

# Organocatalytic Stereoselective Synthesis of Organophosphorus and Organoselenium Compounds

**THESIS**  
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**BABASAHEB BHIMRAO AMBEDKAR UNIVERSITY**  
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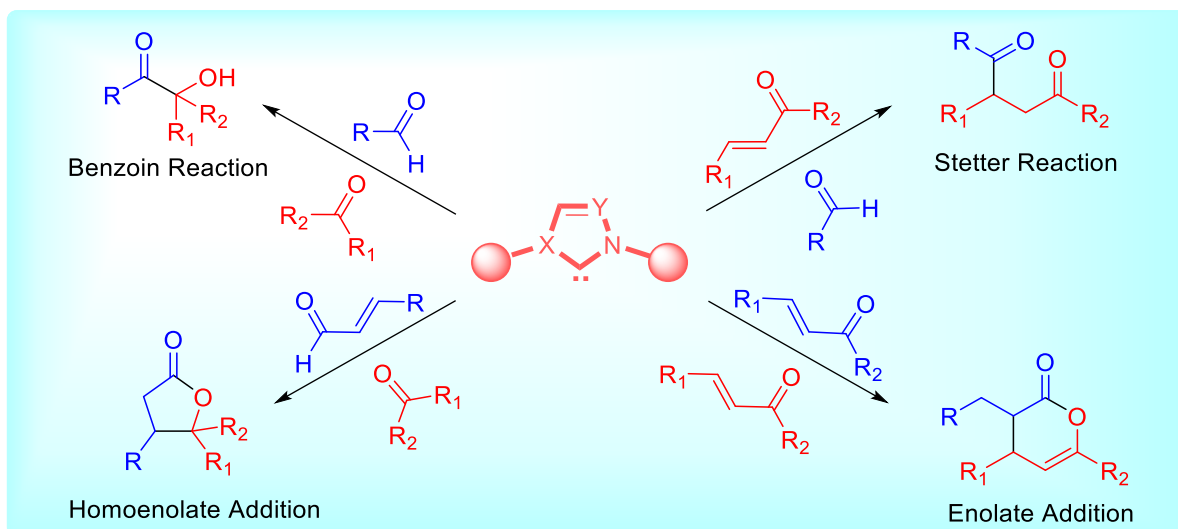
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## ABSTRACT

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

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

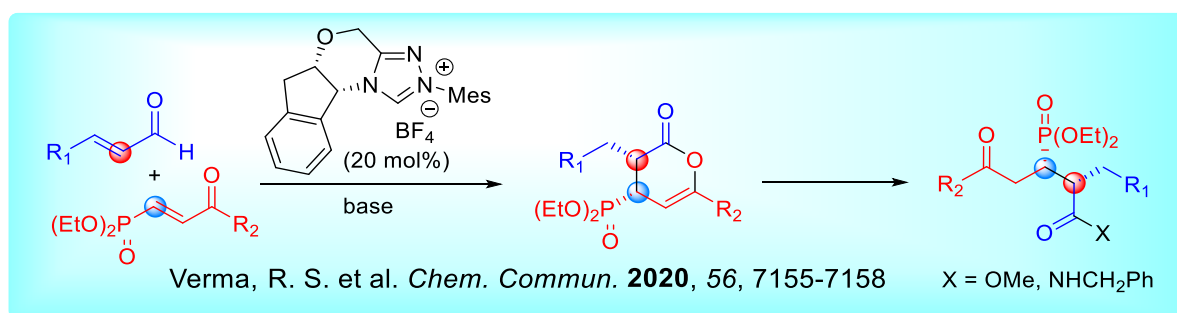
The development of numerous synthetic methods over the last several decades has enabled the chemist to complete the synthesis of even highly complex molecules. However, these methods have mainly relied on the use of different metal-based reagents and catalysts. Pharmaceutical industries prefer transition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



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

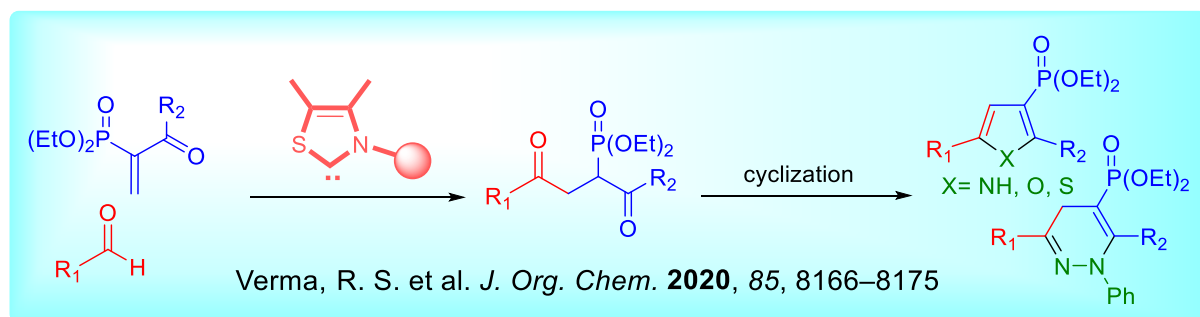
## Chapter 2: Carbene Catalyzed Highly Enantioselective Preparation of 4-Phosphorylated $\delta$ -Lactones

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



### Chapter 3: Carbene Catalyzed Synthesis of $\alpha$ -Phosphorylated 1,4-Diketones: Access of 3/4-Phosphorylated Heterocycles

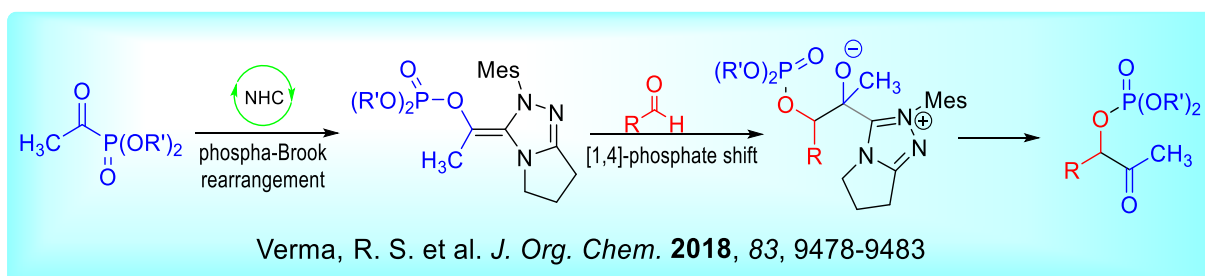
Heterocyclic motifs such as pyrroles, furans, thiophenes and dihydropyridazines are abundantly found in numerous biologically active natural, non-natural, pharmaceuticals and agrochemicals products. On the other hand, phosphoryl groups are omnipresent in the biological system and other vital molecules.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



### Chapter 4: Carbene-Catalyzed Phospha-Brook Rearrangement: Preparation of $\alpha$ -Ketophosphates from Acylphosphonates and Aldehydes

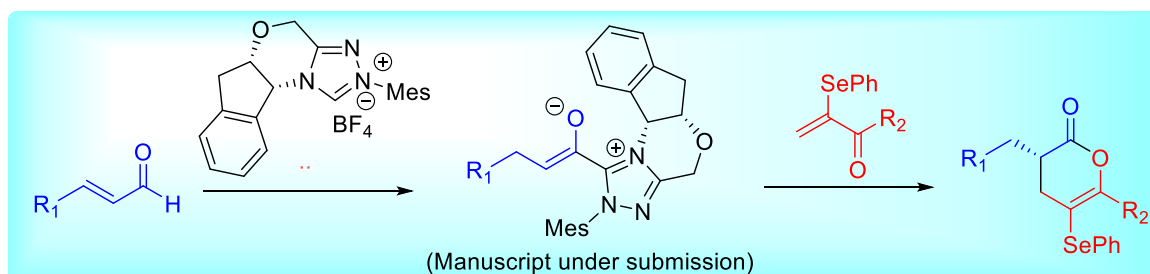
The organophosphorus compounds have an indispensable role as the key biomolecules, such as DNA, RNA and ATP. In addition, they are used in pharmaceuticals, organometallics, organic synthesis and photoelectric materials. They have high chelation affinity with transition metals, therefore, they are widely used as ligands in organic synthesis. Phosphate esters are used in the pesticides and in prodrugs to enhance their aqueous solubility. Among them,  $\alpha$ -ketophosphates are the key intermediates for the synthesis of phospholipids and oligonucleotides. Herein, we have developed the first *N*-heterocyclic carbene catalyzed controlled cross acyloin

condensation of acyl phosphonates and aldehydes *via* phospho-Brook rearrangement. This is the first organocatalytic phospho-Brook rearrangement that generally required metal cyanides as the catalysts previously. In addition, acyl anions from the acyl phosphonates has been generated under carbene catalyst for the first time.



### Chapter 5: Carbene Catalyzed Enantioselective Synthesis of Selenylated $\delta$ -Lactones from Vinyl selenides and Enals

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



To achieve this, we have used vinylselenides as the new Michael acceptor under carbene catalysis. This study is a valuable addition to the limited literature methods available for the

preparation of C4-unsubstituted chiral  $\delta$ -lactones. These class of  $\beta$ -unsubstituted enones have remained challenging substrates for the cycloaddition reaction under NHC-catalysis via homoenolate intermediates.

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