STEREOSELECTIVE VINYLOGOUS ALDOL REACTIONS OF 3-ALKYLIDENE-2-OXINDOLES

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by

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Submitted

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to the

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Dedicated

to

my beloved Parents

and Family

CERTIFICATE

This is to certify that the thesis entitled," **Stereoselective Vinylogous Aldol Reactions of 3-Alkylidene-2-oxindoles** " being submitted by **Mr. Krishna Kumar** 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. Krishna Kumar** 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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Krishna Kumar

ABSTRACT

The thesis entitled "**Stereoselective Vinylogous Aldol Reactions of 3-Alkylidene-2-oxindoles**" deals with development of stereoselective vinylogous aldol reactions of 3-alkylidene-2-oxindole with activated carbonyl compounds and vinylogous nucleophilic addition of 3-alkenyl-2-silyloindole to reactive isobenzopyrolium intermediate for the synthesis of various highly functionalized scaffolds. The highlight of the work described in this thesis lies in the highly stereoselective reaction described that enables realization of challenging reaction yielding stereochemically pure compounds that are utmost importance for pharmaceutical application.

This thesis is mainly focused on the stereoselective synthesis of vinylogous adducts and has been divided into four chapters. The first chapter describes the importance of stereochemistry and methodology to develop the stereoselective molecule as well as the concept of vinylogy and different type of vinylogous nucleophile. This chapter emphasizes the organocatalytic approaches to obtain the stereoselective adduct.

Chapter 2 describes the reactivity of vinylogous 3-alkylidene-2-oxindole for asymmetric aldol methodology. In this chapter, we have established an enantioselective vinylogous aldol reaction of 3-alkylidene 2-oxindoles with α-ketoesters providing a chiral quaternary δ−hydroxy−3-alkylidene oxindoles catalyzed by bifunctional quinine derived thiourea. The activation of vinylogous nucleophile and electrophile through synchronized H-bond afforded aldol adduct in high yield (upto 92%) while obtaining high levels of regio- (100% γ-selective), diastereo (*E/Z* = >19:1) and enantio-control (upto 99% ee). A broad range of enantio-enriched tertiary alcohols have been synthesized. The regio, *E/Z* selectivity and absolute configuration of chiral centre of the aldol products were established by single crystal X-ray analysis of an analogue.

Chapter 3, deals with the asymmetric synthesis of chiral 4-hydroxy 4′-substituted pyrazolones by vinylogous aldol reaction of pyrazole-4,5-diones with 3-alkylidene-2-oxindoles. In this chapter we describe the enantioselective vinylogous aldol reaction

of 3-alkylidene 2-oxindoles with pyrazole-4,5-diones providing a chiral 4-hydroxy 4′-subsituted pyrazolone catalyzed by bifunctional quinine derived amide catalyst. An extensive optimization of quinine catalysts has been performed. This reaction proceeds by the activation of vinylogous nucleophile and electrophile through formation of instantaneous H-bond affording high yield (upto 98%) with high levels of regio- (100% γ-selective), diastereo (*E/Z* = >19:1) with moderate enantiocontrol (upto 72% *ee*). With this reaction a broad range of 4-hydroxy 4′-substituted pyrazolone has been synthesized.

Chapter 4 describes the silver tetrafluoroborate catalyzed vinylogous addition to reactive isochromenylium intermediate generated *in situ* for the synthesis of functionalized 1*H*-isochromenes. A series of functionalized 1*H*-isochromenes comprising of oxindole core have been synthesized. The aliphatic, as well as aromatic substituted alkynes, of *ortho*-alkynyl arylaldehydes were successfully tested for the regioselective intramolecular 6-endo-*dig*-cyclization followed by vinylogous addition of substituted 3-alkenyl-2-silyloxindole leading to functionalized 1*H*-isochromene in high yield (upto 82%) and high levels of regio- (100% γ-selective), diastereo (*E/Z* = >19:1) control.

सारांश

"3-एल्काईलीडीन-2-ऑक्सीइण्डोल्स के स्टीरिओसेलेक्टिव विनाइलोजस एल्डोल रिएक्शन्स " नामक यह थीसिस, 3-एल्काईलीडीन-2-ऑक्सीइण्डोल्स की सक्रीय कार्बोनिल यौगिकों स्टीरिओसेलेक्टिव विनाइलोजस एल्डोल रिएक्शन्स तथा 3-एल्किलीनिल-2-सिलाईलोइण्डोल की सक्रीय आइसोबेंजोपाइरोलिनियम इंटरमीडिएट के साथ, अत्यधिक अभिक्रियाशील स्काफ्फ़ोल्ड्स के निर्माण हेतु विनाइलोजस न्युक्लियोफिलिक संयोग अभिक्रियाओ के विकास से सम्बंधित है। थीसिस में वर्णित कार्य को विशेषता, उच्च कोटि की उन स्टीरिओसेलेक्टिव अभिक्रियाओं में है जो की फार्मास्युटिकल एप्लिकेशन के लिए अत्यधिक महत्व रखने वाले त्रिविमीय रूप से शुद्ध यौगिकों के उत्पादन करने वाली अभिक्रियाओं को साकार करने की चुनौती को पूर्ण करने में सक्षम बनाता है।

यह थीसिस मुख्य रूप से विनियोजस एडक्ट्स के स्टिरियोसेलेक्टिव संश्लेषण पर केंद्रित है और इसे चार अध्यायों में विभाजित किया गया है। पहला अध्याय स्टिरियोकेमिस्ट्री और कार्यप्रणाली के महत्व का वर्णन करता है जो कि स्टिरियोसेलेक्टिव अणु विकसित किया जा सके और साथ ही साथ विनियोलॉजी और विभिन्न प्रकार के विनियोलोजी न्यूक्लियोफाइल की अवधारणा को विकसित किया जा सके। यह अध्याय स्टिरियोसेलेक्टिव एडक्ट्स तो प्राप्त करने के लिए ऑर्गेनोलेटिक पद्धति पर जोर देता है।

अध्याय 2 विनियोजस 3-एल्काइलीडीन-2-ओक्सीइंडोल्स की असममित एल्डोल पद्धति के प्रति क्रियाशीलता का वर्णन करता है। इस अध्याय में 3-एल्काइलीडीन-2-ओक्सीइंडोल्स की α-कीटो एस्टर के साथ बाईफंक्शनल क्विनीन से प्राप्त थायोयूरिया द्वारा उत्प्रेरित इनंशियो सेलेक्टिव विनियोलोजस अभिक्रिया को स्थापित किया गया है जिस से काइरल कवाटरनरी δ-हाइड्रोक्सी 3-एल्काइलीडीन-2-ओक्सीइन्डोल्स प्राप्त होता है। विनियोलोजस न्यूक्लियो फाइल तथा इलेक्ट्रोफाइल के सक्रियण ने सिंक्रोनाइअज्ड H- बंध द्वारा एल्डोल एडक्ट की उच्च मात्रा (92 % तक), उच्च स्तर रेजिओ - (100% γ-सेलेक्टिव), डाई स्टीरियो (E/Z ≥ 19:1) तथा इनंशियो – नियंत्रण (99% तक) में प्राप्ति करवाई। इनंशियो-प्रचुर तृतीयक अल्कोहोलों की एक विस्तृत श्रंखला संश्लेषित की गई। एल्डोल उत्पादों के चिराल केन्द्रों की रेजिओ, E/Z सेलेक्टिविटी तथा निरपेक्ष विन्यास को एक समजातीय के एकल क्रिस्टल X- किरण विश्लेषण द्वारा स्थापित की गई।

अध्याय 3 पाईराजोल -4,5- डाईओंस की 3-एल्काइलीडीन-2-ओक्सीइंडोल्स की विनाईलोजस एल्डोल अभिक्रिया द्वारा काइरल 4- हाइड्रोक्सी 4'–प्रतिस्थापित पाईराजोलोन्स के असममित

संश्लेषण से सम्बंधित है। इस अध्याय में 3-एल्काइलीडीन-2-ओक्सीइंडोल्स की पाईराजोल-4,5-डाईओंस के साथ इनंशियो सेलेक्टिव विनियोलोजस एल्डोल अभिक्रिया का वर्णन किया गया है जिसमे बाईफंक्शनल क्विनीन से प्राप्त एमाइड उत्प्रेरक द्वारा उत्प्रेरण होने पर काईरल 4-हाइड्रोक्सी 4'-प्रतिस्थापित पाईराजोलोन की प्राप्ति होती है। कुनैन उत्प्रेरक का एक व्यापक ओप्टीमाईजेशन प्राप्त किया गया। यह अभिक्रिया तात्कालिक H-बंध के निर्माण द्वारा विनाईलोजस न्यूक्लियोफाइल तथा इलेक्ट्रोफाइल के सक्रियण द्वारा अग्रसर होती है जिससे कि रेजिओ (100% γ-सेलेक्टिव), डाई स्टीरियो (E/Z ≥ 19:1) तथा माध्यम इनंशियो नियंत्रण (72% ee तक) के साथ उच्च लब्धि (98% तक) प्राप्त होती हैं।

अध्याय 4 में फंक्शनलाइज्ड 1H-आइसोक्रोमीन के संश्लेषण हेतु स्वस्थाने उत्पन्न आइसोक्रोमिलिनियम इंटरमीडिएट से सिल्वर टेट्राफ्लुओरोबोरेट द्वारा उत्प्रेरित विनाईलोजस संयोग का वर्णन किया गया है। ओक्सी इन्डोल्स केंद्र वाले फंक्शनलाइज्ड 1H-आइसोक्रोमीनों की एक श्रंखला का संश्लेषण किया गया। ओर्थो-एल्काईनिलएराईलएल्डीहाईड के एलीफैटिक तथा साथ ही एरोमेटिक प्रतिस्थापित एल्काईन्स का रेजिओ सेलेक्टिव अंतराणुक 6- एंडो–dig–चक्रीयकरण तथा तत्पश्चात प्रतिस्थापित 3 – एल्कीनिल – 2- साइलोक्सी इण्डोल के विनाईलोजस संयोग का सफलता पूर्वक परीक्षण किया गया जिससे फंक्शनलाईज्ड *1H*-आइसोक्रोमीन उच्च लब्धि (82% तक) तथा रेजिओ – (100% γ-चयनात्मक), डिया स्टीरियो (E / Z ≥19: 1) नियंत्रण की प्राप्ति संभव हुई।

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List of Abbreviations

Abbreviation	*Full form*
Ar	Aryl
AcOLi	Lithium acetate
ACN	Acetonitrile
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
$CHCl_2CHCl_2$	Tetrachloroethane
cm^{-1}	Wavenumbers
°C	Degrees Celsius
Cu(OAc)	Copper acetate
Cs_2CO_3	Cesium carbonate
CH_3ONa	Sodium methoxide
CsF	Cesium fluoride
DCM	Dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMA	Dimethylacetamide
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
LED	Light-emitting diode
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
μL	Microlitre

NaOMe	Sodium methoxide
NaOAc	Sodium acetate
PC	Photocatalyst
PhONa	Sodium phenoxide
p-TsOH	*para*-Toluenesulfonic acid
s	Singlet
$Sc(OTf)_3$	Scandium trifluoromethanesulfonate
Na_2CO_3	Sodium carbonate
rt	Room temprature
NaO^tBu	Sodium *tert*-butoxide
TBHP	*tert*-butyl hydroperoxide
TBAF	Tetra-*N*-butylammonium floride
TFA	Trifluoroacetoc acid
TFAA	Trifluoroacetic anhydride
TBS	*tert*-butyldimethylsilyl
TBPB	*tert*-butylperoxybenzoate
TIPS	Triisopropylsilyl
^tBuOH	*tert*-Butyl alcohol
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TMSAN	Trimethylsilyl acetonirile
Tr	Trityl or triphenylmethyl
UV	Ultraviolet
$Yb(OTf)_3$	Ytterbium trifluoromethanesulfonate
Zn	Zinc