Organocatalytic Stereoselective Synthesis of Organophosphorus and Organoselenium Compounds

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Submitted by

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2021

Dedicated
To
My Beloved Parents
and
Teachers

For Stronger and Consistent Support

CERTIFICATE

This is to certify that the thesis titled **"Organocatalytic Stereoselective Synthesis of Organophosphorus and Organoselenium Compounds"** submitted by Mr. **Ram Subhawan Verma** is an original research work and has not been previously submitted in part or full for the award of any other degree or diploma to this or any other university.

The thesis submitted to Babasaheb Bhimrao Ambedkar University, Lucknow satisfies all the requirements as stipulated in the *Doctor of Philosophy (Ph.D.) regulations-1999 as amended in 2008/2010/2013* and it is fit for submission and evaluation for the award of the degree of Doctor of Philosophy of the University.

Date:

Co-Supervisor **Supervisor**

Head of Department

DECLARATION

I hereby declare that the thesis titled "**Organocatalytic Stereoselective Synthesis of Organophosphorus and Organoselenium Compounds**" submitted by me for the degree of Doctor of Philosophy, is the record of work carried out by me under the supervision of **Dr**, **Shailesh Kumar**, Assistant Professor, Department of Applied Chemistry, School of Physical Sciences, Babasaheb Bhimrao Ambedkar University (A Central University), Lucknow, India, and co-supervision of **Dr. Bhoopendra Tiwari**, Associate Professor, Department of Molecular Synthesis and Drug Discovery, Centre of Biomedical Research, Lucknow, India and I further confirm that said work has not been submitted anywhere else for the award of any degree, diploma, fellowship, etc. either in this or any other University or other institution of higher learning. I further declare that the material obtained from other sources has been duly acknowledged in the thesis. I, Ram Subhawan Verma also declare that the thesis submitted by me is essentially free from all kinds of plagiarism (checked by URKUND).

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Place:

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Ram Subhawan Verma

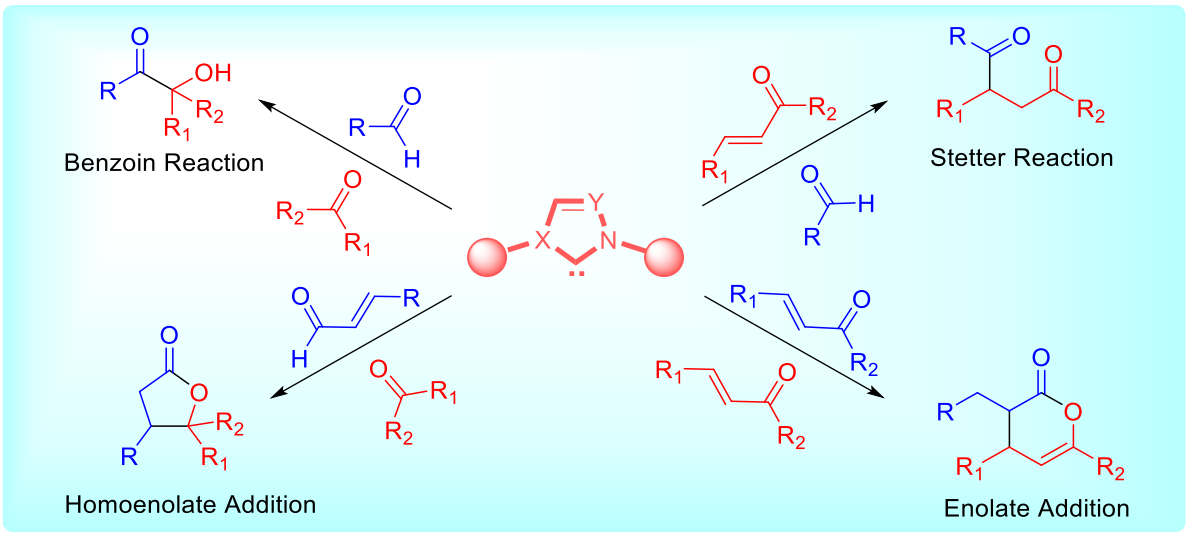
(Research Scholar, BBAU, Lucknow)

ABSTRACT

The thesis entitled "**Organocatalytic Stereoselective Synthesis of Organophosphorus and Organoselenium Compounds**" has been discussed in five chapters. Recent developments of *N*-heterocyclic carbenes as powerful organocatalysts has unlocked a new era in the field of organocatalysis for the construction of simple or complex, chiral and achiral organic molecules. In this context, we have developed the NHC-catalyzed synthesis of chiral and achiral organophosphorus compounds *via* enolate addition, Setter reaction and cross-acyloin condensation reactions. We also discovered the first synthetic protocol to access chiral organoselenium compounds *via* enolate addition under carbene catalysis. These catalytic methods are direct, one-pot, atom-economical, transition-metal free and organocatalytic. All the methodologies discussed in this thesis are developed by using phosphorus and selenium containing electrophiles.

Chapter 1: Organocatalysis: Reactions Catalyzed by N-Heterocyclic Carbenes

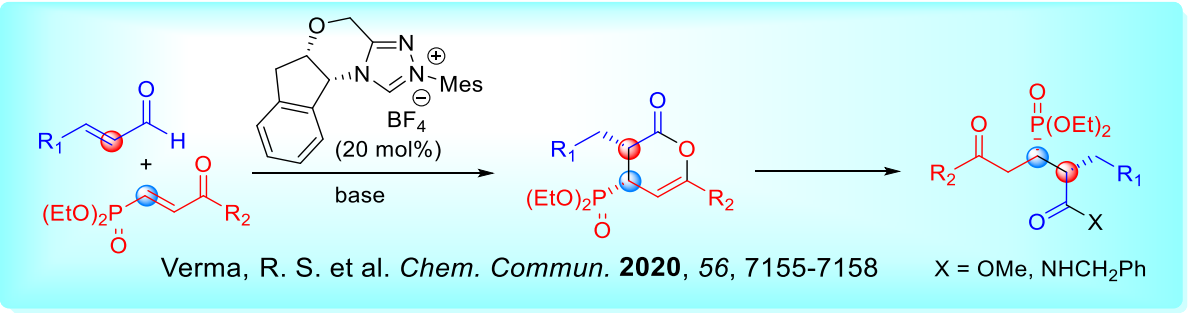
The development of numerous synthetic methods over the last several decades has enabled the chemist to complete the synthesis of even highly complex molecules. However, these methods have mainly relied on the use of different metal-based reagents and catalysts. Pharmaceutical industries prefer transition metal-free catalytic reactions due to metal-leaching, high toxicity and expensiveness of these organometallic catalysts. In that direction, organocatalysts have emerged as the natural alternate choice due to their environmental benign nature, lower toxicity and typically inertness to moisture and air.



Among the various class of organocatalysts developed in the last couple of decades, *N*-Heterocyclic Carbenes (NHCs) have gained increased significance due to their several intrinsic properties and unique modes of activation. The NHCs plays a key role in the polarity reversal of the several function group (umpolung) as in the case of benzoin condensations, Stetter reactions, etc. These catalysts generate homoenolates, enolates or acyl anion intermediates from the same substrates, leading to the formation of three or more different products from the same sets of substrates under different reaction condition. This chapter describes briefly the major class of reactions catalyzed by NHCs.

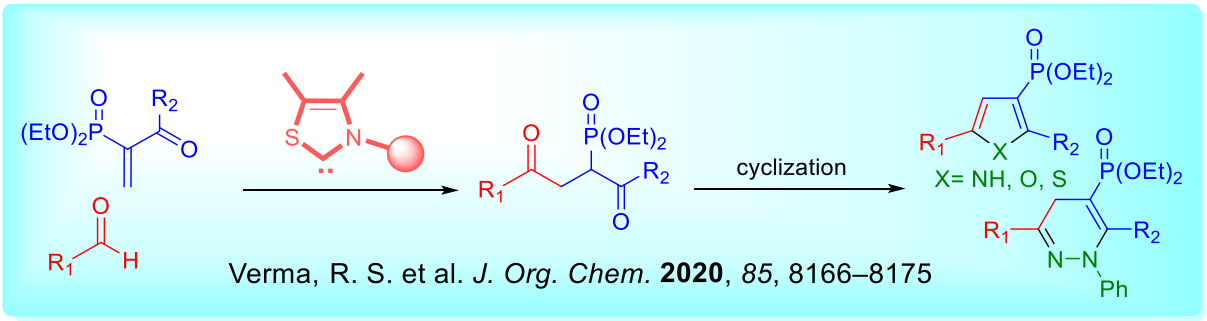
Chapter 2: Carbene Catalyzed Highly Enantioselective Preparation of 4-Phosphorylated δ-Lactones

Organophosphorus compounds exhibit numerous biological properties with potential applications as enzyme inhibitors, pharmaceuticals, agrochemicals, antibacterial, antiviral, and antifungal agents. Among them, phosphorylated lactones have been used in the treatment of numerous antiviral diseases in humans. While 2-pyranylphosphonates (a *δ*-lactones), perform antibacterial and antiviral action against X. *oryzae pv. oryzae* and Tobacco Mosaic Virus respectively. On account of their valuable bioactive properties, the metal-free organocatalyzed enantioselective preparation of organophosphorus compounds has gained significant attention. Herein, we have developed the first, *N*-heterocyclic carbene catalyzed highly enantioselective method for intermolecular enolate addition of *α,β*-unsaturated aldehydes to *β*-phosphorylenones. This class of Michael acceptors with a very bulkier substituent at the *β*-position has remained challenging under carbene-catalysis. The phosphorylated *δ*-lactones were obtained in excellent yields and enantioselectivity. The 4-phosphorylated *δ*-lactones produced multi-functionalized chiral *γ*-ketophosphoryl esters and amides is in quantitative yield.



Chapter 3: Carbene Catalyzed Synthesis of α-Phosphorylated 1,4-Diketones: Access of 3/4-Phosphorylated Heterocycles

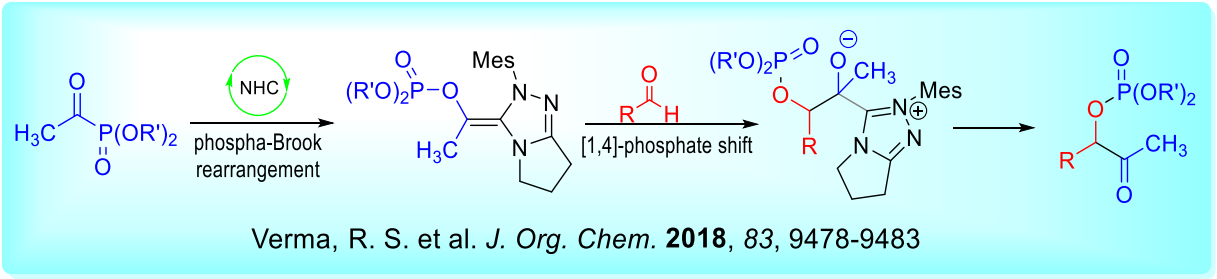
Heterocyclic motifs such as pyrroles, furans, thiophenes and dihydropyridazines are abundantly found in numerous biologically active natural, non-natural, pharmaceuticals and agrochemicals products. On the other hand, phosphoryl groups are omnipresent in the biological system and other vital molecules. So, the phosphorylated heterocycles constitute the virtues of both the phosphorus moiety and the heterocyclic scaffolds. Accordingly, the preparation of these class of compounds has constantly attracted the attention of both the industries as well as the academia. Despite of progress, the preparation of these class of compounds has remained challenging and often requires multi-steps synthesis and transition metal catalyzed cross coupling reaction. Herein, we have developed a global method for the preparation of C3-phosphorylated pyrroles, furans and thiophenes and 4-phosphorylated dihydropyridazines under a metal-free organocatalytic reaction condition. To achieve this, we have developed the first NHC-catalyzed Stetter reaction between vinylphosphonates and aldehydes to access *α*-phosphorylated 1,4-diketones, followed by a cyclization reaction. These phosphorylated 1,4-diketones could be efficiently converted into C3-phosphorylated pyrroles, furans and thiophenes, and C4-phosphorylated dihydropyridazines.



Chapter 4: Carbene-Catalyzed Phospha-Brook Rearrangement: Preparation of α-Ketophosphates from Acylphosphonates and Aldehydes

The organophosphorus compounds have an indispensable role as the key biomolecules, such as DNA, RNA and ATP. In addition, they are used in pharmaceutics, organometallics, organic synthesis and photoelectric materials. They have high chelation affinity with transition metals, therefore, they are widely used as ligands in organic synthesis. Phosphate esters are used in the pesticides and in prodrugs to enhance their aqueous solubility. Among them, *α*-ketophosphates are the key intermediates for the synthesis of phospholipids and

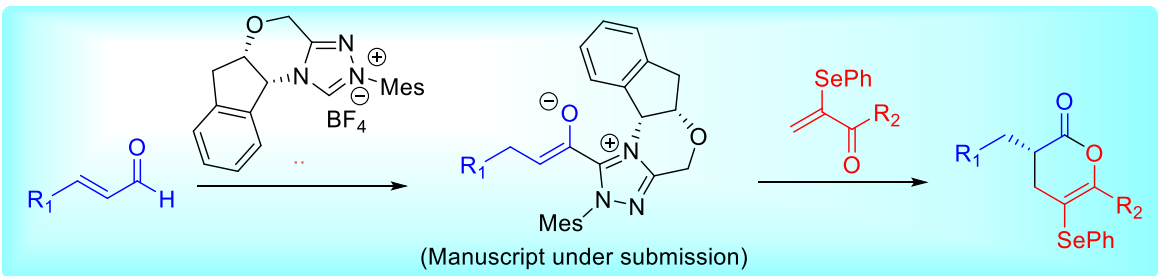
oligonucleotides. Herein, we have developed the first *N*-heterocyclic carbene catalyzed controlled cross acyloin condensation of acyl phosphonates and aldehydes *via* phospha-Brook rearrangement. This is the first organocatalytic phospha-Brook rearrangement that generally required metal cyanides as the catalysts previously. In addition, acyl anions from the acyl phosphonates has been generated under carbene catalyst for the first time.



Verma, R. S. et al. *J. Org. Chem.* **2018**, *83*, 9478-9483

Chapter 5: Carbene Catalyzed Enantioselective Synthesis of Selenylated δ-Lactones from Vinyl selenides and Enals

Selenium is an essential micronutrient for humans and animals and is used in the prevention and treatment of several diseases. It plays a vital role in the immune system functioning and also regulates the progression of viruses. The endemic selenium deficiency can cause Keshan disease (disease of the heart muscles) and Kashin–Beck disease (a disease of the bone). In addition, organoselenium compounds are widely used in the form of dietary supplement due its unique properties such as antioxidative, enzymatic modulator, anticancer and for the inhibition of cell growth. They are also used as synthetic intermediates and as Lewis base/acid catalysts in numerous organic transformations. In this context, the first *N*-heterocyclic carbene (NHC)-catalyzed highly enantioselective synthesis of selenylated *δ*-lactones *via* [4+2] annulation of *α,β*-unsaturated aldehydes with vinylselenides has been developed. This method is highly atom economical and proceeds under transition metal-free condition.



(Manuscript under submission)

To achieve this, we have used vinylselenides as the new Michael acceptor under carbene catalysis. This study is a valuable addition to the limited literature methods available for the preparation of C4-unsubstituted chiral δ-lactones. These class of β-unsubstituted enones have remained challenging substrates for the cycloaddition reaction under NHC-catalysis via homoenolate intermediates.

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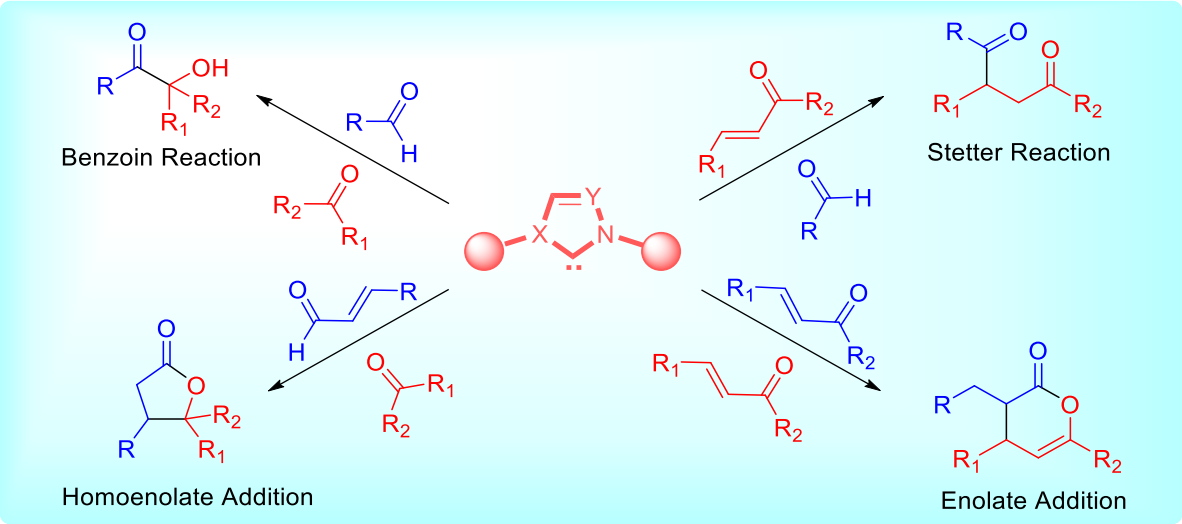
Chapter 1

Organocatalysis: Reactions Catalyzed by *N*-Heterocyclic Carbenes

The development of numerous synthetic methods over the last several decades has enabled the chemist to complete the synthesis of even highly complex molecules. However, these methods have mainly relied on the use of different metal-based reagents and catalysts. Pharmaceutical industries prefer transition metal-free catalytic reactions due to metal-leaching, high toxicity and expensiveness of these organometallic catalysts. In that direction, organocatalysts have emerged as the natural alternate choice due to their environmental benign nature, lower toxicity and typically inertness to moisture and air. Among the various class of organocatalysts developed in the last couple of decades, *N*-Heterocyclic Carbenes (NHCs) have gained increased significance due to their several intrinsic properties and unique modes of activation. The NHCs plays a key role in the polarity reversal of the several function group (umpolung) as in the case of benzoin condensations, Stetter reactions, etc. These catalysts generate homoenolates, enolates or acyl anion intermediates from the same substrates, leading to the formation of three or more different products from the same sets of substrates under different reaction condition. This chapter describes briefly the major class of reactions catalyzed by NHCs.



1.1. Introduction

The term "organocatalyst" is applied to the small organic molecules which can catalyze a reaction in a sub-stoichiometric quantity for the synthesis of simple or complex chiral and achiral compounds. In 2000, David W. C. MacMillan first introduced the term organocatalysis to classify the organic transformations using organic molecules with a low molecular weight as the catalysts.[1] Organocatalysts may be chiral as well as achiral and are mainly composed of organic C, H, N, S, P, Se, O, I, etc. The main advantages of organocatalysts over the traditional metal catalysts include their low sensitivity against aerial oxygen, moisture, good shelf-life, easy availability, easy to handle, low cost, and low toxicity. All these properties of the organocatalysts make them valuable tools in organic synthesis. They are increasingly gaining applications in the synthesis of pharmaceutical, agricultural and natural products.[2] Organocatalysts acts *via* either HOMO and/or LUMO activation. Organocatalysts can be classified based on their mode of interaction with the substrates as covalent, non-covalent, or synzymes (Figure. 1.1). In covalent catalysis, a covalent bond is formed between an organocatalyst and the substrate(s), which results in a

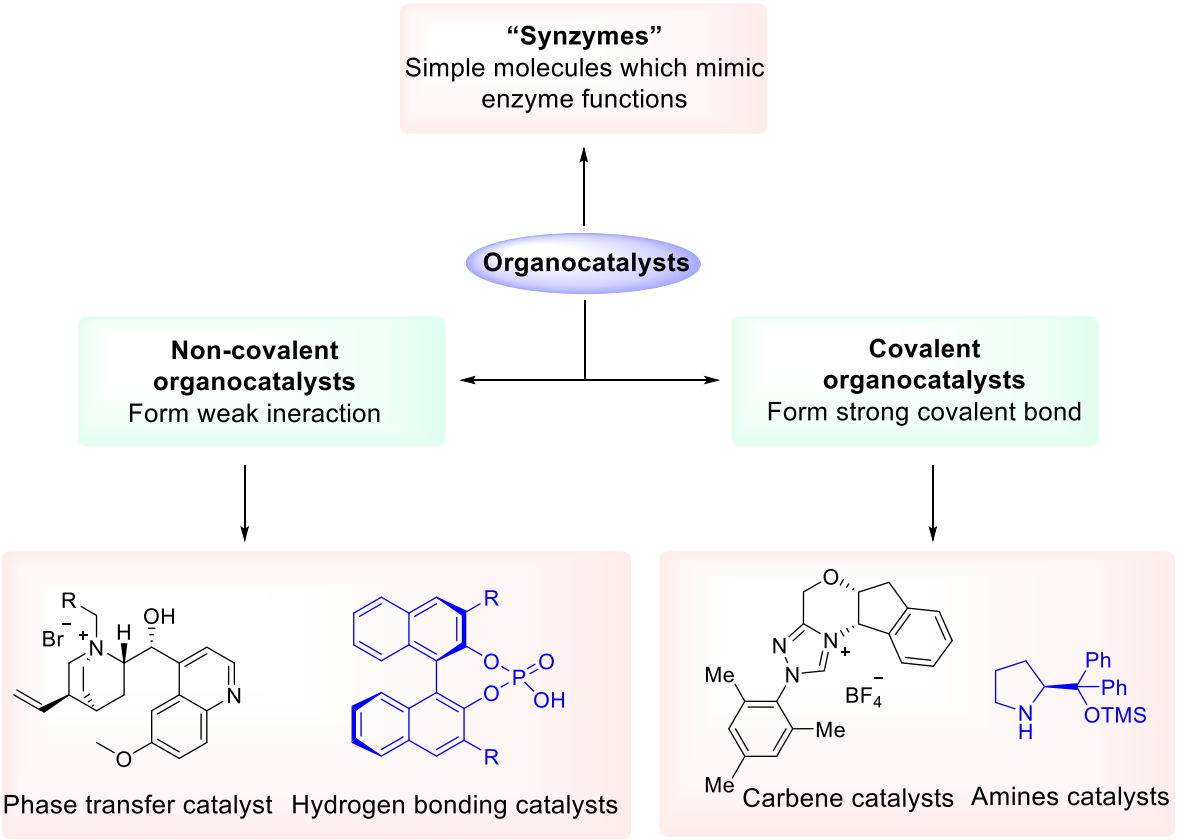


Figure 1.1. Classification of organocatalysts based on their mode of interaction

strong interaction between the catalyst and the substrate(s), for example, in the case of aminocatalysis and *N*-heterocyclic carbene catalysis. In the case of non-covalent interactions, the activation of the substrate occurs *via* the formation of hydrogen bonds (e.g., phosphoric acids, and thiourea catalysts) or *via* ionic interactions, e.g., phase-transfer catalysts (PTC) derived from chiral bases such as cinchona alkaloids (quinine and quinidine).[3]

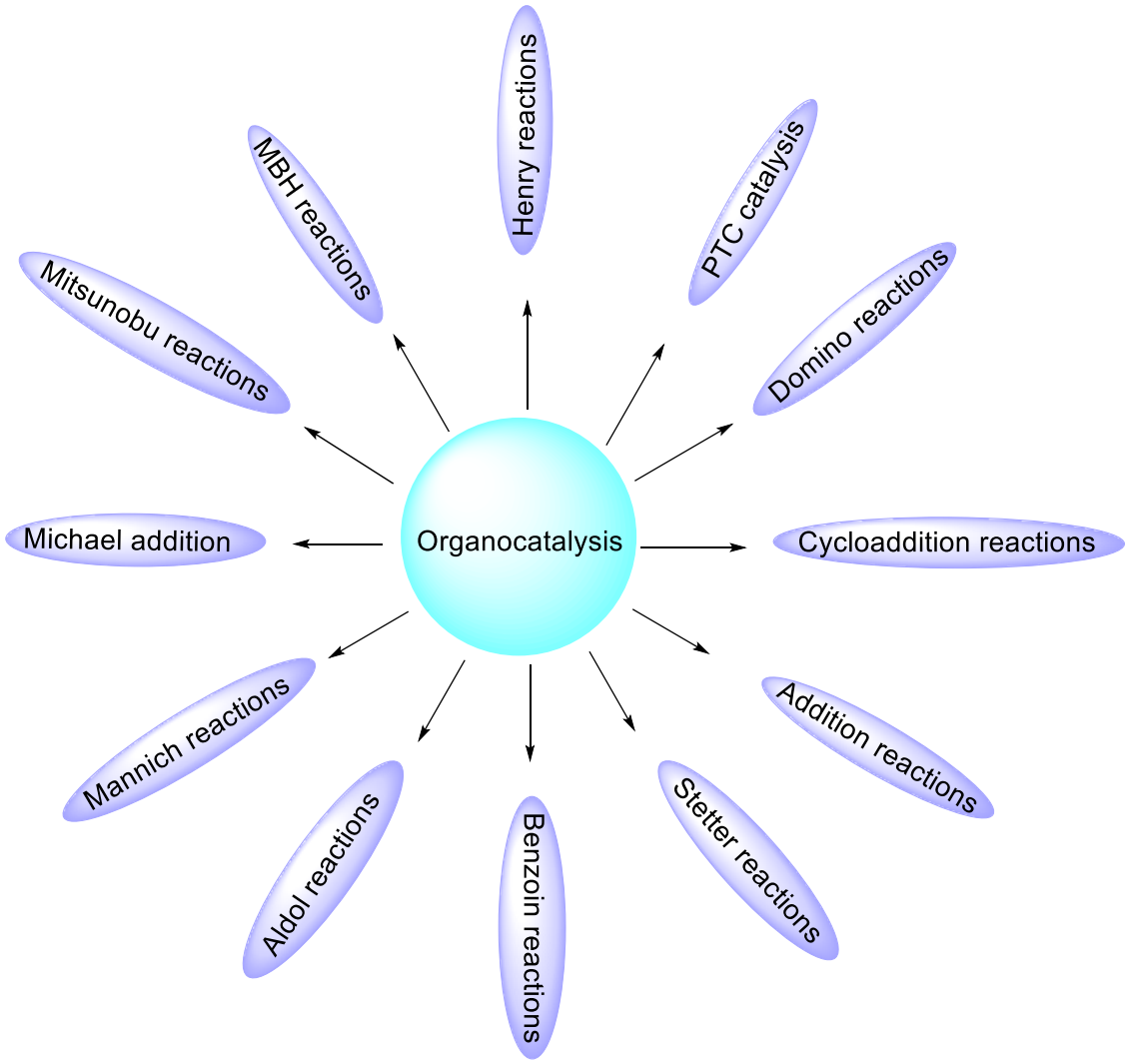


Figure 1.2. Selected examples of the reactions catalyzed by the organocatalysts

For the last two decades, organocatalysts are widely used as powerful tools for the construction of simple and complex organic skeletons and have become complementary to the metal and enzyme catalysis. They are extensively used in the numerous valuable transformations in the field of organic chemistry, e.g., Michael addition, aldol condensation, benzoin condensation, Mitsunobu reaction, Mannich reaction, Stetter reaction, Morita-Baylis-Hillman (MBH) reaction, and so on (Figure 1.2).

Carbenes are an electronically neutral highly reactive transient species containing a divalent carbon atom with two bonding and two non-bonding electrons. The general formula of carbene is R_1R_2C**:** where R_1 and R_2 represent the substituents bonded with the central carbon atom. Based on the arrangement of electrons in the p-orbitals of the central carbon atom, carbenes are classified into two categories, singlet, and triplet (Figure 1.3).

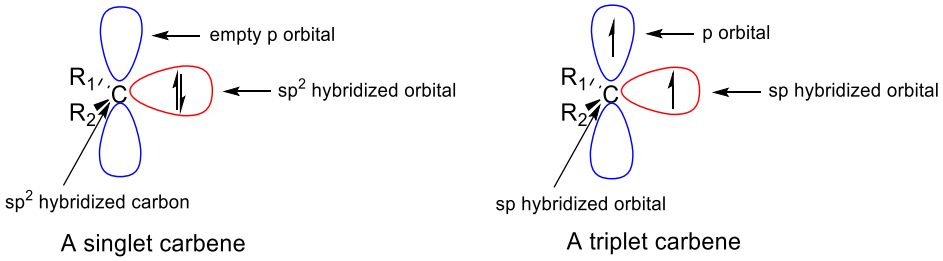


Figure 1.3. Structure of the singlet and triplet carbenes

Singlet and triplet carbenes exhibit divergent reactivity due to their different electronic arrangements. The two nonbonding electrons in singlet carbene are spin paired and occur in the highest occupied molecular orbital (HOMO) of sp^2 hybridized orbital of the carbon atom, whereas p orbital remains vacant and possess nucleophilic and electrophilic properties. While the two non-bonding electrons in the triplet carbenes have parallel spins and occupied in two different p orbital of carbon atom (Figure 1.4).[4] The triplet carbene are paramagnetic in nature due to the presence of unpaired electron, thus it can be detected by using an electron spin resonance spectroscopy (ESR). Therefore, triplet carbene is considered as a biradical species and can participate in stepwise radical additions.

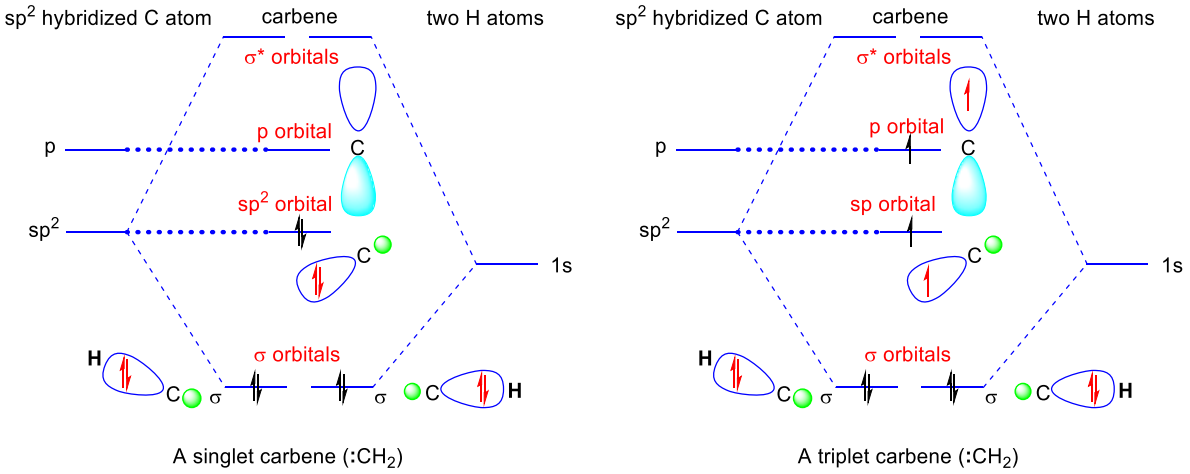


Figure 1.4. Molecular orbital diagram of singlet and triplet carbene

Buchner, Curtius, Staudinger, and Kupfer first reported the existence of carbenes during the late 19th and early 20th centuries.[5] But, due to the extreme reactivity and short life span of the carbenes, it could not be isolated during initial attempts and regarded as an extremely reactive intermediate. Bertrand and co-workers[6] were the first to report a stable carbene phosphinosilylcarbene **1** in 1988.

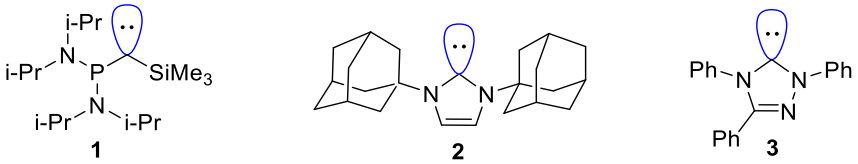


Figure 1.5. Structures of the **1**, **2** first isolated stable carbenes and **3** is the first commercially available NHC catalysts

Later on, in 1991 Arduengo et *al.*[7] first succeeded to isolate the crystalline cyclic diaminocarbene **2**, while triphenyl triazol-5-ylidene **3** was synthesized in 1995 by the group of Enders and co-workers (Figure 1.5).[8a] The evolution of the carbene catalysts in organic synthesis can be understood with the below flow chart (Figure 1.6).[8b]

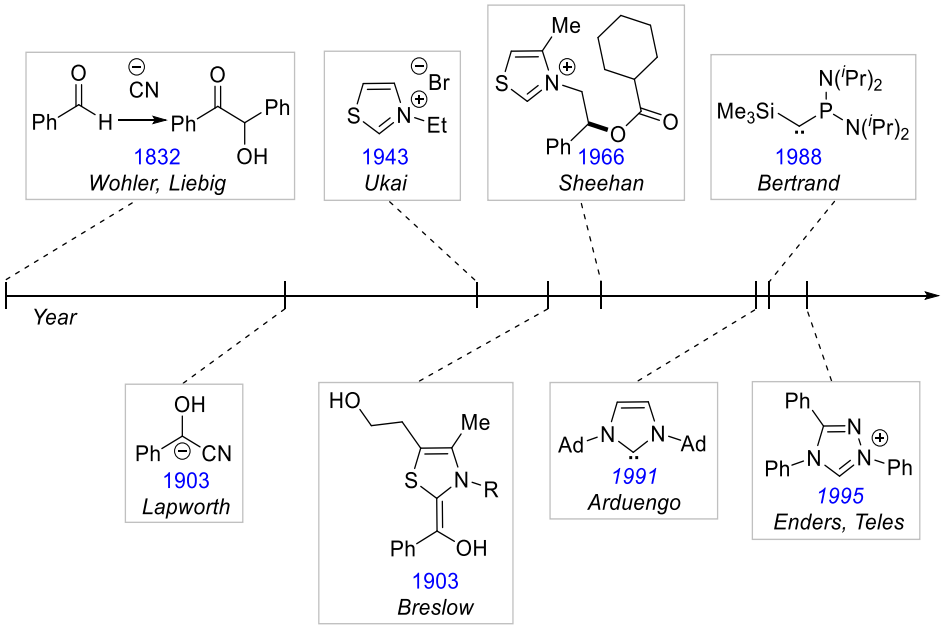


Figure 1.6. Development of NHCs as the organocatalysts

After the first report by Bertrand and Arduengo on the isolation of stable nucleophilic carbenes, the extensive application of *N*-heterocyclic carbenes was demonstrated in the organic synthesis. The four major class of NHCs employed for catalytic reactions are:

thiazolium- (**A**), triazolium- (**B**), imidazolium- (**C**), and imidazolin-2-ylidenes (**D**) (Figure 1.7).

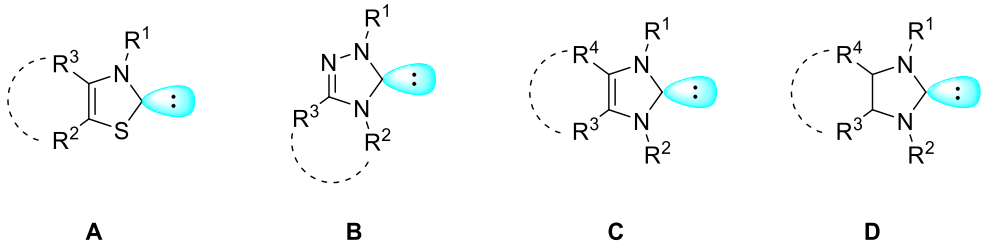


Figure 1.7. The major category of nucleophilic *N*-heterocyclic carbenes

In the stabilization of *N*-heterocyclic carbenes (NHCs), the push-push mesomeric effect plays a crucial role. The two lone pairs of electrons of nitrogen atoms interacted effectively with the p_π orbital of the carbon atom of the carbene centre. The property of nitrogen atoms to withdraw σ-electron relative to carbon atom also assists in the stabilization of *N*-heterocyclic carbenes. More importantly, the mesomeric and inductive effects assists equally to maintain the electron-neutrality in the NHCs (Figure 1.8). The strong electronic interaction among both the nitrogen atoms as well as central carbene carbon destabilizes the p_π orbital, which results in a large s–p_π energy gap.[9] Thus, *N*-heterocyclic carbenes behave like a nucleophilic species rather than electrophilic species.

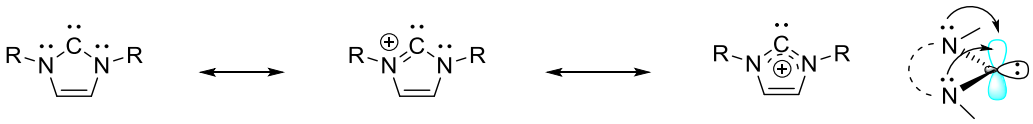


Figure 1.8. The stabilization of the NHCs by the mesomeric and inductive effects

Currently, *N*-heterocyclic carbenes (NHCs) belongs to one of the most investigated species as the organocatalysts in the arena of organic synthesis. They play a key role to maintain the efficiency of the chemical transformations because of their facile reaction mode, selectivity, and environmental friendliness. One of the most salient features of the *N*-heterocyclic carbene catalysis is the inversion of the reactivity of the functional groups in comparison to their normal mode of reactivity (umpolung), which opens up new synthetic pathways in the area of organic synthesis.[10] The well-known coenzyme thiamine (vitamin B_1 **4**, Figure 1.9), which is naturally a thiazolium salt, is utilized in nature as a catalytic agent in the biochemical processes for nucleophilic acylations.

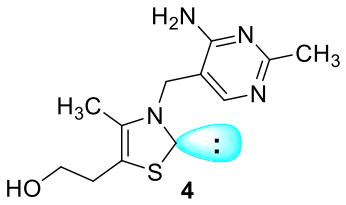
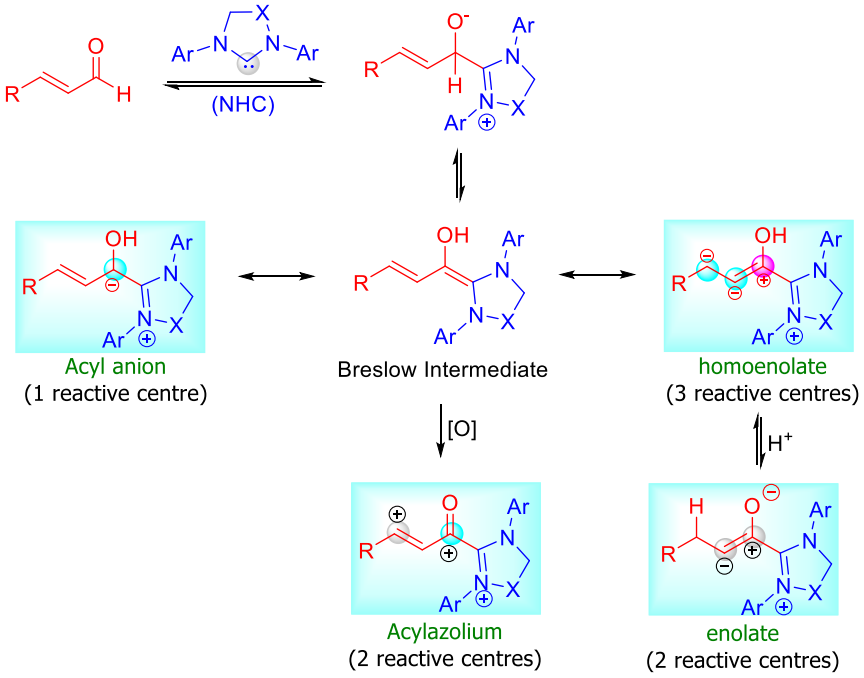


Figure 1.9. Structure of the coenzyme thiamine (Vitamin B_1)

The *N*-heterocyclic carbene catalysis started growing exponentially from the year 2004 onwards after two seminal reports from the groups of Bode and Glorius using *α,β*-unsaturated aldehydes as the substrates.[11] Whereas the aldehydes reacts via only acyl anion intermediate under carbene catalysis, the use of *α,β*-unsaturated aldehydes could produce three different intermediates such as acyl anions, homo-enolates, and enolates selectively in the reaction medium (Scheme 1.1).[11]



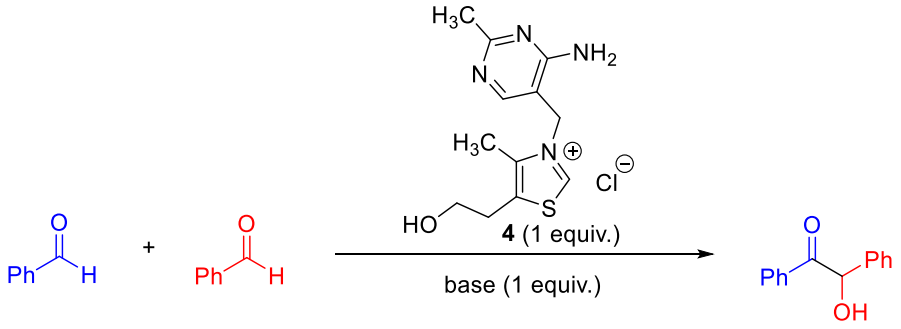
Scheme 1.1. Reactive intermediates generated by NHC from enals

Thus, it turns out to be possible to functionalize *α*-, *β*- and/or *γ*-position of various carbonyl compounds such as aldehydes, enals, esters, ketenes under NHC-catalysis.

1.2. Benzoin Condensation

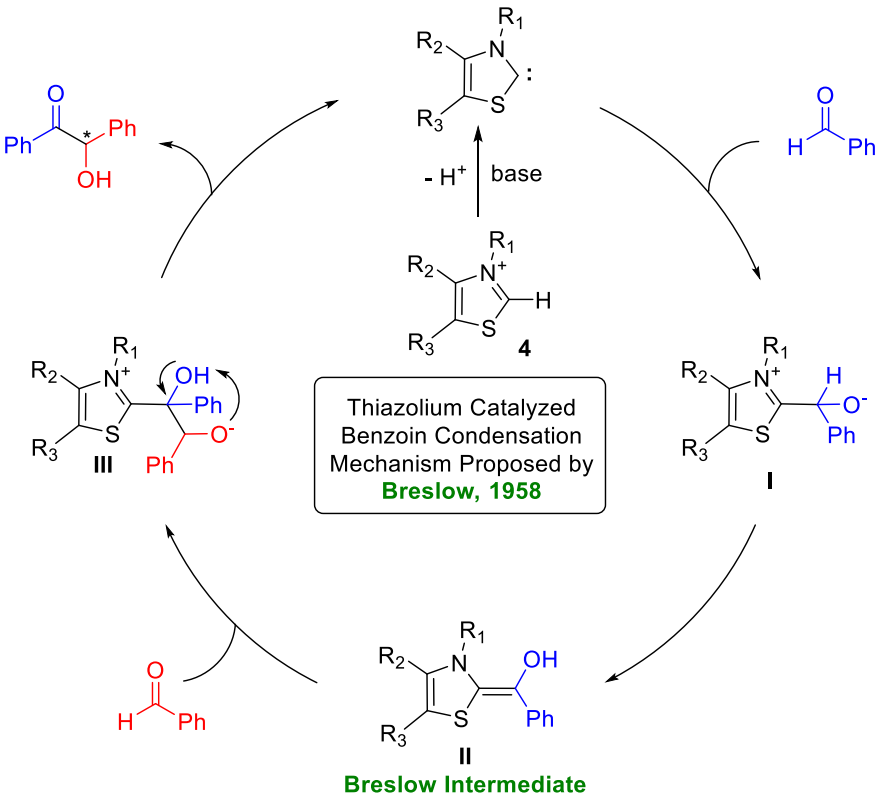
The benzoin condensation is an addition reaction in which two molecules of aldehydes catalytically react to form a benzoin product. The *N*-heterocyclic carbenes catalyzed benzoin

condensation was one of the most investigated reactions in the field of organic chemistry. Notably, in 1832 Wohler and Liebig established the first cyanide catalyzed benzoin condensation by the coupling of two molecules aromatic aldehydes to obtain benzoins (*α*-hydroxyketones).[12a] The mechanism of this reaction was postulated by Lapworth in 1903, in which a carbanion intermediate is formed by the addition of cyanide ion to benzaldehyde *via* 1,2-proton shift.[12b] It was also observed that the general electrophilic reactivity of carbonyl carbon was reversed to nucleophilic in this case. Similarly, activated aldehyde (intermediate **I**) is formed by the addition of carbene catalysts Scheme 1.3, likewise the classical non-NHC variant in benzoin condensation, illustrating the "Ümpolung" concept of Seebach and coworkers.[13] After the discovery of benzoin condensation by Wöhler's and Liebig's, in 1943 Ukai and co-workers recognized that the same transformation could be performed by using a stoichiometric amount of naturally occurring thiamin in the presence of base (Scheme 1.2).[14]



Scheme 1.2. Naturally occurring thiamine catalyzed benzoin reaction

Building upon the postulation of Lapworth, Breslow in 1958 stated that a mild base easily deprotonates thiazolium **4** to produce a reactive species (thiazolylidene) which can further adds to an formyl group to reverse the polarity i.e., (Ümpolung). The mechanistic model of the thiazolium catalyzed benzoin reaction was introduced by Breslow as presented in Scheme 1.3.[15] The mechanism of this reaction was initiated by the in-situ generation of active carbene species (thiazolin-2-ylidene) by the deprotonation of thiazolium salt **4** in the presence of a base. The catalytically active carbene species i.e., nucleophilic thiazolidene moiety further reacts with aldehyde to generate thiazolium salt adduct **I**. A further deprotonation/protonation of **I** resulted in the formation of resonance stabilized enaminol-type Breslow intermediate **II**. In the next step, nucleophilic Breslow intermediate **II** further reacts to another molecule of electrophilic aldehyde to form an intermediate **III**. A thiazolium moiety departs from the intermediate **III** to afford the benzoin product.



Scheme 1.3. The mechanistic model of the benzoin reaction proposed by Breslow

Stetter and co-workers, first successfully prepared the acyloins and benzoin products on a preparative scale by utilizing several thiazolium salts as catalysts. They applied this synthetic concept for the preparation of a wide variety of α-hydroxy ketones (Benzoins). The catalyst **5a** demonstrate admirable efficiency with aliphatic aldehydes, while thiazolium salts **5b** or **5c** proved more suitable catalysts in the coupling of aromatic aldehydes (Figure 1.10).[16]

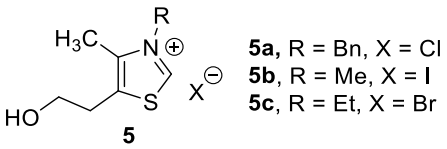
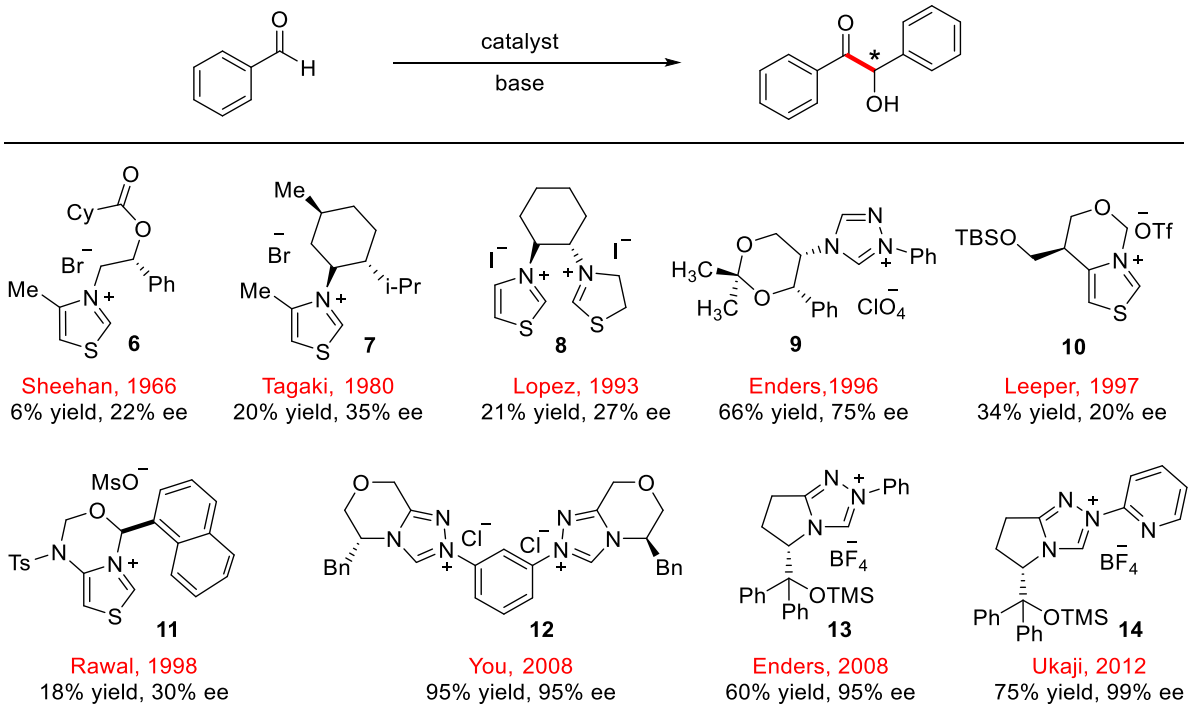


Figure 1.10. Thiazolium salts utilized by Stetter and co-workers

1.2.1. Asymmetric Benzoin Condensation

Asymmetric benzoin condensation usually produces α-hydroxyketones which consist a stereogenic center. Thus, it provides an opportunity for chemists to develop efficient protocols for the asymmetric benzoin or acyloin condensation. In this context, many chemists have made their efforts to develop hetero-azolium catalyzed asymmetric benzoin condensation (Scheme 1.4). Sheehan and Hunneman in 1996 reported the first outcome of the

enantioselective benzoin condensation with a chiral thiazolium NHC precatalyst **6**, however they got the benzoin product in very low yield 6% and enantiomeric excess only 22%.[17] Later to this report, several other chemists like Takagi, Lopez, Leeper, and Rawal also attempted to improve the yield and enantioselectivity of product by varying in the core structure of thiazolium catalysts.[18] Notably, they obtained the benzoin products in modest yield and enantioselectivity with thiazolium-derived NHC catalysts. The major breakthrough in this field was achieved by the Enders and co-workers in 1996, when they established the asymmetric benzoin reaction with 1.25 mol%. of chiral triazolium catalyst **9** to obtain the benzoin product in good yield and enantiomeric excess.[19] Later, it was observed that the use of bicyclic triazolium NHCs catalyst (**12-14**) proved more fruitful rather than a bicyclic thiazolium catalyst, which enhances the yield and enantioselectivities of the products.[20] Afterwards, the computational studies revealed that the triazolium derived precatalyst is more superior than thiazolium derived NHCs catalyst.

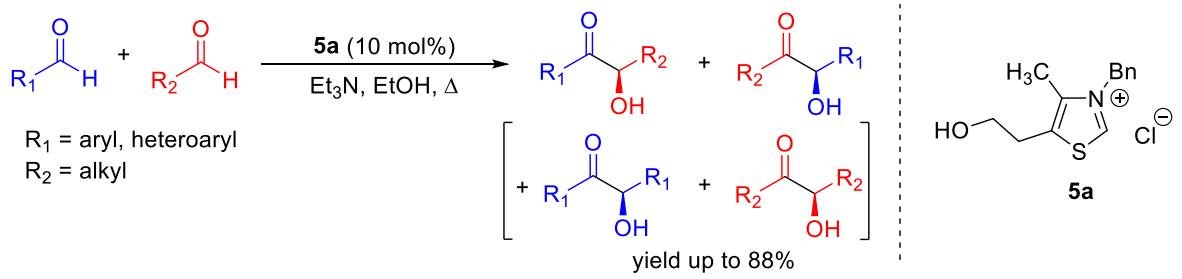


Scheme 1.4. Development of stereoselective benzoin condensation

1.2.2. Intermolecular Crossed Benzoin Condensation

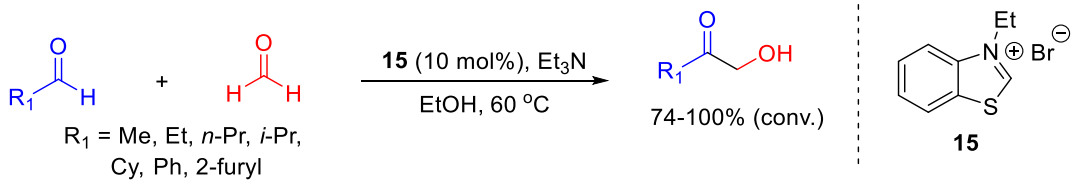
In the NHC-catalyzed crossed benzoin reaction aldehyde molecule coupled with another class of aldehyde, ketone, or imine molecule. The major problem arises in the intermolecular cross-benzoin condensation, is the formation of a mixture of all four possible symmetric and

asymmetric acyloin products. Stetter and co-workers showed that, in some special cases, acyloin condensation could selectively produce one of the two asymmetric acyloins (Scheme 1.5).[21] The observed chemoselectivity of the reaction can be interpreted on the basis of the formation of more stable Breslow intermediate predominantly by one class of aldehydes, which selectively adds to the another class of aldehyde molecule.



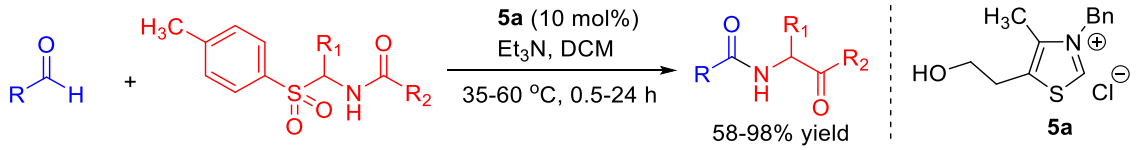
Scheme 1.5. Crossed benzoin condensation of aldehydes

Inoue and co-workers developed the bicyclic thiazolium salt **15** catalyzed selective cross-acyloin condensation of alkyl, aryl, and heteroaryl aldehydes with formaldehyde.[22] This reaction resulted in the formation of exclusively α-hydroxyketone products in good to excellent yields, rather than self-benzoin products. The observed selectivity in this reaction is due to the more stabilizing effects of R-group in the case of alkyl, aryl, and heteroaryl aldehydes (Scheme 1.6).



Scheme 1.6. Selective cross-acyloin condensation of aldehydes with formaldehyde

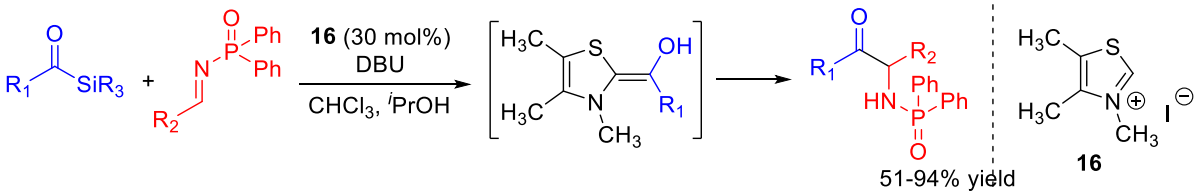
The cross-benzoin reaction is not limited only to the coupling of one aldehyde with another aldehyde molecule, the coupling of aldehydes with imines is also presumable. In this context, Murry et al. first in 2001 developed the preparation of azabenzoin products by the coupling of aldehydes to imines catalyzed by a thiazolium salt **5a**.[23]



Scheme 1.7. Thiazolium catalyzed synthesis of azabenzoin products

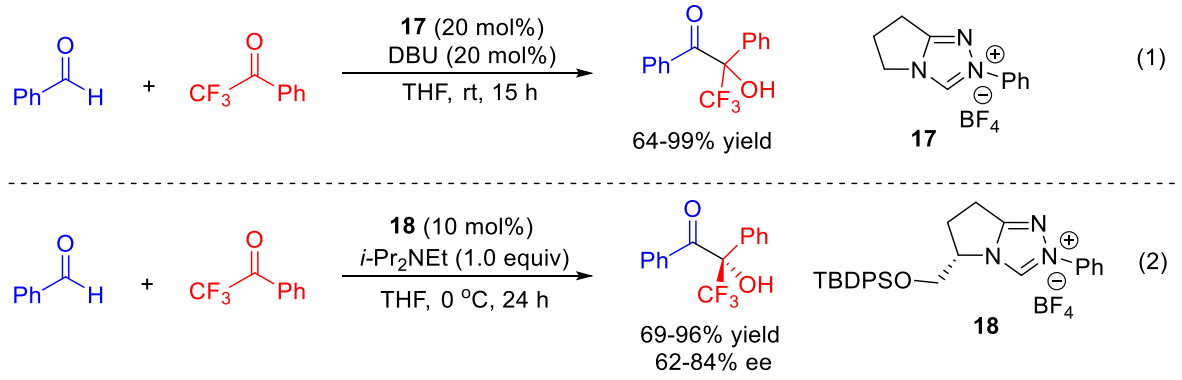
Moreover, in this reaction acyl anion generated from an aldehyde by the action of carbene catalyst, which further reacts with *N*-acylimines to give azabenzoin products in good to excellent yield (Scheme 1.7). Notably, in this reaction, the acylimines are in situ generated from the sulfonylamide in the presence of a base.

Mattson and Scheidt reported the synthesis of *α*-aminoketones *via* the catalytic addition of acylsilanes to *N*-phosphorylimines.[24] In this reaction they used a readily available thiazolium salt **16** as carbene precursor, which adds to acylsilane to form Breslow intermediate *via* demasking of silicon groups in the presence of *i*-PrOH. This acyl anion further reacts with *N*-phosphorylimines to produce *N*-phosphinylated aminoketone products in good to excellent yield (Scheme 1.8). This protocol completely eliminates the possibility of the formation of undesired benzoin products by the self-condensation of aldehydes.



Scheme 1.8. Carbene catalyzed cross-acyloin condensation with acylsilanes

The NHC catalyzed cross-benzoin condensation beyond the coupling of aldehyde to aldehyde offered only limited success. There are limited reports available for the intermolecular cross-benzoin condensation *via* the coupling of aldehydes with ketones.



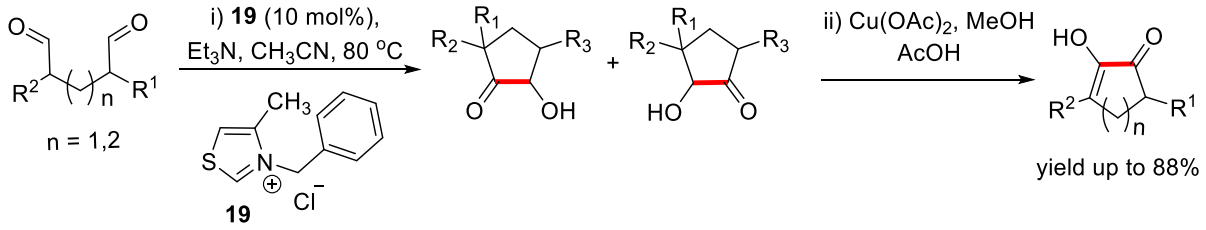
Scheme 1.9. NHC catalyzed preparation of *α*-hydroxy-*α*-trifluoromethyl ketones

In 2009, Enders and Henseler reported a direct intermolecular condensation of aryl aldehydes with aryl trifluoromethyl ketones catalyzed by an achiral NHC catalyst **17** (Scheme 1.9, Eq. 1).[25a] This protocol resulted in the formation of *α*-hydroxy-*α*-trifluoromethyl ketone products

in good to excellent yield (64-99%) and chemo-selectivity. Later, in 2010 the group of Enders also established the chiral triazolium **18** catalyzed synthesis of enantioenriched α-hydroxy-α-trifluoromethyl ketones products in good to excellent yield (69-96%) with good enantioselectivity (Scheme 1.9, Eq. 2).[25b]

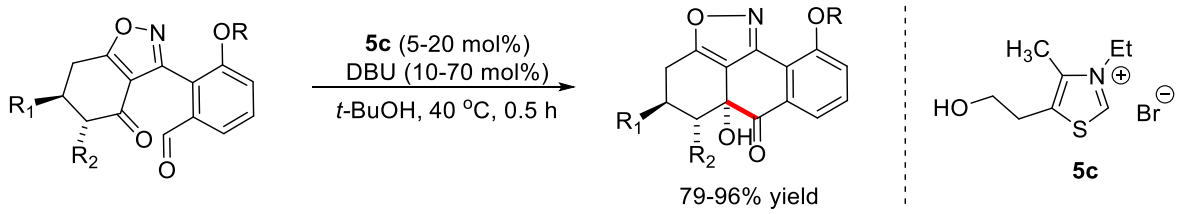
1.2.3. Intramolecular Crossed Benzoin Condensation

As we discussed earlier the NHC-catalyzed acyloin/benzoin reaction and intermolecular benzoin/acyloin reaction, the intramolecular crossed benzoin condensation were also explored. Cookson and Lane in 1976 successfully developed the first intramolecular cross-benzoin reaction using glutaraldehyde derivatives.[26] This reaction resulted in the formation of corresponding 2-hydroxycyclopentanone products by the cyclization of the anhydrous glutaraldehyde derivatives catalyzed by a thiazolium precatalyst **19**. They also showed that the hydroxycyclopentanone undergoes oxidation in the presence of Copper (II) acetate to produce the 2-hydroxycyclopent-2-en-1-one products (Scheme 1.10).



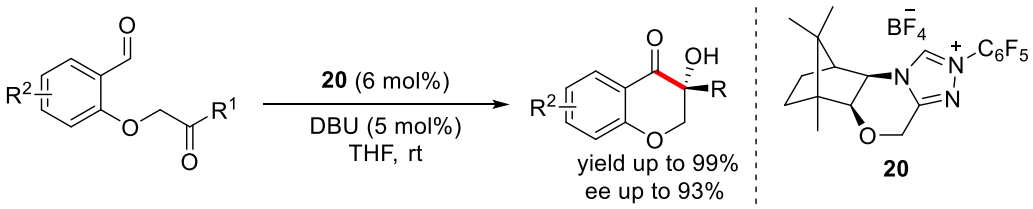
Scheme 1.10. Thiazolium catalyzed intramolecular benzoin condensation of glutaraldehydes

Suzuki and co-workers reported an elegant method for the stereoselective intramolecular crossed benzoin condensation for the preparation of pre-anthraquinones by employing the highly functionalized isoxazole as substrate.[27] The thiazolium salt **5c** catalyzed this reaction to afford the tetracyclic α-hydroxy ketone products in good to excellent yield and diastereoselectivity (Scheme 1.11). The pre-existing stereocenters in the substrates induced the diastereoselective formation of the products.



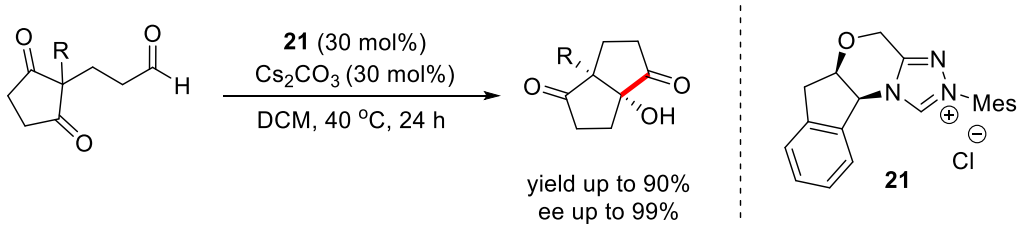
Scheme 1.11. Intramolecular crossed benzoin condensation reported by Suzuki et al.

You and co-workers established the synthesis of chromanone derivatives by the camphor-derived triazolium precatalyst **20** *via* stereoselective intramolecular hetero-coupling of aldehyde and ketone in excellent yield and enantiomeric excess (Scheme 1.12).[28]



Scheme 1.12. NHC-catalyzed enantioselective synthesis of chromanone

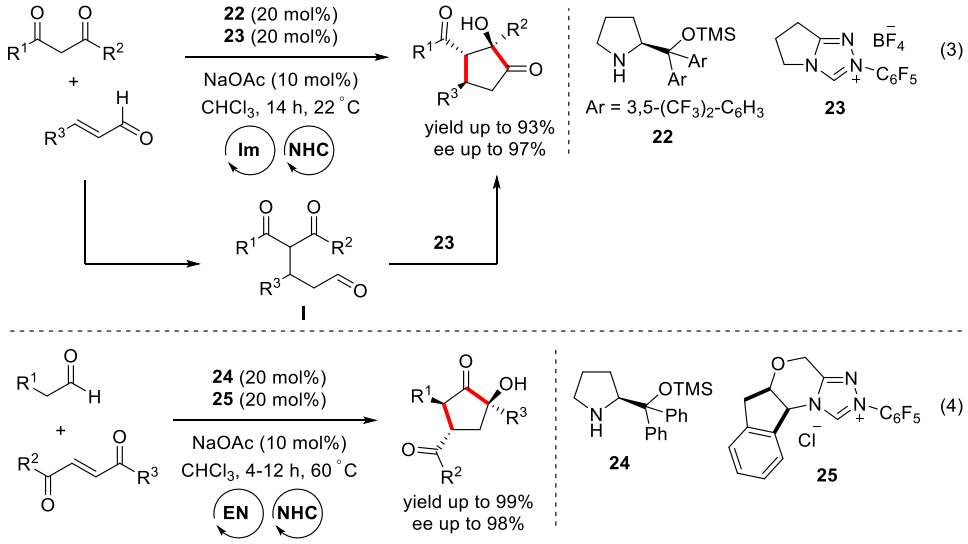
The group of Ema and Sakai developed the chiral NHC catalyst **21** catalyzed synthesis of bicyclic tertiary alcohols *via* intramolecular cross-benzoin condensation.[29] They obtain the bicyclic cyclopentanone products in modest to good yield and enantioselectivity. The most important feature of this product that it consist two stereogenic center adjacent to the both bridgehead carbons (Scheme 1.13)



Scheme 1.13. Synthesis of bicyclic tertiary alcohols by intramolecular cross-benzoin reaction

In 2009, Rovis and co-workers reported the preparation of highly functionalized cyclopentanones by following a multi-catalytic strategy. In this reaction *α,β*-unsaturated aldehydes undergoes Michael addition to diketones, followed by an intramolecular benzoin reaction to afford the product in good to excellent yield with enantiomeric excess (Scheme 1.14, Eq. 3).[30a] This reaction is initiated by the formation of *α,β*-unsaturated iminium by the reaction of enal with amine catalyst **22**, which further undergoes Michael addition with diketone to produce the *δ*-ketoaldehyde intermediate **I**. Thereafter, the NHC catalysts **23** catalyzed the intramolecular cross-benzoin condensation with *δ*-ketoaldehyde to afford the desired product. The stereoselectivity in this reaction was controlled by the chiral amine catalyst **22** not by achiral NHC precatalyst **23**. The control experiments revealed that the Michael addition in this reaction is reversible but the NHC catalysts reacted very quickly with

δ-ketoaldehyde intermediate **I** to give desired product *via* intramolecular cross-benzoin reaction without the destruction of stereoselectivity.

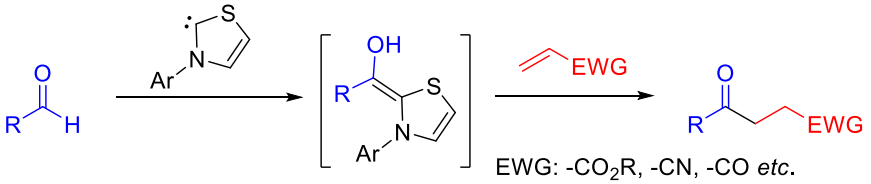


Scheme 1.14. Multicatalytic enantioselective synthesis of cyclopentanols

Later, in 2011 they established conceptually the same protocols with amine/NHC catalyzed cascade reaction with aldehydes and ketones (Scheme 1.14, Eq. 4).[30b] This reaction was started by the addition of amine catalysts **24** to aldehyde to form an enamine, which further reacts with enone (Michael acceptor) to give a δ-ketoaldehyde intermediate **I**. This δ-ketoaldehyde intermediate further reacts in the presence of NHC catalysts **25** *via* an intramolecular cyclization to afford the multi-functionalized cyclopentanol products.

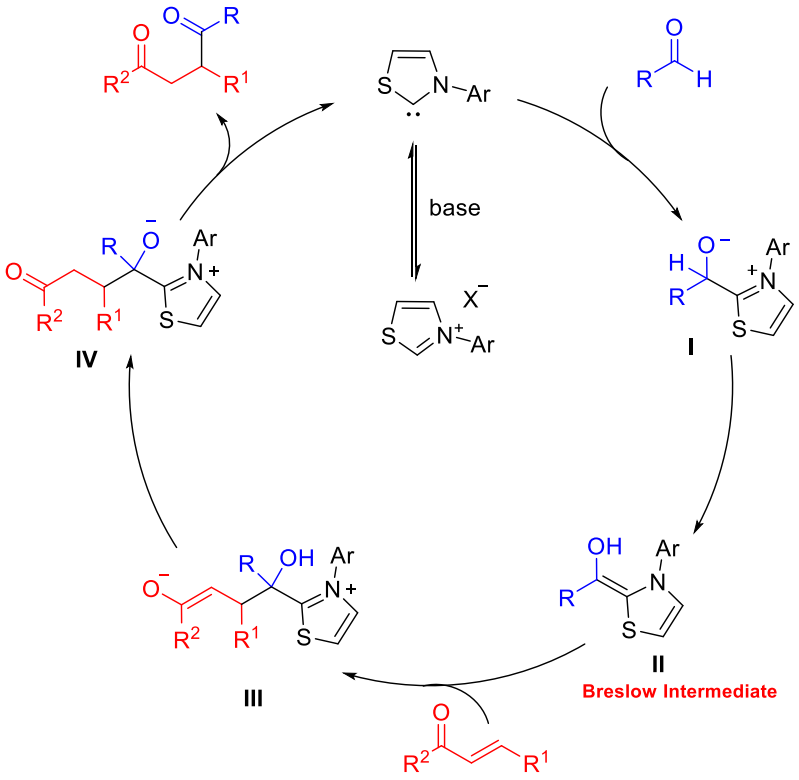
1.3. Stetter Reaction

The addition of an acyl anion generated from aldehydes to the α,β-unsaturated compounds (Michael acceptor) is known as the Stetter reaction. This reaction provides synthetically valuable 1,4-bifunctional compounds, which cannot be easily prepared by using other conventional methods. In 1973 Stetter first addressed the cyanide catalyzed direct addition of aromatic aldehydes to α,β-unsaturated nitriles, and ketones.[31a]



Scheme 1.15. Addition of acyl anion to electron-deficient olefins reported by Stetter

Later in 1976, he explored this reaction by employing thiazolium salt, for the highly selective 1,4-conjugate addition of (hetero)aromatic and aliphatic aldehydes to a variety of electron-deficient olefins (Scheme 1.15).[31b]

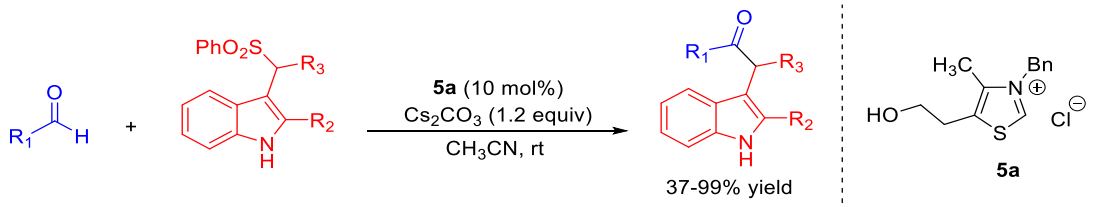


Scheme 1.16. Proposed mechanism for the Stetter reaction

Mechanistically, this Stetter reaction was initiated similarly as in the case of benzoin condensation (Scheme 1.16). First, the NHC catalysts reacts with the aldehyde to form a tetrahedral intermediate **I**. This intermediate **I** further undergoes to 1,2-proton transfer to generate Breslow intermediate **II**. This Breslow intermediate **II** further adds to the Michael acceptor in a 1,4-fashion to form intermediate **III**. The intermediate **III** further gives intermediate **IV** *via* a proton transfer, which after the release of active carbene catalyst afford the desired product.

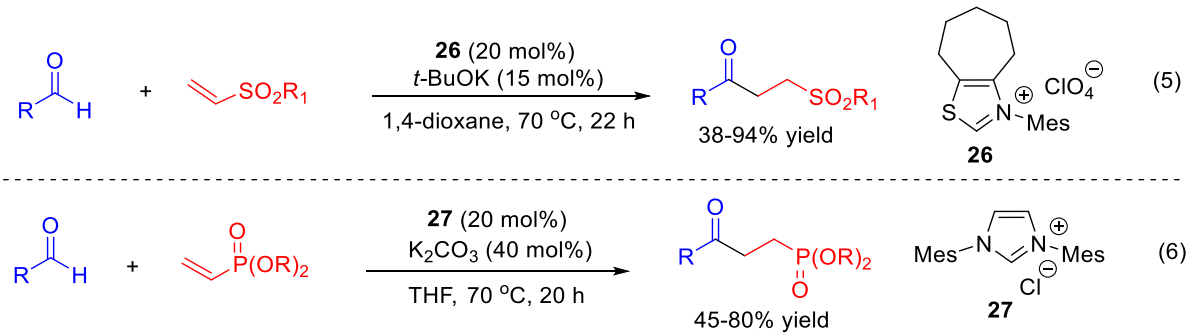
1.3.1. Intermolecular Stetter Reaction

The intermolecular Stetter reactions are very useful to access numerous useful organic precursors. More importantly, most of the intermolecular Stetter reaction was studied by Stetter in 1970s, by using achiral catalysts. In this context, You and co-workers established the thiazolium NHC **5a** catalyzed coupling of aldehydes with aryl-sulfonyl indoles to obtain the desired products in modest to excellent yield (Scheme 1.17).[32]



Scheme 1.17. NHC catalyzed intermolecular coupling of aldehydes with arylsulfonyl indoles

In 2012, Biju and co-workers reported the intermolecular Stetter reaction employing vinyl sulfones as the Michael acceptor.[33a] In this reaction they utilized a bridged thiazolium salt **26** which reacts with aldehydes to form acyl anion that further reacts with vinyl sulfone. This reaction resulted in the formation of *γ*-ketosulfones in modest to excellent yield (Scheme 1.18, Eq. 5). Later to this work in 2014, they successfully reported the coupling of vinylphosphonates with aldehydes in the presence of imidazolium salt **27**. [33b] This reaction produced the valuable *γ*-ketophosphonate in modest to good yield (Scheme 1.18, Eq. 6).

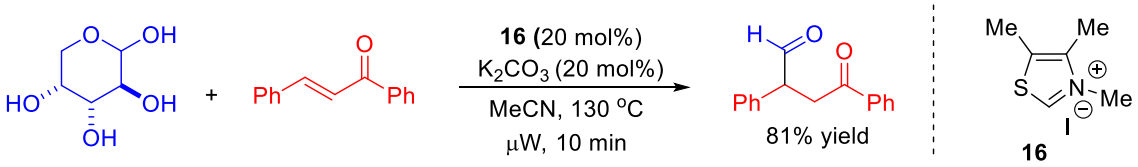


Scheme 1.18. Intermolecular Stetter reaction with vinylsulfones and vinylphosphonates

Unfortunately this reaction was not performed well with unsubstituted aryl, electron-rich aryl, aliphatic and *α,β*-unsaturated aldehyde substrates.

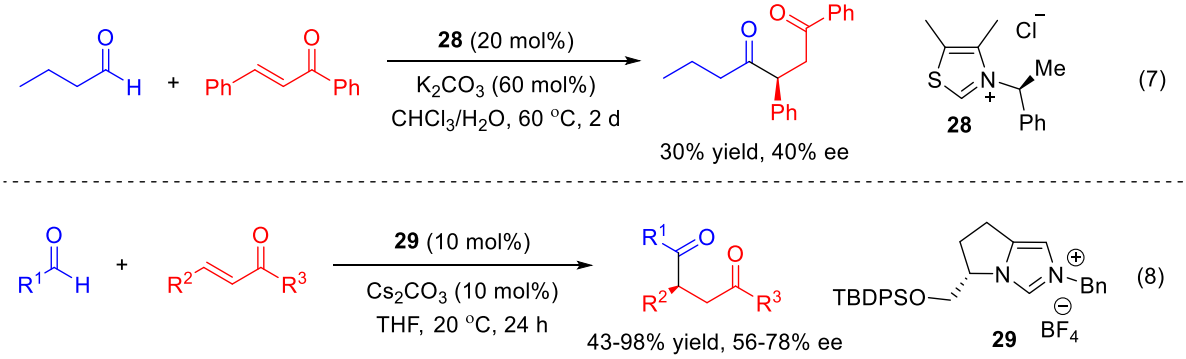
In 2013, Chi and co-workers established the first intermolecular Stetter reaction by the catalytic activation of carbohydrates using thiazolium salt **16**.[34] They used carbohydrates for the formation of formaldehyde equivalents, which subsequently reacts with carbene catalyst to give acyl anion (one-carbon nucleophile). In the process of the generation of acyl anion from carbohydrates involves the NHC catalyzed cleavage of C−C bond *via* a retro-benzoin-type reaction. More importantly, the formaldehyde equivalent was generated from the carbohydrates, which can be easily obtained from readily available biomass. In this Stetter

reaction the acyl anion generated from formaldehyde reacts with chalcones to afford *β*-formyl ketones in good yield (Scheme 1.19).



Scheme 1.19. NHC catalyzed hydroformylation of chalcone derivatives

Despite the achiral NHC catalyzed intermolecular Stetter reaction, the asymmetric intermolecular setter reaction has remained unexplored for many years. In 1989, Enders and co-workers attempted first variant of the asymmetric intermolecual Stetter reaction by the coupling of n-butanal with diphenyl chalcone. The coupling of n-butanal with chalcones was catalyzed by a chiral thiazolium pre-catalyst **28** to afford the valuable 1,4-diketones in 29% yield with 30% ee (Scheme 1.20, Eq. 7).[35a]

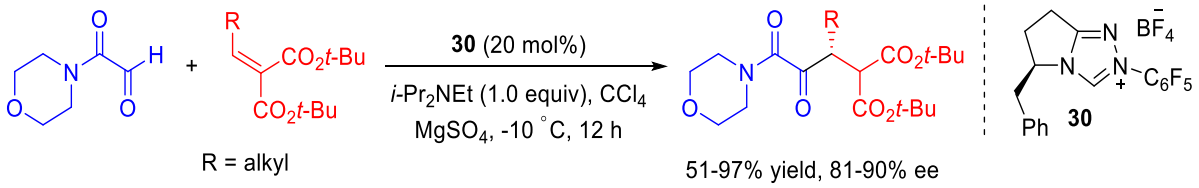


Scheme 1.20. NHC catalyzed enantioselective intermolecular Stetter reaction

However, it was not explored further until unless when in 2008 Enders and Rovis advances the asymmetric intermolecular Stetter reaction. In that direction, Enders and co-workers described the enantioselective synthesis of 1,4-diketones from aryl aldehydes and chalcones.[35b] This reaction was catalyzed by a chiral pyrrolidine derived triazolium catalyst **29**, which frnish 1,4-diketones in good to excellent yield and good enantioselectivity (Scheme 1.20, Eq. 8).

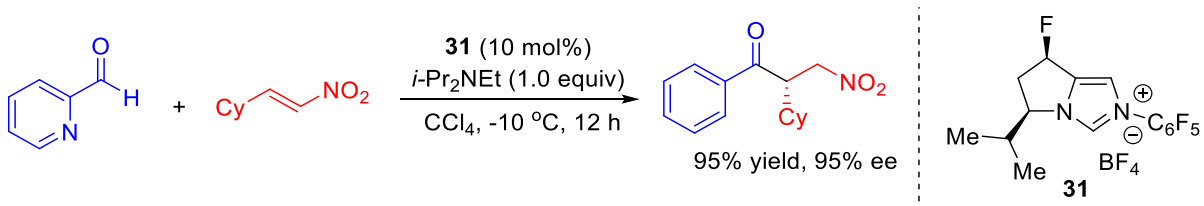
Later, Rovis and co-workers further expanded this asymmetric intermolecular Stetter reaction by using alkylidene malonates and glyoxamides.[36] They reported a highly enantioselective addition of glyoxamides to alkylidene malonates catalyzed by NHC catalyst **30**, which

furnishs the desired Stetter products in 51-97% yield with enantioselectivity up to 99% ee (Scheme 1.21).



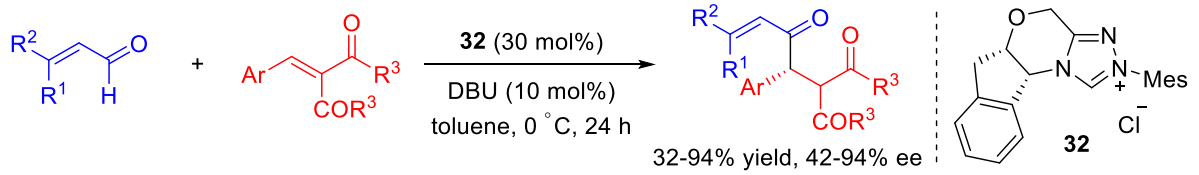
Scheme 1.21. Enantioselective intermolecular Stetter reaction with glyoxamides

Thereafter, Rovis and co-workers also successfully developed the addition of the acyl anion of heteroaromatic aldehydes to nitroalkenes.[37] More importantly, in this reaction fluorine-containing NHC chiral carbene catalyst **31** showed better efficiency and selectivity in comparison to des-fluoro analog. This reaction produces the desired *γ*-keto-nitrones in up to 95% yield and 95% enantioselectivity (Scheme 1.22).



Scheme 1.22. NHC catalyzed coupling of heteroaldehydes with nitroalkenes

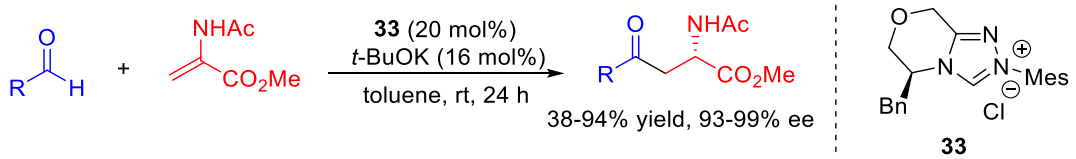
Recently in 2011, Chi and co-workers reported the enantioselective Stetter reaction using *α,β*-unsaturated aldehydes as a coupling partner with modified chalcones.[38] The coupling of *α,β*-unsaturated aldehydes with derivatives of chalcone was catalyzed by NHC catalyst **32**, Which afforded the 1,2,3-tricarbonyl compounds in good to excellent yield and enantioselectivity (Scheme 1.23).



Scheme 1.23. NHC catalyzed Stetter reaction with modified chalcones and enals

In addition, Glorius and co-workers reported the enantioselective intermolecular Stetter reaction by employing methyl 2-acetamidoacrylate as a coupling partner with aldehydes.[39]

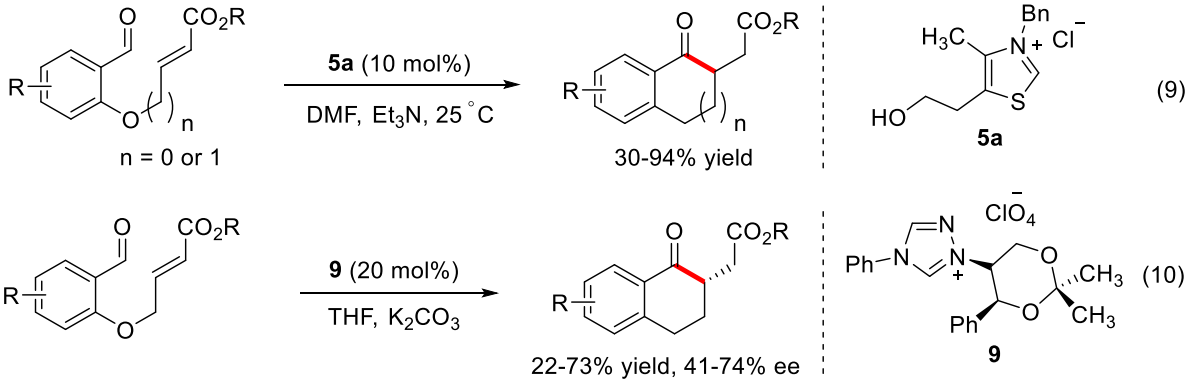
This chiral NHC catalyst **33** catalyzed reaction furnishes the γ-aminoketones in modest to excellent yield and enantioselectivity (Scheme 1.24).



Scheme 1.24. NHC catalyzed Stetter reaction of methyl 2-acetamidoacrylate with aldehydes

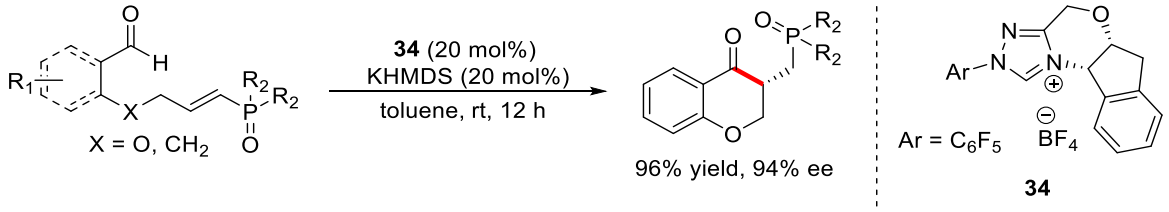
1.3.2. Intramolecular Stetter Reaction

The *N*-heterocyclic carbene catalyzed intramolecular Stetter reaction was remained unexplored until unless when in 1995 Ciganek achieved the thiazolium catalyzed cyclization of 2-formylaryloxycrotonates.[40a] This intramolecular Stetter reaction produces the benzo-annulated pyranones from 2-formylaryloxycrotonates catalyzed by thiazolium catalyst **5a** in 30-94% yield (Scheme 1.25, Eq. 9). Thereafter, in 1996 the group of Ender reported the first NHC-catalyzed stereoselective intramolecular Stetter reaction using 2-formylaryl-oxycrotonates.[40b] The derivatives of 2-formylaryloxycrotonates undergoes cyclization in the presence of chiral triazolium salt **9** to produce the desired chromanones in moderate to good yield and enantioselectivity (Scheme 1.25, Eq. 10).



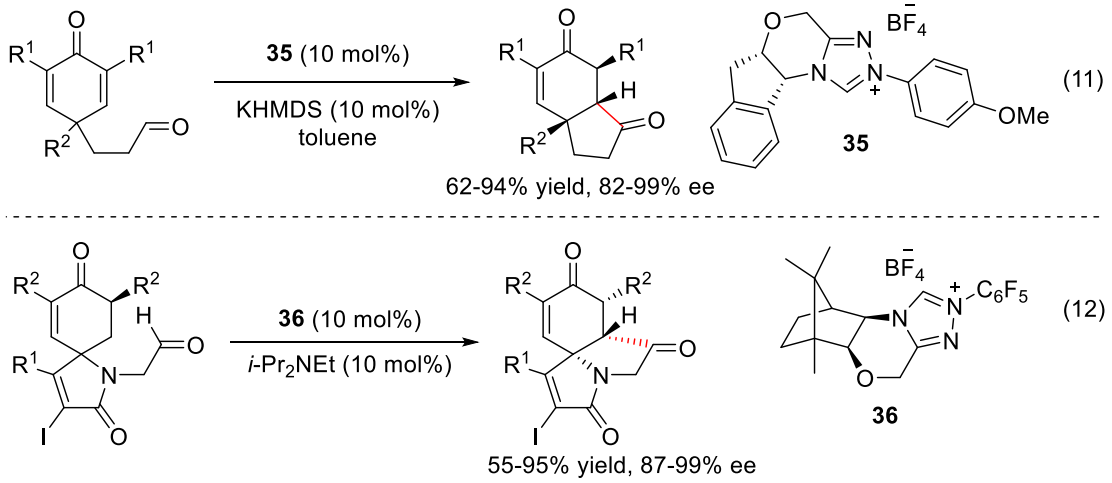
Scheme 1.25. NHC catalyzed intramolecular Stetter reaction of formylaryloxycrotonates

Rovis and colleagues independently, explored this reaction using indanol derived chiral NHC catalyst **34**, by varying heteroatom linkers in the vinylphosphonate, vinylphosphine oxide (Scheme 1.26) etc.[41] This reaction resulted in the formation of benzo-annulated pyranone products in up to 96% yield and enantioselectivity up to 94%.



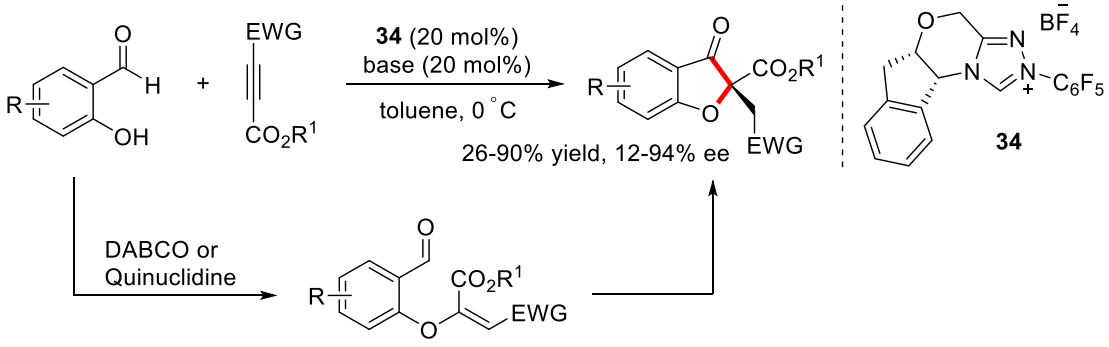
Scheme 1.26. Enantioselective intramolecular Stetter reactions reported by Rovis

In 2006, Rovis and Liu developed an elegant method for the synthesis of hydrobenzofurans by desymmetrization of cyclohexadienones.[42a] In this reaction active carbene is generated from a chiral indanol catalysts **35** in the presence of KHMDS base. Which further reacts with cyclohexadienoes to furnish the desired product in good to excellent yield and enantioselectivity (Scheme 1.27, Eq. 11). Thereafter, You and co-workers developed the desymmetrization of cyclohexadienone by following a similar strategy in the presence of camphor-derived NHC catalysts **36**. This reaction resulted in the formation of a fused tricyclic cyclohexenone product containing three contiguous stereocenters in good to excellent yield and enantioselectivity (Scheme 1.27, Eq. 12).[42b]



Scheme 1.27. NHC-catalyzed desymmetrization of cyclohexadienones

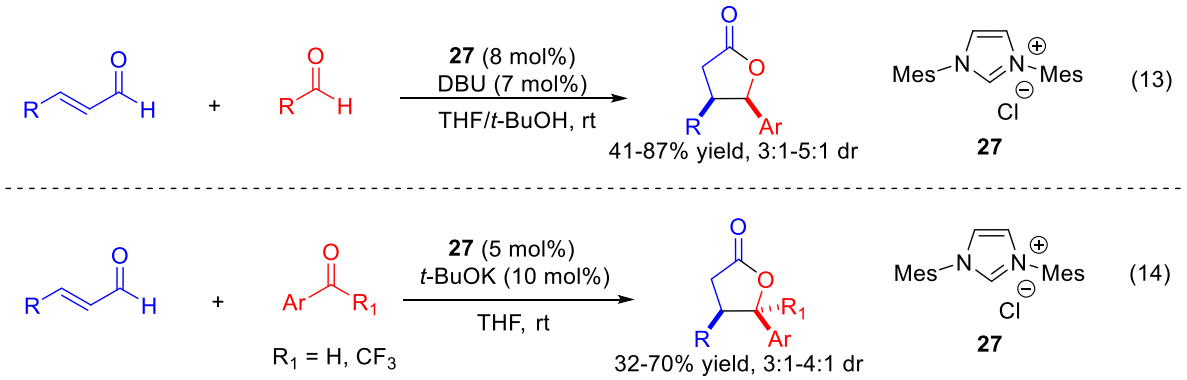
In 2010, Rovis et al. established the one-pot multi-catalytic strategy for the synthesis of benzofuranone derivatives.[43] In this reaction, first DABCO or quinuclidine catalyzed the Michael addition of salicylaldehydes to electrophilic alkynes. Thereafter, indanol derived chiral catalyst **34** catalyzed the enantioselective intramolecular Stetter reaction to afford the desired benzofuranone products (Scheme 1.28).



Scheme 1.28. NHC-catalyzed enantioselective preparation of benzofuranone

1.4. NHC-Catalyzed Reaction *via* Homoenolate Intermediate

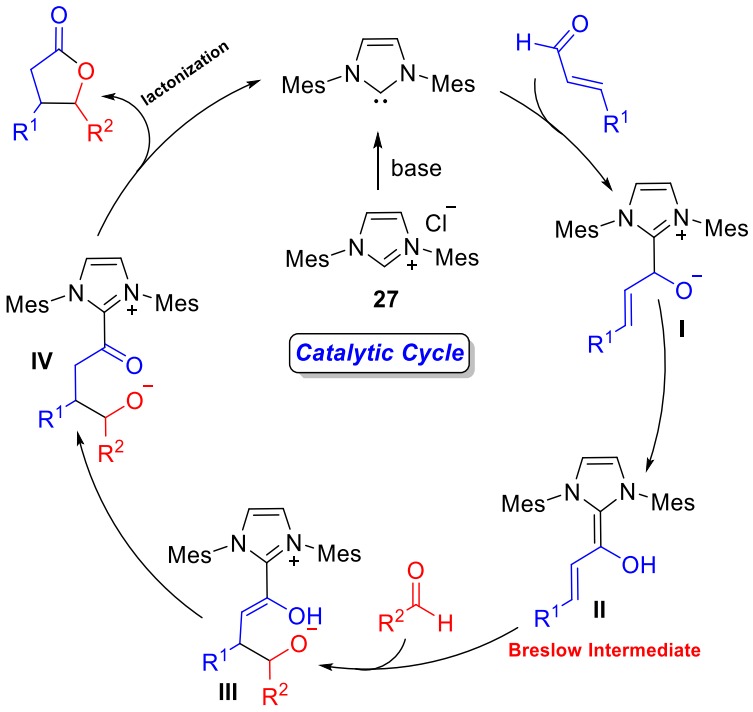
The *N*-heterocyclic carbene catalyzed generation of homoenolate intermediate from *α,β*-unsaturated aldehydes opened a new arena in the organic synthetic chemistry. In 2004, Bode and Glorius independently reported a conceptually new strategy to generate homoenolate from *α,β*-unsaturated aldehydes using NHC catalyst. Eventually, these seminal reports assisted in the exploration of the field of *N*-heterocyclic carbene catalysis *via* homoenolate reactivity. This led to a plethora of new synthetic protocols to access numerous valuable organic products in a single operation. First Bode and co-workers, addressed the homoenolate addition using aryl and propargyl enals with aryl aldehydes for the synthsis of desired *γ*-lactones in moderate to good yields with moderate diastereoselectivity (Scheme 1.29, Eq. 13).[44a] Thereafter, Glorius and co-workers reported the synthesis of *γ*-lactones by using *α,β*-unsaturated aldehydes with aryl aldehydes and trifluoromethyl ketones catalyzed by NHC catalyst **27** in 32-70% yield with 3:1 to 4:1 dr. (Scheme 1.29, Eq. 14).[44b]



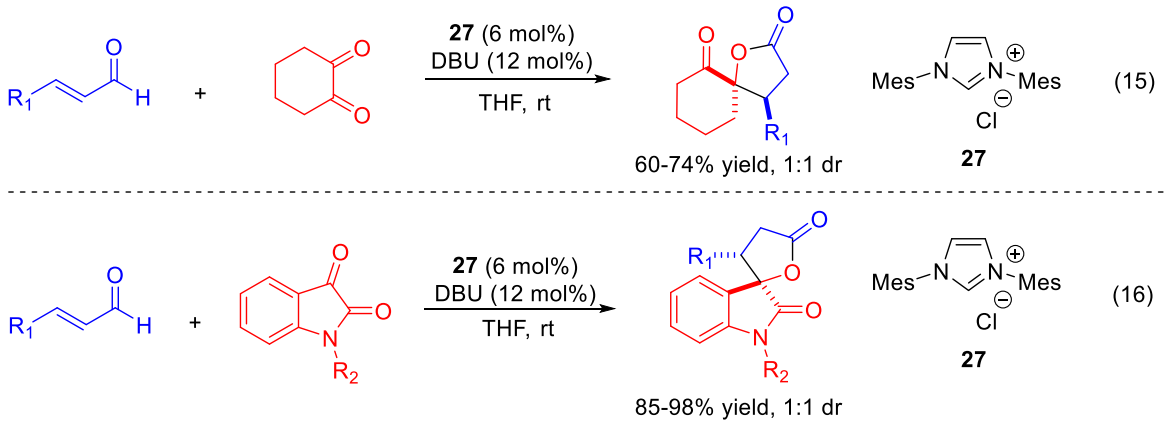
Scheme 1.29. NHC catalyzed synthesis of the *γ*-lactones from enals

These homoenolate addition reactions were proceeded via the formation of extended Breslow intermediate **II** by the addition of carbene catalyst to enals. This extended Breslow

intermediate further reacts with another molecule of aldehyde or ketone *via* the *β*-carbon to form intermediate **III**. This intermediate **III** further undergoes tautomerization to give acyl azolium **IV**. Thereafter, this intermediate *via* an intramolecular cyclization afforded the lactone product and the active NHC catalyst is regenerated (Scheme 1.30).



Scheme 1.30. The postulated mechanism for the NHC catalyzed *γ*-butyrolactone synthesis

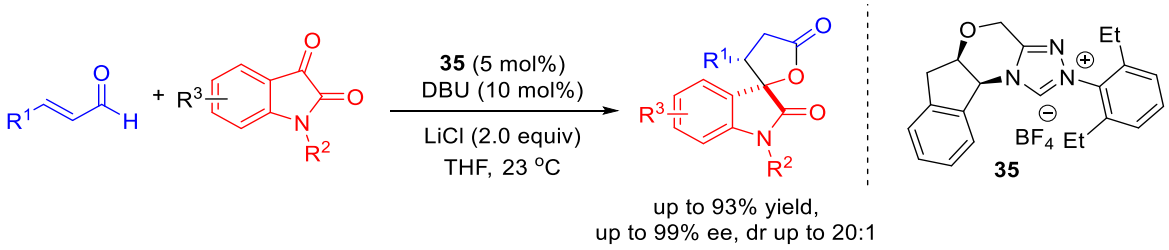


Scheme 1.31. NHC-catalyzed synthesis of *γ*-butyrolactone from 1,2-dicarbonyl compounds

The group of Nair in 2006 developed the preparation of *γ*-lactones *via* homoenolate addition of *α,β*-unsaturated aldehydes to cyclohexane-1,2-dione catalyzed by imidazolium catalyst **27**. This reaction afforded the lactones in good to excellent yield (Scheme 1.31, Eq. 15).[45] Later,

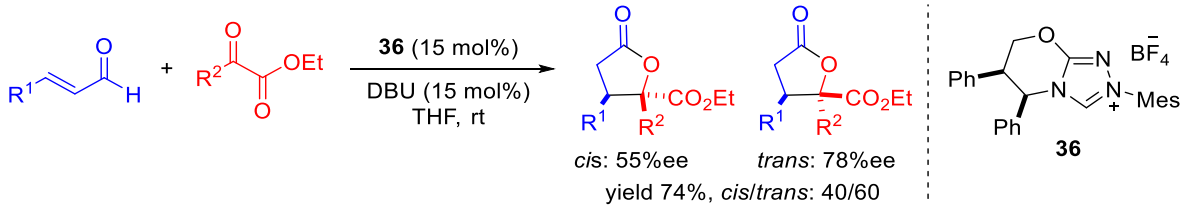
it was recognized that cyclohexane-1,2-dione and *N*-protected isatins are competent electrophiles for this reaction with *α,β*-unsaturated aldehydes. In this reaction to produce spiro-cyclohexanone products in 60-74% yield, and spiro-oxindole *γ*-lactones in 85-98% yield with low diastereoselectivity (1:1) (Scheme 1.31, Eq. 16).

Later, this work was further extended by Scheidt and co-workers, they used the concept of co-operative catalysis for the enantioselective synthesis of *γ*-lactones.[46a] In this raction the homoenolate intermediate generated from *α,β*-unsaturated aldehydes that reacts with isatins. The NHC/LiCl co-operative catalysis strategy produces the corresponding lactones in good to excellent yield (70-93%) and enantioselectivity (86-99%) ee (Scheme 1.32).

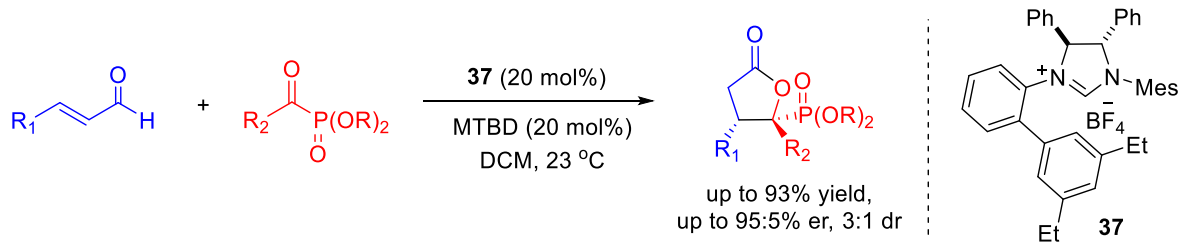


Scheme 1.32. NHC catalyzed enantioselective synthesis of the *γ*-butyrolactone with isatins

You and co-workers reported the enantioselective preparation of *γ*-lactones using enals and glyoxylate derivatives catalyzed by *N*-heterocyclic carbene catalyst **36**.[46b] This reaction preferably produces trans lactones as the major isomer in moderate to good yield and enantioselectivity (Scheme 1.33).



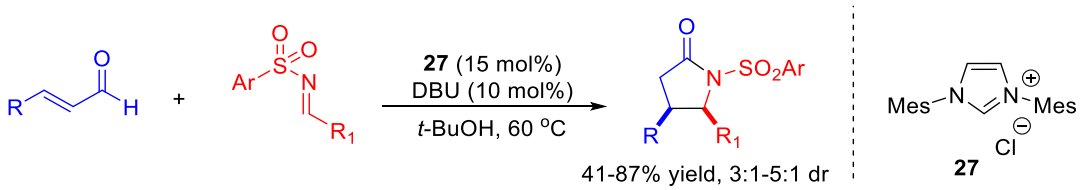
Scheme 1.33. NHC catalyzed synthesis of the *γ*-butyrolactone from glyoxylate derivatives



Scheme 1.34. NHC catalyzed preparation of phosphorylated lactones

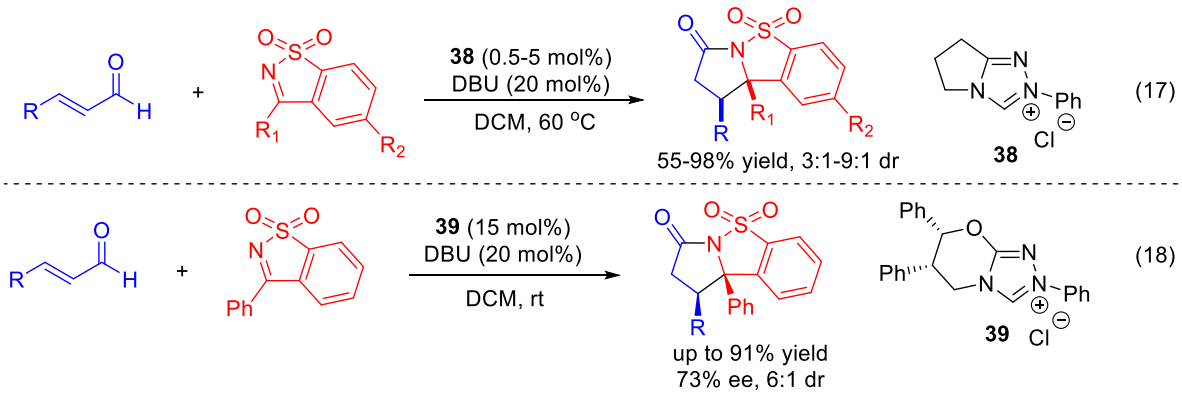
Recently in 2013, Scheidt and co-workers reported the NHC-catalyzed enantioselective homoenolate addition of *α,β*-unsaturated aldehydes with acylphosphonates. This reaction resulted in the formation of phosphorylated *γ*-butyrolactones in good to excellent yield and enantioselectivity.[46c] To develop this strategy they utlized a new designed C_1-symmetric biaryl-saturated imidazolium catalyst. In this reaction *α,β*-unsaturated aldehydes smoothly reacted with acylphosphonates to furnish the desired phosphorylated *γ*-lactones in good to excellent yield and enantioselectivity (Scheme 1.34).

He and Bode in 2005, reported the first time for the NHC catalyzed homoenolate addition of *α,β*-unsaturated aldehydes with imines.[47a] This reaction produced the *γ*-lactam products catalyzed by imidazolium catalyst **27** in modest to good yield and diastereoselectivity (Scheme 1.35).



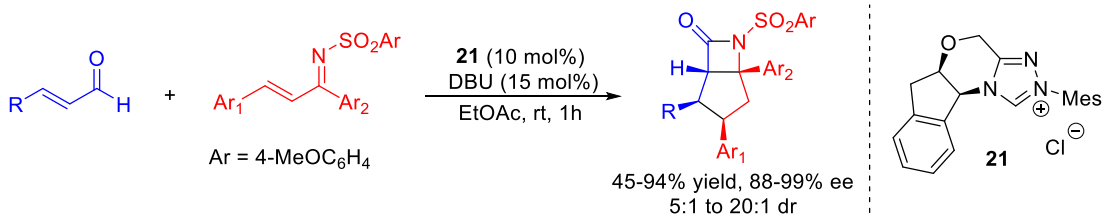
Scheme 1.35. Carbene catalyzed homoenolate addition of enals to sulfonylimines

Later, Bode and co-workers solved the issue of low diastereoselectivity in the formation of *γ*-lactam products by utilizing a cyclic imines.[47b] For this purpose they used saccharin derived ketimines, which is reacted smoothly with aryl and aliphatic enals to furnish the *γ*-lactams in 55-98% yield with dr ranging 1:1 to >20:1 (Scheme 1.36, Eq. 17). The authors also disclosed an asymmetric variant for the same reaction using a chiral NHC catalyst **39**, with saccharin derived ketimines and enals to obtain the *γ*-lactam products in excellent yield 91% and good stereoselectivity (Scheme 1.36, Eq. 1.18).



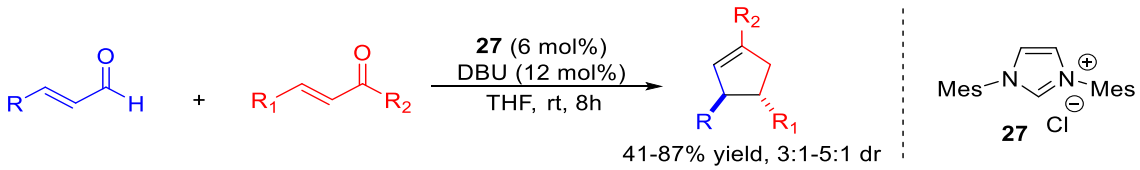
Scheme 1.36. NHC catalyzed homoenolate addition of enals to cyclic sulfonylimines

Later, He and Bode developed the enantioselective preparation of highly substituted cyclopentane fused *β*-lactams from *α,β*-unsaturated *N*-sulfonyl ketimines and enals.[47c] Moreover, this reaction was driven by a chiral indanol derived triazolium catalyst **21**, this reaction was compatible with a variety of *α,β*-unsaturated *N*-sulfonyl ketimines and *α,β*-unsaturated aldehydes. This reaction favoured the formation of *β*-lactam, instead of the dimerization of *α,β*-unsaturated aldehydes or following hetero-Diels-Alder route. This reaction resulted in the formation of *β*-lactams in moderate to excellent yield (45-94%), with excellent enantiomeric excess and stereoselectivity (Scheme 1.37).



Scheme 1.37. NHC catalyzed enantioselective preparation of lactams

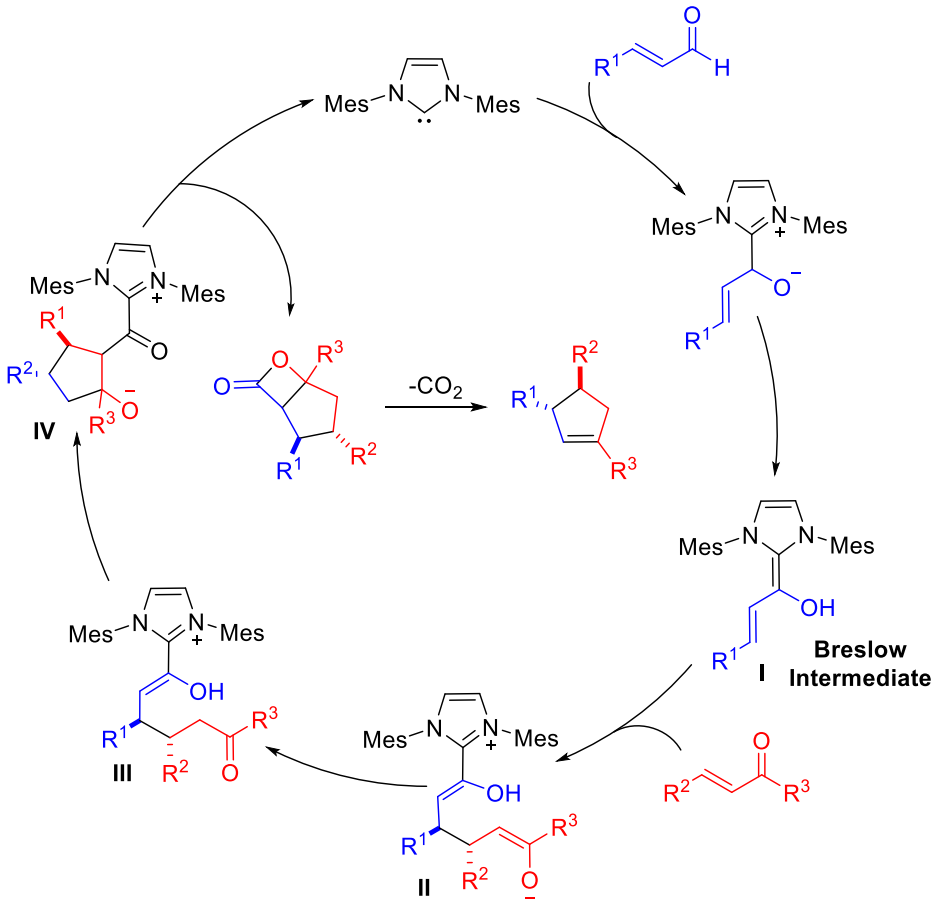
In 2006, Nair et al. reported the first homo-enolate addition of *α,β*-unsaturated aldehydes to chalcones for the synthesis of 1,3,4-trisubstituted cyclopentenes.[48] In this reaction the imidazolium catalyst **27** catalyzed the formaton of bicyclic lactone, which further gives the cyclopentenes by the elimination of CO_2. This reaction was facile with various aryl enals and chalcones to afford cyclopentenes in moderate to good yield (55-88%) and diastereoselectivity (dr 20:1, Scheme 1.38).



Scheme 1.38. NHC catalyzed synthesis of cyclopentenes with enals and enones

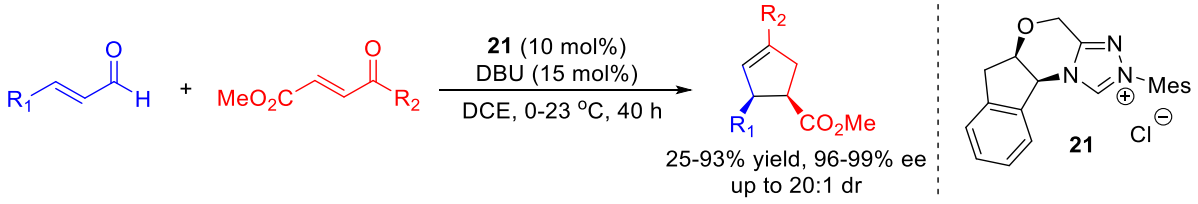
Most accepted mechanism for this reaction is presented in the Scheme 1.39. This reaction begins with the generation of the extended Breslow intermediate **I** form the *α,β*-unsaturated aldehydes by the addition carbene catalyst, thereafter 1,4 addition of the homoenolate intermediate to the chalcone give rise to intermediate **II**. This intermediate **II** further undergoes to tautomerization, which led to the formation of ketone intermediate **III**. This intermediate *via* the enolate addition to carbonyl functionality gives the alkoxide intermediate **IV**. This alkoxide intermediate after the cyclization and the liberation of active carbene

catalyst to produces β-lactone. This β-lactone after the decarboxylation furnishes the trisubstituted cyclopentene product.



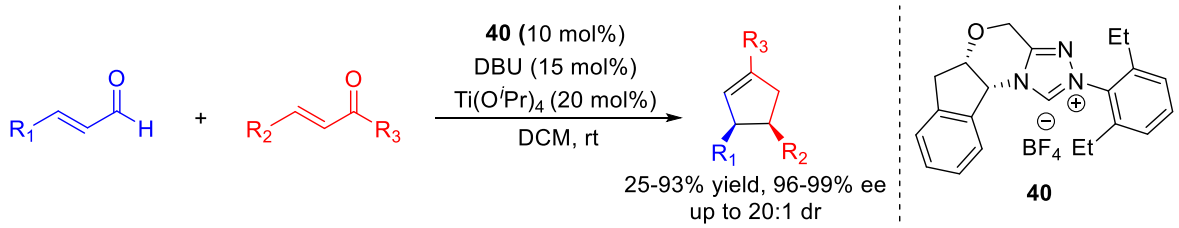
Scheme 1.39. A plausible mechanism for cyclopentene formation.

Shortly after the seminal breakthrough by Nair et al., in 2007 Bode and co-workers, demonstrated an enantioselective synthesis of cyclopentenes by coupling of enals with 4-oxoenoates. In context to the previous work developed by Nair and coworkers, which mainly gives *trans* cyclopentene, in this work exclusively produced *cis*-isomer of cyclopentenes. This reaction gives the cyclopentenes in good to excellent yield with excellent enantioselectivity (Scheme 1.40).[49a]



Scheme 1.40. NHC catalyzed enantioselective synthesis of tri-substituted cyclopentenes

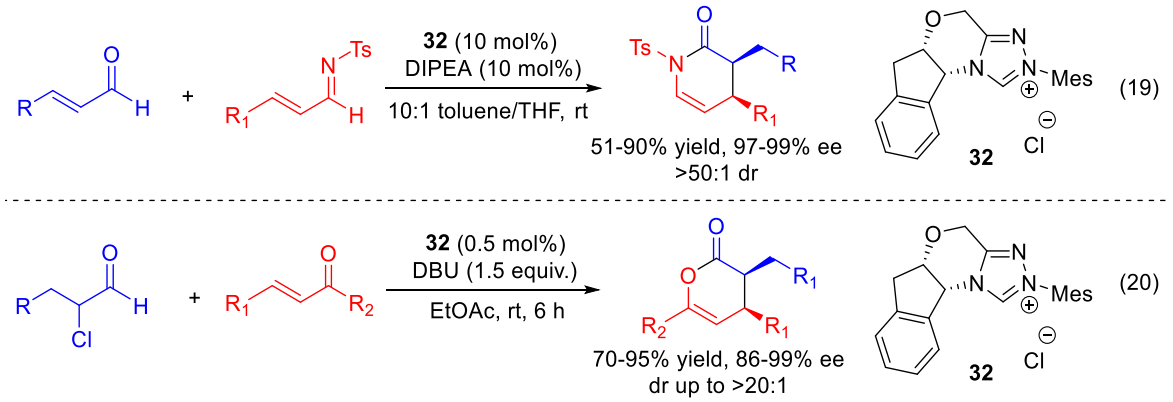
Similarly, in 2010 the group of Scheidt developed the selective preparation of tri-substituted *cis*-cyclopentene with the same starting materials used in the previous work.[49b] The observed selectivity in this reaction was achieved by employing a titanium isopropoxide Lewis acid co-catalyst with the chiral NHC catalyst **40**. This reaction gives cyclopentenes in moderate to excellent yield and enantioselectivity (98-99%, Scheme 1.41).



Scheme 1.41. NHC and cocatalyst catalyzed synthesis of trisubstituted cyclopentenes

1.5. NHC-Catalyzed Reaction *via* Enolate Intermediate

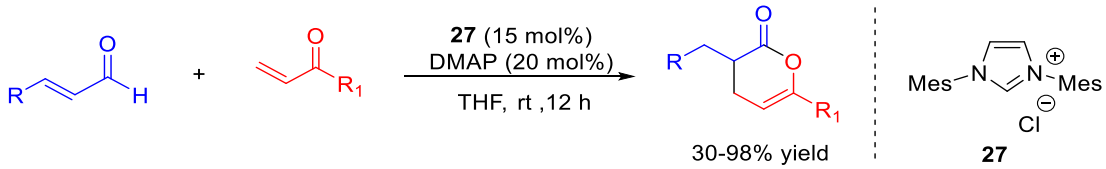
An enolate intermediate is usually formed by the *β*-protonation of the homoenolate intermediate generated by the reaction between *α,β*-unsaturated aldehydes and NHC catalyst. The NHC-catalyzed enolate addition were mainly explored in 2006, after the pioneering work reported by Bode and colleagues. They developed the carbene-catalyzed enantioselective synthesis of dihydropyridinone derivatives by using enals bearing a electron-withdrawing groups (EWGs) at the *β*-position with *α,β*-unsaturated imines (Scheme 1.42, Eq. 19).[50a] Subsequently, in the same year they also successfully developed an elegant protocol for the NHC-catalyzed synthesis of enantioenriched *δ*-lactones *via* enolate addition of *α*-chloro aldehydes with *α,β*-unsaturated enones.[50b] This reaction is compatible with the various derivatives of *α*-chloro aldehydes and chalcones catalyzed by NHC catalyst **32**. More importantly, this reaction proceeds with low catalyst loading of NHC catalyst 0.5 mol% to



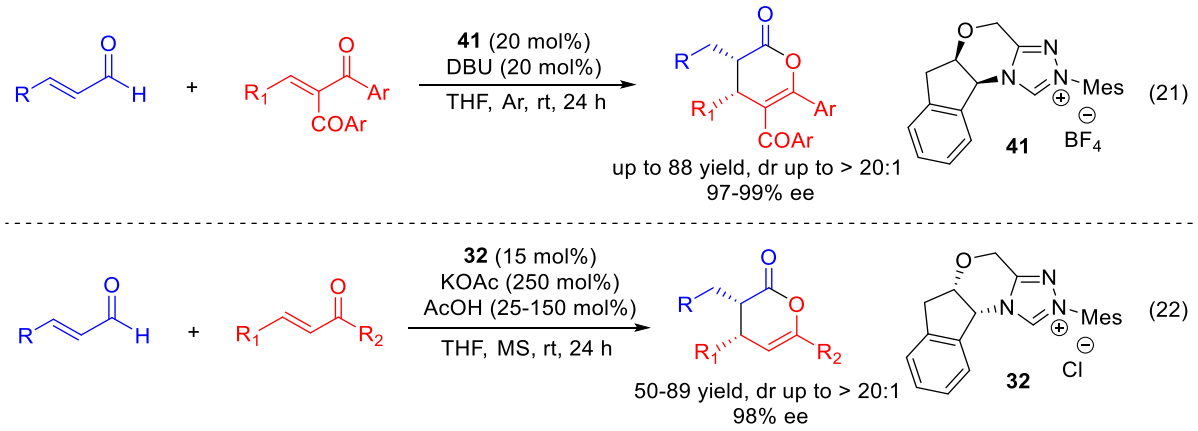
Scheme 1.42. NHC-catalyzed preparation of dihydropyridines and dihydropyranones

afford the δ-lactones in 70-95% yield with excellent enantioselectivity (Scheme 1.42, Eq. 20).

Later in 2010, the research group of Nair developed the first NHC catalyzed enolate addition by using α,β-unsaturated aldehydes with β-unsubstituted vinyl ketones as the electrophiles (Scheme 1.43).[51] This reaction produced δ-lactones in good yields, but unfortunately, phenyl vinyl ketone not worked well under their standard reaction condition and produced the desired product in a very low amount.



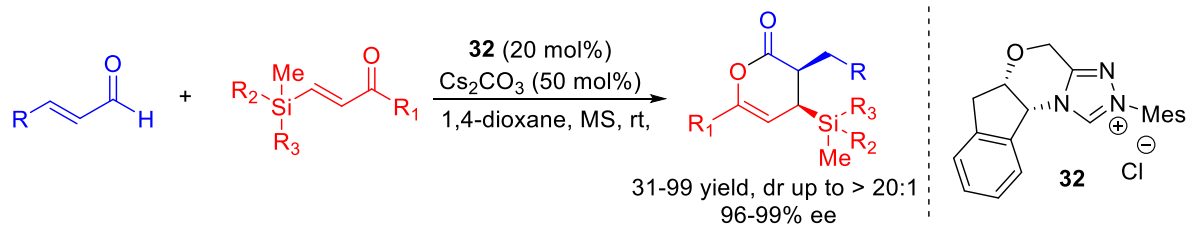
Scheme 1.43. NHC catalyzed enolate addition of enals to vinyl ketones



Scheme 1.44. NHC catalyzed enolate addition reported by Chi and co-workers using enones

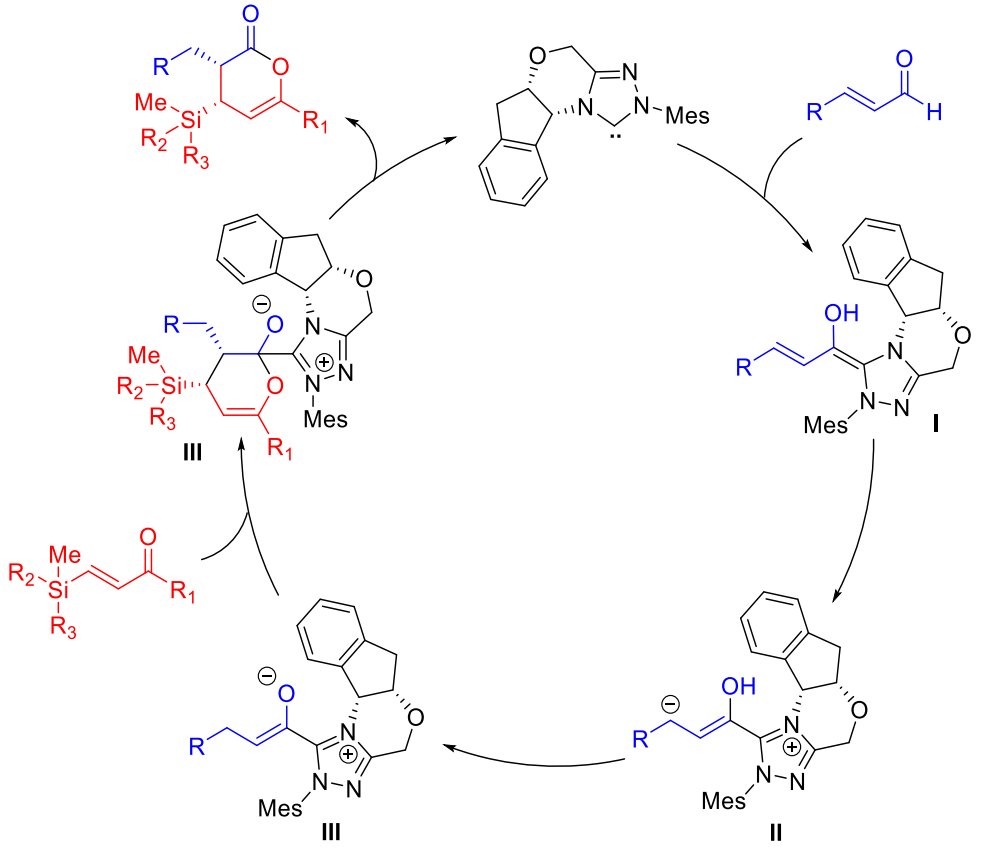
Chi and co-workers in 2011, developed the *N*-heterocyclic carbene **41** catalyzed enolate addition using modified chalcones as the electrophiles bearing an additional carbonyl group with α,β-unsaturated aldehydes.[52a] This reaction predominantly afforded the δ-lactones rather than cyclopentenes in good yield and enantioselectivity (Scheme 1.44, Eq. 21).

Afterward, in 2013, Chi and co-workers yet again reported the NHC **32** catalyzed controlled enolate addition of chalcones to α,β-unsaturated aldehydes in presence of acetic acid.[52b] They developed this reaction by controlling the formation of homoenolate intermediate in the presence of acid co-catalysts, which resulted in the selective formation of enolate intermediate from α,β-unsaturated aldehydes under carbene catalysis. This reaction resulted in the formation of trisubstituted δ-lactones in 50-89% yield with excellent enantioselectivity (Scheme 1.44, Eq. 22).



Scheme 1.45. NHC catalyzed enolate addition of enals to *β*-silylenones

Recently, in 2018, Fu and Huwang established an *N*-heterocyclic carbene catalyzed highly efficient route to access enantioenriched organosilanes from *α,β*-unsaturated aldehydes and *β*-silylenones.[53] For the development of this reaction they used *β*-silylenones as a new electrophile under the carbene catalysis. This reaction resulted in the formation of 4-silylated *δ*-lactones containing two adjacent stereo-centers in excellent yields with excellent stereoselectivity (Scheme 1.45).



Scheme 1.46. Proposed mechanism of the enolate addition of enals to *β*-silylenones

The proposed mechanism for this transformation is shown in (Scheme 1.46). The reaction was started by the addition of carbene catalyst to *α,β*-unsaturated aldehydes, which led to the formation of extended Breslow intermediate *via* 1,2-proton shift. This extended Breslow

intermediate **I** further undergo *β*-protonation to generate enolate intermediate **II**. This enolate intermediate **II** further reacts with *β*-silylenones to form Diels-alder cycloadduct **III**. This Diels-alder cycloadduct further produces the silylated lactones after release of the active carbene catalyst.

1.6. Conclusion

In conclusion, the organocatalysts have been recognized as an attractive alternative tool over transition metal-based catalysts due to their benign nature, lower cost, robustness and non-toxicity. Among them, *N*-heterocyclic carbene catalysts have made a broad impact on the field of organic chemistry due to their unique mode of activation of the substrates. Interestingly, different products can be prepared from the same set of substrates by varying the reaction conditions. These catalysts have been efficiently used even for the remote functionalization of the substrates, such as the *β*- and *γ*-carbons in enals. Despite this notable development in the field of NHC-catalysis, the literature has a very limited reports on the metal-free organocatalytic stereoselective methods for the preparation of organophosphorus and organoselenium compounds. Therefore, a further study in this area is highly desired.

1.7. Aim of the Thesis

The aim of the thesis is to develop novel metal-free methods for the preparation of different class of organophosphorus and organoselenium compounds, as described briefly below:

In this context, in chapter 2 we have described the first *N*-heterocyclic carbene catalyzed highly enantioselective method for intermolecular enolate addition of *α,β*-unsaturated aldehydes to *β*-phosphorylenones. This class of Michael acceptors with a very bulkier substituent at the *β*-position has remained challenging under carbene-catalysis. The phosphorylated *δ*-lactones were obtained in excellent yields and enantioselectivity. The 4-phosphorylated *δ*-lactones produced multi-functionalized chiral *γ*-ketophosphoryl esters and amides is in quantitative yield.

In chapter 3 we have decribed a global method for the preparation of C3-phosphorylated pyrroles, furans and thiophenes and 4-phosphorylated dihydropyridazines under a metal-free organocatalytic reaction condition. To achieve this, we have developed the first NHC-catalyzed Stetter reaction between vinylphosphonates and aldehydes to access *α*-phosphorylated 1,4-diketones, followed by a cyclization reaction. These phosphorylated 1,4-

diketones could be efficiently converted into C3-phosphorylated pyrroles, furans and thiophenes, and C4-phosphorylated dihydropyridazines.

In chapter 4 we have presented the first *N*-heterocyclic carbene catalyzed controlled cross acyloin condensation of acyl phosphonates and aldehydes *via* phospha-Brook rearrangement. This is the first organocatalytic phospha-Brook rearrangement that generally required metal cyanides as the catalysts previously. In addition, acyl anions from the acyl phosphonates has been generated under carbene catalyst for the first time.

In chapter 5 we described the first *N*-heterocyclic Carbene (NHC)-catalyzed highly enantioselective synthesis of selenylated *δ*-lactones *via* [4+2] annulation of *α,β*-unsaturated aldehydes with vinylselenides. This method is highly atom economical and proceeds under transition metal-free condition. To achieve this, we have used vinylselenides as the new Michael acceptor under carbene catalysis. This study is a valuable addition to the limited literature methods available for the preparation of C4-unsubstituted chiral *δ*-lactones. These class of *β*-unsubstituted enones have remained challenging substrates for the cycloaddition reaction under NHC-catalysis *via* homoenolate intermediates.

1.8. References

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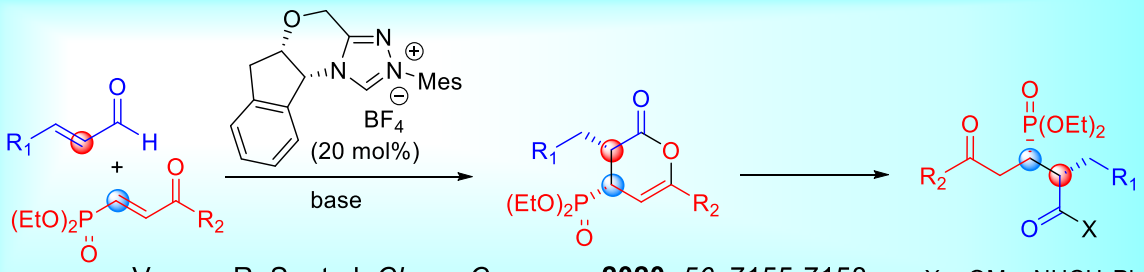
Chapter 2

Carbene Catalyzed Highly Enantioselective Preparation of 4-Phosphorylated δ-Lactones

Organophosphorus compounds exhibit numerous biological properties with potential applications as enzyme inhibitors, pharmaceuticals, agrochemicals, antibacterial, antiviral, and antifungal agents. Among them, phosphorylated lactones have been used in the treatment of numerous antiviral diseases in humans. While 2-pyranylphosphonates (a *δ*-lactones), perform antibacterial and antiviral action against X. *oryzae pv. oryzae* and Tobacco Mosaic Virus respectively. On account of their valuable bioactive properties, the metal-free organocatalyzed enantioselective preparation of organophosphorus compounds has gained significant attention. Herein, we have developed the first, *N*-heterocyclic carbene catalyzed highly enantioselective method for intermolecular enolate addition of *α,β*-unsaturated aldehydes to *β*-phosphorylenones. This class of Michael acceptors with a very bulkier substituent at the *β*-position has remained challenging under carbene-catalysis. The phosphorylated *δ*-lactones were obtained in excellent yields and enantioselectivity. The 4-phosphorylated *δ*-lactones produced multi-functionalized chiral *γ*-ketophosphoryl esters and amides is in quantitative yield.



Verma, R. S. et al. *Chem. Commun.* **2020**, *56*, 7155-7158

X = OMe, $NHCH_2Ph$

2.1. Introduction

The *δ*-lactones are the six-membered hetero-cyclic compounds, consisting oxygen atom in the ring (Figure 2.1). The substituted enol *δ*-lactones are well known as 3,4-dihydropyranones, and are extensively recognized as essential building blocks in the synthesis of numerous biologically active compounds.[1] Apart from that, they are attractive intermediates for the synthesis of cyclic enamines, 2-pyranones, *γ*-lactones, etc.

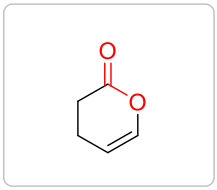


Figure 2.1. General structure of *δ*-lactones

In addition, the phosphorus containing compounds show biological properties with unbroken potential applications as enzyme inhibitors, pharmaceuticals, agrochemicals, antibacterial, antiviral and antifungal agents (Figure 3.1).[2] Compounds **A** and **B** are used as enzyme inhibitor, compound **C** is used for the treatment of osteoporosis (a bone disease) and compound **D** is used as herbicide and fungicide. The compound **E** and **F** used in the treatment of bacterial and cardiovascular disease. Among them, phosphorus-containing lactones **G** used in the treatment of numerous antiviral diseases in humans. While 2-pyranylphosphonates (a *δ*-lactone) **H** perform antibacterial action against X. *oryzae pv. oryzae* and antiviral action against Tobacco Mosaic Virus.[3] In addition, they are also inseparable part of metal catalysts and used as ligands in the various organic transformations.[4]

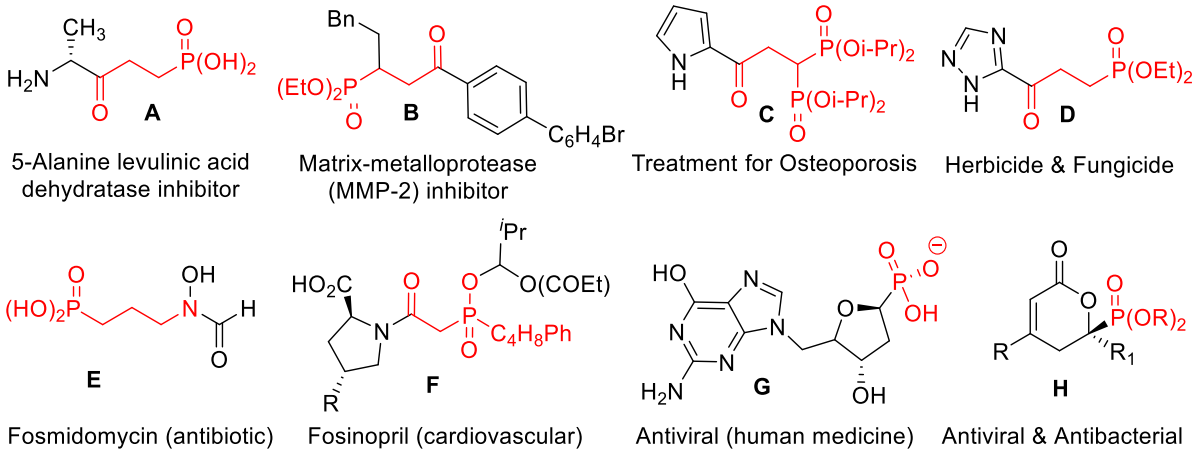


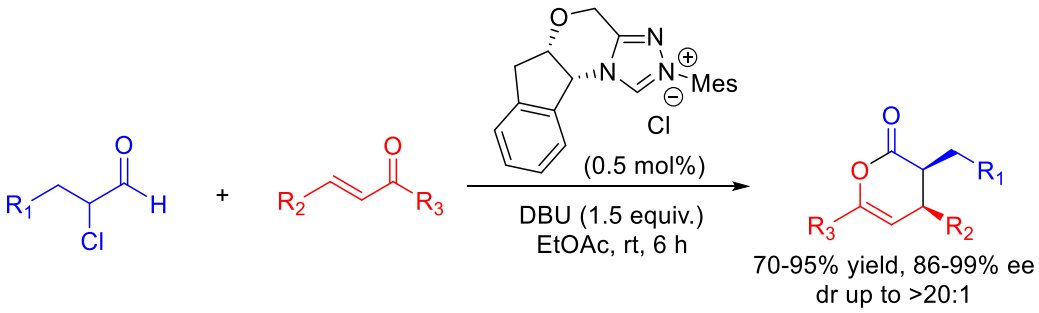
Figure 2.2: Biologically active phosphorylated lactones and *γ*-ketophosphonates

The phosphorylated *δ*-lactones behaves as a synthetic precursor for the preparation of challenging multi-functionalized chiral *β*-ketophosphoryl esters and amides. Thus, the organocatalytic transition metal-free enantioselective synthesis of phosphorus-containing *δ*-lactones is highly desired.

2.2. Literature Review for the Carbene Catalyzed Preparation of Lactones

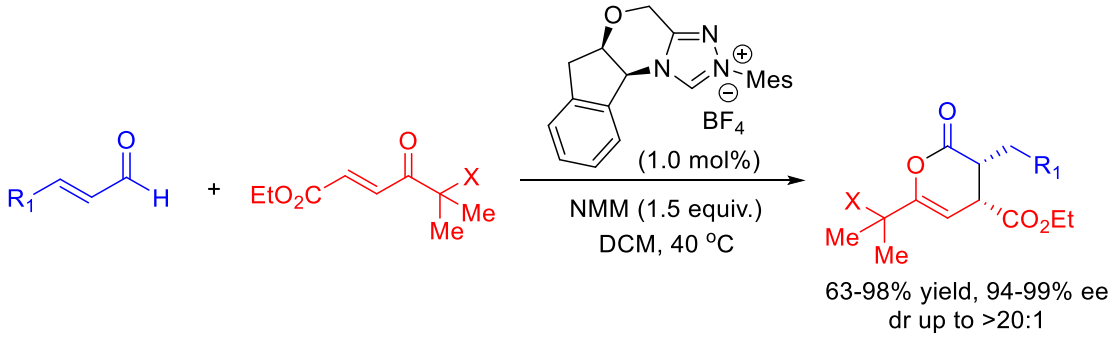
2.2.1. NHC-Catalyzed Preparation of *δ*-Lactones

The *N*-heterocyclic carbene catalysis has emerged as powerful tools for the construction of *δ*-lactones *via* enolate additions. In 2006, Bode and co-workers established the NHC-catalyzed enolate addition of *α*-chloro aldehydes with *α,β*-unsaturated enones for the enantioselective synthesis of *δ*-lactones.[5] In this reaction *α*-chloro aldehydes having aryl and alkyl substituents reacted with a variety of electron-withdrawing *α,β*-unsaturated enones to produce the desired lactones in good to excellent yield and enantioselectivity. Notably, low catalyst loading of carbene precursor required for the synthesis of *δ*-lactones in good to excellent yield with excellent enantioselectivity and diastereoselectivity. The (Z)-enolate generated from *α*-chloro aldehydes preferably reacts with chalcones in endo mode of cycloaddition to produce *cis*-diastereoselectivity in the products (Scheme 2.6).



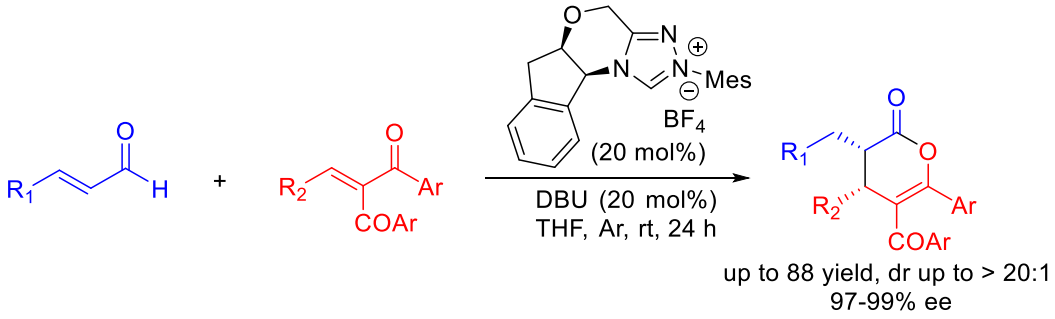
Scheme 2.6. Carbene catalyzed enantioselective synthesis of *δ*-lactones from enones

Later, they found that *α,β*-unsaturated aldehydes (enals) can also be utilized for the enantioselective preparation of dihydropranones.[6] The enolate intermediate could be generated from *α,β*-unsaturated aldehydes by the treatment of a mild base NMM (*N*-methylmorpholine), which further reacts with different *α*-hydroxy enones or *α*-amino enones to form pyranone products (Scheme 2.7). Furthermore, the computational experiments are used to explain the great amount of enantioselectivity which indicates the formation of the non-conjugated complex with azolium and the enolate olefin.

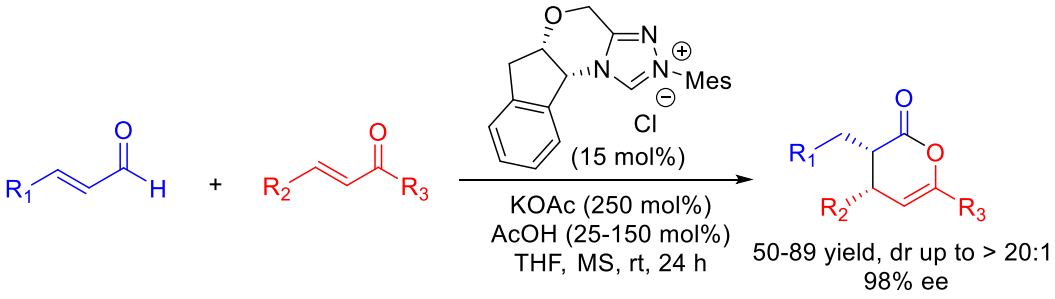


Scheme 2.7. NHC-catalyzed enolate addition to *α*-hydroxy enones

Chi and coworkers in 2011 developed the NHC catalyzed enolate addition using modified chalcones (alkylidene diketones) as the electrophiles with enals.[7] The enolate reactivity of *α,β*-unsaturated aldehydes is observed under carbene catalysis with *α,β*-unsaturated enones bearing an electron-withdrawing group at the *α*-position. The *α,β*-unsaturated aldehydes bearing aryl and heteroaryl substituent reacted smoothly with *α,β*-unsaturated enones to afford the lactones in good yields and enantioselectivities (Scheme 2.8).



Scheme 2.8. NHC-catalyzed synthesis of *δ*-lactones from modified chalcones



Scheme 2.9. NHC-catalyzed controlled enolate addition to chalcones

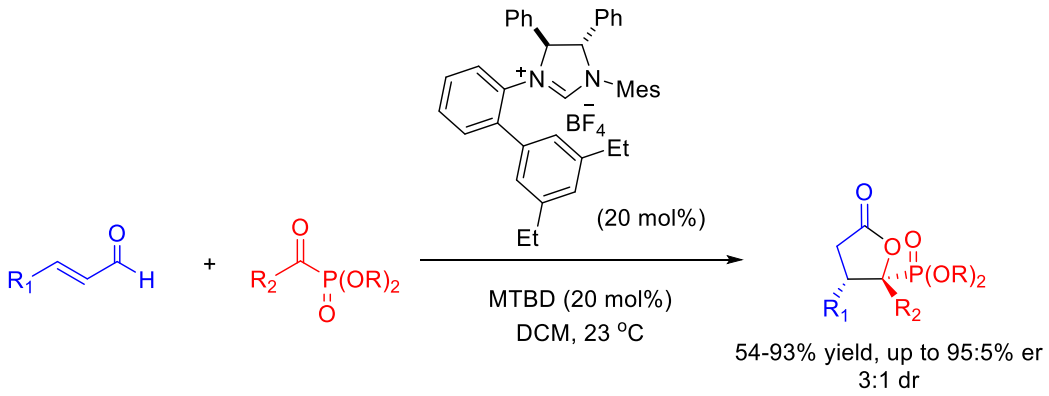
In 2013, Chi and coworkers successfully reported the controlled enolate addition of chalcones with *α,β*-unsaturated aldehydes in presence of acid and NHC catalyst.[8] In this reaction, a substrate-controlled selective formation of enolates over homoenolate intermediate using NHC-catalyst was observed. The *α,β*-unsaturated aldehydes reacts with a variety of chalcones

to produce trisubstituted *δ*-lactones with excellent enantioselectivity (Scheme 1.32). The acetic acid (AcOH) are used as co-catalysts to control the reaction pathways, allowing for individual preparation of the diverse products from the same substrates (Scheme 2.9).

2.2.2. NHC-Catalyzed Preparation of Phosphorylated Lactones

As discussed , there are many elegant methods available for the preparation of *γ*-lactones and *δ*-lactones, but there are very limited reports for the enantioselective preparation of phosphorylated lactones.

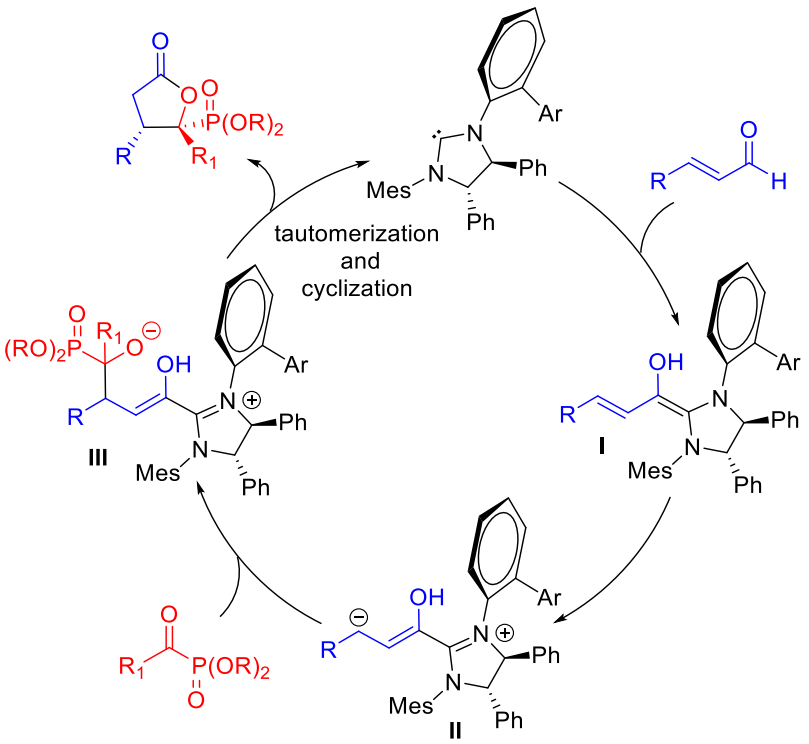
First in 2013, the group of Scheidt developed the NHC-catalyzed enantioselective preparation of phosphorylated *γ*-butyrolactones *via* the homoenolate addition of *α,β*-unsaturated aldehydes and acylphosphonates.[9] In the discovery of this protocol, the literature known standard chiral *N*-heterocyclic carbene catalysts were found unsuitable for this conversion. Thus, they used a newly designed C_1-symmetric biaryl-saturated imidazolium catalyst.



Scheme 2.1: NHC-catalyzed preparation of phosphorylated *γ*-butyrolactones

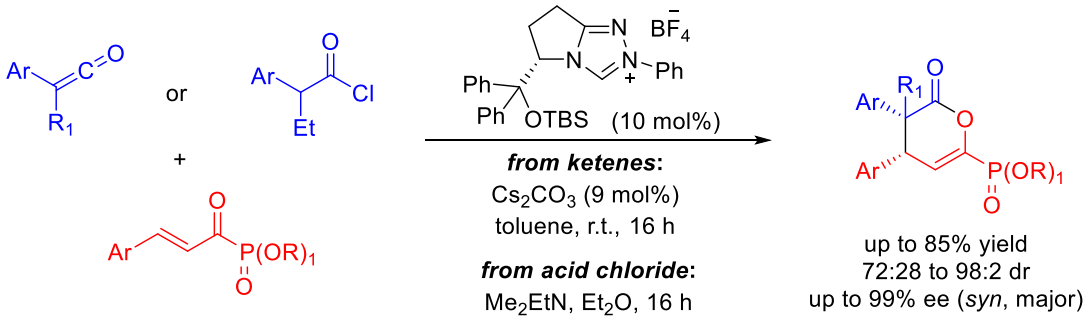
The aryl and heteroaryl substituted *α,β*-unsaturated aldehydes reacted with various derivative of acylphosphonates to furnish the phosphorylated *γ*-butyrolactones in good to excellent yield (54-93%) and good enantioselectivity (Scheme 2.1).

A plausible mechanism of this reaction is presented in Scheme 2.2. This reaction was initiated by the addition of carbene catalyst to *α,β*-unsaturated aldehydes, which led to the formation of extended Breslow intermediate **I** by 1,2-proton shift. In next step homoenolate intermediate **II** was generated from extended Breslow intermediate **I** through *β*-protonation. This homoenolate intermediate **II** further undergoes 1,4-addition with acylphosphonate, to give enol intermediate **III**. Which in next step undergoes tautomerization and followed by cyclization to afford the *γ*-butyrolactone product and release the active carbene catalyst.



Scheme 2.2. Plausible mechanism

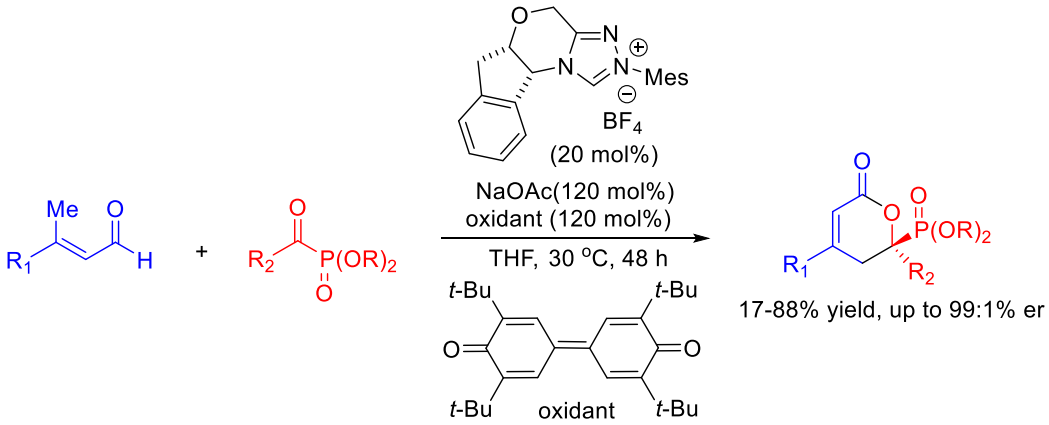
In the same year, Smith and co-workers reported the enantioselective synthesis phosphorylated lactones *via* formal [4+2] cycloadditions of *γ*-substituted-*β*,*γ*-unsaturated *α*-ketophosphonates and alkylarylketenes (Scheme 2.3).[10] In this reaction, a substrate-dependent switch in diastereoselectivity resulted in the formation of the *syn*-phosphorylated lactones with *γ*-aryl *α*-ketophosphonates, while *γ*-methyl *α*-ketophosphonates



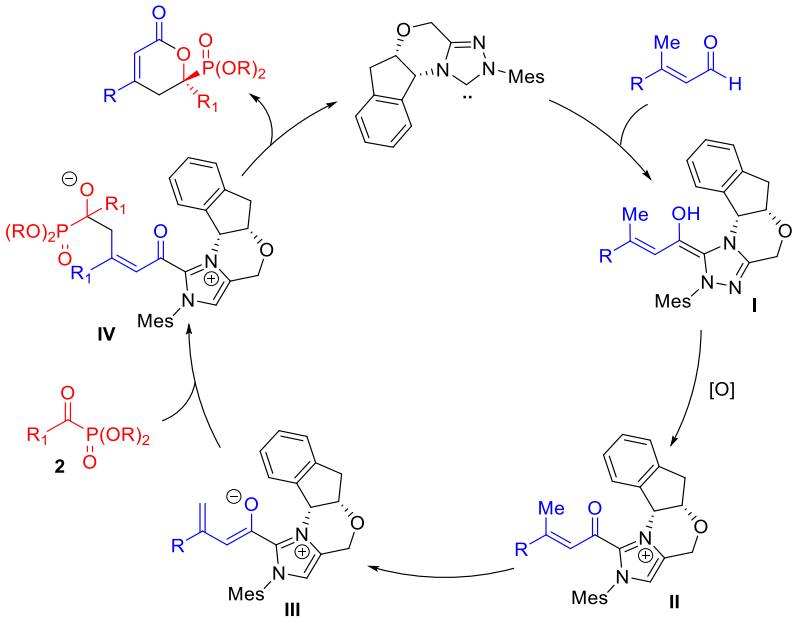
Scheme 2.3: NHC-catalyzed enantioselective synthesis of phosphorylated *δ*-lactones

preferentially gave the *anti*-phosphorylated lactones. In this reaction the in-situ generation of ketene from acyl chloride derivatives retained the high levels of stereoselectivity, which resulted in the improvement of the yield in comparison to the two-step protocols.

Recently in 2018, Chi and co-workers developed the NHC-catalyzed synthesis of 6-phosphorylated *δ*-lactones by [4+2] cyclo-addition of *α,β*-unsaturated aldehydes *via γ*-activation with acyl phosphonates in the presence of an oxidant (Scheme 2.4).[3] In this work the aromatic *α,β*-unsaturated aldehydes and aromatic acylphosphonates reacted smoothly, while the aliphatic *α,β*-unsaturated aldehydes and aliphatic acylphosphonates substrates did not worked well under their optimized reaction condition.



Scheme 2.4: Preparation of phosphorylated *δ*-lactones by the *γ*-activation of enals



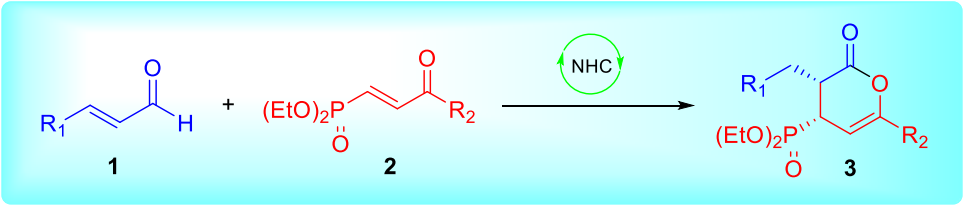
Scheme 2.5. Plausible mechanism

Mechanistically, this reaction proceeded *via* the addition of NHC catalysts to *α,β*-unsaturated aldehyde to form an extended Breslow intermediate **I** (Scheme 2.5). This Breslow intermediate **I** oxidized in the presence of an oxidant to produce acylazolium intermediate **II**,

which subsequently generates vinyl enolate intermediate **III** through base assisted proton abstraction from sp^3 γ-carbon of α,β-unsaturated aldehyde. The γ-carbon of vinyl enolate intermediate **III** reacted with the acylphosphonate to give intermediate **IV**. In the final step, the intermediate **IV** underwent cyclization to produce the lactone product and the active NHC catalyst was regenerated.

2.3. Objective of the Work

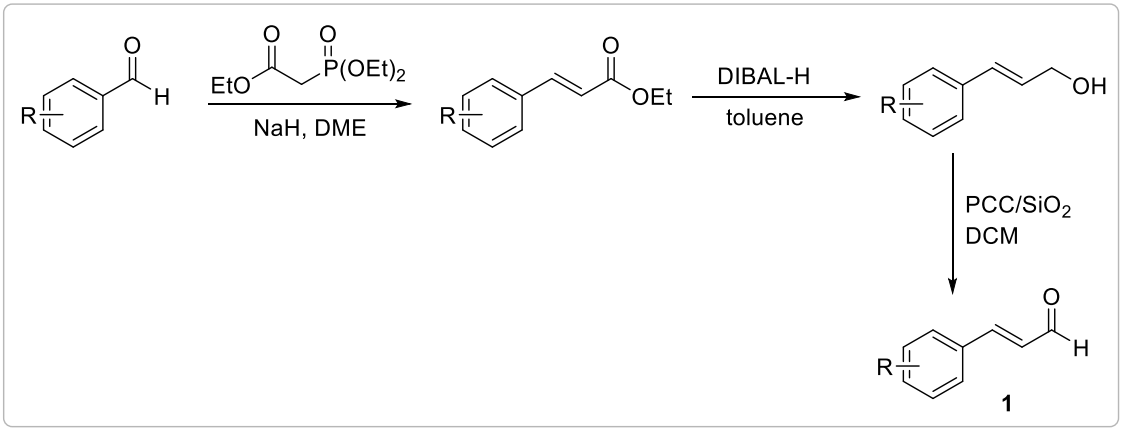
To the best of our knowledge, the literature has no precedence on methods for the preparation of chiral 4-phosphorylated δ-lactones. Herein, we wish to develop the first direct metal-free organocatalytic method for the enantioselective construction of 4-phosphorylated δ-lactones using widely available starting materials such as α,β-unsaturated aldehydes and β-phosphorylenones. The sterically demanding β-phosphorylenones has remained a challenging substrates under NHC catalysis. The reaction is expected to involve the addition of enolates from α,β-unsaturated aldehydes to β-phosphorylenones (Scheme 2.10).



Scheme 2.10. Synthesis of 4-phosphorylated lactones from enals and β-phosphorylenones

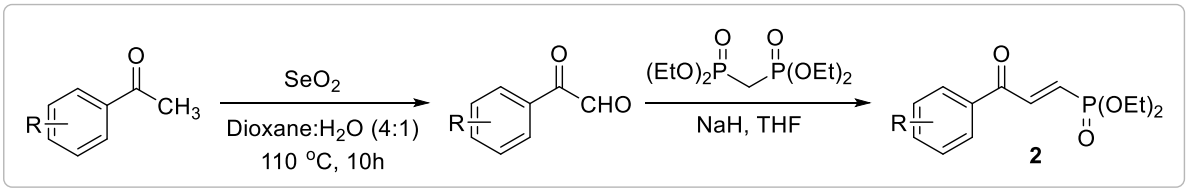
2.4. Results and Discussion

2.4.1. Preparation of Starting Materials



Scheme 2.11. Synthesis of α,β-unsaturated aldehydes **1**

In context to the development of this methodology, we have prepared *α,β*-unsaturated aldehydes **1** in three steps by following the literature procedure (Scheme 2.11).[11] In the first step of the reaction *α,β*-unsaturated esters were prepared by the reaction of aryl aldehydes with triethyl phosphonoacetate in the presence of sodium hydride. In the second step of this reaction *α,β*-unsaturated esters were converted in the allyl alcohols, which in the next step of reaction gives *α,β*-unsaturated aldehydes by the oxidation in the presence of PCC/SiO_2 in DCM solvent. We also prepared the *β*-phosphorylenones **2** in two steps, the first step involves the oxidation of the commercially available acetophenone derivatives using selenium oxide into aldehydes, thereafter in the next step we used this aldehyde substrate for the preparation of *β*-phosphorylenones in the presence of tetraethyl methylenediaphosphonate



Scheme 2.12. Synthesis of *β*-phosphorylenones **2**

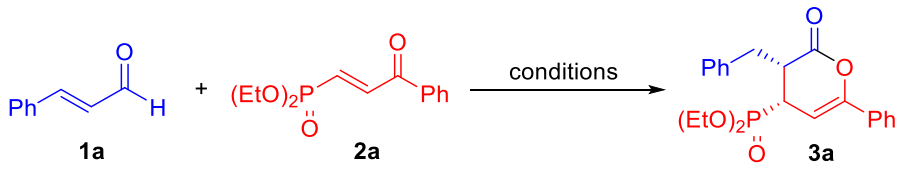
and sodium hydride base as reported in the literature (Scheme 2.12).[12] The indanol-derived triazolium catalyst **K** was prepared according to the literature reported method.[13]

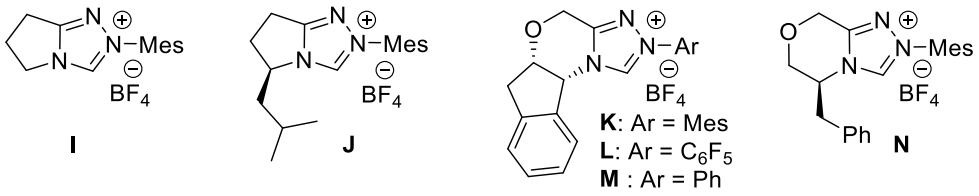
2.4.2. Optimization Studies of the Reaction

To expand the core objective of our research group's in developing various unexplored or less explored NHC catalyzed synthesis of organophosphorus compounds, we have developed the carbene catalyzed synthesis of phosphorylated lactones using *α,β*-unsaturated aldehydes and *β*-phosphorylenones. We started our study employing commercially available cinnamaldehyde **1a** and easily available *β*-phosphorylenone **2a** as the model substrates. The results of all the reactions performed in different conditions are shown in the optimization study Table 2.1. The achiral triazolium salt **I** in the presence of 1,8-Diazabicycloundec-7-ene (DBU) in tetrahydrofuran (THF) solvent afforded the 4-phosphorylated *δ*-lactones **3a** in 21% yield with high diastereoselectivity at room temperature (entry 1). The *N*-Mes protected NHC salt **J** produced **3a** in 27% yield (entry 2). Among the aminoindanol-derived triazolium salts **K**, **L**, and **M**, the *N*-Mes protected precatalyst **K** resulted in the formation of the desired product in a moderate yield of 57% with excellent enantioselectivity of more than 99% as a single diastereomer (entry 3). The indanol derived *N*-C_6F_5 and *N*-Ph protected NHC salts

were failed to afford the desired product (entries 4-5), the same was also true for the phenylalanine derived NHC salt **N** (entry 6). Next, we further move to screen the solvents the *N*-Mes protected precatalyst **K** in 1,2-dichloroethane afford the product in 59% yield with 99% ee (entry 7). The use of chlorinated solvents dichloromethane was proved beneficial to produce the corresponding 4-phosphorylated *δ*-lactones **3a** in 79% yield and 99% enantiomeric excess (ee) as a single diastereomer (entry 8). To our delight, the use of inorganic base Cs_2CO_3 as the base in DCM solvent produced the 4-phosphorylated *δ*-lactones **3a** in an excellent yield of 95% with excellent enantiomeric excess 99% (entry 11).

Table 2.1. Optimization of the reaction condition[a]





entry	cat.	solvent	base	yield (%)[b]	d.r.[c]	ee (%)[d]
1	**I**	THF	DBU	21	>20:1	-
2	**J**	THF	DBU	27	>20:1	-
3	**K**	THF	DBU	57	>20:1	99
4	**L**	THF	DBU	0	-	-
5	**M**	THF	DBU	0	-	-
6	**N**	THF	DBU	29	-	-
7	**K**	$(CH_2Cl)_2$	DBU	59	>20:1	99
8	**K**	$(CH_2Cl)_2$	DBU	79	>20:1	99
9	**K**	$(CH_2Cl)_2$	TMG	23	>20:1	-
10	**K**	$(CH_2Cl)_2$	K_2CO_3	88	>20:1	99
11	**K**	$(CH_2Cl)_2$	Cs_2CO_3	95	>20:1	99

[a]General reaction condition: *α,β*-unsaturated aldehyde **1a** (0.2 mmol), *β*-phosphorylenone **2a** (0.1 mmol), cat. **I**-**N** (20 mol %), base (40 mol %), solvent (1.0 mL) at rt for 16 h.

2.4.3. X-ray Data of Compound 3a

The stereochemistry of the product **3a** was determind by using single crystal X-ray analysis (Figure 2.3). The data collection of compound **3a** was carried out with 'Bruker APEX2' at

ambient temperature. The refinement and data reduction of compound **3a** was done with 'Bruker SAINT'. The 'SHELXS-97 (Sheldrick 2008)' was used for the structure solution of compound **3a**. The structure refinement of compound **3a** was done with 'SHELXL-2014 (Sheldrick 2014)'. The X-ray analysis of compound **3a** is shown in the Table 2.2. The CCDC 1936122 contains the crystallographic information of the compound **3a**. Which can be obtained free of charge from Cambridge Data Centre with the following link http://www.ccdc.cam.ac.uk/data_request/cif.[14]

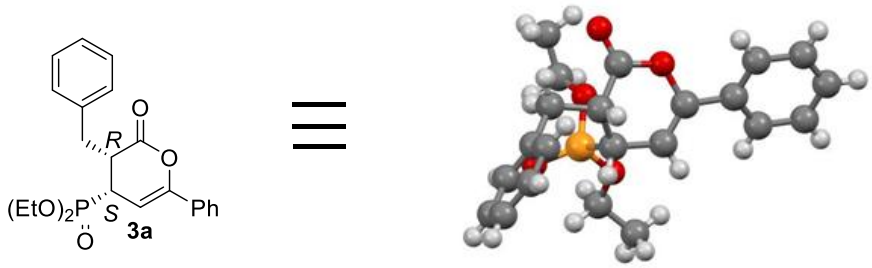


Figure 2.3: Single-crystal X-ray structure of the 4-phosphorylated *δ*-lactones **3a**

Table 2.2. Crystallographic data for compound **3a**

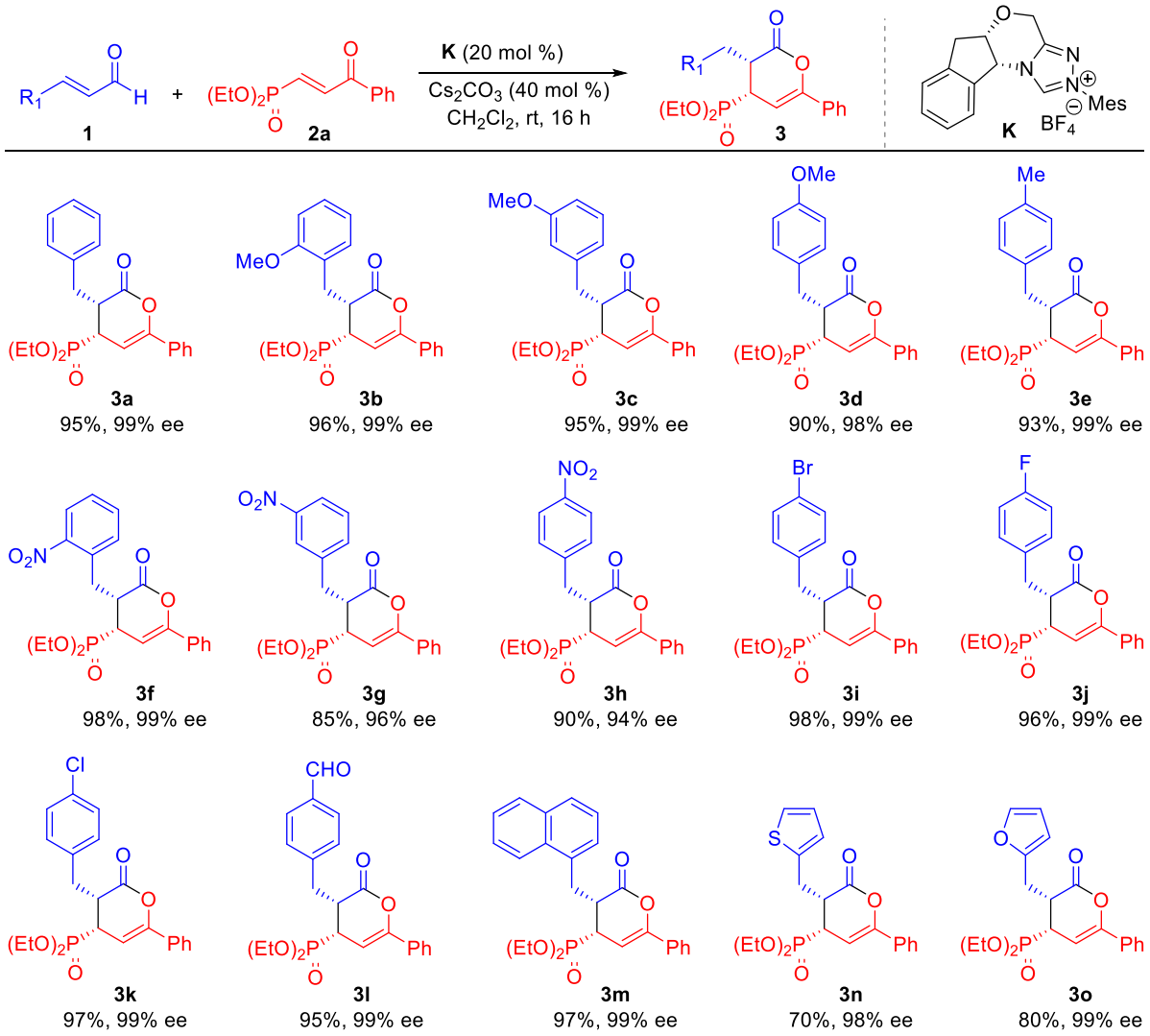
Identification code	**3a**
Empirical formula	$C_{22}H_{25}O_5P$
Formula weight	400.39
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 10.2137(18) Å α= 90°.
	b = 9.2639(15) Å β= 110.270(5)°.
	c = 11.792(2) Å γ = 90°.
Volume	1046.7(3)Å^3
Z	2

Density (calculated)	1.27 g/cm^3
Absorption coefficient	0.161 mm^{-1}
F(000)	424
Crystal size	0.300x 0.300x 0.300 mm^3
Theta range for data collection	2.87° to 28.210°.
Independent reflections	4307 [R(int) = 0.0525]
Completeness to theta = 24.639°	99.8%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4307 / 1 / 256
Goodness-of-fit on F^2	1.014
R indices (all data)	R1 = 0. 1151, wR2 = 0. 0.0950
CCDC	1936122

2.4.4. Substrate Scope of the Variation of Enals

After optimizing the reaction condition, we next moved to test the compatibility of the various derivatives of *α*,*β*-unsaturated aldehydes (enals) with *β*-phosphorylenone **2a** under carbene catalysis (Scheme 2.13). The *α*,*β*-unsaturated aldehydes bearing electron-rich substituents such as methoxy or methyl substituent at the *ortho*, *meta* or *para* position of the aryl ring performed well to produce the corresponding 4-phosphorylated *δ*-lactones in up to 96% yield and up to 99% enantiomeric excess, without influencing the diastereoselectivity of products (**3b**-**3e**). Importantly, the highly electron-deficient *α*,*β*-unsaturated aldehydes having nitro (-NO_2) substituent at the *ortho*, *meta* or *para* position over the ring were also reacted smoothly and affording the 4-phosphorylated *δ*-lactones in good to excellent yield 85-98% (**3f**-**3h**). The *α*,*β*-unsaturated aldehydes bearing Br-, Cl- and I- groups were also found compatible under the optimized reaction condition to produce the 4-phosphorylated *δ*-lactones in excellent yields 96-98% and excellent enantioselectivity (**3i**-**3k**). The *α*,*β*-unsaturated aldehydes having -CHO functionality at *para*-position at the aryl ring, which is a reactive functionality towards *N*-heterocyclic carbene catalysis for the generation of acyl anions, chemoselectively reacted to produce only the 4-phosphorylated *δ*-lactones in excellent yield and stereoselectivity (**3l**). Notably, in this reaction, the sterically demanding

naphthyl- and heteroaryl substituted *α,β*-unsaturated aldehydes also afforded the 4-phosphorylated *δ*-lactones in 70-97% yields with 98-99% enantiomeric excess (**3m-3o**).

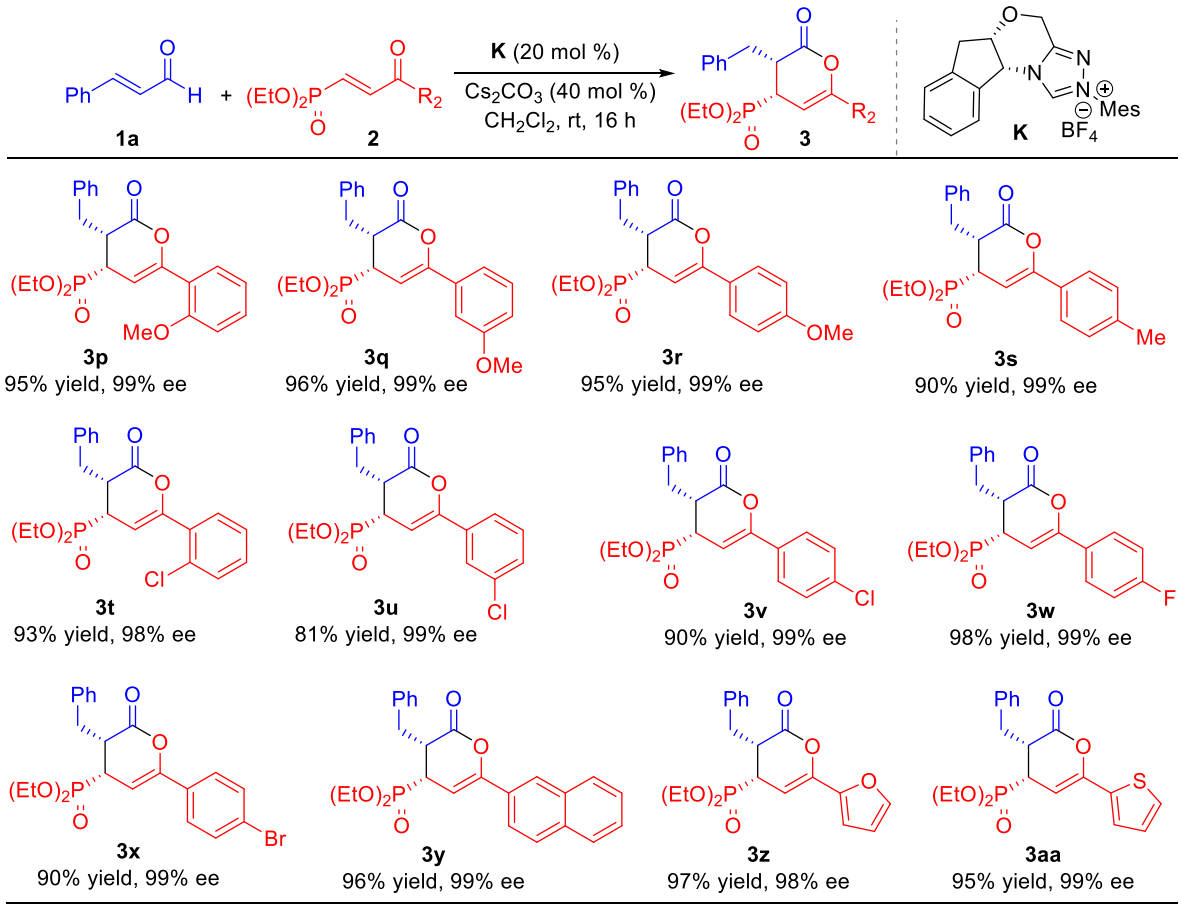


Scheme 2.13. Preparation of 4-phosphorylated *δ*-lactones using derivatives of enals[a]

The use of *α,β*-unsaturated aldehydes having alkyl substituent (e. g., R = Me or –CH_2CH_2Ph) at the *β*-position resulted in the formation of 4-phosphorylated *δ*-lactones (**3**) as an inseparable mixture with some unidentified products. This method was found compatible at the larger scale on performing the reaction using **2a** (0.70 g, 2.61 mmol) resulted in the formation of 4-phosphorylated *δ*-lactones **3a** (0.96 g) slightly low yield 91% rather than 95% yield without any loss in stereoselectivity (Scheme 2.13).

2.4.5. Substrate Scope of the Variation of *β*-Phosphorylenones

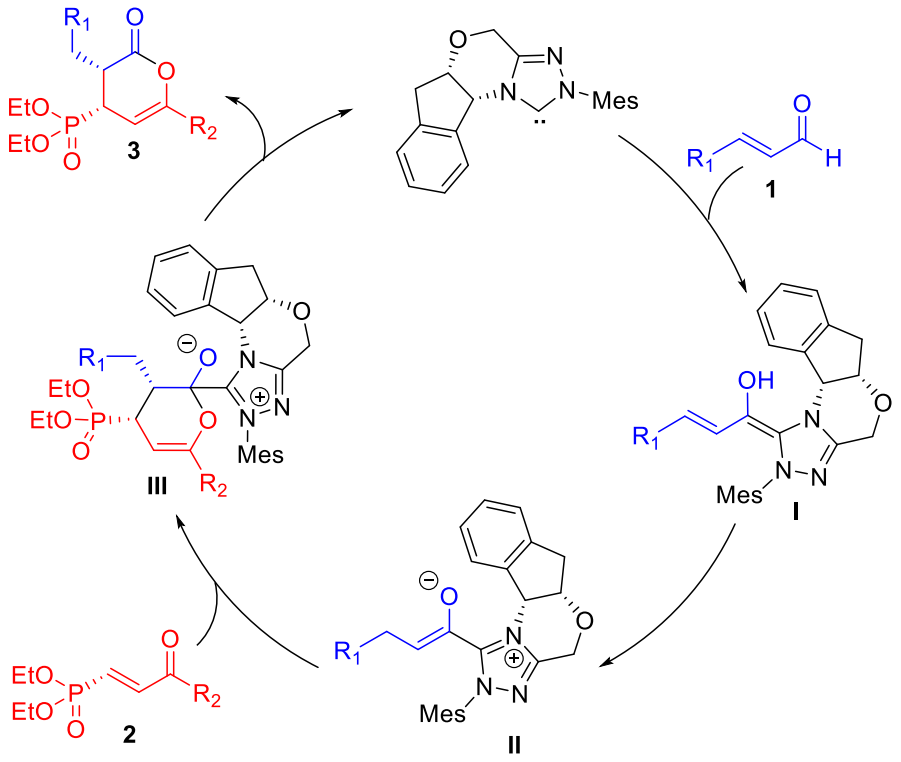
Next, we further proceed to investigate the generality of the reaction using various derivatives of *β*-phosphorylenones under the optimized reaction condition as shown in Table 1, entry 11 (Scheme 2.14). We found that *β*-phosphorylenones having electron-donating groups like methyl or methoxy, at the *ortho*, *meta*, or *para* positions at the aryl ring, performed well with cinnamaldehyde to produce the 4-phosphorylated *δ*-lactones in excellent yields with 99% enantiomeric excess and >20:1 dr (**3p**-**3s**). The *β*-phosphorylenones bearing electron-withdrawing groups (EWG) on the aryl rings like bromo, chloro-, and fluoro- functionalities reacted smoothly to produce the 4-phosphorylated *δ*-lactones in good to excellent yield (**3t**-**3x**). No generality in the reactivity of *β*-phosphorylenones **2** was observed bearing substituent at any position (*ortho*, *meta*, or *para*) of aryl rings (**3t**-**3v**). The naphthyl- and heteroaryl-substituted *β*-phosphorylenones also performed well and produced the phosphorylated *δ*-lactones in excellent yields 95-97% with enantioselectivity 98-99% (**3y**-**3aa**).



Scheme 2.14. Synthesis of phosphorylated *δ*-lactones by the variation of *β*-Phosphorylenones[a]

2.4.6. Proposed Mechanism of the reaction

The proposed mechanism for this NHC-catalyzed enolate addition of *α,β*-unsaturated aldehydes **1** to the *β*-phosphorylenone **2** is shown in (Scheme 2.15). The reaction was initiated by the initial addition of carbene catalysts to *α,β*-unsaturated aldehydes **1** to give rise the extended Breslow intermediate **I**. This extended Breslow intermediate **I** further generates the enolate intermediate **II** *via* *β*-protonation, which then adds to a *β*-phosphorylenone **2** by an endo-Diels-Alder cycloaddition to form the intermediate **III**. Finally, the active carbene are released from **III**, to give enantioenriched cis-phosphorylated *δ*-lactone **3** containing two consecutive stereogenic centers.

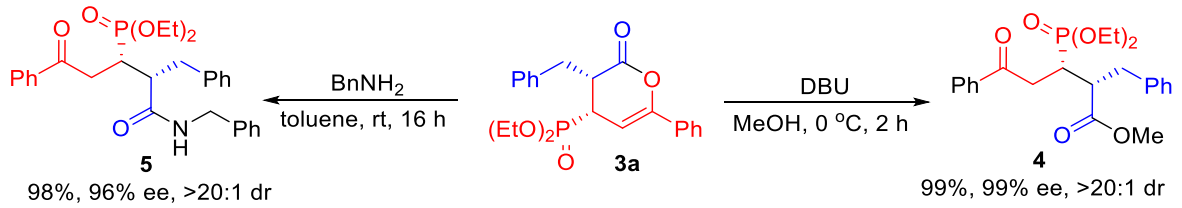


Scheme 2.15. Plausible mechanism

2.4.7. Synthetic Transformations of Functionalized 4-phosphorylated *δ*-lactones

These chiral 4-phosphorylated *δ*-lactones could be efficiently converted into multi-functionalized chiral *γ*-ketophosphoryl esters and amides. Herein we have transformed lactone **3a** in the presence of the catalytic amount of DBU in MeOH solvent in the highly functionalized *γ*-ketophosphoryl esters **4**. We also converted the lactone **3a** in the multi-functionalized *γ*-ketophosphoryl amides **5** in the presence of benzylamine in toluene solvent

without compromising the ee and dr (Scheme 2.16). More importantly, that these classes of ketophosphoryl compounds possess interesting bioactivities, such as enzyme inhibitors,



Scheme 2.16. Preparation of ketophosphoryl ester and ketophosphoryl amide from **3a**

agrochemicals, antibiotics, antifungal, and antiviral agents.

2.5. Conclusion

In summary, we have established the first highly enantioenriched *N*-heterocyclic carbene catalyzed direct protocol for the preparation of 4-phosphorylated *δ*-lactones having two consecutive stereogenic centres using *α,β*-unsaturated aldehydes and *β*-phosphorylenones. This is the first asymmetric intermolecular enolate addition of enals to the sterically demanding *β*-phosphorylenones. The obtained phosphorylated dihydropyranones could be easily transformed into useful *γ*-ketophosphoryl esters and ketophosphoryl amides. The biological activity evaluation of these synthesized valuable 4-phosphorylated *δ*-lactones, *γ*-ketophosphonate esters, and amides are underway.

2.6. Experimental Section

2.6.1. General Information

All reactions were carried out under the argon atmosphere in oven-dried glassware. Chemicals and reagents were purchased from commercial sources (Avra, Spectrochem, Sigma Aldrich, and Alfa-aesar) and used without further purification. The *α,β*-unsaturated aldehydes (enals) **1b** to **1o** were prepared according to literature known methods.[14] The *β*-phosphorylenones **2a** to **2aa** were prepared by using a literature known procedure.[15] Solvents were dried and distilled by following the standard protocols, TLC of the reactions was carried out on pre-coated plates (Merck silica gel 60, F_{254}), and the spots were visualized under the UV light or by charring the TLC plates by dipping in PMA (phosphomolybdic acid) charring solution. Compounds were purified by flash column chromatography using silica gel (100-200 mess) with distilled hexane and ethyl acetate. Enantiomeric excess (*ee*) of the products

were determined by high-performance liquid chromatography (HPLC) analysis using a chiral stationary phase. ^{1}H, ^{13}C, and ^{31}P NMR for compounds were recorded at 400 MHz, 100 MHz, and 162 MHz instruments respectively using $CDCl_3$ as the solvent. 98% PPh_3 as an external standard for ^{31}P NMR. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), and dt (doublet of triplets); m (multiplets), etc. High-resolution mass spectral analysis (HRMS) was performed on Q-TOF Premier mass spectrometer. The optical rotation of compounds measured on an Autopol III, serial number 30700 polarimeter at wavelength 589 nm.

2.6.2. General Procedure for the NHC-Catalyzed Synthesis of Product 3

To an oven-dried Schlenk tube equipped with a magnetic stir bar was added aldehyde **1** (0.2 mmol, 2.0 equiv.), *β*-phosphoryl enones **2** (0.1 mmol, 1.0 equiv.) and catalyst **K** (8.4 mg, 0.02 mmol). The Schlenk tube evacuated and backfilled with argon, after the addition of $CHCl_3$ (1.0 mL) and $CsCO_3$ (13.0 mg, 0.04 mmol) and the reaction chamber was closed. After stirring at rt for 16 h, the reaction was monitored by TLC, the solvent was removed under reduced pressure, and the reaction mixture purified by silica gel column chromatography with EtOAc/Hexane (8:2) to obtain the desired product **3**.

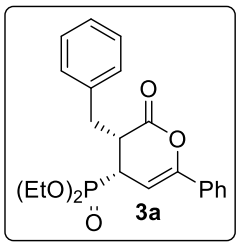
2.6.3. Synthetic Transformations of Compounds 3a

Compound 4: To a dry Schlenk tube equipped with magnetic stir bar lactone **3a** (40.0 mg, 0.1 mmol) was and MeOH 1.0 mL was added and reaction mixture cooled to 0 ^{o}C and DBU (3.0 µL, 0.02) was added. After stirring the reaction mixture at 0 ^{o}C for 2 h, the reaction was monitored by TLC, and solvent was removed under reduced pressure through rotavapor, followed by column chromatography on silica gel with EtOAc produced the desired product **4** in **(**43 mg) 99% yield.

Compound 5: To a dry Schlenk tube equipped with magnetic stir bar lactone **3a** (40.0 mg, 0.1 mmol), toluene 1.0 mL, and benzylamine (28.0 µL, 0.30 mmol) was added and the reaction stirred at rt for 16 h. The reaction was monitored by TLC and solvent was evaporated under reduced pressure through rotavapor, followed by column chromatography on silica gel with EtOAc afforded the desired product **5** in (50 mg) 98% yield.

2.6.4. Characterization of the Products

***Diethyl ((3R,4S)-3-benzyl-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3a)**:



Yield: 38 mg (95%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{25}O_5PNa^+$ $[M+Na]^+$: 423.1332, found: 423.1327.

$[\alpha]_D^{28}$ = +121.60 (c 0.1, $CHCl_3$).

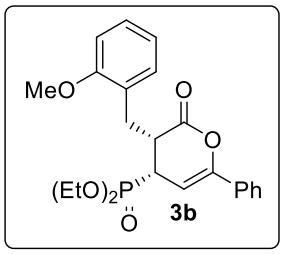
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.30 (6H, m), 2.84-3.18 (3H, m), 3.36-3.52 (1H, m), 3.97-4.16 (4H, m), 5.72 (1H, dd, J = 6.8, 4.8 Hz), 7.11-7.19 (1H, m), 7.20-7.35 (7H, m), 7.47-7.60 (2H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 32.5 (d, $J_{C\text{-}P}$ = 1.0 Hz), 33.8 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.7 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.3 (d, $J_{C\text{-}P}$ = 11.0 Hz), 124.6 (d, $J_{C\text{-}P}$ = 1.0 Hz), 126.5, 128.4, 129.0, 129.3, 131.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 138.9, 151.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.6 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.1.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, UV 254 nm), Rt_1 (minor) = 34.9 min, Rt_2 (major) = 38.4 min; >99% ee.

***Diethyl ((3R,4S)-3-(2-methoxybenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3b)**:



Yield: 42 mg (96%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1438, found: 453.1459;

$[\alpha]_D^{25}$ = +84.80 (c 0.1, $CHCl_3$).

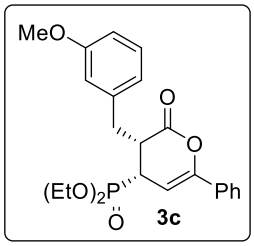
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28-1.40 (6H, m), 2.96-3.18 (2H, m), 3.21-3.42 (1H, m), 3.51 (1H, dd, J = 14.0, 5.6 Hz), 3.79 (3H, s), 4.09-4.24 (4H, m), 5.82 (1H, t, J = 5.6 Hz), 6.84 (1H, d, J = 8.4 Hz), 6.91 (1H, t, J = 7.6 Hz), 7.21 (1H, t, J = 8.0 Hz), 7.36 (3H, t, J = 5.6 Hz), 7.51 (1H, d, J = 7.6 Hz), 7.62 (2H, t, J = 5.6 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 28.3, 34.4 (d, $J_{C\text{-}P}$ = 140.0 Hz), 40.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 55.1, 62.6 (q, $J_{C\text{-}P}$ = 8.0 Hz), 98.4 (d, $J_{C\text{-}P}$ = 11.0 Hz), 110.0, 120.3, 124.6, 124.7, 127.0, 128.4, 129.2, 131.8, 131.9 (d, $J_{C\text{-}P}$ = 4.0 Hz), 151.5 (d, $J_{C\text{-}P}$ = 11.0 Hz), 157.4, 168.9 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 23.6.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, UV 254 nm), Rt_1 (minor) = 26.5 min, Rt_2 (major) = 33.4 min; >99% ee.

***Diethyl ((3R,4S)-3-(3-methoxybenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3c)**:



Yield: 41 mg (95%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{28}O_6P^+$ $[M+H]^+$: 431.1619, found: 431.1608.

$[\alpha]_D^{25}$ = +67.40 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.30 (6H, m), 2.87-3.17 (3H, m), 3.42 (1H, dd, J = 14.0, 3.6 Hz), 3.71 (3H, s), 4.0-4.14 (4H, m), 5.73 (1H, dd, J = 6.8, 4.4 Hz), 6.66-6.73 (1H, m), 6.82-6.91 (2H, m), 7.13 (1H, t, J = 8.0 Hz), 7.25-7.33 (3H, m), 7.49-7.57 (2H, m).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 32.4, 33.7 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 55.0, 62.7 (q, $J_{C\text{-}P}$ = 8.0 Hz), 98.3 (d, $J_{C\text{-}P}$ = 10.0 Hz), 111.9, 114.7, 121.2, 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.4, 129.3, 129.4, 131.8 (d, $J_{C\text{-}P}$ = 5.0 Hz), 140.4, 151.5 (d, $J_{C\text{-}P}$ = 11.0 Hz), 159.6, 168.8 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 23.1.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, UV 254 nm), Rt_1 (minor) = 24.5 min, Rt_2 (major) = 26.8 min; >99% ee.

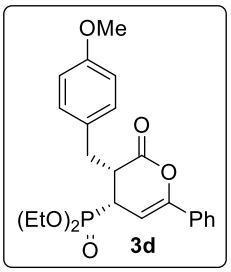
***Diethyl ((3R,4S)-3-(4-methoxybenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3d)**:

Yield: 39 mg (90%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{28}O_6P^+$ $[M+H]^+$: 431.1619, found: 431.1602.

$[\alpha]_D^{25}$ = +72.60 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28-1.39 (6H, m), 2.91-3.22 (3H, m), 3.46 (1H, d, J = 10.0 Hz), 3.79 (3H, s), 4.06-4.24 (4H, m), 5.80 (1H, t, J = 4.0 Hz), 6.85 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 6.8 Hz), 7.36 (3H, d, J = 5.2 Hz), 7.61 (2H, t, J = 4.8 Hz).

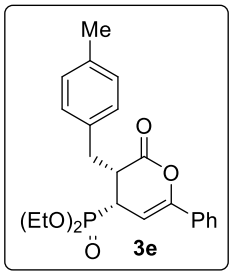


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 31.6, 33.8 (d, $J_{C\text{-}P}$ = 139.0 Hz), 43.2 (d, $J_{C\text{-}P}$ = 4.0 Hz), 55.2, 62.7 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.3 (d, $J_{C\text{-}P}$ = 11.0 Hz), 113.9, 124.7 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.5, 129.3, 130.0, 130.9, 131.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 151.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 158.2, 168.7 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.3.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 25.4 min, Rt_2 (major) = 30.1 min; >98% ee.

***Diethyl ((3R,4S)-3-(4-methylbenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3e)**: **Yield:** 39 mg (93%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).



HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{28}O_5P^+$ $[M+H]^+$: 415.1669, found: 415.1665.

$[\alpha]_D^{28}$ = +59.80 (c 0.1, $CHCl_3$).

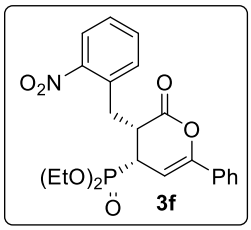
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19-1.31 (6H, m), 2.24 (3H, s), 2.86-3.16 (3H, m), 3.38 (1H, t, J = 3.6 Hz), 3.99-4.15 (4H, m), 5.72 (1H, dd, J = 4.8 Hz), 7.04 (2H, d, J = 7.6 Hz), 7.17 (2H, d, J = 8.0 Hz), 7.24-7.33 (3H, m), 7.48-7.57 (2H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 32.0, 33.7 (d, $J_{C\text{-}P}$ = 139.0 Hz), 42.9 (d, $J_{C\text{-}P}$ = 4.0 Hz), 55.2, 62.7 (q, $J_{C\text{-}P}$ = 8.0 Hz), 98.3 (d, $J_{C\text{-}P}$ = 10.0 Hz), 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.4, 128.8, 129.1, 129.3, 131.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 135.7, 136.0, 151.6 (d, $J_{C\text{-}P}$ = 12.0 Hz), 168.6 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.2.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 28.1 min, Rt_2 (major) = 42.1 min; >99% ee.

***Diethyl ((3R,4S)-3-(2-nitrobenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3f)**:



Yield: 44 mg (98%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}NO_7PNa^+$ $[M+Na]^+$: 468.1183, found: 468.1152.

$[\alpha]_D^{27}$ = +214.2 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22-1.31 (6H, m), 3.13-3.31 (2H, m), 3.36 (1H, dd, J = 14.0, 4.0 Hz), 3.55 (1H, dd, J = 14.0, 8.0 Hz), 4.02-4.18 (4H, m), 5.79 (1H, dd, J = 6.8, 4.4 Hz), 7.23-7.37 (4H, m), 7.45-7.57 (3H, m), 7.85 (1H, dd, J = 7.6, 1.2 Hz), 7.92 (1H, dd, J = 8.4, 1.2 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 31.5, 35.6 (d, $J_{C\text{-}P}$ = 139.0 Hz), 41.9 (d, $J_{C\text{-}P}$ = 5.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.0 (d, $J_{C\text{-}P}$ = 10.0 Hz), 124.6 (d, $J_{C\text{-}P}$ = 1.0 Hz), 124.9, 127.9, 128.4, 129.3, 131.6 (d, $J_{C\text{-}P}$ = 4.0 Hz), 133.3, 134.2, 135.0, 148.7, 151.5 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.4 (d, $J_{C\text{-}P}$ = 4.0 Hz).

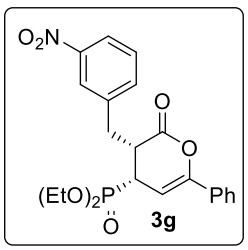
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.0.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 30:70, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 23.9 min, Rt_2 (minor) = 27.3 min; >99% ee.

***Diethyl ((3R,4S)-3-(3-nitrobenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3g)**:

Yield: 38 mg (85% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}NO_7PNa^+$ $[M+Na]^+$: 468.1183, found: 468.1208.



$[\alpha]_D^{26}$ = +79.20 (c 0.1, $CHCl_3$).

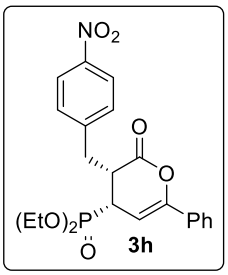
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23-1.32 (6H, m), 2.85-2.99 (1H, m), 3.03-3.28 (2H, m), 3.54 (1H, dd, J = 14.0, 5.2 Hz), 4.03-4.17 (4H, m), 5.75 (1H, dd, J = 6.8, 4.4 Hz), 7.25-7.34 (3H, m), 7.41 (1H, t, J = 7.6 Hz), 7.48-7.57 (2H, m), 7.69 (1H, d, J = 8.0 Hz), 7.98-8.05 (1H, m), 8.17 (1H, t, J = 1.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 32.6, 34.2 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.4 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.9 (q, $J_{C\text{-}P}$ = 7.0 Hz), 97.8 (d, $J_{C\text{-}P}$ = 11.0 Hz), 121.7, 123.9, 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.5, 129.4, 129.5, 131.6 (d, $J_{C\text{-}P}$ = 5.0 Hz), 135.6, 141.0, 148.3, 151.7 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.0 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.5.

HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 21.3 min, Rt_2 (major) = 36.9 min; >96% ee.

***Diethyl ((3R,4S)-3-(4-nitrobenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3h)**:



Yield: 41 mg (90% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}NO_7PNa^+$ $[M+Na]^+$: 468.1183, found: 468.1180.

$[\alpha]_D^{25}$ = +68.40 (c 0.1, $CHCl_3$).

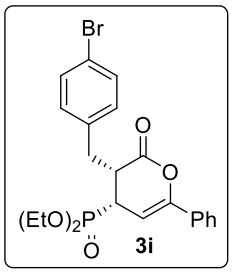
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21-1.32 (6H, m), 2.89 (1H, dt, *J* = 21.2, 6.8 Hz), 3.01-3.19 (1H, m), 3.23 (1H, dd, J = 14.4, 8.4), 3.53 (1H, dd, *J* = 14.4, 6.0 Hz), 4.01-4.17 (4H, m), 5.74 (1H, dd, *J* = 6.8, 4.4 Hz), 7.25-7.33 (3H, m), 7.46-7.57 (4H, m), 8.09 (2H, dd, *J* = 6.8, 4.0 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 32.8, 34.2 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.3 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.9 (q, $J_{C\text{-}P}$ = 7.0 Hz), 97.8 (d, $J_{C\text{-}P}$ = 11.0 Hz), 123.6, 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.5, 129.5, 130.0, 131.5 (d, $J_{C\text{-}P}$ = 4.0 Hz), 146.7, 146.8, 151.7 (d, $J_{C\text{-}P}$ = 11.0 Hz), 167.9 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.4.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 30:70, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 24.6 min, Rt_2 (minor) = 33.7 min; >94% ee.

***Diethyl ((3R,4S)-3-(4-bromobenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3i)**:



Yield: 47 mg (98% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}BrO_5PNa^+$ $[M+Na]^+$: 501.0437, found: 501.0426.

$[\alpha]_D^{28}$ = +15.80 (c 0.1, $CHCl_3$).

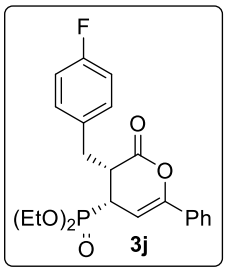
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19-1.30 (6H, m), 2.81-3.16 (3H, m), 3.31-3.46 (1H, m), 3.97-4.16 (4H, m), 5.72 (1H, dd, J = 6.4, 4.4 Hz), 7.18 (2H, d, J = 8.4 Hz), 7.24-7.31 (3H, m), 7.34 (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 4.4 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (t, $J_{C\text{-}P}$ = 6.0 Hz), 32.0, 33.8 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.6 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.7 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.1 (d, $J_{C\text{-}P}$ = 11.0 Hz), 120.3, 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.4, 129.3, 130.8, 131.5, 131.7 (d, $J_{C\text{-}P}$ = 5.0 Hz), 137.9, 151.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.3 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.8.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 14.7 min, Rt_2 (major) = 20.9 min; >99% ee.

***Diethyl ((3R,4S)-3-(4-fluorobenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3j)**:



3j

Yield: 40 mg (96% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}FO_5PNa^+$ $[M+Na]^+$: 441.1238, found: 441.1232.

$[\alpha]_D^{27}$ = +89.00 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.30 (6H, m), 2.82-3.15 (3H, m), 3.32-3.48 (1H, m), 3.99-4.15 (4H, m), 5.73 (1H, dd, J = 6.4, 4.4 Hz), 6.86-6.96 (2H, m), 7.22-7.34 (5H, m), 7.48-7.58 (2H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (t, $J_{C\text{-}P}$ = 6.0 Hz), 31.8, 33.8 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.9 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.7 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.1 (d, $J_{C\text{-}P}$ = 10.0 Hz), 115.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.4, 129.3, 130.6 (d, $J_{C\text{-}F}$ = 8.0 Hz), 131.7 (d, $J_{C\text{-}P}$ = 4.0 Hz), 134.6 (d, $J_{C\text{-}P}$ = 4.0 Hz), 151.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 161.6 (d, $J_{C\text{-}F}$ = 243.0 Hz), 168.4 (d, $J_{C\text{-}P}$ = 5.0 Hz).

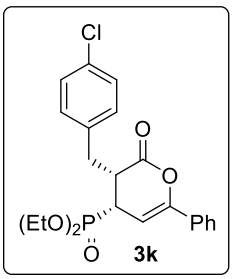
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.9.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 19.9 min, Rt_2 (minor) = 22.9 min; >99% ee.

***Diethyl ((3R,4S)-3-(4-chlorobenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3k)**:

Yield: 43 mg (97% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}ClO_5PNa^+$ $[M+Na]^+$: 457.0943, found: 457.0907.



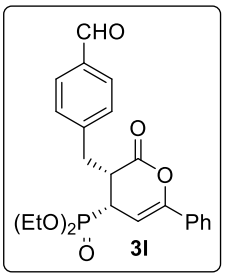
$[\alpha]_D^{28}$ = +18.40 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.30 (6H, m), 2.81-3.15 (3H, m), 3.32-3.47 (1H, m), 3.98-4.15 (4H, m), 5.73 (1H, dd, J = 6.8, 4.8 Hz), 7.16-7.35 (7H, m), 7.52 (2H, t, J = 4.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (t, $J_{C\text{-}P}$ = 5.0 Hz), 32.0, 33.9 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.7 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.7 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.1 (d, $J_{C\text{-}P}$ = 10.0 Hz), 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.4, 128.5, 129.4, 130.4, 131.7 (d, $J_{C\text{-}P}$ = 4.0 Hz), 132.3, 137.4, 151.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.3 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.9.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 20.2 min, Rt_2 (minor) = 22.1 min; >99% ee.

***Diethyl ((3R,4S)-3-(4-formylbenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3l)**:



Yield: 41 mg (95%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{26}O_6P^+$ $[M+H]^+$: 429.1462, found: 429.1460.

$[\alpha]_D^{27}$ = +91.80 (c 0.1, $CHCl_3$).

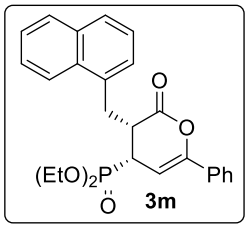
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30-1.40 (6H, m), 2.91-3.08 (1H, m), 3.10-3.73 (2H, m), 3.61 (1H, dd, J = 13.6, 4.8 Hz), 4.09-4.25 (4H, m), 5.82 (1H, dd, J = 6.4, 4.8 Hz), 7.38 (3H, d, J = 4.0 Hz), 7.53-7.68 (4H, m), 7.85 (2H, d, J = 8.0 Hz), 9.99 (1H, s).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (t, $J_{C\text{-}P}$ = 5.0 Hz), 33.0, 34.2 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.3 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 8.0 Hz), 97.9 (d, $J_{C\text{-}P}$ = 11.0 Hz), 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.4, 128.5, 128.8, 129.4, 129.8, 129.9, 131.6 (d, $J_{C\text{-}P}$ = 4.0 Hz), 135.0, 146.3, 151.7 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.1 (d, $J_{C\text{-}P}$ = 5.0 Hz), 191.7.

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.6.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 40:60, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 36.1 min, Rt_2 (minor) = 45.2 min; >99% ee.

***Diethyl ((3R,4S)-3-(naphthalen-1-ylmethyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3m)**: **Yield:** 44 mg (97%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).



HRMS (ESI-TOF) m/z: Mass calcd. for $C_{26}H_{28}O_5P^+$ $[M+H]^+$: 451.1669, found: 451.1666.

$[\alpha]_D^{27}$ = +125.80 (c 0.1, $CHCl_3$).

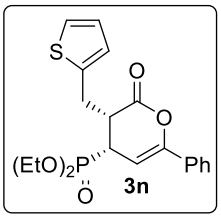
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.30 (6H, m), 2.97 (1H, dt, *J* = 21.6, 6.8 Hz), 3.09-3.31 (1H, m), 3.55 (1H, dd, *J* = 14.8, 8.4 Hz), 3.93-4.22 (5H, m), 5.68 (1H, dd, *J* = 7.2, 4.8 Hz), 7.20-7.29 (3H, m), 7.30-7.45 (3H, m), 7.45-7.53 (2H, m), 7.63(2H, dd, *J* = 6.8 Hz), 7.75 (1H, d, *J* = 2.8 Hz), 7.88 (1H, d, *J* = 8.0 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 29.1, 34.1 (d, $J_{C\text{-}P}$ = 139.0 Hz), 41.5 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.2 (d, $J_{C\text{-}P}$ = 11.0 Hz), 123.0, 124.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 125.4, 125.5, 126.2, 127.3, 127.5, 128.4, 129.0, 129.3, 131.3, 131.7 (d, $J_{C\text{-}P}$ = 4.0 Hz), 133.9, 134.6, 151.5 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.6 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 23.3.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 25.4 min, Rt_2 (major) = 38.7 min; >99% ee.

***Diethyl ((3R,4S)-2-oxo-6-phenyl-3-(thiophen-2-ylmethyl)-3,4-dihydro-2H-pyran-4-yl)phosphon-ate* (3n)**:



Yield: 29 mg (70% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{20}H_{24}O_5PS^+$ $[M+H]^+$: 407.1077, found: 407.1076.

$[\alpha]_D^{27}$ = +129.60 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.31 (6H, m), 2.90-3.20 (2H, m), 3.35 (1H, dd, *J* = 15.2, 9.2 Hz), 3.64 (1H, dd, *J* = 15.2, 4.8 Hz), 3.98-4.17 (4H, m), 5.77 (1H, dd, *J* = 7.2, 4.8

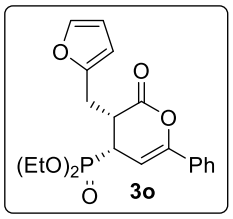
Hz), 6.88 (1H, dd, *J* = 5.2, 3.6 Hz), 6.94 (1H, d, *J* = 7.0 Hz), 7.08 (1H, q, *J* = 0.8 Hz), 7.24-7.37 (3H, m), 7.50-7.58 (2H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (t, J_{C-P} = 2.0 Hz), 27.2, 33.7 (d, J_{C-P} = 140.0 Hz), 43.2 (d, J_{C-P} = 4.0 Hz), 62.7 (q, J_{C-P} = 7.0 Hz), 98.06 (d, J_{C-P} = 11.0 Hz), 123.9, 124.6 (d, J_{C-P} = 2.0 Hz), 126.3, 126.9, 128.4, 129.4, 131.7 (d, J_{C-P} = 4.0 Hz), 140.9, 151.7 (d, J_{C-P} = 11.0 Hz), 168.1 (d, J_{C-P} = 5.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.8.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 37.7 min, Rt_2 (major) = 41.4 min; >98% ee.

***Diethyl ((3R,4S)-3-(furan-2-ylmethyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phospho-nate* (3o)**:



Yield: 32 mg (80% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

$[\alpha]_D^{28}$ = +132.80 (c 0.1, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (6H, q, *J* = 7.2 Hz), 2.98 (1H, dt, *J* = 22.4, 7.2 Hz), 3.10-3.33 (2H, m), 3.37-3.52 (1H, m), 3.97-4.14 (4H, m), 5.78 (1H, dd, *J* = 6.8, 4.4 Hz), 6.14 (1H, d, *J* = 2.8 Hz), 6.23 (1H, s), 7.24 (1H, s), 7.29 (3H, d, *J* = 5.2 Hz), 7.54 (2H, q, *J* = 4.4 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (t, J_{C-P} = 5.0 Hz), 25.7, 33.8 (d, J_{C-P} = 139.0 Hz), 39.6 (d, J_{C-P} = 5.0 Hz), 62.6 (q, J_{C-P} = 8.0 Hz), 98.0 (d, J_{C-P} = 10.0 Hz), 107.2, 110.3, 124.6 (d, J_{C-P} = 2.0 Hz), 128.4, 129.3, 131.7 (d, J_{C-P} = 4.0 Hz), 141.2, 151.6 (d, J_{C-P} = 11.0 Hz), 152.2, 168.1 (d, J_{C-P} = 5.0 Hz).

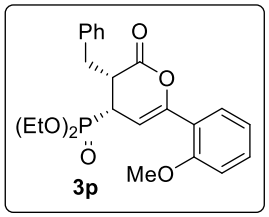
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.9; HRMS (ESI-TOF) m/z: Mass calcd. for $C_{20}H_{23}O_6PNa^+$ $[M+Na]^+$: 413.1125, found: 413.1117.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 37.3 min, Rt_2 (minor) = 41.5 min; >99% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(2-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phospho-nate* (3p)**:

Yield: 41 mg (95% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1438, found: 453.1450.



$[\alpha]_D^{26}$ = +83.80 (c 0.1, $CHCl_3$).

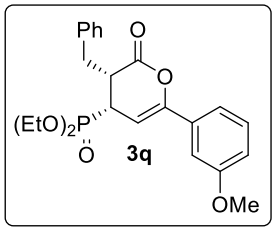
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17-1.39 (6H, m), 3.01 (1H, dt, J = 21.6, 6.8 Hz), 3.08-3.26 (2H, m), 3.52 (1H, t, J = 3.6 Hz), 3.85 (3H, s), 4.09-4.23 (4H, m), 6.19 (1H, dd, J = 6.8, 5.2 Hz), 6.93 (1H, d, J = 8.0 Hz), 6.97 (1H, t, J = 7.6 Hz), 7.22 (1H, t, J = 7.2 Hz), 7.30 (3H, t, J = 7.6 Hz), 7.38 (2H, d, J = 7.6 Hz), 7.65 (1H, d, J = 7.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (q, $J_{C\text{-}P}$ = 1.0 Hz), 32.4 (d, $J_{C\text{-}P}$ = 1.0 Hz), 34.1 (d, $J_{C\text{-}P}$ = 139.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 55.4, 62.6 (q, $J_{C\text{-}P}$ = 8.0 Hz), 103.5 (d, $J_{C\text{-}P}$ = 10.0 Hz), 111.1, 120.4, 120.7 (d, $J_{C\text{-}P}$ = 5.0 Hz), 126.4, 128.0 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.4, 129.1, 130.1, 139.1, 148.4 (d, $J_{C\text{-}P}$ = 11.0 Hz), 157.0 (d, $J_{C\text{-}P}$ = 1.0 Hz), 168.9 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.4.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 38.2 min, Rt_2 (major) = 55.8 min; >99% ee.

***Diethyl ((3R,4S)-3-(3-methoxybenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3q)**:



Yield: 42 mg (96%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1438, found: 453.1436.

$[\alpha]_D^{27}$ = +17.40 (c 0.1, $CHCl_3$).

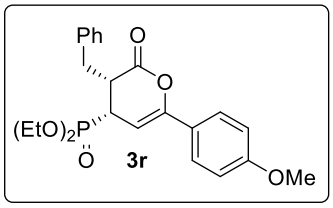
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29-1.38 (6H, m), 2.93-3.26 (3H, m), 3.52 (1H, dd, J = 13.6, 4.0 Hz), 3.82 (3H, s), 4.09-4.21 (4H, m), 5.82 (1H, dd, J = 6.4, 4.8 Hz), 6.91 (1H, d, J = 8.0 Hz), 7.14 (1H, s), 7.16-7.41 (7H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 32.5, 33.8 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 55.3, 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 110.0 (d, $J_{C\text{-}P}$ = 1.0 Hz), 115.2, 117.1 (d, $J_{C\text{-}P}$ = 2.0 Hz), 126.5, 128.5, 129.0, 129.5, 133.2 (d, $J_{C\text{-}P}$ = 4.0 Hz), 138.9, 151.4 (d, $J_{C\text{-}P}$ = 11.0 Hz), 159.7, 168.6 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.1.

HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 15.3 min, Rt_2 (minor) = 20.3 min; >99% ee.

***Diethyl ((3R,4S)-3-(4-methoxybenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3r)**:



Yield: 41 mg (95%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1438, found: 453.1450;

$[\alpha]_D^{29}$ = +68.80 (c 0.05, $CHCl_3$).

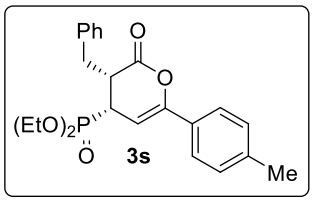
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28-1.39 (6H, m), 2.91-3.25 (3H, m), 3.52 (1H, dd, J = 13.6, 3.6 Hz), 3.81 (3H, s), 4.07-4.22 (4H, m), 5.68 (1H, dd, J = 6.4, 4.8 Hz), 6.88 (2H, d, J = 8.8 Hz), 7.22 (1H, t, J = 6.8 Hz), 7.28-7.40 (4H, m), 7.54 (2H, d, J = 8.8 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 32.5, 33.7 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.9 (d, $J_{C\text{-}P}$ = 4.0 Hz), 55.2, 62.6 (q, $J_{C\text{-}P}$ = 7.0 Hz), 96.2 (d, $J_{C\text{-}P}$ = 10.0 Hz), 113.8, 124.4 (d, $J_{C\text{-}P}$ = 4.0 Hz), 126.1 (d, $J_{C\text{-}P}$ = 2.0 Hz), 126.5, 128.4, 129.0, 139.0, 151.4 (d, $J_{C\text{-}P}$ = 11.0 Hz), 160.4, 168.7 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.5.

HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (major) = 15.0 min, Rt_2 (minor) = 20.8 min; >99% ee.

***Diethyl ((3R,4S)-3-(4-methylbenzyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3s)**:



Yield: 37 mg (90%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{28}O_5P^+$ $[M+H]^+$: 415.1669, found: 415.1668.

$[\alpha]_D^{27}$ = +59.60 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19-1.30 (6H, m), 2.27 (3H, s), 2.85-3.18 (3H, m), 3.43 (1H, dd, J = 13.2, 4.0 Hz), 3.98-4.14 (4H, m), 5.68 (1H, dd, J = 6.8, 4.8 Hz), 7.09 (2H, d, J =

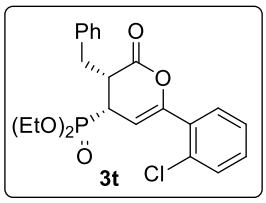
8.0 Hz), 7.13 (1H, t, *J* = 7.2 Hz), 7.22 (2H, t, *J* = 7.6 Hz), 7.28 (2H, d, *J* = 7.6 Hz), 7.42 (2H, t, *J* = 8.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (d, J_{C-P} = 5.0 Hz), 21.1, 32.4, 33.7 (d, J_{C-P} = 140.0 Hz), 42.8 (d, J_{C-P} = 4.0 Hz), 62.7 (q, J_{C-P} = 7.0 Hz), 97.2 (d, J_{C-P} = 10.0 Hz), 124.5 (d, J_{C-P} = 2.0 Hz), 126.4, 128.4, 129.0, 129.1, 138.9, 139.4, 151.6, 151.7, 168.7 (d, J_{C-P} = 5.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 23.3.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 29.3 min, Rt_2 (major) = 42.2 min; >99% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(2-chlorophenyl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3t)**:



Yield: 40 mg (93%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}ClO_5PNa^+$ $[M+Na]^+$: 457.0943, found: 457.0935.

$[\alpha]_D^{28}$ = +108.00 (c 0.1, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 1.31-1.40 (6H, m), 3.01 (1H, dt, *J* = 21.6, 6.4 Hz), 3.10-3.31 (2H, m), 3.54 (1H, dd, *J* = 13.2, 3.6 Hz), 4.10-4.26 (4H, m), 5.70 (1H, dd, *J* = 6.8, 4.4 Hz), 7.21-7.37 (5H, m), 7.40 (3H, d, *J* = 8.0 Hz), 7.47 (1H, t, *J* = 1.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (d, J_{C-P} = 5.0 Hz), 32.4, 33.8 (d, J_{C-P} = 140.0 Hz), 42.7 (d, J_{C-P} = 5.0 Hz), 62.7 (q, J_{C-P} = 7.0 Hz), 104.4 (d, J_{C-P} = 10.0 Hz), 126.5, 126.7, 128.5, 129.1, 130.2, 130.3 (d, J_{C-P} = 2.0 Hz), 130.4, 131.7 (d, J_{C-P} = 3.0 Hz), 132.6 (d, J_{C-P} = 3.0 Hz), 138.8, 150.0 (d, J_{C-P} = 11.0 Hz), 168.5 (d, J_{C-P} = 5.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 23.0.

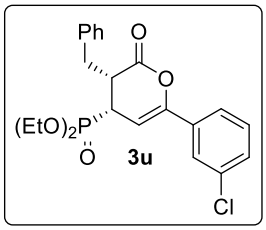
HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 36.6 min, Rt_2 (major) = 39.6 min; >98% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(3-chlorophenyl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3u)**:

Yield: 35 mg (81%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{25}ClO_5P^+$ $[M+H]^+$: 435.1123, found: 435.1119;

[α]$_D^{27}$ = +53.20 (c 0.1, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29-1.39 (6H, m), 2.92-3.26 (3H, m), 3.44-3.60 (1H, m), 4.08-4.23 (4H, m), 5.84 (1H, dd, J = 6.4, 4.4 Hz), 7.20-7.40 (7H, m), 7.48 (1H, d, J = 6.8 Hz), 7.60 (1H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (q, $J_{C\text{-}P}$ = 2.0 Hz), 32.4, 33.8 (d, $J_{C\text{-}P}$ = 139.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 6.0 Hz), 99.6 (d, $J_{C\text{-}P}$ = 10.0 Hz), 122.8 (d, $J_{C\text{-}P}$ = 2.0 Hz), 124.8 (d, $J_{C\text{-}P}$ = 2.0 Hz), 126.6, 128.5, 129.0, 129.3, 129.7, 133.6 (d, $J_{C\text{-}P}$ = 5.0 Hz), 137.7, 138.8, 151.3 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.2 (d, $J_{C\text{-}P}$ = 4.0 Hz);

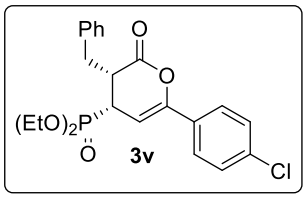
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.9.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 27.6 min, Rt_2 (major) = 37.6 min; >99% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(4-chlorophenyl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3v)**:

Yield: 39 mg (90%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{24}ClO_5PNa^+$ $[M+Na]^+$: 457.0943, found: 457.0915.



[α]$_D^{29}$ = +52.57 (c 0.035, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28-1.39 (6H, m), 2.93-3.25 (3H, m), 3.46-3.58 (1H, m), 4.07-4.22 (4H, m), 5.80 (1H, dd, J = 6.4, 4.8 Hz), 7.22 (1H, t, J = 6.8 Hz), 7.28-7.40 (6H, m), 7.54 (2H, d, J = 8.4 Hz).

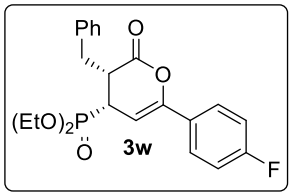
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 32.4, 33.8 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 8.0 Hz), 98.8 (d, $J_{C\text{-}P}$ = 11.0 Hz), 125.9 (d, $J_{C\text{-}P}$ = 2.0 Hz), 126.5, 128.5, 128.7, 129.0, 130.3 (d, $J_{C\text{-}P}$ = 4.0 Hz), 135.3, 138.8, 150.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.3 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.0.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 34.7 min, Rt_2 (major) = 39.5 min; >99% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(4-fluorophenyl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3w)**:

Yield: 42 mg (98%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).



HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{25}FO_5P^+$ $[M+H]^+$: 419.1419, found: 419.1417;

$[\alpha]_D^{27}$ = +105.40 (c 0.1, $CHCl_3$).

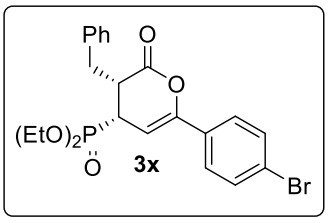
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29-1.39 (6H, m), 2.92-3.28 (3H, m), 3.52 (1H, dd, J = 13.2, 3.6 Hz), 4.07-4.22 (4H, m), 5.75 (1H, dd, J = 6.4, 4.8 Hz), 7.04 (2H, t, J = 8.4 Hz), 7.22 (1H, t, J = 7.2 Hz), 7.28-7.41 (4H, m), 7.59 (2H, dd, J = 8.4, 5.2 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.4 (d, $J_{C\text{-}P}$ = 5.0 Hz), 32.5, 33.9 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 5.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.1 (d, $J_{C\text{-}P}$ = 9.0 Hz), 115.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 126.6, 126.6 (d, $J_{C\text{-}P}$ = 2.0 Hz), 126.7 (d, $J_{C\text{-}F}$ = 1.0 Hz), 128.1 (d, $J_{C\text{-}P}$ = 7.0 Hz), 128.2 (d, $J_{C\text{-}F}$ = 27.0 Hz), 128.5, 129.0, 138.9, 150.8 (d, $J_{C\text{-}P}$ = 11.0 Hz), 163.4 (d, $J_{C\text{-}F}$ = 249.0 Hz), 168.5 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 23.1.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 34.3 min, Rt_2 (major) = 39.4 min; >99% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(4-bromophenyl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3x)**:



Yield: 44 mg (90%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{22}H_{25}BrO_5P^+$ $[M+H]^+$: 479.0618, found: 479.0614;

$[\alpha]_D^{27}$ = +19.00 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27-1.38 (6H, m), 2.91-3.27 (3H, m), 3.45-3.59 (1H, m), 4.06-4.22 (4H, m), 5.82 (1H, dd, J = 6.4, 4.8 Hz), 7.22 (1H, t, J = 6.8 Hz), 7.28-7.40 (4H, m), 7.42-7.55 (4H, m).

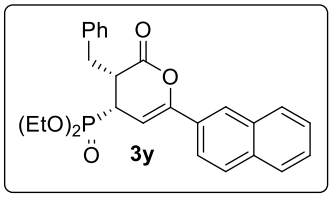
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (t, $J_{C\text{-}P}$ = 6.0 Hz), 32.5, 33.9 (d, $J_{C\text{-}P}$ = 139.0 Hz), 42.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 8.0 Hz), 98.9 (d, $J_{C\text{-}P}$ = 11.0 Hz), 123.6, 126.2 (d, $J_{C\text{-}P}$ =

2.0 Hz), 126.6, 128.5, 129.0, 130.7 (d, $J_{C\text{-}P}$ = 4.0 Hz), 131.7, 138.8, 150.7 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.3 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.8.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 36.3 min, Rt_2 (major) = 40.4 min; >99% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(naphthalen-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3y)**:



Yield: 44 mg (96% yield), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{26}H_{27}O_5PNa^+$ $[M+Na]^+$: 473.1489, found: 473.1484;

$[\alpha]_D^{26}$ = +61.60 (c 0.1, $CHCl_3$).

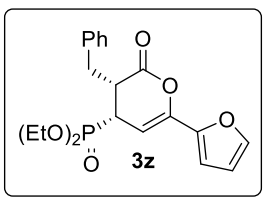
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29-1.39 (6H, m), 2.97-3.32 (3H, m), 3.56 (1H, dd, *J* = 13.2, 3.2 Hz), 4.08-4.24 (4H, m), 5.96 (1H, dd, *J* = 6.4, 4.8 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 7.31 (2H, t, *J* = 7.6 Hz), 7.38 (2H, d, *J* = 7.6 Hz), 7.46-7.54 (2H, m), 7.63 (1H, d, *J* = 8.4 Hz), 7.81 (2H, d, *J* = 8.8 Hz), 7.86 (1H, t, *J* = 5.6 Hz), 8.16 (1H, s).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 32.5, 33.9 (d, $J_{C\text{-}P}$ = 140.0 Hz), 42.9 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.7 (q, $J_{C\text{-}P}$ = 7.0 Hz), 98.8 (d, $J_{C\text{-}P}$ = 10.0 Hz), 121.8, 124.2 (d, $J_{C\text{-}P}$ = 3.0 Hz), 126.5, 126.6, 126.8, 127.5, 128.2, 128.5, 128.6, 128.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 129.0, 132.9, 133.5, 138.9, 151.5 (d, $J_{C\text{-}P}$ = 11.0 Hz), 168.7 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 23.1.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 42.8 min, Rt_2 (major) = 50.3 min; >99% ee.

***Diethyl ((3R,4S)-3-benzyl-6-(furan-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-yl)phosphonate* (3z)**:



Yield: 38 mg (97%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{20}H_{23}O_6PNa^+$ $[M+Na]^+$: 413.1125, found: 413.1114.

[α]D^{26} = +6.00 (c 0.1, $CHCl_3$).

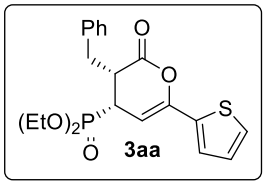
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21-1.31 (6H, m), 2.82-3.19 (3H, m), 3.35-3.51 (1H, m), 3.99-4.17 (4H, m), 5.67 (1H, dd, *J* = 6.8, 4.8 Hz), 6.34 (1H, t, *J* = 3.2 Hz), 6.53 (1H, d, *J* = 2.0 Hz), 7.14 (1H, t, *J* = 6.8 Hz), 7.19-7.35 (5H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.2 (q, $J_{C\text{-}P}$ = 3.0 Hz), 32.5, 33.6 (d, $J_{C\text{-}P}$ = 140.0 Hz), 43.1 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 3.0 Hz), 96.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 108.2 (d, $J_{C\text{-}P}$ = 3.0 Hz), 111.4, 126.5, 128.4, 129.0, 138.8, 143.3, 131.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 146.5 (d, $J_{C\text{-}P}$ = 6.0 Hz), 168.1 (d, $J_{C\text{-}P}$ = 5.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.9.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 41.4 min, Rt_2 (major) = 57.6 min; >98% ee.

Diethyl ((3R,4S)-3-benzyl-2-oxo-6-(thiophen-2-yl)-3,4-dihydro-2H-pyran-4-yl)phosphonate **(3aa)**:



Yield: 38 mg (95%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{20}H_{24}O_5PS^+$ $[M+H]^+$: 407.1077, found: 407.1076.

[α]D^{27} = +86.40 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31-1.40 (6H, m), 2.98 (1H, dt, *J* = 21.6, 6.4 Hz), 3.08-3.30 (2H, m), 3.53 (1H, dd, *J* = 13.2, 3.6 Hz), 4.08-4.25 (4H, m), 5.69 (1H, dd, *J* = 7.2, 4.8 Hz), 7.02 (1H, t, *J* = 4.4 Hz), 7.20-7.43 (7H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 32.5, 33.8 (d, $J_{C\text{-}P}$ = 140.0 Hz), 43.0 (d, $J_{C\text{-}P}$ = 4.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 97.2 (d, $J_{C\text{-}P}$ = 11.0 Hz), 125.0 (d, $J_{C\text{-}P}$ = 2.0 Hz), 126.1, 126.5, 127.5, 128.5, 129.0, 135.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 138.8, 147.5 (d, $J_{C\text{-}P}$ = 12.0 Hz), 168.1 (d, $J_{C\text{-}P}$ = 5.0 Hz).

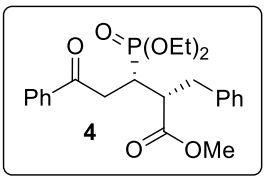
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.9.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 25.6 min, Rt_2 (major) = 27.9 min; >99% ee.

Methyl (2R,3S)-2-benzyl-3-(diethoxyphosphoryl)-5-oxo-5-phenylpentanoate **(4)**:

Yield: 43 mg (99%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{23}H_{29}O_6PNa^+$ $[M+Na]^+$: 455.1594, found: 455.1592;



$[\alpha]_D^{28}$ = -20.80 (c 0.1, $CHCl_3$).

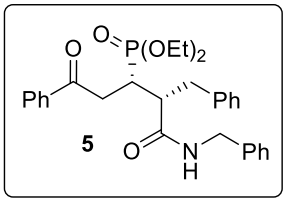
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15-1.30 (6H, m), 2.87-3.18 (3H, m), 3.19-3.32 (1H, m), 3.33-3.43 (2H, m), 3.46 (3H, s), 3.97-4.15 (4H, m), 7.04-7.24 (5H, m), 7.40 (2H, t, J = 7.6 Hz), 7.50 (1H, t, J = 7.2 Hz), 7.92 (2H, d, J = 7.2 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3 (d, $J_{C\text{-}P}$ = 4.0 Hz), 33.0 (d, $J_{C\text{-}P}$ = 142.0 Hz), 34.4 (d, $J_{C\text{-}P}$ = 3.0 Hz), 46.1 (d, $J_{C\text{-}P}$ = 1.0 Hz), 51.8, 62.1 (q, $J_{C\text{-}P}$ = 7.0 Hz), 126.3, 128.1, 128.3, 128.6, 128.9, 133.2, 136.5, 139.2, 173.5 (d, $J_{C\text{-}P}$ = 17.0 Hz), 196.7 (d, $J_{C\text{-}P}$ = 10.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 30.2.

HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, UV 254 nm), Rt_1 (major) = 30.2 min, Rt_2 (minor) = 41.3 min; >99% ee.

***Diethyl ((2R,3S)-2-benzyl-1-(benzylamino)-1,5-dioxo-5-phenylpentan-3-yl)phosphonate* (5)**:



Yield: 50 mg (98%), pale yellow gummy liquid, eluent: EtOAc/Hexane (8:2).

HRMS (ESI-TOF) m/z: Mass calcd. for $C_{29}H_{35}NO_5P^+$ $[M+H]^+$: 508.2248, found: 508.2248.

$[\alpha]_D^{28}$ = -83.00 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, t, J = 6.8 Hz), 3.02-3.19 (3H, m), 3.27-3.56 (2H, m), 3.63-3.80 (1H, m), 3.97-4.20 (5H, m), 4.37 (1H, dd, J = 6.4 Hz), 6.42 (1H, t, J = 5.6), 6.92 (2H, t, J = 3.6 Hz), 7.16-7.31 (8H, m), 7.48 (2H, t, J = 7.6 Hz), 7.57 (1H, t, J = 7.2 Hz), 8.01 (2H, d, J = 7.2 Hz).

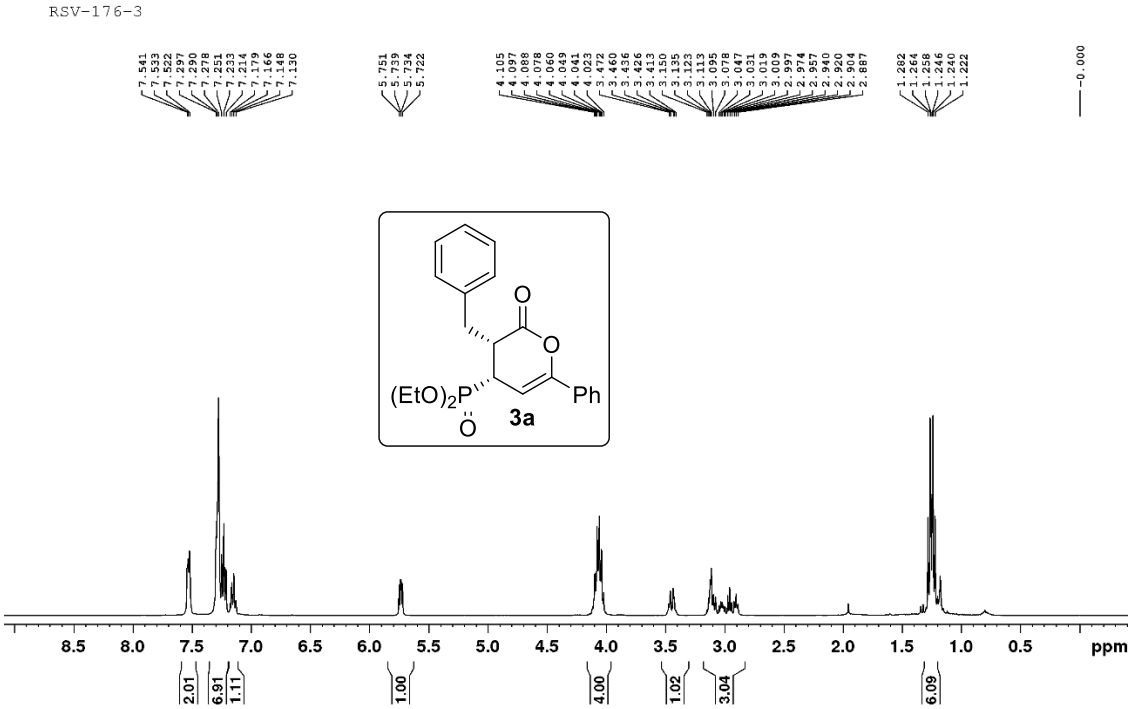
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.2 (t, $J_{C\text{-}P}$ = 6.0 Hz), 33.3 (d, $J_{C\text{-}P}$ = 140.0 Hz), 34.5 (d, $J_{C\text{-}P}$ = 3.0 Hz), 34.7 (d, $J_{C\text{-}P}$ = 4.0 Hz), 43.1, 47.3 (d, $J_{C\text{-}P}$ = 2.0 Hz), 61.7 (q, $J_{C\text{-}P}$ = 7.0 Hz), 126.2, 126.9, 127.3, 128.0, 128.3, 128.4, 128.5, 129.0, 133.0, 136.7, 137.9, 139.3, 172.3 (d, $J_{C\text{-}P}$ = 15.0 Hz), 196.9 (d, $J_{C\text{-}P}$ = 6.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 30.9.

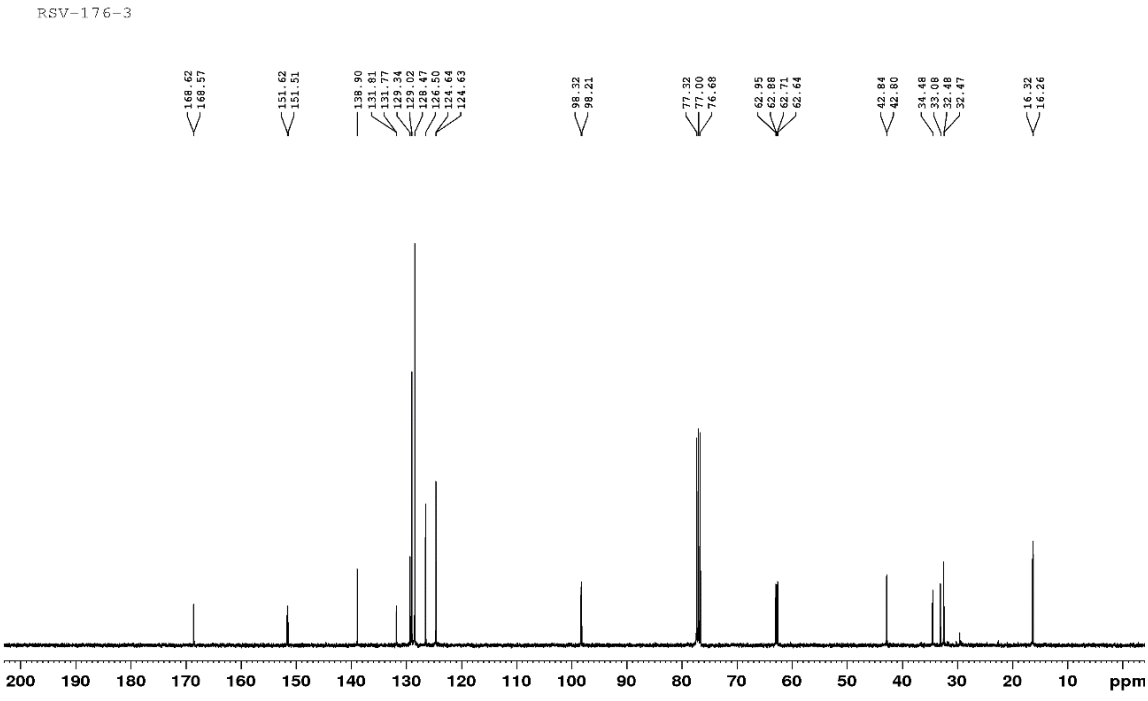
HPLC analysis: (Chiralcel IC; hexane/*i*-PrOH 40:60, flow rate 0.5 mL/min, UV 254 nm), Rt_1 (minor) = 15.8 min, Rt_2 (major) = 18.6 min; >96% ee.

2.6.5. ^{1}H and $^{13}C\{^{1}H\}$ Spectra of the Products

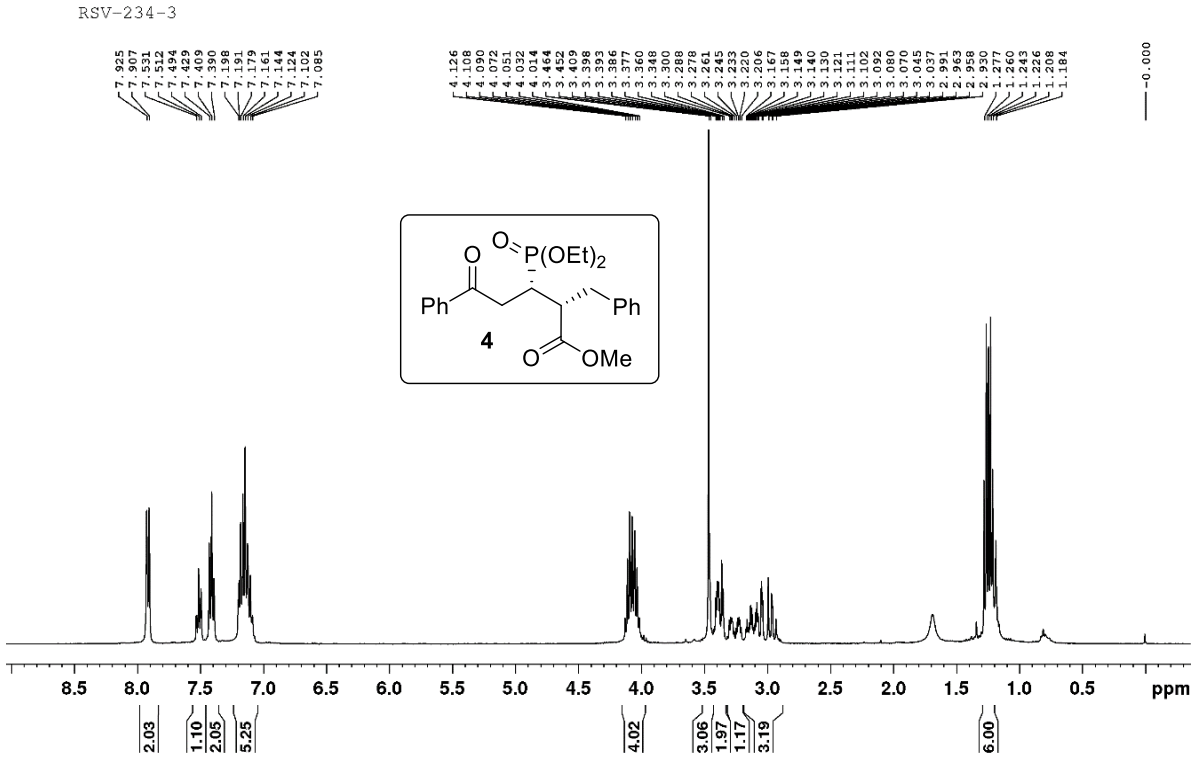
^{1}H NMR of compound 3a (400 MHz/$CDCl_3$)



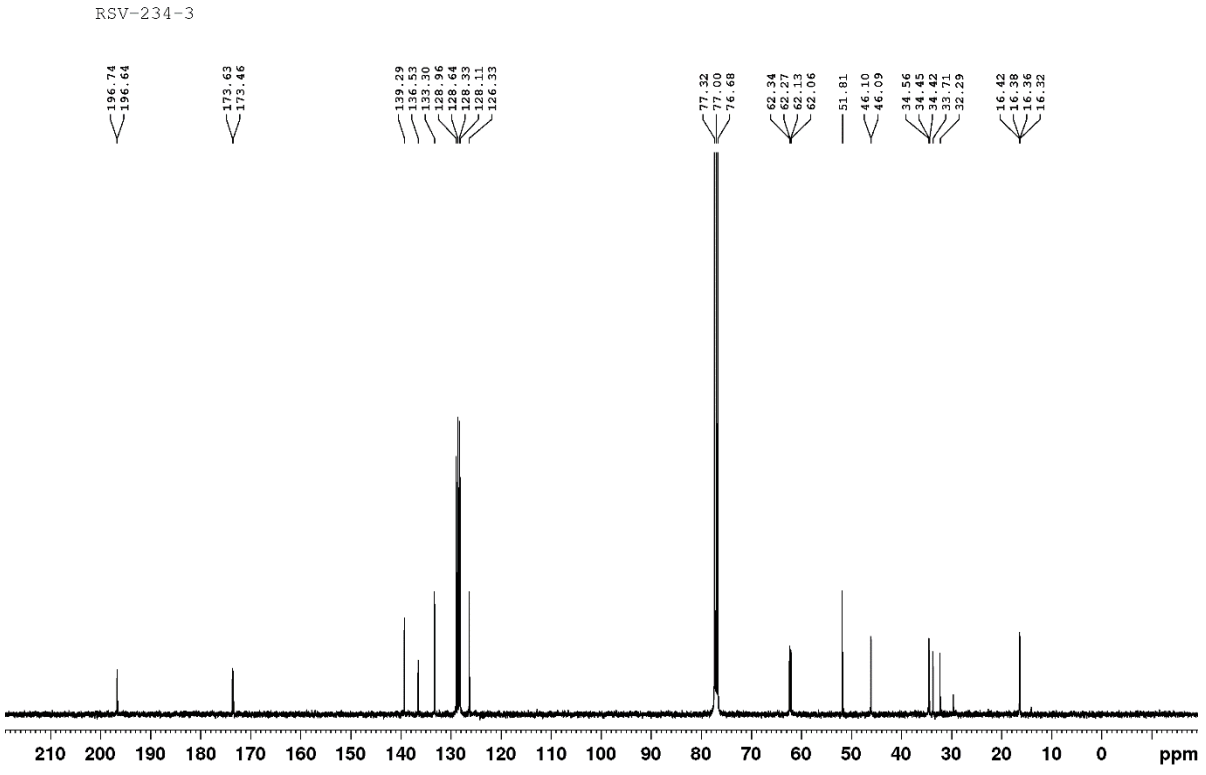
$^{13}C\{^{1}H\}$ NMR of compound 3a (100 MHz/$CDCl_3$)



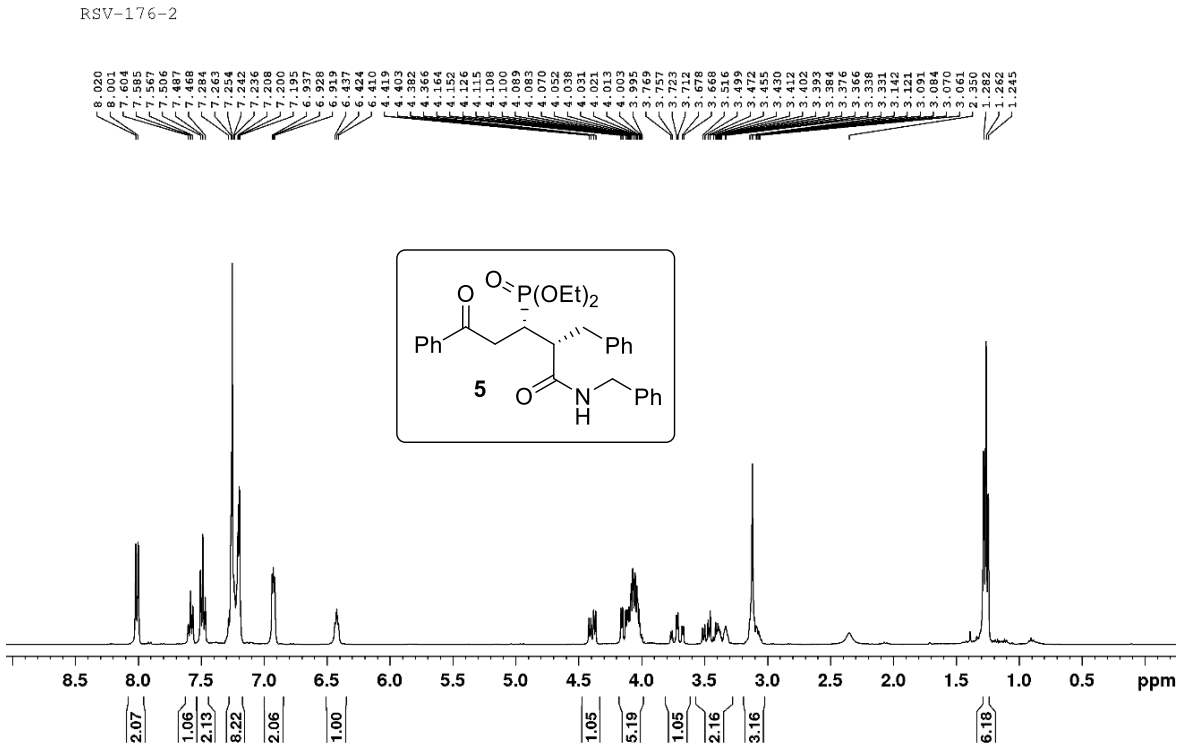
^{1}H NMR of compound 4 (400 MHz/$CDCl_3$)



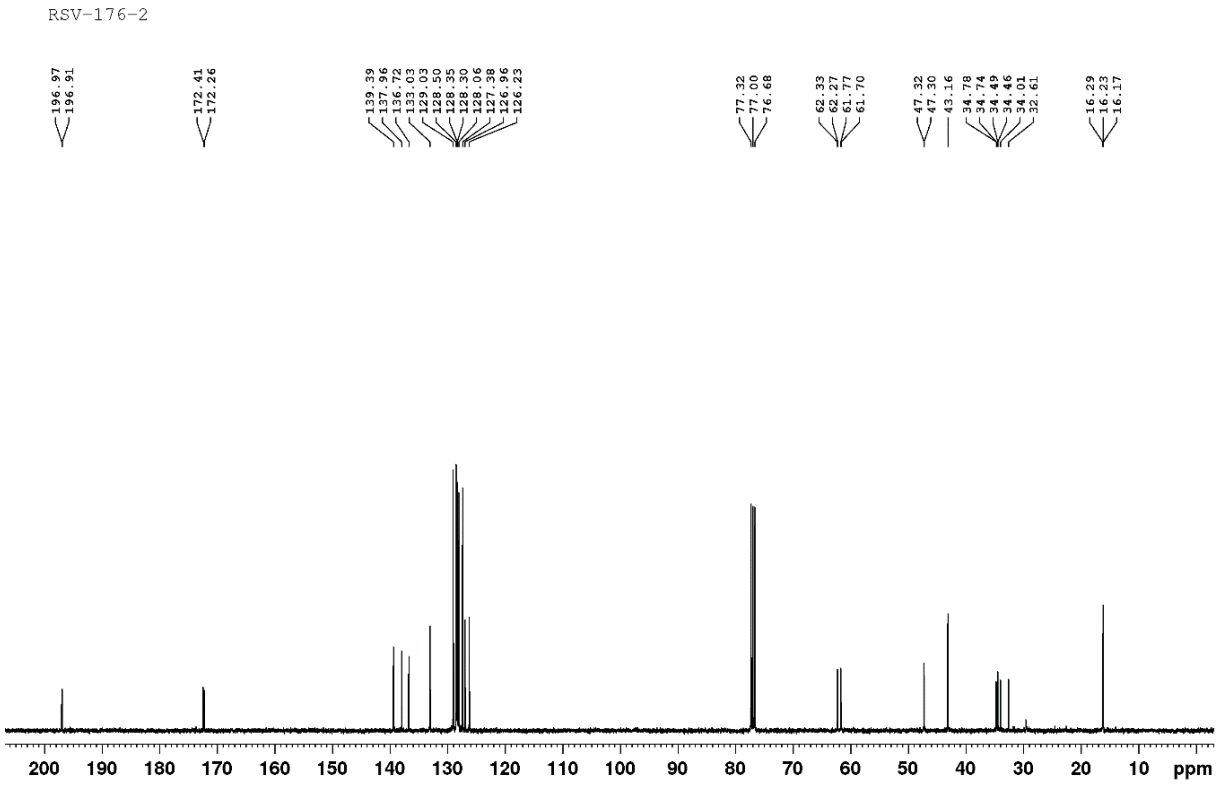
^{13}C{^{1}H} NMR of compound 4 (100 MHz/$CDCl_3$)



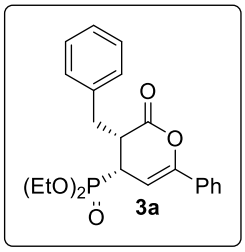
^{1}H NMR of compound 5 (400 MHz/$CDCl_3$)

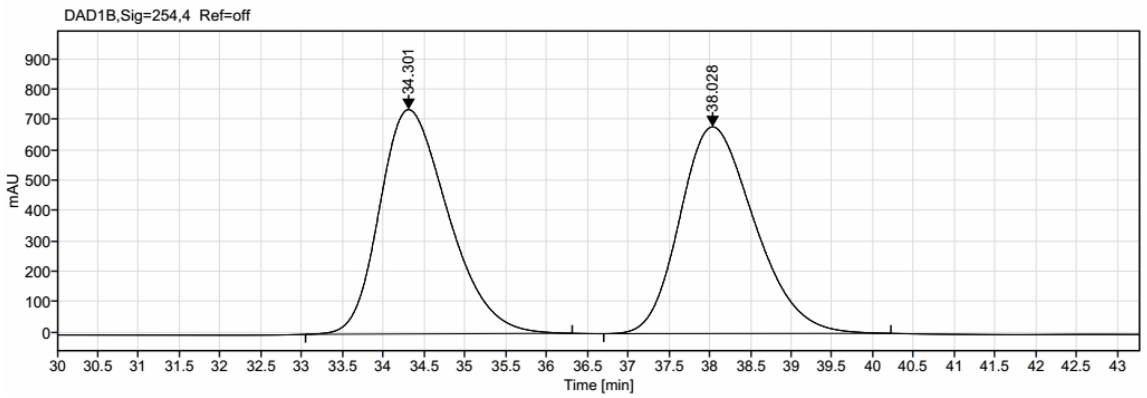


^{13}C{^{1}H} NMR of compound 5 (100 MHz/$CDCl_3$)



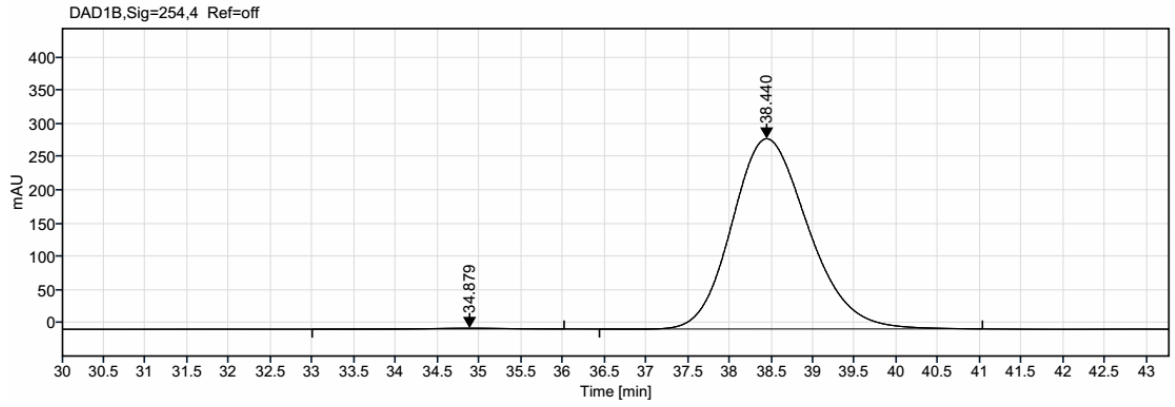
2.6.6. HPLC Chromatogram of the Products





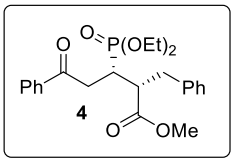
Signal: DAD1B,Sig=254,4 Ref=off

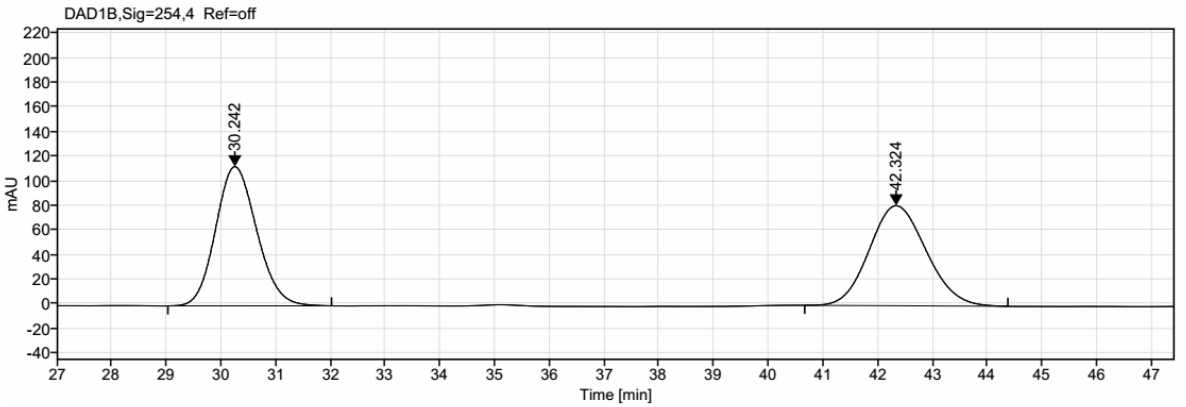
RT [min]	Type	Width [min]	Area	Height	Area%	Name
34.301	MM m	0.91	43209.50	738.91	49.88	
38.028	MM m	0.98	43413.15	680.96	50.12	
		Sum	86622.64			



Signal: DAD1B,Sig=254,4 Ref=off

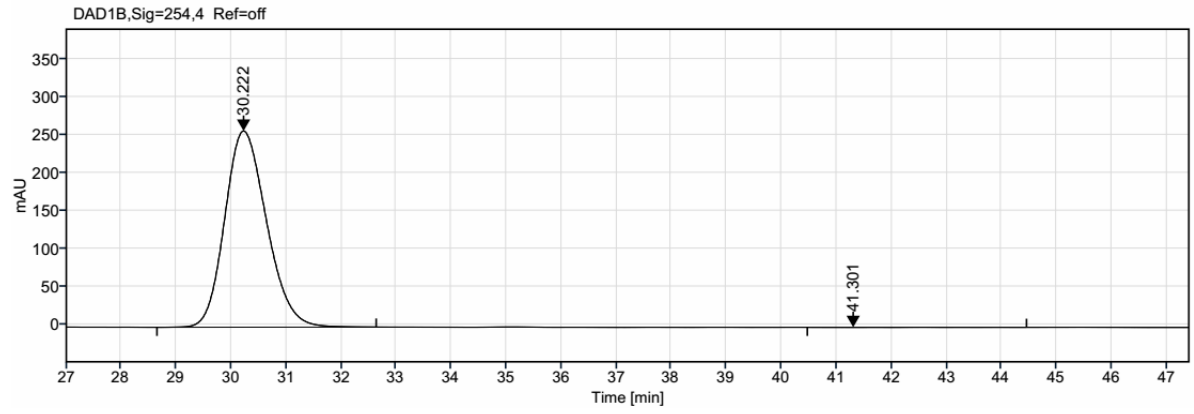
RT [min]	Type	Width [min]	Area	Height	Area%	Name
34.879	MM m	0.75	78.08	1.24	0.43	
38.440	MM m	0.98	18195.35	286.36	99.57	
		Sum	18273.42			





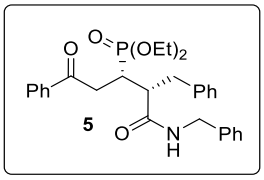
Signal: DAD1B,Sig=254,4 Ref=off

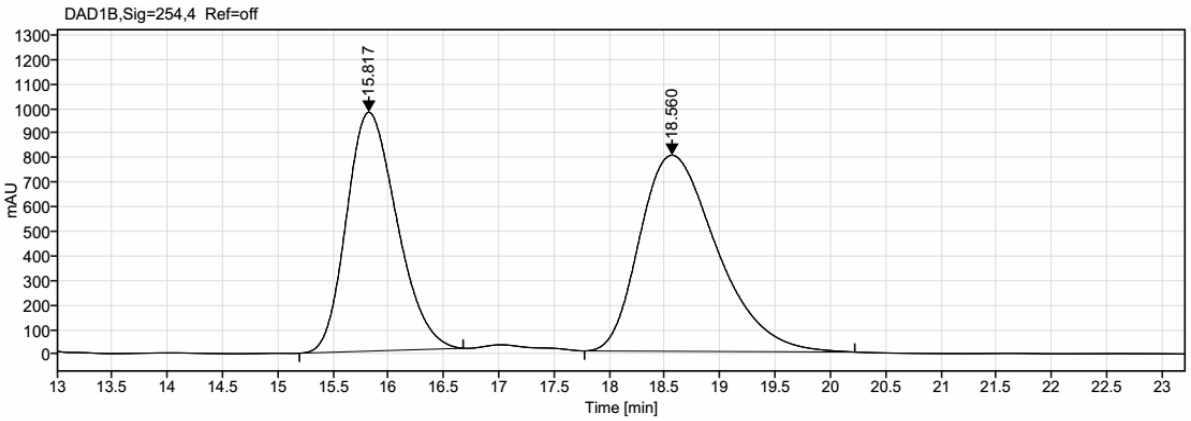
RT [min]	Type	Width [min]	Area	Height	Area%	Name
30.242	MM m	0.81	5905.24	113.24	50.06	
42.324	MM m	1.10	5892.08	81.38	49.94	
		Sum	11797.32			



Signal: DAD1B,Sig=254,4 Ref=off

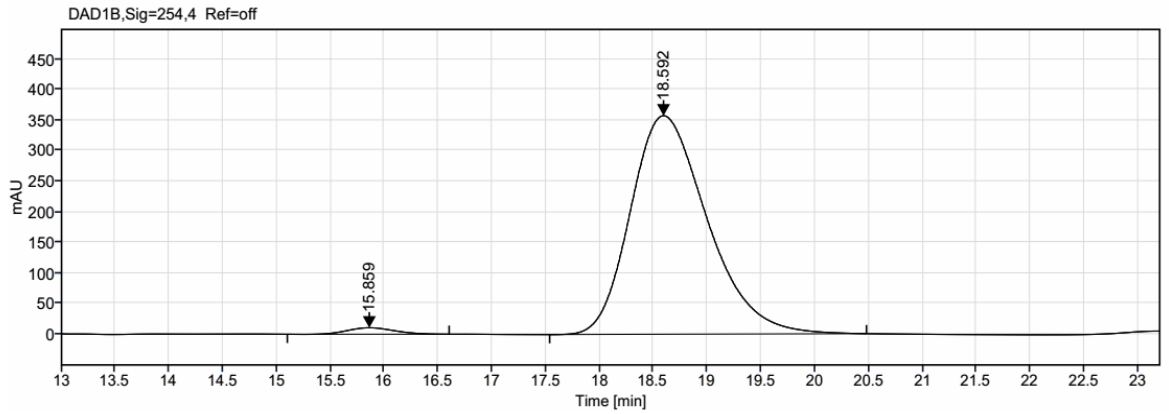
RT [min]	Type	Width [min]	Area	Height	Area%	Name
30.222	MM m	0.80	13607.33	257.73	99.99	
41.301	MM n	0.16	0.96	0.07	0.01	
		Sum	13608.29			





Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
15.817	MM m	0.49	30798.47	972.18	44.29	
18.560	MM m	0.75	38742.57	797.83	55.71	
		Sum	69541.04			



Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
15.859	MM m	0.47	319.57	10.62	1.77	
18.592	MM m	0.76	17728.78	357.53	98.23	
		Sum	18048.34			

2.7. References

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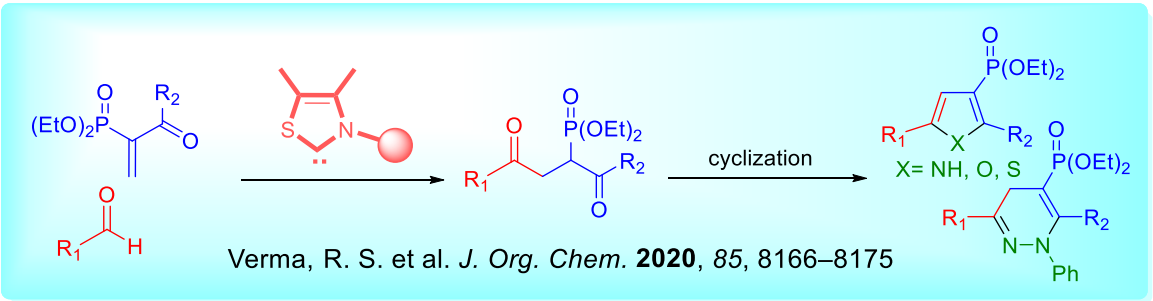
Chapter 3

Carbene Catalyzed Synthesis of *α*-phosphorylated 1,4-diketones: Access of 3/4-Phosphorylated Heterocycles

Heterocyclic motifs such as pyrroles, furans, thiophenes and dihydropyridazines are abundantly found in numerous biologically active natural, non-natural, pharmaceuticals and agrochemicals products. On the other hand, phosphoryl groups are omnipresent in the biological system and other vital molecules. So, the phosphorylated heterocycles constitute the virtues of both the phosphorus moiety and the heterocyclic scaffolds. Accordingly, the preparation of these class of compounds has constantly attracted the attention of both the industries as well as the academia. Despite of progress, the preparation of these class of compounds has remained challenging and often requires multi-steps synthesis and transition metal catalyzed cross coupling reaction. Herein, we have developed a global method for the preparation of C3-phosphorylated pyrroles, furans and thiophenes and 4-phosphorylated dihydropyridazines under a metal-free organocatalytic reaction condition. To achieve this, we have developed the first NHC-catalyzed Stetter reaction between vinylphosphonates and aldehydes to access *α*-phosphorylated 1,4-diketones, followed by a cyclization reaction. These phosphorylated 1,4-diketones could be efficiently converted into C3-phosphorylated pyrroles, furans and thiophenes, and C4-phosphorylated dihydropyridazines.



3.1. Introduction

Heterocyclic compounds are abundantly found in numerous biologically active natural and non-natural products, pharmaceuticals, and agrochemicals.[1] In addition, phosphorus-containing organic compounds have received significant attention due to their biological applications and as ligands in material science.[2] Organophosphorus compounds are also used as organocatalysts for many valuable synthetic transformations, building scaffolds in synthetic chemistry as ligands and particularly it serves as directing groups in the C-H bond activation.[3] Phosphorylated heterocycles have the virtues of both the phosphorus moiety and the heterocycle scaffolds. They demonstrate excellent biological properties as enzyme inhibitors, pharmaceuticals, agrochemicals, antiviral and antibacterial (Figure 3.1). Therefore, the preparation of these class of compounds have increasingly attracted the attention of both the industries as well as academia.[4,5]

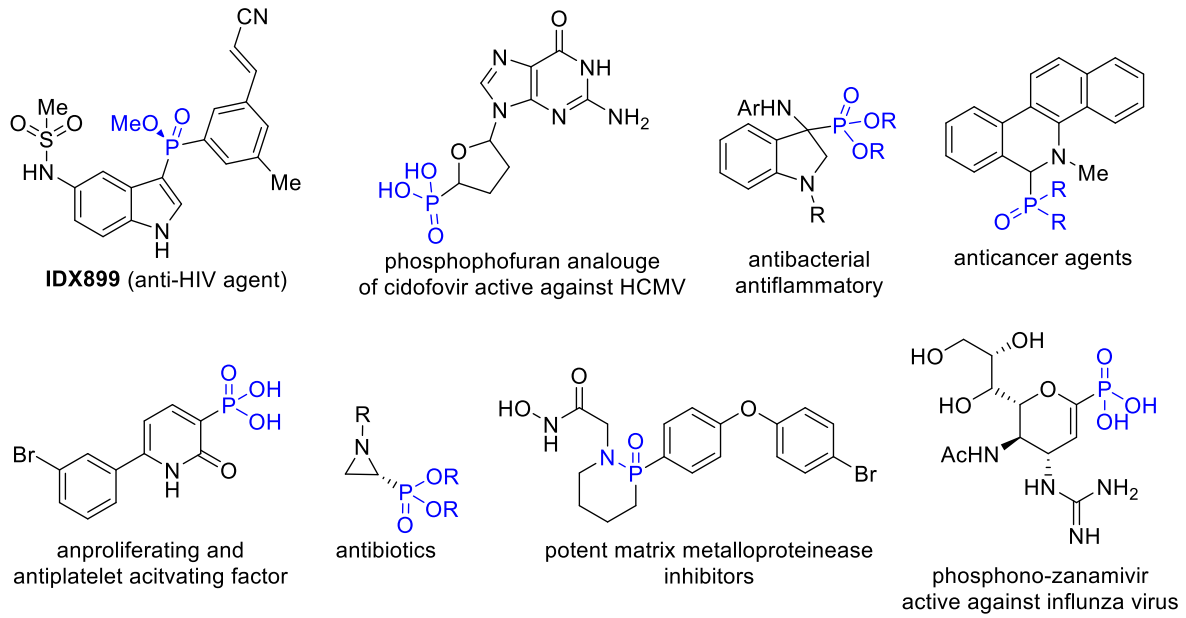
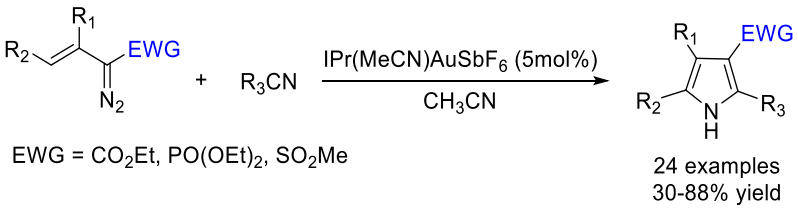


Figure 3.1. Biologically active phosphorus-containing heterocyclic compounds

The construction of 3/4-phosphorylated derivatives of heterocycles like pyrroles, furans, thiophenes and dihydropyridazines has remained difficult in comparison to 2-phosphorylated heterocycles due to the lower reactivity of the C-3/4 positions. Several valuable literature protocols for the synthesis of these compounds have been developed. These reported approaches are generally based on metal-catalyzed cyclization of the phosphorus containing functionalized starting materials. In addition, a directing group-assisted functionalization or metal-catalyzed substitution of heteroaryl halides have also been reported.

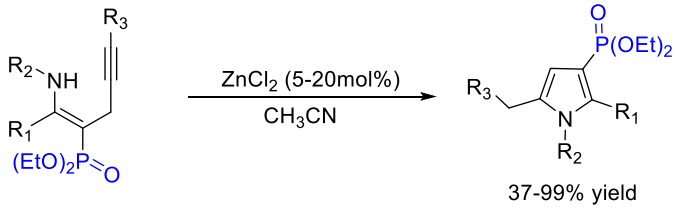
3.2. Literature methods for the preparation of phosphorylated heterocycles

In 2013, Lopez and co-workers developed the synthesis of 3-phosphorylated pyrroles by the reaction of alkenyldiazo compounds with nitriles catalyzed by *i*-Pr(CH_3CN)$AuSbF_6$ catalysts in modest to good yield (Scheme 3.1).[6a] This reaction shows complete regiochemical control in the formal [3+2] cyclization. The terminal position of alkenylgold carbenoid intermediate reacted with nitrile to induce regiochemical outcome in the reaction. A variety of nitriles were found compatible with this [3+2] cyclization reaction to afford the products.



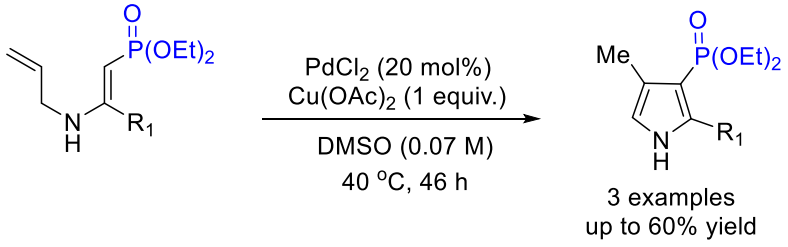
Scheme 3.1. Synthesis of 3-phosphorylated pyrroles from alkenyldiazo compounds

In 2014, Steven and co-workers developed the $ZnCl_2$-catalyzed cyclization of propargylic enamines to obtain phosphorylated pyrroles.[6b] To achieve this, they prepared the starting materials in two steps using *β*-ketophosphonates. This method was well tolerated with a wide variety of 1,2- and 5-position substituted pyrroles to produce the 3-phosphorylated pyrroles in moderate to good yield (Scheme 3.2).



Scheme 3.2. Zinc chloride catalyzed synthesis of 3-phosphorylated pyrroles

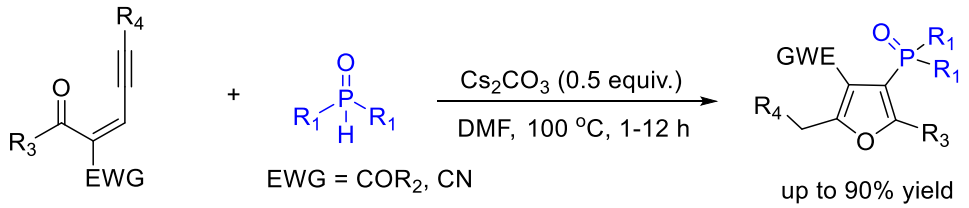
Deb and co-workers in 2016 reported the preparation of 3-phosphorylated pyrroles by the cyclization of imino-/enaminophosphonates. The cyclization of imino-/enaminophosphonates was catalyzed by $PdCl_2$/$Cu(OAc)_2$ in dimethyl oxide (DMSO) solvent.



Scheme 3.3. Palladium chloride catalyzed synthesis of 3-phosphorylated pyrroles

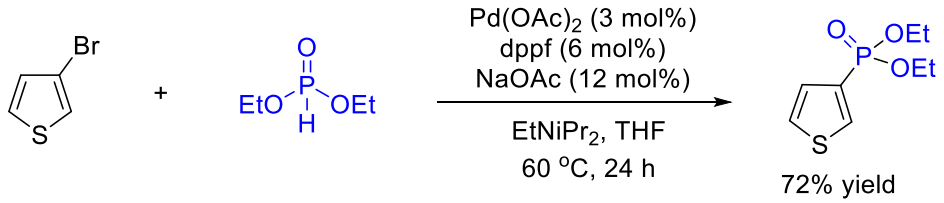
This resulted in the formation of 3-phosphorylated pyrroles in moderate to good yield 37-99% (Scheme 3.3).[6c]

In 2016, Jiang and co-workers developed the preparation of 3-phosphorylated furans using ene-yne-ketones with H-phosphonates.[7] In this reaction, Cs_2CO_3 was used as the base to promote the cyclization of various derivatives of ene-yne-ketones to produce the phosphorylated furans in moderate to good yield (Scheme 3.4).



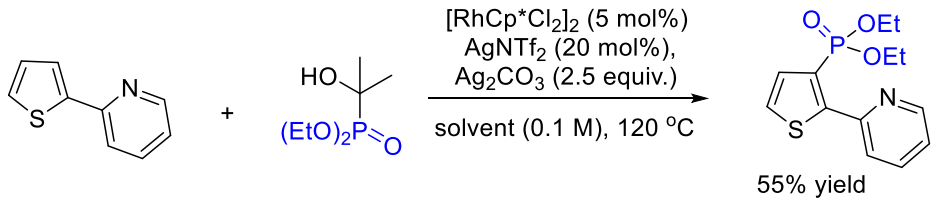
Scheme 3.4. Recent approaches for the synthesis of 3-phosphorylated furans

Muimo and co-workers in 2014 reported the preparation of 3-phosphorylated thiophenes in the presence of $Pd(OAc)_2$/dppf/NaOAc and $EtNiPr_2$ in THF solvent. The $Pd(OAc)_2$/dppf/NaOAc catalyzed the coupling of 3-bromo thiophene with $(EtO)_2P(O)H$ to produce 3-phosphorylated thiophenes in 72% yield (Scheme 3.5).[8a]



Scheme 3.5. Recent approaches for the synthesis of 3-phosphorylated furans

In 2016, Hong and co-workers developed the synthesis of 3-phosphorylated thiophenes using a phosphorylating agent catalyzed by $[RhCp^*Cl_2]_2/AgNTf_2/Ag_2CO_3$ in 55% yield (Scheme 3.6).[8b]



Scheme 3.6. Recent literature protocols for the synthesis of 3-phosphorylated thiophenes

Recently, in 2018 Yamaguchi and co-workers established the decarbonylative phosphorylation of thiophenes catalyzed by $Ni(OAc)_2$/dcypt to obtain the 3-phosphorylated

thiophene in 65% yield (Scheme 3.3, Eq. 3)[8c] Despite the success, these reported protocols suffer from severe multiple limitations like: (i) suitable for one specific category of heterocycle, (ii) multistep preparation of complex advanced starting materials, (iii) catalyzed by transition-metal, and (iv) requires a suitable directing group on the ring. To the best of our knowledge, a global method for the preparation 3-phosphorylated-pyrroles, -furans, and -thiophenes is elusive. In addition, there is no literature report for the preparation of 4-phosphorylated 2,5-dihydropyridazines.

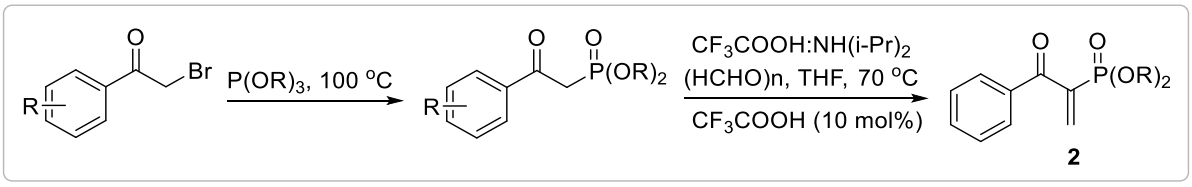
3.3. Objective of the Work

With a long interest in developing metal-free reactions, we were interested to establish the first global method for the preparation of these challenging 3-phosphorylated-pyrroles, -furans, and -thiophenes, and 4-phosphorylated 2,5-dihydropyridazines. We envisioned that all these heterocycles can be prepared from a common starting material, *α*-phosphorylated 1,4-diketones. Our literature survey did not lead to any metal- or organo-catalyzed protocols for the synthesis of *α*-phosphorylated 1,4-diketones. These *α*-phosphorylated 1,4-diketones can be prepared from vinylphosphonates and aldehydes *via* Stetter reaction using NHC organocatalysts. Consequently, the development of an effective approach for the synthesis of *α*-phosphorylated 1,4-diketone, possibly metal-free and organocatalytic, is highly desired. These *α*-phosphorylated 1,4-diketone could be converted to these phosphorylated heterocyclic compounds in one step via simple transformations.[9,10]

3.4. Results and Discussion

3.4.1. Preparation of the Starting Materials

In the development of this methodology, we have prepared vinylphosphonates (*α*-phosphoryl enones) **2** in two steps using commercially available *α*-bromoketones. In the first step of the reaction we prepared *β*-ketophosphonates from the *α*-bromoketones in the presence of tri-alkylphosphite.[11] In the last step of the reaction vinylphosphonates was synthesized from the *β*-ketophosphonates in the presence of paraformaldehyde, CF_3COOH:HN(i-Pr_2) salt and 10 mol% of the trifluoroacetic acid as reported in the literature (Scheme 3.7).[12] Aryl and alkyl aldehydes were obtained from commercial sources, while *α,β*-unsaturated aldehydes were prepared by following the literature protocol as discussed in chapter 2.[13] The thiazolium catalyst **L** used in this methodology was purchased from a commercial source.

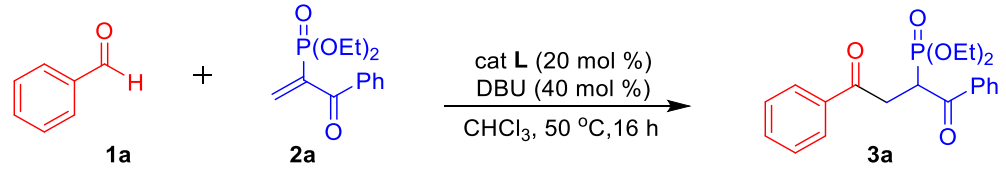


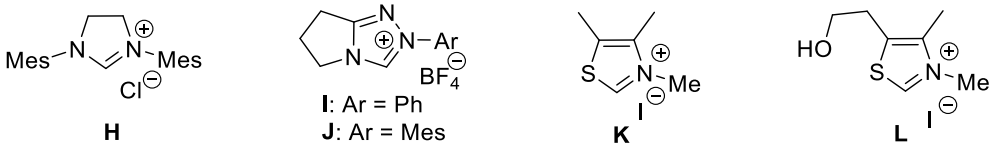
Scheme 3.7. Synthesis of vinylphosphonates

3.4.2. Optimization Studies of the Reaction

We started our investigation for the carbene catalyzed preparation of *α*-phosphorylated 1,4-diketone by employing commercially available benzaldehyde **1a** with vinylphosphonates

Table 3.1. Optimization of the reaction condition[a]





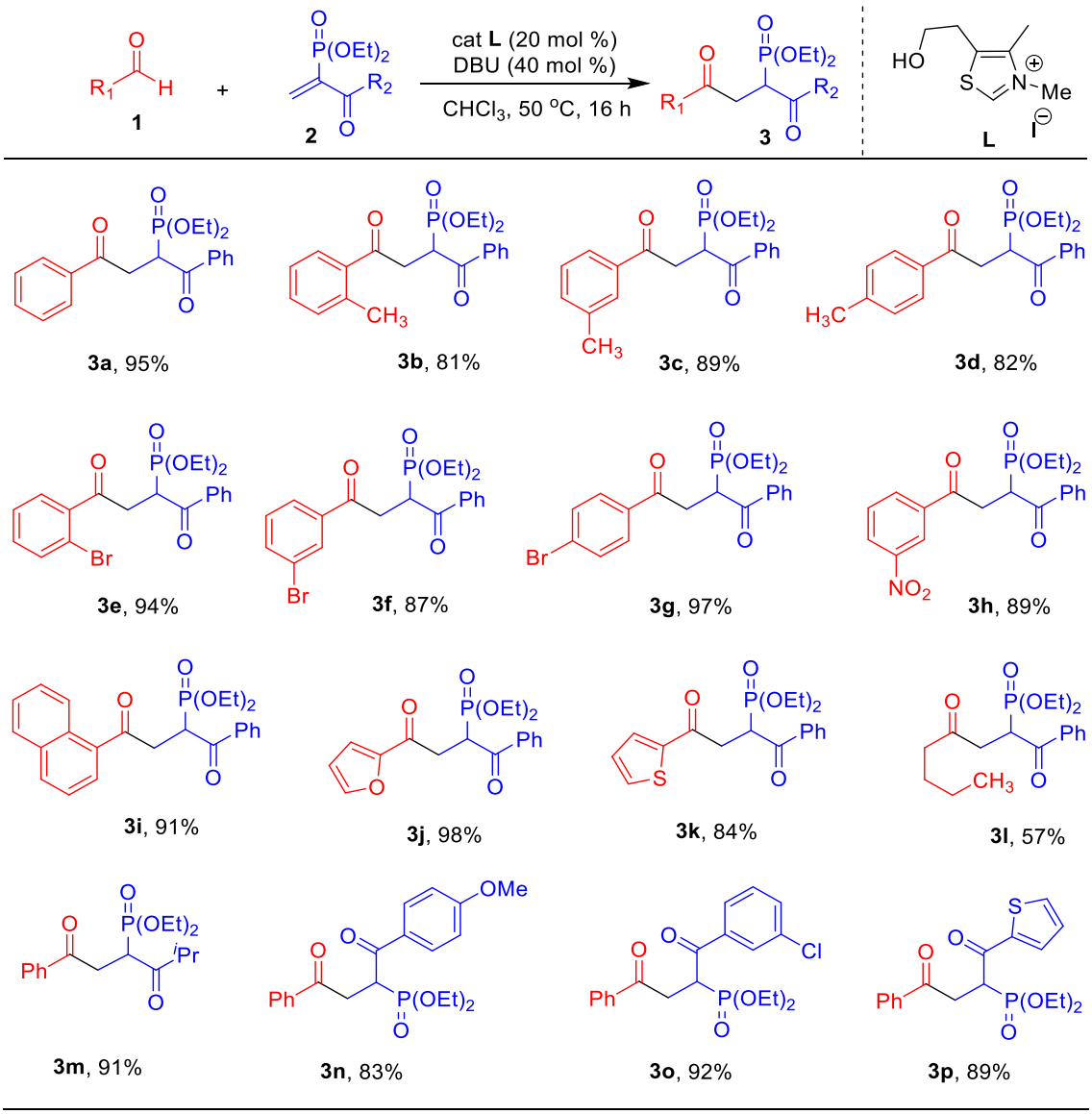
entry	NHC	solvent	base	yield (%)
1	-	$CHCl_3$	DBU	0
2	**H**	$CHCl_3$	DBU	48
3	**I**	$CHCl_3$	DBU	trace
4	**J**	$CHCl_3$	DBU	trace
5	**K**	$CHCl_3$	DBU	64
6	**L**	$CHCl_3$	DBU	95
7	**L**	CH_2Cl_2	DBU	77
8	**L**	$(CH_2Cl)_2$	DBU	61
9	**L**	$CHCl_3$	DABCO	21
10	**L**	$CHCl_3$	^{t}BuOK	26
11	**L**	$CHCl_3$	TMG	89
12	**L**	$CHCl_3$	DBU	67

[a]General reaction condition: benzaldehyde **1a** (0.15 mmol), vinylphosphonates **2a** (0.10 mmol), cat. (20 mol%), base (40 mol%), solvent (1.0 mL) at 50 °C for 16 h.

(*α*-phosphoryl enones) **2a** as model substrates. The screening results of the this NHC-catalyzed Stetter reaction are presented in Table 3.1. First, we performed this reaction in absence of NHC catalyst to evaluate that reaction is catalytic or not. But there is no product formation was observed in absence of carbene catalyst, it clearly indicates the coupling of aldehyde with vinylphosphonate is catalyzed by NHC catalyst. Next, we performed this reaction in the presence of imidazolium NHC salt **H** using an organic base DBU in $CHCl_3$ solvent at 50 ^oC, which afforded the desired product **3a** in moderate yield 48% (entry 2). Afterward, we evaluate this reaction with pyrrolidine derived *N*-Ph- and *N*-Mes-protected triazolium precatalyst **I** and **J**, which failed to produce the *α*-phosphorylated 1,4-diketone product (entry 3-4). Next, we preformed this reaction using thiazolium precatalyst **K**, which produced the corresponding *α*-phosphorylated 1,4-diketone **3a** in good yield 64% (entry 5). Gratifyingly, the use of thiazolium precatalyst **L** proved fruitful, which afforded the *α*-phosphorylated 1,4-diketone **3a** in 95% yield (entry 6). On performing this reaction in dichloromethane and 1,2-dichloroethane solvent instead of chloroform gives the desired product in 77 % and 61% yield respectively (entry 7-8). We also tested this reaction in the presence of DABCO and ^{t}BuOK bases, which produced the desired product in very low yield (entry 9-10). Performing this reaction in the presence of TMG base instead of DBU, produces the desired product in 89% yield (entry 11). This reaction at room temperature instead of heating produced the *α*-phosphorylated 1,4-diketone in moderate yield 55% (entry12).

3.4.3. Stetter Reaction of Aromatic and Aliphatic Aldehydes with Vinylphosphonates

After getting the best result, we next thought to test the compatibility of this thiazolium catalyzed Stetter reaction by employing a wide variety of aldehydes and *α*-phosphoryl enones (Scheme 3.8). Performing this reaction with electron rich aldehyde derivatives such as 2-methylbenzaldehyde, 3-methylbenzaldehyde and 4-methylbenzaldehyde furnish the corresponding *α*-phosphorylated 1,4-diketones in 81-89% yield (**3b**-**3d**). Similarly, electron deficient arylaldehydes such as bromobenzaldehyde derivates and 3-nitrobenzaldehyde reacted smoothly to produce *α*-phosphorylated 1,4-diketones in 87-97% yield (**3e**-**3h**). The naphthyl- and heteroaromatic aldehydes under the optimized reaction condition were efficiently converted into diketone products **3i**-**3k** in 84-98% yields. Notably, in this reaction aliphatic aldehyde (n-valeraldehyde) are also found compatible substrate to produce the desired 1,4-diketone **3l** in moderate yield 57%.

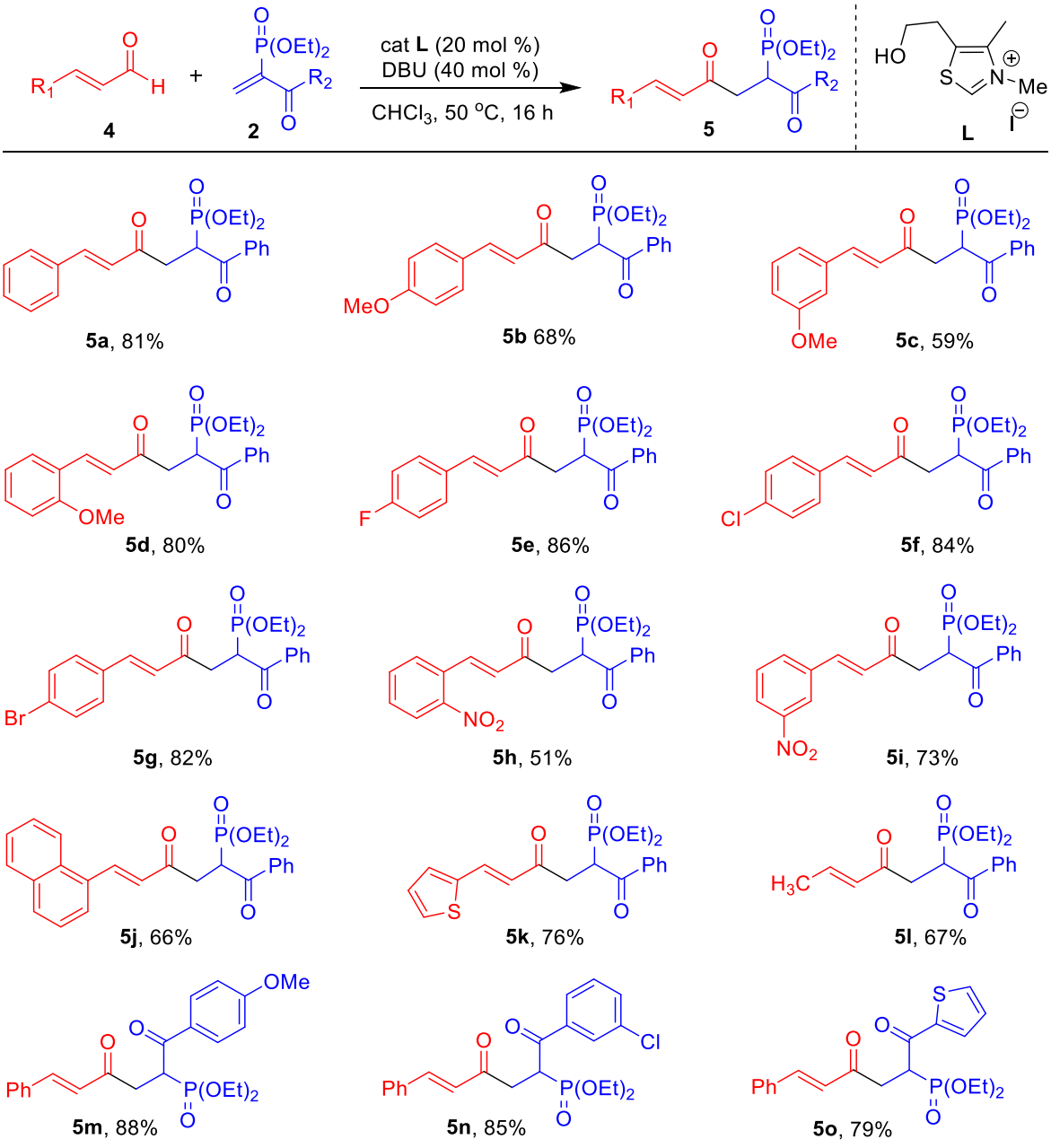


Scheme 3.8. Stetter reaction of aldehydes with vinylphosphonates[a]

We next moved to evaluate the reactivity of several derivatives of vinylphosphonates **2** under the standard condition with benzaldehyde. This reaction was found compatible with alkyl, electron-rich, electron-deficient, and heterocyclic substituted *α*-phosphoryl enones **2** to furnish the *α*-phosphorylated 1,4-diketones in 83-92% yields (**3m-3o**). We also tested the compatibility of the reaction by performing this reaction on larger scale 2.24 mmol (0.60 g) of *α*-phosphoryl enone **2a** under the optimize condition afforded the desired *α*-phosphorylated 1,4-diketone **3a** in 91% yield.

3.4.4. Stetter Reaction of *α,β*-Unsaturated Aldehydes with Vinylphosphonates

We next proceed to expand the substrate scopes of this Stetter reaction, by choosing a variety



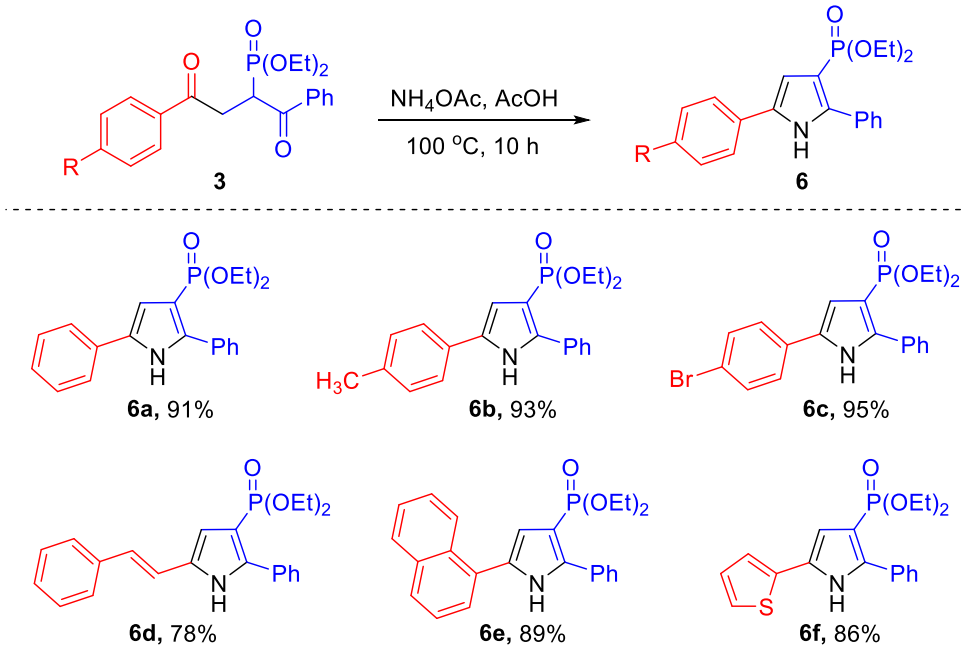
Scheme 3.9. Stetter reaction of *α,β*-unsaturated aldehydes with vinylphosphosphonates[a]

of *α,β*-unsaturated aldehydes 4 as shown in (Scheme 3.9). Notably, it was observed that the NHC-catalyzed Stetter reaction to access diketone products are less explored due to the competing enolate and homoenolate reaction pathways. On performing this reaction with *α,β*-unsaturated aldehydes having electron-deficient as well as electron-rich substituents respective to their *ortho*, *meta* and *para*-positions reacted smoothly and produced the *α*-phosphorylated 1,4-diketone products in 51-86% yield (**5a-5i**). As we observe, that in the case of aromatic aldehydes, here with *α,β*-unsaturated aldehydes also no generality was found

on the reaction outcomes with having substituent present at *ortho*, *meta* and *para*-position of the aryl rings. Polyaromatic and heteroaromatic *α,β*-unsaturated aldehydes were also well tolerated for this Stetter reaction under standard reaction condition and produced the *α*-phosphorylated 1,4-diketones in good yield 66-76% (**5j-5k**). The *β*-Methyl-substituted α,β-unsaturated aldehydes was also smoothly produced the desired product **5l** in 67% yield. We next tested the generality of the reaction with different vinylphosphonates **2** with *α,β*-unsaturated aldehydes **4a**. Vinylphosphonates bearing electron-rich and electron-deficient groups at aryl rings as well as heteroaryl substituent reacted smoothly with cinnamaldehyde to produce the *α*-phosphorylated 1,4-diketones in 79-88% yield (**5m-5o**).

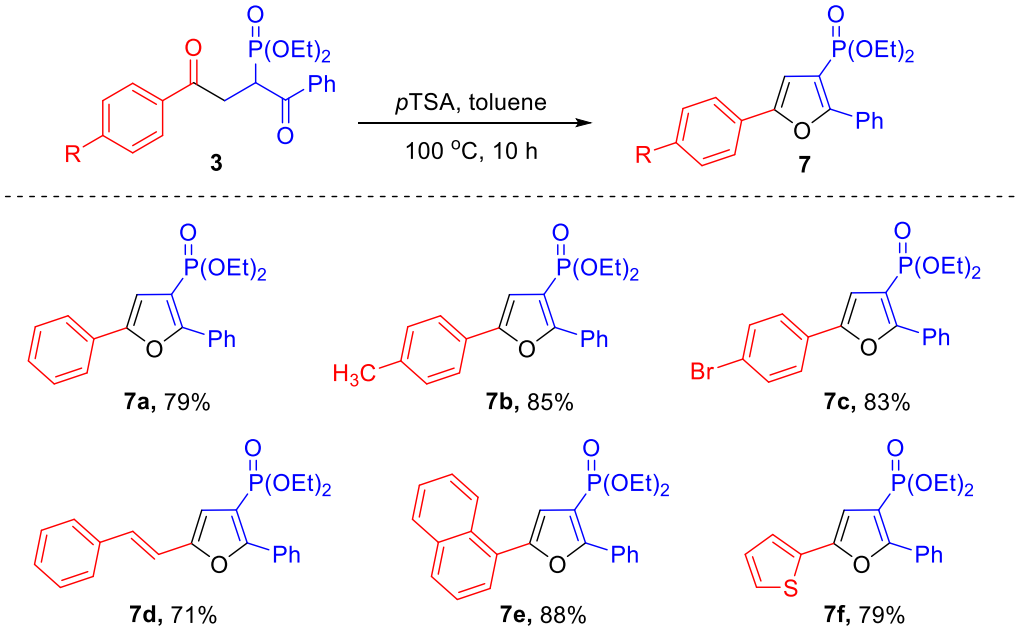
3.4.5. Synthesis of Phosphorylated Heterocycles from *α*-Phosphorylated 1,4-diketones

After developing the thiazolium catalyzed Stetter reaction for the synthesis of a wide variety of 1,4-diketones bearing valuable phosphoryl group, we next move to accept the challenges for the construction of a various class of 3/4-phosphorylated heterocycles. Herein, we have successfully prepared the different category of 3-phosphorylated heterocycles such as pyrroles, furans, thiophenes, as well 4-phosphorylated 2,5-dihydropyradazines. We also demonstrated the compatibility of this approaches by perforing the condensation of diverse class of *α*-phosphorylated 1,4-diketones having electron-deficient electron-rich, and (hetero)aryl-groups.



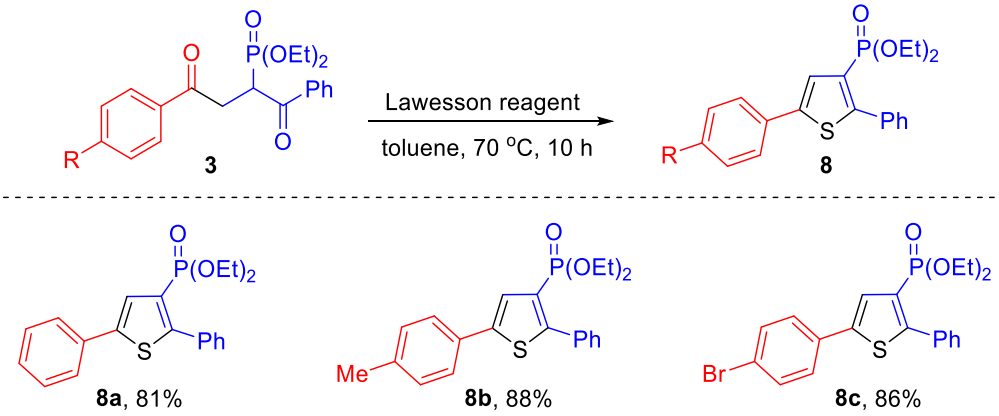
Scheme 3.10. Synthesis of 3-phosphorylated pyrroles

The α-phosphorylated 1,4-diketones **3a, 3d, 3g** and **5a** in the presence of NH_4OAc in AcOH at an elevated temperature smoothly converted into the 3-phosphorylated pyrroles **6a-6d** in good to excellent yield 78-95% (Scheme 3.10).[14]



Scheme 3.11. Synthesis of 3-phosphorylated furans

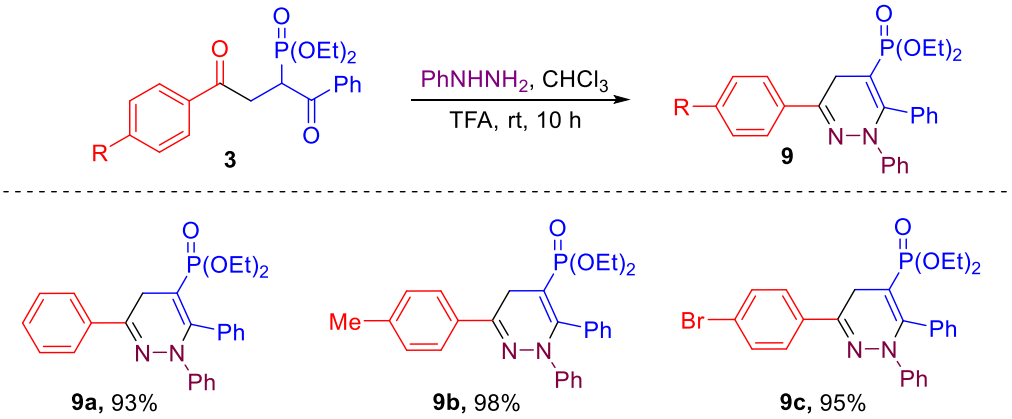
These set of α-phosphorylated 1,4-diketones were efficiently converted in 3-phosphorylated furans **7a-7d** upon treatment with *p*TSA in toluene in good to excellent yield 71-85% (Scheme 3.11).[15]



Scheme 3.12. Preparation of 3-phosphorylated thiophenes

The 3-phosphorylated thiophenes **8a-8c** was prepared by subjecting the α-phosphorylated 1,4-diketones **3a**, **3d** and **3g** in the presence of Lawesson's reagent in toluene solvent over 70 °C, in good to excellent yield (81-88%, Scheme 3.12).[16]

In last, we have prepared the 4-phosphorylated 2,5-dihydropyridazines **9a-9c** from *α*-phosphorylated 1,4-diketones **3a**, **3d**, **3g** and **5a** in the presence of $PhNHNH_2$ (phenyl hydrazine) and TFA (trifluoracetic acid) in 93-98% yield (Scheme 3.13).[17] The regioselectivity observed in the preparation of dihyderopyridazines was may be due to the steric hindrance of the phosphoryl group of *α*-phosphorylated 1,4-diketones with the neighbouring carbonyl groups.



Scheme 3.13. Preparation of 4-phosphorylated 2,5-dihydropyridazines

3.5. Conclusion

In conclusion, we have established the first general protocols for the construction of 3-phosphorylated heterocycles such as pyrroles, furans and thiophenes from *α*-phosphorylated 1,4-diketones. The phosphorylated 1,4-diketones were also used for the synthesis of 4-phosphorylated 2,5-dihydropyridazines. To achieve this, the first carbene catalysed method for the preparation of *α*-phosphorylated 1,4-diketones *via* intermolecular Stetter reaction from *α*-phosphoryl enones and aldehydes was developed. This two-step protocol provides highly efficient and metal-free method for the preparation of different categories of phosphorylated heterocycles which are difficult to prepare otherwise.

3.6. Experimental Section

3.6.1. General Information

Aldehydes and other reagents were purchased from a commercial supplier and used without further purification. All reactions were performed in oven-dried glasswares. The *α,β*-unsaturated aldehydes **4** and vinylphosphonates **2** were prepared following literature known methods.[11,12] Solvents were dried and distilled following the standard procedures; TLC was carried out on pre-coated plates (Merck silica gel 60, F_{254}), and the spots were visualized with

UV light or by charring the plates dipped in PMA charring solution. Flash chromatography was performed using silica gel (230-400 mess) with distilled solvents. ^{1}H, ^{13}C and ^{31}P NMR for compounds were recorded at 400 MHz, 100 MHz and 162 MHz instrument respectively using $CDCl_3$ as the solvent. 98% PPh_3 was used as an external standard for ^{31}P NMR. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), etc. High-resolution mass spectral analysis (HRMS) was performed on Q-TOF Premier mass spectrometer. The melting points were recorded on Buchi M-560 melting point apparatus and are uncorrected.

3.6.2. General Procedure for the Synthesis of *α*-Phosphorylated 1,4-diketones 3 and 5

To an oven-dried Schlenk tube equipped with a magnetic stir bar, was added aldehyde **1** or **4** (0.15 mmol, 1.5 equiv.), vinylphosphonate **2** (0.1 mmol, 1.0 equiv.) and catalyst **L** (20 mol %) in $CHCl_3$ (1.0 mL) at room temperature. The reaction chamber was purged with argon and DBU (40 mol %) was added. After stirring this reaction mixture at 50 ^{o}C in an oil bath for 16 h, the solvent was evaporated under the reduced pressure. The crude mass was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired products **3** or **5**.

*The preparation of **3a** on gram scale:* The product **3a** was obtained in 91% yield (0.76 g) when the reaction was run using **1a** (0.356 g, 3.36 mmol) and **2a** (0.60 g, 2.24 mmol) under the optimized reaction condition.

3.6.3. General Procedure for the Synthesis of Heterocycles 6, 7, 8 and 9

3-Phosphorylated pyrroles 6: To an oven-dried sealed tube equipped with a magnetic stir bar, was added ketophosphonates **3** or **5** (0.10 mmol), NH_4OAc (0.115 g, 1.50 mmol) in AcOH (1.0 mL) and the reaction chamber was sealed. After stirring at 100 ^{o}C in an oil bath for 10 h, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2 (2 x 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired product **6**.

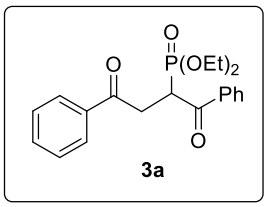
3-Phosphorylated furans 7: To an oven-dried sealed tube equipped with a magnetic stir bar, ketophosphonates **3** or **5** (0.10 mmol), *p*-TSA (0.028 g, 0.15 mmol) and toluene (1.0 mL) was added and the reaction chamber was sealed. After stirring the reaction mixture at 100 ^{o}C in an oil bath for 10 h, the solvent was evaporated under a reduced pressure and the compound was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired product **7**.

3-Phosphorylated thiophenes 8: To an oven-dried sealed tube equipped with a magnetic stir bar, was added ketophosphonates **3** (0.10 mmol), Lawesson's reagent (0.048 g, 0.12 mmol) and toluene (1.0 mL) and the reaction chamber was sealed. After being stirred at 70 ^{o}C in an oil bath for 10 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under a reduced pressure. The crude product was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure furans **8**.

3-Phosphorylated 2,5-dihydropyridazines 9: To an oven-dried sealed tube equipped with a magnetic stir bar, was added ketophosphonates **3** (0.10 mmol), $PhNHNH_2$ (17.8 µL, 0.15 mmol), $CHCl_3$ (1.0 mL) and TFA (10.0 µL, 0.13 mmol) was added, and the reaction chamber was sealed. After stirring the reaction mixture for 10 h at room temperature, the solvent was evaporated under a reduced pressure. The crude product was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired product **9**.

3.6.4. Characterization of the Products

***Diethyl (1,4-dioxo-1,4-diphenylbutan-2-yl)phosphonate* (3a):**



3a

Yield: 36 mg (95%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

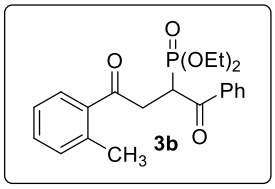
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{23}O_5PNa^+$ 397.1176, found: 397.1171.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, t, J = 6.8 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.47-3.64 (1H, m), 3.85-4.22 (5H, m), 4.63-4.87 (1H, m), 7.28-7.56 (6H, m), 7.91 (2H, d, J = 7.2 Hz), 8.04 (2H, d, J = 7.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 7.0 Hz), 37.3 (d, $J_{C\text{-}P}$ = 1 Hz), 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.9 (t, $J_{C\text{-}P}$ = 7.0 Hz), 128.2, 128.4, 128.6, 128.9, 133.2, 133.5, 135.9, 137.4, 195.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.6 (d, $J_{C\text{-}P}$ = 15.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.3.

***Diethyl (1,4-dioxo-1-phenyl-4-(o-tolyl)butan-2-yl)phosphonate* (3b):**



Yield: 32 mg (81%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

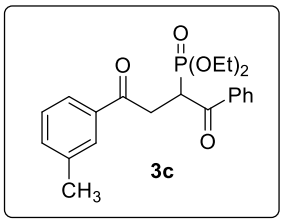
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{21}H_{25}O_5PNa^+$ $[M+Na]^+$: 411.1332, found: 411.1329.

^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 6.8 Hz), 2.34 (3H, s), 3.33-3.35 (1H, m), 3.85-4.16 (5H, m), 4.61-4.84 (1H, m), 7.10-7.26 (2H, m), 7.30 (1H, t, J = 7.2 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.50 (1H, t, J = 7.2 Hz), 7.74 (1H, d, J = 7.6 Hz), 8.04 (2H, d, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 21.3, 39.6 (q, $J_{C\text{-}P}$ = 1.0 Hz), 42.7 (d, $J_{C\text{-}P}$ = 127.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 7.0 Hz), 125.7, 128.4, 128.9, 128.9, 131.7, 131.9, 133.2, 136.6, 137.4, 138.5, 195.3 (d, $J_{C\text{-}P}$ = 4.0 Hz), 200.1 (d, $J_{C\text{-}P}$ = 16.0 Hz);

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.3.

***Diethyl (1,4-dioxo-1-phenyl-4-(m-tolyl)butan-2-yl)phosphon-ate* (3c):**



Yield: 35 mg (89%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

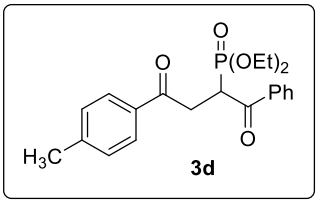
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{21}H_{25}O_5PNa^+$ $[M+Na]^+$: 411.1332, found: 411.1328.

^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 2.32 (3H, s), 3.44-3.62 (1H, m), 3.88-4.20 (5H, m), 4.62-4.82 (1H, m), 7.22-7.35 (2H, m), 7.41 (2H, t, J = 7.2 Hz), 7.50 (1H, t, J = 7.6 Hz), 7.71 (2H, d, J = 6.4 Hz), 8.04 (2H, t, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 21.2, 37.3, 42.4 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 8.0 Hz), 125.4, 128.4, 128.5, 128.8, 128.9, 133.1, 134.2, 135.9, 137.4, 138.4, 195.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.7 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.3.

Diethyl (1,4-dioxo-1-phenyl-4-(p-tolyl)butan-2-yl)phosphon-ate (**3d**):



Yield: 32 mg (82%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

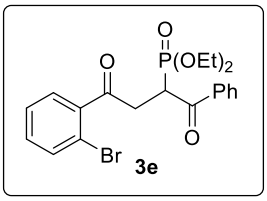
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{21}H_{25}O_5PNa^+$ $[M+Na]^+$: 411.1332, found: 411.1330.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 6.8 Hz), 2.33 (3H, s), 3.42-3.62 (1H, m), 3.87-4.17 (5H, m), 4.60-4.83 (1H, m), 7.18 (2H, d, J = 8.4 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.50 (1H, t, J = 7.2 Hz), 7.81 (2H, d, J = 8.4 Hz), 8.04 (2H, t, J = 7.2 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 21.7, 37.2, 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 7.0 Hz), 128.4, 128.5, 128.9, 129.3, 133.1, 133.5, 137.5, 144.4, 195.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.2 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.4.

Diethyl (4-(2-bromophenyl)-1,4-dioxo-1-phenylbutan-2-yl)ph-osphonate (**3e**):



Yield: 43 mg (94%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

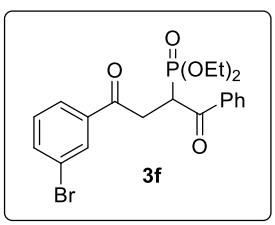
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{22}BrO_5PNa^+$ $[M+Na]^+$: 475.0281, found: 475.0274.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, t, J = 6.8 Hz), 1.15 (3H, t, J = 6.8 Hz), 3.38-3.53 (1H, m), 3.86-4.09 (5H, m), 4.61-4.83 (1H, m), 7.15-7.36 (2H, m), 7.37-7.59 (5H, m), 8.02 (2H, d, J = 7.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 7.0 Hz), 37.2, 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 6.0 Hz), 128.4, 128.7, 128.9, 129.7, 131.9, 133.2, 134.6, 137.2, 195.1 (d, $J_{C\text{-}P}$ = 5.0 Hz), 195.6 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.9.

Diethyl (4-(3-bromophenyl)-1,4-dioxo-1-phenylbutan-2-yl)ph-osphonate (**3f**):



Yield: 40 mg (87%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{22}BrO_5PNa^+$

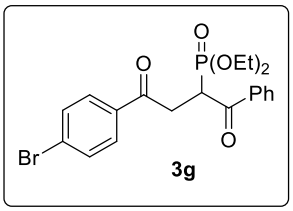
$[M+Na]^+$: 475.0281, found: 475.0276.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.39-3.57 (1H, m), 3.89-4.16 (5H, m), 4.61-4.79 (1H, m), 7.25 (1H, t, J = 8.0 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.51 (1H, t, J = 7.2 Hz), 7.62 (1H, d, J = 8.0 Hz), 7.83 (1H, d, J = 7.6 Hz), 8.02 (3H, t, J = 5.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 37.3, 42.4 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 6.0 Hz), 122.9, 126.7, 128.4, 128.9, 130.2, 131.2, 133.2, 136.3, 137.3, 137.6, 195.0 (d, $J_{C\text{-}P}$ = 5.0 Hz), 195.3 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.8.

Diethyl (4-(4-bromophenyl)-1,4-dioxo-1-phenylbutan-2-yl)ph-osphonate (**3g**):



3g

Yield: 45 mg (97%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

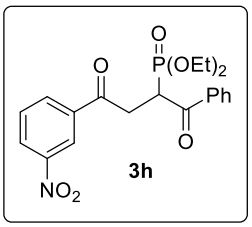
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{22}BrO_5PNa^+$ $[M+Na]^+$: 475.0281, found: 475.0278.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.42-3.55 (1H, m), 3.88-4.15 (5H, m), 4.60-4.80 (1H, m), 7.41 (2H, t, J = 7.2 Hz), 7.50 (3H, t, J = 7.2 Hz), 7.77 (2H, d, J = 8.4 Hz), 8.02 (2H, d, J = 7.2 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 37.2, 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.9 (q, $J_{C\text{-}P}$ = 6.0 Hz), 128.4, 128.7, 128.9, 129.7, 131.9, 133.2, 134.5, 137.2, 195.1 (d, $J_{C\text{-}P}$ = 5.0 Hz), 200.1 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.5.

Diethyl (4-(3-nitrophenyl)-1,4-dioxo-1-phenylbutan-2-yl)pho-sphonate (**3h**):



3h

Yield: 38 mg (89%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{22}NO_7PNa^+$ $[M+Na]^+$: 442.1027, found: 442.1029.

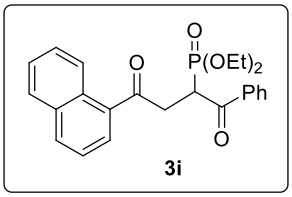
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 7.2 Hz), 3.48-3.63 (1H, m), 3.90-4.08 (4H, m), 4.08-4.21 (1H, m), 4.65-4.82 (1H, m), 7.43 (2H, t, J = 7.2 Hz),

7.53 (1H, t, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 8.0 Hz), 8.03 (2H, t, *J* = 7.2 Hz), 8.23 (1H, d, *J* = 8.0 Hz), 8.35 (1H, dd, *J* = 1.2 Hz), 8.74 (1H, t, *J* = 1.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 3.0 Hz), 37.5, 42.5 (d, $J_{C\text{-}P}$ = 129.0 Hz), 63.1 (t, $J_{C\text{-}P}$ = 3.0 Hz), 123.2, 127.8, 128.5, 128.9, 130.0, 133.5, 133.8, 137.2, 148.5, 194.8 (d, $J_{C\text{-}P}$ = 6.0 Hz), 195.0 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 21.5.

Diethyl (4-(naphthalen-1-yl)-1,4-dioxo-1-phenylbutan-2-yl)phosphonate (**3i**):



3i

Yield: 39 mg (91%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

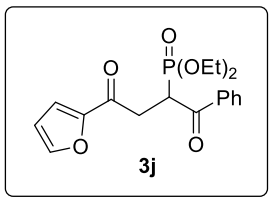
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{25}O_5PNa^+$ $[M+Na]^+$: 447.1332, found: 447.1335.

^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, t, *J* = 7.2 Hz), 1.16 (3H, t, *J* = 6.8 Hz), 3.49-3.67 (1H, m), 3.91-4.09 (4H, m), 4.14-4.27 (1H, m), 4.76-4.92 (1H, m), 7.38-7.48 (5H, m), 7.51 (1H, t, *J* = 7.2 Hz), 7.77 (1H, d, *J* = 7.2 Hz), 7.92 (1H, d, *J* = 8.0 Hz), 7.99 (1H, d, *J* = 4.0 Hz), 8.08 (1H, d, *J* = 7.6 Hz), 8.45 (2H, d, *J* = 8.4 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 7.0 Hz), 40.1, 42.9 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 6.0 Hz), 124.3, 125.7, 126.4, 128.0, 128.3, 128.3, 128.4, 128.9, 130.1, 133.1, 133.2, 133.8, 134.3, 137.5, 195.4 (d, $J_{C\text{-}P}$ = 4.0 Hz), 200.3 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.2.

Diethyl (4-(furan-2-yl)-1,4-dioxo-1-phenylbutan-2-yl)phosphonate (**3j**):



3j

Yield: 36 mg (98%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

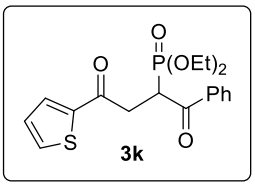
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{18}H_{21}O_6PNa^+$ $[M+Na]^+$: 387.0968, found: 387.0970.

^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, t, *J* = 7.2 Hz), 1.16 (3H, t, *J* = 7.2 Hz), 3.31-3.48 (1H, m), 3.87-4.12 (5H, m), 4.59-4.79 (1H, m), 6.45 (1H, t, *J* = 1.6 Hz), 7.15 (1H, d, *J* = 3.6 Hz), 7.39 (2H, t, *J* = 7.6 Hz), 7.49 (2H, t, *J* = 7.2 Hz), 8.01 (2H, d, *J* = 8.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 36.7 (q, $J_{C\text{-}P}$ = 2.0 Hz), 41.9 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 4.0 Hz), 112.3, 117.6, 128.4, 128.9, 133.2, 137.3, 146.6, 151.9, 185.7 (d, $J_{C\text{-}P}$ = 16.0 Hz), 195.2 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 21.8.

Diethyl (1,4-dioxo-1-phenyl-4-(thiophen-2-yl)butan-2-yl)pho-sphonate (**3k**):



3k

Yield: 32 mg (84%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

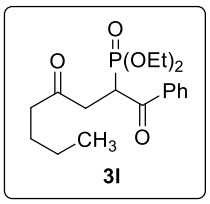
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{18}H_{21}O_5PSNa^+$ $[M+Na]^+$: 403.0740, found: 403.0743.

^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.41-3.57 (1H, m), 3.89-4.14 (5H, m), 4.64-4.81 (1H, m), 7.06 (1H, t, J = 4.4 Hz), 7.40 (2H, t, J = 7.6 Hz), 7.49 (1H, t, J = 7.2 Hz), 7.57 (1H, d, J = 4.8 Hz), 7.76 (1H, d, J = 4.0 Hz), 8.01 (2H, d, J = 7.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 37.5 (d, $J_{C\text{-}P}$ = 1.0 Hz), 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 6.0 Hz), 128.2, 128.4, 128.9, 132.6, 133.2, 134.1, 137.3, 142.7, 189.5 (d, $J_{C\text{-}P}$ = 17.0 Hz), 195.1 (d, $J_{C\text{-}P}$ = 5.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 21.8.

Diethyl (1,4-dioxo-1-phenyloctan-2-yl)phosphonate (**3l**):



3l

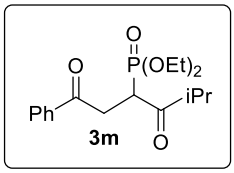
Yield: 20 mg (57%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{18}H_{27}O_5PNa^+$ $[M+Na]^+$: 377.1489, found: 377.1492.

^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, J = 7.2 Hz), 1.05 (3H, t, J = 6.8 Hz), 1.13-1.27 (5H, m), 1.40-1.52 (2H, m), 2.33-2.46 (2H, m), 2.84-3.03 (1H, m), 3.44-3.59 (1H, m), 3.86-4.08 (4H, m), 4.46-4.62 (1H, m), 7.39 (2H, t, J = 7.6 Hz), 7.49 (1H, t, J = 7.2 Hz), 7.96 (2H, d, J = 8.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 13.8, 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 22.2, 25.7, 40.5 (d, $J_{C\text{-}P}$ = 2.0 Hz), 41.6, 42.2 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.7 (q, $J_{C\text{-}P}$ = 6.0 Hz), 128.0, 128.4, 128.7, 128.9, 133.2, 137.4, 195.4 (d, $J_{C\text{-}P}$ = 5.0 Hz), 207.6 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.1.



Diethyl (5-methyl-1,4-dioxo-1-phenylhexan-3-yl)phosphonate (**3m**):

Yield: 31 mg (91%), colorless gummy liquid, eluent: 60% EtOAc in hexane.

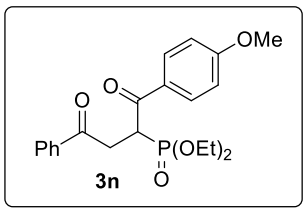
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{17}H_{25}O_5PH^+$ $[M+H]^+$: 341.1513, found: 341.1511.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (3H, d, J = 6.8 Hz), 1.27-1.40 (9H, m), 3.13-3.38 (2H, m), 3.87-4.03 (1H, m), 4.04-4.24 (5H, m), 7.45 (2H, t, J = 8.0 Hz), 7.56 (1H, t, J = 7.2 Hz), 7.98 (2H, d, J = 7.6 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3 (q, $J_{C\text{-}P}$ = 5.0 Hz), 17.6, 19.5, 35.7 (d, $J_{C\text{-}P}$ = 1.0 Hz), 41.4, 45.7 (d, $J_{C\text{-}P}$ = 126.0 Hz), 62.7 (dd, $J_{C\text{-}P}$ = 6.0 Hz, 7.0 Hz), 128.1, 128.5, 133.3, 136.1, 196.6 (d, $J_{C\text{-}P}$ = 16.0 Hz), 208.8 (d, $J_{C\text{-}P}$ = 4.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.8.

Diethyl (1-(4-methoxyphenyl)-1,4-dioxo-4-phenylbutan-2-yl)phosphonate (**3n**):



Yield: 34 mg (83%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{21}H_{25}O_5PNa^+$ $[M+Na]^+$: 427.1281, found: 427.1267.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J = 7.2 Hz), 1.26 (3H, t, J = 6.8 Hz), 3.52-3.65 (1H, m), 3.89 (3H, s), 3.98-4.27 (5H, m), 4.69-4.85 (1H, m), 6.98 (2H, d, J = 8.8 Hz), 7.45 (2H, t, J = 7.6 Hz), 7.57 (1H, t, J = 7.6 Hz), 8.0 (2H, d, J = 8.0 Hz), 8.12 (2H, d, J = 8.8 Hz).

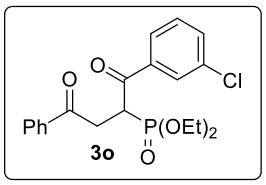
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (t, $J_{C\text{-}P}$ = 6.0 Hz), 37.2, 41.8 (d, $J_{C\text{-}P}$ = 128.0 Hz), 55.5, 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 113.6, 128.2, 128.6, 130.2, 133.4, 133.5, 135.9, 163.7, 193.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.7 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.7.

Diethyl (1-(3-chlorophenyl)-1,4-dioxo-4-phenylbutan-2-yl)phosphonate (**3o**):

Yield: 37 mg (92%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{22}ClO_5PNa^+$ $[M+Na]^+$: 431.0786, found: 431.0786.

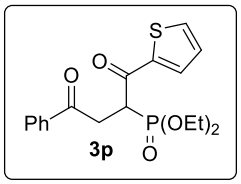


^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, t, J = 6.8 Hz), 1.27 (3H, t, J = 7.2 Hz), 3.56-3.70 (1H, m), 4.01-4.23 (5H, m), 4.60-4.79 (1H, m), 7.41-7.51 (3H, m), 7.54-7.62 (2H, m), 7.94-8.05 (2H, m), 8.07 (1H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, J_{C-P} = 7.0 Hz), 37.4, 42.7 (d, J_{C-P} = 128.0 Hz), 63.0 (d, J_{C-P} = 7.0 Hz), 127.1, 128.2, 128.7, 128.9, 129.7, 133.0, 133.6, 134.7, 135.7, 138.9, 194.2 (d, J_{C-P} = 6.0 Hz), 196.5 (d, J_{C-P} = 16.0 Hz),

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.7.

Diethyl (1,4-dioxo-4-phenyl-1-(thiophen-2-yl)butan-2-yl)phosphonate (**3p**):



Yield: 33 mg (89%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

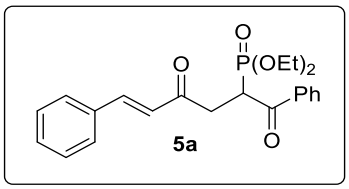
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{18}H_{21}O_5PNa^+$ $[M+Na]^+$: 403.0740, found: 403.0739.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21-1.31 (6H, m), 3.51-3.66 (1H, m), 4.05-4.22 (5H, m), 4.53-4.67 (1H, m), 7.19 (1H, t, J = 4.4 Hz), 7.45 (1H, d, J = 7.6 Hz), 7.57 (1H, t, J = 7.6 Hz), 7.69 (1H, d, J = 5.2 Hz), 7.99 (3H, t, J = 8.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.2 (t, J_{C-P} = 6.0 Hz), 36.8 (d, J_{C-P} = 2.0 Hz), 43.9 (d, J_{C-P} = 127.0 Hz), 62.9 (t, J_{C-P} = 7.0 Hz), 128.1, 128.2, 128.6, 133.5, 133.6, 134.4, 135.8, 144.0, 187.1 (d, J_{C-P} = 5.0 Hz), 196.4 (d, J_{C-P} = 15.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.9.

Diethyl (E)-(1,4-dioxo-1,6-diphenylhex-5-en-2-yl)phosphona-te (**5a**):



Yield: 33 mg (81%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

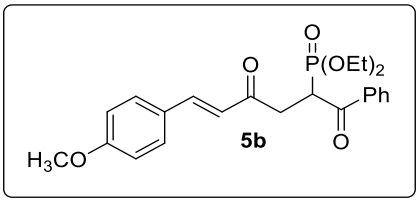
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{25}O_5P$ Na^+ $[M+Na]^+$: 423.1332, found: 423.1329.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, t, J = 6.8 Hz), 1.24 (3H, t, J = 6.8 Hz), 3.23-3.41 (1H, m), 3.78-3.96 (1H, m), 3.97-4.18 (4H, m), 4.63-4.86 (1H, m), 6.74 (1H, d, J = 16.4 Hz), 7.33-7.44 (3H, m), 7.45-7.67 (6H, m), 8.09 (2H, d, J = 7.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (q, $J_{C\text{-}P}$ = 6.0 Hz), 38.8, 42.2 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.7 (t, $J_{C\text{-}P}$ = 8.0 Hz), 124.9, 128.2, 128.3, 128.8, 128.9, 130.6, 133.1, 134.1, 137.3, 143.6, 195.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.2 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.2.

Diethyl (E)-(6-(4-methoxyphenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5b**):



Yield: 30 mg (68%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

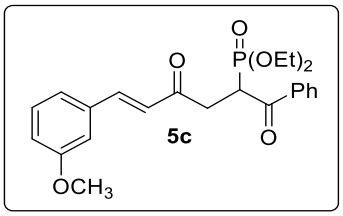
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1437, found: 453.1434.

^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.16-3.28 (1H, m), 3.71-3.84 (1H, m), 3.77 (3H, s), 3.91-4.08 (4H, m), 4.58-4.73 (1H, m), 6.56 (1H, d, J = 16.0 Hz), 6.84 (2H, d, J = 8.8 Hz), 7.41 (4H, t, J = 7.2 Hz), 7.50 (2H, t, J = 6.0 Hz), 8.02 (2H, d, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 38.8, 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 55.4, 62.8 (t, $J_{C\text{-}P}$ = 9.0 Hz), 114.4, 122.9, 126.9, 128.4, 128.9, 130.1, 133.1, 137.5, 143.5, 161.8, 195.4 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.2 (d, $J_{C\text{-}P}$ = 15.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.4.

Diethyl (E)-(6-(3-methoxyphenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5c**):



Yield: 25 mg (59%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

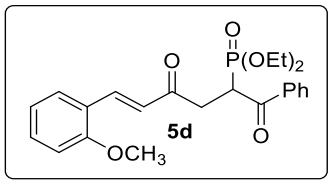
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1437, found: 453.1436.

^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.16-3.32 (1H, m), 3.76 (3H, s), 3.72-3.88 (1H, m), 3.90-4.10 (4H, m), 4.58-4.74 (1H, m), 6.65 (1H, d, J = 16.0 Hz), 6.87 (1H, dd, J = 8 Hz), 6.98 (1H, s), 7.05 (1H, d, J = 7.6 Hz), 7.16-7.31 (1H, m), 7.34-7.59 (4H, m), 8.0 (2H, t, J = 1.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 38.9 (d, $J_{C\text{-}P}$ = 2.0 Hz), 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 55.3, 62.8 (t, $J_{C\text{-}P}$ = 8.0 Hz), 113.1, 116.6, 121.1, 125.4, 128.4, 128.9, 129.9, 133.1, 135.6, 137.4, 143.6, 159.9, 195.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.3 (d, $J_{C\text{-}P}$ = 15.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 21.2.

Diethyl (E)-(6-(2-methoxyphenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5d**):



Yield: 35 mg (80%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

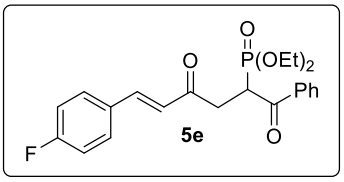
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1437, found: 453.1434.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 6.16 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.19-3.34 (1H, m), 3.73-3.89 (1H, m), 3.82 (3H, s), 3.90-4.09 (4H, m), 4.58-4.75 (1H, m), 6.73 (1H, d, J = 16.0 Hz), 6.80-6.95 (2H, m), 7.25-7.35 (1H, m), 7.36-7.57 (4H, m), 7.89 (1H, d, J = 16.8 Hz), 8.01 (2H, t, J = 1.6 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 7.0 Hz), 38.8, 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 55.4, 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 111.2, 120.7, 123.2, 125.6, 128.4, 128.7, 128.9, 131.9, 133.1, 137.5, 139.1, 158.6, 195.4 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.8 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.4.

Diethyl (E)-(6-(4-fluorophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5e**):



Yield: 36 mg (86%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{24}FO_5PNa^+$ $[M+Na]^+$: 441.1238, found: 441.1229.

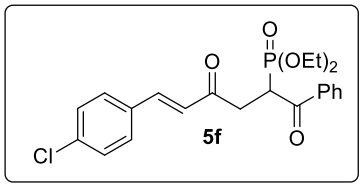
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 6.8 Hz), 3.15-3.31 (1H, m), 3.71-3.87 (1H, m), 3.89-4.11 (4H, m), 4.57-4.74 (1H, m), 6.64 (1H, d, J = 16.4 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.34-7.56 (6H, m), 8.01 (2H, d, J = 7.6 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 7.0 Hz), 38.9 (d, $J_{C\text{-}P}$ = 2.0 Hz), 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (q, $J_{C\text{-}P}$ = 7.0 Hz), 116.1 (d, $J_{C\text{-}F}$ = 22.0 Hz), 124.8 (d, $J_{C\text{-}F}$ = 2.0 Hz), 128.4, 128.9, 130.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.5 (d, $J_{C\text{-}F}$ = 3.5 Hz), 133.2, 137.4, 142.3, 164.1 (d, $J_{C\text{-}F}$ = 250.0 Hz), 195.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.1 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.2.

Diethyl (E)-(6-(4-chlorophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5f**):

Yield: 37 mg (84%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.



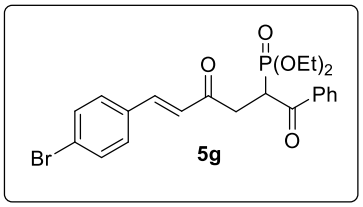
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{24}ClO_5PNa^+$ $[M+Na]^+$: 457.0943, found: 457.0945.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 6.8 Hz), 3.14-3.30 (1H, m), 3.71-3.87 (1H, m), 3.89-4.10 (4H, m), 4.56-4.76 (1H, m), 6.60 (1H, d, J = 16.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.33-7.61 (6H, m), 8.01 (2H, d, J = 7.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (d, $J_{C\text{-}P}$ = 6.0 Hz), 39.0 (d, $J_{C\text{-}P}$ = 2.0 Hz), 42.9 (d, $J_{C\text{-}P}$ = 118.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 8.0 Hz), 125.5, 128.4, 128.9, 129.2, 129.5, 132.7, 133.2, 136.6, 137.3, 142.1, 195.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.1 (d, $J_{C\text{-}P}$ = 15.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.1.

Diethyl (E)-(6-(4-bromophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5g**):



Yield: 40 mg (82%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

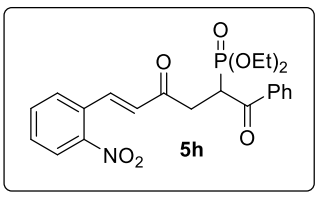
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{24}BrO_5PNa^+$ $[M+Na]^+$: 501.0437, found: 501.0439.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.16-3.28 (1H, m), 3.71-3.86 (1H, m), 3.88-4.11 (4H, m), 4.56-4.74 (1H, m), 6.65 (1H, d, J = 16.0 Hz),), 7.32 (1H, d, J = 8.8 Hz), 7.37-7.55 (6H, m), 8.0 (2H, d, J = 7.2 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 39.0, 42.23 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 8.0 Hz), 124.9, 125.5, 128.4, 128.9, 129.7, 132.2, 133.1, 133.2, 137.3, 142.2, 195.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.2 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.1.

Diethyl (E)-(6-(2-nitrophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5h**):



Yield: 23 mg (51%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

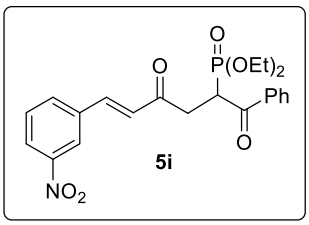
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{24}NO_7PNa^+$ $[M+Na]^+$: 468.1183, found: 468.1179.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 6.8 Hz), 1.18 (3H, t, J = 6.8 Hz), 3.18-3.35 (1H, m), 3.72-3.89 (1H, m), 3.90-4.11 (4H, m), 4.56-4.72 (1H, m), 6.54 (1H, d, J = 16.0 Hz), 7.33-7.66 (7H, m), 7.92-8.10 (4H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 7.0 Hz), 38.8, 42.3 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.9 (d, $J_{C\text{-}P}$ = 8.0 Hz), 125.1, 128.4, 128.9, 129.2, 129.8, 130.6, 130.7, 133.3, 133.7, 137.3, 139.1, 148.4, 195.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.0 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.8.

Diethyl (E)-(6-(3-nitrophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5i**):



5i

Yield: 33 mg (73%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

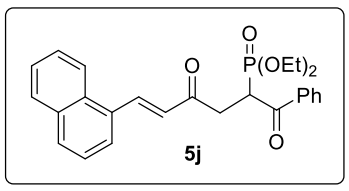
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{24}NO_7PNa^+$ $[M+Na]^+$: 468.1183, found: 468.1177.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.18-3.33 (1H, m), 3.74-3.9 (1H, m) 3.91-4.09 (4H, m), 4.58-4.73 (1H, m), 6.79 (1H, d, J = 16.4 Hz), 7.36-7.63 (5H, m), 7.76 (1H, d, J = 7.6 Hz), 7.9 (2H, dd, J = 1.2 Hz), 8.16 (1H, dd, J = 1.2 Hz), 8.32 (1H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 39.3 (d, $J_{C\text{-}P}$ = 2.0 Hz), 42.4 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.9 (q, $J_{C\text{-}P}$ = 7.0 Hz), 122.6, 124.8, 127.5, 128.4, 128.9, 130.0, 133.3, 133.9, 136.1, 137.3, 140.5, 148.7, 195.9 (d, $J_{C\text{-}P}$ = 5.0 Hz), 195.8 (d, $J_{C\text{-}P}$ = 15.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.8.

Diethyl (E)-(6-(naphthalen-1-yl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5j**):



5j

Yield: 30 mg (66%) pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

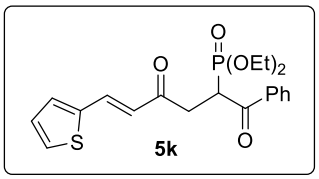
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{26}H_{27}O_5PNa^+$ $[M+Na]^+$: 473.1489, found: 473.1483.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.1 (3H, t, J = 7.2 Hz), 1.19 (3H, t, J = 4.8 Hz), 3.24-3.39 (1H, m), 3.80-3.93 (1H, m), 3.94-4.11 (4H, m), 4.62-4.78 (1H, m), 6.78 (1H, d, J = 15.6 Hz), 7.34-7.58 (6H, m), 7.70 (1H, d, J = 7.2 Hz), 7.76-7.87 (2H, m), 7.99-8.14 (3H, m), 8.38 (2H, d, J = 16.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, J_{C-P} = 6.0 Hz), 39.5 (d, J_{C-P} = 2.0 Hz), 42.4 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 8.0 Hz), 123.2, 125.2, 125.4, 126.2, 126.9, 127.3, 128.5, 128.8, 128.9, 130.9, 131.5, 131.6, 133.2, 133.6, 137.4, 140.4, 195.3 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 15.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.2.

Diethyl (E)-(1,4-dioxo-1-phenyl-6-(thiophen-2-yl)hex-5-en-2-yl)phosphonate (**5k**):



Yield: 31 mg (76%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

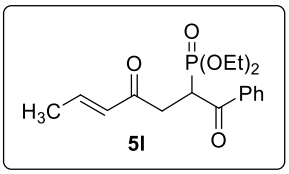
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{23}O_5PSNa^+$ $[M+Na]^+$: 429.0897, found: 429.0893.

^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.11-3.27 (1H, m), 3.66-3.83 (1H, m), 3.88-4.11 (4H, m), 4.56-4.74 (1H, m), 6.48 (1H, d, J = 15.6 Hz), 6.95-7.04 (1H, m), 7.22 (1H, d, J = 4.8 Hz), 7.31-7.56 (4H, m), 7.64 (1H d, J = 16.0 Hz), 7.99 (2H, t, J = 1.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, J_{C-P} = 6.0 Hz), 39.0 (d, J_{C-P} = 2.0 Hz), 42.3 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 7.0 Hz), 123.7, 128.3, 128.4, 128.9, 129.2, 131.9, 133.1, 136.0, 137.4, 139.6, 195.3 (d, J_{C-P} = 5.0 Hz), 195.7 (d, J_{C-P} = 16.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.2.

Diethyl (E)-(1,4-dioxo-1-phenylhept-5-en-2-yl)phosphonate (**5l**):



Yield: 23 mg (67%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

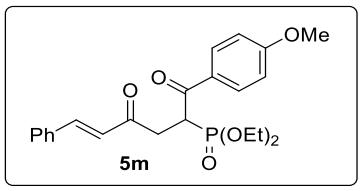
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{17}H_{23}O_5PNa^+$ $[M+Na]^+$: 361.1176, found: 361.1172.

^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (3H, t, J = 6.4 Hz), 1.15 (3H, t, J = 6.8 Hz), 1.84 (3H, d, J = 6.8 Hz), 3.01-3.18 (1H, m), 3.56-3.75 (1H, m), 3.85-4.13 (4H, m), 4.49-4.70 (1H, m), 6.06 (1H, d, J = 16.0 Hz), 6.77-6.99 (1H, m), 7.39 (3H, t, J = 7.6 Hz), 7.48 (2H, t, J = 7.2 Hz), 7.98 (2H, d, J = 7.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (q, $J_{C\text{-}P}$ = 6.0 Hz), 38.1 (d, $J_{C\text{-}P}$ = 2.0 Hz), 42.2 (d, $J_{C\text{-}P}$ = 128.0 Hz), 62.8 (t, $J_{C\text{-}P}$ = 7.0 Hz), 128.4, 128.9, 130.9, 133.1, 137.4, 144.1, 195.4 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.3 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.3.

Diethyl (E)-(1-(4-methoxyphenyl)-1,4-dioxo-6-phenylhex-5-en-2-yl)phosphonate (**5m**):



Yield: 38 mg (88%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

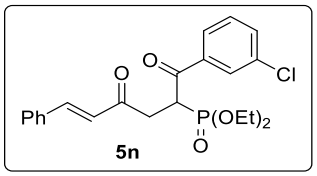
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{23}H_{27}O_6PNa^+$ $[M+Na]^+$: 453.1438, found: 453.1435.

^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J = 6.8 Hz), 1.25 (3H, t, J = 7.2 Hz), 3.21-3.36 (1H, m), 3.80-3.94 (4H, m), 3.99-4.18 (4H, m), 4.62-4.78 (1H, m), 6.74 (1H, d, J = 16.4 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.39 (3H, t, J = 3.6 Hz), 7.53 (2H, t, J = 3.6 Hz), 7.61 (1H, d, J = 16.0 Hz), 8.09 (2H, d, J = 8.4 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (t, $J_{C\text{-}P}$ = 7.0 Hz), 38.8, 41.8 (d, $J_{C\text{-}P}$ = 128.0 Hz), 55.5, 62.8 (t, $J_{C\text{-}P}$ = 6.0 Hz), 113.6, 125.1, 128.3, 128.9, 130.1, 130.6, 131.4, 134.2, 143.6, 163.6, 193.3 (d, $J_{C\text{-}P}$ = 4.0 Hz), 196.5 (d, $J_{C\text{-}P}$ = 15.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 22.7.

Diethyl (E)-(1-(3-chlorophenyl)-1,4-dioxo-6-phenylhex-5-en-2-yl)phosphonate (**5n**):



Yield: 37 mg (85%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

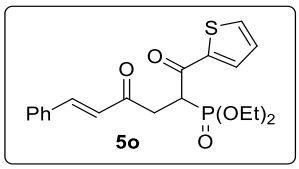
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{24}ClO_5PNa^+$ $[M+Na]^+$: 457.0943, found: 457.0944.

^1H NMR (400 MHz, $CDCl_3$): δ 1.2 (3H, t, J = 6.8 Hz), 1.27 (3H, t, J = 7.2 Hz), 3.26-3.42 (1H, m), 3.79-3.93 (1H, m), 3.99-4.17 (4H, m), 4.55-4.68 (1H, m), 6.74 (1H, d, J = 16.0 Hz), 7.37-7.43 (3H, m), 7.45 (1H, d, J = 7.6 Hz), 7.50-7.58 (3H, m), 7.62 (1H, d, J = 16.4 Hz), 7.98 (1H, d, J = 8.0 Hz), 8.04 (1H, s).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (q, $J_{C\text{-}P}$ = 7.0 Hz), 39.1, 42.6 (d, $J_{C\text{-}P}$ = 129.0 Hz), 62.9 (t, $J_{C\text{-}P}$ = 4.0 Hz), 124.9, 127.0, 128.4, 128.9, 129.0, 129.7, 130.8, 133.0, 134.1, 134.7, 138.9, 143.9, 194.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.2 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 21.6.

Diethyl (E)-(1,4-dioxo-6-phenyl-1-(thiophen-2-yl)hex-5-en-2-yl)phosphonate (**5o**):



Yield: 32 mg (79%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

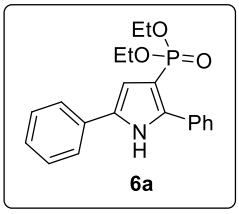
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{20}H_{23}O_5PNa^+$ $[M+Na]^+$: 429.0897, found: 429.0901.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17-1.36 (6H, m), 3.21-3.37 (1H, m), 3.73-3.91 (1H, m), 4.01-4.24 (4H, m), 4.45-4.63 (1H, m), 6.74 (1H, d, J = 16.0 Hz), 7.17 (1H, t, J = 4.4 Hz), 7.40 (3H, t, J = 3.6 Hz), 7.53 (2H, t, J = 3.6 Hz), 7.62 (1H, d, J = 16.0 Hz), 7.68 (1H, d, J = 4.8 Hz), 7.97 (1H, d, J = 3.6 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (t, $J_{C\text{-}P}$ = 5.0 Hz), 38.4, 43.7 (d, $J_{C\text{-}P}$ = 129.0 Hz), 62.9 (t, $J_{C\text{-}P}$ = 7.0 Hz), 125.0, 128.1, 128.3, 128.9, 130.7, 133.7, 134.1, 134.4, 143.7, 144.0, 187.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 196.2 (d, $J_{C\text{-}P}$ = 16.0 Hz).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 21.9.

Diethyl (2,5-diphenyl-1H-pyrrol-3-yl)phosphonate (**6a**):



Yield: 32 mg (91%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{22}NO_3PH^+$: 356.1411, found: 356.1414.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (6H, t, J = 7.2 Hz), 3.85-4.01 (4H, m), 6.86 (1H, q, J = 2.8 Hz), 7.20-7.43 (6H, m), 7.61 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 7.2 Hz), 9.78 (1H, s).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.04 (d, $J_{C\text{-}P}$ = 6.7 Hz), 61.6 (d, $J_{C\text{-}P}$ = 5.2 Hz), 106.8 (d, $J_{C\text{-}P}$ = 214.2 Hz), 112.4 (d, $J_{C\text{-}P}$ = 12.5 Hz), 124.3, 126.8, 128.0, 128.2, 128.3, 128.8, 131.5 (d, $J_{C\text{-}P}$ = 0.9 Hz), 131.8, 132.9 (d, $J_{C\text{-}P}$ = 15.5 Hz), 138.6 (d, $J_{C\text{-}P}$ = 22.7 Hz).

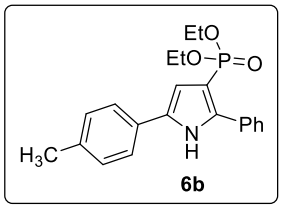
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 17.7.

Diethyl (2-phenyl-5-(p-tolyl)-1H-pyrrol-3-yl)phosphonate (**6b**):

Yield: 34 mg (93%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{24}NO_3PH^+$ 370.1567, found: 370.1566.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (6H, t, J = 6.8 Hz), 2.25 (3H, s) 3.70-3.92 (4H, m), 6.71 (1H, q, J = 2.8 Hz), 7.07 (2H, d, J = 8.0 Hz), 7.13-7.32 (3H, m), 7.43 (2H, d, J = 8.0 Hz), 7.61 (2H, d, J = 7.2 Hz), 9.93 (1H, s).

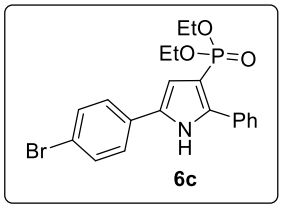


6b

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 21.1, 61.5 (d, $J_{C\text{-}P}$ = 5.2 Hz), 106.4 (d, $J_{C\text{-}P}$ = 214.0 Hz), 111.9 (d, $J_{C\text{-}P}$ = 12.6 Hz), 124.3, 127.8, 128.1, 128.4, 128.8, 129.4, 131.8, 133.2 (d, $J_{C\text{-}P}$ = 16.0 Hz), 136.4, 138.3 (d, $J_{C\text{-}P}$ = 22.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.9.

Diethyl (5-(4-bromophenyl)-2-phenyl-1H-pyrrol-3-yl)phosphonate (**6c**):



6c

Yield: 41 mg (95%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

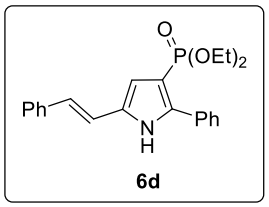
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{21}BrNO_3PH^+$ 434.0516, found: 434.0518.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (6H, t, J = 7.2 Hz), 3.78-4.01 (4H, m), 6.78 (1H, q, J = 4.0 Hz), 7.15-7.31 (3H, m), 7.46 (4H, q, J = 4.8 Hz), 7.67 (2H, d, J = 7.6 Hz), 10.27 (1H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7 Hz), 61.7 (d, $J_{C\text{-}P}$ = 6.0 Hz), 107.0 (d, $J_{C\text{-}P}$ = 214.0 Hz), 112.8 (d, $J_{C\text{-}P}$ = 12.5 Hz), 120.4, 125.9, 128.1, 128.2, 128.4, 130.6, 131.6, 131.8, 131.9 (d, $J_{C\text{-}P}$ = 15.0 Hz), 139.1 (d, $J_{C\text{-}P}$ = 23.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.4.

Diethyl (E)-(2-phenyl-5-styryl-1H-pyrrol-3-yl)phosphonate (**6d**):



6d

Yield: 30 mg (78%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

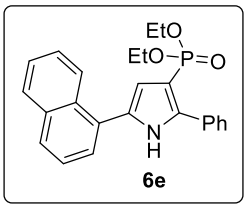
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{22}H_{24}NO_3PH^+$: 382.1567, found: 382.1567.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (6H, t, J = 7.2 Hz), 3.84-4.01 (4H, m), 6.66 (1H, s), 6.91 (2H, s), 7.18 (1H, t, J = 7.2), 7.24-7.34 (5H, m), 7.39 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 7.6 Hz), 10.09 (1H, s).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 61.7 (d, $J_{C\text{-}P}$ = 5.0 Hz), 106.3 (d, $J_{C\text{-}P}$ = 215.0 Hz), 115.1 (d, $J_{C\text{-}P}$ = 12.0 Hz), 117.9, 125.5, 125.9, 127.1, 127.9, 128.1, 128.2, 128.6, 131.6, 131.8 (d, $J_{C\text{-}P}$ = 16.0 Hz), 137.3, 138.7 (d, $J_{C\text{-}P}$ = 23.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 17.7.

Diethyl (2-(naphthalen-1-yl)-5-phenyl-1H-pyrrol-3-yl)phosphonate (**6e**):



6e

Yield: 36 mg (89%), brown gummy liquid, eluent: 60% EtOAc in hexane.

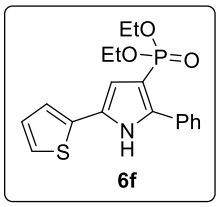
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{24}H_{24}NO_3PH^+$: 406.1567, found: 406.1563.

^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (6H, t, J = 6.8 Hz), 3.82-4.05 (4H, m), 6.79 (1H, s), 7.21-7.41 (3H, m), 7.41-7.60 (4H, m), 7.68-7.90 (4H, m), 8.21-8.33 (1H, m), 9.55 (1H, s).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 61.6 (d, $J_{C\text{-}P}$ = 10.0 Hz), 106.4 (d, $J_{C\text{-}P}$ = 215.0 Hz), 115.8 (d, $J_{C\text{-}P}$ = 12.0 Hz), 122.2, 125.4, 126.0, 126.5, 128.0 (d, $J_{C\text{-}P}$ = 8.0 Hz), 128.1, 128.2, 128.3, 129.9, 131.2, 131.2 (d, $J_{C\text{-}P}$ = 16.0 Hz), 131.7, 133.8, 138.2 (d, $J_{C\text{-}P}$ = 23.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 17.8.

Diethyl (5-phenyl-2-(thiophen-2-yl)-1H-pyrrol-3-yl)phosphonate (**6f**):



6f

Yield: 31 mg (86%), brown gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{18}H_{20}NO_3PSH^+$: 362.0975, found: 362.0970.

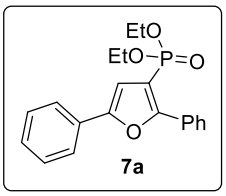
^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (6H, t, J = 6.8 Hz), 3.84-4.08 (4H, m), 6.75 (1H, s), 7.01 (1H, t, J = 4.0 Hz), 7.19 (2H, d, J = 4.4), 7.28-7.42 (3H, m), 7.68 (2H, d, J = 7.6 Hz), 9.37 (1H, s).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 61.7 (d, $J_{C\text{-}P}$ = 5.0 Hz), 106.6 (d, $J_{C\text{-}P}$ = 214.0 Hz), 112.9 (d, $J_{C\text{-}P}$ = 13.0 Hz), 122.2, 123.4, 127.6, 127.6 (d, $J_{C\text{-}P}$ = 16.0 Hz), 128.0, 128.2, 128.3, 131.4, 134.6, 138.3 (d, $J_{C\text{-}P}$ = 23.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 17.3.

Diethyl (2,5-diphenylfuran-3-yl)phosphonate (**7a**):

Yield: 28 mg (79%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.



7a

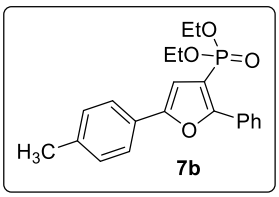
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{21}O_4PH^+$ 357.1251, found: 357.1257.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (6H, t, J = 7.2 Hz), 3.92-4.18 (4H, m), 6.93 (1H, d, J = 3.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.29-7.43 (5H, m), 7.67 (2H, d, J = 7.6 Hz), 7.98 (2H, d, J = 7.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.2 (d, $J_{C\text{-}P}$ = 6.7 Hz), 62.3 (d, $J_{C\text{-}P}$ = 5.3 Hz), 109.5 (d, $J_{C\text{-}P}$ = 210.1 Hz), 110.8, 110.9, 124.0, 127.4, 128.1, 128.4, 128.8, 129.2, 129.6, 152.9 (d, $J_{C\text{-}P}$ = 15.2 Hz), 157.3 (d, $J_{C\text{-}P}$ = 24.3 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 14.0.

Diethyl (2-phenyl-5-(p-tolyl)-furan-3-yl)phosphonate **(7b):**



7b

Yield: 32 mg (85%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

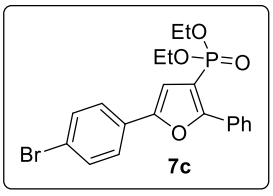
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{23}O_4PH^+$ 371.1407, found: 371.1406.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (6H, t, J = 7.2 Hz), 2.29 (3H, s), 3.91-4.20 (4H, m), 6.87 (1H, d, J = 4.0 Hz), 7.14 (2H, d, J = 7.6 Hz), 7.29 (1H, t, J = 7.2 Hz), 7.36 (2H, t, J = 8.0 Hz), 7.54 (2H, d, J = 8.0 Hz), 7.96 (2H, d, J = 7.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (d, $J_{C\text{-}P}$ = 6.0 Hz), 21.3, 62.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 109.2 (d, $J_{C\text{-}P}$ = 211.0 Hz), 110.0 (d, $J_{C\text{-}P}$ = 11.3 Hz), 123.9, 126.8, 127.3, 128.3, 129.0, 129.4, 129.6, 138.1, 153.2 (d, $J_{C\text{-}P}$ = 15.0 Hz), 156.9 (d, $J_{C\text{-}P}$ = 24.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 14.3.

Diethyl (5-(4-bromophenyl)-2-phenylfuran-3-yl)phosphonate (**7c**):



7c

Yield: 36 mg (83%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

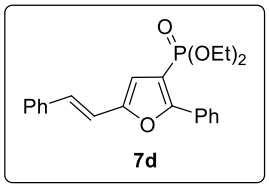
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{20}BrO_4PH^+$ 435.0356, found: 435.0359.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, t, J = 7.2 Hz), 3.98-4.25 (4H, m), 7.0 (1H, d, J = 4.0 Hz), 7.34-7.63 (7H, m), 8.02 (2H, d, J = 8.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (d, $J_{C\text{-}P}$ = 7.0 Hz), 62.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 109.7 (d, $J_{C\text{-}P}$ = 211.0 Hz), 111.3 (d, $J_{C\text{-}P}$ = 11.0 Hz), 121.9, 125.4, 127.4, 128.3, 128.5, 129.2, 129.3, 131.9, 151.8 (d, $J_{C\text{-}P}$ = 16.0 Hz), 157.5 (d, $J_{C\text{-}P}$ = 24.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 13.6.

Diethyl (E)-(2-phenyl-5-styrylfuran-3-yl)phosphonate (**7d**):



7d

Yield: 27 mg (71%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

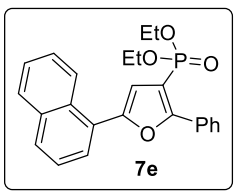
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{22}H_{23}O_4PH^+$ 383.1407, found: 383.1406.

^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, t, J = 6.8 Hz), 3.99-4.21 (4H, m), 6.70 (1H, d, J = 4.0 Hz), 6.89 (1H, d, J = 16.4 Hz), 7.15 (1H, d, J = 16.4 Hz), 7.28 (1H, d, J = 7.2 Hz), 7.33-7.42 (3H, m), 7.43-7.52 (4H, m), 8.04 (2H, d, J = 7.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.1 (d, $J_{C\text{-}P}$ = 6.0 Hz), 62.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 109.4 (d, $J_{C\text{-}P}$ = 211.0 Hz), 114.1 (d, $J_{C\text{-}P}$ = 11.0 Hz), 115.2, 126.4, 127.4, 128.0, 128.3, 128.7, 128.8, 129.2, 129.4, 136.5, 152.2 (d, $J_{C\text{-}P}$ = 15.0 Hz), 157.3 (d, $J_{C\text{-}P}$ = 24.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 13.9.

Diethyl (2-(naphthalen-1-yl)-5-phenylfuran-3-yl)phosphonate (**7e**):



7e

Yield: 36 mg (88%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

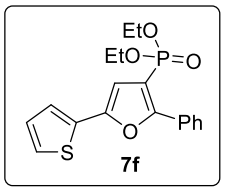
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{24}H_{23}O_4PH^+$: 407.1407, found: 407.1405.

^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (6H, t, J = 6.8 Hz), 4.06-4.28 (4H, m), 7.09 (1H, d, J = 3.6 Hz), 7.34-7.64 (6H, m), 7.81 (1H, d, J = 7.2 Hz), 7.87 (2H, t, J = 9.2 Hz), 8.10 (2H, d, J = 8.0 Hz), 8.44 (1H, d, J = 8.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (d, $J_{C\text{-}P}$ = 7.0 Hz), 62.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 109.3 (d, $J_{C\text{-}P}$ = 211.0 Hz), 114.8 (d, $J_{C\text{-}P}$ = 11.0 Hz), 125.1, 125.2, 126.0, 126.4, 126.9, 127.1, 127.4, 128.4, 128.6, 129.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 129.6, 130.1, 133.9, 152.5 (d, $J_{C\text{-}P}$ = 16.0 Hz), 157.7 (d, $J_{C\text{-}P}$ = 24.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 14.1.

Diethyl (5-phenyl-2-(thiophen-2-yl)furan-3-yl)phosphonate (**7f**):



7f

Yield: 29 mg (79%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

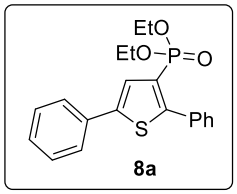
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{18}H_{19}O_4PH^+$: 363.0815, found: 363.0810.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (6H, t, J = 7.2 Hz), 4.01-4.22 (4H, m), 6.85 (1H, d, J = 4.0 Hz), 7.07 (1H, t, J = 4.4 Hz), 7.29 (1H, d, J = 5.2 Hz), 7.35 (1H, d, J = 4.0 Hz) 7.36-7.52 (3H, m), 8.02 (2H, d, J = 7.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (d, $J_{C\text{-}P}$ = 7.0 Hz), 62.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 109.4 (d, $J_{C\text{-}P}$ = 212.0 Hz), 110.6 (d, $J_{C\text{-}P}$ = 11.0 Hz), 123.6, 125.1, 127.3, 127.7, 128.3, 129.2, 129.3, 132.2, 148.6 (d, $J_{C\text{-}P}$ = 16.0 Hz), 156.8 (d, $J_{C\text{-}P}$ = 24.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 13.6.

Diethyl (2,5-diphenylthiophen-3-yl)phosphonate (**8a**):



8a

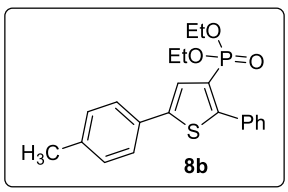
Yield: 30 mg (81%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{21}O_3PSH^+$ 373.1022, found: 373.1023. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (6H, t, J = 6.8 Hz), 3.82-4.05 (4H, m), 7.20 (1H, d, J = 14.4 Hz), 7.28-7.38 (5H, m), 7.53 (3H, t, J = 6.8 Hz), 7.61 (2H, t, J = 2.4 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 6.8 Hz), 62.1 (d, $J_{C\text{-}P}$ = 5.6 Hz), 125.7 (d, $J_{C\text{-}P}$ = 192.5 Hz), 125.8, 128.0, 128.1, 128.2 (d, $J_{C\text{-}P}$ = 16.0 Hz), 128.8, 129.0, 129.6, 133.1, 133.2 (d, $J_{C\text{-}P}$ = 2.0 Hz), 143.7 (d, $J_{C\text{-}P}$ = 19.0 Hz), 151.5 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 12.8.

Diethyl (2-phenyl-5-(p-tolyl)-thiophen-3-yl)phosphonate (**8b**):



8b

Yield: 34 mg (88%), pale yellow gummy liquid, eluent: 60% EtOAc in hexane.

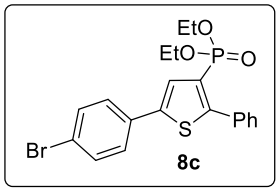
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{23}O_3PSH^+$ 387.1178, found: 387.1178.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (6H, t, J = 6.8 Hz), 2.38 (3H, s), 3.90-4.11 (4H, m), 7.21 (2H, d, J = 8.0 Hz), 7.41 (3H, d, J = 6.8 Hz), 7.50 (2H, d, J = 8.0 Hz), 7.57 (1H, d, J = 4.4 Hz), 7.67 (2H, t, J = 5.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (d, $J_{C\text{-}P}$ = 7.0 Hz), 21.21, 62.1 (d, $J_{C\text{-}P}$ = 6.0 Hz), 125.7 (d, $J_{C\text{-}P}$ = 192.0 Hz), 125.8, 127.7 (d, $J_{C\text{-}P}$ = 16.0 Hz), 128.1, 128.7, 129.6, 129.7, 130.5, 133.3 (d, $J_{C\text{-}P}$ = 2.0 Hz), 138.1, 143.9 (d, $J_{C\text{-}P}$ = 19.0 Hz), 151.0 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 12.9.

Diethyl (5-(4-bromophenyl)-2-phenylthiophen-3-yl) phosphonate (**8c**):



Yield: 39 mg (86%), pale yellow gummy liquid eluent: 60% EtOAc in hexane.

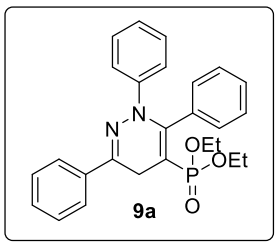
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{20}BrO_3PSH^+$ 451.0127, found: 451.0129.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (6H, t, J = 7.2 Hz), 3.88-4.15 (4H, m), 7.36-7.55 (7H, m), 7.61 (1H, d, J = 4.8 Hz), 7.66 (2H, t, J = 3.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 62.1 (d, $J_{C\text{-}P}$ = 8.0 Hz), 121.9, 126.2 (d, $J_{C\text{-}P}$ = 193.0 Hz), 127.3, 128.2, 128.6 (d, $J_{C\text{-}P}$ = 17.0 Hz), 128.9, 129.6, 132.1, 132.2, 133.0 (d, $J_{C\text{-}P}$ = 3.0 Hz), 142.3 (d, $J_{C\text{-}P}$ = 19.0 Hz), 151.8 (d, $J_{C\text{-}P}$ = 16.0 Hz).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 12.4.

Diethyl (2,3,6-triphenyl-2,5-dihydropyridazin-4-yl)phosphonate (**9a**):



Yield: 41 mg (93%), yellow solid (mp 158-160 ^{o}C), eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{26}H_{27}N_2O_3PH^+$ 447.1833, found: 447.1838.

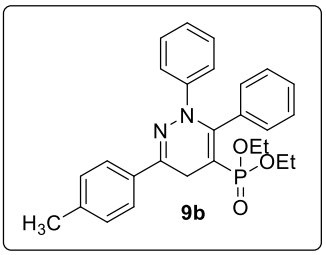
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (6H, t, J = 7.2 Hz), 3.45 (2H, d, J = 9.2 Hz), 3.59-3.70 (2H, m), 3.71-3.82 (2H, m), 6.85 (1H, t, J = 7.2 Hz), 7.03 (2H, t, J = 8.0 Hz), 7.07-7.25 (7H, m), 7.31-7.42 (3H, m), 7.90 (2H, d, J = 6.4 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 6.8 Hz), δ 26.0 (d, $J_{C\text{-}P}$ = 8.7 Hz), 61.3 (d, $J_{C\text{-}P}$ = 5.7 Hz), 90.3 (d, $J_{C\text{-}P}$ = 206.5 Hz), 123.5, 124.2, 126.9, 127.4, 128.1, 128.5, 128.7,

129.6, 130.9, 133.5 (d, $J_{C\text{-}P}$ = 3.1 Hz), 135.1, 143.7 (d, $J_{C\text{-}P}$ = 2.5 Hz), 144.0 (d, $J_{C\text{-}P}$ = 4.3 Hz), 150.2 (d, $J_{C\text{-}P}$ = 21.9 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 19.17.

Diethyl (2,3-diphenyl-6-(p-tolyl)-2,5-dihydropyridazin-4-yl)phosphonate (**9b**):



Yield: 45 mg (98%), yellow solid (mp 160-162 ^oC), eluent: 60% EtOAc in hexane.

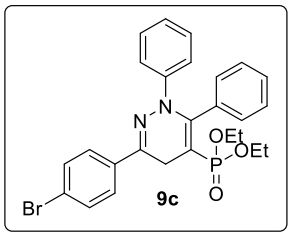
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{27}H_{29}N_2O_3PH^+$ 461.1989, found: 461.1986.

^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (6H, t, J = 7.2 Hz), 2.43 (3H, s), 3.52 (2H, d, J = 9.2 Hz), 3.68-3.79 (2H, m), 3.80-3.91 (2H, m), 6.94 (1H, t, J = 7.2 Hz), 7.12 (2H, t, J = 8.0 Hz), 7.16-7.34 (9H, m), 7.89 (2H, d, J = 8.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 21.4, 26.0 (d, $J_{C\text{-}P}$ = 8.0 Hz), 61.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 90.2 (d, $J_{C\text{-}P}$ = 206.0 Hz), 123.5, 124.1, 126.8, 127.4, 128.1, 128.7, 129.3, 131.0, 132.3, 133.6 (d, $J_{C\text{-}P}$ = 3.0 Hz), 139.8, 143.8 (d, $J_{C\text{-}P}$ = 2.0 Hz), 144.1 (d, $J_{C\text{-}P}$ = 5.0 Hz), 150.3 (d, $J_{C\text{-}P}$ = 22.0 Hz).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 19.3.

Diethyl (6-(4-bromophenyl)-2,3-diphenyl-2,5-dihydrpyridazin-4-yl)phosphonate (**9c**):



Yield: 50 mg (95%), yellow solid (mp 179-182 ^oC), eluent: 60% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{26}H_{26}BrN_2O_3PNa^+$ 547.0757, found: 547.0756.

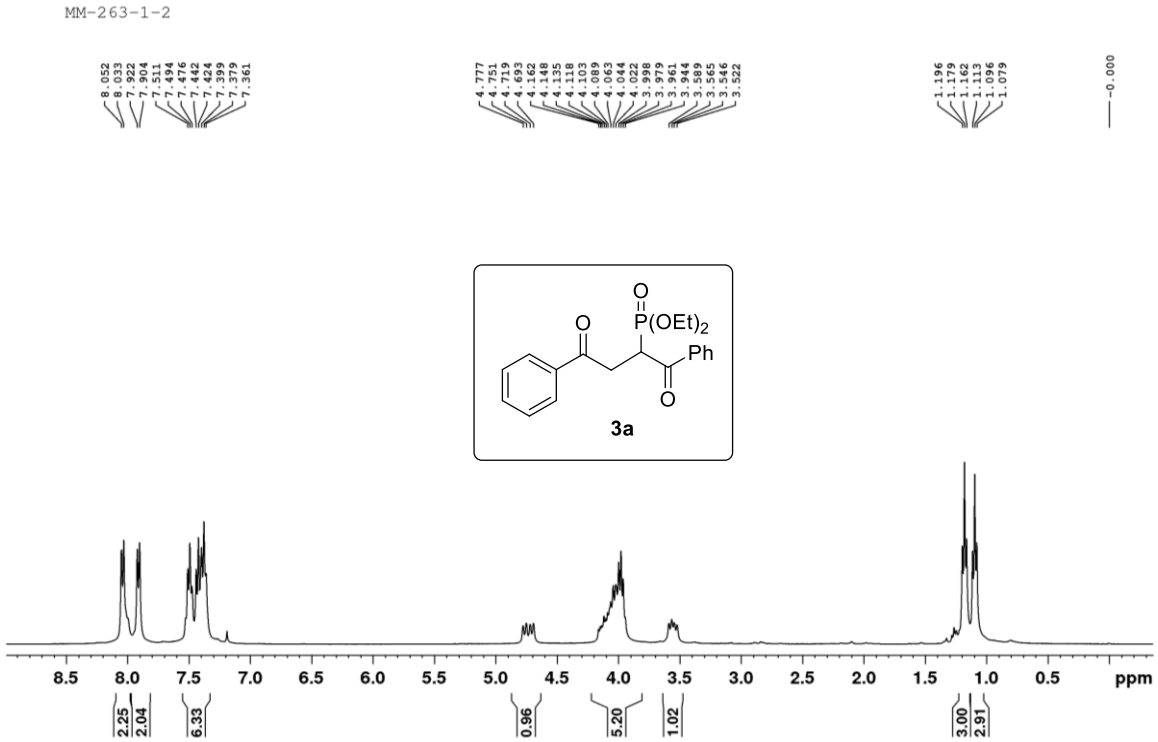
^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (6H, t, J = 7.2 Hz), 3.51 (2H, d, J = 8.8 Hz), 3.67-3.79 (2H, m), 3.80-3.92 (2H, m), 6.96 (1H, t, J = 7.2 Hz), 7.13 (2H, t, J = 8.0 Hz), 7.17-7.33 (7H, m), 7.59 (2H, d, J = 8.4 Hz), 7.86 (2H, d, J = 8.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), δ 25.7 (d, $J_{C\text{-}P}$ = 9.0 Hz), 61.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 90.3 (d, $J_{C\text{-}P}$ = 206.0 Hz), 123.5, 123.9, 124.4, 127.4, 128.1, 128.3, 128.8, 130.9, 131.7, 133.3 (d, $J_{C\text{-}P}$ = 3.0 Hz), 134.0, 142.7 (d, $J_{C\text{-}P}$ = 4.0 Hz), 143.5 (d, $J_{C\text{-}P}$ = 2.0 Hz), 150.1 (d, $J_{C\text{-}P}$ = 22.0 Hz).

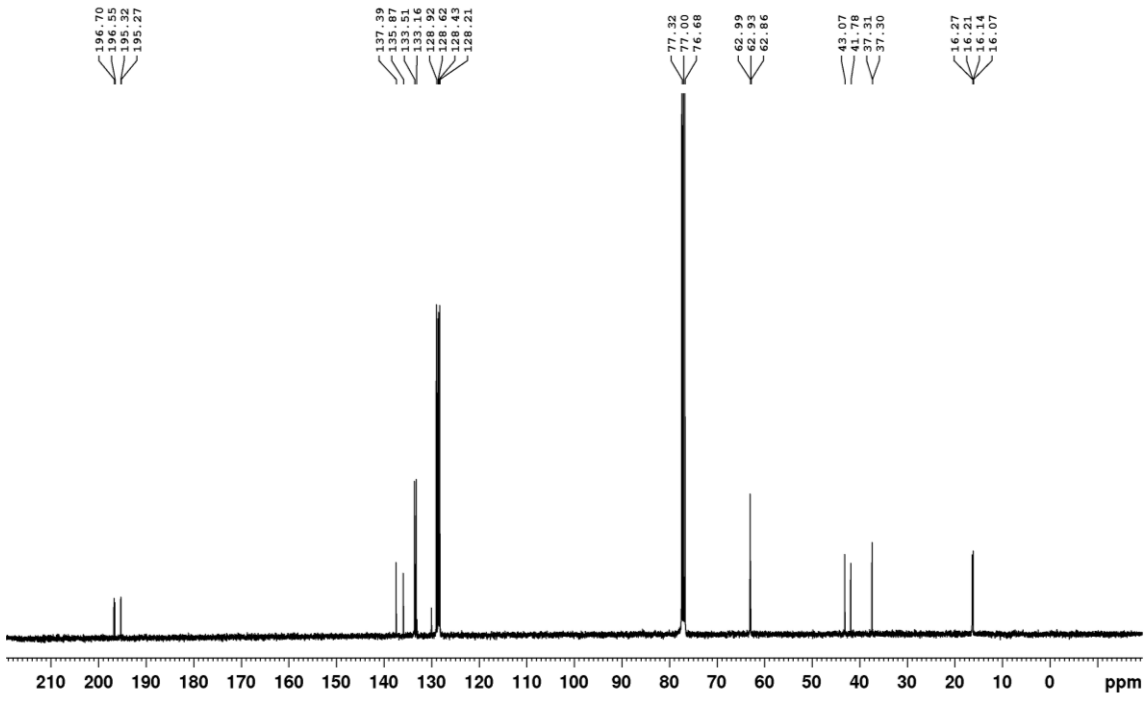
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 19.02.

3.6.5. ^{1}H and $^{13}C\{1H\}$ Spectra of the Products

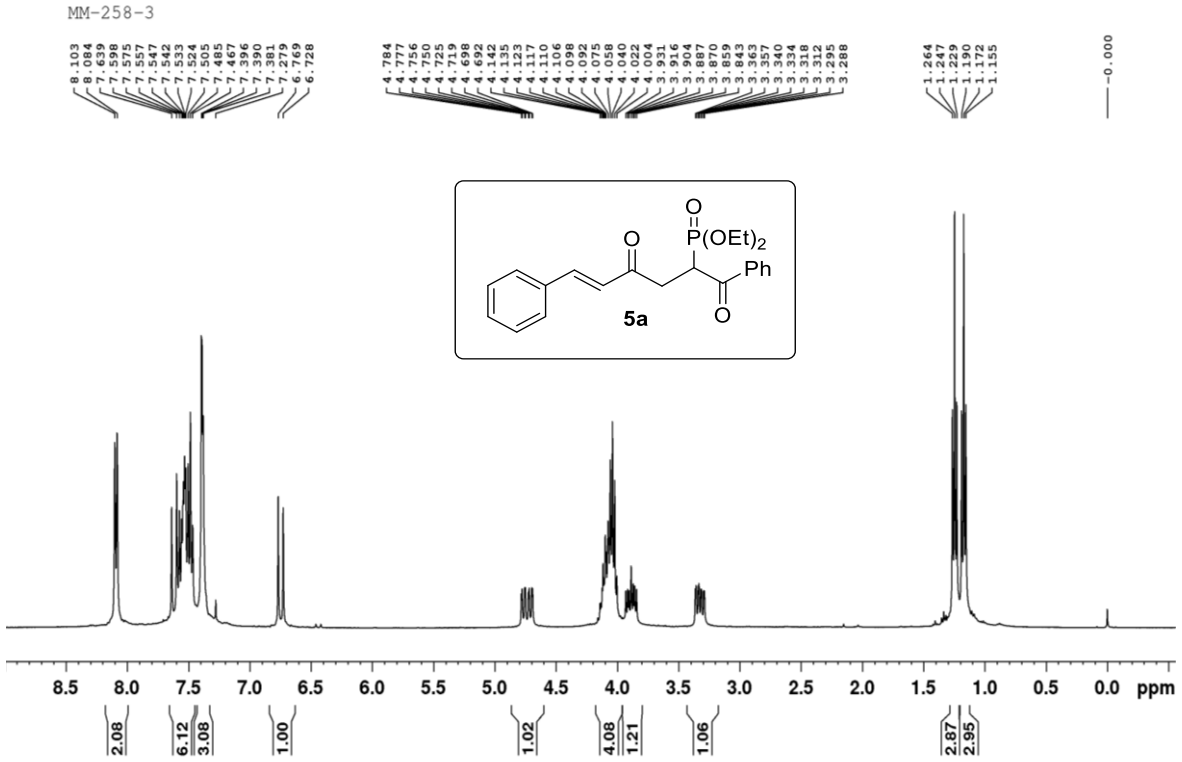
^{1}H NMR of compound 3a (400 MHz/$CDCl_3$)



$^{13}C\{^{1}H\}$ NMR of compound 3a (100 MHz/$CDCl_3$)



^{1}H NMR of compound 5a (400 MHz/$CDCl_3$)



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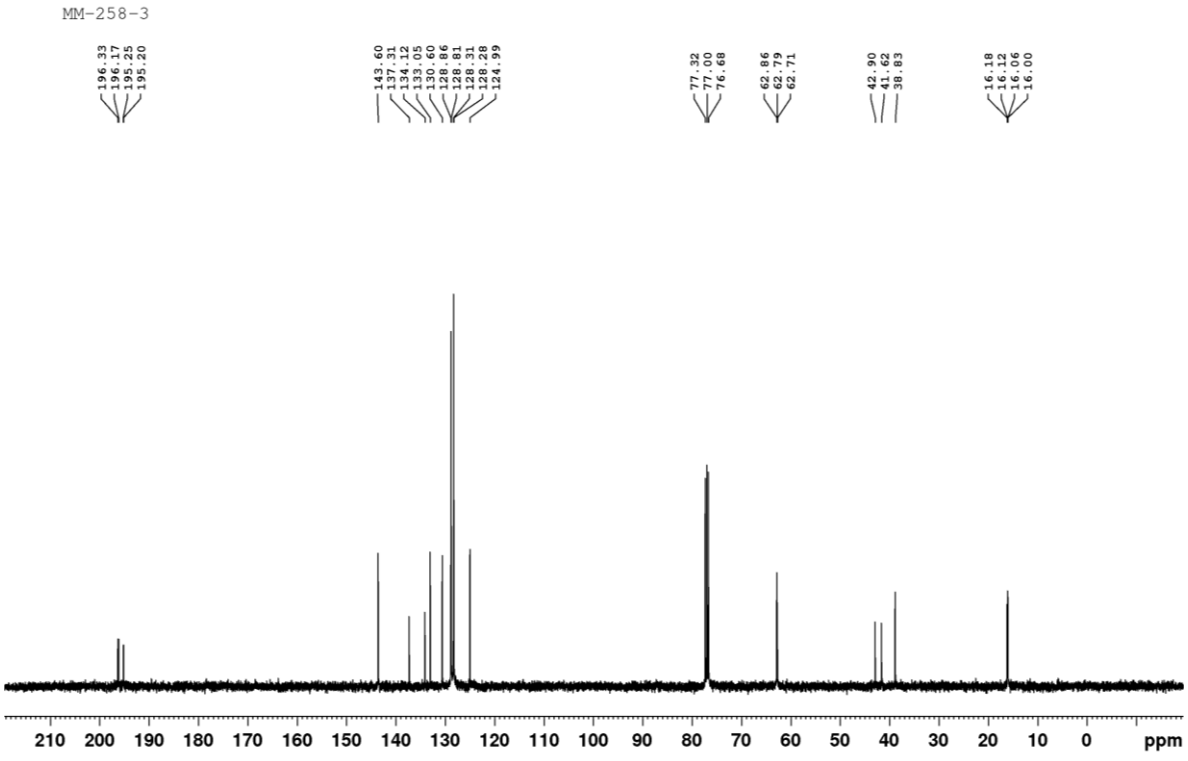
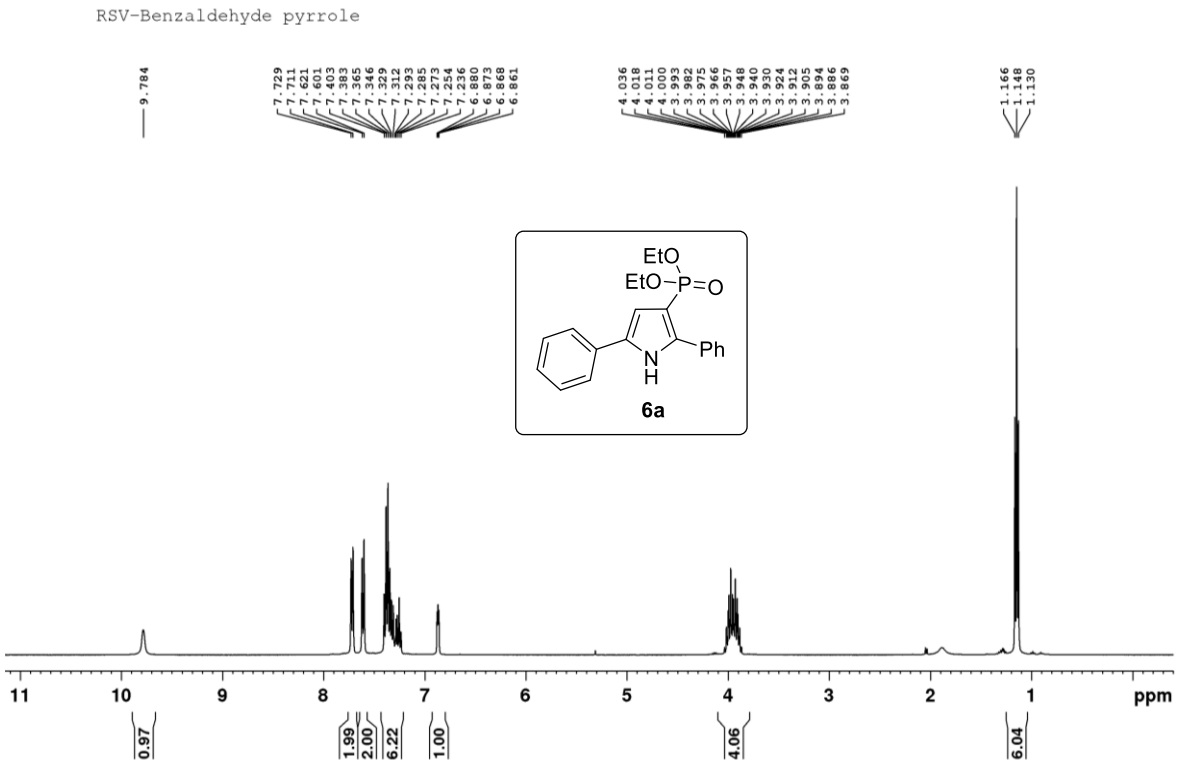
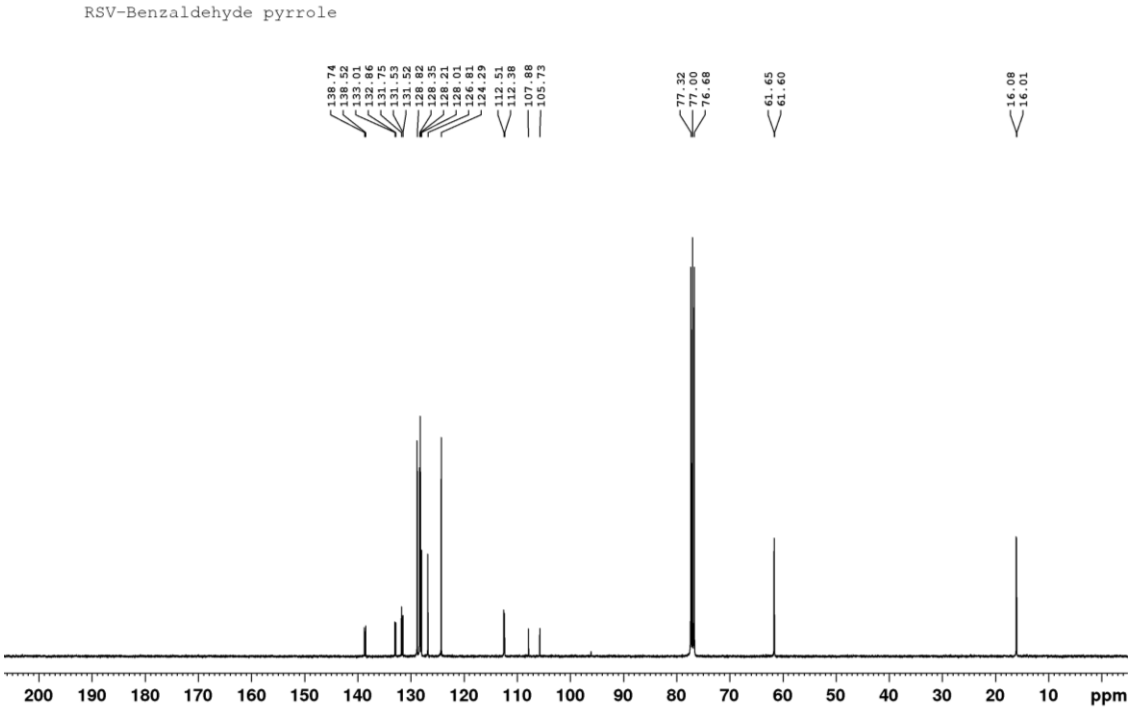


^{1}H NMR of compound 6a (400 MHz/$CDCl_3$)



^{13}C{^{1}H} NMR of compound 6a (100 MHz/$CDCl_3$)



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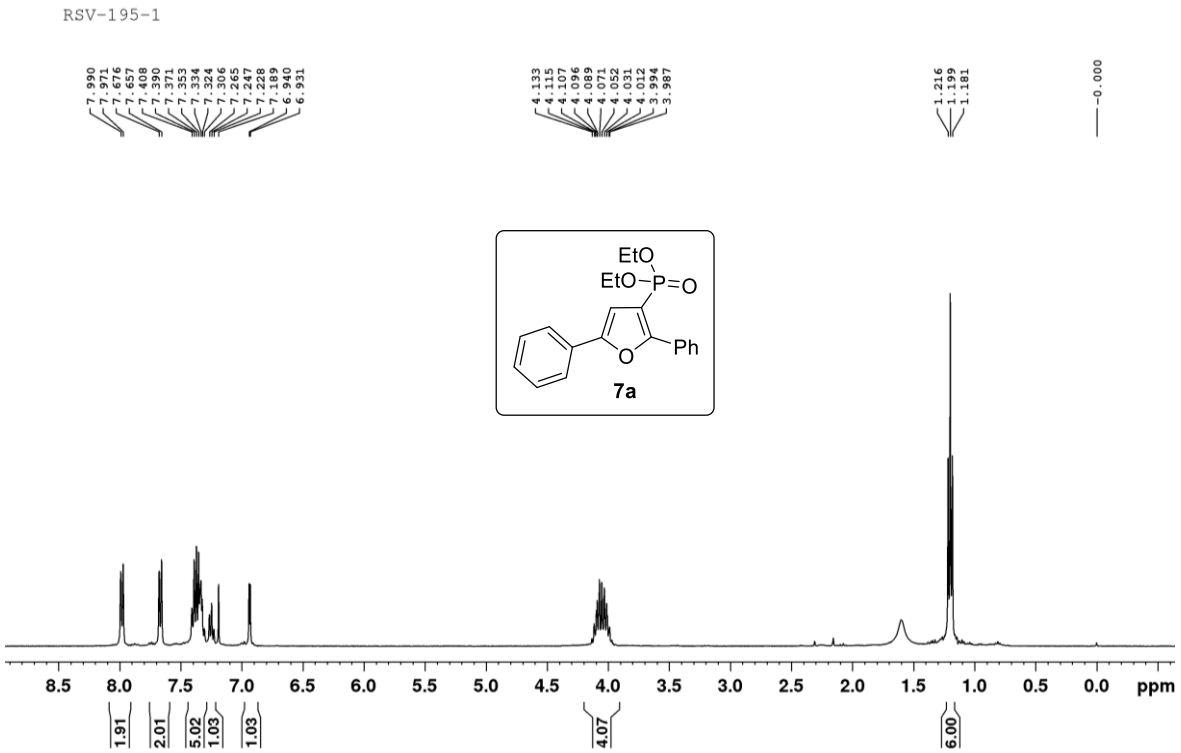
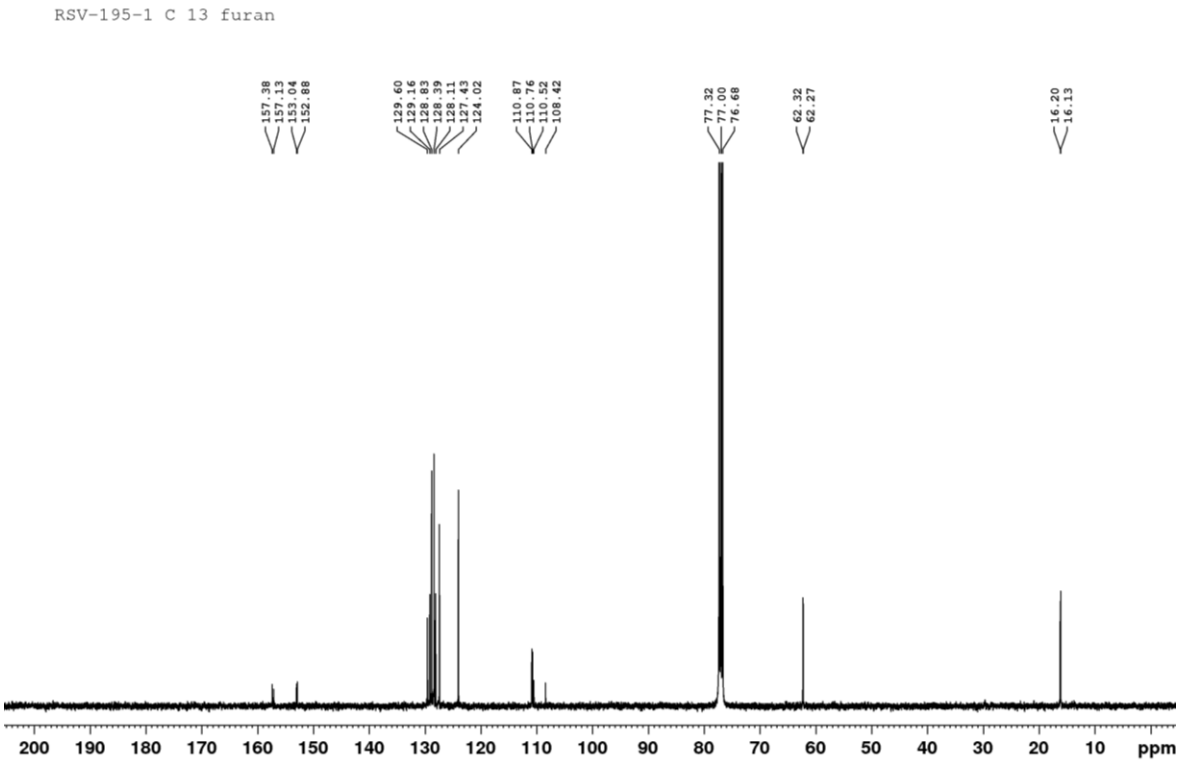


^{13}C{^{1}H} NMR of compound 7a (100 MHz/$CDCl_3$)



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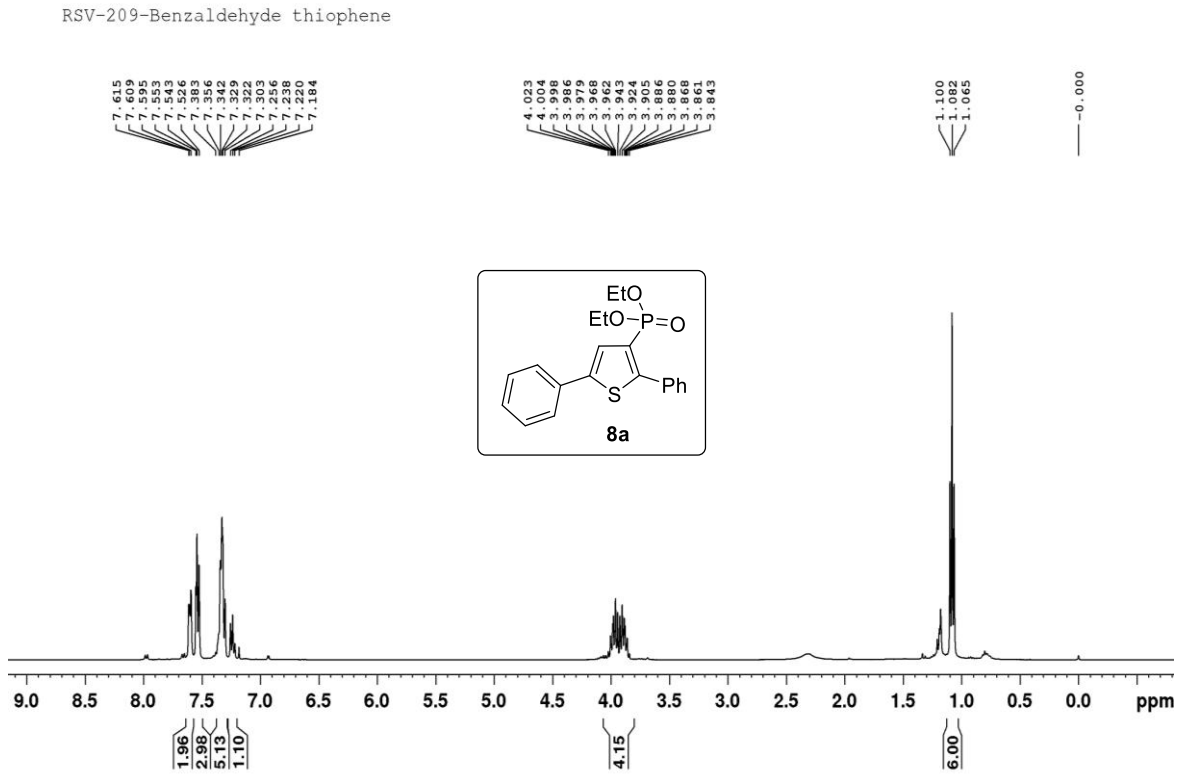

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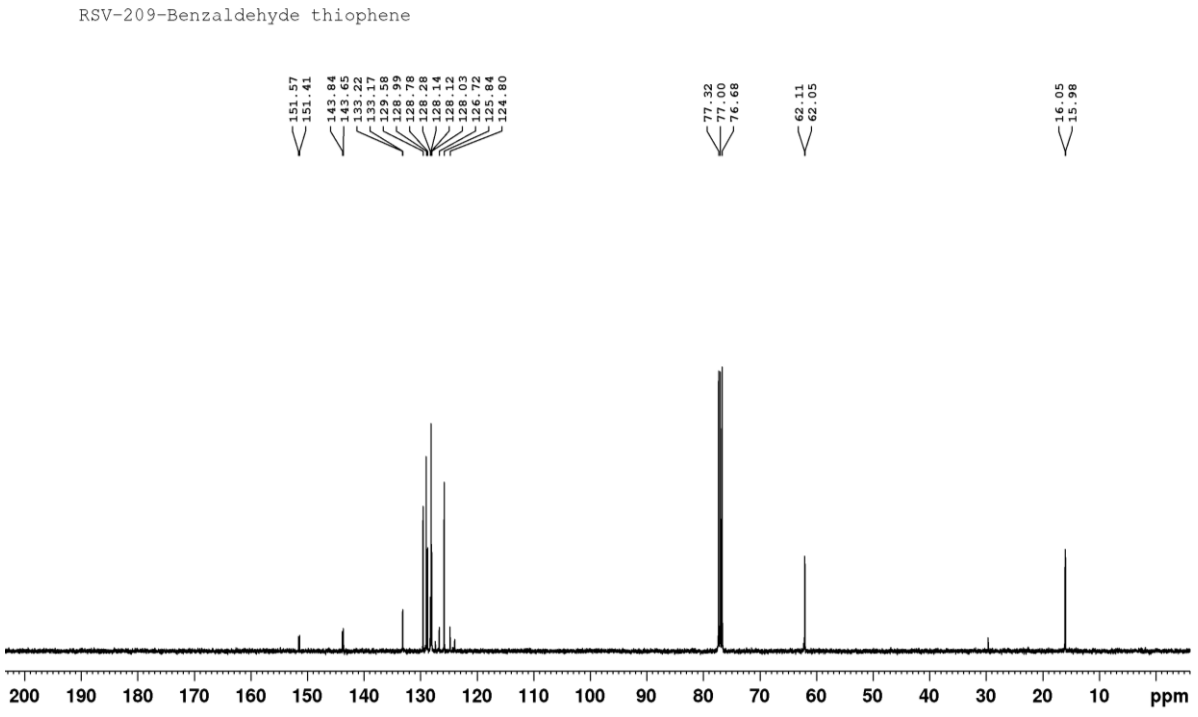

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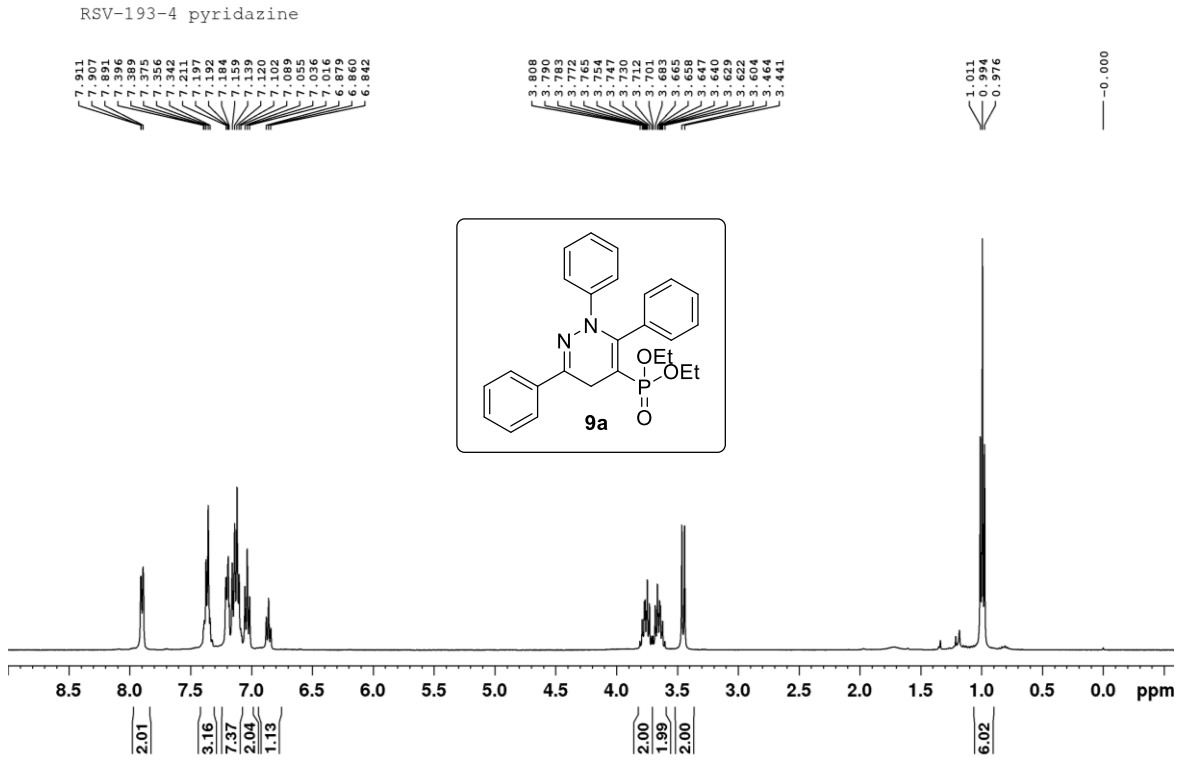
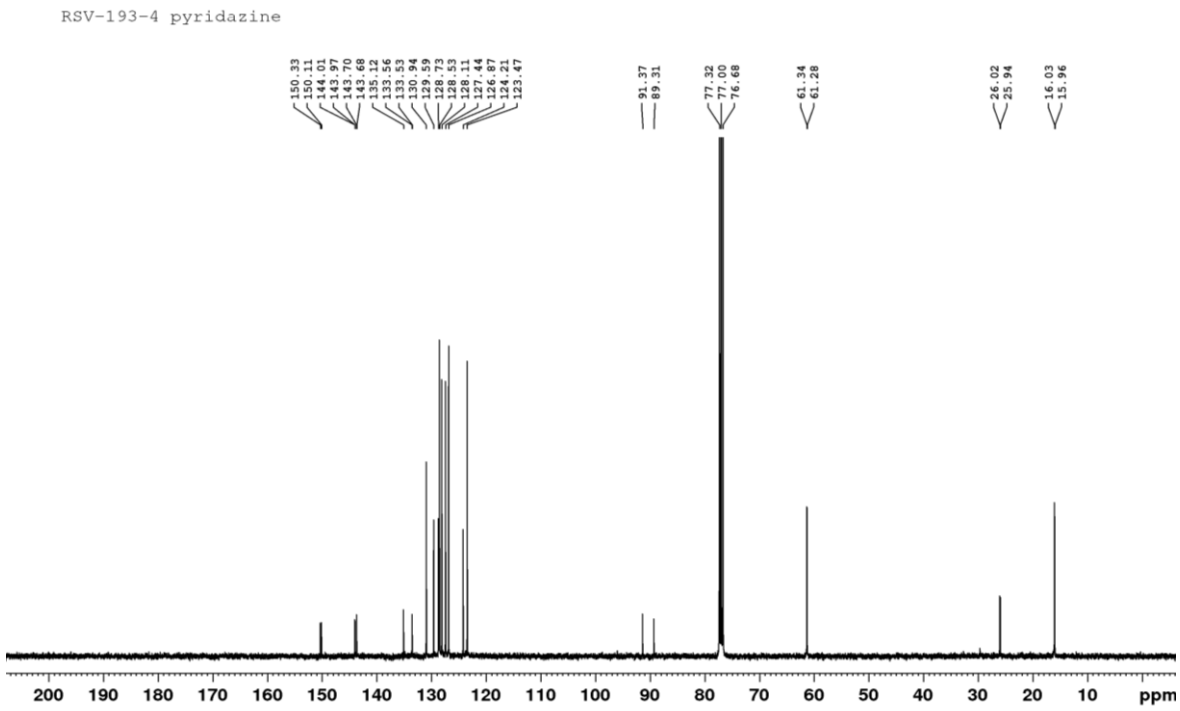


^{13}C{^{1}H} NMR of compound 9a (100 MHz/$CDCl_3$)



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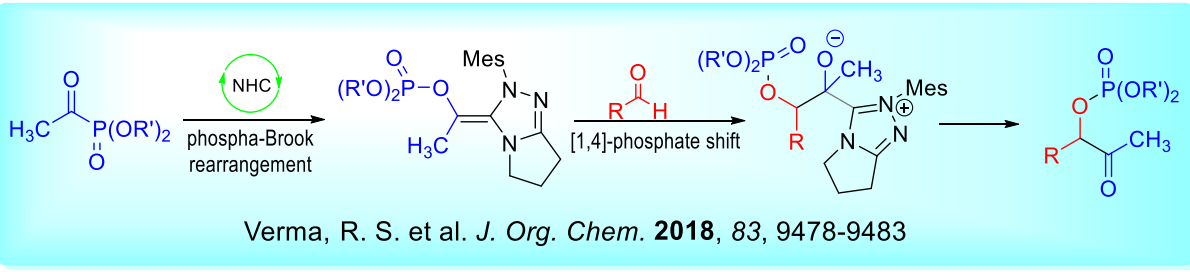
17. For reaction condition, see: Penning, M.; Christoffers, J. *Eur. J. Org. Chem.* **2013**, *2*, 389.

Chapter 4

Carbene Catalyzed Preparation of *α*-Ketophosphates from Acylphosnates and Aldehydes

The organophosphorus compounds have an indispensable role as the key biomolecules, such as DNA, RNA and ATP. In addition, they are used in pharmaceutics, organometallics, organic synthesis and photoelectric materials. They have high chelation affinity with transition metals, therefore, they are widely used as ligands in organic synthesis. Phosphate esters are used in the pesticides and in prodrugs to enhance their aqueous solubility. Among them, *α*-ketophosphates are the key intermediates for the synthesis of phospholipids and oligonucleotides. Herein, we have developed the first *N*-heterocyclic carbene catalyzed controlled cross acyloin condensation of acyl phosphonates and aldehydes *via* phospha-Brook rearrangement. This is the first organocatalytic phospha-Brook rearrangement that generally required metal cyanides as the catalysts previously. In addition, acyl anions from the acyl phosphonates has been generated under carbene catalyst for the first time.



Verma, R. S. et al. *J. Org. Chem.* **2018**, *83*, 9478-9483

4.1. Introduction

Organophosphates (phosphate esters) are a category of organophosphorus compounds that have the general formula $O=P(OR)_3$ (Figure 4.1). The organophosphorus (organophosphates) are the main structural component that occurs in various bioactive molecules.

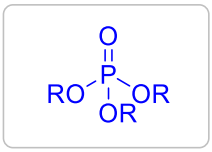


Figure 4.1: General structure of organophosphates

In addition, organophosphorus compounds also have an indispensable role in the key biomolecules such as DNA, RNA and ATP as well as in pharmaceutics, organometallics, organic synthesis and photoelectric materials. Organophosphorus compounds have high chelation affinity with transition metal, therefore, they are widely used as ligands in organic synthesis.[1] Phosphate esters are also found in numerous pesticides and in prodrugs to enhance their aqueous solubility (Figure 4.2).

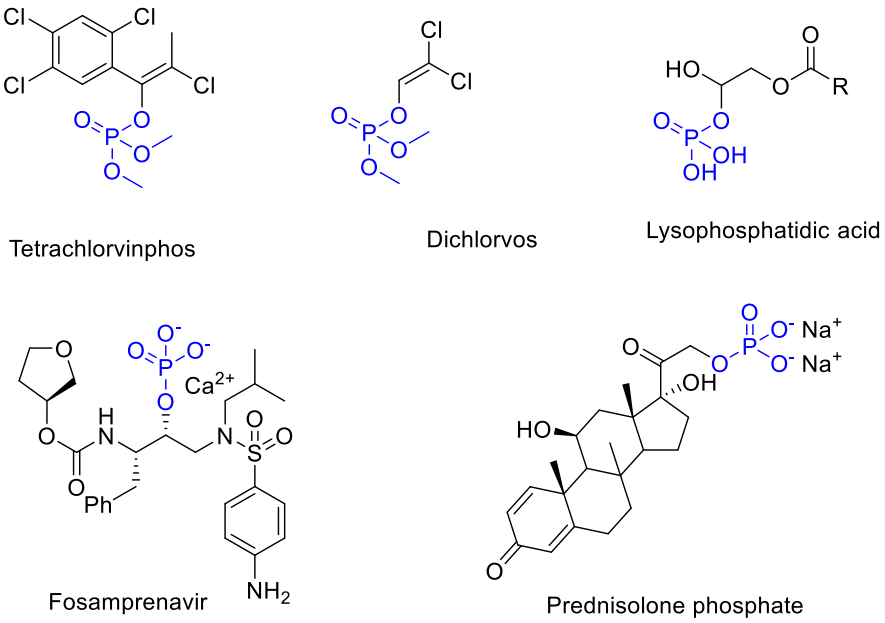


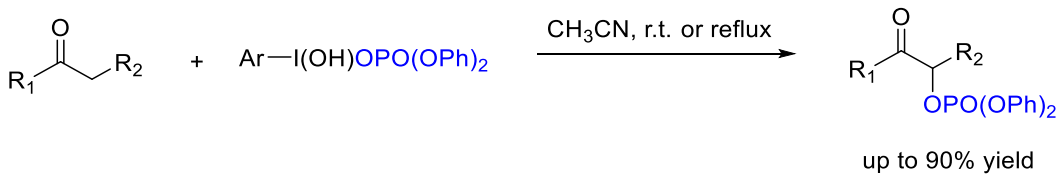
Figure 4.2: Phosphate ester containing biologically active compounds.

One of the important features of the phosphate-containing prodrugs is their chemical stability and rapid rate of bio-conversion by the action of enzymes (phosphatases) present at the intestinal brush border or in the liver.[2] As discussed above phosphate functionality occurs in numerous bioactive compounds. In addition, particularly α-hydroxyketone phosphates are used as key intermediates in the synthesis of phospholipids and oligonucleotides as well it is

serving as sugar analogs.[3] Therefore, the synthesis of α-hydroxyketone phosphates has gained significant attention from the scientists and researchers.

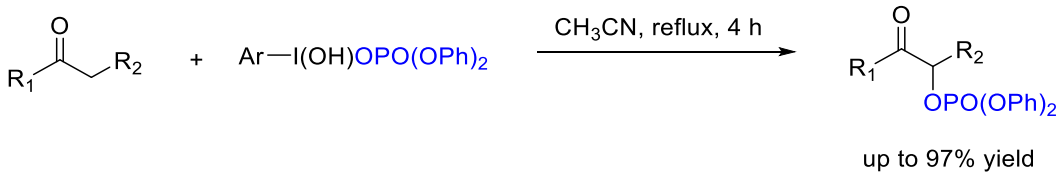
4.2. Literature Reports for the Synthesis of α-Hydroxyketone Phosphates

In view of the biological importance of the phosphate esters, the synthesis of α-hydroxyketone phosphates has received significant attention of the scientific community. The traditional approaches for their synthesis were based on the acidic hydrolysis of 2,2,2-trialkoxy-1,3,2-dioxaphospholene.[4] In 1988, Kokil and co-workers reported the synthesis of α-hydroxyketone phosphates using [hydroxy(phosphoryloxy)iodo]arenes as the phosphorylating agent with ketones in acetonitrile solvent.[5] In this reaction, the α-phosphoryloxylation of various ketones resulted in the formation of α-ketophosphates in moderate to good yields (Scheme 4.1).



Scheme 4.1. α-Phosphoryloxylation of ketones reported by Kokil and co-workers

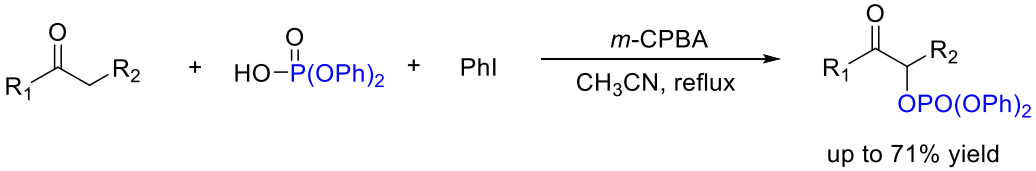
In 2002, the group of Togo reported the α-phosphoryloxylation of ketones by using a [hydroxy(phosphoryloxy)iodo]arenes as the phosphorylating agent.[6] This methodology produced the α-ketophosphates in a very good yield by refluxing the ketones in acetonitrile solvent (Scheme 4.2).



Scheme 4.2. α-Phosphoryloxylation of ketones developed by Togo and co-workers

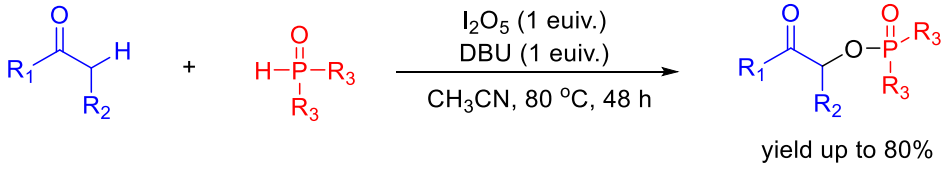
An alternate method for the preparation of α-hydroxyketone phosphates involves the treatment of terminal alkynes with [hydroxy((bis(pheny1oxy)phosphory1)oxy)idolbenzene reagent. In addition, α-hydroxyketone phosphates can also be prepared by oxyphosphorylation of silyl enol ethers in the presence of phosphoric acid and *p*-(difluoroiodo)toluene.[7]

In 2012, the research group of Yan reported the iodobenzene catalyzed *α*-phosphoryloxylation of ketones using aryl phosphate and stoichiometric amounts of *m*-CPBA (*m*-chloroperbenzoic acid).[8] In this reaction, a wide variety of ketones were treated with diphenyl phosphate in the presence of an external oxidizing agent *m*-chloroperbenzoic acid and iodobenzene catalyst in acetonitrile solvent at room temperature producing the corresponding *α*-ketophosphates in moderate to good yields (Scheme 4.3).



Scheme 4.3. *α*-Phosphoryloxylation of ketones catalyzed by iodobenzene

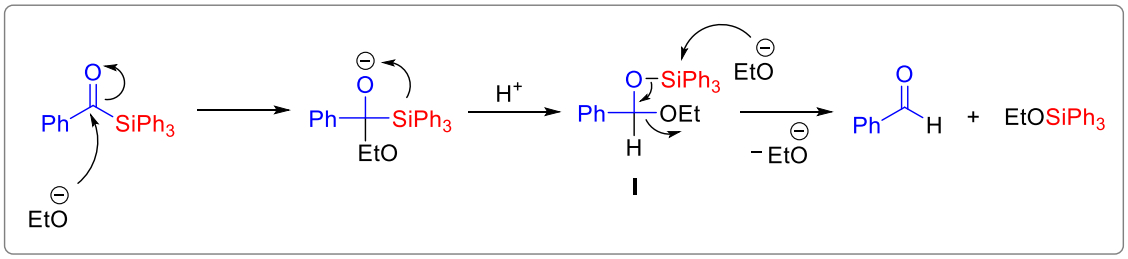
Recently in 2015, Wang and co-workers developed a method for the preparation of *α*-ketophosphates by the direct *α*-phosphoryloxylation of ketones. In this reaction, *α*-ketophosphates were prepared by *α*-phosphoryloxylation of ketones in the presence of H-phosphonates and stochiometric amount of I_2O_5/DBU. In this reaction first ketones undergoes to the *α*-iodination in the presence of I_2O_5. Thereafter, the di-alkylphosphites are oxidized in the di-alkyl hydrogen phosphate in the presence of I_2O_5, they confirmed it by performing the control experiment. Finally, the di-alkyl hydrogen phosphate and *α*-iodo-ketones *via* the nucleophilic substitution to produces *α*-ketophosphates in good yield (Scheme 4.4).[9]



Scheme 4.4. *α*-Phosphoryloxylation of ketones developed by Wang and co-workers

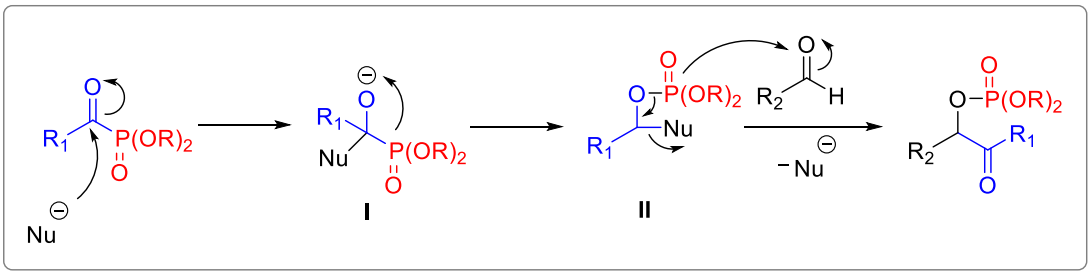
Most of these traditional protocols suffer from one or multiple problems such as additional steps for synthesis of starting materials, substrate scope limitation, poor atom economy, low yields, toxic chemical wastes, and use of potentially hazardous peroxide as oxidants. Consequently, the development of organocatalytic simple, atom economical, highly efficient and convenient approach for the preparation of *α*-ketophosphates is highly desired. In this context, the phospha-Brook rearrangement plays a vital role for the preparation of *α*-ketophosphates.

The Brook rearrangement is an intramolecular 1,2-silyl migration in acylsilanes or in silyl carbinols from the carbon to oxygen in the presence of a base. The mechanism of this rearrangement was described by Brook in 1974 (Scheme 4.5).[10] The mechanism of this reaction is imitated by the nucleophilic addition of ethoxide anion to the acylsilane, which later undergoes a 1,2-silyl migration to give silylether intermediate **I**. Finally, the oxygen silicon bonds cleaved by the ethoxide anion to produce aldehyde product.



Scheme 4.5. Brook rearrangement in acylsilane

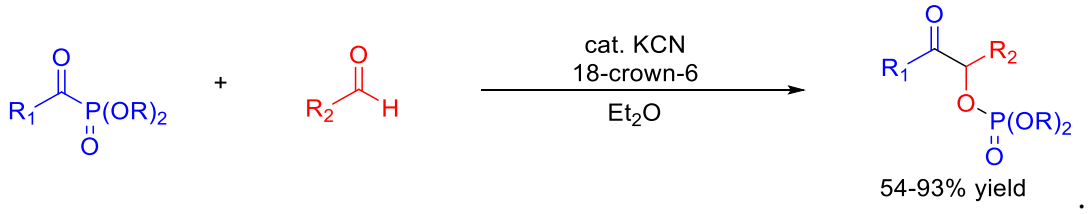
The phospha-Brook rearrangement is an intramolecular 1,2-phosphoryl group migration in acylphosphonate in the presence of a base or catalysts (Scheme 4.6).[11] Mechanistically, this reaction was initiated by the addition of a nucleophile to the acylphosphonate to give intermediate **I**. The intermediate **I** subsequently undergo to 1,2-phosphoryl group migration (1,2-phospha Brook rearrangement) to form a carbanion intermediate **II**. Which further adds to a aldehyde molecule. Thereafter, 1,4-phosphoryl group migration from oxygen to oxygen gives the desired product with release of the nucleophile.



Scheme 4.6. Phospha-Brook rearrangement in acylphosphonate

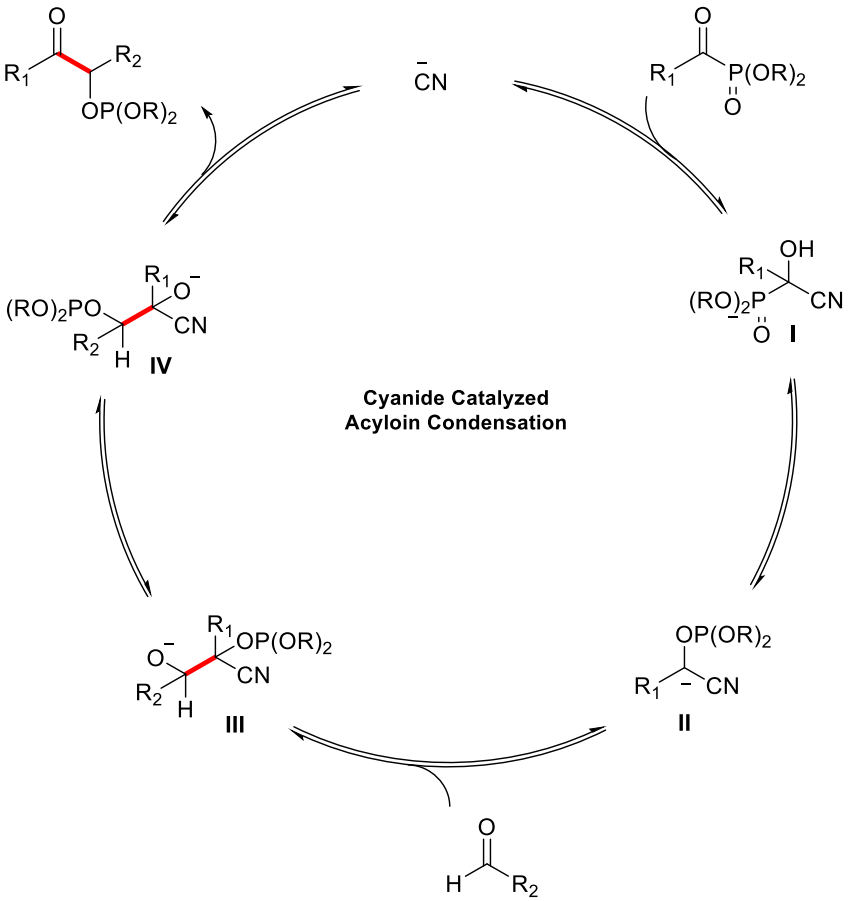
The preparation of *α*-keto-phosphates *via* phospha-Brook rearrangement has great advantages because this method is direct, one-pot and have high atom economy as well as the process is catalytic. In 2005, the group of Johnson and Bausch independently developed the cyanide-catalyzed generation of acyl anion from acyl phosphonates. These acyl anions added to aromatic and heteroaromatic aldehydes resulting in the formation of *α*-keto-phosphates in

good to excellent yields (Scheme 4.7).[12] This reaction produced the desired products in a very low yield with alkyl acylphosphonates and aliphatic aldehydes.

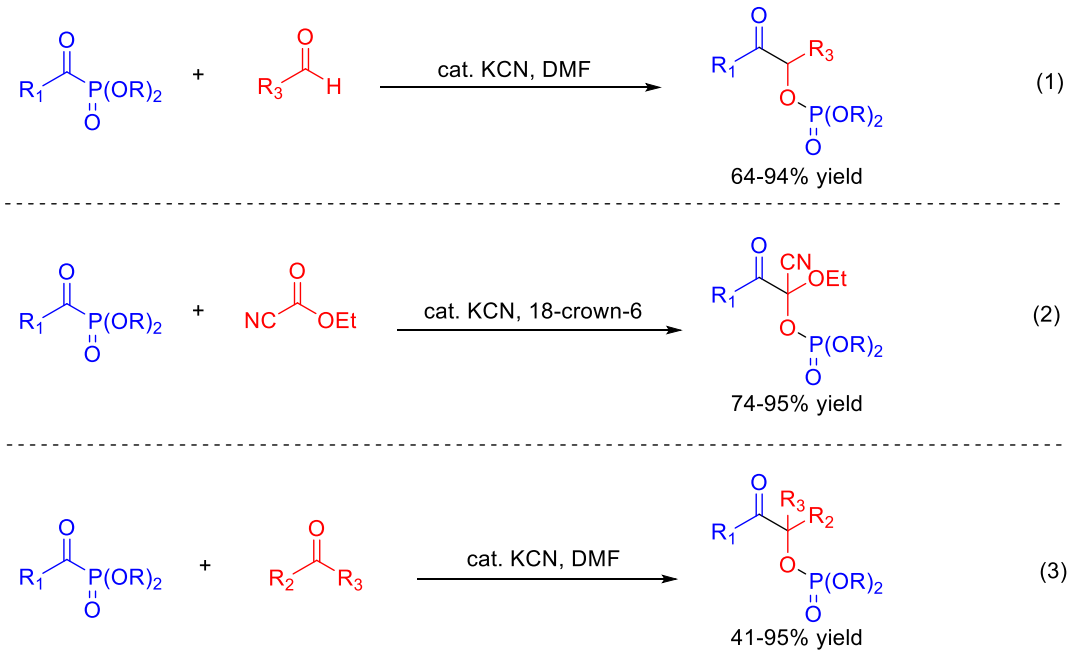


Scheme 4.7. Cyanide catalyzed addition of acylphosphnates to aldehydes

Mechanistically, this reaction was initiated by the addition of the cyanide ion to the acylphosphonate to form an intermediate **I**. This intermediate **I** give a carbanion intermediate **II** *via* 1,2-phosphoryl group migration (1,2-phospha Brook rearrangement). This intermediate **II** further reacts with the aldehydes molecule to generate intermediate **III**, which further undergoes 1,4-phosphoryl group migration to form intermediate **IV**. Finally, this intermediate **IV** after the release of cyanide ion produces the *α*-keto-phosphate product (Scheme 4.8).



Scheme 4.8. Postulated mechanism for the cyanide catalyzed addition of acylphosphonate



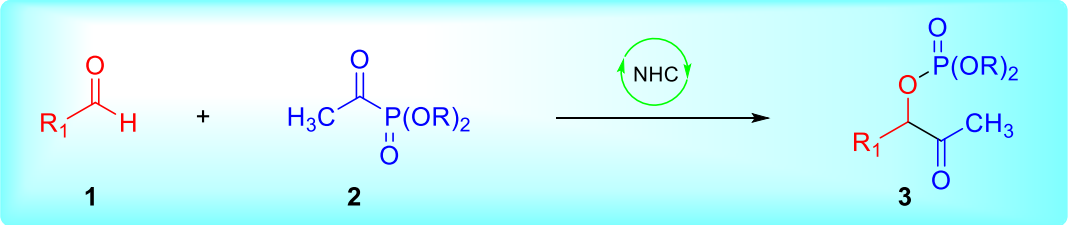
Scheme 4.9. Cyanide catalyzed synthesis of α-ketophosphates reported by Demir's.

In 2005, Demir and co-workers reported the cyanide catalyzed synthesis of α-keto-phosphates by the addition of acylphosphonates to aldehydes. This reaction was well tolerated with aromatic, aliphatic and alicyclic acylphosphonates and with the different class of aromatic and aliphatic aldehydes to afford the desired products in 64-94% yield (Scheme 4.9, Eq. 1).[13a] In 2007, they also developed the cyanide catalyzed addition of acylphosphonates to cyanoformates for the synthesis of α-keto-phosphates in good to excellent yield (Scheme 4.9, Eq. 2).[13b] Similarly, they also successfully established the cyanide catalyzed addition of acylphosphonates to a variety of ketones for the preparation of α-keto-phosphates in good excellent yields (Scheme 4.9, Eq. 3).[13c]

These catalytic literature process produced the densely charged oxygen anion by the migration of phosphoryl group from carbon to oxygen in the presence of cyanides. To the best of our knowledge, there is no literature reports on NHC-catalyzed tandem [1,2]-phospha-Brook/[1,4]-phosphate rearrangement or [1,2]-phosphoryl migration). The two major challenges in achieving the NHC catalysed phospha-Brook rearrangement are: (i) the lower reactivity of acyl phosphonates in comparison to acyl silanes under carbene catalysis is a stronger C-P bond in acyl phosphonates in comparison to C-Si bond in acyl silanes.[14,15] (ii) Unlike metal-cyanides, the NHC produces less nucleophilic intermediate from acyl phosphonate so, it does not facilitate the [1,2]-phosphoryl group migration in acyl phosphonate so easily.[10]

4.3. Objective of the Work

The main objective of this study is to develop the first carbene catalyzed synthesis of α-keto-phosphates using acylphosphonates and aldehydes. The aliphatic-aliphatic cross-coupling of acylphosphonates with aldehydes has remained elusive for the literature protocol. Herein, we have developed the carbene catalyzed synthesis of α-keto-phosphate *via* [1,2]-phospha-Brook/[1,4]-phosphate rearrangement using acylphosphonates and aldehydes (Scheme 4.10).

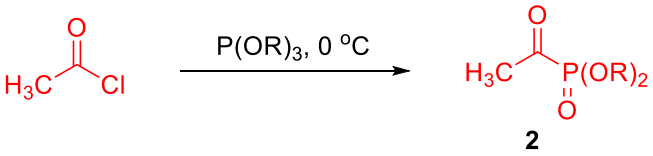


Scheme 4.10. Carbene-catalyzed synthesis of α-ketophosphates

4.4. Results and Discussion

4.4.1. Preparation of the Starting Materials

To develop this methodology, we have prepared acylphosphonates in the presence of acetyl chloride and tri-alkylphosphites by following the reported literature protocol (Scheme 4.11).[16] All aldehydes used in this reaction were obtained from commercial sources and triazolium catalyst **C**[17] was prepared according to the reported literature methods.

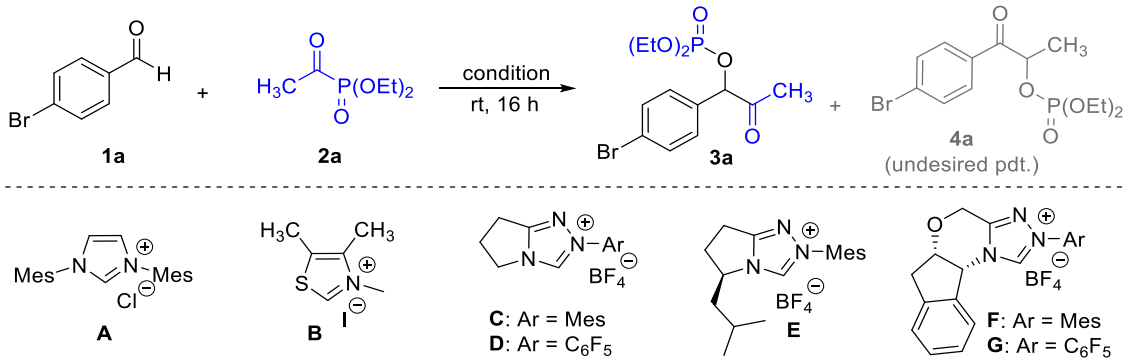


Scheme 4.11. Preparation of acylphosphonates

4.4.2. Optimization Studies of the Reaction

We started our optimization for the NHC catalyzed preparation of α-keto-phosphate by the treatment of 4-bromobenzaldehyde **1a** with the acyl phosphonate **2a** as model substrate (Table 1). First, we perform this reaction in presence of Cs_2CO_3 in DCM solvent without using NHC catalyst, which did not produce any products (entry 1). Next, we used NHC precatalyst **A** under similar conditions, which did not afford the desired product, while thiazolium salt **B** produced α-keto-phosphate **3a** in 23% yield (entry 2-3). Thereafter, we performed this reaction by using triazolium NHC precatalyst **C**, which produced the α-keto-phosphate **3a** in good yield 57% yield with excellent chemoselectivity (entry 4).

Table 4.1. Optimization of the Reaction Condition[a]



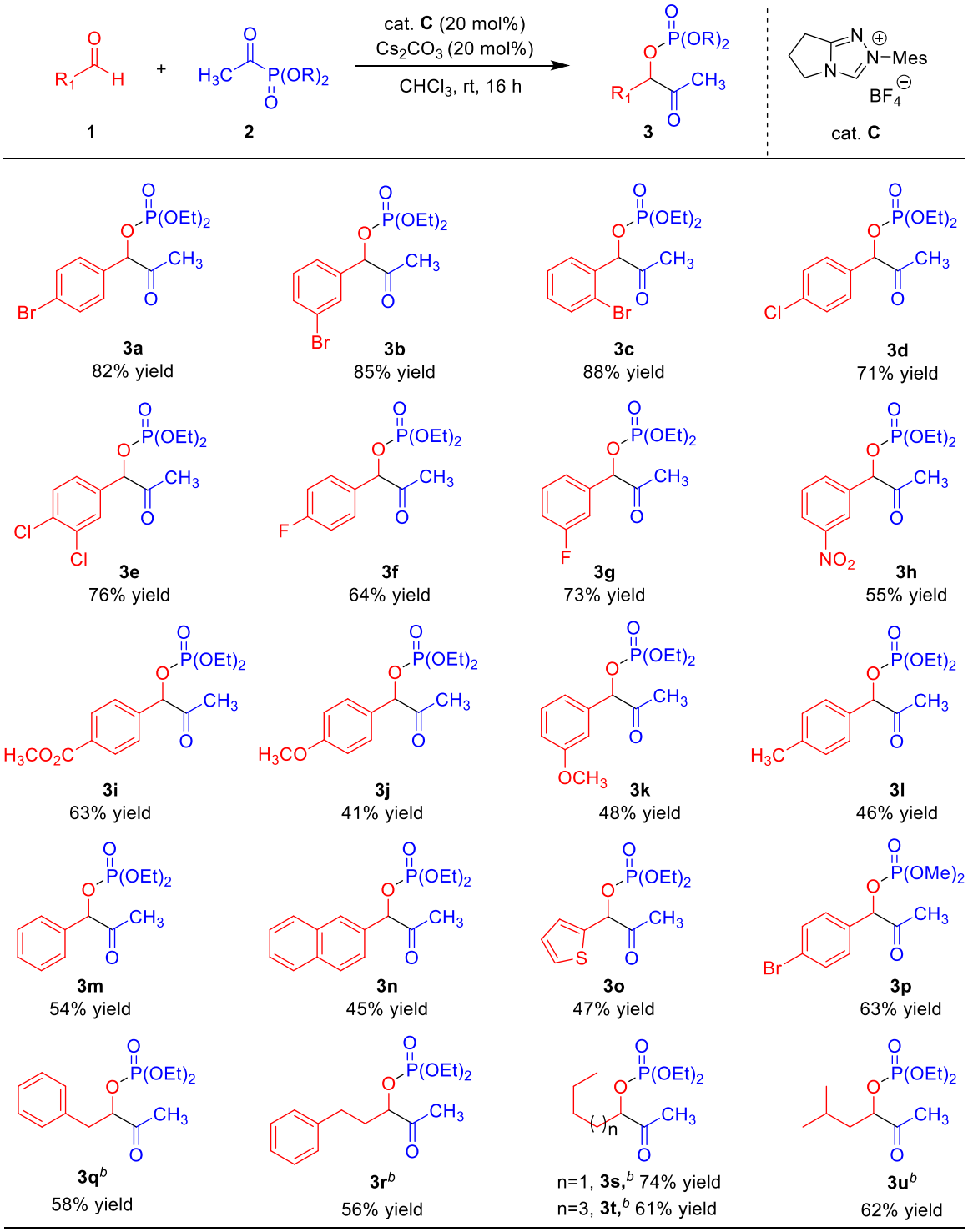
entry	NHC	solvent	base	3a/4a[b]	yield (%)[c]
1	-	CH_2Cl_2	Cs_2CO_3	-	0
2	**A**	CH_2Cl_2	Cs_2CO_3	-	trace
3	**B**	CH_2Cl_2	Cs_2CO_3	100/0	23
4	**C**	CH_2Cl_2	Cs_2CO_3	100/0	57
5	**D**	CH_2Cl_2	Cs_2CO_3	-	trace
6	**E**	CH_2Cl_2	Cs_2CO_3	100/0	17
7	**F**	CH_2Cl_2	Cs_2CO_3	-	trace
8	**G**	CH_2Cl_2	Cs_2CO_3	-	trace
9	**C**	THF	Cs_2CO_3	90/10	51
10	**C**	Et_2O	Cs_2CO_3	56/44	49(33)
11	**C**	toluene	Cs_2CO_3	62/38	47(27)
12	**C**	*p*-xylene	Cs_2CO_3	100/0	48
13	**C**	$CHCl_3$	Cs_2CO_3	100/0	82
14[d]	**C**	$CHCl_3$	Cs_2CO_3	47/53	29(33)
15[e]	**C**	$CHCl_3$	Cs_2CO_3	100/0	83
16	**C**	$CHCl_3$	CsOH	100/0	76
17	**C**	$CHCl_3$	K_2CO_3	100/0	44
18	**C**	$CHCl_3$	KO^tBu	-	trace
19	**C**	$CHCl_3$	DBU	100/0	39
20	**C**	$CHCl_3$	DMAP	-	trace
21	**C**	$CHCl_3$	$CaCO_3$	-	trace

[a]General reaction condition: 4-bromobenzaldehyde **1a** (0.22 mmol), acylphosphonate **2a** (0.11 mmol), cat. (20 mol%), base (20 mol%), solvent (1.0 mL) at rt for 16 h.

When we used -C_6F_5-Ar protected pyrrolidine salt **D** no product formation was observed (entry 5). The use of Chiral NHC catalyst **E** results in the formation of product in 17% yield (entry 6). The indanol derived chiral catalyst **F** and **G** were failed to produce the desired product (entry 7-8). After completion of our catalyst screening, we further moved to screen the solvents using catalyst **E**. The use of solvents such as THF, Et_2O, toluene and *p*-xylene afforded the *α*-keto-phosphate **3a** in moderate yield (entry 9-12). Gratifyingly, the use of $CHCl_3$ solvent proved fruitful in the presence of Cs_2CO_3 and NHC catalyst **E** and produced the *α*-keto-phosphate **3a** in excellent yield 82% with 100% chemoselectivity (entry 13). On performing this reaction at 60 ^oC for overnight the loss of chemoselectivity and deterioration in the yield of desired product was observed (entry 14). Further increasing of the molar ratios of reactants or catalysts, did not show any further noticeable improvement in the reaction outcome (entry 15). The use of other inorganic bases like CsOH, K_2CO_3, KO^tBu, and Ca_2CO_3 in place of Cs_2CO_3 only CsOH produced the desired product in good yield 76%. rest of other either produced in moderate or traces of the products **3a**. The use of organic bases such as DBU and DMAP produced the desired product in diminished yield (entry 16-21).

4.4.3. Carbene Catalyzed Synthesis of *α*-Ketophosphates from Aldehydes

After finding the optimized condition in hand, we moved to evaluate the generality of this cross-acyloin condensation by employing different class of aromatic heteroaryl and aliphatic aldehydes (Scheme 4.12). First, we have tested the tolerance of halogen group respective to -*o*, -*m* and -*p*-positions at aryl rings, di-substituted 3,4-dichlorobenzaldehyde also reacted smoothly. In all cases we obtained the corresponding *α*-ketophosphates in good to excellent yield 64-88% (**3a**-**3g**). In addition, aryl aldehydes having nitro and ester functionalities reacted well and affording the desired products in good yields (**3h**-**3i**). our delight, electron-deficient aldehydes were well swallow under the optimized reaction condition. Notably, it was observed that electron-rich aromatic aldehydes bearing electron donating groups such as methyl or methoxy groups, produced the *α*-ketophosphates in low yield 41-48% (**3j**-**3l**). The substitution effect was also observed with aromatic aldehydes having substituent such as electron withdrawing and electron donating groups at different position on aryl ring in the formation *α*-ketophosphates the yield was improved from *para*- to *meta*- to *ortho*-substituted arylaldehydes (**3a**-**3c**, **3f**-**3g** and **3j**-**3k**). Performing this reaction in standard condition with 1-napthaldehyde and thiophene-2-carboxaldehyde the *α*-ketophosphate products was obtained



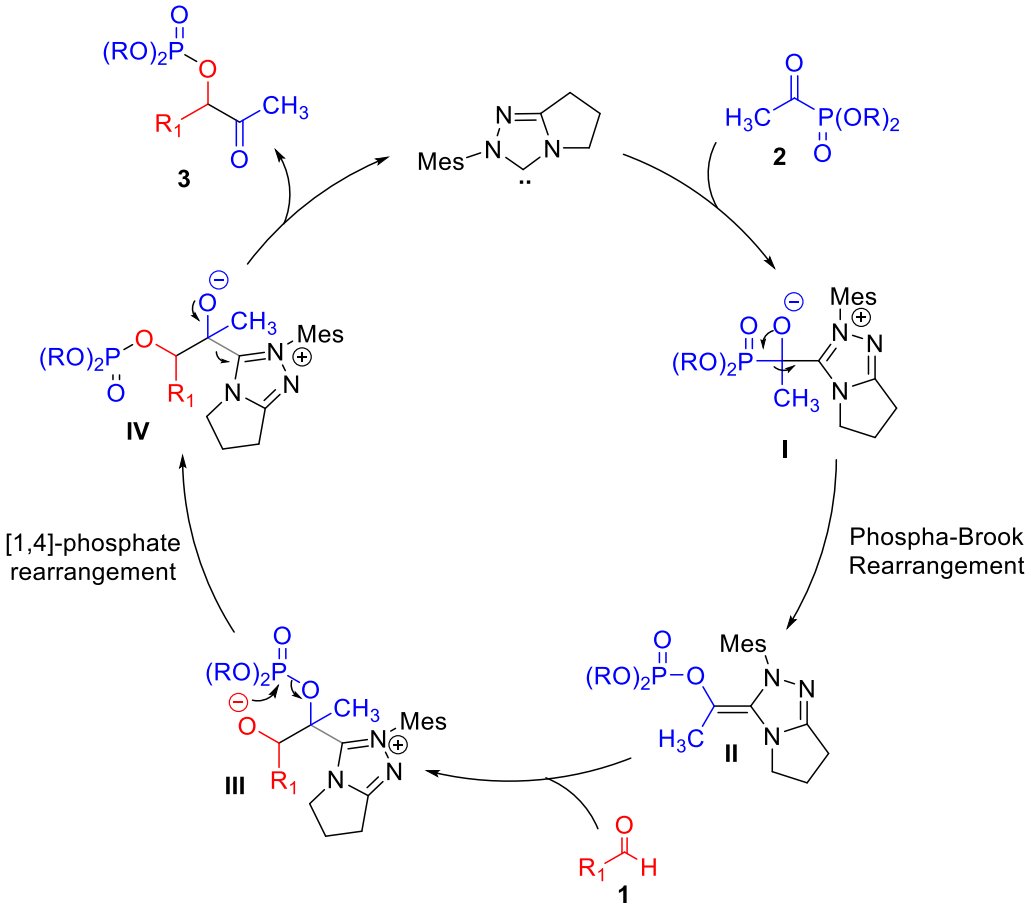
Scheme 4.12. Substrate Scope of aldehydes and acylphosphonates[a]

in moderate yield 45-47% (**3n-3o**).Variation in phosphonate group (-OEt to -OMe) of acyl phosphonate resulted in the formation of *α*-ketophosphates in slightly low yield 63% (**3p**). The loading of higher amount of phenyl acetaldehyde and 3-phenyl propionaldehyde rather than standard condition afforded the desired products in 56-58 % yield (**3q-3r**). The aliphatic

aldehydes are also compatible for this reaction, but it requires the higher amount to produce corresponding α-ketophosphates in good yields 61-74 % (**3s**-**3u**). Notably, these aliphatic aldehydes are challenging for other literature methods to furnish α-ketophosphate products in good yields.

4.4.4. Proposed Mechanism of the Reaction

The proposed mechanism for this NHC-catalyzed addition of the acyl anion generated from acylphosphonates to aldehydes is shown in Scheme 4.13.



Scheme 4.13. Proposed Mechanism

The reaction was initiated by the addition of carbene catalyst to acylphosphonate to produce tetrahedral intermediate **I**, which further undergoes [1,2]-phosphoryl group migration (phospa-Brook rearrangement) from carbon to oxygen to generate intermediate **II**. The formation of intermediate **II** was confirmed by getting a molecular ion peak corresponding to phosphonate protected variant of Breslow-intermediate **II** was found in HRMS [at m/z 408.2054 $(M+H)^+$] in a controlled experiment on performing reaction of acyl phosphonate and carbene catalyst under the standard condition in absence of aldehyde. The intermediate **II**

further reacts with the aldehyde molecule to give intermediate **III**, which further undergoes [1,4]-phosphate shift to generate intermediate **IV**. This intermediate **IV** gives desired ketophosphate product **3** with the regeneration of active NHC catalyst.

4.5. Conclusion

In conclusion, we have developed the first *N*-heterocyclic carbene catalyzed synthesis of *α*-hydroxyketone phosphates from acyl phosphonates and aldehydes. This is the first reported protocol employing acyl phosphonates for the generation of acyl anion using carbene catalyst. This cross-acyloin condensation is one pot, direct, highly atom economical. The coupling of acetyl phosphonates with aliphatic aldehydes is challenging for previously reported methods for the synthesis of *α*-hydroxyketone phosphates.

4.6. Experimental Section

4.6.1. General Information

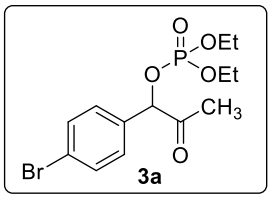
Unless otherwise specified, all reactions were carried out under an atmosphere of argon in a dry Schlenk tube. All aldehydes were of commercial quality and used without further purification. Solvents were dried and distilled following the standard procedures. TLC was carried out on pre-coated plates (Merck silica gel 60, f254), and the spots were visualized with UV light or by charring the plates dipped in vanillin-5% H_2SO_4-EtOH solution. The compounds were purified by flash column chromatography using silica gel (230-400 mesh) with distilled solvents. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 600 MHz instrument, and 100 and 150 MHz instrument, respectively, in $CDCl_3$ as the solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.0 ppm). High-resolution mass spectrometry (HRMS) was performed on agilent 6530 Q-TOF using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

4.6.2. General Procedure for the Catalytic Synthesis of *α*-Ketophosphates 3 and 4a

To a dry Schlenk tube equipped with a magnetic stir bar was added acyl phosphonate **2** (20.0 mg, 0.111 mmol, 1.0 equiv), aldehyde **1** (0.222 mmol, 2.0 equiv), and catalyst **C** (6.93 mg, 20 mol %). The tube was closed after the addition of $CHCl_3$ (1.0 mL) and Cs_2CO_3 (7.15 mg, 20 mol %). The reaction chamber was flashed with argon, and the mixture was stirred at room temperature for 24 h. The reaction mixture was then directly applied to silica gel column chromatography to obtain product **3**.

4.6.3. Characterization of the Products

1-(4-bromophenyl)-2-oxopropyl diethyl phosphate (**3a**)**:**



Yield: 33 mg (82%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

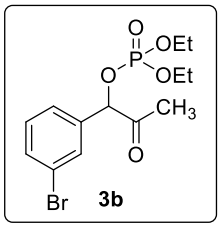
HRMS (ESI): calcd for $C_{13}H_{19}BrO_5P$ $[M+H]^+$: 365.0157, found: 365.0153.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, dt, *J* = 0.8, 6.8 Hz), 1.31 (3H, dt, *J* = 0.8, 6.8 Hz), 2.16 (3H, s), 3.93 - 4.03 (2H, m), 4.06 - 4.25 (2H, m), 5.60 (1H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.0 Hz), 7.53 (2H, d, *J* = 8.4 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 15.9 (d, *J* = 7.0 Hz), 16.0 (d, *J* = 7.0 Hz), 25.4, 64.1 (d, *J* = 6.0 Hz), 64.4 (d, *J* = 6.0 Hz), 82.5 (d, *J* = 5.0 Hz), 123.5, 128.6, 132.1, 133.5 (d, *J* = 5.0 Hz), 202.3 (d, *J* = 5.0 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -2.02.

1-(3-bromophenyl)-2-oxopropyl diethyl phosphate (**3b**)**:**



Yield: 34 mg (85%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

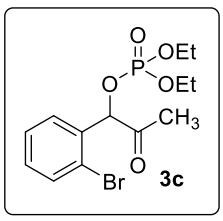
HRMS (ESI): calcd. for $C_{13}H_{19}BrO_5P$ $[M+H]^+$: 365.0152, found: 365.0153.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, dt, *J* = 1.2, 7.2 Hz), 1.32 (3H, dt, *J* = 1.2, 6.8 Hz), 2.18 (3H, s), 3.95 - 4.05 (2H, m), 4.10 - 4.26 (2H, m), 5.60 (1H, d, *J* = 8.4 Hz), 7.26 (1H, t, *J* = 7.6 Hz), 7.35 (1H, d, *J* = 7.6 Hz), 7.48 - 7.53 (1H, m), 7.57 (1H, t, *J* = 1.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 15.8 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 7.0 Hz), 25.5, 64.2 (d, *J* = 6.0 Hz), 64.5 (d, *J* = 5.0 Hz), 82.3 (d, *J* = 5.0 Hz), 122.9, 125.6,129.8, 130.4, 132.3, 136.5 (d, *J* = 5.0 Hz), 202.3 (d, *J* = 5.0 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -2.05.

1-(2-bromophenyl)-2-oxopropyl diethyl phosphate (**3c**)**:**



Yield: 35 mg (88%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

HRMS (ESI): calcd. for $C_{13}H_{19}BrO_5P$ $[M+H]^+$: 365.0150, found: 365.0153.

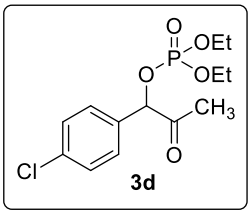
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (3H, dt, *J* = 0.8, 7.2 Hz), 1.32 (3H,

dt, *J* = 1.2, 7.2 Hz), 2.19 (3H, s), 3.92 - 4.02 (2H, m), 4.10 - 4.27 (2H, m), 6.14 (1H, d, *J* = 8.8 Hz), 7.21 - 7.28 (1H, m), 7.32 - 7.43 (2H, m), 7.61 (1H, dd, *J* = 1.3 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 15.8 (d, *J* = 7.0 Hz), 15.9 (d, *J* = 7.0 Hz), 26.4, 64.0 (d, *J* = 6.0 Hz), 64.3 (d, *J* = 6.0 Hz), 81.6 (d, *J* = 6.0 Hz), 123.5, 128.0, 129.6, 130.7, 133.3, 134.5, 201.2 (d, *J* = 5.0 Hz).

$^{31}P\{^1H\}$ (161 MHz, $CDCl_3$): δ -2.03.

1-(4-chlorophenyl)-2-oxopropyl diethyl phosphate (**3d**)**:**



3d

Yield: 25 mg (71%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

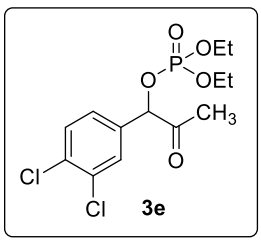
HRMS (ESI): calcd. for $C_{13}H_{19}ClO_5P$ $[M+H]^+$: 321.0662, found: 321.0654.

^1H NMR (600 MHz, $CDCl_3$): δ 1.21 (3H, dt, *J* = 0.6, 7.2 Hz), 1.32 (3H, dt, *J* = 1.2, 7.2 Hz), 2.16 (3H, s), 3.95 - 4.02 (2H, m), 4.11 - 4.24 (2H, m), 5.62 (1H, d, *J* = 8.4 Hz), 7.34 - 7.39 (4H, m).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 15.9 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 6.0 Hz), 25.5, 64.1 (d, *J* = 6.0 Hz), 64.4 (d, *J* = 6.0 Hz), 82.4 (d, *J* = 6.0 Hz), 128.3, 129.2, 133.0 (d, *J* = 6.0 Hz), 135.3, 202.4 (d, *J* = 6.0 Hz).

$^{31}P\{^1H\}$ (161 MHz, $CDCl_3$): δ -2.02.

1-(3,4-dichlorophenyl)-2-oxopropyl diethyl phosphate **(3e):**



3e

Yield: 41 mg (76%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

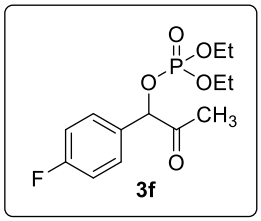
HRMS (ESI): calcd. for $C_{13}H_{18}Cl_2O_5P$ $[M+H]^+$: 355.0272, found: 355.0264.

^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, dt, *J* = 1.2, 7.2 Hz), 1.32 (3H, dt, *J* = 1.2, 7.2 Hz), 2.19 (3H, s), 3.97 - 4.07 (2H, m), 4.10 - 4.26 (2H, m), 5.57 (1H, d, *J* = 8.4 Hz), 7.24 - 7.29 (1H, m), 7.47 (1H, d, *J* = 8.4 Hz), 7.52 (1H, d, *J* = 2.0 Hz).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 15.9 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 7.5 Hz), 25.4, 64.3 (d, *J* = 6.0 Hz), 64.5 (d, *J* = 6.0 Hz), 81.8 (d, *J* = 6.0 Hz), 126.1, 128.7, 130.9, 133.2, 133.5, 134.5 (d, *J* = 6.0 Hz), 202.2 (d, *J* = 4.5 Hz).

$^{31}P\{^1H\}$ (161 MHz, $CDCl_3$): δ -2.03.

Diethyl (1-(4-fluorophenyl)-2-oxopropyl) phosphate (**3f**)**:**



Yield: 22 mg (64%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

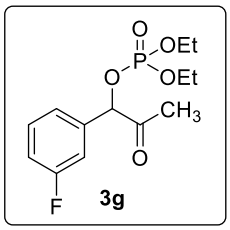
HRMS (ESI): calcd. for $C_{13}H_{19}FO_5P$ $[M+H]^+$: 305.0958, found: 305.0949.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.19 (3H, dt, *J* = 1.2, 7.2 Hz), 1.31 (3H, dt, *J* = 1.2, 6.8 Hz), 2.16 (3H, s), 3.93 - 4.01 (2H, m), 4.09 - 4.24 (2H, m), 5.65 (1H, d, *J* = 8.4 Hz), 7.06 - 7.13 (2H, m), 7.38 - 7.44 (2H, m).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 7.5 Hz), 16.0 (d, *J* = 7.5 Hz), 25.5, 64.1 (d, *J* = 6.0 Hz), 64.4 (d, *J* = 6.0 Hz), 82.4 (d, *J* = 4.5 Hz), 116.0 (d, *J* = 21.0 Hz), 129.0 (d, *J* = 7.5 Hz), 130.4, 163.2 (d, *J* = 247.5 Hz), 202.5 (d, *J* = 4.5 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -1.97.

Diethyl (1-(3-fluorophenyl)-2-oxopropyl) phosphate (**3g**)**:**



Yield: 25 mg (73%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

HRMS (ESI): calcd. for $C_{13}H_{19}FO_5P$ $[M+H]^+$: 305.0958, found: 305.0949.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.21 (3H, dt, *J* = 1.2, 7.2 Hz), 1.33 (3H, dt, *J* = 0.6, 7.2 Hz), 2.18 (3H, s), 3.96 - 4.04 (2H, m), 4.12 - 4.25 (2H, m), 5.64 (1H, d, *J* = 8.4 Hz), 7.04 - 7.09 (1H, m), 7.13 - 7.17 (1H, m), 7.21 (1H, d, *J* = 7.8 Hz), 7.34 - 7.39 (1H, m).

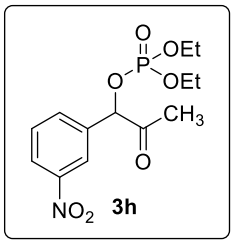
^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 6.0 Hz), 25.4, 64.2 (d, *J* = 6.0 Hz), 64.5 (d, *J* = 6.0 Hz), 82.4 (t, *J* = 6.0 Hz), 113.9 (d, *J* = 22.5 Hz), 116.2 (d, *J* = 21.0 Hz), 122.7 (d, *J* = 4.5 Hz), 130.6 (d, *J* = 7.5 Hz), 136.8 (t, *J* = 4.5 Hz), 162.9 (d, *J* = 246.0 Hz), 202.3 (d, *J* = 4.5 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -2.09.

Diethyl (1-(3-nitrophenyl)-2-oxopropyl) phosphate (**3h**)**:**

Yield: 20 mg (55%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

HRMS (ESI): calcd. for $C_{13}H_{19}NO_7P$ $[M+H]^+$: 332.0902, found: 332.0894.

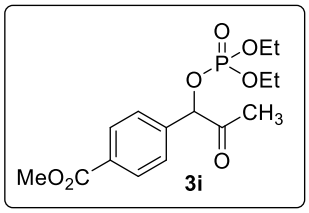


^{1}H NMR (600 MHz, $CDCl_3$): δ 1.24 (3H, dt, *J* = 0.6, 6.6 Hz), 1.34 (3H, dt, *J* = 0.6, 7.2 Hz), 2.25 (3H, s), 4.02 - 4.09 (2H, m), 4.15 - 4.26 (2H, m), 5.72 (1H, d, *J* = 8.4 Hz), 7.59 (1H, t, *J* = 7.8 Hz), 7.76 (1H, d, *J* = 7.8 Hz), 8.22 - 8.26 (1H, m), 8.31 (1H, t, *J* = 1.8 Hz).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): 15.9 (d, *J* = 7.5 Hz), 16.0 (d, *J* = 7.5 Hz), 25.6, 64.4 (d, *J* = 6.0 Hz), 64.7 (d, *J* = 6.0 Hz), 81.92 (d, *J* = 5.0 Hz), 121.6, 124.0, 129.9, 132.8, 136.7 (d, *J* = 6.0 Hz), 148.5, 202.4 (d, *J* = 4.5 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -1.90.

***Methyl 4-(1-((diethoxyphosphoryl)oxy)-2-oxopropyl)benzoate* (3i):**



Yield: 24 mg (63%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

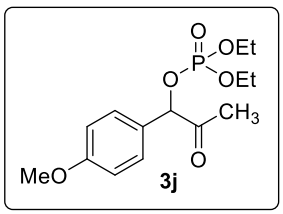
HRMS (ESI): calcd. for $C_{15}H_{22}O_7P$ $[M+H]^+$: 345.1087, found: 345.1098.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, dt, *J* = 1.2, 7.2 Hz), 1.31 (3H, dt, *J* = 1.2, 6.8 Hz), 2.17 (3H, s), 3.92 (3H, s), 3.94 - 4.05 (2H, m), 4.10 - 4.26 (2H, m), 5.68 (1H, d, *J* = 8.4 Hz), 7.51 (2H, d, *J* = 8.0 Hz), 8.06 (2H, d, *J* = 8.4 Hz).

^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$): δ 15.9 (d, *J* = 7.0 Hz), 16.0 (d, *J* = 7.0 Hz), 25.5, 52.2, 64.2 (d, *J* = 6.0 Hz), 64.5 (d, *J* = 6.0 Hz), 82.7 (d, *J* = 5.0 Hz), 126.8, 130.1, 130.9, 139.1 (d, *J* = 5.0 Hz), 166.3, 202.3 (d, *J* = 5.0 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -1.96.

***Diethyl (1-(4-methoxyphenyl)-2-oxopropyl) phosphate* (3j):**



Yield: 15 mg (41%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

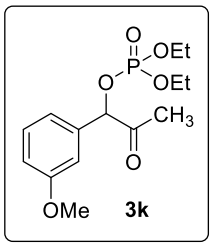
HRMS (ESI): calcd. for $C_{14}H_{22}O_6P$ $[M+H]^+$: 317.1154, found: 317.1149.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (3H, dt, *J* = 1.2, 7.2 Hz), 1.32 (3H, dt, *J* = 1.2, 7.2 Hz), 3.81 (3H, s), 2.14 (3H, s), 3.91 - 3.98 (2H, m), 4.11 - 4.23 (2H, m), 5.63 (1H, d, *J* = 7.8 Hz), 6.91 (2H, d, *J* = 8.4 Hz), 7.33 (2H, d, *J* = 8.4 Hz).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 7.5 Hz), 25.6, 55.3, 63.9 (d, *J* = 6.0 Hz), 64.2 (d, *J* = 6.0 Hz), 82.9 (d, *J* = 4.5 Hz), 114.4, 126.5 (d, *J* = 4.5 Hz), 128.7, 160.4, 202.6 (d, *J* = 6.0 Hz).

$^{31}P\{^{1}H\}$ (161 MHz, $CDCl_3$): δ -1.96.

Diethyl (1-(3-methoxyphenyl)-2-oxopropyl) phosphate (**3k**)**:**



Yield: 17 mg (48%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

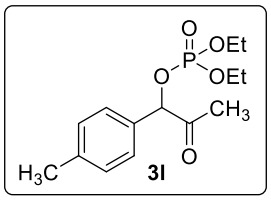
HRMS (ESI): calcd. for $C_{14}H_{22}O_6P$ $[M+H]^+$: 317.1152, found: 317.1149.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.20 (3H, dt, *J* = 1.2, 7.2 Hz), 1.32 (3H, dt, *J* = 0.6, 7.2 Hz), 2.15 (3H, s), 3.81 (3H, s), 3.94 - 4.02 (2H, m), 4.12 - 4.24 (2H, m), 5.63 (1H, d, *J* = 8.4 Hz), 6.89 - 6.92 (1H, m), 6.94 (1H, t, *J* = 1.4 Hz), 7.00 (1H, d, *J* = 7.8 Hz), 7.29 (1H, t, *J* = 7.8 Hz).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 6.0 Hz),16.0 (d, *J* = 6.0 Hz), 25.4, 55.3, 64.0 (d, *J* = 4.5 Hz), 64.3 (d, *J* = 6.0 Hz), 83.1 (d, *J* = 4.5 Hz), 112.4, 114.9, 119.4, 130.0, 135.9 (d, *J* = 4.5 Hz), 160.0, 202.5 (d, *J* = 4.5 Hz).

$^{31}P\{^{1}H\}$ (161 MHz, $CDCl_3$): δ -2.02.

Diethyl (2-oxo-1-(p-tolyl)propyl) phosphate (**3l**)**:**



Yield: 15 mg (46%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

HRMS (ESI): calcd. for $C_{14}H_{22}O_5P$ $[M+H]^+$: 301.1193, found: 301.1199.

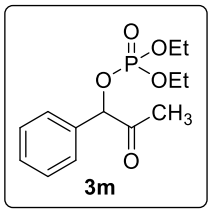
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (3H, dt, *J* = 0.6, 6.6 Hz), 1.32 (3H, dt, *J* = 0.6, 7.2 Hz), 2.14 (3H, s), 2.35 (3H, s), 3.90 - 4.00 (2H, m), 4.12 - 4.24 (2H, m), 5.64 (1H, d, *J* = 8.4 Hz), 7.19 (2H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 7.8 Hz).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 6.0 Hz), 16.0 (d, *J* =7.5 Hz), 21.1, 25.5, 63.9 (d, *J* = 6.0 Hz), 64.3 (d, *J* = 4.5 Hz), 83.2 (d, *J* = 6.0 Hz), 127.1, 129.6, 131.5 (d, *J* = 4.5 Hz), 139.2, 202.7 (d, *J* = 4.5 Hz).

$^{31}P\{^{1}H\}$ (161 MHz, $CDCl_3$): δ -2.00.

Diethyl (2-oxo-1-phenylpropyl) phosphate (**3m**)**:**

Yield: 18 mg (54%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).



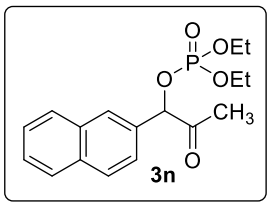
HRMS (ESI): calcd. for $C_{13}H_{20}O_5P$ $[M+H]^+$: 287.1037, found: 287.1048.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (3H, t, *J* = 7.2 Hz), 1.32 (3H, t, *J* = 6.6 Hz), 2.15 (3H, s), 3.91 - 4.01 (2H, m), 4.11 - 4.25 (2H, m), 5.67 (1H, d, *J* = 8.4 Hz), 7.34 - 7.47 (5H, m).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 7.5 Hz), 16.0 (d, *J* = 7.5 Hz), 25.5, 64.0 (d, *J* = 6.0 Hz), 64.3 (d, *J* = 6.0 Hz), 83.3 (d, *J* = 6.0 Hz), 127.1, 128.9, 129.2, 134.5 (d, *J* = 6.0 Hz), 202.6 (d, *J* = 4.5 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -2.00.

Diethyl (1-(naphthalen-2-yl)-2-oxopropyl) phosphate (**3n**)**:**



Yield: 17 mg (45%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

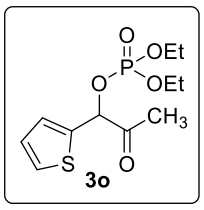
HRMS (ESI): calcd. for $C_{17}H_{22}O_5P$ $[M+H]^+$: 337.121, found: 337.1205.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.15 (3H, dt, *J* = 1.2, 7.2 Hz), 1.33 (3H, dt, *J* = 1.2, 7.2 Hz), 2.19 (3H, s), 3.91 - 4.01 (2H, m), 4.15 - 4.27 (2H, m), 5.85 (1H, d, *J* = 8.4 Hz), 7.47 - 7.50 (1H, m), 7.51 - 7.55 (2H, m), 7.83 - 7.89 (3H, m), 7.94 (1H, s).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 7.5 Hz), 16.0 (d, *J* = 7.5 Hz), 25.65, 64.1 (d, *J* = 6.0 Hz), 64.42 (d, *J* = 6.0 Hz), , 83.4 (d, *J* = 4.5 Hz), 123.9, 126.9, 127.0, 127.7, 128.1, 128.9, 131.8 (d, *J* = 4.5 Hz), 133.1, 133.5, 202.6 (d, *J* = 6.0 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -1.90.

Diethyl (2-oxo-1-(thiophen-2-yl)propyl) phosphate (**3o**)**:**



Yield: 16 mg (47%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

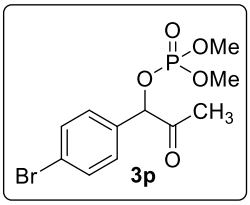
HRMS (ESI): calcd. for $C_{11}H_{18}O_5PS$ $[M+H]^+$: 293.0598, found: 293.0607.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.20 (3H, dt, *J* = 1.2, 7.2 Hz), δ 1.32 (3H, dt, *J* = 0.6, 7.2 Hz), 2.18 (3H, s), 3.93 - 4.02 (2H, m), 4.11 - 4.24 (2H, m), 5.77 (1H, d, *J* = 8.4 Hz), 7.07 - 7.10 (1H, m), 7.33 - 7.36 (1H, m), 7.42 (1H, d, *J* = 3.0 Hz).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 15.8 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 7.5 Hz), 25.5, 64.1 (d, *J* = 6.0 Hz), 64.3 (d, *J* = 6.0 Hz), 79.4 (d, *J* = 4.5 Hz), 124.6, 125.8, 127.0, 135.1 (d, *J* = 4.5 Hz), 202.3 (d, *J* = 4.5 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -2.17.

1-(4-bromophenyl)-2-oxopropyl dimethyl phosphate (**3p**)**:**



Yield: 24 mg (63%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

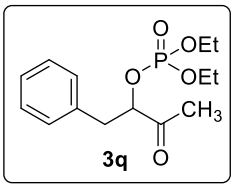
HRMS (ESI): calcd. for $C_{11}H_{15}BrO_5P$ $[M+H]^+$: 336.9826, found: 336.9840.

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.15 (3H, s), 3.63 (3H, d, *J* = 10.8 Hz), 3.83 (3H, d, *J* = 11.4 Hz), 5.64 (1H, d, *J* = 8.4 Hz), 7.30 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8.4 Hz).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 25.6, 54.4 (d, *J* = 6.0 Hz), 54.8 (d, *J* = 4.5 Hz), 82.6 (d, *J* = 6.0 Hz), 123.7, 128.7, 132.2, 133.3 (d, *J* = 4.5 Hz), 201.9 (d, *J* = 4.5 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -2.01.

Diethyl (3-oxo-1-phenylbutan-2-yl) phosphate (**3q**)**:**



Yield: 20 mg (58%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

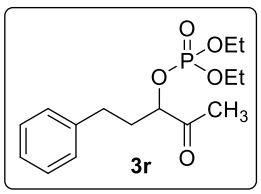
HRMS (ESI): calcd. for $C_{14}H_{22}O_5P$ $[M+H]^+$: 301.1196, found: 301.1199.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.17 (3H, dt, *J* = 0.6, 7.2 Hz), 1.23 (3H, dt, *J* = 0.6, 6.6 Hz), 2.16 (3H, s), 2.95 - 3.03 (1H, m), 3.10 - 3.18 (1H, m), 3.78 - 3.94 (3H, m), 4.00 - 4.08 (1H, m), 4.81 - 4.87 (1H, m), 7.22 - 7.26 (3H, m), 7.28 - 7.32 (2H, m).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 15.9 (d, *J* = 7.5 Hz), 15.9 (d, *J* = 6.0 Hz), 26.5, 38.7 (d, *J* = 6.0 Hz), 63.8 (d, *J* = 6.0 Hz), 64.0 (d, *J* = 6.0 Hz), 82.3 (d, *J* = 6.0 Hz), 127.0, 128.5, 129.6, 135.4, 206.4 (d, *J* = 3.0 Hz).

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -2.07.

Diethyl (4-oxo-1-phenylpentan-3-yl) phosphate (**3r**)**:**



Yield: 20 mg (56%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

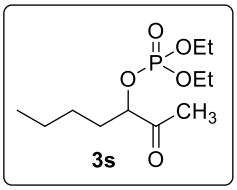
HRMS (ESI): calcd. for $C_{15}H_{24}O_5P$ $[M+H]^+$: 315.1378, found: 315.1356.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 - 1.41 (6H, m), 2.05 - 2.14 (2H, m), 2.23 (3H, s), 2.69 - 2.78 (2H, m), 4.09 - 4.25 (4H, m), 4.63 - 4.73 (1H, m) 7.15 - 7.24 (3H, m), 7.24 - 7.33 (2H, m).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 16.0 (d, *J* = 6.0 Hz), 26.0, 30.7, 34.1 (d, *J* = 6.0 Hz), 64.1 (d, *J* = 6.0 Hz), 64.2 (d, *J* = 6.0 Hz), 81.3 (d, *J* = 6.0 Hz), 126.2, 128.4, 128.5, 140.3, 206.2 (d, *J* = 3.0 Hz).

$^{31}P\{^{1}H\}$ (161 MHz, $CDCl_3$): δ -1.56.

***Diethyl (2-oxoheptan-3-yl) phosphate* (3s):**



Yield: 22 mg (74%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

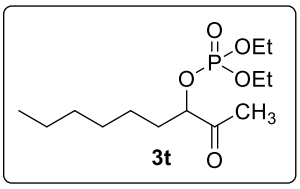
HRMS (ESI): calcd. for $C_{11}H_{24}O_5P$ $[M+H]^+$: 267.1375, found: 267.1361.

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 5.4 Hz), 1.28 - 1.45 (10H, m), 1.74 - 1.82 (2H, m), 2.22 (3H, s), 4.09 - 4.21 (4H, m), 4.59 - 4.67 (1H, m).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 13.7, 16.0 (d, *J* = 6.0 Hz), 22.2, 25.9, 26.5, 32.1 (d, *J* = 4.5 Hz), 64.0 (d, *J* = 6.0 Hz), 64.1 (d, *J* = 6.0 Hz), 82.0 (d, *J* = 6.0 Hz), 206.4 (d, *J* = 4.5 Hz).

$^{31}P\{^{1}H\}$ (161 MHz, $CDCl_3$): δ -1.64.

***Diethyl (2-oxononan-3-yl) phosphate* (3t):**



Yield: 20 mg (61%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

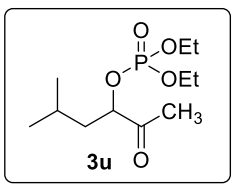
HRMS (ESI): calcd. for $C_{13}H_{28}O_5P$ $[M+H]^+$: 295.1667, found: 295.1669.

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 7.2 Hz), 1.21 - 1.46 (14H, m), 1.73 - 1.79 (2H, m), 2.22 (3H, s), 4.09 - 4.19 (4H, m), 4.60 - 4.65 (1H, m).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 13.9, 16.0, 16.0 (d, *J* = 6.0 Hz) 22.4, 24.4, 25.9, 26.7, 31.4, 32.4 (d, *J* = 4.5 Hz), 64.0 (d, *J* = 7.5 Hz), 64.1 (d, *J* = 4.5 Hz), 82.0 (d, *J* = 6.0 Hz), 206.6 (d, *J* = 3.0 Hz).

$^{31}P\{^{1}H\}$ (161 MHz, $CDCl_3$): δ -1.64.

***Diethyl (5-methyl-2-oxohexan-3-yl) phosphate* (3u):**



Yield: 18 mg (62%), pale yellow liquid, eluent: EtOAc:pet ether (1:4).

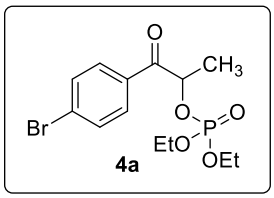
HRMS (ESI): calcd. for $C_{11}H_{24}O_5P$ $[M+H]^+$: 267.1354, found: 267.1356.

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.91 - 1.01 (6H, m), 1.30 - 1.38 (6H, m), 1.45 - 1.53 (1H, m), 1.65 - 1.72 (1H, m), 1.77 - 1.88 (1H, m), 2.22 (3H, d, *J* = 1.2 Hz), 4.08 - 4.21 (4H, m), 4.63 - 4.70 (1H, m).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 16.0 (d, *J* = 6.0 Hz) 21.4, 23.1, 24.1, 25.5, 41.2 (d, *J* = 7.5 Hz), 64.0 (d, *J* = 6.0 Hz), 64.2 (d, *J* = 6.0 Hz), 80.7 (d, *J* = 7.5 Hz), 206.6.

^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -1.64.

1-(4-Bromophenyl)-1-oxopropan-2-yl diethyl phosphate (**4a**)**:**



4a

Yield: 11 mg (27%), colorless liquid, eluent: EtOAc:pet ether (1:4).

HRMS (ESI): calcd. for $C_{13}H_{19}BrO_5P$ $[M+H]^+$: 365.0155, found: 365.0153.

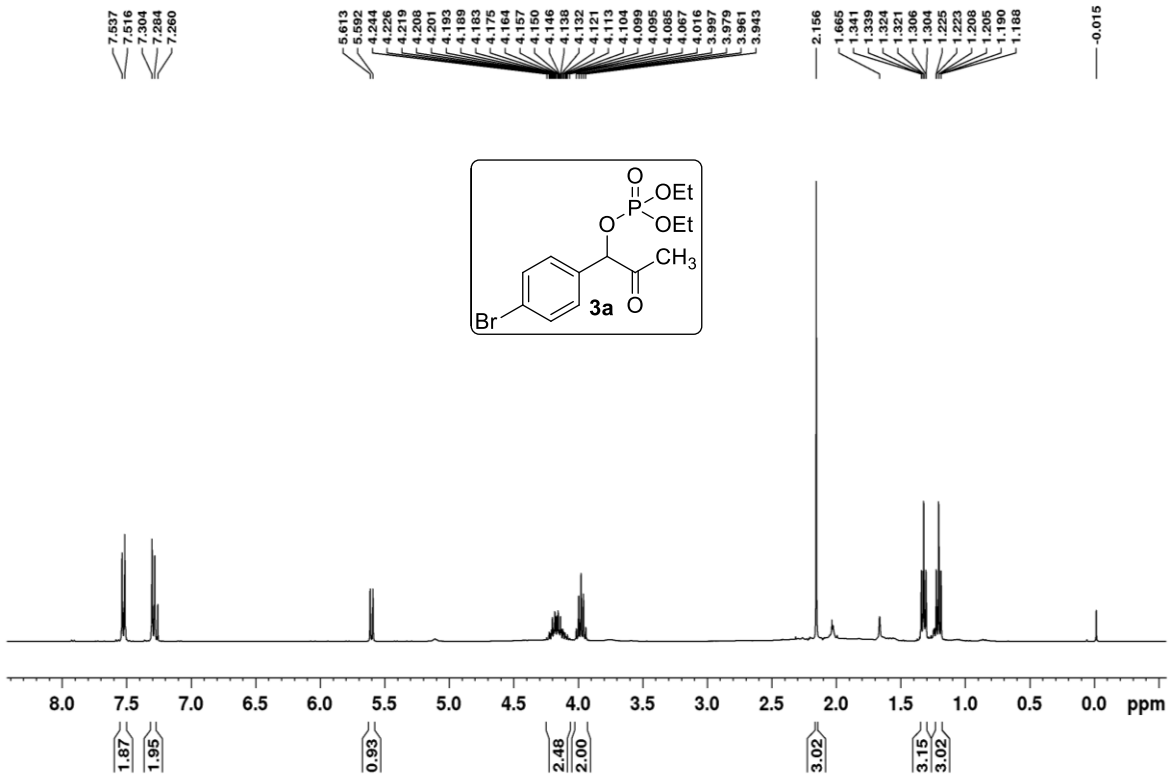
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.27 (3H, dt, *J* = 0.6, 7.2, Hz), 1.32 (3H, dt, *J* = 0.6, 6.6, Hz), 1.60 (3H, d, *J* = 6.6 Hz), 4.04 - 4.18 (4H, m), 5.61 - 5.70 (1H, m) 7.63 (2H, d, *J* = 9.0 Hz), 7.85 (2H, d, *J* = 8.4 Hz).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 15.9, 16.0, (d, *J* = 7.5 Hz) 19.1, (d, *J* = 4.5 Hz) 64.1, (d, *J* = 6.0 Hz), 64.2, (d, *J* = 6.0 Hz), 74.5, (d, *J* = 4.5 Hz), 128.9, 130.3, 132.1, 132.9, 195.4, (d, *J* = 6.0 Hz).

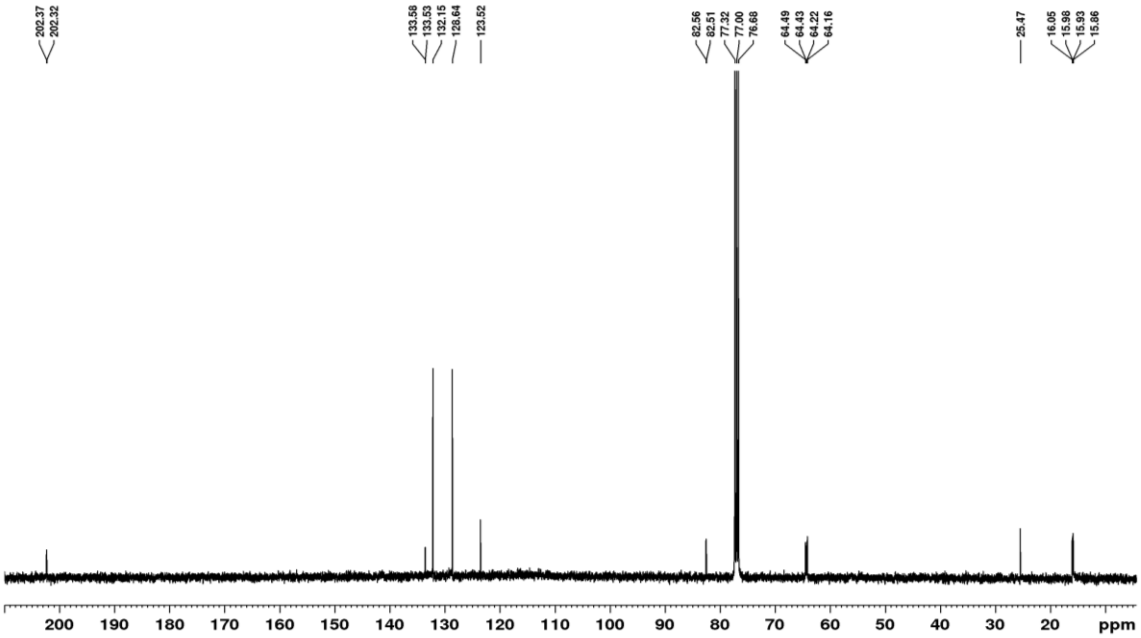
^{31}P{^{1}H} (161 MHz, $CDCl_3$): δ -1.97.

4.6.4. ^{1}H NMR and ^{13}C{^{1}H} NMR Spectra of Products

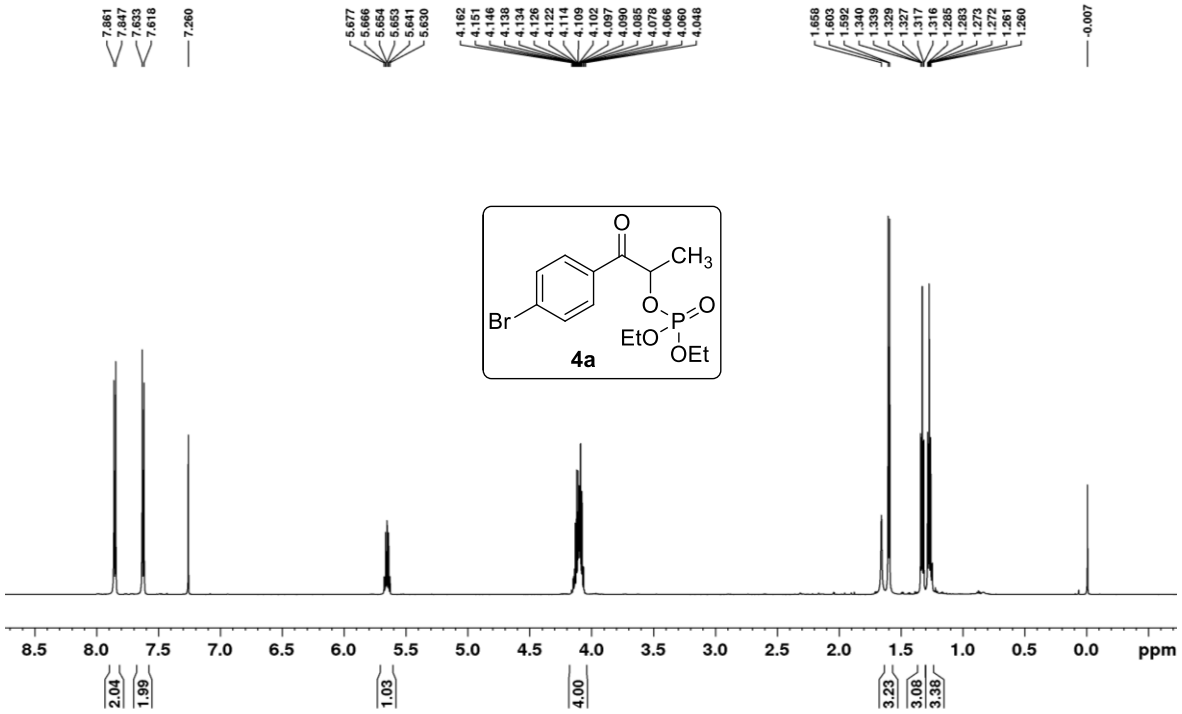
^{1}H NMR spectrum of compound 3a (400 MHz/$CDCl_3$)



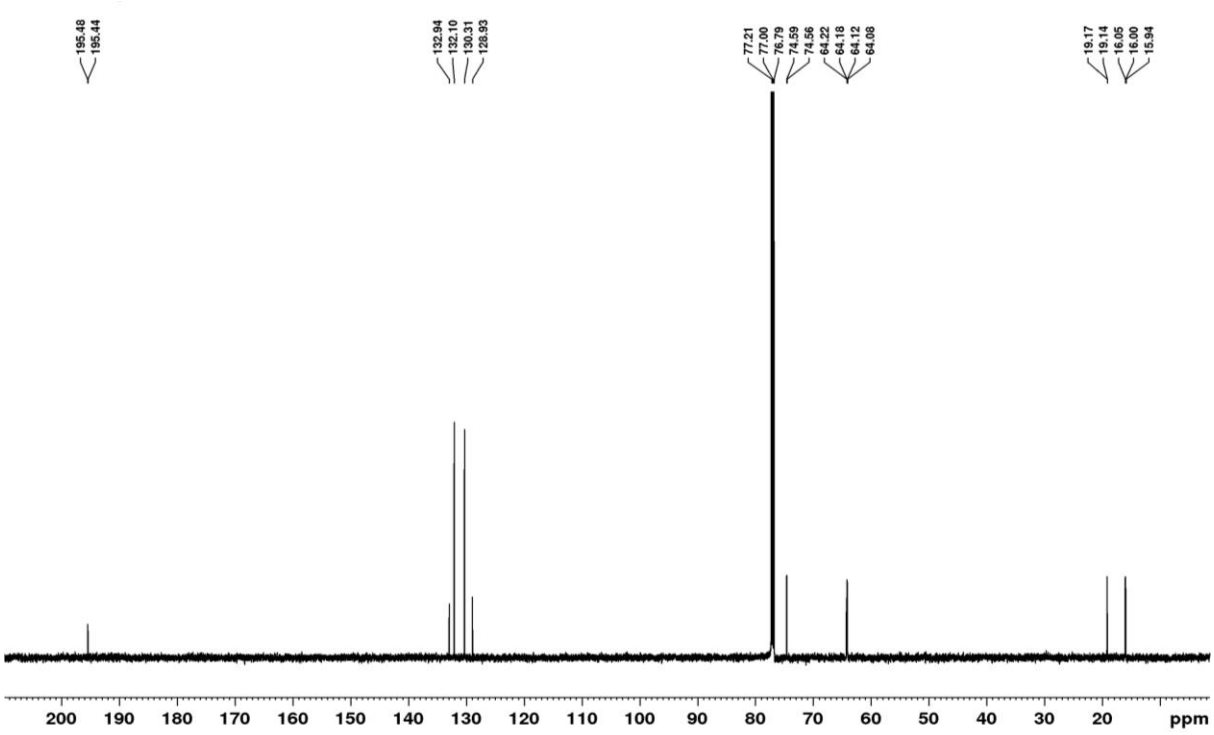
^{13}C NMR spectrum of compound 3a (100 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound 4a (600 MHz/$CDCl_3$)



^{13}C NMR spectrum of compound 4a (150 MHz/$CDCl_3$)



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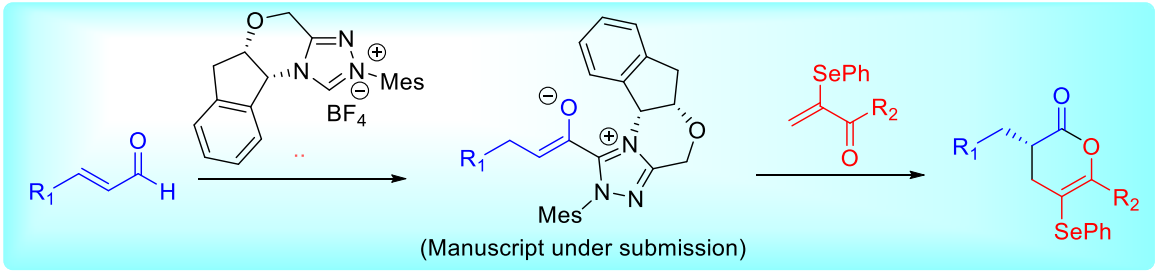
Chapter 5

Carbene catalyzed Enantioselective Synthesis of Selenylated δ-Lactones from Vinyl selenides and Enals

Selenium is an essential micronutrient for humans and animals and is used in the prevention and treatment of several diseases. It plays a vital role in the immune system functioning and also regulates the progression of viruses. The endemic selenium deficiency can cause Keshan disease (disease of the heart muscles) and Kashin–Beck disease (a disease of the bone). In addition, organoselenium compounds are widely used in the form of dietary supplement due its unique properties such as antioxidative, enzymatic modulator, anticancer and for the inhibition of cell growth. They are also used as synthetic intermediates and as Lewis base/acid catalysts in numerous organic transformations. In this context, the first *N*-heterocyclic carbene (NHC)-catalyzed highly enantioselective synthesis of selenylated *δ*-lactones *via* [4+2] annulation of *α,β*-unsaturated aldehydes with vinylselenides has been developed. This method is highly atom economical and proceeds under transition metal-free condition.



(Manuscript under submission)

5.1. Introduction

Selenium is an essential micronutrient for humans and animals, that has probable role in the prevention and treatment of disease. Selenium was discovered in 1817 by the Swedish chemist Jons Jacob Berzelius, as it causes the death of several livestocks in some parts of the US due to its high content in cereal grains.[1] First selenium was named as Selene after the Greek goddess of the moon. Later in 1950s, its essentiality was recognized in mammals,[2] while in 1973, the first selenoprotein glutathione peroxidase (GPx) was identified.[3,4] Organic forms of selenium occur in the speciation of grains such as in vegetables and legumes, however selenate is also detected in some of these foods. Commonly, *Allium* and *Crussiferae* families such as garlic, onions, and broccoli are good sources of MeSeCys proteins (and related species) and the grains and legumes are good sources of SeMet proteins.[5] Currently, 25 selenoproteins comprising selenocysteine (SeCys) residues at their active sites, are recognized in humans. Selenoproteins have many applications in humans as antioxidants (GPxs), in selenium transport (selenoprotein P) in thyroid hormone production

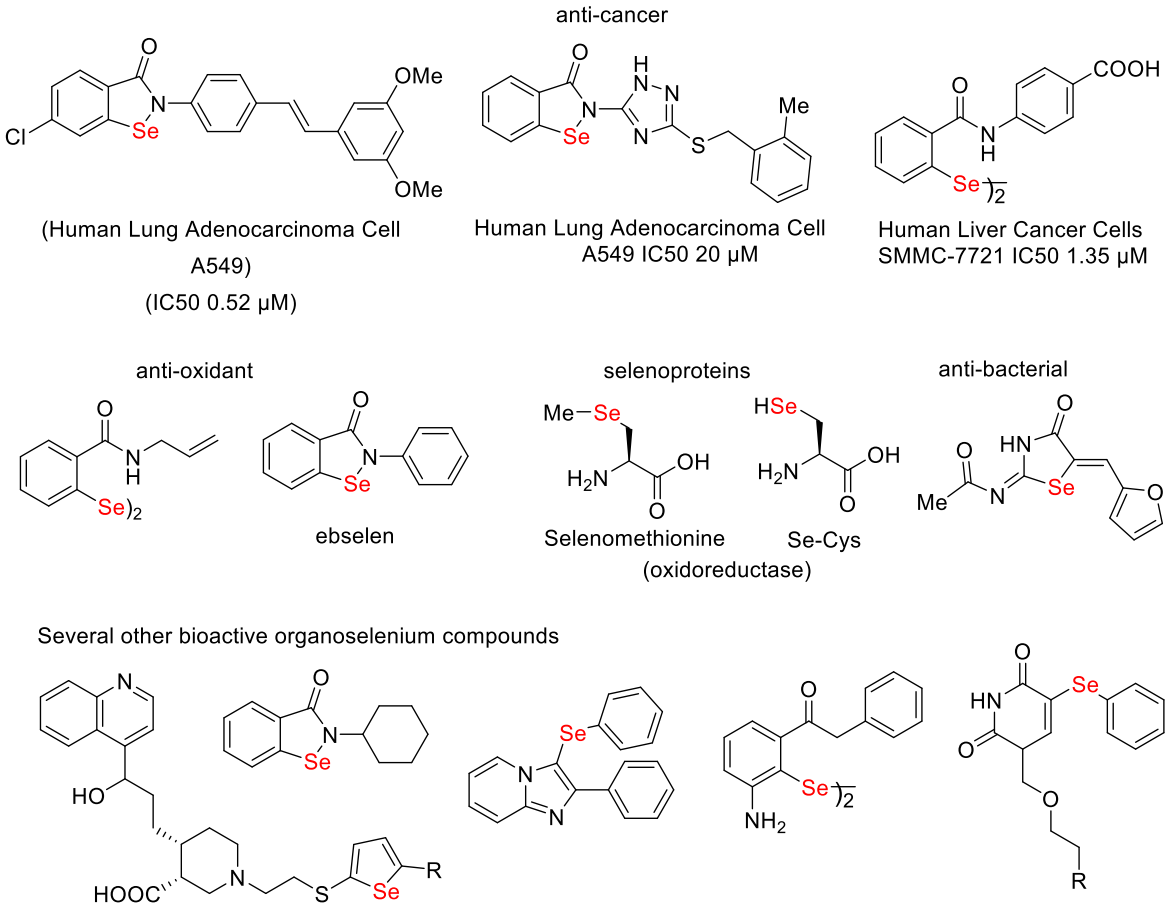


Figure 5.1. Selected bioactive organoselenium compounds

(iodothyronine deiodinases), and in maintaining the intracellular redox status (thioredoxin reductases), among other functions; some of which yet to be determined.

Selenium also plays a vital role in the immune system functioning and it also regulates the progression of viruses. The endemic selenium deficiency can cause Keshan disease (disease of the heart muscles) and Kashin–Beck disease (disease of the bone).[6] In addition, organoselenium compounds are widely used in the form of dietary supplement due its unique properties such as antioxidative, enzymatic modulator, anticancer and for the inhibition of cell growth (Figure 5.1). The average recommended daily dose of selenium by scientist in adults is 60 mg per day for men and 53 mg per day for women.[7]

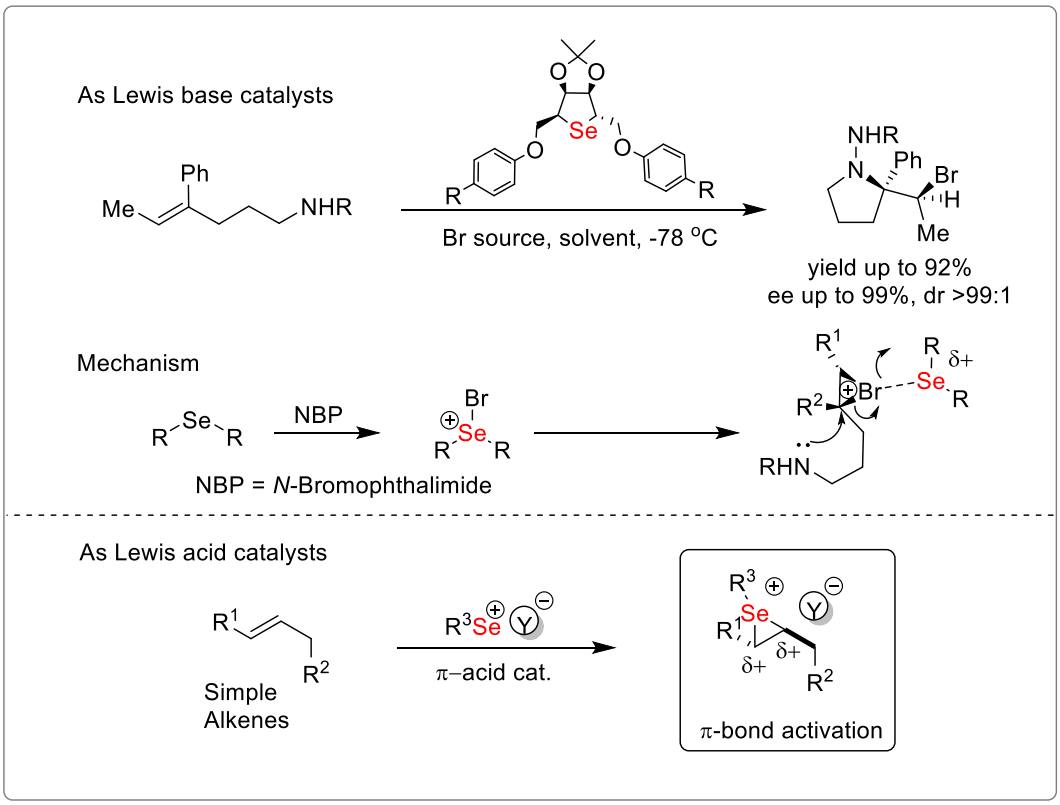


Figure 5.2. Important selenium compounds as Lewis base and acid catalysts

Besides this, organoselenium compounds are prominently used as synthetic intermediates, ligands and as Lewis base/acid catalysts in numerous organic transformations (Figure 5.2).[8] The structure and reactivity of organoselenium compounds have a similarity with sulphur analogs. At the same time, certain properties of selenium make it more valuable in comparison to sulfur. As the selenium forms weaker σ-bonds in comparison to sulfur, the C–Se, O–Se, and N–Se bonds can be cleaved under milder reaction conditions. The versatile

reactivities of selenium as an electrophile, a nucleophile and as a radical species along with its unique metallic and non-metallic properties has been summarized in Figure 5.3.

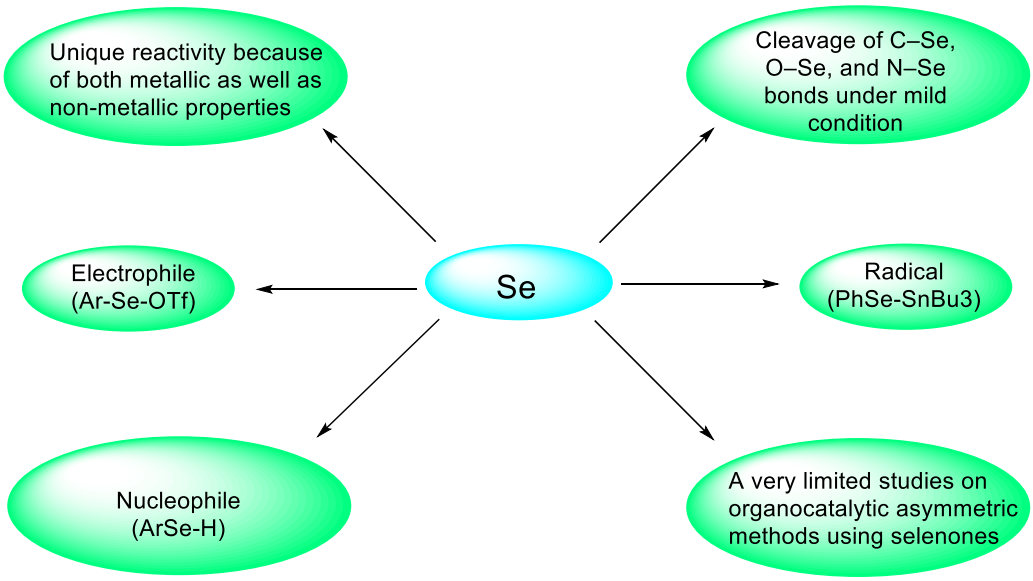


Figure 5.3. Different role and exploration of selenium in the field of organic chemistry

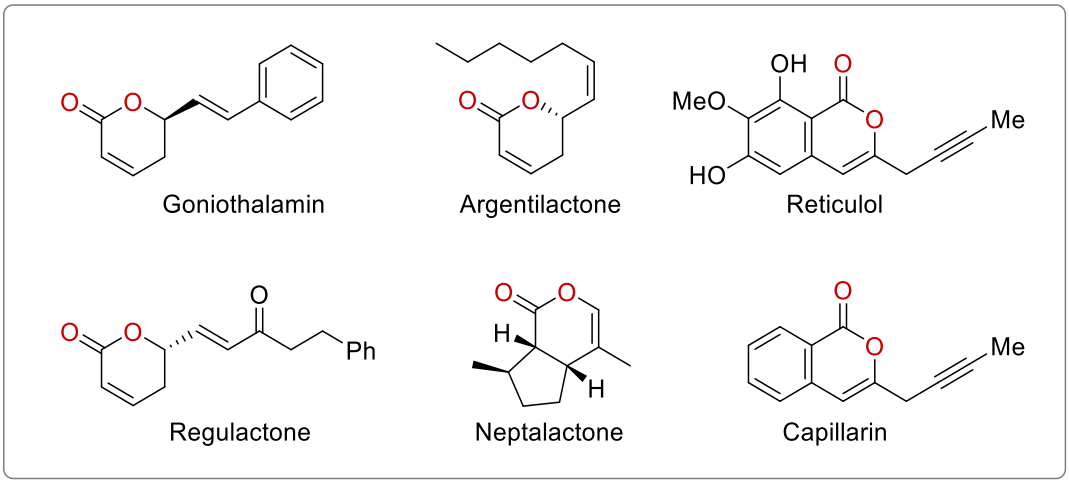
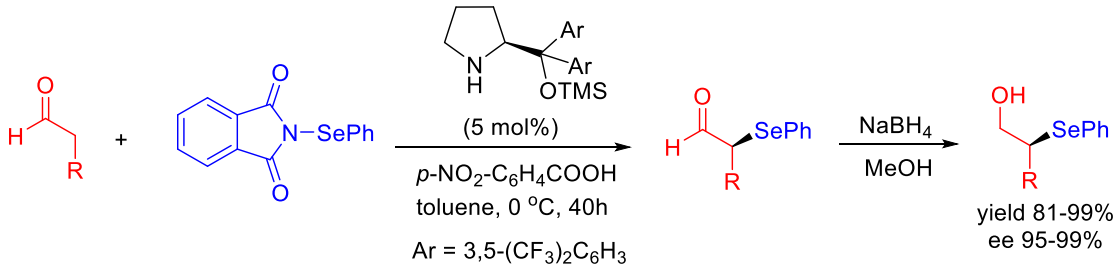


Figure 5.4. *δ*-lactone containing biologically active compounds

The *δ*-lactones are the important core structural unit of isocoumarins and pyrones and occurs in many naturally occurring compounds with biological activities including antifungal, antimicrobial, phytotoxic, androgen-like and pheromonal effects (Figure 5.4).[9] In this context, many researches have made their contribution to incorporate selenium in the lactones.

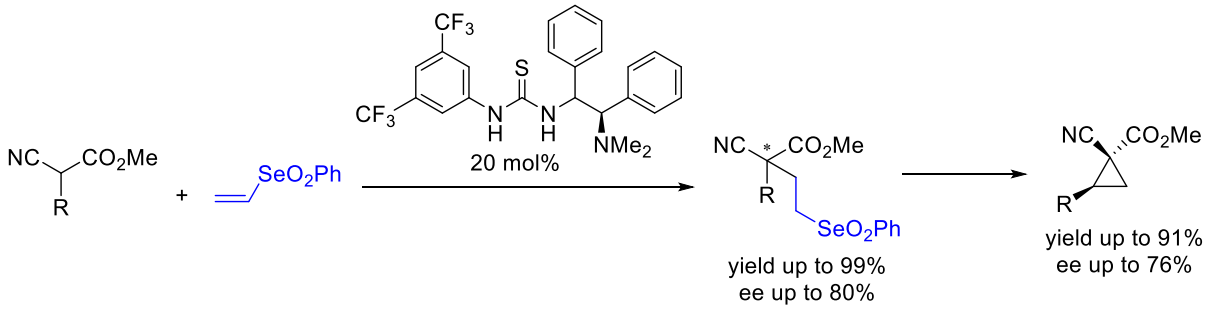
5.2. Literature Reports for the Organocatalyzed Enantioselective Synthesis of Organoselenium Compounds

In 2007, Marini and co-workers developed a highly enantioselective *α*-selenylation of aldehydes catalyzed by an amine catalyst (Scheme 5.1).[10] For this reaction, they used phenylselenyl phthalimide as the selenylating agent for the preparation of *α*-seleno aldehydes. This reaction produced *α*-seleno aldehydes in good to excellent yield with excellent enantiomeric excess of 95-99%.



Scheme 5.1. Amine catalyzed enantioselective synthesis of *a*-seleno aldehydes

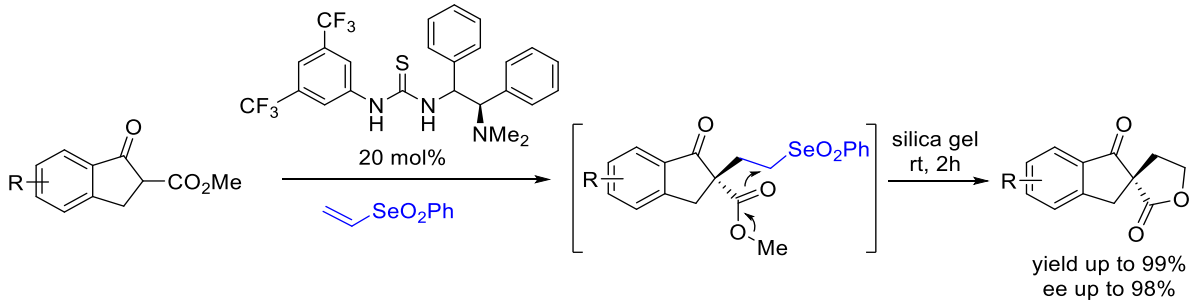
Later in 2009, Tiecco and co-workers reported the enantioselective synthesis of organoselenium compounds using vinylselenone and *a*-substituted cyanoacetates catalyzed by a bifunctional hydrogen bonding catalyst (Scheme 5.2).[11] This reaction proceeded by the Michael addition of *a*-substituted cyanoacetates to vinyl selenones, followed by an intramolecular cyclization to give the highly substituted cyclopropanes in moderate to good yield and enantioselectivities.



Scheme 5.2. Stereoselective preparation of cyclopropanes

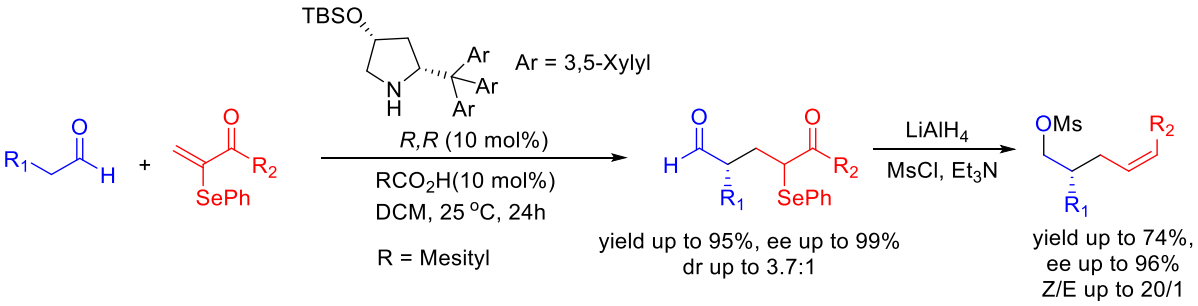
In 2011, the group of Marini established the cinchona alkaloid catalyzed Michael addition/cyclization using vinylselenone and cyclic *β*-ketoesters (Scheme 5.3).[12] This reaction proceeded *via* the Michael addition of *β*-ketoesters to vinylselenone, followed by an intramolecular cyclization with removal of phenylseleno group. This one-pot reaction

afforded the functionalized spirolactones under milder reaction condition in good to excellent yield and enantioselectivities.



Scheme 5.3. Enantioselective preparation of spirolactones catalyzed by chinchona alkaloid

Recently in 2018, Maruoka and co-workers achieved the chiral amine catalyzed enantioselective preparation of organoselenium compounds using *α*-phenylselenoenones (Scheme 5.4).[13] In this reaction, first chiral amine reacts with aldehydes to form an enamine which further adds to *α*-phenylselenoenones to afford the selenium-containing 1,5-dicarbonyl compounds in moderate to good yields. After the development of the synthesis of 1,5-dicarbonyl compounds, they further used it as the synthetic precursor for the preparation of *Z*-olefins in good yield with excellent enantioselectivity.

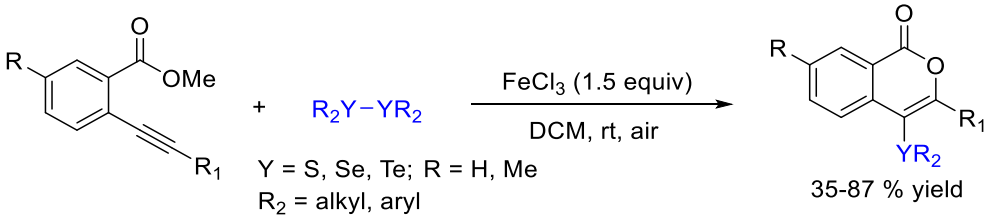


Scheme 5.4. Amine catalyzed enantioselective Michael addition of *α*-phenylselenoenones

5.3. Literature Reports for the Preparation of Selenylated *δ*-Lactones

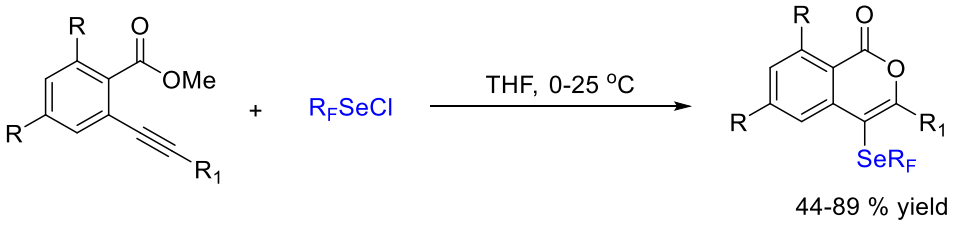
In context to the development of new efficient methods for the synthesis of organoselenium compounds, the construction of selenide-containing *δ*-lactones has received significant interest from the researchers. It is worth mentioning here that all the literature reported protocols are based on the cyclization of *o*-alkynylbenzoates using diselenides or selenyl chlorides. In 2011, the group of Zeni developed the first $FeCl_3$-mediated cyclization of 2-alkynylaryl esters using a variety of diorganyl dichalcogenides to afford selenylated isochromenones in good yields (Scheme 5.5).[14] This reaction was performed at room

temperature with inexpensive iron reagent in DCM solvent under the air atmosphere. The reaction was compatible with various diorganyl dichalcogenides bearing different substituents on the aromatic ring and with alkyl substituents bonded with chalcogen.



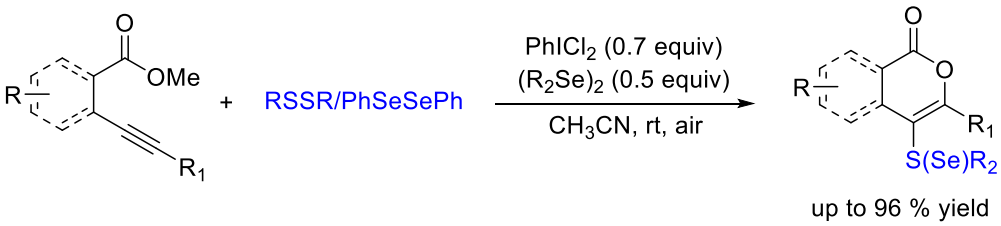
Scheme 5.5. $FeCl_3$-mediated cyclization of 2-alkynylaryl esters

In 2018, Billard and co-workers developed a method for the preparation of fluoroalkyl selenylated isocoumarins using CF_3SeCl and other fluorinated selenenyl chlorides (Scheme 5.6).[15] This reaction produced selenylated isocoumarins through intramolecular cyclization of 2-alkynylaryl esters promoted by CF_3SeCl reagent.



Scheme 5.6. CF_3SeCl promoted cyclization of 2-alkynylaryl esters

Recently in 2019, Du and co-workers reported the synthesis of trifluoromethylselanyl isocoumarins by regioselective intramolecular cyclization of alkynes using trifluoromethylselanyl chlorides and hypervalent iodine reagent (Scheme 5.7).[16] In this reaction, organosulfenyl chloride and organoselenyl chloride are generated in situ from the disulfides and diselenides in the presence of hypervalent iodine catalyst ($PhICl_2$) in acetonitrile solvent. Which further enables the regioselective intramolecular cyclization of



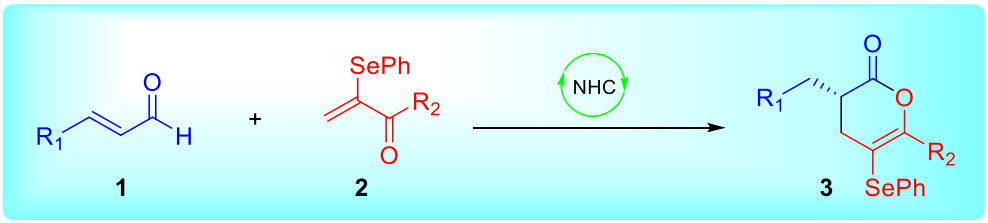
Scheme 5.7. Hypervalent iodine catalyzed cyclization of 2-alkynylaryl esters

o-alkynylbenzoates to afford selenium-containing isocumarins/pyrones in good to excellent yield.

In conclusion, the enantioselective preparation of organoselenium compounds has scarcely been studied, especially under metal-free organocatalytic reaction conndition. It was also found that a very limited literature methods are available for the synthesis of selenylated *δ*-lactones. All these literature methods furnish only non-chiral benzo-fused δ-lactones. Therefore, further study is required to explore this area.

5.4. Objective of the Work

As we discussed in the previous section, the selenium-derived compounds have important roles in the organic synthesis as catalysts or as the substrates. These compounds also show important biological activity, e.g., ebselen is a commercial drug. To the best of our knowledge, there is no precedence in the literature on the preparation of chiral selenylated *δ*-lactones. Herein, we wish to develop the first direct metal-free NHC-organocatalyzed asymmetric method for the preparation of these challenging molecule from *α,β*-unsaturated aldehydes and vinylselenides (*α*-phenylselanyl enones) (Scheme 5.8). Our approach of constructing these selenylated lactones offers a complementary approach over the known methods.

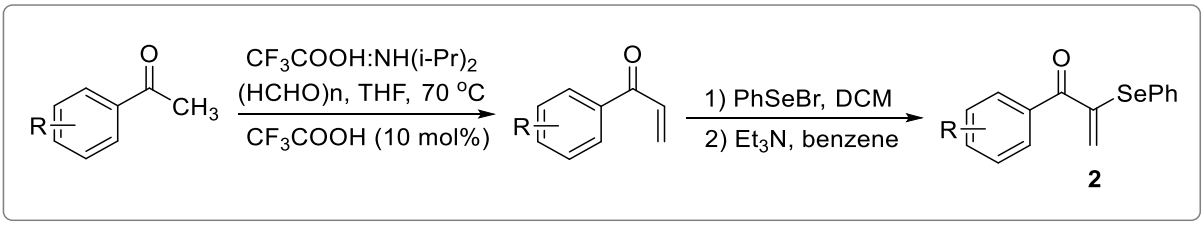


Scheme 5.8. Carbene catalyzed preparation of selenylated *δ*-lactones

5.5. Results and Discussion

5.5.1. Preparation of the Starting Materials

The derivative of vinyl ketones were prepared from acetophenone derivatives by following the reported literature protocols.[17] .All derivative of vinylselenides **2** were prepared by following the reported literature protocol using vinyl ketones in the presence of phenylselanyl bromide (Scheme 5.9).[18] and *α,β*-unsaturated aldehydes were used in this reaction were prepared according to the same procedure reported in chapter 2.[19] While the NHC catalyst **C** used in this reaction was prepared similarly according to the reported literature method.[20]

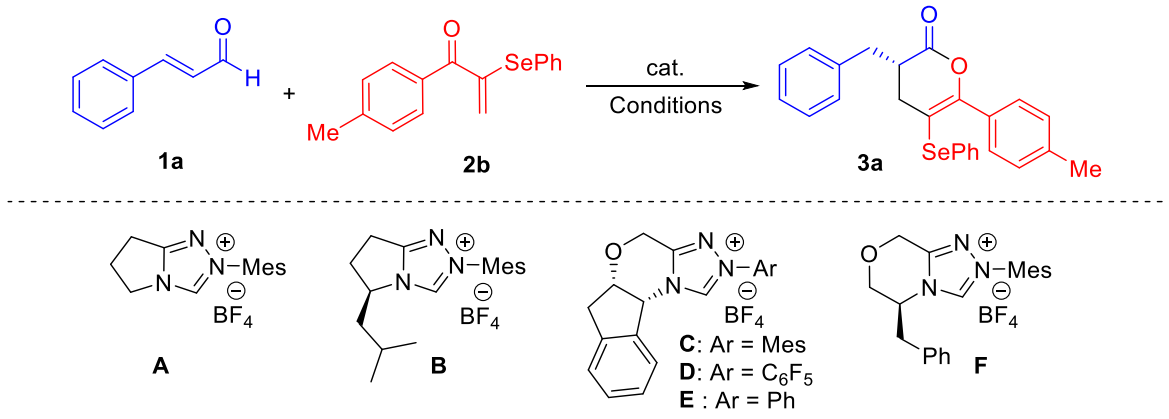


Scheme 5.9. Synthesis of vinylselenides

5.5.2. Optimization Studies of the Reaction

We selected cinnamaldehyde **1a** and vinyl selenide **2a** as a model substrate and the key results of the optimization of reaction conditions are summarized in Table 1. We started our investigation by examining different NHC pre-catalyst salts in the presence of Cs_2CO_3 in $CHCl_3$ solvent (Table 1). The triazolium pre-catalyst salts **A** furnished the desired product in very low yield 10%, while chiral triazolium salts **B** afforded the product **3a** in 25% (entries 1-2). The use of mes- protected amino-indanol precatalyst **C** resulted in the formation of desired product **3a** in moderate yield 39%, with excellent enantioselectivity 99% (entry 3). The other amino-indaol precatalyst **D** and **E** are found ineffective to produce the desired product (entries 4-5). An amino-acid derived precatalyst **F** afforded the product **3a** in 27% yield (entry 6). Switching to solvents like CH_2Cl_2, $(CH_2)_2Cl_2$, and THF does not show any noticeable improvement in the yield (entry 7-9). Gratifyingly, NHC precatalyst **E** in the presence of Cs_2CO_3 in non-polar toluene solvent produced the product **3a** in 75% yield and 99% ee (entry 10). The use of inorganic base K_2CO_3 gives the selenylated *δ*-lactones **3a** in 65% yield, while the organic bases TMG and DBU furnish the product in very low yield (entry 11-14). Performing this reaction under a similar condition as (entry 10) on 50 °C rather than rt did not show any noticeable improvement in the yield (entry 15).

Table 5.1. Optimization of the reaction condition[a]



entry	cat.	solvent	base	yield %[b]	ee %[c]
1	**A**	$CHCl_3$	Cs_2CO_3	10	0
2	**B**	$CHCl_3$	Cs_2CO_3	25	0
3	**C**	$CHCl_3$	Cs_2CO_3	39	99
4	**D**	$CHCl_3$	Cs_2CO_3	<5	0
5	**E**	$CHCl_3$	Cs_2CO_3	<5	0
6	**F**	$CHCl_3$	Cs_2CO_3	23	0
7	**C**	CH_2Cl_2	Cs_2CO_3	41	99
8	**C**	$(CH)_2Cl_2$	Cs_2CO_3	32	99
9	**C**	THF	Cs_2CO_3	44	99
10	**C**	toluene	Cs_2CO_3	75	99
11	**C**	toluene	K_2CO_3	65	99
12	**C**	toluene	TMG	26	0
14	**C**	toluene	DBU	15	0
15[d]	**C**	toluene	Cs_2CO_3	72	0

[a]General reaction condition: cinnamaldehyde **1a** (0.15 mmol), vinylselenide **2a** (0.1 mmol), cat. (20 mol %), solvent (1.0 mL) at rt 15 h. [b]Isolated yields of **3a** based on vinylselenides. [c]Enantiomeric excess was determined by chiral phase HPLC analysis. [d]Reaction performed at 50 °C.

5.5.3. X-ray Data of Compound 3a

The stereochemistry of the product **3a** was determind by using single crystal X-ray analysis (Figure 5.5).[21] The data collection of compound **3a** was carried out with 'Bruker APEX2' at ambient temperature. The refinement and data reduction of compound **3a** was done with 'Bruker SAINT'. The 'SHELXS-97 (Sheldrick 2008)' was used for the structure solution of compound **3a**. The structure refinement of compound **3a** was done with 'SHELXL-2014 (Sheldrick 2014)'. The X-ray analysis of compound **3a** is shown in the Table 5.2. The CCDC 2055769 contains the crystallographic information of the compound **3a** which can be obtained free of charge from Cambridge Data Centre with the following link http://www.ccdc.cam.ac.uk/data_request/cif.

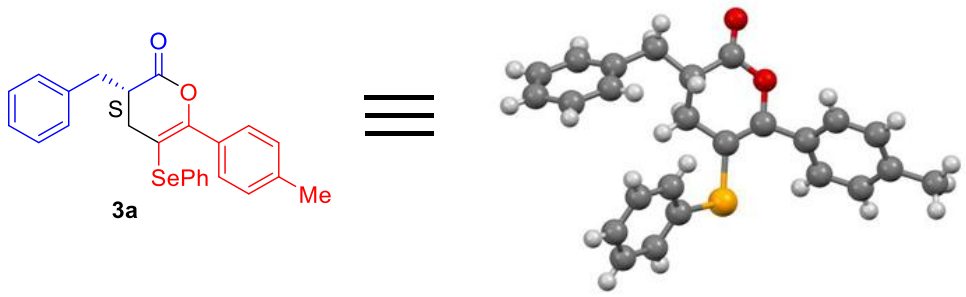


Figure 5.5. Single-crystal X-ray structure of the selenylated *δ*-lactones **3a**

Table 5.2. Crystallographic data and structure refinement for compound **3a**

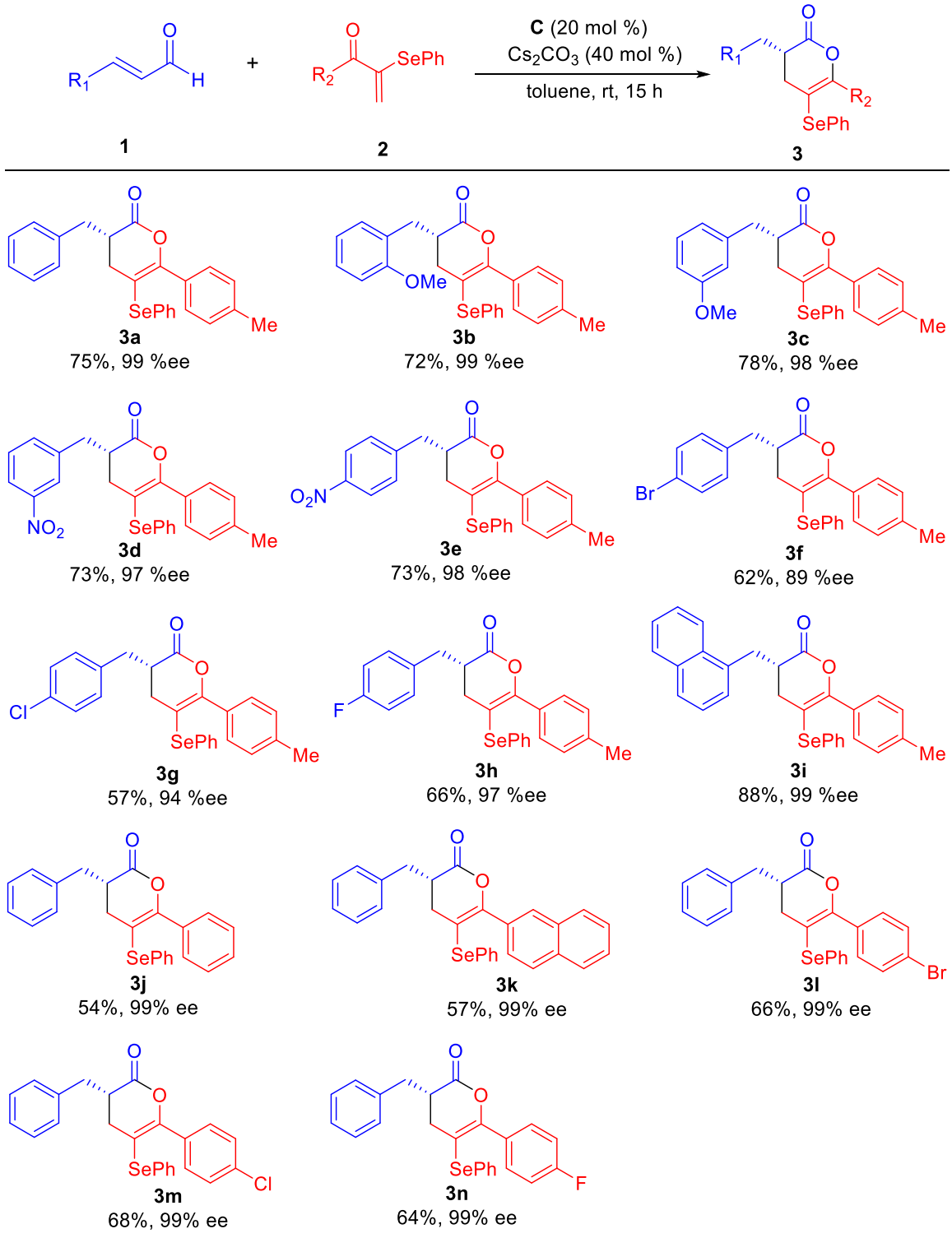
Identification code	**3a**
Chemical formula	$C_{25}H_{22}O_2Se$
Formula weight	433.38
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P21
Unit cell dimensions	a = 9.3022(5) Å α= 90°.
	b = 9.9995(5) Å β= 90°.
	c = 21.2668(12) Å γ = 90°.
Volume	1978.18(18)$Å^3$
Z	4
Density (calculated)	1.455 g/cm^3
Absorption coefficient	1.916 mm^{-1}
F(000)	888
Crystal size	0.300x 0.300x 0.300 mm^3
Theta range for data collection	2.80° to 28.31°.
Independent reflections	4916 [R(int) = 0.0447]
Completeness to theta = 24.639°	99.8%

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4916 / 0 / 255
Goodness-of-fit on F^2	1.037
R indices (all data)	R1 = 0. 0229, wR2 = 0. 0.0490
CCDC	2057769

5.5.4. Substrate Scope of Vinylselenides and *α,β*-Unsaturated Aldehydes

After getting the optimized condition in hand, we further moved to evaluate the compatibility of the reactions with the derivatives of *α,β*-unsaturated aldehydes and vinylselenides **2a** (Scheme 5.10). The *α,β*-unsaturated aldehydes having methoxy substituent at *ortho* and *meta* position at the aryl ring were found compatible under the optimized reaction condition and gives the selenylated *δ*-lactones in good yields 72-78% and 98-99% ee (**3b**-**3c**). The electron-deficient aldehydes bearing -NO_2 substituent at *meta* or *para* position on the aryl ring are also found compatible and produced the desired products in 73% yield with excellent enantioselectivity (**3d**-**3e**). The *α,β*-unsaturated aldehydes bearing halogen (bromo, chloro, and fluoro) at the *para* position over aryl rings were also reacted smoothly under the standard reaction condition and furnish the selenylated *δ*-lactones in 57-66% yield and excellent stereoselectivity (**3f**-**3h**). The Naphthyl- substituent present at the *β*-position on enals reacted well and gives the desired product in the excellent yield 88% with enantioselectivity 99% (**3i**).

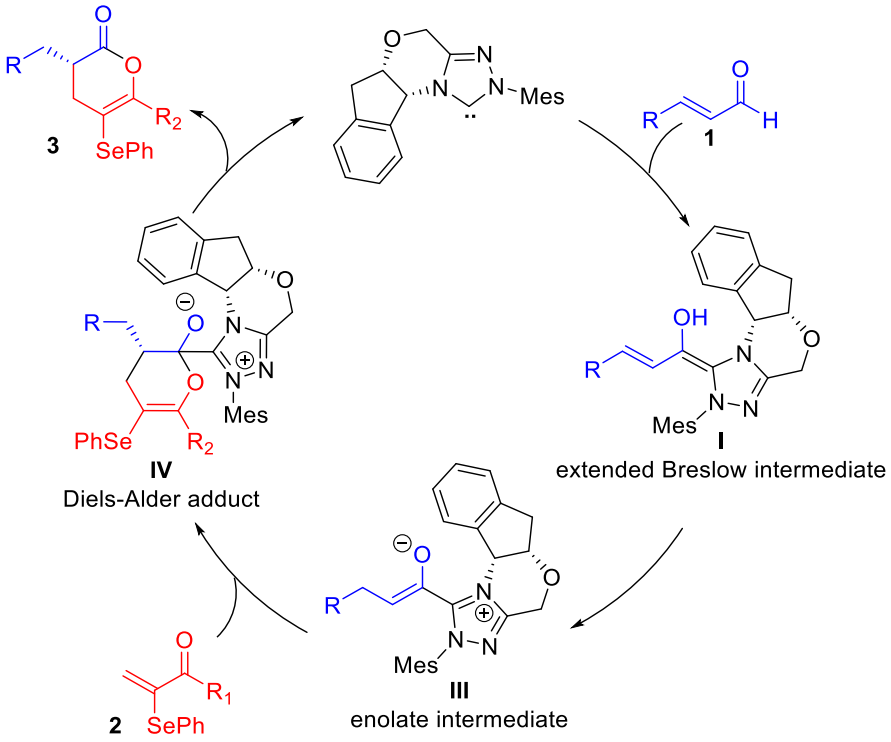
We next moved to investigate the generality of the derivatives of vinylselenides with respect to cinnamaldehyde under the optimized reaction condition (Scheme 5.10). The unsubstituted aryl and naphthyl substituted vinylselenides were found compatible under the optimized reaction condition with cinnamaldehyde and produced the desired selenylated lactones in good yield 54-57% with 99% enantioselectivity (**3j**-**3k**). The vinylselenides bearing halogen functionality such as -Br, -Cl, and -F at *para*- position on the aryl ring also reacted smoothly to give desired lactone products in 64-68% yield with 99% enantioselectivity (**3l**-**3n**).



Scheme 5.10. Scope of different substituted aldehydes[a]

5.5.5. Proposed Mechanism of the Reaction

The mechanism of this reaction was initiated by the addition of NHC catalysts to *α,β*-unsaturated aldehyde, which resulted in the formation of the extended Breslow intermediate **I**



Scheme 5.11. Proposed catalytic cycle for the synthesis of selenylated *δ*-lactones

(Scheme 5.11). The intermediate **I** undergo *β*-protonation to generate enolate intermediate **II**, further reacts with the vinylselenides to form a cyclize Diels-Alder adduct **III**. Subsequently, the regeneration of the catalyst from **III** gives rise to the desired selenylated dihydropyranone product **3**.

5.6. Conclusion

In conclusion, we have developed the first *N*-heterocyclic carbene (NHC)-catalyzed highly enantioselective method for the preparation of selenylated *δ*-lactones *via* [4+2] annulation of *α,β*-unsaturated aldehydes with vinylselenides. The reaction condition was compatible with a variety of enals and vinylselenides to give the selenylated lactones in good yield with excellent enantioselectivity. The structure and the absolute configuration of the product was unambiguously determined by the X-ray crystallography.

5.7. Experimental Section

5.7.1. General Information

The reactions were performed under an argon atmosphere in oven-dried glassware. Solvents were dried and distilled following the standard procedures, TLC was carried out on pre-coated plates (Merck silica gel 60, F_{254}), and the spots were visualized with UV light or by

charring the plates dipped in phosphomolybdic acid (PMA) or vanillin charring solution. Flash chromatography was performed using silica gel (100-200 mess) with distilled solvents. Enantiomeric excess (*ee*) of the products were determined by high-performance liquid chromatography (HPLC) analysis using a chiral stationary phase. ^{1}H and ^{13}C NMR for compounds were recorded at 400 MHz and 100 MHz instrument respectively using $CDCl_3$ as the solvent. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), and dt (doublet of triplets); m (multiplets), etc. High-resolution mass spectral analysis (HRMS) was performed on Q-TOF Premier mass spectrometer.

5.7.2. *N*-Heterocyclic Carbene Catalyzed Preparation of Selenylated *δ*-Lactones 3

To an oven-dried Schlenk tube equipped with a magnetic stir bar, was added *α,β*-unsaturated aldehydes **1** (0.2 mmol, 2.0 equiv.), vinylselenides **2** (0.1 mmol, 1.0 equiv.) and catalyst **C** (20 mol %) in toluene (1.0 mL) at room temperature. Thereafter, the reaction chamber was purged with argon, and Cs_2CO_3 (40 mol%) was added. After stirring this reaction mixture at room temperature for 16 h, the solvent was evaporated under reduced pressure. The crude mass was purified by flash column chromatography on silica gel using EtOAc in hexane.

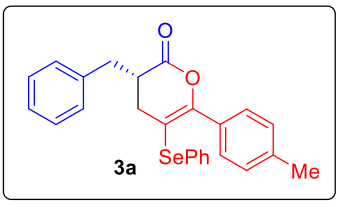
5.7.3. Characterization of the Products

(*S*)-3-Benzyl-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3a):

Yield: 75% (33 mg), white solid, eluent: 5% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{25}H_{22}O_2SeNa^+$ 457.0678, found: 457.0679.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.34-2.54 (5H, m), 2.71 (1H, dd, *J* = 4.8, 9.2 Hz), 2.85-2.98 (1H, m), 3.35 (1H, dd, *J* = 9.6, 4.4 Hz), 7.08 (2H, d, *J* = 7.2 Hz), 7.17-7.31 (8H,m), 7.37 (2H, d, *J* = 7.6 Hz), 7.48 (2H, d, *J* = 8.0 Hz).

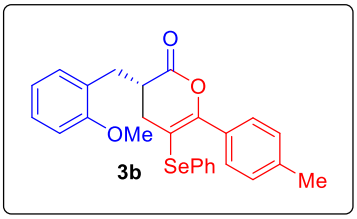


3a

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): *δ* 21.4, 32.3, 35.3, 41.5, 104.9, 126.5, 127.7, 128.5, 128.6, 128.7, 128.9, 129.0, 129.2, 130.3, 132.8, 137.8, 139.6, 150.7, 170.1; 457.0677.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 21.34 min, Rt_2 (major) = 26.53 min; >99% ee.

(*S*)-3-(2-Methoxybenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3b):



Yield: 72% (32 mg), pale yellow gummy liquid, eluent: 10% EtOAc in hexane.

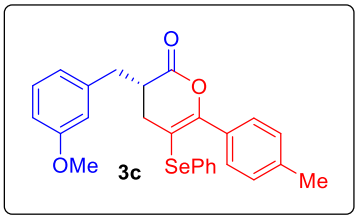
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{26}H_{25}O_3Se^+$ 465.0964, found: 465.0961.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31-2.46 (5H, m), 2.64 (1H, dd, J = 4.4, 9.2 Hz), 2.91-3.07 (1H, m), 3.35 (1H, dd, J = 8.4, 5.2 Hz), 3.69 (3H, s), 6.72-6.85 (2H, m), 7.01 (1H, d, J = 7.2 Hz), 7.11-7.28 (6H, m), 7.33 (2H, d, J = 6.8 Hz), 7.44 (2H, d, J = 8.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.3, 30.4, 32.6, 39.7, 55.0, 105.0, 110.1, 120.3, 126.2, 127.5, 127.9, 128.5, 128.7, 129.1, 130.4, 130.8, 132.7, 139.4, 150.6, 157.3, 170.1.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 11.71 min, Rt_2 (major) = 15.19 min; >99% ee.

(*S*)-3-(3-Methoxybenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3c):



Yield: 78% (35 mg), pale yellow gummy liquid, eluent: 10% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{26}H_{25}O_3Se^+$ 465.0964, found: 465.0969.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31-2.49 (5H, m), 2.64 (1H, dd, J = 4.4, 9.6 Hz), 2.79-2.94 (1H, m), 3.29 (1H, dd, J = 9.6, 4.4 Hz), 3.75 (3H, s), 6.58-6.67 (2H, m), 6.72 (1H, d, J = 8.8 Hz), 7.12 (1H, t, J = 8.0 Hz), 7.15-7.27 (5H, m), 7.33 (2H, d, J = 7.6 Hz), 7.44 (2H, d, J = 7.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.3, 32.2, 35.3, 41.4, 55.0, 105.0, 112.1, 114.4, 121.1, 127.6, 128.5, 128.6, 128.9, 129.2, 129.4, 130.2, 132.7, 139.4, 139.6, 150.5, 159.5, 170.1.

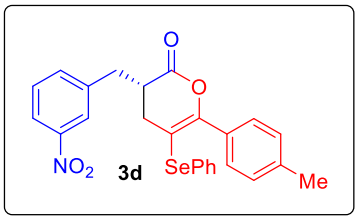
HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 70:30, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 13.40 min, Rt_2 (major) = 15.41 min; >98% ee.

(*S*)-3-(3-Nitrobenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3d):

Yield: 73% (35 mg), pale yellow gummy liquid, eluent: 15% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{25}H_{22}NO_4Se^+$ 480.0709, found: 480.0709.

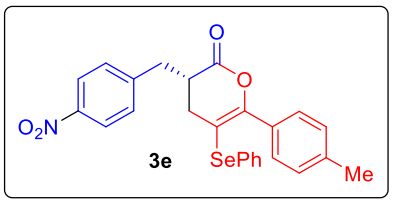
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24-2.47 (5H, m), 2.79 (1H, dd, J = 4.8, 8.8 Hz), 2.83-2.96 (1H, m), 3.39 (1H, dd, J = 9.2, 4.8 Hz), 7.12-7.25 (5H, m), 7.34 (2H, d, J = 6.8 Hz), 7.36-7.48 (4H, m), 7.92 (1H, s), 8.04 (1H, d, J = 7.6 Hz).



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.4, 32.2, 34.9, 41.2, 105.0, 121.8, 123.6, 127.9, 128.6, 129.2, 129.4, 129.9, 133.1, 135.2, 139.8, 140.0, 148.2, 150.4, 169.5.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 16.94 min, Rt_2 (major) = 20.20 min; >97% ee.

(*S*)-3-(4-Nitrobenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3e):



Yield: 73% (35 mg), white solid, eluent: 15% EtOAc in hexane.

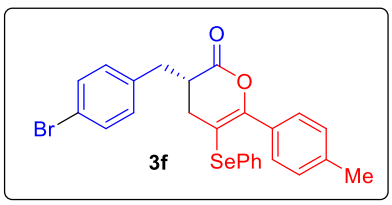
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{25}H_{22}NO_4Se^+$ 480.0709, found: 480.0709.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19-2.39 (5H, m), 2.71 (1H, dd, J = 4.8, 8.8 Hz), 2.75-2.85 (1H, m), 3.31 (1H, dd, J = 8.8, 4.8 Hz), 7.08-7.21 (7H, m), 7.24-7.31 (2H, m), 7.36 (2H, d, J = 8.4 Hz), 7.96-8.02 (2H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.4, 32.2, 35.0, 41.2, 105.0, 123.7, 127.9, 128.6, 128.7, 129.3, 129.7, 129.9, 133.2, 139.8, 145.7, 146.7, 150.5, 169.4.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 60:40, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 19.34 min, Rt_2 (major) = 22.10 min; >98% ee.

(*S*)-3-(4-Bromobenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3f):



Yield: 62% (32 mg), white solid, eluent: 5% EtOAc in hexane.

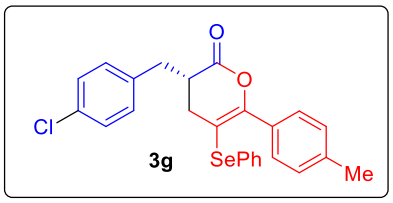
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{25}H_{22}BrO_2Se^+$ 512.9963, found: 512.9965.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33-2.44 (5H, m), 2.65 (1H, dd, J = 4.8, 9.2 Hz), 2.76-2.89 (1H, m), 3.27 (1H, dd, J = 9.6, 4.4 Hz), 6.93 (2H, d, J = 8.4 Hz), 7.18-7.27 (4H, m), 7.27-7.41 (5H, m), 7.46 (2H, d, J = 8.4 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.4, 32.0, 34.6, 41.4, 105.2, 120.5, 127.9, 128.6, 128.7, 128.8, 129.3, 130.1, 130.6, 131.5, 133.1, 136.8, 139.7, 150.4, 169.9.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 20.86 min, Rt_2 (major) = 23.09 min; >89% ee.

(*S*)-3-(4-Chlorobenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3g):



Yield: 57% (27 mg), white solid, eluent: 5% EtOAc in hexane.

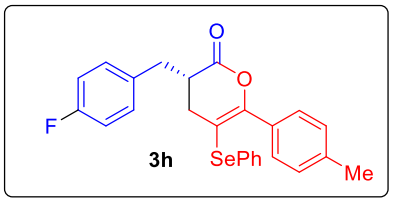
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{25}H_{22}ClO_2Se^+$ 469.0469, found: 469.0474.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30-2.42 (5H, m), 2.64 (1H, dd, J = 4.8, 9.2 Hz), 2.73-2.86 (1H, m), 3.25 (1H, dd, J = 9.6, 4.4 Hz), 6.96 (2H, d, J = 8.0 Hz), 7.13-7.23 (6H, m), 7.23-7.31 (1H, m), 7.33 (2H, d, J = 7.6 Hz), 7.43 (2H, d, J = 8.0 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.4, 32.0, 34.5, 41.4, 105.1, 127.8, 128.6, 128.6, 128.7, 128.8, 129.2, 130.1, 130.2, 132.4, 133.0, 136.3, 139.7, 150.4, 169.9.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 19.59 min, Rt_2 (major) = 22.20 min; >94% ee.

(*S*)-3-(4-Fluorobenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3h):



Yield: 66% (30 mg), white solid, eluent: 5% EtOAc in hexane.

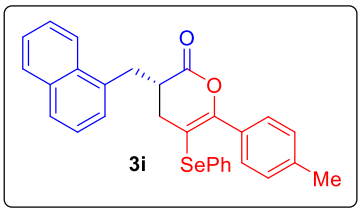
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{25}H_{22}FO_2Se^+$ 453.0764, found: 453.0765.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32-2.42 (5H, m), 2.66 (1H, dd, J = 4.8, 9.2 Hz), 2.74-2.87 (1H, m), 3.25 (1H, dd, J = 9.2, 4.8 Hz), 6.89 (2H, t, J = 8.4 Hz), 6.95-7.05 (2H, m), 7.16-7.30 (5H, m), 7.34 (2H, d, J = 7.6 Hz), 7.44 (2H, d, J = 8.0 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.4, 32.1, 34.4, 41.5, 105.0, 115.3 (d, $J_{C\text{-}F}$ = 21.0 Hz), 127.8, 128.6, 128.7, 128.8, 129.2, 130.1, 130.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 133.0, 133.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 139.7, 150.5, 161.6 (d, $J_{C\text{-}F}$ = 243.0 Hz), 170.0.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 18.96 min, Rt_2 (major) = 21.95 min; >97% ee.

Naphthalen-1-ylmethyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3i):



Yield: 88% (43 mg), pale yellow gummy liquid, eluent: 5% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{29}H_{25}O_2Se^+$ 485.1015, found: 485.1011.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20-2.52 (5H, m), 2.85-3.12 (2H, m), 3.93 (1H, dd, J = 10.4, 3.2 Hz), 6.97 (2H, t, J = 7.6 Hz), 7.09 (2H, t, J = 6.4 Hz), 7.15-7.31 (5H, m), 7.40-7.55 (4H, m), 7.68 (1H, d, J = 8.4 Hz), 7.79-7.96 (2H, m).

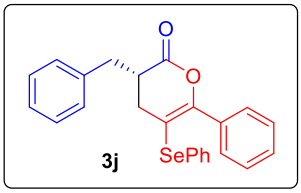
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.3, 32.5, 32.6, 40.5, 105.3, 123.1, 125.2, 125.6, 126.2, 127.3, 127.5, 127.6, 128.5, 128.6, 128.9, 129.0, 130.2, 131.3, 132.8, 133.8, 133.9, 139.5, 150.3, 170.4.

HPLC analysis: (Chiralcel IA; hexane/*i*-PrOH 80:20, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 13.14 min, Rt_2 (major) = 17.68 min; >99% ee.

(*S*)-3-Benzyl-6-phenyl-5-(phenylselanyl)-3,4-dihydro-2*H*-pyran-2-one (3j):

Yield: 54% yield (23 mg), white solid, eluent: 5% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{20}O_2SeNa^+$ 443.0521, found: 443.0520.

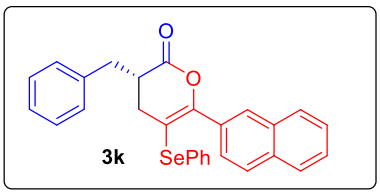


^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32-2.52 (2H, m), 2.68 (1H, dd, J = 4.4, 9.2 Hz), 2.81-2.97 (1H, m), 3.31 (1H, dd, J = 9.2, 4.8 Hz), 7.05 (2H, d, J = 7.2 Hz), 7.13-7.28 (6H, m), 7.29-7.44 (5H, m), 7.50-7.62 (2H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 32.3, 35.2, 41.4, 105.6, 126.5, 127.7, 127.9, 128.5, 128.8, 128.9, 129.2, 129.4, 132.9, 133.1, 137.7, 150.5, 170.0.

HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 22.92 min, Rt_2 (major) = 24.51 min; >99% ee.

(*S*)-3-benzyl-6-(naphthalen-2-yl)-5-(phenylselanyl)-3,4-dihydro-2*H*-pyran-2-one (3k):



Yield: 57% (27 mg), white solid, eluent: 5% EtOAc in hexane.

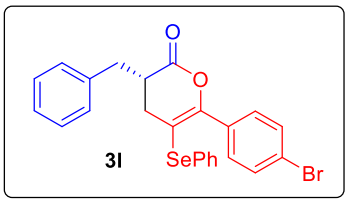
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{28}H_{22}O_2SeNa^+$ 493.0678, found: 493.0679;

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34-2.58 (2H, m), 2.72 (1H, dd, J = 4.4, 9.2 Hz), 2.85-3.02 (1H, m), 3.34 (1H, dd, J = 9.2, 4.8 Hz), 7.07 (2H, d, J = 6.8 Hz), 7.13-7.29 (6H, m), 7.35 (2H, d, J = 8.0 Hz), 7.44-7.57 (2H, m), 7.68 (1H, d, J = 8.8 Hz), 7.76-7.93 (3H, m), 8.01 (1H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 32.4, 35.3, 41.4, 106.2, 125.7, 126.4, 126.6, 126.9, 127.5, 127.6, 127.8, 128.4, 128.5, 128.8, 128.8, 128.9, 129.3, 130.4, 132.4, 133.0, 133.5, 137.8, 150.3, 170.1.

HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 32.31 min, Rt_2 (major) = 45.32 min; >99% ee.

(*S*)-3-benzyl-6-(4-bromophenyl)-5-(phenylselanyl)-3,4-dihydro-2*H*-pyran-2-one (3l):



Yield: 66% (33 mg), white solid, eluent: 5% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{24}H_{20}BrO_2Se^+$ 498.9807, found: 498.9800.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30-2.52 (2H, m), 2.68 (1H, dd, J = 4.8, 9.2 Hz), 2.80-2.95 (1H, m), 3.30 (1H, dd, J = 9.6, 4.8 Hz), 7.04 (2H, d, J = 7.2 Hz), 7.15-7.28 (6H, m), 7.32 (2H, d, J = 7.6 Hz), 7.43 (2H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.0 Hz).

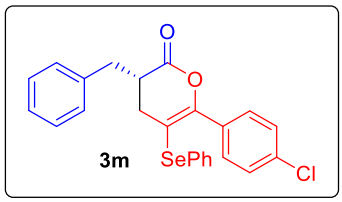
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 32.3, 35.2, 41.3, 106.4, 123.6, 126.6, 127.9, 128.5, 128.8, 129.3, 130.3, 131.1, 131.9, 132.9, 137.6, 149.3, 169.8.

HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 19.11 min, Rt_2 (major) = 30.62 min; >99% ee.

(*S*)-3-(4-Chlorobenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3m):

Yield: 68% (31 mg), white solid, eluent: 5% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{19}ClO_2SeNa^+$ 477.0131, found: 477.0132.

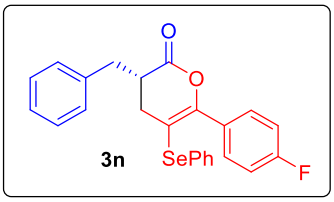


^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31-2.52 (2H, m), 2.68 (1H, dd, J = 4.8, 9.2 Hz), 2.80-2.97 (1H, m), 3.30 (1H, dd, J = 9.6, 4.4 Hz), 7.04 (2H, d, J = 6.4 Hz), 7.15-7.29 (6H, m), 7.29-7.40 (4H, m), 7.50 (2H, d, J = 8.4 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 32.3, 35.2, 41.3, 106.3, 126.6, 127.9, 128.1, 128.5, 128.6, 128.9, 129.3, 130.1, 131.5, 132.8, 135.3, 137.6, 149.3, 169.8.

HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 18.91 min, Rt_2 (major) = 28.95 min; >99% ee.

(*S*)-3-(4-Fluorobenzyl)-5-(phenylselanyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (3n):



Yield: 64% (28 mg), white solid, eluent: 5% EtOAc in hexane.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{24}H_{20}FO_2Se^+$ 439.0608, found: 439.0610.

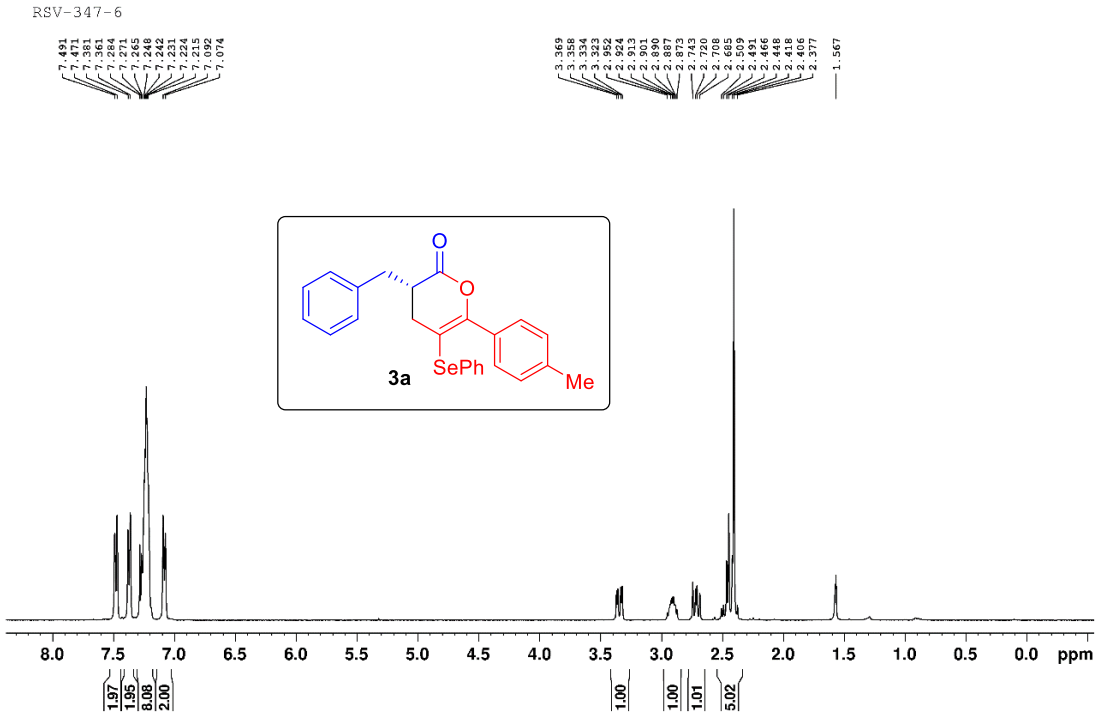
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30-2.53 (2H, m), 2.68 (1H, dd, J = 4.8, 9.2 Hz), 2.80-2.97 (1H, m), 3.31 (1H, dd, J = 9.2, 4.8 Hz), 7.06 (4H, t, J = 7.6 Hz), 7.14-7.28 (6H, m), 7.32 (2H, d, J = 7.6 Hz), 7.54 (2H, q, J = 8.4 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 32.3, 35.2, 41.3, 105.7, 115.0 (d, $J_{C\text{-}F}$ = 22.0 Hz), 126.6, 127.8, 128.5, 128.7, 128.8, 129.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.3, 130.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 132.7, 137.7, 149.6, 163.1 (d, $J_{C\text{-}F}$ = 249.0 Hz), 169.9.

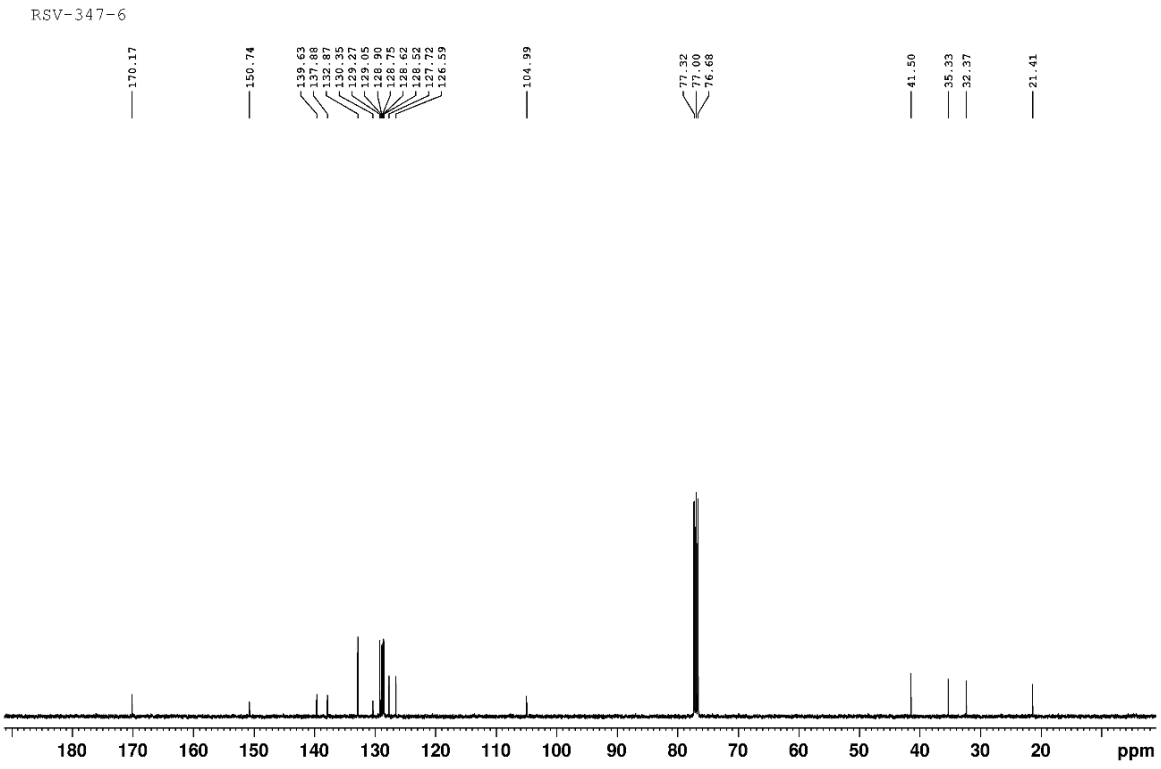
HPLC analysis: (Chiralcel ODH; hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, 254 nm), Rt_1 (minor) = 23.59 min, Rt_2 (major) = 35.81 min; >99% ee.

5.7.4. ^{1}H and $^{13}C\{^{1}H\}$ NMR Spectra of Products

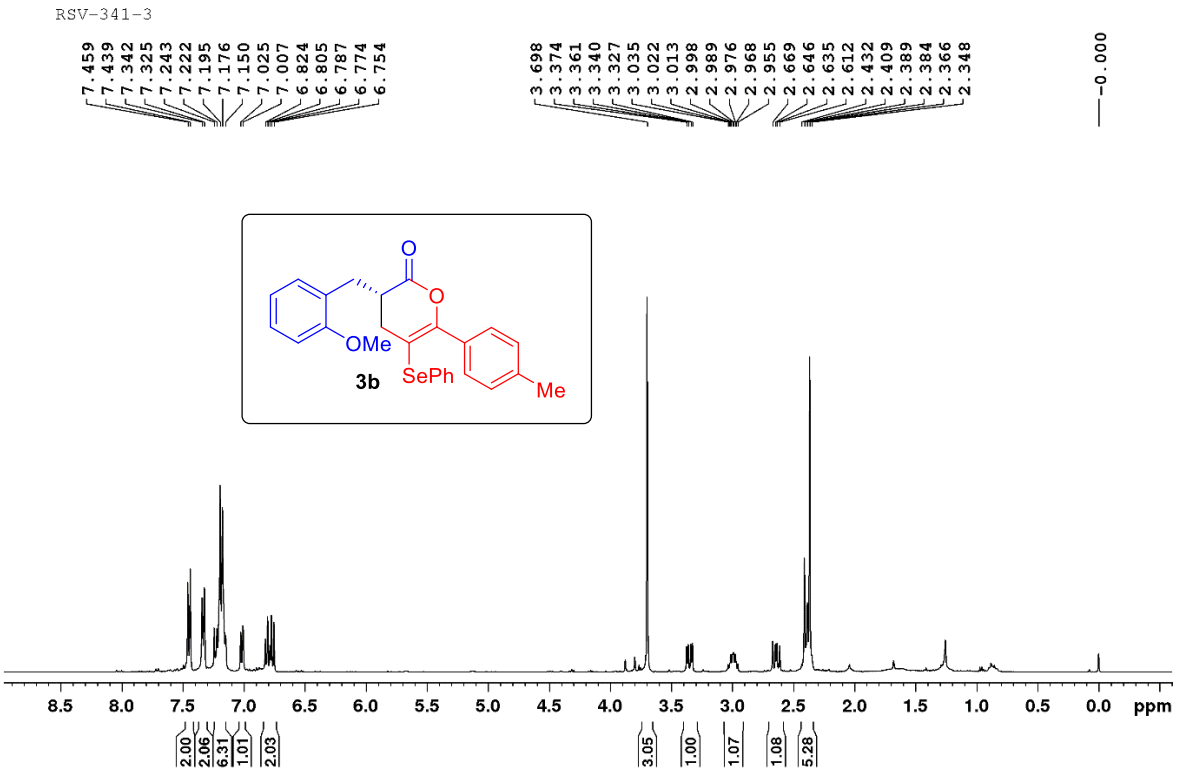
^{1}H NMR in $CDCl_3$ 400MHz 3a



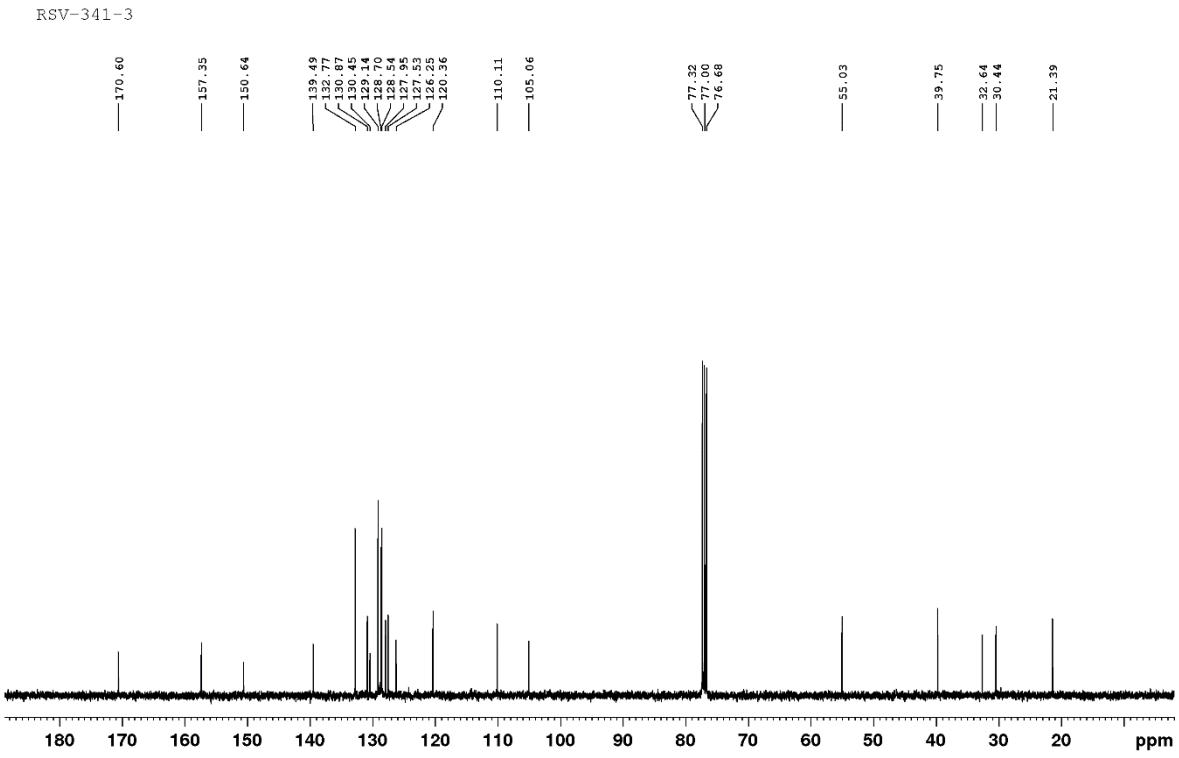
$^{13}C\{^{1}H\}$ NMR in $CDCl_3$ 400MHz 3a



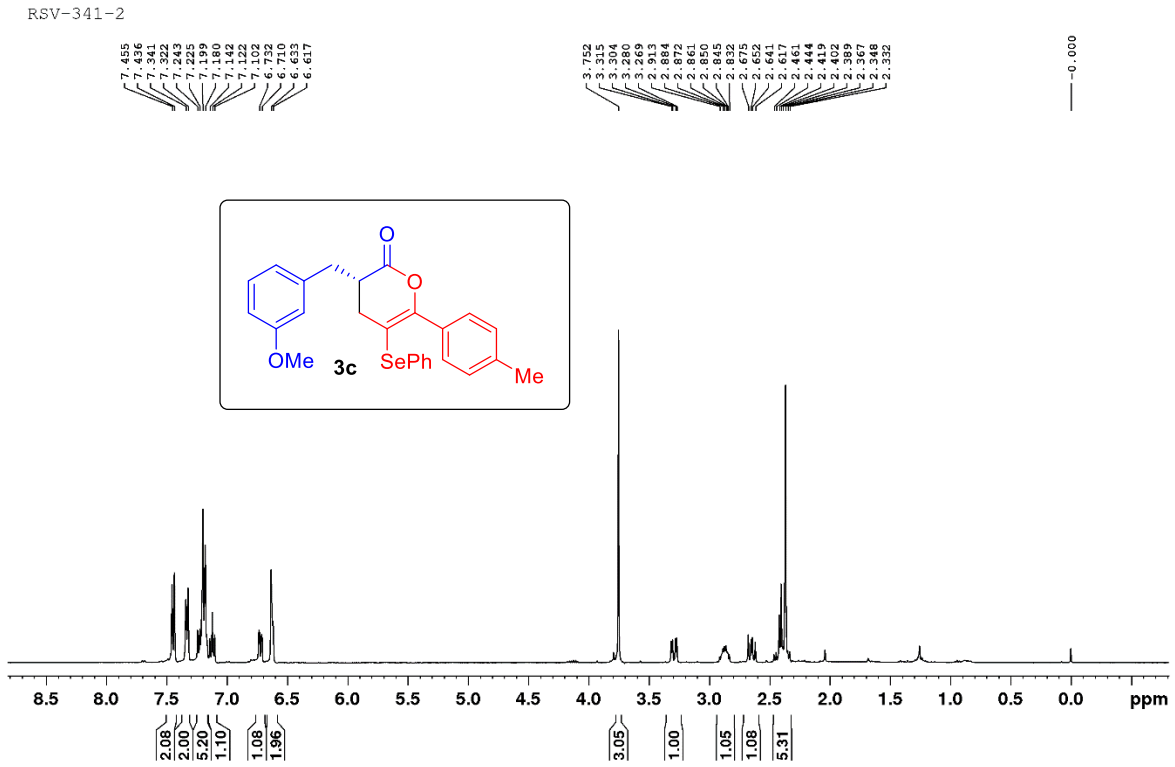
^{1}H NMR in $CDCl_3$ 400MHz 3b



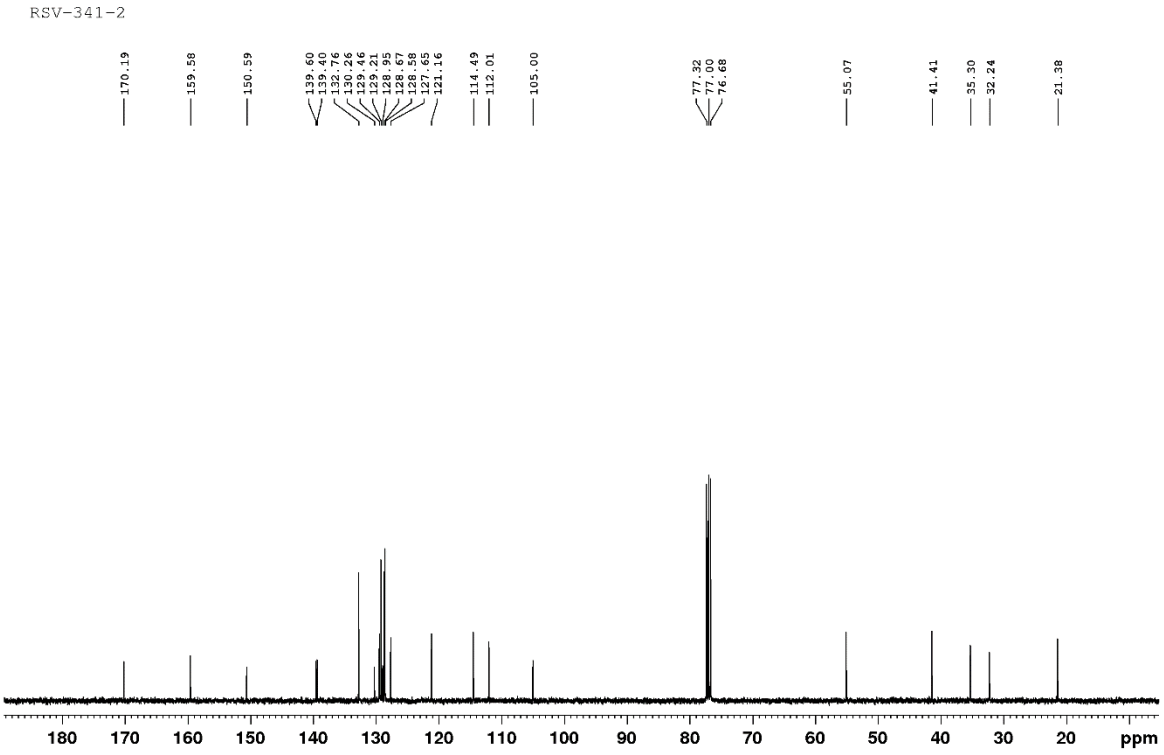
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3b



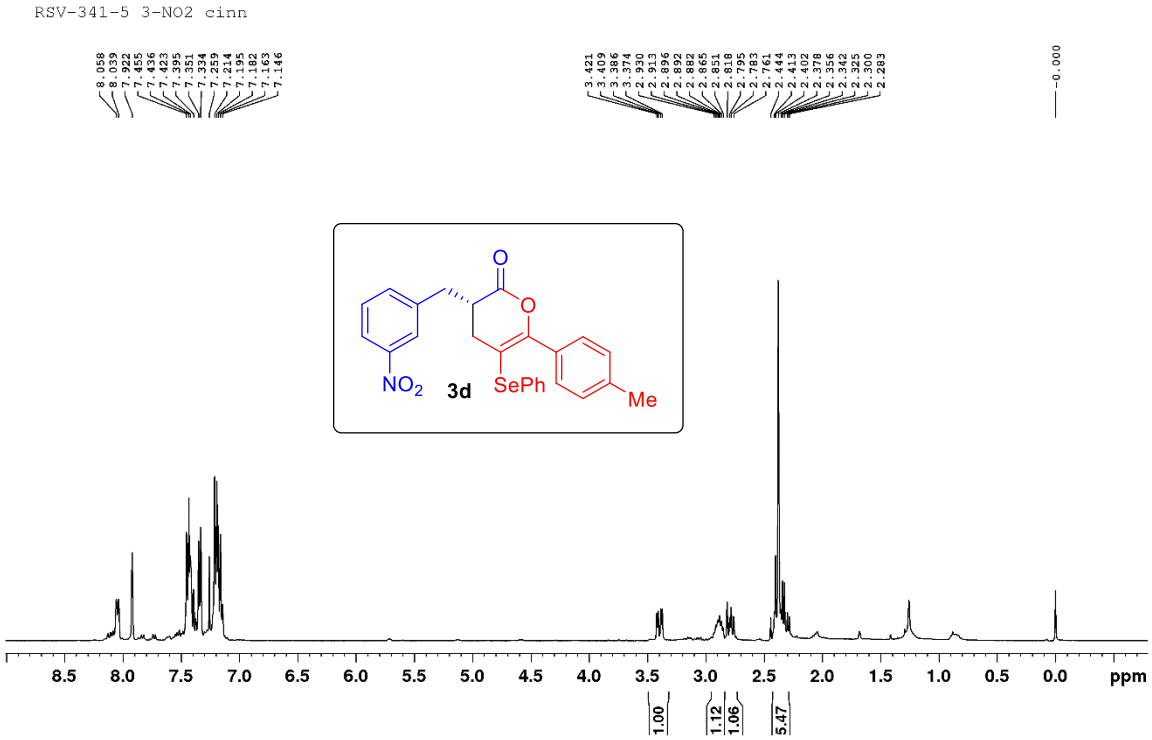
^{1}H NMR in $CDCl_3$ 400MHz 3c



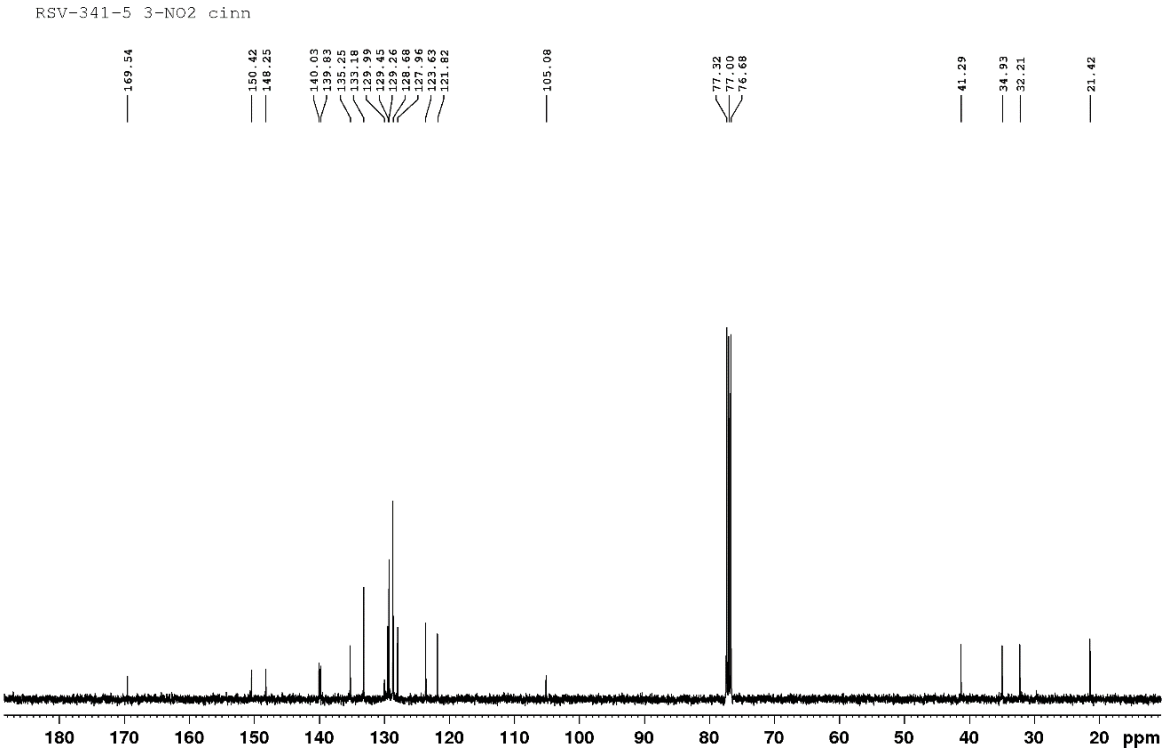
$^{13}C\{^{1}H\}$ NMR in $CDCl_3$ 400MHz 3c



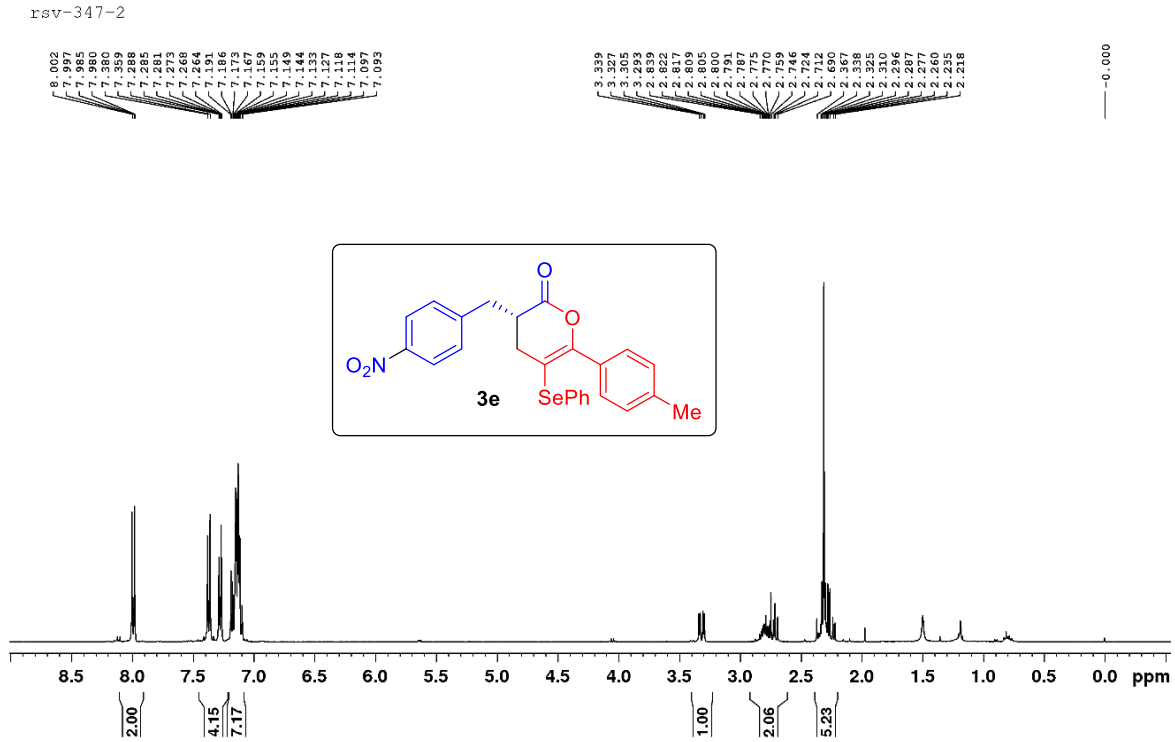
^{1}H NMR in $CDCl_3$ 400MHz 3d



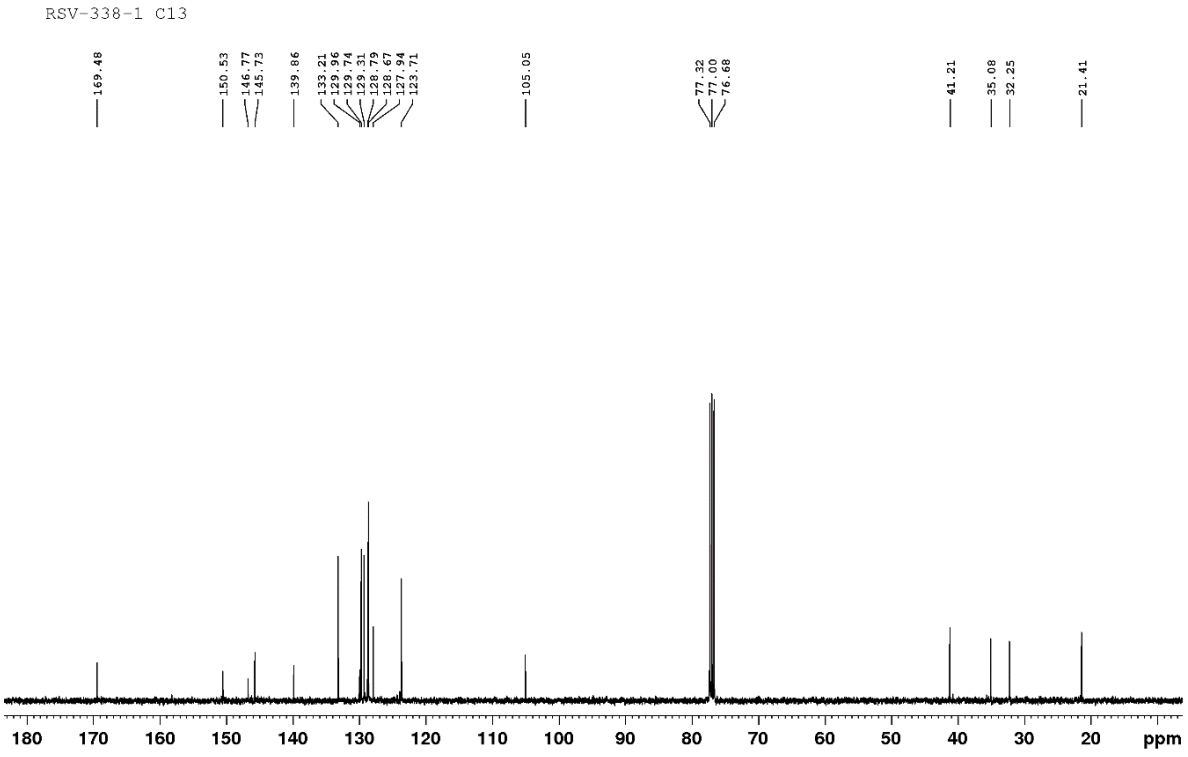
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3d



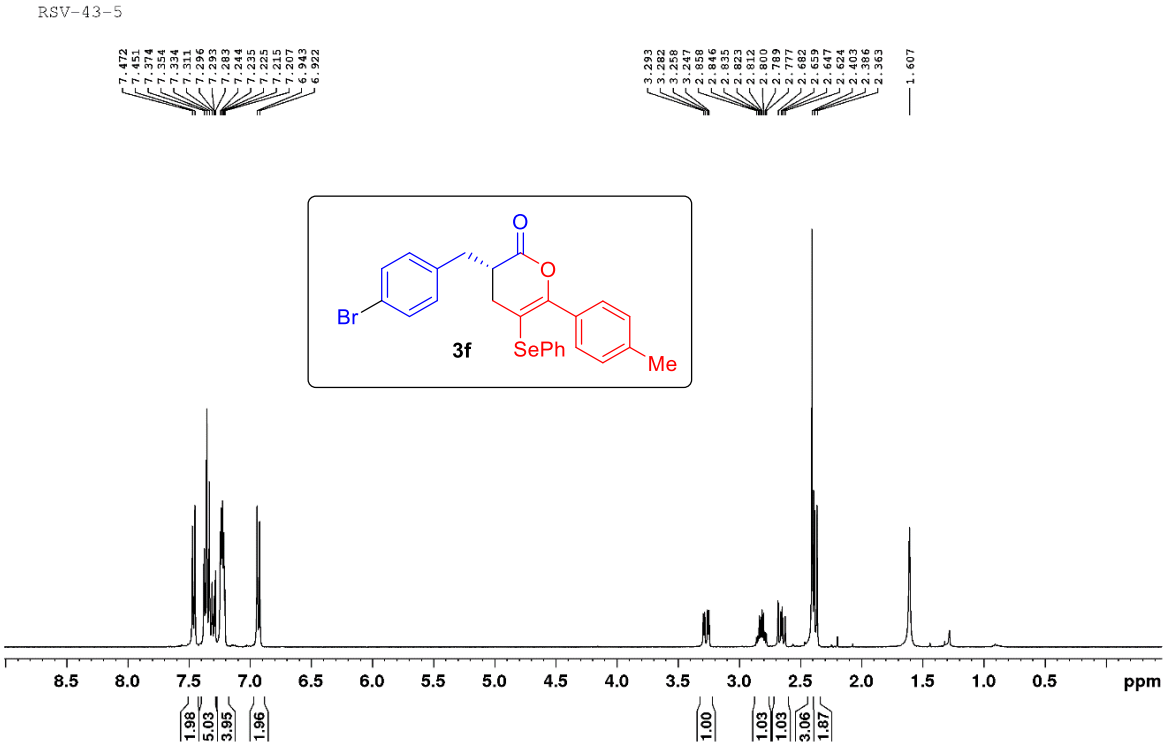
^{1}H NMR in $CDCl_3$ 400MHz 3e



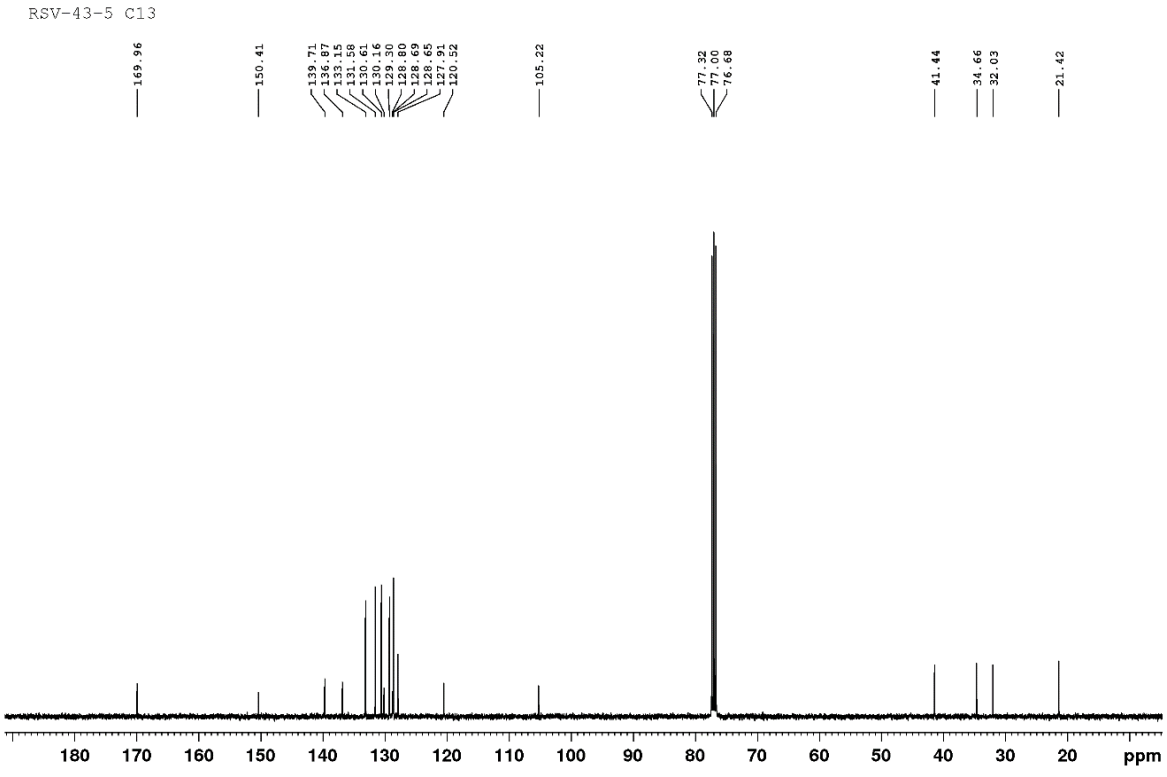
$^{13}C\{^{1}H\}$ NMR in $CDCl_3$ 400MHz 3e



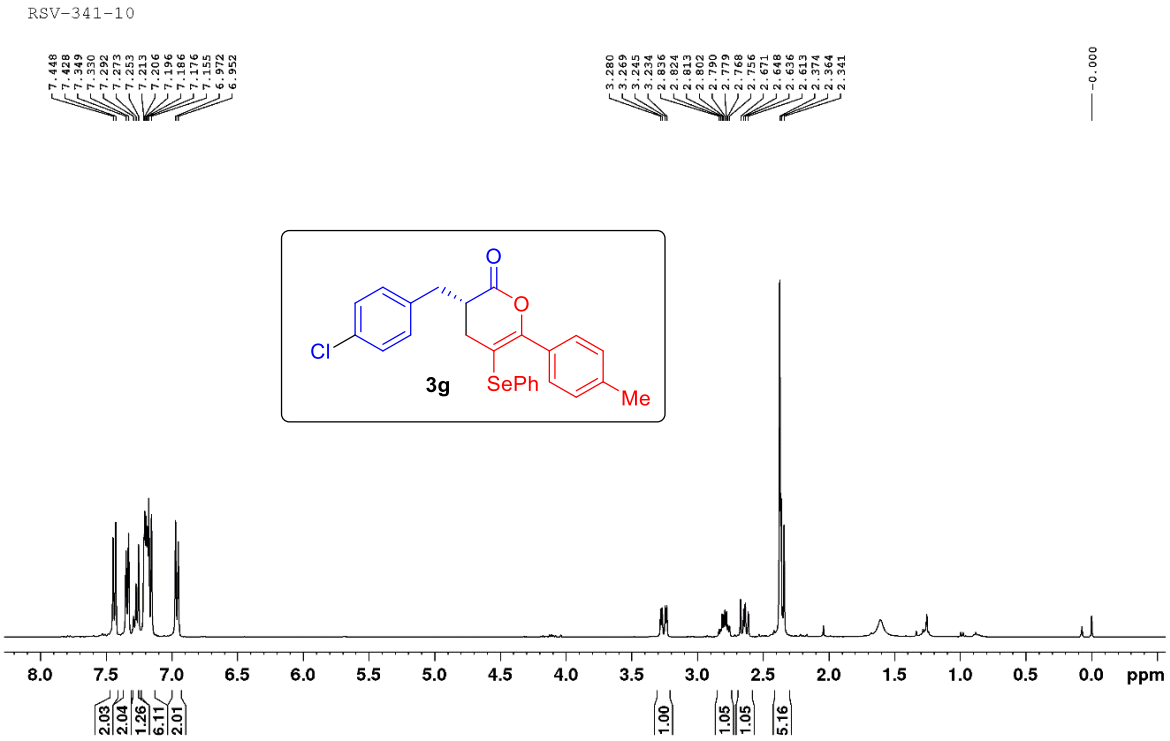
^{1}H NMR in $CDCl_3$ 400MHz 3f



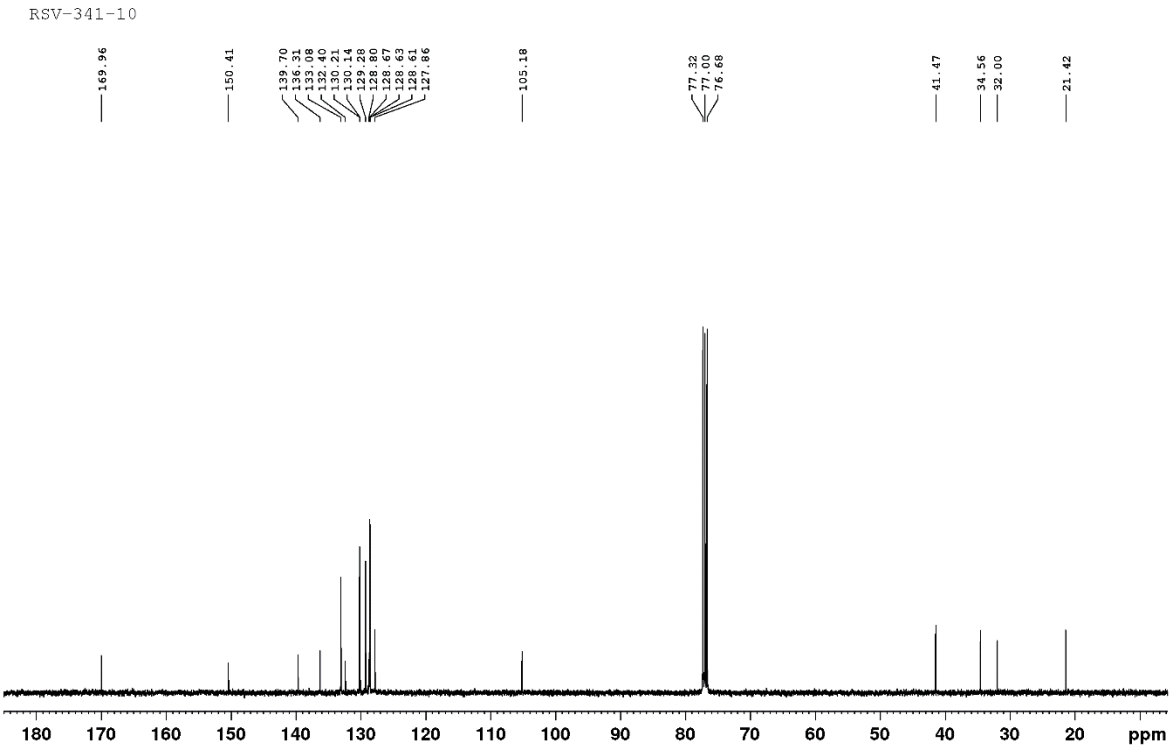
^{13}C^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3f



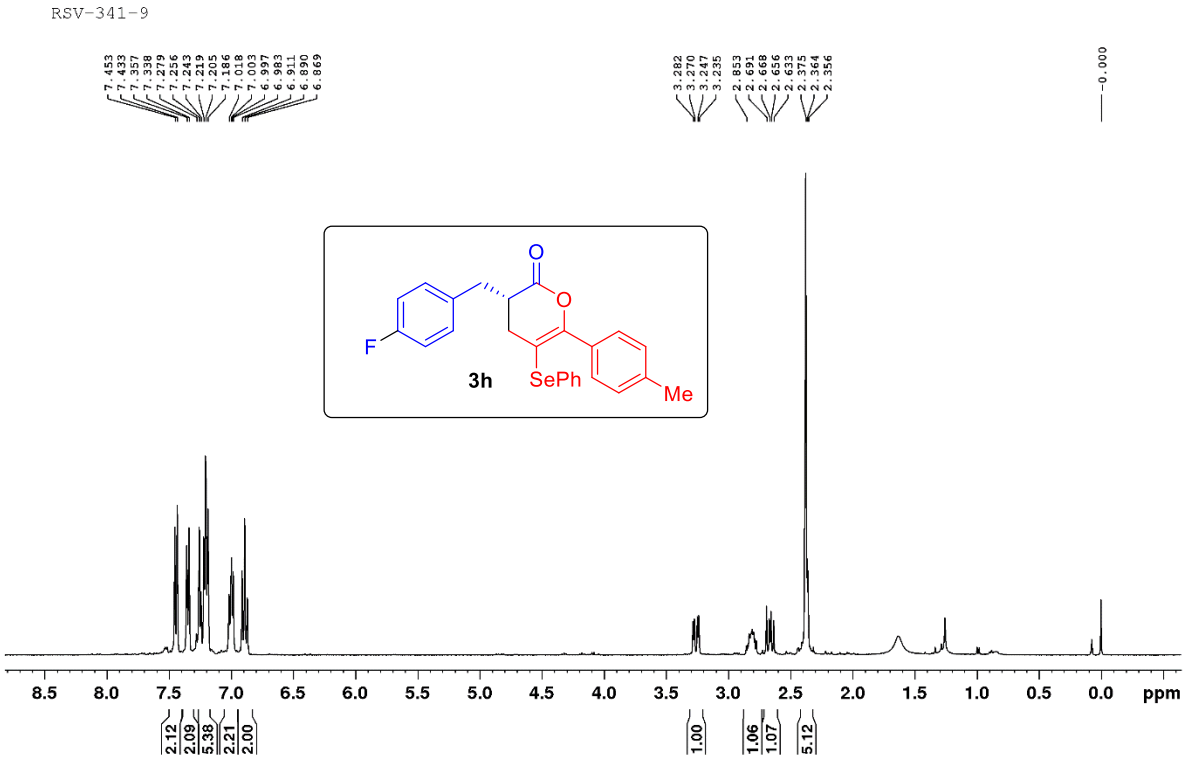
^{1}H NMR in $CDCl_3$ 400MHz 3g



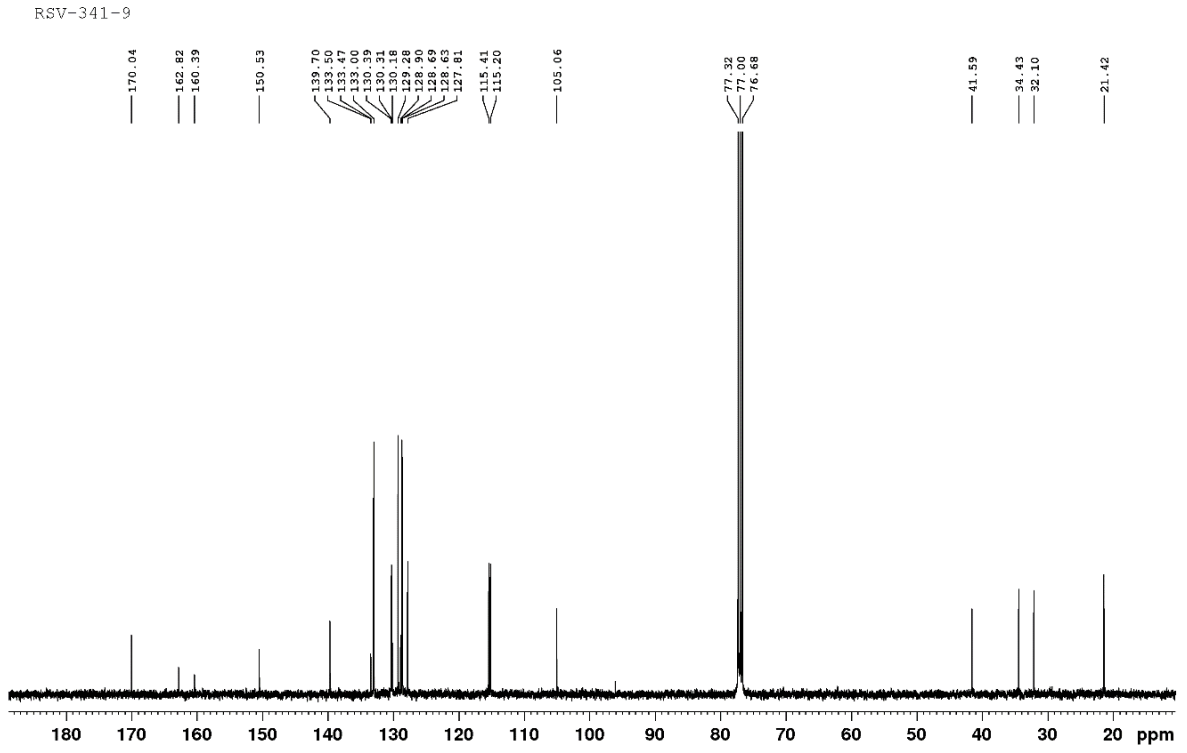
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3g



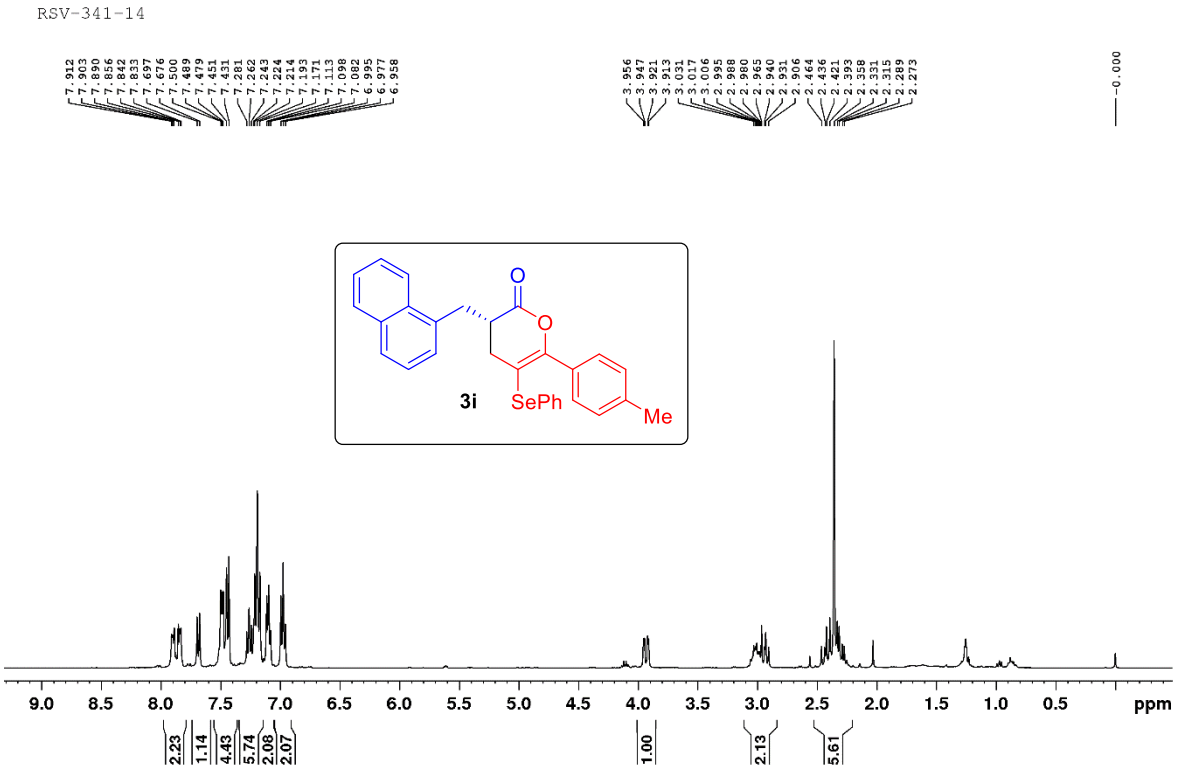
^{1}H NMR in $CDCl_3$ 400MHz 3h



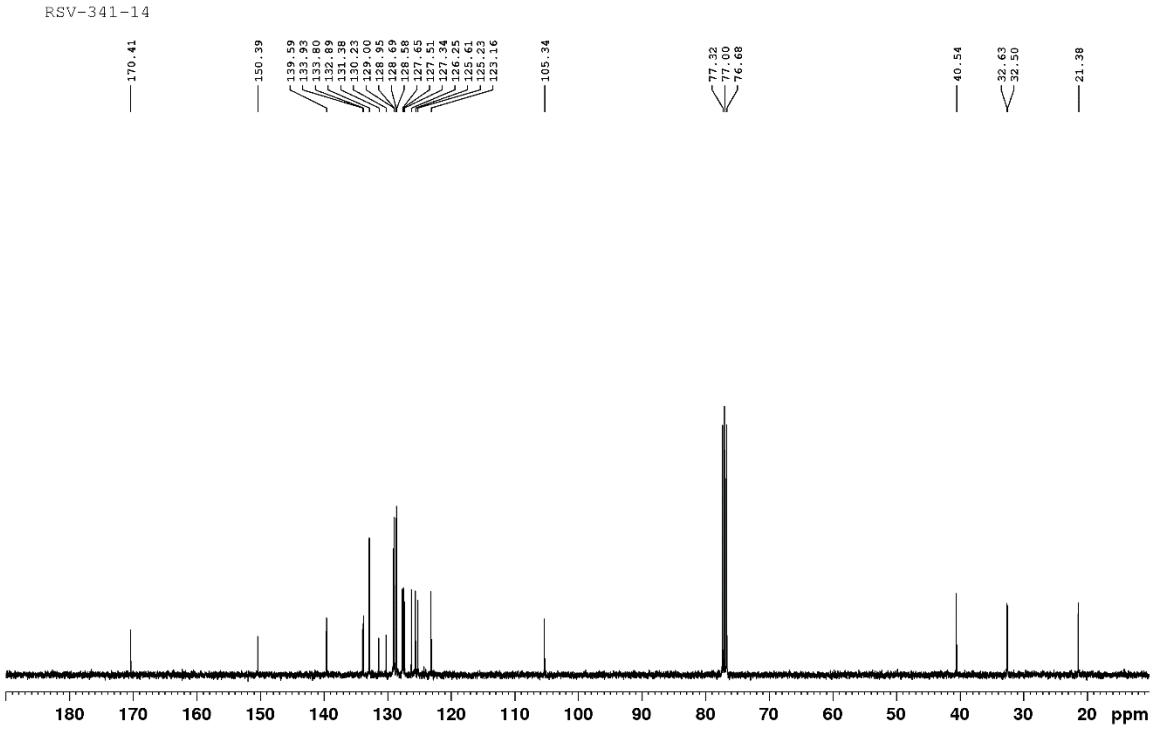
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3h



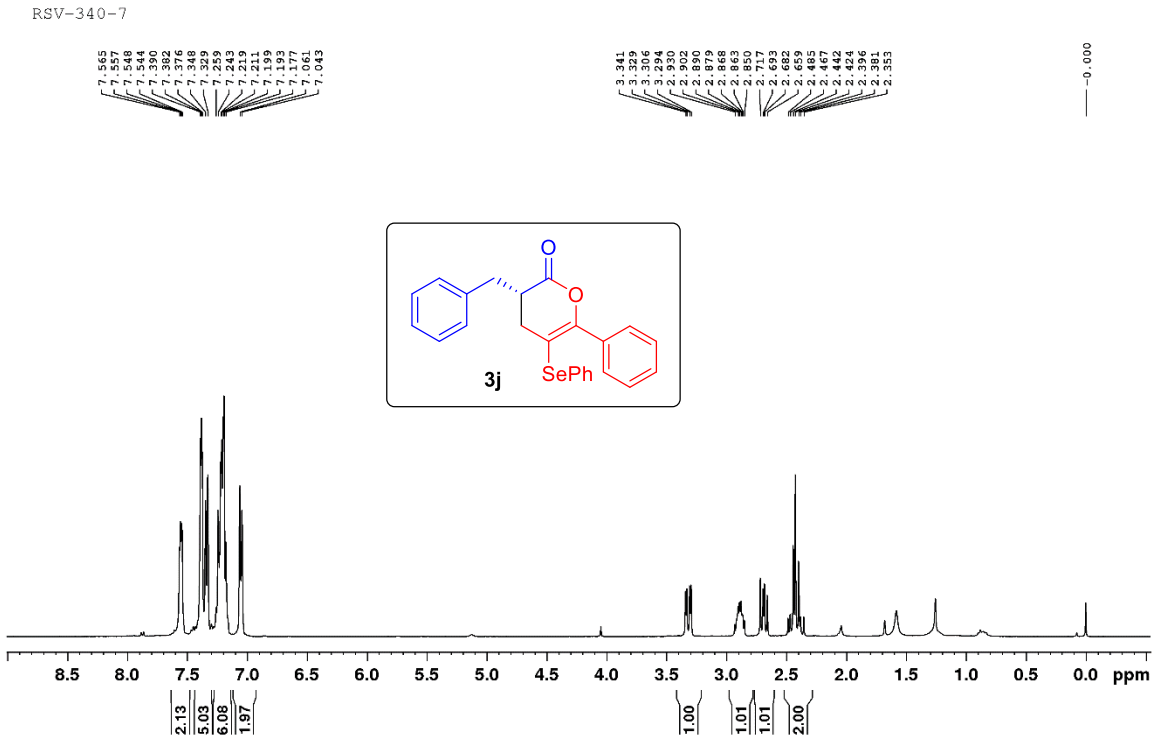
^{1}H NMR in $CDCl_3$ 400MHz 3i



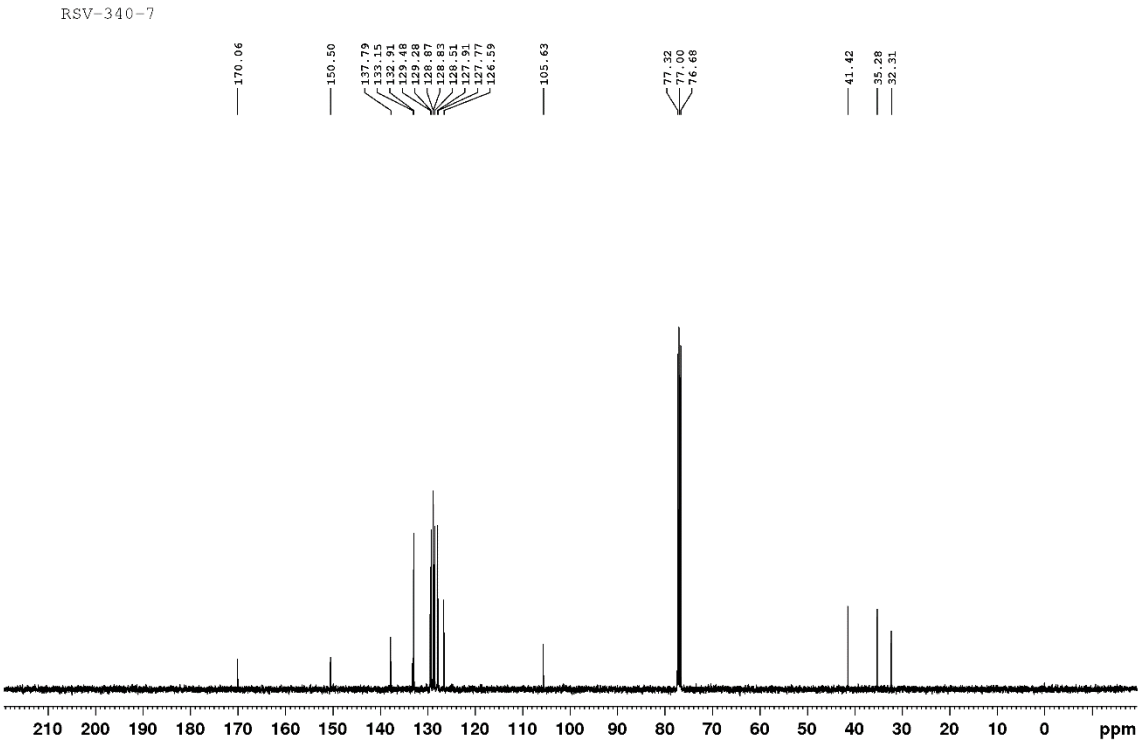
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3i



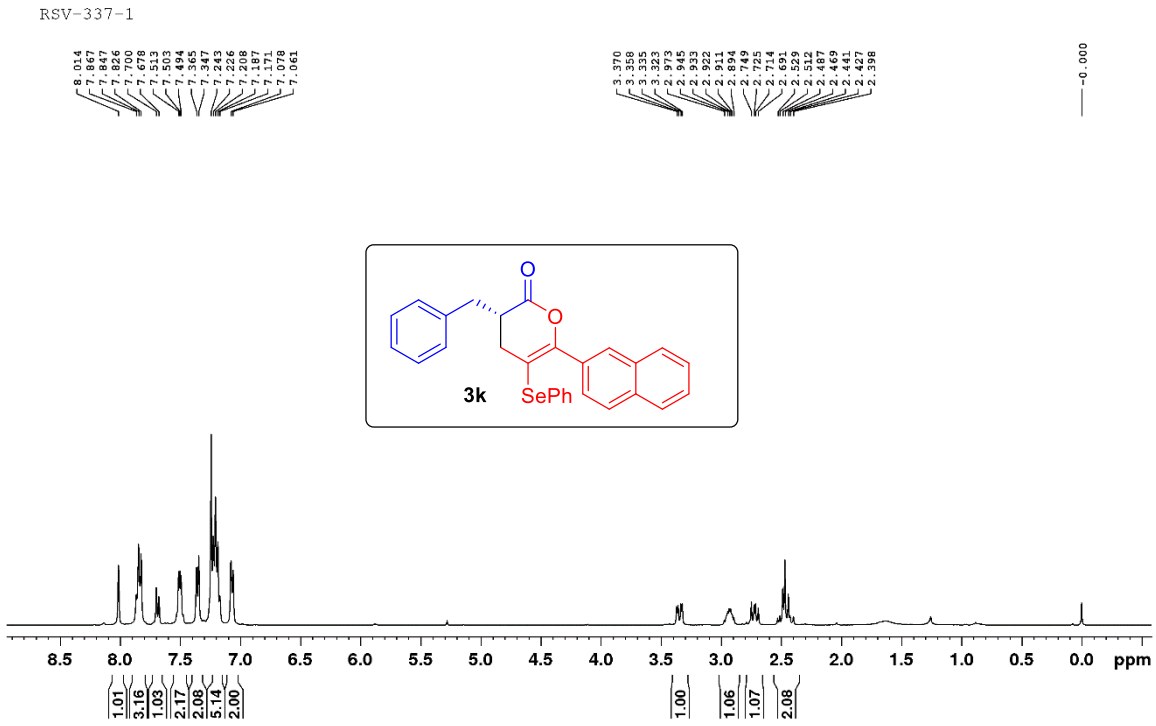
^{1}H NMR in $CDCl_3$ 400MHz 3j



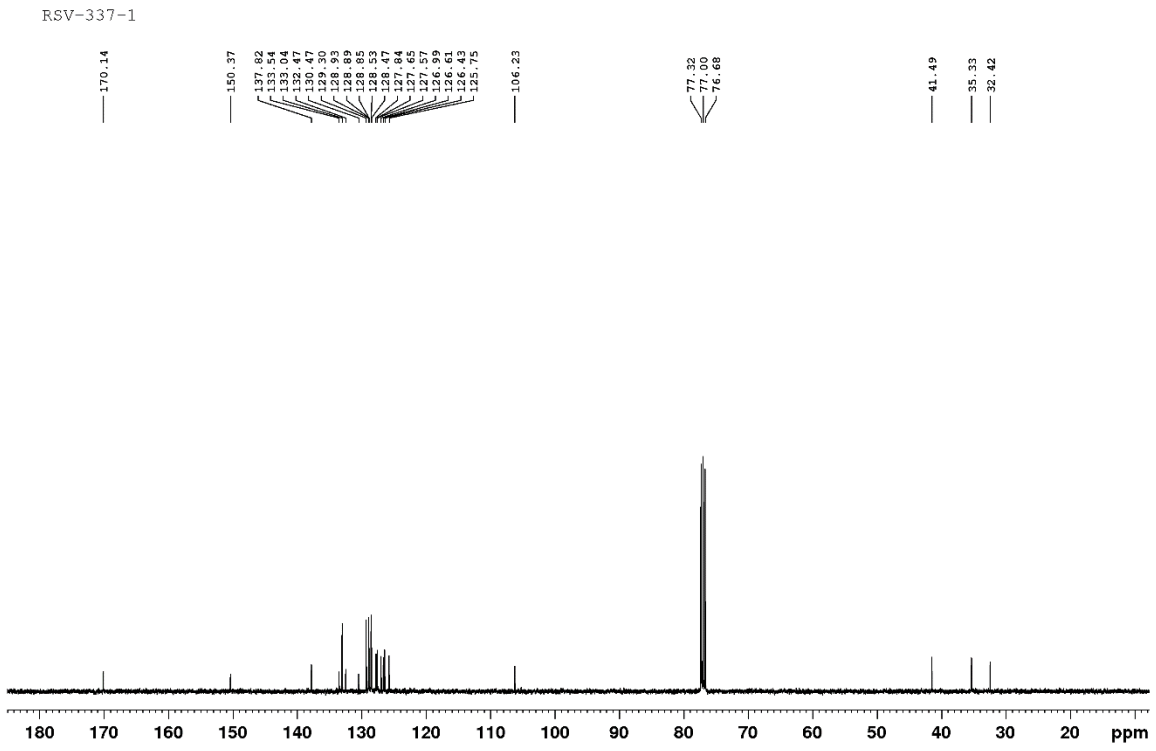
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3j



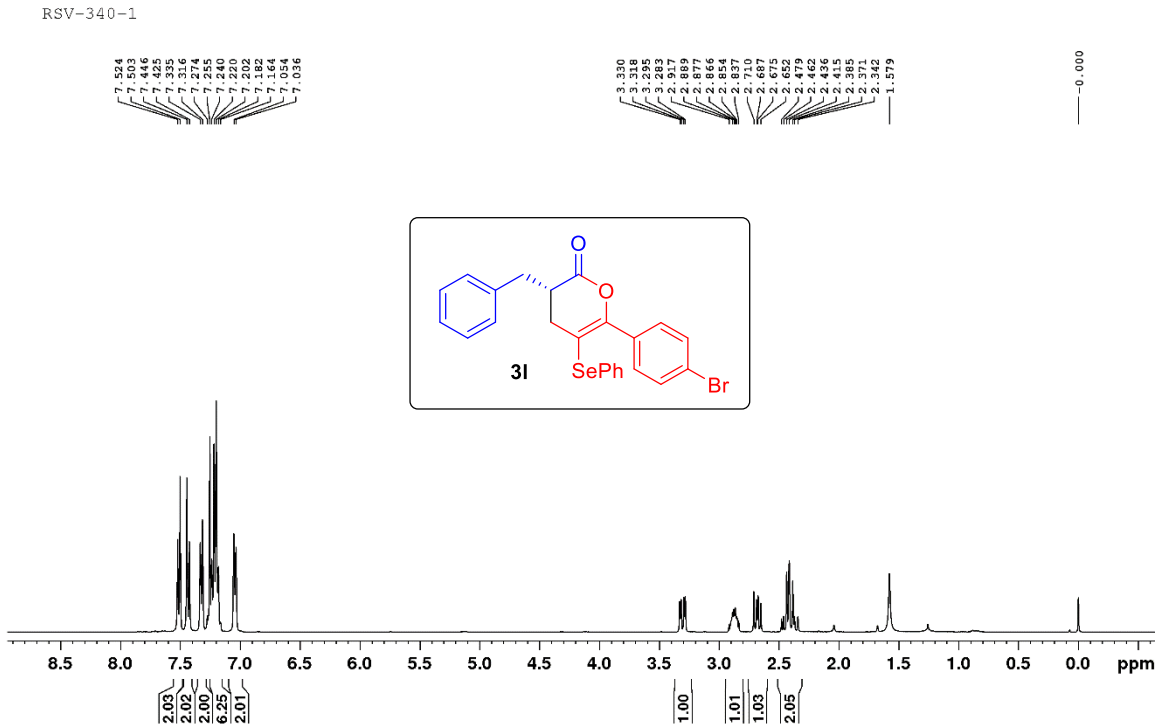
^{1}H NMR in $CDCl_3$ 400MHz 3k



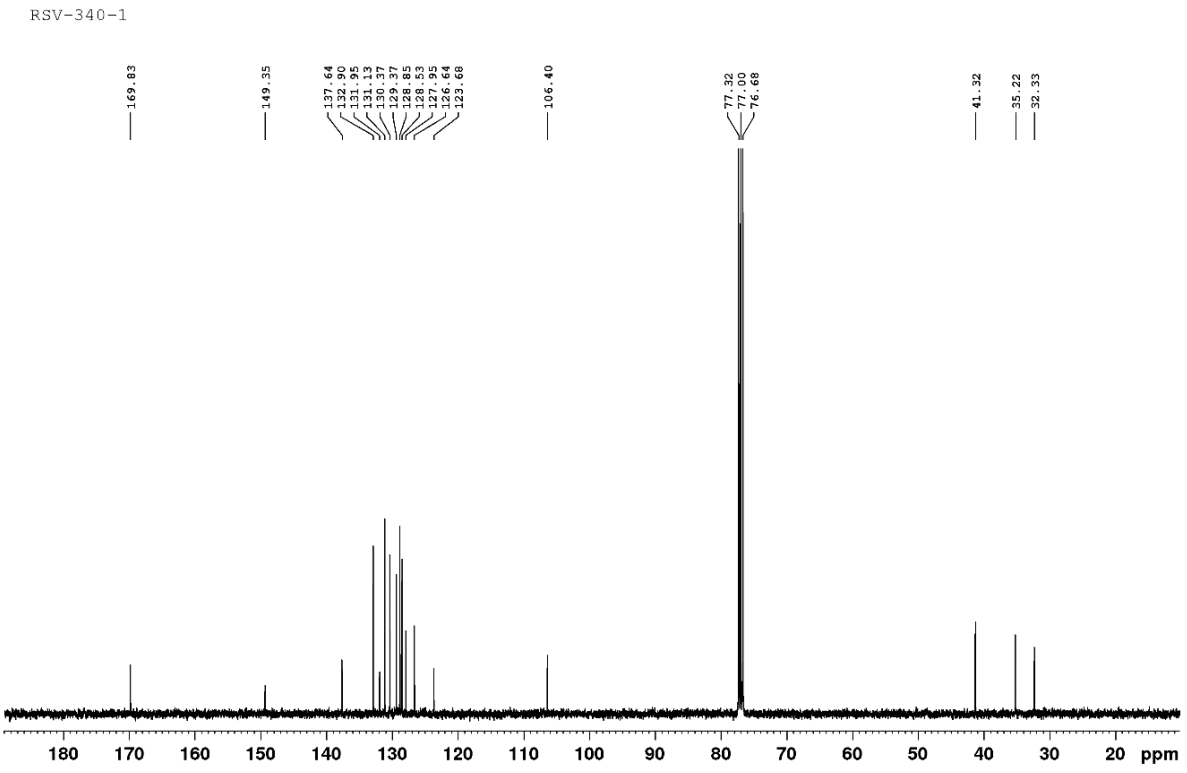
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3k



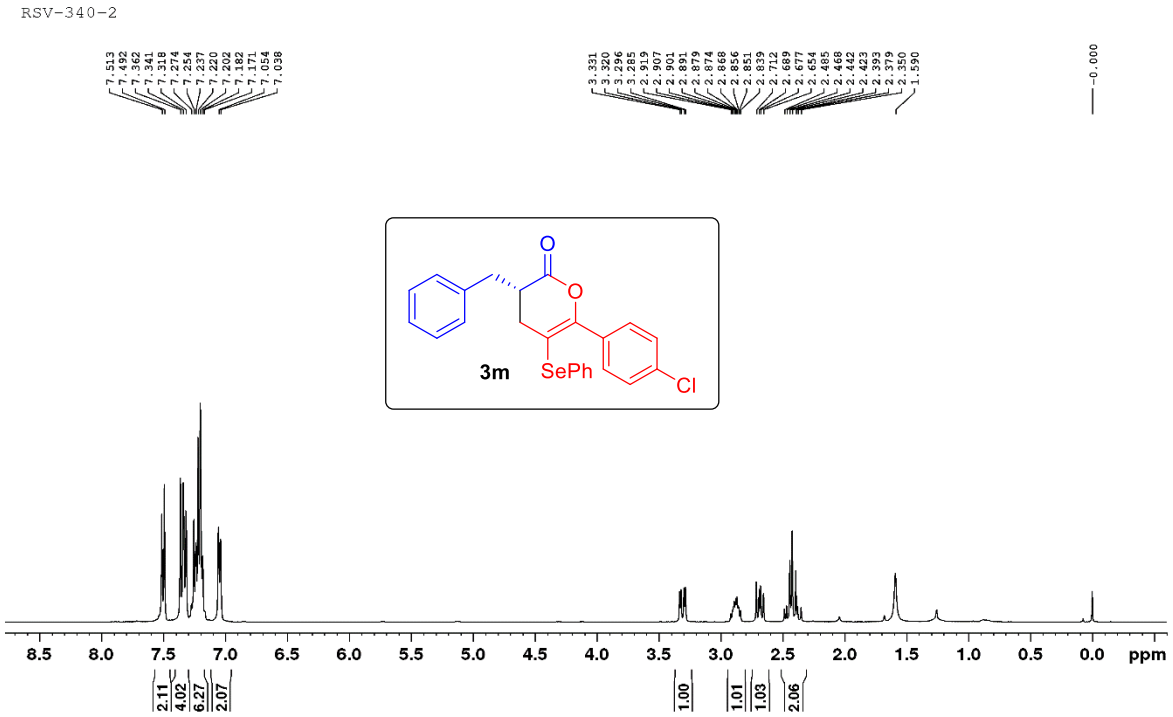
^{1}H NMR in $CDCl_3$ 400MHz 3l



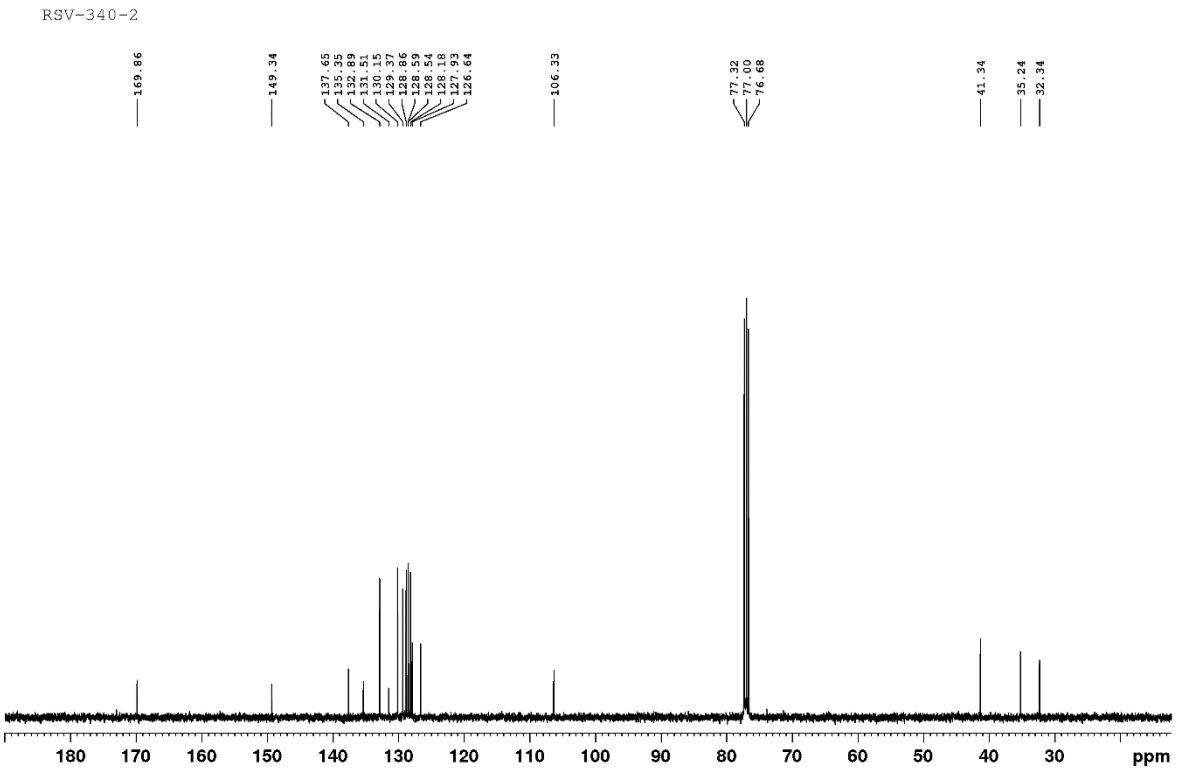
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3l



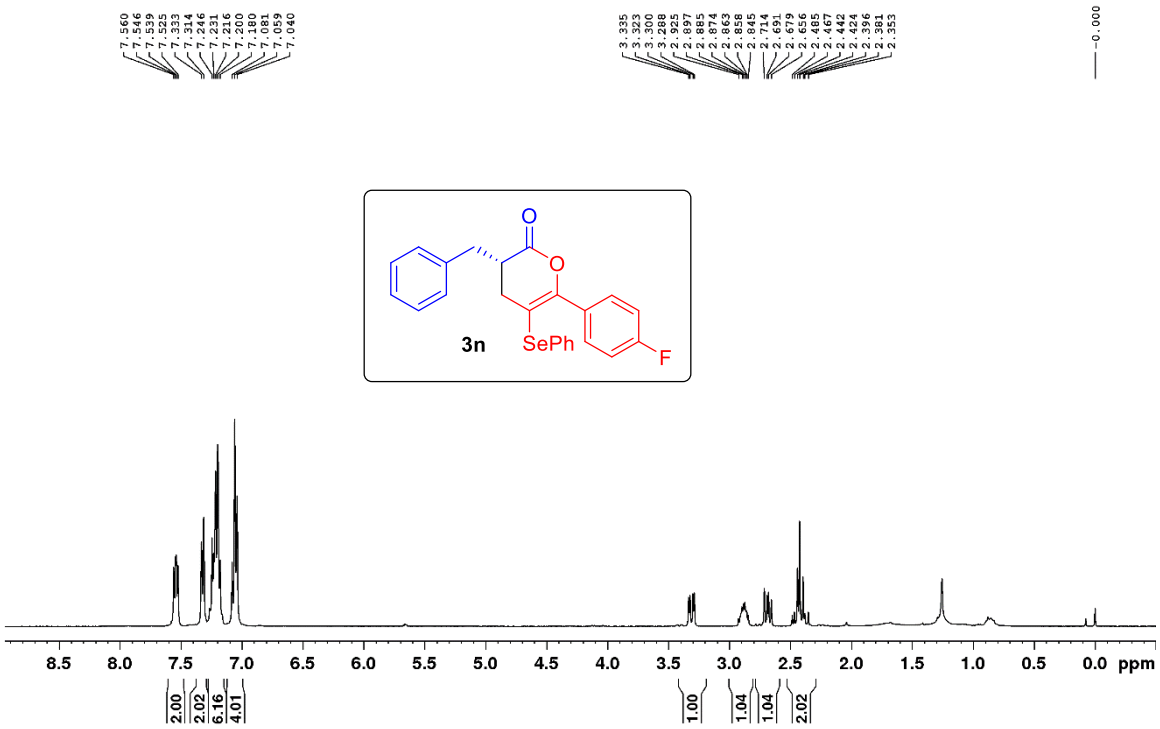
^{1}H NMR in $CDCl_3$ 400MHz 3m



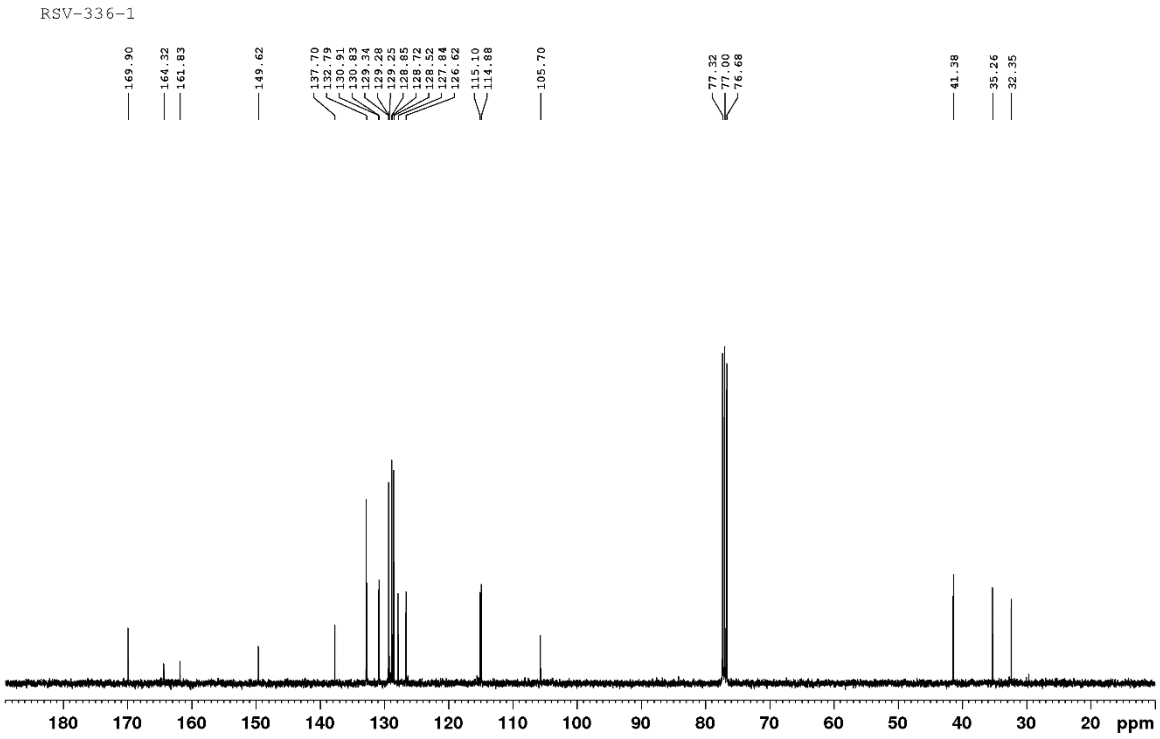
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3m



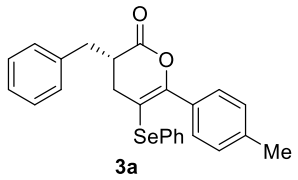
^{1}H NMR in $CDCl_3$ 400MHz 3n



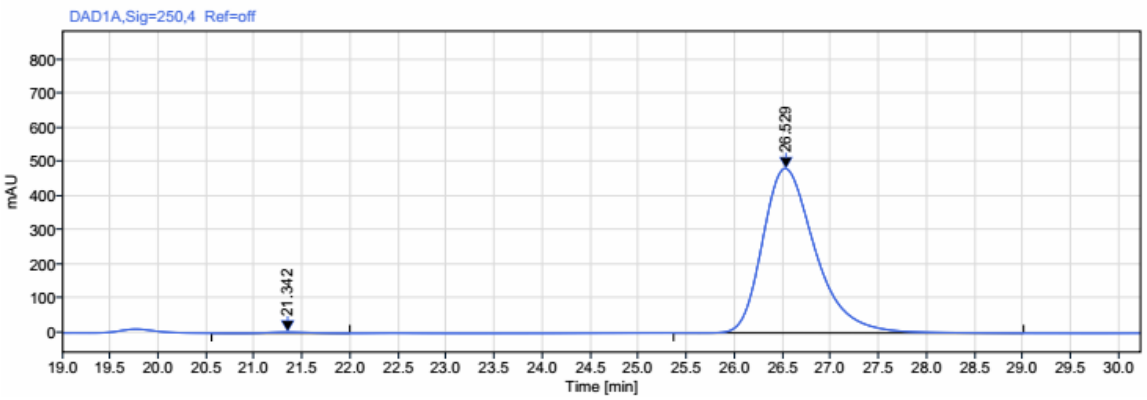
^{13}C{^{1}H} NMR in $CDCl_3$ 400MHz 3n



5.7.5. HPLC Spectra of the Products

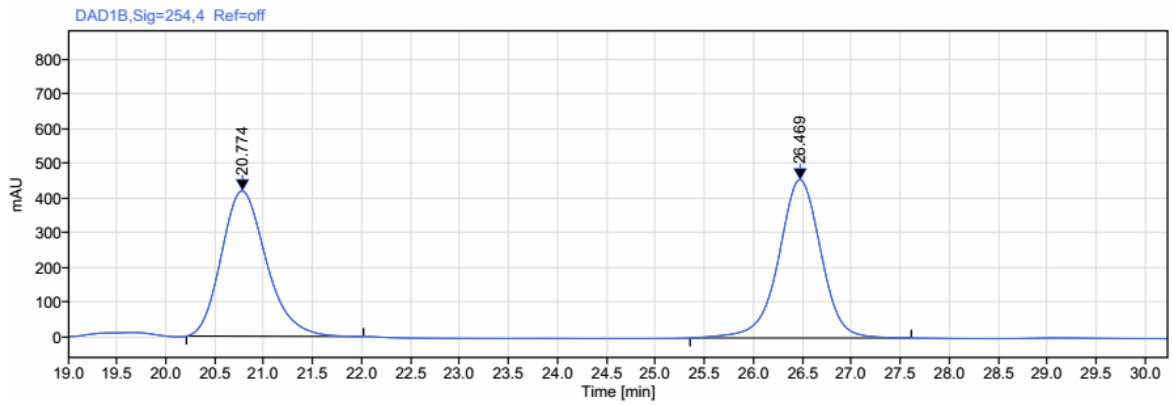


3a



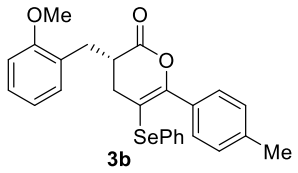
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
21.342	MM m	1.44	71.00	2.62	0.38	
26.529	BM m	3.64	18378.15	480.84	99.62	
		Sum	**18449.15**			

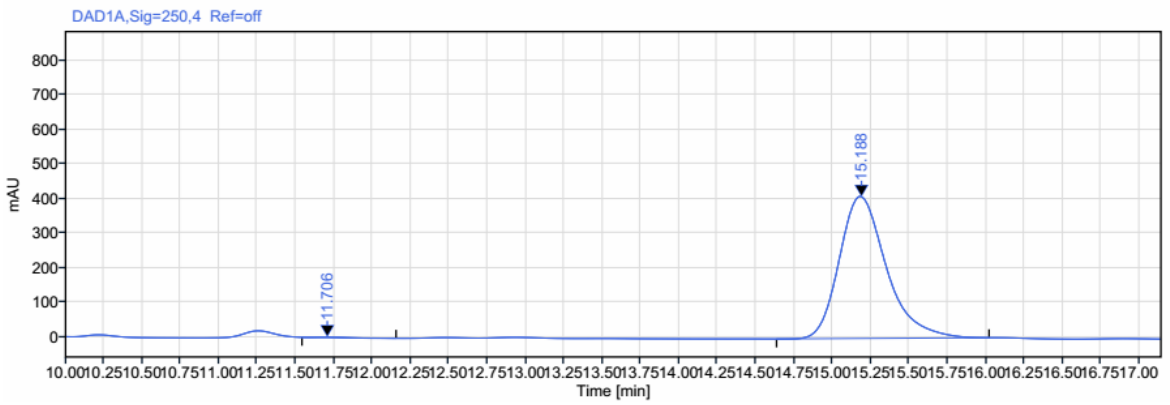


Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
20.774	MM m	1.81	13304.07	417.23	49.22	
26.469	MM m	2.26	13723.84	454.04	50.78	
		Sum	**27027.91**			

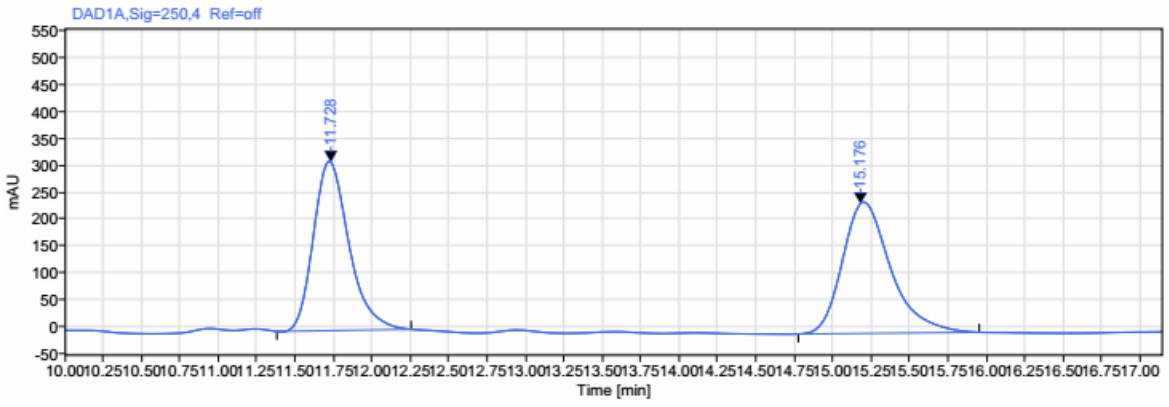


3b



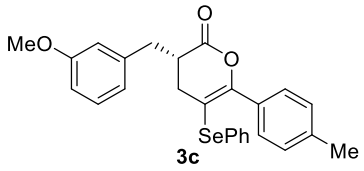
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
11.706	MM m	0.61	4.81	1.14	0.05	
15.188	MM m	1.39	8767.23	409.09	99.95	
		Sum	**8772.04**			

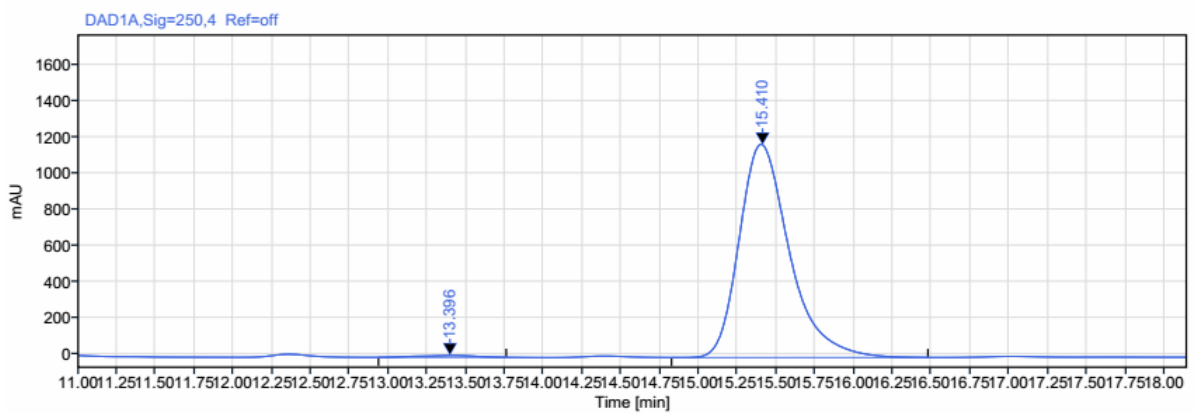


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
11.728	MM m	0.87	5040.22	311.05	48.81	
15.176	MM m	1.18	5285.29	238.77	51.19	
		Sum	**10325.50**			

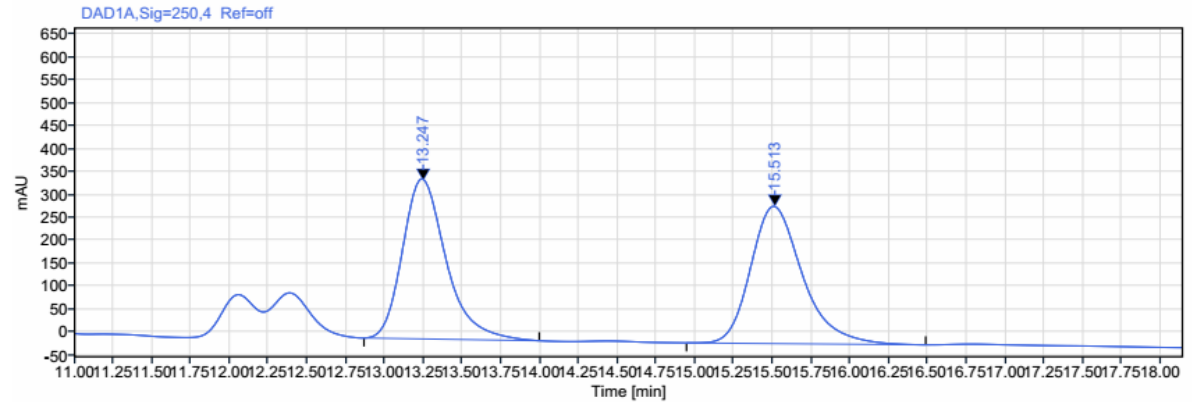


3c



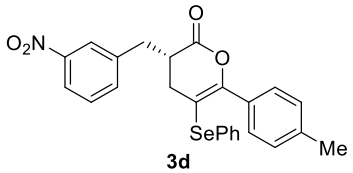
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
13.396	MM m	0.82	260.72	10.57	0.97	
15.410	MM m	1.65	26525.45	1176.09	99.03	
		Sum	**26786.16**			

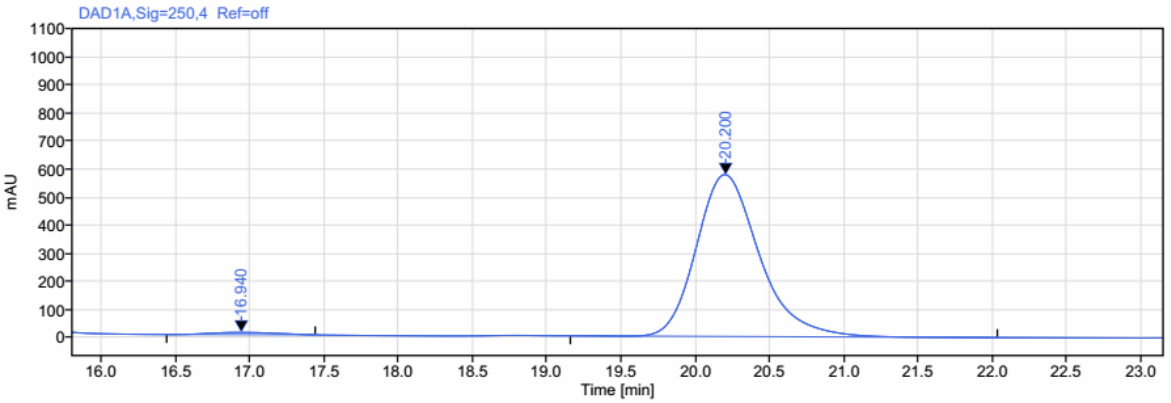


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
13.247	MM m	1.13	6810.59	344.52	49.48	
15.513	MM m	1.54	6954.33	298.37	50.52	
		Sum	**13764.92**			

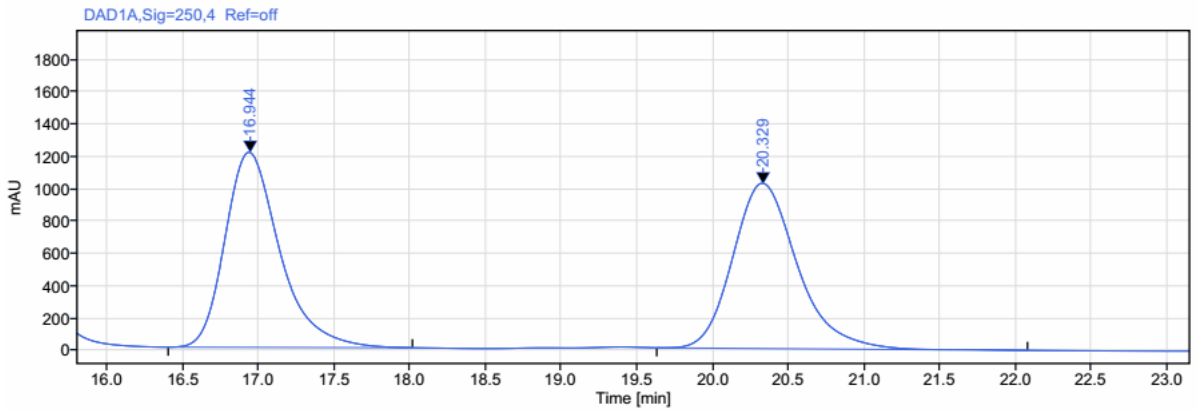


3d



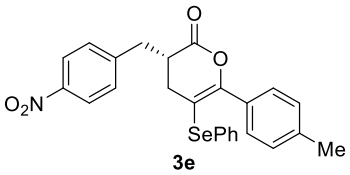
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
16.940	MM m	1.00	240.09	7.77	1.39	
20.200	MM m	2.87	16982.90	574.77	98.61	
		Sum	**17222.99**			

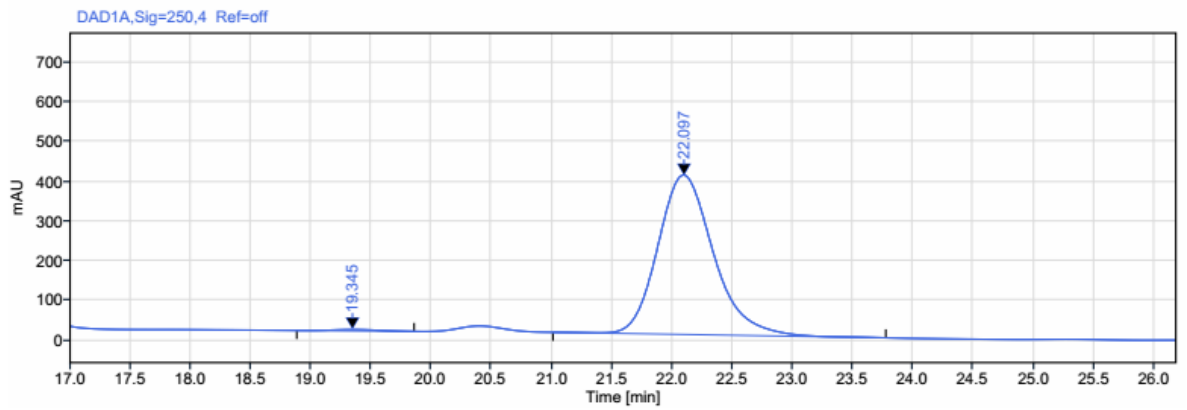


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
16.944	MM m	1.61	30317.03	1202.72	49.97	
20.329	MM m	2.45	30347.64	1015.25	50.03	
		Sum	**60664.67**			

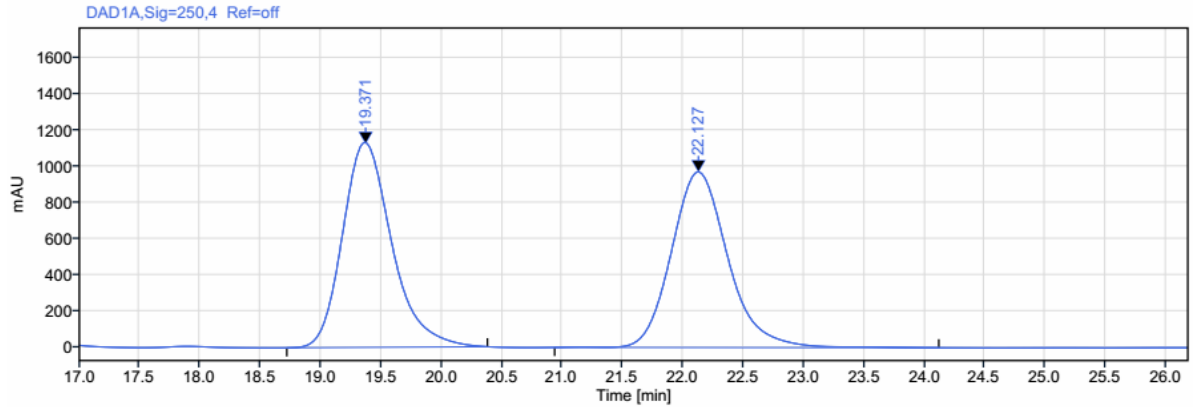


3e



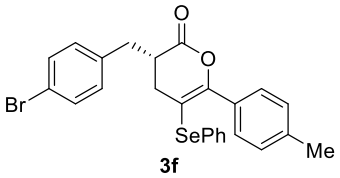
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
19.345	MM m	0.97	87.90	3.31	0.68	
22.097	MM m	2.76	12863.03	398.97	99.32	
		Sum	**12950.93**			

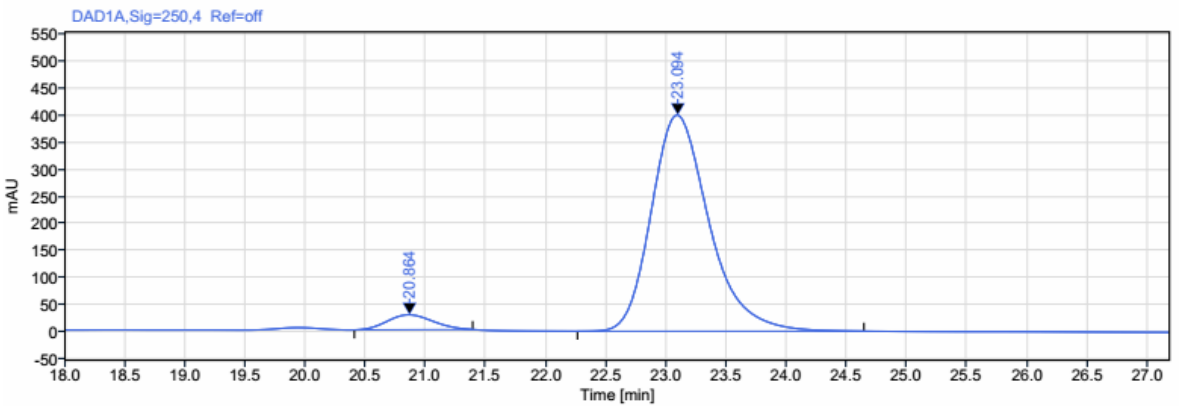


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
19.371	MM m	1.66	32104.70	1122.36	50.41	
22.127	MM m	3.18	31579.60	966.91	49.59	
		Sum	**63684.30**			

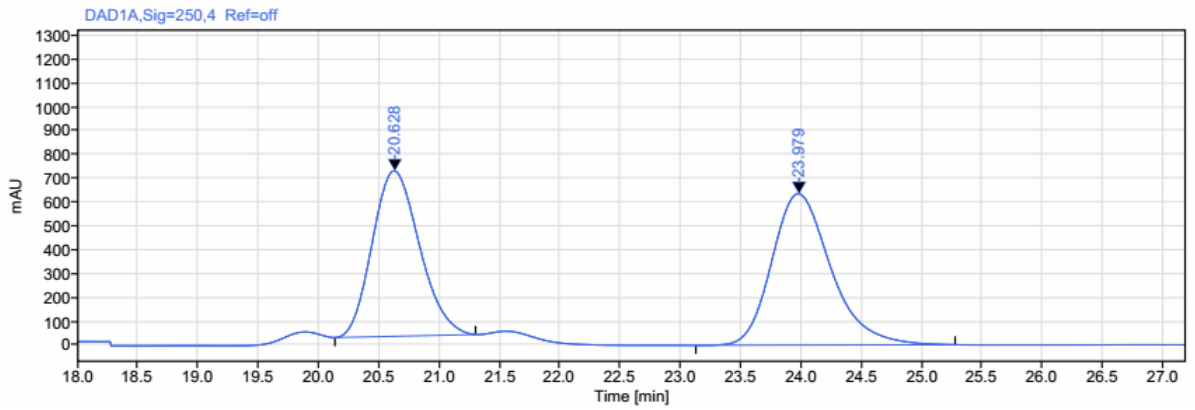


3f



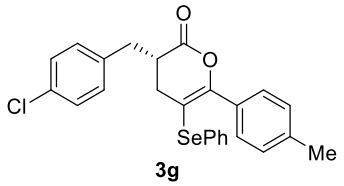
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
20.864	MM m	0.98	726.30	27.26	5.18	
23.094	MM m	2.38	13286.21	397.65	94.82	
		Sum	**14012.51**			

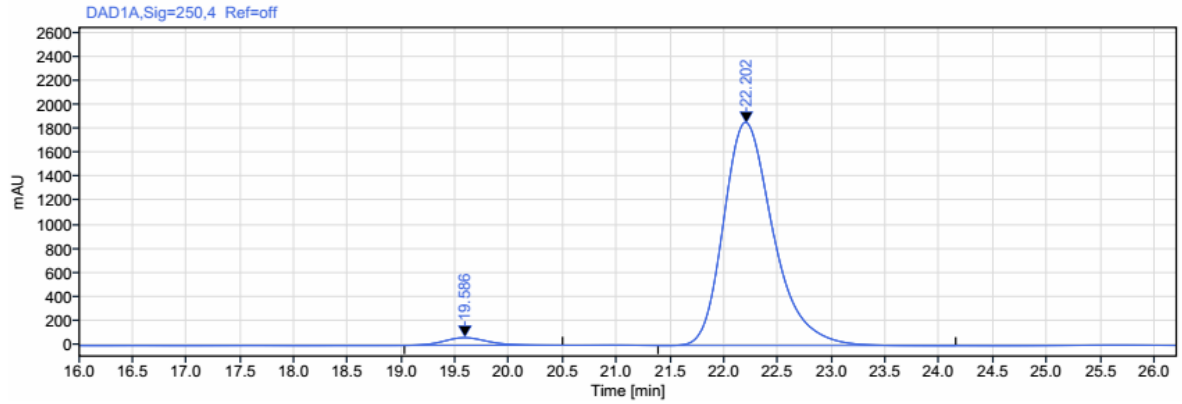


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
20.628	MM m	1.17	18837.42	692.12	46.63	
23.979	MM m	2.15	21563.06	633.51	53.37	
		Sum	**40400.48**			

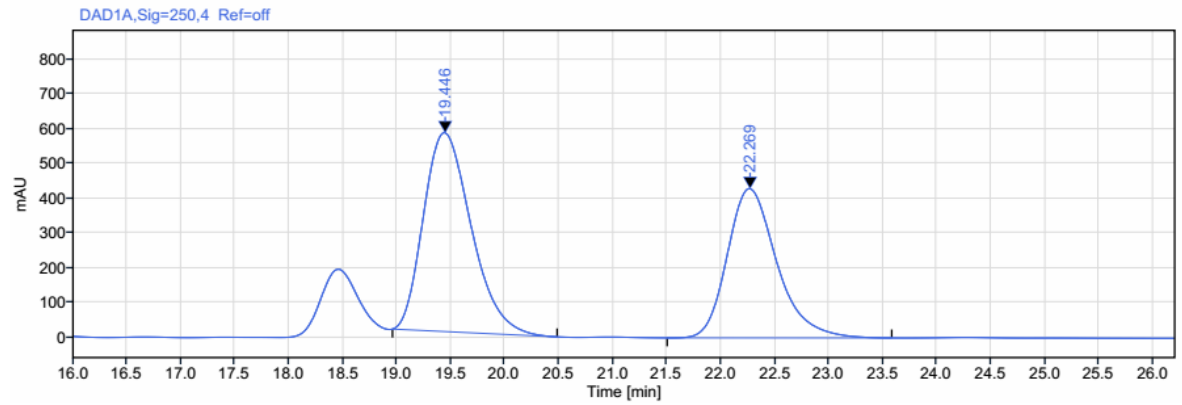


3g



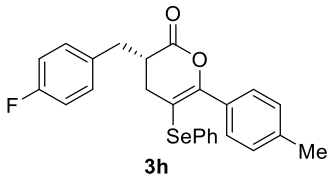
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
19.586	MM m	1.47	1812.58	63.26	2.96	
22.202	MM m	2.77	59504.10	1844.74	97.04	
		Sum	**61316.69**			

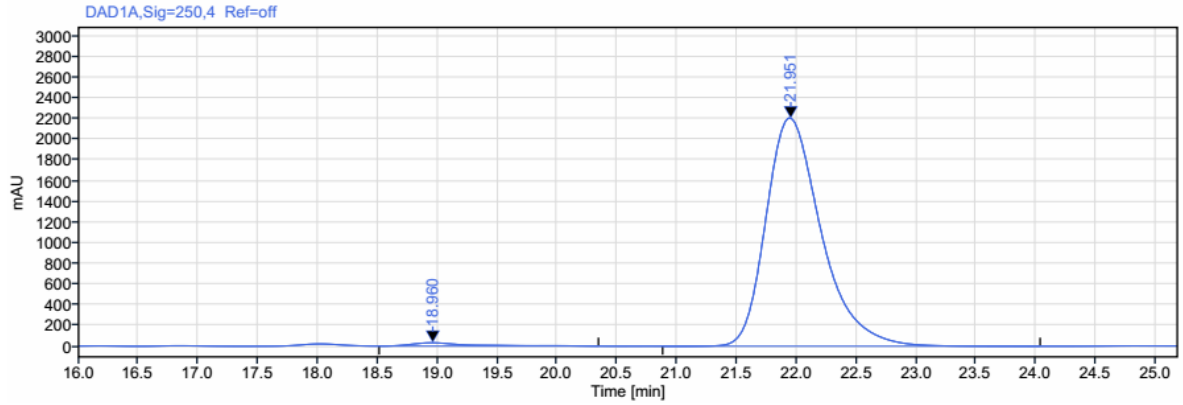


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
19.446	MM m	1.52	17578.13	570.40	56.25	
22.269	MM m	2.08	13670.92	427.89	43.75	
		Sum	**31249.04**			

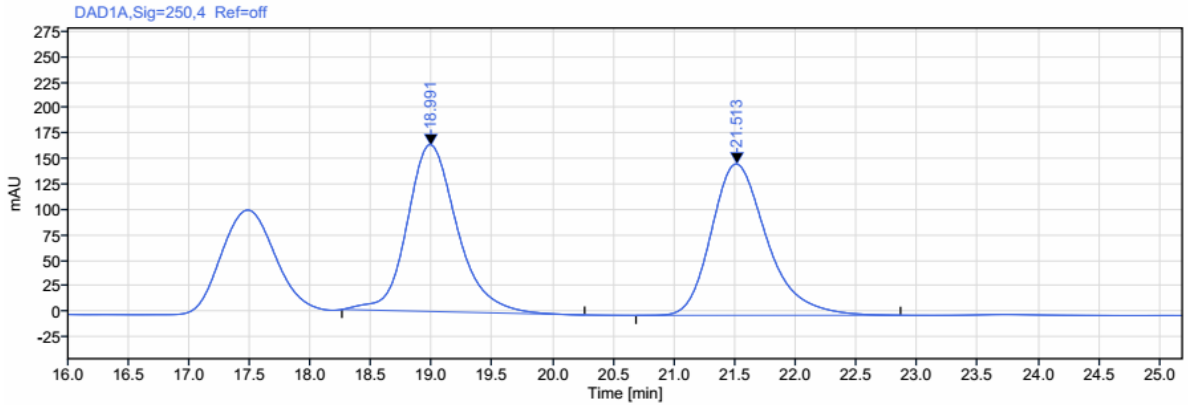


3h



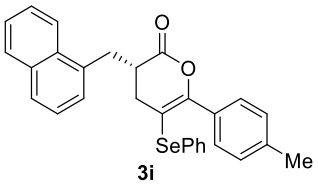
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.960	MM m	1.83	1019.00	31.44	1.42	
21.951	MM m	3.15	70557.84	2197.97	98.58	
		Sum	**71576.84**			

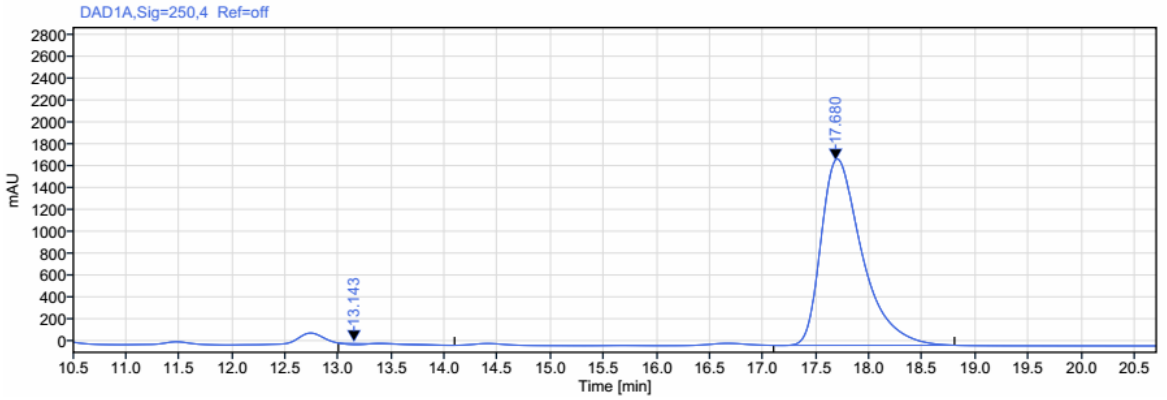


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.991	MM m	2.00	4688.95	162.34	49.77	
21.513	MM m	2.18	4731.77	148.03	50.23	
		Sum	**9420.71**			

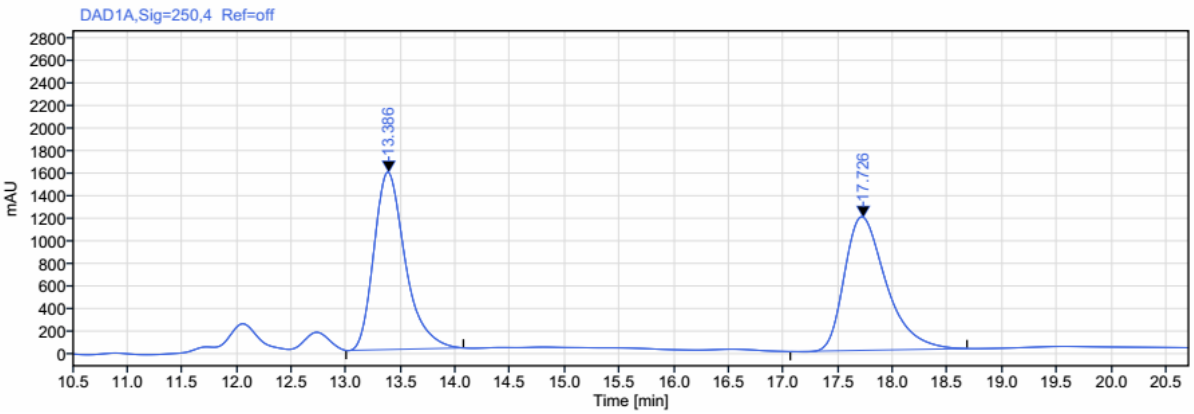


3i



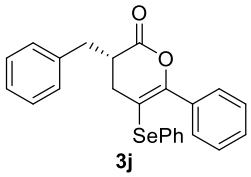
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
13.143	MM n	1.09	114.56	10.86	0.25	
17.680	MM m	1.70	45471.64	1680.78	99.75	
		Sum	**45586.20**			

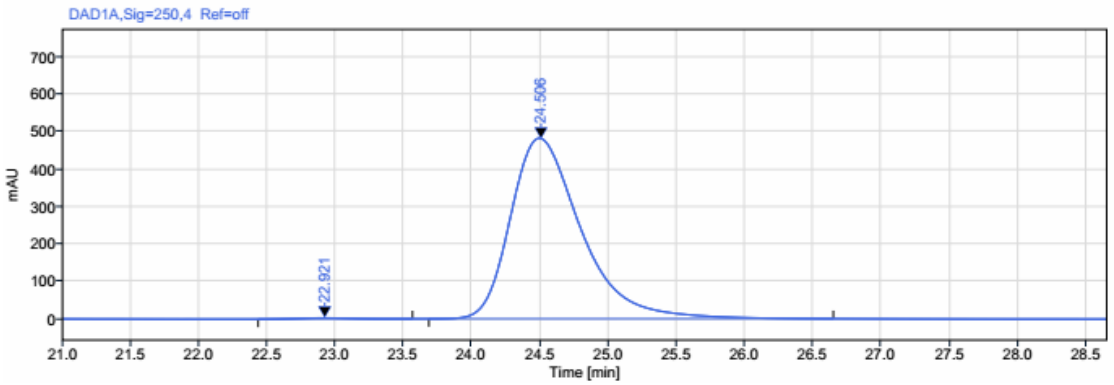


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
13.386	MM m	1.07	31165.66	1557.16	50.00	
17.726	MM m	1.62	31167.61	1165.96	50.00	
		Sum	**62333.27**			

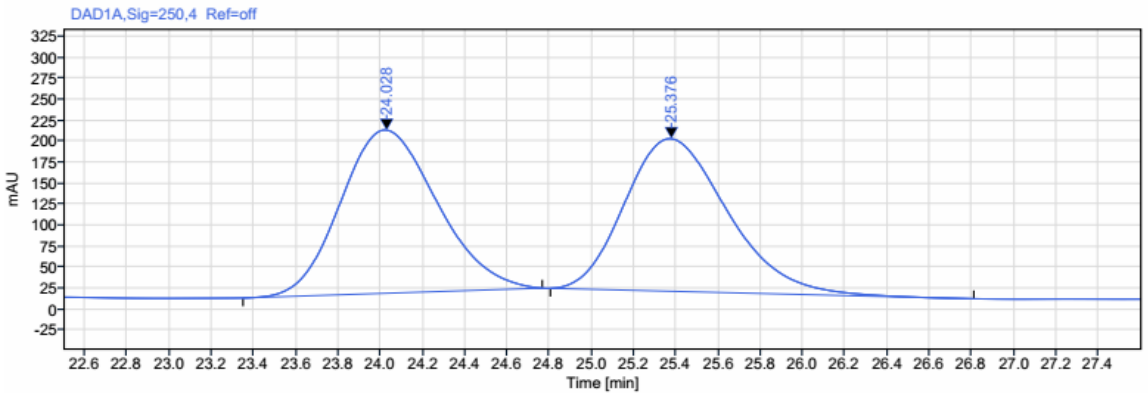


3j



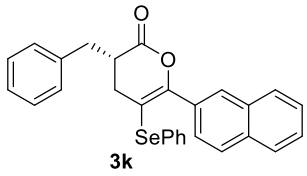
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
22.921	MM m	1.13	73.93	2.77	0.43	
24.506	MM m	2.96	17288.58	479.42	99.57	
		Sum	**17362.51**			

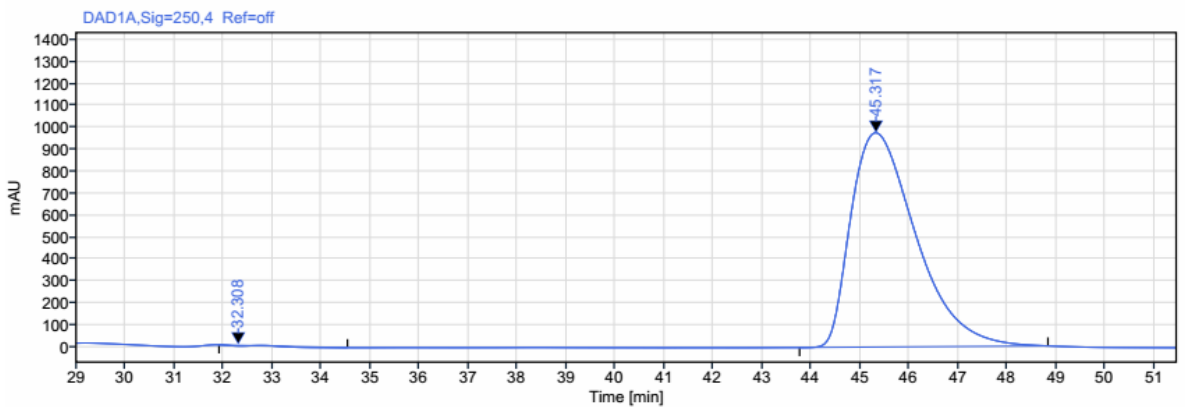


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
24.028	MM m	1.42	6174.14	193.72	50.10	
25.376	MM m	2.01	6148.56	181.47	49.90	
		Sum	**12322.70**			

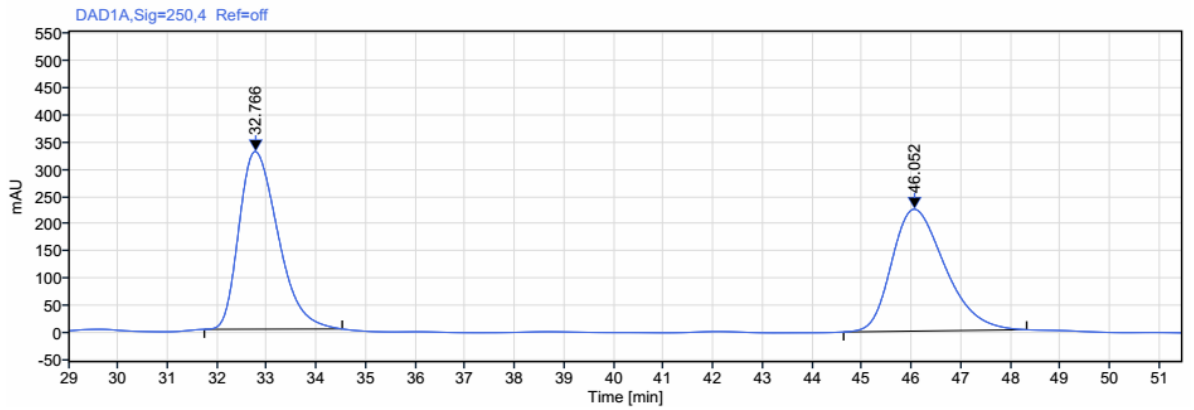


3k



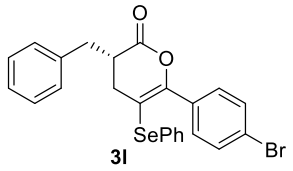
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
32.308	MM n	2.62	223.57	3.35	0.25	
45.317	MM m	5.07	90001.23	975.78	99.75	
		Sum	**90224.79**			

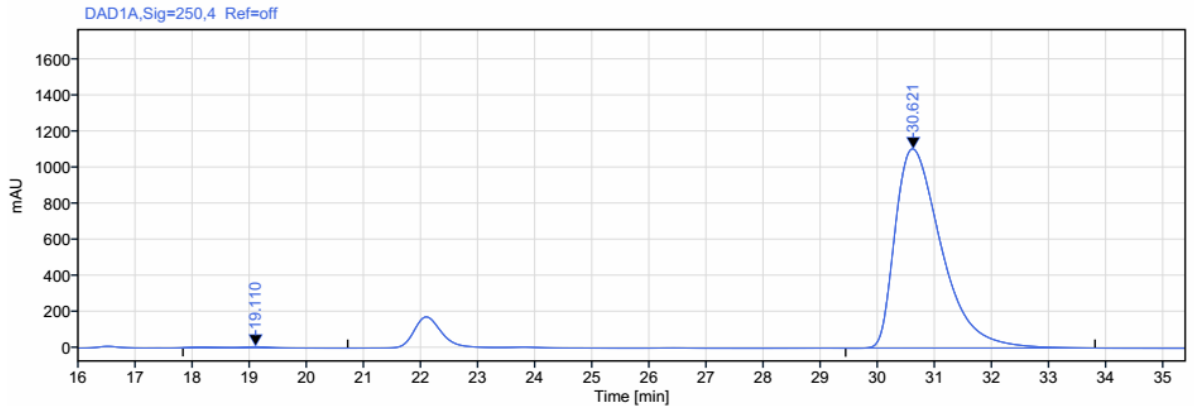


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
32.766	MM m	2.78	17772.72	324.60	51.68	
46.052	MM m	3.69	16614.58	222.92	48.32	
		Sum	**34387.30**			

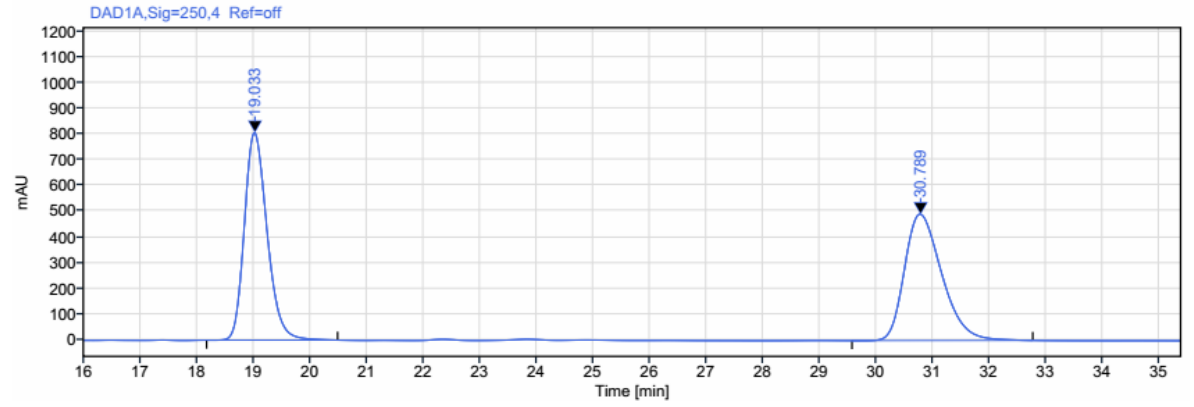


3l



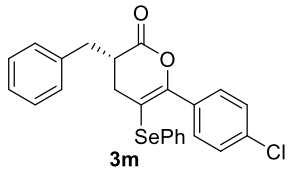
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
19.110	MM m	2.88	297.35	6.75	0.48	
30.621	MM m	4.36	62100.85	1101.89	99.52	
		Sum	**62398.20**			

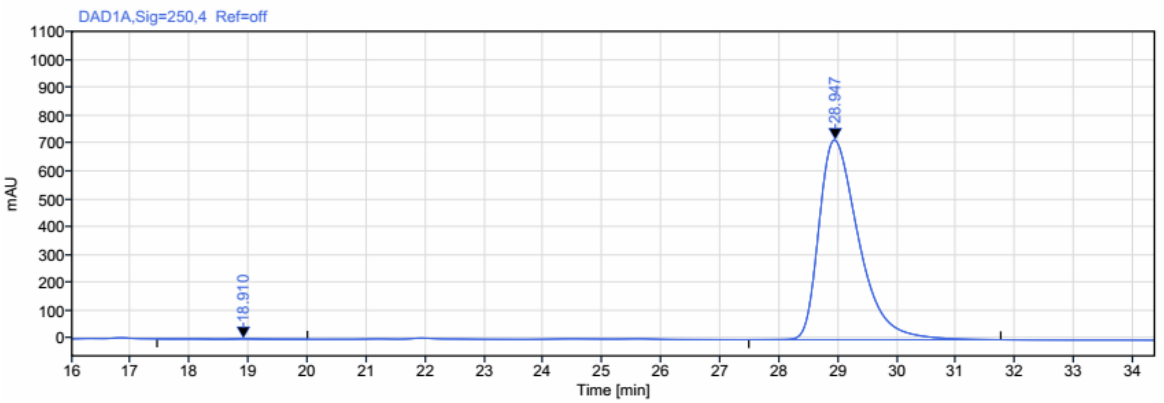


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
19.033	MM m	2.31	22453.89	805.37	50.03	
30.789	MM m	3.19	22430.74	489.51	49.97	
		Sum	**44884.63**			

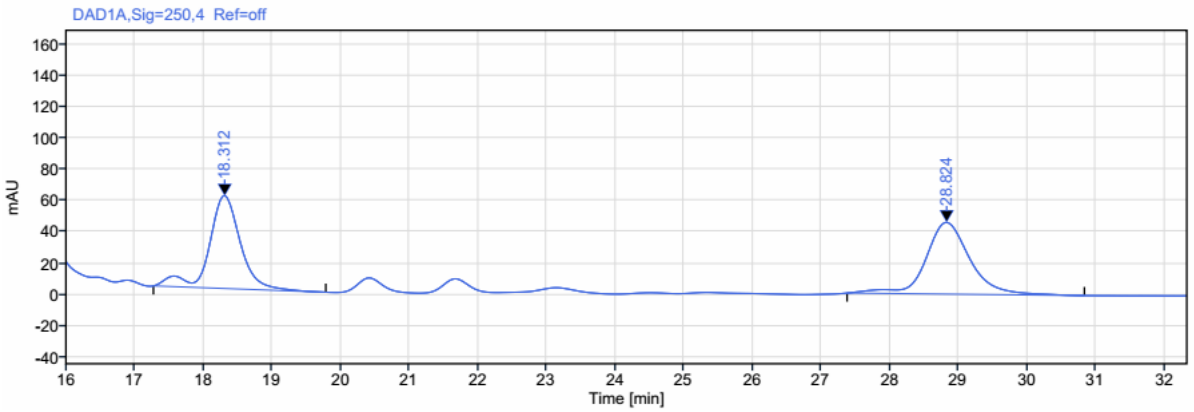


3m



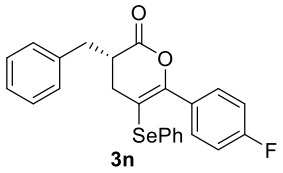
Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.910	MM m	2.55	12.35	1.33	0.04	
28.947	MM m	4.27	33513.07	716.30	99.96	
		Sum	**33525.42**			

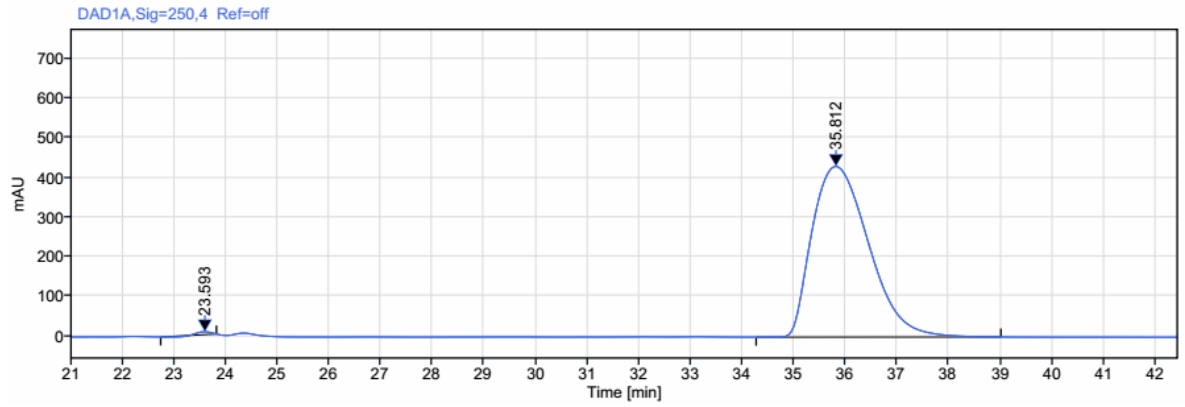


Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.312	MM m	2.51	1880.72	58.90	48.01	
28.824	MM m	3.46	2036.99	45.63	51.99	
		Sum	**3917.70**			

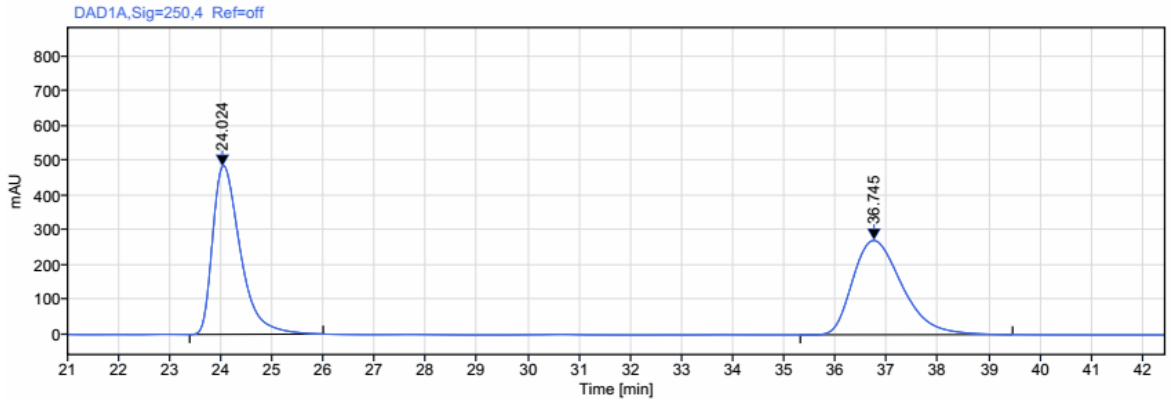


3n



Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
23.593	MM m	1.08	91.49	7.08	0.28	
35.812	MM m	4.74	32789.00	430.24	99.72	
		Sum	**32880.49**			



Signal: DAD1A,Sig=250,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
24.024	MM m	2.61	18198.67	482.22	50.05	
36.745	MM m	4.14	18160.13	270.91	49.95	
		Sum	**36358.79**			

5.8. References

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(21) CCDC 2057769 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/daa_request/cif.

List of Publications:

1. Verma, R. S.; Khatana, A. K.; Mishra, M.; Kumar S.; Tiwari B. Access to enantioenriched 4-phosphorylated δ-lactones from β-phosphorylenones and enals *via* carbene organocatalysis. *Chem. Commun.* **2020**, *56*, 7155-7158.

2. Verma, R. S.; Mishra, M.; Pandey, C. B.; Kumar S.; Tiwari B. Global Access to 3/4-Phosphorylated Heterocycles via a Carbene-Catalyzed Stetter Reaction of Vinylphosphonates and Aldehydes. *J. Org. Chem.* **2020**, *85*, 8166–8175.

3. Pandey, C. B., Azaz T.; Verma, R. S.; Mishra M.; Jat, J. L.; Tiwari B. Stereoselective Oxidative Rearrangement of Disubstituted Unactivated Alkenes Using Hypervalent Iodine (III) Reagent. *J. Org. Chem.* **2020**, *85*, 10175–10181.

4. Singh, V.; Verma, R. S.; Khatana, A. K.; Tiwari B. Construction of Phenanthrenes and Chrysenes from β-Bromovinylarenes via Aryne Diels–Alder Reaction/Aromatization. *J. Org. Chem.* **2019**, *84*, 14161–14167.

5. Verma, R. S.; Pandey, C. B.; Kumar S.; Tiwari B. Carbene-Catalyzed Tandem [1,2]-Phospha-Brook/[1,4]-Phosphate Rearrangement: Access to α-Ketophosphates via Controlled Cross- Acyloin Condensation. *J. Org. Chem.* **2018**, *83*, 9478–9483.

6. Bhaumik, A.; Verma, R. S. Tiwari, B. Direct Construction of 2,3-Dihydroxy-2,3-diaryltetrahydrofurans via *N*-Heterocyclic Carbene/Base-Mediated Domino Reactions of Aromatic Aldehydes and Vinyl Selenone. *Org. Lett.* **2017**, *19*, 444-447.

7. Verma, R. S.; Khatana, A. K.; Tiwari B. One-Pot Metal-Free Construction of Functionalized 3-Pyridylphosphonates (Manuscript under submission).

8. Verma, R. S.; Mishra, M.; Talukdar, R.; Kumar S.; Tiwari B. Carbene catalyzed Enantioselective Synthesis of Selenylated δ-Lactones from Vinyl selenides and Enals (Manuscript under submission).

Attended Conferences and Workshop:

1. XIII J-NOST Conference held at Department of Chemistry Institute of Science Banaras Hindu University, Varanasi, India (9-12th Nov' 2017). Topic of the presented poster: *Direct Construction of 2,3-Dihydroxy-2,3-diaryltetrahydrofurans via N-Heterocyclic Carbene/Base-Mediated Domino Reactions of Aromatic Aldehydes and Vinyl Selenone.*

2. Participated in Science of Synthesis Workshop held at Centre of Biomedical Research, Lucknow, India (25th Sep'2018).

3. Global Conference on the Control of Green House Gases at the Source by Physical and Chemical Technology in Chemistry held at Babasaheb Bhimrao Ambedkar University, Lucknow, India (22nd April 2019). Topic of the oral presentation: *Carbene-Catalyzed Tandem [1,2]-Phospha-Brook/[1,4]-Phosphate Rearrangement: Access to α-Ketophosphates via Controlled Cross-Acyloin Condensation J. Org. Chem. 2018, 83, 9478–9483.*

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Access to enantioenriched 4-phosphorylated δ-lactones from β-phosphorylenones and enals *via* carbene organocatalysis†

Ram Subhawan Verma,[a] Anil Kumar Khatana,[a] Monika Mishra,[a] Shailesh Kumar[b] and Bhoopendra Tiwari *[a]

N-heterocyclic carbene (NHC) catalyzed direct access to enantioenriched 4-phosphorylated δ-lactones from β-phosphorylenones and enals has been achieved. The sterically demanding β-phosphonate-substituted enones, having competing regiomeric reaction centres, have remained elusive so far in intermolecular cycloaddition reactions under NHC catalysis. All the products were obtained in excellent yield and enantioselectivity. These phosphorylated δ-lactones could be transformed into challenging multi-functionalized chiral esters and amides loaded with a β-ketophosphonate functionality.

The catalytic enantioselective preparation of organophosphorus compounds has received considerable efforts as they exhibit a wide range of biological activities.[1] They also form an integral part of metal catalysis as ligands.[2] Among them, phosphorylated lactones and β-ketophosphorylesters/acids have garnered significant attention in recent years owing to their promising properties with applications as enzyme inhibitors, agrochemicals, antibiotics, antifungals and antiviral agents (Fig. 1).[3] For instance, phosphorylated δ-lactones have shown antibacterial and antiviral activities against *X. oryzae pv. oryzae* and Tobacco Mosaic Virus.[4] In addition, the phosphorylated δ-lactones can be further directly transformed into the challenging multi-functionalized chiral β-ketophosphoryl derivatives. Thus, the organocatalytic transition metal-free construction of chiral phosphorylated δ-lactones is highly desired. The group of Scheidt reported an N-heterocyclic carbene (NHC)-catalyzed asymmetric [3+2] cycloaddition of acylphosphonates and enals to afford phosphorylated γ-butyrolactones (Scheme 1a).[5] Chi and coworkers achieved the synthesis of 6-phosphorylated δ-lactones from acylphosphonates *via* γ-activation of enals using NHC in the presence of an oxidant (Scheme 1b).[4]

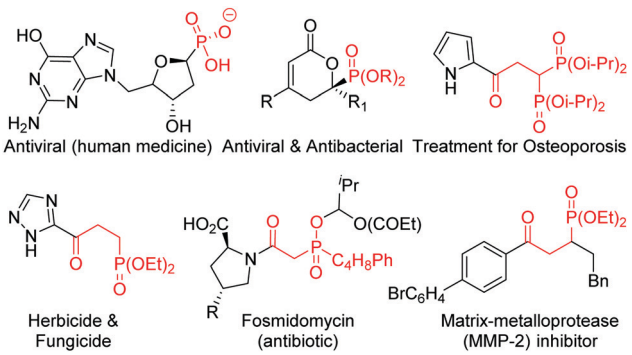

Fig. 1 Bioactive phosphorylated lactones, ketones and others.

Considering the high stakes in biological systems and very limited reports on direct catalytic enantioselective synthetic methods, we were interested in developing a carbene-catalysed method for the preparation of chiral 4-phosphorylated δ-lactones from β-phosphorylenones and enals (Scheme 1d).[6] The major challenges enroute were the addition of enolate intermediate **II** to the sterically demanding β-phosphorylenones **2** and the regioselectivity due to the two competing polarising functionalities on **2** (a vinyl phosphonate derivative) to generate intermediate **III**. All the previous attempts at the enantioselective intermolecular addition of acyl anions, enolates or homoenolates to β-phosphorylenones or their derivatives have remained yet unrealised.[7] It is worth mentioning that very recently, Fu and Huwang reported an elegant method for the preparation of 4-silylated δ-lactones from sterically hindered β-silylenones.[8] The groups of Bode, Rovis, Scheidt, Smith, Chi, Nair, You, and others have pioneered and enriched the literature through their novel methods for addition of enolate intermediates to chalcones substituted with aryl, aliphatic chain, CF_3, and CO_2R groups at the β-position.[9–12]

Expanding our group's core objective in developing carbene catalysed methods, we commenced our study using enal **1a** and β-phosphorylenone **2a** as the model substrates.[13] The key results of the optimization study are listed in Table 1. The precatalyst salt **A** in the presence of DBU in THF solvent produced the desired

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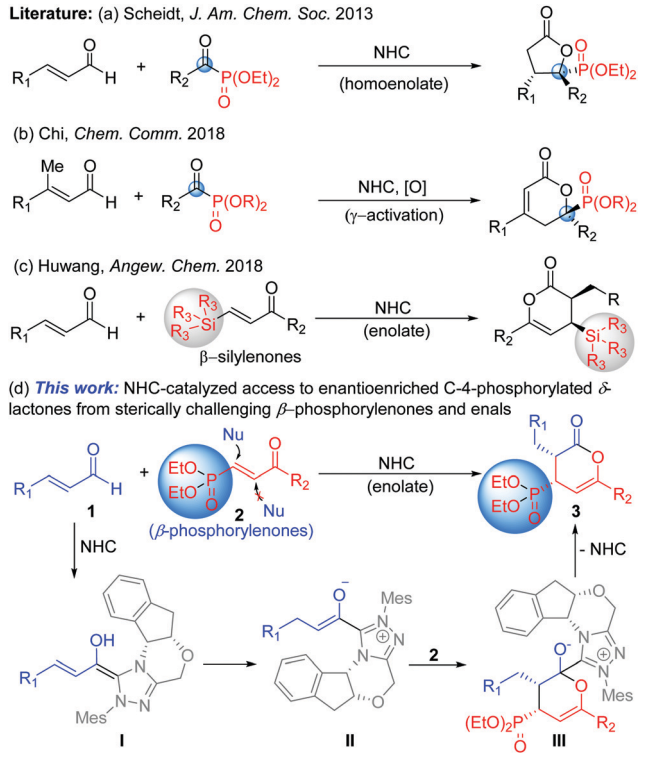
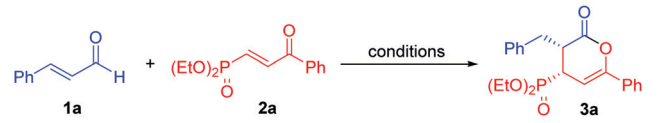
† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR and HPLC spectra. CCDC 1936122. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc03204b

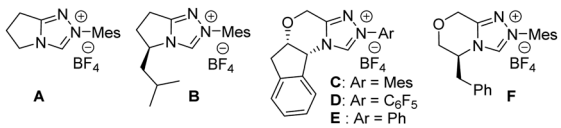


Scheme 1 NHC-catalyzed preparation of phosphorylated lactones.

Table 1 Optimization of the reaction conditions[a]



Entry	Conditions	Yield[b] (%)	dr[c]	ee[d] (%)
1	**A**/DBU/THF	21	>20 : 1	—
2	**B**/DBU/THF	27	>20 : 1	—
3	**C**/DBU/THF	57	>20 : 1	99
4	**D**/DBU/THF	0	—	—
5	**E**/DBU/THF	0	—	—
6	**F**/DBU/THF	29	—	—
7	**C**/DBU/$(CH_2Cl)_2$	59	>20 : 1	99
8	**C**/DBU/CH_2Cl_2	79	>20 : 1	99
9	**C**/TMG/CH_2Cl_2	23	>20 : 1	—
10	**C**/K_2CO_3/CH_2Cl_2	88	>20 : 1	99
11	**C**/Cs_2CO_3/CH_2Cl_2	95	>20 : 1	99



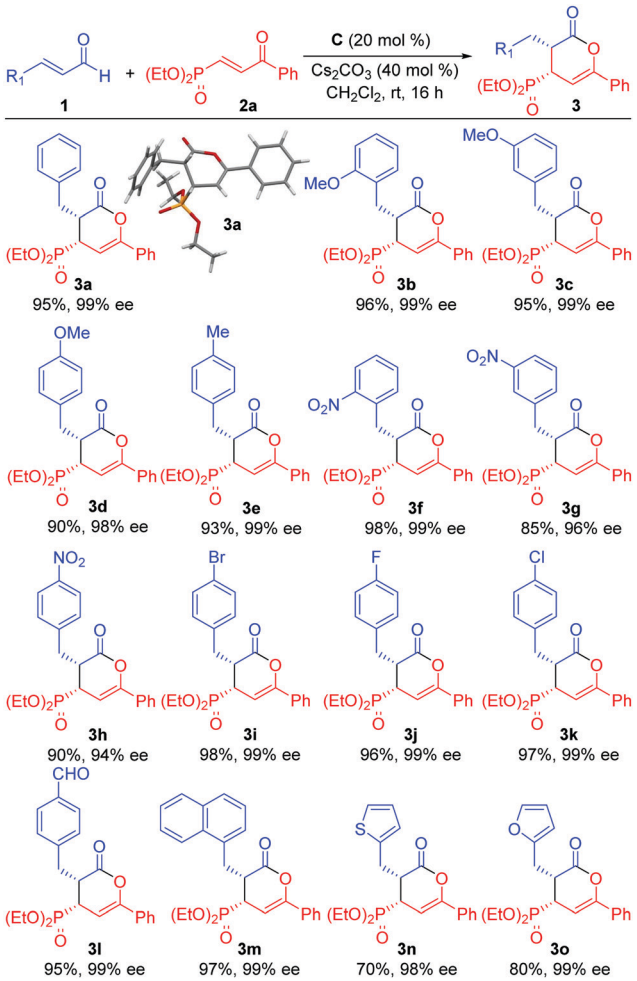
[a] Standard reaction conditions, unless otherwise specified: **1a** (0.2 mmol), **2a** (0.1 mmol), NHC **A–F** (20 mol%), base (40 mol%), solvent (1.0 mL) at rt for 16 h. [b] Isolated yield of **3a**. [c] Diastereomeric ratio was determined by the ^{1}H NMR analysis of the crude reaction mixture. [d] Eantiomeric excess was determined by chiral-phase HPLC analysis. In all cases, the regiomeric product was neither detected by the ^{1}H NMR analysis of the crude reaction mixture nor isolated after chromatographic purification. DBU = 1,8-diazabicycloundec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, TMG = 1,1,3,3-tetramethyl guanidine.

product **3a** in 21% yield with a high diastereoselectivity at room temperature (entry 1). The *N*-Mes protected salt **B** afforded **3a** in 27% yield (entry 2). Among aminoindanol-derived triazolium salts, the *N*-Mes protected precatalyst **C** led to the formation of the desired product with a descent yield of 57%, and excellent enantio- (>99% ee) and diastereo-selectivity (entry 3). The corresponding *N*-C_6F_5 and *N*-Ph protected salts were unsuitable for this reaction (entries 4 and 5). The phenylalanine-derived salt **F** was no better and produced **3a** in a poor yield (entry 6). The use of chlorinated solvents in place of THF proved fruitful, affording **3a** in CH_2Cl_2 with 79% yield and 99% ee as a single diastereomer (entry 8). Gratifyingly, the use of Cs_2CO_3 as the base in CH_2Cl_2 furnished the desired product **3a** in an excellent yield of 95% and 99% ee (entry 11). The absolute configuration of the product was determined by single crystal X-ray analysis of **3a**.[14]

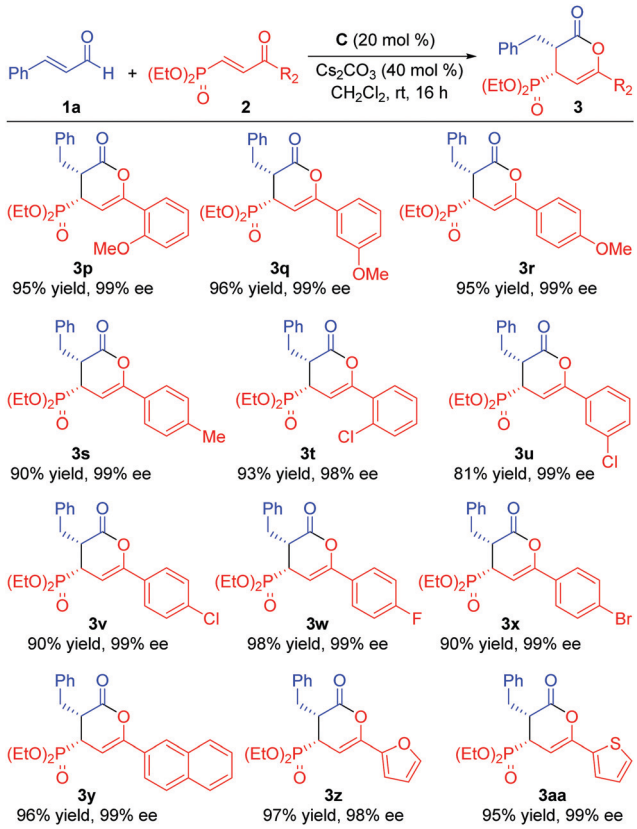
Having the optimal conditions in hand, we next examined different enals for enolate addition to β-phosphorylenone **2a** to expand the utility of this method (Scheme 2). Aldehydes substituted with electron-donating groups such as OMe or Me at the *ortho*, *meta* or *para*-positions on the phenyl ring reacted well to give the desired products in excellent yields (90–96%) and 98–99% ee without affecting the diastereoselectivity (**3b–3e**). The electron-deficient aldehydes bearing an NO_2-substitution at any position on the ring also proved to be suitable substrates, giving the desired products in 85–98% yield (**3f–3h**). Halogen (bromo, chloro and fluoro) substituted aldehydes were also well tolerated under the reaction conditions to afford the desired products in 96–98% yield and excellent stereoselectivity (**3i–3k**). The enal bearing a formyl group on the ring, which is generally a reactive functionality under NHC-catalysis, reacted chemoselectively to produce exclusively the δ-lactone product in excellent yield and selectivity (**3l**). The sterically demanding biaryl as well as heteroaryl substitution at the β-position on enals produced the desired product in excellent yields and stereoselectivity (98–99% ee and >20 : 1 dr, **3m–3o**). The enals bearing aliphatic substitution (*e.g.*, R = Me or $-CH_2$ CH_2Ph) at the β-position yielded the desired products as an inseparable mixture with some uncharacterised products. This method was demonstrated on a larger scale by preparing **3a** (0.96 g) from **2a** (0.70 g, 2.61 mmol) in 91% yield without any loss of stereoselectivity.

We next investigated the generality of β-phosphorylenones under our optimized conditions (Scheme 3). We were pleased to observe that enones bearing electron-rich substituents like Me or OMe groups, irrespective of its position being *ortho*, *meta* or *para* on the aryl ring, furnished the desired products in 90–96% yield with 99% ee and >20 : 1 dr (**3p–3s**). Electron withdrawing groups like bromo, chloro and fluoro on the aryl rings were well tolerated (**3t–3x**). No general effect on the reactivity was observed based on the substitution pattern among *ortho*, *meta* and *para* substituted enones **2** (**3t–3v**). Biaryl and heteroaryl substituted enones also furnished the desired products in 95–97% yield with 98–99% ee.

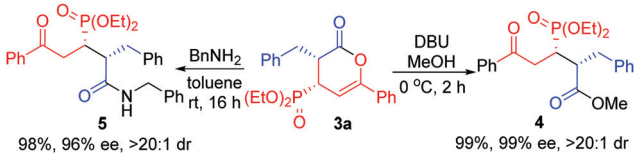
The chiral 4-phosphorylated δ-lactone **3a** could be efficiently converted to multi-functionalized chiral ester **4** and amide **5** with a β-ketophosphoryl functionality under mild reaction



Scheme 2 Scope of enals[a]. [a]Isolated yields under the standard conditions as in entry 11, Table 1. Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture and in all cases the dr was >20 : 1. Enantiomeric excess was determined by chiral-phase HPLC analysis.



Scheme 3 Scope of β-phosphorylenones[a]. [a]Isolated yields under the standard conditions as in entry 11, Table 1. Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture and in all cases the dr was >20 : 1. Enantiomeric excess was determined by chiral-phase HPLC analysis.



Scheme 4 Synthetic transformations of **3a**.

conditions without compromising the ee and dr (Scheme 4). It is noteworthy that this class of ketophosphoryl compounds possesses interesting bioactivity, for example as enzyme inhibitors, agrochemicals, antibiotics, antifungals and antiviral agents.

In conclusion, we have developed a highly enantioselective NHC-catalyzed direct method for the preparation of 4-phosphorylated δ-lactones from enals and β-phosphorylenones. This is the first enantioselective report on intermolecular addition of enolates to the challenging β-phosphorylenones. These phosphorylated δ-lactones could be efficiently converted to valuable esters and amides containing β-ketophosphoryl units. The biological activity evaluation of lactones and their ester and amide derivatives is underway.

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Conflicts of interest

There are no conflicts to declare.

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14 CCDC 1936122 contains the supplementary crystallographic data for this paper†.

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Global Access to 3/4-Phosphorylated Heterocycles via a Carbene-Catalyzed Stetter Reaction of Vinylphosphonates and Aldehydes

Ram Subhawan Verma, Monika Mishra, Chandra Bhan Pandey, Shailesh Kumar, and Bhoopendra Tiwari*

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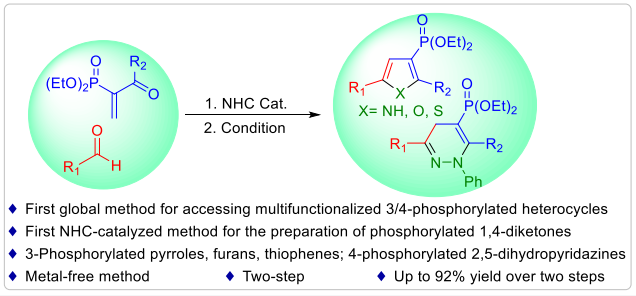
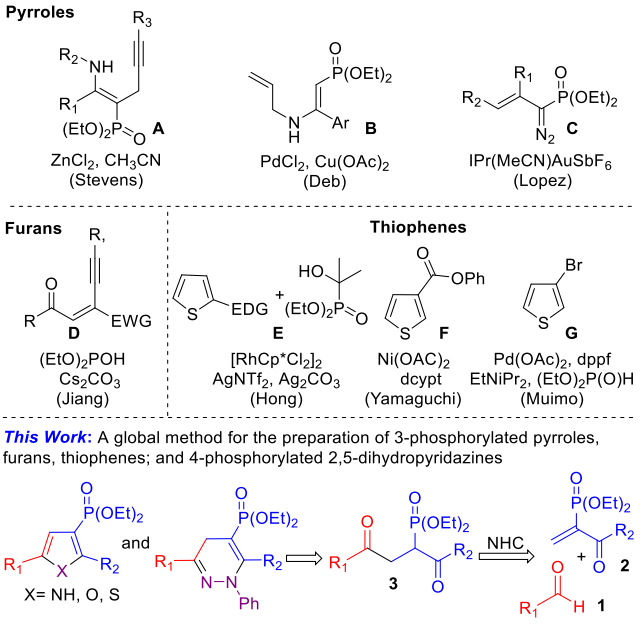
ABSTRACT: The first global method for the preparation of 3-phosphorylated-pyrroles, -furans, -thiophenes, and 4-phosphorylated 2,5-dihydropyridazines is reported. To achieve this, the first protocol for the direct synthesis of α-phosphorylated 1,4-diketones has been developed through a carbene-catalyzed Stetter reaction of vinylphosphonates and aldehydes. This is the first synthetic method for accessing 4-phosphorylated 2,5-dihydropyridazines. This process is metal-free and produces multifunctionalized heterocycles.



Phosphorylated aryls and heteroaryls have ubiquitous occurrence in pharmaceutics, agrochemicals, functionalized materials, organic synthesis as ligands and intermediates and are closely related to life science.[1] They show unique bioactivities by virtue of the P═O group acting as a strong hydrogen bond acceptor with proteins.[2] For heterocycles like pyrroles, furans, and thiophenes, accessing 3/4-phosphorylated derivatives has remained challenging compared to 2-substituted analogues due to a lower reactivity of the C-3/4. Several valuable methods for their preparation have been developed. These methods generally rely on metal-catalyzed cyclization of phosphoryl-functionalized substrates, directing group-assisted functionalization or metal-catalyzed substitution in aryl halides. Some of the recent reports for the preparation of pyrroles include Steven's $ZnCl_2$-catalyzed cyclization of **A**, Deb's $PdCl_2/Cu(OAc)_2$-catalyzed cyclization of **B**, and Lopez's $IPr(CH_3CN)AuSbF_6$-catalyzed cyclization of **C** (Scheme 1).[3] The group of Jiang prepared furans using $(EtO)_2POH/Cs_2CO_3$ from **D**.[4] Hong, Yamaguchi, and Muimo achieved phosphorylation of **E**, **F**, and **G** using $[RhCp^*Cl_2]_2/AgNTf_2/Ag_2CO_3$, $Ni(OAc)_2$/dcypt, and $Pd(OAc)_2$/dppf/$EtNiPr_2$/$(EtO)_2P(O)H$, respectively.[5] Despite the success, these methods suffer from one or multiple limitations: (i) suitable for one specific class of heterocycle, (ii) multistep preparation of complex advanced substrates, (iii) transition-metal-catalyzed, and (iv) require directing group on the ring. To our knowledge, the literature is elusive of any general method suitable for the preparation of 3-phosphorylated-pyrroles, -furans, and -thiophenes. In addition, the synthesis of 4-phosphorylated 2,5-dihydropyridazines is yet to be achieved.

We hypothesized that all these challenging heterocycles could be obtained from a common α-phosphorylated 1,4-

Scheme 1. Recent Approaches for the Preparation of 3-Phosphorylated Pyrroles, Furans, and Thiophenes



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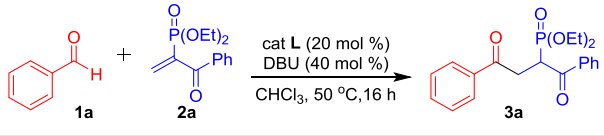
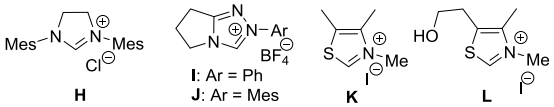
diketone, intermediate **3** (Scheme 1). Our literature survey did not lead to any precedence, either metal- or organo-catalyzed, on the synthesis of **3**. Consequently, developing an effective synthetic method for **3**, possibly metal-free and organo-catalytic, was key to the success of this study. With a long interest in metal-free catalysis, we were interested in developing the first *N*-heterocyclic harbene (NHC)-catalyzed method for the preparation of **3** through the Stetter reaction of aldehyde **1** with vinylphosphonate **2**.[6,7]

Our study commenced using aldehyde **1a** and vinylphosphonate **2a**. The key results of reaction condition optimization are enlisted in Table 1. Precatalyst **H** in $CHCl_3$

Table 1. Optimization of the Reaction Conditions[a]



Entry	Deviation from the standard condition	Yield (%)[b]
1	no catalyst	0
2	**H** instead of **L**	48
3	**I** and **J** instead of **L**	trace
4	**K** instead of **L**	64
5	none	95
6	CH_2Cl_2 instead of $CHCl_3$	77
7	$(CH_2Cl)_2$ instead of $CHCl_3$	61
8	DABCO instead of DBU	21
9	^{t}BuOK instead of DBU	26
10	TMG instead of DBU	89
11	rt instead of 50 °C	67

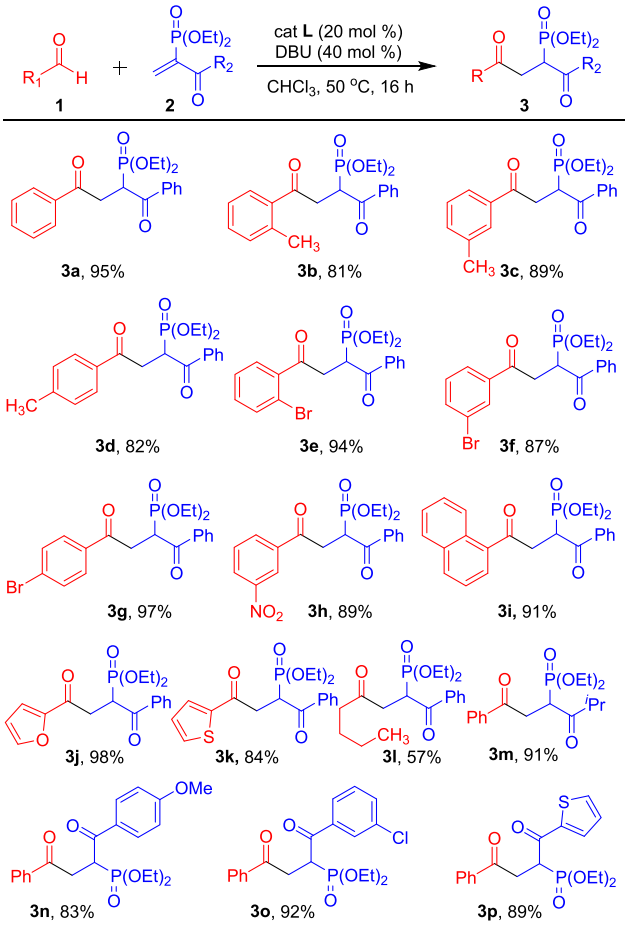


[a]Standard reaction conditions, unless otherwise specified: **1a** (0.15 mmol), **2a** (0.10 mmol), **L** (20 mol %), DBU (40 mol %), and $CHCl_3$ (1.0 mL) at 50 °C for 16 h. [b]Isolated yield of **3a**. DBU = 1,8-diazabicycloundec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, TMG = 1,1,3,3-tetramethylguanidine.

in the presence of DBU base at 50 °C produced **3a** in 48% yield (entry 2). The *N*-Ph- and *N*-Mes-protected pyrrolidinone-based triazolium salts were not suitable for this reaction (**I** and **J**, entry 3). The use of thiazolium salt **K** improved the yield to 64% (entry 4). Switching to salt **L** gratifyingly produced **3a** in an excellent yield of 95% (entry 5). Screening of several other solvents and bases under a condition similar to entry 5 generated the desired product with a diminished yield (entries 6−10).

We next sought to examine the generality of this Stetter reaction using different aldehydes and vinylphosphonates under the standard condition. As demonstrated in Scheme 2, arylaldehydes substituted with electron-donating groups (EDG), such as methyl, at the *ortho*, *meta*, or *para*-position reacted well to give the desired product in 81−89% yields (**3b**−**3d**). Likewise, the electron-withdrawing groups (EWG) on arylaldehydes were well tolerated, giving the diketones in 87−97% yields (**3e**−**3h**). The substitution pattern (*ortho*/*meta*/*para*) on the aryl rings did not show any general effect on the reactivity. Next, polyaromatic and heteroaromatic

Scheme 2. Scope of Aldehydes and Vinylphosphonates[a]



[a]Standard reaction condition as in entry 1, Table 1. Yields are the isolated yields after column chromatography.

aldehydes were efficiently converted to produce **3i**−**3k** in excellent yields. Notably, an aliphatic aldehyde also reacted smoothly to afford the phosphorylated diketone **3l** in a decent yield. We next examined the substitution effect on vinylphosphonates **2** in the reaction with **1a**. The reactions tolerated aliphatic, both electron-rich as well as electron-deficient aryl, and heteroaryl-derived **2** to produce the desired products in excellent yields (**3m**−**3p**). *β*-Phenyl-substituted vinylphosphonate (a derivative of **2a**) under this reaction condition remained largely unconsumed. Performing the reaction on a 2.24 mmol scale (0.60 g) of vinylphosphonate **2a** produced the desired product **3a** in a 91% isolated yield.

Further expanding the scope of the reaction, we used different enals **4** (Scheme 3). These *α*,*β*-unsaturated aldehydes have remained comparatively challenging substrates for the Stetter-type reaction due to a competing homoenolate and enolate reaction pathways. In general, both electron-deficient and electron-rich enals underwent this coupling reaction to afford the Stetter products in good to excellent yields (**5a**−**5i**). As in the case of aryl aldehydes, here also no generality on the reaction outcome among *ortho*, *meta*, and *para*-substitution was observed. Polyaromatic and heteroaromatic enals were equally compatible under the optimized condition and gave the corresponding products in excellent yields (**5j**−**5k**).

β-Methyl-substituted enal was also tolerated to produce **5l** in 67% yield. We next examined the scope of vinylphosphonates

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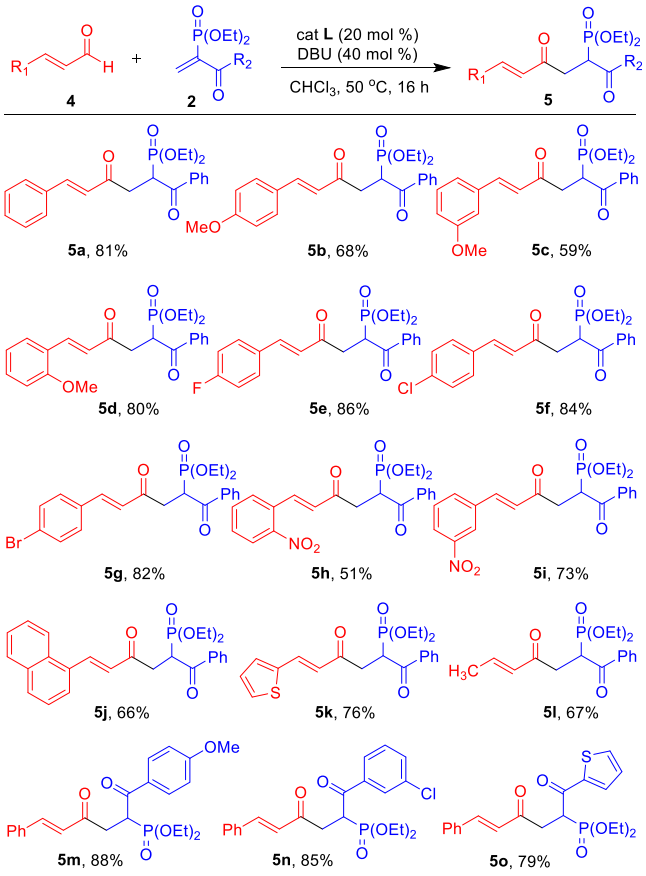
Scheme 3. Scope of Enals and Vinylphosphonates[a]



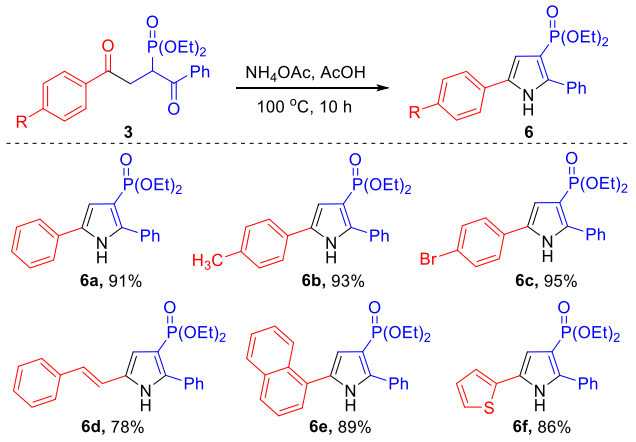
[a]Standard reaction condition as in entry 1, Table 1. Yields are the isolated yields after column chromatography.

2. Electron-rich as well as, deficient aryl, and heteroaryl-substituted vinylphosphonates reacted well with **4a** to generate the desired products in 79−88% yields (**5m**−**5o**).

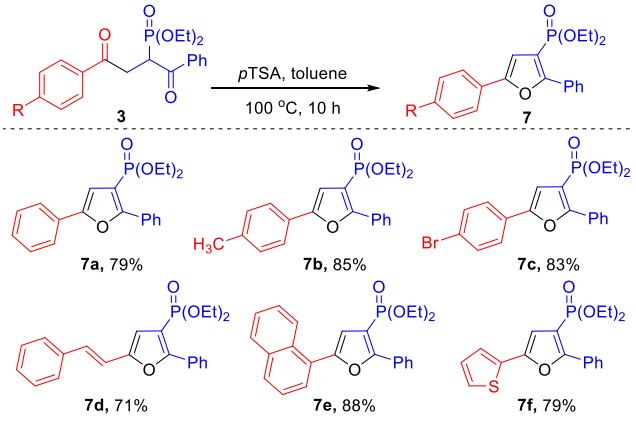
After successfully developing the catalytic method for the preparation of a wide range of α-phosphorylated 1,4-diketones, we next undertook the preparation of a different class of 3/4-phosphorylated heterocycles. For all classes of heterocycles prepared here, such as 3-phosphorylated-pyrroles, -furans and thiophenes, and 4-phosphorylated 2,5-dihydropyridazines, we demonstrated the efficiency of our method using electron-rich and electron-deficient (hetero)aryl-substituted 1,4-diketones. The diketones **3a**, **3d**, **3g**, **3i**, **3k**, and **5a** smoothly converted to 3-phosphorylated pyrroles **6a**−**6f** in the presence of NH_4OAc in AcOH at an elevated temperature in 78−95% yields (Scheme 4).[8] When this set of diketones were treated with *p*TSA in toluene, the 3-phosphorylated furans **7a**−**7f** were obtained in 71−88% yields (Scheme 5).[9] Upon subjecting **3a**, **3d**, and **3g** with Lawesson's reagent in toluene at 70 °C, 3-phosphorylated thiophenes **8a**−**8c** were obtained in 81−88% yields (Scheme 6).[10] Finally, these diketones could be converted to 4-phosphorylated 2,5-dihydropyridazines **9a**−**9c** using $PhNHNH_2$ in excellent yields of 93−98% (Scheme 7).[11] The observed regioselectivity may be attributed to the steric hindrance from the phosphoryl group to the neighboring carbonyl functionality.

In summary, we have developed the first general method for the preparation of highly functionalized 3-phosphorylated-pyrroles, -furans, and -thiophenes, and 4-phosphorylated 2,5-dihydropyridazines from vinylphosphonates and aldehydes. To achieve this, the first NHC-catalyzed Stetter reaction was developed for the preparation of α-phosphorylated-1,4-

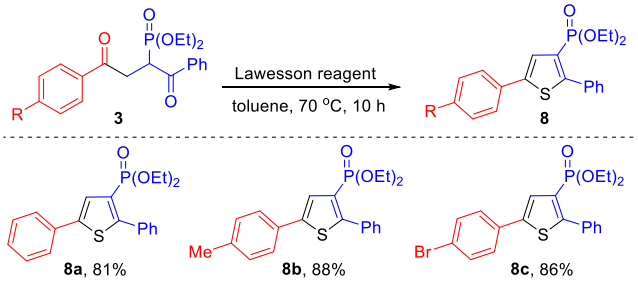
Scheme 4. Preparation of 3-Phosphorylated Pyrroles



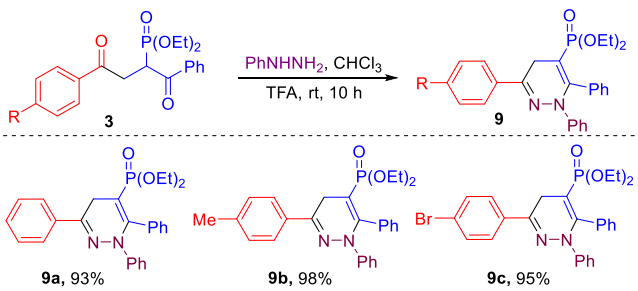
Scheme 5. Preparation of 3-Phosphorylated Furans



Scheme 6. Preparation of 3-Phosphorylated Thiophenes



Scheme 7. Preparation of 4-Phosphorylated 2,5-Dihydropyridazines



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diketones for a wide range of aldehydes, enals, and vinylphosphonates. This is the first method to synthesize 4-phosphorylated 2,5-dihydropyridazines. This two-step method is metal-free and highly efficient. This study is expected to further augment the bioactivity evaluation of a different class of phosphorylated heterocycles.

EXPERIMENTAL SECTION

General Information. Aldehydes and other reagents were purchased from a commercial supplier and used without further purification. All reactions were performed in oven-dried glassware. The α,β-unsaturated aldehydes **4** and vinylphosphonates **2** were prepared following the literature known methods.[12,13] Solvents were dried and distilled, following the standard procedures; TLC was carried out on precoated plates (Merck silica gel 60, f_{254}), and the spots were visualized with UV light or by charring the plates dipped in PMA charring solution. Flash chromatography was performed using silica gel (230−400 mess) with distilled solvents. ^{1}H, ^{13}C, and ^{31}P NMR for compounds were recorded at 400, 100, and 162 MHz, respectively, using $CDCl_3$ as the solvent, and 98% PPh_3 was used as an external standard for ^{31}P NMR. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), m (multiplets), etc. High-resolution mass spectral analysis (HRMS) was performed on a Q-TOF Premier mass spectrometer. The melting points were recorded on the Buchi M-560 melting point apparatus and are uncorrected.

General Procedure for the NHC-Catalyzed Synthesis of 3 and 5. To an oven-dried Schlenk tube equipped with a magnetic stir bar were added aldehyde **1** or **4** (0.15 mmol, 1.5 equiv), vinylphosphonate **2** (0.1 mmol, 1.0 equiv), and catalyst **L** (20 mol %) in $CHCl_3$ (1.0 mL) at room temperature. The reaction chamber was purged with argon, and DBU (40 mol %) was added. After stirring this reaction mixture at 50 °C in an oil bath for 16 h, the solvent was evaporated under the reduced pressure. The crude mass was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired products **3** or **5**.

*Preparation of **3a** on a Gram Scale.* The product **3a** was obtained in 91% yield (0.76 g) when the reaction was run using **1a** (0.356 g, 3.36 mmol) and **2a** (0.60 g, 2.24 mmol) under the optimized reaction conditions.

General Procedure for the Synthesis of Compounds 6, 7, 8, and 9. *Pyrroles **6**.* To an oven-dried sealed tube equipped with a magnetic stir bar were added ketophosphonates **3** or **5** (0.10 mmol) and NH_4OAc (0.115 g, 1.50 mmol) in AcOH (1.0 mL), and the reaction chamber was sealed. After stirring at 100 °C in an oil bath for 10 h, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired product **6**.

*Furans **7**.* To an oven-dried sealed tube equipped with a magnetic stir bar were added ketophosphonates **3** or **5** (0.10 mmol), *p*-TSA (0.028 g, 0.15 mmol), and toluene (1.0 mL), and the reaction chamber was sealed. After stirring the reaction mixture at 100 °C in an oil bath for 10 h, the solvent was evaporated under reduced pressure, and the compound was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired product **7**.

*Thiophenes **8**.* To an oven-dried sealed tube equipped with a magnetic stir bar were added ketophosphonates **3** (0.10 mmol), Lawesson's reagent (0.048 g, 0.12 mmol), and toluene (1.0 mL), and the reaction chamber was sealed. After being stirred at 70 °C in an oil bath for 10 h, the reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure furans **8**.

*2,5-Dihydropyridazines **9**.* To an oven-dried sealed tube equipped with a magnetic stir bar were added ketophosphonates **3** (0.10 mmol), $PhNHNH_2$ (17.8 μL, 0.15 mmol), $CHCl_3$ (1.0 mL), and TFA (10.0 μL, 0.13 mmol), and the reaction chamber was sealed. After stirring the reaction mixture for 10 h at room temperature, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using 60% EtOAc in hexane to obtain the pure desired product **9**.

Characterization of the Products. *Diethyl (1,4-Dioxo-1,4-diphenylbutan-2-yl)phosphonate (**3a**):* 95% yield (36 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 6.8 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.47−3.64 (1H, m), 3.85−4.22 (5H, m), 4.63−4.87 (1H, m), 7.28−7.56 (6H, m), 7.91 (2H, d, J = 7.2 Hz), 8.04 (2H, d, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 7.0 Hz), 37.3 (d, J_{C-P} = 1 Hz), 42.3 (d, J_{C-P} = 128.0 Hz), 62.9 (t, J_{C-P} = 7.0 Hz), 128.2, 128.4, 128.6, 128.9, 133.2, 133.5, 135.9, 137.4, 195.2 (d, J_{C-P} = 5.0 Hz), 196.6 (d, J_{C-P} = 15.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{23}O_5PNa^+$, 397.1176; found, 397.1171.

*Diethyl (1,4-Dioxo-1-phenyl-4-(o-tolyl)butan-2-yl)phosphonate (**3b**):* 81% yield (32 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 6.8 Hz), 2.34 (3H, s), 3.33−3.35 (1H, m), 3.85−4.16 (5H, m), 4.61−4.84 (1H, m), 7.10−7.26 (2H, m), 7.30 (1H, t, J = 7.2 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.50 (1H, t, J = 7.2 Hz), 7.74 (1H, d, J = 7.6 Hz), 8.04 (2H, d, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 21.3, 39.6 (q, J_{C-P} = 1.0 Hz), 42.7 (d, J_{C-P} = 127.0 Hz), 62.8 (t, J_{C-P} = 7.0 Hz), 125.7, 128.4, 128.9, 128.9, 131.7, 131.9, 133.2, 136.6, 137.4, 138.5, 195.3 (d, J_{C-P} = 4.0 Hz), 200.1 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{25}O_5PNa^+$ [M + Na]$^+$, 411.1332; found, 411.1329.

*Diethyl (1,4-Dioxo-1-phenyl-4-(m-tolyl)butan-2-yl)phosphonate (**3c**):* 89% yield (35 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 2.32 (3H, s), 3.44−3.62 (1H, m), 3.88−4.20 (5H, m), 4.62−4.82 (1H, m), 7.22−7.35 (2H, m), 7.41 (2H, t, J = 7.2 Hz), 7.50 (1H, t, J = 7.6 Hz), 7.71 (2H, d, J = 6.4 Hz), 8.04 (2H, t, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 21.2, 37.3, 42.4 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 8.0 Hz), 125.4, 128.4, 128.5, 128.8, 128.9, 133.1, 134.2, 135.9, 137.4, 138.4, 195.3 (d, J_{C-P} = 5.0 Hz), 196.7 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{25}O_5PNa^+$ [M + Na]$^+$, 411.1332; found, 411.1328.

*Diethyl (1,4-Dioxo-1-phenyl-4-(p-tolyl)butan-2-yl)phosphonate (**3d**):* 82% yield (32 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 6.8 Hz), 2.33 (3H, s), 3.42−3.62 (1H, m), 3.87−4.17 (5H, m), 4.60−4.83 (1H, m), 7.18 (2H, d, J = 8.4 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.50 (1H, t, J = 7.2 Hz), 7.81 (2H, d, J = 8.4 Hz), 8.04 (2H, t, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 21.7, 37.2, 42.3 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 7.0 Hz), 128.4, 128.5, 128.9, 129.3, 133.1, 133.5, 137.5, 144.4, 195.3 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{25}O_5PNa^+$ [M + Na]$^+$, 411.1332; found, 411.1330.

*Diethyl (4-(2-Bromophenyl)-1,4-dioxo-1-phenylbutan-2-yl)-phosphonate (**3e**):* 94% yield (43 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 6.8 Hz), 1.15 (3H, t, J = 6.8 Hz), 3.38−3.53 (1H, m), 3.86−4.09 (5H, m), 4.61−4.83 (1H, m), 7.15−7.36 (2H, m), 7.37−7.59 (5H, m), 8.02 (2H, d, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 7.0 Hz), 37.2, 42.3 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 6.0 Hz), 128.4, 128.7, 128.9, 129.7, 131.9, 133.2, 134.6, 137.2, 195.1 (d, J_{C-P} = 5.0 Hz), 195.6 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.9; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}BrO_5PNa^+$ [M + Na]$^+$, 475.0281; found, 475.0274.

*Diethyl (4-(3-Bromophenyl)-1,4-dioxo-1-phenylbutan-2-yl)-phosphonate (**3f**):* 87% yield (40 mg), pale yellow gummy liquid,

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eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.39−3.57 (1H, m), 3.89−4.16 (5H, m), 4.61−4.79 (1H, m), 7.25 (1H, t, J = 8.0 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.51 (1H, t, J = 7.2 Hz), 7.62 (1H, d, J = 8.0 Hz), 7.83 (1H, d, J = 7.6 Hz), 8.02 (3H, t, J = 5.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 37.3, 42.4 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 6.0 Hz), 122.9, 126.7, 128.4, 128.9, 130.2, 131.2, 133.2, 136.3, 137.3, 137.6, 195.0 (d, J_{C-P} = 5.0 Hz), 195.3 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}BrO_5PNa^+$ [M + Na]$^+$, 475.0281; found, 475.0276.

*Diethyl (4-(4-Bromophenyl)-1,4-dioxo-1-phenylbutan-2-yl)-phosphonate (**3g**):* 97% yield (45 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.42−3.55 (1H, m), 3.88−4.15 (5H, m), 4.60−4.80 (1H, m), 7.41 (2H, t, J = 7.2 Hz), 7.50 (3H, t, J = 7.2 Hz), 7.77 (2H, d, J = 8.4 Hz), 8.02 (2H, d, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 37.2, 42.3 (d, J_{C-P} = 128.0 Hz), 62.9 (q, J_{C-P} = 6.0 Hz), 128.4, 128.7, 128.9, 129.7, 131.9, 133.2, 134.5, 137.2, 195.1 (d, J_{C-P} = 5.0 Hz), 200.1 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}BrO_5PNa^+$ [M + Na]$^+$, 475.0281; found, 475.0278.

*Diethyl (4-(3-Nitrophenyl)-1,4-dioxo-1-phenylbutan-2-yl)-phosphonate (**3h**):* 89% yield (38 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 7.2 Hz), 3.48−3.63 (1H, m), 3.90−4.08 (4H, m), 4.08−4.21 (1H, m), 4.65−4.82 (1H, m), 7.43 (2H, t, J = 7.2 Hz), 7.53 (1H, t, J = 7.6 Hz), 7.60 (1H, t, J = 8.0 Hz), 8.03 (2H, t, J = 7.2 Hz), 8.23 (1H, d, J = 8.0 Hz), 8.35 (1H, dd, J = 1.2 Hz), 8.74 (1H, t, J = 1.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 3.0 Hz), 37.5, 42.5 (d, J_{C-P} = 129.0 Hz), 63.1 (t, J_{C-P} = 3.0 Hz), 123.2, 127.8, 128.5, 128.9, 130.0, 133.5, 133.8, 137.2, 148.5, 194.8 (d, J_{C-P} = 6.0 Hz), 195.0 (d, J_{C-P} = 5.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}NO_7PNa^+$ [M + Na]$^+$, 442.1027; found, 442.1029.

*Diethyl (4-(Naphthalen-1-yl)-1,4-dioxo-1-phenylbutan-2-yl)-phosphonate (**3i**):* 91% yield (39 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 6.8 Hz), 3.49−3.67 (1H, m), 3.91−4.09 (4H, m), 4.14−4.27 (1H, m), 4.76−4.92 (1H, m), 7.38−7.48 (5H, m), 7.51 (1H, t, J = 7.2 Hz), 7.77 (1H, d, J = 7.2 Hz), 7.92 (1H, d, J = 8.0 Hz), 7.99 (1H, d, J = 4.0 Hz), 8.08 (1H, d, J = 7.6 Hz), 8.45 (2H, d, J = 8.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 7.0 Hz), 40.1, 42.9 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 6.0 Hz), 124.3, 125.7, 126.4, 128.0, 128.3, 128.3, 128.4, 128.9, 130.1, 133.1, 133.2, 133.8, 134.3, 137.5, 195.4 (d, J_{C-P} = 4.0 Hz), 200.3 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{25}O_5PNa^+$ [M + Na]$^+$, 447.1332; found, 447.1335.

*Diethyl (4-(Furan-2-yl)-1,4-dioxo-1-phenylbutan-2-yl)-phosphonate (**3j**):* 98% yield (36 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.31−3.48 (1H, m), 3.87−4.12 (5H, m), 4.59−4.79 (1H, m), 6.45 (1H, t, J = 1.6 Hz), 7.15 (1H, d, J = 3.6 Hz), 7.39 (2H, t, J = 7.6 Hz), 7.49 (2H, t, J = 7.2 Hz), 8.01 (2H, d, J = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 36.7 (q, J_{C-P} = 2.0 Hz), 41.9 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 4.0 Hz), 112.3, 117.6, 128.4, 128.9, 133.2, 137.3, 146.6, 151.9, 185.7 (d, J_{C-P} = 16.0 Hz), 195.2 (d, J_{C-P} = 5.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{21}O_6PNa^+$ [M + Na]$^+$, 387.0968; found, 387.0970.

*Diethyl (1,4-Dioxo-1-phenyl-4-(thiophen-2-yl)butan-2-yl)-phosphonate (**3k**):* 84% yield (32 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.41−3.57 (1H, m), 3.89−4.14 (5H, m), 4.64−4.81 (1H, m), 7.06 (1H, t, J = 4.4 Hz), 7.40 (2H, t, J = 7.6 Hz), 7.49 (1H, t, J = 7.2 Hz), 7.57 (1H, d, J = 4.8 Hz), 7.76 (1H, d, J = 4.0 Hz), 8.01 (2H, d, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 37.5 (d, J_{C-P} = 1.0 Hz), 42.3 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 6.0 Hz), 128.2, 128.4, 128.9, 132.6, 133.2, 134.1, 137.3, 142.7, 189.5 (d, J_{C-P} = 17.0 Hz), 195.1 (d, J_{C-P} = 5.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{21}O_5PSNa^+$ [M + Na]$^+$, 403.0740; found, 403.0743.

*Diethyl (1,4-Dioxo-1-phenyloctan-2-yl)phosphonate (**3l**):* 57% yield (20 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, t, J = 7.2 Hz), 1.05 (3H, t, J = 6.8 Hz), 1.13−1.27 (5H, m), 1.40−1.52 (2H, m), 2.33−2.46 (2H, m), 2.84−3.03 (1H, m), 3.44−3.59 (1H, m), 3.86−4.08 (4H, m), 4.46−4.62 (1H, m), 7.39 (2H, t, J = 7.6 Hz), 7.49 (1H, t, J = 7.2 Hz), 7.96 (2H, d, J = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 13.8, 16.1 (q, J_{C-P} = 6.0 Hz), 22.2, 25.7, 40.5 (d, J_{C-P} = 2.0 Hz), 41.6, 42.2 (d, J_{C-P} = 128.0 Hz), 62.7 (q, J_{C-P} = 6.0 Hz), 128.0, 128.4, 128.7, 128.9, 133.2, 137.4, 195.4 (d, J_{C-P} = 5.0 Hz), 207.6 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{27}O_5PNa^+$ [M + Na]$^+$, 377.1489; found, 377.1492.

*Diethyl (5-Methyl-1,4-dioxo-1-phenylhexan-3-yl)phosphonate (**3m**):* 91% yield (31 mg), colorless gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.8 Hz), 1.27−1.40 (9H, m), 3.13−3.38 (2H, m), 3.87−4.03 (1H, m), 4.04−4.24 (5H, m), 7.45 (2H, t, J = 8.0 Hz), 7.56 (1H, t, J = 7.2 Hz), 7.98 (2H, d, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.3 (q, J_{C-P} = 5.0 Hz), 17.6, 19.5, 35.7 (d, J_{C-P} = 1.0 Hz), 41.4, 45.7 (d, J_{C-P} = 126.0 Hz), 62.7 (dd, J_{C-P} = 6.0 Hz, 7.0 Hz), 128.1, 128.5, 133.3, 136.1, 196.6 (d, J_{C-P} = 16.0 Hz), 208.8 (d, J_{C-P} = 4.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{25}O_5PH^+$ [M + H]$^+$, 341.1513; found, 341.1511.

*Diethyl (1-(4-Methoxyphenyl)-1,4-dioxo-4-phenylbutan-2-yl)-phosphonate (**3n**):* 83% yield (34 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t, J = 7.2 Hz), 1.26 (3H, t, J = 6.8 Hz), 3.52−3.65 (1H, m), 3.89 (3H, s), 3.98−4.27 (5H, m), 4.69−4.85 (1H, m), 6.98 (2H, d, J = 8.8 Hz), 7.45 (2H, t, J = 7.6 Hz), 7.57 (1H, t, J = 7.6 Hz), 8.0 (2H, d, J = 8.0 Hz), 8.12 (2H, d, J = 8.8 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.2 (t, J_{C-P} = 6.0 Hz), 37.2, 41.8 (d, J_{C-P} = 128.0 Hz), 55.5, 62.8 (q, J_{C-P} = 7.0 Hz), 113.6, 128.2, 128.6, 130.2, 133.4, 133.5, 135.9, 163.7, 193.3 (d, J_{C-P} = 5.0 Hz), 196.7 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 22.7; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{25}O_5PNa^+$ [M + Na]$^+$, 427.1281; found, 427.1267.

*Diethyl (1-(3-Chlorophenyl)-1,4-dioxo-4-phenylbutan-2-yl)-phosphonate (**3o**):* 92% yield (37 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, J = 6.8 Hz), 1.27 (3H, t, J = 7.2 Hz), 3.56−3.70 (1H, m), 4.01−4.23 (5H, m), 4.60−4.79 (1H, m), 7.41−7.51 (3H, m), 7.54−7.62 (2H, m), 7.94−8.05 (2H, m), 8.07 (1H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 7.0 Hz), 37.4, 42.7 (d, J_{C-P} = 128.0 Hz), 63.0 (d, J_{C-P} = 7.0 Hz), 127.1, 128.2, 128.7, 128.9, 129.7, 133.0, 133.6, 134.7, 135.7, 138.9, 194.2 (d, J_{C-P} = 6.0 Hz), 196.5 (d, J_{C-P} = 16.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.7; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}ClO_5PNa^+$ [M + Na]$^+$, 431.0786; found, 431.0786.

*Diethyl (1,4-Dioxo-4-phenyl-1-(thiophen-2-yl)butan-2-yl)-phosphonate (**3p**):* 89% yield (33 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.31 (6H, m), 3.51−3.66 (1H, m), 4.05−4.22 (5H, m), 4.53−4.67 (1H, m), 7.19 (1H, t, J = 4.4 Hz), 7.45 (1H, d, J = 7.6 Hz), 7.57 (1H, t, J = 7.6 Hz), 7.69 (1H, d, J = 5.2 Hz), 7.99 (3H, t, J = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.2 (t, J_{C-P} = 6.0 Hz), 36.8 (d, J_{C-P} = 2.0 Hz), 43.9 (d, J_{C-P} = 127.0 Hz), 62.9 (t, J_{C-P} = 7.0 Hz), 128.1, 128.2, 128.6, 133.5, 133.6, 134.4, 135.8, 144.0, 187.1 (d, J_{C-P} = 5.0 Hz), 196.4 (d, J_{C-P} = 15.0 Hz); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 21.9; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{21}O_5PNa^+$ [M + Na]$^+$, 403.0740; found, 403.0739.

*Diethyl (E)-(1,4-Dioxo-1,6-diphenylhex-5-en-2-yl)phosphonate (**5a**):* 81% yield (33 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t, J = 6.8

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Hz), 1.24 (3H, t, J = 6.8 Hz), 3.23−3.41 (1H, m), 3.78−3.96 (1H, m), 3.97−4.18 (4H, m), 4.63−4.86 (1H, m), 6.74 (1H, d, J = 16.4 Hz), 7.33−7.44 (3H, m), 7.45−7.67 (6H, m), 8.09 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (q, J_{C-P} = 6.0 Hz), 38.8, 42.2 (d, J_{C-P} = 128.0 Hz), 62.7 (t, J_{C-P} = 8.0 Hz), 124.9, 128.2, 128.3, 128.8, 128.9, 130.6, 133.1, 134.1, 137.3, 143.6, 195.2 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{25}O_5P\ Na^+$ $[M + Na]^+$, 423.1332; found, 423.1329.

*Diethyl (E)-(6-(4-Methoxyphenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5b**):* 68% yield (30 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.16−3.28 (1H, m), 3.71−3.84 (1H, m), 3.77 (3H, s), 3.91−4.08 (4H, m), 4.58−4.73 (1H, m), 6.56 (1H, d, J = 16.0 Hz), 6.84 (2H, d, J = 8.8 Hz), 7.41 (4H, t, J = 7.2 Hz), 7.50 (2H, t, J = 6.0 Hz), 8.02 (2H, d, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 38.8, 42.3 (d, J_{C-P} = 128.0 Hz), 55.4, 62.8 (t, J_{C-P} = 9.0 Hz), 114.4, 122.9, 126.9, 128.4, 128.9, 130.1, 133.1, 137.5, 143.5, 161.8, 195.4 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 15.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{27}O_6PNa^+$ $[M + Na]^+$, 453.1437; found, 453.1434.

*Diethyl (E)-(6-(3-Methoxyphenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5c**):* 59% yield (25 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.16−3.32 (1H, m), 3.76 (3H, s), 3.72−3.88 (1H, m), 3.90−4.10 (4H, m), 4.58−4.74 (1H, m), 6.65 (1H, d, J = 16.0 Hz), 6.87 (1H, dd, J = 8 Hz), 6.98 (1H, s), 7.05 (1H, d, J = 7.6 Hz), 7.16−7.31 (1H, m), 7.34−7.59 (4H, m), 8.0 (2H, t, J = 1.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 38.9 (d, J_{C-P} = 2.0 Hz), 42.3 (d, J_{C-P} = 128.0 Hz), 55.3, 62.8 (t, J_{C-P} = 8.0 Hz), 113.1, 116.6, 121.1, 125.4, 128.4, 128.9, 129.9, 133.1, 135.6, 137.4, 143.6, 159.9, 195.3 (d, J_{C-P} = 5.0 Hz), 196.3 (d, J_{C-P} = 15.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 21.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{27}O_6PNa^+$ $[M + Na]^+$, 453.1437; found, 453.1436.

*Diethyl (E)-(6-(2-Methoxyphenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5d**):* 80% yield (35 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 6.16 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.19−3.34 (1H, m), 3.73−3.89 (1H, m), 3.82 (3H, s), 3.90−4.09 (4H, m), 4.58−4.75 (1H, m), 6.73 (1H, d, J = 16.0 Hz), 6.80−6.95 (2H, m), 7.25−7.35 (1H, m), 7.36−7.57 (4H, m), 7.89 (1H, d, J = 16.8 Hz), 8.01 (2H, t, J = 1.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 7.0 Hz), 38.8, 42.3 (d, J_{C-P} = 128.0 Hz), 55.4, 62.8 (q, J_{C-P} = 7.0 Hz), 111.2, 120.7, 123.2, 125.6, 128.4, 128.7, 128.9, 131.9, 133.1, 137.5, 139.1, 158.6, 195.4 (d, J_{C-P} = 5.0 Hz), 196.8 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{27}O_6PNa^+$ $[M + Na]^+$, 453.1437; found, 453.1434.

*Diethyl (E)-(6-(4-Fluorophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5e**):* 86% yield (36 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 6.8 Hz), 1.16 (3H, t, J = 6.8 Hz), 3.15−3.31 (1H, m), 3.71−3.87 (1H, m), 3.89−4.11 (4H, m), 4.57−4.74 (1H, m), 6.64 (1H, d, J = 16.4 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.34−7.56 (6H, m), 8.01 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 7.0 Hz), 38.9 (d, J_{C-P} = 2.0 Hz), 42.3 (d, J_{C-P} = 128.0 Hz), 62.8 (q, J_{C-P} = 7.0 Hz), 116.1 (d, J_{C-F} = 22.0 Hz), 124.8 (d, J_{C-F} = 2.0 Hz), 128.4, 128.9, 130.3 (d, J_{C-F} = 8.0 Hz), 130.5 (d, J_{C-F} = 3.5 Hz), 133.2, 137.4, 142.3, 164.1 (d, J_{C-F} = 250.0 Hz), 195.2 (d, J_{C-P} = 5.0 Hz), 196.1 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}FO_5PNa^+$ $[M + Na]^+$, 441.1238; found, 441.1229.

*Diethyl (E)-(6-(4-Chlorophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5f**):* 84% yield (37 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 6.8 Hz), 3.14−3.30 (1H, m), 3.71−3.87 (1H, m), 3.89−4.10 (4H, m), 4.56−4.76 (1H, m), 6.60 (1H, d, J = 16.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.33−7.61 (6H, m), 8.01 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (d, J_{C-P} = 6.0 Hz), 39.0 (d, J_{C-P} = 2.0 Hz), 42.9 (d, J_{C-P} = 118.0 Hz), 62.8 (t, J_{C-P} = 8.0 Hz), 125.5, 128.4, 128.9, 129.2, 129.5, 132.7, 133.2, 136.6, 137.3, 142.1, 195.2 (d, J_{C-P} = 5.0 Hz), 196.1 (d, J_{C-P} = 15.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}ClO_5PNa^+$ $[M + Na]^+$, 457.0943; found, 457.0945.

*Diethyl (E)-(6-(4-Bromophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5g**):* 82% yield (40 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.16−3.28 (1H, m), 3.71−3.86 (1H, m), 3.88−4.11 (4H, m), 4.56−4.74 (1H, m), 6.65 (1H, d, J = 16.0 Hz),), 7.32 (1H, d, J = 8.8 Hz), 7.37−7.55 (6H, m), 8.0 (2H, d, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 39.0, 42.23 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 8.0 Hz), 124.9, 125.5, 128.4, 128.9, 129.7, 132.2, 133.1, 133.2, 137.3, 142.2, 195.2 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}BrO_5PNa^+$ $[M + Na]^+$, 501.0437; found, 501.0439.

*Diethyl (E)-(6-(2-Nitrophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)-phosphonate (**5h**):* 51% yield (23 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 6.8 Hz), 1.18 (3H, t, J = 6.8 Hz), 3.18−3.35 (1H, m), 3.72−3.89 (1H, m), 3.90−4.11 (4H, m), 4.56−4.72 (1H, m), 6.54 (1H, d, J = 16.0 Hz), 7.33−7.66 (7H, m), 7.92−8.10 (4H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 7.0 Hz), 38.8, 42.3 (d, J_{C-P} = 128.0 Hz), 62.9 (d, J_{C-P} = 8.0 Hz), 125.1, 128.4, 128.9, 129.2, 129.8, 130.6, 130.7, 133.3, 133.7, 137.3, 139.1, 148.4, 195.2 (d, J_{C-P} = 5.0 Hz), 196.0 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 21.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}NO_7PNa^+$ $[M + Na]^+$, 468.1183; found, 468.1179.

*Diethyl (E)-(6-(3-Nitrophenyl)-1,4-dioxo-1-phenylhex-5-en-2-yl)-phosphonate (**5i**):* 73% yield (33 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 6.8 Hz), 3.18−3.33 (1H, m), 3.74−3.9 (1H, m) 3.91−4.09 (4H, m), 4.58−4.73 (1H, m), 6.79 (1H, d, J = 16.4 Hz), 7.36−7.63 (5H, m), 7.76 (1H, d, J = 7.6 Hz), 7.9 (2H, dd, J = 1.2 Hz), 8.16 (1H, dd, J = 1.2 Hz), 8.32 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 39.3 (d, J_{C-P} = 2.0 Hz), 42.4 (d, J_{C-P} = 128.0 Hz), 62.9 (q, J_{C-P} = 7.0 Hz), 122.6, 124.8, 127.5, 128.4, 128.9, 130.0, 133.3, 133.9, 136.1, 137.3, 140.5, 148.7, 195.9 (d, J_{C-P} = 5.0 Hz), 195.8 (d, J_{C-P} = 15.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 21.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}NO_7PNa^+$ $[M + Na]^+$, 468.1183; found, 468.1177.

*Diethyl (E)-(6-(Naphthalen-1-yl)-1,4-dioxo-1-phenylhex-5-en-2-yl)phosphonate (**5j**):* 66% yield (30 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.1 (3H, t, J = 7.2 Hz), 1.19 (3H, t, J = 4.8 Hz), 3.24−3.39 (1H, m), 3.80−3.93 (1H, m), 3.94−4.11 (4H, m), 4.62−4.78 (1H, m), 6.78 (1H, d, J = 15.6 Hz), 7.34−7.58 (6H, m), 7.70 (1H, d, J = 7.2 Hz), 7.76−7.87 (2H, m), 7.99−8.14 (3H, m), 8.38 (2H, d, J = 16.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 39.5 (d, J_{C-P} = 2.0 Hz), 42.4 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 8.0 Hz), 123.2, 125.2, 125.4, 126.2, 126.9, 127.3, 128.5, 128.8, 128.9, 130.9, 131.5, 131.6, 133.2, 133.6, 137.4, 140.4, 195.3 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 15.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{26}H_{27}O_5PNa^+$ $[M + Na]^+$, 473.1489; found, 473.1483.

*Diethyl (E)-(1,4-Dioxo-1-phenyl-6-(thiophen-2-yl)hex-5-en-2-yl)-phosphonate (**5k**):* 76% yield (31 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 3.11−3.27 (1H, m), 3.66−3.83 (1H, m), 3.88−4.11 (4H, m), 4.56−4.74 (1H, m), 6.48 (1H, d, J = 15.6 Hz), 6.95−7.04 (1H, m), 7.22 (1H, d, J = 4.8 Hz), 7.31−7.56 (4H, m), 7.64 (1H d, J = 16.0 Hz), 7.99 (2H, t, J = 1.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 39.0 (d, J_{C-P} = 2.0 Hz), 42.3 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 7.0 Hz), 123.7, 128.3, 128.4, 128.9, 129.2, 131.9, 133.1, 136.0, 137.4, 139.6, 195.3 (d, J_{C-P} = 5.0 Hz), 195.7 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$

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NMR (162 MHz, $CDCl_3$) δ 22.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{23}O_5PSNa^+$ $[M + Na]^+$, 429.0897; found, 429.0893.

*Diethyl (E)-(1,4-Dioxo-1-phenylhept-5-en-2-yl)phosphonate (**5l**):* 67% yield (23 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, t, J = 6.4 Hz), 1.15 (3H, t, J = 6.8 Hz), 1.84 (3H, d, J = 6.8 Hz), 3.01−3.18 (1H, m), 3.56−3.75 (1H, m), 3.85−4.13 (4H, m), 4.49−4.70 (1H, m), 6.06 (1H, d, J = 16.0 Hz), 6.77−6.99 (1H, m), 7.39 (3H, t, J = 7.6 Hz), 7.48 (2H, t, J = 7.2 Hz), 7.98 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (q, J_{C-P} = 6.0 Hz), 38.1 (d, J_{C-P} = 2.0 Hz), 42.2 (d, J_{C-P} = 128.0 Hz), 62.8 (t, J_{C-P} = 7.0 Hz), 128.4, 128.9, 130.9, 133.1, 137.4, 144.1, 195.4 (d, J_{C-P} = 5.0 Hz), 196.3 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.3; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{23}O_5PNa^+$ $[M + Na]^+$, 361.1176; found, 361.1172.

*Diethyl (E)-(1-(4-Methoxyphenyl)-1,4-dioxo-6-phenylhex-5-en-2-yl)phosphonate (**5m**):* 88% yield (38 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t, J = 6.8 Hz), 1.25 (3H, t, J = 7.2 Hz), 3.21−3.36 (1H, m), 3.80−3.94 (4H, m), 3.99−4.18 (4H, m), 4.62−4.78 (1H, m), 6.74 (1H, d, J = 16.4 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.39 (3H, t, J = 3.6 Hz), 7.53 (2H, t, J = 3.6 Hz), 7.61 (1H, d, J = 16.0 Hz), 8.09 (2H, d, J = 8.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.2 (t, J_{C-P} = 7.0 Hz), 38.8, 41.8 (d, J_{C-P} = 128.0 Hz), 55.5, 62.8 (t, J_{C-P} = 6.0 Hz), 113.6, 125.1, 128.3, 128.9, 130.1, 130.6, 131.4, 134.2, 143.6, 163.6, 193.3 (d, J_{C-P} = 4.0 Hz), 196.5 (d, J_{C-P} = 15.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 22.7; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{27}O_6PNa^+$ $[M + Na]^+$, 453.1438; found, 453.1435.

*Diethyl (E)-(1-(3-Chlorophenyl)-1,4-dioxo-6-phenylhex-5-en-2-yl)phosphonate (**5n**):* 85% yield (37 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.2 (3H, t, J = 6.8 Hz), 1.27 (3H, t, J = 7.2 Hz), 3.26−3.42 (1H, m), 3.79−3.93 (1H, m), 3.99−4.17 (4H, m), 4.55−4.68 (1H, m), 6.74 (1H, d, J = 16.0 Hz), 7.37−7.43 (3H, m), 7.45 (1H, d, J = 7.6 Hz), 7.50−7.58 (3H, m), 7.62 (1H, d, J = 16.4 Hz), 7.98 (1H, d, J = 8.0 Hz), 8.04 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.2 (q, J_{C-P} = 7.0 Hz), 39.1, 42.6 (d, J_{C-P} = 129.0 Hz), 62.9 (t, J_{C-P} = 4.0 Hz), 124.9, 127.0, 128.4, 128.9, 129.0, 129.7, 130.8, 133.0, 134.1, 134.7, 138.9, 143.9, 194.2 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}ClO_5PNa^+$ $[M + Na]^+$, 457.0943; found, 457.0944.

*Diethyl (E)-(1,4-Dioxo-6-phenyl-1-(thiophen-2-yl)hex-5-en-2-yl)-phosphonate (**5o**):* 79% yield (32 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17−1.36 (6H, m), 3.21−3.37 (1H, m), 3.73−3.91 (1H, m), 4.01−4.24 (4H, m), 4.45−4.63 (1H, m), 6.74 (1H, d, J = 16.0 Hz), 7.17 (1H, t, J = 4.4 Hz), 7.40 (3H, t, J = 3.6 Hz), 7.53 (2H, t, J = 3.6 Hz), 7.62 (1H, d, J = 16.0 Hz), 7.68 (1H, d, J = 4.8 Hz), 7.97 (1H, d, J = 3.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.2 (t, J_{C-P} = 5.0 Hz), 38.4, 43.7 (d, J_{C-P} = 129.0 Hz), 62.9 (t, J_{C-P} = 7.0 Hz), 125.0, 128.1, 128.3, 128.9, 130.7, 133.7, 134.1, 134.4, 143.7, 144.0, 187.2 (d, J_{C-P} = 5.0 Hz), 196.2 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 21.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{23}O_5PNa^+$ $[M + Na]^+$, 429.0897; found, 429.0901.

*Diethyl (2,5-Diphenyl-1H-pyrrol-3-yl)phosphonate (**6a**):* 91% yield (32 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (6H, t, J = 7.2 Hz), 3.85−4.01 (4H, m), 6.86 (1H, q, J = 2.8 Hz), 7.20−7.43 (6H, m), 7.61 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 7.2 Hz), 9.78 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.04 (d, J_{C-P} = 6.7 Hz), 61.6 (d, J_{C-P} = 5.2 Hz), 106.8 (d, J_{C-P} = 214.2 Hz), 112.4 (d, J_{C-P} = 12.5 Hz), 124.3, 126.8, 128.0, 128.2, 128.3, 128.8, 131.5 (d, J_{C-P} = 0.9 Hz), 131.8, 132.9 (d, J_{C-P} = 15.5 Hz), 138.6 (d, J_{C-P} = 22.7 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 17.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{22}NO_3PH^+$, 356.1411; found, 356.1414.

*Diethyl (2-Phenyl-5-(p-tolyl)-1H-pyrrol-3-yl)phosphonate (**6b**):* 93% yield (34 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (6H, t, J = 6.8 Hz), 2.25 (3H, s) 3.70−3.92 (4H, m), 6.71 (1H, q, J = 2.8 Hz), 7.07 (2H, d, J = 8.0 Hz), 7.13−7.32 (3H, m), 7.43 (2H, d, J = 8.0 Hz), 7.61 (2H, d, J = 7.2 Hz), 9.93 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7.0 Hz), 21.1, 61.5 (d, J_{C-P} = 5.2 Hz), 106.4 (d, J_{C-P} = 214.0 Hz), 111.9 (d, J_{C-P} = 12.6 Hz), 124.3, 127.8, 128.1, 128.4, 128.8, 129.4, 131.8, 133.2 (d, J_{C-P} = 16.0 Hz), 136.4, 138.3 (d, J_{C-P} = 22.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 17.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{24}NO_3PH^+$, 370.1567; found, 370.1566.

*Diethyl (5-(4-Bromophenyl)-2-phenyl-1H-pyrrol-3-yl)-phosphonate (**6c**):* 95% yield (41 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (6H, t, J = 7.2 Hz), 3.78−4.01 (4H, m), 6.78 (1H, q, J = 4.0 Hz), 7.15−7.31 (3H, m), 7.46 (4H, q, J = 4.8 Hz), 7.67 (2H, d, J = 7.6 Hz), 10.27 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7 Hz), 61.7 (d, J_{C-P} = 6.0 Hz), 107.0 (d, J_{C-P} = 214.0 Hz), 112.8 (d, J_{C-P} = 12.5 Hz), 120.4, 125.9, 128.1, 128.2, 128.4, 130.6, 131.6, 131.8, 131.9 (d, J_{C-P} = 15.0 Hz), 139.1 (d, J_{C-P} = 23.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 17.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{21}BrNO_3PH^+$, 434.0516; found, 434.0518.

*Diethyl (E)-(2-Phenyl-5-styryl-1H-pyrrol-3-yl)phosphonate (**6d**):* 78% yield (30 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (6H, t, J = 7.2 Hz), 3.84−4.01 (4H, m), 6.66 (1H, s), 6.91 (2H, s), 7.18 (1H, t, J = 7.2), 7.24−7.34 (5H, m), 7.39 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 7.6 Hz), 10.09 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7.0 Hz), 61.7 (d, J_{C-P} = 5.0 Hz), 106.3 (d, J_{C-P} = 215.0 Hz), 115.1 (d, J_{C-P} = 12.0 Hz), 117.9, 125.5, 125.9, 127.1, 127.9, 128.1, 128.2, 128.6, 131.6, 131.8 (d, J_{C-P} = 16.0 Hz), 137.3, 138.7 (d, J_{C-P} = 23.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 17.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{24}NO_3PH^+$, 382.1567; found, 382.1567.

*Diethyl (2-(Naphthalen-1-yl)-5-phenyl-1H-pyrrol-3-yl)-phosphonate (**6e**):* 89% yield (36 mg), brown gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (6H, t, J = 6.8 Hz), 3.82−4.05 (4H, m), 6.79 (1H, s), 7.21−7.41 (3H, m), 7.41−7.60 (4H, m), 7.68−7.90 (4H, m), 8.21−8.33 (1H, m), 9.55 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7.0 Hz), 61.6 (d, J_{C-P} = 10.0 Hz), 106.4 (d, J_{C-P} = 215.0 Hz), 115.8 (d, J_{C-P} = 12.0 Hz), 122.2, 125.4, 126.0, 126.5, 128.0 (d, J_{C-P} = 8.0 Hz), 128.1, 128.2, 128.3, 129.9, 131.2, 131.2 (d, J_{C-P} = 16.0 Hz), 131.7, 133.8, 138.2 (d, J_{C-P} = 23.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 17.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{24}NO_3PH^+$, 406.1567; found, 406.1563.

*Diethyl (5-Phenyl-2-(thiophen-2-yl)-1H-pyrrol-3-yl)phosphonate (**6f**):* 86% yield (31 mg), brown gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (6H, t, J = 6.8 Hz), 3.84−4.08 (4H, m), 6.75 (1H, s), 7.01 (1H, t, J = 4.0 Hz), 7.19 (2H, d, J = 4.4), 7.28−7.42 (3H, m), 7.68 (2H, d, J = 7.6 Hz), 9.37 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7.0 Hz), 61.7 (d, J_{C-P} = 5.0 Hz), 106.6 (d, J_{C-P} = 214.0 Hz), 112.9 (d, J_{C-P} = 13.0 Hz), 122.2, 123.4, 127.6, 127.6 (d, J_{C-P} = 16.0 Hz), 128.0, 128.2, 128.3, 131.4, 134.6, 138.3 (d, J_{C-P} = 23.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 17.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{20}NO_3PSH^+$, 362.0975; found, 362.0970.

*Diethyl (2,5-Diphenylfuran-3-yl)phosphonate (**7a**):* 79% yield (28 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (6H, t, J = 7.2 Hz), 3.92−4.18 (4H, m), 6.93 (1H, d, J = 3.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.29−7.43 (5H, m), 7.67 (2H, d, J = 7.6 Hz), 7.98 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J_{C-P} = 6.7 Hz), 62.3 (d, J_{C-P} = 5.3 Hz), 109.5 (d, J_{C-P} = 210.1 Hz), 110.8, 110.9, 124.0, 127.4, 128.1, 128.4, 128.8, 129.2, 129.6, 152.9 (d, J_{C-P} = 15.2 Hz), 157.3 (d, J_{C-P} = 24.3 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 14.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{21}O_4PH^+$, 357.1251; found, 357.1257.

*Diethyl (2-Phenyl-5-(p-tolyl)-furan-3-yl)phosphonate (**7b**):* 85% yield (32 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (6H, t, J = 7.2 Hz), 2.29 (3H, s), 3.91−4.20 (4H, m), 6.87 (1H, d, J = 4.0 Hz), 7.14 (2H, d, J = 7.6 Hz), 7.29 (1H, t, J = 7.2 Hz), 7.36 (2H, t, J = 8.0 Hz), 7.54 (2H,

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d, J = 8.0 Hz), 7.96 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (d, J_{C-P} = 6.0 Hz), 21.3, 62.2 (d, J_{C-P} = 5.0 Hz), 109.2 (d, J_{C-P} = 211.0 Hz), 110.0 (d, J_{C-P} = 11.3 Hz), 123.9, 126.8, 127.3, 128.3, 129.0, 129.4, 129.6, 138.1, 153.2 (d, J_{C-P} = 15.0 Hz), 156.9 (d, J_{C-P} = 24.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 14.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{23}O_4PH^+$, 371.1407; found, 371.1406.

*Diethyl (5-(4-Bromophenyl)-2-phenylfuran-3-yl)phosphonate (**7c**):* 83% yield (36 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (6H, t, J = 7.2 Hz), 3.98−4.25 (4H, m), 7.0 (1H, d, J = 4.0 Hz), 7.34−7.63 (7H, m), 8.02 (2H, d, J = 8.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (d, J_{C-P} = 7.0 Hz), 62.3 (d, J_{C-P} = 6.0 Hz), 109.7 (d, J_{C-P} = 211.0 Hz), 111.3 (d, J_{C-P} = 11.0 Hz), 121.9, 125.4, 127.4, 128.3, 128.5, 129.2, 129.3, 131.9, 151.8 (d, J_{C-P} = 16.0 Hz), 157.5 (d, J_{C-P} = 24.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 13.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{20}BrO_4PH^+$, 435.0356; found, 435.0359.

*Diethyl (E)-(2-Phenyl-5-styrylfuran-3-yl)phosphonate (**7d**):* 71% yield (27 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (6H, t, J = 6.8 Hz), 3.99−4.21 (4H, m), 6.70 (1H, d, J = 4.0 Hz), 6.89 (1H, d, J = 16.4 Hz), 7.15 (1H, d, J = 16.4 Hz), 7.28 (1H, d, J = 7.2 Hz), 7.33−7.42 (3H, m), 7.43−7.52 (4H, m), 8.04 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (d, J_{C-P} = 6.0 Hz), 62.3 (d, J_{C-P} = 6.0 Hz), 109.4 (d, J_{C-P} = 211.0 Hz), 114.1 (d, J_{C-P} = 11.0 Hz), 115.2, 126.4, 127.4, 128.0, 128.3, 128.7, 128.8, 129.2, 129.4, 136.5, 152.2 (d, J_{C-P} = 15.0 Hz), 157.3 (d, J_{C-P} = 24.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 13.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{23}O_4PH^+$, 383.1407; found, 383.1406.

*Diethyl (2-(Naphthalen-1-yl)-5-phenylfuran-3-yl)phosphonate (**7e**):* 88% yield (36 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (6H, t, J = 6.8 Hz), 4.06−4.28 (4H, m), 7.09 (1H, d, J = 3.6 Hz), 7.34−7.64 (6H, m), 7.81 (1H, d, J = 7.2 Hz), 7.87 (2H, t, J = 9.2 Hz), 8.10 (2H, d, J = 8.0 Hz), 8.44 (1H, d, J = 8.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J_{C-P} = 7.0 Hz), 62.3 (d, J_{C-P} = 6.0 Hz), 109.3 (d, J_{C-P} = 211.0 Hz), 114.8 (d, J_{C-P} = 11.0 Hz), 125.1, 125.2, 126.0, 126.4, 126.9, 127.1, 127.4, 128.4, 128.6, 129.2 (d, J_{C-P} = 5.0 Hz), 129.6, 130.1, 133.9, 152.5 (d, J_{C-P} = 16.0 Hz), 157.7 (d, J_{C-P} = 24.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 14.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{23}O_4PH^+$, 407.1407; found, 407.1405.

*Diethyl (5-Phenyl-2-(thiophen-2-yl)furan-3-yl)phosphonate (**7f**):* 79% yield (29 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (6H, t, J = 7.2 Hz), 4.01−4.22 (4H, m), 6.85 (1H, d, J = 4.0 Hz), 7.07 (1H, t, J = 4.4 Hz), 7.29 (1H, d, J = 5.2 Hz), 7.35 (1H, d, J = 4.0 Hz) 7.36−7.52 (3H, m), 8.02 (2H, d, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (d, J_{C-P} = 7.0 Hz), 62.3 (d, J_{C-P} = 5.0 Hz), 109.4 (d, J_{C-P} = 212.0 Hz), 110.6 (d, J_{C-P} = 11.0 Hz), 123.6, 125.1, 127.3, 127.7, 128.3, 129.2, 129.3, 132.2, 148.6 (d, J_{C-P} = 16.0 Hz), 156.8 (d, J_{C-P} = 24.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 13.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{19}O_4PH^+$, 363.0815; found, 363.0810.

*Diethyl (2,5-Diphenylthiophen-3-yl)phosphonate (**8a**):* 81% yield (30 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (6H, t, J = 6.8 Hz), 3.82−4.05 (4H, m), 7.20 (1H, d, J = 14.4 Hz), 7.28−7.38 (5H, m), 7.53 (3H, t, J = 6.8 Hz), 7.61 (2H, t, J = 2.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 6.8 Hz), 62.1 (d, J_{C-P} = 5.6 Hz), 125.7 (d, J_{C-P} = 192.5 Hz), 125.8, 128.0, 128.1, 128.2 (d, J_{C-P} = 16.0 Hz), 128.8, 129.0, 129.6, 133.1, 133.2 (d, J_{C-P} = 2.0 Hz), 143.7 (d, J_{C-P} = 19.0 Hz), 151.5 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 12.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{21}O_3PSH^+$, 373.1022; found, 373.1023.

*Diethyl (2-Phenyl-5-(p-tolyl)-thiophen-3-yl)phosphonate (**8b**):* 88% yield (34 mg), pale yellow gummy liquid, eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (6H, t, J = 6.8 Hz), 2.38 (3H, s), 3.90−4.11 (4H, m), 7.21 (2H, d, J = 8.0 Hz), 7.41 (3H, d, J = 6.8 Hz), 7.50 (2H, d, J = 8.0 Hz), 7.57 (1H, d, J = 4.4 Hz), 7.67 (2H, t, J = 5.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.1 (d, J_{C-P} = 7.0 Hz), 21.21, 62.1 (d, J_{C-P} = 6.0 Hz), 125.7 (d, J_{C-P} = 192.0 Hz), 125.8, 127.7 (d, J_{C-P} = 16.0 Hz), 128.1, 128.7, 129.6, 129.7, 130.5, 133.3 (d, J_{C-P} = 2.0 Hz), 138.1, 143.9 (d, J_{C-P} = 19.0 Hz), 151.0 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 12.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{23}O_3PSH^+$, 387.1178; found, 387.1178.

*Diethyl (5-(4-Bromophenyl)-2-phenylthiophen-3-yl)-phosphonate (**8c**):* 86% yield (39 mg), pale yellow gummy liquid eluent: 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (6H, t, J = 7.2 Hz), 3.88−4.15 (4H, m), 7.36−7.55 (7H, m), 7.61 (1H, d, J = 4.8 Hz), 7.66 (2H, t, J = 3.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7.0 Hz), 62.1 (d, J_{C-P} = 8.0 Hz), 121.9, 126.2 (d, J_{C-P} = 193.0 Hz), 127.3, 128.2, 128.6 (d, J_{C-P} = 17.0 Hz), 128.9, 129.6, 132.1, 132.2, 133.0 (d, J_{C-P} = 3.0 Hz), 142.3 (d, J_{C-P} = 19.0 Hz), 151.8 (d, J_{C-P} = 16.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 12.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{20}BrO_3PSH^+$, 451.0127; found, 451.0129.

*Diethyl (2,3,6-Triphenyl-2,5-dihydropyridazin-4-yl)phosphonate (**9a**):* 93% yield (41 mg), yellow solid (mp 158−160 °C), eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (6H, t, J = 7.2 Hz), 3.45 (2H, d, J = 9.2 Hz), 3.59−3.70 (2H, m), 3.71−3.82 (2H, m), 6.85 (1H, t, J = 7.2 Hz), 7.03 (2H, t, J = 8.0 Hz), 7.07−7.25 (7H, m), 7.31−7.42 (3H, m), 7.90 (2H, d, J = 6.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 6.8 Hz), δ 26.0 (d, J_{C-P} = 8.7 Hz), 61.3 (d, J_{C-P} = 5.7 Hz), 90.3 (d, J_{C-P} = 206.5 Hz), 123.5, 124.2, 126.9, 127.4, 128.1, 128.5, 128.7, 129.6, 130.9, 133.5 (d, J_{C-P} = 3.1 Hz), 135.1, 143.7 (d, J_{C-P} = 2.5 Hz), 144.0 (d, J_{C-P} = 4.3 Hz), 150.2 (d, J_{C-P} = 21.9 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 19.17; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_3PH^+$, 447.1833; found, 447.1838.

*Diethyl (2,3-Diphenyl-6-(p-tolyl)-2,5-dihydropyridazin-4-yl)-phosphonate (**9b**):* 98% yield (45 mg), yellow solid (mp 160−162 °C), eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (6H, t, J = 7.2 Hz), 2.43 (3H, s), 3.52 (2H, d, J = 9.2 Hz), 3.68−3.79 (2H, m), 3.80−3.91 (2H, m), 6.94 (1H, t, J = 7.2 Hz), 7.12 (2H, t, J = 8.0 Hz), 7.16−7.34 (9H, m), 7.89 (2H, d, J = 8.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7.0 Hz), 21.4, 26.0 (d, J_{C-P} = 8.0 Hz), 61.3 (d, J_{C-P} = 6.0 Hz), 90.2 (d, J_{C-P} = 206.0 Hz), 123.5, 124.1, 126.8, 127.4, 128.1, 128.7, 129.3, 131.0, 132.3, 133.6 (d, J_{C-P} = 3.0 Hz), 139.8, 143.8 (d, J_{C-P} = 2.0 Hz), 144.1 (d, J_{C-P} = 5.0 Hz), 150.3 (d, J_{C-P} = 22.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 19.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_3PH^+$, 461.1989; found, 461.1986.

*Diethyl (6-(4-Bromophenyl)-2,3-diphenyl-2,5-dihydrpyridazin-4-yl)phosphonate (**9c**):* 95% yield (50 mg), yellow solid (mp 179−182 °C), eluent = 60% EtOAc in hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (6H, t, J = 7.2 Hz), 3.51 (2H, d, J = 8.8 Hz), 3.67−3.79 (2H, m), 3.80−3.92 (2H, m), 6.96 (1H, t, J = 7.2 Hz), 7.13 (2H, t, J = 8.0 Hz), 7.17−7.33 (7H, m), 7.59 (2H, d, J = 8.4 Hz), 7.86 (2H, d, J = 8.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J_{C-P} = 7.0 Hz), δ 25.7 (d, J_{C-P} = 9.0 Hz), 61.3 (d, J_{C-P} = 6.0 Hz), 90.3 (d, J_{C-P} = 206.0 Hz), 123.5, 123.9, 124.4, 127.4, 128.1, 128.3, 128.8, 130.9, 131.7, 133.3 (d, J_{C-P} = 3.0 Hz), 134.0, 142.7 (d, J_{C-P} = 4.0 Hz), 143.5 (d, J_{C-P} = 2.0 Hz), 150.1 (d, J_{C-P} = 22.0 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 19.02; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{26}H_{26}BrN_2O_3PNa^+$, 547.0757; found, 547.0756

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00150.

^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Carbene-Catalyzed Tandem [1,2]-Phospha-Brook/[1,4]-Phosphate Rearrangement: Access to α-Ketophosphates via Controlled Cross-Acyloin Condensation

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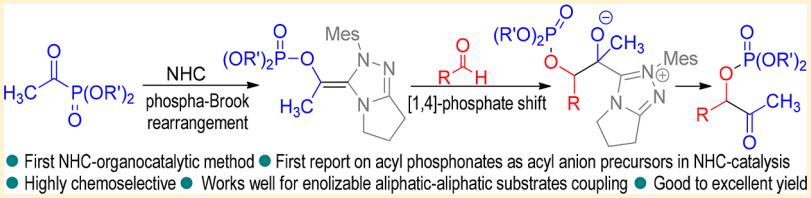
Supporting Information

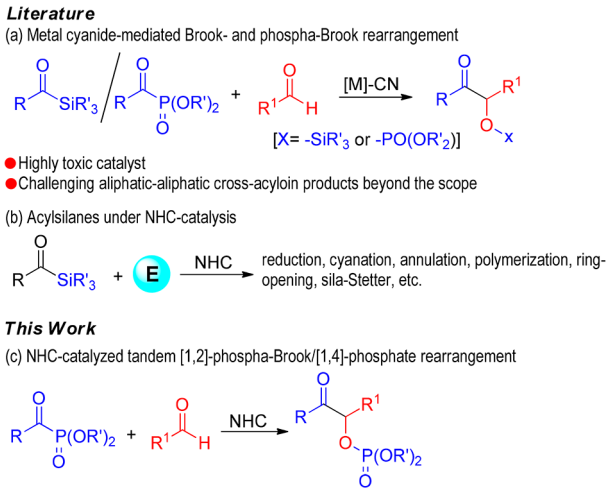


ABSTRACT: The first *N*-heterocyclic carbene (NHC)-organocatalytic tandem [1,2]-phospha-Brook/[1,4]-phosphate rearrangement is reported. Acyl phosphonates, unlike acyl silanes that are well-exploited, make entry as the acyl anion precursors under NHC catalysis. The reactions proceed with absolute chemoselectivity via cross-acyloin condensation between acyl phosphonates and aldehydes giving the products α-ketophosphates in good to excellent yields. The challenging (enolizable) aliphatic−aliphatic substrates coupling also furnished the desired product in a good yield.

The Brook rearrangement is an intramolecular anionic migration of a silyl group in silyl carbinols from carbon to oxygen in the presence of a base.[1] The corresponding phosphonate to phosphate rearrangement is commonly known as phospha-Brook rearrangement.[2] Organic phosphorus compounds, e.g., α-keto- and α-hydroxy-phosphates, are the key structural motifs in numerous molecules of biological significance. They also have an inevitable role in organic synthesis, organometallics, pharmaceutics, and photoelectric materials due to their high chelation affinity and easy manipulation to useful functionalities.[3] Among the traditional methods to access these compounds, the [1,2]-phospha-Brook rearrangement, followed by an in situ [1,4]-phosphate shift, has clear advantages, such as having a high atom economy and being direct, one-pot, and catalytic.[4] First, Johnson and co-workers in 2005, and later the group of Demir, accomplished the synthesis of α-keto-phosphates using this approach (Scheme 1a).[5] These protocols, otherwise elegant methods, require the use of highly nucleophilic (toxic) metal cyanides (e.g., KCN) as the catalyst, partly, to facilitate the migration of the phosphonate group from carbon to oxygen by enabling the generation of a densely charged oxygen anion.

N-Heterocyclic carbene (NHC) organocatalysis has enabled the discovery of numerous new methods by virtue of its unparalleled mode of substrate activation.[6] Despite the tremendous advancement in this field, to the best of our knowledge, there is no literature precedence on NHC-catalyzed either [1,2]-phospha-Brook itself or tandem [1,2]-phospha-Brook/[1,4]-phosphate rearrangement (Scheme 1c). One of the probable reasons may be the lower reactivity of the

Scheme 1. NHC-Catalyzed Tandem [1,2]-Phospha-Brook/[1,4]-Phosphate Rearrangement



acyl phosphonates as acyl anion precursors, unlike acyl silanes, under NHC catalysis due to a stronger carbon−phosphorus bond compared to a carbon−silicon bond (Scheme 1b).[7,8] Second, unlike metal cyanides, the NHC normally does not produce an intermediate from acyl phosphonate with a very high charge density on oxygen to promote [1,2]-phosphoryl

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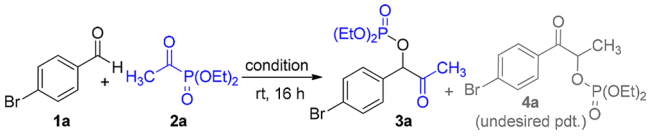
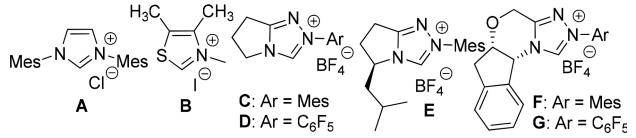
group migration.[1] Several other factors contributing equally to its conspicuous absence may include competing undesired reactions like self-benzoin condensation of the aldehydes as well as acyl phosphonates and cross-acyloin condensation (acyl anion of aldehydes adding to acyl phosphonates). Herein we report the first NHC-organocatalytic tandem [1,2]-phospha-Brook/[1,4]-phosphate rearrangement of acyl phosphonates and aldehydes. This is also the first example of using the challenging acyl phosphonates as the masked acyl anion under NHC catalysis. In addition, this protocol works well even for the challenging enolizable aliphatic−aliphatic substrates coupling/rearrangement.

Continuing our work in NHC catalysis, we commenced this study by examining the reaction of *p*-bromo benzaldehyde **1a** and acyl phosphonate **2a** in CH_2Cl_2 with Cs_2CO_3 as the base (Table 1).[9] Under this condition, the imidazolium precatalyst **A** did not work, whereas the thiazolium precatalyst **B** gave the desired product **3a** in a poor yield (23% yield; entries 2 and 3). Pyrrolidinone-based triazolium salt **C**[10] resulted in the formation of the desired product **3a** with a significant increase in the yield (57% yield) with absolute chemoselectivity (entry 4). Further inquiries into the core structure of the catalysts using precatalysts **D**, **E**, **F**, and **G** either failed completely or produced the desired product in a low yield (entries 5−8). We next surveyed several solvents with varying polarity using precatalyst **C** and Cs_2CO_3. Switching the solvent to THF resulted in the lowering of the yield as well as selectivity, giving product **3a** along with the undesired isomer **4a** in a 90:10 ratio (entry 9). The use of nonpolar solvents like Et_2O, toluene, and *p*-xylene led to further deterioration in the yield as well as selectivity (entries 10−12). Gratifyingly, carrying out this reaction in $CHCl_3$ turned out be beneficial, forming the product **3a** in an excellent yield of 82% with absolute chemoselectivity (entry 13). Several organic as well as inorganic bases were also tried, but most of them turned out be detrimental (entries 16−21). Raising the reaction temperature, using a longer reaction time and higher catalyst loading, and changing the molar ratios of the substrates did not lead to any improvement in the reaction outcome.

Table 1. Optimization of the Reaction Conditions[a]



entry	NHC	base	solvent	3a/4a[b]	yield (%)[c]
1		Cs_2CO_3	CH_2Cl_2		0
2	**A**	Cs_2CO_3	CH_2Cl_2		trace
3	**B**	Cs_2CO_3	CH_2Cl_2	100:0	23
4	**C**	Cs_2CO_3	CH_2Cl_2	100:0	57
5	**D**	Cs_2CO_3	CH_2Cl_2		trace
6	**E**	Cs_2CO_3	CH_2Cl_2	100:0	17
7	**F**	Cs_2CO_3	CH_2Cl_2		trace
8	**G**	Cs_2CO_3	CH_2Cl_2		trace
9	**C**	Cs_2CO_3	THF	90:10	51
10	**C**	Cs_2CO_3	Et_2O	56:44	49 (33)
11	**C**	Cs_2CO_3	toluene	62:38	47 (27)
12	**C**	Cs_2CO_3	*p*-xylene	100:0	48
13	**C**	Cs_2CO_3	$CHCl_3$	100:0	82
14[d]	**C**	Cs_2CO_3	$CHCl_3$	47:53	29 (33)
15[e]	**C**	Cs_2CO_3	$CHCl_3$	100:0	83
16	**C**	CsOH	$CHCl_3$	100:0	76
17	**C**	K_2CO_3	$CHCl_3$	100:0	44
18	**C**	KO^{t}Bu	$CHCl_3$		trace
19	**C**	DBU	$CHCl_3$	100:0	39
20	**C**	DMAP	$CHCl_3$		trace
21	**C**	$CaCO_3$	$CHCl_3$		trace



[a]Reaction condition unless otherwise specified: **1a** (0.22 mmol), **2a** (0.11 mmol), NHC (20 mol %), base (20 mol %), solvent (1.0 mL) at rt for 16 h. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield of **3a**. Number in the parentheses is the isolated yield of **4a**. [d]Reaction performed at 60 °C overnight. [e]30 mol % C was used. DBU = 1,8-diazabicycloundec-7-ene. DMAP = 4-dimethylaminopyridine.

With optimized conditions balancing the selectivity as well as the yield identified, we next explored the generality of this transformation. To our delight, both electron-deficient as well as electron-rich aldehydes were well-tolerated under the reaction conditions (Scheme 2). For example, electron-deficient aryl aldehydes bearing bromo, chloro, fluoro, nitro, and ester functionalities provided the corresponding ketophosphates in good to excellent yields with the exclusive formation of the desired isomer only (**3a**−**3i**). On the other hand, electron-rich aryl aldehydes substituted with methyl or methoxy groups, in general, furnished the product with a diminished yield compared to the electron-deficient aldehydes (**3j**−**3l**). A limited effect of the substitution pattern was also observed as the yield slightly improved from *para*- to *meta*- to *ortho*-substituted aldehydes (**3a**−**3c**, **3f**, **3g**, **3j**, **3k**). The biphenyl ring-based aldehyde as well as heteroaromatic aldehyde reacted under the optimized conditions but with diminished yields (**3n**, **3o**). Switching to dimethyl acyl phosphonate led to the product formation in a lower yield (**3p**). We next moved on to investigate the more challenging enolizable aliphatic aldehydes. It is noteworthy that this class of aldehydes (aliphatic aldehyde−aliphatic phosphonate coupling) performed badly under the literature known protocols using a cyanide-based catalyst.[5] Benzylic, homobenzylic, branched, and long-chain aldehydes all reacted well giving the desired products in good yields, albeit requiring a little higher loading of the aldehyde (**3q**−**3u**). This reaction also worked well on a 1.0 g scale of acyl phosphonate, giving the desired product **3a** in 71% isolated yield.

Our postulated mechanism for this tandem [1,2]-phospha-Brook/[1,4]-phosphate rearrangement is detailed in Scheme 3. NHC reacts with acyl phosphonate to generate intermediate **I**, which undergoes [1,2]-migration of the phosphonate group from carbon to oxygen (called phospha-Brook rearrangement) producing a protected variant of the Breslow intermediate (**II**). A molecular ion peak was observed in HRMS [at *m*/*z* 408.2054 $(M + H)^+$] corresponding to the intermediate **II** in a controlled experiment using acyl phosphonate and NHC under the optimized condition without an aldehyde. Intermediate **II** reacts with the aldehyde to generate intermediate **III**, which further participates in an intramolecular [1,4]-phosphate shift to produce intermediate **IV**. Subsequent regeneration of the catalyst from **IV** giving the desired ketophosphate product **3** completes the catalytic cycle.

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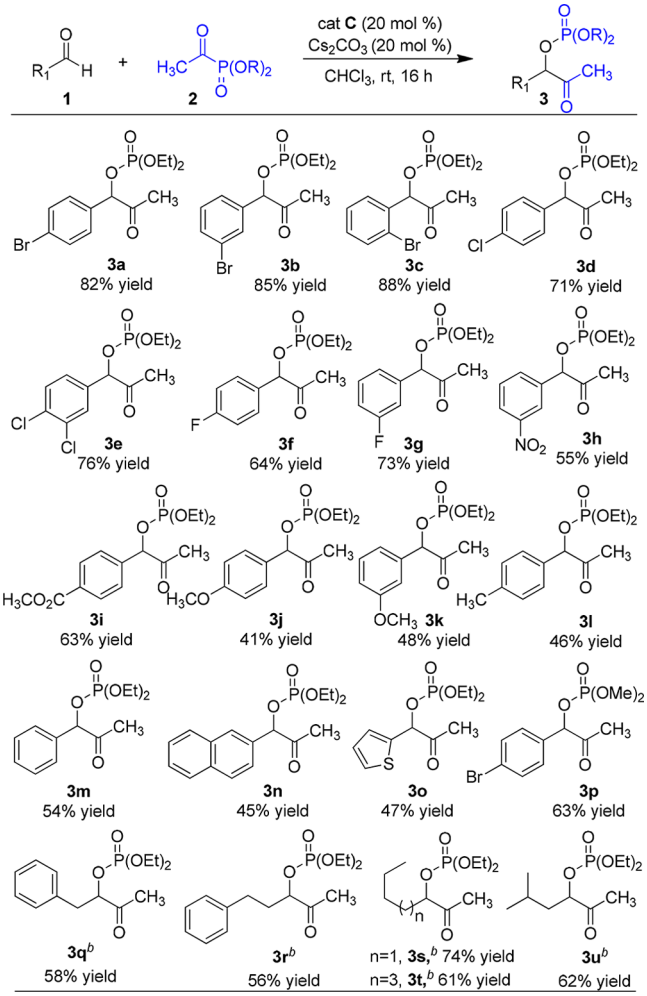
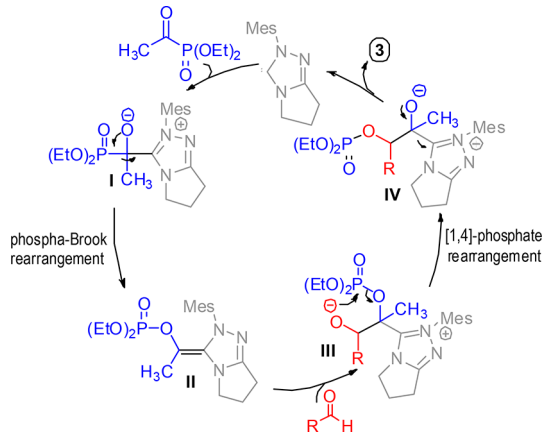
Scheme 2. Substrate Scope of Aldehydes and Acyl Phosphonates[a]



[a]Isolated yields under the optimized condition (as in entry 13, Table 1) unless otherwise mentioned. All of the products were obtained as a single isomer. [b]0.33 mmol of the corresponding aldehyde was used.

Scheme 3. Proposed Mechanism



In conclusion, we have established the first NHC-organo-catalyzed tandem [1,2]-phospha-Brook/[1,4]-phosphate rearrangement. It is the first report on using acyl phosphonates as acyl anion equivalents that has remained elusive until now under NHC catalysis. This study provides a toxic (metal) cyanide-free, direct, one-pot, highly atom economical method for the preparation of α-ketophosphates. The aliphatic–aliphatic substrates coupling, which remained sluggish under literature methods, produced the desired products in good yields under this protocol. We expect that this report on using acyl phosphonates as the acyl anion equivalent will lead to the development of several novel methods under NHC catalysis.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified, all reactions were carried out under an atmosphere of argon in a dry Schlenk tube. All aldehydes were of commercial quality and used without further purification. Solvents were dried and distilled following the standard procedures. TLC was carried out on precoated plates (Merck silica gel 60, f254), and the spots were visualized with UV light or by charring the plates dipped in vanillin–5% H_2SO_4–EtOH solution. The compounds were purified by flash column chromatography using silica gel (230–400 mesh) with distilled solvents. ^{1}H and ^{13}C NMR spectra were recorded with a 400 and 600 MHz instrument and 100 and 150 MHz instrument, respectively, in $CDCl_3$ as the solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.0 ppm). High-resolution mass spectrometry (HRMS) was performed on an Agilent 6530 Q-TOF using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

General Procedure for the Catalytic Synthesis of α-Ketophosphate 3 and 4a. To a dry Schlenk tube equipped with a magnetic stir bar was added acyl phosphonate **2** (20.0 mg, 0.111 mmol, 1.0 equiv), aldehyde **1** (0.222 mmol, 2.0 equiv), and catalyst **C** (6.93 mg, 20 mol %). The tube was closed after the addition of $CHCl_3$ (1.0 mL) and Cs_2CO_3 (7.15 mg, 20 mol %). The reaction chamber was flashed with argon, and the mixture was stirred at room temperature for 24 h. The reaction mixture was then directly applied to silica gel column chromatography to obtain product **3**.

Characterization of the Products. *1-(4-Bromophenyl)-2-oxopropyl Diethyl Phosphate (**3a**).* The title compound was prepared according to the general procedure as described above in 82% yield: pale yellow liquid, 33 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, dt, J = 0.8, 6.8 Hz), 1.31 (3H, dt, J = 0.8, 6.8 Hz), 2.16 (3H, s), 3.93–4.03 (2H, m), 4.06–4.25 (2H, m), 5.60 (1H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.0 Hz), 7.53 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (d, J = 7.0 Hz), 16.0 (d, J = 7.0 Hz), 25.4, 64.1 (d, J = 6.0 Hz), 64.4 (d, J = 6.0 Hz), 82.5 (d, J = 5.0 Hz), 123.5, 128.6, 132.1, 133.5 (d, J = 5.0 Hz), 202.3 (d, J = 5.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.02; HRMS (ESI) calcd for $C_{13}H_{19}BrO_5P$ $[M + H]^+$ 365.0157, found 365.0153.

*1-(3-Bromophenyl)-2-oxopropyl Diethyl Phosphate (**3b**).* The title compound was prepared according to the general procedure as described above in 85% yield: pale yellow liquid, 34 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, dt, J = 1.2, 7.2 Hz), 1.32 (3H, dt, J = 1.2, 6.8 Hz), 2.18 (3H, s), 3.95–4.05 (2H, m), 4.10–4.26 (2H, m), 5.60 (1H, d, J = 8.4 Hz), 7.26 (1H, t, J = 7.6 Hz), 7.35 (1H, d, J = 7.6 Hz), 7.48–7.53 (1H, m), 7.57 (1H, t, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (d, J = 6.0 Hz), 16.0 (d, J = 7.0 Hz), 25.5, 64.2 (d, J = 6.0 Hz), 64.5 (d, J = 5.0 Hz), 82.3 (d, J = 5.0 Hz), 122.9, 125.6,129.8, 130.4, 132.3, 136.5 (d, J = 5.0 Hz), 202.3 (d, J = 5.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.05; HRMS (ESI) calcd for $C_{13}H_{19}BrO_5P$ $[M + H]^+$ 365.0152, found 365.0153.

*1-(2-Bromophenyl)-2-oxopropyl Diethyl Phosphate (**3c**).* The title compound was prepared according to the general procedure as described above in 88% yield: pale yellow liquid, 35 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, dt, J = 0.8, 7.2 Hz), 1.32 (3H, dt, J = 1.2, 7.2 Hz), 2.19 (3H, s), 3.92–4.02 (2H, m), 4.10–4.27 (2H, m), 6.14 (1H, d, J = 8.8 Hz), 7.21–7.28 (1H, m), 7.32–7.43 (2H, m), 7.61 (1H, dd, J = 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (d, J = 7.0 Hz), 15.9 (d, J = 7.0

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Hz), 26.4, 64.0 (d, J = 6.0 Hz), 64.3 (d, J = 6.0 Hz), 81.6 (d, J = 6.0 Hz), 123.5, 128.0, 129.6, 130.7, 133.3, 134.5, 201.2 (d, J = 5.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.03; HRMS (ESI) calcd for $C_{13}H_{19}BrO_5P$ $[M + H]^+$ 365.0150, found 365.0153.

*1-(4-Chlorophenyl)-2-oxopropyl Diethyl Phosphate (**3d**).* The title compound was prepared according to the general procedure as described above in 71% yield: pale yellow liquid, 25 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (3H, dt, J = 0.6, 7.2 Hz), 1.32 (3H, dt, J = 1.2, 7.2 Hz), 2.16 (3H, s), 3.95−4.02 (2H, m), 4.11−4.24 (2H, m), 5.62 (1H, d, J = 8.4 Hz), 7.34−7.39 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9 (d, J = 6.0 Hz), 16.0 (d, J = 6.0 Hz), 25.5, 64.1 (d, J = 6.0 Hz), 64.4 (d, J = 6.0 Hz), 82.4 (d, J = 6.0 Hz), 128.3, 129.2, 133.0 (d, J = 6.0 Hz), 135.3, 202.4 (d, J = 6.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.02; HRMS (ESI) calcd for $C_{13}H_{19}ClO_5P$ $[M + H]^+$ 321.0662, found 321.0654.

*1-(3,4-Dichlorophenyl)-2-oxopropyl Diethyl Phosphate (**3e**).* The title compound was prepared according to the general procedure as described above in 76% yield: pale yellow liquid, 41 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, dt, J = 1.2, 7.2 Hz), 1.32 (3H, dt, J = 1.2, 7.2 Hz), 2.19 (3H, s), 3.97−4.07 (2H, m), 4.10−4.26 (2H, m), 5.57 (1H, d, J = 8.4 Hz), 7.24−7.29 (1H, m), 7.47 (1H, d, J = 8.4 Hz), 7.52 (1H, d, J = 2.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9 (d, J = 6.0 Hz), 16.0 (d, J = 7.5 Hz), 25.4, 64.3 (d, J = 6.0 Hz), 64.5 (d, J = 6.0 Hz), 81.8 (d, J = 6.0 Hz), 126.1, 128.7, 130.9, 133.2, 133.5, 134.5 (d, J = 6.0 Hz), 202.2 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.03; HRMS (ESI) calcd for $C_{13}H_{18}Cl_2O_5P$ $[M + H]^+$ 355.0272, found 355.0264.

*Diethyl (1-(4-Fluorophenyl)-2-oxopropyl) Phosphate (**3f**).* The title compound was prepared according to the general procedure as described above in 64% yield: pale yellow liquid, 22 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (3H, dt, J = 1.2, 7.2 Hz), 1.31 (3H, dt, J = 1.2, 6.8 Hz), 2.16 (3H, s), 3.93−4.01 (2H, m), 4.09−4.24 (2H, m), 5.65 (1H, d, J = 8.4 Hz), 7.06−7.13 (2H, m), 7.38−7.44 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 7.5 Hz), 16.0 (d, J = 7.5 Hz), 25.5, 64.1 (d, J = 6.0 Hz), 64.4 (d, J = 6.0 Hz), 82.4 (d, J = 4.5 Hz), 116.0 (d, J = 21.0 Hz), 129.0 (d, J = 7.5 Hz), 130.4, 163.2 (d, J = 247.5 Hz), 202.5 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.97; HRMS (ESI) calcd for $C_{13}H_{19}FO_5P$ $[M + H]^+$ 305.0958, found 305.0949.

*Diethyl (1-(3-Fluorophenyl)-2-oxopropyl) Phosphate (**3g**).* The title compound was prepared according to the general procedure as described above in 73% yield: pale yellow liquid, 25 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (3H, dt, J = 1.2, 7.2 Hz), 1.33 (3H, dt, J = 0.6, 7.2 Hz), 2.18 (3H, s), 3.96−4.04 (2H, m), 4.12−4.25 (2H, m), 5.64 (1H, d, J = 8.4 Hz), 7.04−7.09 (1H, m), 7.13−7.17 (1H, m), 7.21 (1H, d, J = 7.8 Hz), 7.34−7.39 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 6.0 Hz), 16.0 (d, J = 6.0 Hz), 25.4, 64.2 (d, J = 6.0 Hz), 64.5 (d, J = 6.0 Hz), 82.4 (t, J = 6.0 Hz), 113.9 (d, J = 22.5 Hz), 116.2 (d, J = 21.0 Hz), 122.7 (d, J = 4.5 Hz), 130.6 (d, J = 7.5 Hz), 136.8 (t, J = 4.5 Hz), 162.9 (d, J = 246.0 Hz), 202.3 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.09; HRMS (ESI) calcd for $C_{13}H_{19}FO_5P$ $[M + H]^+$ 305.0958, found 305.0949.

*Diethyl (1-(3-Nitrophenyl)-2-oxopropyl) Phosphate (**3h**).* The title compound was prepared according to the general procedure as described above in 55% yield: pale yellow liquid, 20 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.24 (3H, dt, J = 0.6, 6.6 Hz), 1.34 (3H, dt, J = 0.6, 7.2 Hz), 2.25 (3H, s), 4.02−4.09 (2H, m), 4.15−4.26 (2H, m), 5.72 (1H, d, J = 8.4 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.76 (1H, d, J = 7.8 Hz), 8.22−8.26 (1H, m), 8.31 (1H, t, J = 1.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) 15.9 (d, J = 7.5 Hz), 16.0 (d, J = 7.5 Hz), 25.6, 64.4 (d, J = 6.0 Hz), 64.7 (d, J = 6.0 Hz), 81.92 (d, J = 5.0 Hz), 121.6, 124.0, 129.9, 132.8, 136.7 (d, J = 6.0 Hz), 148.5, 202.4 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.90; HRMS (ESI) calcd for $C_{13}H_{19}NO_7P$ $[M + H]^+$ 332.0902, found 332.0894.

*Methyl 4-(1-((Diethoxyphosphoryl)oxy)-2-oxopropyl) Benzoate (**3i**).* The title compound was prepared according to the general procedure as described above in 63% yield: pale yellow liquid, 24 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, dt, J = 1.2, 7.2 Hz), 1.31 (3H, dt, J = 1.2, 6.8 Hz), 2.17 (3H, s), 3.92 (3H, s), 3.94−4.05 (2H, m), 4.10−4.26 (2H, m), 5.68 (1H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.0 Hz), 8.06 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (d, J = 7.0 Hz), 16.0 (d, J = 7.0 Hz), 25.5, 52.2, 64.2 (d, J = 6.0 Hz), 64.5 (d, J = 6.0 Hz), 82.7 (d, J = 5.0 Hz), 126.8, 130.1, 130.9, 139.1 (d, J = 5.0 Hz), 166.3, 202.3 (d, J = 5.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.96; HRMS (ESI) calcd for $C_{15}H_{22}O_7P$ $[M + H]^+$ 345.1087, found 345.1098.

*Diethyl (1-(4-Methoxyphenyl)-2-oxopropyl) Phosphate (**3j**).* The title compound was prepared according to the general procedure as described above in 41% yield: pale yellow liquid, 15 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (3H, dt, J = 1.2, 7.2 Hz), 1.32 (3H, dt, J = 1.2, 7.2 Hz), 3.81 (3H, s), 2.14 (3H, s), 3.91−3.98 (2H, m), 4.11−4.23 (2H, m), 5.63 (1H, d, J = 7.8 Hz), 6.91 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 6.0 Hz), 16.0 (d, J = 7.5 Hz), 25.6, 55.3, 63.9 (d, J = 6.0 Hz), 64.2 (d, J = 6.0 Hz), 82.9 (d, J = 4.5 Hz), 114.4, 126.5 (d, J = 4.5 Hz), 128.7, 160.4, 202.6 (d, J = 6.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.96; HRMS (ESI) calcd for $C_{14}H_{22}O_6P$ $[M + H]^+$ 317.1154, found 317.1149.

*Diethyl (1-(3-Methoxyphenyl)-2-oxopropyl) Phosphate (**3k**).* The title compound was prepared according to the general procedure as described above in 48% yield: pale yellow liquid, 17 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (3H, dt, J = 1.2, 7.2 Hz), 1.32 (3H, dt, J = 0.6, 7.2 Hz), 2.15 (3H, s), 3.81 (3H, s), 3.94−4.02 (2H, m), 4.12−4.24 (2H, m), 5.63 (1H, d, J = 8.4 Hz), 6.89−6.92 (1H, m), 6.94 (1H, t, J = 1.4 Hz), 7.00 (1H, d, J = 7.8 Hz), 7.29 (1H, t, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 6.0 Hz),16.0 (d, J = 6.0 Hz), 25.4, 55.3, 64.0 (d, J = 4.5 Hz), 64.3 (d, J = 6.0 Hz), 83.1 (d, J = 4.5 Hz), 112.4, 114.9, 119.4, 130.0, 135.9 (d, J = 4.5 Hz), 160.0, 202.5 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.02; HRMS (ESI) calcd for $C_{14}H_{22}O_6P$ $[M + H]^+$ 317.1152, found 317.1149.

*Diethyl (2-Oxo-1-(p-tolyl)propyl) Phosphate (**3l**).* The title compound was prepared according to the general procedure as described above in 46% yield: pale yellow liquid, 15 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (3H, dt, J = 0.6, 6.6 Hz), 1.32 (3H, dt, J = 0.6, 7.2 Hz), 2.14 (3H, s), 2.35 (3H, s), 3.90−4.00 (2H, m), 4.12−4.24 (2H, m), 5.64 (1H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 6.0 Hz), 16.0 (d, J = 7.5 Hz), 21.1, 25.5, 63.9 (d, J = 6.0 Hz), 64.3 (d, J = 4.5 Hz), 83.2 (d, J = 6.0 Hz), 127.1, 129.6, 131.5 (d, J = 4.5 Hz), 139.2, 202.7 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.00; HRMS (ESI) calcd for $C_{14}H_{22}O_5P$ $[M + H]^+$ 301.1193, found 301.1199.

*Diethyl (2-Oxo-1-phenylpropyl) Phosphate (**3m**).* The title compound was prepared according to the general procedure as described above in 54% yield: pale yellow liquid, 18 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (3H, t, J = 7.2 Hz), 1.32 (3H, t, J = 6.6 Hz), 2.15 (3H, s), 3.91−4.01 (2H, m), 4.11−4.25 (2H, m), 5.67 (1H, d, J = 8.4 Hz), 7.34−7.47 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 7.5 Hz), 16.0 (d, J = 7.5 Hz), 25.5, 64.0 (d, J = 6.0 Hz), 64.3 (d, J = 6.0 Hz), 83.3 (d, J = 6.0 Hz), 127.1, 128.9, 129.2, 134.5 (d, J = 6.0 Hz), 202.6 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.00; HRMS (ESI) calcd for $C_{13}H_{20}O_5P$ $[M + H]^+$ 287.1037, found 287.1048.

*Diethyl (1-(Naphthalen-2-yl)-2-oxopropyl) Phosphate (**3n**).* The title compound was prepared according to the general procedure as described above in 45% yield: pale yellow liquid, 17 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.15 (3H, dt, J = 1.2, 7.2 Hz), 1.33 (3H, dt, J = 1.2, 7.2 Hz), 2.19 (3H, s), 3.91−4.01 (2H, m), 4.15−4.27 (2H, m), 5.85 (1H, d, J = 8.4 Hz), 7.47−7.50 (1H, m), 7.51−7.55 (2H, m), 7.83−7.89 (3H, m), 7.94 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 7.5 Hz), 16.0 (d, J = 7.5 Hz), 25.65, 64.1 (d, J = 6.0 Hz), 64.42 (d, J = 6.0 Hz), 83.4 (d, J = 4.5 Hz), 123.9, 126.9, 127.0, 127.7, 128.1, 128.9, 131.8 (d, J = 4.5 Hz), 133.1, 133.5, 202.6 (d, J = 6.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.90; HRMS (ESI) calcd for $C_{17}H_{22}O_5P$ $[M + H]^+$ 337.121, found 337.1205.

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*Diethyl (2-Oxo-1-(thiophen-2-yl)propyl) Phosphate (**3o**).* The title compound was prepared according to the general procedure as described above in 47% yield: pale yellow liquid, 16 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (3H, dt, J = 1.2, 7.2 Hz), δ 1.32 (3H, dt, J = 0.6, 7.2 Hz), 2.18 (3H, s), 3.93−4.02 (2H, m), 4.11−4.24 (2H, m), 5.77 (1H, d, J = 8.4 Hz), 7.07−7.10 (1H, m), 7.33−7.36 (1H, m), 7.42 (1H, d, J = 3.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8 (d, J = 6.0 Hz), 16.0 (d, J = 7.5 Hz), 25.5, 64.1 (d, J = 6.0 Hz), 64.3 (d, J = 6.0 Hz), 79.4 (d, J = 4.5 Hz), 124.6, 125.8, 127.0, 135.1 (d, J = 4.5 Hz), 202.3 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.17; HRMS (ESI) calcd for $C_{11}H_{18}O_5PS$ [M + H]$^+$ 293.0598, found 293.0607.

*1-(4-Bromophenyl)-2-oxopropyl Dimethyl Phosphate (**3p**).* The title compound was prepared according to the general procedure as described above in 63% yield: pale yellow liquid, 24 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.15 (3H, s), 3.63 (3H, d, J = 10.8 Hz), 3.83 (3H, d, J = 11.4 Hz), 5.64 (1H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.54 (2H, d, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.6, 54.4 (d, J = 6.0 Hz), 54.8 (d, J = 4.5 Hz), 82.6 (d, J = 6.0 Hz), 123.7, 128.7, 132.2, 133.3 (d, J = 4.5 Hz), 201.9 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.01; HRMS (ESI) calcd for $C_{11}H_{15}BrO_5P$ [M + H]$^+$ 336.9826, found 336.9840.

*Diethyl (3-Oxo-1-phenylbutan-2-yl) Phosphate (**3q**).* The title compound was prepared according to the general procedure as described above in 58% yield: pale yellow liquid, 20 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.17 (3H, dt, J = 0.6, 7.2 Hz), 1.23 (3H, dt, J = 0.6, 6.6 Hz), 2.16 (3H, s), 2.95−3.03 (1H, m), 3.10−3.18 (1H, m), 3.78−3.94 (3H, m), 4.00−4.08 (1H, m), 4.81−4.87 (1H, m), 7.22−7.26 (3H, m), 7.28−7.32 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9 (d, J = 7.5 Hz), 15.9 (d, J = 6.0 Hz), 26.5, 38.7 (d, J = 6.0 Hz), 63.8 (d, J = 6.0 Hz), 64.0 (d, J = 6.0 Hz), 82.3 (d, J = 6.0 Hz), 127.0, 128.5, 129.6, 135.4, 206.4 (d, J = 3.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −2.07; HRMS (ESI) calcd for $C_{14}H_{22}O_5P$ [M + H]$^+$ 301.1196, found 301.1199.

*Diethyl (4-Oxo-1-phenylpentan-3-yl) Phosphate (**3r**).* The title compound was prepared according to the general procedure as described above in 56% yield: pale yellow liquid, 20 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31−1.41 (6H, m), 2.05−2.14 (2H, m), 2.23 (3H, s), 2.69−2.78 (2H, m), 4.09−4.25 (4H, m), 4.63−4.73 (1H, m) 7.15−7.24 (3H, m), 7.24−7.33 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.0 (d, J = 6.0 Hz), 26.0, 30.7, 34.1 (d, J = 6.0 Hz), 64.1 (d, J = 6.0 Hz), 64.2 (d, J = 6.0 Hz), 81.3 (d, J = 6.0 Hz), 126.2, 128.4, 128.5, 140.3, 206.2 (d, J = 3.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.56; HRMS (ESI) calcd for $C_{15}H_{24}O_5P$ [M + H]$^+$ 315.1378, found 315.1356.

*Diethyl (2-Oxoheptan-3-yl) Phosphate (**3s**).* The title compound was prepared according to the general procedure as described above in 74% yield: pale yellow liquid, 22 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 5.4 Hz), 1.28−1.45 (10H, m), 1.74−1.82 (2H, m), 2.22 (3H, s), 4.09−4.21 (4H, m), 4.59−4.67 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 16.0 (d, J = 6.0 Hz), 22.2, 25.9, 26.5, 32.1 (d, J = 4.5 Hz), 64.0 (d, J = 6.0 Hz), 64.1 (d, J = 6.0 Hz), 82.0 (d, J = 6.0 Hz), 206.4 (d, J = 4.5 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.64; HRMS (ESI) calcd for $C_{11}H_{24}O_5P$ [M + H]$^+$ 267.1375, found 267.1361.

*Diethyl (2-Oxononan-3-yl) Phosphate (**3t**).* The title compound was prepared according to the general procedure as described above in 61% yield: pale yellow liquid, 20 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.2 Hz), 1.21−1.46 (14H, m), 1.73−1.79 (2H, m), 2.22 (3H, s), 4.09−4.19 (4H, m), 4.60−4.65 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 16.0, 16.0 (d, J = 6.0 Hz), 22.4, 24.4, 25.9, 26.7, 31.4, 32.4 (d, J = 4.5 Hz), 64.0 (d, J = 7.5 Hz), 64.1 (d, J = 4.5 Hz), 82.0 (d, J = 6.0 Hz), 206.6 (d, J = 3.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.64; HRMS (ESI) calcd for $C_{13}H_{28}O_5P$ [M + H]$^+$ 295.1667, found 295.1669.

*Diethyl (5-Methyl-2-oxohexan-3-yl) Phosphate (**3u**).* The title compound was prepared according to the general procedure as described above in 62% yield: pale yellow liquid, 18 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91−1.01 (6H, m), 1.30−1.38 (6H, m), 1.45−1.53 (1H, m), 1.65−1.72 (1H, m), 1.77−1.88 (1H, m), 2.22 (3H, d, J = 1.2 Hz), 4.08−4.21 (4H, m), 4.63−4.70 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.0 (d, J = 6.0 Hz) 21.4, 23.1, 24.1, 25.5, 41.2 (d, J = 7.5 Hz), 64.0 (d, J = 6.0 Hz), 64.2 (d, J = 6.0 Hz), 80.7 (d, J = 7.5 Hz), 206.6; ^{31}P (161 MHz, $CDCl_3$) δ −1.64; HRMS (ESI) calcd for $C_{11}H_{24}O_5P$ [M + H]$^+$ 267.1354, found 267.1356.

*1-(4-Bromophenyl)-1-oxopropan-2-yl Diethyl Phosphate (**4a**).* The title compound was prepared according to the general procedure as described above in 27% yield: colorless liquid, 11 mg, eluent EtOAc/petroleum ether (1:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (3H, dt, J = 0.6, 7.2, Hz), 1.32 (3H, dt, J = 0.6, 6.6, Hz), 1.60 (3H, d, J = 6.6 Hz), 4.04−4.18 (4H, m), 5.61−5.70 (1H, m), 7.63 (2H, d, J = 9.0 Hz), 7.85 (2H, d, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 16.0 (d, J = 7.5 Hz) 19.1 (d, J = 4.5 Hz), 64.1 (d, J = 6.0 Hz), 64.2 (d, J = 6.0 Hz), 74.5 (d, J = 4.5 Hz), 128.9, 130.3, 132.1, 132.9, 195.4(d, J = 6.0 Hz); ^{31}P (161 MHz, $CDCl_3$) δ −1.97; HRMS (ESI) calcd for $C_{13}H_{19}BrO_5P$ [M + H]$^+$ 365.0155, found 365.0153.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01172.

^{1}H, ^{13}C, and ^{31}P NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Direct Construction of 2,3-Dihydroxy-2,3-diaryltetrahydrofurans via *N*-Heterocyclic Carbene/Base-Mediated Domino Reactions of Aromatic Aldehydes and Vinyl Selenone

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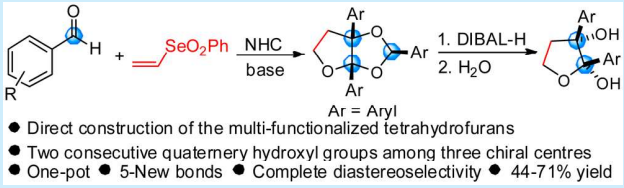
Supporting Information

ABSTRACT: A one-pot, stereoselective construction of 2,3-dihydroxy-2,3-diaryltetrahydrofurans has been achieved via *N*-heterocyclic carbene (NHC)/base-mediated domino reactions of aldehydes and vinyl selenone. The products containing two contiguous quaternary hydroxyl functionalities among the three stereocenters are obtained advantageously as either acetals or ketals through the formation of five new chemical bonds in a single operation. This report constitutes an altogether different reactivity of vinyl selenone in comparison with the corresponding sulfones and phosphonates under NHC/base-mediated reactions.

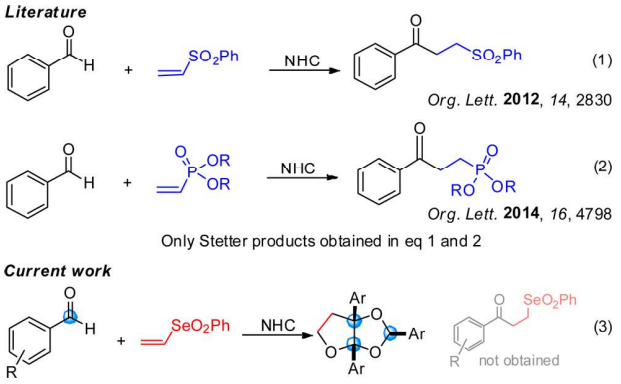


The catalytic stereoselective synthesis of functionalized scaffolds in a concise manner is a highly desirable and challenging endeavor in organic synthesis; e.g., multisubstituted tetrahydrofuran moieties present in numerous natural products and pharmaceutical ingredients.[1] In that direction, one-pot multicomponent reactions[2] and domino reactions[3] are vital tools. *N*-Heterocyclic carbenes (NHC) alone, or in combination with co-catalysts like Bronsted acids, Lewis acids, or transition-metal complexes, have enabled the discovery of a wide range of such reactions via new modes of activation.[4,5]

The synthesis of organoselenides/-selenones has recently attracted considerable attention because of their biological properties.[6] More significantly, the insertion of a selenide/selenone group is often accompanied by self-induced unexpected, yet interesting, transformations like vicinal group functionalization and the formation of rings/stereocenters via rearrangement because of a weaker C−Se σ-bond than even a closely resembling C−S bond.[7] Despite these aforesaid properties, metal-free catalytic asymmetric synthesis has remained relatively unexplored. Marini and Melchiorre's amine catalyzed α-selenenylation of aldehydes,[8i] Jacobsen's selenocyclization of alkenes in the presence of hydrogen-bond donor catalyst,[8e] and Zhu's Bronsted base-catalyzed addition of isocyanoacetates to vinyl selenones[7g] are some of the elegant methods for preparing chiral organoselenium compounds.[8] The group of Marini prepared spirolactones[7h] and cyclopropanes,[7k] whereas Zhu et al. reported oxazolidin-2-one[7c] and 1,3-oxazinan-2-one[7e] synthesis, taking advantage of the unprecedented self-rearrangement of the in situ generated organoselenones.

Our interest in expanding the horizons of NHC catalysis to unexplored or less explored domains,[9] on one hand, and the attractive properties of organoselenones, on the other hand, led us to explore the NHC-catalyzed addition of acyl anions, enolates, and homoenolates of aldehydes and enals to vinyl selenone and its other derivatives, which has so far proven elusive in the literature. It is worth noting here that Biju and co-workers reported Stetter reactions of aldehydes first with vinyl sulfones in 2012 and later with vinyl phosphonates in 2014 (eqs 1 and 2, Scheme 1).[10,11] We began our studies using 4-bromobenzaldehyde and vinyl selenone (Table 1). In analogy with sulfones and phosphonates, due to their comparable reactivity, the formation of the Stetter product via addition of an acyl anion equivalent to the vinyl selenone was anticipated. To our surprise, we obtained a highly functionalized

Scheme 1. NHC/Base-Mediated Reaction of Aldehydes and Vinyl Selenone



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Construction of Phenanthrenes and Chrysenes from β-Bromovinylarenes via Aryne Diels−Alder Reaction/Aromatization

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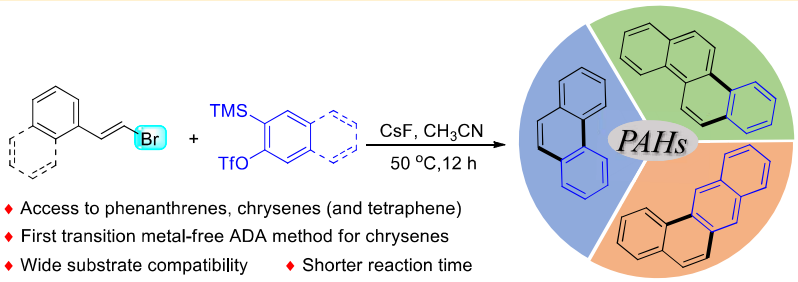
Supporting Information

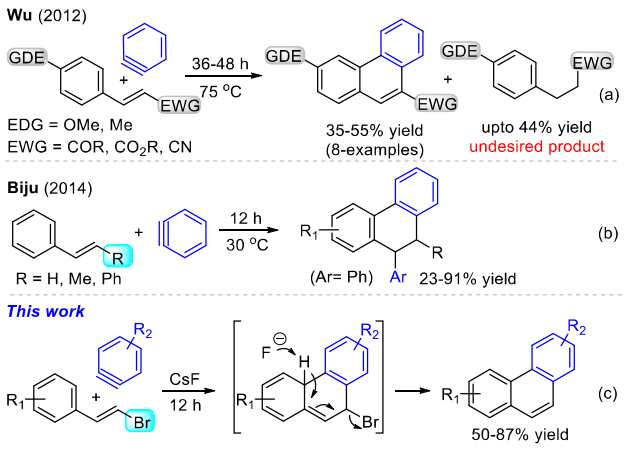


ABSTRACT: A highly efficient transition-metal-free general method for the synthesis of polycyclic aromatic hydrocarbons like phenanthrenes and chrysenes (and tetraphene) from β-bromovinylarenes and arynes has been developed. The reactions proceed via an aryne Diels−Alder (ADA) reaction, followed by a facile aromatization. This is the first report on direct construction of chrysenes (and tetraphene) using the ADA approach. Unlike the literature method which is limited to only 9/10-substituted derivatives, this method gives access to a wide variety of functionalized phenanthrenes.

The preparation of phenanthrenes has received significant attention among the various polycyclic aromatic hydrocarbons (PAHs) because of their presence in natural products and pharmaceutics like antiviral, anticancer, and antimalarial agents.[1] Apart from this, they also find a huge application in material chemistry due to their photochemical and electroluminescent properties.[2] Classically, phenanthrenes have been accessed via metal-catalyzed Ullman−McMurry,[3a] Pschorr,[3b] Mallory cyclization of stilbenes,[3c] radical coupling,[3d,e] photochemical cyclization,[3f,g] ring-closing metathesis,[3h] etc.[3i−n] On the other hand, arynes, unlike strain-free alkynes, have a high electrophilic reactivity due to a lower LUMO.[4] Therefore, the recent approach for phenanthrene synthesis includes cocyclization of arynes with alkynes/allenes/halostyrenes/halobiaryls, biaryls, haloaryls, etc.[5] This approach, primarily driven by the groups of Larock, Guitian, Yamamoto, and Yao, allows for the direct assembly of functionalized phenanthrenes.[5] Nevertheless, all of these methods are transition-metal-catalyzed and often suffer from one or the other limitations like *cyclotrimerizations of arynes* due to their electrophilic nature, accessibility of the advanced starting materials, relatively lower overall yield, compatibility of functional groups, formation of undesired side products, etc.

In continuation of our work in developing (transition)metal-free reactions,[6] we were interested in preparing phenanthrenes under transition-metal-free conditions from arynes. The preparation of phenanthrenes from arynes under transition-metal-free conditions has scarcely been studied. The group of Wu established the preparation of 3,9-disubstituted phenanthrenes using styrenes compulsorily substituted with a strong electron-donating group (EDG) at the *para*-position on the aromatic ring and an electron-withdrawing group (EWG) such as keto, ester, and cyanide at the β-position of the styrenes (Scheme 1a).[7a] This method afforded the desired products in 35−55% yield along with an undesired byproduct (saturated

Scheme 1. Preparation of PAHs from Arynes under Transition-Metal-Free Conditions



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Stereoselective Oxidative Rearrangement of Disubstituted Unactivated Alkenes Using Hypervalent Iodine(III) Reagent

Chandra Bhan Pandey, Tazeen Azaz, Ram Subhawan Verma, Monika Mishra, Jawahar L. Jat, and Bhoopendra Tiwari*

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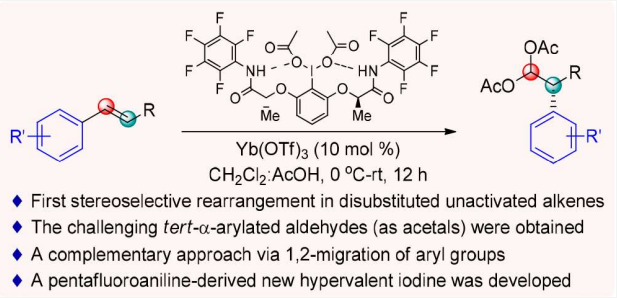
ABSTRACT: The stereoselective oxidative rearrangement of disubstituted unactivated olefins has been achieved using a hypervalent iodine(III) reagent. The aryl group undergoes 1,2-migration to give *tert*-α-arylated aldehydes (as acetals). The preparation of these aldehydes/acetals, especially containing a *tert*-benzylic stereocenter, has remained challenging. This migration-based method provides a complementary approach over the known α-substitution-based methods for accessing this class of molecules.

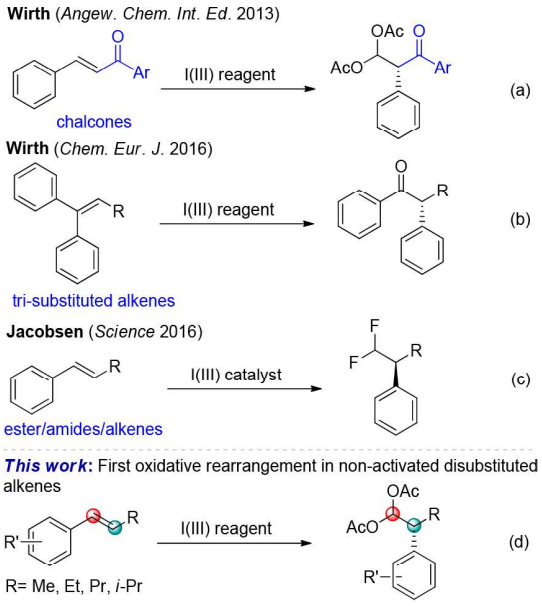


The stereoselective functionalization of olefins has been a long-standing interest as they unarguably possess one of the most diverse reactivities. Accordingly, a plethora of synthetic methodologies has been discovered using both transition metal as well as metal-free organocatalytic approaches.[1] Given the latter's promising advantages, several different classes of organocatalysts have emerged.[2] Among them, hypervalent iodines have more recently gained tremendous attention due to their intrinsic properties.[3,4] For instance, the highly electrophilic nature coupled with an excellent leaving ability of iodoaryls(III) enable them to induce exclusive rearrangements through aryl migration, ring-expansion, or ring-contraction to generate complexity and new stereocenters in a single step operation. With chiral hypervalent iodines, much of the success has come from the direct functionalization of the olefinic double bonds, as investigated by the groups of Jacobsen, Muniz, Fujita, Gilmour, and others.[5] On the other hand, the stereoselective rearrangement through a migration of one of the substituents on the double bond has remained challenging, with a very limited success. In 2013, the group of Wirth reported the first asymmetric migration of aryl groups in chalcones to produce α-arylated ketones using lactate-based chiral hypervalent reagent[6] in 52−96% ee and moderate to excellent yield (Scheme 1a).[7d] The same group later achieved a similar rearrangement in trisubstituted alkenes to give α-arylated ketones (Scheme 1b).[7b]

Very recently, the group of Jacobsen reported an excellent catalytic asymmetric migratory germinal difluorination of di- and trisubstituted alkenes/ester/amides to generate a difluoromethylated stereocenter (Scheme 1c).[7a]

α-Aryl substituted aldehydes, containing a benzylic stereocenter, are an important class of synthons for bioactive

Scheme 1. Hypervalent Iodine-Mediated Stereoselective Rearrangement of Alkenes



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