

ORGANOCATALYTIC ASYMMETRIC VINYLOGOUS C-C BOND FORMATION AND STEREOSELECTIVE [3+3] CYCLOADDITION REACTION WITH 3-ALKYLIDENE-2-OXINDOLES

MANISH KUMAR JAISWAL



**DEPARTMENT OF CHEMISTRY
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ORGANOCATALYTIC ASYMMETRIC VINYLOGOUS C-C BOND FORMATION AND STEREOSELECTIVE [3+3] CYCLOADDITION REACTION WITH 3-ALKYLIDENE-2-OXINDOLES

by

MANISH KUMAR JAISWAL

Department of Chemistry

Submitted

in fulfilment of the requirements of the degree of Doctor of Philosophy

to the



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Dedicated to my beloved Parents

CERTIFICATE

This is to certify that the thesis entitled, “**Organocatalytic Asymmetric Vinylogous C-C Bond Formation and Stereoselective [3+3] Cycloaddition Reaction with 3-Alkylidene-2-Oxindoles**”, being submitted by **Mr. Manish Kumar Jaiswal** 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. Manish Kumar Jaiswal 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.

(Dr. Ravi P. Singh)

Associate Professor,

Department of Chemistry

Indian Institute of Technology Delhi

New Delhi-110016

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ABSTRACT

The thesis entitled “**Organocatalytic Asymmetric Vinylogous C-C Bond Formation and Stereoselective [3+3] Cycloaddition Reaction with 3-Alkylidene-2-Oxindoles**” deals with the evolution of stereoselective reactions for the synthesis of functionalized oxindole scaffolds. Different stereoisomers of a molecule are responsible for many important properties like the biological activity, effect on taste, odour and pharmaceutical activity. Therefore, it is crucial to selectively synthesize the desired enantiomers and diastereomers through smart synthetic design and conscious choice of catalysts and reaction conditions. We have developed organocatalytic highly diastereoselective and enantioselective methods for C-C bond forming reactions leading to functionally rich moieties of oxindole core.

This thesis has been divided into four chapters. In the **first chapter**, significance of chirality with various interesting examples has been explained. Synthetic routes to diastereomerically and/or enantiomerically pure compounds has been explained. The chapter has an introduction to asymmetric catalysis and detailed description of organocatalysis. Also highlighted are the various modes of organocatalysis such as covalent and non-covalent catalysis. Additionally, asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea has been described. Then, a brief introduction to the principle of vinylogy with example of 3-alkylidene-oxindole as a vinylogous nucleophile in asymmetric vinylogous aldol reaction, asymmetric vinylogous Michael reaction and cycloaddition strategy for synthesis of spirocyclohexene-oxindole has been described.

Chapter 2 describes an organocatalytic highly enantioselective vinylogous Aldol reaction of 3-alkylidene oxindole with α -ketophosphonates. Biological importance of oxindole scaffolds and α -Hydroxy phosphonic acid and their derivatives in particular quaternary α -hydroxy phosphonates has been described. The chapter also describes synthetic routes to asymmetric aldol reaction and vinylogous aldol reactions, along with discussion on asymmetric organocatalyzed vinylogous aldol reaction. In this chapter, the development of a cinchona alkaloid derivative, and a chiral organic catalyst system that effectively promotes the asymmetric vinylogous aldol reactions yielding, chiral δ -quaternary α -hydroxyphosphonato-3-alkylidene-2-oxindole and their derivatives is described. The scaffolds developed are unique as they are hybrid of oxindole and hydroxy-phosphonate moieties. Since, both type of scaffold has their own biological and pharmaceutical importance and they are the building blocks for the synthesis of biologically active compounds.

Chapter 3, deals with the synthesis of chiral γ -substituted 3-alkylidene oxindoles through enantioselective vinylogous Michael addition reaction of 3-alkylidene oxindole to β,γ -unsaturated α -ketoesters in presence of bifunctional amine-thiourea catalyst. Various nucleophiles that have been used for asymmetric Michael addition on β,γ -unsaturated α -ketoesters are also described. The lack of methodologies for asymmetric vinylogous Michael addition with biologically active vinylogous nucleophile such as 3-alkylidene-2-oxindoles is also highlighted. Among cyclic and acyclic vinylogous nucleophiles, particularly 3-alkylidene-2-oxindoles have shown great potential as nucleophiles for providing a functionalized indole or oxindole containing backbones. In this chapter, we have demonstrated the reaction can create highly functionalized vinylic scaffolds in regio- and stereoselective manner. Synthetic utility of the developed Michael adducts is exemplified by common synthetic transformations.

In **chapter 4**, formal [3+3] annulation of 3-alkylidene-2-oxindole with β,γ -unsaturated α -keto esters have been described for the diastereoselective synthesis of spirocyclohexene-oxindole. Numerous bioactive alkaloid natural products and pharmaceutically important compounds containing spirocyclohexene(-ane) oxindole core with a quaternary stereo center at the C3 position is shown. Also described the synthetic route for synthesis of cyclohexene-oxindole. This chapter discloses a novel route for the construction of these scaffolds in high yields and excellent selectivity through [3+3] cycloaddition reaction with DABCO as an organocatalyst. We have reported a preliminary bioactivity studies of these compounds that suggests its strong anti-cancer property.

सार

थीसिस हकदार “ऑर्गेनोकटेलिटिक एसिमेट्रिक विनायलोगस सी-सी बॉन्ड फॉर्मेशन और स्टेरियोसेलेक्टिव [3 + 3] साइक्लोएडिशन रिएक्शन के साथ 3-एल्केलाइडीन-2-ऑक्सिंडोल” के साथ कार्य करता है। यह क्रियाकारक ऑक्सिंडोल स्कैफोल्ड के संश्लेषण के लिए स्टेरियोसेलेक्टिव प्रतिक्रियाओं के विकास के साथ होता है। एक अणु के विभिन्न स्टेरियोइसोमर्स जैविक गतिविधि, स्वाद पर प्रभाव, गंध और दवा गतिविधि जैसे कई महत्वपूर्ण गुणों के लिए जिम्मेदार हैं। इसलिए, स्मार्ट सिंथेटिक डिजाइन और उत्प्रेरकों और प्रतिक्रिया की स्थितियों के प्रति सचेत पसंद के माध्यम से वांछित एनेन्सिओमेर्स और डायस्टेरियोमर्स को चुनिंदा रूप से संश्लेषित करना महत्वपूर्ण है। हमने ऑक्सिंडोल कोर के कार्यात्मक रूप से समृद्ध मोईटीस के लिए सी-सी बॉन्ड बनाने वाली प्रतिक्रियाओं के लिए ऑर्गेनोकटेलिटिक अत्यधिक डायस्टेरोसेलेक्टिव और एनेन्सिओमेर्स तरीके विकसित किए हैं।

इस थीसिस को चार अध्यायों में विभाजित किया गया है। **पहले अध्याय** में, विभिन्न दिलचस्प उदाहरणों के साथ काइरलिटी के महत्व को समझाया गया है। सिंथेटिक मार्गों को डायस्टेरोमेरिक और / या एनेन्सिओमेरिकली शुद्ध यौगिकों के लिए समझाया गया है। अध्याय में एसिमेट्रिक कटैलिसिस का परिचय है और ऑर्गेनोकटेलिसिस का विस्तृत विवरण है। इसके अलावा हाइलाइट किए गए ऑर्गेनोकटेलिसिस के विभिन्न तरीके जैसे सहसंयोजक और गैर-सहसंयोजक कटैलिसिस हैं। इसके अतिरिक्त, द्विभाषी सिनकोना अल्कलॉइड-आधारित यूरिया और थायोरिया के साथ एसिमेट्रिक कटैलिसिस का वर्णन किया गया है। फिर, एसिमेट्रिक विनायलोगस एल्डोल प्रतिक्रिया में एक विनायलोगस न्यूक्लियोफाइल के रूप में 3-एल्केलाइडीन-ऑक्सिंडोल के उदाहरण के साथ विनायलोजी के सिद्धांत का एक संक्षिप्त परिचय, एसिमेट्रिक विनायलोगस माइकल प्रतिक्रिया और स्पाइरोसाइक्लोहेक्सीन - ऑक्सिंडोल के संश्लेषण के लिए साइक्लोएडिशन रणनीति का वर्णन किया गया है।

अध्याय 2 में α -किटोफोस्फोनेट्स के साथ 3-एल्केलाइडीन ऑक्सिंडोल के एक ऑर्गेनोकटेलिटिक अत्यधिक एनेन्सियोसेलेक्टिव विनायलोगस प्रतिक्रिया का वर्णन है। ऑक्सिंडोल स्कैफोल्ड और एन-हाइड्रॉक्सी फॉस्फोनिक एसिड के जैविक महत्व और विशेष रूप से चतुर्धातुक α -हाइड्रॉक्सीफोस्फोनेट्स में उनके डेरिवेटिव का वर्णन किया गया है। अध्याय में एसिमेट्रिक एल्डोल प्रतिक्रिया और विनायलोगस एल्डोल प्रतिक्रियाओं के लिए सिंथेटिक मार्गों का भी वर्णन किया गया है, साथ ही एसिमेट्रिक ऑर्गेनोक्लाटाइज्ड विनायलोगस एल्डोल प्रतिक्रिया पर चर्चा की गई है। इस अध्याय में, एक सिनकोना अल्कलॉइड व्युत्पन्न का विकास, और एक काइरल

कार्बनिक उत्प्रेरक प्रणाली है जो प्रभावी रूप से एसिमेट्रिक विनायलोगस अल्डोल प्रतिक्रियाओं को उपजाने, काइरल δ - चतुर्धातुक α - हाइड्रोक्सी फॉस्फोनटो-3- एल्केलाइडीन-2- ऑक्सिंडोल और उनके वर्णन को बढ़ावा देता है। विकसित किए गए स्कैफोल्ड अनूठे हैं क्योंकि वे ऑक्सिंडोल और हाइड्रोक्सी-फॉस्फोनेट मोईटीस के संकर हैं। चूंकि, दोनों प्रकार के स्कैफोल्ड का अपना जैविक और औषधीय महत्व है और वे जैविक रूप से सक्रिय यौगिकों के संश्लेषण के लिए बिल्डिंग ब्लॉक हैं।

अध्याय 3, काइरल γ - प्रतिस्थापित 3- एल्केलाइडीन ऑक्सिंडोल के संश्लेषण से संबंधित है, जो 3- एल्केलाइडीन ऑक्सिंडोल की एनन्सिओसेलेक्टिव विनायलोगस के माध्यम से β -असंतृप्त α - किटोएस्टर के लिए द्विभाजक अमीन- थायोयूरिया उत्प्रेरक की उपस्थिति में है। β, γ - असंतृप्त α - किटोएस्टर पर असिमेट्रिक माइकल एडिशन के लिए उपयोग किए जाने वाले विभिन्न न्यूक्लियोफाइल भी वर्णित हैं। जैविक रूप से सक्रिय विनायलोगस न्यूक्लियोफाइल जैसे कि 3-एल्केलाइडीन-2-ऑक्सिंडोल्स के साथ एसिमेट्रिक विनायलोगस माइकल एडिशन के लिए कार्यप्रणाली की कमी को भी रेखांकित किया गया है। चक्रीय और अचक्रीय विनायलोगस न्यूक्लियोफाइल के बीच, विशेष रूप से 3-एल्केलाइडीन-2-ऑक्सिंडोल्स ने एक कार्यात्मक रूप से इंडोल या आधारयुक्त ऑक्सिंडोल प्रदान करने के लिए न्यूक्लियोफाइल के रूप में बड़ी क्षमता दिखाई है। इस अध्याय में, हमने यह प्रदर्शित किया है कि प्रतिक्रिया रेजियो- और स्टिरियोसेलेक्टिव तरीके से अत्यधिक कार्यात्मक विनायलिक स्कैफोल्ड बना सकती है। विकसित माइकल अडॉक्ट की सिंथेटिक उपयोगिता आम सिंथेटिक परिवर्तनों द्वारा अनुकरणीय है।

अध्याय 4 में, फॉर्मल [3 + 3] β, γ - असंतृप्त α - किटोएस्टर के साथ 3-एल्केलाइडीन-2-ऑक्सिंडोल की घोषणा की गई है जो कि स्पाइरोसाइक्लोहेक्सीन-ऑक्सिंडोल के डायस्टेरोसेलेक्टिव संश्लेषण के लिए वर्णित है। कई बायोएक्टिव अल्कलॉइड प्राकृतिक उत्पादों और फार्मास्यूटिकल रूप से महत्वपूर्ण यौगिकों जिनमें सी-3 स्थिति में एक चतुर्धातुक स्टीरियो केंद्र के साथ स्पाइरोसाइक्लोहेक्सीन (-एन) ऑक्सिंडोल कोर होता है। साइक्लोहेक्सिन-ऑक्सिंडोल के संश्लेषण के लिए सिंथेटिक मार्ग का भी वर्णन किया गया है। यह अध्याय उच्च पैदावार में इन स्कैफोल्ड के निर्माण के लिए एक उपन्यास मार्ग का खुलासा करता है और ऑर्गेनोकटेलिस्ट DABCO के साथ [3 + 3] साइक्लोएडिशन प्रतिक्रिया के माध्यम से उत्कृष्ट चयनात्मकता प्रदान करता है। हमने इन यौगिकों की प्रारंभिक जैव-सक्रियता अध्ययनों की सूचना दी है जो इसके मजबूत कैंसर-रोधी गुण का सुझाव देते हैं।

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List of Abbreviations

Abbreviations	Full form
Ar	Aryl
Bn	Benzyl
Boc	tert-butyloxycarbonyl
<i>t</i> -Bu	<i>tert</i> -Butyl
CDCl ₃	Deuterated chloroform
DCM	Dichloromethane
THF	Tetrahydrofuran
DCE	Dichloroethane
cm ⁻¹	Wavenumbers
°C	Degrees Celsius
<i>ee</i>	Enantiomeric excess
<i>dr</i>	Diastereomeric ratio
QETU	Quinine derived thiourea
QDTU	Quinidine derived thiourea
DIPEA	<i>N, N</i> -Diisopropylethylamine
DMAP	<i>N, N</i> -Dimethylpyridin-4-amine
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
Cs ₂ CO ₃	Cesium carbonate
K ₂ CO ₃	Potassium carbonate
TFA	Trifluoroacetic acid
TBS	<i>tert</i> -butyldimethylsilyl
d	Doublet
dd	Doublet of doublet
<i>J</i>	Coupling constant
m	Multiplet

s	Singlet
d ₆ -Toluene	Deuterated toluene
MHz	Mega-hertz
δ	Chemical shift
<i>er</i>	Enantiomeric ratio
ESI-TOF	Electrospray ionization-Time-of-flight
EtOAc	Ethyl acetate
EtOH	Ethanol
FTIR	Fourier transform infrared
H ₂ O	Water
mL	Millilitre
μ L	Microlitre
h	Hour