STEREOSELECTIVE CASCADE APPROACHES INVOLVING 1,2-PHOSPHA BROOK REARRANGEMENT/CONJUGATE ADDITION AND CYCLOADDITION REACTIONS

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JUNE 2025

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by

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Submitted

In fulfillment of the requirements of the degree of Doctor of Philosophy

to the

INDIAN INSTITUTE OF TECHNOLOGY, DELHI

JUNE 2025

This Ph.D. thesis is dedicated to my Family.

Special gratitude to my parents and my brother for their blessings, unconditional love, friendship and support.

CERTIFICATE

This is to certify that the thesis entitled, **"Stereoselective Cascade Approaches involving 1,2-Phospha Brook Rearrangement/Conjugate Addition and Cycloaddition Reactions"**, being submitted by **Ms. Ravneet Kaur** to the ***Indian Institute of Technology Delhi*** for the award of the degree of **Doctor of Philosophy** in Chemistry is a record of bonafide research work carried out by her. **Ms. Ravneet Kaur** worked under my guidance and supervision and has fulfilled the requirements for the submission of a Ph.D. thesis, which to my knowledge has reached the requisite standard.

The results illustrated and incorporated in this dissertation have not been submitted in part or full to any other University or Institute for the award of any degree or diploma.

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Acknowledgments

I extend my heartfelt gratitude to all those who have contributed to the completion of this doctoral dissertation. First and foremost, I want to thank my supervisor ***Prof. Ravi P. Singh*** *without his enthusiasm, encouragement, support, and continuous optimism, this thesis would hardly have been completed. I am also very grateful to him for his scientific advice and knowledge and many insightful discussions and suggestions. He showed me different dimensions to approach a research problem and the need to be persistent to accomplish any goal. His advice on both research as well as on my career has been invaluable. I also must thank the members of my SRC committee,* ***Prof. A. J. Elias****,* ***Prof. V. Haridas****, and* ***Prof. Josemon Jacob*** *for their valuable suggestions and advice in general. I also thank all the past and the present Head of the Department of Chemistry, for the academic support and the facilities provided to carry out my research work. I would also like to thank* ***Prof. Shashank Deep*** *(Chairman, DRC) for streamlining curricular formalities. I would like to express my special gratitude towards* ***Prof. V. Haridas****, for his timely encouragement, valuable suggestions and support. I gratefully acknowledge all the faculty members and staff for providing the necessary facilities to pursue my research activities. I would also like to thank* ***Prof. Neetu Singh****, for her kind and generous nature, constant support, and encouragement. I would also like to thank MHRD-India, India, for providing the research fellowship that allowed me to undertake this research program. I would also like to greatly acknowledge* ***Prof. S. Nagendran****, coordinator of the X-ray facility, for providing me an opportunity to learn and operate the single crystal X-ray diffractometer. I would like to thank Mr. Bhuvnesh, Mr. Abhijit, Dr. Pritam, Dr. Vivek, and Dr. Prakash for helping me to learn and solve the X-ray Crystal data. I would like to extend my sincere thanks to all the teachers of the chemistry department for their support whenever it was required. I also thank Mr. Keshav, Mr. Manoj, Mrs. Poornima, Mrs. Priyanka and Mr. Narugopal for helping me in recording NMR and HRMS. I also thank Mr. Virender Sharma, in-charge III of central glass blowing facility for his timely help. I am thankful to all the members of this department who helped me in one way or the other to carry out my work successfully.*

The foundation stone of this group was laid down by my senior lab mates Dr. Amol P Jadhav, Dr. Bhaskara Rao, Dr. Amjad Ali, and Dr. Devalina Ray. I would like to thank them for not only creating a cordial working environment in the lab but also for timely guidance and enduring support in continuing and completing my research projects. I feel very lucky to have such seniors in my life and I express my special thank of gratitude to them. I would like to thank

Dr. Md. Belal, Dr. Abhijeet Srivastava, Dr. Krishna Kumar, Dr. Vijay Gupta, Dr. Krishna Nand Tripathi, Dr. Manish Kumar Jaiswal, Dr. Soumyadip Hore, Dr. Diksha Gambhir for the support, and guidance at various times.

I would like to extend my heartfelt gratitude to my juniors Dr. Bhuvnesh Singh, Ravi Saini, Abhijit, Shreya and Chandan for their support and encouragement throughout my PhD journey. Their camaraderie, insightful discussions, and willingness to assist whenever needed have made this challenging journey much more manageable and enjoyable. A special thanks to Dr. Sanjay Singh for his invaluable contributions, whether it was through brainstorming ideas, sharing resources, or simply being a friend and a source of motivation during tough times. His enthusiasm and dedication have been truly inspiring. I thank all my colleagues (present and past) Dr. Roshayed Ali Lashker, Dr. Dinesh Singla, Dr. Shashank Singh, Dr. Manju Devi, Harish, Arindam, Kalyan, Najmuddin, Aarti, Satish, Priyankar, Rajesh, Sunil, Akash, Neha, Gyanshree, Surjeet, Anjum, Dhyanesh, Payal, Altaf, Rajnish, Lalit, Gayatri and Imran. I extend my heartfelt gratitude to Saurabh and Mubarik for being exceptional students and for their significant contributions to my research work. It is a pleasure to thank my teacher Mr. Pawandeep Singh Brar for creating my interest in chemistry. I shared one of most memorable times during my PhD with my friends Dr. Shivani Goyal Singhal, and Dr. Ritu.

Words cannot express how grateful I am to my family: my parents Mr. Gurmeet Singh Sandhu and Mrs. Baljinder Kaur Sandhu and my brother Mr. Navreet Singh Sandhu for their unconditional love, support, and sacrifices that have been the foundation of my journey. I thank them for instilling in me the values of hard work, resilience, and curiosity. Their belief in my potential has been my greatest motivation. My brother has been my steadfast cheerleader, always there to uplift my spirits and celebrate my achievements. I would like to express my deepest gratitude to my best friend Mr. Sagar Khera, whose unwavering support, understanding, and encouragement have been my anchor throughout this PhD journey. His belief in me, even during the most challenging moments, has been a source of strength and inspiration.

In closing, I wish to thank Waheguru for showering me with benevolent blessings and infusing me with unwavering strength and boundless courage to fearlessly confront the formidable challenges that have graced my path.

Ravneet Kaur

ABSTRACT

The thesis titled ***"Stereoselective Cascade Approaches Involving [1,2]-Phospha Brook Rearrangement/Conjugate Addition and Cycloaddition Reactions"*** is structured into four chapters that primarily focus on the development of stereoselective C-C and C-X bond-forming methodologies involving [1,2]-phospha Brook rearrangement, conjugate addition, and cycloaddition reactions. Chapters 2 and 3 detail the role of the [1,2]-phospha Brook rearrangement in stereoselective addition reactions, while Chapter 4 focuses on (5+2) cycloaddition reactions for constructing complex cyclic molecules.

Chapter 1: This chapter provides a concise overview of general organic chemistry, chirality, and its significance in everyday life, along with a discussion on asymmetric catalysis, with a particular focus on organocatalysis and its various activation modes. The chapter further elaborates on the concepts of aminocatalysis, the [1,2]-Phospha Brook Rearrangement, and cycloaddition reactions.

Chapter 2: This chapter introduces an aminocatalytic enantioselective conjugate addition reaction involving [1,2]-phospha-Brook rearrangement. Here, a simple aminocatalyst featuring both primary/secondary amine and tertiary amine functionalities, enabling the simultaneous activation of *α,β*-unsaturated enones and the generation of anionic nucleophiles *via* the Pudovik addition/[1,2]-phospha-Brook rearrangement. The approach provides a simple one-pot process employing a stable, additive-free catalytic system, yielding a variety of oxindole derivatives with two adjacent stereocenters, achieved in high yields and exceptional stereoselectivities.

Chapter 3: This work describes a highly regio- and diastereoselective approach for synthesizing phosphate-substituted dihydrocoumarins through the [1,2]-phospha-Brook rearrangement catalysed by a Brønsted base. The method employs a two-step, one-pot process involving the Michael addition of *α*-phosphonyloxy enolates formed through the coupling of dialkyl phosphite with *α*-ketoesters to *o*-quinone methides, followed by intramolecular cyclization. This strategy efficiently produces 3,4-dihydrocoumarin frameworks in high yields with excellent diastereoselectivity.

Chapter 4: This section presents a base-catalysed intermolecular (5+2) cycloaddition/oxa-Michael addition between α-arylidene pyrazolones and acylated pyranone acetals. The reaction proceeds through a sequential vinylogous aldol-Michael addition of alkylidene pyrazolones to

oxidopyrylium ylides, generated in situ from the acylated pyranone acetals. This process yields bridged cycloaddition products, which subsequently undergo oxa-Michael addition. The method offers a highly regioselective and stereoselective route to synthesize 8-oxobicyclo[3.2.1]octane cores, achieving moderate to good yields with excellent diastereoselectivity.

सार

इस शोधप्रबंध का शीर्षक "स्टीरियोसिलेक्टिव कैस्केड दृष्टिकोण जिनमें [1,2]-फॉस्फा ब्रूक पुनर्व्यवस्था/संयुग्मित अभिक्रिया और साइक्लोऐडिशन अभिक्रियाएं शामिल हैं" है। यह चार अध्यायों में विभाजित है, जो मुख्य रूप से [1,2]-फॉस्फा ब्रूक पुनर्व्यवस्था, संयुग्मित अभिक्रिया, और साइक्लोऐडिशन अभिक्रियाओं के माध्यम से स्टीरियोसिलेक्टिव C-C और C-X बंध निर्माण पद्धतियों के विकास पर केंद्रित हैं। अध्याय 2 और 3 में स्टीरियोसिलेक्टिव संयोजन अभिक्रियाओं में [1,2]-फॉस्फा ब्रूक पुनर्व्यवस्था की भूमिका का विवरण दिया गया है, जबकि अध्याय 4 जटिल चक्रीय अणुओं के निर्माण के लिए (5+2) साइक्लोऐडिशन अभिक्रियाओं पर केंद्रित है।

अध्याय 1: यह अध्याय सामान्य कार्बनिक रसायन विज्ञान, चिरलिटी और इसके दैनिक जीवन में महत्व का संक्षिप्त अवलोकन प्रस्तुत करता है। इसमें विषम उत्प्रेरण पर चर्चा की गई है, जिसमें विशेष रूप से ऑर्गेनोकैटालिसिस और इसके विभिन्न सक्रियण विधियों पर ध्यान केंद्रित किया गया है। अध्याय में आगे अमीनोकैटालिसिस, [1,2]-फॉस्फा ब्रूक पुनर्व्यवस्था, और साइक्लोऐडिशन अभिक्रियाओं की अवधारणाओं को विस्तार से समझाया गया है।

अध्याय 2: यह अध्याय [1,2]-फॉस्फा ब्रूक पुनर्व्यवस्था से संबंधित अमीनोकैटालिटिक एंटियोसिलेक्टिव संयुग्मित अभिक्रिया का परिचय देता है। इसमें एक साधारण अमीनोकैटालिस्ट का उपयोग किया गया है, जिसमें प्राथमिक/माध्यमिक अमीन और तृतीयक अमीन कार्यात्मकताएं शामिल हैं, जो α,β-असंतृप्त इनोन्स को सक्रिय करने और पुदोविक अभिक्रिया/[1,2]-फॉस्फा ब्रूक पुनर्व्यवस्था के माध्यम से एनीऑनिक न्यूक्लियोफाइल उत्पन्न करने में सक्षम हैं। यह प्रक्रिया एक सरल वन-पॉट विधि प्रदान करती है, जिसमें स्थिर और एडिटिव-मुक्त उत्प्रेरक प्रणाली का उपयोग किया गया है, जिससे दो निकटवर्ती स्टीरियोसेंटर्स के साथ ऑक्सिंडोल व्युत्पन्न उच्च उपज और उत्कृष्ट स्टीरियोसेलेक्टिविटी के साथ प्राप्त होते हैं।

अध्याय 3: यह कार्य [1,2]-फॉस्फा ब्रूक पुनर्व्यवस्था द्वारा ब्रोंस्टेड बेस उत्प्रेरण के तहत फॉस्फेट-प्रतिस्थापित डाइहाइड्रोकोमरिन्स के संश्लेषण के लिए एक अत्यधिक क्षेत्र- और डायस्टेरियोसेलेक्टिव दृष्टिकोण का वर्णन करता है। यह विधि एक दो-चरणीय, वन-पॉट प्रक्रिया का उपयोग करती है, जिसमें डायल्काइल फॉस्फाइट और α-किटोएस्टर्स के संयोजन से बने α-फॉस्फोनिओक्सी एनोलाट्स का माइकल अभिक्रिया o-क्विनोन मिथाइड्स के साथ किया जाता है, जिसके बाद अंतःआणविक चक्रीकरण

होता है। यह रणनीति उच्च उपज और उत्कृष्ट डायस्टेरियोसेलेक्टिविटी के साथ 3,4-डाइहाइड्रोकोमरिन ढांचे का कुशलतापूर्वक निर्माण करती है।

अध्याय 4: यह खंड α-एरिलिडीन पायराज़ोलोंस और एसीलेटेड पायरोनोन एसीटल्स के बीच एक बेस-कैटालाइज्ड इंटरमॉलिक्यूलर (5+2) साइक्लोऐडिशन/ऑक्सा-माइकल अभिक्रिया प्रस्तुत करता है। यह अभिक्रिया एसीलेटेड पायरोनोन एसीटल्स से इन-सीटू उत्पन्न ऑक्सीडोपायरीलियम यलाइड्स के साथ अल्काइलिडीन पायराज़ोलोंस के क्रमिक विनाइलोगस एल्डोल-माइकल अभिक्रिया के माध्यम से होती है। इस प्रक्रिया से बने ब्रिज्ड साइक्लोऐडिशन उत्पादों में आगे ऑक्सा-माइकल अभिक्रिया होती है। यह विधि 8-ऑक्सोबाइसाइक्लो[3.2.1]ऑक्टेन कोर के संश्लेषण के लिए एक अत्यधिक क्षेत्र- और स्टीरियोसेलेक्टिव मार्ग प्रदान करती है, जो मध्यम से अच्छी उपज और उत्कृष्ट डायस्टेरियोसेलेक्टिविटी के साथ प्राप्त होती है।

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Abbreviation	Full form
Ac	Acetate
MeCN/CH_3CN/ACN	Acetonitrile
Ar	Aryl
AI	Artificial Intelligence
^{t}Bu	*tert*-Butyl
$CDCl_3$	Deuterated chloroform
CH_2Cl_2 /DCM	Dichloromethane
CPA	Chiral Phosphoric Acid
cm^{-1}	Wavenumbers
°C	Degrees Celsius
dr	Diastereomeric ratio
d	Doublet
dd	Doublet of doublets
DMSO-d_6	Deuterated dimethyl sulfoxide
δ	Chemical shift
er	Enantiomeric ratio
ee	Enantiomeric excess
ESI-TOF	Electrospray ionization - Time-of-flight
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
H_2O	Water
hr	Hour
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectroscopy
J	Coupling constant
λ	Wavelength
LUMO	Lowest unoccupied molecular orbital
min	Minute
MTBE	Methyl *tert*-butyl ether

m	Multiplet
MHz	Megahertz
mL	Millilitre
μL	Microlitre
NHC	N-Heterocyclic carbenes
Na_2SO_4	Sodium Sulphate
NBS	N-Bromosuccinimide
$NaHCO_3$	Sodium bicarbonate
NaCl	Sodium chloride
NMR	Nuclear Magnetic Resonance
N_2	Nitrogen gas
o	Ortho
p-TsOH	*para*-Toluenesulfonic acid
PTC	Phase Transfer Catalyst
PhCl	Chlorobenzene
^{i}Pr	Isopropyl
p	para
rt	room temperature
s	Singlet
SOMO	Singly unoccupied molecular orbital
TLC	Thin Layer Chromatography
TfOH	Triflic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
UV	Ultraviolet