

Vinyl Sulfoxonium Ylides: A Sustainable Platform for X-H Bond Insertions and Rearrangement Reactions

The thesis to be submitted for the award of the degree

DOCTOR OF PHILOSOPHY

By

SRASHTI BHARDWAJ

Entry No: 2020CYZ8066

Under the supervision of

Prof. JANAKIRAM VAITLA

To



Department of Chemistry

Indian Institute of Technology, Delhi

New Delhi - 110016, India

December 2025

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CERTIFICATE

This is to certify that the thesis entitled “**VINYL SULFOXONIUM YLIDES: A SUSTAINABLE PLATFORM FOR X-H BOND INSERTIONS AND REARRANGEMENT REACTIONS**” being submitted by Ms. Srashti Bhardwaj to the Department of Chemistry, Indian Institute of Technology Delhi, for the award of the degree of Doctor of Philosophy is a record of bonafide research work carried out by her.

She has worked under my guidance and supervision and has fulfilled the requirements for the submission of the thesis, which to my knowledge, has reached the requisite standard.

The results contained in this thesis have not been submitted in part or in full to any other University or Institute for the award of any degree or diploma.

Prof. Janakiram Vaitla

Department of Chemistry,

Indian Institute of Technology Delhi,

New Delhi-110016, India.

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Srashti Bhardwaj

ABSTRACT

The thesis work entitled “*Vinyl Sulfoxonium Ylides: A Sustainable Platform for X-H Bond Insertions and Rearrangement Reactions*” presents a metal-free strategy for the synthesis of the insertion products utilizing vinyl sulfoxonium in combination with various nucleophiles. It further highlights the synthesis of diverse rearrangement products derived from insertion intermediates, offering new methodologies, mechanistic insights, and synthetic applications. Additionally, the work also presents a bidirectional iterative strategy for the synthesis of unsaturated esters, further expanding the versatility of this platform.

Chapter 1: In this chapter, we report metal and reagent-free insertion reactions of vinyl sulfoxonium ylides into X-H (X = O, N, S, C, halogen) bonds of acids, thiols, amines, phenols, enols, indoles, and halogen acids under mild reaction conditions. This strategy demonstrates a broad substrate scope (>50 examples, up to 99% yield) with excellent regioselectivity. Mechanistic studies further reveal that the rate-limiting step varies depending on the type of X-H bond undergoing insertion.

Chapter 2: In this chapter, we employed the acid insertion product of vinyl sulfoxonium ylide as a key building block for the bidirectional synthesis of sequence-defined unsaturated polyesters. In nature, peptides exemplify sequence-defined bidirectional synthesis, where chain elongation can proceed in both the C→N and N→C directions. However, no such strategies have been reported for the bidirectional sequence-defined synthesis of unsaturated oligoesters. Given the wide-ranging applications of unsaturated oligoesters in biomedicine, coatings and insulating materials, and lightweight fibre-reinforced composites for the automotive industry and inspired by the structural analogy with vinylogous oligopeptides, we developed a novel bidirectional X-H insertion strategy to access these scaffolds from aryl-substituted vinyl sulfoxonium ylides under metal- and reagent-free conditions. We envisioned that vinyl sulfoxonium ylide-derived acid intermediates could serve as templates for the stereoselective synthesis of *Z*-configured unsaturated oligoesters, either through sequential acid iteration or sequential ylide iteration. We believe this simple and convenient approach provides a promising platform for the design of functional oligoesters with potential applications in pharmaceutical and medicinal chemistry.

Chapter 3: Classical rearrangements such as the Fries and Claisen reactions are well-established strategies for constructing phenol derivatives, and numerous sigmatropic

rearrangements involving heteroatoms (X, Y = C, O, N, S, I) have further expanded access to *ortho*-substituted phenols. However, despite their synthetic utility, these transformations often proceed *via* a temporary loss of aromaticity, resulting in high energy barriers. Notably, the Baker–Venkataraman rearrangement avoids perturbing the phenolic core, highlighting the potential of rearrangements that preserve aromaticity. Inspired by this concept, we developed a phenol-based rearrangement reaction using insertion-derived *O*-substituted salicylaldehyde *N*-tosylhydrazones as substrates. This base-mediated *O*-to-*N* group transfer enables the direct synthesis of *Z*-configured 2,3-diaza-1,3,5-hexatrienes, representing a rearrangement pathway distinct from classical phenol migrations. The transformation proceeds under mild, metal-free conditions, exhibits a broad substrate scope, and displays excellent functional group tolerance and scalability. The resulting diazatrienes serve as precursors for heterocycles and photoswitches. This rearrangement introduces a new synthetic strategy, distinct from classical phenol-based rearrangements.

Chapter 4:

Part A: In this chapter, we describe a novel multicomponent reaction involving two distinct carbene precursors and a nucleophile under metalloradical catalysis. Several competing pathways were possible: (i) both carbenes could undergo direct X–H insertion with the nucleophile; (ii) homo- or cross-dimerization of carbenes could furnish different geometrical isomers of alkenes; and (iii) the dimerized product of an electron-deficient carbene precursor could act as a Michael acceptor, undergoing conjugate addition with the nucleophilic heteroatom of the X–H bond. Despite these challenges, we successfully achieved the stereoselective difunctionalization of diazo compounds with nucleophiles under metalloradical conditions. The success of this transformation arises from the intrinsic difference in reactivity between vinyl sulfoxonium ylides and diazo compounds toward nucleophiles and carbene radical sources. The vinyl sulfoxonium ylide reacts preferentially with the nucleophile to generate an allyl sulfide intermediate, while the diazo compound is activated by the cobalt catalyst to form an α -Co(III)–alkyl radical complex. The *in situ* convergence of these intermediates furnishes a sulfonium ylide, which subsequently undergoes a [2,3]-sigmatropic rearrangement. This methodology provides access to a broad array of architecturally complex and functionally diverse tertiary sulfide scaffolds in good yields with moderate to good diastereoselectivity. Combined experimental and computational studies have elucidated the mechanistic details of this multicomponent process, while theoretical investigations of noncovalent interactions uncovered the origin of the observed diastereoselectivity.

Part B: Towards the goal of sustainable and green chemistry, we developed a multicomponent reaction of vinyl sulfoxonium ylide, aryl diazoacetate, and thiol under blue light irradiation. This catalyst- and additive-free strategy exhibits a broad substrate scope and furnishes structurally complex tertiary sulfide scaffolds. Mechanistic investigations, supported by control experiments, indicate that the transformation proceeds *via* an *in situ*-generated sulfonium ylide, which undergoes a [2,3]-sigmatropic rearrangement. The success of this approach stems from the complementary reactivity of vinyl sulfoxonium ylide and aryl diazoester, enabling highly selective and efficient product formation.

Chapter 5: In this chapter, we investigated the reactivity of activated pyridines as electrophilic partners with vinyl sulfoxonium ylides. According to the previous reports, we expected the cyclopropane-fused derivatives, but our reaction followed an unexpected rearrangement pathway, leading to the formation of 4-dienyl-1,4-dihydropyridines. This study establishes a regioselective dearomatization of activated pyridines using vinyl sulfoxonium ylides as nucleophiles, delivering 4-dienyl-1,4-dihydropyridines with excellent E/Z selectivity. The transformation proceeds through a sequential cascade involving ylide addition, a [2,3]-sigmatropic rearrangement, and subsequent elimination. Moreover, the aromatization of the dihydropyridines with sulfur powder under thermal conditions afforded pyridine–thiophene-linked bis-heterocycles, further showcasing the synthetic versatility of this methodology. Finally, combined experimental and theoretical investigations provided mechanistic insights, elucidating the key steps of this unique dearomatization process.

सार

“विनाइल सल्फोक्सोनियम यलाइड्स: X-H बॉन्ड इंसर्शन और रिअरेंजमेंट रिएक्शन के लिए एक सस्टेनेबल प्लेटफॉर्म” शीर्षक वाला यह थीसिस वर्क विभिन्न न्यूक्लियोफाइल्स के साथ विनाइल सल्फोक्सोनियम का उपयोग करके इंसर्शन प्रोडक्ट्स के सिंथेसिस के लिए एक मेटल-फ्री रणनीति प्रस्तुत करता है। यह इंसर्शन इंटरमीडिएट्स से प्राप्त विभिन्न रिअरेंजमेंट प्रोडक्ट्स के सिंथेसिस पर भी प्रकाश डालता है, जो नई कार्यप्रणाली, मैकेनिस्टिक अंतर्दृष्टि और सिंथेटिक अनुप्रयोग प्रदान करता है। इसके अतिरिक्त, यह कार्य अनसैचुरेटेड एस्टर के सिंथेसिस के लिए एक द्विदिशीय पुनरावृत्ति रणनीति भी प्रस्तुत करता है, जो इस प्लेटफॉर्म की बहुमुखी प्रतिभा का और विस्तार करता है।

अध्याय 1: इस अध्याय में, हम हल्के रिएक्शन स्थितियों के तहत एसिड, थायोल्स, एमाइन, फिनोल, एनोल्स, इंडोल्स और हैलोजन एसिड के X-H (X = O, N, S, C, हैलोजन) बॉन्ड में विनाइल सल्फोक्सोनियम यलाइड्स के मेटल और रिएजेंट मुक्त इंसर्शन रिएक्शन की रिपोर्ट करते हैं। यह रणनीति उत्कृष्ट रीजियोसेलेक्टिविटी के साथ एक व्यापक सबस्ट्रेट स्कोप (>50 उदाहरण, 99% तक यील्ड) प्रदर्शित करती है। मैकेनिस्टिक अध्ययन से पता चलता है कि दर-सीमित चरण इंसर्शन से गुजरने वाले X-H बॉन्ड के प्रकार के आधार पर भिन्न होता है।

अध्याय 2: इस अध्याय में, हमने अनुक्रम-परिभाषित अनसैचुरेटेड पॉलीएस्टर के द्विदिशीय सिंथेसिस के लिए एक प्रमुख बिल्डिंग ब्लॉक के रूप में विनाइल सल्फोक्सोनियम यलाइड के एसिड इंसर्शन उत्पाद का उपयोग किया। प्रकृति में, पेप्टाइड्स अनुक्रम-परिभाषित द्विदिशीय सिंथेसिस का उदाहरण देते हैं, जहां श्रृंखला विस्तार $C \rightarrow N$ और $N \rightarrow C$ दोनों दिशाओं में आगे बढ़ सकता है। हालांकि, अनसैचुरेटेड ओलिगोएस्टर के द्विदिशीय अनुक्रम-परिभाषित सिंथेसिस के लिए ऐसी कोई रणनीति रिपोर्ट नहीं की गई है। बायोमेडिसिन, कोटिंग्स और इन्सुलेंटिंग सामग्री, और ऑटोमोटिव उद्योग के लिए हल्के फाइबर-प्रबलित कंपोजिट में अनसैचुरेटेड ओलिगोएस्टर के व्यापक अनुप्रयोगों को देखते हुए और विनाइलॉग्स ओलिगोपेप्टाइड्स के साथ संरचनात्मक समानता से प्रेरित होकर, हमने मेटल- और रिएजेंट-मुक्त स्थितियों के तहत एरिल-प्रतिस्थापित विनाइल सल्फोक्सोनियम यलाइड्स से इन स्कैफोल्ड तक पहुंचने के लिए एक नई द्विदिशीय X-H इंसर्शन रणनीति विकसित की। हमने कल्पना की कि विनाइल सल्फोक्सोनियम यलाइड-व्युत्पन्न एसिड इंटरमीडिएट अनुक्रमिक एसिड पुनरावृत्ति या अनुक्रमिक यलाइड पुनरावृत्ति के माध्यम से Z-कॉन्फ़िगर अनसैचुरेटेड ओलिगोएस्टर के स्टीरियोसेलेक्टिव सिंथेसिस के लिए टेम्पलेट के रूप में काम कर सकते हैं। हमारा मानना है कि यह सरल और सुविधाजनक दृष्टिकोण फार्मास्युटिकल और औषधीय रसायन विज्ञान में संभावित अनुप्रयोगों के साथ कार्यात्मक ओलिगोएस्टर के डिजाइन के लिए एक आशाजनक मंच प्रदान करता है।

अध्याय 3: फ्राइज़ और क्लेज़न रिएक्शन जैसे क्लासिकल पुनर्व्यवस्थाएं फिनोल डेरिवेटिव बनाने के लिए अच्छी तरह से स्थापित रणनीतियाँ हैं, और हेटेरोएटम (X, Y = C, O, N, S, I) से जुड़ी कई सिग्माट्रोपिक पुनर्व्यवस्थाओं ने

ऑर्थो-सब्सटिट्यूटेड फिनोल तक पहुँच को और बढ़ाया है। हालाँकि, उनकी सिंथेटिक उपयोगिता के बावजूद, ये परिवर्तन अक्सर एरोमैटिसिटी के अस्थायी नुकसान के माध्यम से होते हैं, जिसके परिणामस्वरूप उच्च ऊर्जा बाधाएँ आती हैं। विशेष रूप से, बेकर-वेंकटरामन पुनर्व्यवस्था फेनोलिक कोर को परेशान करने से बचती है, जो एरोमैटिसिटी को बनाए रखने वाली पुनर्व्यवस्थाओं की क्षमता को उजागर करती है। इस अवधारणा से प्रेरित होकर, हमने सबस्ट्रेट के रूप में इंसर्शन-व्युत्पन्न O-सब्सटिट्यूटेड सैलिसिलिडिहाइड N-टॉसिलहाइड्राज़ोन का उपयोग करके एक फिनोल-आधारित पुनर्व्यवस्था प्रतिक्रिया विकसित की। यह बेस-मध्यस्थ O-से-N समूह स्थानांतरण Z-कॉन्फ़िगर 2,3-डायज़ा-1,3,5-हेक्साट्रिएन के प्रत्यक्ष संश्लेषण को सक्षम बनाता है, जो क्लासिकल फिनोल माइग्रेशन से अलग एक पुनर्व्यवस्था मार्ग का प्रतिनिधित्व करता है। यह परिवर्तन हल्के, धातु-मुक्त परिस्थितियों में होता है, एक व्यापक सबस्ट्रेट स्कोप प्रदर्शित करता है, और उत्कृष्ट कार्यात्मक समूह सहनशीलता और स्केलेबिलिटी दिखाता है। परिणामी डायज़ाट्रिएन हेट्रोसायकल और फोटोस्विच के लिए अग्रदूत के रूप में कार्य करते हैं। यह पुनर्व्यवस्था एक नई सिंथेटिक रणनीति पेश करती है, जो क्लासिकल फिनोल-आधारित पुनर्व्यवस्थाओं से अलग है।

अध्याय 4:

भाग A: इस अध्याय में, हम मेटालोरेडिकल उत्प्रेरण के तहत दो अलग-अलग कार्बिन अग्रदूतों और एक न्यूक्लियोफाइल से जुड़ी एक उपन्यास मल्टीकंपोनेंट प्रतिक्रिया का वर्णन करते हैं। कई प्रतिस्पर्धी मार्ग संभव थे: (i) दोनों कार्बिन न्यूक्लियोफाइल के साथ सीधे X-H इंसर्शन से गुजर सकते थे; (ii) कार्बिन का होमो- या क्रॉस-डिमराइज़ेशन एल्कीन के विभिन्न ज्यामितीय आइसोमर प्रदान कर सकता था; और (iii) एक इलेक्ट्रॉन-कमी वाले कार्बिन अग्रदूत का डिमराइज़्ड उत्पाद एक माइकल स्वीकर्ता के रूप में कार्य कर सकता है, जो X-H बंधन के न्यूक्लियोफिलिक हेटेरोएटम के साथ संयुग्म जोड़ से गुजरता है। इन चुनौतियों के बावजूद, हमने मेटालोरेडिकल परिस्थितियों में न्यूक्लियोफाइल के साथ डायज़ो यौगिकों के स्टीरियोसेलेक्टिव डिफंक्शनलाइज़ेशन को सफलतापूर्वक प्राप्त किया। इस परिवर्तन की सफलता विनाइल सल्फोक्सोनियम यलाइड और डायज़ो यौगिकों के बीच न्यूक्लियोफाइल और कार्बिन रेडिकल स्रोतों के प्रति प्रतिक्रियाशीलता में आंतरिक अंतर से उत्पन्न होती है। विनाइल सल्फोक्सोनियम यलाइड अधिमानतः न्यूक्लियोफाइल के साथ प्रतिक्रिया करके एक एलिल सल्फाइड मध्यवर्ती उत्पन्न करता है, जबकि डायज़ो यौगिक कोबाल्ट उत्प्रेरक द्वारा सक्रिय होकर एक α -Co(III)-अल्काइल रेडिकल कॉम्प्लेक्स बनाता है। इन इंटरमीडिएट के इन-सीटू कन्वर्जेंस से एक सल्फोनियम यलाइड बनता है, जो बाद में एक [2,3]-सिग्माट्रोपिक पुनर्व्यवस्था से गुजरता है। यह कार्यप्रणाली मध्यम से अच्छी डायस्टीरियोसेलेक्टिविटी के साथ अच्छी उपज में संरचनात्मक रूप से जटिल और कार्यात्मक रूप से विविध तृतीयक सल्फाइड स्कैफोल्ड की एक विस्तृत श्रृंखला तक पहुँच प्रदान करती है। संयुक्त प्रायोगिक और कम्प्यूटेशनल अध्ययनों ने इस बहुघटक प्रक्रिया के यांत्रिक विवरणों को स्पष्ट किया है, जबकि गैर-सहसंयोजक इंटरैक्शन की सैद्धांतिक जांच ने देखी गई डायस्टीरियोसेलेक्टिविटी के मूल का पता लगाया है।

भाग B: स्थायी और हरित रसायन विज्ञान के लक्ष्य की दिशा में, हमने नीली रोशनी विकिरण के तहत विनाइल सल्फोक्सोनियम यलाइड, एरिल डायजोएसीटेट और थायोल की एक बहुघटक प्रतिक्रिया विकसित की। यह उत्प्रेरक- और योज्य-मुक्त रणनीति एक व्यापक सबस्ट्रेट दायरे को प्रदर्शित करती है और संरचनात्मक रूप से जटिल तृतीयक सल्फाइड स्कैफोल्ड प्रदान करती है। नियंत्रण प्रयोगों द्वारा समर्थित यांत्रिक जांच से संकेत मिलता है कि परिवर्तन एक इन सीटू-जनित सल्फोनियम यलाइड के माध्यम से आगे बढ़ता है, जो एक [2,3]-सिग्माट्रोपिक पुनर्व्यवस्था से गुजरता है। इस दृष्टिकोण की सफलता विनाइल सल्फोक्सोनियम यलाइड और एरिल डायजोएस्टर की पूरक प्रतिक्रियाशीलता से उत्पन्न होती है, जो अत्यधिक चयनात्मक और कुशल उत्पाद निर्माण को सक्षम बनाती है।

अध्याय 5: इस अध्याय में, हमने विनाइल सल्फोक्सोनियम यलाइड्स के साथ इलेक्ट्रोफिलिक पार्टनर के रूप में एक्टिवेटेड पाइरिडीन की रिएक्टिविटी की जांच की। पिछली रिपोर्टों के अनुसार, हमें साइक्लोप्रोपेन-फ्यूज्ड डेरिवेटिव्स की उम्मीद थी, लेकिन हमारी रिएक्शन एक अप्रत्याशित रिअरेजमेंट रास्ते से हुई, जिससे 4-डाइनिल-1,4-डाइहाइड्रोपाइरिडीन बने। यह अध्ययन न्यूक्लियोफाइल के रूप में विनाइल सल्फोक्सोनियम यलाइड्स का उपयोग करके एक्टिवेटेड पाइरिडीन के एक रीजियोसेलेक्टिव डीएरोमेटाइजेशन को स्थापित करता है, जिससे बेहतर *E/Z* सेलेक्टिविटी के साथ 4-डाइनिल-1,4-डाइहाइड्रोपाइरिडीन मिलते हैं। यह ट्रांसफॉर्मेशन एक सीकेंस में होता है जिसमें यलाइड एडिशन, एक [2,3]-सिग्माट्रोपिक रिअरेजमेंट, और उसके बाद एलिमिनेशन शामिल है। इसके अलावा, थर्मल स्थितियों में सल्फर पाउडर के साथ डाइहाइड्रोपाइरिडीन के एरोमेटाइजेशन से पाइरिडीन-थियोफीन-लिंकड बिस-हेटेरोसाइकिल मिले, जो इस मेथोडोलॉजी की सिंथेटिक बहुमुखी प्रतिभा को और दिखाता है। अंत में, संयुक्त प्रायोगिक और सैद्धांतिक जांचों ने मैकेनिस्टिक जानकारी प्रदान की, जिससे इस अनोखी डीएरोमेटाइजेशन प्रक्रिया के मुख्य चरणों को स्पष्ट किया गया।

TABLE OF CONTENTS

| | |
|----------------------------|-------|
| Certificate..... | ii |
| Acknowledgments..... | iii |
| Abstract..... | v |
| Table of contents..... | xi |
| List of Figures..... | xv |
| List of Tables..... | xviii |
| List of Schemes..... | xix |
| List of abbreviations..... | xxiii |

Table of Contents

| | |
|--|----|
| Introduction | 1 |
| Origin of vinyl sulfoxonium ylide | 1 |
| Reactivity of vinyl sulfoxonium ylide as allylic intermediates | 2 |
| Previously reported allylation reactions and its importance | 2 |
| Present approach for metal-free allylation reactions | 3 |
| Thesis Outline | 5 |
| References | 6 |
| Chapter 1..... | 8 |
| 1.1 Introduction | 8 |
| 1.2 Results and Discussion..... | 10 |
| 1.2.1 Optimization Studies | 10 |
| 1.2.2 Substrate scope of acid insertion reactions | 12 |
| 1.2.3 Substrate scope of thiol insertion reactions | 14 |
| 1.2.4 Substrate scope of amines, phenols and halogen acids insertion reactions | 15 |
| 1.2.5 Gram-Scale synthesis of 3aa | 16 |
| 1.2.6 Mechanistic studies..... | 16 |
| 1.3 Conclusion..... | 20 |
| 1.4 Experimental studies..... | 20 |
| 1.4.1 General procedure for the synthesis of vinyl sulfoxonium ylides | 20 |
| 1.4.2 General procedure for the synthesis of acid insertion products | 20 |
| 1.4.3 Characterization data of the acid insertion products | 21 |
| 1.4.4 General procedure for the synthesis of thiol insertion products..... | 31 |

| | |
|---|-------------------------------------|
| 1.4.5 Characterization data of the thiol insertion products | 31 |
| 1.4.6 General procedure for the synthesis of amines, phenols, indole C-H inserted product and enol insertion products | 37 |
| 1.4.7 Characterization data of the amines, phenols, indole C-H inserted product and enol insertion products..... | 37 |
| 1.4.8 Characterization data of the halogen acid inserted products..... | 40 |
| 1.4.9 General procedure for the gram-scale synthesis of 3aa | 41 |
| 1.4.10 Spectral data for the selected compounds..... | 41 |
| 1.5 References..... | 56 |
| Chapter 2..... | 58 |
| 2.1 Introduction..... | 58 |
| 2.2 Results and discussion | 61 |
| 2.2.1 Acid iteration..... | 61 |
| 2.2.2 Ylide iteration..... | 68 |
| 2.3 Conclusion..... | 69 |
| 2.4 Experimental Studies..... | 69 |
| 2.4.1 General procedure for synthesis of vinyl sulfoxonium ylide with protected ester functional group | 69 |
| 2.4.2 General procedure for the Synthesis of acid 6 (TBAF deprotection)..... | 71 |
| 2.4.3 General procedure for the synthesis of acid insertion products | 71 |
| 2.4.4 General procedure for the synthesis of thiol insertion products..... | 71 |
| 2.4.5 Characterization data of the iterative sequences | 71 |
| 2.4.6 X-Ray crystallographic studies of 8 | Error! Bookmark not defined. |
| 2.4.6 Spectral data of the selected compounds | Error! Bookmark not defined. |
| 2.5 References..... | 97 |
| Chapter 3..... | 99 |
| 3.1. Introduction..... | 99 |
| 3.2 Preliminary Investigation..... | 102 |
| 3.3 Result and Discussion..... | 104 |
| 3.3.1 Reaction Optimization | 104 |
| 3.3.2 Substrate scope..... | 108 |
| 3.3.3. Applications | 110 |
| 3.3.4 Mechanistic Studies | 111 |
| 3.3.5 Mechanism..... | 118 |
| 3.4 Conclusion..... | 119 |
| 3.5 Experimental Studies..... | 119 |

| | |
|---|------------|
| 3.5.1. General procedure for the synthesis of Vinyl Sulfoxonium Ylide | 119 |
| 3.5.2 General procedure for the synthesis of <i>N</i> -Tosylhydrazones | 120 |
| 3.5.3 Synthesis and Characterization of 2,3-diaza-1,3,5-hexatrienes | 121 |
| 3.5.4 Experimental procedure and characterisation data for the Applications | 136 |
| 3.5.5 X-ray crystallographic data of 4f (CCDC No: 2475651) | 141 |
| 3.5.6 Spectral data | 143 |
| 3.6 References | 156 |
| Chapter 4a | 158 |
| 4a.1 Introduction | 158 |
| 4a.2 Preliminary Studies | 164 |
| 4a.3 Results and Discussion | 171 |
| 4a.3.1 Optimization Studies | 171 |
| 4a.3.2 Substrate Scope | 173 |
| 4a.3.3 Gram-scale synthesis | 179 |
| 4a.3.4 Synthetic applications | 179 |
| 4a.3.5 Mechanistic Studies | 180 |
| 4a.3.6 Determination of diastereomeric ratio | 192 |
| 4a.3.7 Proposed Mechanism | 194 |
| 4a.4 Conclusion | 194 |
| 4a.5 Experimental studies | 195 |
| 4a.5.1 General procedure for the synthesis of vinyl sulfoxonium ylides | 195 |
| 4a.5.2 General procedure for the synthesis of Diazo esters | 195 |
| 4a.5.3 Synthesis and Characterization of tertiary sulfide scaffolds | 196 |
| 4a.5.4 General procedure and characterization data of applications | 219 |
| 4a.5.5 X-ray crystallographic data of 4n (CCDC No: 2298973) | 224 |
| 4a.5.6 Density Functional Theory calculations and NCI plot analysis | 227 |
| 4a.5.7. Spectral data | 229 |
| 4a.6 References | 246 |
| Chapter 4b | 249 |
| 4b.1 Introduction | 249 |
| 4b.2 Results and Discussion | 252 |
| 4b.2.1 Optimization Studies | 252 |
| 4b.2.2 Substrate Scope | 255 |
| 4b.2.3 Mechanistic Studies | 257 |
| 4b.2.4 Mechanism | 267 |
| 4b.3 Conclusion | 268 |

| | |
|--|------------|
| 4b.4 Experimental Studies | 269 |
| 4b.4.1 General procedure for the synthesis of Vinyl Sulfoxonium Ylide..... | 269 |
| 4b.4.2 General procedure for the synthesis of Diazo esters..... | 269 |
| 4b.4.3 General procedure for the photoinduced Doyle-Kirmse reaction..... | 269 |
| 4b.4.4 Characterization of tertiary sulfide scaffolds..... | 270 |
| 4b.4.5 Spectral data..... | 286 |
| 4b.5 References | 292 |
| Chapter 5 | 294 |
| 5.1 Introduction | 294 |
| 5.2 Results and Discussion | 296 |
| 5.2.1 Optimization Studies..... | 296 |
| 5.2.2 Substrate scope for the synthesis of dihydropyridine products 3 | 300 |
| 5.2.3 Stereochemistry of the compound 3 | 302 |
| 5.2.4 Reaction with isoquinolines..... | 304 |
| 5.2.5 Applications..... | 305 |
| 5.2.4 Mechanistic Studies..... | 308 |
| 5.2.5 Proposed Mechanism..... | 320 |
| 5.3 Conclusion | 321 |
| 5.4 Experimental Studies | 321 |
| 5.4.1 General procedure for the synthesis of vinyl sulfoxonium ylide..... | 321 |
| 5.4.2 General procedure for the synthesis of dihydropyridines products..... | 322 |
| 5.4.3 Characterization data of dihydropyridines products..... | 322 |
| 5.4.4 Experimental procedure and characterisation data for the Applications..... | 335 |
| 5.4.5 X-ray crystallographic data of 5 (CCDC No: 2388366) and 6f (CCDC No: 2390291) | 339 |
| 5.4.6 Stereoselectivity determining transition state..... | 343 |
| 5.4.7 Spectral data..... | 344 |
| 5.5 References | 351 |

LIST OF FIGURES

| Figure No. | Figure Caption | Page No. |
|------------|---|----------|
| 1.1 | Origin of vinyl sulfoxonium ylides. | 1 |
| 1.2 | Vinyl sulfoxonium ylides as multifaceted allylic intermediates. | 2 |
| 1.3 | Previous approaches for the metal-mediated allylation reactions. | 3 |
| 1.4 | Present approach for the metal-free allylation reactions. | 4 |
| 1.5 | Outline of the thesis. | 5 |
| 2.1 | Reaction analysis of vinyl sulfoxonium ylide insertion to the benzoic acid using React-IR studies. | 16 |
| 2.2 | <i>In-situ</i> React-IR monitoring of the insertion of vinyl sulfoxonium ylides into benzoic acids. | 17 |
| 2.3 | <i>In-situ</i> React-IR monitoring of the insertion of vinyl sulfoxonium ylides into thiols. | 18 |
| 2.4 | Reaction analysis of vinyl sulfoxonium ylide insertion to the thiophenol using React-IR studies. | 18 |
| 3.1 | Unsaturated oligoester-based drug molecules. | 67 |
| 3.2 | Iterative building blocks used in this study. | 69 |
| 3.3 | Iterative terminating blocks used in this study. | 69 |
| 3.4 | ORTEP representation of the X-ray structure of 8 with Thermal ellipsoid at 30% probability. (All hydrogens are omitted for clarity). | 80 |
| 4.1 | HRMS spectra of crossover experiment of 4e and 4u . | 111 |
| 4.2 | NMR spectra of the deuterated vinyl sulfoxonium ylide 1a-D . | 112 |
| 4.3 | NMR spectra of the deuterated vinyl sulfoxonium ylide 3a-D . | 113 |
| 4.4 | NMR spectra of the deuterated vinyl sulfoxonium ylide 4a-D . | 114 |
| 4.5 | ORTEP representation of the X-ray structure of 4f with Thermal ellipsoid at 40% probability. | 141 |
| 5.1 | The metalloporphyrin catalyst explored for synthesis of tertiary sulfide scaffolds. | 158 |
| 5.2 | Benzenethiol insertion with vinyl sulfoxonium ylide and diazo compound. | 162 |
| 5.3 | Computational analysis of the insertion reaction between ylides and diazoesters. | 163 |
| 5.4 | React-IR spectra of benzenethiol insertion study with vinyl sulfoxonium ylide and diazo compound. | 164 |
| 5.5 | 3D-Surface Reaction analysis of benzenethiol insertion with vinyl sulfoxonium ylide and diazo compound. | 165 |

| | | |
|------|---|-----|
| 5.6 | ¹ H NMR Spectra of dimerized product 3aa' . | 173 |
| 5.7 | HRMS spectra for formation of C-H insertion product 15 . | 180 |
| 5.8 | ¹ H NMR spectra of compound 11a . | 183 |
| 5.9 | ¹ H NMR spectra of compound 11a-D . | 183 |
| 5.10 | ¹ H NMR spectra of compound 4c . | 185 |
| 5.11 | ¹ H NMR spectra of compound 4c-D . | 185 |
| 5.12 | EPR Spectra of the compound 3c with the Co ^(III) TMPP. | 188 |
| 5.13 | Mechanism for TEMPO trapped adduct 20 . | 189 |
| 5.14 | HRMS Spectra for TEMPO trapped adduct 20 . | 190 |
| 5.15 | ¹ H NMR Spectrum of Major Diastereomer (4c). | 191 |
| 5.16 | ¹ H NMR Spectrum of Major Diastereomer (4c'). | 191 |
| 5.17 | ¹ H NMR Spectrum of crude reaction mixture consisting of 4c and 4c' . | 192 |
| 5.18 | ORTEP representation of the X-ray structure of 4n with Thermal ellipsoid at 40% probability. (All hydrogens are omitted for clarity) | 225 |
| 5.19 | Computed energy profile (kcal/mol) for the S-H insertion of sulfoxonium ylide and diazo ester. | 226 |
| 6.1 | Reactivity of ylide and diazoester under photochemical conditions. | 256 |
| 6.2 | ¹ H NMR Spectra of homodimerized product 6 . | 257 |
| 6.3 | Benzenethiol reactivity with vinyl sulfoxonium ylide and diazo compound. | 258 |
| 6.4 | NMR spectra of a mixture of dimerized product 6 and S-H insertion product 7 . | 259 |
| 6.5 | Reaction analysis of vinyl sulfoxonium ylide insertion to the thiophenol. | 260 |
| 6.6 | TEMPO Experiment. | 262 |
| 6.7 | Deuterium Labelling Experiment. | 263 |
| 6.8 | ¹ H NMR Spectra for deuterium labelling experiment of 5-D and 4b-D . | 264 |
| 6.9 | Multicomponent reaction in the dark conditions. | 265 |
| 7.1 | ¹ H NMR (CDCl ₃ , 400 MHz) of deuterated vinyl sulfoxonium ylide 1a-D . | 308 |
| 7.2 | ¹ H NMR Spectra (CDCl ₃ , 400MHz) of deuterated product 3a-D . | 309 |
| 7.3 | ¹ H NMR Spectra (CDCl ₃ , 500MHz) of Diene 13 . | 311 |
| 7.4 | HRMS spectra for the formation of the [2,3]-sigmatropic rearranged product 12 as reaction intermediate. | 312 |
| 7.5 | Crude ¹ H NMR spectra (CDCl ₃ , 500 MHz) recorded at the intervals of 10 mins for 1 hour. | 313 |

| | | |
|------|--|------------|
| 7.6 | Formation of rearrangement product 12 . (a) Crude ¹ H NMR (CDCl ₃ , 500 MHz) spectra for the formation of the [2,3]-sigmatropic rearranged product 12 as reaction intermediate (b) The enlarged view of spectra shows the diastereotopic ratio (dr 3:1) of the proton at 5.68 ppm. | 314 |
| 7.7 | ¹ H NMR Spectra (CDCl ₃ , 400MHz) and ¹³ C NMR Spectra (CDCl ₃ , 101MHz) of product 15 . | 316 |
| 7.8 | COSY (Correlated Spectroscopy) (CDCl ₃ , 400MHz) of compound 15 . | 317 |
| 7.9 | Mechanism for the formation of product 15 . | 317 |
| 7.10 | ¹ H NMR Spectra (CDCl ₃ , 500MHz) of product 3a . | 319 |
| 7.11 | ORTEP representation of the X-ray structure of 5 with Thermal ellipsoid at 40% probability. (All hydrogens are omitted for clarity) | 341 |
| 7.12 | ORTEP representation of the X-ray structure of 6f with Thermal ellipsoid at 40% probability. (All hydrogens are omitted for clarity) | 342 |
| 7.13 | Origin of stereoselectivity of the dihydropyridine scaffolds. | 343 |

LIST OF TABLES

| Table No. | Table Caption | Page No. |
|-----------|---|------------|
| 2.1 | Optimization studies for metal-free insertion reaction. ^a | 10 |
| 3.1 | Effect of metal catalyst in the reaction. ^a | 102 |
| 3.2 | Effect of different bases on the yield of product 4a ^a | 104 |
| 3.3 | Base concentration effect on the yield of product 4a ^a | 104 |
| 3.4 | Effect of various solvent and temperature on the reaction yield of 4a ^a | 106 |
| 3.5 | Crystal data and structure refinement for (4f). | 140 |
| 4.1 | (a) Reactivity of vinyl sulfoxonium ylide with various metal catalyst. (b) Reactivity of diazo compound with various metal catalyst. | 166 |
| 4.2 | Reaction optimization studies for the synthesis of tertiary thiol scaffolds. ^a | 169 |
| 4.3 | Crystal data and structure refinement for (4n). | 224 |
| 5.1 | Light source optimization for the synthesis of 4a . ^a | 251 |
| 5.2 | Solvent optimization for the synthesis of 4a . ^a | 252 |
| 5.3 | Effect of Diazo Compound Concentration on the Reaction Outcome ^a | 253 |
| 5.4 | Effect of vinyl sulfoxonium ylide concentration on the reaction outcome ^a | 253 |
| 6.1 | Reaction Optimization using various solvents at different temperatures ^a | 296 |
| 6.2 | Concentration effects of (Boc) ₂ O and pyridine ^b | 297 |
| 6.3 | Optimization of the activation source of pyridine ^a | 298 |
| 6.4 | Crystal data and structure refinement for (5). | 340 |
| 6.5 | Crystal data and structure refinement for (6f). | 341 |

LIST OF SCHEMES

| Scheme No. | Scheme Caption | Page No. |
|------------|---|------------|
| 2.1 | Reported methodologies for vinyl diazo-mediated X-H bond insertion. | 8 |
| 2.2 | Present hypothesis for metal-free X-H bond insertion. | 9 |
| 2.3 | Present approach for the insertion reaction of vinyl sulfoxonium ylide with various nucleophiles. | 10 |
| 2.4 | Substrate scope of acids insertion reaction with vinyl sulfoxonium ylides. | 12 |
| 2.5 | Substrate scope of thiols insertion reaction with vinyl sulfoxonium ylides. | 14 |
| 2.6 | Substrate scope of amines, phenols and halogen acids insertion reaction with vinyl sulfoxonium ylide. | 15 |
| 2.7 | Scale-up synthesis of 3aa . | 15 |
| 2.8 | Proposed mechanism for the synthesis of the insertion products. | 19 |
| 3.1 | Principle of iterative synthesis. | 57 |
| 3.2 | Previous approach for the synthesis of the polyalkyl chains via iterative strategy. | 58 |
| 3.3 | Present objective for the synthesis of the unsaturated oligoesters. | 59 |
| 3.4 | Concept of bidirectional iterative process. | 60 |
| 3.5 | General reaction scheme for the acid-iteration process. | 61 |
| 3.6 | Iterative Sequence for the synthesis of unsaturated oligoester 7a . | 62 |
| 3.7 | Iterative Sequence for the synthesis of unsaturated oligoester 7b . | 63 |
| 3.8 | Iterative Sequence for the synthesis of unsaturated oligoester 7c . | 63 |
| 3.9 | Iterative Sequence for the synthesis of unsaturated oligoester 7d . | 64 |
| 3.10 | Iterative Sequence for the synthesis of unsaturated oligoester 7e . | 65 |
| 3.11 | Iterative Sequence for the synthesis of unsaturated oligoester 7f . | 65 |
| 3.12 | Iterative Sequence for the synthesis of unsaturated oligoester 7g . | 66 |
| 3.13 | Ylide iteration for the synthesis of unsaturated oligoester. | 68 |
| 4.1 | Classical rearrangements for the synthesis of <i>o</i> -substituted phenols. | 99 |
| 4.2 | Baker-Vanketraman rearrangement for the synthesis of <i>o</i> -substituted phenols. | 99 |
| 4.3 | Substrate scope for the synthesis of diazahexatrienes scaffolds. | 100 |
| 4.4 | Unsuccessful substrates for the rearrangement product. | 108 |

| | | |
|------|---|------------|
| 4.5 | Synthetic applications of rearrangement product 4 . | 110 |
| 4.6 | Possible pathways for the synthesis of diazahexatrienes based on the deuterium labelling studies. | 114 |
| 4.7 | Comparative analysis of reaction pathways with and without vinylogous anion participation. | 116 |
| 4.8 | Proposed mechanism for the synthesis of 4 . | 117 |
| 5.1 | Previous strategies for one-pot carbene-mediated alkylation reactions. | 157 |
| 5.2 | Present concept for the one-pot reaction involving two carbene precursors and nucleophile. | 158 |
| 5.3 | Major challenges of the present reaction design. | 160 |
| 5.4 | Working hypothesis for the synthesis of [2,3]-sigmatropic rearrangement product. | 161 |
| 5.5 | Reactivity comparison of diazo compound and vinyl sulfoxonium ylide with benzenethiol in presence of cobalt catalyst. | 168 |
| 5.6 | Substrate scope of diazo compounds for the synthesis of tertiary thiol scaffolds. | 172 |
| 5.7 | Substrate scope of thiol compounds for the synthesis of tertiary thiol scaffolds. | 174 |
| 5.8 | Substrate scope of vinyl sulfoxonium ylide for the synthesis of tertiary thiol scaffolds. | 175 |
| 5.9 | Gram-scale synthesis of the rearrangement product 4c . | 176 |
| 5.10 | Synthetic applications of the rearrangement product. | 178 |
| 5.11 | Plausible mechanism for the synthesis of tertiary thiol scaffolds 4 . | 193 |
| 6.1 | Coupling reactions of diazo compounds with the sulfur ylides. | 249 |
| 6.2 | Present approach for the metal free synthesis of tertiary thiol scaffolds. | 250 |
| 6.3 | Substrate scope for the synthesis of 4 . | 255 |
| 6.4 | Plausible mechanism for the synthesis of 4 . | 267 |
| 7.1 | Nucleophilic species commonly involved in pyridine dearomatization. | 294 |
| 7.2 | Previous methodologies employing unconjugated sulfur ylides. | 294 |
| 7.3 | Our approach toward the synthesis of 4-dienyl 1,4-dihydropyridine derivatives. | 295 |
| 7.4 | Substrate scope of the dienyl 1,4-dihydropyridine scaffolds. | 300 |
| 7.5 | Proposed mechanistic pathway for the generation of benzo-fused aza-barbaralane scaffolds 5 . | 303 |
| 7.6 | Metal-mediated strategies for the synthesis of <i>bis</i> -heterocycles. | 304 |
| 7.7 | Proposed mechanism for the formation of the thiophene frameworks. | 306 |
| 7.8 | Metal-free approach for the synthesis of pyridine-pyrrole <i>bis</i> -heterocycles. | 307 |
| 7.9 | Plausible mechanism for the formation of the pyridine-pyrrole <i>bis</i> -heterocycle. | 307 |

| | | |
|------|---|------------|
| 7.10 | Mechanistic study to elucidate the reaction sequence. | 310 |
| 7.11 | Proposed mechanism for the formation of dienyl 1,4-dihydropyridine scaffolds. | 320 |

LIST OF ABBREVIATIONS

| | |
|--------|---|
| Å | Angstrom |
| ° | degree |
| °C | degree centigrade |
| α | alpha |
| β | Beta |
| δ | chemical shift |
| μ | mu |
| o | ortho |
| % | percentage |
| Ar | aryl |
| Ac | acetyl |
| bs | broad singlet |
| bd | broad doublet |
| Bn | benzyl |
| Bu | butyl |
| Calcd. | calculated |
| d | doublet |
| dd | doublet of doublets |
| dt | doublet of triplets |
| ddd | doublet of doublets of doublets |
| dddd | doublet of doublets of doublets of doublets |
| dq | doublet of quartets |
| dr | diastereomeric ratio |
| DCM | dichloromethane |
| DMF | dimethyl formamide |
| DMSO | dimethyl sulfoxide |
| DMAP | 4-dimethylaminopyridine |

| | |
|--------------|-----------------------------------|
| DABCO | 1,4-diaza bicyclo[2.2.2]octane |
| DFT | density functional theory |
| EWG | electron withdrawing group |
| EDG | electron donating group |
| EtOAc | ethyl acetate |
| Et | ethyl |
| gem | geminal |
| HRMS | high-resolution mass spectrometry |
| iPr | isopropyl |
| K | Kelvin |
| Me | methyl |
| MeOH | methanol |
| MS | molecular sieves |
| mg | milligram |
| M | molarity |
| mmol | millimole |
| mol | mole |
| MHz | mega hertz |
| m | multiplet |
| nm | nanometer |
| NMR | nuclear magnetic resonance |
| NBS | N-bromosuccinimide |

| | |
|--------------|---|
| Ph | phenyl |
| ppm | parts per million |
| q | quartet |
| qd | quartet of doublets |
| Rf | retention factor |
| t | triplet |
| td | triplet of doublets |
| Ts | tosyl |
| tBu | tertiary butyl |
| THF | tetrahydrofuran |
| TEMPO | 2,2,6,6-tetramethyl-1-piperidinyloxy |
| TLC | thin layer chromatography |
| VSX | vinyl sulfoxonium ylide |