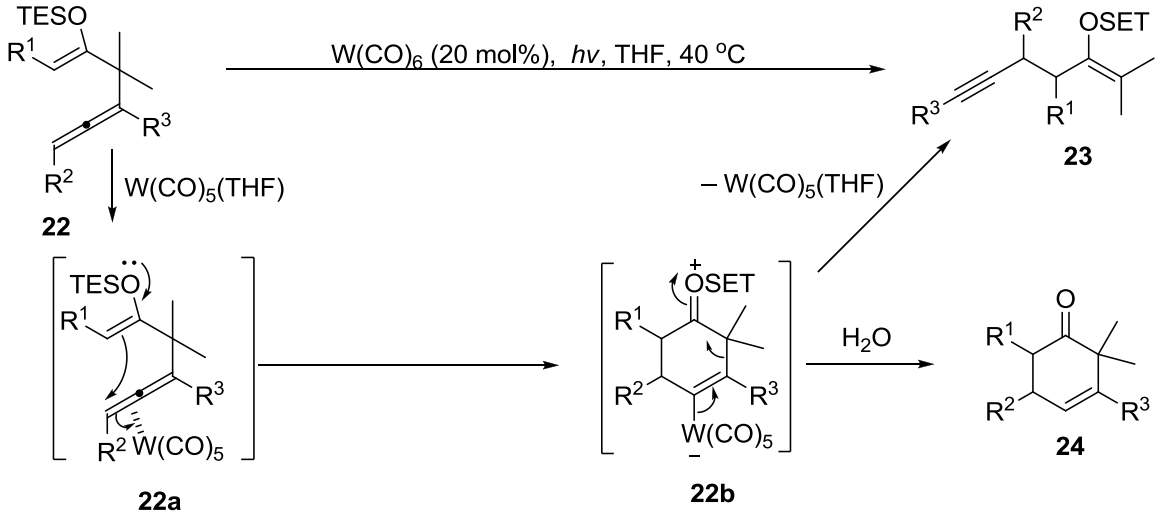
Scheme 1.4 Tungsten-Catalyzed Cyclization of Iodoalkynes



Scheme 1.5 Tungsten-Catalyzed Cyclization of ω-Acetylenic Silyl Enol Ethers



Scheme 1.6 Tungsten-Catalyzed Formal Cope Rearrangement of Allenyl Enol Ethers



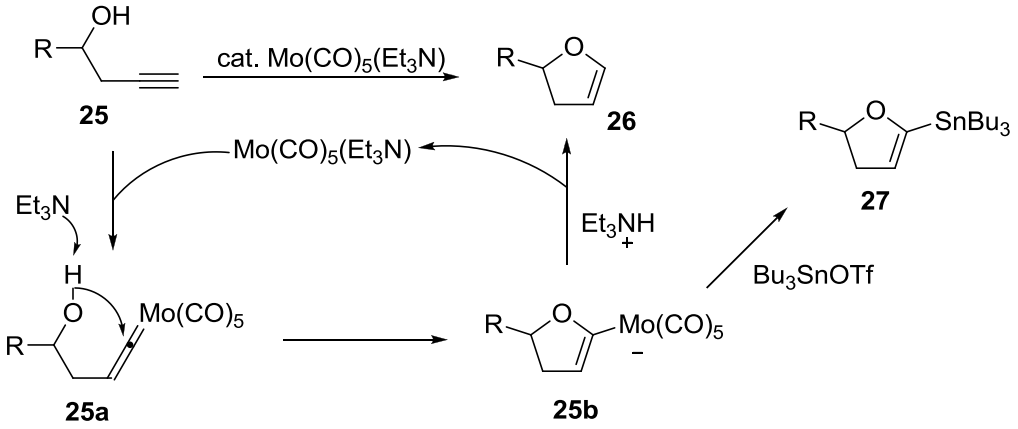
This synthetic strategy was further extended to prepare *N*-heterocycle **20** and **21** via 6-*endo* and 5-*exo* ring closure (Scheme 1.5).[33] The ratio of *endo*- and *exo*-products was very sensitive to the reaction conditions in this case.

Apart from activating alkynes, $W(CO)_6$ also has the ability to activate allene functional group to initiate the formal Cope rearrangememt of **22** to to form **23** in good yields under photoirradiation (Scheme 1.6).[34] The reaction proceeded strictly via 6-*endo* mode to afford the corresponding products and the substitutions on silyl enol ether moiety or allene moiety were well tolorated. The extrusion of water is essential to the reaction system since the conversion of vinylmetallic intermediate to furnish β,γ-unsaturated ketone **24** occurred in the presence of water.

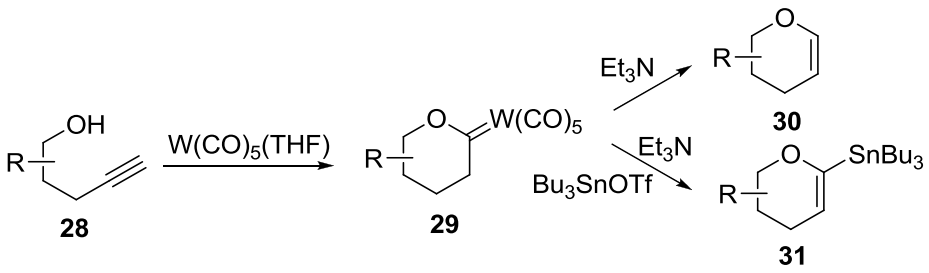
1.2.2 Cyclization of Alkyne Derivatives Using Alcohol as Nucleophilic Group

McDonald's group investigated intensively the use of $Mo(CO)_5(Et_3N)$ and $W(CO)_5(THF)$ catalysts for the *endo*-selective alkynol cycloisomerization reactions and employed such strategy to synthesize important natural products and bioactive substrates.[9-11,35] Their contributions were divided into two parts. Firstly, a catalytic or a stoichiometric amount of $Mo(CO)_5(Et_3N)$ was required to promote cyclization of different 1-alkyne-4-ols **25**.[36]

Scheme 1.7 Molybdenum-Catalyzed Alkynol Cyclization



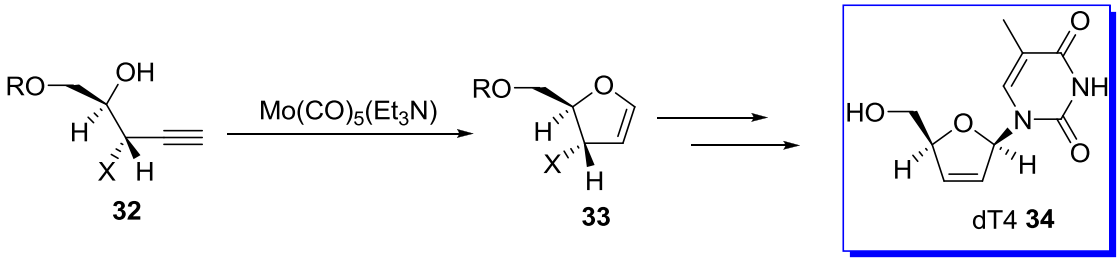
Scheme 1.8 Tungsten-Catalyzed Alkynol Cyclization



Through such approach, a variety of valuable 2,3-dihydrofuran isomers **26** were prepared. However, this method was mainly limited to the formation of five-membered heterocycles (Scheme 1.7). The other contribution was the development of $W(CO)_5$(THF)-mediated cyclization reactions of 1-alkyn-5-ols **28** to construct six-membered rings **30** (Scheme 1.8).[37] The key intermediates of both reactions were confirmed by intercepting them with stannyl reagents leading to the corresponding α-stannyl vinyl ethers **27** and **31**, respectively.

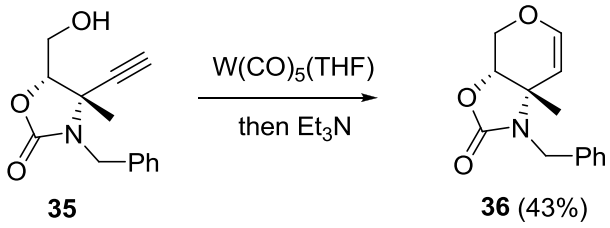
An early example of McDonald's group work involved the formation of a variety of biologically active deoxygenated furanose glycals by $Mo(CO)_5$ mediated cycloisomerization of alkynyl alcohols (Scheme 1.9).[38] The scope of this catalytic system is wide and could tolerate valuable functional groups such as amide and ester. The anti-AIDS β-nucleoside stavudine (d4T) and its derivatives could be stereoselectively

Scheme 1.9 Application in Enantioselective Synthesis of HIV Reverse Transcriptase Inhibitor dT 4



prepared via molybdenum-catalyzed cyclization of 2,3-dideoxyfuranose glycols **32**. Detailed mechanistic studies were carried out and proved that cyclic molybdenum carbene anion was the key intermediate in this catalytic system.

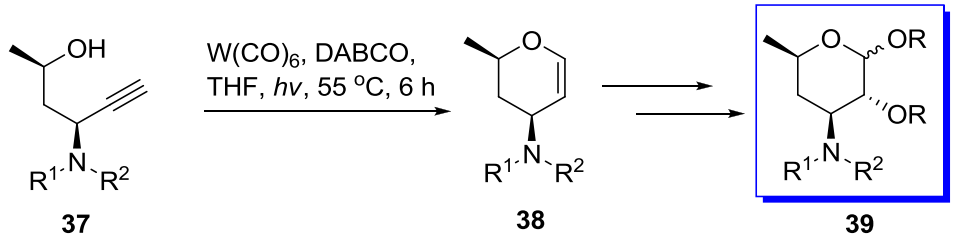
Scheme 1.10 Tungsten-Catalyzed Cyclization of Alkynols



Later, McDonald's group extended their study and also developed the tungsten pentacarbonyl-catalyzed cycloisomerization of alkynyl alcohols to synthesize a variety of pyranose glucals **36** (Scheme 1.10).[39] In this system, free amino group was incompatible due to the coordination with Group *VI* metal carbonyls. Additionally, molybdenum carbonyl complex catalysts were also applicable and provided an alternative procedure to this kind of pyranose glucals.

McDonald's group also applied the tungsten-mediated cycloisomerization of amino-alkynols **37** for stereoselective synthesis of D-desosamine diacetate ester and related Glycals **39** (Scheme 1.11).[40] A serial of different N-substituents were compatible with this methodology. The reaction proceeded via the nearly exclusive *endo*-cyclization for various alkynol substrates to afford stereoselective cyclized products, which was notable

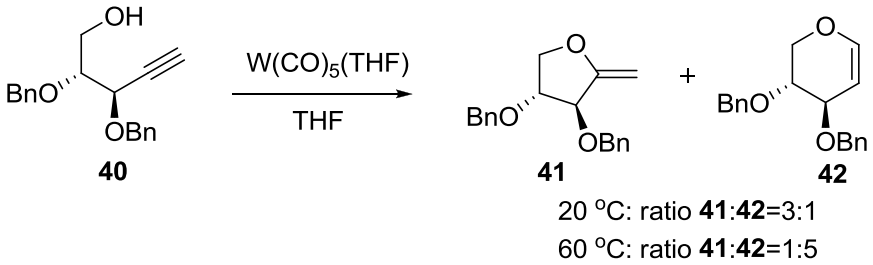
Scheme 1.11 Tungsten-Catalyzed Alkynol *endo*-Cyclization reaction



because the previous methodology could not provide higher regioselectivity for the similar alkynol compounds.

Although *endo*-mode cyclization mostly occurred in tungsten-catalyzed cyclization of alkynols, 1-alkyn-5-ol **40** tended to provide a mixture of *endo* and *exo*-cyclized products (Scheme 1.12).[41] The reaction system was very sensitive to the temperature. For example, the *exo*-product **41** was the major isomer when the reaction temperature was 20 °C, however, the reaction favored *endo*-cyclization at 60 °C.

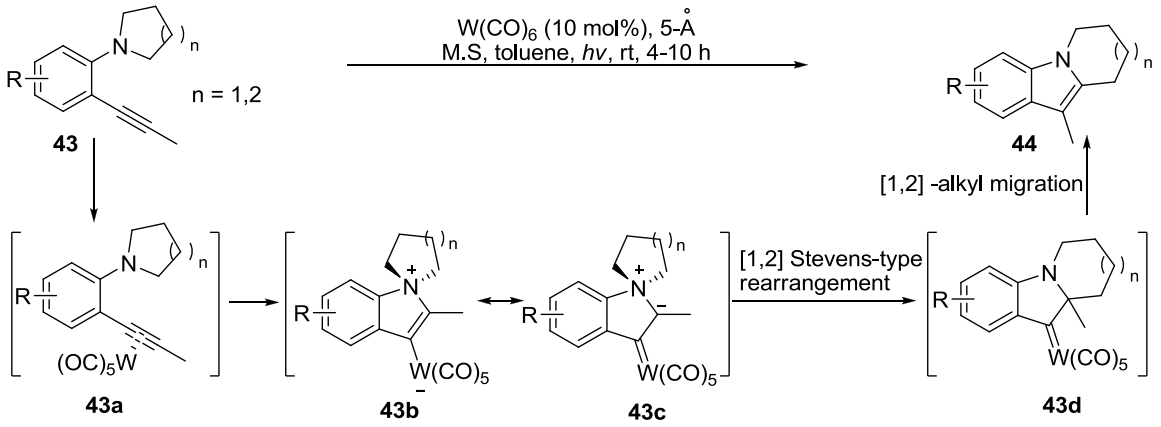
Scheme 1.12 Temperature Dependence on Regioselectivity



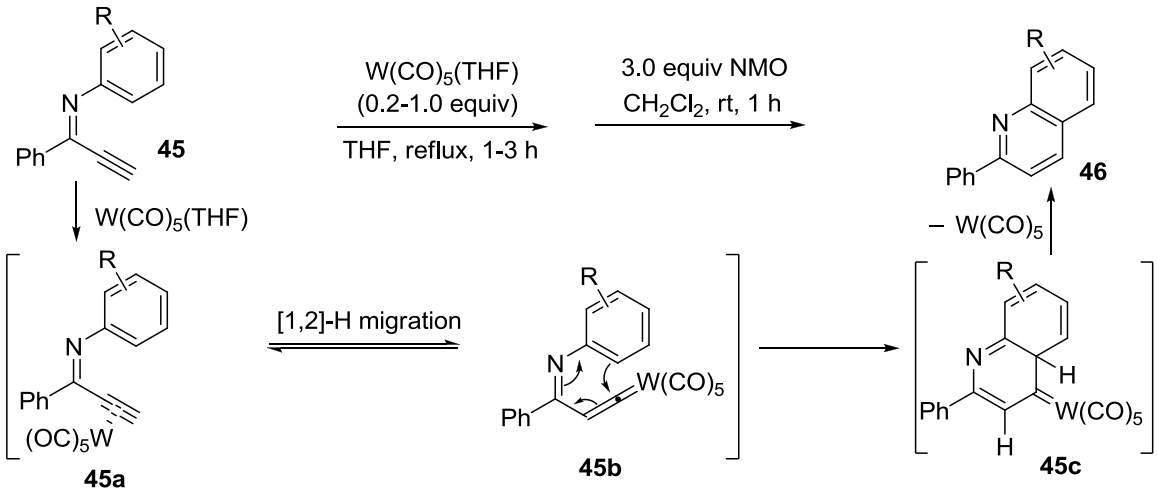
1.2.3 Cyclization of Alkyne Derivatives Using Amine, Carbon and Thiol Nucleophiles

Other nucleophiles involving amine, thiol and carbon anion have also been investigated. For example, an approach to efficiently construct various functionalized *N*-fused tricyclic indoles using $W(CO)_6$ catalyst in toluene under photo conditions has been reported by Iwasawa's group (Scheme 1.13).[42] The use of tertiary amine as the nucleophile to attack the electrophilically activated alkyne-π-complex **43a** provided **43c**, which then underwent

Scheme 1.13 Tungsten-Catalyzed Cyclization of *N*-(2-Alkynylphenyl) Amines



Scheme 1.14 Tungsten-Catalyzed Cyclization of Alkynyl Imines



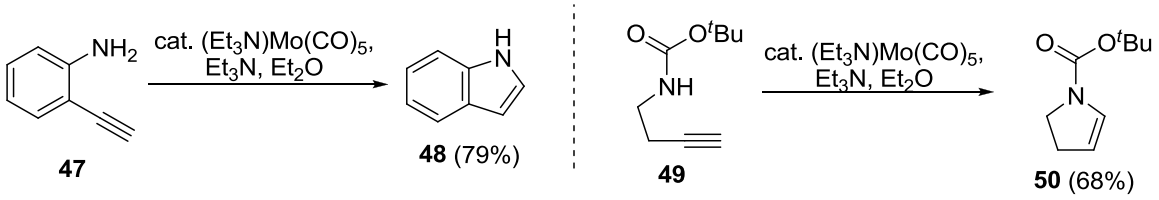
ring expansion to afford carbene complex **43d**. Carbene **43d** then underwent 1,2-alkyl migration to achieve the corresponding indole **44** along with the regeneration of the catalyst.

In 2004, Akiyama's group developed a novel method to construct quinoline skeletons using 20 mol% of $W(CO)_5(THF)$ as the catalyst to promote the [4+2] electrocyclization of alkynyl imines **45** in refluxing THF (Scheme 1.14).[43] Alkynyl imines containing electron -donating or electron-withdrawn substituents on the aniline ring or imine carbon all led to the corresponding products in good yields. The oxidant NMO (*N*-methylmorpholine *N*-

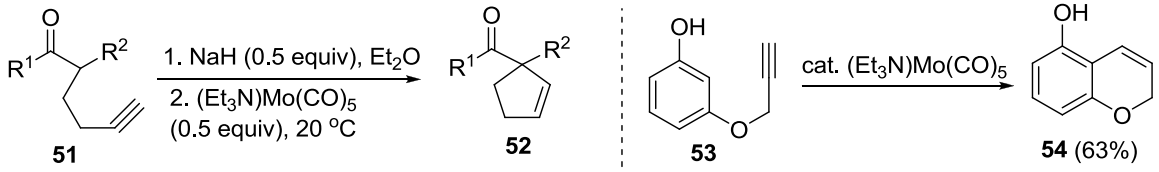
oxide) was used to regenerate the catalyst and the products and thus improving the overall yield.

McDonald's group has studied the effectiveness of several functional groups towards the Group *VI* pentacarbonyl-activated alkynes. They briefly pointed out that alkynyl nitrogen-based substrates such as alkynylaniline **47** and alkynylcarbanate **49** were smoothly cyclized to afford the corresponding indoles and cyclic enecarbamates respectively (Scheme 1.15).[44] Carbon nucleophiles such as activated methylene **51** and phenolic **53** were also successfully employed in the cyclo-isomerization with terminal alkynes (Scheme 1.16).[45] The cyclization of thiol-alkyne substrates **55** in the presence of molybdenum or chromium carbonyls had also been achieved (Scheme 1.17).[38] In this system, the chromium-catalyst procedure appeared to provide better yields. The

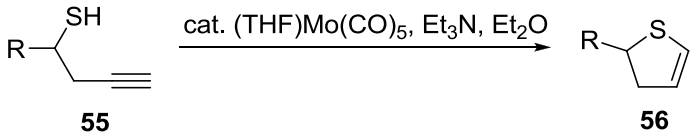
Scheme 1.15 Azacycloisomerization of Alkynyl-nitrogen Compounds



Scheme 1.16 Carbocycloisomerization of Alkynyl-carbon Compounds



Scheme 1.17 Thiacycloisomerization of Alkynyl-sulfur Compounds



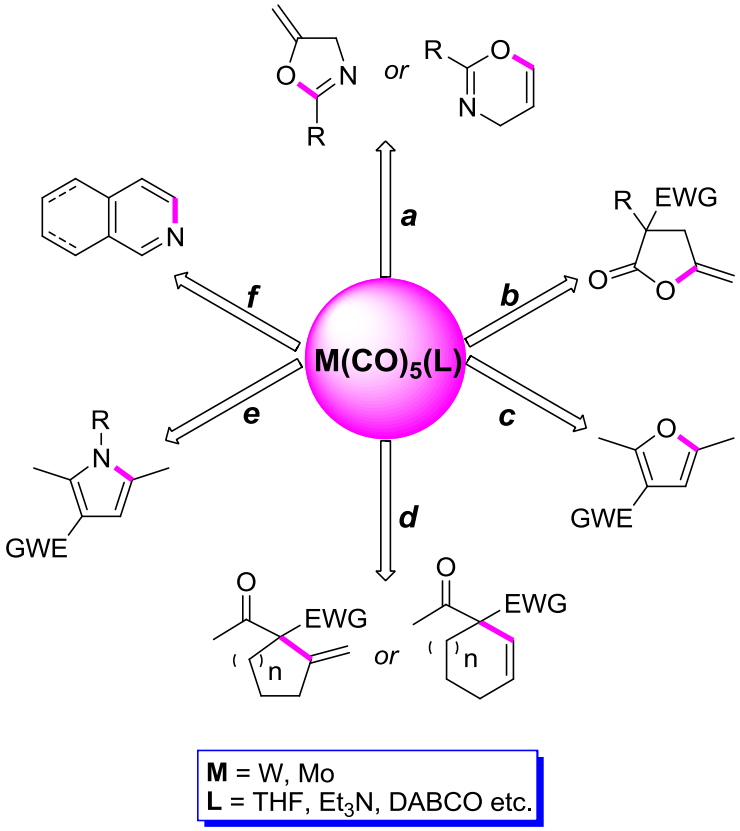
functional group compatibility as shown in earlier schemes remained somehow limited, but the successful results open the possibility of wide application of Group *VI* metal carbonyls in organic transformation.

1.3 Proposed Work

We have been interested in W- and Mo-mediated synthesis of heterocycles and carcycles by activation of alkynes with W and Mo-catalysts togrther with approciate nucleophiles.

In chapter 2, W- and Mo-catalyzed cyclization of *N*-propargyl amides (Figure 1.3a) is investigated and the selectivity of *exo*- and *endo*-cyclization depends very much on the structure of the starting material and the nature of catalysts. In chapter 3, W-catalyzed cyclization of *α*-alkynyl-*β*-dicarbonyl derivatives to afford methylenelactones, furans, and methylenecyclopentanes under photo irradiation conditions (Figure 1.3b-1.3d). In addition, the synthesis of pyrroles, pyridines and isoquinolines via cyclization of terminal alkynes tethered to nitrogen nucleophiles is also presented (Figure 1.3e, 1.3f). The newly

Figure 1.3 W- and Mo-Catalyzed Cyclization of Alkyne Derivatives



developed methods would provide synthetically useful approaches to important heterocyclic compounds.

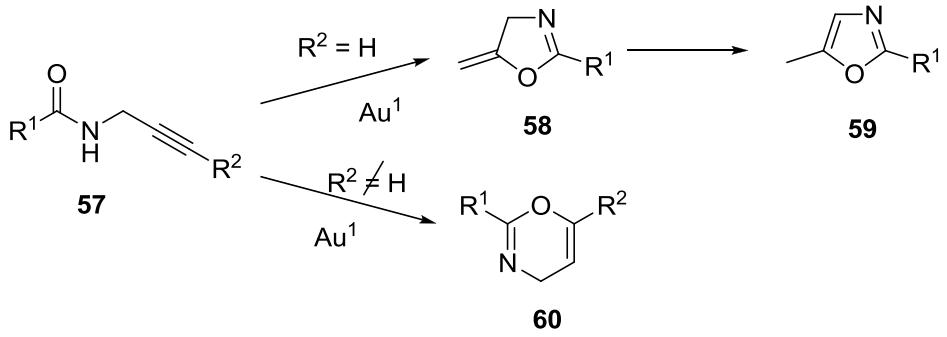
Chapter 2. Tungsten and Molybdenum-Catalyzed Cyclization of *N*-Propargyl Amides

2.1 Introduction

The intramolecular *endo*-selective cyclization of nucleophilic addition onto alkynes is one of the important organic transformations for efficient access to commercially available reagents and useful bioactive compounds.[46] A variety of late transition metals complexes such as Pd, Au and Ru etc have been widely employed to furnish this type of reactions over the several past decades. [47]

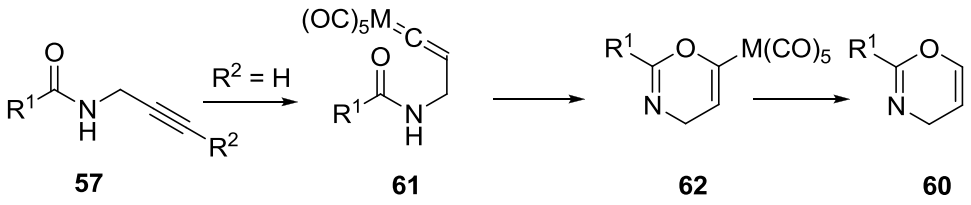
Comparing the numerous novel strategies promoted by late transition metals, related transformations mediated by early transition-metal catalysts such as Mo and W have not been intensively investigated and have scarcely been found in literatures. This is because they are relatively unreactive species as catalysts in synthetic reactions.[48] However, Group *VI* metal carbonyl complexes exhibit special ability of electrophilic activation of terminal alkynes to preferentially afford vinylidene metal complexes, which resulted in the *endo*-selective cyclized products.[49] Therefore, it would be interesting and highly valuable to study the synthetic usefulness of Group *VI* metals for the transformations of alkyne derivatives.

Scheme 2.1 Gold(I)-Catalyzed Cyclization of Propargylic Amides



It is known that a widespread variety of transition metal catalysts including Au,[50] Ag,[51] Cu[52] and Pd[53] have been employed in promoting cyclization of propargylic amides to provide access to oxazoline derivatives. Based on the previously reported literatures, this synthetic approach mainly proceeds via two pathways (Scheme 2.1). The *endo*-mode cyclization reactions occurred usually for alkyl-substituted alkynes, but terminal alkynes preferentially undergo *exo*-mode cyclization in the presence of metals. Additionally, selective synthesis of the oxazoline derivatives without the formation of the corresponding isomerized products remained challenging because they were very sensitive to the reaction conditions and easily undergo aromatization.[54]

Scheme 2.2 Proposed Pathway for Tungsten- or Molybdenum-Mediated Cyclization of Propargylic Amides

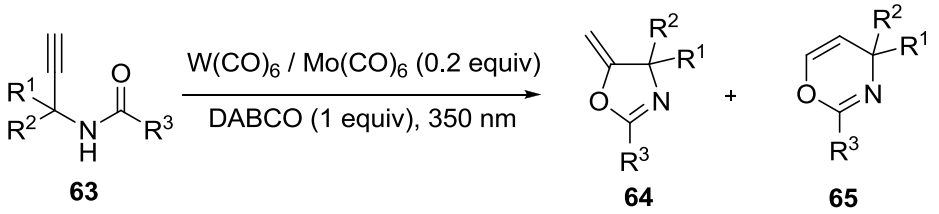


57 **61** **62** **60**

The synthetic utility of Group *VI* carbonyl complexes would be significantly increased by establishing a synthetic method using propargylic amides as starting materials to selectively produce oxazolines or oxazines via the 5-*exo* or 6-*endo* mode cyclization. The selective synthesis of oxazines was difficult, because such mode of cyclization generally occured only for alkyl-substituted alkynes in the presence of transition metals, as mentioned above.[55] Group *VI* carbonyl complexes are known to exhibit the ability to afford vinylidene carbene species in the presence of terminal alkynes. Mechanistically, the *endo*-cyclized oxazines **60** could be selectively obtained via vinylidene complex **61** (Scheme 2.2).[56] On the basis of this hypothesis, we speculated that a Group *VI* carbonyl complexes-catalyzed cyclization of propargylic amides would undergo a *endo*-mode cyclization, thereby leading to the formation of oxazines.

In this chapter, we present the W-and Mo-catalyzed cyclization of propargylic amides to provide access to oxazolines **64** and/or oxazines **65** via the 5-*exo* mode and/or 6-*endo* mode cyclization under photo-assisted conditions (Scheme 2.3). The divergence in product selectivity depends on the structures of the substrates and the employed catalysts.

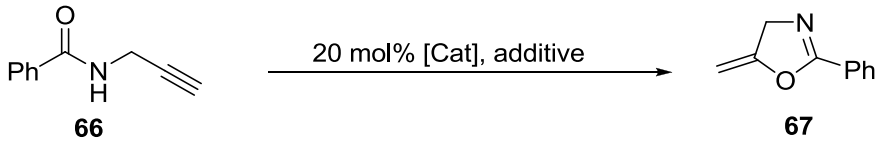
Scheme 2.3 $W(CO)_6$ / $Mo(CO)_6$ -Catalyzed Cyclization of *N*-Propargyl Amides



2.2 Results and Discusssion

At the outset of our investgation, we focused on finding the suitable catalyst under thermal conditions for the cyclization of *N*-propynylbenzamide (**66**) (Table 2.1), which was prepared by treating commercially available propargyl amine with benzoyl chloride in the presence of Et_3N in dichloromethane at room temperature. Trace amount of the cyclized product was initially observed under conditions when using $W(CO)_3(CH_3CN)_3$ as catalyst in refluxing toluene (entry 1).[57] Based on this intriguing observation, the reactions in refluxing CH_3CN and THF were then studied (entries 2 and 3). Unfortunately, no products were isolated and the starting material was recovered. $Mo(CO)_3(DMF)_3$ catalyst was not effective as well and led to the recovery of the model substrate, even after heating the reaction for 20 hours in refluxing THF (entry 4).[58] When using 20 mol% $W(CO)_6$ and 1 equiv Et_3N in refluxing toluene, only a trace amount of product **67** was isolated (entry 5). Similarly, the use of $Mo(CO)_6$ catalyst showed no improvement (entry 6). We then explored this transformation under photo conditions. Treatment of **66** with 20 mol% $W(CO)_6$ and 1 equiv Et_3N in THF under irradiation at 350 nm provided the desired oxazoline **67** in 40 % yield (entry 7). But the reaction did not proceed in the absence of

Table 2.1 $M(CO)_5(L)$-Catalyzed Cyclization of Propargyl Amide **66**



66 **67**

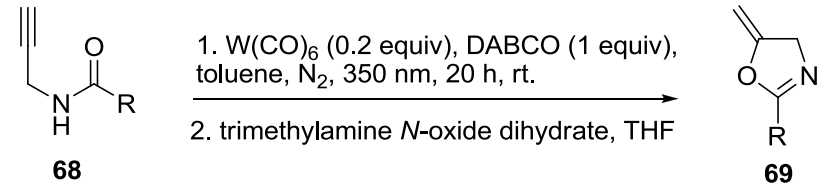
Entry	Cat.	Additive	Solvent	Condition	Time (h)	Yield (%)
1	$W(CO)_3(CH_3CN)_3$	-	Toluene	reflux	10	trace
2	$W(CO)_3(CH_3CN)_3$	-	CH_3CN	reflux	10	0
3	$W(CO)_3(CH_3CN)_3$	-	THF	reflux	20	0
4	$Mo(CO)_3(DMF)_3$	-	THF	reflux	20	0
5	$W(CO)_6$	Et_3N	Toluene	reflux	12	trace
6	$Mo(CO)_6$	Et_3N	Toluene	reflux	12	trace
7	$W(CO)_6$	Et_3N	THF	350 nm	12	40
8	$W(CO)_6$	-	THF	350 nm	12	trace
9	$W(CO)_6$	DABCO	THF	350 nm	12	63
10	$W(CO)_6$	DABCO	Toluene	350 nm	12	73
11	$W(CO)_6$	DABCO	Toluene	350 nm	24	65
12	$Mo(CO)_6$	DABCO	Toluene	350 nm	12	45
13	-	DABCO	Toluene	reflux	10	0

Et_3N and the starting material was recovered quantitatlvely (entry 8). Realizing the importance of a base in this system, the reaction was then performed with DABCO as the alternative base. Good yield was achieved when using tungsten catalyst in the presence of 1 equiv DABCO (entry 9).[59] The yield was improved to 73% by using toluene as the solvent instead of THF under the similar conditions (entry 10). Prolonging the reaction time to 24 hours did not improve the yield at all (entry 11). Changing the catalyst from W to Mo under the same conditions slightly decreased the reaction yield to 45% (entry 12),

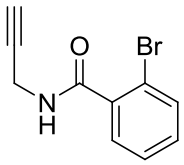
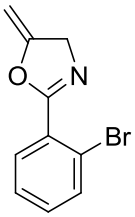
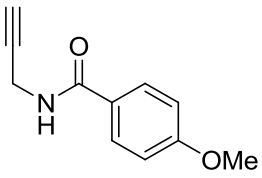
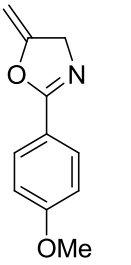
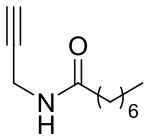
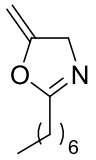
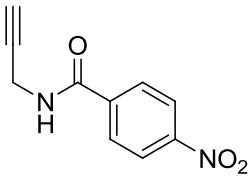
and no reaction was observed when treating the starting material under thermal conditions (entry 13). The reaction conditions leading to 73 % isolated yield were not appealing. The ^{1}H NMR spectrum of the isolated polar complex showed similar characteristics as the corresponding product. The complex was weakly soluble in organic solvent, thus indicating it might be an inorganic complex. Based on the reported literature, [60] we suspected that the corresponding oxazoline product might have coordinated with the tungsten complex, hence resulting in decreasing the overall yield. The oxazoline product was freed from the tungsten-complex after an oxidative treatment with triethylamine *N*-oxide dihydrate, and the overall yield was then improved to 84%. As such, we have obtained the optimized cyclized conditions using 20 mol% $W(CO)_6$ and 1 equiv DABCO in toluene under irradiation at 350 nm for 20 h, followed by the oxidative treatment with triethylamine *N*-oxide dihydrate, to furnish oxazoline compounds. This current approach is attractive because it allows selective formation of an oxazoline via exclusive *exo*-mode cyclization. In addition, the formation of oxazole derived from the isomerization of the corresponding oxazoline was not observed, probably attributing to the mildness of our present photo conditions.

We next examined the influence of an amide moiety by exploring several aromatic substates with different substituents in arene and alkyl amides (Table 2.2). The unsubstituted propargylic amides **68** were easily synthesized by treating commercially available propargyl amine with the corresponding acid chlorides in the presence of triethylamine in dichloromethane at room temperature. 2-Bromo-propargylic amide **68a** was very reactive in current reaction system, thus leading to the corresponding product **69a** with excellent yield (entry 1). The cyclization of 4-methoxy-propargylic amide **68b** proceeded smoothly when employing this catalytic protocol (entry 2). Similarly, alkyl propargylic amide **68c** also cyclized nicely to afford **69c** (entry 3).

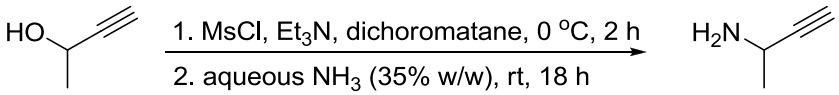
Table 2.2 $W(CO)_6$-Catalyzed Cyclization of Unsubstituted Propargyl Amides



68 **69**

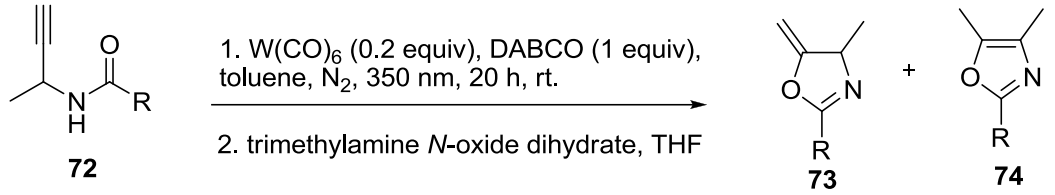
Entry	Substrate		Product		Yield (%)
1		**68a**		**69a**	89
2		**68b**		**69b**	91
3		**68c**		**69c**	83
4		**68d**	-	-	-

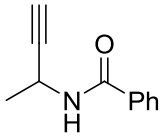
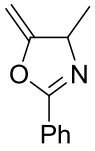
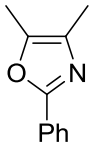
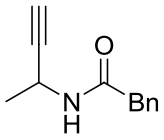
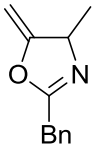
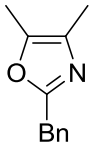
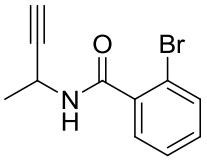
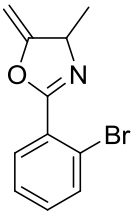
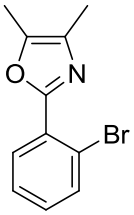
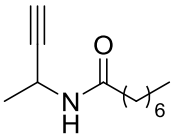
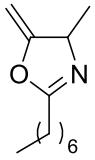
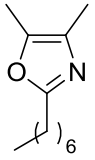
Scheme 2.4 Preparation of 1-Methyl-2-Propynylamine (**71)**



70 **71**

Table 2.3 $W(CO)_6$-Catalyzed Cyclization of Monosubstituted Propargyl Amides



Entry	Substrate	Products		Yield (%) (**73**:**74**)
1	 **72a**	 **73a**	 **74a**	65:33
2	 **72b**	 **73b**	 **74b**	20:83
3	 **72c**	 **73c**	 **74c**	72:22
4	 **72d**	 **73d**	 **74d**	67:25

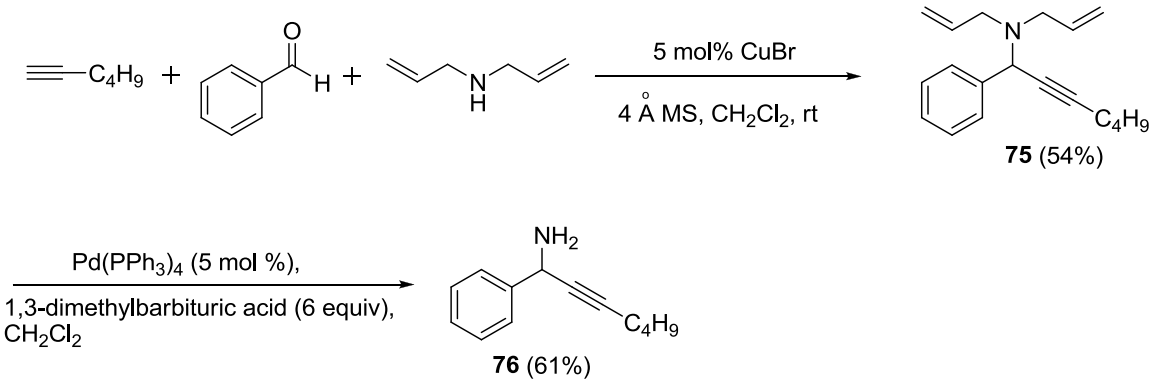
Unfortunately, 4-nitro-propargylic amide **68d** did not undergo cyclization, presumably because of the strongly withdrawing electronic influence of the nitro group (entry 4).

To increase the generality of this W-catalyzed cyclization process, we next examined monoalkyl substituted propargylic amides (Table 2.3). The study was initiated with the

preparation of 1-methyl-2-propynylamine (**71)** in two steps from commercially available 3-butyn-2-ol (**70)** by the reported procedure.[61] The crude 1-methyl-2-propy-nylamine in dicholomethane was used directly for subsequent amidation with the corresponding acid chlorides to give **72** as shown in Table 2.3.

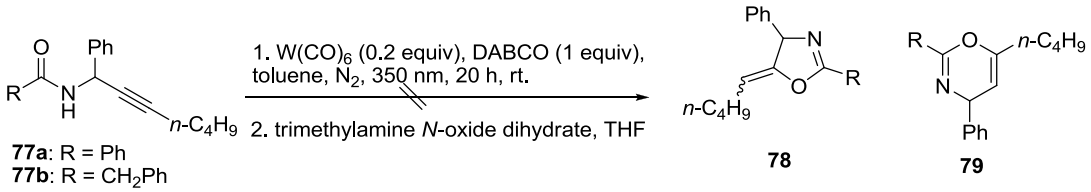
Subsequent cyclization reactions were investigated under optimized conditions. Surprisingly, the isomeric mixture of the oxazoline **73** and oxazole **74** was isolated for *mono*-substituted propargylic amide substrates. This transformation was compatible with the representative functional groups, including phenyl and benzyl groups (entries 1 and 2). In addition, aryl bromide substrate **72c** was also well tolerated (entry 3), which is particularly valuable because the corresponding product could be served as an important coupling partner in further applications. Finally, the reaction with alkyl substrate **72d** proceeded well to give the desired products (**73d**, **74d**) with excellent overall yields (entry 4). We next turned our attention to achieve the complete isomerizarion of oxazoline to oxazole. After completion of the reaction, when the crude mixture of **73a** and **74a** was treated with 2 equiv DABCO for 12 hours at 80 ^{o}C, the isomerization was incomplete, showing 1:1 mixture of **73a** and **74a**. DBU was much more effective than DABCO. Treatment of a mixture of **73a** and **74a** with DBU in benzene at room temperature afforded **74a** in 97% yield.

Scheme 2.5 Preparation of *mono*-Substituted *N*-Propargylic Amine **76**



We then turned our attention to study the cyclization of substituted *N*-propargylic amides in order to extend this catalytic system further. Based on the reported literature procedures, the substituted propargylic amine **76** was prepared as shown in Scheme 2.5. Alkyne, aldehyde and diallylamine was first mixed together in the presence of CuBr catalyst to form the corresponding tertiary amine **75**,[62] followed by removal of the allyl protecting group,[63] to afford the desired substituted propargylic amine **76**. Amidation of newly formed substituted propargylic amine **76** with benzoyl chloride and phenylacetyl chloride afforded **77a** and **77b**, respectively. The optimized cyclization conditions were then applied to substituted *N*-propargylic amides (**77a**, **77b**) as shown in Scheme 2.6. Unfortunately, the reaction did not undergo cyclization to give the corresponding 5-membered oxazoline **78** or 6-membered oxazine **79** and the starting material was revovered quantitatively.[64]

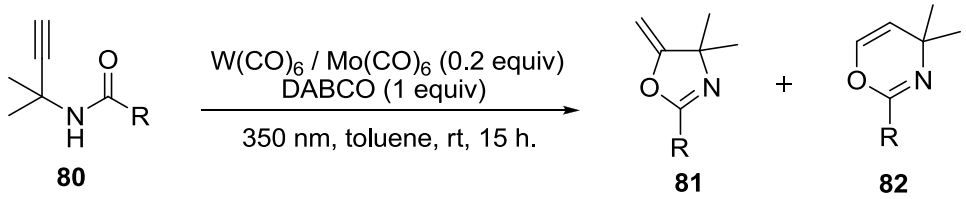
Scheme 2.6 Cyclization of Substituted *N*-Propargylic Amides

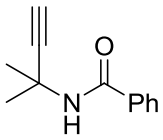
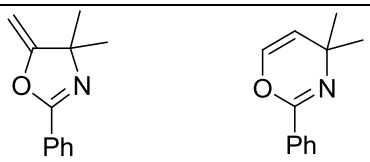
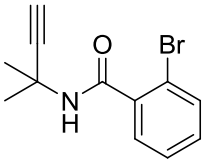
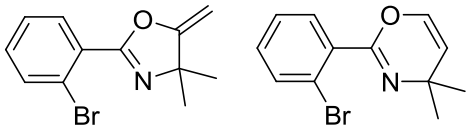
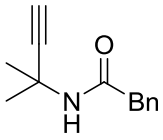
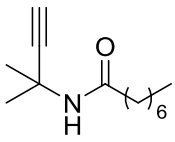
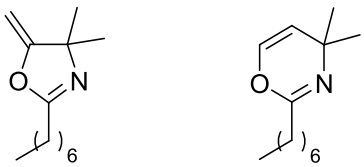


The success of smooth cyclization achieved using unsubstituted and monoalkyl substituted *N*-propargylic amides encouraged us to examine the possibility of cyclizing disubstituted propargylic amides using W and Mo catalysts under the present conditions. The disubstituted propargylic amides illustrated on Table 2.4 were easily prepared by treating the commercially available 1,1-dimethyl-2-propynylamine with the corresponding acid chlorides.

Surprisingly, reaction of disubstituted propargylic amides **80** with W and Mo under optimized conditions as shown in Table 2.4 afforded *endo*-cyclized product oxazines along with oxazolines. The structural versatility of the disubstituted propargylic amides

Table 2.4 Cyclization of Dimethy Substituted Propargyl Amides

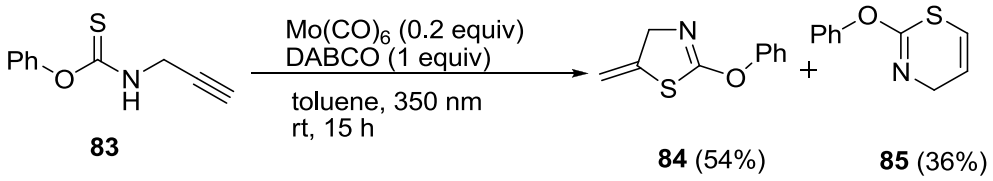


Entry	Substrate	Cat.	Products	Yield (%) (**81**:**82**)
				
1		W		17:78
	80a		**81a** **82a**	
2		Mo		10:85
				
3		W		49:49
	80b		**81b** **82b**	
4		Mo		16:82
				
5		W		69:23
	80c		**81c** **82c**	
6		Mo		8:86
				
7		W		32:63
	80d		**81d** **82d**	
8		Mo		68:27

was then exploited. When the substrate **80a** was employed in the presence of W catalyst, *endo*-mode cyclization was favored, providing the oxazine **82a** as the major product along with trace amont of oxazoline **81a** (entry 1). The Mo catalyst gave the similar result for this substrate (entry 2). However, the similar result was not observed when the reaction was performed with 2-bromo-*N*-propargylic amide **80b** (entry 3). In this case, the catalysts had resulted in different ratio of the corresponding products. Benzyl propargylic amide **80c** gave **81c** (69%) as the major product when using W catalyst, but afforded **82c** with 86% yield when using Mo catalyst (entry 4). For alkyl disubstituted propargylic amide **80d**, $Mo(CO)_6$ preferred to furnish the 6-membered compound **82d** while $W(CO)_6$ favored the formation of the 5-membered compound **81d** (entry 5). Based on the above results, we concluded that the ratio of oxazoline **81** and oxazine **82** depended very much on the structures of the starting materials and the characteristics of the catalyst.

We also used our standard conditions to test the cyclization of thiocarbamate **83**. When substrate **83** was treated with 20 mol% $W(CO)_6$ and 1 equiv DABCO in toluene under irradiation at 350 nm for 15 hours, the reaction did not proceed and the starting material was recovered quantitatively. However, after switching $W(CO)_6$ to $Mo(CO)_6$ catalyst the

Scheme 2.7 Mo-Catalyzed Cyclization of Thiocarbamate

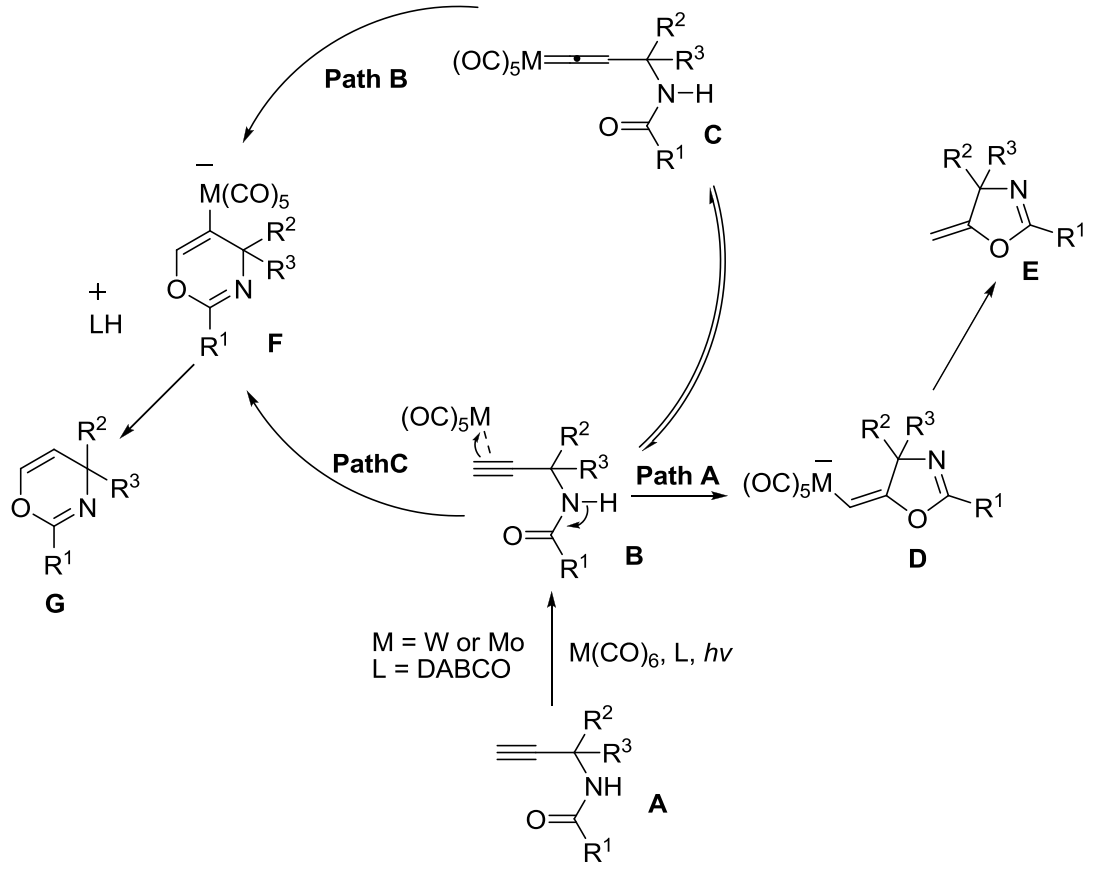


83 **84** (54%) **85** (36%)

Scheme 2.8 Carbamate and Urea

86 **87**

Scheme 2.9 Two Possible Mechanisms



cyclization proceeded well and afforded a mixture of 54% thiazolidine **84** and 36% thiaoxazine **85**. Meanwhile, this cyclization system was also applied to the carbamate **86** and urea **87** (Scheme 2.8). Unfortunately, the cyclization did not proceed at all.

There are two possible mechanistic pathways as shown in Scheme 2.9. The reaction was initiated by the activation of the alkynyl functionality of propargylic amides by coordinating with W and Mo catalysts, resulting in the foramation of π-alkyne complex **B**, whereby **B** and the vinylidene complex **C** were reversible.[11] Intramolecular nucleophilic attack of the carbonyl oxygen on the amides to intermediate **B** via 5-*exo* or 6-*endo* mode, followed by the protonation of the corresponding carbene compounds **D** or **F** would produce oxazoline **E** or oxazine **G**.

2.3 Conclusion

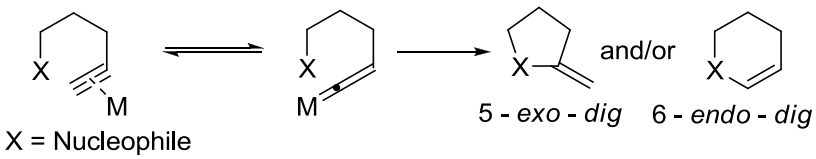
In this work, we have developed a novel and efficient W- and Mo-catalyzed synthetic approach that allowed for the formation of oxazolines and oxazines based on the cyclization of propargylic amides. The value of this method was to generate *endo*-oxazine products efficiently under photo conditions, which were not easily prepared in traditional methods. However, the selectivity of *exo*-and *endo*-cyclization varied as it depended on the structure of the starting materials and the used catalysts. Efforts to address the ratio of two products via adjusting reaction conditions and expanding the scope of this method are required.

Chapter 3. $W(CO)_5(L)$-Catalyzed Cyclization of Alkynyl-Nucleophile Substrates to Methylenelactones, Furans, Methylenecyclopentanes, Pyrroles, Pyridines and Isoquinolines

3.1 Introduction

Transition metal-catalyzed cyclization of alkyne derivatives is one of the important transformations in organic synthesis.[65] Therefore, studies to probe the relationship between the nature of nucleophiles and *exo*- or *endo*-mode ring closure issues in transition metal-mediated reactions remained challenging for synthetic chemists (Scheme 3.1).[66]

Scheme 3.1 Transition Metal-Mediated *exo*-or *endo*-Cyclization



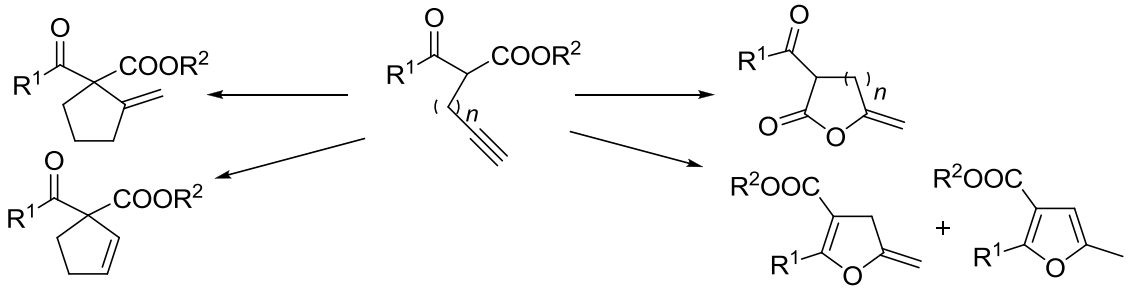
Based on Baldwin's rule, cyclizations of alkynes via 5-*exo*-dig and 6-*endo*-dig are favorable and competitive (Scheme 3.1).[67] Therefore, the regeoselectivity of 5-*exo* and 6-*endo* closures depends upon the nature of the Lewis acid, alkynyl substitution and the nucleophile.[68]

In the previous chapter, we presented tungsten and molybdenum carbonyl-catalyzed *exo*- or *endo*-cyclization of *N*-propargyl amides to oxazolines and oxazines, respectively.[69] Due to the inspiration of this work and our keen pursuit in exploiting the catalytic activity of Group *VI* carbonyl complexes in functionalization of alkynes, we next turned our attention to cyclization of easily available α-alkynyl-β-ketocarbonyl substrates. Oxygen nucleophiles generated from carbonyl group or carbon nucleophiles from the α-position can attack the tungsten-activated alkyne complex. We reasoned that, in the

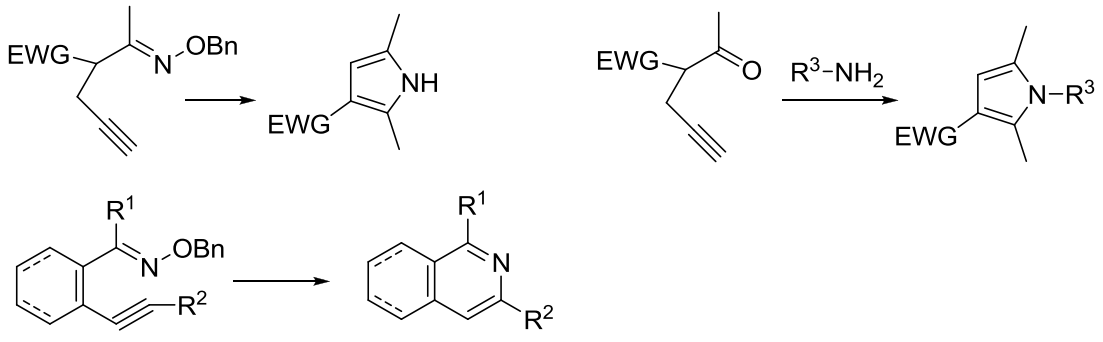
presence of tungsten pentacarbonyl complex, *α*-alkynyl-*β*- ketocarbonyl derivatives would undergo *endo*- or *exo*-cyclization to afford the corresponding methylenelactones, furans and cyclopentenes under mild conditions. Similarly, pyrroles might also be obtained via cyclization of imine derivatives, which were prepared from *α*-alkynyl-*β*-dicarbonyl derivatives and primary amines.

In this chapter, we will describe the preparation of methylenelactones, furans, and methylenecyclopentanes by tungsten-catalyzed cyclization of *α*-alkynyl-*β*-dicarbonyl derivatives under photo conditions (Scheme 3.2). In addition, pyrroles, pyridines, and isoquinolines were also efficiently synthesized via cyclization of alkyne derivatives tethered to nitrogen nucleophiles under thermal conditions in the presence of tungsten catalyst (Scheme 3.3).

Scheme 3.2 Synthesis of Methylenelactones, Furans, Methylenecyclopentanes.



Scheme 3.3 Synthesis of Pyrroles and Isoquinolines

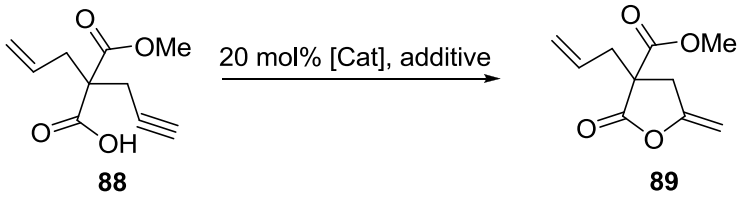


3.2 Results and Discussion

3.2.1 Synthesis of Methylenelactone Derivatives

A lot of transition metal catalysts involving Pd,[70] Rh,[71] Au,[72] Ag[73] etc[74] have been employed for the cyclization of alkynoic acids to enol lactones. However, transition metal-catalyzed cyclization reactions involving alkynoic acids had not been exploited under Group *VI* carbonyl complexes catalysis. Our initial efforts towards cyclization of alkynoic acids using model substrate **88** concentrated on $W(CO)_6$ catalyst under thermal conditions. As illustrated in Table 3.1, the reactions were optimized with respect to the catalyst, the reaction condition, the solvent, and the absence or presence of additive. We found that a trace amount of the corresponding alkylidene lactone **89** was isolated when

Table 3.1 Optimization of Reaction Conditions



88 **89**

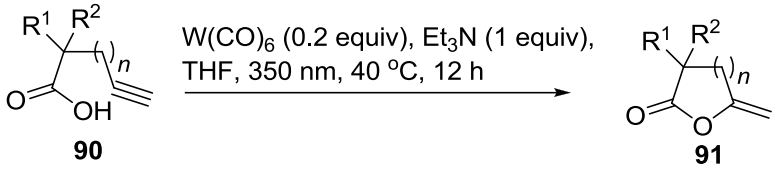
entry	cat.	additive	solvent	condition	time (h)	yield (%)
1	$W(CO)_6$	-	THF	80 ^oC	12	trace
2	$W(CO)_6$	Et_3N	THF	80 ^oC	12	trace
3	$W(CO)_6$	Et_3N	CH_3CN	80 ^oC	12	trace
4	$W(CO)_6$	-	CH_3CN	80 ^oC	12	trace
5	$W(CO)_6$	-	THF	350 nm	16	93
6	$W(CO)_6$	Et_3N	THF	350 nm	6	95
7	$Mo(CO)_3(CH_3CN)_3$	-	CH_3CN	80 ^oC	16	0
8	$Mo(CO)_3(DMF)_3$	-	CH_3CN	80 ^oC	16	0
9	$Mo(CO)_6$	-	THF	80 ^oC	16	0

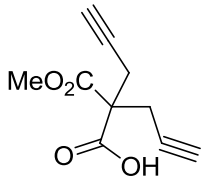
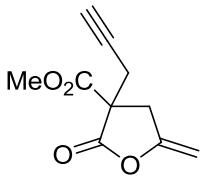
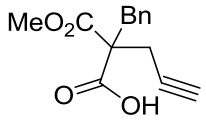
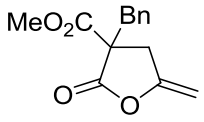
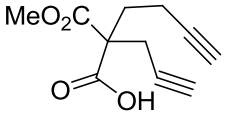
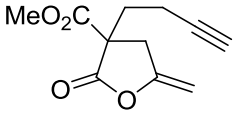
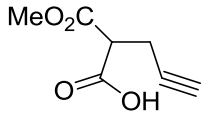
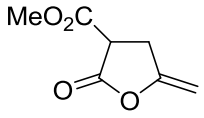
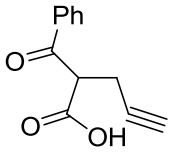
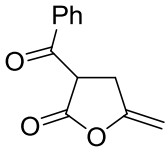
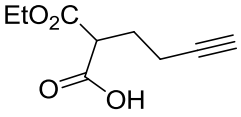
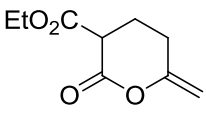
the mixture was refluxed in THF or acetonitrile for 12 h (entries 1, 4). However, the yield was not improved even in the presence of triethylamine (entries 2 and 3). Gratifyingly, substrate **88** went to complete conversion with *exo*-mode regiocontrol under irradiation at 350 nm for 16 h, thus affording methylenelactone **89** in 93% yield upon isolation (entry 5). Such result highlighted the easy formation of reactive species of tungsten pentacarbonyl under photo irradiation. In addition, the reaction time was shortened to 6 h in the presence of 1 equiv triethylamine (entry 6). Surprisingly, the reaction failed to undergo under thermal conditions using several molybdenum catalysts (entries 7-9). Therefore, the cyclization was carried out by irradiating a THF solution of alkynoic acids, 20 mol% $W(CO)_6$ and 1 equiv of Et_3N at 350 nm for 12 h.

As shown in Table 3.2, tungsten-catalyzed cyclization could be extended to a variety of alkynoic acids. For example, the cyclization of bis-propargylic substrate **90a** provided the desired product **91a** in 92% isolated yield (entry 1). Compound **90c** bearing a homo-propargylic group cyclized cleanly to generate **91c** in 95% yield, without observing any *endo*-cyclization or other undesired side reactions (entry 3). Di-substituted and mono-substituted propargyl malonic esters also performed well to afford the desired lactones (entries 2, 4). Moreover, phenyl ketone substrate **90e** cyclized smoothly to give **91e** in 96% isolated yield (entry 5). The 6-*exo* cyclization could be achieved in the absence of the propargylic group, but the reaction proceeded slower and required 36 h for completion (entry 6).

We next turn our attention to the cyclization of ketoacid **92** under our model system (Scheme 3.4). Surprisingly, the result was somewhat different from that of **90e** and decarboxylation proceeded faster than cyclization for substrate **92**, and produced oct-7-yn-4-one in 93% isolated yield under the same conditions. Interestingly, treatment of **92**

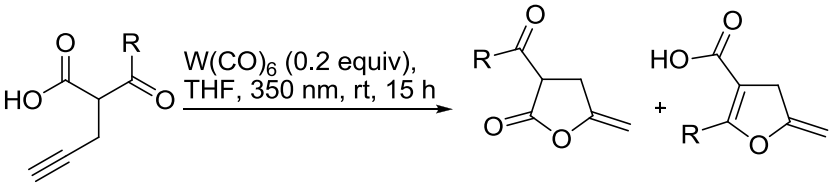
Table 3.2 Cyclization of Acetylenic Acids for the Formation of Alkylidene Lactones



entry	acid		product		yield (%)
1		**90a**		**91a**	92
2		**90b**		**91b**	91
3		**90c**		**91c**	95
4		**90d**		**91d**	93
5		**90e**		**91e**	96
6[a]		**90f**		**91f**	87

[a] The reaction was carried out for 36 h

Scheme 3.4 Tungsten-Catalyzed Cyclization of Ketoacid **92**



92a: R= *n*-C_3H_7 **93a** (50%) **94a** (10%)

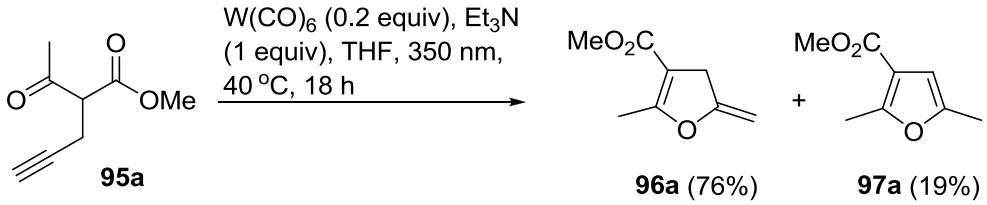
92b: R= CH_3 **93b** (55%) **94a** (11%)

with $W(CO)_6$ in the absence of triethylamine provided a mixture of **93a** and **94a** in moderate yield along with the decarboxylation as a side reaction. The ratio of the isolated yields of **93a** and **94a** indicated that the oxygen from the carboxyl group was more nucleophic than the enol towards attacking activated alkynyl tungsten complex in this case. Similarly, substrate **92b** also gave rise to the corresponding products **93b** and **94a**.

3.2.2 Synthesis of Furan Derivatives

Furan derivatives dominate the properties of a lot of drugs, materials and bioactive natural products.[75] Thus, development of novel synthetic methods for the synthesis of furan structural framework has always attracted much attention. The nucleophilic addition of the carbonyl oxygen onto alkyne-metal complex represents one of the important approaches for construction of furans.[76] To the best of our knowledge, pioneering studies related to Group *VI* metal carbonyl complexes as catalyst in cyclization reactions have been proposed via vinylidene carbene species and few synthetic methodologies on them have been disclosed since then.[77]

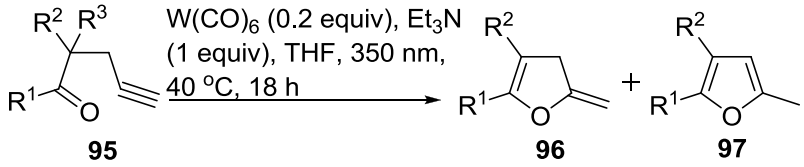
Scheme 3.5 Tungsten-Catalyzed Cyclization of Ketoester **95a**



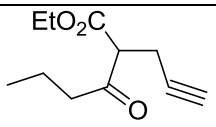
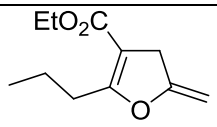
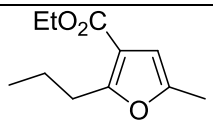
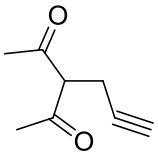
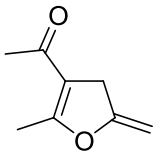
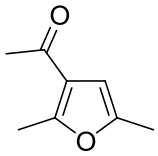
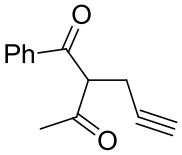
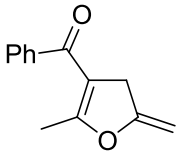
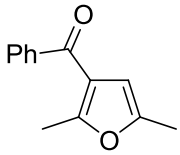
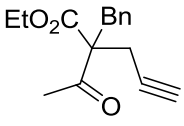
Guided by the reported results, we envisioned that Group *VI* metal carbonyl complexes can promote cyclization of α-alkynyl-*β*-dicarbonyl derivatives to produce furans. Substrate **95a** was first performed with a catalytic amount of $W(CO)_6$ and 1 equiv Et_3N in THF under irradiation at 350 nm for 15 h, and only *exo*-cyclized products **96a** and **97a** were obtained under this preliminary study. Such result indicated that the cyclization proceed via the *π*-alkyne metal intermediate instead of the vinylidene carbene complex.

With this optimized condition in hand, we next explored the substrate scope as shown in Table 3.3. 1,3-Dimethylketone **95c** provided dihydrofuran **96c** with 94% isolated yield without the observation of its isomerized furan (entry 2). However, the 1,3-phenyl methyl ketone **95d** cyclized to afford a mixture of dihydrofuran **96d** and isomerized furan **97c** (entry 3), indicating that the stability of the initially formed dihydrofuran derivatives depended on the structure of the substrates under the current conditions.

Table 3.3 Formation of Dihydrofurans and Furans

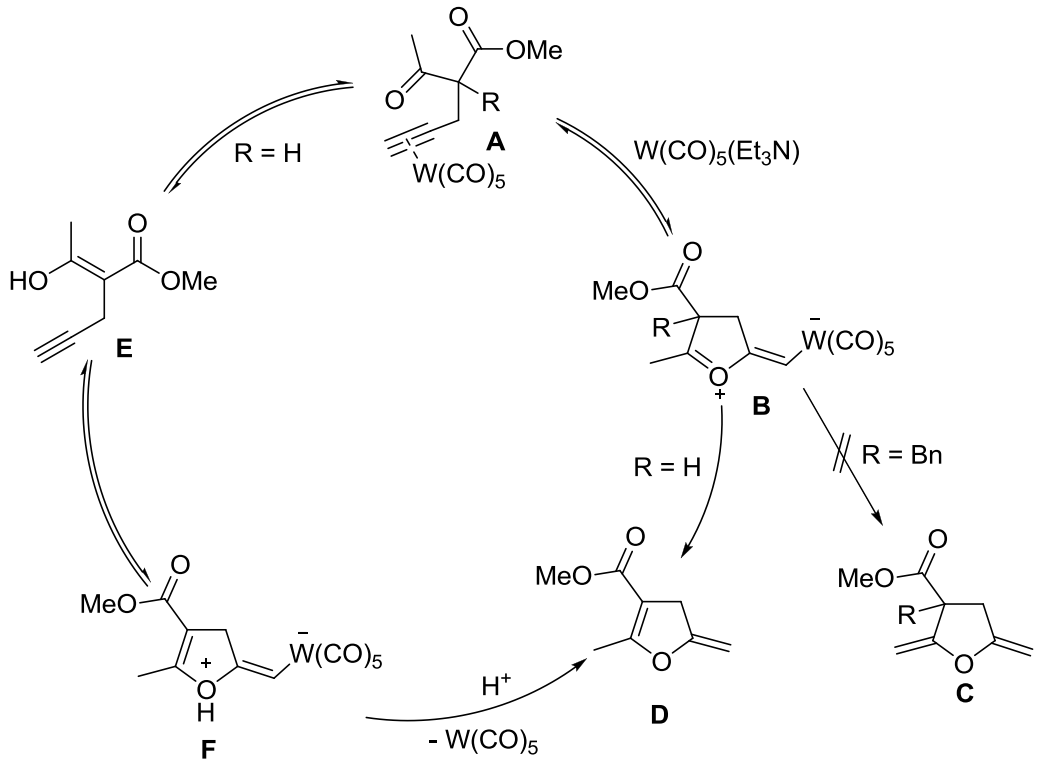


95 **96** **97**

entry	ketone	product		yield (%) (**96**:**97**)
1				78:17
	95b	**96b**	**97b**	
2				94:0
	95c	**96c**	**97c**	
3				66:21
	95d	**96d**	**97d**	
4		-	-	-
	95e			

Meanwhile, the newly formed dihydrofuran compounds could be easily isomerized to the corresponding furans by treating with Amberlist or DBU according to the previously reported procedures.[78] In addition, the fully-substituted ketoester **95e** failed to give the corresponding product with this established cyclization protocol (entry **4**).

Scheme 3.6 Plausible Catalytic Cycle

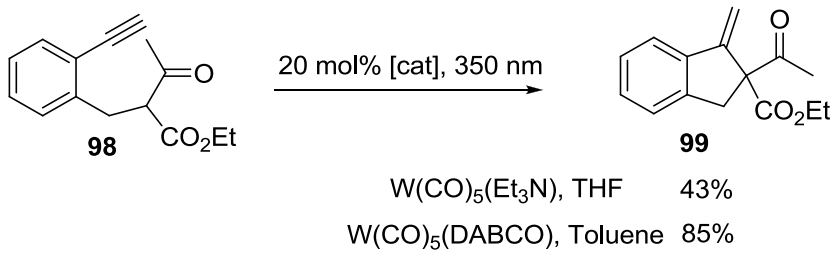


Two mechanistic pathways for this cyclization would be possible (Scheme 3.6). The reaction may proceed *via* keto–enol tautomerization to generate enol ester **E**, followed by nucleophilic addition of enol onto alkyne complex to afford the intermediate **F**. Fast protonation would provide access to dihydrofuran **D** and the regeneration of tungsten species. Alternatively, a mechanism involving facile deprotonation in **B** might also be considered. But the failure of cyclization for unsubstituted keto ester **95e** (R=CH_2Ph) may exclude the present pathway.

3.2.3 Synthesis of Methylenecyclopentane Derivatives

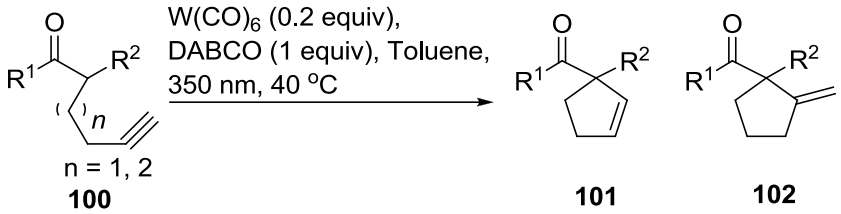
To further demonstrate the synthetic utility of this methodology, Conia-ene type reaction was studied by employing ketoester **98** as model substrate under the same conditions. Several transition metal catalysts have been used to achieve the Conia-ene type reactions.[79] In fact, Group *VI* metal catalysts were also employed in such kind of reactions, in which newly formed enolate anions attacked activated alkynes to achieve *endo*-carbocyclization.[80] As shown in Scheme 3.7, it was found that substrate **98** is compatible with this novel cyclization approach. However, the starting material **98** was not consumed completely and only gave *exo*-cyclized product **99**, without observing 6-*endo*-cyclized product in this case.

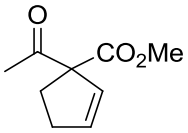
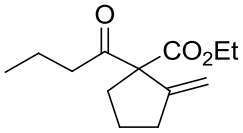
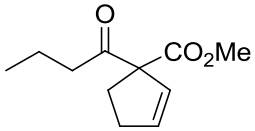
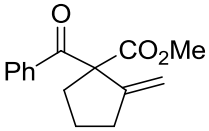
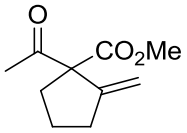
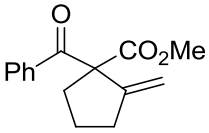
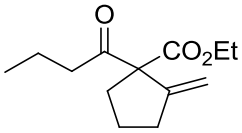
Scheme 3.7 Tungsten-Catalyzed Cyclization of Ketoester **98**



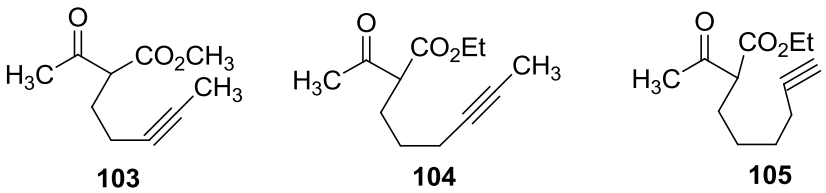
As demonstrated in Table 3.4, similar transformations were achieved using Et_3N in THF (entries 5 and 7). However, the starting materials were not consumed completely even after irradiating the mixture for 48 h. Luckily, switching to DABCO and toluene increased the reaction efficiency dramatically. A comparison of the experiment for substrate **98** using DABCO in toluene instead of Et_3N in THF revealed that the reaction time was reduced and **99** was obtained with a significantly enhanced 85% isolated yield. Under this optimized conditions, substrates containing alkyl ketone and phenyl ketone were successfully cyclized to produce methylenecyclopentane derivatives **102** with excellent yields (entries 3, 4, 6). Interestingly, the current methodology could be further employed to the 5-*endo*-mode cyclization of *homo*-propargylic substrates. **100a** and **100b**

Table 3.4 Tungsten -Catalyzed Cornia-ene type reactions



entry	product	yield (%)	entry	product	Yield (%)
1	 **101a**	94	5[a]	 **102d**	44 (45)[b]
2	 **101b**	82	6	 **102e**	87
3	 **102c**	91	7[a]	 **102e**	15 (80)[b]
4	 **102d**	84			

[a] The reaction was studied in the presence of Et_3N (1 equiv). [b] Recovered starting material



cyclized smoothly to generate 5-*endo*-cyclized products respectively under the present conditions (entry 1 and 2). Although the reaction was slow, the cyclization proceeded smoothly in all cases.

Unfortunately, this catalytic system was not applicable for cyclization of substituted alkynes. Substrates **103** and **104** failed to provide the cyclization products and were recovered intact. Moreover, 6-*exo*-*dig* cyclization of **105** was also studied under the present conditions but the reaction did not proceed at all.

3.2.4 Synthesis of Pyrrole Derivatives

Guided by our previous results that tungsten-activated terminal alkynes could be easily attacked by nucleophiles, we subsequently turned our attention to the feasibility of the tungsten-mediated addition of an imino group to the alkynyl group to afford a dihydropyrrol or a pyrrole derivative (Scheme 3.8).

Following our established standard conditions, the THF solution of the model iminoester **109**, 20 mol% of $W(CO)_6$ and 1 equiv Et_3N was irradiated at 350 nm for 15 h. The reaction did not occur and the starting material was recovered (Table 3.5, entry 1). Switching Et_3N to DABCO did not have any improvement (entry 2). In the absence of base, no reaction occurred even under photo-assisted conditions (entry 3). Next, we then treated the reaction under thermal conditions. Gratifyingly, we found that the cyclization occurred using $W(CO)_6$ catalyst in refluxed THF for 15 h and 35 % isolated yield of the

Scheme 3.8 Tungsten-Catalyzed Cyclization of Iminoester

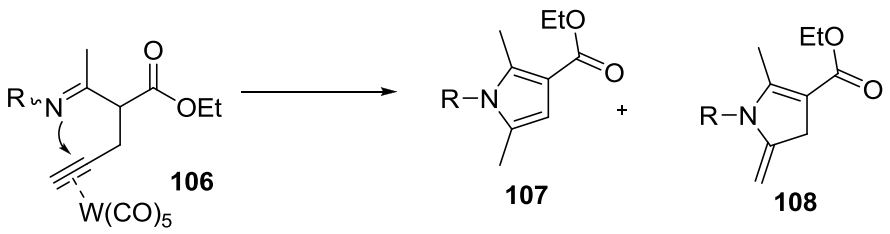
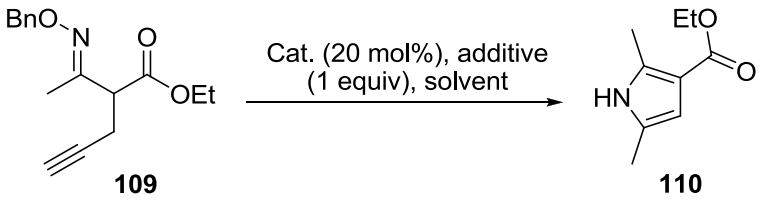


Table 3.5 Tungsten-Catalyzed Cyclization of Iminoester **109**



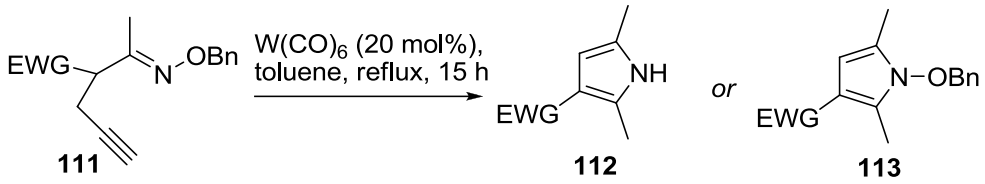
109 **110**

entry	cat.	additive (1 equiv)	solvent	condition	time (h)	yield (%)
1	$W(CO)_6$	Et_3N	THF	350 nm	15	0
2	$W(CO)_6$	DABCO	THF	350 nm	15	0
3	$W(CO)_6$	-	THF	350 nm	15	0
4	$W(CO)_6$	-	THF	110 ^oC	15	25
5	$W(CO)_6$	-	toluene	110 ^oC	15	88
6	$W(CO)_6$	Et_3N	toluene	110 ^oC	15	62
7	$Mo(CO)_6$	-	toluene	110 ^oC	15	39
8	$Mo(CO)_3(CH_3CN)_3$	-	toluene	110 ^oC	15	trace
9	$Mo(CO)_3(DMF)_3$	-	toluene	110 ^oC	15	trace

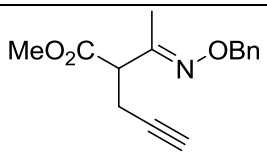
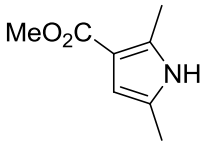
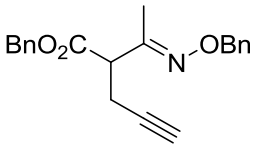
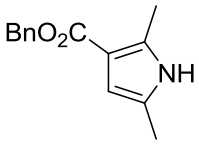
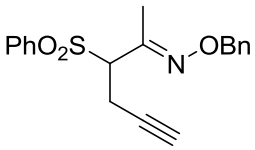
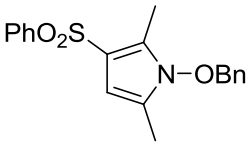
corresponding pyrrole **110** was obtained (entry 4). The catalysts were then briefly examined under thermal conditions (entries 5-9). It was found that $W(CO)_6$ was the most effective catalyst (entry 5) and the isolated yield of the product dropped in the presence of Et_3N (entry 6). It was noteworthy that dihydropyrrole was not observed during the reaction.

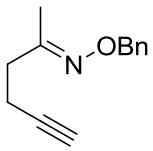
With the optimized conditions in hand, several imino substrates were examined to study the scope of present cyclization protocol. Substrates bearing ester ketone (**111a**, **111b**) could smoothly be cyclized, affording the corresponding pyrroles in 85% and 75%, respectively. Phenyl-sulfone substrate (**111c**) was also cyclized under present conditions,

Table 3.6 Tungsten-Catalyzed Cyclization of Iminoesters

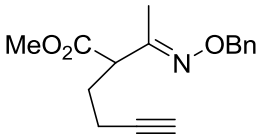


111 **112** **113**

entry	substrate	product	yield (%)
1			85
	111a	**112a**	
2			75
	111b	**112b**	
3			63
	111c	**113c**	



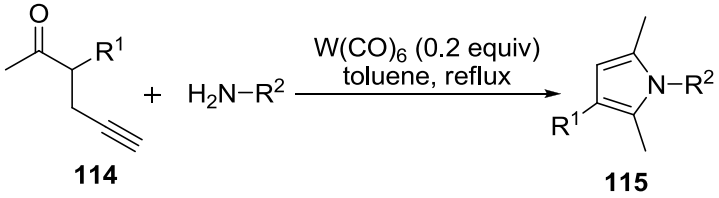
111d



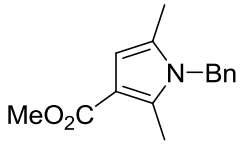
111e

and it gave the substituted pyrrole (**113c**) The cyclization did not take place at all for substrate **111d** without the withdrawing-group. Unfortunately, the present conditions were not applicable to homo-propargylic substrate. Substrates **111e** failed to give the cyclization product and it was recovered quantitatively.

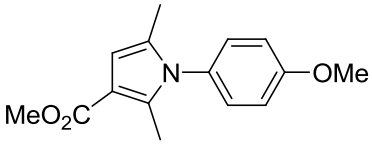
Table 3.7 Tungsten-Catalyzed Synthesis of Pyrroles



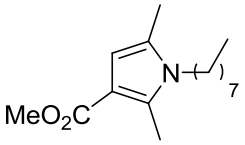
114 **115**



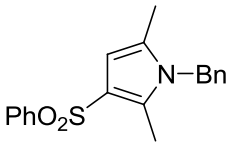
115a (94%)



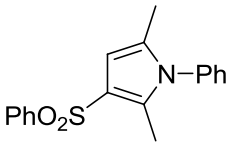
115b (83%)



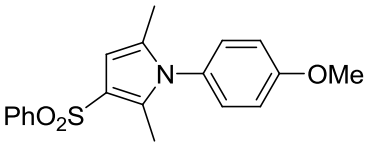
115c (96%)



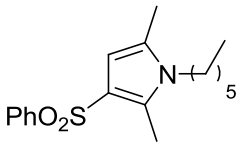
115d (87%)



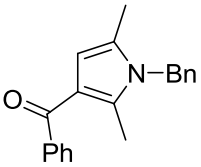
115e (85%)



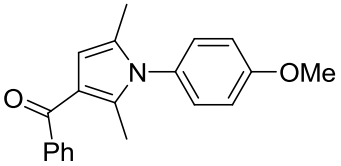
115f (89%)



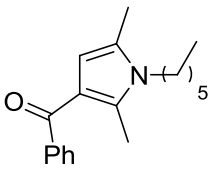
115g (92%)



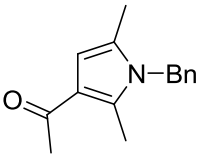
115h (91%)



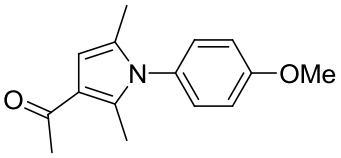
115i (84%)



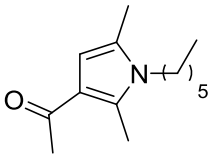
115j (95%)



115k (86%)



115l (90%)



115m (93%)

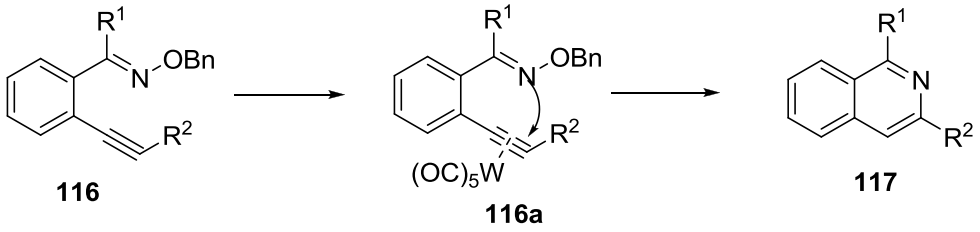
Furthermore, it would be possible to perform a one-pot reaction if the imine formation is faster than the cyclization to form furan derivative. Treatment of alkynyl keto-ester **114** with benzylamine (1.2 equiv) in the presence of $W(CO)_6$ (0.2 equiv) in refluxing toluene

for 24 h afforded pyrrole **115a** in 94% yield. Apparently, the dihydropyrroles underwent isomerization to the pyrroles during prolonged refluxing conditions. This one-pot reaction exhibits broad scope with respect to both alkynyl group and primary amine (Table 3.4). Benzylamine, analine and alkylamine are compatible on the alkynyl keto-esters (**115a**-**115c**). Strong electron-withdrawing group such as keto-sulfones may also be employed (**115d**-**115g**). Dimethyl diketones (**115h**-**115j**), and methyl phenyl ketones (**115k**-**115m**) also worked well with *n*-hexylamine, benzylamine, and 4- methoxyaniline to afford the corresponding pyrroles. In all cases, the yield was consistently high, ranging from 85% to 96%.

3.2.5 Synthesis of Isoquinoline and Pyridine Derivatives

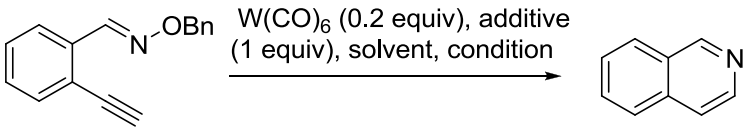
Continuing our interest, we further investigated the utility of tungsten in cyclization reactions, and chose to study the tungsten-mediated cyclization of ethynylbenzaldehyde oxime ethers and expected to generate various kinds of isoquinolines.[81]

Scheme 3.9 Tungsten-Catalyzed Cyclization of Ethynyl Oxime



Transition metals such as palladium[82] and silver[83] etc[84] were already employed in mediating cyclization reactions for the synthesis of isoquinolines. However, to the best of our knowledge, no tungsten-catalyzed process exists for the synthesis of isoquinolines. Based on our success of cyclization of imino alkynyl substrtates, we envisioned that ethynyl oxime **116** should permit the cyclization to afford isoquinoline **117** (Scheme 3.9). (*E*)-2-ethynylbenzaldehyde *O*-benzyl oxime (**118**) was employed as model substrate for

Table 3.8 Reaction optimization



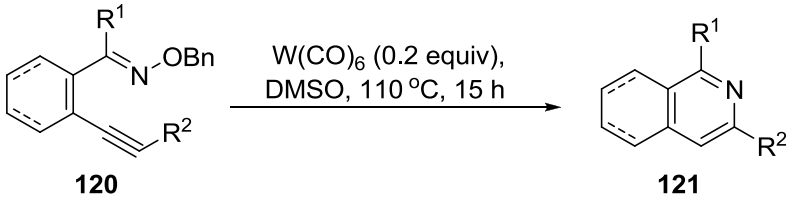
118 **119**

entry	cat.	additive (1 equiv)	solvent	condition	time (h)	yield (%)
1	$W(CO)_6$	Et_3N	THF	350 nm	15	0
2	$W(CO)_6$	Et_3N	THF	reflux	15	0
3	$W(CO)_6$	-	toluene	reflux	15	0
4	$W(CO)_6$	Et_3N	toluene	reflux	15	0
5	$W(CO)_6$	-	DMSO	110 ^oC	15	92
6	$W(CO)_6$	-	DMF	110 ^oC	15	81
7	-	-	DMSO	110 ^oC	15	0

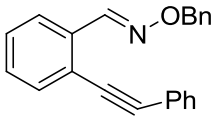
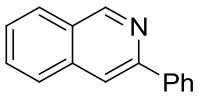
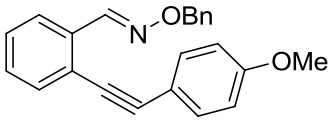
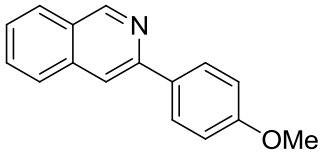
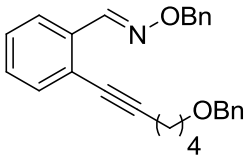
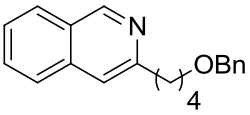
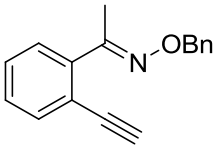
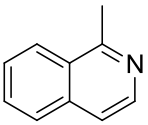
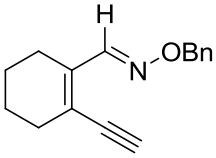
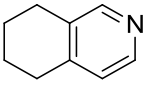
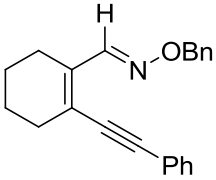
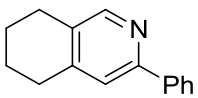
screening the optimized reaction conditions. Under photo-assisted conditions as shown in entry 1 (Table 3.8), the reaction did not occur and the starting material was recovered quantitatively. No improvement was observed even after heating the reaction mixture at reflux (entry 2). For imino alkynyl substrates **118**, the starting material was consumed, however, the reaction was messy and the corresponding product was not isolated (entry 3). In the presence of a base, a similar result was observed (entry 4). Luckily, when we used DMSO as the solvent, the reaction was clean and excellent yield was obtained (entry 5). DMF also worked well (entry 6). Expectedly, the reaction did not take place in the absence of tungsten metal.

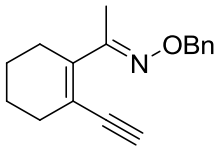
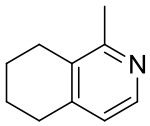
With the optimization conditions in hand, we next screened other substrates to survey the generality of this cyclization using $W(CO)_6$ as catalyst and DMSO as solvent. Phenyl-

Table 3.9 Tungsten-Catalyzed Synthesis of Isoquinolines and Pyridines



120 **121**

entry	substrate		product		yield (%)
1		**120a**		**121a**	81
2		**120b**		**121b**	76
3		**120c**		**121c**	75
4		**120d**		**121d**	94
5		**120e**		**121e**	89
6		**120f**		**121f**	63

7		**120g**		**121g**	91

substituted alkynyl oxime substrate **120a** delivered the corresponding isoquinoline **121a** with 81% isolated yield (entry 1, Table 3.9). 4-Methoxy phenyl-substituted substrate provided the product **121b** with 76% isolated yield (entry 2). Alkyl-substituted substrate **120c** was also tested and cyclized smoothly to give the desired isoquinoline **121c** in good yield (entry 3). Although substrate **120d** with benzyl substituent was blocked by the methyl group, it worked well to produce the corresponding isoquinoline **121d** with excellent yield under the catalytic system (entry 4).

To increase the generality of this cyclization process, we subsequently prepared pyridine derivatives using the similar idea as above. We were pleased to find that substrate **120e** was cyclized to the desired pyridine **121e** with the same conditions for synthesis of isoquinolines (entry 5, Table 3.9). For phenyl-substituted substrate **120f**, the reaction also worked well and provided the corresponding pyridine with moderate yield (entry 6). The excellent yield was obtained when substrate **120g** was treated with the standard conditions (entry 7).

3.3 Conclusion

In summary, the efficient and reliable tungsten-catalyzed methods were established for the preparation of methylenelactones, furans and methylenecyclopentanes using α-alkynyl-β-dicarbonyl derivatives under photo conditions. Pyrroles, pyridines and isoquinolines were also efficiently prepared via the tungsten-catalyzed cyclization of alkyne derivatives tethered to nitrogen nucleophiles under thermal conditions. These protocols accomodated remarkably mild conditions and proceeded mainly through a 5-

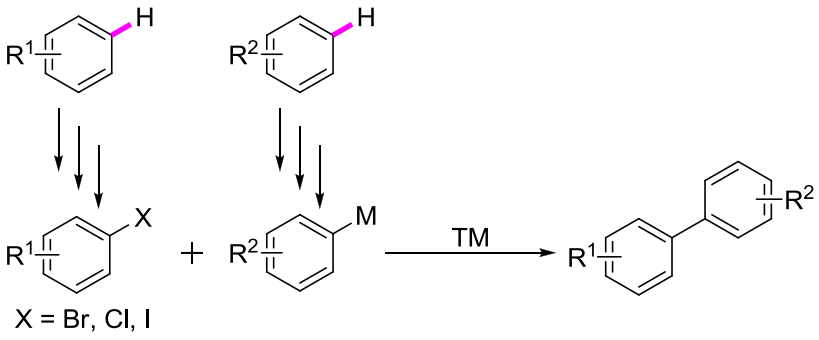
exo-mode cyclization. In addition, the present methodology also allows the formation of 5-membered rings *via endo*-cyclization. Ongoing efforts are focused on gaining further insights into the mechanisms of these transformations and synthetic usefulness of $W(CO)_5(L)$ catalyst in functionalization of alkyne derivatives.

Chapter 4. Transition-Metal-Catalyzed C−H Bond Functionzalization

4.1 Introduction

Traditional methods to synthesize pharmaceuticals, dyes, herbicides, natural products, agrochemicals, and polymers rely on the classical cross-coupling reactions in key steps, such as Suzuki-Miyaura, Heck, Hiyama, Negishi, Tsuji-Trost allylation, and Buchwald-Hartwig reactions etc (Scheme 4.1).[85] Such cross-coupling reactions have matured to be reliable tools for the formation of a wide variety of basic and useful functional groups. Unfortunately, these useful and powerful approaches conducted transformations on preactivated reaction partners for reactivity and selectivity, including organometallic and halides reagents.[86] It will cost time and produce waste to prepare these coupling fragments to access in the context of complex molecular synthesis. Furthermore, preparation of preactivated substrates often requires several steps, which may waste time and resources.

Scheme 4.1 Traditional Cross-Coupling Reactions



Although much improvement has been made in these classic reactions in the industrial and academic area, there is still a need to discover more efficient routes. We are inspired to obtain the same outcome with shorter synthetic routes, but avoiding the formation of

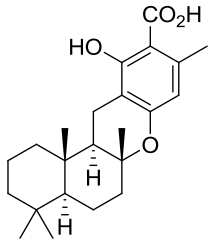
undesired byproducts. In order to optimize resources and circumvent the accumulation of unnecessary steps, direct and selective C−H functionalization represents an environmentally and economically more attractive strategy because the C–H bond is the most common chemical bond in organic compounds.

Direct C−H transformation to new functional groups is a research area of long history, such as various kinds of classic C−H bond oxidation reactions.[87] Most of the reactions described at that time commonly relied on the use of either harsh conditions or stoichiometric amounts of expensive or toxic agents. These drawbacks surely made the methodologies for selective hydrocarbons functionalization underdeveloped and poorly applied in organic synthesis. However, these disadvantages were decreased dramatically since the organic chemists applied transition metals to devise catalytic C−H bond transformation reactions to enhance efficiency and exquisite selectivity. Over the last several decades, spectacular advancement in the area of C−H bond functionalization methodology has been uncovered in the synthesis of new C−C and C−X bonds using various transition-metal catalysts, including palladium, [88] rhodium, [89] ruthenium, [90] copper,[91] iron,[92] cobalt[93] etc complex.

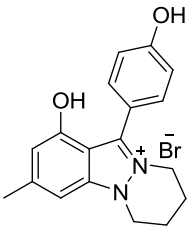
4.2 Directing-Group-Assisted Functionalization of C−H Bonds

In order to broaden the synthetic value of C−H activation reactions, the problem of site selective C−H bond activation must be preferentially considered because a molecule has many different C−H bonds and a variety of potentially reactive functional groups. Especially for arene substrates, the reactivity of C−H bonds in arene rings is generally less distinct, so the reactive sites are required for controlling the regioselectivity issues. In these conditions, directing group-based C−H activation has become one of the important approaches to furnish site-selective C−H bond transformations. Meanwhile, C−H functionalization methodologies were already successfully employed in the construction

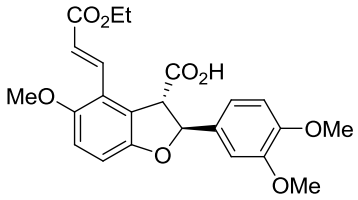
Scheme 4.2 Application of C−H Functionalization Logic to the Synthesis of Natural Products and Bioactive Molecules



(+)-hongoquercin A **122**



Nigellidine Hydrobromide **123**



core for lithospermic acid faminly **124**

of bioactive natural products and bioactive molecules (Scheme 4.2).[94]

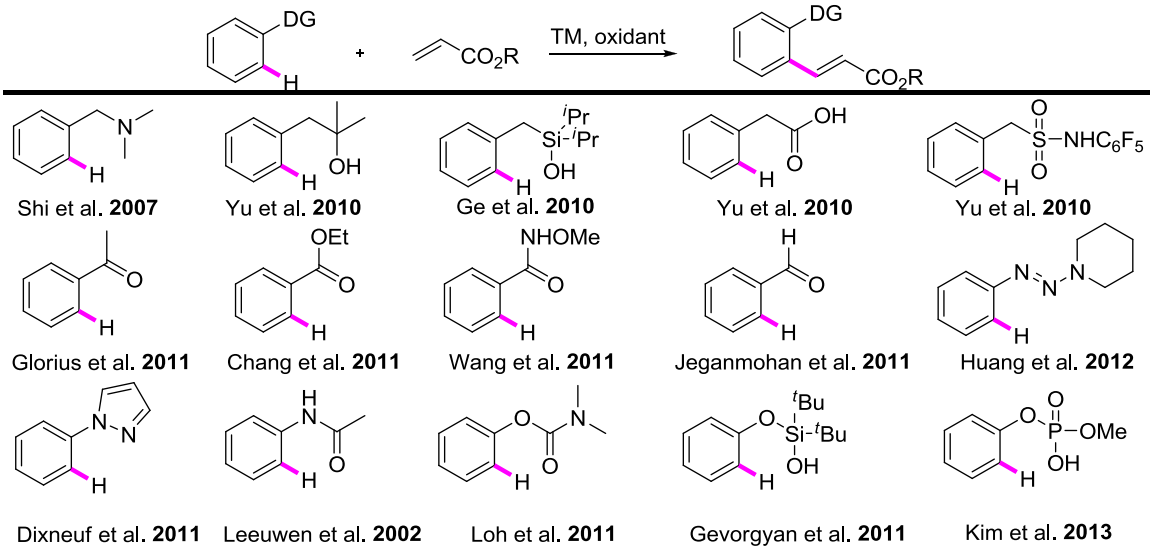
Palladium complexes are particularly attractive as catalysts for direct C−H transformations. Palladium catalysts have significantly broadened the applications of sp^2 C−H activation processes to new C-X bond formation within the past several decades. The current chapter will specifically focus on palladium-catalyzed directing-group-assisted *ortho*-olefination, and *ortho*-arylation of aryl C−H bonds.

4.2.1 Palladium-Catalyzed Direct Olefination of C−H Bonds

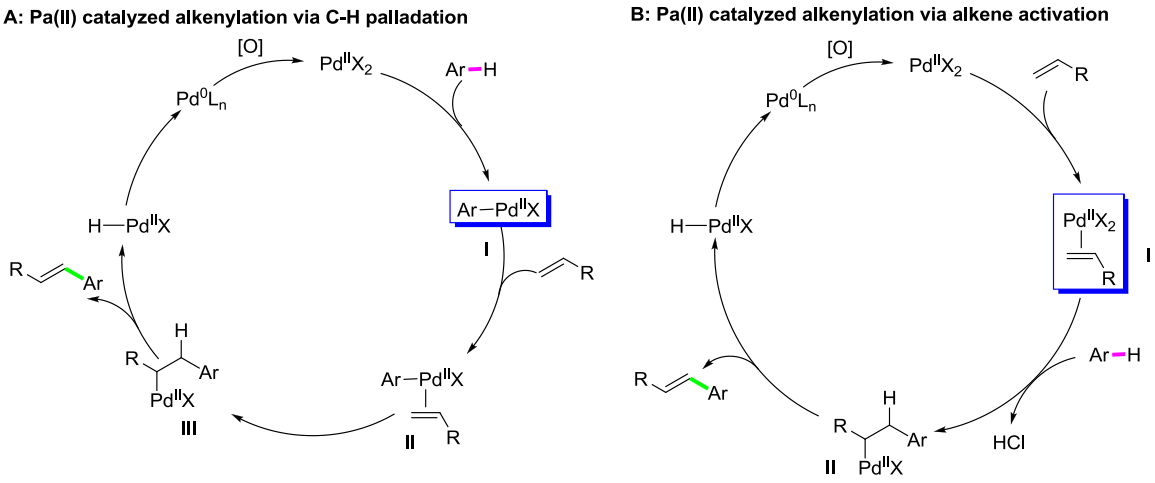
Over the last few years, transition-metal-catalyzed directing group-based C−H activation approach has been well-developed and tremendous research literatures have already been reported.[95] Without a doubt, a direct olefination of arene C−H bonds is not only synthetically useful in transitional-metal-catalyzed C−H bond functionalization reactions, but also among the most mechanistically investigated reactions in C−H activation reactions. Therefore, it is not surprising that numerous reviews have been published in this field.[83-87] In particular, directing-group-assisted C−H olefination reactions flourished during the last decade.

Various kinds of directing groups have been employed to direct functionalization of arene C−H bonds in the presence of various metal catalysts. For examples, Shi, Yu, Chang, Loh, Glorius, et al, have developed palladium-catalyzed or rhodium-catalyzed

Scheme 4.3 Directing-Group-Assisted C−H Olefination



Scheme 4.4 General mechanisms for Pd-catalyzed C−H olefination

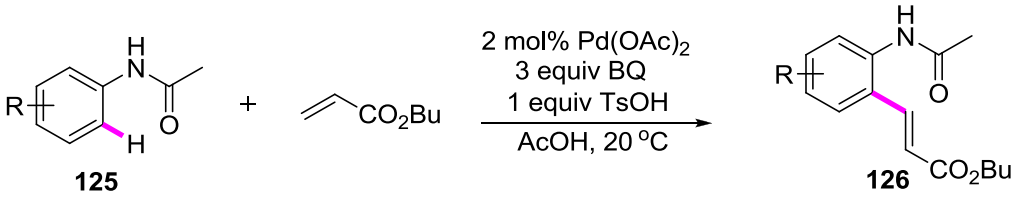


synthetic methodologies for the olefination of arenes with the assistance of synthetically valuable directing groups, involving amines, alcohols, carboxylic acids, amides, esters, ketones, and aldehdyes (Scheme 4.3). [96]

In general, there are two typical mechanisms applied for Pd-catalyzed direct olefination of sp^2 C−H bond, initially proposed by Fujiwara and Moritoni in the late 1960s.[97] First, electrophilic substitution of aromatic C−H bond by palladium species gives the key complex **I** as shown in pathway A of Scheme 4.4, from which coordination with olefins would afford intermediate **II**. Subsequent 1,2-migratory insertion and *β*-hydride

elimination would provide the olefinated aromatic molecule along with HPd^{II}-X species, followed by liberation of HX and the regeneration of the active Pd^0 to Pd^{II} species by oxidants. A second pathway involves the initial olefin activation with Pd^{II} species to generate the complex **I**, followed by subsequent nucleophilic attack from an electron-rich arene to form the same intermediate **II** and proceed similarly as shown in pathway A (B, Scheme 4.4).

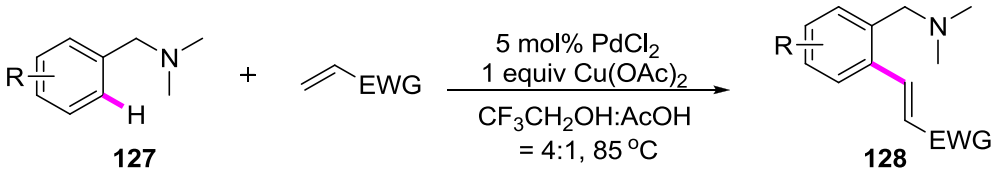
Scheme 4.5 Palladium-Catalyzed *ortho*-Olefination of Amides



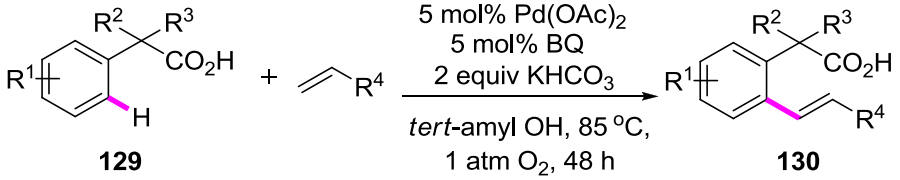
In 2002, Leeuwen reported the amide-directed coupling reaction of arene and olefins using palladium catalysis and a stoichiometric amount of *p*-toluenesulfonic acid in AcOH (Scheme 4.5).[98] In this system, a free N-H bond on the amide functionality is crucial and the C−H palladation process was promoted by $Pd(OTs)_2$ instead of $Pd(OAc)_2$. Benzoquinone works not only as the oxidant, but also probably serves as a ligand for palladium. Ar-H activation of *ortho*-substituted aromatic substrate proceeded in lower yield due to the sterically hindered effect. The electron-rich anilides undergo olefination in moderate to excellent yield, while low yield was obtained with electron-deficient substrates and olefins.

The *ortho*-olefination of *N*,*N*-dimethylbenzylamines **127** with various alkenes has been achieved using 5 mol% $PdCl_2$ and 1 equivalent of $Cu(OAc)_2$ (Scheme 4.6).[99] With electron-donating and electron-withdrawing groups on the aryl ring, this coupling reaction system provided the corresponding olefinated *N*,*N*-dimethylbenzyl amine with moderate to good yield. However, the reaction did not proceed at all for styrene coupling partners.

Scheme 4.6 Palladium-Catalyzed *ortho*-Olefination of *N*,*N*-dimethyl benzylamines

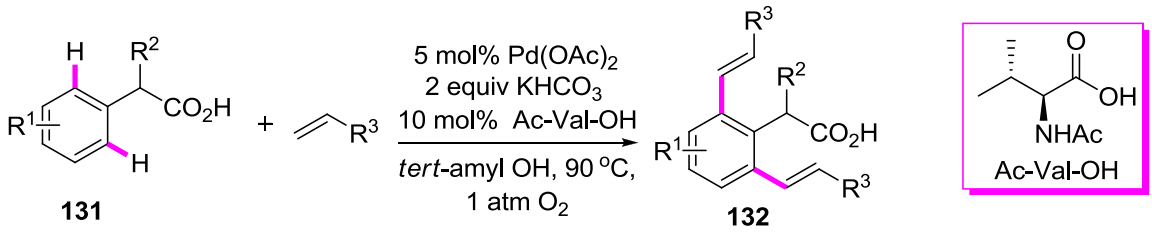


Scheme 4.7 Palladium-Catalyzed *ortho*-Olefination of Phenylacetic Acids



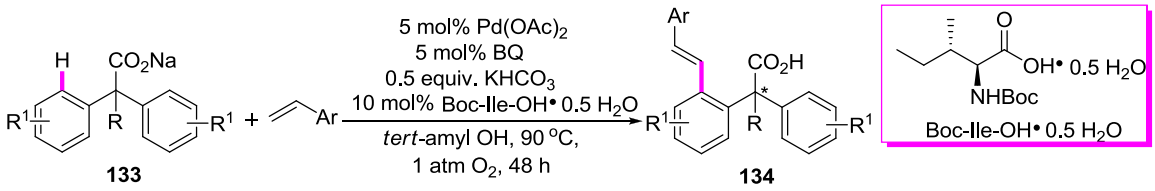
In 2010, Yu and co-workers reported a carboxylic acid directing group for the Pd(II)-catalyzed *ortho*-olefination of phenylacetic acids **129** with alkenes in the presence of 1,4-benzoquinone, oxygen, K_2CO_3 in *tert*-amyl alcohol (Scheme 4.7).[100] They proposed that the reaction was initiated through weak coordination between the C=O of the carboxylate and $Pd(OAc)_2$ and the inorganic additive ($KHCO_3$) was crucial to improve the reaction efficiency. Regioselective mono-olefination of a range of electron-rich and electron-poor phenylacetic acids was achieved with good to excellent yield under such mild conditions. Arene olefination with styrene also proceeded well.

Scheme 4.8 Palladium-Catalyzed *ortho*-Olefination of Phenylacetic Acids



A more efficient palladium-catalyzed oxidative cross-coupling between phenylacetic acids **131** and olefins in the presence of amino acid ligands was subsequently demonstrated by Yu's group (Scheme 4.8).[101] A wide range of phenylacetic acids with

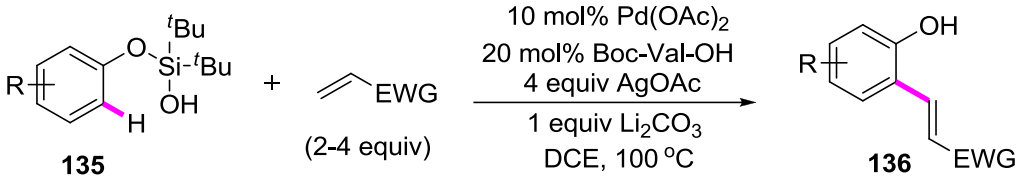
Scheme 4.9 Palladium-Catalyzed *ortho*-Olefination of Phenylacetic Acids



electron-rich and electron-poor substitutes was reacted with olefins to provide the *di*-olefinated products. Facial olefination still occurred even when *meta*-positions were blocked.

Yu also applied the similar conditions to study the asymmetric reaction by using the coordination of palladium and a chiral amino acid ligand to control the regioselectivity and enantioselectivity (Scheme 4.9).[102] In this case, the sodium salts was an important parameter in improving the efficiency of the reaction. Corresponding monoolefinated products were obtained with moderate to good yield in good to excellent enantioselectivity.

Scheme 4.10 Palladium-Catalyzed *ortho*-Olefination of Silanol-Tethered Phenols

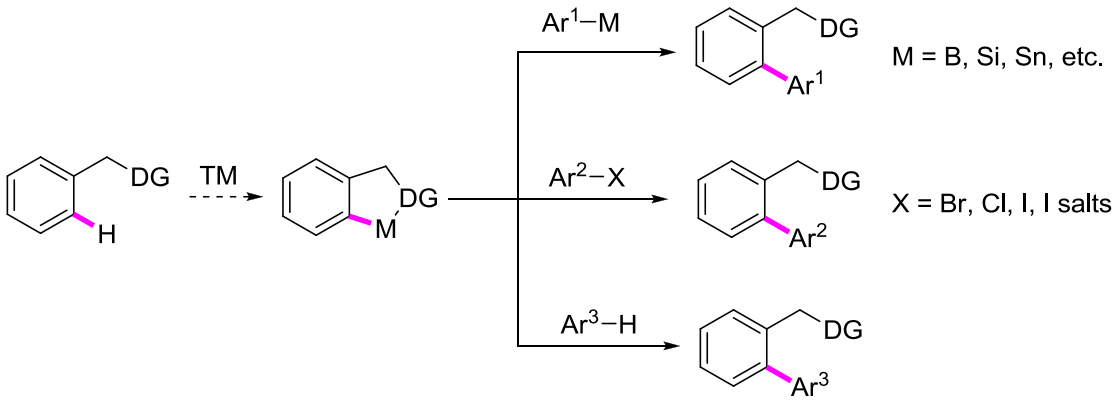


A related synthesis of olefinated phenols from silanol-tethered phenols **135** and olefins using palladium catalysis and amino acids ligand has been developed by Gevorgyan's groups in 2011 (Scheme 4.10).[103] Silanol serves as an ideal directing group for creating various kinds of olefinated phenols, after acidic cleavage of the silyl groups. Under this condition, such transformation shows broad scope and functional group compatibility.

4.2.2 Palladium-Catalyzed Directing-Group-Assisted Arylation of C−H Bonds

In general, transition-metal-catalyzed directing-group-assisted direct arylation of aryl C−H bonds can be broadly divided into three classes as shown in Scheme 4.11. The three classes are: (i) the coupling of an aromatic molecule with organometallic species; (ii) the coupling of an aromatic molecule with aryl halides; and (iii) dehydrogenative cross-couplings reactions in which both reaction partners are simple arenes. Such three strategies have been achieved by various transition-metal catalysts including Pd, Rh, Ru, Cu, Fe etc in recent years. However, palladium and rhodium salts have emerged as the most popular catalysts to promote the C−H bond cleavage in catalytic direct arylation reactions.

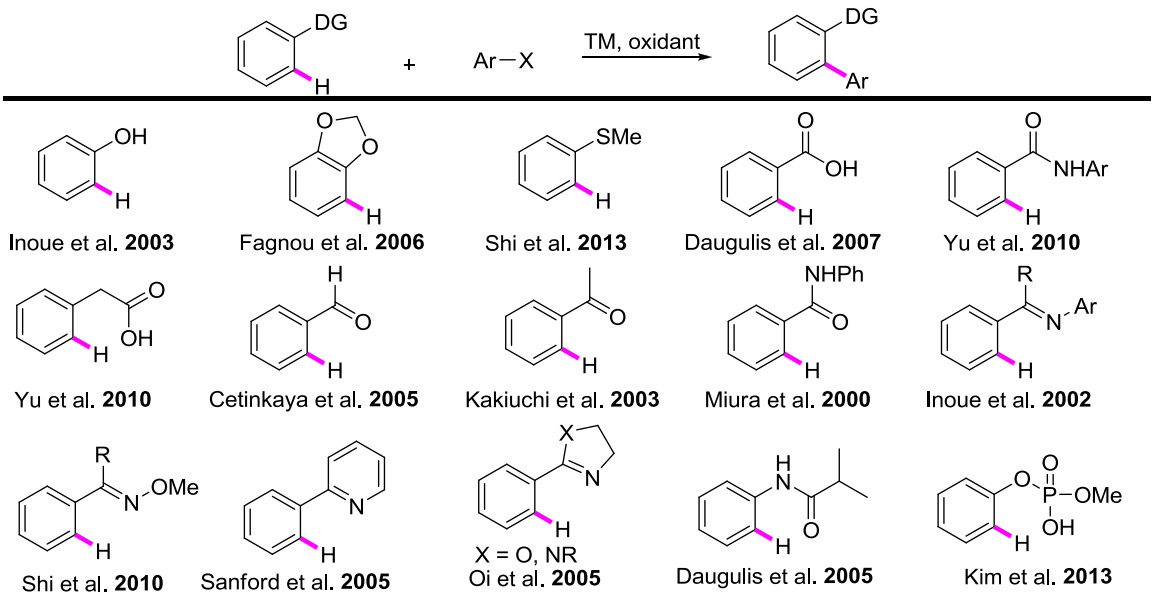
Scheme 4.11 Transition-Metal-Catalyzed Direct Arylation of sp^2 C−H Bonds



Transition metal-catalyzed directing group-based arylation approaches have flourished in recent decades. As shown in Scheme 4.12, various synthetic functional groups such as acid, ketone, aldehyde, etc have been employed to functionalize aryl C−H bonds using palladium and rhodium catalysts.

Palladium (II) salts have emerged as the preferred catalysts to promote the C−H bond cleavage in catalytic direct arylation reactions. The activation of sp^2 C−H bonds by palladium catalysis is crucial to initiate the reaction cycle. Depending on the catalytic conditions and substrates involved, the mechanisms to cleave sp^2 C−H bonds by

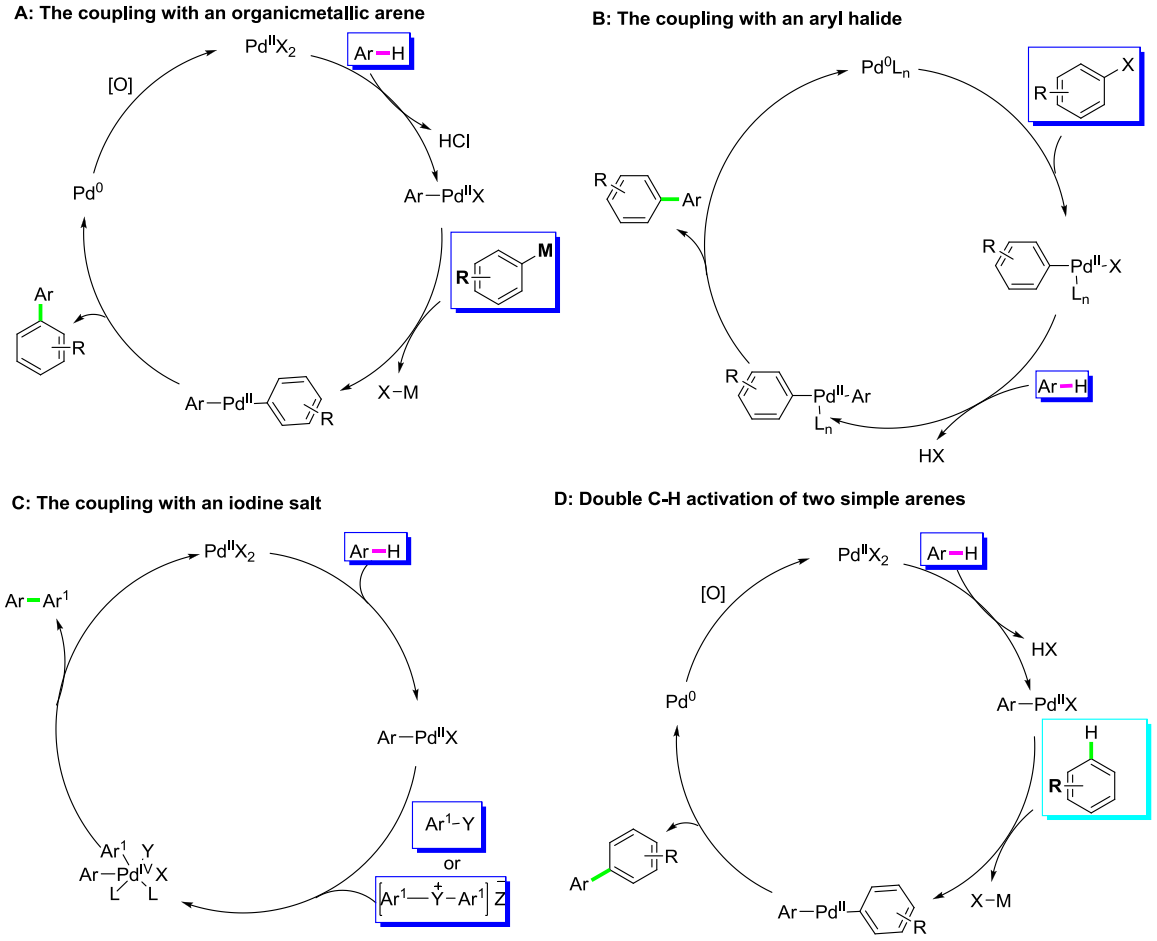
Scheme 4.12 Scheme 4.3 Directing-Group-Assisted C−H Arylation



palladium to form metal-carbon bond or cyclo-palladium intermediates was proposed to belong to one of the four general categories: (i) oxidation addition at electron-rich palladium centers; (ii) *σ*-bond metathesis; (iii) electrophilic activation; (iv) converted base-assisted metalation (Scheme 3). [104]

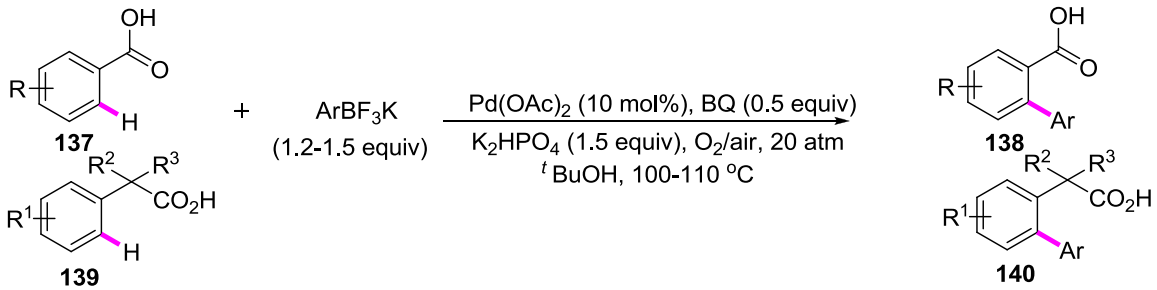
For the direct arylation of arenes with organometallic arene via a Pd(0)/Pd(II) cycle (A, Scheme 4.13), the reaction is initiated by C−H bond palladation with a Pd(II) catalyst, followed by a transmetallation with an organometallic arenes. Reductive elimination to afford the desired arylated product and releases Pd(0), which was oxidized to regenerate the Pd(II) catalyst. For the direct arylation of arenes with aryl halides via a Pd(0)/Pd(II) cycle (B, Scheme 4.13), the oxidative insertion of Pd(0) into the aryl halides takes place earlier than the C−H bond activation. New C−C bond is then produced along with the liberation of Pd(0). A novel catalytic system involving a Pd(II)/Pd(IV) cycle was shown in pathway C for direct arylation via C−H bond activation. The Pd(II) complex is first inserted into the C−H bond, followed by the oxidative addition of an Ar-X type compound, generating the corresponding Pd(IV) species. Reductive elimination would then form a new C−C bond and release Pd(II) back into the cycle. The most economic and

Scheme 4.13 General Mechanisms for Pd-Catalyzed C−H Arylation



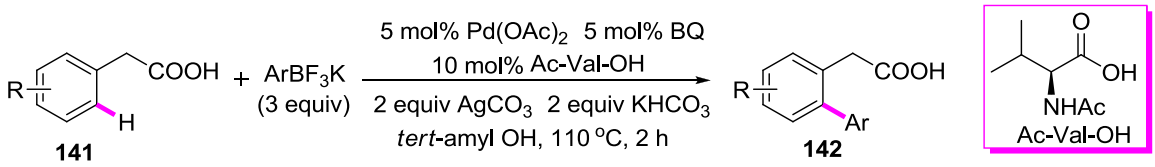
attractive method should be the coupling of two simple arenes (D, Scheme 4.13). In such catalytic reactions, one of the coupling partners contains the directing group which coordinates with palladium complex, and activates the first C−H bond. Transmetallation and subsequent reductive elimination processes provide the biaryl product together with Pd(0). In the presence of oxidant, the Pd(II) is obtained again.

Scheme 4.14 Palladium-Catalyzed *ortho*-Arylation of Aryl Acids



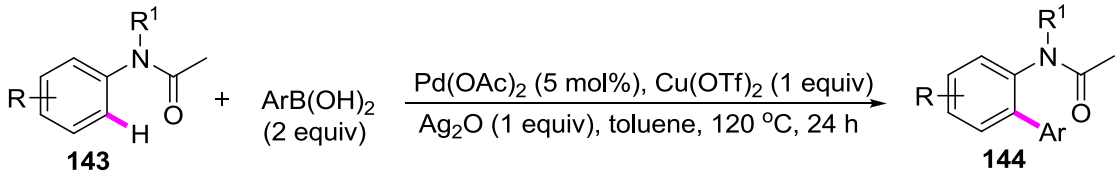
Using an carboxylic acid directing group, Yu and co-workers accomplished palladium-catalyzed direct *ortho*-arylation of benzoic acids **137** and phenylacetic acids **138** with potassium aryltrifluroborates, along with oxygen as the oxidant in *t*-BuOH as the solvent (Scheme 4.14).[105] The nature of stoichiometic additive K_2HPO_4 and cocatalytic amount of 1,4-benzoquinone was found to be of prime importance for achieving satisfactory results.

Scheme 4.15 Palladium-Catalyzed *ortho*-Arylation of Phenylacetic Acids



The addition of an amino acid ligand has shown to improve the efficiency of the reactions in palladium-catalyzed *ortho*-olefination of phenylacetic acids, done by Yu's group (Schem 4.15).[106] Electron-deficient phenylacetic acids also worked well with this methodology and reacted with potassium aryltrifluroborates to furnish the desired products in excellent yield. It was found to proceed well under 1 atm O_2 as the sole oxidant instead of Ag_2CO_3, which suggests the possibility of developing optimized ligands for constructing biaryl molecules via aerobic C−H /arylboron cross-coupling reactions.

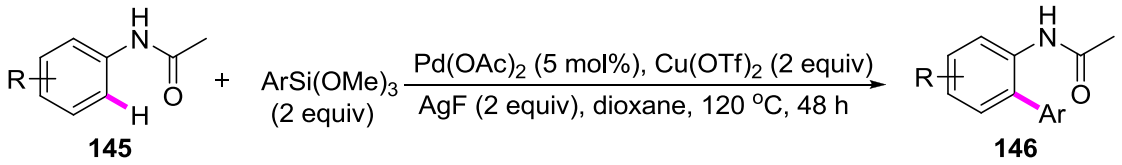
Scheme 4.16 Palladium-Catalyzed *ortho*-Arylation of Amides



Shi and co-workers recently demonstrated a set of conditions for the arylation of a wide range of aryl amides **143** with various aryl boronic acids using palladium catalysis (Scheme 4.16).[107] In one example, the coupling reaction of amides with 2-methyl phenyl

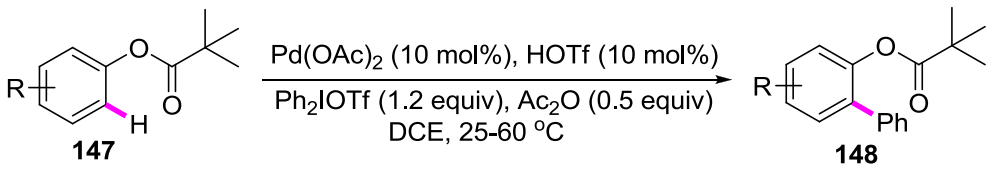
boron acid only provided a 20% isolated yield of the corresponding *ortho*-arylated product, probably arising from an increasing steric effect at the reaction site. The boronic acids with electron-withdrawing groups also did not perform well, likely due to the strong electron-withdrawing nature of nitro group.

Scheme 4.17 Palladium-Catalyzed *ortho*-Arylation of Amides



While the approach used by Shi employed aryl boron acids as coupling partners to *ortho*-arylate aryl amides, Loh used similar reaction conditions to construct biaryl amides **146** with a free N-H bond, whereby trialkoxylarylsilanes was used as coupling partner (Scheme 4.17).[108] The scope of this transformation is very broad. A variety of substitutes may be presented on the aryl ring or trialkoxylarylsilanes, including methyl, methoxyl, halide and phenyl groups.

Scheme 4.18 Palladium-Catalyzed *ortho*-Arylation of Phenol Esters



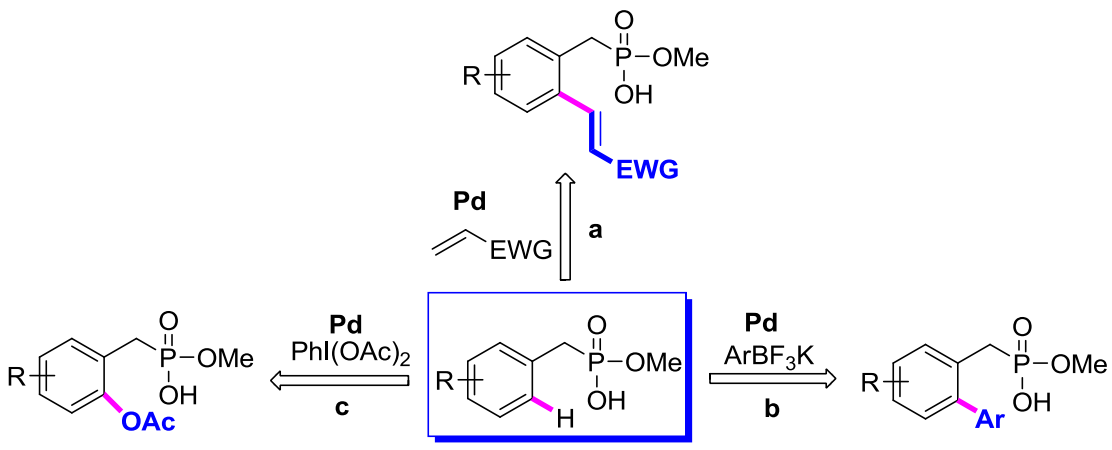
Ortho-arylation of phenol derivatives **147** with Ph_2IOTf using an ester directing group was illustrated by Liu and co-worker in 2010 (Scheme 4.18).[109] They proposed the reaction mechanism to proceed via a Pd(II)/Pd(IV) catalytic process, while Ph_2IOTf played the dual role of phenyl source and an oxidant. The reactions are mild to provide the corresponding *ortho*-arylated products in good to excellent yields. High functional group tolerance, high regioselectivity and good substrate scope were noticed.

4.3 Proposed Work

Our work for the following two chapters has been directed towards the development of new organophosphonate directing groups in C−H acitivation. We have focused on C−H functionalization of benzylic phosphonic acid using phosphonic monoester directing group. These newly developed methods enable the delivery of phosphorus containing compounds of biological and material interest in an efficient and selective manner.

In chapter 5, an efficient and convenient route to olefinated organic phosphonates is described via palladium-catalyzed C−H bond olefination of benzylic phosphonic compounds (Figure 4.1a). The newly olefinated benzylic phosphonates were achieved in Horner-Wadsworth-Emmons reactions. In chapter 6, we describe an *ortho*-arylation reaction of benzylic phosphonic monoesters with potassium aryltrifluoroborates using palladium catalyst (Figure 4.1b). In addition, the above successful approaches led us to investigate the potential of installing other useful functional groups, such as OAc (Figure 4.1c). The mechanism of direct *ortho*-acetoxylation reaction was thought to occur via a Pd^{II}/Pd^{IV} process. Finally, we concluded that organic phosphonates would be feasible for functionalization via transition metal-catalyzed C−H bond activation approach and provide an efficient and straightforward method to different kinds of organic phosphonates.

Figure 4.1 Functionzalization of Benzylic Phosphonic Monoesters



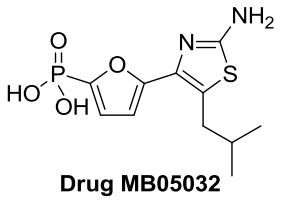
Chapter 5. Palladium (II)-Catalyzed *ortho*-Olefination and -Acetoxylation of Benzylic Phosphonic Monoesters

5.1 Introduction

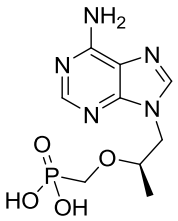
During the recent decades, there is a significant progress in transition metal-catalyzed C−H bond functionalizations to construct new C−C and C−X bonds.[110] In particular, directing group-based C−H activation approach has been well developed. Tremendous research literatures on transition metal-catalyzed C−H transformations have already been reported with the assistance of nitrogen- (including pyridines, amide, imine, oximes and oxazolines etc)[111] and oxygen-based directing groups (such as ketone, aldehyde, acid and phenol etc).[112] Despite the tremendous progress made in this area, C−H transformation still constitutes a remarkable synthetic challenge.

Phosphorus containing organic molecules have numerous biological functions and play a crucial role in the search for new pharmaceutical compounds.[113] For example, phosphonic acid functional group is an essential moiety of several therapeutic candidates as shown in Figure 5.1, which consist of anticancer, antibacterial, and anti-HIV.[114] Additionally, organophosphonates have wide application in organic chemistry, medicinal chemistry, and material science.[115] Therefore, tremendous efforts have been directed at the development of novel synthetic methods to generate phosphonate derivatives.

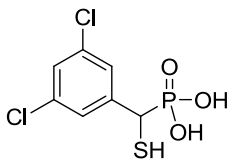
Figure 5.1 Drugs and Potential Therapeutic Agents contained a Phosponic Acid Moiety



Drug MB05032
Fructose 1,6-bisphophatase inhibitor
149



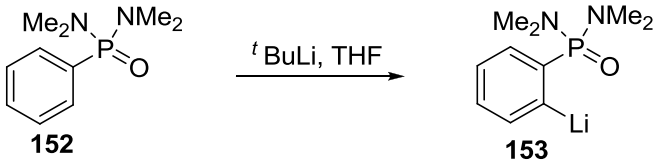
Drug Tenofovir
Used in AIDS (HIV) and HBV
150



Used in co-administration with antibiotic therapy
151

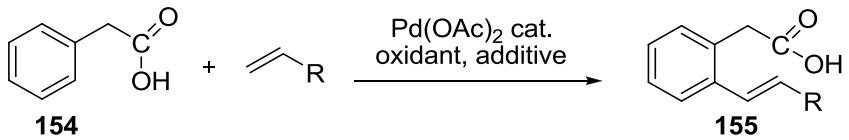
The phosphonic acid and its derivatives are widely used as important intermediates or reagents in synthetic chemistry.[116] Benzylic phosphonates are common structural motifs in biological chemistry. A useful method in the construction of alkene derivatives via Horner-Wadsworth-Emmons reactions in synthetic organic chemistry also required phosphonate functionality.[117] Traditional routes to this functional group were commonly depended on the Michaelis-Arbuzov reaction,[118] which employed a large quantity of Lewis acid or high temperature, or Michaelis-Berker reactions which required stoichiometric quantities of a strong base.[119] As a result, many functional groups were not compatible because of these harsh conditions. However, the direct functionalization of arene nucleus could avoid such limitation and provide access to the required functional groups.

Scheme 5.1 the *ortho*-Lithiation of Phosphonic Amide



152 **153**

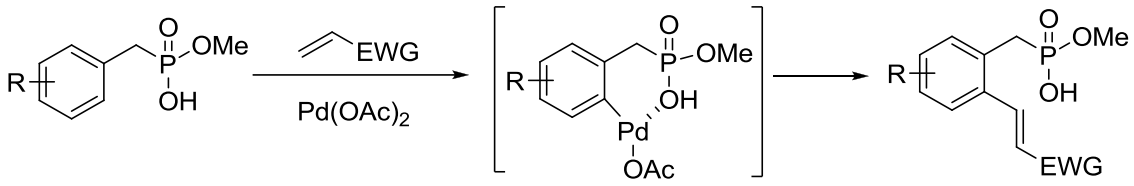
Scheme 5.2 Yu's Work on *ortho*-Olefination of Phenylacetic Acid



154 **155**

Based on reported literatures, the P=O bond of phosphonic amides has been employed as the chelation element in achieving *ortho*-lithiation (Scheme 5.1).[120,121] To the best of our knowledge, the use of phosphoryl-related groups to direct C−H activation has not been described before we published our work.[122] Previously, Yu developed Pd(II)-catalyzed *ortho*-olefination and *ortho*-arylation of C−H bonds in phenylacetic acids **154** using carboxylic acid as the directing group (Scheme 5.2).[123] Inspired by this result, we

Scheme 5.3 Palladium-Catalyzed *ortho*-Olefination of Benzylic Phosphonic Acids

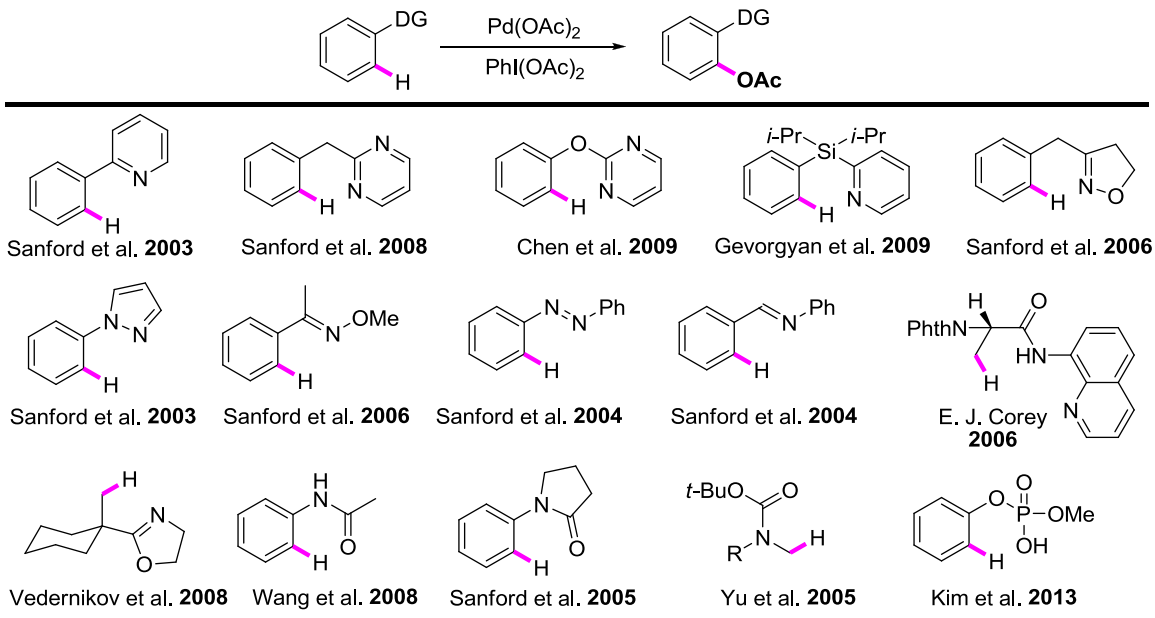


envisioned to establish a phosphonic acid-directed Pd(II)-catalyzed C−H activation on organophosphonates derivatives.

In this chapter, we disclosed a synthetic methodology for phosphonic acid assisted Pd(II)-catalyzed *ortho*-olefination of sp^2 C−H bonds of benzylic phosphonic mono esters (Scheme 5.3). The proposed reaction mechanism was also presented. In addition, the newly formed olefinated products were well tolerated in the Horner-Wadsworth-Emmons reaction.

A wide variety of directing groups, including pyridines, oxime ethers, imines, pyrazoles, amides, etc have been employed to furnish sp^2 C−H bond acetoxylation as shown in Scheme 5.4.[124] Extensive mechanistic studies of C−O bond formation via Pd(II)/Pd(IV) catalytic cycle were done by Sanford's group.[125] In our recent studies, we also proved

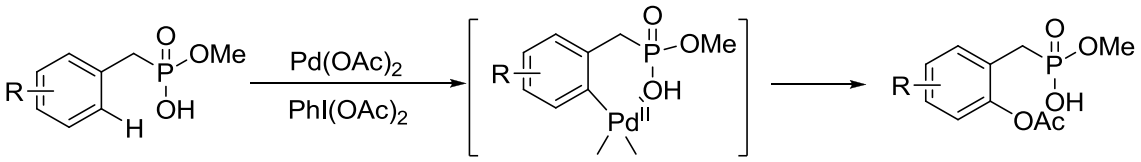
Scheme 5.4 Directing-Group-Assisted C−H Acetoxylation



the feasibility of Pd(II)/Pd(IV) catalysis in *ortho*-arylation in the presence of various aryl iodonium salts.[126] Therefore, we were motivated to further explore the diversity of C−H functionalization of such aryl organophosphonates.

In the second part of this chapter, we describe a Pd(II)-catalyzed *ortho*-acetoxylation of sp^2 C−H bonds of benzylic phosphonic monoesters (Scheme 5.5) and provided the possible reaction mechanism.

Scheme 5.5 Palladium-Catalyzed *ortho*-Acetoxylation of Benzylic Phosphonic Acids



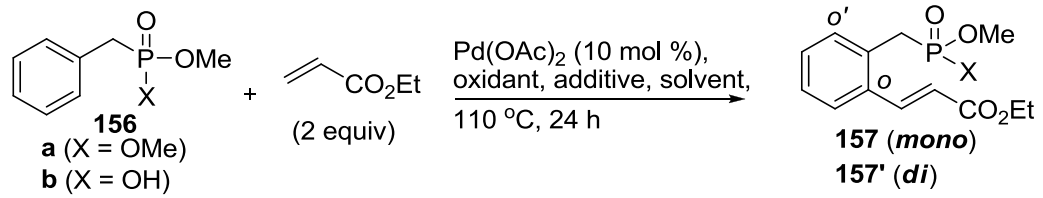
5.2 Results and Discussion

5.2.1 Palladium-Catalyzed *ortho*-Olefination of Benzylic Phosphonic Monoesters

The Pd-catalyzed *ortho*-olefination of dimethyl benzyl phosphonate **156a** with ethyl acrylate (2 equiv) as the olefin coupling partner was investigated and as shown in Table 5.1. Initially, the effectiveness of several common oxidants in C−H activation approach was tested. Reaction conducted with $Na_2S_2O_8$ oxidant did not afford the desired arylated products under palladium catalysis (Table 5.1 entry 1). The reactions still did not proceed after switching to AgOAc or $Cu(OAc)_2$ oxidant, and the model substrate **156a** was recovered in both cases (entries 2, 3).

Recently, several reports on palladium-catalyzed direct C−H bond transformations using hydroxyl moiety as coordinating site have been disclosed.[127] For example, Yu and coworkers have reported Pd(II)-catalyzed *ortho*-functionalization of phenyl actetic acids using an acid directing group and alcohol-directed C−H activation/C−O cyclization for construction of dihydrobenzofurans.[128] Gevorgyan and coworkers have reported

Table 5.1 Optimization of C−H Bond Olefination of Phosphonates **156a** and **156b**

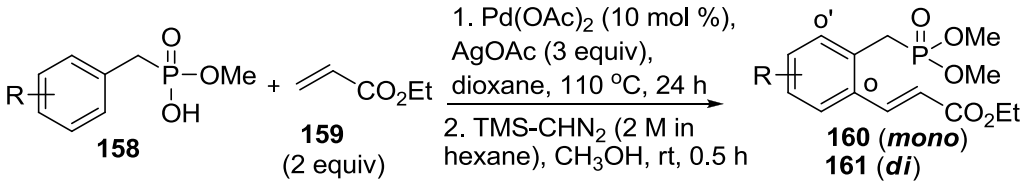


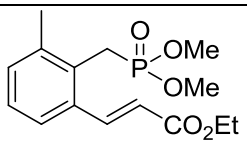
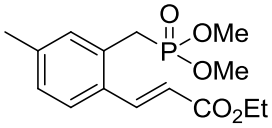
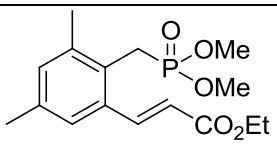
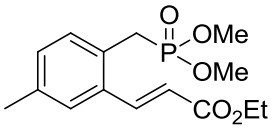
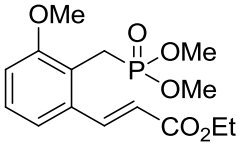
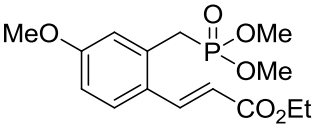
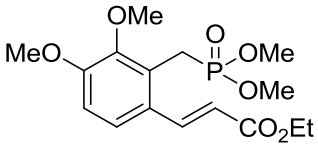
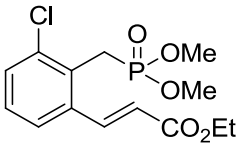
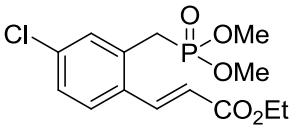
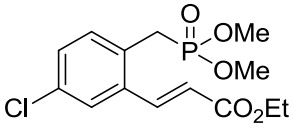
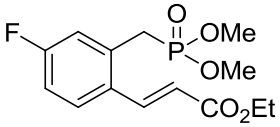
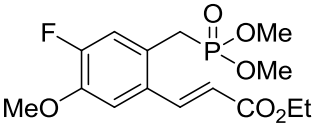
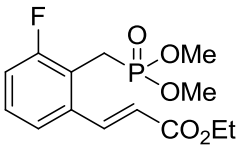
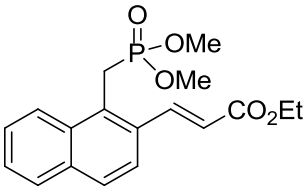
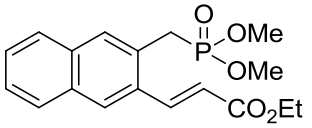
entry	substrate	ligand (20 mol%)	additive (1 equiv)	oxidant (equiv)	solvent	yield (%)[a] **157**:**157'**:**156**
1	**156a**	-	-	$Na_2S_2O_8$ (2)	DCE	0:0:100
2	**156a**	-	-	AgOAc (3)	Dioxane	0:0:100
3	**156a**	-	-	$Cu(OAc)_2$(2)	DCE	0:0:100
4	**156b**	-	Li_2CO_3	$Cu(OAc)_2$ (2) Ag_2O (2)	^{t}Amyl OH	10:5:85
5	**156b**	-	Li_2CO_3	AgOAc (3)	^{t}Amyl OH	38:27:35
6	**156b**	Boc-Val-OH	Li_2CO_3	AgOAc (3)	^{t}Amyl OH	55:22:27
7	**156b**	Boc-Leu-OH	Li_2CO_3	AgOAc (3)	^{t}Amyl OH	54:35:11
8	**156b**	Boc-Val-OH	Li_2CO_3	AgOAc (3)	DMF	5:0:95
9	**156b**	Boc-Val-OH	Li_2CO_3	AgOAc (3)	Toluene	39:26:35
10	**156b**	-	Li_2CO_3	AgOAc (3)	Dioxane	52:35:13
11	**156b**	-	Li_2CO_3	Ag_2O (2)	Dioxane	41:16:43
12	**156b**	-	Li_2CO_3	Ag_2CO_3 (2)	Dioxane	25:7:68
13	**156b**	-	-	AgOAc (3)	Dioxane	48:47:5
14[b]	**156b**	-	-	AgOAc (2)	Dioxane	51:20:29

[a] The yield and ratio was determined by ^{1}H NMR analysis.
[b] using 1 equiv of ethyl acrylate.

ortho-olefination of phenol derivatives using silanol as directing group.[129] The above works inspired us to employ phosphonic acid as the directing group. We next focused on using methyl hydrogen benzylphosphonate **156b** as the model substrate. Luckily, the reaction of methyl hydrogen benzylphosphonate **156b** with ethyl acrylate in the presence of $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv), Ag_2O (2 equiv) and Li_2CO_3 (1 equiv) in *t*-amyl alcohol at 110 ^oC for 24 h provided a small amount of the Heck-type products **157** and **157'** with excellent *E*-stereoselectivity (entry 4). In order to improve the yield, the reaction was then screened with various palladium catalysts, oxidants, and solvent. As shown in entry 5, AgOAc improved the conversion of the starting materials significantly, leading to a more promising result along with a small amount of recovered starting material. Inspired by the exciting effect of amino acid ligands in palladium-catalyzed *ortho*-olefination of phenyl actetic acids and silanol alcohol,[130] we added Boc-Val-OH (20 mol%) to the reaction mixture, and the result was slightly improved (entry 6). Changing the amino acid to Boc-Leu-OH almost gave the same results. (entry 7). Solvent played an important role in this reaction (entries 6–9). In fact, changing the solvent to dioxane improved the reaction and afforded the *mono*- and *bis*-olefinated products in better yields in the absence of the amino acid using AgOAc as oxidant (entry 10). As shown in entries 10 and 11, when the oxidant AgOAc was replaced with Ag_2O or Ag_2CO_3, lower yields were observed under these conditions (entries11 and 12). Surprisingly, a better result was obtained if the additive was removed from the reaction system (entry 13). In order to suppress the double arylation, we reduced the loading of AgOAc and ethyl acrylate. However, the result was not encouraging and a mixture of *mono*- and *bis*-olefinated product was again isolated with the unreacted starting material (entry 14). Therefore, 1 equiv of methyl hydrogen benzylphosphonate, 2 equiv of olefin coupling partner, 10 mol % $Pd(OAc)_2$ and 3 equiv AgOAc in refluxing 1,4-dioxane for 24 h were established as the optimized conditions.

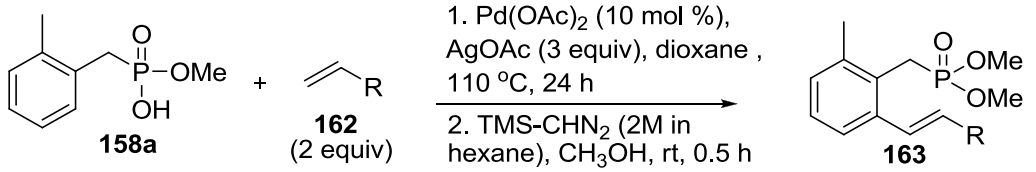
Table 5.2. Scope of the Olefination of Benzylic Phosphonates Derivatives

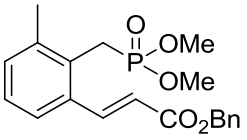


		
160a (91%)	**160b** (85%)	**160c** (97%)
		
160d (47%), **161d** (45%)	**160e** (90%)	**160f** (91%)
		
160g (95%)	**160h** (86%)	**160i** (81%)
		
160j (48%), **161j** (43%)	**160k** (74%)	**160l** (83%)
		
160m (36%) (61%)[a]	**160n** (85%)	**160o** (73%)

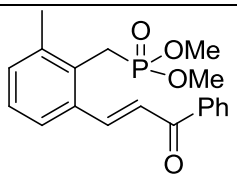
[a] The yield of the unconverted starting material.

Table 5.3. Scope of the Olefination of Alkene Derivatives with **158a**

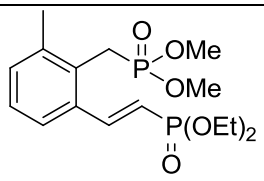




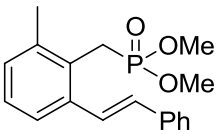
163a (91%)



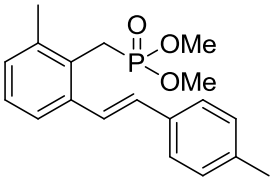
163b (63%) (30%)[a]



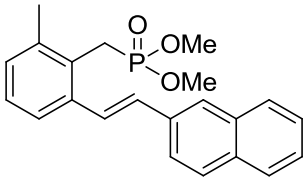
163c (76%)



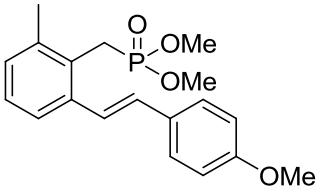
163d (85%)



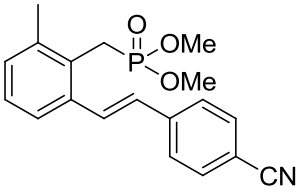
163e (81%)



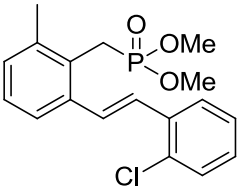
163f (71 %)



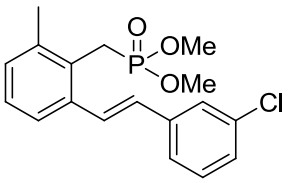
163g (55%) (40%)[a]



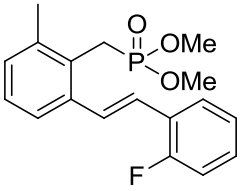
163h (73%)



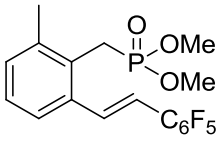
163i (84%)



163j (86%)



163k (93%)



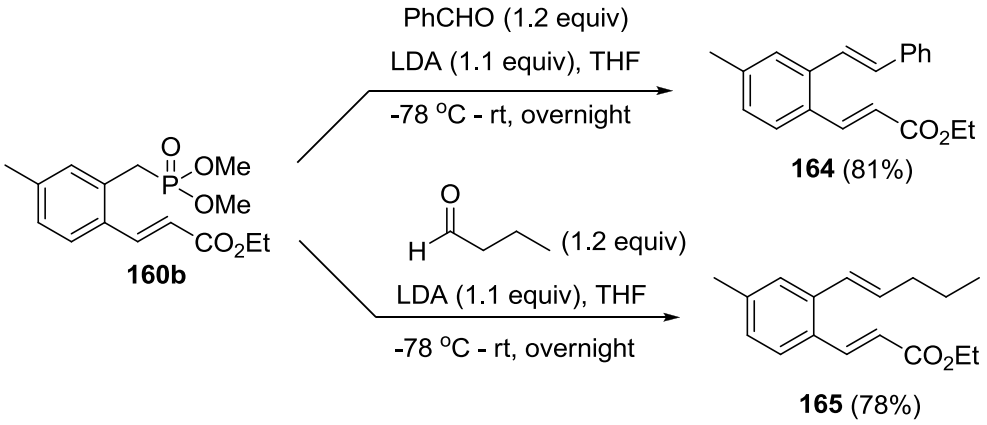
163l (96%)

[a] The yield of the unconverted starting material.

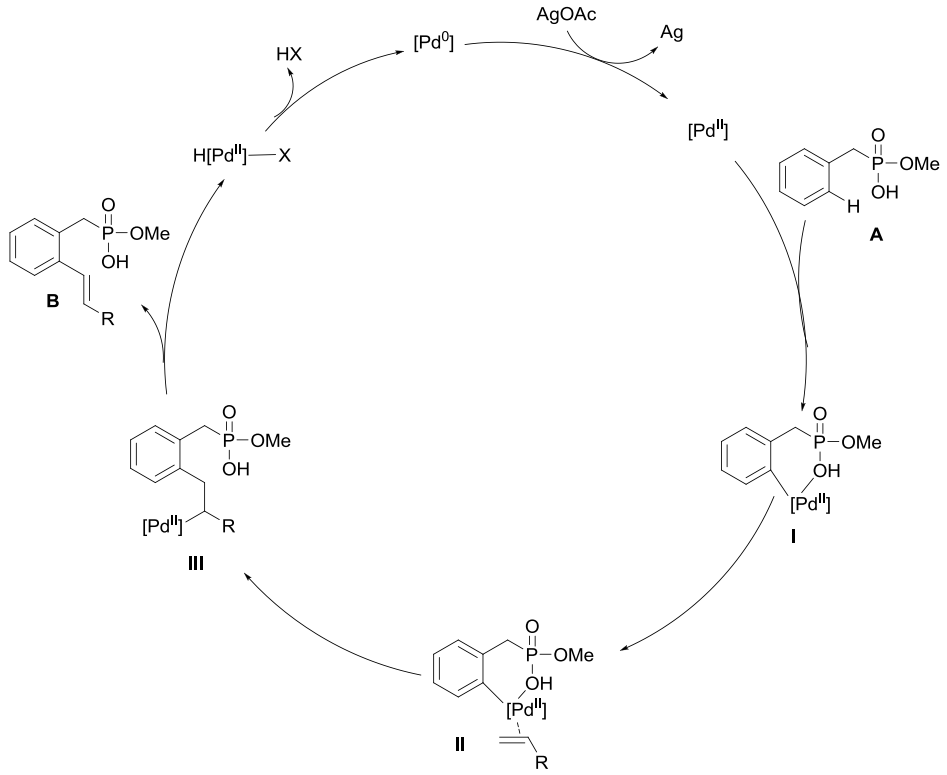
The standard optimization conditions were applied to various methyl hydrogen benzylphosphonates and ethyl acrylate. The results obtained were included in Table 5.2. For facile purifications, the newly formed crude products were methylated with TMS-diazomethane, leading to *mono*-olefinated product **160** and *bis*-olefinated product **161**. As we expected, a mixture of *mono*- and *bis*-olefinated products was isolated for methyl hydrogen benzylphosphonates lacking *ortho*- or *meta*-substitutent (**161d**, **161j**). *Ortho*-substituted substrates resulted in *ortho*-selective alkenylation process and *meta*-substituted molecules achieved regioselective *mono*-olefinations at the sterically less hindered site. Coincided with the above conclusion, the *ortho*-, *meta*-methyl, and dimethyl substituted moleculars reacted smoothly with ethyl acrylate to provide the corresponding *mono*-olefinated products at the less hindered sites (**160a**, **160b**, **160c**). Similarly, compounds (**158e**-**158g**) bearing electron-donating methoxy groups underwent clean olefination. The halogen-containing substrates are completely tolerated under the optimized condition. The chloride substituent had little effect on the yield of the C−H olefination and greater than 80% isolated yields of the olefinated products **160h** and **160i** were obtained. However, fluoride substituent had some effect on the reaction. The substituted position of fluride on the aromatic ring also makes a difference, probably arising from the electronic influence. The *meta*-fluoro substituted substrates gave the corresponding mono-olefinated products with good yield (**158k**, **158l**) but *ortho*-fluoro substituted **158m** resulted in lower yield along with the recovery of 61% unreacted starting material. In addition, naphthyl derivatives **158n** and **158o** also provided the corresponding *ortho*-olefinated product with good yield.

After investigating the functional group tolerance of such catalytic sysyem with benzylic phosphonic acid *mono*-esters, we next turned our attention to the reactivity of various alkene coupling partners by varying the functional group. As shown in Table 5.3, olefins with electron-withdrawing groups such as benzyl acrylate and vinyl phosphate

Scheme 5.6 Horner-Wadsworth-Emmons Reaction with **160b**



Scheme 5.7 Possible Reaction Mechanism



efficiently reacted with **158a** under the present conditions to produce the corresponding Heck-type products **163a** and **163c** in 91% and 76% yield, respectively. When the catalytic system was also tested on phenyl vinyl ketone, the starting material did not consume completely, leading to **163b** in 63% yield and the recovery of starting material **158a** (30%). Olefination proceeded with high efficiency using various styrene derivatives.

Styrene derivatives bearing electron-withdrawing substituents provided the corresponding olefinated products with good efficiency (**163h**-**163l**), while the reaction did not go to completion for the electron-donating methoxy group (**163g**). Unfortunately, when ethyl crotonate and allylbenzene were employed as the coupling patarner, the corresponding olefinated products were not observed and the starting material was isolated quantitatively.

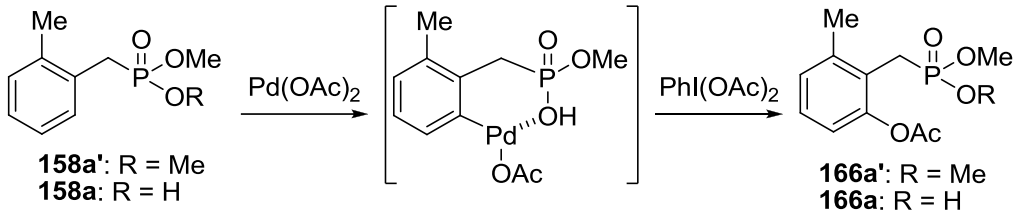
To explore the application of the current methodology, we performed the Horner-Wadsworth-Emmons reaction onto the newly formed olefinated products (Scheme 5.6). Fortunately, the reactions proceeded smoothly to produce the desired alkenes **164** and **165** in high yield.

Based on the reported palladium(II)-catalyzed directing group-based C−H *ortho*-olefination reactions, we proposed the reaction to follow the mechanism as shown in Scheme 5.7. First of all, the weaker coordination of Pd(II) with the hydroxyl moiety of **A** could cleave C−H bond in a similar fashion to that of phenylacetic acid substrates. Then, the arylpalladium(II) complex **I** would coordinate with olefin to generate species **II**. Subsequent 1,2-migratory insertion led to metal complex **III**, which underwent *β*-hydride elimination to afford olfinated product **B** and H[Pd^{II}]-X species. Then fast liberation of HX gives Pd(0). In the presence of an oxidant reagent, Pd(0) was reoxidized to complete the cycle of the reaction.

5.2.2 Palladium-Catalyzed *ortho*-Acetoxylation of Benzylic Phosphonic Monoesters

For *ortho*-acetoxylation of benzylic phosphonic monoesters, we initially chose dimethyl 2-methylbenzylphosphonate (**158a'**) as the model substrate for the preliminary studies as shown in Table 5.4. No corresponding product was observed when **158a'** was treated with 10 mol % $Pd(OAc)_2$, 2 equiv of $PhI(OAc)_2$ at 110 ^oC for 15 h in both 1,2-dichloroethane

Table 5.4 Optimizing Reaction Conditions of *ortho*-Acetoxylation for **158** [a]

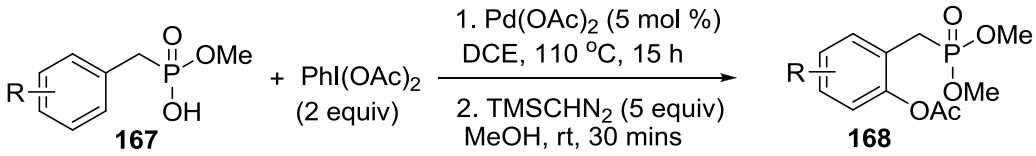


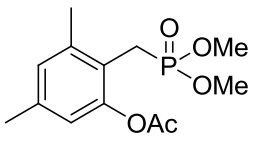
entry	substrate	temp (^{o}C)	solvent	conv (%)[b]
1	**158a'**	110	DCE	0
2	**158a'**	110	dioxane	0
3	**158a**	110	dioxane	0
4	**158a**	110	MeOH	0
5	**158a**	110	DMSO	0
6	**158a**	110	DMF	13
7	**158a**	110	AcOH	53
8	**158a**	110	toluene	56
9	**158a**	110	DCE	91
10[c]	**158a**	110	DCE	93 (91)[d]

[a] Conditions: 0.15 mmol of **158a**, 2 equiv of $PhI(OAc)_2$, 10 mol % of $Pd(OAc)_2$ in 1 mL of solvent for 15 h at 110 ^{o}C. [b] Conversion of starting material **158a**, based on crude NMR. [c] 5 mol % of $Pd(OAc)_2$ was used. [d] Isolated yield after methylation with $TMSCHN_2$.

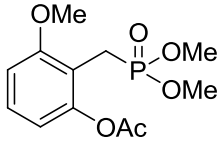
and 1,4-dioxane (entries 1 and 2). Intrigued by the above results obtained from *ortho*-olefination of phosphonic acids, we then used methyl hydrogen 2-methylbenzylphosphonate **158a** to examine various solvents for *ortho*-acetoxylation reactions. When **158a** was performed under various solvents such as 1,4-dioxane, methanol, and DMSO, the reaction did not proceed and the starting material **158a** was recovered quantitatively (entries 3-5). Using DMF as solvent, the reaction occurred and delivered the product **166a** in a low yield of 13% (entry 6). This result indicated that the

Table 5.5 Substrate Scope in *ortho*-Acetoxylation[a]

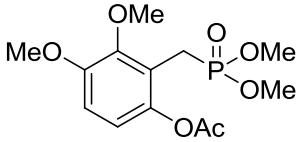




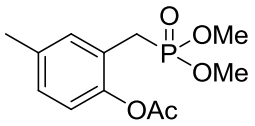
168a (93%)



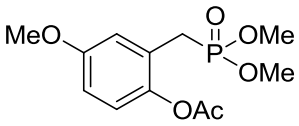
168b (92%)



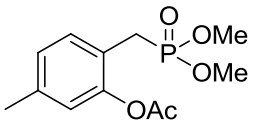
168c (94%)



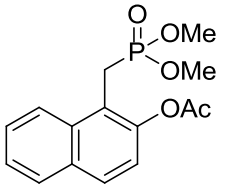
168d (85%)



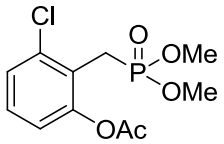
168e (83%)



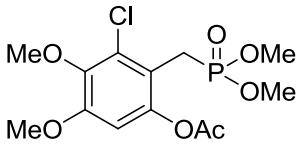
168f[b] (53%) (15%)[c] (17%)[d]



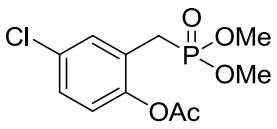
168g (76%)



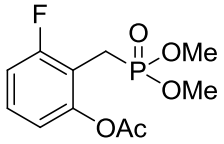
168h (86%)



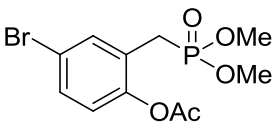
168i (95%)



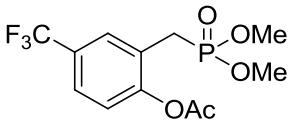
168j (82%)



168k (81%)



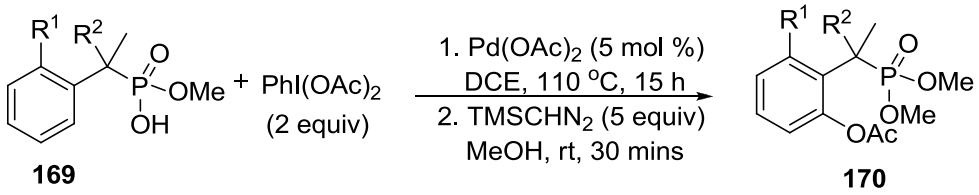
168l (93%)



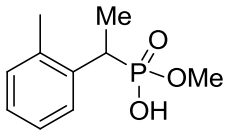
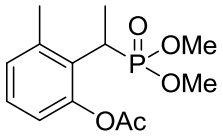
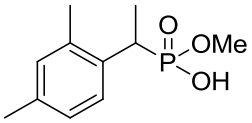
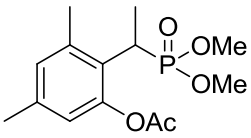
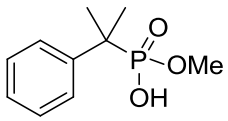
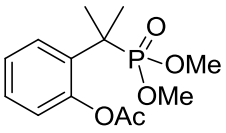
168m (91%)

[a] Isolated yield. [b] 1.1 equiv of $PhI(OAc)_2$ was used. [c] Yield of diacetoxylated product. [d] Recovery yield of methylated starting material.

Table 5.6 *ortho*-Acetoxylation of **169**



169 **170**

entry	substrate		product		yield (%)
1		**169a**		**170a**	88
2		**169b**		**170b**	90
3		**169c**		**170c**	93

solvent used was crucial for the success of this process. When changing the solvent to AcOH or toluene, the mixture of **158a**, 10 mol % $Pd(OAc)_2$, 2 equiv of $PhI(OAc)_2$ at 110 ^oC afforded the product **166a** in a promising yield of 53% and 56%, respectively (entries 7-8). Gratifyingly, 1,2-dichloroethane has proven to be the most ideal solvent in this *ortho*- acetoxylation (entries 9-10), and reducing the catalyst loading to 5 mol % did not hinder the reaction (entry 10), with an isolated 91% yield of product after methylation.

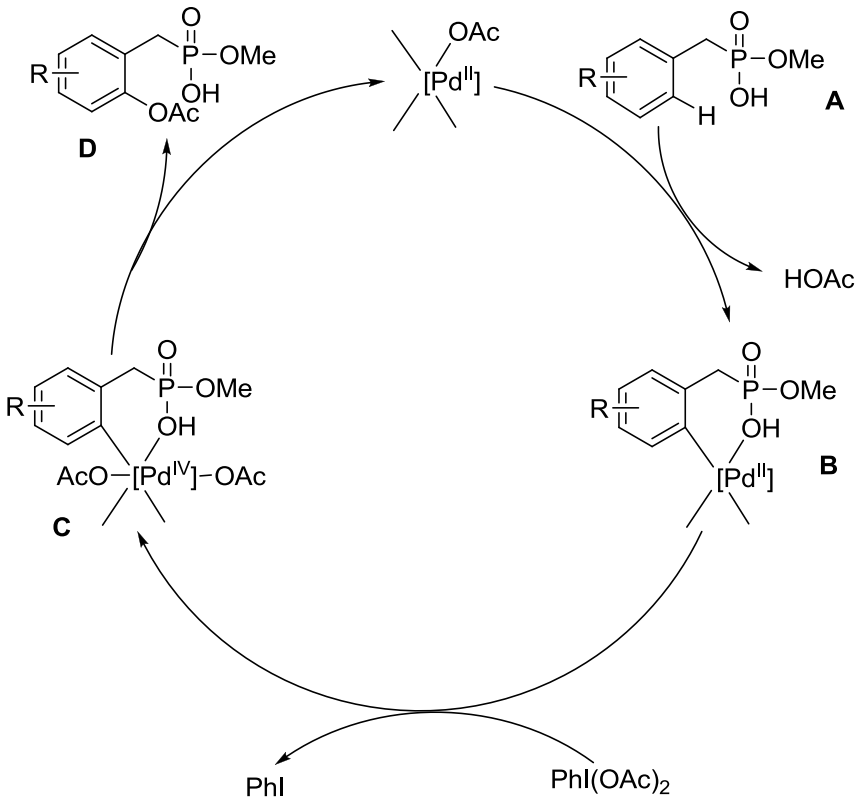
With the optimized conditions in hand, the scope of Pd-catalyzed *ortho*-acetoxylation of benzylic phosphonic acid was then investigated as shown in Table 5.5. For facile purification, the crude acetoxylated benzylic phosphonic acids were first methylated using TMS-diazomethane to afford the respective methyl phosphonate esters **168**. The reaction

went smoothly for alkyl or alkoxyl substitutents at the *ortho*- or *meta*-position (**168a**-**168e**). Undoubtly, the *mono*-acetoxylated products were obtained for *ortho*-substituted substrates (**168a**-**168c**). Excellent regioselectivities were observed for substrates that were blocked at the *meta*-position because the reaction preferred to proceed at the less-hinded C−H bonds to provide *mono*-acetoxylated products (**168d**, **168e**). However, further *ortho*-acetoxylation was observed when using **168f** with methyl substituted at the *para*-position (**168f**), and 15% of *di*-acetoxylated product was also isolated even when only 1.1 equiv $PhI(OAc)_2$ was used. The reaction also occurred nicely for naphthalene derivative (**168g**). Chlorosubstituted benzylic phosphonic acids were completely compatible in this optimized condition and gave the corresponding products in high yield (**168h**-**168j**). Similarly, the substrate containing fluoride was compatible under present conditions (**168k**). The Acetoxylated substrated **168l** containing bromide could be used for further coupling reactions. In addition, benzylic phosphonic acid containing a strong electron-withdrawing CF_3 group at the *meta* position also worked well in this protocol (**168m**).

The efficiency of this catalytic process encouraged us to examine the regioselectivity of substrates **169** bearing *α*-substituents (Table 5.6). Secondary substrates **170a** and **170b** with methyl substituent at the *ortho*-position gave the desired products in 88% and 90% yield, respectively. Tertiary substrate **170c** with sufficient steric hindrance only delivered *mono*-acetoxyled product **170c** in 93% yield.

Based on reported literatures on palladium-catalyzed *ortho*-acetoxylation, a possible reaction pathway was proposed as shown in Sccheme 5.8. Initially, a phosphonic acid-directed Pd insertion afforded a cyclopalladated intermediate **B** and subsequent oxidation of the palladacycle by $PhI(OAc)_2$ provided Pd(IV) intermediate **C**. Reductive elimination of the Pd(IV) achieves C-O bond formation to generate the product **D** along with the

Scheme 5.8 Possible Reaction Mechanism



liberation of Pd(II) catalyst. An alternative Pd(II)/Pd(III) redox catalysis with I(III) oxidants as demonstrated by Ritter's group offered another insight into the mechanism.[131]

5.3 Conclusion

We have developed a novel and general approach for the Pd(II)-catalyzed *ortho*-alkenylation and *ortho*-acetoxylation of benzylic phosphonates using the phosphonic monoester directing group. This transformation has a wide substrate scope for the direct functionalization of aromatic molecules containing phosphate functional groups. Moreover, Horner-Wadsworth-Emmons reactions could be easily applied onto the products obtained, making it an attractive method. Further studies on metal-catalyzed C−H activation reactions using phosphate group as directing group would be feasible.

Chapter 6. Palladium(II)-Catalyzed *ortho*-Arylation of Benzylic Phosphonic Monoesters with Potassium Aryltrifluoroborates

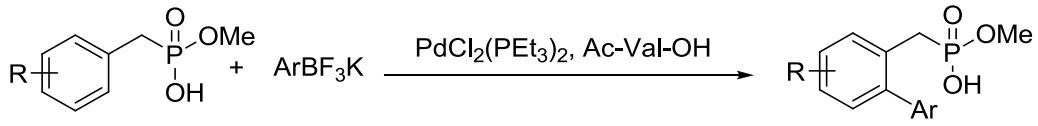
6.1 Introduction

Palladium-catalyzed and coordination-assisted direct *ortho*-arylation of functionalized arenes is an atom- and step-economic tool for making various biaryls and thus has been extensively studied.[132] Recently, our group and several other research groups have focused on the application of Pd-catalyzed C−H activations using mono-phosphoric acid derivatives as a new class of such "modern" directing groups.[133] In previous chapter, we have reported Pd-catalyzed *ortho*-alkenylation and acetoxylation of benzylic phosphonic monoesters. In addition, our group has also achieved Pd-catalyzed C−H bond functionalization of phosphoric acids and phosphoramidates.[128c-128e] Meanwhile, Lee and several other research groups have focused on Rh-catalyzed C−H activations using phosphonic-acid directing groups.[134]

The success of our work using new mono-phosphonic acid directing groups in C−H activation indicated the possibility of installing other functional groups on phosphoryl-related arene substrates via transition metal-catalyzed C−H activation process. As an extension of our work, we investigated the *ortho*-arylation of benzylic phosphonate *mono*-esters. In analogous studies, Yu reported the Pd(II)-catalyzed *ortho*-arylation of phenylacetic acids using arylboron reagents and found remarkable beneficial effects of amino acid ligands.[135]

In this chapter, we describe our results on Pd(II)-catalyzed *ortho*-arylation of benzylic phosphonic *mono*-esters with potassium aryltrifluoroborates (Scheme 6.1). The

Scheme 6.1 Palladium-Catalyzed *ortho*-Arylation of Benzylic Phosphonic Acids



mechanistic studies were carried out using a deuterated substrate and the proposed reaction pathway is also provided. Additionally, the application of the newly formed arylated products in Horner-Wadsworth-Emmons reaction is presented.

6.2 Results and Discussion

Recently, our group reported Pd(II)-catalyzed cross-coupling of C(sp^2)-H bond of **171** and diaryliodonium triflates.[5d] Encouraged by this successful protocol, Initially, the same conditions were employed using aryl benzylic phosphonate **158a**. Surprisingly, *O*-phenylation occurred to some extent instead, without observing the formation of desired product **173b** (Scheme 6.2). *O*-Arylation of phenols derivatives with diaryliodonium triflates was reported in recent years.[136] The reaction was sensitive to the oxidant used and the desired product **173b** was not isolated in any cases.

We next turned our attention to arylboron coupling partners as shown in Table 6.1. Using 10 mol % $Pd(OAc)_2$ catalyst and AgOAc oxidant (3 equiv) in refluxing dioxane, various arylboron coupling partners were examined. It was found that both the phenylboronic acid pinacol ester and the phenylboronic acid neopentylglycol ester provided lower yields of *mono*-arylated product **174,** along with the recovery of starting material, without observing any *di*-arylated product **175** (entries 1, 2). However, phenylboronic acid pyrocatechol ester, phenylboronic acid and 2,4,6-triphenylboroxin were totally ineffective and no reaction occurred (entries 3, 4 and 5). When we next used potassium aryltrifluoroborate salts as a coupling partner.[137,138] No reaction occurred in refluxing dioxane (entry 6). Gratifyingly, the phenylation occurred to some extent

Scheme 6.2 Reaction of **171** and **158a** with Ph_2IOTf

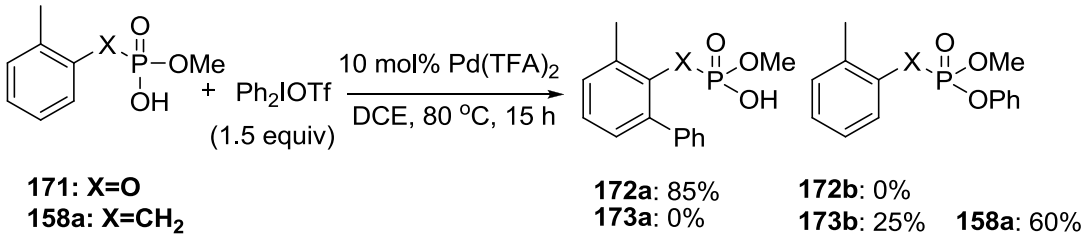
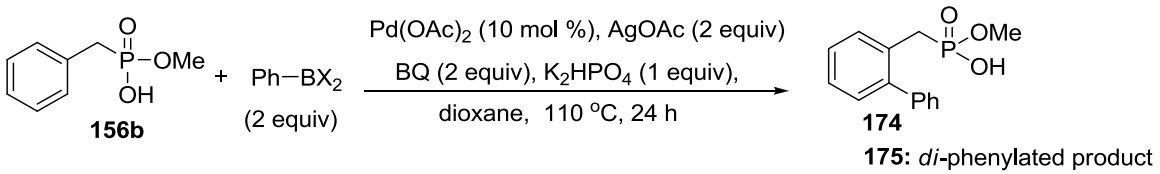
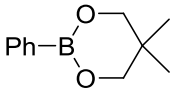
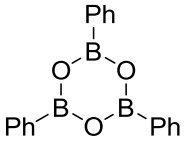
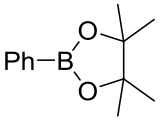
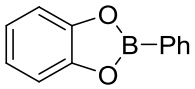


Table 6.1 Arylboron Coupling Partners Optimization

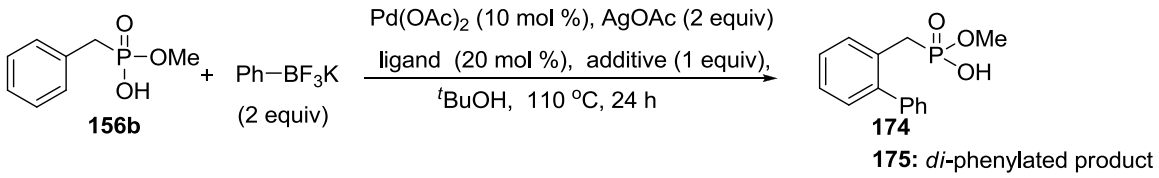


entry	Ph-BX_2	yield (%)[a] (**174**:**175**:**156b**)[b]	entry	Ph-BX_2	yield (%)[a] (**174**:**175**:**156b**)[b]
1		30:0:70	5		0:0:100
2		17:0:83	6	Ph−BF_3K	0:0:100
3		0:0:100	7[c]	Ph−BF_3K	28:10:62
4	Ph−$B(OH)_2$	0:0:100	8[c,d]	Ph−BF_3K	31:15:54

[a] The yield and ratio was determined by ^{1}H NMR analysis. [b] The mixture was converted to its methyl ester with diazomethane. [c] The reaction was carried out using ^{t}BuOH as solvent. [d] The reaction was carried out without BQ.

after changing the solvent from dioxane to *t*-BuOH, yielding a 28:10:62 mixture of **174**, **175** and **156b** (entry 7). Without BQ, a slightly better result was obtained (entry 8). Obviously, these initial results were not very promising.

Table 6.2 Ligands and Additive Optimization

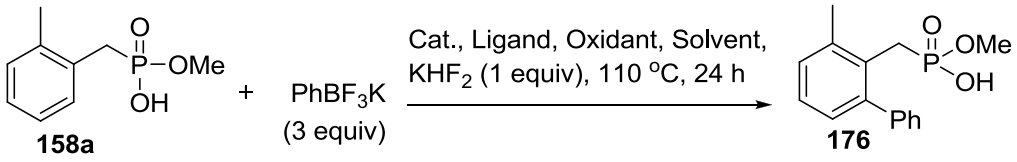


entry	ligand	additive	yield (%)[a] (**174**:**175**:**156b**)[b]
1	Boc-Ala-OH	$KHCO_3$	35:15:50
2	Boc-Val-OH	$KHCO_3$	42:29:29
3	Boc-Ile-OH • 0.5 H_2O	$KHCO_3$	50:23:27
4	Boc-Leu-OH	$KHCO_3$	46:20:34
5	Ac-Val-OH	$KHCO_3$	43:32:25
6	Ac-Val-OH	K_2HPO_4	39:13:48
7	Ac-Val-OH	Li_2CO_3	38:20:42
8	Ac-Val-OH	KHF_2	57:25:18

[a] The yield and ratio was determined by ^{1}H NMR analysis. [b] The mixture was converted to its methyl ester with diazomethane.

Inspired by Yu's work on C−H arylation of phenylacetic acids using amino acids as ligands,[8] several amino acids were screened (entries 1-5). To our delight, the yields of *mono*-and *di*-arylated products could be dramatically improved when amino acid ligands were employed. The results also indicated that the nature of amino acid ligands did not influence the reaction greatly. Compared to *mono-N*-Boc-protected amino acids, the *mono-N*-Ac-protected amino acid improved the yield slightly (entry 5), but the conversion of the starting material **156b** to **174** was not complete. Among several additives tested, KHF_2 gave the best effect (entries 6-8), however, the starting material **156b** was not consumed totally. We then turned our attention on screening catalyst, ligand, oxidant, and solvent, in order to achieve full conversion of the starting materials to the

Table 6.3 Optimization of Reaction Conditions



Entry	Cat. (10 mol %)	Ligand (20 mol %)	Oxidant (2 equiv)	Solvent	Yield (%)[a] (**176**:**158a**)
1	$Pd(OAc)_2$	Ac-Val-OH	AgOAc	^{t}BuOH	63:32
2	$Pd(OAc)_2$	Ac-Val-OH	Ag_2O	^{t}BuOH	65:26
3	$Pd(OAc)_2$	Boc-Val-OH	Ag_2O	^{t}BuOH	49:43
4	$PdCl_2$	Ac-Val-OH	Ag_2O	^{t}BuOH	11:76
5	$PdCl_2(PPh_3)_2$	Ac-Val-OH	Ag_2O	^{t}BuOH	62:27
6	**$PdCl_2(PEt_3)_2$**	**Ac-Val-OH**	**Ag_2O**	**^{t}BuOH**	**85:8**[b]
7	$PdCl_2(PEt_3)_2$	-	Ag_2O	^{t}BuOH	62:28
8	$PdCl_2(PEt_3)_2$	Boc-Val-OH	Ag_2O	^{t}BuOH	60:34
9	$PdCl_2(PEt_3)_2$	Ac-Val-OH	AgOAc	^{t}BuOH	23:70
10	$PdCl_2(PEt_3)_2$	Ac-Val-OH	Ag_2CO_3	^{t}BuOH	10:81
11	$PdCl_2(PEt_3)_2$	Ac-Val-OH	$Na_2S_2O_8$	^{t}BuOH	0:100
12	$PdCl_2(PEt_3)_2$	Ac-Val-OH	$Cu(OAc)_2$	^{t}BuOH	0:100
13	$PdCl_2(PEt_3)_2$	Ac-Val-OH	Ag_2O	DMSO	12:80
14	$PdCl_2(PEt_3)_2$	Ac-Val-OH	Ag_2O	Toluene	35:21
15	$PdCl_2(PEt_3)_2$	Ac-Val-OH	Ag_2O	Dioxane	36:17
16	$PdCl_2(PEt_3)_2$	Ac-Val-OH	Ag_2O	DMF	62:30

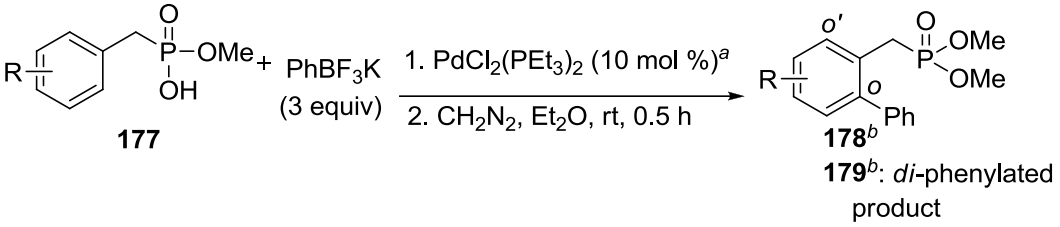
[a] The yield and ratio was determined by ^{1}H NMR analysis. [b] **176** was converted to its methyl ester (**176a**) with diazomethane.

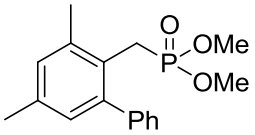
arylated products. Methyl hydrogen 2-methylbenzylphosphonate (**158a**) was then chosen as the substrate for optimization.

When **158a** was treated with $PhBF_3K$ using 10 mol % $Pd(OAc)_2$ catalyst, 20 mol % Ac-Val-OH ligand, and AgOAc oxidant in refluxing *t*-butanol for 24 h, a 63:32 mixture of **176** and **158a** was obtained (entry 1, Table 6.3). Ag_2O oxidant was equally effective (entry 2) but Boc-Val-OH ligand was slightly less effective (entry 3). After many futile experiments, the effectiveness of other Pd(II) catalysts was investigated. $PdCl_2$ was inferior to $Pd(OAc)_2$ (entry 4), whereas $PdCl_2(PPh_3)_2$ was equally effective as $Pd(OAc)_2$, but not the best choice (entry 5). Gratifyingly, $PdCl_2(PEt_3)_2$ catalyst was found to be most effective for arylation of **158a** under the same conditions (entry 6).[139] Among the oxidants tested in this study, $Na_2S_2O_8$ and $Cu(OAc)_2$ were totally ineffective (entries 11 and 12) and Ag_2O gave the best results (entry 6). Furthermore, the reaction was sensitive to solvent and *t*-butanol was found to be the superior solvent (entries 13–16).

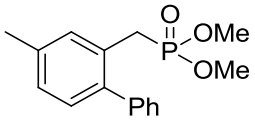
Under the optimized conditions, we tested the scope of this catalytic protocol with benzylic phosphonic monoesters carrying a number of substituents as shown in Table 6.4. For facile purification, the crude arylated products were methylated using diazomethane to achieve the corresponding methyl esters **178**. Both electron-rich and electron-poor substrates worked well. For instance, substrates containing electron-donating groups (Me and OMe) were converted to the arylated products in good to excellent yield (**178a**-**178e**), with high *ortho* selectivity. Undoubtly, mono-arylated products were obtained when using substrate with *ortho*-substitutent (**178a**, **178d**). In the case of *meta*-substituted phosphonic acids, the reaction occurred at the less sterically hindered position to give only the mono-arylated products (**178b**, **178e**). When the reaction was carried out with methyl hydrogen phenylphosphonate (**177c**) using 1.1 equiv of $PhBF_3K$, a 51:15 mixture of **178c** and **179c** was obtained, along with the recovery of **177c** (23%). For *para*-substituted substrate **177i**, a similar result was obtained. The *ortho*- and

Table 6.4 Substrate Scope of Benzyl Phosphoric Acids

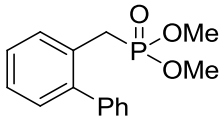




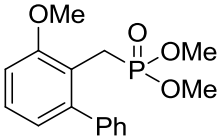
178a (91 %)



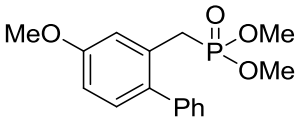
178b (86 %)



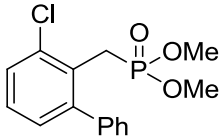
178c[b] (51 %) **179c** (15 %)



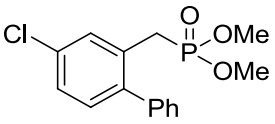
178d (90 %)



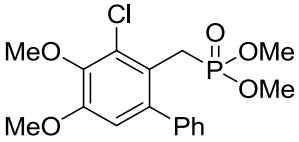
178e (85 %)



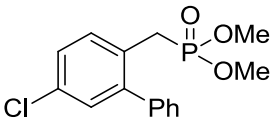
178f (83 %)



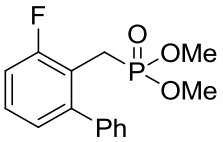
178g (82 %)



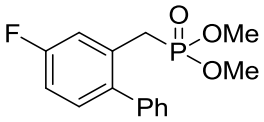
178h (93 %)



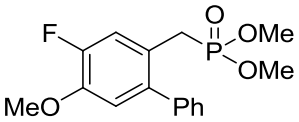
178i[b] (47 %) **179i** (12 %)



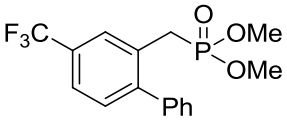
178j (71 %) (25 %)[c]



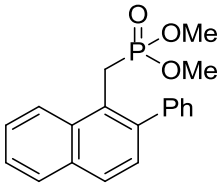
178k (80 %)



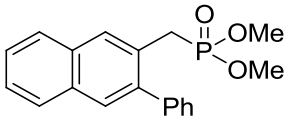
178l (81 %)



178m (92 %)



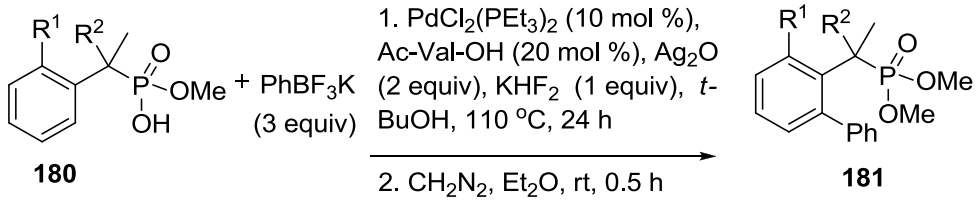
178n (87%)



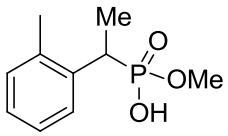
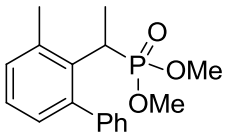
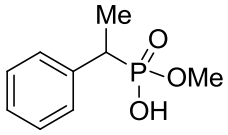
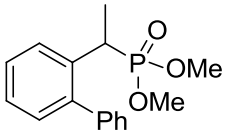
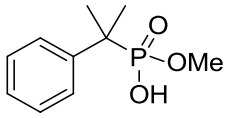
178o (76%)

[a] The reaction was carried out with Ac-Val-OH (20 mol %), Ag_2O (2 equiv), KHF_2 (1 equiv) in *t*-BuOH at 110 °C for 24 h. [b] Isolated yield. [c] 1.1 equiv of $PhBF_3K$ was used. [d] The isolated yield of the recovered starting material.

Table 6.5 *ortho*-Phenylation of **180** with $PhBF_3K$



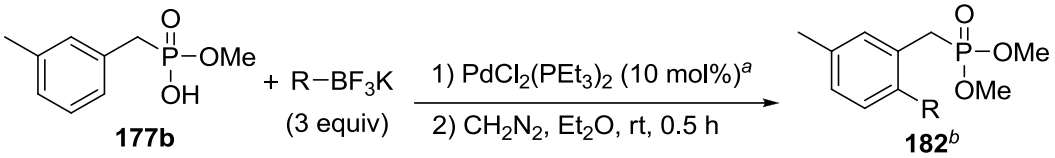
180 **181**

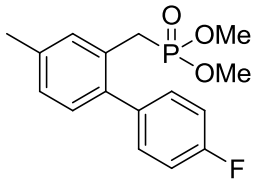
entry	substrate		product		yield (%)
1		**180a**		**181a**	88
2		**180b**		**181b**	75 (20)[a]
3		**180c**	-		-

[a] The isolated yield of the recovered starting material.

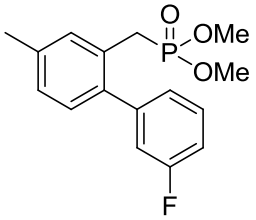
meta-chloro-substituted substrates underwent *ortho*-phenylation cleanly, giving the desired products (**178f**, **178g**, **178h**) in high yield, whereas the fluoro-substituted substrates were influenced to some extent by the position of substitution. The *meta*-substituted substrates worked well to afford the products in excellent yields (**178k**, **178l**), while the *ortho*-substituted substrate slowed down the reaction, yielding **178j** in 71% yield together with the recovery of starting material **177j** (25%). Notably, phosphonic monoester **177m** bearing a strong electron-withdrawing CF_3 group underwent clean phenylation to give **178m** in 92% yield. Naphthyl derivatives also worked well to give the corresponding arylated products **178n** and **178o** in 87% and 76%, respectively. As shown in Table 6.5, the phenylation of a secondary and a tertiary benzylic substrate was briefly

Table 6.6 Substrate Scope of Potassium Aryltrifluoroborates

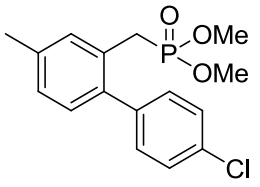




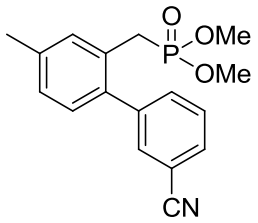
182a (93 %)



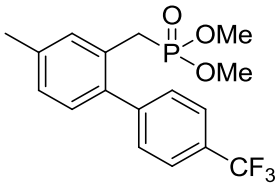
182b (89 %)



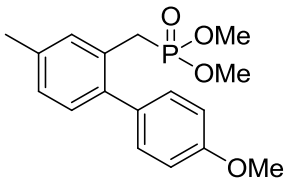
182c (95 %)



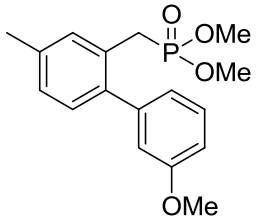
182d (91 %)



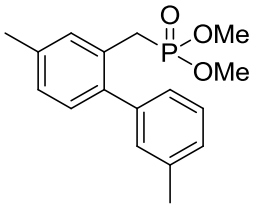
182e (73 %) (20 %) [b]



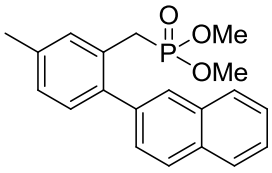
182f (92 %)



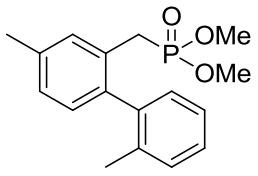
182g (76 %) (18 %) [b]



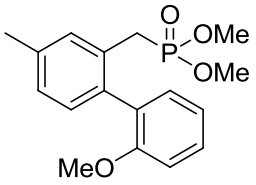
182h (71 %) (25 %) [b]



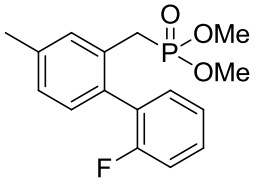
182i (88 %)



182j (0 %) (92 %)[b]



182k (0 %) (88 %) [b]



182l (13 %) (80 %) [b]

[a] The reaction was carried out with Ac-Val-OH (20 mol%), Ag_2O (2 equiv), KHF_2 (1 equiv) in *t*-BuOH at 110 °C for 24 h. [b] Isolated yield. [c] Isolated yield of the recovered **177b**.

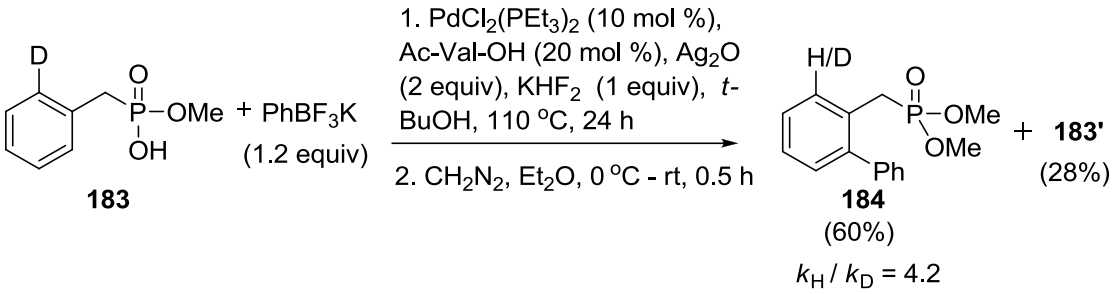
examined and two noteworthy features were found. Firstly, secondary substrate **180a** underwent smooth phenylation to give **181a** in 88% yield but tertiary substrate **180c** failed, probably due to steric hindrance. Secondly, selective mono-phenylation at the *ortho*-position was achieved with **180b**.

To further determine the scope of the method, structurally different potassium aryltrifluoroborates were utilized under the standard conditions (Table 6.6). Potassium aryltrifluoroborates containing electron-withdrawing groups (F, Cl, CN) reacted with **177b** to afford the corresponding *ortho*-arylated products in high yields (**182a-182d**). In the case of strong electron-withdrawing CF_3 group, the arylation was slowed down, yielding **182e** (73%) along with the recovery of **177b** (20%). This catalytic system also effectively promoted the cross-coupling of **177b** with boron reagents bearing electron-donating groups (OMe and Me) to provide the desired products in moderate to excellent yields. Although potassium 4-methoxyphenyltrifluoroborate worked as an excellent coupling partner as shown in **182f**, the *meta*-substituted boron reagents slowed down the reaction considerably (**182g** and **182h**), probably arising from the steric hindrance of the *meta*-substituents. Consistent with the observation, *ortho*-substituted aryltrifluoroborates could not be used as the coupling partners. Thus, the formation of **182j** and **182k** were not observed, while **182l** was isolated only in 13% yield. Furthermore, potassium vinyl and *n*-butyl trifluoroborate failed to undergo *ortho*-alkenylation and alkylation under the standard conditions.

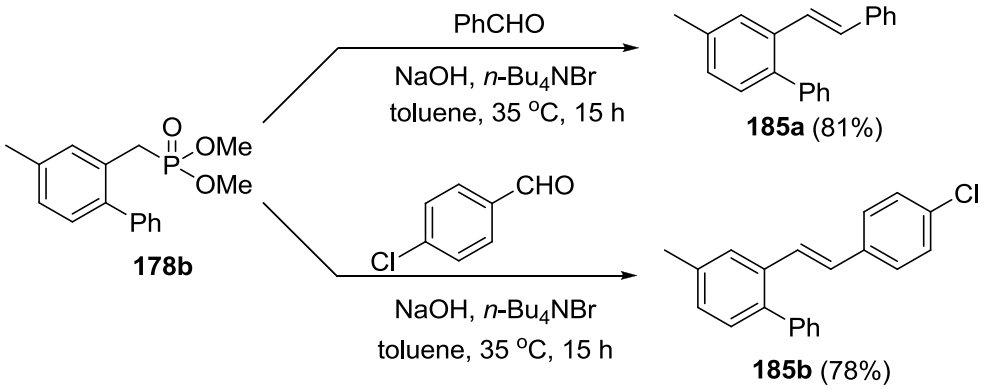
To understand the reaction mechanism of the reaction, a deuterium-labeling experiment was studied briefly using deuterated substrate **183** (Scheme 6.3). An intramolecular isotope effect (k_H/k_D = 4.2) was observed. This result suggested that the cleavage of the C−H bond was involved in the rate-determing step.

To test the feasibility and further application of the *ortho*-arylated products in the Horner-Wadsworth-Emmons reaction (Scheme 6.4),[140] substrate **178b** was reacted with

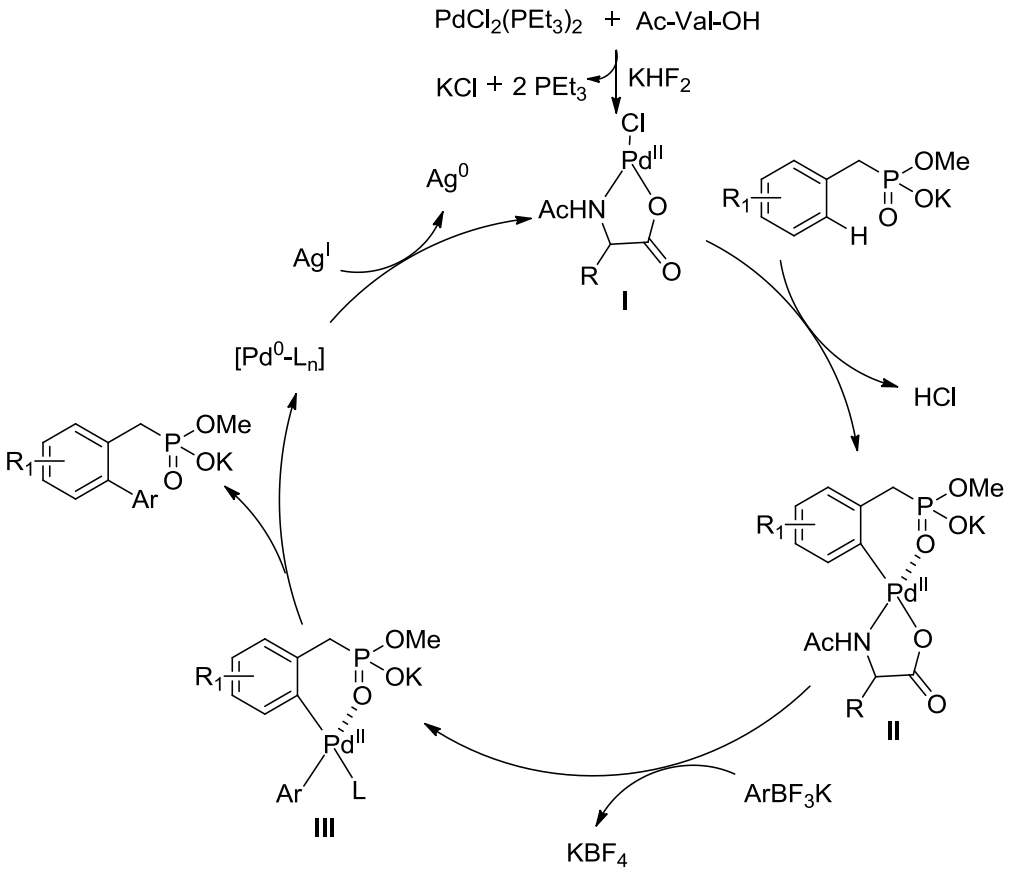
Scheme 6.3 Kinetic Isotope Study



Scheme 6.4 The Horner-Wadworth-Emmons Reaction of **178b**



Scheme 6.5 A Plausible Mechanism



benzaldehyde using sodium hydroxide and *n*-tetrabutylammonium bromide in toluene at 35 ^{o}C for 15 h to give the desired product **185a** in 81% yield. Chloride-containing aldehyde was also tolerated and a similar result was obtained, giving 78 % of **185b**.

Based on Yu's mechanistic studies of Pd(II)-catalyzed C−H olefination and arylation of phenylacetic acids in assistance of amino acids,[9] we envisioned our reaction mechanism to undergo a similar pathway (Scheme 6.5). The process might be promoted by the Pd(II) species **I**, which afforded the palladacyclic complex **II** after incertion into the C−H bond, with the assistance of phosphonic directing group. Subsequent transmetalation and reductive elimination would afford the *ortho*-arylated product along with the liberation of Pd(0). Reoxidation with silver (I) oxide regenerated the active Pd(II) species **I**.

6.3 Conclusion

In conclusion, a Pd(II)-catalyzed *ortho*-arylation of benzylic phosphonic monoesters with potassium aryltrifluoroborates was achieved using a phosphonic monoesters directing group. The present arylation protocol exhibited good compatibility with a variety of synthetically important functional groups in two coupling partners. Furthermore, the newly formed products were further applied in Horner-Wadsworth-Emmons reactions.

Chapter 7. Experimental Section

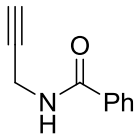
7.1 General Methods.

A variety of chemical reagents were commercially purchased and used without further purification. Analytical TLC was carried out on pre-coated plates and visualized with UV light or stained with potassium permanganate. ^{1}H and ^{13}C NMR spectra were measured at 298 K on 400 Fourier Transform NMR spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of TMS. The signals observed were described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The number of protons (n) for a given resonance was indicated as nH. Coupling constants are reported as *J* value in Hz. ^{13}C NMR is 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 Shimadzu IR Perstige-21 FTIR spectrometer. Mass spectrometry was obtained using a Q-tof high resolution mass spectrometer.

7.2 Tungsten and Molybdenum Catalyst-catalyzed Cyclization of *N*-Propargyl Amides

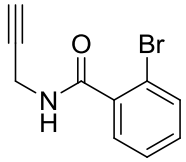
General methods for preparation of propargylic amides. To a solution of Et_3N (101.0 mg, 1.0 mmol), DMAP (6.1 mg, 0.05 mmol), and propargylamine (55.8 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) in an oven-dried flask was added the acid chloride (1.0 mmol) at 0 ^oC. The reaction mixture was allowed to warm to ambient temperature and stirred for 12 h. The reaction mixture was quenched with water (1 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 10:1) to afford the corresponding propagylic amide.

***N*-(Prop-2-ynyl)benzamide (66)**[141]



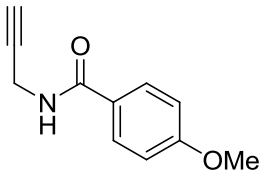
Yield: 142.5 mg, 89%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.57 -7.49 (m, 1H), 7.45 (dd, *J* = 8.1, 6.7 Hz, 2H), 6.26 (s, 1H), 4.27 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.29 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 133.8, 131.8, 128.7, 127.0, 79.48, 71.9, 29.8; IR (film) *v* 1645, 1487, 1215, 756, 677; HRMS (ESI) *m / z* calcd for $C_{10}H_9NO$ $(M + H)^+$ 160.0762, found 160.0762.

2-Bromo-*N*-(prop-2-ynyl)benzamide (68a)



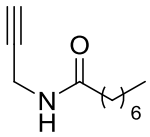
Yield: 202.2 mg, 85%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (ddd, *J* = 13.1, 7.8, 1.4 Hz, 2H), 7.37 (td, *J* = 7.5, 1.2 Hz, 1H), 7.29 (td, *J* = 7.7, 1.8 Hz, 1H), 6.21 (s, 1H), 4.27 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.29 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 167.2, 136.9, 133.4, 131.5, 129.7, 127.6, 119.4, 78.9, 72.1, 29.5; IR(film) *v* 1736, 1375, 1240, 1047, 847, 607; HRMS (ESI) *m / z* calcd for $C_{10}H_8BrNO$ $(M + H)^+$ 237.9868, found 237.9860.

4-Methoxy-*N*-(prop-2-ynyl)benzamide (68b)[142]



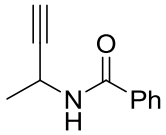
Yield: 180.5 mg, 95%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 -7.24 (m, 3H), 7.06 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H), 6.25 (s, 1H), 4.26 (dd, *J* = 5.2, 2.6 Hz, 2H), 3.85 (s, 3H), 2.29 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 159.8, 135.2, 129.6, 118.9, 118.0, 112.5, 79.6, 71.8, 55.4, 29.8; IR (film) *v* 1643, 1555, 1215, 754, 669; HRMS (ESI) *m / z* calcd for $C_{11}H_{11}NO_2$ $(M + H)^+$ 190.0868, found 190.0868.

***N*-(Prop-2-ynyl)Octanamide (68c)**



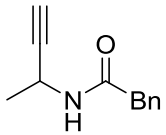
Yield: 154.6 mg, 92%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (s, 1H), 4.06 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.21 (dt, *J* = 15.3, 5.2 Hz, 3H), 1.63 (dd, *J* = 14.7, 7.1 Hz, 2H), 1.42 – 1.17 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 79.6, 71.3, 36.4, 31.5, 29.1, 28.9, 25.5 , 22.5, 13.9; IR (film) *v* 1666, 1510, 1421, 928, 740; HRMS (ESI) *m / z* calcd for $C_{10}H_{17}NO$ $(M + H)^+$ 168.1388, found 168.1389.

_N_-(But-3-yn-2-yl)benzamide (71a)



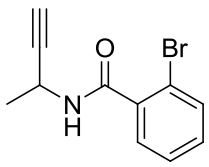
Yield: 156.6 mg, 90%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.50 (dd, *J* = 6.3, 3.8 Hz, 1H), 7.44 (dt, *J* = 11.4, 5.8 Hz, 2H), 6.35 -6.28 (m, 1H), 5.06 -5.00 (m, 1H), 2.31 (t, *J* = 1.9 Hz, 1H), 1.53 (dd, *J* = 6.8, 3.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 133.9, 131.7, 128.6, 127.0, 84.2, 81.5, 70.7, 37.5, 22.4; IR (film) *v* 1647, 1510, 1215, 928,748; HRMS (ESI) *m / z* calcd for $C_{11}H_{11}NO$ $(M + H)^+$ 174.0919, found 174.0914.

_N_-(But-3-yn-2-yl)-2-phenylacetamide (71b)



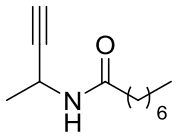
Yield: 171.1 mg, 91%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.9, 6.4 Hz, 2H), 7.33 -7.28 (m, 1H), 7.26 (t, *J* = 3.3 Hz, 2H), 5.54 (s, 1H), 4.81 (dqd, *J* = 13.8, 6.9, 2.3 Hz, 1H), 3.57 (s, 2H), 2.21 (d, *J* = 2.3 Hz, 1H), 1.34 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 134.5, 129.4, 129.1, 127.4, 83.9, 70.4, 43.6, 37.0, 22.1; IR (film) *v* 1647, 1535, 1355, 1134,754, 511; HRMS (ESI) *m / z* calcd for $C_{12}H_{13}NO$ $(M + H)^+$ 188.1075, found 188.1076.

2-Bromo-_N_-(but-3-yn-2-yl)benzamide (71c)



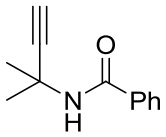
Yield: 211.7 mg, 84%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 16.1, 7.8, 1.4 Hz, 2H), 7.37 (td, *J* = 7.5, 1.1 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.18 (s, 1H), 5.03 (dqd, *J* = 13.8, 6.9, 2.3 Hz, 1H), 2.32 (d, *J* = 2.3 Hz, 1H), 1.55 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.41, 137.2, 133.3, 131.4, 129.6, 127.5, 119.3, 83.6, 70.9, 37.6, 22.1; ; IR (film) *v* 1666, 1504, 1265, 740, 704; HRMS (ESI) *m / z* calcd for $C_{11}H_{10}BrNO$ $(M + H)^+$ 252.0024, found 252.0017.

_N_-(But-3-yn-2-yl)octanamide (71d)



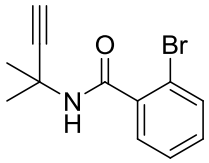
Yield: 160.2 mg, 88%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (s, 1H), 4.83 (ddd, *J* = 8.1, 6.9, 2.3 Hz, 1H), 2.25 (d, *J* = 2.3 Hz, 1H), 2.21 -2.05 (m, 2H), 1.71 -1.56 (m, 3H), 1.41 (d, *J* = 6.9 Hz, 3H), 1.33 -1.27 (m, 5H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 84.3, 70.3, 36.8, 36.7, 31.5, 28.9, 25.5, 22.5, 22.4, 14.0; IR (film) *v* 1645, 1504, 1215, 1140, 748; HRMS (ESI) *m / z* calcd for $C_{11}H_{19}NO$ $(M + H)^+$ 182.1545, found 182.1558.

_N_-(2-Methylbut-3-yn-2-yl)benzamide (80a)[143]



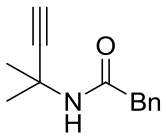
Yield: 157.9 mg, 84%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 5.3, 3.4 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 6.21 (s, 1H), 2.39 (s, 1H); 13C NMR (101 MHz, CDCl3) δ 166.5, 134.8, 131.5, 128.5, 126.9, 87.2, 69.4, 47.9, 29.0; IR (film) *v* 1645, 1508, 1283, 1215, 756; HRMS (ESI) *m / z* calcd for $C_{12}H_{13}NO$ $(M + H)^+$ 188.1075, found 188.1073.

2-Bromo-*N*-(2-methylbut-3-yn-2-yl)benzamide (80b)



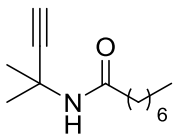
Yield: 218.1 mg, 82%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 7.3, 5.0, 1.3 Hz, 2H), 7.35 (td, *J* = 7.5, 1.1 Hz, 1H), 7.30 -7.26 (m, 1H), 6.08 (s, 1H), 2.40 (s, 1H), 1.78 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 137.9, 133.3, 131.2, 129.6, 127.6, 119.2, 86.8, 69.7, 48.5, 28.8; IR (film) *v* 1666, 1504, 1298, 1215, 744; HRMS (ESI) *m / z* calcd for $C_{12}H_{12}BrNO$ $(M + H)^+$ 266.0181, found 266.0181.

***N*-(2-Methylbut-3-yn-2-yl)-2-phenylacetamide (80c)**



Yield: 171.8 mg, 85%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.25 (s, 1H), 5.45 (s, 1H), 3.54 (s, 2H), 2.31 (s, 1H), 1.57 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 134.9, 129.3, 129.0, 127.3, 86.9, 69.2, 47.7, 44.4, 28.8; IR (film) *v* 1643, 1537, 1210, 748, 655; HRMS (ESI) *m / z* calcd for $C_{32}H_{15}NO$ $(M + H)^+$ 202.1232, found 202.1230.

***N*-(2-Methylbut-3-yn-2-yl)octanamide (80d)**

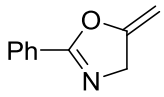


Yield: 180.3 mg, 92%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 1H), 2.33 (s, 1H), 2.18 -2.05 (m, 2H), 1.64 (s, 6H), 1.63 -1.57 (m, 2H), 1.30 (t, *J* = 4.8 Hz, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.27, 87.40, 68.93, 47.44, 37.22, 31.52,

28.89, 25.49, 22.46, 13.98; IR (film) *v* 1647, 1535, 1383, 1190, 756, 699; HRMS (ESI) *m / z* calcd for $C_{12}H_{21}NO$ $(M + H)^+$ 196.1701, found 196.1699.

General methods for $W(CO)_6$ catalyzed cyclization of unsubstituted and monosubstituted propargyl amides (Table 2.2, **Table 2.3).** To a solution of the propargyl amide (0.2 mmol) and DABCO (22.4 mg, 0.2 mmol) in 1.5 mL of toluene in an oven-dried flask under nitrogen was added $W(CO)_6$ (14.1 mg, 0.04 mmol) at room temperature. The mixture was irradiated under 350 nm in a Rayonet photoreactor for 20 h at room temperature. After the completion of the reaction, the solvent was evaporated under reduced pressure. The residue was filtered through a short pad of Celite silica gel and washed with CH_2Cl_2 (5 mL). After concentration in vacuo, the residue was diluted with THF (5 mL) and treated with trimethylamine *N*-oxide dihydrate (22.2 mg, 0.4 mmol) at room temperature. The mixture was stirred for 4 h and then quenched with water (1 mL). THF was removed in vaco and the residue was diluted with diethyl ether (2 × 10 mL). The organic layer was collected, washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 30:1) to afford the corresponding cyclized product.

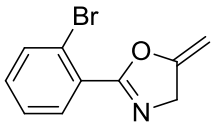
5-Methylene-2-phenyl-4,5-dihydrooxazole (67)[144]



Yield: 25.6 mg, 80%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 -7.90 (m, 2H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.44 (dd, *J* = 8.1, 6.8 Hz, 2H), 4.82 (d, *J* = 2.9 Hz, 1H), 4.65 (t, *J* = 2.8 Hz, 2H), 4.37 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 158.9, 131.8,

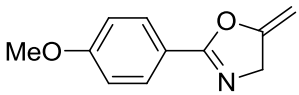
128.5, 128.0, 126.8, 83.8, 57.8; IR (film) *v* 1691, 1647, 1327, 1217, 1060, 692; HRMS (ESI) *m / z* calcd for $C_{10}H_9NO$ $(M + H)^+$ 160.0762, found 160.0764.

2-(2-Bromophenyl)-5-methylene-4,5-dihydrooxazole (69a)



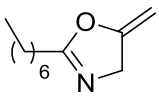
Yield: 42.3 mg, 89%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.36 (dtd, *J* = 17.2, 7.5, 1.5 Hz, 2H), 4.86 -4.74 (m, 1H), 4.72 (t, *J* = 2.9 Hz, 2H), 4.39 (q, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 158.4, 134.3, 132.1, 131.5, 128.4, 127.2, 121.9, 84.1, 58.2; IR (film) *v* 1693, 1651, 1433, 1315, 1024, 729; HRMS (ESI) *m / z* calcd for $C_{10}H_8BrNO$ $(M + H)^+$ 237.9868, found 237.9874.

2-(4-Methoxyphenyl)-5-methylene-4,5-dihydrooxazole (69b)



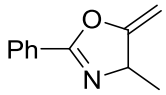
Yield: 34.6 mg, 91%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.79 (d, *J* = 2.9 Hz, 1H), 4.62 (t, *J* = 2.8 Hz, 2H), 4.34 (d, *J* = 2.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 162.4, 159.0, 129.8, 127.6, 123.9, 119.3, 113.9, 113.9, 83.4, 57.7, 55.4; IR (film) *v* 1645, 1435, 1309, 1186, 910, 731; HRMS (ESI) *m / z* calcd for $C_{11}H_{11}NO_2$ $(M + H)^+$ 190.0868, found 190.0873.

2-Heptyl-5-methylene-4,5-dihydrooxazole (69c)



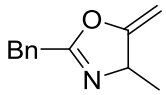
Yield: 27.9 mg, 83%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (q, *J* = 3.0 Hz, 1H), 4.40 (dq, *J* = 4.3, 1.5 Hz, 2H), 4.24 (q, *J* = 2.6 Hz, 1H), 2.34 (dd, *J* = 10.9, 4.5 Hz, 2H), 1.76 – 1.64 (m, 2H), 1.35 -1.26 (m, 6H), 0.92 -0.83 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 159.6, 82.6, 57.20 (s), 31.40 (s), 28.81 (s), 28.17 (s), 25.46 (s), 22.49 (s), 14.01 (s); IR (film) *v* 1667, 1510, 1421, 927, 603; HRMS (ESI) *m / z* calcd for $C_{10}H_{17}NO$ (M + H)$^{+}$ 168.1388, found 168.1396.

4-Methyl-5-methylene-2-phenyl-4,5-dihydrooxazole (73a)



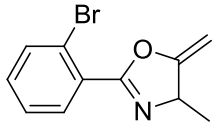
Yield: 22.5 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 -7.98 (m, 2H), 7.48 -7.34 (m, 3H), 4.79 (dt, *J* = 6.8, 2.7 Hz, 2H), 4.31 (t, *J* = 2.6 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 3H).

2-Benzyl-4-methyl-5-methylene-4,5-dihydrooxazole (73b)



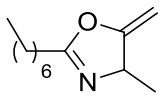
Yield: 7.5 mg, 20%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 -7.22 (m, 5H), 4.62 (t, *J* = 2.6 Hz,, 1H), 4.56 – 4.53 (m,1H), 4.19 (t, *J* = 4.9 Hz, 1H), 3.68 (s, 2H), 1.36 (d, *J* = 7.0 Hz, 3H).

2-(2-Bromophenyl)-4-methyl-5-methylene-4,5-dihydrooxazole (73c)



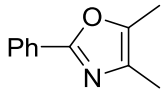
Yield: 36.1 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.41 -7.28 (m, 2H), 4.85 – 4.83 (m, 1 H), 4.82 (dd, *J* = 6.9, 2.6 Hz, 1H), 4.32 (t, *J* = 2.6 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H).

2-Heptyl-4-methyl-5-methylene-4,5-dihydrooxazole (73d)



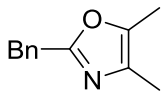
Yield: 24.3mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (t, *J* = 2.7 Hz, 1H), 4.53 (d, *J* = 6.9 Hz, 1H), 4.18 (t, *J* = 2.5 Hz, 1H), 2.34 (t, *J* = 7.6 Hz, 2H), 1.74 -1.63 (m, 2H), 1.45 - 1.25 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H).

4,5-Dimethyl-2-phenyloxazole (74a)[145]



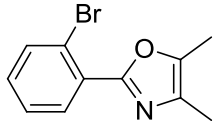
Yield: 11.4 mg, 33%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.41 (t, *J* = 4.9 Hz, 3H), 2.32 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 143.4, 131.9, 129.7, 128.7, 128.5, 128.1, 127.9, 125.8, 11.30, 10.11; IR (film) *v* 1645, 1448, 1085, 1026, 910, 775, 732; HRMS (ESI) *m / z* calcd for $C_{11}H_{11}NO$ $(M + H)^+$ 174.0919, found 174.0915.

2-Benzyl-4,5-dimethyloxazole (74b)[142]



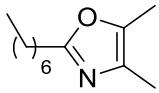
Yield: 31.0 mg, 83%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 -7.22 (m, 5H), 4.01 (s, 2H), 2.17 (s, 3H), 2.05 (d, *J* = 0.8 Hz, 3H).

2-(2-Bromophenyl)-4,5-dimethyloxazole (74c)



Yield: 11.0 mg, 22%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.29 -7.20 (m, 1H), 2.33 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 144.1, 134.3, 131.9, 131.0, 130.6, 128.9, 127.3, 120.8, 11.3, 10.1; IR (film) *v* 1645, 1610,1514, 1257, 1172, 1068, 731; HRMS (ESI) *m / z* calcd for $C_{11}H_{10}BrNO$ $(M + H)^+$ 252.0024, found 252.0024.

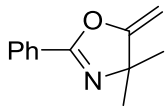
2-Heptyl-4,5-dimethyloxazole (74d)



Yield: 9.1 mg, 25%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (t, *J* = 7.7 Hz, 2H), 2.18 (s, 3H), 2.04 (s, 3H), 1.74 -1.63 (m, 2H), 1.45 -1.25 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H).

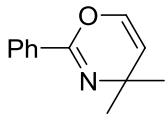
General methods for $W(CO)_6$ catalyzed cyclization of disubstituted propargyl amides (Table 2.4). To a solution of the propargyl amide (0.2 mmol) and DABCO (22.4 mg, 0.2 mmol) in 1.5 mL of toluene in an oven-dried flask under nitrogen was added $W(CO)_6$ (14.1 mg, 0.04 mmol) or $Mo(CO)_6$ (10.6 mg, 0.04 mmol) at room temperature. The mixture was irradiated under 350 nm in a Rayonet photoreactor for 15 h at room temperature. The reaction was quenched with H_2O (1 mL) and toluene was removed under reduced pressure. The residue was diluted with diethyl ether (2 × 10 mL). The organic layer was collected, washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/ethyl acetate = 30:1) to afford the corresponding cyclized product.

4,4-Dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole (81a)[146]



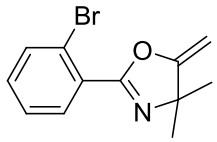
Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 -7.91 (m, 2H), 7.56 -7.46 (m, 1H), 7.46 - 7.34 (m, 2H), 4.74 (d, *J* = 2.8 Hz, 1H), 4.25 (d, *J* = 2.8 Hz, 1H), 1.46 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 159.9, 131.7, 128.5, 128.1, 127.0, 82.3, 69.1, 29.8; IR (film) *v* 1697, 1668, 1497, 1263, 976, 955, 733; HRMS (ESI) *m / z* calcd for $C_{12}H_{13}NO$ $(M + H)^+$ 188.1075, found 188.1090.

4,4-Dimethyl-2-phenyl-4H-1,3-oxazine (82a)



Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.52 -7.30 (m, 3H), 6.52 (d, *J* = 6.2 Hz, 1H), 5.01 (d, *J* = 6.2 Hz, 1H), 1.33 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 137.2 132.7 130.5 128.1, 127.2, 111.5, 49.5, 32.6; IR (film) *v* 1686, 1635, 1449, 1290, 1056, 694; HRMS (ESI) *m / z* calcd for $C_{12}H_{13}NO$ $(M + H)^+$ 188.1075, found 188.1078.

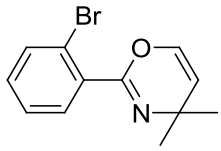
2-(2-Bromophenyl)-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (81b)



Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.36 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.32 (dd, *J* = 7.8, 1.9 Hz, 1H), 4.73 (d, *J* = 2.9 Hz, 1H), 4.27 (d, *J* = 2.9 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 159.2, 133.9, 131.9, 131.4, 129.1, 127.1, 121.9, 82.6, 69.6, 29.9; IR (film) *v* 1693, 1638,

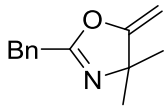
1300, 1033, 759, 731; HRMS (ESI) *m / z* calcd for $C_{12}H_{12}BrNO$ $(M + H)^+$ 266.0181, found 266.0189.

2-(2-Bromophenyl)-4,4-dimethyl-4H-1,3-oxazine (82b)



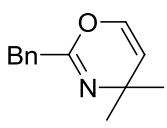
Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 7.26 -7.18 (m, 1H), 6.48 (d, *J* = 6.2 Hz, 1H), 5.03 (d, *J* = 6.2 Hz, 1H), 1.38 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 137.4, 135.2, 133.3, 130.9, 130.3, 127.3, 121.4, 111.6, 50.3, 32.5; IR (film) *v* 1693, 1657, 1643, 1450, 1327, 1060, 926, 777; HRMS (ESI) *m / z* calcd for $C_{12}H_{12}BrNO$ $(M + H)^+$ 266.1081, found 266.0173.

2-Benzyl-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (81c)



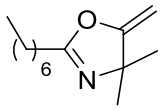
Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 -7.28 (m, 5H), 4.58 (d, *J* = 2.8 Hz, 1H), 4.15 (d, *J* = 2.8 Hz, 1H), 3.71 (s, 2H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 161.9, 134.5, 128.9, 128.7, 127.1, 82.1, 68.6, 34.9, 29.5; IR (film) *v* 1697, 1672, 1496, 1265, 954, 732; HRMS (ESI) *m / z* calcd for $C_{13}H_{15}NO$ $(M + H)^+$ 202.1232, found 202.1238.

2-Benzyl-4,4-dimethyl-4H-1,3-oxazine (82c)



Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.4 Hz, 4H), 7.29 -7.25 (m, 1H), 6.30 (d, *J* = 6.2 Hz, 1H), 4.91 (d, *J* = 6.2 Hz, 1H), 3.54 (s, 2H), 1.29 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 137.2, 136.0, 128.8, 128.5, 126.8, 111.1, 49.3 , 41.6, 32.6; IR (film) *v* 1697, 1673, 1454, 1184, 955, 705; HRMS (ESI) *m / z* calcd for $C_{13}H_{15}NO$ $(M + H)^+$ 202.1232, found 202.1228.

2-Heptyl-4,4-dimethyl-5-methylene-4,5-dihydrooxazole (81d)



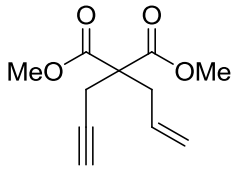
Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (d, J = 2.7 Hz, 1H), 4.13 (d, J = 2.7 Hz, 1H), 2.49 -2.22 (m, 2H), 1.66 (dt, J = 15.2, 7.5 Hz, 2H), 1.33 (s, 6H), 1.43 -1.18 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.3, 163.8, 81.4, 68.3, 31.4, 29.6, 28.7, 28.1, 25.6, 22.5, 13.9; IR (film) *v* 1672, 1573, 1199, 910, 733; HRMS (ESI) *m / z* calcd for $C_{12}H_{21}NO$ $(M + H)^+$ 196.1701, found 196.1722.

7.3 $W(CO)_5(L)$-Catalyzed Cyclization of Alkynyl-Nucleophile Substrates to Methylenelactones, Furans, Methylenecyclopentanes, Pyrroles, Pyridines and Isoquinolines

7.3.1 Synthesis of Methylenelacetone Derivatives.

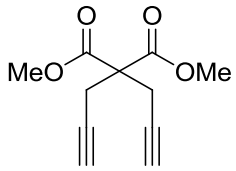
General procedure for preparation of alkylated malonates. To a stirred suspension of NaH (44.0 mg, 1.1 mmol, 60 % dispersion in mineral oil) in THF was added the corresponding malonate (1.0 mmol) at 0 ^oC, The reaction mixture was allowed to warm to ambient temperature and stirred for 0.5 h. Propargyl bromide (148.8 mg, 1.0 mmol, 80 wt. % in toluene) was then added to the solution at 0 ^oC. The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (1 mL) and diluted with Et_2O (10 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 30:1) to afford the corresponding alkylated malonate.

Dimethyl 2-allyl-2-(prop-2-ynyl)malonate[147]



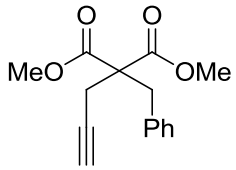
Yield: 191.1 mg, 91 %; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 -5.55 (m, 1H), 5.15 (dddd, *J* = 16.1, 10.1, 1.9, 1.1 Hz, 2H), 3.73 (s, 6H), 2.79 (t, *J* = 4.5 Hz, 4H), 2.01 (t, *J* = 2.7 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 131.6, 119.9, 78.7, 71.5, 56.8, 52.8, 36.5, 22.7.

Dimethyl 2,2-di(prop-2-ynyl)malonate[143]



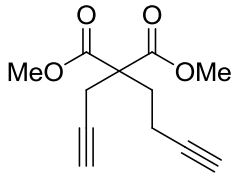
Yield: 197.6 mg, 95 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (d, *J* = 2.3 Hz, 3H), 3.00 (d, *J* = 2.6 Hz, 2H), 2.05 (t, *J* = 2.6 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.05, 78.28, 71.79, 56.42, 53.17, 22.65.

Dimethyl 2-benzyl-2-(prop-2-ynyl)malonate[148]



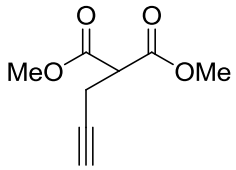
Yield: 226.3 mg, 87 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 -7.24 (m, 3H), 7.21 -7.04 (m, 2H), 3.75 (s, 6H), 3.41 (s, 2H), 2.68 (d, *J* = 2.7 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 135.4, 129.8, 128.5, 127.3, 79.2, 72.3, 58.3, 52.8, 37.5, 22.2.

Dimethyl 2-(but-3-ynyl)-2-(prop-2-ynyl)malonate[149]



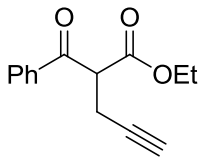
Yield: 188.7 mg, 85 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 6H), 2.86 (d, *J* = 2.2 Hz, 2H), 2.35 (t, *J* = 7.7 Hz, 2H), 2.24 (dd, *J* = 8.2, 2.5 Hz, 2H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.97 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 82.7, 78.2, 71.7, 68.9, 56.1, 52.8, 30.9, 22.9, 13.8.

Dimethyl 2-(prop-2-ynyl)malonate[150]



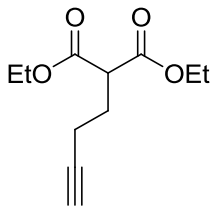
Yield: 134.3 mg, 79 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H), 3.62 (t, *J* = 7.7 Hz, 1H), 2.80 (dd, *J* = 7.7, 2.7 Hz, 2H), 2.03 (t, *J* = 2.7 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 79.8, 70.5, 52.9, 50.9, 18.5.

Ethyl 2-benzoylpent-4-ynoate[151]



Yield: 172.6 mg, 75 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 -7.26 (m, 5H), 4.16 (dddd, *J* = 15.2, 10.8, 7.1, 3.7 Hz, 2H), 3.83 -3.68 (m, 1H), 2.93 (ddd, *J* = 16.8, 8.3, 2.6 Hz, 1H), 2.63 (ddd, *J* = 16.8, 7.1, 2.6 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 137.9, 128.7, 127.8, 127.7, 81.4, 69.9, 61.1, 50.8, 23.1, 14.1.

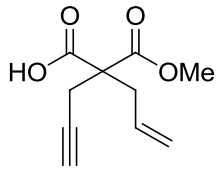
Diethyl 2-(but-3-ynyl)malonate[152]



Yield: 95.4 mg, 45 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (qd, *J* = 7.1, 2.0 Hz, 4H), 3.57 (t, *J* = 7.4 Hz, 1H), 2.29 (dd, *J* = 6.8, 2.6 Hz, 2H), 2.13 (t, *J* = 7.1 Hz, 2H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 6H).;^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 82.4, 69.7, 61.5, 50.6, 27.4, 16.4, 14.1.

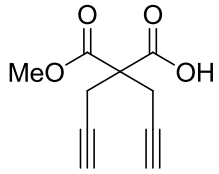
General procedure for the preparation of acetylenic acids. To a stirred solution of acetylenic esters (0.5 mmol) in H_2O (2 mL) was slowly added 5 % KOH solution (0.5 mL, 0.5 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was extracted with Et_2O (2 × 10 mL). The aqueous phase was acidified to pH = 1 with 2 N HCl and extracted with Et_2O (3 × 10 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography (hexane/ethyl acetate = 5:1) to give the corresponding product.

2-(Methoxycarbonyl)-2-(prop-2-ynyl)pent-4-enoic acid (88)[143]



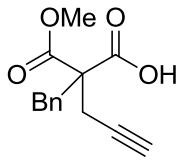
Yield: 58.8 mg, 60 %; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 -5.60 (m, 1H), 5.24 -5.15 (m, 2H), 3.79 (s, 3H), 3.03 -2.57 (m, 4H), 2.07 -2.04 (m, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 170.3, 131.3, 120.3, 78.4, 71.8, 56.9, 53.1, 36.8, 22.9.

2-(Methoxycarbonyl)-2-(prop-2-ynyl)pent-4-ynoic acid (90a)[143]



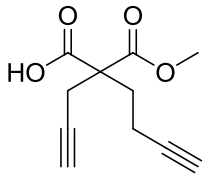
Yield: 53.4 mg, 55 %; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.02 (d, *J* = 2.0 Hz, 4H), 2.07 (t, *J* = 2.6 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 168.9, 77.9, 72.1, 56.4, 53.4, 22.7.

2-Benzyl-2-(methoxycarbonyl)pent-4-ynoic acid (90b)



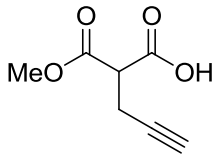
Yield: 49.2 mg, 40 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 -7.26 (m, 3H), 7.19 (dd, *J* = 7.5, 1.7 Hz, 2H), 3.80 (s, 3H), 3.40 (q, *J* = 13.8 Hz, 2H), 2.83 -2.64 (m, 2H), 2.18 (t, *J* = 2.6 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 170.3, 135.0, 129.8, 128.6, 127.5, 78.8, 72.5, 58.4, 53.1, 38.0, 22.7.; IR (film) *v* 3288, 2954, 1732, 1714, 1435, 1211, 1085, 704..; HRMS (ESI) *m / z* calcd for $C_{14}H_{15}O_4$ $(M + H)^+$ 247.0970, found 247.0968.

2-(Methoxycarbonyl)-2-(prop-2-ynyl)hex-5-ynoic acid (90c)[153]



Yield: 72.8 mg, 70 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 2.88 (dd, *J* = 5.0, 2.7 Hz, 2H), 2.38 -2.32 (m, 2H), 2.29 -2.22 (m, 2H), 2.07 (dd, *J* = 6.9, 4.3 Hz, 1H), 1.98 (t, *J* = 2.5 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 170.2, 82.5, 78.1, 72.1, 69.3, 56.2, 53.1, 31.1, 23.1, 13.9.

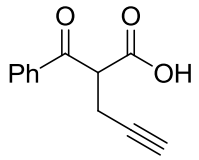
2-(Methoxycarbonyl)pent-4-ynoic acid (90d)



Yield: 44.5 mg, 57 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.65 (t, *J* = 7.5 Hz, 1H), 2.82 (dt, *J* = 7.5, 2.8 Hz, 2H), 2.06 (t, *J* = 2.6 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 168.2, 79.4, 70.9, 53.1, 50.6, 18.5.; IR (film) *v* 3417, 2360, 1728,

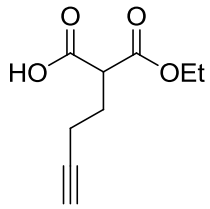
1634, 1445, 1249, 1024, 677; HRMS (ESI) *m / z* calcd for $C_7H_9O_4$ $(M + H)^+$ 157.0501, found 157.0507.

2-Benzoylpent-4-ynoic acid (90e)



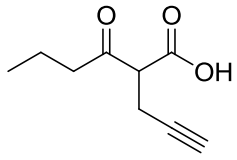
Yield: 91.0 mg, 82 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 -7.28 (m, 5H), 3.83 (t, *J* = 7.6 Hz, 1H), 2.93 (ddd, *J* = 16.8, 8.1, 2.6 Hz, 1H), 2.65 (ddd, *J* = 16.8, 7.2, 2.6 Hz, 1H), 1.97 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 128.9, 128.0, 127.9, 81.0, 70.2, 50.6, 22.6.; IR (film) *v* 3422, 1711, 1627, 1403, 914, 724.; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}O_3$ $(M + H)^+$ 203.0708, found 203.0706.

2-(Ethoxycarbonyl)hex-5-ynoic acid (90f)[148]



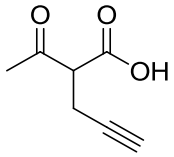
Yield: 58.0 mg, 63 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (q, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 7.3 Hz, 1H), 2.45 -2.24 (m, 2H), 2.15 (dd, *J* = 10.5, 4.9 Hz, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 168.9, 82.1, 69.9, 61.9, 50.1, 27.4, 16.4, 14.0.

3-Oxo-2-(prop-2-ynyl)hexanoic acid (92a)



Yield: 63.0 mg, 75 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (t, *J* = 7.4 Hz, 1H), 2.77 -2.57 (m, 4H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.66 (dd, *J* = 14.5, 7.1 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 173.6, 80.1, 70.6, 57.0, 45.0, 17.5, 16.8, 13.5.; IR (film) *v* 2933, 2389, 1712, 1176, 655.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3$ $(M + H)^+$ 169.0856, found 169.0870.

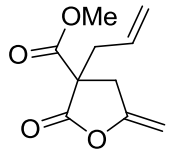
2-Acetylpent-4-ynoic acid (92b)



Yield: 56.0 mg, 80 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (t, *J* = 7.4 Hz, 1H), 2.75 (ddd, *J* = 7.7, 5.3, 2.7 Hz, 2H), 2.38 (s, 3H), 2.04 (t, *J* = 2.7 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 173.2, 79.9, 70.7, 57.7, 29.9, 17.4.; IR (film) *v* 3422, 2253, 1627, 1377, 914, 731; HRMS (ESI) *m / z* calcd for $C_7H_9O_3$ $(M + H)^+$ 141.0552, found 141.0552.

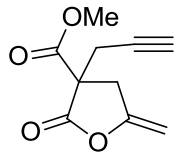
General methods for $W(CO)_6$ catalyzed cyclization of acetylenc acids (Table 3.2). To a solution of an acetylenc acid (0.2 mmol) in THF (1.5 mL) was added Et_3N (22.0 mg, 0.2 mmol) and $W(CO)_6$ (14.0 mg, 0.04 mmol) under nitrogen atmosphere at room temperature. The mixture was irradiated at 350 nm in a photo reactor for 12 h. After the completion of the reaction, the mixture was quenched with water (0.5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate = 30: 1) to give the corresponding product.

Methyl 3-allyl-5-methylene-2-oxotetrahydrofuran-3-carboxylate (89)[143]



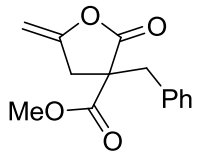
Yield: 37.2 mg, 95 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 -5.58 (m, 1H), 5.23 (s, 1H), 5.22 -5.17 (m, 1H), 4.80 (d, *J* = 1.8 Hz, 1H), 4.38 (d, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.29 (d, *J* = 16.7 Hz, 1H), 2.91 (d, *J* = 16.7 Hz, 1H), 2.77 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.67 (dd, *J* = 14.0, 7.1 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 169.3, 152.6, 130.9, 121.1, 89.7, 54.8, 53.4, 38.2, 34.3.

Methyl 5-methylene-2-oxo-3-(prop-2-ynyl)tetrahydrofuran-3-carboxylate (91a)[143]



Yield: 35.7 mg, 92 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 4.6, 2.4 Hz, 1H), 4.43 (dt, *J* = 2.9, 1.9 Hz, 1H), 3.81 (s, 3H), 3.39 -3.17 (m, 2H), 2.91 (dd, *J* = 2.6, 0.6 Hz, 2H), 2.09 (t, *J* = 2.6 Hz, 1H).

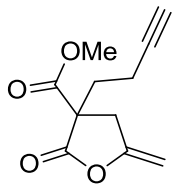
Methyl 3-benzyl-5-methylene-2-oxotetrahydrofuran-3-carboxylate (91b)



Yield: 44.8 mg, 91 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 -7.26 (m, 3H), 7.17 (dd, *J* = 7.6, 1.8 Hz, 2H), 4.64 (d, *J* = 2.6 Hz, 1H), 4.22 (dd, *J* = 1.7, 1.1 Hz, 1H), 3.82 (s, 3H), 3.33 (q, *J* = 14.0 Hz, 2H), 3.23 (dt, *J* = 16.6, 1.7 Hz, 1H), 2.90 (dd, *J* = 10.3, 8.3 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 135.4, 129.8, 128.5, 127.3, 79.2, 72.2, 58.3,

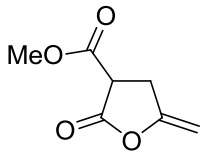
52.8, 37.5, 22.2.; IR (film) *v* 3026, 1803, 1741, 1249, 1217, 1145, 751.; HRMS (ESI) *m / z* calcd for $C_{14}H_{15}O_4$ $(M + H)^+$ 247.0970, found 247.0975.

Methyl 3-(but-3-ynyl)-5-methylene-2-oxotetrahydrofuran-3-carboxylate (91c)[149]



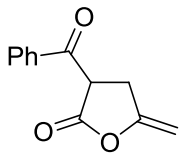
Yield: 39.5 mg, 95 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (dd, *J* = 4.7, 2.1 Hz, 1H), 4.41 (dt, *J* = 2.8, 1.8 Hz, 1H), 3.80 (s, 3H), 3.39 (dt, *J* = 16.6, 1.7 Hz, 1H), 2.98 (dt, *J* = 16.6, 2.0 Hz, 1H), 2.43 -2.25 (m, 3H), 2.22 -2.12 (m, 1H), 2.01 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 168.9, 152.3, 89.9, 82.1, 69.8, 54.7, 53.5, 35.4, 32.7, 14.4.

Methyl 5-methylene-2-oxotetrahydrofuran-3-carboxylate (91d)



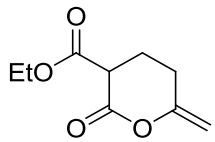
Yield: 29.0 mg, 93 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (dd, *J* = 4.6, 2.3 Hz, 1H), 4.42 (dt, *J* = 2.8, 1.9 Hz, 1H), 3.83 (s, 3H), 3.76 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.32 (dd, *J* = 16.6, 7.6 Hz, 1H), 3.15 -3.03 (m, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 167.3, 153.1, 89.9, 53.4, 46.2, 29.4.; IR (film) *v* 2253, 1728, 1639, 1445, 1216, 914, 624.; HRMS (ESI) *m / z* calcd for $C_7H_9O_4$ $(M + H)^+$ 157.0501, found 157.0501.

3-Benzoyl-5-methylenedihydrofuran-2(3H)-one (91e)



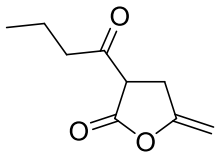
Yield: 38.8 mg, 96 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.9, 6.4 Hz, 2H), 7.35 -7.30 (m, 1H), 7.29 -7.22 (m, 2H), 4.84 (dd, *J* = 4.3, 2.2 Hz, 1H), 4.42 (dd, *J* = 4.1, 1.9 Hz, 1H), 3.99 (dd, *J* = 10.1, 7.8 Hz, 1H), 3.33 (ddd, *J* = 10.1, 9.0, 5.9 Hz, 1H), 3.03 (ddd, *J* = 16.4, 9.2, 4.9 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 154.0, 136.6, 129.1, 128.0, 127.5, 89.2, 46.0, 34.5.; IR (film) *v* 3461, 1636, 1249, 907, 735, 522; HRMS (ESI) *m / z* calcd for $C_{12}H_{11}O_3$ $(M + H)^+$ 203.0708, found 203.0702.

Ethyl 6-methylene-2-oxotetrahydro-2H-pyran-3-carboxylate (91f)



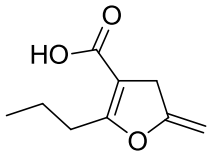
Yield: 32.0 mg, 87 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 -4.65 (m, 1H), 4.37 (d, *J* = 1.5 Hz, 1H), 4.30 -4.17 (m, 2H), 3.60 (dd, *J* = 7.7, 6.5 Hz, 1H), 2.71 -2.57 (m, 1H), 2.56 -2.43 (m, 1H), 2.25 (dtd, *J* = 13.4, 7.9, 5.5 Hz, 1H), 2.12 (ddt, *J* = 13.5, 7.7, 6.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 164.3, 154.2, 95.1, 62.2, 47.7, 24.8, 22.1, 14.0.; IR (film) *v* 3422, 1640, 1151, 908, 733, 650.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_4$ $(M + H)^+$ 185.0814, found 185.0813.

3-Butyryl-5-methylenedihydrofuran-2(3H)-one (93a)



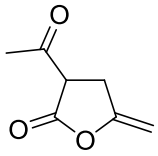
Yield: 16.8 mg, 50 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (dd, *J* = 4.8, 2.3 Hz, 1H), 4.39 (dd, *J* = 4.6, 1.9 Hz, 1H), 3.85 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.53 -3.38 (m, 1H), 3.05 -2.80 (m, 2H), 2.60 (dt, *J* = 18.0, 7.0 Hz, 1H), 1.66 (dd, *J* = 14.6, 7.3 Hz, 2H), 0.96 (dt, *J* = 12.6, 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 170.3, 153.6, 89.5, 52.7, 44.0, 26.7, 16.8, 13.5.

5-Methylene-2-propyl-4,5-dihydrofuran-3-carboxylic acid (94a)



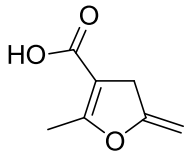
Yield: 3.4 mg, 10 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 4.80 -4.78 (m, 1H), 4.32 (d, *J* = 2.5 Hz, 1H), 3.49 -3.43 (m, 1H), 3.02 -2.84 (m, 2H), 2.64 -2.56 (m, 1H), 2.19 (d, *J* = 7.6 Hz, 2H), 1.69 -1.63 (m, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 171.8, 153.6, 94.1, 88.8, 35.1, 28.1, 19.2, 13.7.

3-Acetyl-5-methylenedihydrofuran-2(3H)-one (93b)



Yield: 15.4 mg, 55 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 -4.67 (m, 1H), 4.33 (d, *J* = 2.3 Hz, 1H), 3.80 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.48 -3.33 (m, 1H), 2.81 (ddt, *J* = 17.0, 10.2, 1.7 Hz, 1H), 2.41 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 170.1, 153.5, 89.7, 53.5, 26.5, 26.4.

2-Methyl-5-methylene-4,5-dihydrofuran-3-carboxylic acid (94b)

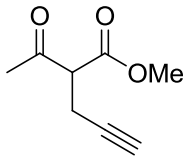


Yield: 3.1 mg, 11 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 4.79 -4.67 (m, 1H), 4.26 (d, *J* = 2.3 Hz, 1H), 3.48 -3.33 (m, 2H), 1.92 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 168.5, 153.7, 94.4, 88.9, 28.2, 19.2.

7.3.2 Synthesis of Furan Derivatives.

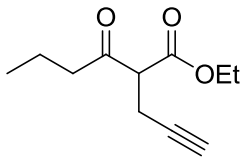
General procedure for preparation of *α*-alkynyl-*β*-dicarbonyl derivatives. To a stirred suspension of NaH (44.0 mg, 1.1 mmol, 60 % dispersion in mineral oil) in THF (5 mL) was added the corresponding dicarbonyl compound (1.0 mmol) at 0 ^{o}C, The reaction mixture was allowed to warm to ambient temperature and stirred for 0.5 h. Propargyl bromide (148.8 mg, 1.0 mmol, 80 wt. % in toluene) was then added to the solution at 0 ^{o}C. The mixture was stirred for 12 h at room temperature and quenched with water (1 mL), and diluted with Et_2O (10 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 50:1) to afford the corresponding product.

Methyl 2-acetylpent-4-ynoate (95a)[154]



Yield: 104.8 mg, 68 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.83 - 3.58 (m, 1H), 2.71 (dt, *J* = 7.3, 2.4 Hz, 2H), 2.30 (s, 3H), 2.00 (t, *J* = 2.6 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 168.6, 80.3, 70.4, 58.0, 52.8, 29.7, 17.4.

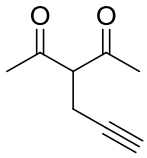
Ethyl 3-oxo-2-(prop-2-ynyl)hexanoate (95b)



Yield: 149.0 mg, 76 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.70 (t, *J* = 7.5 Hz, 1H), 2.72 (dt, *J* = 7.4, 2.8 Hz, 2H), 2.66 -2.48 (m, 2H), 1.98

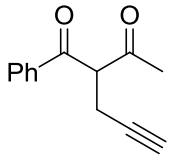
(t, *J* = 2.6 Hz, 1H), 1.64 (dd, *J* = 14.6, 7.3 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 168.1, 80.5, 70.2, 61.7, 57.5, 44.5, 17.4, 16.8, 14.0, 13.5.; IR (film) *v* 1711, 1627, 1377, 1095, 914, 733.; HRMS (ESI) *m / z* calcd for $C_{11}H_{17}O_3(M + H)^+$ 197.1178, found 197.1174.

3-(Prop-2-ynyl)pentane-2,4-dione (95c)[155]



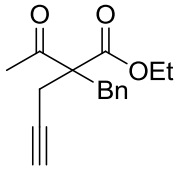
Yield: 76.0 mg, 55 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (t, *J* = 7.5 Hz, 1H), 2.70 (dd, *J* = 7.6, 2.7 Hz, 2H), 2.26 (s, 6H), 2.03 (t, *J* = 2.7 Hz, 1H).

1-Phenyl-2-(prop-2-ynyl)butane-1,3-dione (95d)



Yield: 166.0 mg, 83 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 -7.85 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 4.71 (t, *J* = 7.4 Hz, 1H), 2.95 (ddd, *J* = 17.2, 8.0, 2.7 Hz, 1H), 2.80 (ddd, *J* = 17.2, 6.8, 2.7 Hz, 1H), 2.20 (s, 3H), 2.01 (t, *J* = 2.7 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1, 194.8, 136.2, 134.3, 129.2, 129.1, 80.7, 71.1, 61.7, 28.6, 18.4.; IR (film) *v* 1711, 1579, 1216, 914, 734, 649.; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}O_2$ $(M + H)^+$ 201.0916, found 209.0909.

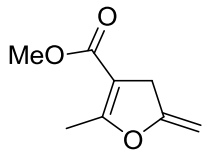
Ethyl 2-acetyl-2-benzylpent-4-ynoate (95e)[156]



Yield: 232.2 mg, 90 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 -7.22 (m, 3H), 7.14 (dd, *J* = 7.7, 1.6 Hz, 2H), 4.34 -4.13 (m, 2H), 3.35 (dd, *J* = 36.2, 14.1 Hz, 2H), 2.65 (qd, *J* = 17.5, 2.6 Hz, 2H), 2.23 (s, 3H), 2.14 (t, *J* = 2.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 170.3, 135.7, 129.8, 128.5, 127.2, 79.3, 72.4, 64.0, 61.9, 36.9, 26.7, 21.5, 14.0.

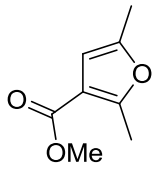
General methods for $W(CO)_6$ catalyzed cyclization of *α*-alkynyl-*β*-dicarbonyl derivatives (Table 3.3). To a solution of an *α*-alkynyl-*β*-dicarbonyl compound (0.2 mmol) in THF (1.5 mL) was added Et_3N (22.0 mg, 0.2 mmol) and $W(CO)_6$ (14.0 mg, 0.04 mmol) under nitrogen atmosphere at room temperature. The mixture was irradiated at 350 nm in a photo reactor for 18 h. After the completion of the reaction, the mixture was quenched with water (0.5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate = 30: 1) to give the corresponding product.

Methyl 2-methyl-5-methylene-4,5-dihydrofuran-3-carboxylate (96a)[157]



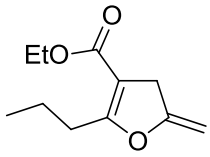
Yield: 23.4 mg, 76 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, *J* = 2.7 Hz, 1H), 4.27 (d, *J* = 2.6 Hz, 1H), 3.72 (s, 3H), 3.56 (dd, *J* = 4.6, 2.7 Hz, 2H), 2.26 (t, *J* = 1.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.2, 159.8, 103.7, 85.9, 51.1, 33.4, 13.6.

Methyl 2,5-dimethylfuran-3-carboxylate (97a)[152]



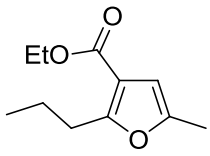
Yield: 5.9 mg, 19 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 0.6 Hz, 1H), 3.80 (s, 3H), 2.52 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 157.7, 149.9, 113.7, 106.1, 51.2, 13.6, 13.2.

Ethyl 5-methylene-2-propyl-4,5-dihydrofuran-3-carboxylate (96b)



Yield: 26.4 mg, 78 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (dd, *J* = 5.5, 2.8 Hz, 1H), 4.30 -4.24 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.57 (s, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 1.63 (dd, *J* = 15.0, 7.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).;^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 164.7, 160.0, 103.7, 85.7, 59.8, 33.5, 29.2, 20.1, 14.4, 13.8.; IR (film) *v* 2931, 1714, 1691, 1382, 1205, 1095, 1053.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3$ $(M + H)^+$ 169.0865, found 169.0861.

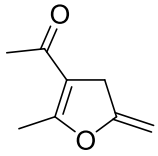
Ethyl 5-methyl-2-propylfuran-3-carboxylate (97b)



Yield: 5.7 mg, 17 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.24 (s, 3H), 1.68 (dd, *J* = 14.9, 7.4 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 161.5, 149.9, 113.7, 106.2, 59.9, 29.5, 21.6, 14.3, 13.7, 13.2.; IR (film) *v* 2926, 1714, 1583, 1382,

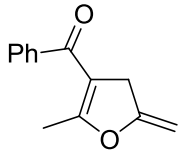
1205, 1093, 1053.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3$ $(M + H)^+$ 169.0865, found 169.0860.

1-(2-Methyl-5-methylene-4,5-dihydrofuran-3-yl)ethanone (96c)[152]



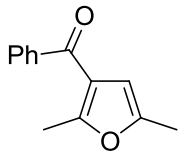
Yield: 25.9 mg, 94 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (dd, *J* = 5.6, 2.9 Hz, 1H), 4.29 (q, *J* = 2.6 Hz, 1H), 3.63 (dd, *J* = 4.6, 2.8 Hz, 2H), 2.29 (t, *J* = 1.8 Hz, 3H), 2.23 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 165.2, 159.5, 113.6, 86.2, 33.9, 29.4, 14.5.

(2-Methyl-5-methylene-4,5-dihydrofuran-3-yl)(phenyl)methanone (96d)[158]



Yield: 26.4 mg, 66 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 -7.55 (m, 2H), 7.56 -7.46 (m, 1H), 7.43 (dd, *J* = 8.0, 6.7 Hz, 2H), 4.67 (d, *J* = 2.7 Hz, 1H), 4.32 (d, *J* = 2.6 Hz, 1H), 3.77 (dd, *J* = 4.5, 2.7 Hz, 2H), 1.90 (t, *J* = 1.8 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 165.8, 159.7, 140.3, 131.5, 128.4, 127.9, 113.8, 86.1, 34.7, 14.9.; IR (film) *v* 2253, 2100, 1645, 1627, 1216, 914, 734.; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}O_2$ $(M + H)^+$ 201.0916, found 201.0910.

(2,5-Dimethylfuran-3-yl)(phenyl)methanone (97d)[159]



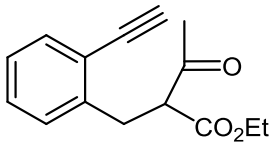
Yield: 8.04 mg, 21 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 -7.74 (m, 2H), 7.53

(d, *J* = 7.4 Hz, 1H), 7.49 -7.40 (m, 2H), 6.16 (d, *J* = 0.7 Hz, 1H), 2.48 (s, 3H), 2.28 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 157.9, 149.8, 139.4, 131.9, 129.9, 129.3, 121.3, 107.5, 14.2, 13.2.; IR (film) *v* 2922, 2387, 1651, 1566, 1392, 1232, 907.; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}O_2$ $(M + H)^+$ 201.0916, found 201.0917.

7.3.3 Synthesis of Methylenecyclopentane Derivatives

Preparation of ketoester 11. Ethyl acetoacetate (260 mg, 2 mmol) was slowly added to a stirred suspension of NaH (88 mg, 2.2 mmol, 60 % w/w in mineral oil) in THF (5 mL) at 0 ^{o}C and then the mixture was stirred for 0.5 h at room temperature. 1-(Bromomethyl)-2 -ethynylbenzene (427 mg, 2.2 mmol) was added to the solution at 0 ^{o}C and then the mixture was stirred overnight at room temperature. After the completion of the reaction, the reaction was quenched with water (1 mL) and extracted with Et_2O (3 × 10 mL). The organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification of the crude product by silica gel flash column chromatography (hexane: ethyl acetate = 20:1) afforded **98** (376.0 mg, 77 %).

Ethyl 2-(2-ethynylbenzyl)-3-oxobutanoate (98)

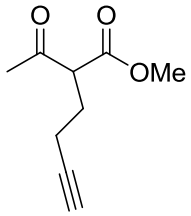


Yield: 376.0 mg, 77 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.22 (ddd, *J* = 9.2, 8.7, 5.2 Hz, 4H), 4.14 (ddd, *J* = 10.7, 7.2, 3.6 Hz, 2H), 4.01 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.44 -3.22 (m, 3H), 2.22 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 169.1, 140.6, 133.1, 129.9, 129.0, 126.7, 121.6, 81.8, 61.4,

59.6, 32.7, 29.5, 14.0.; IR (film) *v* 3020, 1737, 1715, 1485, 1217, 756.; HRMS (ESI) *m / z* calcd for $C_{15}H_{17}O$ $(M + H)^+$ 245.1178, found 245.1181.

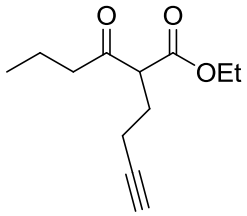
General procedure for preparation of *α*-alkynyl-*β*-dicarbonyl compounds. Under a nitrogen atmosphere, the *α*-alkynyl-*β*-dicarbonyl (2.0 mmol) was slowly added to a stirred suspension of NaH (88 mg, 2.2 mmol, 60 % w/w in mineral oil) in anhydrous DMF (5 mL) at 0 ^oC, then the mixture was stirred for 0.5 h at room temperature. *p*-tolylsulfonyloxyalkyne (2.2 mmol) and KI (332 mg, 2.0 mmol) were then slowly added to the solution at 0 ^oC. The mixture was heated at 100 ^oC overnight. Then the mixture was quenched with water (1 mL) and extracted with Et_2O (3 × 10 mL). The organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification of the crude product by silica gel flash column chromatography (hexane/ethyl acetate = 50:1) afforded the corresponding *α*-alkynyl-*β*-dicarbonyl ester **100a**-**100e**.

Methyl 2-acetylhex-5-ynoate (100a)[160]



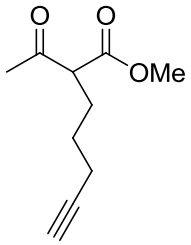
Yield: 215.0 mg, 64 %; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.83 -3.69 (m, 1H), 2.25 (s, 3H), 2.32 -2.22 (m, 2H), 2.11 -2.03 (m, 2H), 2.01 (t, *J* = 2.6 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 169.7, 82.4, 69.8, 57.6, 52.5, 29.4, 26.4, 16.3.

Ethyl 2-butyrylhex-5-ynoate (100b)



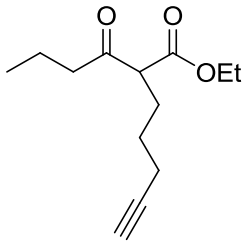
Yield: 294.0 mg, 70 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.73 (t, *J* = 7.2 Hz, 1H), 2.67 -2.47 (m, 2H), 2.25 (td, *J* = 6.7, 2.1 Hz, 2H), 2.10 -1.97 (m, 3H), 1.63 (dd, *J* = 14.7, 7.3 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9, 169.3, 82.6, 69.7, 61.4, 57.1, 44.3, 26.4, 16.9, 16.3, 14.1, 13.5.; IR (film) *v* 2920, 1732, 1440, 1280, 1085, 704.; HRMS (ESI) *m / z* calcd for $C_{12}H1_9O_3$ $(M + H)^+$ 211.1334, found 211.1334.

Methyl 2-acetylhept-6-ynoate (100c)[161]



Yield: 294.0 mg, 53 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.47 (t, *J* = 7.4 Hz, 1H), 2.24 (s, 3H), 2.29 -2.17 (m, 2H), 2.01 -1.92 (m, 3H), 1.57 -1.46 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 170.0, 83.4, 68.9, 59.0, 52.4, 28.8, 27.1, 26.0, 18.1.

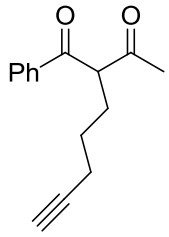
Ethyl 2-butyrylhept-6-ynoate (100d)



Yield: 197.1 mg, 44 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 -4.09 (m, 2H),

3.43 (d, *J* = 5.9 Hz, 1H), 2.66 -2.34 (m, 2H), 2.19 (d, *J* = 4.3 Hz, 2H), 1.96 -1.91 (m, 3H), 1.68 -1.44 (m, 4H), 1.31 -1.15 (m, 3H), 1.02 -0.72 (m, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9, 169.6, 83.5, 68.9, 61.3, 58.6, 43.7, 27.1, 26.2, 18.2, 16.9, 14.1, 13.5.; IR (film) *v* 3020, 2922, 1737, 1712, 1215, 1149, 1022.; HRMS (ESI) *m / z* calcd for $C_{13}H_{21}O_3$ $(M + H)^+$ 225.1491, found 225.1486.

2-(Pent-4-ynyl)-1-phenylbutane-1,3-dione (100e)

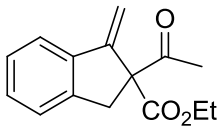


Yield: 195.8 mg, 39 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 -7.99 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 4.47 (t, *J* = 7.1 Hz, 1H), 2.24 (td, *J* = 6.9, 2.6 Hz, 2H), 2.19 -2.05 (m, 2H), 2.15 (s, 3 H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.57 -1.52 (m, 2H),; ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3, 196.3, 136.5, 134.0, 129.1, 128.9, 83.6, 69.2, 63.0, 28.1, 28.0, 26.5, 18.4.; IR (film) *v* 3019, 1722, 1674, 1359, 1217, 756.; HRMS (ESI) *m / z* calcd for $C_{15}H_{16}O_2Na$ $(M + Na)^+$ 251.1048, found 251.1047.

General methods for $W(CO)_6$ catalyzed cyclization of *α*-alkynyl-*β*-dicarbonyl esters (Table 3.4). To a solution of an *α*-alkynyl-*β*-dicarbonyl compound (0.2 mmol) in THF (1.5 mL) was added DABCO (22.4 mg, 0.2 mmol) and $W(CO)_6$ (14.0 mg, 0.04 mmol) under nitrogen atmosphere at room temperature. The mixture was irradiated at 350 nm in a photo reactor. After the completion of the reaction, the mixture was quenched with water (0.5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude

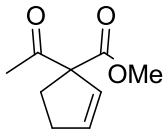
product was purified by silica gel flash column chromatography (hexane/ethyl acetate = 30:1) to give the corresponding product.

Ethyl 2-acetyl-1-methylene-2,3-dihydro-1H-indene-2-carboxylate (99)



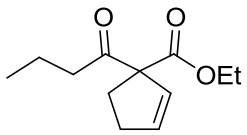
Yield: 41.7 mg, 85 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 6.7 Hz, 1H), 7.30 -7.23 (m, 3H), 5.89 (s, 1H), 5.51 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.75 (d, *J* = 17.2 Hz, 1H), 3.49 (d, *J* = 17.2 Hz, 1H), 2.23 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4, 170.5, 146.8, 142.0, 138.8, 129.4, 127.3, 125.0, 120.9, 109.5, 70.3, 61.9, 38.4, 25.9, 14.0.; IR (film) *v* 2984, 2358, 1714, 1355, 1240, 1022, 756.; HRMS (ESI) *m / z* calcd for $C_{15}H_{17}O_3$ $(M + H)^+$ 245.1178, found 245.1180.

Methyl 1-acetylcyclopent-2-enecarboxylate (101a)[162]



Yield: 31.6 mg, 94 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 -5.97 (m, 1H), 5.95 -5.79 (m, 1H), 3.74 (s, 3H), 2.59 -2.35 (m, 4H), 2.18 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 172.3, 136.4, 128.7, 73.6, 52.6, 31.9, 30.1, 26.4.

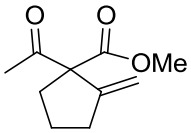
Ethyl 1-butyrylcyclopent-2-enecarboxylate (101b)



Yield: 34.4 mg, 82 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 5.6 Hz, 1H), 5.94 -5.77 (m, 1H), 4.19 (qd, *J* = 7.1, 0.9 Hz, 2H), 2.47 -2.37 (m, 6H), 1.61 (dd, *J* = 14.6,

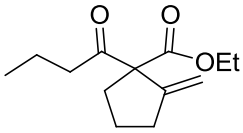
7.3 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0, 172.0, 136.1, 128.8, 73.4, 61.4, 40.7, 31.9, 30.1, 17.1, 14.1, 13.6.; IR (film) *v* 2964.6, 1741.7, 1732.6, 1463.9, 1249.9, 1018.4, 758.0.; HRMS (ESI) *m / z* calcd for $C_{12}H1_9O_3$ $(M + H)^+$ 211.1334, found 211.1336.

Methyl 1-acetyl-2-methylenecyclopentanecarboxylate (102c)



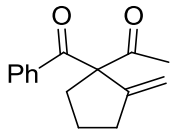
Yield: 33.1 mg, 91 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 5.23 (s, 1H), 3.75 (s, 3H), 2.43 (ddd, *J* = 19.0, 9.1, 4.5 Hz, 3H), 2.22 (s, 3H), 2.25 -2.16 (m, 1H), 1.82 -1.64 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, 171.7, 148.7, 112.2, 70.5, 52.7, 35.1, 33.9, 26.6, 24.1.

Ethyl 1-butyryl-2-methylenecyclopentanecarboxylate (102d)



Yield: 37.6 mg, 84 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (t, *J* = 2.0 Hz, 1H), 5.23 (t, *J* = 2.3 Hz, 1H), 4.20 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.57 -2.34 (m, 5H), 2.18 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.76 -1.60 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7, 171.3, 148.6, 112.0, 70.3, 61.5, 40.9, 35.0, 34.0, 24.0, 17.6, 14.0, 13.6.; IR (film) *v* 2962, 739, 1464, 1236, 899, 756.; HRMS (ESI) *m / z* calcd for $C_{13}H_{21}O_3$ $(M + H)^+$ 225.1491, found 225.1490.

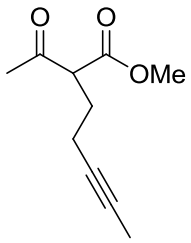
1-(1-Benzoyl-2-methylenecyclopentyl)ethanone (102e)



Yield: 43.7 mg, 87 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 5.41 (s, 1H), 5.13 (s, 1H), 2.84 -2.68 (m, 1H), 2.52 (d, *J* = 7.5 Hz, 2H), 2.32 -2.16 (m, 1H), 2.24 (s, 3H), 1.79 (dd, *J* = 15.5, 7.5 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5, 198.0, 149.0, 135.5, 132.8, 129.3, 128.5, 113.3, 75.5, 35.8, 34.3, 27.2, 24.2.; IR (film) *v* 1742.8, 1686.9,1604.5, 1421.5, 1248.2, 948.0, 756.1.; HRMS (ESI) *m / z* calcd for $C_{15}H_{16}O_2Na$ $(M + Na)^+$ 251.1048, found 251.1045.

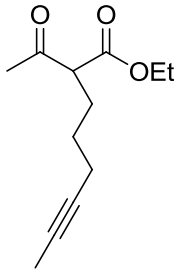
Preparation of ketoesters 103-105. Under a nitrogen atmosphere methyl acetoacetate (232 mg, 2 mmol) was slowly added to a stirred suspension of NaH (88 mg, 2.2 mmol, 60 % w/w in mineral oil) in THF (5 mL) at 0 ^{o} C, then the mixture was stirred for 0.5 h at room temperature. 1-iodo-3-pentyne (426 mg, 2.2 equiv) was then added to the solution at room temperature. The mixture was stirred overnight at reflux. After the completion of the reaction, the reaction was quenched with water (1 mL) and extracted with Et_2O (2 × 10 mL). The organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification of the crude product by silica gel flash column chromatography (hexane/ethyl acetate = 50:1) afforded **103** (265 mg, 73%).

Methyl 2-acetylhept-5-ynoate (103)



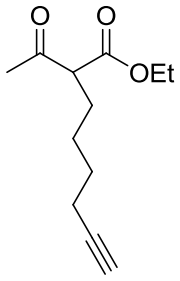
Yield: 265 mg, 73 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 1 3.69 (m, 1H), 3.74 (s, 3H), 2.26 (s, 3H), 2.18 (dd, *J* = 6.2, 3.7 Hz, 2H), 2.02 (t, *J* = 7.0 Hz, 2H), 1.76 (t, *J* = 2.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 169.9, 77.2, 77.2, 58.0, 52.5, 29.4, 27.1, 16.7, 3.4.; IR (film) *v* 2953, 1746, 1714, 1435, 1359, 1176, 1051, 733.; HRMS (ESI) *m / z* calcd for $C_{10}H_{15}O_3$ $(M + H)^+$ 183.1021, found 183.1024.

Ethyl 2-acetyloct-6-ynoate (104)



Yield: 244.8 mg, 58 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 - 4.15 (m, 2H), 3.44 (t, *J* = 7.4 Hz, 1H), 2.24 (s, 3H), 2.16 (d, *J* = 2.6 Hz, 2H), 1.93 (t, *J* = 7.8 Hz, 2H), 1.77 (dd, *J* = 5.5, 3.0 Hz, 3H), 1.48 -1.45 (m, 2H), 1.28 (dd, *J* = 12.3, 5.2 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 169.7, 78.2, 76.2, 61.4, 59.4, 28.8, 27.3, 26.7, 18.5, 14.1, 3.5.; IR (film) *v* 2953, 1746, 1714, 1435, 1359, 1176, 1051, 733.; HRMS (ESI) *m / z* calcd for $C_{12}H_{19}O_3$ $(M + H)^+$ 211.1334, found 211.1330.

Ethyl 2-acetyloct-7-ynoate (105)



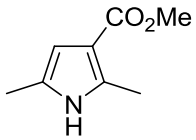
Yield: 206.8 mg, 49 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.0 Hz, 2H), 3.39 (t, *J* = 7.4 Hz, 1H), 2.23 -2.14 (m, 5H), 1.92 (dd, *J* = 3.5, 1.7 Hz, 1H), 1.88 -

1.77 (m, 2H), 1.56 -1.50 (m, 2H), 1.44 - 1.33 (m, 2H), 1.26 (td, *J* = 7.1, 1.0 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 169.8, 84.0, 68.5, 61.4, 59.7, 28.8, 28.1, 27.6, 26.4, 18.1, 14.1; IR (film) *v* 2938, 1740, 1714, 1360, 1244, 1148, 624.; HRMS (ESI) *m / z* calcd for $C_{12}H_{19}O_3$ $(M + H)^+$ 211.1334, found 211.1340.

7.3.4 Synthesis of Pyrrole Derivatives.

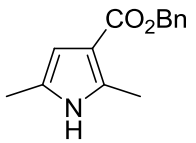
General methods for $W(CO)_6$ catalyzed cyclization of imino substrates (Table 3.6). To a solution of the imino compound (0.2 mmol) in toluene (1.5 mL) was added $W(CO)_6$ (14.0 mg, 0.04 mmol) at room temperature. The mixture was stirred for 15 h at 110 ^oC. After the completion of the reaction, the mixture was quenched with water (0.5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate = 10:1) to give the corresponding product.

Methyl 2,5-dimethyl-1H-pyrrole-3-carboxylate (112a)[163]



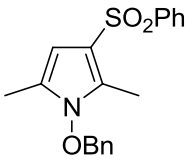
Yield: 26.0 mg, 85 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 6.18 (s, 1H), 3.78 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 134.5, 125.8, 111.2, 107.4, 50.7, 13.1, 12.6.

Benzyl 2,5-dimethyl-1H-pyrrole-3-carboxylate (112b)



Yield: 34.4 mg, 75 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.1 Hz, 1H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.46 (dt, *J* = 25.4, 7.2 Hz, 3H), 6.06 (s, 1H), 2.53 (s, 3H), 2.22 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 140.8, 135.6, 130.9, 128.9, 127.9, 125.2, 119.9, 109.7, 13.8, 12.6.; IR (film) *v* 3020, 2922, 1787, 1377, 1216, 1024, 908, 734.; HRMS (ESI) *m / z* calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 229.1105, found 229.1103.

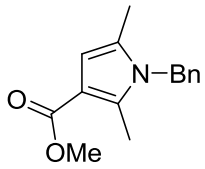
1-(Benzyloxy)-2,5-dimethyl-3-(phenylsulfonyl)-1H-pyrrole (113c)



Yield: 43.0 mg, 63 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.80 (m, 2H), 7.58 - 7.45 (m, 3H), 7.41 - 7.33 (m, 3H), 7.29 (dd, *J* = 8.1, 1.4 Hz, 2H), 6.15 (d, *J* = 0.9 Hz, 1H), 4.97 (s, 2H), 2.31 (s, 3H), 2.15 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 133.1, 132.1, 129.7, 128.9, 128.9, 128.6, 126.3, 125.1, 114.4, 103.1, 80.8, 10.54 (s), 9.3.; IR (film) *v* 3025, 2978, 1637, 1357, 1218, 1024, 908, 734.; HRMS (ESI) *m / z* calcd for $C_{19}H_{20}NO_3S$ $(M + H)^+$ 342.1084, found 342.1087.

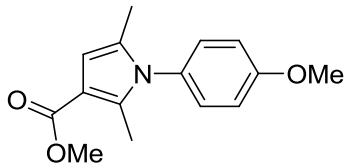
General methods for $W(CO)_6$ catalyzed synthesis of pyrroles (Table 3.7). To a solution of the ketone ester (0.2 mmol) and the corresponding primary amine (0.2 mmol) in toluene (1.5 mL) was added $W(CO)_6$ (14.0 mg, 0.04 mmol) at room temperature. The mixture was stirred for 15 h at reflux. After the completion of the reaction, the mixture was quenched with water (0.5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate = 10:1) to give the corresponding product.

Methyl 1-benzyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (115a)



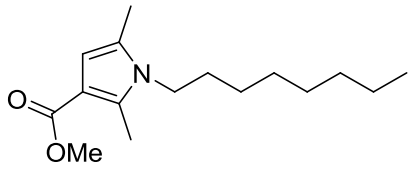
Yield: 45.9 mg, 94%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 -7.23 (m, 3H), 6.88 (d, *J* = 7.1 Hz, 2H), 6.33 (d, *J* = 0.7 Hz, 1H), 5.03 (s, 2H), 3.79 (s, 3H), 2.45 (s, 3H), 2.11 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 137.0, 135.8, 128.9, 128.1, 127.4, 125.6, 110.9, 107.7, 50.7, 46.8, 12.2, 11.3.; IR (film) *v* 2947, 1703, 1537, 1438, 1219, 1072, 911, 729.; HRMS (ESI) *m / z* calcd for $C_{15}H_{18}NO_2$ $(M + H)^+$ 244.1338, found 244.1335.

Methyl 1-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (115b)



Yield: 43.2 mg, 83%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.33 (d, *J* = 0.9 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 2.27 (s, 3H), 1.96 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 159.5, 136.7, 130.4, 129.2, 129.1, 114.5, 110.9, 107.2, 55.5, 50.7, 12.6, 12.3.; IR (film) *v* 2948, 1693, 1515, 1437, 1221, 755.; HRMS (ESI) *m / z* calcd for $C_{15}H_{18}NO_3$ $(M + H)^+$ 260.1287, found 260.1283.

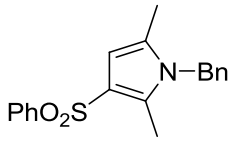
Methyl 2,5-dimethyl-1-octyl-1H-pyrrole-3-carboxylate (115c)



Yield: 51.0 mg, 96%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 0.9 Hz, 1H), 3.76 (s, 3H), 3.75 -3.71 (m, 2 H), 2.51 (s, 3H), 2.19 (s, 3H), 1.64 - 1.56 (m, 2H), 1.38 -

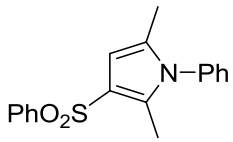
1.18 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 135.1, 127.4, 110.3, 107.4, 50.6, 43.7, 31.8, 30.6, 29.3, 29.2, 26.9, 22.6, 14.1, 12.2, 11.3.; IR (film) *v* 2927, 1701, 1533, 1437, 1222, 1071, 772.; HRMS (ESI) *m / z* calcd for $C_{16}H_{28}NO_2$ $(M + H)^+$ 266.2120, found 266.2111.

1-Benzyl-2,5-dimethyl-3-(phenylsulfonyl)-1H-pyrrole (115d)



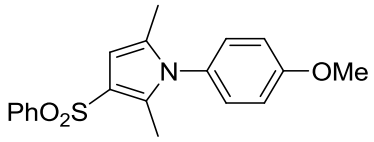
Yield: 56.7 mg, 87%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.61 -7.42 (m, 3H), 7.35 -7.29 (m, 3H), 6.87 (d, *J* = 6.9 Hz, 2H), 6.36 (s, 1H), 5.02 (s, 2H), 2.42 (s, 3H), 2.12 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 136.1, 132.7, 132.0, 129.2, 129.0, 128.9, 127.7, 126.4, 125.5, 118.9, 107.4, 47.2, 12.2, 10.6.; IR (film) *v* 2921, 2360, 1520, 1407, 1300, 1148, 1095, 719.; HRMS (ESI) *m / z* calcd for $C_{19}H_{20}NO_2S$ $(M + H)^+$ 326.1215, found 326.1224.

2,5-Dimethyl-1-phenyl-3-(phenylsulfonyl)-1H-pyrrole (115e)



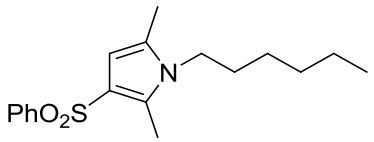
Yield: 53.0 mg, 85%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.58 -7.39 (m, 6H), 7.13 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.34 (s, 1H), 2.23 (s, 3H), 1.93 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 136.9, 133.2, 132.2, 129.9, 129.6, 129.0, 128.9, 128.1, 126.6, 119.3, 106.9, 12.7, 11.5.; IR (film) *v* 2921, 2360, 1597, 1499, 1301, 1103, 734, 689.; HRMS (ESI) *m / z* calcd for $C_{18}H_{18}NO_2S$ $(M + H)^+$ 312.1058, found 312.1068.

1-(4-Methoxyphenyl)-2,5-dimethyl-3-(phenylsulfonyl)-1H-pyrrole (115f)



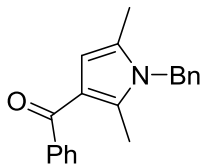
Yield: 55.5 mg, 89%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 -7.85 (m, 2H), 7.58 -7.41 (m, 3H), 7.09 -6.99 (m, 2H), 7.01 -6.88 (m, 2H), 6.31 (d, *J* = 0.9 Hz, 1H), 3.85 (s, 3H), 2.21 (s, 3H), 1.92 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 144.4, 133.6, 132.1, 130.1, 129.6, 129.1, 128.9 126.6, 119.0, 114.7, 106.6, 55.6, 12.6, 11.5.; IR (film) *v* 2921, 2253, 1513, 1301, 1152, 914, 734.; HRMS (ESI) *m / z* calcd for $C_{19}H_{20}NO_3S$ $(M + H)^+$ 342.1164, found 312.1166.

1-Hexyl-2,5-dimethyl-3-(phenylsulfonyl)-1H-pyrrole (115g)



Yield: 58.9 mg, 92%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.51 -7.39 (m, 3H), 6.22 (d, *J* = 0.7 Hz, 1H), 3.77 -3.56 (m, 2H), 2.44 (s, 3H), 2.16 (s, 3H), 1.58 -1.53 (m, 2H), 1.32 -1.28 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 131.9, 131.8, 128.8, 128.4, 126.4, 118.2, 107.1, 44.2, 31.3, 30.4, 26.5, 22.5, 13.9, 12.2, 10.6.; IR (film) *v* 2921, 2360, 1579, 1445, 1306, 1216, 1151, 755.; HRMS (ESI) *m / z* calcd for $C_{18}H_{26}NO_2S$ $(M + H)^+$ 320.1684, found 320.1681.

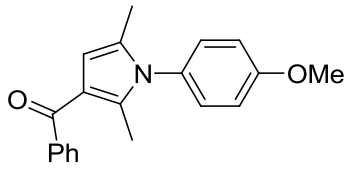
(1-Benzyl-2,5-dimethyl-1H-pyrrol-3-yl)(phenyl)methanone (115h)



Yield: 52.2mg, 91%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 -7.73 (m, 2H), 7.46 (ddd, *J* = 14.4, 7.8, 6.4 Hz, 3H), 7.35 -7.25 (m, 3H), 6.94 (d, *J* = 7.1 Hz, 2H), 6.16 (d, *J* =

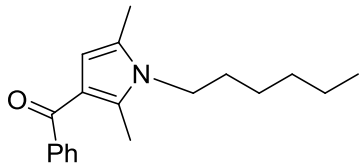
0.8 Hz, 1H), 5.09 (s, 2H), 2.51 (s, 3H), 2.13 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 141.1, 136.8, 136.7, 130.9, 129.1, 129.0, 127.9, 127.7, 127.5, 125.7, 119.5, 110.4, 46.8, 12.2, 12.0.; IR (film) *v* 2253, 1627, 1520, 1377, 1024, 908, 733.; HRMS (ESI) *m / z* calcd for $C_{20}H_{20}NO$ $(M + H)^+$ 290.1545, found 290.1549.

(1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrol-3-yl)(phenyl)methanone (115i)



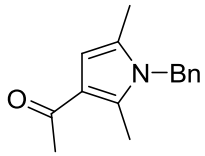
Yield: 51.4 mg, 84%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 -7.76 (m, 2H), 7.47 (ddd, *J* = 13.1, 7.8, 6.3 Hz, 3H), 7.18 -7.08 (m, 2H), 7.06 -6.93 (m, 2H), 6.18 (d, *J* = 0.9 Hz, 1H), 3.88 (s, 3H), 2.33 (s, 3H), 1.98 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 159.6, 141.0, 137.8, 130.9, 130.2, 129.1, 129.0, 128.7, 127.9, 119.4, 114.6, 109.7, 55.5, 13.1, 12.7.; IR (film) *v* 1627, 1514, 1250, 907, 732.; HRMS (ESI) *m / z* calcd for $C_{20}H_{20}NO_2$ $(M + H)^+$ 306.1494, found 306.1493.

(1-Hexyl-2,5-dimethyl-1H-pyrrol-3-yl)(phenyl)methanone (115j)



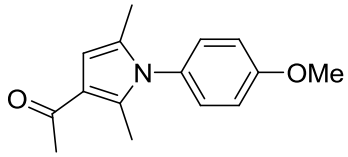
Yield: 54.0 mg, 95%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 -7.70 (m, 2H), 7.54 -7.33 (m, 3H), 6.05 (d, *J* = 0.8 Hz, 1H), 3.85 -3.67 (m, 2H), 2.57 (s, 3H), 2.20 (s, 3H), 1.68 -1.64 (m, 2H), 1.38 -1.32 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 141.2, 136.2, 130.7, 129.0, 127.8, 127.0, 110.2, 43.7, 31.5, 30.5, 26.6, 22.6, 14.0, 12.3, 12.0.; IR (film) *v* 1629, 1520, 1417, 1246, 914, 726.; HRMS (ESI) *m / z* calcd for $C_{19}H_{26}NO$ $(M + H)^+$ 284.2014, found 284.2018.

1-(1-Benzyl-2,5-dimethyl-1H-pyrrol-3-yl)ethanone (115k)



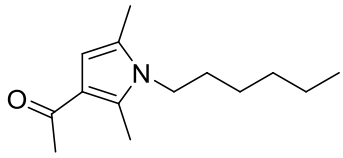
Yield: 39.2 mg, 86%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 -7.25 (m, 3H), 6.89 (d, *J* = 7.1 Hz, 2H), 6.29 (d, *J* = 0.8 Hz, 1H), 5.04 (s, 2H), 2.49 (s, 3H), 2.40 (s, 3H), 2.13 (s, 3 H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 137.0, 135.4, 129.1, 128.1, 127.7, 125.8, 120.5, 108.6, 46.8, 28.8, 12.4, 12.0.; IR (film) *v* 1627, 1520, 1377, 1216, 914, 733.; HRMS (ESI) *m / z* calcd for $C_{15}H_{18}NO$ $(M + H)^+$ 228.1388, found 228.1387.

1-(1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrol-3-yl)ethanone (115l)



Yield: 43.9 mg, 90%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.9 Hz, 2H), 7.04 -6.92 (m, 2H), 6.30 (d, *J* = 0.9 Hz, 1H), 3.87 (s, 3H), 2.42 (s, 3H), 2.30 (s, 3H), 1.98 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 159.6, 136.2, 130.1, 129.1, 128.9, 120.3, 114.6, 107.7, 55.5, 28.6, 12.9, 12.7.; IR (film) *v* 1643, 1514,1249, 1216, 907, 734.; HRMS (ESI) *m / z* calcd for $C_{15}H_{18}NO_2$ $(M + H)^+$ 244.1338, found 244.1339.

1-(1-Hexyl-2,5-dimethyl-1H-pyrrol-3-yl)ethanone (115m)



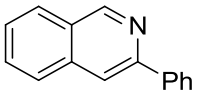
Yield: 45.8 mg, 93%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 0.7 Hz, 1H), 3.80 -3.66 (m, 2H), 2.54 (s, 3H), 2.35 (s, 3H), 2.21 (s, 3H), 1.60 -1.42 (m, 2H), 1.30 (dd, *J* = 15.0, 3.6 Hz, 12H), 0.87 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9,

134.6, 127.1, 119.9, 108.2, 43.5, 31.8, 30.5, 29.2, 29.1, 28.5, 26.9, 22.6, 14.1, 12.3, 11.9.; IR (film) *v* 1627, 1377, 1216, 1024, 908, 734.; HRMS (ESI) *m / z* calcd for $C_{14}H_{23}NONa$ $(M + Na)^+$ 244.1677, found 246.1687.

3.2.5 Synthesis of Isoquinoline and Pyridine Derivatives

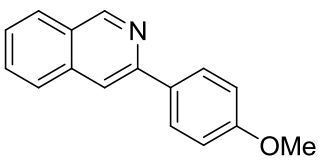
General methods for $W(CO)_6$ catalyzed synthesis of isoquinolines and pyridines (Table 3.8). To a solution of the oxime ether (0.2 mmol) in DMSO (1.5 mL) was added $W(CO)_6$ (14.0 mg, 0.04 mmol) at room temperature. The mixture was stirred for 15 h at 110 ^oC. The mixture was then quenched with water (5 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate = 30:1) to give the corresponding product.

3-Phenylisoquinoline (121a)[158]



Yield: 33.2 mg, 81%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.7 Hz, 3H), 8.11 (d, *J* = 8.5 Hz, 3H), 7.89 (d, *J* = 8.2 Hz, 3H), 7.70 (dd, *J* = 7.9, 1.5 Hz, 8H), 7.66 (d, *J* = 5.7 Hz, 3H), 7.58 – 7.48 (m, 12H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 142.2, 139.6, 136.9,130.0, 129.9, 128.6, 128.4, 127.6, 127.2, 127.0, 126.7, 119.9.

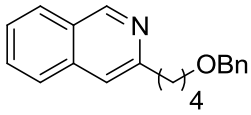
3-(4-Methoxyphenyl)isoquinoline (121b)



Yield: 35.7 mg, 76 %; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.14 – 8.05

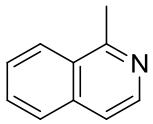
(m, 2H), 8.01 – 7.95 (m, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 7.1 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 152.3, 151.1, 136.8, 132.3, 130.5, 128.2, 127.5, 127.4, 126.7, 126.6, 115.4, 114.2, 55.4.; IR (film) *v* 2987, 1617, 1374, 1213, 1024, 926, 714.; HRMS (ESI) *m / z* calcd for $C_{16}H_{14}NO$ $(M + H)^+$ 235.0997, found 235.0992.

3-(4-(Benzyloxy)butyl)isoquinoline (121c)



Yield: 43.7 mg, 75 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (d, *J* = 0.8 Hz, 1H), 7.98 – 7.83 (m, 1H), 7.56 – 7.42 (m, 2H), 7.38 (d, *J* = 0.9 Hz, 1H), 7.33 (dd, *J* = 12.3, 8.1 Hz, 4H), 7.29 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 2H), 3.54 (t, *J* = 6.0 Hz, 2H), 2.52 (s, 2H), 1.78 (ddd, *J* = 6.7, 5.6, 2.3 Hz, 4H), 1.58 (d, *J* = 2.1 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 138.5, 135.9, 133.7, 133.3, 128.4, 127.9, 127.6, 127.5, 126.9, 97.8, 72.9, 69.7, 29.1, 25.4, 19.5.; IR (film) *v* 2934, 1647, 1377, 1256, 1024, 938, 708.; HRMS (ESI) *m / z* calcd for $C_{20}H_{22}NO_2$ $(M + H)^+$ 291.1635, found 291.1638.

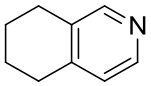
1-Methylisoquinoline (121d)



Yield: 26.9 mg, 94 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 5.8 Hz, 1H), 8.14 – 8.08 (m, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.59 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.51 (d, *J* = 5.8 Hz, 1H), 2.97 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 141.8, 135.9, 129.9, 127.5, 127.2, 127.0, 125.6, 119.3, 22.4.; IR (film) *v* 3002, 1602, 1352, 1200, 1028, 932, 708.; HRMS (ESI) *m / z* calcd for $C_{10}H_{10}N$ $(M + H)^+$ 143.0751, found

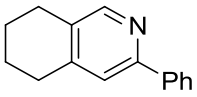
143.0753.

5,6,7,8-Tetrahydroisoquinoline (121e)



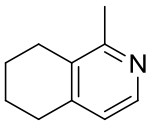
Yield: 23.7 mg, 89 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.19 (m, 2H), 6.96 (d, *J* = 5.0 Hz, 1H), 2.74 (s, 4H), 1.89 - 1.76 (m, 4H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 146.4, 146.1, 133.0, 123.9, 28.6, 26.2, 22.6, 22.4.; IR (film) *v* 3014, 1653, 1377, 1216, 1008, 931, 716.; HRMS (ESI) *m / z* calcd for $C_9H_{12}N$ $(M + H)^+$ 133.0889, found 133.0891.

3-Phenyl-5,6,7,8-tetrahydroisoquinoline (121f)



Yield: 26.3 mg, 63 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.42 (dt, *J* = 22.8, 7.4 Hz, 4H), 2.88 - 2.72 (m, 4H), 1.94 - 1.79 (m, 4H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 150.3, 146.7, 139.8, 131.7, 128.6, 128.4, 126.7, 120.7, 29.0, 26.1, 22.7, 22.5.; IR (film) *v* 3024, 1653, 1308, 1219, 1024, 908, 756.; HRMS (ESI) *m / z* calcd for $C_{15}H_{16}N$ $(M + H)^+$ 209.1208, found 209.1201.

1-Methyl-5,6,7,8-tetrahydroisoquinoline (121g)



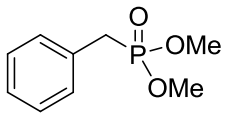
Yield: 26.8 mg, 91 %; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 5.1 Hz, 1H), 6.83 (d, *J* = 5.1 Hz, 1H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.43 (s, 3H), 1.85 (dd, *J* = 11.8, 5.9 Hz, 2H), 1.80 – 1.72 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ

157.0, 146.0, 145.2, 130.9, 122.1, 29.4, 26.0, 23.0, 22.1, 22.0.; IR (film) *v* 2988, 1627, 1377, 1219, 1014, 938, 713.; HRMS (ESI) *m / z* calcd for $C_{10}H_{14}NO$ $(M + H)^+$ 147.1043, found 147.1041.

7.3 Palladium (II)-Catalyzed *ortho*-Olefination and -Acetoxylation of Benzylic Phosphonic Monoesters

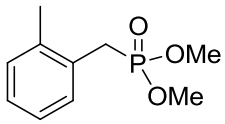
General procedure for preparation of dimethyl benzylic phosphonates.[147] To a solution of benzylic alcohol (1.0 mmol) in anhydrous toluene (10 mL) was added ZnI_2 (1.5 mmol) and $P(OMe)_3$ (2.0 mmol) under nitrogen. The reaction mixture was heated to 110 ^oC for 15 h under nitrogen. After being cooled to room temperature, the solvent was removed in vacuo. The residue was diluted with diethyl ether (20 mL), washed with 2 N NaOH (2 × 5 mL) and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified via flash column chromatography on silica gel (hexane/ethyl acetate = 2:1) to afford dimethyl benzylic phosphonate.

Dimethyl benzylphosphonate[147]



Yield: 162.0 mg, 81 %, colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 -7.25 (m, 5H), 3.70 -3.59 (m, 6H), 3.18 (d, *J* = 5.2 Hz, 1H), 3.13 (d, *J* = 5.2 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.2 (d, *J* = 9.2 Hz), 129.7 (d, *J* = 6.6 Hz), 128.6 (d, *J* = 2.8 Hz), 127.0 (d, *J* = 3.5 Hz), 52.8 (d, *J* = 6.8 Hz), 32.8 (d, *J* = 137.4 Hz).

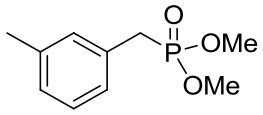
Dimethyl 2-methylbenzylphosphonate



Yield: 163.4 mg, 76 %, colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 1.5 Hz, 1H), 7.15 (d, *J* = 1.7 Hz, 3H), 3.65 (d, *J* = 1.9 Hz, 3H), 3.62 (d, *J* = 1.9 Hz, 3H), 3.21 (d, *J*

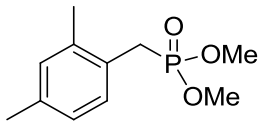
= 1.7 Hz, 1H), 3.15 (d, *J* = 1.7 Hz, 1H), 2.38 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (d, *J* = 6.7 Hz), 130.5 (d, *J* = 4.9 Hz), 129.7 (d, *J* = 9.5 Hz), 127.2 (d, *J* = 3.9 Hz), 126.1 (d, *J* = 3.5 Hz), 52.8 (d, *J* = 6.9 Hz), 30.2 (d, *J* = 138.0 Hz), 19.9.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; IR (film) *v* 3053, 2304, 1421, 1265, 895, 740, 108, 704.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_3P$ $(M + H)^+$ 215.0837, found 215.0831.

Dimethyl 3-methylbenzylphosphonate



Yield: 154.8 mg, 72 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.5 Hz, 1H), 7.17 -6.96 (m, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.15 (s, 1H), 3.10 (s, 1H), 2.33 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (d, *J* = 3.1 Hz), 131.0 (d, *J* = 9.2 Hz), 130.4 (d, *J* = 6.6 Hz), 128.5 (d, *J* = 3.1 Hz), 127.8 (d, *J* = 3.6 Hz), 126.7 (d, *J* = 6.6 Hz), 52.9 (d, *J* = 6.8 Hz), 32.7 (d, *J* = 138.0 Hz), 21.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; IR (film) *v* 3425, 2954, 1514, 1234, 1031, 862, 816.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_3P$ $(M + H)^+$ 215.0837, found 215.0835.

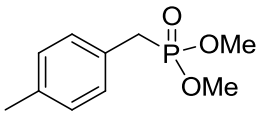
Dimethyl 2,4-dimethylbenzylphosphonate



Yield: 190.1 mg, 83 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 7.7, 2.8 Hz, 1H), 7.02 -6.93 (m, 2H), 3.66 (s, 3H), 3.63 (s, 3H), 3.17 (s, 1H), 3.12 (s, 1H), 2.34 (d, *J* = 1.4 Hz, 3H), 2.28 (d, *J* = 2.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (dd, *J* = 7.1, 5.5 Hz, 2C), 131.3 (d, *J* = 3.4 Hz), 130.4 (d, *J* = 5.5 Hz), 126.8 (d, *J* = 3.6 Hz), 126.4 (d, *J* = 9.6 Hz), 52.8 (d, *J* = 6.9 Hz), 29.8 (d, *J* = 138.0 Hz), 21.0 (d, *J* = 1.2 Hz), 19.8 (d, *J*

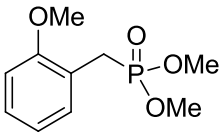
= 1.1 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5.; IR (film) *v* 2954, 1245, 1061, 1038, 907, 731, 650.; HRMS (ESI) *m / z* calcd for $C_{11}H_{18}O_3P$ $(M + H)^+$ 229.0994, found 229.0993.

Dimethyl 4-methylbenzylphosphonate



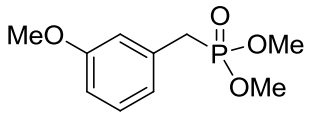
Yield: 157.0 mg, 73 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.1, 2.2 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 3.66 (s, 3H), 3.64 (s, 3H), 3.14 (s, 1H), 3.09 (s, 1H), 2.31 (d, *J* = 2.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6 (d, *J* = 3.8 Hz), 129.5 (d, *J* = 6.6 Hz), 129.3 (d, *J* = 3.1 Hz), 127.9 (d, *J* = 9.3 Hz), 52.8 (d, *J* = 6.8 Hz), 32.3 (d, *J* = 138.4 Hz), 21.0.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; IR (film) *v* 2953, 2235, 1516, 1250, 1057, 862, 729.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_3P$ $(M + H)^+$ 215.0837, found 215.0834.

Dimethyl 2-methoxybenzylphosphonate



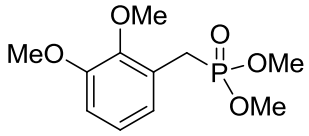
Yield: 173.3 mg, 75 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 -7.27 (m, 1H), 7.23 (t, *J* = 4.8 Hz, 1H), 6.94 -6.86 (m, 2H), 3.85 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.30 (s, 1H), 3.25 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (d, *J* = 6.7 Hz), 131.2 (d, *J* = 5.7 Hz), 128.4 (d, *J* = 3.7 Hz), 120.7 (d, *J* = 3.5 Hz), 119.8 (d, *J* = 9.6 Hz), 110.7 (d, *J* = 3.0 Hz), 55.5, 52.8 (d, *J* = 6.6 Hz), 25.8 (d, *J* = 138.4 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.8.; IR (film) *v* 2955, 1601, 1250, 1050, 735.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_4P$ $(M + H)^+$ 231.0786, found 231.0786.

Dimethyl 3-methoxybenzylphosphonate



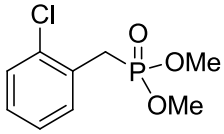
Yield: 184.8 mg, 80 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.9 Hz, 1H), 6.90 -6.83 (m, 2H), 6.83 -6.79 (m, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.17 (s, 1H), 3.12 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, *J* = 3.1 Hz), 132.6 (d, *J* = 9.1 Hz), 129.6 (d, *J* = 3.0 Hz), 122.1 (d, *J* = 6.7 Hz), 115.4 (d, *J* = 6.6 Hz), 112.6 (d, *J* = 3.5 Hz), 55.2, 53.0 (d, *J* = 6.8 Hz), 32.9 (d, *J* = 137.5 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9.; IR (film) *v* 2955, 1601, 1489, 1251, 1031, 807.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_4P$ $(M + H)^+$ 231.0786, found 231.0785.

Dimethyl 2,3-dimethoxybenzylphosphonate



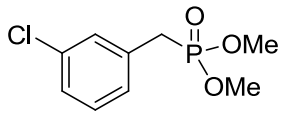
Yield: 224.5 mg, 86 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (t, *J* = 7.9 Hz, 1H), 6.97 -6.93 (m, 1H), 6.83 (dt, *J* = 8.0, 1.8 Hz, 1H), 3.72 (d, *J* = 4.2 Hz, 6H), 3.72 (s, 3H), 3.69 (s, 3H), 3.30 (s, 1H), 3.25 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 147.3, 125.2, 123.9 (d, *J* = 3.3 Hz), 122.8 (d, *J* = 4.8 Hz), 111.3 (d, *J* = 3.3 Hz), 60.7 (s), 55.7 (s), 52.8 (d, *J* = 6.7 Hz), 25.9 (d, *J* = 138.4 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.3.; IR (film) *v* 2955, 1586, 1486, 1271, 1057, 1032, 731.; HRMS (ESI) *m / z* calcd for $C_{11}H_{18}O_5P$ $(M + H)^+$ 261.0892, found 261.0892.

Dimethyl 2-chlorobenzylphosphonate



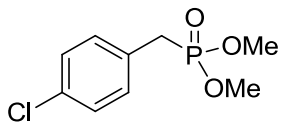
Yield: 168.9 mg, 71 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.1 Hz, 1H), 7.39 (d, *J* = 6.8 Hz, 1H), 7.26 -7.18 (m, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.42 (s, 1H), 3.37 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.2 (d, *J* = 8.3 Hz), 131.7 (d, *J* = 5.2 Hz), 129.7 (dd, *J* = 6.2, 3.1 Hz, 2C), 128.5 (d, *J* = 3.7 Hz), 127.0 (d, *J* = 3.4 Hz), 52.9 (d, *J* = 6.7 Hz), 29.9 (d, *J* = 138.5 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.7.; IR (film) *v* 2955, 2852, 1479, 1267, 1050, 867, 734.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3PCl$ $(M + H)^+$ 235.0291, found 235.0292.

Dimethyl 3-chlorobenzylphosphonate



Yield: 171.6 mg, 73 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 -7.27 (m, 1H), 7.27 -7.23 (m, 2H), 7.20 (s, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.16 (s, 1H), 3.11 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (d, *J* = 3.4 Hz), 133.3 (d, *J* = 9.1 Hz), 129.80 (dd, *J* = 9.1, 4.9 Hz 2C), 127.9 (d, *J* = 6.5 Hz), 127.3 (d, *J* = 3.6 Hz), 53.0 (d, *J* = 6.8 Hz), 29.9 (d, *J* = 138.5 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.1.; IR (film) *v* 2956, 1720, 1597, 1265, 1034, 882, 737.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3PCl$ $(M + H)^+$ 235.0291, found 235.0289.

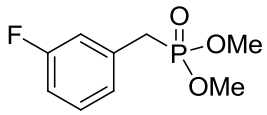
Dimethyl 4-chlorobenzylphosphonate



Yield: 185.7 mg, 79 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 7.16 (dd, *J* = 8.6, 2.4 Hz, 2H), 3.62 (s, 3H), 3.59 (s, 3H), 3.08 (s, 1H), 3.03 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0 (d, *J* = 4.4 Hz), 131.0 (d, *J* = 6.7 Hz), 129.8 (d, *J* = 9.3 Hz), 128.8 (d, *J* = 3.1 Hz), 52.9 (d, *J* = 6.9 Hz), 32.2 (d, *J* = 138.0 Hz).; ^{31}P NMR (162

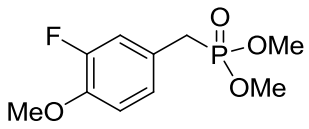
MHz, $CDCl_3$) δ 28.2.; IR (film) *v* 2955, 1491, 1247, 1031, 865, 788.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3PCl$ $(M + H)^+$ 235.0291, found 235.0293.

Dimethyl 3-fluorobenzylphosphonate



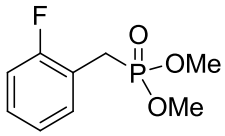
Yield: 151.1 mg, 69 %, colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 11.4, 5.2 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.02 (dd, *J* = 9.7, 1.9 Hz, 1H), 6.96 (dd, *J* = 9.4, 7.4 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.19 (s, 1H), 3.13 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 247.1 Hz). 133.7 (t, *J* = 8.6 Hz), 133.0 (t, *J* = 8.6 Hz), 125.4 (dd, *J* = 6.8, 2.9 Hz), 116.7 (dd, *J* = 22.0, 6.5 Hz), 113.9 (d, *J* = 17.1 Hz), 52.90 (d, *J* = 6.8 Hz), 32.5 (d, *J* = 138.0 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.0.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.9.; IR (film) *v* 2955, 1493, 1456, 1234, 1033, 758.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3PF$ $(M + H)^+$ 219.0586, found 219.0585.

Dimethyl 3-fluoro-4-methoxybenzylphosphonate



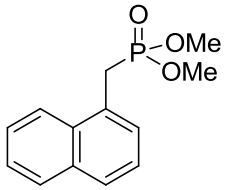
Yield: 179.3 mg, 72 %, colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 -6.98 (m, 2H), 6.91 (t, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 3.11 (s, 1H), 3.06 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4 (dd, *J* = 32.0, 241.5 Hz), 146.7 (dd, *J* = 10.6, 3.5 Hz), 125.5 (dd, *J* = 7.1, 3.6 Hz), 124.0 (dd, *J* = 9.3, 6.9 Hz), 117.4 (dd, *J* = 19.0, 6.3 Hz), 113.8, 56.3, 52.92 (d, *J* = 6.8 Hz), 31.8 (d, *J* = 138.9 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.5.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -134.8.; IR (film) *v* 2957, 1520, 1314, 1234, 1057, 916, 823.; HRMS (ESI) *m / z* calcd for $C_{10}H_{15}O_4PF$ $(M + H)^+$ 249.0692, found 249.0689.

Dimethyl 2-fluorobenzylphosphonate



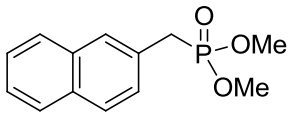
Yield: 142.4 mg, 65 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.25 (d, *J* = 13.0 Hz, 1H), 7.14 -7.02 (m, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.25 (s, 1H), 3.20 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8 (d, *J* = 246.3 Hz), 131.8, 128.9, 124.3, 118.8, 115.5 (d, *J* = 22.1 Hz), 52.9 (d, *J* = 6.5 Hz), 25.4 (d, *J* = 139.6 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8 (d, *J* = 4.9 Hz).; ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.4 (d, *J* = 3.8 Hz).; IR (film) *v* 2957, 1586, 1496, 1268, 1031, 872, 735.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_3PF$ $(M + H)^+$ 219.0586, found 219.0585.

Dimethyl naphthalen-1-ylmethylphosphonate



Yield: 178.2 mg, 71 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.79-7.72 (m, 1H), 7.57-7.51 (m, 1H), 7.50-7.44 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 3.67 (s, 1H), 3.61 (s, 1H), 3.59 (s, 3H), 3.56 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9 (d, *J* = 2.8 Hz), 131.9 (d, *J* = 5.3 Hz), 128.7, 128.5 (d, *J* = 7.6 Hz), 127.94(d, *J* = 4.2 Hz), 127.5 (d, *J* = 10.0 Hz), 126.3, 125.8, 125.4 (d, *J* = 4.2 Hz), 124.1 (d, *J* = 1.7 Hz), 53.0 (d, *J* = 6.9 Hz), 29.9 (d, *J* = 139.5 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.7.; IR (film) *v* 2955, 1597, 1255, 1030, 854, 778.; HRMS (ESI) *m / z* calcd for $C_{13}H_{16}O_3P$ $(M + H)^+$ 251.0837, found 251.0837.

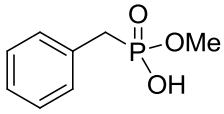
Dimethyl naphthalen-2-ylmethylphosphonate



Yield: 153.2 mg, 61 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 3H), 7.76 (s, 1H), 7.55-7.38 (m, 3H), 3.72-3.59 (m, 6H), 3.37 (s, 1H), 3.32 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.5 (d, *J* = 3.2 Hz), 132.4 (d, *J* = 2.6 Hz), 128.7 (d, *J* = 9.6 Hz), 128.5 (d, *J* = 8.6 Hz), 128.3 (d, *J* = 2.5 Hz), 127.7 (d, *J* = 5.1 Hz), 127.7 (d, *J* = 1.6 Hz), 127.6 (d, *J* = 1.4 Hz), 126.2, 125.9, 53.0 (d, *J* = 6.9 Hz), 33.1 (d, *J* = 138.3 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.3.; IR (film) *v* 2953, 1631, 1601, 1250, 1030, 813.; HRMS (ESI) *m / z* calcd for $C_{13}H_{16}O_3P$ $(M + H)^+$ 251.0837, found 251.0834.

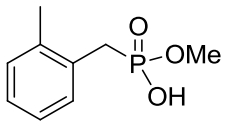
General procedure for preparation of methyl hydrogen benzylic phosphonate.[148] To a solution of dimethyl benzylic phosphonate (0.5 mmol) in $SOCl_2$ (0.5 mL) was added a catalytic amount of DMF (3.7 mg, 0.05 mmol) at room temperature. The reaction mixture was allowed to stir at reflux for 3 h. Excess $SOCl_2$ was removed and the residue was diluted with dichloromethane (10 mL). Cool water (1 mL) was then added to the solution at 0 ^{o}C and the mixture was stirred for 10 min. The organic layer was separated and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (dichloromethane/methanol = 20:1) to afford the corresponding methyl hydrogen benzylic phosphonate.

Methyl hydrogen benzylphosphonate (156b)



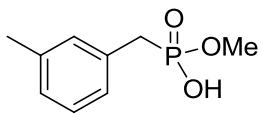
Yield: 80.4 mg, 86 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dt, *J* = 13.4, 7.5 Hz, 5H), 3.52 (d, *J* = 11.1 Hz, 3H), 3.07 (s, 1H), 3.02 (s, 1H). ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.3, 129.9 (d, *J* = 6.3 Hz), 128.5 (t, *J* = 6.3 Hz), 126.9 (d, *J* = 3.3 Hz), 52.0, 33.3 (d, *J* = 140.6 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.7.; IR (film) *v* 3055, 2358, 1495, 1265, 1049, 988, 738, 698.; HRMS (ESI) *m / z* calcd for $C_8H_{12}O_3P$ $(M + H)^+$ 187.0524, found 187.0521.

Methyl hydrogen 2-methylbenzylphosphonate (158a)



Yield: 78.4 mg, 78 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.13 (d, *J* = 9.3 Hz, 3H), 3.50 (d, *J* = 10.9 Hz, 3H), 3.11 (s, 1H), 3.05 (s, 1H), 2.35 (s, 3H). ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1 (d, *J* = 6.6 Hz), 130.8 (d, *J* = 5.3 Hz), 130.4 (d, *J* = 2.9 Hz), 129.8 (d, *J* = 9.3 Hz), 127.1 (d, *J* = 3.5 Hz), 126.0 (d, *J* = 3.2 Hz), 51.9 (d, *J* = 6.9 Hz), 30.6 (d, *J* = 139.2 Hz), 19.9 (s).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.2.; IR (film) *v* 3053, 2986, 1422, 1265, 1049, 728, 704.; HRMS (ESI) *m / z* calcd for $C_9H_{14}O_3P$ $(M + H)^+$ 201.0681, found 201.0679.

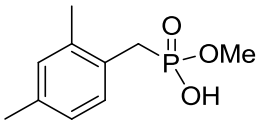
Methyl hydrogen 3-methylbenzylphosphonate (158b)



Yield: 71.4 mg, 71 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.5 Hz, 1H), 7.05 (dd, *J* = 12.4, 7.5 Hz, 3H), 3.55 (d, *J* = 10.9 Hz, 3H), 3.05 (s, 1H), 3.00 (s, 1H), 2.32 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 131.2 (d, *J* = 8.9 Hz), 130.6 (d, *J* = 6.5 Hz), 128.4 (d, *J* = 2.6 Hz), 127.7 (d, *J* = 3.2 Hz), 126.9 (d, *J* = 6.4 Hz), 52.0 (d, *J* = 6.9 Hz), 30.6 (d, *J* = 142.0 Hz), 21.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.9.; IR (film) *v* 2953,

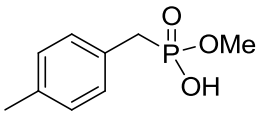
1606, 1487, 1045, 895, 810, 694.; HRMS (ESI) *m / z* calcd for $C_9H_{14}O_3P$ $(M + H)^+$ 201.0681, found 201.0679.

Methyl hydrogen 2,4-dimethylbenzylphosphonate (158c)



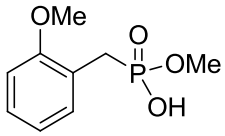
Yield: 81.7 mg, 76 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.4 Hz, 1H), 6.99 -6.90 (m, 2H), 3.50 (d, *J* = 10.8 Hz, 3H), 3.06 (s, 1H), 3.01 (s, 1H), 2.30 (s, 3H), 2.24 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (d, *J* = 6.2 Hz), 136.6 (d, *J* = 3.4 Hz), 131.2 (d, *J* = 2.2 Hz), 130.6 (d, *J* = 4.9 Hz), 126.6 (dd, *J* = 17.7, 6.0 Hz, 2C), 51.7 (d, *J* = 6.8 Hz), 30.9, 30.2 (d, *J* = 140.7 Hz), 19.8.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.3.; IR (film) *v* 2955, 1505, 1412, 1188, 1048, 910, 733.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_3P$ $(M + H)^+$ 215.0837, found 215.0841.

Methyl hydrogen 4-methylbenzylphosphonate (158d)



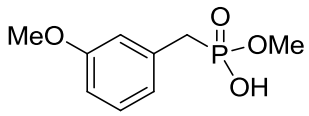
Yield: 79.4 mg, 79 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 -7.07 (m, 4H), 3.54 (d, *J* = 7.0 Hz, 3H), 3.05 (s, 1H), 3.00 (s, 1H), 2.31 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 129.7 (d, *J* = 5.8 Hz), 129.2 (d, *J* = 14.6 Hz), 128.2, 52.0, 32.9 (d, *J* = 140.2 Hz), 21.0.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.3.; IR (film) *v* 2953, 2351, 1514, 1265, 1051, 989, 137.; HRMS (ESI) *m / z* calcd for $C_9H_{14}O_3P$ $(M + H)^+$ 201.0681, found 201.0680.

Methyl hydrogen 2-methoxybenzylphosphonate (158e)



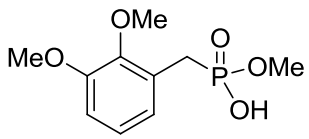
Yield: 82.5 mg, 76 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 -7.25 (m, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.90 -6.82 (m, 2H), 3.81 (s, 3H), 3.57 (d, *J* = 8.9 Hz, 3H), 3.22 (s, 1H), 3.17 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 131.3, 128.2, 120.5, 120.1 (d, *J* = 7.5 Hz), 110.8, 55.6, 52.0 (d, *J* = 3.9 Hz), 26.6 (d, *J* = 141.6 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.3.; IR (film) *v* 3053, 2986, 1600, 1495, 1265, 1049, 983, 748.; HRMS (ESI) *m / z* calcd for $C_9H_{14}O_4P$ $(M + H)^+$ 217.0630, found 217.0629.

Methyl hydrogen 3-methoxybenzylphosphonate (158f)



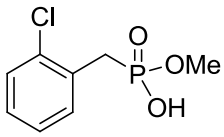
Yield: 70.5 mg, 65 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 3.76 (s, 3H), 3.55 (d, *J* = 11.1 Hz, 3H), 3.06 (s, 1H), 3.00 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (d, *J* = 2.9 Hz), 132.8 (d, *J* = 9.1 Hz), 129.4 (d, *J* = 2.8 Hz), 122.2 (d, *J* = 6.7 Hz), 115.4 (d, *J* = 6.5 Hz), 112.5 (d, *J* = 3.4 Hz), 55.1 (s), 52.1 (d, *J* = 7.1 Hz), 33.3 (d, *J* = 139.0 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.3.; IR (film) *v* 2984, 1732, 1373, 1242, 1047, 736.; HRMS (ESI) *m / z* calcd for $C_9H_{14}O_4P$ $(M + H)^+$ 217.0630, found 217.0632.

Methyl hydrogen 2,3-dimethoxybenzylphosphonate (158g)



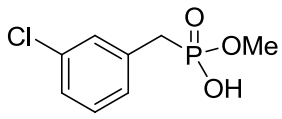
Yield: 77.8 mg, 63 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.61 (d, *J* = 11.2 Hz, 3H), 3.23 (s, 1H), 3.18 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (d, *J* = 3.0 Hz), 147.5 (d, *J* = 8.0 Hz), 125.3 (d, *J* = 8.9 Hz), 123.7 (d, *J* = 3.4 Hz), 123.0 (d, *J* = 4.9 Hz), 111.3 (d, *J* = 3.4 Hz), 60.8 (d, *J* = 1.7 Hz), 55.7, 51.9 (d, *J* = 7.5 Hz), 26.5 (d, *J* = 141.0 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.9.; IR (film) *v* 2952, 1585, 1485, 1273, 1051, 750.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_5P$ $(M + H)^+$ 247.0735, found 247.0732.

Methyl hydrogen 2-chlorobenzylphosphonate (158h)



Yield: 85.1 mg, 77 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, *J* = 8.7 Hz, 2H), 7.19 (dd, *J* = 14.4, 7.4 Hz, 2H), 3.61 (d, *J* = 11.1 Hz, 3H), 3.34 (s, 1H), 3.29 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (d, *J* = 8.3 Hz), 131.7 (d, *J* = 5.1 Hz), 129.7 (dd, *J* = 9.6, 6.0 Hz, 2C), 128.4 (d, *J* = 3.4 Hz), 126.8 (d, *J* = 3.1 Hz), 52.3 (d, *J* = 6.9 Hz), 30.5 (d, *J* = 140.0 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; IR (film) *v* 2955, 1479, 1442, 1189, 989, 750.; HRMS (ESI) *m / z* calcd for $C_8H_{11}O_3PCl$ $(M + H)^+$ 221.0134, found 221.0135.

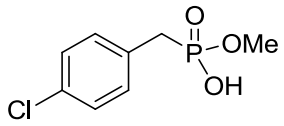
Methyl hydrogen 3-chlorobenzylphosphonate (158i)



Yield: 88.4 mg, 80 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.22 (d, *J* = 6.3 Hz, 2H), 7.15 (s, 1H), 3.59 (d, *J* = 11.2 Hz, 3H), 3.07 (s, 1H), 3.02 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.3 (d, *J* = 3.6 Hz), 133.4 (d, *J* = 9.2 Hz), 129.8 (dd, *J* = 12.6, 4.9 Hz, 2C), 128.1 (d, *J* = 6.6 Hz), 127.2 (d, *J* = 3.6 Hz), 52.1 (d, *J* = 7.1 Hz), 32.9

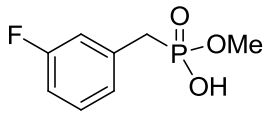
(d, *J* = 140.2 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.1.; IR (film) *v* 2985, 1473, 1265, 1199, 1049, 738.; HRMS (ESI) *m / z* calcd for $C_8H_{11}O_3PCl$ $(M + H)^+$ 221.0134, found 221.0130.

Methyl hydrogen 4-chlorobenzylphosphonate (158j)



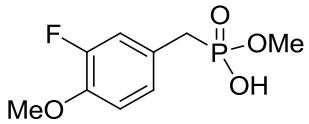
Yield: 90.6 mg, 82 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.2 Hz, 2H), 7.23 -7.11 (m, 2H), 3.55 (d, *J* = 11.1 Hz, 3H), 3.05 (s, 1H), 3.00 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9 (d, *J* = 4.5 Hz), 131.2 (d, *J* = 6.6 Hz), 129.8 (d, *J* = 9.4 Hz), 128.7 (d, *J* = 3.2 Hz), 52.0 (d, *J* = 7.1 Hz), 32.7 (d, *J* = 141.2 Hz).;).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.6.; IR (film) *v* 3053, 1490, 1265, 1051, 985, 738.; HRMS (ESI) *m / z* calcd for $C_8H_{11}O_3PCl$ $(M + H)^+$ 221.0134, found 221.0137.

Methyl hydrogen 3-fluorobenzylphosphonate (158k)



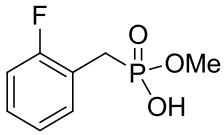
Yield: 78.9 mg, 77 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 13.3, 6.8 Hz, 1H), 7.04 (t, *J* = 9.9 Hz, 2H), 6.94 (t, *J* = 8.4 Hz, 1H), 3.59 (d, *J* = 7.4 Hz, 3H), 3.12 (s, 1H), 3.07 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (d, *J* = 254.1 Hz), 134.2, 129.9 (d, *J* = 8.3 Hz), 125.6, 116.8 (d, *J* = 21.0 Hz), 113.8 (d, *J* = 27.0 Hz), 52.2, 33.4 (d, *J* = 166.4 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.2.; IR (film) *v* 2955, 1580, 1500, 1253, 982, 738.; HRMS (ESI) *m / z* calcd for $C_8H_{11}O_3PF$ $(M + H)^+$ 205.0430, found 205.0430.

Methyl hydrogen 3-fluoro-4-methoxybenzylphosphonate (158l)



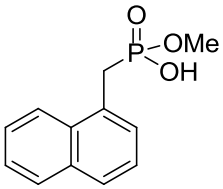
Yield: 74.0 mg, 63 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 12.0 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.88 (t, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 3.59 (d, *J* = 10.9 Hz, 3H), 3.03 (s, 1H), 2.98 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (d, *J* = 244.4 Hz), 146.7 (d, *J* = 7.9 Hz), 125.6 (d, *J* = 3.4 Hz), 124.0 (d, *J* = 8.7 Hz), 117.5 (dd, *J* = 19.0, 5.7 Hz), 113.4, 56.2, 52.0 (d, *J* = 6.8 Hz), 33.3 (d, *J* = 139.0 Hz).;).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.9.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -135.0.; IR (film) *v* 3053, 1265, 1116, 993, 736.; HRMS (ESI) *m / z* calcd for $C_9H_{13}O_4PF$ $(M + H)^+$ 235.0536, found 235.0531.

Methyl hydrogen 2-fluorobenzylphosphonate (158m)



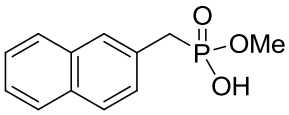
Yield: 83.0 mg, 81 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.4 Hz, 1H), 7.25 -7.15 (m, 1H), 7.11 -7.01 (m, 2H), 3.60 (d, *J* = 11.1 Hz, 3H), 3.17 (s, 1H), 3.11 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4 (dd, *J* = 243.0, 245.0 Hz), 131.8 (dd, *J* = 5.2, 3.5 Hz), 128.8 (dd, *J* = 8.1, 3.6 Hz), 124.1 (t, *J* = 3.5 Hz), 118.7 (dd, *J* = 15.6, 9.4 Hz), 115.4 (dd, *J* = 22.0, 3.0 Hz), 52.2 (d, *J* = 6.9 Hz), 25.9 (d, *J* = 140.0 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.0.; IR (film) *v* 3053, 1494, 1456, 1265, 1049, 738.; HRMS (ESI) *m / z* calcd for $C_8H_{11}O_3PF$ $(M + H)^+$ 205.0430, found 205.0429.

Methyl hydrogen naphthalen-1-ylmethylphosphonate (158n)



Yield: 103.1 mg, 87 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 11.6, 7.8 Hz, 2H), 7.36 (dt, *J* = 10.0, 7.0 Hz, 2H), 3.45 (s, 1H), 3.39 (s, 1H), 3.35 (d, *J* = 11.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8 (d, *J* = 2.6 Hz), 132.0 (d, *J* = 5.1 Hz), 128.7 (d, *J* = 7.6 Hz), 128.5, 127.74(d, *J* = 4.3 Hz), 127.7 (d, *J* = 5.4 Hz), 126.2, 125.7, 125.4 (d, *J* = 4.0 Hz), 124.4, 65.9, 51.9 (d, *J* = 7.1 Hz), 30.3 (d, *J* = 141.5 Hz), 15.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.3.; IR (film) *v* 3051, 1508, 1265, 1049, 983, 736.; HRMS (ESI) *m / z* calcd for $C_{12}H_{14}O_3P$ $(M + H)^+$ 237.0681, found 237.0679.

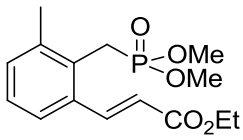
Methyl hydrogen naphthalen-2-ylmethylphosphonate (158o)



Yield: 79.7 mg, 69 %, colorless oil; ^{1}H NMR (400 MHz, DMSO) δ 7.84 (dd, *J* = 21.5, 12.4 Hz, 4H), 7.52 -7.46 (m, 3H), 3.56 (d, *J* = 10.8 Hz, 3H), 3.31 (s, 1H), 3.26 (s, 1H).; ^{13}C NMR (101 MHz, DMSO) δ 133.5 (d, *J* = 3.0 Hz), 132.1 (d, *J* = 2.4 Hz), 131.5 (d, *J* = 9.2 Hz), 128.8 (d, *J* = 5.0 Hz), 128.4 (d, *J* = 8.3 Hz), 127.948 (d, *J* = 1.7 Hz), 127.8 (d, *J* = 1.3 Hz), 126.6, 126.0 (s), 52.0 (d, *J* = 6.2 Hz), 33.7 (d, *J* = 133.2 Hz).; ^{31}P NMR (162 MHz, DMSO) δ 24.6.; IR (film) *v* 3053, 1653, 1265, 1130, 993, 738.; HRMS (ESI) *m / z* calcd for $C_{12}H_{14}O_3P$ $(M + H)^+$ 237.0681, found 231.0672.

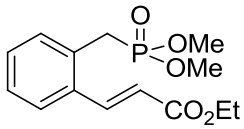
Typical procedure for *ortho* C–H olefination of methyl hydrogen 2-methylbenzylphosphonate (158a). **158a** (43.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.8 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol), ethyl acrylate (40 mg, 43 μL, 0.4 mmol) and dioxane (1.5 mL) were mixed in a sealed vial. The reaction mixture was stirred at 110 °C for 24 h. The mixture was then cooled to 0 °C and 2.0 N HCl solution (1 mL) was added. The mixture was extracted with EtOAc (2 × 10 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield the crude product, which was diluted with methanol (5 mL) and treated with TMS-CHN_2 (0.5 mL, 2M in hexane) at room temperature for 0.5 h. The mixture was evaporated under reduced pressure and purified by silica gel flash column chromatography (dichloromethane/acetone = 20:1) to afford product **160a** (56.9 mg, 91%).

(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-3-methylphenyl)acrylate (160a)



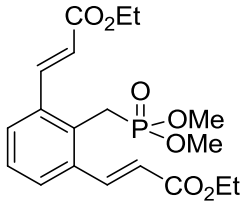
Yield: 56.9 mg, 91 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 15.7 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.12 – 7.08 (m, 1H), 6.26 (d, *J* = 15.7 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 143.0 (d, *J* = 2.2 Hz), 138.5 (d, *J* = 6.0 Hz), 134.6 (d, *J* = 5.9 Hz), 132.3 (d, *J* = 3.7 Hz), 129.5 (d, *J* = 9.9 Hz), 127.3 (d, *J* = 3.9 Hz), 124.9 (d, *J* = 3.6 Hz), 120.4, 60.5, 52.8 (d, *J* = 6.9 Hz), 27.2 (d, *J* = 138.1 Hz), 20.64 (s), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.9.; IR (film) *v* 2980, 1713, 1614, 1238, 1031, 846, 791.; HRMS (ESI) *m / z* calcd for $C_{15}H_{22}O_5P$ $(M + H)^+$ 313.1205, found 313.1203.

(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)phenyl)acrylate (157)



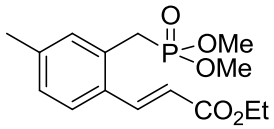
Yield: 22.0 mg, 48 %, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 15.8 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.38-7.33 (m, 2H), 7.33-7.28 (m, 1H), 6.38 (d, *J* = 15.7 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.35 (s, 1H), 3.29 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 141.8 (d, *J* = 2.0 Hz), 134.0 (d, *J* = 6.6 Hz), 131.6 (d, *J* = 5.7 Hz), 131.0 (d, *J* = 9.6 Hz), 130.1 (d, *J* = 3.5 Hz), 127.7 (d, *J* = 3.7 Hz), 127.0 (d, *J* = 3.2 Hz), 120.5, 60.6, 52.9 (d, *J* = 6.9 Hz), 30.2 (d, *J* = 137.7 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.7.; IR (film) *v* 2958, 1713, 1634, 1260, 1029, 802.; HRMS (ESI) *m / z* calcd for $C_{14}H_{20}O_5P$ $(M + H)^+$ 229.1048, found 229.1049.

(2*E*,2'*E*)-Diethyl 3,3'-(2-((dimethoxyphosphoryl)methyl)-1,3-phenylene)diacrylate (157')



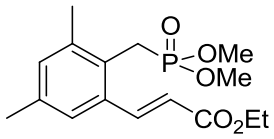
Yield: 37.3 mg, 47 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 15.7 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.31 (td, *J* = 7.8, 2.2 Hz, 1H), 6.34 (d, *J* = 15.7 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 4H), 3.70 (s, 3H), 3.67 (s, 3H), 3.47 (s, 1H), 3.42 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 142.3, 135.7, 130.1, 128.7, 127.8, 121.8, 60.7, 52.9 (d, *J* = 6.8 Hz), 27.1 (d, *J* = 138.0 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.5.; IR (film) *v* 2983, 1714, 1633, 1315, 1176, 1031, 848.; HRMS (ESI) *m / z* calcd for $C_{19}H_{26}O_7P$ $(M + H)^+$ 397.1416, found 397.1413.

(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-4-methylphenyl)acrylate (160b)



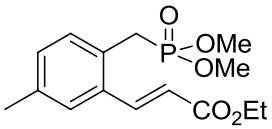
Yield: 53.2 mg, 85 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 15.7 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.31 (s, 1H), 3.26 (s, 1H), 2.35 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 141.7 (d, *J* = 2.0 Hz), 132.2 (d, *J* = 5.7 Hz), 128.6 (d, *J* = 3.6 Hz), 126.8 (d, *J* = 3.2 Hz), 119.3, 60.5, 52.9 (d, *J* = 6.9 Hz), 30.1 (d, *J* = 137.5 Hz), 21.3, 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8.; IR (film) *v* 2955, 1713, 1634, 1315, 1182, 1032, 814.; HRMS (ESI) *m / z* calcd for $C_{15}H_{22}O_5P$ $(M + H)^+$ 313.1205, found 313.1200.

(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-3,5-dimethylphenyl)acrylate (160c)



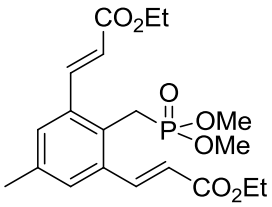
Yield: 63.4 mg, 97 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 15.7 Hz, 1H), 7.25 (s, 1H), 7.06 (s, 1H), 6.34 (d, *J* = 15.7 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 3.64 (s, 3H), 3.35 (s, 1H), 3.30 (s, 1H), 2.41 (s, 3H), 2.30 (d, *J* = 2.4 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 143.1 (d, *J* = 2.3 Hz), 138.3 (d, *J* = 6.0 Hz), 136.8 (d, *J* = 4.1 Hz), 134.3 (d, *J* = 5.8 Hz), 133.3 (d, *J* = 3.8 Hz), 126.6 (d, *J* = 10.0 Hz), 125.4 (d, *J* = 3.6 Hz), 120.1, 77.4, 77.0, 76.7, 60.5, 52.8 (d, *J* = 7.0 Hz), 27.5 (d, *J* = 138.3 Hz), 20.9 (d, *J* = 1.2 Hz), 20.6 (d, *J* = 1.2 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.2.; IR (film) *v* 2955, 1712, 1634, 1269, 1034, 856, 731.; HRMS (ESI) *m / z* calcd for $C_{16}H_{24}O_5P$ $(M + H)^+$ 327.1361, found 327.1358.

(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-5-methylphenyl)acrylate (160d)



Yield: 29.4 mg, 47 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 15.8 Hz, 1H), 7.40 (s, 1H), 7.24 (dd, *J* = 7.8, 2.7 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.37 (d, *J* = 15.7 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 3.65 (s, 3H), 3.31 (s, 1H), 3.25 (s, 1H), 2.34 (d, *J* = 2.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 142.0 (d, *J* = 2.0 Hz), 137.3 (d, *J* = 3.9 Hz), 133.7 (d, *J* = 6.6 Hz), 131.5 (d, *J* = 5.7 Hz), 131.0 (d, *J* = 3.5 Hz), 128.0 (d, *J* = 9.8 Hz), 127.5 (d, *J* = 3.2 Hz), 120.2, 60.5, 52.9 (d, *J* = 6.9 Hz), 29.8 (d, *J* = 137.9 Hz), 21.0, 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.9.; IR (film) *v* 2981, 1713, 1633, 1180, 1030, 862.; HRMS (ESI) *m / z* calcd for $C_{15}H_{22}O_5P$ $(M + H)^+$ 313.1205, found 313.1205.

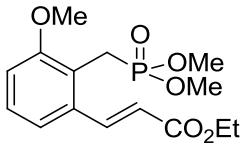
(2*E*,2'*E*)-Diethyl 3,3'-(2-((dimethoxyphosphoryl)methyl)-5-methyl-1,3-phenylene) Diacrylate (161d)



Yield: 37.0 mg, 45 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 15.7 Hz, 2H), 7.41 (s, 2H), 6.34 (d, *J* = 15.7 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 4H), 3.70 (s, 3H), 3.67 (s, 3H), 3.44 (s, 1H), 3.38 (s, 1H), 2.36 (d, *J* = 2.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 142.4 (d, *J* = 2.2 Hz), 137.4 (d, *J* = 4.0 Hz), 135.5 (d, *J* = 6.0 Hz), 129.4 (d, *J* = 3.6 Hz), 127.3 (d, *J* = 10.2 Hz), 121.5, 60.6, 52.9 (d, *J* = 6.9 Hz), 26.7 (d, *J* = 138.2 Hz), 21.0, 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.8.; IR (film) *v* 2955,

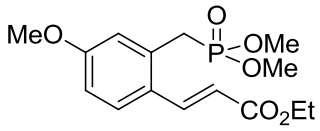
1713, 1633, 1183, 1031, 860.; HRMS (ESI) *m / z* calcd for $C_{20}H_{28}O_7P$ $(M + H)^+$ 411.1573, found 411.1566.

(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-3-methoxyphenyl)acrylate (160e)



Yield: 59.2 mg, 90 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 15.7 Hz, 1H), 7.27 -7.19 (m, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.36 (d, *J* = 16.1 Hz, 1H), 4.30 -4.24 (m, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.48 (s, 1H), 3.42 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 157.7 (d, *J* = 5.8 Hz), 142.2 (d, *J* = 2.3 Hz), 135.3 (d, *J* = 6.0 Hz), 128.1 (d, *J* = 3.8 Hz), 120.7, 120.4 (d, *J* = 10.6 Hz), 119.1 (d, *J* = 3.6 Hz), 111.7 (d, *J* = 3.3 Hz), 60.5, 55.9, 52.7 (d, *J* = 6.6 Hz), 23.3 (d, *J* = 138.5 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.0.; IR (film) *v* 2982, 1713, 1633, 1261, 1030, 848.; HRMS (ESI) *m / z* calcd for $C_{15}H_{22}O_6P$ $(M + H)^+$ 329.1154, found 329.1160.

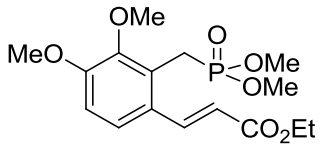
(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-4-methoxyphenyl)acrylate (160f)



Yield: 59.9 mg, 91 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 15.7 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 6.88 (t, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.29 (d, *J* = 15.7 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.69 (d, *J* = 3.2 Hz, 3H), 3.67 (s, 3H), 3.33 (s, 1H), 3.28 (s, 1H), 1.33 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 160.9 (d, *J* = 3.5 Hz), 141.2 (d, *J* = 1.9 Hz), 132.9 (d, *J* = 9.4 Hz), 128.4 (d, *J* = 3.1 Hz), 126.4 (d, *J* = 6.5 Hz), 117.9, 116.4 (d, *J* = 5.6 Hz), 113.9 (d, *J* = 3.5 Hz), 60.4, 55.4, 52.9 (d, *J* = 6.9 Hz), 30.3 (d, *J* = 137.6 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ

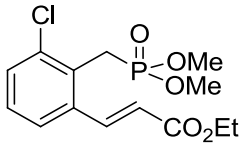
27.5.; IR (film) *v* 2957, 1713, 1604, 1504, 1258, 1030, 813.; HRMS (ESI) *m / z* calcd for $C_{15}H_{22}O_6P$ $(M + H)^+$ 329.1154, found 329.1160.

(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-3,4-dimethoxyphenyl)acrylate (160g)



Yield: 68.2 mg, 95 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 15.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.28 (d, *J* = 15.7 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.48 (s, 1H), 3.43 (s, 1H), 1.33 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 154.0 (d, *J* = 3.4 Hz), 147.5 (d, *J* = 6.7 Hz), 142.1 (d, *J* = 1.9 Hz), 127.2 (d, *J* = 5.1 Hz), 125.9 (d, *J* = 10.0 Hz), 122.6 (d, *J* = 3.3 Hz), 118.0, 111.4 (d, *J* = 3.5 Hz), 60.7 (d, *J* = 1.8 Hz), 60.4, 55.7, 52.8 (d, *J* = 6.7 Hz), 23.8 (d, *J* = 138.7 Hz), 14.4.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.0.; IR (film) *v* 2955, 1707, 1637, 1482, 1182, 1036, 910, 731.; HRMS (ESI) *m / z* calcd for $C_{16}H_{24}O_7P$ $(M + H)^+$ 359.1260, found 359.1268.

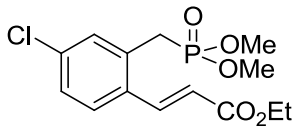
(*E*)-Ethyl 3-(3-chloro-2-((dimethoxyphosphoryl)methyl)phenyl)acrylate (160h)



Yield: 57.3 mg, 86 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 15.7 Hz, 1H), 7.46 (dd, *J* = 17.4, 7.9 Hz, 2H), 7.23 (td, *J* = 8.0, 2.4 Hz, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 3.60 (s, 1H), 3.55 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (d, *J* = 2.1 Hz), 136.6 (d, *J* = 5.6 Hz), 135.8 (d, *J* = 7.0 Hz), 131.0 (d, *J* = 3.5 Hz), 129.5 (d, *J* = 10.3 Hz), 128.3 (d, *J* = 3.9 Hz), 125.6 (d, *J* = 3.5 Hz), 121.9, 60.6, 52.9 (d, *J* = 6.8 Hz), 28.0 (d, *J* = 138.7 Hz), 14.4.;

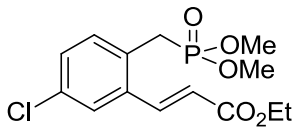
^{31}P NMR (162 MHz, $CDCl_3$) δ 26.5.; IR (film) *v* 2957, 1713, 1635, 1271, 1181, 1030, 789.; HRMS (ESI) *m / z* calcd for $C_{14}H_{19}O_5PCl$ $(M + H)^+$ 333.0659, found 333.0658.

(*E*)-Ethyl 3-(4-chloro-2-((dimethoxyphosphoryl)methyl)phenyl)acrylate (160i)



Yield: 53.9 mg, 81 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 15.7 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.34 (t, *J* = 2.4 Hz, 1H), 7.27 (d, *J* = 4.2 Hz, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.27 (d, *J* = 22.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 140.6, 135.9, 132.8 (d, *J* = 9.7 Hz), 132.5 (d, *J* = 6.5 Hz), 131.4 (d, *J* = 5.7 Hz), 128.2 (d, *J* = 3.3 Hz), 128.0 (d, *J* = 3.7 Hz), 121.0, 60.7, 53.0 (d, *J* = 6.8 Hz), 30.1 (d, *J* = 138.0 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.7.; IR (film) *v* 2955, 1714, 1634, 1593, 1250, 1210, 813.; HRMS (ESI) *m / z* calcd for $C_{14}H_{19}O_5PCl$ $(M + H)^+$ 333.0659, found 333.0654.

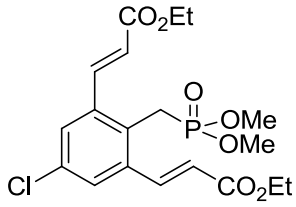
(*E*)-Ethyl 3-(5-chloro-2-((dimethoxyphosphoryl)methyl)phenyl)acrylate (160j)



Yield: 32.0 mg, 48 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 15.7 Hz, 1H), 7.55 (s, 1H), 7.30 (t, *J* = 2.3 Hz, 2H), 6.38 (d, *J* = 15.7 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.29 (s, 1H), 3.24 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 140.5 (d, *J* = 1.9 Hz), 135.6 (d, *J* = 6.7 Hz), 133.6 (d, *J* = 4.5 Hz), 132.8 (d, *J* = 5.6 Hz), 129.9 (d, *J* = 3.5 Hz), 129.5 (d, *J* = 9.7 Hz), 126.8 (d, *J* = 3.2 Hz), 121.8, 60.8, 53.0 (d, *J* = 6.9 Hz), 29.7 (d, *J* = 138.2 Hz), 14.3; ^{31}P NMR (162

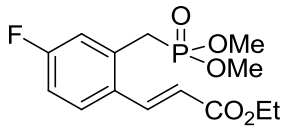
MHz, $CDCl_3$) δ 27.0.; IR (film) *v* 2957, 1713, 1634, 1315, 1182, 1031, 866.; HRMS (ESI) *m / z* calcd for $C_{14}H_{19}O_5PCl$ $(M + H)^+$ 333.0659, found 333.0657.

(2*E*,2'*E*)-Diethyl 3,3'-(5-chloro-2-((dimethoxyphosphoryl)methyl)-1,3-phenylene) Diacrylate (161j)



Yield: 37.1 mg, 43 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 15.7 Hz, 2H), 7.54 (s, 2H), 6.34 (d, *J* = 15.7 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 4H), 3.71 (s, 3H), 3.69 (s, 3H), 3.41 (s, 1H), 3.35 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 141.0 (d, *J* = 2.1 Hz), 137.4 (d, *J* = 5.9 Hz), 133.8 (d, *J* = 4.6 Hz), 128.6 (d, *J* = 10.1 Hz), 128.2 (d, *J* = 3.5 Hz), 123.0, 60.8, 53.0 (d, *J* = 6.8 Hz), 26.9 (d, *J* = 139.1 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.0.; IR (film) *v* 2957, 1714, 1634, 1271, 1180, 1031, 861.; HRMS (ESI) *m / z* calcd for $C_{19}H_{25}O_7PCl$ $(M + H)^+$ 431.1026, found 431.1023.

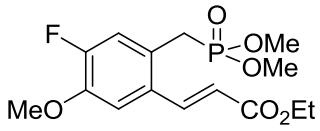
(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-4-fluorophenyl)acrylate (160k)



Yield: 46.9 mg, 74 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 15.7 Hz, 1H), 7.58 (dd, *J* = 8.7, 5.8 Hz, 1H), 7.08 (dt, *J* = 9.4, 2.7 Hz, 1H), 7.03 -6.96 (m, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.32 (s, 1H), 3.27 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 163.4 (dd, *J* = 3.9, 249.5 Hz), 140.7, 133.6 (d, *J* = 9.5 Hz), 130.2 (dd, *J* = 6.6, 3.4 Hz), 128.9 (dd, *J* =

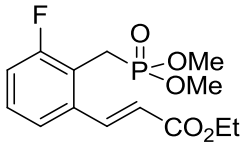
8.7, 3.2 Hz), 120.3, 118.2 (dd, *J* = 22.3, 5.6 Hz), 115.1 (dd, *J* = 21.7, 3.6 Hz), 60.6, 53.0 (d, *J* = 6.9 Hz), 30.3 (d, *J* = 138.0 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.8.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -110.2.; IR (film) *v* 2957, 1714, 1633, 1606, 1495, 1180, 1030, 814.; HRMS (ESI) *m / z* calcd for $C_{14}H_{19}O_5PF$ $(M + H)^+$ 317.0954, found 317.0956.

(*E*)-Ethyl-3-(2-((dimethoxyphosphoryl)methyl)-4-fluoro-5-methoxyphenyl)acrylate (160l)



Yield: 57.6 mg, 83 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 15.7 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.08 (dd, *J* = 11.7, 2.4 Hz, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 4.31 -4.24 (m, 2H), 3.91 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.26 (s, 1H), 3.20 (s, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 153.3 (dd, *J* = 250.3, 4.0 Hz), 147.1 (dd, *J* = 11.1, 3.4 Hz), 140.9, 130.1 (dd, *J* = 7.0, 3.9 Hz), 124.5 (dd, *J* = 9.9, 6.9 Hz), 120.2, 118.9 (dd, *J* = 19.3, 5.4 Hz), 111.5, 60.7, 56.3, 52.3 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 139.0 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.2.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.3.; IR (film) *v* 2957, 1713, 1634, 1514, 1249, 1180, 1029, 866, 813.; HRMS (ESI) *m / z* calcd for $C_{15}H_{21}O_6PF$ $(M + H)^+$ 347.1060, found 347.1056.

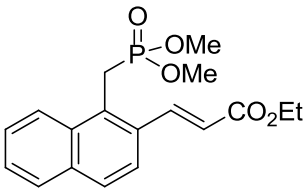
(*E*)-Ethyl 3-(2-((dimethoxyphosphoryl)methyl)-3-fluorophenyl)acrylate (160m)



Yield: 22.8 mg, 36 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 15.8 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 3.9 Hz, 1H), 7.11 (t, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.40 (d, *J* = 1.5 Hz,

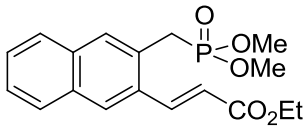
1H), 3.35 (d, *J* = 1.5 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.40 (s), 162.3 (dd, *J* = 245.0, 6.2 Hz), 140.8 (dd, *J* = 3.3, 2.3 Hz), 136.3 (dd, *J* = 5.6, 3.7 Hz), 128.6 (dd, *J* = 9.1, 3.8 Hz), 122.5 (t, *J* = 3.3 Hz), 121.7 (d, *J* = 0.9 Hz), 119.1 (dd, *J* = 15.8, 10.4 Hz), 116.5 (dd, *J* = 23.1, 3.4 Hz), 60.7, 52.9 (d, *J* = 6.6 Hz), 23.0 (dd, *J* = 139.5, 4.5 Hz), 14.3.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.6 (d, *J* = 4.9 Hz).; ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.9 (d, *J* = 3.8 Hz).; IR (film) *v* 2955, 1712, 1636, 1456, 1244, 1031, 848, 793.; HRMS (ESI) *m / z* calcd for $C_{14}H_{19}O_5PF$ $(M + H)^+$ 317.0954, found 317.0959.

(*E*)-Ethyl 3-(1-((dimethoxyphosphoryl)methyl)naphthalen-2-yl)acrylate (160n)



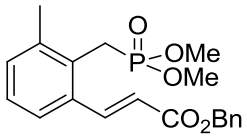
Yield: 59.3 mg, 85 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 15.7 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.79 -7.75 (m, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.62 -7.57 (m, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 1H), 3.82 (s, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 142.4 (d, *J* = 3.2 Hz), 134.3 (d, *J* = 2.9 Hz), 132.4 (d, *J* = 4.6 Hz), 131.6 (d, *J* = 7.9 Hz), 128.6, 128.2 (dd, *J* = 12.4, 7.4 Hz), 126.9 (d, *J* = 9.1 Hz), 125.3 (d, *J* = 2.2 Hz), 123.7 (d, *J* = 4.1 Hz), 121.0 (s), 60.6, 52.9 (d, *J* = 6.9 Hz), 30.4 (d, *J* = 137.0 Hz), 14.4.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.1.; IR (film) *v* 2955, 1713, 1632, 1300, 1180, 1031, 815, 731.; HRMS (ESI) *m / z* calcd for $C_{18}H_{22}O_5P$ $(M + H)^+$ 349.1205, found 349.1201.

(*E*)-Ethyl 3-(3-((dimethoxyphosphoryl)methyl)naphthalen-2-yl)acrylate (160o)



Yield: 51.0 mg, 73 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 15.7 Hz, 1H), 8.08 (s, 1H), 7.81 (t, *J* = 5.1 Hz, 3H), 7.51 – 7.46 (m, 2H), 6.51 (d, *J* = 15.7 Hz, 1H), 4.30 (d, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 3.67 (s, 3H), 3.49 (s, 1H), 3.43 (s, 1H), 1.36 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 142.4, 133.9 (d, *J* = 3.6 Hz), 132.4 (t, *J* = 4.0 Hz), 130.4 (d, *J* = 7.4 Hz), 128.1 (d, *J* = 1.7 Hz), 127.8 (d, *J* = 9.8 Hz), 127.4 (d, *J* = 13.4 Hz), 127.0 (d, *J* = 2.6 Hz), 126.6, 121.0, 60.6, 53.0 (d, *J* = 6.9 Hz), 26.5 (d, *J* = 138.8 Hz), 14.4.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8.; IR (film) *v* 2955, 1715, 1634, 1464, 1267, 1180, 1031, 810, 752.; HRMS (ESI) *m / z* calcd for $C_{18}H_{22}O_5P$ $(M + H)^+$ 349.1205, found 349.1201.

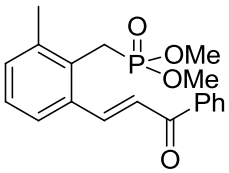
(*E*)-Benzyl 3-(2-((dimethoxyphosphoryl)methyl)-3-methylphenyl)acrylate (163a)



Yield: 68.3 mg, 91 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 15.7 Hz, 1H), 7.42 (dd, *J* = 10.6, 4.1 Hz, 3H), 7.40 -7.32 (m, 3H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.20 - 7.15 (m, 1H), 6.39 (d, *J* = 15.7 Hz, 1H), 5.26 (s, 2H), 3.63 (s, 3H), 3.61 (s, 3H), 3.39 (s, 1H), 3.33 (s, 1H), 2.45 (d, *J* = 1.2 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.61 (s), 143.60 (d, *J* = 2.3 Hz), 138.52 (d, *J* = 6.0 Hz), 136.11 (s), 134.45 (d, *J* = 5.8 Hz), 132.42 (d, *J* = 3.6 Hz), 129.67 (d, *J* = 9.9 Hz), 128.58 (s), 128.24 (s), 127.32 (d, *J* = 4.0 Hz), 124.88 (d, *J* = 3.6 Hz), 120.00 (s), 66.35 (s), 52.79 (d, *J* = 7.0 Hz), 27.22 (d, *J* = 138.9 Hz), 20.66 (s).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8.; IR (film) *v* 2955, 1714, 1634, 1451, 1249,

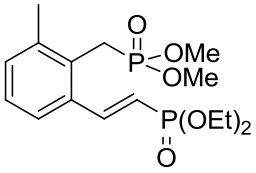
1163, 1030, 849.; HRMS (ESI) *m / z* calcd for $C_{20}H_{24}O_5P$ $(M + H)^+$ 375.1361, found 375.1361.

(*E*)-Dimethyl 2-methyl-6-(3-oxo-3-phenylprop-1-enyl)benzylphosphonate (163b)



Yield: 43.5 mg, 63 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 15.4 Hz, 1H), 8.07 -8.02 (m, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 15.4 Hz, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.44 (s, 1H), 3.38 (s, 1H), 2.48 (d, *J* = 1.2 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 143.3 (d, *J* = 2.3 Hz), 138.7 (d, *J* = 6.0 Hz), 135.1 (d, *J* = 5.8 Hz), 132.8, 132.6 (d, *J* = 3.7 Hz), 130.3 (d, *J* = 9.9 Hz), 128.6 (d, *J* = 6.2 Hz), 127.3 (d, *J* = 3.9 Hz), 124.9 (d, *J* = 3.6 Hz), 124.4, 52.8 (d, *J* = 7.0 Hz), 27.3 (d, *J* = 137.9 Hz), 20.7.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8.; IR (film) *v* 2955, 1661, 1602, 1238, 1031, 839.; HRMS (ESI) *m / z* calcd for $C_{19}H_{22}O_4P$ $(M + H)^+$ 345.1256, found 345.1252.

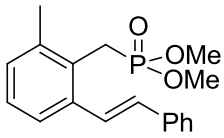
(*E*)-Dimethyl 2-methyl-6-(diethyl vinylphosphonate)benzylphosphonate (163c)



Yield: 57.3 mg, 76 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 22.6, 17.2 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.19 (dt, *J* = 7.6, 4.7 Hz, 2H), 6.17 (dd, *J* = 18.8, 17.4 Hz, 1H), 4.20 – 4.10 (m, 4H), 3.66 (s, 3H), 3.63 (s, 3H), 3.37 (s, 1H), 3.31 (s, 1H), 2.43 (d, *J* = 1.2 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (d, *J* = 7.2 Hz), 138.4 (d, *J* = 5.9 Hz), 135.4 (dd, *J* = 22.6, 5.9 Hz), 132.2 (d, *J* = 3.7 Hz), 129.1 (d, *J*

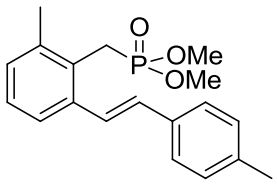
= 9.8 Hz), 127.3 (d, *J* = 3.9 Hz), 124.7 (d, *J* = 2.1 Hz), 117.8, 115.9, 61.9 (d, *J* = 5.6 Hz), 52.8 (d, *J* = 7.0 Hz), 27.1 (d, *J* = 137.9 Hz), 20.6 (d, *J* = 1.3 Hz), 16.4 (d, *J* = 6.4 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.9, 18.9.; IR (film) *v* 2983, 1620, 1469, 1392, 1238, 1051, 966, 792.; HRMS (ESI) *m / z* calcd for $C_{16}H_{27}O_6P_2$ $(M + H)^+$ 377.1283, found 377.1281.

(*E*)-Dimethyl 2-methyl-6-styrylbenzylphosphonate (163d)



Yield: 53.9 mg, 85 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.37 (dd, *J* = 10.4, 4.7 Hz, 2H), 7.28 (dd, *J* = 5.9, 1.5 Hz, 1H), 7.19 -7.12 (m, 2H), 6.95 (d, *J* = 16.0 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.42 (s, 1H), 3.36 (s, 1H), 2.44 (d, *J* = 1.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 137.6, 131.4 (d, *J* = 1.3 Hz), 130.0 (d, *J* = 3.7 Hz), 128.7, 127.7, 127.3 (dd, *J* = 15.6, 3.2 Hz), 126.7, 124.3 (d, *J* = 3.6 Hz), 52.9 (d, *J* = 7.0 Hz), 27.5 (d, *J* = 138.0 Hz), 20.7 (d, *J* = 1.3 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9.; IR (film) *v* 2953, 1454, 1250, 1030, 840, 781, 692.; HRMS (ESI) *m / z* calcd for $C_{18}H_{22}O_3P$ $(M + H)^+$ 317.1307, found 317.1313.

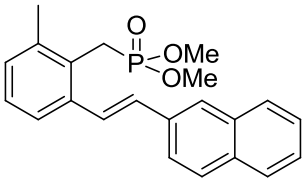
(*E*)-Dimethyl 2-methyl-6-(4-methylstyryl)benzylphosphonate (163e)



Yield: 53.6 mg, 81 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.3 Hz, 1H), 7.51 -7.44 (m, 2H), 7.25 -7.12 (m, 6H), 3.66 (s, 3H), 3.64 (s, 3H), 3.41 (s, 1H), 3.36 (s, 1H), 2.45 (d, *J* = 1.3 Hz, 3H), 2.42 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (d, *J* =

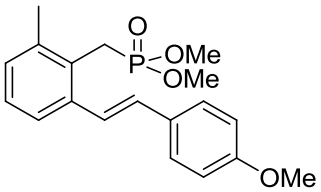
5.9 Hz), 137.9 (d, *J* = 6.1 Hz), 136.7, 135.8, 130.4, 130.0 (d, *J* = 3.7 Hz), 129.4, 128.8 (d, *J* = 2.2 Hz), 127.9 (d, *J* = 9.7 Hz), 127.6, 127.2 (d, *J* = 4.0 Hz), 126.3, 125.8, 124.5 (d, *J* = 3.6 Hz), 52.8 (d, *J* = 7.0 Hz), 28.3, 27.6 (d, *J* = 138.0 Hz), 20.7, 19.9.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9.; IR (film) *v* 2953, 1487, 1454, 1250, 1030, 842, 748.; HRMS (ESI) *m / z* calcd for $C_{19}H_{24}O_3P$ $(M + H)^+$ 331.1463, found 331.1461.

(*E*)-Dimethyl 2-methyl-6-(2-(naphthalen-2-yl)vinyl)benzylphosphonate (163f)



Yield: 52.1 mg, 71 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 3H), 7.82 -7.68 (m, 3H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.50 -7.42 (m, 2H), 7.20 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.17 -7.07 (m, 2H), 3.68 (s, 3H), 3.65 (s, 3H), 3.45 (s, 1H), 3.40 (s, 1H), 2.46 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (d, *J* = 6.3 Hz), 135.1, 133.7, 133.1, 131.5, 130.1 (d, *J* = 3.7 Hz), 128.4, 128.0 (d, *J* = 6.2 Hz), 127.7, 127.3 (d, *J* = 3.9 Hz), 126.8, 126.4, 126.0, 124.3 (d, *J* = 3.6 Hz), 123.6, 52.9 (d, *J* = 7.0 Hz), 27.6 (d, *J* = 137.9 Hz), 20.7.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.0.; IR (film) *v* 2955, 1593, 1463, 1250, 1030, 842, 750.; HRMS (ESI) *m / z* calcd for $C_{22}H_{24}O_3P$ $(M + H)^+$ 367.1463, found 367.1464.

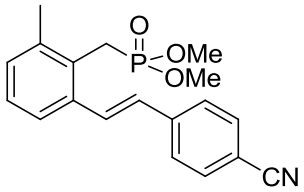
(*E*)-Dimethyl 2-(4-methoxystyryl)-6-methylbenzylphosphonate (163g)



Yield: 38.2 mg, 55 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 -7.42 (m, 4H), 7.19 -7.14 (m, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.93 -6.87 (m, 3H), 3.83 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.41 (s, 1H), 3.35 (s, 1H), 2.44 (d, *J* = 1.1 Hz, 3H).; ^{13}C NMR (101 MHz,

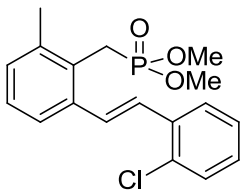
$CDCl_3$) δ 159.4, 138.1 (d, *J* = 5.9 Hz), 137.8 (d, *J* = 6.0 Hz), 130.9, 130.5, 129.7 (d, *J* = 3.7 Hz), 127.9, 127.7, 127.6, 127.2 (d, *J* = 4.0 Hz), 125.3 (d, *J* = 2.4 Hz), 124.2, 114.2, 55.4, 52.8 (d, *J* = 6.9 Hz), 27.6 (d, *J* = 138.7 Hz), 20.7.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9.; IR (film) *v* 2955, 1606, 1152, 1251, 1032, 840, 735.; HRMS (ESI) *m / z* calcd for $C_{19}H_{24}O_4P$ $(M + H)^+$ 347.1412, found 347.1414.

(*E*)-Dimethyl 2-(4-cyanostyryl)-6-methylbenzylphosphonate (163h)



Yield: 49.9 mg, 73 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 16.0 Hz, 1H), 7.74 -7.56 (m, 4H), 7.51 -7.44 (m, 1H), 7.23 -7.11 (m, 2H), 6.94 (d, *J* = 16.0 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.40 (s, 1H), 3.34 (s, 1H), 2.43 (d, *J* = 1.3 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 138.1 (d, *J* = 6.2 Hz), 136.91 (d, *J* = 5.8 Hz), 132.6, 131.3 (d, *J* = 2.4 Hz), 130.9 (d, *J* = 3.6 Hz), 129.3, 128.3 (d, *J* = 9.6 Hz), 127.4 (d, *J* = 3.9 Hz), 127.1, 124.4 (d, *J* = 3.6 Hz), 119.1, 110.7, 52.9 (d, *J* = 7.0 Hz), 27.5 (d, *J* = 138.0 Hz), 20.6.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.6.; IR (film) *v* 2955, 2226, 1601, 1505, 1248, 1030, 844, 738.; HRMS (ESI) *m / z* calcd for $C_{19}H_{21}NO_3P$ $(M + H)^+$ 342.1259, found 342.1260.

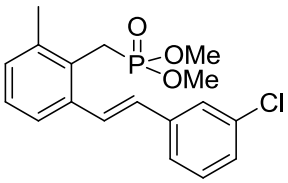
(*E*)-Dimethyl 2-(2-chlorostyryl)-6-methylbenzylphosphonate (163i)



Yield: 59.0 mg, 84 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.59 (d, *J* = 15.9 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.35 (ddd, *J* = 34.8, 13.4, 4.4 Hz,

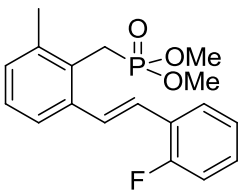
3H), 7.23 -7.13 (m, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.41 (s, 1H), 3.36 (s, 1H), 2.45 (d, *J* = 1.3 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (dd, *J* = 25.0, 6.0 Hz), 135.8, 133.4, 130.4 (d, *J* = 3.7 Hz), 130.1 (d, *J* = 2.3 Hz), 129.8, 128.6, 128.0 (d, *J* = 9.7 Hz), 127.4 (dd, *J* = 15.0, 2.7 Hz), 127.0 (d, *J* = 15.2 Hz), 124.7 (d, *J* = 3.6 Hz), 52.8 (d, *J* = 7.0 Hz), 27.6 (d, *J* = 138.0 Hz), 20.7.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.8.; IR (film) *v* 2953, 1596, 1475, 1250, 1030, 869, 783.; HRMS (ESI) *m / z* calcd for $C_{18}H_{21}O_3PCl$ $(M + H)^+$ 351.0917, found 351.0920.

(*E*)-Dimethyl 2-(3-chlorostyryl)-6-methylbenzylphosphonate (163j)



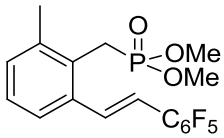
Yield: 60.4 mg, 86 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.49 (s, 1H), 7.43 (dd, *J* = 11.4, 7.3 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.20 (ddd, *J* = 11.2, 8.4, 1.4 Hz, 3H), 6.87 (d, *J* = 16.0 Hz, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.40 (s, 1H), 3.35 (s, 1H), 2.44 (d, *J* = 1.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 138.0 (d, *J* = 6.1 Hz), 137.4 (d, *J* = 5.8 Hz), 134.7, 130.4 (d, *J* = 3.7 Hz), 130.09 – 129.70 (m), 128.9 (d, *J* = 2.3 Hz), 128.1 (d, *J* = 9.7 Hz), 127.6, 127.3 (d, *J* = 4.0 Hz), 126.7, 124.7, 124.4 (d, *J* = 3.6 Hz), 52.8 (d, *J* = 7.0 Hz), 27.6 (d, *J* = 138.0 Hz), 20.7 (d, *J* = 1.3 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9.; IR (film) *v* 2953, 1591, 1475, 1250, 1030, 787, 684.; HRMS (ESI) *m / z* calcd for $C_{18}H_{21}O_3PCl$ $(M + H)^+$ 351.0917, found 351.0912.

(*E*)-Dimethyl 2-(2-fluorostyryl)-6-methylbenzylphosphonate (163k)



Yield: 62.3 mg, 93 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (ddd, *J* = 10.2, 9.5, 6.3 Hz, 2H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.25 -7.21 (m, 1H), 7.20 -7.04 (m, 5H), 3.66 (s, 3H), 3.64 (s, 3H), 3.41 (s, 1H), 3.36 (s, 1H), 2.45 (d, *J* = 1.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5 (d, *J* = 247.9 Hz), 137.9 (dd, *J* = 11.8, 6.0 Hz), 130.3 (d, *J* = 3.7 Hz), 129.8, 128.9 (d, *J* = 8.4 Hz), 128.0 (d, *J* = 9.7 Hz), 127.3 (dd, *J* = 10.9, 3.8 Hz), 125.5 (d, *J* = 12.0 Hz), 124.4 (dd, *J* = 13.7, 3.6 Hz), 124.0, 115.8 (d, *J* = 22.1 Hz), 52.8 (d, *J* = 7.0 Hz), 27.5 (d, *J* = 138.8 Hz), 20.7.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.8.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -118.1.; IR (film) *v* 2953, 1489, 1456, 1229, 1030, 840, 754.; HRMS (ESI) *m / z* calcd for $C_{18}H_{21}O_3PF$ $(M + H)^+$ 335.1212, found 335.1211.

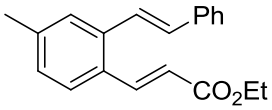
(*E*)-Dimethyl 2-(penta-fluorostyryl)-6-methylbenzylphosphonate (163l)



Yield: 78.1 mg, 96 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 16.5 Hz, 1H), 7.45 (d, *J* = 5.8 Hz, 1H), 7.21 (dd, *J* = 4.6, 2.6 Hz, 2H), 6.82 (d, *J* = 16.5 Hz, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 3.36 (s, 1H), 3.31 (s, 1H), 2.46 (d, *J* = 1.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (d, *J* = 6.0 Hz), 137.2 (d, *J* = 5.9 Hz), 136.4 (d, *J* = 8.1 Hz), 131.2 (d, *J* = 3.7 Hz), 128.4 (d, *J* = 9.6 Hz), 127.4 (d, *J* = 4.0 Hz), 124.4 (d, *J* = 3.6 Hz), 115.2, 52.8 (d, *J* = 7.0 Hz), 27.5 (d, *J* = 138.9 Hz), 20.6 (d, *J* = 1.3 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -142.9 (dd, *J* = 21.7, 7.8 Hz), -156.4 (t, *J* = 20.8 Hz), -159.7 --166.3 (m).; IR (film) *v* 3424, 1520, 1497, 1462, 1377, 1032, 814, 791.; HRMS (ESI) *m / z* calcd for $C_{18}H_{17}O_3PF_5$ $(M + H)^+$ 407.0835, found 407.0833.

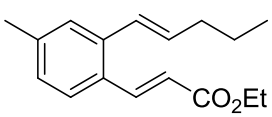
Typical procedure for the Horner-Wadsworth-Emmons reactions of 160b. To a solution of **160b** (31.3 mg, 0.1 mmol) in THF (1 mL) was added freshly prepared LDA (0.11 mmol) in THF at -78 °C. After the mixture was stirred at -78 °C for 30 min, benzylaldehyde (15.9 mg, 0.15 mmol) in THF (0.5 mL) was added. After being stirred at -78 °C for 1 h, the mixture was gradually warmed to room temperature. Then aqueous NH_4Cl (1 mL) was added to the reaction mixture and the mixture was extracted with Et_2O (2 × 10 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification of the crude mixture by silica gel flash chromatography (hexane/ethyl acetate = 100:1) afforded product **164** (23.6 mg, 81%).

(*E*)-Ethyl 3-(4-methyl-2-styrylphenyl)acrylate (164)



Yield: 23.6 mg, 81 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 15.8 Hz, 1H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.45 -7.35 (m, 4H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 16.1 Hz, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 142.2, 140.3, 137.5, 137.2, 132.4, 130.2, 128.8, 128.0, 127.5, 127.2, 126.8, 125.6, 119.4, 60.5, 21.5, 14.4.; IR (film) *v* 3026, 1711, 1695, 1604, 1314, 1180, 908, 732.; HRMS (ESI) *m / z* calcd for $C_{20}H_{20}O_2Na$ $(M + Na)^+$ 315.1361, found 315.1368.

(*E*)-Ethyl 3-(4-methyl-2-((E)-pent-1-enyl)phenyl)acrylate (165)

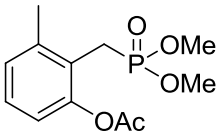


Yield: 20.2 mg, 78 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 15.9 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 15.6 Hz,

1H), 6.31 (d, *J* = 15.8 Hz, 1H), 6.06 (dt, *J* = 15.6, 7.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 2.23 (ddd, *J* = 14.6, 7.3, 1.4 Hz, 2H), 1.54 – 1.45 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 142.7, 140.1, 138.3, 135.3, 129.4, 128.0, 127.7, 127.1, 126.8, 118.6, 60.4, 35.4, 22.5, 21.4, 14.3, 13.7.; IR (film) *v* 1719, 1606, 1314, 1179, 1037, 912, 732.; HRMS (ESI) *m / z* calcd for $C_{17}H_{23}O_2$ $(M + H)^+$ 259.1698, found 259.1703.

General experimental procedure for the *ortho*-acetoxylation of mono-benzylic phosphonic acid 167. $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol) and $PhI(OAc)_2$ (96.6 mg, 0.30 mmol) was carefully weighed to a vial equipped with a magnetic stirrer bar and a tightly-screwed cap. Mono-benzylic phosphonic acid **167** (0.15 mmol, 1.0 equiv) in 1,2-dichloroethane (1 mL) was then added and stirred at 110 ^{o}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, 2.0 M 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 silica gel flash chromatography (dichloromethane/acetone = 20:1) to afford the desired acetoxylated product **168**.

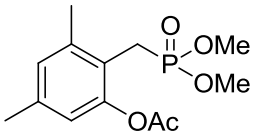
2-((Dimethoxyphosphoryl)methyl)-3-methylphenyl acetate (166a)



Yield: 37.2 mg, 91%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.16 (dd, *J* = 7.9, 2.5 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 3.23 (s, 1H), 3.17 (s, 1H), 2.41 (d, *J* = 1.4 Hz, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz,

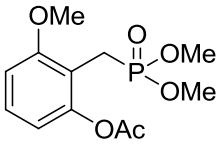
$CDCl_3$) δ 169.1, 149.1 (d, J = 6.4 Hz), 139.1 (d, J = 5.8 Hz), 127.8 (d, J = 3.5 Hz), 127.4 (d, J = 4.0 Hz), 122.3 (d, J = 9.8 Hz), 120.4 (d, J = 3.6 Hz), 52.9 (d, J = 6.9 Hz), 24.9 (d, J = 140.9 Hz), 21.1, 20.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3; FTIR (NaCl, neat): v 1768, 1471, 1208, 1034, 909, 731; HRMS (ESI, $C_{12}H_{18}O_5P$ (M+)): calcd.: 273.0892; found: 273.0894.

2-((Dimethoxyphosphoryl)methyl)-3,5-dimethylphenyl acetate (168a)



Yield: 39.9 mg, 93%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.79 (s, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.18 (s, 1H), 3.12 (s, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 2.29 (d, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 149.0 (d, J = 6.4 Hz), 138.7 (d, J = 5.8 Hz), 137.5 (d, J = 4.2 Hz), 128.8 (d, J = 3.6 Hz), 120.9 (d, J = 3.6 Hz), 119.1 (d, J = 9.9 Hz), 52.8 (d, J = 7.0 Hz), 24.6 (d, J = 141.3 Hz), 21.2, 21.0, 20.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.6; FTIR (NaCl, neat): v 1767, 1368, 1209, 1034, 854, 731; HRMS (ESI, $C_{13}H_{20}O_5P$ (M+)): calcd.: 287.1048; found: 287.1048.

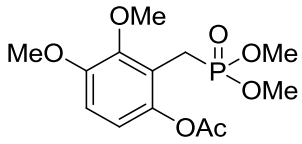
2-((Dimethoxyphosphoryl)methyl)-3-methoxyphenyl acetate (168b)



Yield: 39.8 mg, 92%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 1H), 6.78 (s, 1H), 6.76 (s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 3.29 (s, 1H), 3.24 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 158.2 (d, J = 5.7 Hz), 149.7 (d, J = 6.5 Hz), 127.9 (d, J = 3.9 Hz), 115.3 (d, J = 3.5 Hz), 113.2 (d, J = 10.5 Hz), 107.9 (d, J = 3.2 Hz), 56.0, 52.7 (d, J = 6.6 Hz), 21.3 (d, J = 141.2 Hz), 21.1; ^{31}P NMR (162 MHz,

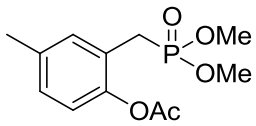
$CDCl_3$) δ 28.7; FTIR (NaCl, neat): ν 1767, 1606, 1369, 1209, 1071, 1033, 731; HRMS (ESI, $C_{12}H_{18}O_6P$ (M+)): calcd.: 289.0841; found: 289.0837.

2-((Dimethoxyphosphoryl)methyl)-3,4-dimethoxyphenyl acetate (168c)



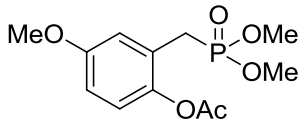
Yield: 44.9 mg, 94%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 1.5 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.27 (s, 1H), 3.22 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 150.4 (d, J = 3.4 Hz), 147.7 (d, J = 6.6 Hz), 142.5 (d, J = 5.8 Hz), 118.7 (d, J = 10.1 Hz), 117.7 (d, J = 3.3 Hz), 111.0 (d, J = 3.7 Hz), 60.8 (d, J = 1.6 Hz), 56.0, 52.8 (d, J = 6.7 Hz), 22.1 (d, J = 141.4 Hz), 21.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.2; FTIR (NaCl, neat): ν 1767, 1488, 1207, 1043, 807, 733; HRMS (ESI, $C_{13}H_{20}O_7P$ (M+)): calcd.: 319.0947; found: 319.0949.

2-((Dimethoxyphosphoryl)methyl)-4-methylphenyl acetate (168d)



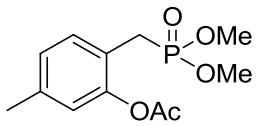
Yield: 34.7 mg, 85%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ .18 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 3.13 (s, 1H), 3.08 (s, 1H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 146.6 (d, J = 7.4 Hz), 135.8 (d, J = 3.3 Hz), 131.9 (d, J = 5.5 Hz), 128.9 (d, J = 3.7 Hz), 123.1 (d, J = 9.2 Hz), 122.5 (d, J = 3.1 Hz), 52.9 (d, J = 6.8 Hz), 27.2 (d, J = 140.5 Hz), 21.0, 20.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.2; FTIR (NaCl, neat): ν 1761, 1500, 1370, 1218, 1044, 811; HRMS (ESI, $C_{12}H_{18}O_5P$ (M+)): calcd.: 273.0892; found: 273.0897.

2-((Dimethoxyphosphoryl)methyl)-4-methoxyphenyl acetate (168e)



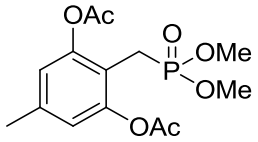
Yield: 35.9 mg, 83%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.9 Hz, 1H), 6.90 (t, J = 2.8 Hz, 1H), 6.80 (dt, J = 8.9, 2.6 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.12 (s, 1H), 3.07 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.41, 157.1 (d, J = 3.4 Hz), 142.4 (d, J = 7.5 Hz), 124.5 (d, J = 9.1 Hz), 123.5 (d, J = 3.1 Hz), 116.3 (d, J = 5.5 Hz), 113.5 (d, J = 3.6 Hz), 55.6, 52.9 (d, J = 6.8 Hz), 27.4 (d, J = 140.5 Hz), 21.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8; FTIR (NaCl, neat): ν 1761, 1606, 1501, 1370, 1243, 867, 733; HRMS (ESI, $C_{12}H_{18}O_6P$ (M+)): calcd.: 289.0841; found: 289.0838.

2-((Dimethoxyphosphoryl)methyl)-5-methylphenyl acetate (168f)



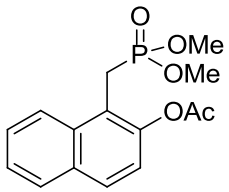
Yield: 21.6 mg, 53%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (q, J = 2.4 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.93 (s, 1H), 3.68 (d, J = 3.2 Hz, 3H), 3.65 (d, J = 3.2 Hz, 3H), 3.13 (s, 1H), 3.08 (s, 1H), 2.33 (d, J = 2.3 Hz, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 148.7 (d, J = 7.5 Hz), 138.4 (d, J = 3.8 Hz), 131.1 (d, J = 5.5 Hz), 127.0 (d, J = 3.3 Hz), 123.4 (d, J = 3.1 Hz), 120.3 (d, J = 9.3 Hz), 52.9 (d, J = 6.8 Hz), 26.8 (d, J = 140.9 Hz), 21.0 (d, J = 1.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3; FTIR (NaCl, neat): ν 2955, 1751, 1636, 1211, 1038, 908, 733, 650; HRMS (ESI, $C_{12}H_{18}O_5P$ (M+)): calcd.: 273.0892; found: 273.0890.

2-((Dimethoxyphosphoryl)methyl)-5-methylphenyl acetate (168f')



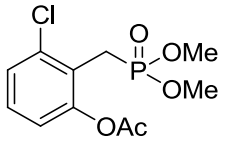
Yield: 7.4 mg, 15%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 3.65 (s, 3H), 3.62 (s, 3H), 3.15 (s, 1H), 3.10 (s, 1H), 2.34 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 149.3 (d, J = 6.2 Hz), 138.2 (d, J = 4.0 Hz), 121.0 (d, J = 3.4 Hz), 113.9 (d, J = 10.0 Hz), 52.9 (d, J = 6.9 Hz), 21.4 (d, J = 26.1 Hz), 21.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.3; FTIR (NaCl, neat): ν 2953, 1770, 1761, 1626, 1369, 1198, 1147, 1040, 735, 702; HRMS (ESI, $C_{14}H_{20}O_7P$ (M+)): calcd.: 331.0947; found: 331.0951.

1-((Dimethoxyphosphoryl)methyl)naphthalen-2-yl acetate (168g)



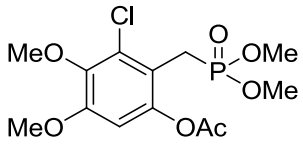
Yield: 35.1 mg, 76%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.80 (dd, J = 9.0, 2.1 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 3.68 (s, 1H), 3.63 (s, 1H), 3.60 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 147.0 (d, J = 8.5 Hz), 132.6 (d, J = 4.3 Hz), 131.8 (d, J = 3.0 Hz), 128.6 (d, J = 3.6 Hz), 128.6, 126.8, 125.6, 124.4 (d, J = 1.9 Hz), 121.8 (d, J = 4.2 Hz), 118.3 (d, J = 10.4 Hz), 52.9 (d, J = 6.9 Hz), 24.0 (d, J = 141.8 Hz), 21.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.6; FTIR (NaCl, neat): ν 2955, 1763, 1630, 1516, 1205, 1036, 908, 732, 650; HRMS (ESI, $C_{15}H_{18}O_5P$ (M+)): calcd.: 309.0892; found: 309.0900.

3-Chloro-2-((dimethoxyphosphoryl)methyl)phenyl acetate (168h)



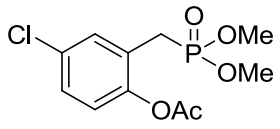
Yield: 37.8 mg, 86%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.1 Hz, 1H), 7.23 (dd, J = 8.1, 2.4 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.44 (s, 1H), 3.38 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 149.8 (d, J = 6.1 Hz), 135.3 (d, J = 6.8 Hz), 128.1 (d, J = 3.9 Hz), 126.9 (d, J = 3.4 Hz), 123.2 (d, J = 10.3 Hz), 121.8 (d, J = 3.5 Hz), 52.9 (d, J = 6.8 Hz), 25.6 (d, J = 141.3 Hz), 21.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.7; FTIR (NaCl, neat): ν 1776, 1451, 1201, 1034, 911, 731; HRMS (ESI, $C_{11}H_{15}ClO_5P$ (M+)): calcd.: 293.0344; found: 293.0349.

3-Chloro-2-((dimethoxyphosphoryl)methyl)-4,5-dimethoxyphenyl acetate (168i)



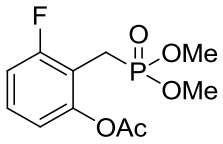
Yield: 50.3 mg, 95%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 3.84 (d, J = 1.5 Hz, 6H), 3.68 (s, 3H), 3.66 (s, 3H), 3.35 (s, 1H), 3.29 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 152.4 (d, J = 3.6 Hz), 145.2 (d, J = 6.3 Hz), 143.6 (d, J = 3.4 Hz), 129.4 (d, J = 6.1 Hz), 115.3 (d, J = 10.3 Hz), 106.3 (d, J = 3.5 Hz), 60.7, 56.1, 52.9 (d, J = 6.8 Hz), 25.4 (d, J = 142.5 Hz), 21.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.2; FTIR (NaCl, neat): ν 1768, 1485, 1205, 1036, 908, 732; HRMS (ESI, $C_{13}H_{19}ClO_7P$ (M+)): calcd.: 353.0557; found: 353.0559.

4-Chloro-2-((dimethoxyphosphoryl)methyl)phenyl acetate (168j)



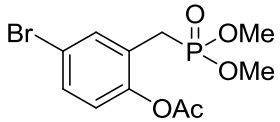
Yield: 36.0 mg, 82%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 2.6 Hz, 1H), 7.25 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.14 (s, 1H), 3.08 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 147.3 (d, J = 7.3 Hz), 131.3 (d, J = 3.8 Hz), 131.2 (d, J = 5.6 Hz), 128.3 (d, J = 3.6 Hz), 125.6 (d, J = 9.4 Hz), 124.2 (d, J = 3.1 Hz), 53.0 (d, J = 6.9 Hz), 27.2 (d, J = 140.9 Hz), 21.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.0; FTIR (NaCl, neat): ν 1767, 1486, 1204, 1170, 1030, 886; HRMS (ESI, $C_{11}H_{15}ClO_5P$ (M+)): calcd.: 293.0346; found: 293.0355.

2-((Dimethoxyphosphoryl)methyl)-3-fluorophenyl acetate (168k)



Yield: 33.6 mg, 81%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 1H), 6.98 (t, J = 8.0 Hz, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.25 (d, J = 1.5 Hz, 1H), 3.20 (d, J = 1.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 161.2 (d, J = 247.6 Hz), 149.7 (d, J = 6.1 Hz), 128.2 (dd, J = 9.9, 3.8 Hz), 118.8 (t, J = 3.4 Hz), 112.8 (d, J = 3.3 Hz), 112.6 (d, J = 3.3 Hz), 52.9 (d, J = 6.6 Hz), 21.8 (d, J = 3.2 Hz), 21.0 (s), 20.4 (d, J = 3.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.8; ^{19}F NMR (162 MHz, $CDCl_3$) δ -114.00 (d, J = 4.5 Hz); FTIR (NaCl, neat): ν 1775, 1469, 1205, 1029, 845, 734; HRMS (ESI, $C_{11}H_{15}FO_5P$ (M+)): calcd.: 277.0641; found: 277.0646.

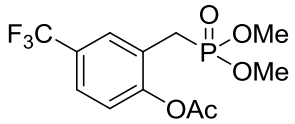
4-Bromo-2-((dimethoxyphosphoryl)methyl)phenyl acetate (168l)



Yield: 47.0 mg, 93%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 2.5 Hz, 1H), 7.39 (dt, J = 8.6, 2.3 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H),

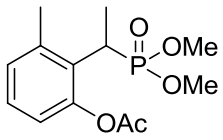
3.13 (s, 1H), 3.07 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 147.9 (d, J = 7.2 Hz), 134.1 (d, J = 5.6 Hz), 131.2 (d, J = 3.7 Hz), 126.0 (d, J = 9.3 Hz), 124.6 (d, J = 3.1 Hz), 118.9 (d, J = 3.9 Hz), 53.0 (d, J = 6.8 Hz), 27.2 (d, J = 140.9 Hz), 21.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.0; FTIR (NaCl, neat): ν 1767, 1484, 1203, 1030, 872, 735; HRMS (ESI, $C_{11}H_{15}BrO_5P$ (M+)): calcd.: 336.9840; found: 336.9837.

2-((Dimethoxyphosphoryl)methyl)-4-(trifluoromethyl)phenyl acetate (168m)



Yield: 44.5 mg, 91%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 6.9 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.23 (s, 1H), 3.17 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 151.3 (d, J = 6.0 Hz), 128.6 (dd, J = 5.4, 3.8 Hz), 125.3 (t, J = 3.6 Hz), 125.0 (d, J = 9.4 Hz), 123.6 (d, J = 3.0 Hz), 53.0 (d, J = 6.8 Hz), 27.4 (d, J = 141.0 Hz), 21.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.29; FTIR (NaCl, neat): ν 2957, 1771, 1425, 1335, 1267, 1034, 893, 739, 704; HRMS (ESI, $C_{12}H_{15}F_3O_5P$ (M+)): calcd.: 327.0609; found: 327.0615.

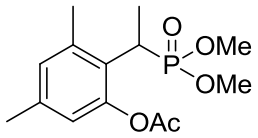
2-(1-(Dimethoxyphosphoryl)ethyl)-3-methylphenyl acetate (170a)



Yield: 37.8 mg, 88%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, J = 7.8, 1.8 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 3.71 (d, J = 10.7 Hz, 3H), 3.60 – 3.49 (m, 1H), 3.46 (d, J = 10.5 Hz, 3H), 2.38 (s, 3H), 1.63 (dd, J = 18.5, 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 149.9 (d, J = 5.2 Hz), 138.5 (d, J = 8.3 Hz), 128.1 (d, J = 5.9 Hz), 127.8 (d, J = 1.9 Hz), 127.5 (d, J = 3.0 Hz), 122.2 (d, J = 2.9 Hz),

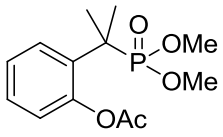
53.0 (dd, *J* = 117.3, 7.1 Hz), 32.4 (d, *J* = 141.3 Hz), 21.7, 20.8, 13.7 (d, *J* = 4.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.9; FTIR (NaCl, neat): *v* 1767, 1464, 1368, 1206, 1024, 825, 734; HRMS (ESI, $C_{13}H_{20}O_5P$ (M+)): calcd.: 287.1048; found: 287.1041.

2-(1-(Dimethoxyphosphoryl)ethyl)-3,5-dimethylphenyl acetate (170b)



Yield: 40.5 mg, 90%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.77 (s, 1H), 3.70 (d, *J* = 10.7 Hz, 3H), 3.47 (d, *J* = 10.5 Hz, 3H), 3.47 – 3.45 (m, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.28 (d, *J* = 1.3 Hz, 3H), 1.60 (dd, *J* = 18.5, 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 149.7 (d, *J* = 5.1 Hz), 138.1 (d, *J* = 8.3 Hz), 137.5 (d, *J* = 3.2 Hz), 128.8 (d, *J* = 1.8 Hz), 125.0 (d, *J* = 5.9 Hz), 122.7 (d, *J* = 2.9 Hz), 53.5 (d, *J* = 6.9 Hz), 52.4 (d, *J* = 7.3 Hz), 32.1 (d, *J* = 141.3 Hz), 21.8, 20.8 (d, *J* = 12.0 Hz), 13.8 (d, *J* = 4.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.1; FTIR (NaCl, neat): *v* 1761, 1447, 1208, 1037; HRMS (ESI, $C_{14}H_{22}O_5P$ (M+)): calcd.: 301.1205; found: 301.1201.

2-(2-(Dimethoxyphosphoryl)propan-2-yl)phenyl acetate (170c)



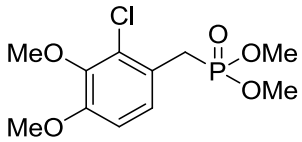
Yield: 39.9 mg, 93%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 3.50 (s, 3H), 3.48 (s, 3H), 2.28 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 149.7 (d, *J* = 5.4 Hz), 132.4 (d, *J* = 4.6 Hz), 129.8 (d, *J* = 5.6 Hz), 128.1 (d, *J* = 3.1 Hz), 125.6 (d, *J* = 2.4 Hz), 124.9 (d, *J* = 2.8 Hz), 53.4 (d, *J* = 7.4 Hz), 39.2 (d, *J* = 138.0 Hz), 24.7 (d, *J* = 4.5 Hz), 21.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.3; FTIR (NaCl, neat): *v*

2955, 1767, 1370, 1211, 1192, 1028, 825, 800, 735.; HRMS (ESI, $C_{13}H_{20}O_5P$ (M+)): calcd.: 287.1048; found: 287.1053.

7.4 Palladium(II)-Catalyzed *ortho*-Arylation of Benzylic Phosphonic Monoesters with Potassium Aryltrifluoroborates

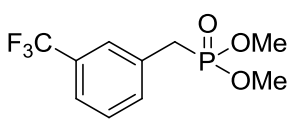
General procedure for preparation of dimethyl benzylic phosphonates.[147] To a solution of benzylic alcohol (1.0 mmol) in anhydrous toluene (10 mL) was added ZnI_2 (1.5 mmol) and $P(OMe)_3$ (2.0 mmol) under nitrogen. The reaction mixture was heated to 110 ^oC for 15 h under nitrogen. After being cooled to room temperature, the solvent was removed in vacuo. The residue was diluted with diethyl ether (20 mL), washed with 2 N NaOH (2 × 5 mL) and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified via flash column chromatography on silica gel (hexane/ethyl acetate = 2:1) to afford dimethyl benzylic phosphonate.

Dimethyl 2-chloro-3,4-dimethoxybenzylphosphonate



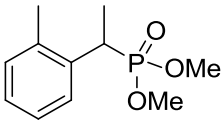
Yield: 229.4 mg, 78 %, colorless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 3.84 (d, *J* = 2.6 Hz, 6H), 3.69 (s, 3H), 3.66 (s, 3H), 3.33 (s, 1H), 3.28 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (d, *J* = 3.5 Hz), 145.7 (d, *J* = 3.0 Hz), 128.9 (d, *J* = 8.0 Hz), 126.1 (d, *J* = 5.5 Hz), 122.4 (d, *J* = 9.1 Hz), 110.8 (d, *J* = 3.4 Hz), 60.6, 56.1, 52.8 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 140.3 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.2.; IR (film) *v* 2953, 2358, 1597, 1490, 1267, 1031, 860, 734.; HRMS (ESI) *m / z* calcd for $C_{11}H_{17}O_5PCl$ $(M + H)^+$ 295.0502, found 295.0504.

Dimethyl 3-(trifluoromethyl)benzylphosphonate



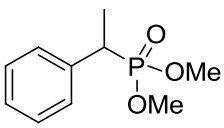
Yield: 180.0 mg, 67 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 3H), 7.45 (t, *J* = 7.9 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.24 (s, 1H), 3.19 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1 (d, *J* = 6.2 Hz), 132.5 (d, *J* = 9.0 Hz), 131.0 (dd, *J* = 33.0, 2.2 Hz), 129.1 (d, *J* = 3.0 Hz), 126.4 (dd, *J* = 6.9, 3.7 Hz), 124.0 (q, *J* = 270.6 Hz), 123.9 (t, *J* = 3.7 Hz), 52.9 (d, *J* = 6.8 Hz), 32.8 (d, *J* = 139.0 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.6.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.7.; IR (film) *v* 2956, 1450, 1330, 1126, 1033, 889, 702.; HRMS (ESI) *m / z* calcd for $C_{10}H_{13}O_3F_3P$ $(M + H)^+$ 269.0554, found 269.0554.

Dimethyl 1-o-tolylethylphosphonate



Yield: 171.0 mg, 75 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 1H), 7.23 – 7.09 (m, 3H), 3.68 (d, *J* = 10.6 Hz, 3H), 3.50 – 3.48 (m, 1H), 3.48 (d, *J* = 10.5 Hz, 3H), 2.37 (d, *J* = 1.1 Hz, 3H), 1.54 (dd, *J* = 18.7, 7.3 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3 (d, *J* = 6.0 Hz), 136.1 (d, *J* = 7.0 Hz), 130.4 (d, *J* = 2.4 Hz), 127.9 (d, *J* = 4.8 Hz), 126.9 (d, *J* = 3.2 Hz), 126.3 (d, *J* = 3.1 Hz), 53.3 (d, *J* = 7.1 Hz), 52.8 (d, *J* = 7.4 Hz), 33.1 (d, *J* = 138.0 Hz), 19.9, 15.8 (d, *J* = 5.2 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.9.; IR (film) *v* 3051, 2953, 2357, 1462, 1265, 1037, 827, 732.; HRMS (ESI) *m / z* calcd for $C_{11}H_{18}O_3P$ $(M + H)^+$ 229.0994, found 229.0995.

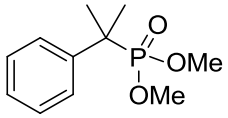
Dimethyl 1-phenylethylphosphonate



Yield: 154.1 mg, 72 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m,

4H), 7.19 (dd, *J* = 4.7, 2.2 Hz, 1H), 3.62 (d, *J* = 10.6 Hz, 3H), 3.46 (d, *J* = 10.5 Hz, 3H), 3.14 (dd, *J* = 22.7, 7.4 Hz, 1H), 1.51 (dd, *J* = 18.5, 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.68 (d, *J* = 6.9 Hz), 128.60 (d, *J* = 6.7 Hz), 128.54 (d, *J* = 2.7 Hz), 127.18 (d, *J* = 3.2 Hz), 53.04 (dd, *J* = 48.9, 7.1 Hz), 38.08 (d, *J* = 137.8 Hz), 15.54 (d, *J* = 5.1 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.1.; IR (film) *v* 2954, 1633, 1494, 1454, 1219, 1029,823, 763, 700.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_3P$ $(M + H)^+$ 215.0837, found 215.0842.

Dimethyl 2-phenylpropan-2-ylphosphonate

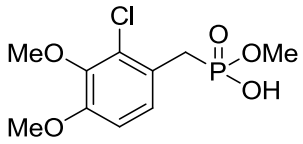


Yield: 157.3 mg, 69 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.54 (m, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.26 – 7.25 (m, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3 (d, *J* = 5.0 Hz), 128.1 (d, *J* = 2.7 Hz), 127.6 (d, *J* = 5.3 Hz), 126.8 (d, *J* = 3.2 Hz), 53.4 (d, *J* = 7.4 Hz), 39.3 (d, *J* = 136.4 Hz), 23.9 (d, *J* = 4.1 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.6.; IR (film) *v* 2955, 1645, 1497, 1231, 1053, 1028, 806, 698.; HRMS (ESI) *m / z* calcd for $C_{11}H_{18}O_3P$ $(M + H)^+$ 229.0994, found 229.0992.

General procedure for preparation of methyl hydrogen benzylic phosphonate.[148] To a solution of dimethyl benzylic phosphonate (0.5 mmol) in $SOCl_2$ (0.5 mL) was added a catalytic amount of DMF (3.7 mg, 0.05 mmol) at room temperature. The reaction mixture was allowed to stir at reflux for 3 h. Excess $SOCl_2$ was removed and the residue was diluted with dichloromethane (10 mL). Cool water (1 mL) was then added to the solution at 0 ^{o}C and the mixture was stirred for 10 min. The organic layer was separated and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel

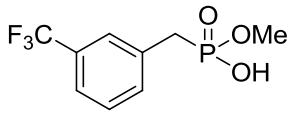
(dichloromethane/methanol = 20:1) to afford the corresponding methyl hydrogen benzylic phosphonate.

Methyl hydrogen 2-chloro-3,4-dimethoxybenzylphosphonate (177i)



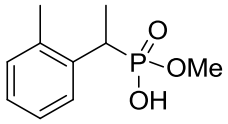
Yield: 122.0 mg, 83 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.88 – 3.77 (m, 6H), 3.63 – 3.58 (m, 3H), 3.28 (s, 1H), 3.23 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7 (d, *J* = 2.9 Hz), 145.6, 129.1 (d, *J* = 7.9 Hz), 126.1 (d, *J* = 5.6 Hz), 122.5 (d, *J* = 9.0 Hz), 110.6 (d, *J* = 3.4 Hz), 60.5, 56.0, 52.2 (d, *J* = 6.8 Hz), 29.9 (d, *J* = 142.0 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.9.; IR (film) *v* 2852, 2358, 1635, 1489, 1043, 989.; HRMS (ESI) *m / z* calcd for $C_{10}H_{15}O_5PCl$ $(M + H)^+$ 281.0346, found 281.0343.

Methyl hydrogen 3-(trifluoromethyl)benzylphosphonate (177m)



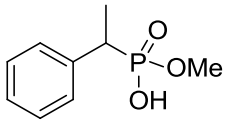
Yield: 108.6 mg, 81 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br, 1H), 7.51 (d, *J* = 11.3 Hz, 2H), 7.47 – 7.38 (m, 2H), 3.55 (d, *J* = 11.2 Hz, 3H), 3.13 (s, 1H), 3.08 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3 (d, *J* = 6.3 Hz), 132.4 (d, *J* = 9.2 Hz), 130.9 (dd, *J* = 32.3, 3.1 Hz), 128.9 (d, *J* = 3.0 Hz), 126.5 (dd, *J* = 6.7, 3.7 Hz), 123.9 (q, *J* = 272.7 Hz), 123.8 (t, *J* = 3.6 Hz), 52.0 (d, *J* = 7.1 Hz), 33.1 (d, *J* = 141.2 Hz).; IR (film) *v* 2987, 1450, 1330, 1167, 1126, 1049, 740, 702.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.1.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.7.; HRMS (ESI) *m / z* calcd for $C_9H_{11}O_3PF_3$ $(M + H)^+$ 255.0398, found 255.0397.

Methyl hydrogen 1-o-tolylethylphosphonate (180a)



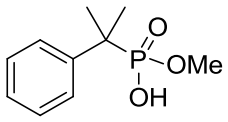
Yield: 90.1 mg, 79 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 1H), 7.22 – 7.08 (m, 3H), 3.54 – 3.47 (m, 3H), 3.47 – 3.36 (m, 1H), 2.36 (s, 3H), 1.52 (dd, *J* = 18.7, 7.3 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6 (d, *J* = 8.1 Hz), 136.2 (d, *J* = 6.7 Hz), 130.3 (d, *J* = 2.5 Hz), 127.8 (d, *J* = 4.8 Hz), 126.8 (d, *J* = 3.2 Hz), 126.2 (d, *J* = 3.2 Hz), 51.9 (d, *J* = 7.5 Hz), 32.9 (d, *J* = 140.0 Hz), 19.9, 15.5 (d, *J* = 5.1 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.2.; IR (film) *v* 3003, 2250, 1705, 1361, 1223, 1051, 918, 732.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_3P$ $(M + H)^+$ 215.0837, found 215.0836.

Methyl hydrogen 1-phenylethylphosphonate (180b)



Yield: 73.0 mg, 73 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (br, 1H), 7.34 – 7.25 (m, 4H), 7.25 – 7.17 (m, 1H), 3.48 (d, *J* = 10.8 Hz, 3H), 3.12 (dd, *J* = 23.2, 7.4 Hz, 1H), 1.52 (dd, *J* = 18.7, 7.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (d, *J* = 7.1 Hz), 128.7 (d, *J* = 6.5 Hz), 128.4 (d, *J* = 2.6 Hz), 127.0 (d, *J* = 3.2 Hz), 52.0 (d, *J* = 7.4 Hz), 37.9 (d, *J* = 140.1 Hz), 15.2 (d, *J* = 5.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.7.; IR (film) *v* 2953, 2850, 1602, 1494, 1454, 821, 783, 765, 732, 698.; HRMS (ESI) *m / z* calcd for $C_9H_{14}O_3P$ $(M + H)^+$ 201.0681, found 201.0688.

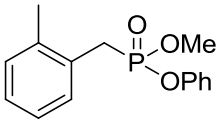
Methyl hydrogen 2-phenylpropan-2-ylphosphonate (180c)



Yield: 75.3 mg, 66 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (br, 1H), 7.43 (d, *J* = 1.7 Hz, 1H), 7.37 (ddd, *J* = 7.1, 3.7, 1.9 Hz, 1H), 7.23 – 7.13 (m, 2H), 3.59 (d, *J* = 11.2 Hz, 3H), 3.06 (s, 1H), 3.01 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 128.0, 127.7 (d, *J* = 4.3 Hz), 126.6, 52.2 (d, *J* = 7.2 Hz), 38.5 (d, *J* = 140.1 Hz), 23.6.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.7.; IR (film) *v* 3053, 2985, 1419, 1265, 1047, 976, 895, 739, 704.; HRMS (ESI) *m / z* calcd for $C_{10}H_{16}O_3P$ $(M + H)^+$ 215.0837, found 215.0841.

Pd(TFA)$_2$-catalyzed reaction of benzylic phosphonic monoester 158a with diphenyliododium triflate. To a mixture of benzylic phosphonic monoester **158a** (20.0 mg, 0.1 mmol) and Ph_2IOTf (64.5 mg, 0.15 mmol) in 1,2-dichloroethane (1.5 mL) was added Pd(TFA)$_2$ (3.3 mg, 0.01 mmol). The reaction mixture was heated at 110 °C for 15 h in a sealed vial, and then 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 (3 mL), and washed with saturated aqueous $Na_2S_2O_3$ (1 mL). The aqueous layer was further extracted with EtOAc (3 × 5 mL), and the combined organic layer was concentrated in vacuo. The residue was purified by silica gel flash chromatography (dichloromethane/acetone = 20:1) to afford the *O*-phenylated product **173b** (6.9 mg, 25%) and the starting material **158a** (12.0 mg, 60%).

Methyl phenyl 2-methylbenzylphosphonate (173b)

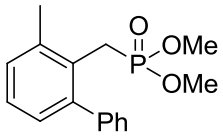


Yield: 6.9 mg, 25 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 3H), 7.21 – 7.11 (m, 4H), 7.10 – 7.06 (m, 2H), 3.69 (d, *J* = 11.0 Hz, 3H), 3.38 (s, 1H), 3.33 (d, *J* = 0.9 Hz, 1H), 2.39 (d, *J* = 1.7 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (d, *J* = 9.0 Hz), 137.1 (d, *J* = 6.9 Hz), 130.7 (d, *J* = 5.7 Hz), 130.6 (d, *J* = 3.5 Hz), 129.2 (d, *J* =

9.7 Hz), 127.4 (d, *J* = 3.9 Hz), 126.2 (d, *J* = 3.6 Hz), 124.8, 120.3 (d, *J* = 4.4 Hz), 53.4 (d, *J* = 7.3 Hz), 30.7 (d, *J* = 139.1 Hz), 20.0.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.7.; IR (film) *v* 2958, 1591, 1489, 1261, 1205, 1041, 927, 802.; HRMS (ESI) *m / z* calcd for $C_{15}H_{18}O_3P$ $(M + H)^+$ 277.0994, found 277.0992.

Typical procedure for the ortho-arylation of benzylic phosphonic monoester 158a. To a mixture of benzylic phosphonic monoester **158a** (21.5 mg, 0.1 mmol) and $PhBF_3K$ (50.2 mg, 0.3 mmol) in *t*-butanol (1.5 mL) was added $PdCl_2(PEt_3)_2$ (4.2 mg, 0.01 mmol), Ac-Val-OH (3.5 mg, 0.02 mmol), KHF_2 (7.8 mg, 0.1 mmol) and Ag_2O (46.4 mg, 0.2 mmol). The reaction mixture was heated at 110 °C for 24 h in a sealed vial. After the reaction mixture was cooled to 0 °C, EtOAc (10 mL) and 2.0 N HCl solution (1 mL) were added. The organic layer was separated and washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield the crude product, which was subjected to silica gel column chromatography (dichloromethane/acetone = 10:1) to get the acid. The crude acid was dissolved in diethyl ether and treated with an excess amount of CH_2N_2 in diethyl ether at room temperature for 0.5 h. Diethyl ether was evaporated under reduced pressure and the crude product was purified by passing through silica gel flash column (dichloromethane/acetone = 20:1) to afford **178a** (27.6 mg, 91%).

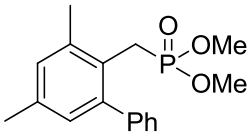
Dimethyl (3-methylbiphenyl-2-yl)methylphosphonate (176a)



Yield: 23.6 mg, 81 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.34 (dd, *J* = 7.2, 5.5 Hz, 3H), 7.19 (dd, *J* = 4.0, 2.7 Hz, 2H), 7.08 – 7.05 (m, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.36 (s, 1H), 3.31 (s, 1H), 2.51 (d, *J* = 1.5 Hz, 3H).; ^{13}C NMR (101

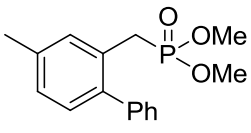
MHz, $CDCl_3$) δ 143.3 (d, *J* = 6.4 Hz), 142.1, 138.1 (d, *J* = 5.5 Hz), 129.8 (d, *J* = 3.8 Hz), 129.6, 128.4 (d, *J* = 3.6 Hz), 128.1, 127.8 (d, *J* = 3.1 Hz), 127.0 (s), 126.7 (d, *J* = 4.1 Hz), 52.3 (d, *J* = 6.9 Hz), 27.4 (d, *J* = 137.5 Hz), 20.9 (d, *J* = 1.4 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.0.; IR (film) *v* 2953, 1462, 1252, 1055, 1029, 888, 839,704.; HRMS (ESI) *m / z* calcd for $C_{16}H_{20}O_3P$ $(M + H)^+$ 291.1150, found 291.1148.

Dimethyl (3,5-dimethylbiphenyl-2-yl)methylphosphonate (178a)



Yield: 27.6 mg, 91 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 10.2, 4.4 Hz, 2H), 7.32 (dd, *J* = 7.1, 5.2 Hz, 3H), 7.02 (s, 1H), 6.89 (s, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.32 (s, 1H), 3.26 (s, 1H), 2.46 (d, *J* = 1.4 Hz, 3H), 2.30 (d, *J* = 2.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (d, *J* = 6.3 Hz), 142.2, 137.9 (d, *J* = 5.4 Hz), 136.2 (d, *J* = 4.2 Hz), 130.7 (d, *J* = 3.8 Hz), 129.5, 129.2 (d, *J* = 3.6 Hz), 128.1, 126.9, 124.5 (d, *J* = 10.0 Hz), 52.3 (d, *J* = 6.9 Hz), 27.0 (d, *J* = 137.8 Hz), 20.8 (d, *J* = 5.7 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.3.; IR (film) *v* 2953, 1472, 1251, 1055, 1029, 819, 779, 704.; HRMS (ESI) *m / z* calcd for $C_{17}H_{22}O_3P$ $(M + H)^+$ 305.1307, found 305.1308.

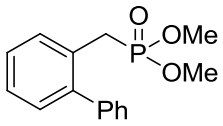
Dimethyl (4-methylbiphenyl-2-yl)methylphosphonate (178b)



Yield: 25.0 mg, 86 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 6H), 7.14 (t, *J* = 7.3 Hz, 2H), 3.59 (s, 3H), 3.56 (s, 3H), 3.21 (s, 1H), 3.15 (s, 1H), 2.39 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 139.8 (d, *J* = 8.1 Hz), 137.2 (d, *J* = 3.2 Hz), 131.1 (d, *J* = 4.6 Hz), 130.4 (d, *J* = 2.7 Hz), 129.6, 128.2, 127.8 (d, *J* = 3.3 Hz), 127.0, 52.6 (d, *J*

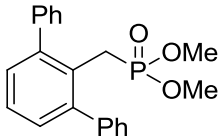
= 6.8 Hz), 29.3 (d, *J* = 138.1 Hz), 21.1.; IR (film) *v* 2954, 1458, 1257, 1057, 1031, 867, 761, 704.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5.; HRMS (ESI) *m / z* calcd for $C_{16}H_{20}O_3P$ $(M + H)^+$ 291.1150, found 291.1152.

Dimethyl biphenyl-2-ylmethylphosphonate (178c)



Yield: 14.1 mg, 51 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 1H), 7.46 – 7.40 (m, 2H), 7.40 – 7.35 (m, 3H), 7.33 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.30 (dd, *J* = 5.4, 3.7 Hz, 1H), 7.25 (d, *J* = 5.4 Hz, 1H), 3.59 (s, 3H), 3.56 (s, 3H), 3.24 (s, 1H), 3.18 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (d, *J* = 8.3 Hz), 141.1, 130.5 (d, *J* = 0.8 Hz), 130.5 (d, *J* = 3.3 Hz), 129.5, 128.7 (d, *J* = 8.7 Hz), 128.3, 127.5 (d, *J* = 3.4 Hz), 127.2, 127.0 (d, *J* = 3.5 Hz), 52.7 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 138.3 Hz).; IR (film) *v* 2953, 1481, 1254, 1051, 1030, 858, 746, 704.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.3.; HRMS (ESI) *m / z* calcd for $C_{15}H_{18}O_3P$ $(M + H)^+$ 277.0994, found 277.0994.

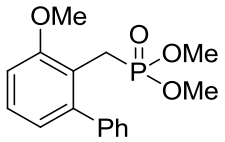
Dimethyl (3-phenylbiphenyl-2-yl)methylphosphonate (179c)



Yield: 5.3 mg, 15 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 8H), 7.37 – 7.33 (m, 2H), 7.32 – 7.30 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 3.45 (s, 1H), 3.39 (s, 1H), 3.18 (s, 3H), 3.15 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (d, *J* = 6.0 Hz), 142.1, 130.0 (d, *J* = 3.7 Hz), 129.7, 128.2, 127.1, 126.9 (d, *J* = 10.2 Hz), 126.6 (d, *J* = 4.0 Hz), 51.8 (d, *J* = 6.8 Hz), 27.0 (d, *J* = 136.3 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.7.; IR

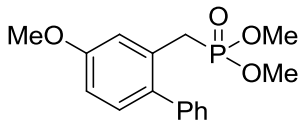
(film) *v* 2951, 1456, 1256, 1057, 1032, 868,761, 704.; HRMS (ESI) *m / z* calcd for $C_{21}H_{22}O_3P$ $(M + H)^+$ 353.1307, found 353.1304.

Dimethyl (3-methoxybiphenyl-2-yl)methylphosphonate (178d)



Yield: 27.6 mg, 90 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.37 – 7.32 (m, 3H), 7.239 – 7.239 (m, 1H), 6.88 (dd, *J* = 16.7, 8.0 Hz, 2H), 3.91 (s, 3H), 3.50 (s, 3H), 3.47 (s, 3H), 3.35 (s, 1H), 3.30 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (d, *J* = 5.3 Hz), 144.0 (d, *J* = 6.7 Hz), 141.2, 129.5, 128.1, 127.5 (d, *J* = 3.9 Hz), 127.1, 122.9 (d, *J* = 3.5 Hz), 118.5 (d, *J* = 10.4 Hz), 109.4 (d, *J* = 3.4 Hz), 55.7, 52.2 (d, *J* = 6.5 Hz), 24.1 (d, *J* = 138.3 Hz).; IR (film) *v* 2953, 1573, 1470, 1260, 1032, 886, 764, 706.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.8.; HRMS (ESI) *m / z* calcd for $C_{16}H_{20}O_4P$ $(M + H)^+$ 307.1099, found 307.1092.

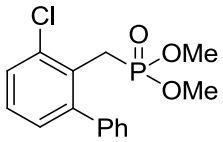
Dimethyl (4-methoxybiphenyl-2-yl)methylphosphonate (178e)



Yield: 26.1 mg, 85 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 3H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.10 (s, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 3.60 (s, 3H), 3.58 (s, 3H), 3.21 (s, 1H), 3.16 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 140.8, 135.2 (d, *J* = 8.3 Hz), 131.5 (d, *J* = 2.7 Hz), 129.9 (d, *J* = 8.8 Hz), 129.7, 128.3, 126.9, 115.5 (d, *J* = 4.8 Hz), 112.9 (d, *J* = 3.4 Hz), 55.4, 52.7 (d, *J* = 6.8 Hz), 29.6 (d, *J* = 138.1 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; IR (film) *v* 2955,

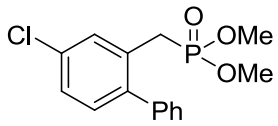
1608, 1485, 1234, 1030, 712, 705.; HRMS (ESI) *m / z* calcd for $C_{16}H_{20}O_4P$ $(M + H)^+$ 307.1099, found 307.1097.

Dimethyl (3-chlorobiphenyl-2-yl)methylphosphonate (178f)



Yield: 25.8 mg, 83 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.5 Hz, 3H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.2 Hz, 2H), 7.15 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 3.45 (s, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.41 (s, 1H),; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (d, *J* = 6.1 Hz), 140.9, 135.3 (d, *J* = 6.5 Hz), 129.4, 129.2 (d, *J* = 3.6 Hz), 128.9 (d, *J* = 3.6 Hz), 128.3, 127.7 (d, *J* = 3.9 Hz), 127.5, 52.4 (d, *J* = 6.7 Hz), 28.1 (d, *J* = 138.3 Hz).; IR (film) *v* 2953, 1562, 1452, 1265, 1031, 870, 793, 164, 704.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.5.; HRMS (ESI) *m / z* calcd for $C_{15}H_{17}O_3PCl$ $(M + H)^+$ 311.0604, found 311.0608.

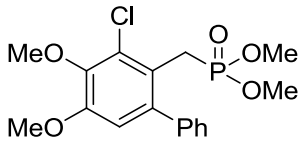
Dimethyl (4-chlorobiphenyl-2-yl)methylphosphonate (178g)



Yield: 25.5 mg, 82 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 2.4 Hz, 1H), 7.43 (dd, *J* = 7.9, 6.3 Hz, 2H), 7.36 (ddd, *J* = 8.3, 6.9, 1.5 Hz, 3H), 7.30 – 7.26 (m, 1H), 7.21 – 7.17 (m, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 3.19 (s, 1H), 3.13 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (d, *J* = 8.2 Hz), 139.9, 133.3 (d, *J* = 4.0 Hz), 131.7 (d, *J* = 2.8 Hz), 130.8 (d, *J* = 8.8 Hz), 130.2 (d, *J* = 4.9 Hz), 129.4, 128.4, 127.5, 127.2 (d, *J* = 3.5 Hz), 52.8 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 138.7 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.4.; IR

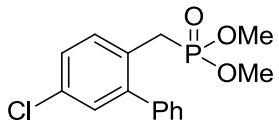
(film) *v* 2953, 1635, 1476, 1252, 1030, 888, 809, 704.; HRMS (ESI) *m / z* calcd for $C_{15}H_{17}O_3PCl$ $(M + H)^+$ 311.0604, found 311.0607.

Dimethyl (3-chloro-4,5-dimethoxybiphenyl-2-yl)methylphosphonate (178h)



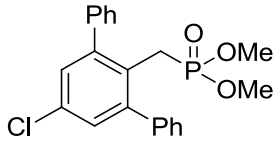
Yield: 34.4 mg, 93 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.39 – 7.31 (m, 3H), 7.26 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.50 (s, 3H), 3.47 (s, 3H), 3.43 (s, 1H), 3.37 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (d, *J* = 3.8 Hz), 144.9, 141.1 (d, *J* = 1.6 Hz), 139.5 (d, *J* = 6.5 Hz), 129.8 (d, *J* = 6.0 Hz), 129.5, 128.3, 127.5, 120.9 (d, *J* = 10.5 Hz), 113.1 (d, *J* = 3.6 Hz), 60.6, 56.1, 52.3 (d, *J* = 6.7 Hz), 27.9 (d, *J* = 139.5 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.0.; IR (film) *v* 2955, 1562, 1487, 1349, 1273, 1031, 886, 704.; HRMS (ESI) *m / z* calcd for $C_{17}H_{20}O_5PClNa$ $(M + Na)^+$ 393.0635, found 393.0630.

Dimethyl (5-chlorobiphenyl-2-yl)methylphosphonate (178i)



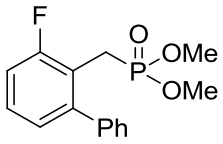
Yield: 14.6 mg, 47 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.41 (m, 3H), 7.41 – 7.28 (m, 5H), 3.60 (s, 3H), 3.58 (s, 3H), 3.18 (s, 1H), 3.12 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2 (d, *J* = 8.3 Hz), 139.8, 132.7 (d, *J* = 4.2 Hz), 131.8 (d, *J* = 4.9 Hz), 130.3 (d, *J* = 2.9 Hz), 129.3, 128.4, 127.7, 127.6 (d, *J* = 3.4 Hz), 127.4 (d, *J* = 8.7 Hz), 52.7 (d, *J* = 6.7 Hz), 28.9 (d, *J* = 138.8 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.7.; IR (film) *v* 2955, 1636. 1472, 1250, 1057, 1031, 864, 806, 704.; HRMS (ESI) *m / z* calcd for $C_{15}H_{17}O_3PCl$ $(M + H)^+$ 311.0604, found 311.0600.

Dimethyl (5-chloro-3-phenylbiphenyl-2-yl)methylphosphonate (179i)



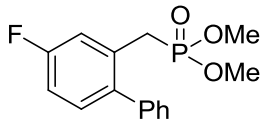
Yield: 4.6 mg, 12 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 17.0, 7.0 Hz, 10H), 7.24 (d, *J* = 0.8 Hz, 2H), 3.38 (s, 1H), 3.32 (s, 1H), 3.19 (s, 3H), 3.16 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (d, *J* = 6.0 Hz), 140.8, 132.2 (d, *J* = 4.9 Hz), 129.7 (d, *J* = 3.8 Hz), 129.5, 128.3, 127.5, 125.8 (d, *J* = 10.3 Hz), 51.9 (d, *J* = 6.7 Hz), 26.6 (d, *J* = 136.8 Hz).; IR (film) *v* 2954, 1636, 1570, 1423, 1265, 1058, 1034, 736, 702.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.1.; HRMS (ESI) *m / z* calcd for $C_{21}H_{21}O_3PCl$ $(M + H)^+$ 387.0917, found 387.0917.

Dimethyl (3-fluorobiphenyl-2-yl)methylphosphonate (178j)



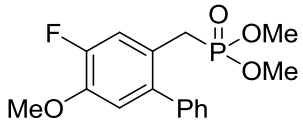
Yield: 21.0 mg, 71 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 10.2, 4.2 Hz, 2H), 7.30 (ddd, *J* = 4.6, 3.3, 2.2 Hz, 3H), 7.23 – 7.19 (m, 1H), 7.00 (dd, *J* = 16.4, 8.2 Hz, 2H), 3.48 (s, 3H), 3.45 (s, 3H), 3.25 (d, *J* = 2.3 Hz, 1H), 3.19 (d, *J* = 2.3 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3(dd, *J* = 246.9, 5.9 Hz), 144.8 (d, *J* = 3.5 Hz), 140.0, 129.4, 128.3, 128.1 (dd, *J* = 9.3, 3.8 Hz), 127.5, 126.2 (t, *J* = 3.2 Hz), 117.5 (dd, *J* = 15.7, 10.1 Hz), 114.3 (dd, *J* = 22.8, 3.5 Hz), 52.5 (d, *J* = 6.4 Hz), 23.5 (dd, *J* = 139.4, 3.3 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8 (d, *J* = 3.6 Hz).; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.3 (d, *J* = 3.7 Hz).; IR (film) *v* 2953, 1636, 1464, 1265, 1032, 902, 736, 702.; HRMS (ESI) *m / z* calcd for $C_{15}H_{17}O_3PF$ $(M + H)^+$ 295.0899, found 295.0899.

Dimethyl (4-fluorobiphenyl-2-yl)methylphosphonate (178k)



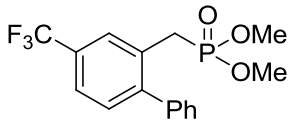
Yield: 23.6 mg, 80 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.35 (dd, *J* = 12.8, 7.3 Hz, 3H), 7.23 (dd, *J* = 12.4, 5.4 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 3.20 (s, 1H), 3.14 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 242.4 Hz), 140.1, 138.7 (dd, *J* = 9.5, 4.8 Hz), 131.9 (dd, *J* = 8.2, 2.8 Hz), 131.0 (t, *J* = 8.4 Hz), 129.6, 128.4, 127.4, 117.0 (dd, *J* = 22.3, 4.8 Hz), 114.0 (dd, *J* = 21.1, 3.4 Hz), 52.7 (d, *J* = 6.7 Hz), 29.6 (d, *J* = 138.6 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.5 (d, *J* = 2.1 Hz).; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (d, *J* = 2.6 Hz).; IR (film) *v* 2955, 1609, 1483, 1252, 1031, 956, 816, 708.; HRMS (ESI) *m / z* calcd for $C_{15}H_{17}O_3PF$ $(M + H)^+$ 295.0899, found 295.0898.

Dimethyl (4-fluoro-5-methoxybiphenyl-2-yl)methylphosphonate (178l)



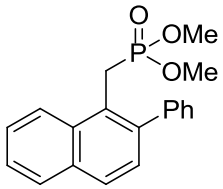
Yield: 26.3 mg, 81 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 2H), 7.37 (dd, *J* = 9.1, 7.6 Hz, 3H), 7.25 (d, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.63 (s, 3H), 3.60 (s, 3H), 3.11 (s, 1H), 3.05 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (dd, *J* = 246.1, 3.8 Hz), 146.2 (dd, *J* = 10.8, 3.3 Hz), 140.4, 139.4 – 13.0 (m), 129.5, 128.4, 127.5, 121.3 (dd, *J* = 9.0, 6.8 Hz), 117.7 (dd, *J* = 19.1, 4.5 Hz), 115.4, 56.3, 52.7 (d, *J* = 6.8 Hz), 28.7 (d, *J* = 139.5 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9.; ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.7 (d, *J* = 2.5 Hz).; IR (film) *v* 2955, 1636, 1516, 1232, 1034, 830, 704.; HRMS (ESI) *m / z* calcd for $C_{16}H_{19}O_4P$ F $(M + H)^+$ 325.1005, found 325.1010.

Dimethyl (4-(trifluoromethyl)biphenyl-2-yl)methylphosphonate (178m)



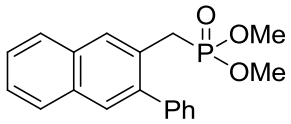
Yield: 31.7 mg, 92 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.35 (m, 6H), 3.63 (s, 3H), 3.60 (s, 3H), 3.26 (s, 1H), 3.20 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2 (d, *J* = 9.2 Hz), 139.8, 131.0 (d, *J* = 2.8 Hz), 130.1 (d, *J* = 8.8 Hz), 129.2, 128.5, 127.9, 127.5 – 127.0 (m), 123.7 (t, *J* = 3.6 Hz), 52.8 (d, *J* = 6.8 Hz), 29.5 (d, *J* = 138.8 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.1.; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5.; IR (film) *v* 2954, 1636, 1332, 1126, 1032, 899, 704.; HRMS (ESI) *m / z* calcd for $C_{16}H_{17}O_3PF_3$ $(M + H)^+$ 345.0866, found 345.0867.

Dimethyl (2-phenylnaphthalen-1-yl)methylphosphonate (178n)



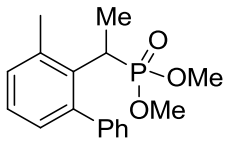
Yield: 28.5 mg, 87 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 3.6 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.83 – 7.77 (m, 1H), 7.74 (s, 1H), 7.50 – 7.42 (m, 6H), 7.40 (dd, *J* = 6.1, 2.6 Hz, 1H), 3.58 (s, 3H), 3.55 (s, 3H), 3.39 (s, 1H), 3.33 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 140.7 (d, *J* = 7.0 Hz), 132.6 (d, *J* = 3.5 Hz), 132.3 (d, *J* = 2.6 Hz), 129.7, 129.5 (d, *J* = 6.6 Hz), 129.3, 128.3, 127.5 (d, *J* = 7.4 Hz), 127.3, 127.1 (d, *J* = 8.9 Hz), 126.2, 52.7 (d, *J* = 6.8 Hz), 29.5 (d, *J* = 138.4 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; IR (film) *v* 2953, 1636, 1497, 1265, 1057, 1034, 815, 736, 702.; HRMS (ESI) *m / z* calcd for $C_{19}H_{20}O_3P$ $(M + H)^+$ 327.1150, found 327.1148.

Dimethyl (3-phenylnaphthalen-2-yl)methylphosphonate (178o)



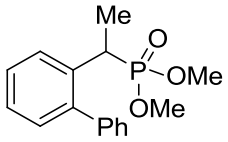
Yield: 24.8 mg, 76 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 3.6 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.82 – 7.79 (m, 1H), 7.74 (s, 1H), 7.50 – 7.44 (m, 6H), 7.41 (dd, *J* = 6.2, 2.5 Hz, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 3.39 (s, 1H), 3.34 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 140.7 (d, *J* = 7.1 Hz), 132.6 (d, *J* = 3.5 Hz), 132.3 (d, *J* = 2.5 Hz), 129.7, 129.5, 129.4, 129.3 (d, *J* = 2.2 Hz), 127.9 (d, *J* = 1.5 Hz), 127.5 (d, *J* = 1.2 Hz), 127.1, 127.0, 126.3, 126.2, 52.7 (d, *J* = 6.8 Hz), 29.5 (d, *J* = 138.5 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.1.; IR (film) *v* 3055, 2953, 2237, 1409, 1246, 1031, 910, 731, 704.; HRMS (ESI) *m / z* calcd for $C_{19}H_{20}O_3P$ $(M + H)^+$ 327.1150, found 327.1143.

Dimethyl 1-(3-methylbiphenyl-2-yl)ethylphosphonate (181a)



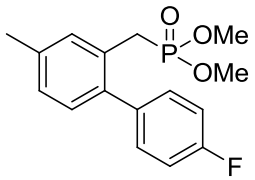
Yield: 26.9 mg, 88 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 4H), 7.18 – 7.16 (m, 3H), 7.04 – 7.03 (m, 1H), 3.75 – 3.63 (m, 1H), 3.55 (d, *J* = 10.7 Hz, 3H), 3.40 (d, *J* = 10.5 Hz, 3H), 2.70 (d, *J* = 1.2 Hz, 3H), 1.53 (dd, *J* = 18.4, 7.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (d, *J* = 9.2 Hz), 142.7, 138.5 (d, *J* = 4.5 Hz), 133.8 (d, *J* = 4.7 Hz), 131.6 (d, *J* = 3.0 Hz), 129.8, 128.1 (d, *J* = 1.6 Hz), 127.9, 127.0, 126.4 (d, *J* = 2.8 Hz), 52.8 (d, *J* = 6.8 Hz), 52.2 (d, *J* = 7.2 Hz), 34.6 (d, *J* = 138.0 Hz), 21.5, 14.4 (d, *J* = 3.9 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.8.; IR (film) *v* 2953, 1630, 1458, 1238, 1036, 820, 702.; HRMS (ESI) *m / z* calcd for $C_{17}H_{22}O_3P$ $(M + H)^+$ 305.1307, found 305.1309.

Dimethyl 1-(biphenyl-2-yl)ethylphosphonate (181b)



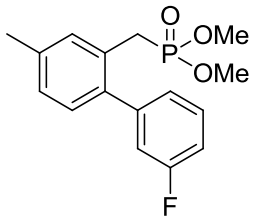
Yield: 23.8 mg, 82 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.28 (m, 7H), 7.23 (d, *J* = 7.6 Hz, 1H), 3.62 (d, *J* = 10.6 Hz, 3H), 3.50 (t, *J* = 8.3 Hz, 3H), 3.55 – 3.39 (m, 1H), 1.49 (dd, *J* = 18.7, 7.3 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2 (d, *J* = 9.7 Hz), 141.2, 135.7 (d, *J* = 5.4 Hz), 130.3 (d, *J* = 2.0 Hz), 129.3, 128.3, 128.4 (d, *J* = 4.5 Hz), 128.3, 127.7 (d, *J* = 2.9 Hz), 126.8 (d, *J* = 2.7 Hz), 52.9 (dd, *J* = 60.5, 7.1 Hz), 33.3 (d, *J* = 138.8 Hz), 17.2 (d, *J* = 4.8 Hz).; ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.0; IR (film) *v* 2953, 1741, 1494, 1234, 1058, 1031, 825, 775, 750, 704.; HRMS (ESI) *m / z* calcd for $C_{16}H_{20}O_3P$ $(M + H)^+$ 291.1150, found 219.1156.

Dimethyl (4'-fluoro-4-methylbiphenyl-2-yl)methylphosphonate (182a)



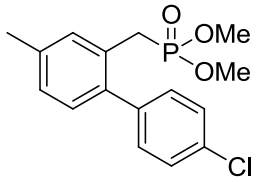
Yield: 28.7 mg, 93 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.6, 5.5 Hz, 3H), 7.10 (dd, *J* = 11.3, 6.1 Hz, 4H), 3.62 (s, 3H), 3.59 (s, 3H), 3.15 (s, 1H), 3.10 (s, 1H), 2.39 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 246.1 Hz), 138.7 (d, *J* = 8.0 Hz), 137.4 (d, *J* = 3.4 Hz), 137.0 (s), 131.2 (d, *J* = 8.6 Hz), 131.1 (d, *J* = 5.5 Hz), 130.4 (d, *J* = 2.6 Hz), 128.5 (d, *J* = 8.6 Hz), 127.9 (d, *J* = 3.5 Hz), 115.1 (d, *J* = 21.2 Hz), 52.7 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 138.5 Hz), 21.1.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.3.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.7 (d, *J* = 3.0 Hz).; IR (film) *v* 2955, 1634, 1489, 1223, 1159, 1032, 816, 735.; HRMS (ESI) *m / z* calcd for $C_{16}H_{19}O_3PF$ $(M + H)^+$ 309.1056, found 309.1053.

Dimethyl (3'-fluoro-4-methylbiphenyl-2-yl)methylphosphonate (182b)



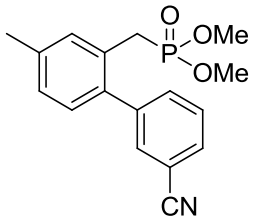
Yield: 27.5 mg, 89 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.15 – 7.10 (m, 3H), 7.10 – 7.05 (m, 2H), 3.62 (s, 3H), 3.59 (s, 3H), 3.18 (s, 1H), 3.12 (s, 1H), 2.39 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (d, *J* = 246.3 Hz), 143.3 (d, *J* = 7.7 Hz), 138.5 (d, *J* = 8.1 Hz), 137.7 (d, *J* = 3.5 Hz), 131.2 (d, *J* = 4.9 Hz), 130.2 (d, *J* = 2.8 Hz), 129.7 (d, *J* = 8.4 Hz), 128.4 (d, *J* = 8.6 Hz), 127.9 (d, *J* = 3.5 Hz), 125.4 (d, *J* = 2.6 Hz), 116.6 (d, *J* = 21.4 Hz), 113.9 (d, *J* = 20.9 Hz), 52.7 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 138.5 Hz), 21.2.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.2.; IR (film) *v* 2956, 1614, 1585, 1265, 1186, 1057, 1031, 852, 736.; HRMS (ESI) *m / z* calcd for $C_{16}H_{19}O_3PF$ $(M + H)^+$ 309.1056, found 309.1053.

Dimethyl (4'-chloro-4-methylbiphenyl-2-yl)methylphosphonate (182c)



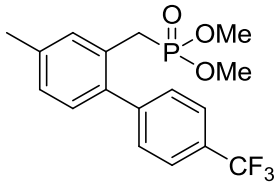
Yield: 30.9 mg, 95 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 3H), 7.11 (s, 2H), 3.62 (s, 3H), 3.60 (s, 3H), 3.15 (s, 1H), 3.09 (s, 1H), 2.39 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 138.6 (d, *J* = 8.1 Hz), 137.6 (d, *J* = 3.4 Hz), 133.1, 131.2 (d, *J* = 4.9 Hz), 130.9, 130.3 (d, *J* = 2.8 Hz), 128.4, 127.9 (d, *J* = 3.5 Hz), 52.7 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 138.6 Hz), 21.1.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2.; IR (film) *v* 2953, 1636, 1481, 1250, 1057, 1031, 815, 735.; HRMS (ESI) *m / z* calcd for $C_{16}H_{19}O_3PCl$ $(M + H)^+$ 325.0760, found 325.0760.

Dimethyl (3'-cyano-4-methylbiphenyl-2-yl)methylphosphonate (182d)



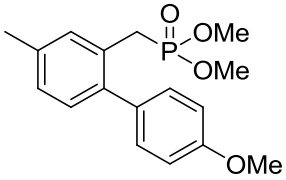
Yield: 28.8 mg, 91 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.07 (s, 1H), 3.02 (s, 1H), 2.40 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 140.3, 139.3 (d, *J* = 7.8 Hz), 137.6 (d, *J* = 3.7 Hz), 132.7, 132.1, 131.8 (d, *J* = 4.6 Hz), 130.1 (d, *J* = 2.9 Hz), 129.3, 128.9, 128.1 (d, *J* = 3.9 Hz), 127.3, 53.0 (d, *J* = 6.9 Hz), 30.3 (d, *J* = 138.8 Hz), 21.1.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.8.; IR (film) *v* 2958, 1635, 1506, 1265, 1057, 1032, 812, 736.; HRMS (ESI) *m / z* calcd for $C_{17}H_{19}NO_3P$ $(M + H)^+$ 316.1103, found 316.1096.

Dimethyl (4-methyl-4'-(trifluoromethyl)biphenyl-2-yl)methylphosphonate (182e)



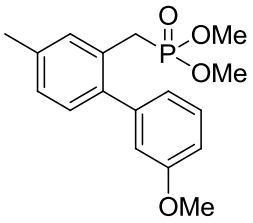
Yield: 26.2 mg, 73 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.35 (s, 1H), 7.13 (s, 2H), 3.63 (s, 3H), 3.60 (s, 3H), 3.14 (s, 1H), 3.08 (s, 1H), 2.40 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 138.4 (d, *J* = 8.1 Hz), 138.0 (d, *J* = 3.4 Hz), 131.3 (d, *J* = 5.0 Hz), 130.2 (d, *J* = 2.5 Hz), 130.0, 125.2 (d, *J* = 3.8 Hz), 52.7 (d, *J* = 6.8 Hz), 29.5 (d, *J* = 138.8 Hz), 21.2.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.0.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.4.; IR (film) *v* 2955, 1635, 1618, 1325, 1166, 1124, 1031, 817, 736.; HRMS (ESI) *m / z* calcd for $C_{17}H_{19}O_3PF_3$ $(M + H)^+$ 359.1024, found 359.1021.

Dimethyl (4'-methoxy-4-methylbiphenyl-2-yl)methylphosphonate (182f)



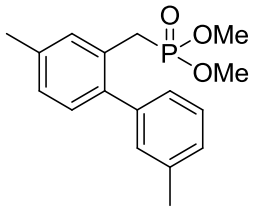
Yield: 29.5 mg, 92 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.30 – 7.24 (m, 2H), 7.12 (t, *J* = 8.3 Hz, 2H), 6.97 – 6.93 (m, 2H), 3.85 (s, 3H), 3.61 (s, 3H), 3.58 (s, 3H), 3.20 (s, 1H), 3.15 (s, 1H), 2.38 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 139.5, 136.9 (d, *J* = 3.4 Hz), 133.5, 131.0 (d, *J* = 4.9 Hz), 130.6, 130.5 (d, *J* = 2.8 Hz), 128.6 (d, *J* = 8.7 Hz), 127.8 (d, *J* = 3.5 Hz), 113.7, 55.3, 52.7 (d, *J* = 6.8 Hz), 29.3 (d, *J* = 138.2 Hz), 21.1.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.6.; IR (film) *v* 2953, 1610, 1493, 1246, 1057, 1034, 812, 735.; HRMS (ESI) *m / z* calcd for $C_{17}H_{22}O_4P$ $(M + H)^+$ 321.1256, found 321.1259.

Dimethyl (3'-methoxy-4-methylbiphenyl-2-yl)methylphosphonate (182g)



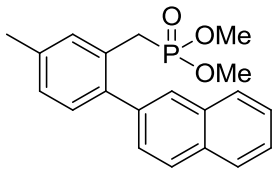
Yield: 24.4 mg, 76 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 13.4, 5.2 Hz, 2H), 7.15 (t, *J* = 10.7 Hz, 2H), 6.96 – 6.88 (m, 3H), 3.84 (s, 3H), 3.62 (s, 3H), 3.59 (s, 3H), 3.21 (s, 1H), 3.16 (s, 1H), 2.39 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 142.5, 139.7 (d, *J* = 10.4 Hz), 137.3, 131.0 (d, *J* = 4.9 Hz), 130.3, 129.2, 128.4 (d, *J* = 8.6 Hz), 127.8 (d, *J* = 3.4 Hz), 122.0, 115.1, 112.9, 55.3, 52.7 (d, *J* = 6.8 Hz), 29.3 (d, *J* = 138.3 Hz), 21.1.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.6.; IR (film) *v* 2955, 1636, 1479, 1223, 1055, 1030, 810, 736, 706.; HRMS (ESI) *m / z* calcd for $C_{17}H_{22}O_4P$ $(M + H)^+$ 321.1256, found 321.1255.

Dimethyl (3',4-dimethylbiphenyl-2-yl)methylphosphonate (182h)



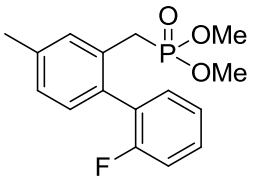
Yield: 21.7 mg, 71 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.32 – 7.27 (m, 1H), 7.19 – 7.08 (m, 5H), 3.59 (s, 3H), 3.56 (s, 3H), 3.21 (s, 1H), 3.15 (s, 1H), 2.39 (s, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 139.9 (d, *J* = 8.2 Hz), 137.8, 137.1 (d, *J* = 3.4 Hz), 131.0 (d, *J* = 4.9 Hz), 130.4, 130.3 (d, *J* = 2.2 Hz), 128.1, 127.7 (d, *J* = 3.5 Hz), 127.7, 126.6, 52.6 (d, *J* = 6.7 Hz), 29.3 (d, *J* = 137.9 Hz), 21.5, 21.1.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5.; IR (film) *v* 2953, 1634, 1614, 1456, 1250, 1056, 1032, 844, 735, 710.; HRMS (ESI) *m / z* calcd for $C_{17}H_{22}O_3P$ $(M + H)^+$ 305.1307, found 305.1308.

Dimethyl 5-methyl-2-(naphthalen-2-yl)benzylphosphonate (182i)



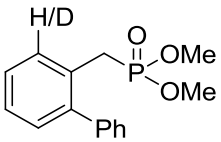
Yield: 30.0 mg, 88 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.81 (m, 4H), 7.56 – 7.47 (m, 3H), 7.39 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 3.24 (s, 1H), 3.18 (s, 1H), 2.42 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (d, *J* = 8.2 Hz), 138.6, 137.3 (d, *J* = 3.4 Hz), 133.3, 132.3, 131.1 (d, *J* = 4.9 Hz), 130.6 (d, *J* = 2.7 Hz), 128.6 (d, *J* = 8.6 Hz), 128.3, 128.0, 127.9, 127.9, 127.8, 127.7, 126.3, 126.0, 52.6 (d, *J* = 6.8 Hz), 29.4 (d, *J* = 138.2 Hz), 21.2.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5.; IR (film) *v* 2953, 1636, 1491, 1265, 1057, 1032, 895, 800, 735, 704.; HRMS (ESI) *m / z* calcd for $C_{20}H_{22}O_3P$ $(M + H)^+$ 341.1307, found 341.1303.

Dimethyl (2'-fluoro-4-methylbiphenyl-2-yl)methylphosphonate (182l)



Yield: 4.0 mg, 13 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 3H), 7.20 (t, *J* = 7.1 Hz, 1H), 7.16 – 7.10 (m, 3H), 3.56 (t, *J* = 13.5 Hz, 6H), 3.13 (d, *J* = 19.3 Hz, 2H), 2.40 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (d, *J* = 245.9 Hz), 138.0 (d, *J* = 3.3 Hz), 133.1 (d, *J* = 8.2 Hz), 132.2, 131.1 (d, *J* = 5.1 Hz), 130.7, 129.7 (d, *J* = 9.0 Hz), 129.3 (d, *J* = 8.0 Hz), 128.3 (d, *J* = 17.6 Hz), 127.9 (d, *J* = 3.3 Hz), 124.1 (d, *J* = 3.6 Hz), 115.7 (d, *J* = 22.5 Hz), 52.6, 29.7 (d, *J* = 138.4 Hz), 21.2.; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.1.; ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.0.; IR (film) *v* 2955, 1483, 1446, 1254, 1057, 1032, 814, 762.; HRMS (ESI) *m / z* calcd for $C_{16}H_{19}O_3PF$ $(M + H)^+$ 309.1056, found 309.1050.

Dimethyl biphenyl-2-ylmethylphosphonate (184)

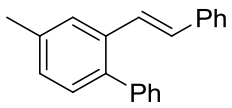


Yield: 14.1 mg, 51 %; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 1H), 7.46 – 7.40 (m, 2H), 7.40 – 7.35 (m, 3H), 7.33 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.30 (dd, *J* = 5.4, 3.7 Hz, 1H), 7.25 (d, *J* = 5.4 Hz, 0.18H), 3.59 (s, 3H), 3.56 (s, 3H), 3.24 (s, 1H), 3.18 (s, 1H).

Typical procedure for the Horner-Wadsworth-Emmons reactions.[151] To a mixture of dimethyl (4-methylbiphenyl-2-yl)methylphosphonate **178b** (29.1 mg, 0.1 mmol), *n*-Bu_4NBr (6.4 mg, 0.02 mmol) and solid NaOH (6.4 mg, 0.02 mmol) in anhydrous toluene

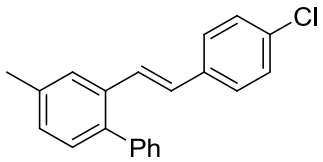
(3 mL) at room temperature was added a toluene solution (1 mL) of benzaldehyde (12.7 mg, 0.12 mmol) and the mixture was vigorously stirred at 35 ^{o}C for 15 h under nitrogen. After completion of the reaction, H_2O (1 mL) was added to the reaction mixture and the mixture was extracted with diethyl ether (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 100:1) to provide compound **185a** (21.9 mg, 81%).

(*E*)-4-Methyl-2-styrylbiphenyl (185a)



Yield: 21.9 mg, 81 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.47 – 7.33 (m, 7H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.19 (dd, *J* = 23.5, 8.1 Hz, 3H), 7.07 (q, *J* = 16.3 Hz, 2H), 2.45 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 138.5, 137.7, 137.2, 135.2, 130.2, 129.9, 129.2, 128.6, 128.4, 128.1, 127.9, 127.4, 126.9, 126.9, 126.5, 21.2.; IR (film) *v* 3024, 2922, 1598, 1261, 1072, 964, 908, 819, 769, 721, 700.; HRMS (ESI) *m / z* calcd for $C_{21}H_{19}$ $(M + H)^+$ 271.1487, found 271.1487.

(*E*)-2-(4-Chlorostyryl)-4-methylbiphenyl (185b)



Yield: 23.7 mg, 78 %, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.48 – 7.32 (m, 5H), 7.31 – 7.23 (m, 5H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 38.9, 16.3 Hz, 2H), 2.44 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 138.6, 137.2, 136.2, 134.8, 133.0, 130.3, 129.9, 128.9, 128.7, 128.6, 128.1, 127.9, 127.7, 127.0, 126.4, 21.2.; IR (film)

v 3024, 2922, 1486, 1089, 1010, 964, 908, 812, 761, 732, 702.; HRMS (ESI) *m / z* calcd for $C_{21}H_{18}Cl$ $(M + H)^+$ 305.1097, found 305.1091.

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