Doctoral Dissertation (Censored)

博士論文 (要約)

Zinc-Catalyzed Phosphonylation Reactions for Efficient Synthesis of Organophosphites/Organophosphates

(触媒的亜リン酸化反応による効率的亜リン酸・リン酸エステル合成)

A Dissertation Submitted for the Degree of Doctor of Philosophy

July 2021

令和 3 年 7 月博士（理学）申請

Department of Chemistry, Graduate School of Science,
The University of Tokyo

東京大学大学院理学系研究科

化学専攻

Soo Min Cho

曺秀旼

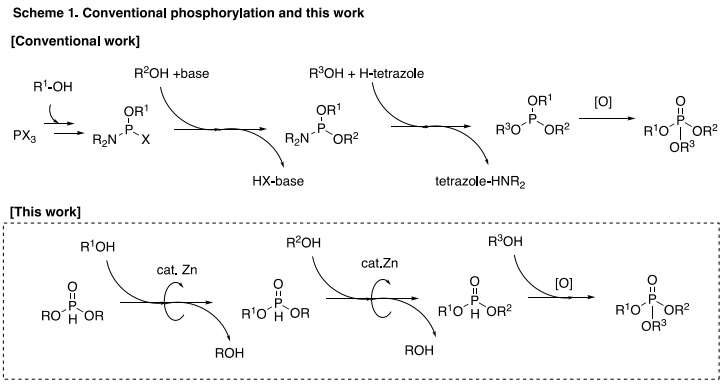
Abstract

Zinc-Catalyzed Phosphonylation Reactions for Efficient Synthesis of Organophosphites/Organophosphates

1. Introduction

Organophosphonates are highly important class of compounds since they are found in various kinds of natural products and pharmaceutical agents and also have applications in oligonucleotide therapeutics. Oligonucleotides are short DNA/RNA molecules, which consist of 2'-deoxyribonucleosides or ribonucleosides joined via phosphodiester linkages. Phosphorylation of alcohols is the most straightforward way to gain organophosphate molecules, and can be achieved by substitution of alcohols on the phosphorus atom. Designing efficient phosphorylating reagents and activating reagents have gained lots of attention, and P(III) phosphites have become one of the most attractive phosphorylating reagents since they are reactive and can be readily oxidized to phosphates.[1] For example, the substitution by a variety of alcohols on phosphoramidites and H- phosphonates enabled highly reliable methods to be developed and are currently used for the manufacture of oligonucleotides, mainly in the solid-phase synthesis. However, these methods have some drawbacks such as requiring stoichiometric amounts of activation reagents and producing a large amount of waste.[1] Some catalytic phosphorylation reactions have also been reported, but they all require harsh reaction conditions and substrate scopes are rather limited. Most importantly, there has been no effort made to introduce second alcohols to obtain phosphite diesters.[2,3] Therefore, I decided to focus on the phosphonylation of alcohols using a catalytic amount of Lewis acid under mild reaction conditions to access various kinds of phosphates/phosphites/phosphonates and further that allows second introduction of alcohols (Scheme 1).

Scheme 1. Conventional phosphorylation and this work

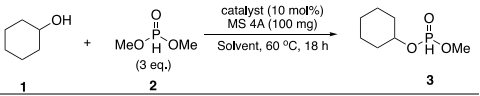


2. Results and Discussion

2.1 Zinc-catalyzed phosphonylation of alcohols with dimethyl phosphites

Various Lewis acids were first examined using cyclohexanol (**1**) as a model alcohol with dimethyl phosphite (**2**) as a phosphonylation reagent since it is an inexpensive and readily available reagent. Molecular sieves were employed to capture the leaving methanol, and therefore efficiency of the transesterification reaction was increased. After screening various Lewis acid catalysts, it was revealed that most of the Zn salts showed the highest catalytic activity than other metal salts (Table 1, entries 1-4), especially square-planar Zn complexes such as $Zn(acac)_2$ and $Zn(salicylate)_2$ (Table 1, entries 5-8). Zn oxo-cluster $Zn_4(TFA)_6O$ also showed catalytic activity that was comparable to that of $Zn(acac)_2$ but further comparison of these active Zn salts at decreased reaction temperature revealed that $Zn(acac)_2$ showed higher catalytic activity than the Zn cluster catalyst (Table 1, entries 10 and 11). After further optimization with $Zn(acac)_2$, I could improve the desired product (**3**) yield to 94%. The reaction hardly proceeded in the absence of molecular sieves. With optimized reaction conditions in hand, substrate scope was

Table 1. Catalyst screening



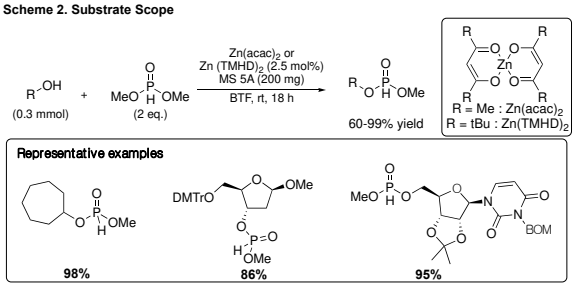
1 2 3

Entry	Catalyst	Solvent	Yield (%)
1	$Sc(OTf)_3$	Toluene	<5
2	$La(OTf)_3$	Toluene	19
3	$Hf(OTf)_4$	Toluene	<5
4	$Co(acac)_2$	Toluene	58
5	$Zn(acac)_2$	Toluene	77
6	$Zn(OTf)_2$	Toluene	56
7	$ZnEt_2$	Toluene	46
8	$Zn(Salicylate)_2$	Toluene	64
9[a]	$Zn_4(TFA)_6O$	Toluene	77
10[b]	$Zn(acac)_2$	Toluene	87
11[a,b]	$Zn_4(TFA)_6O$	Toluene	65
12[a,b,c]	$Zn(acac)_2$	BTF	<5
13[a,b,d]	$Zn(acac)_2$	BTF	94

[a] 2.5 mol% of catalyst was used. [b] Reaction temperature 40 °C. [c] Without molecular sieves. [d] 200 mg of MS 5A was used instead of MS4A.

investigated. Various alcohols including primary, secondary, and even tertiary alcohols of acyclic and cyclic structures, carbohydrates, steroids, and amino acids reacted smoothly with excellent functional group tolerance, and interestingly, a sterically hindered Zn complex, such as bis(2,2,6,6-tetramethyl-3,5-heptanedionato)zinc(II) ($Zn(TMHD)_2$) demonstrated the best activity for sterically hindered alcohols (Scheme 2). Phosphonylation of nucleosides was also investigated using the Zn catalyst, and I confirmed that several oligonucleotides could be synthesized. I also confirmed that a phosphonylated product could be easily oxidized to a biologically important trialkyl phosphate in high yield by a slightly modified, reported procedure,[4] and this result suggests that the currently described method could be combined with the oxidation protocol to access to a wide variety of trialkyl phosphates with high efficiency. In conclusion, I could achieve an efficient zinc-catalyzed phosphonlyation of alcohols using dimethyl phosphite under mild reaction conditions to afford various mono-phosphonylated alcohols.[5]

Scheme 2. Substrate Scope



2.2 Zinc-catalyzed synthesis of phosphite diesters with methyl phosphites

This part is not published because it is scheduled to be published in journals or other publications within five years.

This part is not published because it is scheduled to be published in journals or other publications within five years.

4. References

[1] Beaucage, S. L. *et al. Tetrahedron Lett.* **1981**, *22*, 1859−1862. [2] Ishihara, K. *et al. Angew. Chem., Int. Ed.* **2007**, *46*, 1423−1426. [3] Kanai, M. *et al. ACS Cent. Sci.* **2020**, *6*, 283−292. [4] Prabhu, R. *et al. Org. Lett.* **2013**, *15*, 6062−6065. [5] Kobayashi, S. *et al. Org. Lett.* **2020**, *22*, 3171−3175.

【Publication(s) related to the thesis】

"Zinc-Catalyzed Phosphonylation of Alcohols with Alkyl Phosphites"
Saito Yuki, Cho SooMin, Danieli Alessandro Luca, Kobayashi Shu, *Organic Letters*, **2020**, *22*, 3171–3175.

【Publication(s) not related to the thesis】

"A Convenient and Mild Cyclocondensation Using Water-soluble Aldehydes in Water"
Kitanosono Taku, Cho SooMin, Kobayashi Shu, *Tetrahedron*, **2018**, *74*, 7237-7241.

【Oral presentations】

"Catalytic Phosphonation Reactions of Alcohols"
Cho SooMin, Saito Yuki, Kobayashi Shu
The 100th CSJ Annual Meeting, 2020. Mar.

"Catalytic Phosphonation of Alcohols Towards Synthesizing Bioinspired Phosphates"
Danieli A. Luca, Saito Yuki, Cho SooMin, Kobayashi Shu
The 100th CSJ Annual Meeting, 2020. Mar.

"Zinc-Catalyzed Phosphonylation of Alcohols with Alkyl Phosphites"
Cho SooMin, Danieli A. Luca, Matsunaga Akira, Saito Yuki, Kobayashi Shu
The 101st CSJ Annual Meeting, 2021. Mar.

"Investigation of the Leaving Group Effect of Phosphite Substituents on Catalytic Phosphonylation"
Danieli A. Luca, Saito Yuki, Cho SooMin, Kobayashi Shu
The 101st CSJ Annual Meeting, 2021. Mar.

"Zinc-catalyzed synthesis of disubstituted H-phosphonate"
Matsunaga Akira, Saito Yuki, Cho SooMin, Kobayashi Shu
The 101st CSJ Annual Meeting, 2021. Mar.

Acknowledgement

First, I would like to express my gratitude to Professor Kobayashi for accepting me in his group to study synthetic organic chemistry with his excellent guidance and advices. It was a great chance for me to learn about how to be a true scientist and researcher for this 5 years. Without his encouragement and exciting discussion, I would definitely not have made it.

I would also like to thank Dr. Saito Yuki for guiding me with the excellent project for the past three years. Without his fruitful advices and support, I would not be able to make the progress on this project so fast.

I would like to appreciate Dr. Kitanosono Taku, for guiding and supporting me during my master course. I was able to learn basic knowledge about chemistry and lab techniques through his help and able to graduate master course with one publication. I would also like to thank all the staff members who gave me valuable advices and suggestion in my research. I also appreciate Sakamaki san from Nakamura laboratory for helping me with mass spectrometry.

I am also thankful to my seniors, especially Dr. Xu Pengyu and Dr. Min Hyemin and Mr. Jose Alberto Rodriguez Santamaria for giving me lots of advices towards experiments and also life when I first came to Japan.

I would like to thank my colleagues, Ms. Yang Xi and Mr. Lu Fangqiu for going through this whole graduate school life together for 5 years. It was a great encouragement to continue research with these people. I would especially like to thank Ms. Yang Xi for being wonderful friend who was always there for me whenever I need her help.

I would also like to thank my juniors in this lab, Ms Cho Hyemin, Mr. Danieli Luca Alessandro, Mr. Chen Wenlong, Mr. Nishizawa Ken, Mr. Matsunaga Akira for their help and cooperation. I am also thankful to other members in this laboratory.

I want to thank my friends in Japan, Mr. Oka Yuki, Ms. Ko Jisuk, Mr. Jo Byeongook, Dr. Miller Sam, Dr. Kim Woogyeom, Mr. Ko Jin-ho, Dr. Yun Gwangnam, Dr. Ahn Sohjin, Dr. Kim Jeonghyun, Dr. Choi Saemi who gave me big emotional support and warm encouragement during 5 years of my life in Japan. I would also like to thank my friends in Korea and UK for their support.

Finally, I would like to thank my parents for supporting me financially and emotionally to complete my studies in Japan.

Cho SooMin

Table of Contents

Chapter 1. Introduction

1-1 Primary Metabolism

Every means of life depends on chemistry, which makes the chemical side of biology so fascinating. From simplest single-cell creatures to our human body, it is built up from the same molecules and all the functions are controlled by common metabolism: primary metabolism and secondary metabolism.

Primary metabolism is chemistry common to all living things' growth, development, and reproduction. It usually performs a physiological function in the organism (i.e. an intrinsic function). A primary metabolite, which is also referred to as a central metabolite, is typically present in many organisms or cells. Metabolites are biomolecules, micro as well as macromolecules which are either intermediates or the products of metabolism. They have definite role and function in metabolism and are essential for growth and development.[1]

The chart shown in **Figure 1-1** shows some common examples of primary metabolites and connections between them.[2] The chart shows their origin starts from CO_2 and then develops into some important intermediates, such as glucose, pyruvic acid, citric acid, acetylcoenzyme A (acetyl CoA) and so on. These molecules can be eventually built into nucleic acids and proteins which are mainly responsible for the biological events happening through life.

Nucleic acids are the most important substances since they store genetic information.[2] They are polymers which consist of monomers of nucleotides, a sugar molecule that is connected to a heterocyclic base and a phosphate ester. For example, one of the most important nucleotides is adenosine monophosphate (AMP), a nucleoside containing a pyrimidine base (adenine) with a phosphate ester group (**Figure 1-2**). Adenosine triphosphate (ATP) is another type of important nucleotide that has almost the same structure as AMP but with triple phosphates, and they are very reactive because phosphates are stable anions and good leaving groups. Various hard and soft nucleophiles can attack either phosphate group or CH_2 group on sugar (**Figure 1-2**). The high reactivity of phosphates plays key roles in metabolism since they are added up to compounds to make them to be more reactive while providing stable linkages between molecules.

Proteins are another important substances in nature since they play partial role as enzymes, which are catalysts for biological reactions.[2] A method by which a human body cells can regulate and control the activity of enzymes and change the functionality of proteins is known as covalent modification. This typically involves the addition of a specific functional group onto the enzyme by another molecule. There are many different types of covalent modifications that can take place inside human body and therefore can modify the proteins in many different ways, such as methylation[3], acetylation[4], sulfonation[5] and so on. Phosphorylation of alcohol is one of the most common means of covalent modification.[6] In fact, significant amounts of eukaryotic proteins are phosphorylated. Phosphorylation can be regulated by enzymes like many other reactions, and the family of enzymes that are responsible for this reaction is known as protein kinases (**Figure 1-3**)[7].

They catalyse the transfer of the terminal phosphoryl group (PO_3^{2-}) from adenosine triphosphate (ATP), which produced by the mitochondria of the cell, on to a hydroxyl containing residue (serine, thrconine or tyrosine) of the target protein. The activity of protein phosphorylation plays important roles in many cellular processes including cell cycle, growth, apoptosis and signal transduction pathways. Also, it can regulate enzyme activity, modulate its affinity to other proteins, and cells signalling. For example, cell survival can be regulated after protein kinase B is activated following phosphorylation of its Ser and Thr residues, whereas it can be turned off when proto-oncogene tyrosine-protein kinase (c-Src) is dephosphorylated, causing a block in the regulation of cell growth.

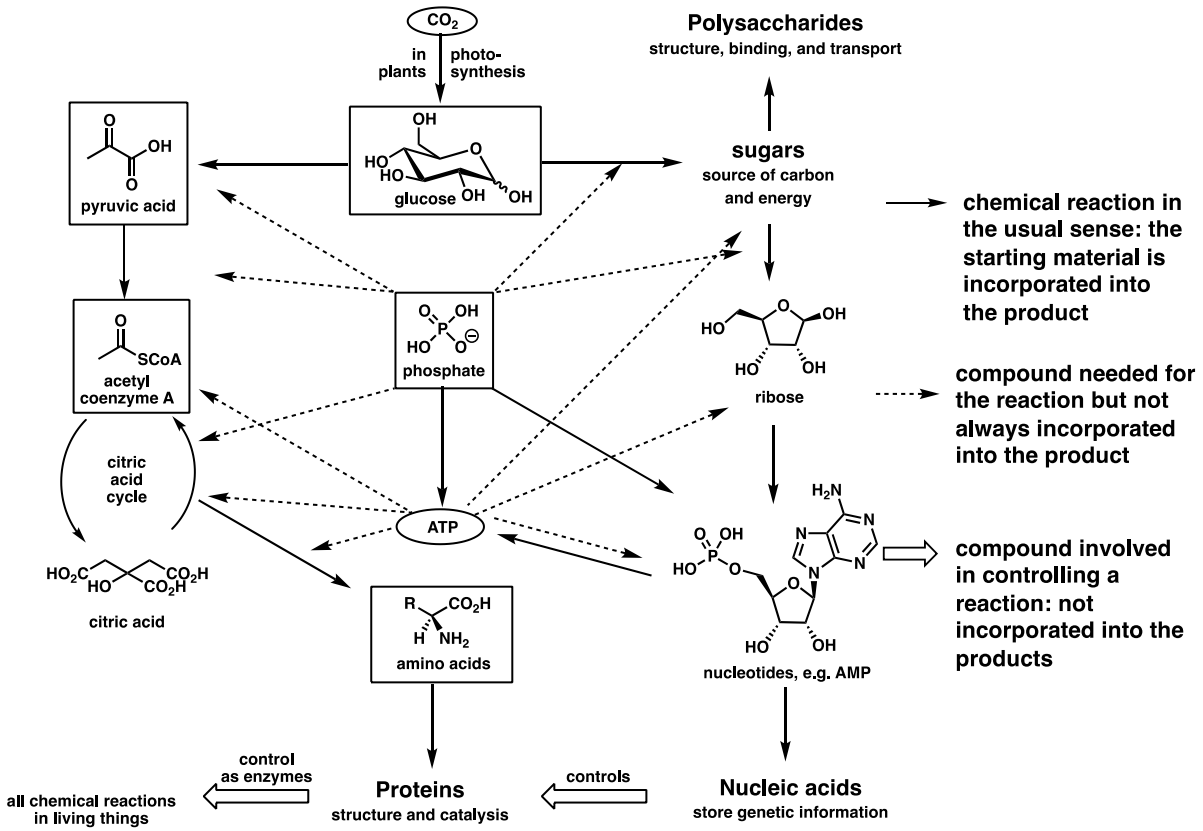


Figure 1-1. Primary Metabolism

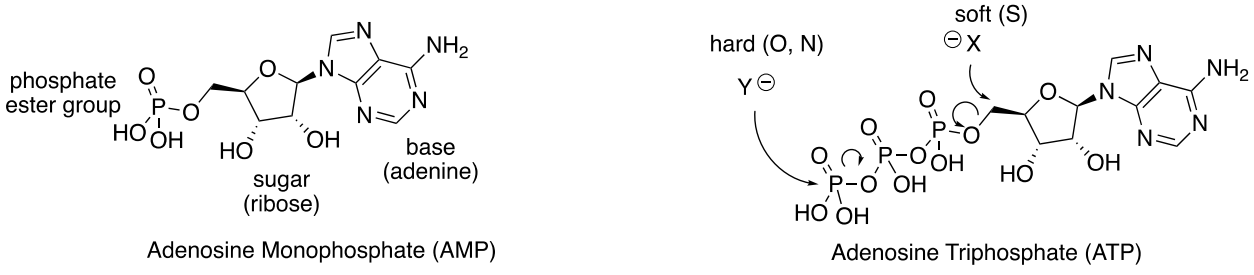


Figure 1-2. Structures of AMP and ATP

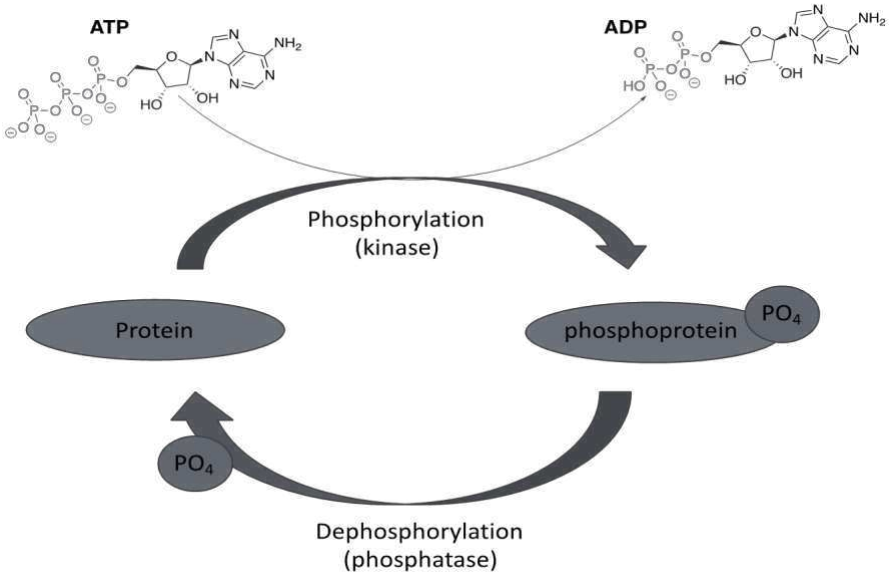


Figure 1-3. Protein Phosphorylation

The phosphate molecules also play key role in glycolysis. Glycolysis is a beginning of cellular respiration. It is a process taking glucose as a fuel and then breaking it up into two pyruvate (conjugate base of pyruvic acids) molecules under aerobic conditions.[8] During the process of glycolysis, it produces two ATPs net with reduced nicotinamide adenine dinucleotide, NADH (**Scheme 1-1**). The next step is the formation of acetyl coenzyme A, which is the initiator of the citric acid cycle. Pyruvate undergoes oxidative decarboxylation to form acetyl-CoA while releasing carbon dioxide. This is called a pyruvate dehydrogenase reaction. It is catalysed by the pyruvate dehydrogenase complex (**Scheme 1-2**).

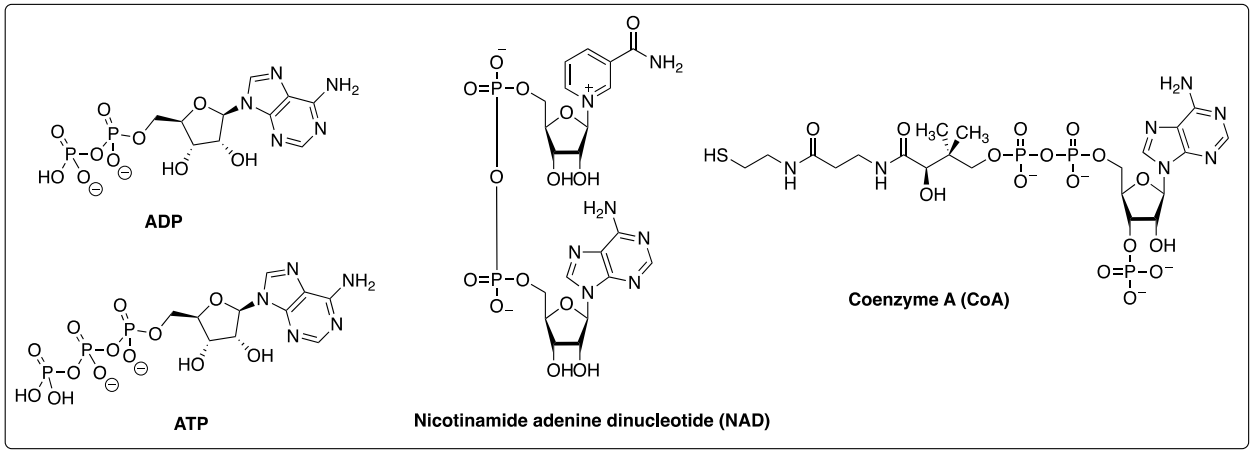
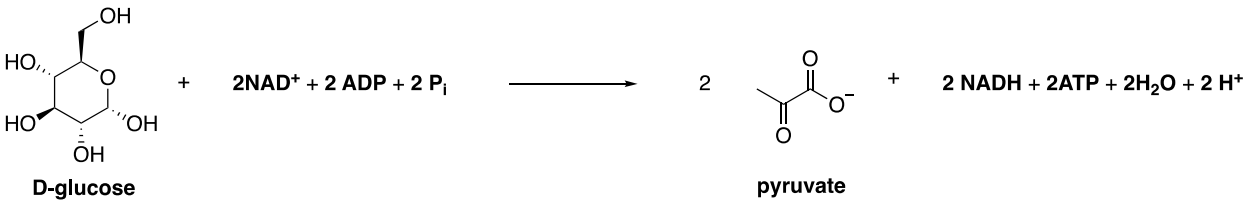
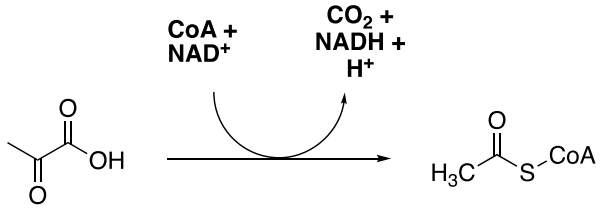


Figure 1-4. Structures of Important Biological Phosphate Molecules

Scheme 1-1. Glycolysis to produce pyruvate molecules

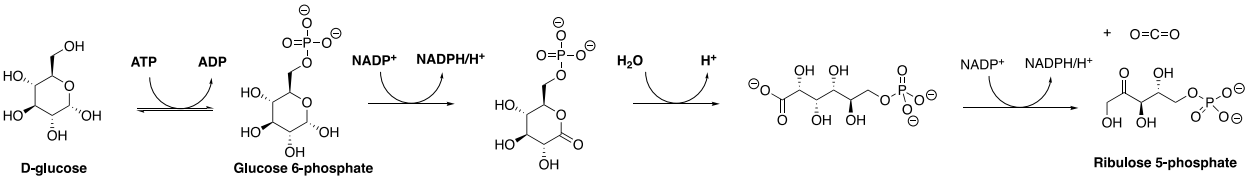


Scheme 1-2. Synthesis of acetyl coenzyme from pyruvic acid



The phosphate molecules also plays key role in synthesizing pentoses (5-carbon sugars) as well as ribose 5-phosphate, a precursor for the synthesis of nucleotides, through pentose phosphate pathway.[9] The pentose phosphate pathway is a metabolic pathway parallel to glycolysis. There are two distinct phases in the pathway; the oxidative phase, in which two NADPHs are generated, and the non-oxidative synthesis of 5-carbon sugars (**Scheme 1-3**).

Scheme 1-3. Pentose phosphate pathway



The reason why phosphorylation is such a common mechanism of regulation is from following reasons. First, phosphorylation gives the enzyme two extra negative charges, which can disrupt old interactions and form new interactions. This can in turn modify the active site and alter the catalytic rate of enzyme. Second, the negatively charged oxygen atoms of the phosphorylated side chain residue can form hydrogen bonds with other molecules, which will increase the specificity of interaction between the active site and the substrate. Third, the speed of which phosphorylation occurs could be easily controlled by the cell. Finally, the high abundancy of ATP allows the cell to utilize them quickly and effectively in phosphorylation.

1-2. Oligonucleotide Synthesis

In the field of organic chemistry, organophosphate molecules are one of the most important class of organic compounds. They are found in various natural products and pharmaceutical agents as well as in functional materials.[10] (**Figure 1-5**). For example, the glucocorticoid class of steroids is phosphorylated when used for medical treatment to improve water solubility.[11]

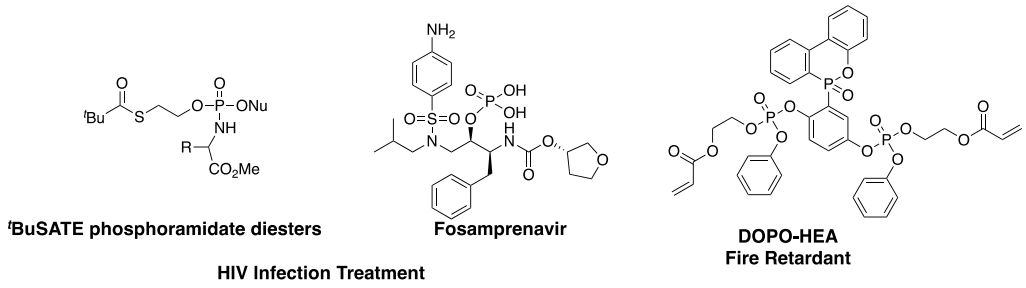


Figure 1-5. Organophosphate molecules

Phosphorylation of alcohols is the most straightforward way to access to organophosphate molecules. One of the most important applications of phosphorylation of alcohol is used in the synthesis of oligonucleotides. Chemists have devoted lots of effort on chemically synthesizing oligonucleotides, which are nucleosides (heterocyclic base connected to sugar molecules) joined via phosphodiester linkages (**Figure 1-6**). Due to its importance in genetic testing, DNA/RNA based therapeutics and forensics, it is extremely important to achieve the oligonucleotide synthesis in high yields and purity.[12] Phosphorylation of alcohols can be achieved by condensation reactions between alcohols and phosphorous reagents, and synthetic chemists have devoted much effort to designing efficient phosphorylating reagents and activating reagents such as phosphoryl chlorides and pyrophosphates to effect such transformations. (**Scheme 1-4** and **Scheme 1-5**)[13,14] However, these reactions have some limitations in terms of substrate scope since only simple alcohols can be employed.

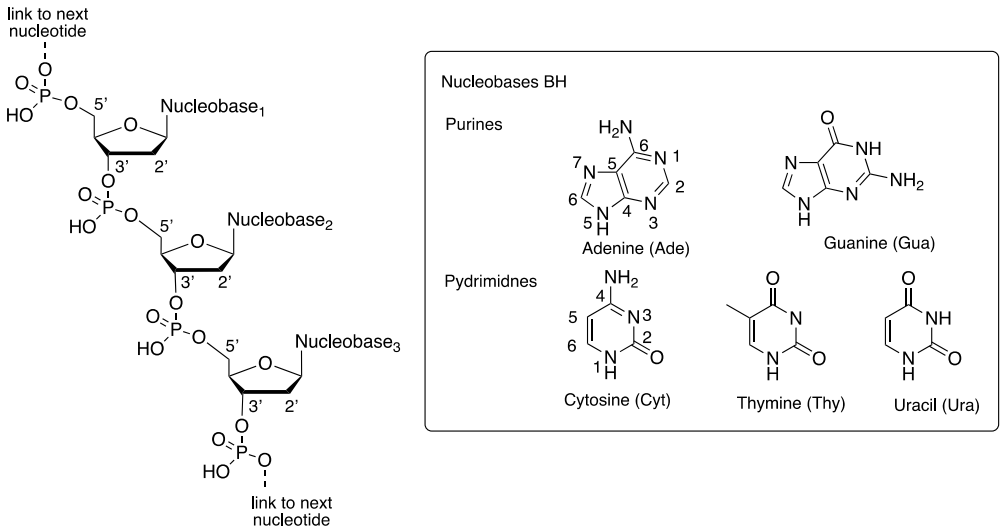
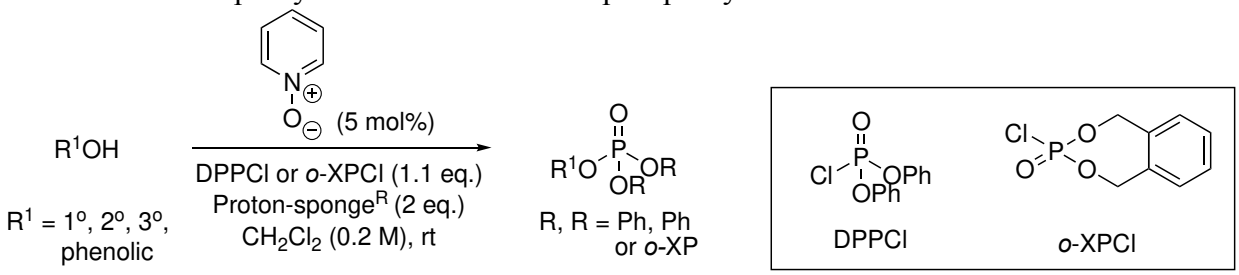
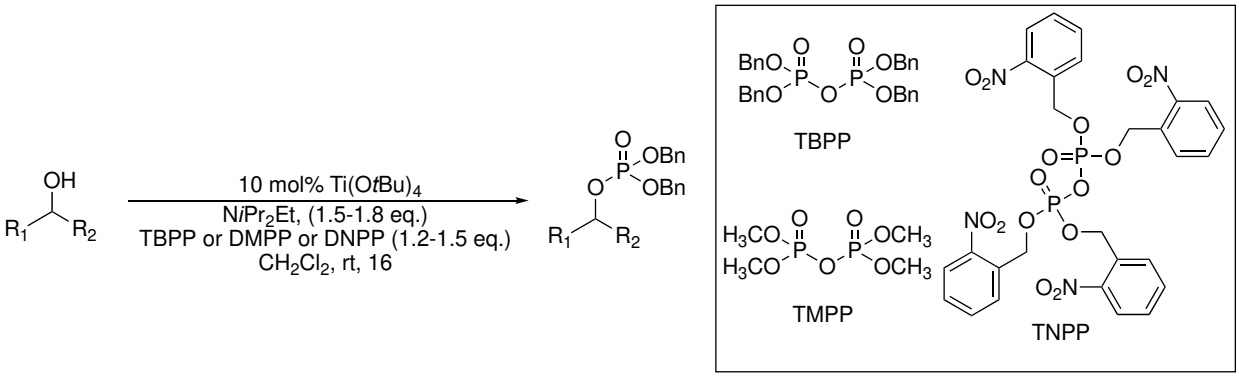


Figure 1-6. General Structure of Oligonucleotide

Scheme 1-4. Phosphorylation of alcohols with phosphoryl chloride[13]

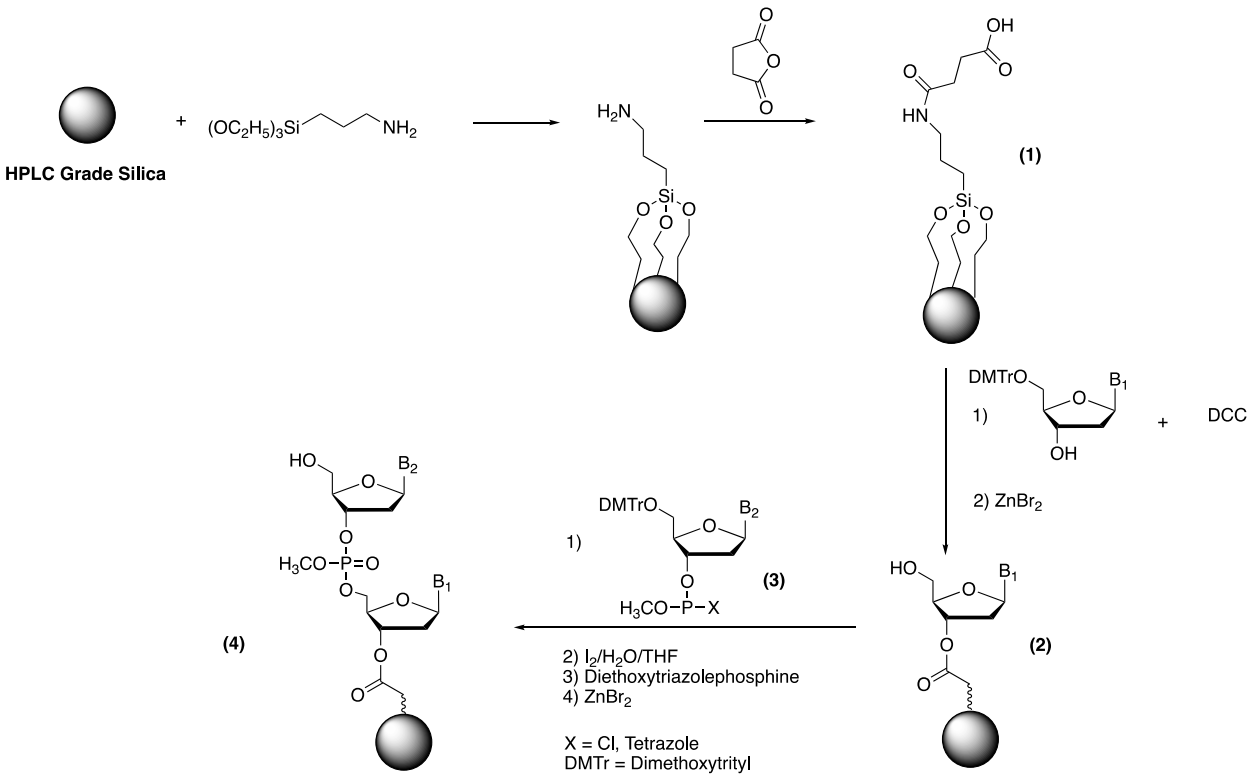


Scheme 1-5. Phosphorylation of alcohols with pyrophosphates[14]



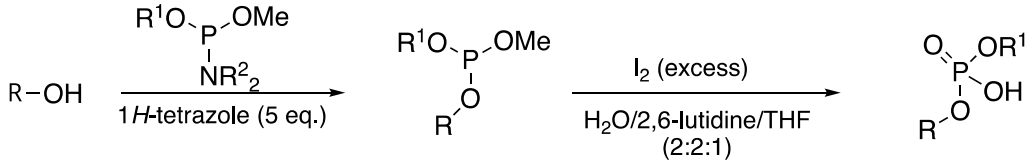
On the other hand, P(III) molecules are found to be more reactive and selective than P(V) reagents, and have been widely employed as starting materials to react with alcohols to provide phosphites/phosphonates, which can be readily oxidized to phosphates efficiently. It was confirmed that chloro- and dichlorophosphites react more rapidly than the corresponding phosphorochloridates with the 3'-hydroxyl group of a 2'-deoxynucleoside.[15] This observation led Caruthers's group to use of 2'-deoxynucleoside P(III) derivatives for synthesizing 2'-deoxyoligonucleotides on polymeric support (**Scheme 1-6**).[16] HPLC-grade silica gel was used as a support due to its chemically inertness, rigidness, and non-swelling nature in organic solvents. Various polymers have been shown to be inappropriate for reasons such as slow diffusion rates into the support, excessive swelling of various macroporous, low crosslinked polymers and irreversible adsorption of reagents onto the polymer.[16] HPLC grade silica was first activated by treating with (3-aminopropyl)triethoxysilane. This activated silica gel was then treated with succinic anhydride to form compound **1**. This then undergoes condensation with 5'-dimethoxytrityl-2'-deoxythymidine to the support using dicyclohexylcarbodiimide (DCC) as an activating agent. 5'-Dimethoxytrityl group was then removed by $ZnBr_2$ to give **2**. This was then further condensed with 2'-deoxynucleoside 3'phosphite **3** and further oxidised to phosphate with aqueous iodine. Any unreacted intermediates and protecting group were removed by diethoxytriazolephosphine and $ZnBr_2$ to give **4.**[18] The strategy seems quite straightforward, but limitation comes from instability of the reactive intermediates (nucleoside phosphomonochloridites or monotetrazolides) towards hydrolysis and air oxidation.

Scheme 1-6. DNA Synthesis on HPLC Silica

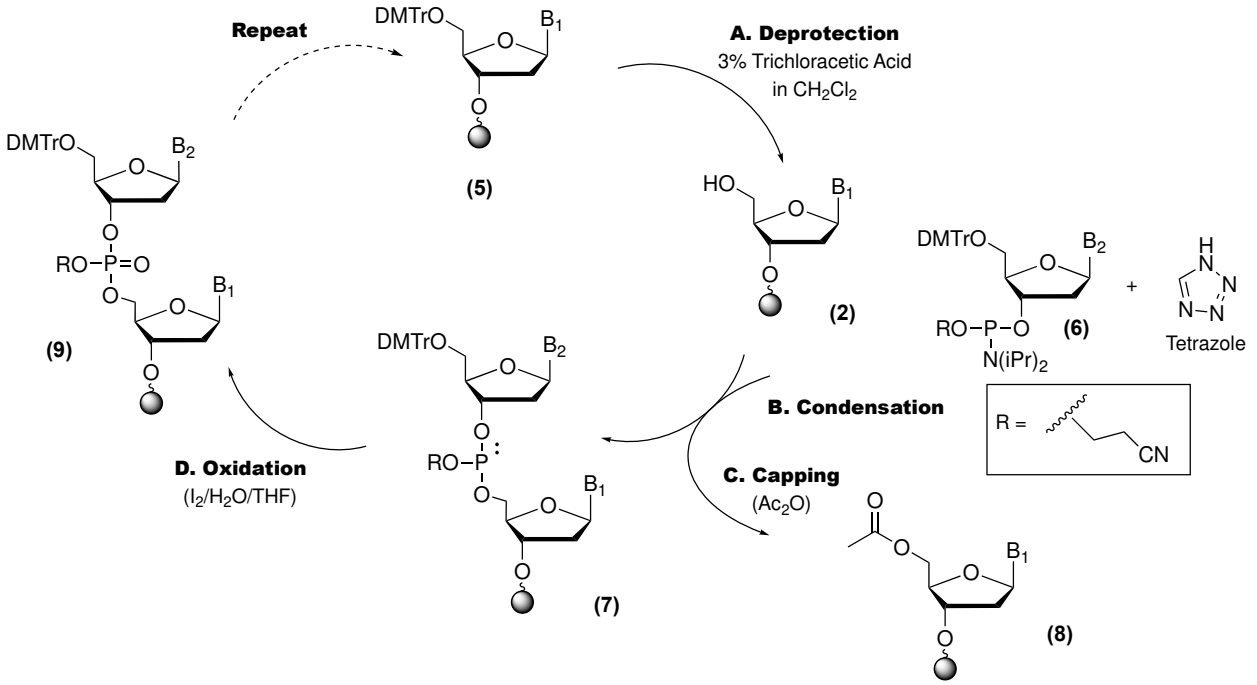


Based on this observation, Caruther's group developed synthesis of deoxypolynucleotide using phosphoramidites as phosphorylating reagent (**Scheme 1-7**). [17] The instability of reactive intermediates could be solved by either preparing the reactive species immediately prior to use or storing the active phosphite as a precipitate in hexanes at -20°C. New class of nucleoside phosphites, N, N-dimethylaminophosphoramidites were prepared and stored as dry, stable powders. They are found to be very stable under air and resistant to hydrolysis and air oxidation. This methodology was combined with the use of HPLC-grade silica gel as a solid support to developed an efficient method for oligonucleotide synthesis (**Scheme 1-8**). **5** was first treated with a solution of 3% trichloroacetic acid to revmove 5'-DMTr in DCM to form **2**. This was then condensed with 5'-dimethoxytrityl-2'-deoxynucleoside 3'-phosphoramidite **6** using tetrazole as an activator to yield phosphite triester **7**. Unreacted 5'-hydroxyl groups is capped using acetic anhydride activated by N-methylimidazole in pyridine (Step C). The intermediate phosphite triester is then finally oxidized to phosphate **9** using aqueous iodine.[18]

Scheme 1-7. Step-wise phosphonylation with phosphoramidites, followed by oxidation

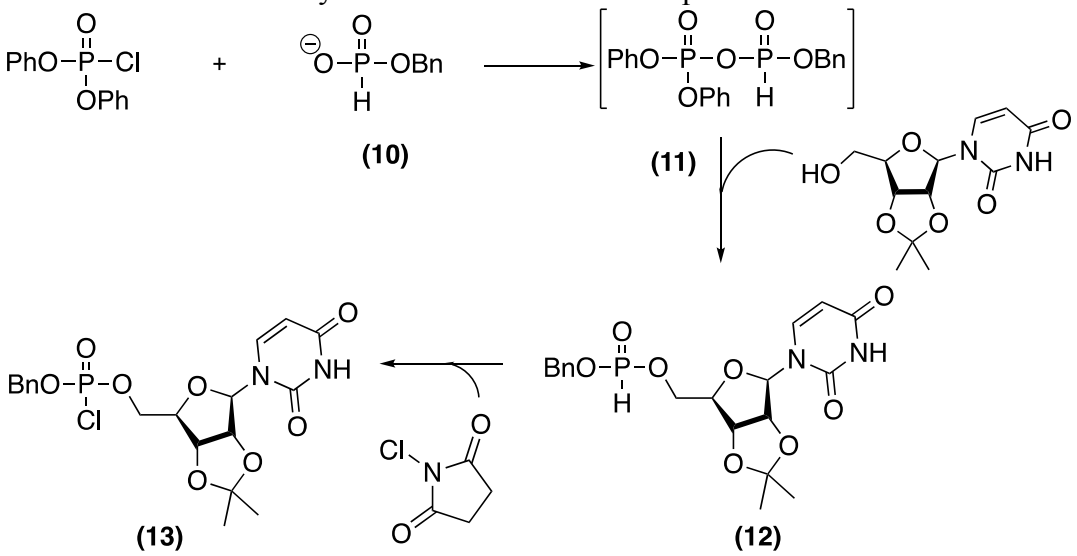


Scheme 1-8. The Phosphoramiditite Approach for Oligonucleotide Synthesis

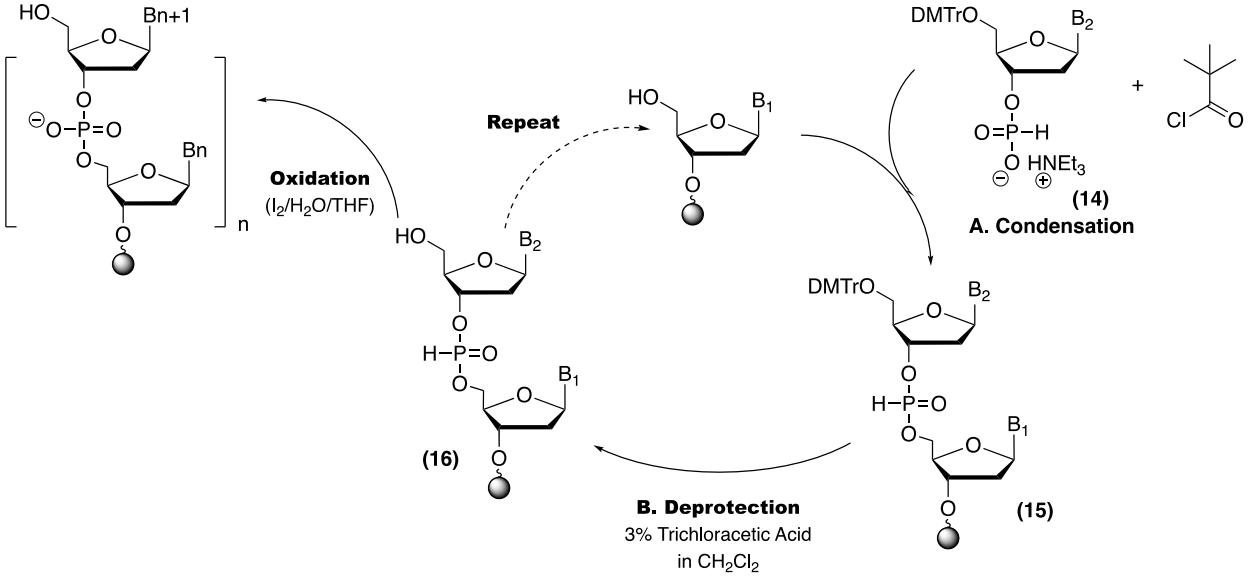


H-phosphonates (dialkyl phosphite) are another class of P(III) molecules that has enabled highly reliable methods to be developed that are currently used in organonucleotide synthesis. They contain phosphoryl group (P=O) and a hydrogen atom bonded to the phosphorous centre. H-phosphonates have the same tetrahedral geometry as P(V) molecules, and the central phosphorus atom has electrophilic nature with lacks of a lone pair of electrons. This provides resistance towards oxidation under ambient conditions. However, high reactivity of H-phosphonate monoesters to nucleophilic substitution makes them attractive candiates for preparing oligonucleotides.[18] H-phosphonates chemistry was first devloped by Sir Alexander Todd and co-workers.[19] They demonstrated that reaction of benzyl H-phosphonate monoester **10** with diphenyl phosphorochloridate will give corresponding activated mixed anhydride **11** as an assumed intermediate (**Scheme 1-9**). This compound was condensed in situ with the 5'-hydroxyl group of a 2'3'-isopropylidine nucleoside to yield the H-phosphonate diester **12** that was further oxdised by N-chlorosuccinimide to the phosphorochloridate diester **13**. This methodology was later adapted by various groups for the synthesis of oligonucleotide in solid phase synthesis.[20] The general scheme is depicted in **Scheme 1-10**. After removal of the 5'-dimethoxytrityl protecting group, condensation was carried out with an 5'-dimethoxytrityl protected 2'-deoxy or ribonucleoside H-phosphonate monoester **14** and an activating agent. The mixed anhydride can be induced to undergo a nucleophilic attack at the phosphorous atom by the 5'-hydroxyl of the nucleoside conncected to a polymeric support to give phosphite diester **15**. After removal of protecting group in acid mediated condition, oxidation was carried out to give final product **16**.

Scheme 1-9. Mixed Anhydride Activation of H-Phosphonates

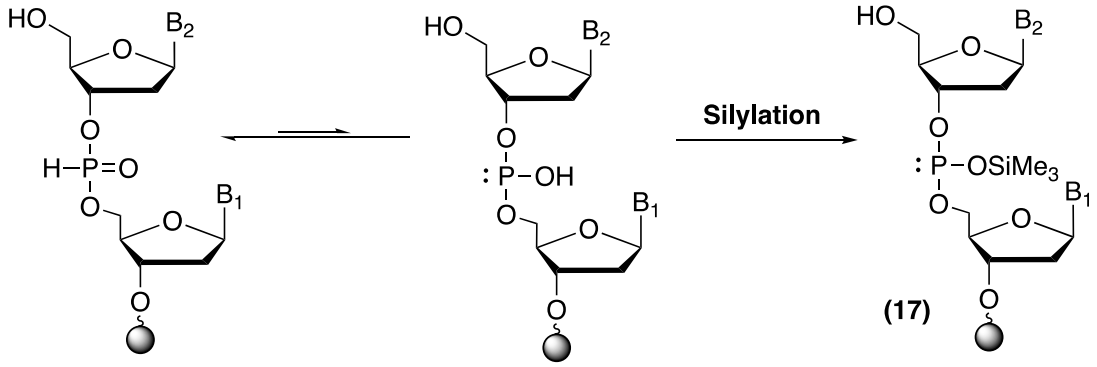


Scheme 1-10. The H-Phosphonate Approach to DNA/RNA Synthesis



The fact that the H-phosphonate diester and its phosphite triester can exist in equilibrium form also attracted additional attention to this methodology (**Scheme 1-11**). This phosphite can be trapped by silylation to form **17**, which creates a nucleophilic phosphorus centre with lone pair of electrons, that enhances reactivity towards electrophiles. This will allow synthesis of various organophosphate molecules. Since the silylation procedure can be performed at the end of the synthetic cycles, it can avoid being exposed to the acidic deprotonation solution, which makes it important when preparing acid sensitive analogues. However, only uniformly modified oligomers can be produced with this strategy.[18]

Scheme 1-11. The equilibrium existed in H-phosphonate diester

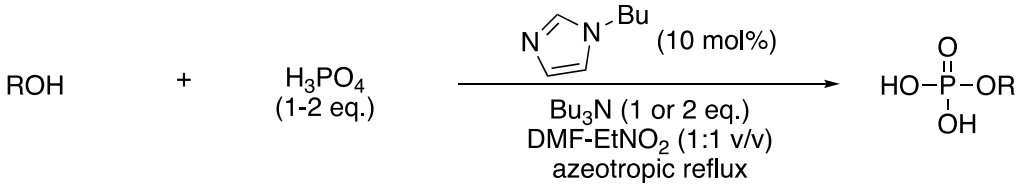


Due to these features, phosphoramidites and H-phosphonates offer a useful routes for the synthesis of oligonucleotide. However, all of these methods need large amount of activating agents and produce significant amount of waste. Also, since all the methods depend on solid-phase synthesis, large scale synthesis of oligonucleotides are quite difficult. Therefore, more efficient, direct catalytic phosphorylation method for synthesis of oligonucleotide that does not depends on solid phase synthesis is needed.

1-3. Development of Catalytic Phosphorylation Reaction

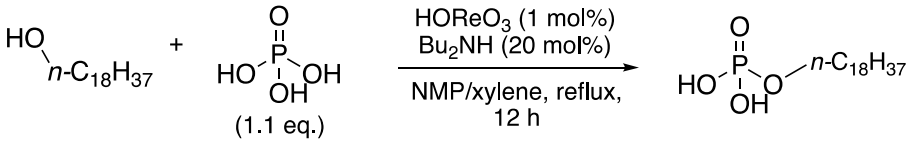
In 2005, Ishihara's group reported condensation reaction of phosphoric acid with alcohols catalysed by nucleophilic bases such as N-butylimidazole in the presence of tributylamine (**Scheme 1-12**).[21] However, this methodology required 2 equivalents of phosphoric acid with 2 equivalents of tributylamine in order to expect catalytic activity of nucleophilic base.

Scheme 1-12. Dehydrative Condensation of Phosphoric Acid and Alcohols Promoted by Nucleophilic Bases.

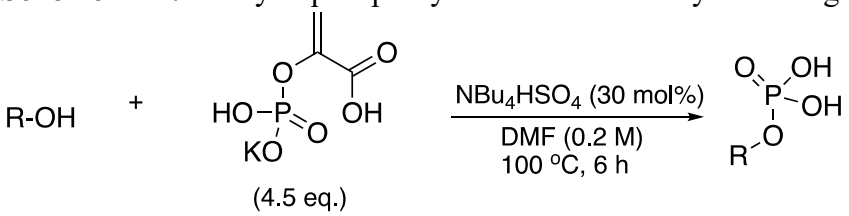


Based on this finding, in 2007, Ishihara's group achieved the direct catalytic condensation of phosphoric acid with an equimolar amount of an alcohol and synthesized several useful phosphoric acid monoesters (**Scheme 1-13**).[22] This catalytic condensation can be readily applied to large-scale processes with high efficiency. However, reaction temperatures above 150 °C were needed for the reaction, and substrates were rather limited. Most importantly, they did not investigate second introduction of alcohol to achieve phosphite diesters. Last year, Kanai's group also reported catalytic and chemoselective phosphorylation of alcohols using phosphoenolpyruvic acid monopotassium salt (PEP-K) as a phosphoryl donor and tetrabutylammonium hydrogen sulfate (TBAHS) as a catalyst (**Scheme 1-14**).[23] They suggested that TBAHS plays a significant role as both a Brønsted acid and a nucleophilic activator. This method enabled broad substrate scope of phosphate monoesters, including functionalized small molecules, carbohydrates, and unprotected peptides with high functional group tolerance. However, this method also required harsh reaction conditions and again, did not put any effort on introducing second alcohols to synthesize phophite diesters. Therefore, I aimed to synthesize various organophosphate molecules by simple phosphonylation under milder reaction conditions that allows second introduction of alcohol.

Scheme 1-13. Catalytic phosphorylation of alcohols by Ishihara's group



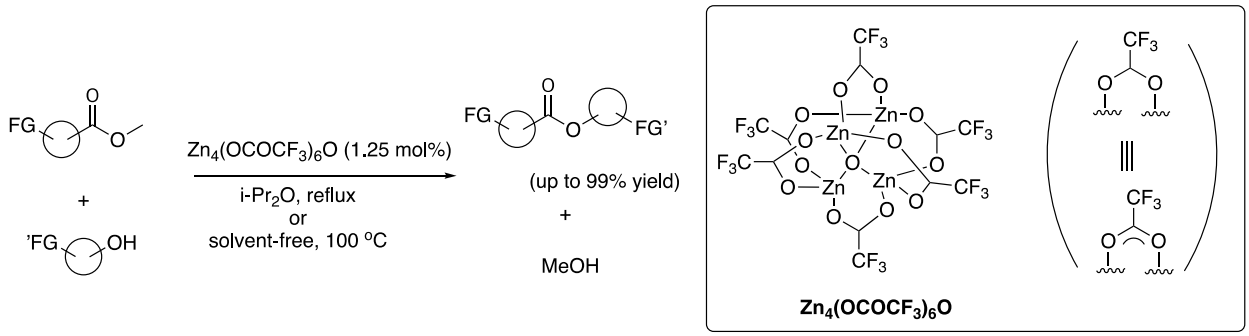
Scheme 1-14. Catalytic phosphorylation of alcohols by Kanai's group



1-4. Motivation and Aim

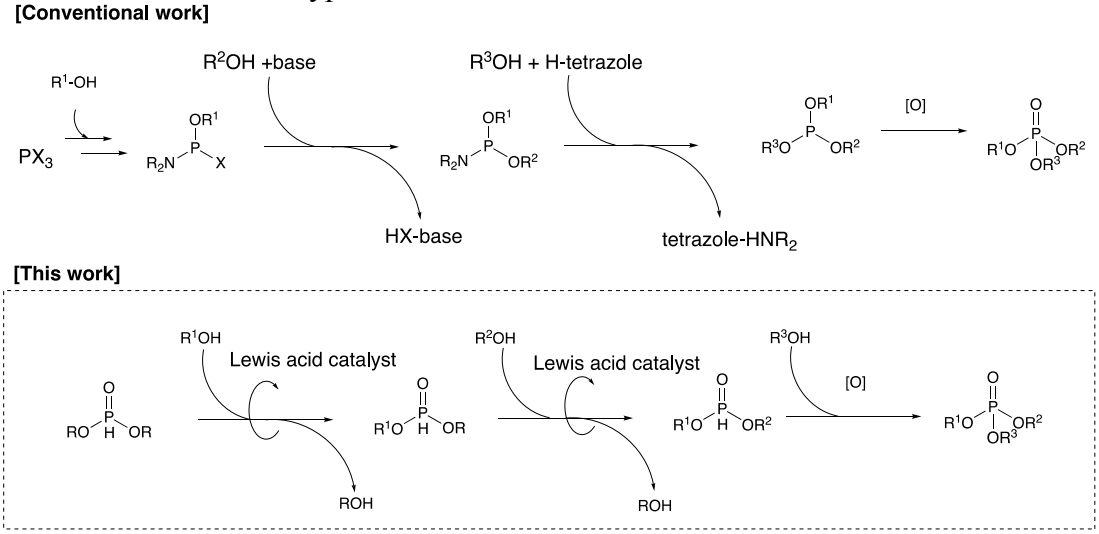
Catalytic protocol for the synthesis of phosphorus esters can be achieved via transesterification of phosphosphours molecules and equimolar of alcohols. Transesterification reactions catalysed by Lewis acids are well known. For example, in 2008, Ohshima's group reported a new catalytic transesterification reaction of carboxylic acids with alcohols catalysed by zinc cluster (**Scheme 1-15**).[24] Broad substrate scope with high functional group tolerance could be achieved in moderate to high yields. Zinc catalysis is also very appealing due to its low toxicity and ease of operation. The reaction could proceed in solvent-free condition, which results low waste.

Scheme 1-15. Transesterification of methyl esters with alcohols catalysed by tetranuclear Zinc cluster

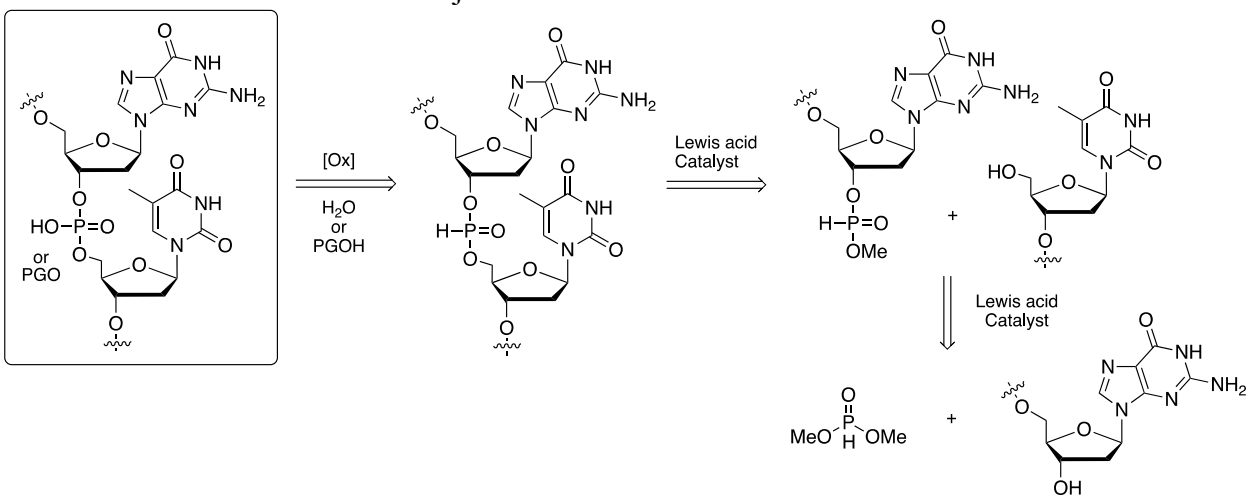


Therefore, I hypothesized that simple phosphonylation of alcohols catalysed by Lewis acids with alkyl phosphites will work and since the only waste is leaving alcohol, the reaction could further undergo reaction with different alcohols under catalytic conditions for the selective synthesis of phosphite diesters. Combination of these two-steps catalytic transformation and reported oxidation procedure would offer various kinds of biological important organophosphate di- and tri- esters (**Scheme 1-16**). If this works well, I could further apply this method to synthesis of actual oligonucleotide (**Scheme 1-17**).

Scheme 1-16. General hypothesis



Scheme 1-17. Final Goal of the Project



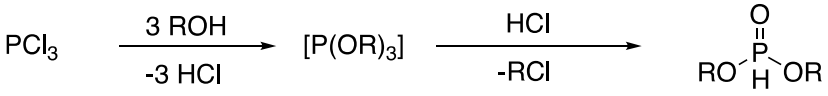
Chapter 2. Zinc-catalyzed Phosphonylation of Alcohols With Dimethyl Phosphites

2-1. Background

Catalytic phosphorylation/phosphitylation/phosphonylation reactions with readily available and nonactivated reagents under mild reaction conditions to provide sustainable synthetic access to various kinds of phosphates/phosphites/phosphonates with minimal waste are desired.[22,23] I decided to focus on simple phosphonylation of alcohols using phosphite diesters (H-phosphonates) as phosphorylating agent. Phosphite diesters are widely used in synthetic organic chemistry and serve as simple building blocks in organophosphorus chemistry.[25] They are used in the addition to carbonyl and imino groups to give α-hydroxyphosphonates or α-aminophosphonate[26], respectively, or addition to olefinic moiety in phospha-Micheal reaction.[27] Their application also involves in the Kabachnik-Fields condensations towards α-aminophosphonates[28] , and Hirao reaction, a P-C coupling reactions with alkyl or aryl halides.[29] They also offer a useful alternative to the phosphoramidite method particularly for oligonucleotides. [30]

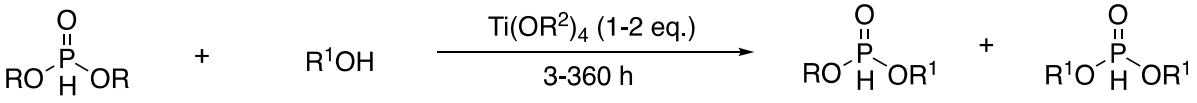
Conventionally, phosphite diesters were synthesized by the reaction of phosphorus trichloride with alcohols in the absence of base (**Scheme 2-1**).[31] The reaction seems quite straightforward, but it is difficult to synthesize H-phosphonates with two different alkyl groups with this method.

Scheme 2-1. Conventional Synthesis of H-phosphonates



Phosphonlyation of alcohols can be conducted through transesterification methods, which provides leaving alcohol as only by-product. However, generally high temperature and large excess amount of alcohols are needed. For example, in 1988, Modro's group reported titanium mediated transesterification reaction with phosphite diesters (**Scheme 2-2**),[32] but solvent amount of alcohols and stochiometric amount of metal was needed for the reaction. Also the main product was phosphite diesters bearing same alkyl groups.

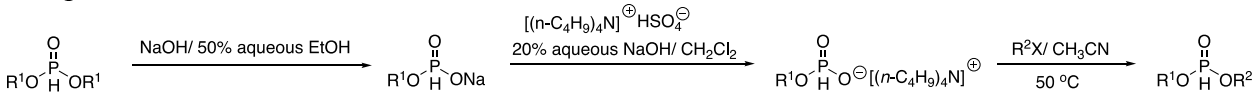
Scheme 2-2. Synthesis of H-phosphonates Mediated by Titanium



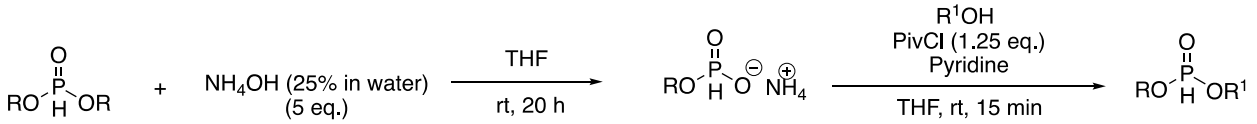
There were some attempts to synthesize phosphite diesters bearing different alkyl groups. For example, phosphite diesters could be synthesized using alkylation of tetra-n-butylaminium alkyl phosphites (**Scheme 2-3**).[33] However, they required 3 steps which can be complicated, and the substrate scope was quite limited with only moderate yield with this method. In addition, there is

also a report of the synthesis of phosphite diesters bearing different alkyl groups using coupling reaction between alcohol with phosphite monoester ammonium salts in the presence of coupling agent (**Scheme 2-4**).[34] However, there are also some drawbacks in this methodology since it requires stoichiometric amount of coupling agents in the presence of base and only simple alcohols with long alkyl chains can be applicable.

Scheme 2-3. Synthesis of H-phosphonates Using Alkylation of Tetra-n-butylammonium Alkyl Phosphites

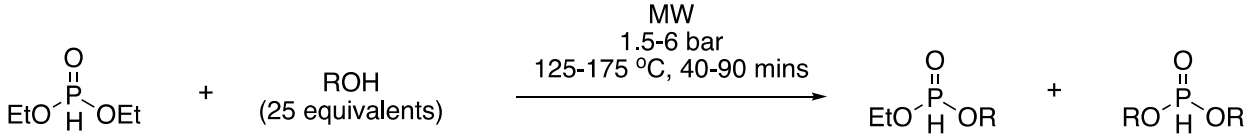


Scheme 2-4. Synthesis of H-phosphonates Using H-phosphonate Monoester Ammonium Salts in the Presence of Coupling Agent



Finally, Keglevich group demonstrated microwave-assisted catalyst-free phosphonylation of alcohol, and further apply to flow-conditions (**Scheme 2-5**).[35] However, they required harsh reaction conditions and only used simple, short chain alcohols and again, did not investigate introduction of second alcohol.

Scheme 2-5. Continuous Flow Alcoholysis of Diethyl Phosphite[36]

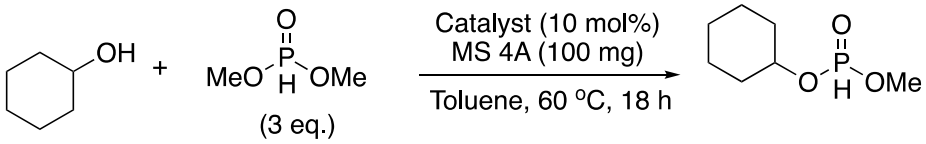


All of the synthesis methods described above have lots of limitations in terms of substrate scope and complicated steps. Therefore, I decided to first focus on simple phosphonylation of alcohols catalyzed by Lewis acids with alkyl phosphites with mild reaction conditions that will allow broad substrate scope with high functional group tolerance. If the reaction works well, I will further introduce second alcohol to synthesize phosphite diesters with different alcohols. Finally, the synthesized phosphite diesters product will be further oxidize to various kinds of biological important organophosphate triesters.

2-2. Initial Catalysts Screening

For the model reaction, I chose dimethyl phosphite as phosphorylating agent since it is cheap and readily available. The reaction was carried out for 18 hours at 60 °C in toluene in the presence of 10 mol% of catalyst and 100 mg of MS 4A as additive. MS 4A was employed as drying agent to capture the leaving methanol and therefore to forward the reaction. Various Lewis acids were screened as catalysts (**Table 2-1**). First, early transition-metal catalysts, such as $Sc(OTf)_3$, $La(OTf)_3$, and $Hf(OTf)_4$, were screened (**Table 2-1**, entries 1−4). However, the best yield for the first screening was only 19% with $La(OTf)_3$. Alkaline earth metals, such as $Mg(OAc)_2$ (**Table 2-1**, entry 5) also showed low reactivity. Late- transition-metal Lewis acids were then screened accordingly (**Table 2-1**, entries 7-11), and interestingly, moderate yield of desired product **3** could be obtained when using $Co(acac)_2$ as catalyst (**Table 2-1**, entries 8). This suggests that square-planar structured Lewis acid is effective for this reaction. Further screening of various Lewis acids finally revealed that $Zn(acac)_2$ had good catalyst activity, affording the desired product in 77% yield (**Table 2-1**, entry 12). Various Zn complexes were then investigated to confirm the effect of the counter anions, and the desired product was obtained in moderate to high yields (**Table 2-1**, entries 12, 14-21). It was revealed that square-planar Zn complexes such as $Zn(acac)_2$ and $Zn(salicylate)_2$ showed higher reactivity compared to other Zn salts, confirming that square-planar structure is important for the reaction (**Table 2-1**, entries 12 and 19). Zn oxo-cluster $Zn_4(TFA)_6O$, which is known to be a good catalyst for transesterification[24] , showed catalytic activity that was comparable to that of $Zn(acac)_2$ (**Table 2-1**, entry 21).

Table 2-1. Catalysts Screening



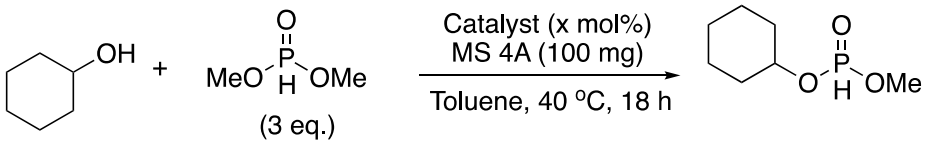
1a **2** **3a**

Entry	Catalyst	Yield(%)
1	$Sc(OTf)_3$	<5
2	$La(OTf)_3$	19
3	$Hf(OTf)_4$	<5
4	$Ti(OiPr)_4$	<5
5	$Mg(OAc)_2$	8
6	$Yb(OAc)_3$	10
7	$Fe(acac)_3$	<5
8	$Co(acac)_2$	58
9	$Co(acac)_3$	<5
10	$Cu(tBuacac)_2$	<5
11	Ag(OAc)	<5
12	$Zn(acac)_2$	77
13	$Bi(OAc)_3$	11
14	$Zn(OAc)_2$	46
15	$Zn(OTf)_2$	56
16	$Zn(ClO_4)_2$	<5

17	$Zn(SO_4)$	10
18	$Zn(PhCO_2)_2$	52
19	$Zn(Salicylate)_2$	64
20	$ZnEt_2$	46
21	$Zn_4(TFA)_6O$	77

Further comparison of these active Zn salts, $Zn(acac)_2$ and $Zn_4(TFA)_6O$, was performed with decreased reaction temperature (**Table 2-2**, entries 1 and 2). It was found that $Zn(acac)_2$ showed higher catalytic activity than the Zn cluster catalyst at 40 °C. It was turned out that the desired reaction proceeded in moderate yield even when the catalyst amount was reduced to 2.5 mol% (**Table 2-2**, entry 4). Based on these results, $Zn(acac)_2$ was selected as the optimal catalyst and the reaction conditions were then investigated.

Table 2-2. Catalysts further screening

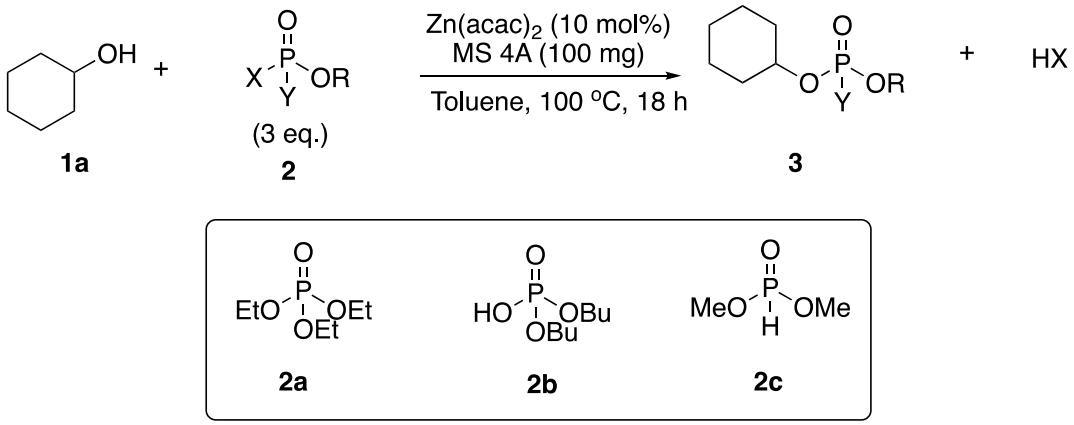


1a **2** **3a**

Entry	Catalyst	x (mol%)	Yield (%)
1	$Zn(acac)_2$	10	87
2	$Zn_4(TFA)_6O$	10	65
3	$Zn(acac)_2$	5	53
4	$Zn(acac)_2$	2.5	41

In the meanwhile, phosphorylating reagent was also investigated (**Table 2-3**). Since $Zn(acac)_2$ was found to be the best catalyst, the reaction was carried out with 10 mol% $Zn(acac)_2$ catalyst. It was confirmed that with P(V) substrates, **2a** and **2b**, reactions did not proceed at all (**Table 2-3**, entries 1 and 2), whereas substrate **2c** gave the desired product in 77% yield (**Table 2-3**, entry 3).

Table 2-3. Phosphorylating Reagent Screening

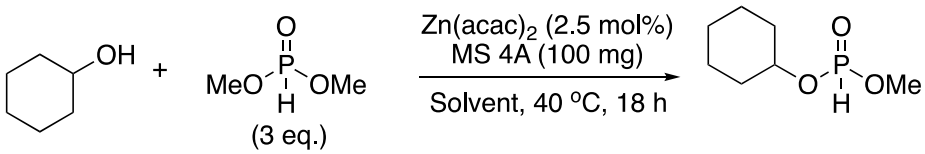


Entry	P reagent	Yield(%)
1	**2a**	NR
2	**2b**	NR
3	**2c**	77

2-3. Optimization

First, solvent screening was conducted, and the reactivity of the catalysts were almost the same when the reaction was conducted in toluene, THF, and EtOAc (**Table 2-4**, entries 1-3). Interestingly, the yield significantly dropped when MeCN was used as solvent, maybe due to the coordinating ability of the solvent, and therefore leading to the deactivation of the catalyst (**Table 2-4**, entries 4). When BTF was used as solvent, the target product was obtained in highest yield (**Table 2-4**, entry 5). Interestingly, the reaction did not proceed well in the absence of MS 4A (**Table 2-4**, entry 6).

Table 2-4. Solvent Screening



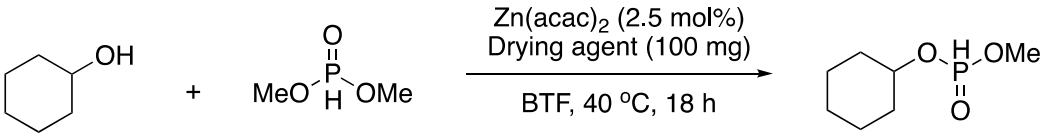
1a **2** **3a**

Entry	Solvent	Yield(%)
1	Toluene	41
2	THF	40
3	EtOAc	49
4	MeCN	18
5	BTF	68
6[a]	BTF	<5

[a] Without MS 4A.

Drying agents were then screened (**Table 2-5**). Among all the different molecular sieves, I got the best results with MS5A and MS3A (**Table 2-5**, entries 3 and 4). Since they showed similar reactivity, I increased the amount of both molecular sieves to 200 mg and conducted the reaction for 16 h, but they still showed similar results (**Table 2-5**, entries 5 and 6). Therefore, I decided to fix molecular sieves to MS5A and continued further optimization.

Table 2-5. Screening of Drying Agents



1a **2** (3 eq.) **3a**

Entry	Drying agent	Yield (%)
1	MS4A	68
2	MS13X	0
3	MS3A	76
4	MS5A	77

5[a]	MS3A	86
6[a]	MS5A	87

[a] 200 mg of molecular sieves were used, 16 h reaction time.

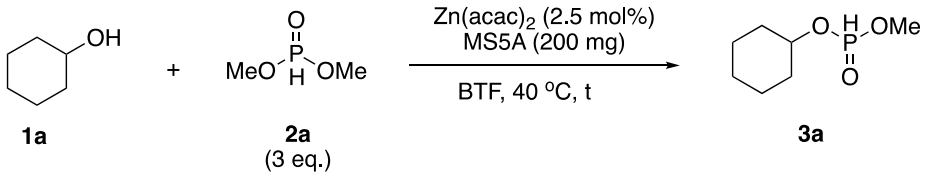
I then screened the different amounts of molecular sieves (**Table 2-6**). It was found out that the more molecular sieves were used to capture methanol, the more efficient the reaction got (**Table 2-6**, entries 1-3). With 200 mg, I could improve the yield up to 88% (**Table 2-6**, entry 3). However, if I increased the molecular sieves amount to 400 mg, the reaction gets saturated and the yields stops at 88% (**Table 2-6**, entry 4).

Table 2-6. Screening of Amounts of Molecular Sieves

1a + **2** (3 eq.) → **3a**

Entry	x	Yield (%)
1	50	58
2	100	77
3	200	88
4	400	88

At the same time, I also checked the reaction profile of this reaction (**Figure 2-1**). The reaction seems to be completed in 18 hours and therefore I decided to set the reaction time to 18 hours.



1a + **2a** (3 eq.) → **3a**

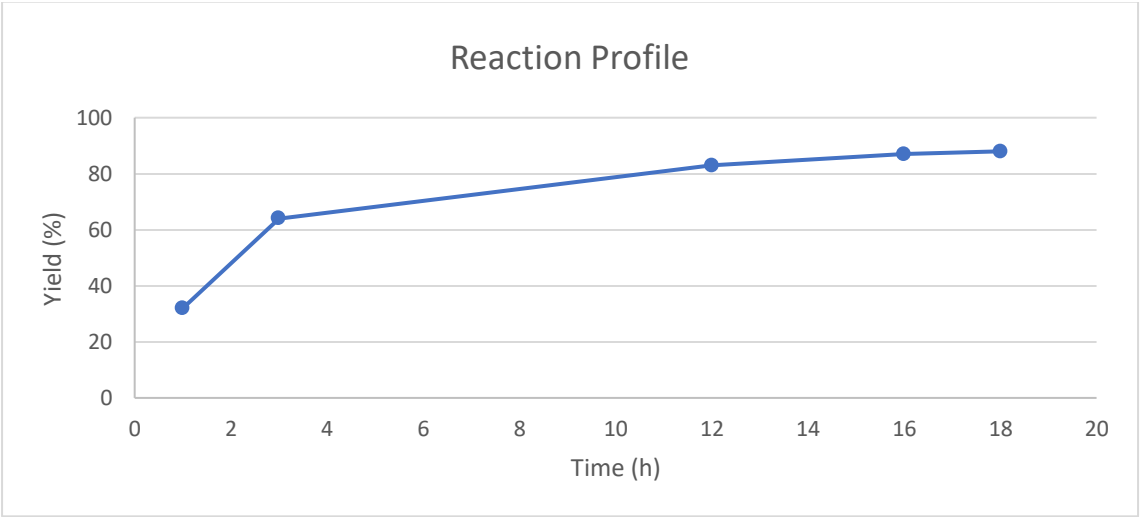
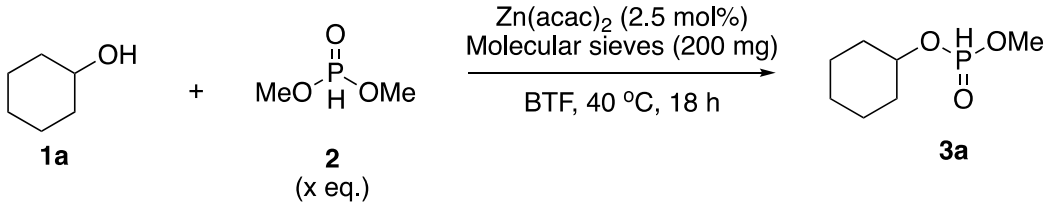


Figure 2-1. Reaction Profile

I also screened different equivalents of dimethyl phosphite (**Table 2-7**). With 2 equivalents of dimethyl phosphite, I could get almost similar results as using 3 equivalents (**Table 2-7**, entries 1 and 3).

Table 2-7. Screening of Equivalents of Dimethyl Phosphite

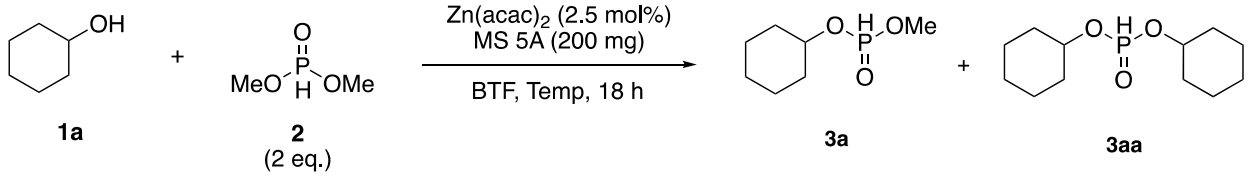


Entry	x	Yield (%)
1	3	88
2	1.5	81
3	2	87

However, even by changing lots of parameters, I could not improve the yield above 90%. By checking NMR spectrum, it seemed that the double adduct was formed as well as product, which indicated that the reaction somehow overran and therefore might need much milder reaction conditions.

I first tried decreasing the reaction temperature to room temperature (**Table 2-8**, entry 2). The yield of the desired product increased with less amount of the by-product. By decreasing the reaction temperature to 0 °C, I could decrease the amount of double adduct further. Mass balance was odd since the sum of the yields were over 100%, but still acceptable since it was within the error range. I decided set this condition as my optimized condition and move on to substrate scope (**Table 2-8**, entry 3).

Table 2-8. Optimization of Reaction Conditions



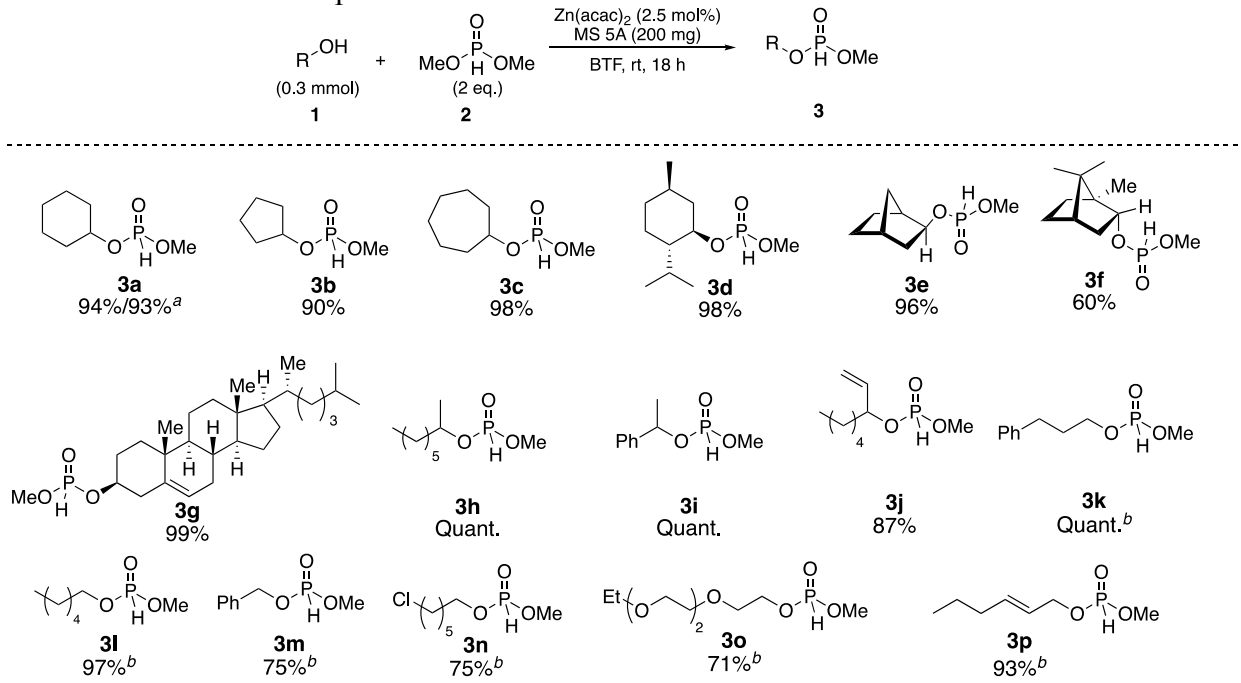
Entry	Temp (°C)	**3a** Yield (%)	**3aa** Yield (%)
1	40	87	18
2	Rt	94	15
3	0	94	11

2-4. Substrate Scope

With optimized conditions in hand, substrate scope of the reaction with structurally simple alcohols was examined (**Scheme 2-6**). Cyclic alcohols, such as cyclopentanol and cycloheptanol, reacted smoothly to give the desired products **3b** and **3c** in high yields. Substituents on the cyclohexyl ring did not affect the reactivity, and phosphonylated menthol **3d** was obtained in excellent yield. Bicyclic structures were also tested, and the desired phosphites **3e** and **3f** were obtained in high yields. Furthermore, cholesterol, which is a structurally complex steroid, reacted smoothly under the standard reaction conditions to afford **3g** in excellent yield. Various acyclic alcohols were then tested, including simple alkyl-substituted alcohol **1h**, phenyl- and vinyl-substituted alcohols **1i** and **1j**, also afforded the corresponding phosphite products in excellent yields.

After screening various secondary alcohols, I then moved on to screening some primary alcohols, and it was found out that primary alcohols showed much higher reactivity than the secondary alcohols, which caused overreactions of the products and therefore resulted in decreased final yields. This problem could be solved by simply decreasing the reaction temperature to 0 °C. Under these reaction conditions, simple alkyl alcohols 3- phenylpropanol (**1k**) and n-hexanol (**1l**) gave the desired products in excellent yields. However, it was difficult to control the reactivity and selectivity for benzyl alcohol (**1m**), and the desired product **3m** was obtained in 75% yield. In contrast, alcohol **1n**, bearing a primary alkyl chloride, gave the corresponding product **3n** in good yield while retaining the potentially electrophilic chloride group. Alcohols bearing polyether and alkene groups, **1o** and **1p**, were also tested, and the desired H-phosphonates, **3o** and **3p** were obtained in high yields with excellent functional group tolerance. For all the substrates except for cholesterol, the volatility of the products was quite high, and the isolated yields were significantly lower than the NMR yields. Therefore all the yields were determined by NMR spectroscopy.

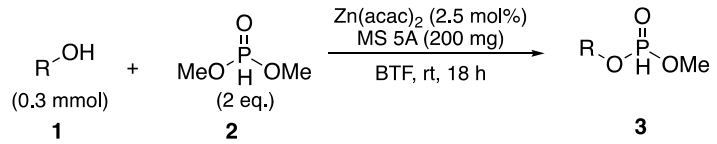
Scheme 2-6. Substrate Scope

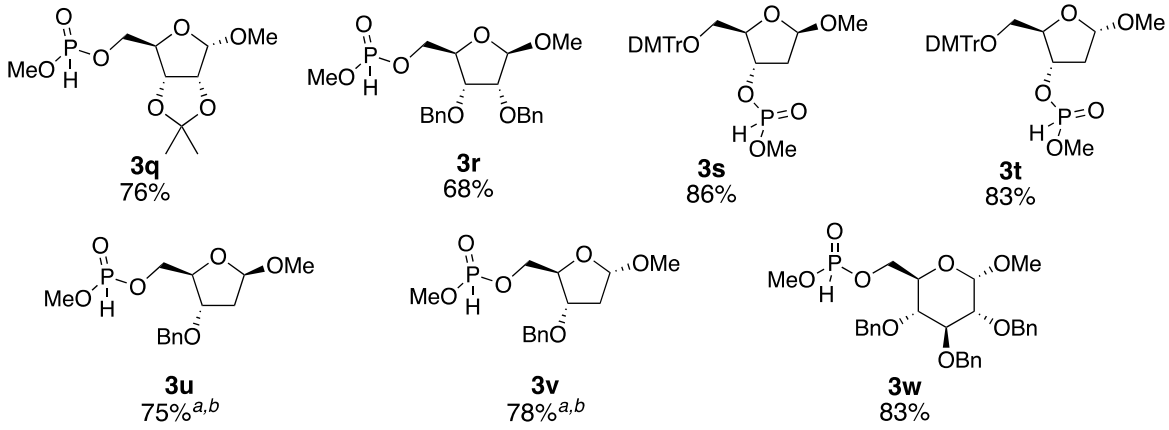


[a] Reaction was performed in 1.2 mmol scale. [b] Reaction was performed at 0 °C.

Carbohydrates were also tested as a part of substrate scope (**Scheme 2-7**). First, 1-O-methyl-2,3-acetonide-protected ribose was employed under the standard reaction conditions, and the desired product **3q** was obtained in high yield. The protecting group at the 2,3- positions could be changed to Bn groups without significant loss of reactivity, and **3r** was obtained in good yield. After several trials of ribose substrates, 2-deoxyribose substrates were then investigated. 5-DMTr- protected 2-deoxyriboses **1s** and **1t** reacted smoothly, and the target products **3s** and **3t**, respectively, were obtained in high yields. The stereocenter at the 1-position (α- and β-) did not affect the reactivity or selectivity. 3- BnO-protected 2-deoxyriboses **1u** and **1v** also worked well to afford 5-phosphonylated compounds **3u** and **3v** in good yields. Protected glucose **1w** also gave the corresponding H-phosphonate diester **3w** in high yield.

Scheme 2-7. Substrate Scope of the Reaction with Carbohydrate Derivatives



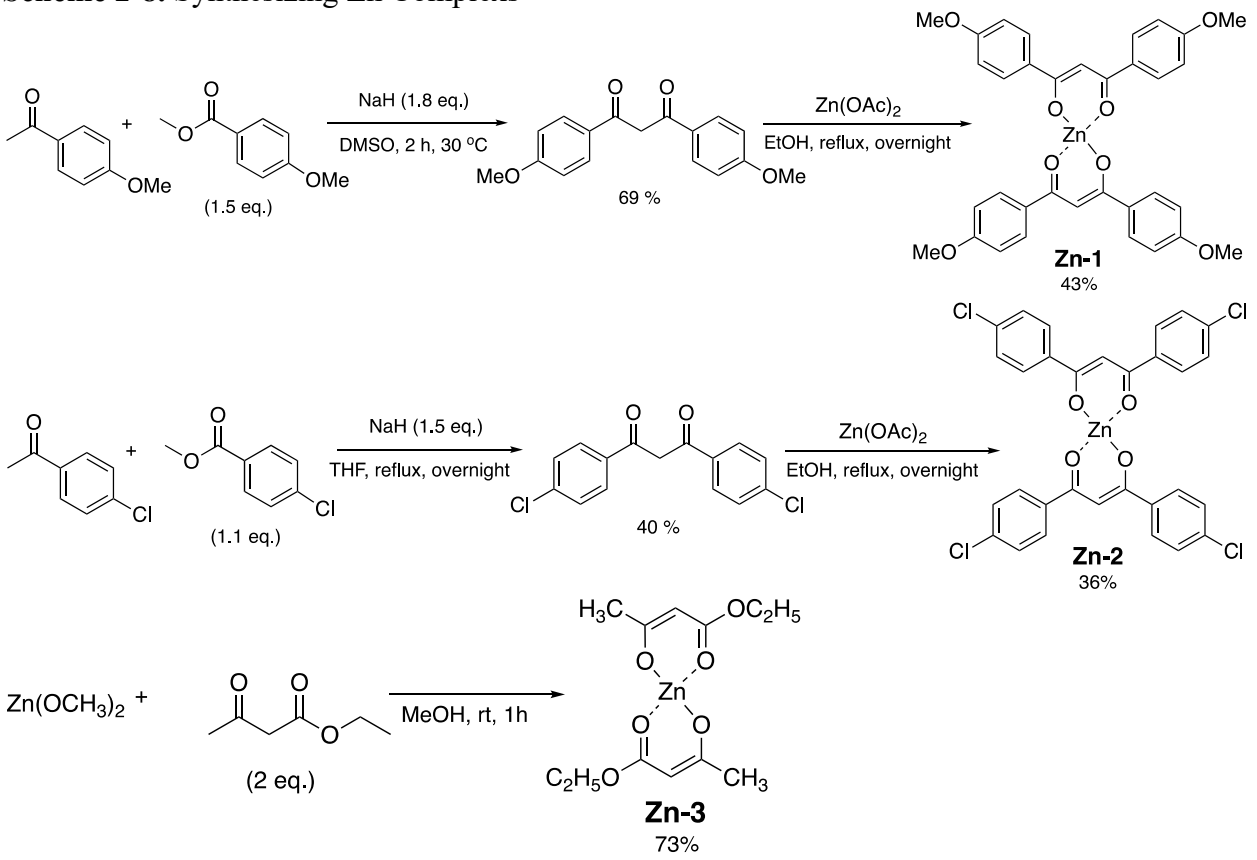


[a] Reaction was performed at 0 °C. [b] Dimethyl phosphite (3 eq.) was used.

2-5. Further Catalyst Screening

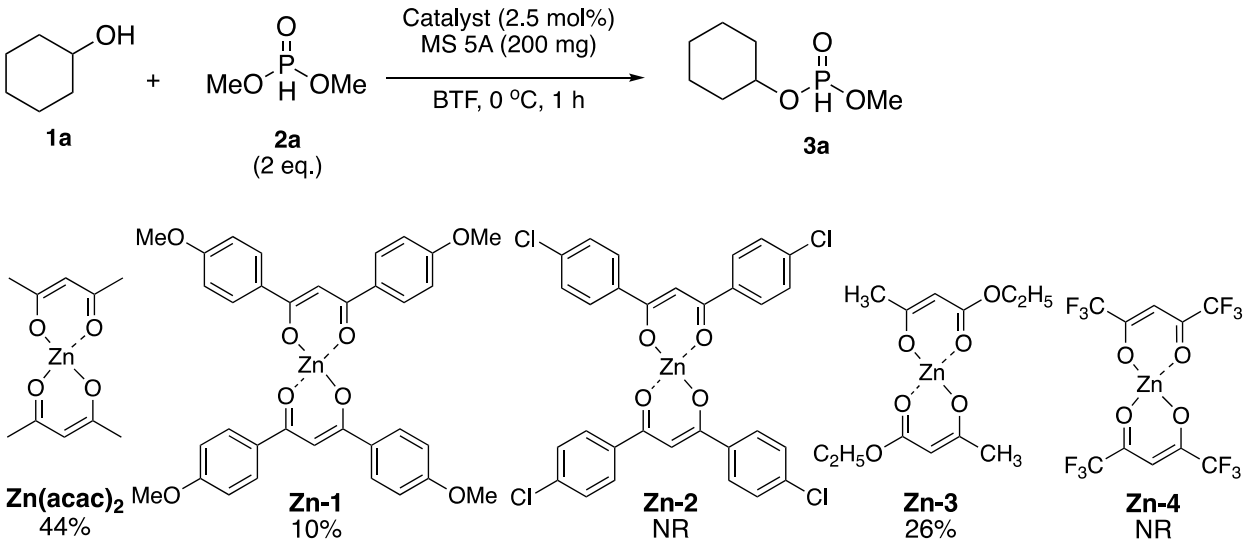
Apart from primary and secondary alcohols, to our knowledge, there has been no successful example of the use of tertiary alcohols in reported catalytic systems. Since tertiary alcohol suffered from low reactivity, I decided to explore more active Zn catalysts for more demanding substrates. I first decided to investigate the electronic effects of substituents on Zn complexes (**Scheme 2-9**). First, Zn complexes containing both electron donating group (OMe) (**Zn-1**) and electron withdrawing group (Cl) (**Zn-2**) (**Scheme 2-8**) were synthesized. Respective diketones had to be synthesized first, and then coordination to $Zn(OAc)_2$ was tried by refluxing in ethanol overnight, which is a standard procedure for synthesizing $Zn(acac)_2$.[36] I could get 36% and 43% of products **Zn-1** and **Zn-2** respectively. A Zn complex with an ester (**Zn-3**) was also synthesized by reacting with $Zn(OCH_3)_2$ in MeOH (**Scheme 2-8**) following reported procedure.[37]

Scheme 2-8. Synthesizing Zn Complexes



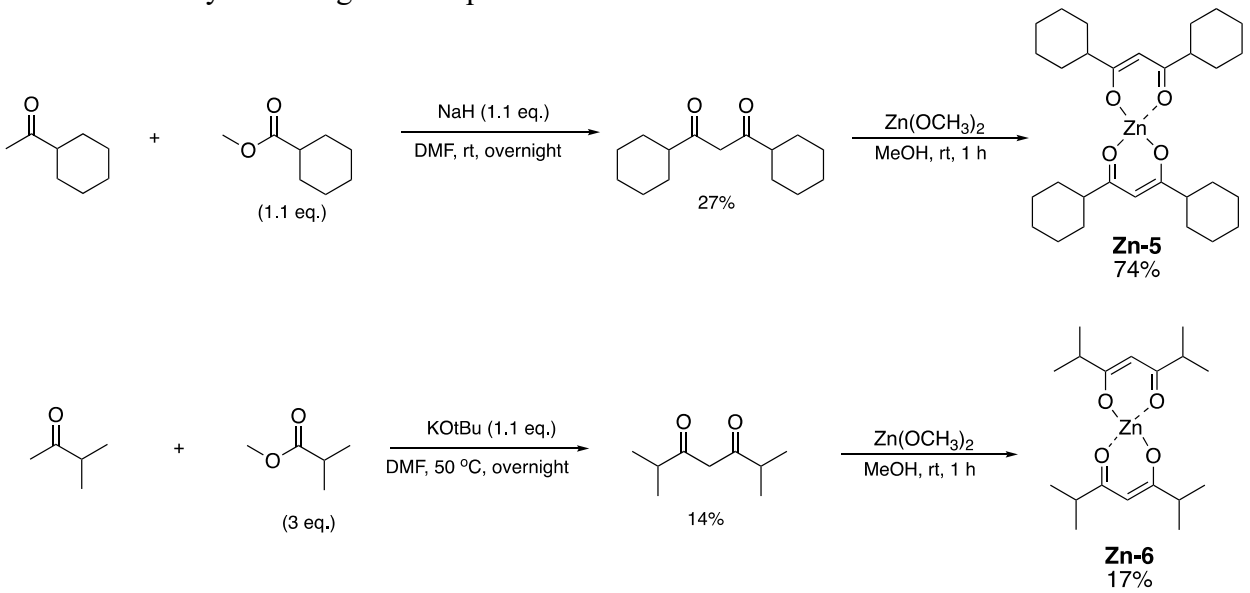
Reactivities of Zn complexes were then compared (**Scheme 2-9**). Commercially available $Zn(C_5HF_6O_2)_2$ (**Zn-4**) was also tried as part of the screening, but no reaction proceeded. Zn complexes with electron donating groups (**Zn-1** and **Zn-3**) had slightly positive effect compared to electron withdrawing groups (**Zn-2** and **Zn-4**). However, all the Zn complexes with both electron withdrawing groups and electron donating groups showed lower reactivities compared to $Zn(acac)_2$. Therefore, I decided to focus on investigation of steric bulkiness of the substituents on Zn complexes.

Scheme 2-9. Further Catalysts Screening



Zn complexes with the cyclohexyl groups and isopropyl groups as substituents were then synthesized (**Scheme 2-10**). Diketones were first synthesized and obtained in 27% and 14% yields respectively. Then I tried to coordinate to Zn by reacting with $Zn(OAc)_2$ in EtOH in reflux condition overnight, but the reaction did not proceed. So I tried using different Zn solution for Zn coordination and could successfully obtained expected complexes (**Zn-5** and **Zn-6**) by using Zn methoxide solution which is standard procedure for synthesizing **Zn-3** complex.[37]

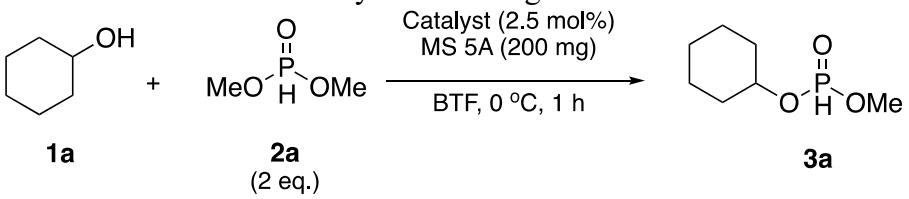
Scheme 2-10. Synthesizing Zn Complexes



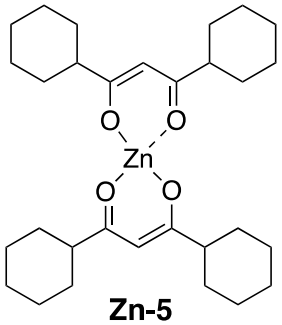
Reactivities of Zn complexes were then compared (**Scheme 2-11**). Commercially available $Zn(TMHD)_2$ (bis(2,2,6,6-tetramethyl-3,5-heptanedionato)zinc(II)) (**Zn-7**) was also tried as part of the screening, and it was turned out the more sterically bulkier the substituents of Zn complexes, the better the reactivity. Finally, the most sterically bulky Zn complex, $Zn(TMHD)_2$ (**Zn-7**),

showed the highest reactivity. I also tried different metal catalyst, such as $Ni(acac)_2$, but the reaction did not proceed at all in this case, which highlights the importance of using Zn metal catalysts.

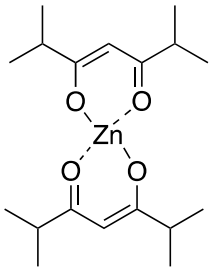
Scheme 2-11. Further Catalysts Screening



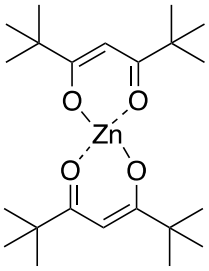
1a **2a** (2 eq.) **3a**



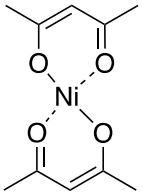
Zn-5
20%



Zn-6
74%



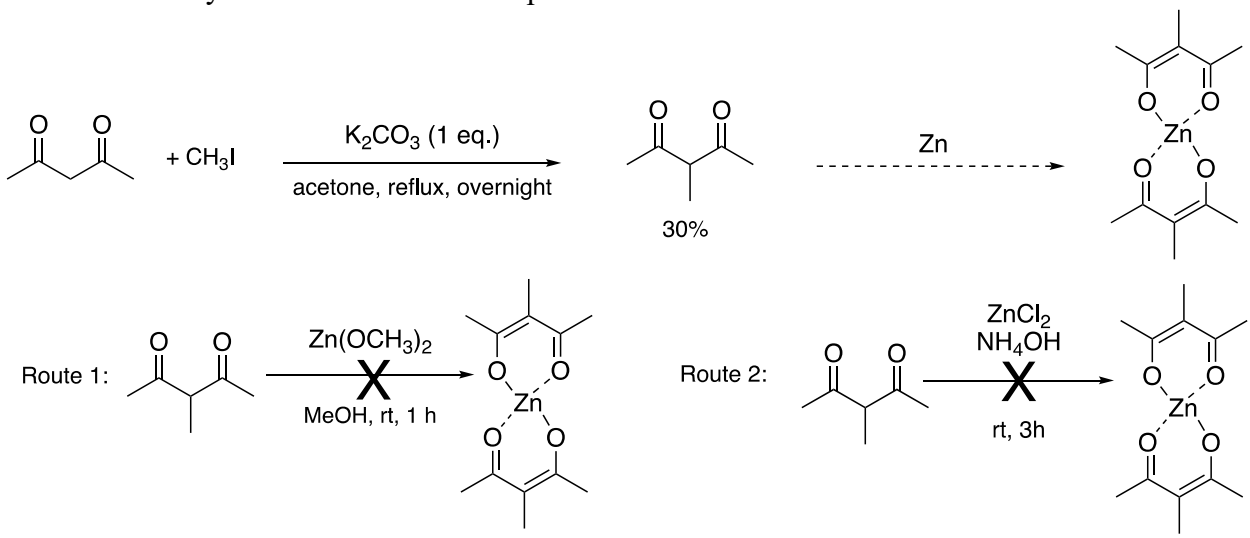
Zn-7
Quant.



$Ni(acac)_2$
N.R

At the same time, since the substituent effect on diketone that coordinate to Zn has never been investigated, I also synthesized 3-methyl 2,4-pentanedione and then tried to coordinate to Zn. For the first attempt to coordinate to Zn, I tried mixing with $Zn(OCH_3)_2$ in MeOH since I previously synthesized other Zn complexes in this method (**Scheme 2-12**, Route 1). However, the desired product was not obtained. I also tried mixing with $ZnCl_2$ in ammonia solution, but the desired product was also not obtained (**Scheme 2-12**, Route 2). Therefore, the reactivity of the Zn complex with diketone that have a substituent in phosphonylation could not be investigated.

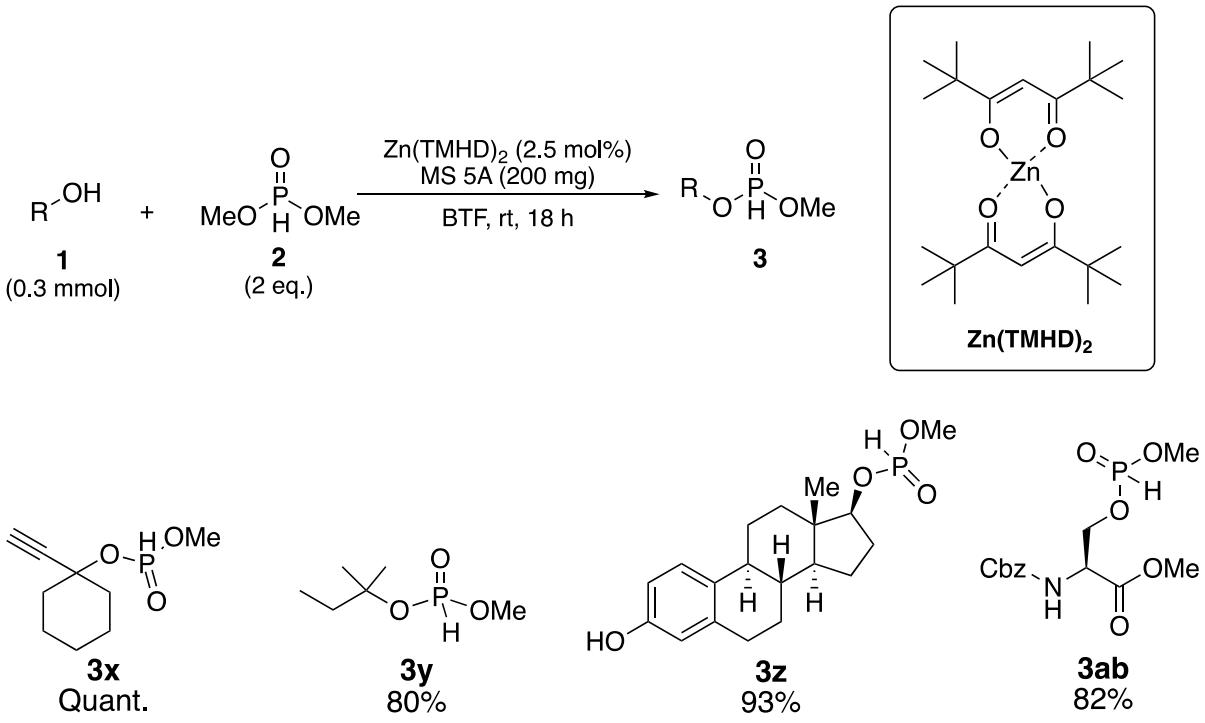
Scheme 2-12. Synthesis of New Zn Complex



2-6. Substrate Scope (tertiary alcohols)

Since sterically hindered bis(2,2,6,6- tetramethyl-3,5-heptanedionato)zinc(II) ($Zn(TMHD)_2$) turned out to be the most active catalyst, the scope of the reaction with challenging alcohols were further investigated (**Scheme 2-13**). A sterically hindered tertiary alcohol **1x** reacted smoothly to give the desired product **3x** in quantitative yield. Acyclic tertiary alcohol **1y** also gave the desired product **3y** in good yield. Surprisingly, steroid **1z**, which features a free phenol group, only the secondary alcohol reacted selectively to afford **3z** in excellent yield, which actually demonstrates the superior functional group tolerance of the catalyst. Substrates with carbamate and ester groups were also tolerated, with CbZ- protected serine ester **1ab** giving the desired H-phosphonate diester **3ab** in high yield.

Scheme 2-13. Further Substrate Scope



2-7. Nucleosides Phosphonylation

This part is not published because it is scheduled to be published in journals or other publications within five years.

Chapter 3. Zinc-catalyzed Synthesis of Phosphite Diesters with Methyl Phosphites

This part is not published because it is scheduled to be published in journals or other publications within five years.

Chapter 4. Investigation of the Leaving Group Effect of Phosphite Substituents on Catalytic Phosphonylation

This part is not published because it is scheduled to be published in journals or other publications within five years.

Chapter 5. Zinc-catalyzed Synthesis of Phosphite Diesters with Trifluoroethyl Phosphites

This part is not published because it is scheduled to be published in journals or other publications within five years.

Chapter 6. Summary

This part is not published because it is scheduled to be published in journals or other publications within five years.

Chapter 7. Experimental Section

General

JEOL JNM-ECA 500 or ECX 600 spectrometers were used for NMR measurement using deuterated chloroform as solvent unless otherwise noted. Tetramethyl silane was used as an internal standard for ^{1}H-NMR (δ = 0 ppm), and deuterated chloroform was used for ^{13}CNMR (δ = 77.36 ppm).

Analysis in Real Time (DART) mass spectra were recorded on JEOL JMS-T100TD mass spectrometer. Mass spectra were also obtained on Shimadzu LCMS-IT-TOF (APCI) mass spectrometer. IR spectra were recorded on Shimadzu IRSpirit-T with QART-S.

Solvents were purchased in anhydrous grade from FUJIFILM Wako Pure Chemical Company and Tokyo Chemical Industry Co., Ltd.. and used as received. Metal salts employed for the screening were purchased from Wako Pure Chemical Company and Tokyo Chemical Industry Co., Ltd. and used as received.

Alcohols **1a**-**1p** and **1x**-**1z** were purchased from FUJIFILM Wako Pure Chemical Company and Tokyo Chemical Industry Co., Ltd. and purified by recrystallization or distillation before use.

Alcohols **1q**-**1w** derived from carbohydrates were synthesized by reported procedure.[1-4] Alcohol **1ab** derived from serine was synthesized by reported procedure.[5]

Alcohols **1ac**-**1ai** derived from nucleosides were synthesized by reported procedure.[7-10]

Dimethyl phosphite, diethyl phosphite and diisopropyl phosphite were purchased from Tokyo Chemical Industry Co., Ltd. and distilled before use. Bis(2,2,2-trifluoroethyl) phosphite was synthesized by reported procedure[6] and kept under argon atmosphere at -20 °C. Powdered molecular sieves were purchased from Sigma-Aldrich Co. LLC., and dried 200 °C under vacuo before use and kept in a glove box.

All commercially available reagents, unless otherwise stated, were used without further purification.

All reactions, unless otherwise stated, were carried out under argon atmosphere.

Chapter 2

1. A typical procedure of optimization of reaction conditions using cyclohexanol 1a (Section 2-2, Table 2-1, entry 12)

To an oven dried test tube equipped with a magnetic stirring bar was added $Zn(acac)_2$ (7.9 mg, 0.03 mmol) and powdered MS 4A (100 mg). The tube was capped with a septum, connected to a vacuum line, then an Ar balloon was equipped. Toluene (1.0 mL) was added to the tube, followed by the addition of dimethyl phosphite **2** (99.0 mg, 0.9 mmol) and cyclohexanol **1a** (30.0 mg, 0.3 mmol)

by syringe. The tube was put in an oil bath heated at 60 °C, and stirred for 18 h. Then, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). The solid material was removed by filtration and washed with ethyl acetate (5 mL*2). The combined organic phase was evaporated and connected to a vacuum line. The ^{1}H NMR was recorded with 1,2,4,5-tetramethyl benzene as internal standard. The crude mixture was purified by column chromatography using hexane/ethyl acetate = 1/2 as eluent (R^f = 0.3). The product **3a** was isolated as colourless oil (41.2 mg, 77% yield).

2. A general procedure of substrate scope with $Zn(acac)_2$ (Section 2-4)

[For liquid alcohols]

To an oven dried test tube equipped with a magnetic stirring bar was added $Zn(acac)_2$ (1.9 mg, 0.0075 mmol) and powdered MS 5A (200 mg). The tube was capped with a septum, connected to a vacuum line, then an Ar balloon was equipped. BTF (1.0 mL) was added to the tube, followed by the addition of dimethyl phosphite **2** (66.0 mg, 0.6 mmol) and alcohol **1** (0.3 mmol) by syringe. The reaction mixture was stirred for 18 h at room temperature. Then, the reaction mixture was diluted with ethyl acetate (5 mL). The solid material was removed by filtration and washed with ethyl acetate (5 mL*2). The combined organic phase was evaporated and connected to a vacuum line. The ^{1}H NMR was recorded with 1,2,4,5-tetramethyl benzene as internal standard. The crude mixture was purified by column chromatography using hexane/ethyl acetate = 1/2. The product **3** was isolated as colourless oil.

[For solid alcohols]

To an oven dried test tube equipped with a magnetic stirring bar was added $Zn(acac)_2$ (1.9 mg, 0.0075 mmol), alcohol **1** (0.3 mmol), and powdered MS 5A (200 mg). The tube was capped with a septum, connected to a vacuum line, then an Ar balloon was equipped. BTF (1.0 mL) was added to the tube, followed by the addition of dimethyl phosphite **2** (66.0 mg, 0.6 mmol) by syringe. The reaction mixture was stirred for 18 h at room temperature. Then, the reaction mixture was diluted with ethyl acetate (5 mL). The solid material was removed by filtration and washed with ethyl acetate (5 mL*2). The combined organic phase was evaporated and connected to a vacuum line. The ^{1}H NMR was recorded with 1,2,4,5-tetramethyl benzene as internal standard. The crude mixture was purified by column chromatography using hexane/ethyl acetate = 1/2. The product **3** was isolated as colourless oil.

3. A general procedure of substrate scope with $Zn(TMHD)_2$ (Section 2-6)

[For liquid alcohols]

To an oven dried test tube equipped with a magnetic stirring bar was added $Zn(TMHD)_2$ (3.2 mg, 0.0075 mmol) and powdered MS 5A (200 mg). The tube was capped with a septum, connected to a vacuum line, then an Ar balloon was equipped. BTF (1.0 mL) was added to the tube, followed by the addition of dimethyl phosphite **2** (66.0 mg, 0.6 mmol) and alcohol **1** (0.3 mmol) by syringe. The reaction mixture was stirred for 18 h at room temperature. Then, the reaction mixture was diluted with ethyl acetate (5 mL). The solid material was removed by filtration and washed with

ethyl acetate (5 mL*2). The combined organic phase was evaporated and connected to a vacuum line. The ^{1}H NMR was recorded with 1,2,4,5-tetramethyl benzene as internal standard. The crude mixture was purified by column chromatography using hexane/ethyl acetate = 1/2. The product **3** was isolated as colourless oil.

[For solid alcohols]

To an oven dried test tube equipped with a magnetic stirring bar was added $Zn(TMHD)_2$ (3.2 mg, 0.0075 mmol), alcohol **1** (0.3 mmol), and powdered MS 5A (200 mg). The tube was capped with a septum, connected to a vacuum line, then an Ar balloon was equipped. BTF (1.0 mL) was added to the tube, followed by the addition of dimethyl phosphite **2** (66.0 mg, 0.6 mmol) by syringe. The reaction mixture was stirred for 18 h at room temperature. Then, the reaction mixture was diluted with ethyl acetate (5 mL). The solid material was removed by filtration and washed with ethyl acetate (5 mL*2). The combined organic phase was evaporated and connected to a vacuum line. The ^{1}H NMR was recorded with 1,2,4,5-tetramethyl benzene as internal standard. The crude mixture was purified by column chromatography using hexane/ethyl acetate = 1/2. The product 3 was isolated as colourless oil.

4. A procedure of oxidation of 3 to 4 (Section 2-7, Scheme 2-15)

To an oven dried 10 mL round bottom flask equipped with magnetic stirring bar was added H-phosphonate **3g** (90.1 mg, 0.19 mmol). The tube was capped with septum, connected to a vacuum line, then an Ar balloon was equipped. EtOH (1 mL) was added to make clear solution. Another solution of I_2 (5.1 mg, 0.02 mmol) and TBHP (30.9 mg, 0.24 mmol) in EtOH (1 mL) was added to the flask slowly. The reaction solution was stirred for 15 h, at which stage full consumption of **3g** was confirmed by TLC and ^{31}P NMR. The reaction was quenched by the addition of NaS_2O_3 aq. (sat. 1 mL) and extracted with DCM (5 mL*3). The combined organic phase was dried over Na_2SO_4 and solvent was removed in vacuo. to give analytically pure phosphonate **4g** as a white solid (91.6 mg).

5. Procedure of 1ah synthesis (Section 2-7)

To an oven dried 300 mL round bottom flask equipped with magnetic stirring bar was added 2',3'-isopropylideneguanosine (2.0 g, 4.57 mmol) and 4-Dimethylaminopyridine (553.8 mg, 4.57 mmol). The flask was connected to a vacuum line then an Ar balloon was equipped before adding dry DCM (30 mL). Di-tert-butyl decarbonate (4.99 g, 22.85 mmol) was then added and the solution was stirred overnight at room temperature. Then the reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (3*30 mL). The combined organic phase was dried over Na_2SO_4 and solvent was removed in vacuo. The crude mixture was purified by column chromatography using hexane/ethyl acetate = 1/2. The product **1ah** was isolated as a colourless solid.

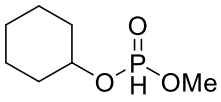
6. Procedure of NMR studies (Section 2-8)

Dimethyl phosphite (33.0 mg, 0.3 mmol) and $Zn(TMHD)_2$ (129.6 mg, 0.3 mmol) were dissolved in toluene-d_6 while stirring. $Zn(TMHD)_2$ was dissolved in the solution and was subsequently

transferred to an NMR tube. ^{1}H NMR spectrum and ^{31}H NMR spectrum were measured to make sure that interaction between dimethyl phosphite and Zn catalyst took place.

Compound data

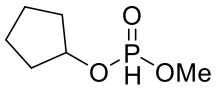
Cyclohexyl methyl phosphonate (**3a**)



Colourless oil, 50.2 mg (94% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.75 (1H, d, $J_{P\text{-}H}$ = 693.3 Hz), 4.43-4.38 (1H, m), 3.69 (3H, d, $J_{P\text{-}H}$ = 11.68 Hz), 1.94-1.82 (2H, m), 1.70-1.65 (3H, m), 1.52-1.48 (3H, m), 1.32-1.19 (2H, m) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 76.03 (d, $J_{P\text{-}C}$ = 7.15 Hz), 51.73 (d, $J_{P\text{-}C}$ = 5.96 Hz), 33.73 (d, $J_{P\text{-}C}$ = 3.58 Hz), 33.49 (d, $J_{P\text{-}C}$ = 4.77 Hz), 25.01 (s), 23.50 (s) ; ^{31}P NMR (240 MHz, $CDCl_3$): δ 8.27 (s) ; IR (neat): 2935 cm^{-1}, 2859 cm^{-1}, 1251 cm^{-1}, 1054 cm^{-1}, 958 cm^{-1}, 892 cm^{-1} ; HRMS (DART): m/z calcd. for $C_7H_{15}O_3P$ ([2M+H]+): 357.15959; found: 357.15912.

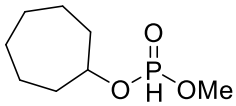
Cyclopentyl methyl phosphonate (**3b**)



Colourless oil, 44.3 mg (90% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.75 (1H, d, $J_{P\text{-}H}$ = 696.0 Hz), 4.96-4.94 (1H, m), 3.73 (3H, d, $J_{P\text{-}H}$ = 11.68 Hz), 1.80-1.76 (6H, m), 1.61-1.58 (2H, m) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 79.66 (d, $J_{P\text{-}C}$ = 7.22 Hz), 51.77 (d, $J_{P\text{-}C}$ = 5.78 Hz), 34.22 (d, $J_{P\text{-}C}$ = 4.33 Hz), 34.00 (d, $J_{P\text{-}C}$ = 4.33 Hz), 22.92 (s) ; ^{31}P NMR (240 MHz, $CDCl_3$): δ 8.61 (s) ; IR (neat): 2964 cm^{-1}, 2877 cm^{-1}, 1254 cm^{-1}, 1053 cm^{-1}, 966 cm^{-1}, 800 cm^{-1}; HRMS (DART): m/z calcd. for $C_6H_{13}O_3P$ ([2M+H]+): 329.12829; found: 329.12934.

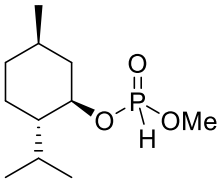
Cycloheptyl methyl phosphonate (**3c**)



Colourless oil, 56.5 mg (98% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.77 (1H, d, $J_{P\text{-}H}$ = 690.0 Hz), 4.64-4.62 (1H, m), 3.73 (3H, d, $J_{P\text{-}H}$ = 11.68 Hz), 1.98-1.96 (2H, m,), 1.80-1.77 (2H, m), 1.67-1.64 (2H, m), 1.55-1.54 (4H, m), 1.43-1.39 (2H, m) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 78.61 (d, $J_{P\text{-}C}$ = 5.78 Hz), 51.72 (d, $J_{P\text{-}C}$ = 5.78 Hz), 35.93(d, $J_{P\text{-}C}$ = 4.33 Hz), 35.71 (d, $J_{P\text{-}C}$ = 4.33 Hz), 27.91 (s), 22.10 (s) ; ^{31}P NMR (240 MHz, $CDCl_3$): δ 8.28 (s) ; IR (neat): 2925 cm^{-1}, 2859 cm^{-1}, 1255 cm^{-1}, 1045 cm^{-1}, 958 cm^{-1}, 790 cm^{-1}; HRMS (DART): m/z calcd. for $C_8H_{17}O_3P$ ([2M+H]+): 385.19089; found: 385.18990.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl methyl phosphonate (**3d**)

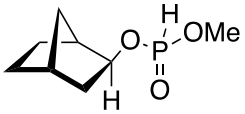


Colourless oil, 84.5 mg (98% yield), dr = 58/42.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.84 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 692.6 Hz), 6.82 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 693.6 Hz), 4.30-4.24 (1H, m), 3.77 (3H, d, J = 12.37 Hz), 3.76 (3H, d, J = 11.68 Hz), 2.18-2.05 (2H, m), 1.69-1.67 (2H, m), 1.51-1.42 (1H, m), 1.41-1.34 (1H, m), 1.22 (1H, q, J = 11.91 Hz), 1.05-0.99 (1H, m), 0.93 (6H, d, J = 6.87 Hz), 0.90-0.85 (1H, m), 0.82 (3H, d, J = 6.87 Hz);

^{13}C NMR (150 MHz, $CDCl_3$): δ 78.23, 78.18, 78.01, 77.96, 51.8, 51.7, 51.6, 51.5, 48.21, 48.18, 43.3, 42.8, 33.85, 33.83, 31.49, 31.47, 25.8, 25.6, 22.8, 21.8, 20.79, 20.76, 15.60, 15.56; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 8.93, 8.33; IR (neat): 2435, 2118, 1652, 1256, 1181, 1026, 983, 952, 881, 826, 778, 549 cm^{-1}; HRMS (DART): m/z calcd. 469.28479 for $C_{22}H_{47}O_6P_2$ ([2M+H]+); found: 469.27741.

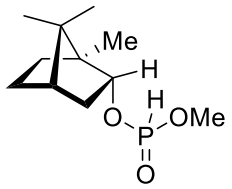
(1*S*,2*R*,4*R*)-Bicyclo[2.2.1]heptan-2-yl methyl phosphonate (**3e**)



Yellow oil, 55.0 mg (96% yield), dr = 47/53.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.73 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 696.0 Hz), 6.73 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 696.0 Hz), 4.38 (1H, q, *J* = 6.0 Hz), 3.71 (3H for one diastereomer, d, *J* = 12.4 Hz), 3.70 (3H for the other diastereomer, d, *J* = 11.7 Hz), 2.36 (1H, d, *J* = 4.1 Hz), 2.26 (1H, s), 1.71-1.67 (1H, m), 1.57-1.54 (2H, m), 1.51-1.45 (1H, m), 1.42-1.36 (1H, m), 1.15 (1H, d, $J_{P\text{-}H}$ = 8.9 Hz), 1.04-0.99 (2H, m) ; ^{13}C NMR (150 MHz, CDCl3): δ 79.65, 79.62 (s), 79.59 (s), 51.73 (s), 51.69 (s), 43.07 (s), 43.04 (s), 42.83 (s), 42.80 (s), 40.68, 40.64, 40.57, 40.53, 35.27, 35.25, 34.71, 34.68, 27.91, 23.80, 23.78 ; ^{31}P NMR (243 MHz, CDCl3) : δ 8.20 ; IR (neat): 2967, 2876, 2367, 2331, 1260, 1083, 974, 813 cm^{-1} ; HRMS (DART): m/z calcd. 381.15959 for $C_{16}H_{31}O_6P_2$ ([2M+1]+); found: 381.15926.

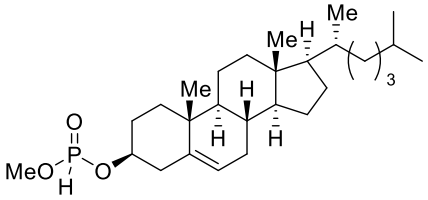
Methyl ((1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl) phosphonate (**3f**)



Colourless oil, 42.0 mg (60% yield), dr = 43/57.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.74 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 696 Hz), 6.74 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 696 Hz), 4.61-4.55 (1H, m), 3.70 (3H for one diastereomer, d, *J* = 13.1 Hz), 3.70 (3H for the other diastereomer, d, *J* = 13.7 Hz), 2.29-2.24 (1H, m), 1.88-1.86 (1H, m), 1.63 (1H, t, *J* = 4.5 Hz), 1.24-1.15 (3H, m), 0.83 (3H for one diastereomer, s), 0.83 (3H for the other diastereomer, s)), 0.82 (6H for one diastereomer, s), 0.80 (6H for the other diastereomer, s) ; ^{13}C NMR (150 MHz, CDCl3): δ 82.72, 82.70, 82.67, 82.65, 51.19, 51.75, 49.65, 49.62, 49.60, 47.71, 47.68, 44.85, 44.83, 37.18, 37.05, 37.03, 27.97, 27.94, 26.39, 26.36, 19.88, 18.70, 13.25, 13.14 ; ^{31}P NMR (243 MHz, CDCl3) : δ 9.88, 9.72 ; IR (neat): 2958, 2879, 1261, 1058, 967, 793 cm^{-1} ; HRMS (DART): m/z calcd. 465.25349 for $C_{22}H_{43}O_6P_2$ ([2M+1]+); found: 465.25231.

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl methyl phosphonate (**3g**)

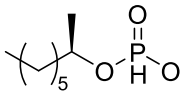


White foam, 138 mg (99% yield).

^{1}H NMR (600 MHz, $CDCl^3$): δ 6.81 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 690 Hz), 6.81 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 690 Hz), 5.37(1H, d, *J* = 1.4), 4.31-4.24 (1H, m), 3.74 (3H for one diastereomer, d, *J* = 11.7), 3.74 (3H for the other diastereomer, d, *J* = 11.7 Hz), 2.45 (1H, t, *J* = 12.0 Hz), 2.41-2.38 (1H, m), 2.00-1.94 (3H, m),

1.86-1.78 (2H, m), 1.72 (1H, q, J = 12.6 Hz), 1.58-1.39 (7H, m), 1.37-1.29 (3H, m), 1.26-1.21 (1H, m), 1.16-1.02 (7H, m), 1.00-0.96 (5H, m), 0.89 (3H, d, J = 6.2 Hz), 0.85-0.81 (6H, m), 0.65 (3H, s) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.88, 123.0, 76.76, 76.72, 56.44, 55.95, 51.75, 51.53, 49.77, 42.12, 42.09, 40.14, 40.12, 39.94, 39.90, 39.49, 39.32, 36.70, 36.19, 35.99, 35.59, 31.67, 31.61, 29.85, 29.83, 29.63, 29.60, 28.03, 27.80, 24.07, 23.65, 22.64, 22.39, 20.84, 19.05, 18.53, 11.65; ^{31}P NMR (243 MHz, $CDCl_3$) : δ 8.15.

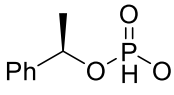
Methyl octan-2-yl phosphonate (**3h**)



Colourless oil, 62.3 mg (>99% yield), dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.73 (1H, d, $J_{P\text{-}H}$ = 692.6 Hz), 4.53-4.47 (1H, m), 3.70-3.68 (3H, m), 1.61-1.58 (1H, m), 1.50-1.46 (1H, m), 1.33-1.22 (11H, m), 0.82-0.80 (3H, m) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 74.63-74.59 (m), 51.48, 51.44, 51.41, 51.37, 37.34, 37.26, 37.23, 31.43, 31.40, 25.03, 25.01, 24.86, 24.83, 22.31, 22.29, 22.25, 21.92, 21.90, 21.57, 21.55, 13.79, 13.77, 13.73; ^{31}P NMR (240 MHz, $CDCl_3$): δ 8.64 (s), 8.31 (s) ; IR (neat): 2924 cm^{-1}, 2856 cm^{-1}, 1257 cm^{-1}, 1058 cm^{-1}, 962 cm^{-1}, 801 cm^{-1} ; HRMS (DART): m/z calcd. for $C_9H_{21}O_3P$ ([M]+): 209.13066; found: 209.13026.

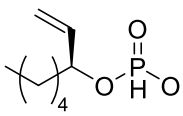
Methyl (1-phenylethyl) phosphonate (**3i**)



Colourless oil, 60.1 mg (>99% yield) dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33-7.23 (6H, m), 6.14 (1H for one diasteromer, d, $J_{P\text{-}H}$ could not be determined due to overlap of other peak), 6.08 (1H for one diasteromer, d, $J_{P\text{-}H}$ could not be determined due to overlap of other peak), 5.55-5.46 (1H, m), 3.65 (3H for one diasteromer, d, $J_{P\text{-}H}$ = 11.68 Hz), 3.47 (3H for one diastereomer, d, $J_{P\text{-}H}$ = 11.68 Hz), 1.59-1.58 (3H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.22, 141.19, 140.96, 140.93, 128.61, 128.59, 128.36, 128.34, 125.84, 125.80, 125.31, 75.46, 75.26, 75.22, 51.63, 51.59, 24.47, 24.18, 24.15; ^{31}P NMR (240 MHz, $CDCl_3$): δ 8.61 (s), 8.28 (s) ; IR (neat): 2432 cm^{-1}, 2353 cm^{-1}, 1253 cm^{-1}, 1065 cm^{-1}, 950 cm^{-1}, 756 cm^{-1}, 698 cm^{-1}; HRMS (DART): m/z calcd. for $C_9H_{13}O_3P$ ([2M+H]+): 401.12829; found: 401.12733.

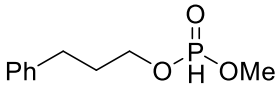
Methyl oct-1-en-3-yl phosphonate (**3j**)



Colourless oil, 53.9 mg (87% yield) dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.81 (1H for one diasteromer, d, $J_{P\text{-}H}$ = 705.0 Hz), 6.81 (1H for one diasteromer, d, $J_{P\text{-}H}$ = 696.1 Hz), 5.87-5.83 (1H, M), 5.34 (1H, d, $J_{P\text{-}H}$ = 17.18 Hz), 5.24 (1H, d, $J_{P\text{-}H}$ = 9.62 Hz), 4.85-4.83 (1H, m), 3.79-3.73 (3H, m), 1.74-1.72 (1H, m), 1.65-1.63 (1H, m), 1.38-1.33 (6H, m), 0.89-0.88 (3H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.80, 136.79, 136.47, 136.44, 117.55, 117.32, 78.64, 78.60, 78.37, 78.33, 51.65, 51.61, 51.59, 51.55, 35.83, 35.79, 35.73, 35.69, 31.31, 31.27, 31.24, 24.43, 24.31, 22.35, 13.84, 13.82, 13.79; ^{31}P NMR (240 MHz, $CDCl_3$): δ 8.61 (s) ; IR (neat): 2930 cm^{-1}, 2859 cm^{-1}, 1257 cm^{-1}, 1082 cm^{-1}, 955 cm^{-1}, 792 cm^{-1}; HRMS (DART): m/z calcd. for $C_6H_{13}O_3P$ ([2M+H]+): 413.22219; found: 413.22014.

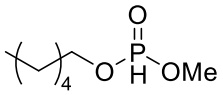
Methyl (3-phenylpropyl) phosphonate (**3k**)



Colourless oil, 64.3 mg (>99% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29-7.27 (2H, m), 7.19 (3H, t, J = 8.25 Hz) 6.78 (1H, d, $J_{P\text{-}H}$ = 696.1 Hz), 4.09-4.05 (2H, m), 3.75 (3H, d, $J_{P\text{-}H}$ = 12.37 Hz), 2.72 (2H, t, J = 7.56 Hz), 2.03-1.98 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 140.71 (s), 128.49 (s), 128.42 (s), 126.13 (s), 64.94 (d, $J_{P\text{-}C}$ = 5.78 Hz), 51.94 (d, $J_{P\text{-}C}$ = 5.78 Hz) 31.94 (s), 31.90 (s), 31.60 (s); ^{31}P NMR (240 MHz, $CDCl_3$): δ 9.83 (s) ; IR (neat): 3027 cm^{-1}, 1255 cm^{-1}, 1051 cm^{-1}, 963 cm^{-1}, 803 cm^{-1}, 745 cm^{-1}, 699 cm^{-1} ; HRMS (DART): m/z calcd. for $C_{10}H_{16}O_3P$ ([M+H]+): 215.08371; found: 215.08427.

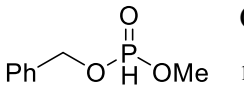
Hexyl methyl phosphonate (**3l**)



Colourless oil, 52.5 mg (97% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.70 (1H, d, $J_{P\text{-}H}$ = 694.7 Hz), 4.03-3.96 (2H, m), 3.69 (3H, d, $J_{P\text{-}H}$ = 11.68 Hz), 1.63-1.58 (2H, m), 1.32-1.19 (6H, m), 0.81 (3H, t, J = 6.87 Hz) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 65.88 (d, $J_{P\text{-}C}$ = 5.78 Hz), 51.81 (d, $J_{P\text{-}C}$ = 5.78 Hz), 31.18 (s), 30.28 (d, $J_{P\text{-}C}$ = 5.78 Hz), 25.05 (s), 22.40 (s), 13.87 (s) ; ^{31}P NMR (240 MHz, $CDCl_3$): δ 9.75 (s) ; IR (neat): 2958 cm^{-1}, 2927 cm^{-1}, 1257 cm^{-1}, 1051 cm^{-1}, 950 cm^{-1}, 781 cm^{-1}; HRMS (DART): m/z calcd. for $C_7H_{17}O_3P$ ([M+H]+): 181.09936; found: 181.09936.

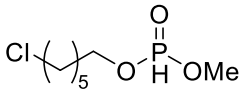
Benzyl methyl phosphonate (**3m**)



Colourless oil, 40.6 mg (75% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29-7.19 (5H, m), 6.70 (1H, d, $J_{P\text{-}H}$ = 11.68 Hz), 4.97 (2H, d, $J_{P\text{-}H}$ = 10.31 Hz), 3.56 (3H, d, $J_{P\text{-}H}$ = 12.37 Hz) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.37 (d, $J_{P\text{-}C}$ = 5.78 Hz), 128.45 (s), 128.44 (s) 127.75 (s), 67.04 (d, $J_{P\text{-}C}$ = 5.78 Hz), 51.66 (d, $J_{P\text{-}C}$ = 5.78 Hz); ^{31}P NMR (240 MHz, $CDCl_3$): δ 9.75 (s) ; IR (neat): 2350 cm^{-1}, 1251 cm^{-1}, 1048 cm^{-1}, 963 cm^{-1}, 829 cm^{-1}, 789 cm^{-1}, 733 cm^{-1}, 696 cm^{-1} ; HRMS (DART): m/z calcd. for $C_8H_{11}O_3P$ ([2M+H]+): 373.09699; found: 373.09803.

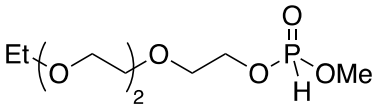
6-Chlorohexyl methyl phosphonate (**3n**)



Yellow oil, 48 mg (75% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.73 (1H, d, $J_{P\text{-}H}$ = 690.0 Hz), 4.05-4.00 (2H, m), 3.71 (3H, d, $J_{P\text{-}H}$ = 11.7 Hz), 3.47 (2H, t, J = 6.5 Hz), 3.74 (3H, d), 1.74-1.70 (2H, m), 1.68-1.63 (2H, m), 1.44-1.39 (2H, m), 1.38-1.33 (2H, m) ; ^{13}C NMR (150 MHz, CDCl3): δ 65.61 (d, $J_{P\text{-}C}$ = 5.8 Hz), 51.96, 44.84, 30.21 (d, $J_{P\text{-}C}$ = 5.8 Hz), 26.31, 24.79 ; ^{31}P NMR (243 MHz, CDCl3) : δ 9.80 ; IR (neat): 2968, 2894, 2837, 1257, 1051, 968, 799 cm^{-1}; HRMS (DART): m/z calcd. 429.11294 for $C_{14}H_{33}O_6P_2$ ([2M+H]+); found: 429.11109.

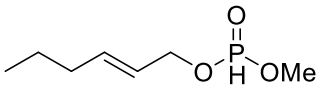
2-(2-(2-Ethoxyethoxy)ethoxy)ethyl methyl phosphonate (**3o**)



colourless oil, 40.6 mg (71% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.81 (1H, d, $J_{P\text{-}H}$ = 708.64 Hz), 4.22-4.18 (1H, m), 4.15-4.10 (1H, m), 3.71 (3H, d, J = 12.37 Hz), 3.66 (2H, t, J = 4.47 Hz), 3.63-3.55 (6H, m), 3.54-3.41 (2H, m), 3.48-3.44 (2H, m), 1.14 (3H, t, J = 6.78 Hz) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 70.6, 70.5 (d, Jc-p = 2.89 Hz), 70.1, 69.7, 66.6, 64.9 (d, Jc-p = 5.78 Hz), 61.7, 51.7 (d, J = 5.78 Hz), 15.1 ; ^{31}P NMR (240 MHz, $CDCl_3$): δ 10.31 (s) ; IR (neat): 2972, 2870, 2359, 1457, 1350, 1257, 974, 810, 548cm–1 ; HRMS (DART): m/z calcd. for $C_{16}H_{23}O_6P_2$ ([M+H]+): 257.1154; found: 257.1146.

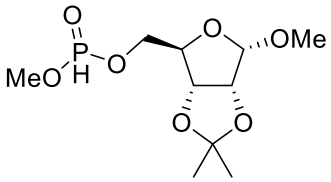
(E)-Hex-2-en-1-yl methyl phosphonate (**3p**)



Yellow oil, 28.0 mg (93% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.78 (1H, d, $J_{P\text{-}H}$ = 696 Hz), 5.80(1H, dt, J = 15.1, 6.9 Hz), 5.60-5.55 (1H, m), 4.51 (2H, dd, J = 10.0, 6.5 Hz), 3.74 (3H, d, J = 12.4 Hz), 2.02 (2H, q, J = 7.1 Hz), 1.39 (2H, td, J = 14.8, 7.1 Hz), 0.88 (3H, t, J = 7.6 H z) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.16, 124.11 (d, $J_{P\text{-}C}$= 5.75 Hz), 66.51 (d, $J_{P\text{-}C}$ = 5.75 Hz), 51.86 (d, $J_{P\text{-}C}$ = 5.75 Hz), 34.14, 21.92, 13.58 ; ^{31}P NMR (243 MHz, $CDCl_3$) : δ 9.72 ; IR (neat): 2966, 2875, 2367, 1257, 1059, 964, 792 cm^{-1} ; HRMS (DART): m/z calcd. 357.15959 for $C_{14}H_{31}O_6P_2$ ([2M+1]+); found: 357.16020.

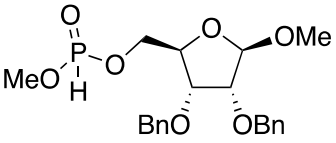
((3a*R*,4*R*,6*S*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4- yl)methyl methyl phosphonate (**3q**)



Colourless oil, 64.3 g (76% yield) dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.78 (1H for one diasteromer, d, $J_{P\text{-}H}$ = 705.0 Hz), 6.77 (1H for one diasteromer, d, $J_{P\text{-}H}$ = 707.1 Hz), 4.91 (1H, s), 4.65-4.64 (1H, m), 4.54-4.53 (1H, m), 4.30 (1H, t, J = 6.87 Hz), 4.06-3.96 (2H, m), 3.74 (3H for one diasteromer, d, $J_{P\text{-}H}$ = 2.06 Hz), 3.72 (3H for one diasteromer, d, $J_{P\text{-}H}$ = 707.1 Hz), 3.28-3.24 (3H, m), 1.42 (3H, s), 1.26 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 112.69, 109.42, 109.39, 84.98, 84.95, 84.86, 84.81, 81.40, 81.35, 65.52, 65.48, 65.23, 65.18, 55.14, 55.12, 52.16, 52.12, 26.37, 24.89; ^{31}P NMR (240 MHz, $CDCl_3$): δ 9.75 (s), 9.69 (s) ; IR (neat): 2993 cm^{-1}, 1258 cm^{-1}, 1210 cm^{-1}, 1161 cm^{-1}, 1090 cm^{-1}, 1045 cm^{-1}, 959 cm^{-1}, 867 cm^{-1}, 822 cm^{-1}, 779 cm^{-1} ; HRMS (DART): m/z calcd. for $C_{10}H_{19}O_7P$ ([M+H]+): 283.09466; found: 283.09347.

((2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-methoxytetrahydrofuran-2-yl)methyl methyl phosphonate (**3r**)

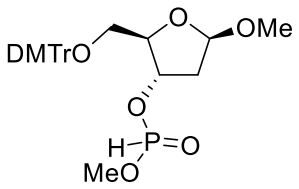


Colorless oil, 88.5 mg (68% yield), dr 50/50

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30-7.19 (10H, m), 6.75 (1H for one diasteromer, d, JP-H = 707.0 Hz), 6.74 (1H for one diasteromer, d, JP-H = 707.1 Hz), 4.82 (1H, s), 4.59-4.52(3H, m), 4.37 (1H, t, J = 11.0 Hz), 4.25-4.24 (1H, m), 4.21-4.17 (1H, m), 4.03-4.02 (1H, m), 3.96-3.93 (1H, m), 3.77 (1H,

t, J = 4.81 Hz), 3.69 (3H for one diasteromer, d, JP-H = 2.75), 3.66 (3H for one diasteromer, d, JP-H = 2.75), 3.27 (3H for one diasteromer, s), 3.26 (3H for one diasteromer, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.5, 137.39, 137.36, 128.49, 128.46, 128.45, 128.43, 128.39, 128.00, 127.97, 127.92, 127.89, 127.87, 106.4, 106.3, 79.7, 79.61, 79.55, 79.5, 79.2, 79.1, 77.7, 77.5, 72.6, 72.39, 72.37, 66.65, 66.6, 65.95, 65.90, 55.19, 55.18, 51.8, 51.5; ^{31}P NMR (240 MHz, $CDCl_3$): 10.48 (s), 10.04 (s) ; IR (neat): 2376 cm–1, 2333, 1106, 988, 931, 869, 798, 700 cm–1; HRMS (DART): m/z calcd. for C21H27O7P1 ([M]+): 422.1494; found: 422.1493.

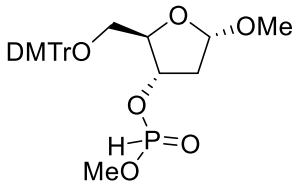
(2*R*,3*S*,5*R*)-2-((Bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5- methoxytetrahydrofuran-3-yl methyl phosphonate (**3s**)



Colourless oil, 150.3 mg (86% yield), dr = 57/43.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (2H, dd, *J* = 7.90, 1.72 Hz), 7.25-7.18 (6H, m), 7.12 (1H, t, *J* = 7.22 Hz), 6.75 (4H, d, *J* = 8.25 Hz), 6.69 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 705.6 Hz), 6.67 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 703.8 Hz), 5.09 (1H, d, *J* = 5.50 Hz), 4.93-4.86 (1H, m), 4.25-4.22 (1H, m), 3.70 (6H, s), 3.64 (3H for one diastereomer, d, *J* = 12.37 Hz), 3.55 (3H for the other diastereomer, d, *J* = 11.00 Hz), 3.33 (3H, s), 3.20 (1H, q, *J* = 4.81 Hz), 3.12 (1H, td, *J* = 9.97, 3.89 Hz), 2.41-2.33 (1H, m), 2.14-2.10 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.4, 144.60, 144.58, 135.78, 125.66, 130.0, 128.1, 127.7, 126.7, 113.1, 105.0, 86.2, 86.1, 83.52, 83.48, 83.3, 83.2, 76.33, 76.29, 76.0, 75.9, 63.1, 63.1, 55.11, 55.08, 51.94, 51.90, 51.86, 40.60, 40.58, 40.21, 40.19; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 9.10; IR (neat): 2439, 2322, 2159, 2026, 1980, 1844, 1701, 1684, 1669, 1653, 1635, 1576, 1569, 1560, 1558, 1541, 1506, 1436, 1419, 1245, 1212, 1177, 1033, 974, 830, 729, 700 cm^{-1} ; HRMS (DART): m/z calcd. 529.19130 for $C_{28}H_{33}O_8P$ ([M+H]+); found: 529.1910.

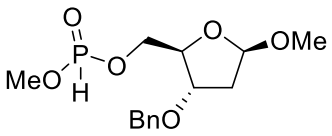
(2*R*,3*S*,5*S*)-2-((Bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5- methoxytetrahydrofuran-3-yl methyl phosphonate (**3t**)



Colourless oil, 131.5 mg (83% yield), dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (2H, d, *J* = 7.37 Hz), 7.53 (4H, d, *J* = 8.50 Hz), 7.28 (2H, t, *J* = 7.65 Hz), 7.22-7.16 (1H, m), 6.83 (4H, d, *J* = 8.50 Hz), 6.76 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 713.0 Hz), 6.74 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 715.0 Hz), 5.17-5.12 (1H, m), 5.07-5.00 (1H, m), 4.22-4.17 (1H, m), 3.78 (6H, s), 3.71 (3H for one diastereomer, d, *J* = 11.90 Hz), 3.68 (3H for the other diastereomer, d, *J* = 11.90 Hz), 3.30 (3H, s), 3.23 (2H, d, *J* = 3.40 Hz), 2.29 (2H, t, *J* = 4.82 Hz) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.4, 144.6, 139.5, 135.9, 135.8, 130.0, 129.1, 128.1, 127.75, 127.72, 127.0, 126.7, 113.0, 105.10, 105.06, 105.0, 86.2, 86.1, 85.9, 83.65, 83.59, 83.5, 83.4, 81.3, 76.9, 76.7, 76.62, 76.57, 63.7, 63.6, 63.3, 60.3, 55.5, 55.34, 55.32, 55.2, 55.1, 52.1, 52.04, 51.96, 51.9, 40.17, 40.16, 40.03, 40.00, 21.0, 14.19; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 8.91, 8.61; IR (neat): 2164, 2030, 1943, 1918, 1845, 1734, 1701, 1684, 1636, 1609, 1505, 1452, 1294, 1249, 1175, 1034, 976, 833, 732, 700 cm^{-1} ; HRMS (DART): m/z calcd. 529.19130 for $C_{28}H_{33}O_8P$ ([M+H]+); found: 529.1911.

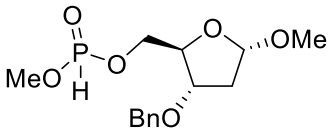
((2*R*,3*S*,5*R*)-3-(Benzyloxy)-5-methoxytetrahydrofuran-2-yl)methyl methyl phosphonate (**3u**)



Colourless oil, 72.1 mg (75% yield), dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33-7.26 (5H, m), 6.83 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 705.0 Hz), 6.82 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 706.2 Hz), 5.07 (1H, d, J = 2.75 Hz), 4.51-4.46 (2H, m), 4.23-4.19 (1H, m), 4.17-4.04 (3H, m), 3.76 (3H for one diastereomer, d, J = 2.75 Hz), 3.74 (3H for one diastereomer, d, J = 3.44 Hz), 3.31 (3H, s), 2.26-2.22 (1H, m), 2.13-2.08 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.5, 128.5, 127.9, 127.7, 105.6, 82.4, 82.3, 82.2, 78.92, 78.87, 71.88, 71.85, 66.8, 66.7, 66.32, 66.28, 55.1, 52.00, 51.96, 51.9, 39.30, 39.27; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 10.15, 9.96; IR (neat): 2433, 2152, 2031, 1734, 5171, 1419, 1246, 1043, 974, 830, 736, 699 cm^{-1} ; HRMS (DART): m/z calcd. 633.22297 for $C_{28}H_{43}O_{12}P_2$ ([2M+H]+); found: 633.22537.

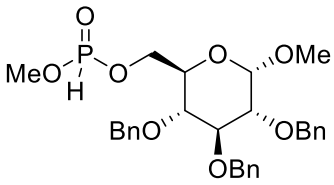
((2*R*,3*S*,5*S*)-3-(Benzyloxy)-5-methoxytetrahydrofuran-2-yl)methyl methyl phosphonate (**3v**)



Colourless oil, 75.2 mg (78% yield), dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.28 (5H, m), 6.83 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 705.0 Hz), 6.82 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 706.2 Hz), 5.07 (1H, d, J = 5.50 Hz), 4.60 (1H, dd, J = 12.03, 3.09 Hz), 4.49 (1H, d, J = 12.37, 2.75 Hz), 4.25-4.12 (2H, m), 4.08-4.02 (1H, m), 3.75 (3H for one diastereomer, d, J = 11.68 Hz), 3.74 (3H for one diastereomer, d, J = 12.37 Hz), 3.40 (3H for one diastereomer, s), 3.39 (3H for the other diastereomer, s), 2.27-2.20 (1H, m), 2.05 (1H, d, J = 13.75 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.7, 128.5, 128.4, 128.0, 127.8, 127.7, 105.1, 81.3, 82.22, 82.20, 81.16, 77.86, 71.9, 71.8, 65.41, 65.37, 65.29, 65.25, 55.2, 51.9, 51.83, 51.80, 38.8,; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 10.15, 9.96; IR (neat): 2439, 2164, 2028, 1977, 1700, 1257, 1215, 1046, 970, 830, 744, 699 cm^{-1} ; HRMS (DART): m/z calcd. 633.22297 for $C_{28}H_{43}O_{12}P_2$ ([2M+H]+); found: 633.22413.

Methyl (((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2H-pyran-2- yl)methyl) phosphonate (**3w**)

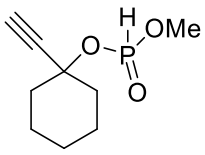


Colourless oil, 135.2 mg (83% yield), dr = 52/48.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36-7.27 (15H, m), 6.80 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 708.6 Hz), 6.75 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 708.6 Hz) 5.00 (1H, d, J = 10.31 Hz), 4.90 (1H, dd, J = 10.31, 8,25 Hz), 4.82 (2H, d, J = 11.00 Hz), 4.79 (2H, d, J = 11.68 Hz), 4.67-4.58 (3H, m), 4.31-4.20 (2H, m), 4.01 (1H, t, J = 8.94 Hz), 3.73 (2H, d, J = 11.68 Hz), 3.72 (2H, d, J = 12.37 Hz), 3.533-3.46 (2H, m), 3.38 (3H for one diastereomer, s), 3.36 (3H for the other diastereomer, s) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.5, 137.93, 137.89, 137.8, 128.5, 128.4, 128.1, 128.02, 127.96, 127.91, 127.89, 127.86, 127.6, 98.11, 98.05, 81.8, 79.9, 79.7, 77.1, 77.0, 75.74, 75.72, 75.07, 75.05, 73.42, 73.37, 69.45, 69.41, 69.32, 69.29, 64.73, 64.70, 64.6, 64.5, 55.4, 55.3, 51.78, 51.74; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 10.75, 10.59 ; IR (neat): 2159, 2031, 1976, 1943, 1918, 1845, 1825, 1718, 1701, 1696, 1685, 1676, 1635, 1577, 1569, 1550, 1540, 1507, 1459,

1250, 1044, 974, 834, 740, 699cm^{-1} ; HRMS (DART): m/z calcd. 543.21478 for $C_{29}H_{36}O_8P$ ([M+H]+); found: 543.20656.

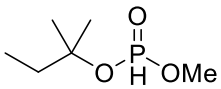
1-Ethynylcyclohexyl methyl phosphonate (**3x**)



Colourless oil, 50.2 mg (99% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.04 (1H, d, $J_{P\text{-}H}$ = 702.2 Hz), 3.79 (3H, d, $J_{P\text{-}H}$ = 12.4 Hz), 2.79 (1H, s), 2.15-2.04 (2H, m), 1.97-1.89 (2H, m), 1.74-1.70 (2H, m), 1.64-1.58 (2H, m), 1.53-1.51 (1H, m), 1.36-1.31 (1H, m) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 82.63 (d, $J_{P\text{-}C}$ = 5.78 Hz), 77.42 (d, $J_{P\text{-}C}$ = 8.67 Hz), 76.45 (s), 51.92 (d, $J_{P\text{-}C}$ = 5.78 Hz), 39.26 (d, $J_{P\text{-}C}$ = 4.33 Hz), 24.57 (s), 22.50 (d, $J_{P\text{-}H}$ = 7.22 Hz) ; ^{31}P (MHz, $CDCl_3$) NMR: δ 5.90 ; IR (neat): 2938, 2862, 2108, 1991, 1447, 1262, 1247, 1144, 1078, 1045, 905, 891, 881, 835, 671, 624, 572 cm^{-1} ; HRMS (DART): m/z calcd. 405.15959 for $C_{18}H_{31}O_6P_2$ ([2M+H]+); found: 405.15608.

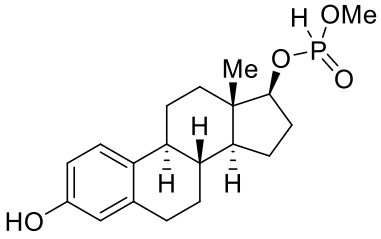
Methyl tert-pentyl phosphonate (**3y**)



Colourless oil, 39.9 mg (80% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.77 (1H, d, $J_{P\text{-}H}$ = 692.0 Hz), 3.67 (3H, d, $J_{P\text{-}H}$ = 11.68 Hz), 1.69 (2H, q, J = 7.33 Hz,), 1.43 (6H, d, J = 3.44 Hz), 0.90 (3H, t, J = 7.56 Hz) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 86.57 (s), 51.67 (d, $J_{P\text{-}C}$ = 5.78 Hz), 35.86 (s), 27.73 (d, $J_{P\text{-}C}$ = 4.33 Hz), 27.62 (d, $J_{P\text{-}C}$ = 4.33 Hz), 8.42 (s) ; ^{31}P NMR (240 MHz, CDCl3): δ 4.60 (s) ; IR (neat): 2976, 1462, 1373, 1257, 963, 794 cm–1; HRMS (DART): m/z calcd. for $C_{12}H_{31}O_6P_2$ ([2M+H]+): 333.1596; found: 333.1592.

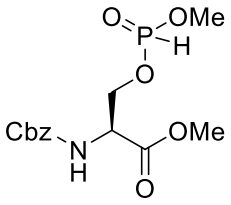
(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6Hcyclopenta[a]phenanthren-17-yl methyl phosphonate (**3z**)



Colorless oil, 96.7 mg (93% yield), dr = 58/42.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 (1H, d, J = 2.06 Hz), 6.84 (1H for one diastereomer, d, $J_{P\text{-}H}$ = 700.0 Hz), 6.83 (1H for the other diastereomer, d, $J_{P\text{-}H}$ = 699.0 Hz), 6.68 (1H, d, J = 2.06 Hz), 6.60 (1H, br), 4.40-4.35 (1H, m), 3.79 (3H for one diastereomer, d, J = 11.68 Hz), 3.78 (3H for the other diastereomer, d, J = 11.68 Hz), 2.85-2.76 (2H, m), 2.29-2.27 (1H, m), 1.96 (1H, t, J = 11.68 Hz), 1.85-1.82 (1H, m), 1.79-1.69 (2H, m), 1.49-1.39 (3H, m), 1.36-1.27 (2H, m), 1.19-1.14 (1H, m), 0.82 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.1, 137.8, 131.6, 126.3, 115.3, 112.9, 99.9, 85.4, 85.33, 85.29, 52.01, 51.99, 51.95, 49.03, 49.01, 43.6, 43.4,0, 43.36, 43.3, 38.6, 36.4, 36.3, 29.5, 28.70, 28.69, 28.53, 28.51, 27.1, 23.06, 23.03, 11.62, 11.56; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 9.20, 9.06; IR (neat): 3225, 2163, 2026, 1972, 1220, 1016, 978, 951, 905, 869, 727, 668, 576, 419 cm^{-1} ; HRMS (DART): m/z calcd. 701.33721 for $C_{38}H_{55}O_8P_2$ ([2M+H]+); found: 701.34725.

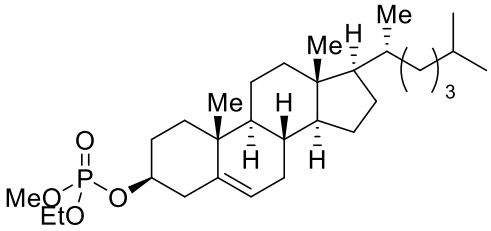
Methyl (methyl ((benzyloxy)carbonyl)-L-serinate) phosphonate (**3ab**)



Colourless oil, 78.0 mg (82% yield), dr = 50/50.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37-7.31 (5H, m), one peak 6.18 (1H for one diastereomer, d, J_{P-H} could not be determined due to overlap of the other peak), one peak 6.15 (1H for one diastereomer, d, J_{P-H} could not be determined due to overlap of the other peak) 5.84 (1H, t, J = 9.97 Hz), 5.16-5.11 (2H, m), 4.62-4.58 (1H, m), 4.49 (1H, tt, J = 13.40, 3.67 Hz), 4.38 (1H, dq, J = 14.43, 3.67 Hz), 3.80 (3H, s), 3.74 (3H for one diastereomer, d, J = 10.31 Hz), 3.72 (3H for one diastereomer, d, J = 11.00 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3, 155.7, 136.0, 135.9, 133.7, 128.5, 128.2, 128.11, 128.09, 67.21, 67.20, 65.4, 65.33, 65.29, 54.37, 56.36, 54.33, 54.29, 53.2, 53.0, 42.9, 52.21, 52.16, 52.14, 52.10; ^{31}P (243 MHz, $CDCl_3$) NMR: δ 10.07 ; IR (neat): 2929, 2162, 2034, 1701, 1696, 1685, 1560, 1507, 1497, 1253, 1181, 1029, 960, 778, 543cm^{-1} ; HRMS (DART): m/z calcd. 663.17200 for $C_{26}H_{37}N_2O_{14}P_2$ ([2M+H]+); found: 663.16846.

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((R)-4-methylpentan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl ethyl methyl phosphate (**4g**)

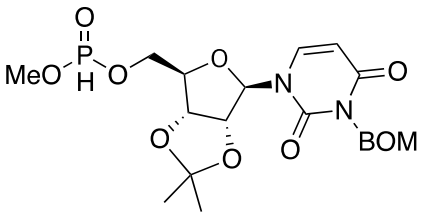


White solid, 91.6 mg (95% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.39 (1H, d, J = 4.12 Hz), 4.20 (1H, dq, J = 21.82, 5.73 Hz), 4.13-4.09 (2H, m), 3.75 (3H, dd, J = 11.34, 1.72 Hz), 2.43 (2H, d, J = 6.87 Hz), 2.02-1.96 (3H, m), 1.87-1.81 (2H, m), 1.70 (1H, dt, J = 29.78, 7.39 Hz), 1.60-1.33 (13H, m), 1.26 (2H, dd, J = 19.59, 12.03 Hz), 1.18-1.04 (7H, m), 1.03-0.96 (5H, m), 0.94-0.91 (4H, m), 0.86 (6H, q, J = 2.98 Hz), 0.67 (3H, s) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.3, 123.0, 78.29, 78.25, 63.7, 63.6, 56.6, 56.1, 54.0, 53.9, 49.9, 42.3, 39.89, 39.86, 39.7, 39.5, 36.8, 36.4, 36.1, 35.7, 31.84, 31.79, 29.55, 29.52, 28.2, 28.0, 25.8, 24.2, 23.8, 22.8, 22.5, 21.0, 19.2, 18.7, 16.12, 16.08, 11.8; ^{31}P (243 MHz, $CDCl_3$) NMR: δ -0.10; IR (neat): 2936, 2159, 2031, 1974, 1465, 1387, 1273, 1052, 971, 905, 827, 760, 732 cm^{-1}; HRMS (DART): m/z calcd. 509.37597 for $C_{30}H_{54}O_4P$ ([M+H]+); found: 509.37026.

All the phosphorylated nucleosides were too unstable, and therefore not able to take ^{13}C NMR, IR, and HRMS (**3ac**-**3ai**).

((3a*R*,4*R*,6*R*,6a*R*)-6-(3-((Benzyloxy)methyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl methyl phosphonate (**3ac**)



^{1}H NMR ($CDCl_3$) δ: 7.29-7.15 (3H, m), 6.73 (1H, d, J = 708.64 Hz), 5.67 (1H, d, J = 7.56 Hz), 5.55 (1H, d, J = 9.62 Hz), 5.41 (1H, dd, J = 9.62, 3.44 Hz), 5.36 (1H, d, J = 9.62 Hz), 4.89 (1H, d, J = 6.87 Hz), 4.79 (1H, td, J = 7.39, 4.12 Hz), 4.62 (2H, s), 4.28-4.19 (3H, m), 3.71 (3H, s), 1.49 (3H, s), 1.28 (3H, s). ^{31}P -NMR ($CDCl_3$) δ: 10.22 (d, J = 85.50 Hz).

This part is not published because it is scheduled to be published in journals or other publications within five years.

Chapter 8. References

[1] a) Dowd C. J.; Kelley, B. *Purification Process Design and the Influence of Product and Technology Platforms, Comprehensive Biotechnology (Second Edition)*, Elsevier Science, **2011**.

b) Chen, H.;Wang, L. *Sugar Strategies for Biomass Biochemical Conversion, Technologies for Biochemical Conversion of Biomass*, Academic Press, an imprint of Elsevier, **2017**.

[2] Clayden, J.; Greeves, N.; Warren, S.; *Organic Chemistry*, Oxford University Press, **2001**.

[3] Cheng, X.; Blumenthal, R.; *Cell Press,* **2007**, *16*, 341-350.

[4] Drazic, A.; Myklebust, L. M.; Ree, R.; Arnesen, T. *Biochimica et Biophysica Acta.* **2016**, *1864* 1372-1401.

[5] Chapman, E.; Best, M. D.; Hanson, S. R.; Wong, C-H. *Angew. Chem. Int. Ed*. **2004**, *43*, 3526–3548.

[6] Garcia-Garcia, T.; Poncet, S.; Derouiche, A.; Shi, L.; Mijakovic, I.; Noirot-Gros, M-F., *Frontiers in Microbiology*, **2006**, *7*, Article 184.

[7] Ardito, F.; Giuliani, M.; Perrone, D.; Trioiano, G.; Muzio, L. L. *Int. J. Mole. Med.* **2017**, *40*, 271-280

[8] Blackstock, J. C. *Guide to Biochemistry*, Wright, **1989**.

[9] Alfarouk, K.; Ahmed, S. B. M.; Elliott, R. L.; Benoit, A.; Alqahtani, S. S.; Ibrahim, M. E.; Bashir A. H. H.; Alhoufie, S. T. S.; Elhassan, G. O.; Wales, C. C.; Schwartz, L. H.; Ali, H. S.; Ahmed, A.; Forde, P. F.; Devesa, J.; Cardone, R. A.; Fais, S.; Harguindey, S.; Reshkin, S. J. *Metabolites* **2020**, *10*, 285-301.

[10] a) McGuigan, C.; Pathirana, R. N.; Balzarini, J.; Declercq, E. *J. Med. Chem.* **1993**, *36*, 1048−1052.

b) Freel Meyers, C. L.; Borch, R. F. *J. Med. Chem.* **2000**, *43*, 4319−4327.

c) Chang, S. L.; Griesgraber, W.; Southern, P. J.; Wagner, C. R. *J. Med. Chem.* **2001**, *44*, 223−231.

d) Egron, D.; Imbach, J. L.; Gosselin, G.; Aubertin, A. M.; Perigaud, C. *J. Med. Chem.* **2003**, *46*, 4564−4571.

e) Wire, M. B.; Shelton, M. J.; Studenberg, S. *Clin. Pharmacokinet.* **2006**, *45*, 137−168.

f) Qian, X. D.; Song, L.; Jiang, S. H.; Tang, G.; Xing, W. Y.; Wang, B. B.; Hu, Y.; Yuen, R. K. K. *Ind. Eng. Chem. Res.* **2013**, *52*, 7307−7315.

[11] Feuer, D. J.; Broadley, K. E. *Ann. Oncol.* **1999**, *10*, 1035−1041.

[12] a) Gragoudas, E. S.; Adamis, A. P.; Cunningham, E. T.; Feinsod, M.; Guyer, D. R.; Neova, V. I. S. O. *N. Engl. J. Med.* **2004**, *351*, 2805−2816.

b) Raal, F. J.; Santos, R. D.; Blom, D. J.; Marais, A. D.; Charng, M. J.; Cromwell, W. C.; Lachmann, R. H.; Gaudet, D.; Tan, J. L.; Chasan- Taber, S.; Tribble, D. L.; Flaim, J. D.; Crooke, S. T. *Lancet* **2010**, *375*, 998−1006.

c) Mendell, J. R.; Rodino-Klapac, L. R.; Sahenk, Z.; Roush, K.; Bird, L.; Lowes, L. P.; Alfano, L.; Gomez, A. M.; Lewis, S.; Kota, J.; Malik, V.; Shontz, K.; Walker, C. M.; Flanigan, K. M.; Corridore, M.; Kean, J. R.; Allen, H. D.; Shilling, C.; Melia, K. R.; Sazani, P.; Saoud, J. B.; Kaye, E. M.; *Ann. Neurol.* **2013**, *74*, 637−647.

[13] Murray,J. I.; Woscholski, R.; Spivey, A. C. *Synlett*. **2015**, *26*, 985-990.

[14] Fenton, O. S.; Allen, E. E.; Pedretty, K. P.; Till, S. D.; Todaro, J. E.; Sculimbrene, B. R. *Tetrahedron* **2012**, *68*, 9023-9028.

[15] Letsinger; R.L.; Lunsford, W.B. *J. Am. Chem. Soc.* **1976**, *98*, 3655–3661.

[16] a) Matteucci, M.D.; Caruthers, M.H. *Tetrahedron Lett.* **1980**, *21*, 719–722.

b) Matteucci, M.D.; Caruthers, M.H. *J. Am. Chem. Soc.* **1981**, *103*, 3185–3191.

[17] Beaucage, S. L; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859-1862.

[18] a) Subhadeep Roy, Marvin Caruthers, *Molecules*, **2013**, *18*, 14268-14284.

b) Wei, X. *Tetrahedron* **2013**, *69*, 3615−3637.

[19] a) Corby, N.S.; Kenner, G.W.; Todd, A.R. *J. Chem Soc.* **1952**, 3669–3675.

b) Hall, R.H.; Todd, A.; Webb, R.F. *J. Chem. Soc.* **1957**, 3291–3296.

[20] a) Froehler, B.C.; Ng, P.G.; Matteucci, M.D. *Nucleic Acids Res.* **1986**, *14*, 5399–5407.

b) Garegg, P.J.; Lindh, I.; Regberg, T.; Stawinski, J.; Strömberg, R.; Henrichson, C. *Tetrahedron Lett.* **1986**, *27*, 4051–4054.

[21] Sakakura, A.; Katsukawa, M.; Ishihara, K. *Org.Lett.* **2005**, *7*, 1999–2002.

[22] Sakakura, A.; Katsukawa, M.; Ishihara, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1423 –1426.

[23] Domon, K.; Puripat, M.; Fujiyoshi, K.; Hatanaka, M.; Kawashima, S.A.; Yamatsugu, K.; Kanai, M. *ACS Cent. Sci.* **2020**, *6*, 283−292.

[24] Iwasaki, T.; Maegawa, T.; Hayashi, Y.; Oshima, T.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944-2945.

[25] Troev, K.D. *Chemistry and Application of H-Phosphonates*, Elsevier, **2006**.

[26] Keglevich, G.; Tóth, V.R.; Drahos, L. *Heteroatom Chem.* **2011**, *22*, 15-17.

[27] a)Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29–49.

b) Bálint, E.; Takács, J.; Drahos, L.; Keglevich, G. *Heteroatom Chem.*, **2012**, *23*, 235-240.

[28] Keglevich, G. *Molecules*, **2012**, *17*, 12821-12835.

[29] a) Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y., Agawa, T. *Bull. Chem. Soc. Jpn.*, **1982**, *55*, 909-913.

b) Henyecz, R.; Keglevich, G. *Organophosphorus Chemistry*, Royal Society of Chemistry, **2018**.

[30] Roy, S.; Caruthers, M. *Molecules* **2013**, *18*, 14268-14284.

[31] a) Gerrard, W. *J. Chem. Soc.* **1940**, 1466–1469.

b) Hardy, E.E.; Anniston, A.; Kosolapoff, G.M. U.S. Patent 2409039.

c) Foss, O. *Acta Chem. Scand.* **1947**, *1*, 8–31.

[32] Froneman, M.; Modro, T.A. Tetrahedron Lett., **1988**, *29*, 3327-3330.

[33] Kluba, M.; Zwierzak, A. *Synthesis* **1978**, *2*, 134–137.

[34] Berchel, M.; Haddad, J.; Le Corre, S.S.; Haelters, J.-P.; Jaffrès, P.-A. *Tetrahedron Lett.* **2015**, *56*, 2345–2348.

[35] a)Bálint, E.; Tajti, A.; Drahos, L.; Ilia, G.; Keglevich, G. *Curr. Org. Chem*. **2013**, 17, 555-562.

b) Bálint, E.; Tajti, A.; Toth, N.; Keglevich, G. *Molecules*, **2018**, *23*, 1618-1633.

[36] Xu, C.; Shi, Y-L.; Huang, J-E.; Wang, B.; Li, H-L. *Journal of Molecular Catalysis A***:** *Chemical*, **2004**, *219*, 351 – 355.

[37] Backus, A. C.; Wood, L. L. U. S. Patent. 3,453,300.

[38] Ohshima, T. *Chem. Pharm. Bull.* **2016**, *64*, 523−539.

[39] Dhineshkumar, J.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 6062−6065.

[40] Saito, Y.; Cho, S.; Danieli, A. L.; Kobayashi, S. *Org. Lett.* **2020**, *22*, 3171-3175.

[41] Timperley C. A.; Arbon R. E.; Saunders, S. A.; Waters, M. J.; *Jour. Fluorine Chem*. **2002**, *113*, 65-78.