ASYMMETRIC VINYLOGOUS MANNICH, ALLYLATION AND DIASTEREOSELECTIVE CYANOMETHYLATION REACTIONS: A DIRECT ACCESS TO 3,3-DISUBSTITUTED OXINDOLES

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by

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Submitted

In fulfillment of requirements of degree of Doctor of Philosophy

to the

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Dedicated to my beloved

Grandparents, Parents and Family

Members

CERTIFICATE

This is to certify that the thesis entitled, **"Asymmetric Vinylogous Mannich, Allylation and diastereoselective Cyanomethylation reactions: A direct access to 3,3-disubstituted oxindoles"**, being submitted by **Mr. U Bhaskara Rao Vippili** 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 him. Mr. U Bhaskara Rao Vippili 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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ABSTRACT

The thesis entitled "**Asymmetric Vinylogous Mannich, Allylation and diastereoselective Cyanomethylation reactions: A direct access to 3,3-disubstituted oxindoles**" 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 chiral auxiliary assisted enantioselective and base mediated diastereoselective methods for C-C bond forming reactions leading to functionally rich moieties.

This thesis has been divided into four chapters. In the first chapter, importance of stereochemistry with various interesting examples has been explained. An introduction to asymmetric catalysis with the emphasis on organocatalysis has been described. A brief history of chiral auxiliaries is followed by a brief introduction to the principle of vinylogy has been described.

Chapter 2, describes a highly practical asymmetric approach for the efficient preparation of chiral tetrasubstituted 3-aminooxindoles. Functionalized chiral oxindoles bearing a 3,3'-disubstituted carbon stereocenter are common structural core in natural products and pharmaceuticals. Such cores also offer valuable chiral building blocks for the enantioselective synthesis of biologically active compounds. Especially, the oxindoles with amino group at the 3-position are vital in drug discovery and considered important for the bioactivity of these molecules. We have disclosed the use of Ellman's chiral auxiliary *tert*-butanesulfinamide for the efficient preparation of chiral tetrasubstituted 3-aminooxindoles; based on a simple Lewis acid mediated diasteroselective vinylogous Mannich process. The method is found to be very efficient and also provides a facile access to sterically challenging 3-aminooxindole butenolides bearing two quaternary centers in continuation. The relative configuration of the major stereoisomer of Mannich adduct was established to be *anti*. Further, versatility of the method is demonstrated by 1,4-addition of nucleophiles on the sterically congested butenolide substructure. The method

provides easy access to a wide range of highly enantiomerically enriched 3-butenolide substitued 3-aminooxindoles, which is the essential structural motif in natural products and biologically active compounds.

Chapter 3, deals with asymmetric allylation of isatin derived ketimines for the efficient preparation of chiral tetra substituted functionalized 3-allyl-3-aminooxindoles. Here also we have used Ellman's chiral auxiliary *tert*-butanesulfinamide, a profoundly useful chiral auxiliary for asymmetric amination reactions and this method has shown to be an efficient preparation of chiral tetra substituted functionalized 3-allyl-3-aminooxindoles; in light of simple zinc mediated highly diasteroselective allylation reaction with the major role of KF as an additive in shaping the reaction. The present methodology is found to be very efficient and also provides a facile access to produce chiral quaternary homoallylic amines *i. e.* 3-allyl-3-aminooxindoles that possess an adjacent tertiary stereocenter.

In chapter 4, we have also demonstrated that, Aldol-type cyanomethylation of isatins by nucleophilic addition provides direct access to 3-substituted-3-hydroxyoxindoles, an important and common structural core in natural products and pharmaceuticals. In the first section of chapter 4, a practically simple and highly efficient CsF mediated cyanomethylation of various *N*-tritylisatins with TMSAN for the synthesis of 3-hydroxy-3-cyanomethyl oxindoles has been established. This method provides *β*-hydroxynitriles in moderate to very good yields and represents a valuable and competitive alternative to the previously reported procedures. Moreover, the synthetic utility of the present methodology has been showed by applying current protocol in the efficient assembly of the intermediates of medicinally important 3-hydroxy indole containing natural products. Further, in the second section an efficient, metal-free approach to 3-substituted 3-hydroxyoxindole by DBU-mediated highly diastereoselective addition of aryl acetonitrile to *N*-protected isatin under mild conditions has been developed. The reaction proceeds smoothly to produce respective cyanomethylated adducts in good yield and excellent diastereoselectivity. The mechanistic insight toward the aldol-type cyanomethylation of *N*-tritylisatin with benzyl cyanide was obtained by DFT calculations. The study indicates that the major diastereoselective product formed would be the *anti* product. The versatility of the cyanomethylation reaction is also validated by converting the cyanomethyl adduct to an advance intermediate of a natural product analogue in simple steps.

सार

थीसिस "**असममित विनीलोगस मैननिच, एलीलाइशन और डायस्टिरोज़ेक्लेक्टीव साइनोमेथिलेशन प्रतिक्रियाएं: 3,3-डिबस्टिट्यूटेड ऑक्सींडोल्स तक सीधी पहुंच**" स्थानिक रूप से परिभाषित कार्यात्मक मचानों के संश्लेषण के लिए स्टीरियोसेलेक्टीव प्रतिक्रियाओं के विकास से संबंधित है। विभिन्न स्टीरियोइज़ोमर मानवीय इंद्रियों जैसे गंध और स्वाद, कीड़ों के व्यवहार और सबसे महत्वपूर्ण रूप से मानव शरीर में उनके औषधीय गतिविधि में विभिन्न प्रतिक्रियाएं दिखा सकते हैं। इस प्रकार, उत्प्रेरक और प्रतिक्रिया की स्थिति की सावधानीपूर्वक पसंद के माध्यम से वांछित एनंटीओमर और डियास्टेरएवमेर चुनिंदा रूप से संश्लेषित करना बहुत महत्वपूर्ण है। हमने सी-सी बंधन के लिए चिराल सहायक सहायक एनेंटियोसेलेक्टीव और बेस मध्यस्थ डायस्टिरोसेलेक्टीव विधियों को विकसित किया है जो कार्यात्मक रूप से समृद्ध आधा भाग के लिए प्रतिक्रिया प्रतिक्रियाओं का निर्माण किया है।

यह थीसिस चार अध्यायों में बांटा गया है। पहले अध्याय में, विभिन्न रोचक उदाहरणों के साथ स्टीरियोकेमिस्ट्री के महत्व को समझाया गया है। ओरगानोकतालयसिस पर जोर के साथ असममित उत्प्रेरण का परिचय दिया गया है। चिराल सहायक के एक संक्षिप्त इतिहास के बाद विनीलॉजी के सिद्धांत के लिए एक संक्षिप्त परिचय दिया गया है।

अध्याय 2, चिराल तेत्रसुब्स्तितुतेद ३-अ्इनूक्सिन्दोलेस की कुशल तैयारी के लिए एक अत्यधिक व्यावहारिक असममित दृष्टिकोण का वर्णन करता है। 3,3'-विघटित कार्बन स्टीरियोसेन्टर वाले कार्यात्मक चिराल ऑक्सींडोल्स प्राकृतिक उत्पादों और फार्मास्यूटिकल्स में सामान्य संरचनात्मक कोर हैं। ऐसे कोर जैविक रूप से सक्रिय यौगिकों के enantioselective संश्लेषण के लिए मूल्यवान चिराल बिल्डिंग ब्लॉक भी प्रदान करते हैं। विशेष रूप से, 3-स्थिति में एमिनो समूह के साथ ऑक्सींडोल दवा की खोज में महत्वपूर्ण हैं और इन अणुओं की जैव-क्रियाशीलता के लिए महत्वपूर्ण माना जाता है। हमने चिड़िया तेत्रसुब्स्तितुतेद ३-अ्इनूक्सिन्दोलेस की कुशल तैयारी के लिए एल्मैन के चिराल सहायक टर्ट-बुतनेसुल्फिनमिदे के उपयोग का खुलासा किया है; एक साधारण लुईस एसिड मध्यस्थ डायस्टरोसेलेक्टीव विन्य्लोगोउस मन्निच प्रक्रिया के आधार पर। यह विधि बहुत ही कुशल साबित हुई है और निरंतर चुनौतीपूर्ण 3-एमिनोक्सिंडोल ब्यूटिनोलाइड्स को निरंतर उपयोग में दो क्वाटरनेरी केंद्रों के साथ एक आसान पहुंच प्रदान करती है। मन्निच अद्दुक्त के प्रमुख स्टीरियोइज़ोमर की सापेक्ष विन्यास विरोधी होने के लिए स्थापित किया गया था। इसके अलावा, विधि की बहुमुखी प्रतिभा 1,4-स्टेरिकली कंजस्टेड ब्यूटिनोलाइड सबस्ट्रक्चर पर न्यूक्लियोफाइल के अतिरिक्त प्रदर्शित होती है। प्रक्रिया अत्यधिक एनन्तिॐएरेरिकल्ली समृद्ध 3-बुतेनोलिदे प्रतिस्थापित 3-अ्इनूक्सिन्दोलेस की एक विस्तृत श्रृंखला तक आसान पहुंच प्रदान करता है, जो प्राकृतिक उत्पादों और जैविक रूप से सक्रिय यौगिकों में आवश्यक संरचनात्मक रूप है।

अध्याय 3, चिराल टेट्रा की कुशल तैयारी के लिए इसाटिन व्युत्पन्न केटिमिन के असममित एलिलिलेशन से संबंधित 3-एलिल-3-एमिनोक्सिंडोल्स को प्रतिस्थापित किया गया है। यहां भी हमने

एल्मैन के चिराल सहायक टर्ट-ब्यूटेनसल्फिनमाइड का उपयोग किया है, जो असममित उत्सर्जन प्रतिक्रियाओं के लिए एक गहन रूप से उपयोगी चिराल सहायक है और यह विधि चिराल टेट्रा प्रतिस्थापित 3-एलिल-3-एमिनोक्सिंडोल्स को प्रतिस्थापित करने की एक कुशल तैयारी साबित हुई है; प्रतिक्रिया को आकार देने में एक योजक के रूप में केएफ की प्रमुख भूमिका के साथ सरल जस्ता मध्यस्थ अत्यधिक डायस्टोसेलेक्टीव एलिलीलेशन प्रतिक्रिया के प्रकाश में। वर्तमान पद्धति बहुत ही कुशल पाई जाती है और चिराल क्वाटरनेरी होमोलिकल अमाइन । का उत्पादन करने के लिए एक आसान पहुंच भी प्रदान करती है । ई। 3-एलिल-3-एमिनोक्सिंडोल्स जिनमें आसन्न तृतीयक स्टीरियोसेन्टर होता है।

अध्याय 4 में, हमने यह भी दर्शाया है कि, न्यूक्लियोफिलिक जोड़ द्वारा इसाटिन के एल्डोल-प्रकार साइनोमाइथिलेशन प्राकृतिक उत्पादों और फार्मास्यूटिकल्स में एक महत्वपूर्ण और सामान्य संरचनात्मक कोर, 3-प्रतिस्थापित-3-हाइड्रोक्साइक्सिंडोल तक सीधे पहुंच प्रदान करता है। अध्याय 4 के पहले खंड में, 3-हाइड्रॉक्सी-3-साइनोमाइथिल ऑक्सीन्डोल के संश्लेषण के लिए टीएमएसएएन के साथ विभिन्न एन-ट्राइटीलिसाटिनों का व्यावहारिक रूप से सरल और अत्यधिक कुशल सीएसएफ मध्यस्थ साइनोमाइथिलेशन स्थापित किया गया है। यह विधि मध्यम से बहुत अच्छी पैदावार में β-ह्य्द्रोक्सिन्त्रतृलेस प्रदान करती है और पहले रिपोर्ट की गई प्रक्रियाओं के लिए एक मूल्यवान और प्रतिस्पर्धी विकल्प का प्रतिनिधित्व करती है। इसके अलावा, वर्तमान पद्धति की सिंथेटिक उपयोगिता प्राकृतिक उत्पादों वाले औषधीय महत्वपूर्ण 3-हाइड्रॉक्सी इंडोल के मध्यवर्ती की कुशल असेंबली में वर्तमान प्रोटोकॉल को लागू करके दिखाया गया है। इसके अलावा, दूसरे खंड में हल्के परिस्थितियों में एन-संरक्षित आइसैटिन के लिए एआरएल एसीटोनिट्रियल के डीबीयू-मध्यस्थ अत्यधिक डायस्टिरोसेलेक्टिव जोड़ द्वारा 3-प्रतिस्थापित 3-हाइड्रोक्साइक्सिंडोल के लिए एक कुशल, धातु मुक्त दृष्टिकोण विकसित किया गया है। प्रतिक्रिया अच्छी उपज और उत्कृष्ट दिअस्तेरेओसेलेक्तिवित्री में संबंधित क्यनोमेथ्य्लतेद अद्दुक्त्स उत्पादन करने के लिए सुचारू रूप से आगे बढ़ती है। बेंजाइल साइनाइड के साथ एन-ट्राइटीलिसाटिन के अलडोल-प्रकार साइनोमाइथिलेशन की ओर यांत्रिक अंतर्दृष्टि डीएफटी गणनाओं द्वारा प्राप्त की गई थी। अध्ययन से संकेत मिलता है कि गठित प्रमुख डायस्टिरोसेलेक्टिव उत्पाद एंटी उत्पाद होगा। साइनोमाइथिलेशन प्रतिक्रिया की बहुमुखी प्रतिभा को सरल चरणों में प्राकृतिक उत्पाद एनालॉग के अग्रिम मध्यवर्ती में साइनोमाइथिल आदी को परिवर्तित करके भी सत्यापित किया जाता है।

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Abbreviation	Full form
Ar	Aryl
AcOLi	Lithium acetate
AgOAc	Silver acetate
$BF_3.OEt_2$	Boron trifluoride etherate
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
^{t}Bu	*tert*-Butyl
BuLi	n-Butyllithium
Bu_3SnH	Tributyltin hydride
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
$CHCl_2CHCl_2$	Tetrachloroethane
cm^{-1}	Wavenumbers
°C	Degrees Celsius
$Cu(OAc)_2$	Copper acetate
Cs_2CO_3	Cesium carbonate
CH_3ONa	Sodium methoxide
CsF	Cesium fluoride
dr	Diastereomeric ratio
DMAP	*N*, *N*-Dimethylpyridin-4-amine
DMF	Dimethylformamide
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

ee	Enantiomeric excess
ESI-TOF	Electrospray ionization - Time-of-flight
EtOAc	Ethyl acetate
EtOH	Ethanol
FTIR	Fourier transform infrared
H_2O	Water
HMPA	Hexamethylphosphoramide
h	Hour
In	Indium
$In(OTf)_3$	Indium trifluoromethanesulfonate
J	Coupling constant
λ	Wavelength
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KOH	Potassium hydroxide
KO^tBu	Potassium *tert*-butoxide
KOAc	Potassium acetate
$La(O^iPr)_3$	Lanthanum isopropoxide
LDA	Lithium diisopropylamide
LiCl	Lithium chloride
LiHMDS	Lithium bis(trimethylsilyl)amide
min	Minute
MTBE	Methyl *tert*-butyl ether
m	Multiplet
MBH	Morita-Baylis-Hillman
MHz	Megahertz
mL	Millilitre
MeOD	Deuterated methanol
μL	Microlitre
NaOMe	Sodium methoxide
NaOAc	Sodium acetate

PMB	*para*-Methoxy benzyl
PhONa	Sodium phenoxide
p-TsOH	*para*-Toluenesulfonic acid
s	Singlet
$Sc(OTf)_3$	Scandium trifluoromethanesulfonate
Na_2CO_3	Sodium carbonate
NaO^tBu	Sodium *tert*-butoxide
TASF	*Tris*(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra-*N*-butylammonium floride
TBS	*tert*-butyldimethylsilyl
^{t}BuOH	*tert*-Butyl alcohol
TEA	Triethyl amine
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TMSAN	Trimethylsilyl acetonirile
Tr	Trityl or triphenylmethyl
UV	Ultraviolet
$Yb(OTf)_3$	Ytterbium trifluoromethanesulfonate
Zn	Zinc