

**ASYMMETRIC VINYLOGOUS MICHAEL REACTION,
STEREOABLATIVE O-ARYLATION, ALKYLATION
AND VINYLOGOUS NUCLEOPHILIC SUBSTITUTION:
TOWARDS FUNCTIONALIZED ORGANIC
FRAMEWORKS**

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INDIAN INSTITUTE OF TECHNOLOGY DELHI
OCTOBER 2017**

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FRAMEWORKS**

by

AMOL P. JADHAV

Department of Chemistry

Submitted

In fulfillment of requirements of degree of Doctor of Philosophy

to the



INDIAN INSTITUTE OF TECHNOLOGY DELHI

OCTOBER 2017

Dedicated to my beloved Parents

and

Sachin Dada

CERTIFICATE

This is to certify that the thesis entitled, “**Asymmetric Vinylogous Michael Reaction, Stereoablative O-Arylation, Alkylation and Vinylogous Nucleophilic Substitution: Towards Functionalized Organic Frameworks**”, being submitted by **Mr. Amol P. Jadhav** to the **Indian Institute of Technology Delhi** for the award of the degree of **Doctor of Philosophy** in Chemistry is a record of bona fide research work carried out by him. Mr. Amol P. Jadhav worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results contained 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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ACKNOWLEDGEMENTS

Completion of this doctoral dissertation was possible with the support of several people. I would like to express my sincere gratitude to all of them. First and foremost I want to thank my advisor **Dr. Ravi P. Singh**. It has been an honor to be his first Ph.D. student. 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 ways 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 have been invaluable.

I also have to thank the members of my SRC committee, Professors J. D. Singh, V. Haridas, and J. Jacob for their helpful 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. N. D. Kurur (Chairman, DRC) for streamlining curricular formalities. I would especially like to express my gratitude towards Prof. N. G. Ramesh and Dr. S. L. Gholap for their timely encouragement 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 Dr. Neetu Singh, for her kind and generous nature, constant support and encouragement. I would like to thank CSIR, India, for providing the research fellowship which allowed me to undertake this research program.

A good support system is important to surviving and staying sane in grad school. I was lucky to be a part of what we like to call as “CCSL Group”. I am forever thankful to my colleagues in the lab for their friendship and support and for creating a cordial working environment. Their presence was very important in a process that is often felt as tremendously solitaire. U. Bhaskara Rao formed the core of my research time and we have been there for one another throughout this journey. I would like to thank all my colleagues (past and present) Dr. Devalina Ray, Dr. T. Palani, Vijay, Krishna Kumar, Pradeep, Arup, Krishna Nand, Manish, Soumyadip, Sanjay, Khushboo, Sonu, Neha, Shrikesh, Ashima, Shweta and Deepak. I also recognize the support and contributions from Amjad and Aarti, not only with the projects but in many ways. I would like to thank all my friends at NCL, Pune and Pune University including Avinash, Manikandan, Dnyaneshwar, Virat, Balaji, Shivcharan, Balu, Rohan, Ganesh, Brijesh, Menaka,

Ravindra, Milind, Praveen, Tukaram and Shubhangi for their personal and scholarly interactions with me. It is a pleasure to thank my friends at IIT Delhi including Rahul, Vimal, Rituraj, Ashish, Lakhbeer, Jagriti, Jatinder, Mayuk, Awadh, Anil, Sonal, Vartika, Smita and Chandrashekhar.

I am also greatly indebted to many teachers in the past including Prof. V. D. Bobade, Prof. A. V. Borhade, Prof. S. Patil and Prof. N. Z. Borse for creating my interest in Chemistry and further in the research field.

Words can not express how grateful I am to my family: my parents, Pandharinath R. Jadhav and Nalini P. Jadhav for educating me the best possible way, for unconditional support, blessings, constant love and encouragement to pursue my interests. I express my deepest gratitude to my brother Sachin and sister in law Pallavi for believing in me and selflessly encouraging me to explore new directions in life and seek my own destiny. Credit to smiles on my face goes to Vighnesh, my nephew, who has been the light of our life and has given me the extra strength and motivation to get things done.

Finally, and most importantly, I would like to thank my wife Dr. Monali. Her support, encouragement, quiet patience and unwavering love were undeniably the basis upon which the past ten years of my life have been built. To have a woman of such infinite talent and dynamism, who put her own professional career on hold to support the dreams of the man she's married is a powerful thing and I have striven every day to live up to that. Without my wife, Monali, none of this would ever have been possible.

Last, but not the least, I would like to thank the almighty God for showers of blessings and for providing me strength and courage to face the challenges laid out before me.

Amol P. Jadhav

ABSTRACT

The thesis entitled “**Asymmetric vinylogous Michael reaction, stereoablative O-arylation, alkylation and vinylogous nucleophilic substitution: Towards functionalized organic frameworks**” deals with development of stereoselective reactions for the synthesis of spatially defined functionalized scaffolds. Different stereoisomers can show varied response towards human senses such as smell and taste, behaviour of insects and most importantly in their pharmacological activity in human body. Thus, it is very important to selectively synthesize the desired enantiomers and diastereomers through meticulous choice of catalysts and reaction conditions. We have developed organocatalytic enantioselective and Lewis acid catalyzed diastereoselective methods for C-C and C-O bond forming reactions leading to functionally rich moieties.

This thesis has been divided into five chapters. In the first chapter, importance of stereochemistry with various interesting examples has been explained. An introduction to asymmetric catalysis with emphasis on organocatalysis has been described. A brief history of organocatalysis is followed by activation modes such as covalent and non-covalent organocatalysis. Then, a brief introduction to the principle of vinylogy and stereoablative strategy has been described.

Chapter 2 describes organocatalytic diastereo- and enantioselective Michael addition of 2-silyloxyfurans with various cyclic enones. Chiral γ -butenolide and their derivatives are present in numerous natural products and are important building blocks for the synthesis of biologically active compounds. Particularly, cycloalkane connected γ -butenolides with chiral quaternary center at cycloalkane-connecting point are of great interest. However, due to the built-in steric repulsion, the asymmetric installation of quaternary all-carbon stereogenic centres remains a difficult and imperative problem in chiral catalysis and has been a domain of large research interest in synthetic organic chemistry. We have disclosed the development of a simple, commercially available chiral organic catalyst system that effectively promotes the asymmetric vinylogous Michael reactions of various 2-silyloxyfurans with cyclic enones and 3-substituted cyclic enones. Furthermore, the synthetic potential of these *syn*-Michael adducts was demonstrated by 1,4-addition of nucleophiles on the butenolide substructure.

Chapter 3, deals with the synthesis of α -Alkylidene- δ -diaryl-2-oxindoles through the vinylogous nucleophilic substitution of the hydroxy Group in diarylmethanols with 3-propenyl-2-silyloxyindoles. Various nucleophiles which have been used for direct nucleophilic substitution of alcohols include carbonyl compounds, alkynes, alkenes, active silanes, active methylene compounds, aromatic compounds and hetero atom donors. However, very few methodologies of alcohol substitution with vinylogous nucleophiles have manner. However, very few methodologies of alcohol substitution with vinylogous nucleophiles have been reported. Among the vinylogous nucleophiles particularly 3-alkylidene-2-oxindoles have shown great potential as nucleophiles for providing a functionalized indole or oxindole containing backbones. It could install highly functionalized vinylic scaffolds in regio- and diastereoselective manner. We have disclosed the first example of a Lewis acid catalyzed highly diastereoselective direct vinylogous nucleophilic substitution reaction of *tert*-butyldimethylsilyloxydienes derived from γ -enolizable 3-alkylidene-2-oxindoles with *in-situ* generated diarylmethyl carbocations obtained from *o*-methoxybenzylic alcohols. This remote functionalization of protocol resulted in *Z*-selective α -alkylidene- δ -diaryl-2-oxindoles.

In chapter 4, enantioselective organocatalytic stereoablative aryloxylation of 3-bromooxindoles with bifunctional catalyst have been described. Numerous bioactive alkaloid natural products and pharmaceutically important compounds contains 3,3'-disubstituted oxindole core with a heteroquaternary stereo center at the C3 position. In particular 3,3'-disubstituted oxindoles exhibiting spatially defined aryloxy group at C3 position have become desirable synthetic targets. We have disclosed a novel route for the construction of these scaffolds in high yields and excellent enantioselectivities through stereoablative aryloxylation of 3-halooxindoles with cinchona alkaloid derived organocatalysts. We have demonstrated synthetic utility of our developed methodology by synthesizing 3-phenoxy analogue of core of alkaloid CPC-1. We also did mechanistic investigation of this developed protocol by HRMS studies, supporting the simultaneous activation of both the *o*-azaxylylene intermediate and aryl alcohol by organocatalyst *via* bifunctional mode of activation.

In chapter 5, we have developed a strategy for diastereoselective stereoablative alkylation of 3-halooxindoles for the synthesis of vicinal all-carbon quaternary stereocenters. Molecules possessing two adjacent all-carbon quaternary stereocenter are present not only in the natural products but also in the compounds of pharmaceutical and medicinal importance. Among these

molecules, those bearing oxindole and indole or bisindole moieties linked through adjacent all carbon quaternary centers are present in many complex indole alkaloids of therapeutic importance. We have developed direct alkylation strategy using inherently nucleophilic 3-substituted indoles with electrophilic oxindole counterpart in diastereoselective fashion, to get indole/oxindole scaffolds bearing adjacent quaternary stereocenters.

सार

थीसिस हकदार “असममित विनायलोगोस माइकल प्रतिक्रिया, स्टेरेओअब्लतिव ओ-अरैलेशन, अल्किलेशन और विनायलोगोस नुक्लेओफिलिक प्रतिस्थापन: कार्यात्मक जैविक चौखटों की ओर” स्थानिक रूप से परिभाषित फंक्शनल स्कैफोल्ड्स के संश्लेषण के लिए स्टेरिओसिलेक्टिव प्रतिक्रियाओं के विकास के साथ संबंधित है। अलग-अलग स्तिरिओइसोमेर मानव इंद्रियों जैसे गंध और स्वाद, कीड़ों के व्यवहार और सबसे महत्वपूर्ण रूप से मानव शरीर में उनके औषधीय गतिविधि में विविध प्रतिक्रियाओं को दिखा सकते हैं। इस प्रकार, उत्प्रेरक और प्रतिक्रिया की स्थितियों के सूक्ष्म चयन के माध्यम से वांछित एनेन्सिओमेर्स और डायस्टेरेओमेर्स को चुनिंदा रूप से संश्लेषित करना बहुत महत्वपूर्ण है। हमने सी-सी और सी-ओ बंधन के लिए संगठनात्मक एनेन्सिओसेलेक्टिव और लुईस एसिड उत्प्रेरित डायस्टेरेओसिलेक्टिव तरीकों को विकसित किया है, जो क्रियात्मक रूप से समृद्ध आधा भाग बनाते हैं।

इस थीसिस को पांच अध्यायों में बांटा गया है। पहले अध्याय में, विभिन्न दिलचस्प उदाहरणों के साथ स्टेरियोकेमिस्ट्री के महत्व को समझाया गया है। जैविक कटैलिसीस पर जोर देने के साथ असममित उत्प्रेरकों का परिचय दिया गया है। संगठनात्मक विश्लेषण का एक संक्षिप्त इतिहास, इसके बाद सहसंयोजक और गैर-सहसंयोजक संगठनात्मकता के रूप में सक्रियण मोडों के बाद होता है। इसके बाद, विनैलोगी और स्टेरेओअब्लतिव रणनीति के सिद्धांत को एक संक्षिप्त परिचय वर्णित किया गया है।

अध्याय दो विभिन्न चक्रीय एनोन के साथ संगठनात्मक डाइस्टेरेयो- और एनेन्सिओसेलेक्टिव माइकल 2-सील्यलॉक्सीफुरन्स के अलावा जोड़ता है। काइरल γ -ब्यूटेनोलिड और उनके डेरिवेटिव कई प्राकृतिक उत्पादों में मौजूद हैं और जैविक रूप से सक्रिय यौगिकों के संश्लेषण के लिए महत्वपूर्ण इमारत ब्लॉकों में उपलब्ध हैं। विशेष रूप से, सैक्लोअल्केन-जोड़ने बिंदु पर काइरल चतुर्भुज केंद्र के साथ γ -ब्यूटेनोलिड से जुड़े सैक्लोअल्केन बहुत रुचि के हैं। हालांकि, अंतर्निहित स्थूलता के प्रतिकूल होने के कारण, काइरल कटैलिसीस में चतुष्कोणीय सभी कार्बन स्तिरियोजेनिक केंद्रों की असममित स्थापना एक कठिन और अनिवार्य समस्या बनी हुई है और सिंथेटिक जैविक रसायन विज्ञान में बड़े शोध वाले हितों का एक डोमेन है। हमने एक सरल, व्यावसायिक रूप से उपलब्ध काइरल कार्बनिक उत्प्रेरक प्रणाली के विकास का खुलासा किया है जो कि चक्रीय एनोन और 3-प्रतिस्थापित चक्रीय एनोन के साथ विभिन्न 2-सील्यलॉक्सीफुरन्स के असममित विनायलोगोस माइकल प्रतिक्रियाओं को प्रभावी ढंग से बढ़ावा

देता है। इसके अलावा, इन सीन-माइकल जोड़ों की सिंथेटिक संभावना को ब्यूटेनोलिड आधार पर न्यूक्लियोफाइल के १, ४ -अतिरिक्त जोड़ द्वारा प्रदर्शित किया गया है।

अध्याय ३, ३-प्रोपेनिल-२-सिलीलॉक्सी इंडोल्स के साथ डाइरेलेमिथेनॉल में हाइड्रॉक्सी ग्रुप के विनायलोगोस नुक्लेओफिलिक प्रतिस्थापन के माध्यम से α -अल्किलिदिन- δ -डाइअरील-२-ऑक्सिनडॉल्स के संश्लेषण से संबंधित है। हालांकि, विनायलोगोस न्यूक्लियोफाइल के साथ अल्कोहोल प्रतिस्थापन के बहुत ही कम तरीके हैं। विशेष रूप से ३-एल्किलिडेन-२-ऑक्सीडोल्स में विनायलोगोस न्यूक्लियोफाइलों में एक कार्यात्मक इन्डोल या ऑक्सीन्डोल युक्त बैकबोन प्रदान करने के लिए न्यूक्लियोफिल्स के रूप में अच्छी संभावनाएं दिखाई हैं। यह बहुत ही कार्यात्मक विनायलोगोस स्कॉफॉल्ड्स को रेजीओ- और डाइस्टेरेयोसेलेक्टिव तरीके से स्थापित कर सकता है। हमने एक लिविस एसिड के पहले उदाहरण का खुलासा किया है जिसमें उच्च-डाइस्टेरेयोसेलेक्टिव डायरेक्ट विनायलोगोस न्यूक्लियोफिलिक सब्सटिशन प्रतिक्रिया के टीट-ब्यूथिलडिमिथिलसिलीक्लॉक्सीडियंस की उत्पत्ति हुई है, जो कि गामा-एनोलिज़ेबल ३-एल्किलिडेन-२-ऑक्सीडोल से उत्पन्न होती है, जिसमें ओ-मेथॉक्सीबेंजाहेड्रिल अल्कोहल से प्राप्त इन-सीटू जनरेटेड डाइरेलेमिथाइल कार्बोक्तायन हैं। प्रोटोकॉल के इस दूरस्थ कार्यात्मककरण के चयनात्मक जी α -अल्किलिदिन- δ -डायअरील-२-ऑक्सिनडॉल्स परिणामस्वरूप प्राप्त किया गया है।

अध्याय ४ में, बाइफंक्शनल उत्प्रेरक के साथ ३-ब्रोमोऑक्सीन्डोल्स के एनन्सिओसेलेक्टिव काइरल कार्बनिक उत्प्रेरक प्रणाली से स्टेरेओअब्लतिव एरिलॉक्सिलेशन को वर्णित किया गया है। कई बायोएक्टिव एल्कालोइड प्राकृतिक उत्पाद और औषधीय रूप से महत्वपूर्ण यौगिकों में सी-३ की स्थिति में एक हेटेरो-चतुर्धातुक स्टीरियो सेंटर के साथ ३,३ '-विहीन ऑक्सीन्डोल कोर शामिल हैं। विशेष रूप से ३,३ में सी-३ की स्थिति में स्थानिक रूप से परिभाषित अरीलॉक्सी समूह का प्रदर्शन करने वाले विघटनित आक्सीडोल वांछनीय कृत्रिम लक्ष्य बन गए हैं। हमने उच्चतम पैदावार में इन स्कॉफॉल्ड्स के निर्माण और ३-हेलोऑक्सिंडोल्स के स्टेरेओअब्लतिव एरिलॉक्सिलेशन के माध्यम से सिन्कोना एल्कालोइड व्युत्पन्न जैविक उत्प्रेरक के साथ उत्कृष्ट उपन्यासों का निर्माण करने के लिए एक उपन्यास मार्ग का खुलासा किया है। हमने एल्कालोइड सीपीसी-१ के कोर के ३-फेनोक्सी अनुरूप को संश्लेषित करके हमारी विकसित कार्यप्रणाली के सिंथेटिक उपयोगिता का प्रदर्शन किया है। हम एचआरएमएस अध्ययनों द्वारा इस विकसित प्रोटोकॉल की तंत्रिकी जांच भी कर चुके हैं, सक्रियण के दोहरे कार्यात्मक मोड के माध्यम से जैविक उत्प्रेरक द्वारा ओ-अझाजायलिन मध्यम और एरिल अल्कोहल दोनों के साथ-साथ सक्रियण को समर्थन देते हैं।

अध्याय ५ में, हमने ३-हेलोऑक्सीन्डोल्स के डायस्टेरेसियोक्लेक्टिव स्टेरेओअब्लतिव अल्किलेशन के लिए एक कार्यनीति विकसित की है जो पड़ोसी दो-कार्बन चतुष्कोणीय अवरोधक के संश्लेषण के लिए है। अणुओं के पास दो

सटे हुए कार्बन चतुर्धातुक स्टिरिओसेंटर न केवल प्राकृतिक उत्पादों में मौजूद हैं बल्कि दवा और औषधीय महत्व के यौगिकों में मौजूद हैं। इन अणुओं में, आसन्न सभी कार्बन चतुष्कोणीय केन्द्रों के माध्यम से जुड़े ऑक्सीन्डोल और इंडोल या दोहरे ऑक्सीन्डोल, रोगी चिकित्सीय महत्व के कई जटिल इंडोल एल्कलॉइड में मौजूद होते हैं। हमने स्वैच्छिक चतुष्कोणीय स्टिरिओसेंटर्स वाले इंडोल / ऑक्सीन्डोल पाइ प्राप्त करने के लिए, डायस्टेरेओअब्लतिव में इलेक्ट्रोफिलिक ऑक्सीडोल समकक्ष वाले स्वाभाविक न्यूक्लियोफिल ३-प्रतिस्थापन इंडॉल्स का प्रयोग करके प्रत्यक्ष अल्किलेशन रणनीति विकसित की है।

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List of Abbreviations

Abbreviation	Full form
Ar	Aryl
Bn	Benzyl
Boc	<i>tert</i> -butyloxycarbonyl
^t Bu	<i>tert</i> -Butyl
CDCl ₃	Deuterated chloroform
CH ₂ Cl ₂	Dichloromethane
CPME	Cyclopentyl methyl ether
cm ⁻¹	Wavenumbers
°C	Degrees Celsius
2,4-DNBA	2,4-Dinitrobenzoic acid
<i>dr</i>	Diastereomeric ratio
DIPEA	<i>N, N</i> -Diisopropylethylamine
DMAP	<i>N, N</i> -Dimethylpyridin-4-amine
DEPT	Distortionless enhancement by polarization transfer
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d	Doublet
dd	Doublet of doublets
d ₆ -DMSO	Deuterated dimethyl sulfoxide
δ	Chemical shift
<i>er</i>	Enantiomeric ratio
<i>ee</i>	Enantiomeric excess
ESI-TOF	Electrospray ionization - Time-of-flight
EtOAc	Ethyl acetate
FTIR	Fourier transform infrared
H ₂ O	Water
h	Hour

HCN	Hydrogen cyanide
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
J	Coupling constant
λ	Wavelength
LUMO	Lowest unoccupied molecular orbital
min	Minute
MTBE	Methyl <i>tert</i> -butyl ether
m	Multiplet
MHz	Megahertz
mL	Millilitre
MeOD	Deuterated methanol
μL	Microlitre
PNBA	<i>para</i> -Nitrobenzoic acid
<i>p</i> -TsOH	<i>para</i> -Toluenesulfonic acid
PMA	Phosphomolybdic acid
s	Singlet
SOMO	Singly unoccupied molecular orbital
TFA	Trifluoroacetic acid
TfOH	Triflic acid
TCA	Trichloroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TBAF	Tetra- <i>N</i> -butylammonium fluoride
UV	Ultraviolet