Asymmetric Synthesis of Non-Biaryl C-C Atropisomers and Spiro-Oxindoles

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Asymmetric Synthesis of Non-Biaryl C-C Atropisomers and Spiro-Oxindoles

by

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This work is dedicated to my parents and

my cherished siblings.

CERTIFICATE

This certifies that the thesis titled "**Asymmetric Synthesis of Non-Biaryl C-C Atropisomers and Spiro-Oxindoles**," submitted by **Ms. Manju Devi** to the Indian Institute of Technology Delhi for the Doctor of Philosophy degree in Chemistry, constitutes a genuine record of her research work. Manju Devi has worked under my guidance and supervision and has met the criteria for the submission of this thesis, which, to my knowledge, has attained the required level of excellence. The findings presented in this dissertation have not been submitted, in whole or in part, to any other university or institution for the conferment of any degree or diploma.

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Manju Devi

ABSTRACT

The doctoral thesis titled "**Asymmetric Synthesis of Non-Biaryl C-C Atropisomers and Spiro-Oxindoles**" encompasses five chapters focused on the advancement of organocatalytic enantioselective C-C and C-O bond formation. Chapter 1 is introductory and briefly explains the terminology and importance of asymmetric catalysis. In chapters 2 and 3, the concept of VQM has been elaborated and axially chiral styrenes containing barbiturates are synthesized in chapter 2 while axially chiral styrenes bearing multiple stereogenic elements are constructed in chapter 3. In chapters 4 and 5, oxindole fused spiro [furo[2,3-d]pyrimidines] and spirodihydrobezofuran are synthesized enantioselectively using organocascade approach.

Chapter 1: provides a concise overview of the importance of chirality and its practical aspects with intriguing examples. It covers methods of asymmetric induction, with special emphasis on organocatalysis, followed by its brief history and modes of activation including covalent and non-covalent organocatalysis. Then, a brief introduction to atropisomerism, axially chiral styrenes, spirocycles and spiro-oxindoles is provided, followed by various challenges and strategies for synthesising them.

Chapter 2: describes the inaugural enantioselective method for axially chiral barbiturate-substituted styrenes from vinylidene *ortho*-quinone methide (VQM) derived from 1-alkynylnaphthalen-2-ols, facilitated by quinidine-derived bifunctional catalyst *via* C-5 functionalization of barbituric acids. This mild and straightforward protocol offers tolerance to a broad range of substrates bearing electronically diverse functional groups to afford axially chiral barbiturate bearing styrenes in excellent yield (up to 99%), diastereo- and enantioselectivities (up to 99%). The scale-up synthesis, post synthetic transformations and stereodivergent synthesis demonstrate its synthetic potential.

Chapter 3: In this chapter, an enantioselective methodology is demonstrated for synthesizing highly functionalized styrenes bearing multiple stereogenic elements. This methodology involves the nucleophilic addition of nucleophile generated from β-keto esters in presence of quinine-derived bifunctional squaramide catalyst on *in situ* generated vinylidene ortho-quinone methide

(VQM) from 1-alkynylnaphthalen-2-ols. A series of axially chiral styrenes bearing axial and central chirality has been synthesized successfully with excellent yield (up to 90%) and stereoselectivity (dr up to 98:2, er up to 96:4) at room temperature.

Chapter 4: Here, we have developed an unparalleled enantioselective methodology to access oxindole-fused spiro [furo[2,3-*d*]pyrimidines] with high bond efficiency, involving the formation of two new C-C bonds and one C-O bond with two contiguous stereocenters. A library of chiral spiro[furo[2,3-d]pyrimidines] with various substitutions has been synthesised with high yields (up to 90%) and exceptional stereoselectivity (dr up to 99:1, er up to 97:3) at room temperature. The scale-up synthesis, while maintaining reactivity and selectivity, showcases its synthetic potential. The reaction mechanism involving ammonium ylide and the subsequent synthesis of spirocyclopropylbarbiturate has been investigated using ^{1}H NMR and HRMS titrations.

Chapter 5: illustrates the unprecedented protocol to access chiral oxindole fused spirodihydrobezofuran *via* organocascade approach, applicable to *N*-unprotected as well as protected 3-chlorooxindoles and the spiro product formed with high bond efficiency (1 new C-C and 1 C-O bond) with two contiguous stereocenters. A series of chiral oxindole fused spirobezofuran has been synthesized successfully with high yield (up to 82%) and excellent stereoselectivity (dr and er up to 99:1) at room temperature. Further, the potential practicality of the protocol is shown by gram scale and stereodivergent synthesis without compromising the reaction outcome. Dynamic HRMS titrations have been conducted to propose the reaction pathway.

सार

डॉक्टोरल शोध प्रबंध *"असाममित संश्लेषण: नॉन-बायरेल C–C एट्रोपआइसोमर्स एवं स्पायरो-ऑक्सिनडोल्स"* में पाँच अध्याय शामिल हैं, जो ऑर्गेनोकैटालिटिक एनैंटियोचयनात्मक C–C और C–O बंध निर्माण में नवीन प्रगति पर केंद्रित हैं।

अध्याय 1 में समरूपता (chirality) के महत्व और उसके व्यावहारिक अनुप्रयोगों की संक्षिप्त रूपरेखा दी गई है। इसमें असाममित प्रेरण (asymmetric induction) की विधियों का उल्लेख किया गया है, विशेष रूप से ऑर्गेनोकैटालिसिस पर बल देते हुए। इसके इतिहास, क्रियाविधि (covalent तथा non-covalent activation) और विभिन्न यौगिकों जैसे एट्रोपआइसोमर्स, अक्षीय सममित स्टाइरीन, स्पायरोसाइक्ल्स और स्पायरो-ऑक्सिनडोल्स की जानकारी दी गई है। साथ ही, इनकी संश्लेषणात्मक चुनौतियों और रणनीतियों का भी वर्णन है।

अध्याय 2 में पहली बार ऐसे एनैंटियोचयनात्मक तरीके का विवरण है, जिसमें 1-ऐल्काइनयुक्त नेफ्थालीन-2-ऑल से व्युत्पन्न विनाइलिडीन ऑर्थो-क्विनोन मिथाइड्स (VQM) के माध्यम से बार्बिट्यूरेट-युक्त अक्षीय सममित स्टाइरीन यौगिकों का निर्माण किया गया है। यह प्रक्रिया क्विनिडीन-आधारित द्विक्रीयात्मक उत्प्रेरक द्वारा बार्बिट्यूरिक अम्लों के C-5 स्थान पर क्रियाशीलता के माध्यम से सम्पन्न होती है। यह सरल और मृदु विधि विभिन्न इलेक्ट्रॉनिक गुणों वाले सब्सट्रेट्स को सहन करते हुए उच्च उपज (99% तक) और असाधारण डायस्टेरियो- तथा एनैंटियोचयनात्मकता (99% तक) प्रदान करती है। इस विधि की उपयोगिता को बड़े पैमाने पर संश्लेषण, उप-संश्लेषणीय रूपांतरण तथा स्टिरियोडायवर्जेंट संश्लेषण द्वारा दर्शाया गया है।

अध्याय 3 में एक ऐसी एनैंटियोचयनात्मक विधि विकसित की गई है, जो बहु-स्टीरियोजेनिक केंद्रों वाले स्टाइरीन यौगिकों के संश्लेषण के लिए सक्षम है। यह प्रक्रिया इन-सीटू उत्पन्न VQM पर β-कीटो एस्टर से जनित न्यूक्लियोफाइल की क्विनिन-आधारित स्क्वैरामाइड उत्प्रेरक की उपस्थिति में न्यूक्लियोफिलिक अभिक्रिया पर आधारित है। परिणामस्वरूप, अक्षीय और केन्द्रीय सममितता वाले स्टाइरीन यौगिक 90% तक उपज और उच्च स्टीरियोचयनात्मकता (dr: 98:2 तक, er: 96:4 तक) के साथ संश्लेषित किए गए हैं।

अध्याय 4 में ऑक्सिनडोल-संलग्न स्पायरो [फ्यूरो[2,3-d]पाइरीमिडिन] यौगिकों के संश्लेषण के लिए एक अद्वितीय एनैंटियोचयनात्मक विधि प्रस्तुत की गई है। इस प्रक्रिया में दो C–C और एक C–O बंध का निर्माण

होता है, जिससे दो सतत स्टीरियोजेनिक केंद्र निर्मित होते हैं। विभिन्न प्रतिस्थापन वाले यौगिकों की एक श्रृंखला 90% तक उपज और असाधारण स्टीरियोचयनात्मकता (dr: 99:1, er: 97:3 तक) के साथ प्राप्त की गई है। संश्लेषण की प्रतिक्रिया प्रक्रिया को ^{1}H NMR और HRMS टाइट्रेशन द्वारा समझा गया है, जिसमें एक अमोनियम ग्लाइड मध्यवर्ती प्रस्तावित किया गया है।

अध्याय 5 में एक अभूतपूर्व ऑर्गेनोकैस्केड विधि द्वारा ऑक्सिनडोल-संलग्न स्पायरोडायहाइड्रोबेंज़ोफ्यूरान का निर्माण प्रस्तुत किया गया है, जो संरक्षित और अप्रतिबंधित 3-क्लोरोऑक्सिनडोल्स दोनों पर लागू होती है। यह प्रक्रिया दो नए बंध (एक C–C और एक C–O) के निर्माण के साथ दो स्टीरियोजेनिक केंद्रों को निर्मित करती है। संश्लेषित उत्पादों की श्रृंखला को 82% तक उपज और उत्कृष्ट स्टीरियोचयनात्मकता (dr: 99:1 तक, er: 99:1 तक)) के साथ प्राप्त किया गया है। इस प्रक्रिया की व्यावहारिकता को ग्राम-स्तरीय संश्लेषण और स्टिरियोडायवर्जेंट विधि द्वारा सिद्ध किया गया है। प्रतिक्रिया तंत्र को समझने हेतु डायनेमिक HRMS टाइट्रेशन किए गए हैं।

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Abbreviation	Full form
Ac	Acetate
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
^{t}Bu	*tert*-Butyl
BuLi	Butyllithium
$CDCl_3$	Deuterated chloroform
Cs_2CO_3	Cesium carbonate
CH_2Cl_2	Dichloromethane
CPME	Cyclopentyl methyl ether
CPA	Chiral Phosphoric Acid
CF_3Ph	Trifluoro toluene
CuI	Copper iodide
cm^{-1}	Wavenumbers
°C	Degrees Celsius
dr	Diastereomeric ratio
DET	Diethyl tartrate
DIPEA	*N*, *N*-Diisopropylethylamine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
d	Doublet
dd	Doublet of doublets
d_6-DMSO	Deuterated dimethyl sulfoxide
δ	Chemical shift
er	Enantiomeric ratio
ee	Enantiomeric excess
ESI-TOF	Electrospray ionization - Time-of-flight

EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
FTIR	Fourier transform infrared
H_2O	Water
h	Hour
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
J	Coupling constant
λ	Wavelength
LUMO	Lowest unoccupied molecular orbital
LDA	Lithium diisopropylamide
min	Minute
MTBE	Methyl *tert*-butyl ether
m	Multiplet
MHz	Megahertz
mL	Millilitre
NBS	*N*-Bromosuccinimide
μL	Microlitre
p-TsOH	*p*ara-Toluenesulfonic acid
s	Singlet
SOMO	Singly unoccupied molecular orbital
TFA	Trifluoroacetic acid
TfOH	Triflic acid
TCA	Trichloroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TBAF	Tetra-*N*-butylammonium floride
UV	Ultraviolet